Leadless Cardiac Pacemaker

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Policy

Aetna considers leadless cardiac pacemakers experimental and investigational for arrhythmias and all other indications because of insufficient evidence of its safety and effectiveness.

Aetna considers the use of combined leadless pacemaker and subcutaneous implantable cardioverter defibrillators for ventricular tachycardia and all indications experimental and investigational because the effectiveness of this approach has not been established.

Aetna considers the use of combined leadless pacemaker and atrioventricular nodal ablation experimental and investigational for the treatment of atrial fibrillation because the effectiveness of this approach has not been established.

See also CPB 0585 - Cardioverter-Defibrillators (../500_599/0585.html).

Background
A leadless cardiac pacemaker system is a pulse generator with built-in battery and electrode for implantation in a cardiac chamber via a transfemoral catheter approach.

Leadless pacemakers are designed to achieve the same pacing results as a standard pacemaker, but the process for implanting the leadless pacemaker is different from standard pacemakers. The leadless pacemaker is placed via a catheter into the right ventricle. Unlike a standard pacemaker, a leadless pacemaker does not require creation of a surgical pocket for the pacemaker, and it requires no leads. The pacemaker battery life is equivalent to that of similar standard single chamber pacemakers.

Advantages of a leadless pacemaker over a standard pacemaker is avoidance of a surgical scar or lump under the skin where the pacemaker sits. Additional potential advantages include avoidance of problems with lead placement and reduction in risk of infections. A number of leadless cardiac pacemakers are currently in development, including the Nanostim Leadless Pacemaker (St. Jude Medical, St. Paul, MN) and the Micra Transcatheter Pacing System (Medtronic, Minneapolis, MN).

Reddy et al (2014) reported on a prospective, non-randomized study of the safety and clinical performance of a leadless cardiac pacemaker (LCP). The primary safety end point was freedom from complications at 90 days. Secondary performance end-points included implant success rate, implant time, and measures of device performance (pacing/sensing thresholds and rate-responsive performance). The mean age of the patient cohort (n = 33) was 77 ± 8 years, and 67 % of the patients were male (n = 22/33). The most common indication for cardiac pacing was permanent atrial fibrillation with atrio-ventricular block (n = 22, 67 %). The implant success rate was 97 % (n = 32). Five patients (15 %) required the use of more than 1 LCP during the procedure. One patient developed right ventricular perforation and cardiac tamponade.
during the implant procedure, and eventually died as the result of a stroke. The overall complication-free rate was 94% (31/33). After 3 months of follow-up, the measures of pacing performance (sensing, impedance, and pacing threshold) either improved or were stable within the accepted range.

Reddy and associates (2015) studied a miniaturized, fully self-contained LCP that is non-surgically implanted in the right ventricle with the use of a catheter. In this multicenter study, these researchers implanted an active-fixation LCP in patients who required permanent single-chamber ventricular pacing. The primary efficacy end-point was both an acceptable pacing threshold (less than or equal to 2.0 V at 0.4 msec) and an acceptable sensing amplitude (R wave greater than or equal to 5.0 mV, or a value equal to or greater than the value at implantation) through 6 months. The primary safety end-point was freedom from device-related serious adverse events through 6 months. In this ongoing study, the pre-specified analysis of the primary end-points was performed on data from the first 300 patients who completed 6 months of follow-up (primary cohort). The rates of the efficacy end-point and safety end-point were compared with performance goals (based on historical data) of 85% and 86%, respectively. Additional outcomes were assessed in all 526 patients who were enrolled as of June 2015 (the total cohort). The LCP was successfully implanted in 504 of the 526 patients in the total cohort (95.8%). The intention-to-treat primary efficacy end-point was met in 270 of the 300 patients in the primary cohort (90.0%; 95% confidence interval [CI]: 86.0 to 93.2, p = 0.007), and the primary safety end-point was met in 280 of the 300 patients (93.3%; 95% CI: 89.9 to 95.9; p < 0.001). At 6 months, device-related serious adverse events were observed in 6.7% of the patients; events included device dislodgement with percutaneous retrieval (in 1.7%), cardiac perforation (in 1.3%), and pacing-threshold elevation requiring percutaneous retrieval and device replacement (in 1.3%). The authors concluded that the LCP met pre-specified pacing and sensing requirements in the large majority of patients; device-related
serious adverse events occurred in approximately 1 in 15 patients. The main drawback of this study was its short-term follow-up.

Miller et al (2015) stated that despite significant advances in battery longevity, lead performance, and programming features since the first implanted permanent pacemaker was developed, the basic design of cardiac pacemakers has remained relatively unchanged over the past 50 years. Because of inherent limitations in their design, conventional (transvenous) pacemakers are prone to multiple potential short- and long-term complications. Accordingly, there has been intense interest in a system that is capable of providing the symptomatic and potentially life-saving therapies of cardiac pacemakers while mitigating many of the risks associated with their weakest link – the transvenous lead. The authors concluded that a LCP system represents the future of cardiac pacing systems, similar to the transition that occurred from the use of epicardial pacing systems to the familiar transvenous systems of today. These researchers summarized the current evidence and potential benefits of LCP systems, which are either commercially available (in Europe) or under clinical investigation.

Knops and colleagues (2015) noted that a LCP system was recently introduced to overcome lead-related complications of conventional pacing systems. To date, long-term results of an LCP system are unknown. These investigators evaluated the complication incidence, electrical performance, and rate response characteristics within the first year of follow-up of patients implanted with an LCP. They retrospectively assessed intermediate-term follow-up data for 31 of 33 patients from the LEADLESS trial cohort who had an indication for single-chamber pacing and received an LCP between December 2012 and April 2013. The mean age of the cohort was 76 ± 8 years, and 65% were male. Between 3 and 12 months of follow-up, there were no pacemaker-related adverse events reported. The pacing performance results at 6- and 12-
month follow-up were, respectively, as follows: mean pacing threshold (at a 0.4-ms pulse width), 0.40 ± 0.26 V and 0.43 ± 0.30 V; R-wave amplitude 10.6 ± 2.6 mV and 10.3 ± 2.2 mV; and impedance 625 ± 205 ohms and 627 ± 209 ohms. At the 12-month follow-up in 61% of the patients (n = 19 of 31), the rate response sensor was activated, and an adequate rate response was observed in all patients. The authors concluded that the LCP demonstrated very stable performance and reassuring safety results during intermediate-term follow-up. They stated that these results support the use of the LCP as a promising alternative to conventional pacemaker systems; continued evaluation is warranted to further characterize this system.

Ritter et al (2015) described the early performance of a novel self-contained miniaturized pacemaker. Patients having Class I or II indication for ventricular demand (VVI) pacing underwent implantation of a Micra transcatheter pacing system, from the femoral vein and fixated in the right ventricle using 4 protractible nitinol tines. Pre-specified objectives were greater than 85% freedom from unanticipated serious adverse device events (safety) and less than 2 V 3-month mean pacing capture threshold at 0.24 ms pulse width (efficacy). Patients were implanted (n = 140) from 23 centers in 11 countries (61% male, mean age of 77.0 ± 10.2 years) for atrio-ventricular block (66%) or sinus node dysfunction (29%) indications. During mean follow-up of 1.9 ± 1.8 months, the safety endpoint was met with no unanticipated serious adverse device events. Thirty adverse events related to the system or procedure occurred, mostly due to transient dysrhythmias or femoral access complications. One peri-cardial effusion without tamponade occurred after 18 device deployments. In 60 patients followed to 3 months, mean pacing threshold was 0.51 ± 0.22 V, and no threshold was ≥2 V, meeting the efficacy endpoint (p < 0.001). Average R-wave was 16.1 ± 5.2 mV and impedance was 650.7 ± 130 ohms. The authors concluded that early assessment showed that the transcatheter
pacemaker can safely and effectively be applied. Moreover, they stated that long-term safety and benefit of the pacemaker will further be evaluated in the trial.

Sperzel et al (2015) stated that despite undisputable benefits, conventional pacemaker therapy is associated with specific complications related to the subcutaneous device and the transvenous leads. Recently, 2 miniaturized LCP, Nanostim™ (St. Jude Medical) and Micra™ (Medtronic), which can be completely implanted inside the right ventricle using steerable delivery systems, entered clinical application. The WiCS™-cardiac resynchronization therapy (CRT) system (wireless cardiac stimulation for CRT, EBR Systems) delivers leadless left ventricular endocardial stimulation for cardiac resynchronization. The authors concluded that in addition to obvious cosmetic benefits, leadless pacing systems may have the potential to overcome some complications of conventional pacing. However, they noted that acute and long-term complications still remains to be determined, as well as the feasibility of device explantation years after device placement.

Neuzil and Reddy (2015) stated that traditional trans-venous approach for permanent cardiac pacing can be associated with significant acute and chronic complications related partly to either the insertion of trans-venous lead or subcutaneous placement of pacemaker device. These researchers summarized the current status of a novel self-contained leadless cardiac pacemaker in the first-in-human and subsequent series of feasibility studies in patients indicated for ventricular rate-responsive pacing (VVI). Using a femoral venous approach, the device is implanted at the right ventricular apical septum region. They described the technical and clinical characterization of this innovative technology – 2 different systems of leadless pacemakers are currently implanted to the patients. Up to now, the electrical parameters, such as pacing thresholds, sensing parameters, and pacing impedances, either improved or remained stable within the accepted range. The authors discussed the
potential benefit of leadless cardiac pacing, and concluded that all available data demonstrated the feasibility of this approach.

Kypta and co-workers (2016) stated that conventional pacemaker therapy is limited by short- and long-term complications, most notably device infection. Leadless transcatheter pacing systems (TPS) may be beneficial in this type of patients as they eliminate the need for a device pocket and leads and thus may reduce the risk of re-infection. These researchers evaluated a novel procedure in 6 patients with severe device infection who were pacemaker-dependent. After lead extraction a single chamber TPS was implanted into the right ventricle. Of the 6 patients who underwent lead extraction due to severe device infection at the authors’ institution, 3 were diagnosed with a pocket infection only, whereas the other 3 showed symptoms of both pocket and lead infection. Successful lead extraction and TPS implantation was accomplished in all patients. Four patients were bridged with a temporary pacemaker between 2 hours and 2 days after lead extraction, whereas 2 patients had the TPS implanted during the same procedure just before traditional pacemaker system removal. All patients stayed free of infection during the follow-up period of 12 weeks. An additional positron emission tomography (PET) scan was performed in each patient and indicated no signs of an infection around the TPS. The authors concluded that transcatheter pacemaker implantation was safe and feasible in 6 patients and did not result in re-infection even if implanted before removal of the infected pacemaker system within the same procedure. Therefore, implantation of a TPS may be an option for patients with severe device infection, especially in those with blocked venous access or who are pacemaker-dependent.

Seriwala and associates (2016) noted that cardiac pacemakers are a critical management option for patients with rhythm disorders. Current efforts to develop leadless
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pacemakers have 2 primary goals: (i) to reduce lead-associated post-procedural morbidity, and (ii) to avoid the surgical scar associated with placement. After extensive studies on animal models and technological advancements, these devices are currently under investigation for human use. These investigators reviewed the evidence from animal studies and the technological advancements that have ushered in the era of use in humans. They also discussed different leadless pacemakers currently under investigation, along with limitations and future developments of this innovative concept.

Arkles and Cooper (2016) noted that the role of leadless devices to treat cardiac rhythm disorders and heart failure (HF) is emerging. Subcutaneous defibrillator (S-ICD) and leadless pacemakers were developed to ameliorate the risks associated with chronic transvenous leads. Potential benefits of leadless pacemakers and S-ICD include more favorable infection profile, less risk of venous stenosis or occlusion, and less risk of tricuspid valve insufficiency. The authors concluded that novel implantable leadless monitors for HF represent a novel diagnostic tool that can guide therapy for congestive HF.

Meyer and colleagues (2016) stated that electrical cardiac pacing today is the standard therapy for symptomatic bradycardia. Importantly, despite technical advantages, complications associated with conventional trans-venous pacing leads and pockets are still challenging in a relevant number of patients. Beyond cosmetic benefits, miniaturized leadless pacemaker may partly overcome these limitations and beneficially influence implantation-related physical restrictions. Initial findings with single-chamber pacemakers for right ventricular pacing, which are completely implanted via a femoral venous vascular access, are promising. The authors concluded that leadless pacing offers novel perspectives.
regarding cardiac implantable electronic devices although acute safety and the long-term performance of these systems needs to be determined in more detail.

An assessment by the Canadian Agency for Drugs and Technologies in Health (CADTH, 2015) concluded: "Differences in safety and pacing performance because of design differences between the two leadless pacemakers are currently unknown. Further evaluation of leadless pacemakers for long-term pacing performance, complication rates, and cost-effectiveness compared with traditional pacemakers is required."

Reynolds and colleagues (2016) stated that a leadless intra-cardiac transcatheter pacing system has been designed to avoid the need for a pacemaker pocket and trans-venous lead. In a prospective, multi-center study without controls, a transcatheter pacemaker was implanted in patients who had guideline-based indications for ventricular pacing. The analysis of the primary end-points began when 300 patients reached 6 months of follow-up. The primary safety end-point was freedom from system-related or procedure-related major complications. The primary efficacy end-point was the percentage of patients with low and stable pacing capture thresholds at 6 months (less than or equal to 2.0 V at a pulse width of 0.24 msec and an increase of less than or equal to 1.5 V from the time of implantation). The safety and efficacy end-points were evaluated against performance goals (based on historical data) of 83 % and 80 %, respectively. These researchers also performed a post-hoc analysis in which the rates of major complications were compared with those in a control cohort of 2,667 patients with trans-venous pacemakers from 6 previously published studies. The device was successfully implanted in 719 of 725 patients (99.2 %). The Kaplan-Meier estimate of the rate of the primary safety end-point was 96.0 % (95 % CI: 93.9 to 97.3; p < 0.001 for the comparison with the safety performance goal of 83 %); there were 28 major complications in 25 of 725 patients, and no
dislodgements. The rate of the primary efficacy end-point was 98.3 % (95 % CI: 96.1 to 99.5; p < 0.001 for the comparison with the efficacy performance goal of 80 %) among 292 of 297 patients with paired 6-month data. Although there were 28 major complications in 25 patients, patients with transcatheter pacemakers had significantly fewer major complications than did the control patients (hazard ratio [HR], 0.49; 95 % CI: 0.33 to 0.75; p = 0.001). The authors concluded that in this historical comparison study, the transcatheter pacemaker met the pre-specified safety and efficacy goals; it had a safety profile similar to that of a trans-venous system while providing low and stable pacing thresholds.

The main drawback of this study was the lack of comparison with a randomized control group. Instead, these investigators compared the outcomes in their patients against separately defined performance criteria for safety and efficacy, and in a post-hoc analysis these researchers compared their patients with outcomes in a group of control patients. Additional drawbacks were that the follow-up data were limited to 6 months and that implantation experience was limited to the 94 physicians who performed the implantations.

Duray and associates (2017) noted that early performance of the Micra transcatheter pacemaker from the global clinical trial reported a 99.2 % implant success rate, low and stable pacing capture thresholds, and a low (4.0 %) rate of major complications up to 6 months. These researchers described the pre-specified long-term safety objective of Micra at 12 months and electrical performance through 24 months. The Micra Transcatheter Pacing Study was a prospective single-arm study designed to assess the safety and effectiveness of the Micra VVIR leadless/intra-cardiac pacemaker. Enrolled patients met class I or II guideline recommendations for de-novo ventricular pacing. The long-term safety objective was freedom from a system- or procedure-related major complication at 12 months. A pre-defined historical control group of 2,667 patients with trans-venous pacemakers was
used to compare major complication rates. The long-term safety objective was achieved with a freedom from major complication rate of 96.0% at 12 months (95% CI: 94.2% to 97.2%; p < 0.0001 versus performance goal). The risk of major complications for patients with Micra (n = 726) was 48% lower than that for patients with trans-venous systems through 12 months post-implant (HR 0.52; 95% CI: 0.35 to 0.77; p = 0.001). Across subgroups of age, sex, and co-morbidities, Micra reduced the risk of major complications compared to trans-venous systems. Electrical performance was excellent through 24 months, with a projected battery longevity of 12.1 years. The authors concluded that long-term performance of the Micra transcatheter pacemaker remained consistent with previously reported data. Few patients experienced major complications through 12 months of follow-up, and all patient subgroups benefited as compared to trans-venous pacemaker historical control group. Moreover, they noted that while these long-term data demonstrated that the beneficial effects of Micra versus trans-venous systems were sustained up to 2 years, these researchers anticipated continued benefit chronically with Micra. Moreover, they stated that long-term data suggested that trans-venous systems remain prone to infections and are associated with complications related to venous obstruction, lead fracture and insulation breach, injury to the tricuspid valve, and Twiddler syndrome; data of transcatheter pacemakers are needed to shed light on the benefits of eliminating these chronic device complications.

A major drawback of this trial was the absence of a randomized control group for comparison. In order to derive a relative comparison to trans-venous systems, a historical control was assembled from 6 trans-venous pacemaker trials and major complications were estimated. The safety analyses, as pre-specified, were restricted to the events meeting major complication criteria, and events not leading to death, hospitalization, prolonged hospitalization by at least 48 hours, or loss of device function were outside the scope of the present analysis. In addition, there were limited data on
system revisions and no patients were followed beyond 2 years. These researchers noted that data from the Micra Transcatheter Pacing System post-approval registry are aimed to address these questions.

Roberts and colleagues (2017) stated that first-in-man studies of leadless pacemakers (LPs) have demonstrated high rates of implant success, and safety and efficacy objectives were achieved. Outside of the investigational setting, there are concerns, particularly over cardiac effusion and perforation, device dislodgement, infection, telemetry, and battery issues. These investigators reported the acute performance of the Micra transcatheter pacing system (TPS) from a worldwide post-approval registry. The registry is an ongoing prospective single-arm observational study designed to assess the safety and effectiveness of Micra in the post-approval setting. The safety end-point was system- or procedure-related major complications at 30 days post-implant. They compared the major complication rate with that of the 726 patients from the investigational study; electrical performance was also characterized. The device was successfully implanted in 792 of 795 registry patients (99.6 %) by 149 implanters at 96 centers in 20 countries. Through 30 days post-implant, a total of 13 major complications occurred in 12 patients, for a major complication rate of 1.51 % (95 % CI: 0.78 % to 2.62 %).

Major complications included cardiac effusion/perforation (1, 0.13 %), device dislodgement (1, 0.13 %), and sepsis (1, 0.13 %). After adjusting for baseline differences, the rate of major complications in the registry trended lower than the investigational trial (odds ratio [OR], 0.58, 95 % CI: 0.27 to 1.25; p = 0.16). Early pacing capture thresholds were low and stable. The authors concluded that performance of the Micra TPS in a real-world setting demonstrated a high rate (99.6 %) of implant success and low rate (1.51 %) of major complications through 30 days post-implant. In particular, the rates of pericardial effusion, device dislodgement, and infection were low, reinforcing the positive results observed in the investigational study.
This study had several drawbacks: (i) the registry was intended to include as many patients as possible over as many centers and geographies as possible. However, there may be some degree of bias in favor of the patients who were approached to join a registry by the recruiting physician, and whereas it is anticipated that this registry represents a real-world population, the data did not include all patients implanted with the Micra TPS worldwide, (ii) this report was an interim analysis with limited follow-up, including patients who had not yet been followed for 30 days, and it reflected the geographies of enrolled patients who were primarily from Europe. However, enrollment of patients in the US is continuing, and patients in the registry will be followed for a minimum of 9 years, and (iii) few patients had follow-up electrical data available, and thus battery projections were preliminary and based on only 54 patients.

Martínez-Sande and colleagues (2017) noted that currently, studies on the LP (Micra) have mostly been limited to clinical trials with less than 6 months' follow-up and they often failed to reflect real population outcomes. In a prospective, observational study, these investigators evaluated electrical parameters at implantation and chronologically during follow-up, as well as the safety of this new technique. This trial included 30 consecutive patients, all 65 years of age or older, with an indication for single-chamber pacemaker implantation. Successful implantation was accomplished in all patients referred for leadless implantation. The mean age was 79.4 ± 6.4 years (range of 66 to 89 years); 20 (66.6%) were men and 28 had permanent atrial fibrillation (AF; 93.3%); 1 had atrial tachycardia and 1 had sinus rhythm. Concomitant atrio-ventricular (AV) node ablation was performed immediately after implantation in 5 patients (16.6%), and implantation was performed after transcatheter aortic valve implantation (TAVI) in 2. The procedure was performed under an uninterrupted anti-coagulation regimen (maximum INR 2.4) in 23 patients.
With the exception of 1 moderate pericardial effusion without tamponade, there were no severe complications. The mean follow-up was 5.3 ± 3.3 months and 4 patients had more than 1 year of follow-up. Sensing and pacing parameters were stable both at implantation and during the short- to mid-term follow-up. The authors concluded that implantation of LPs is feasible, safe and provided advantages over the conventional system. Moreover, they stated that further studies with longer follow-up periods are needed before these devices become widely used in routine clinical practice.

Tjong and Reddy (2017) stated that a new technology, leadless pacemaker therapy, was recently introduced clinically to address lead- and pocket-related complications in conventional trans-venous pacemaker therapy. These leadless devices are self-contained right ventricular single-chamber pacemakers implanted by using a femoral percutaneous approach. In this review of available clinical data on leadless pacemakers, early results with leadless devices were compared with historical results with conventional single-chamber pacing. Both presently manufactured leadless pacemakers showed similar complications, which were mostly related to the implant procedure: cardiac perforation, device dislocation, and femoral vascular access site complications. In comparison with conventional trans-venous single-chamber pacemakers, slightly higher short-term complication rates have been observed: 4.8 % for leadless pacemakers versus 4.1 % for conventional pacemakers. The complication rate of the leadless pacemakers was influenced by the implanter learning curve for this new procedure. No long-term outcome data are yet available for the leadless pacemakers. The authors concluded that larger leadless pacing trials, with long-term follow-up and direct randomized comparison with conventional pacing systems, are needed to define the proper clinical role of these leadless systems. Moreover, they stated that although current leadless pacemakers are limited to right ventricular
pacing, future advanced, communicating, multi-component systems are expected to expand the potential benefits of leadless therapy to a larger patient population.

Vamos and colleagues (2017) noted that 2 leadless pacemaker (PM) systems were recently developed to avoid pocket- and lead-related complications. As leadless PMs are implanted with a large delivery catheter, cardiac perforation remains a major safety concern. These investigators provided a literature review on incidence of cardiac perforation with conventional and with leadless PM systems. They performed a systematic review over the last 25 years for studies reporting data on PM lead perforation; findings were synthesized descriptively. Where control groups were available, data were meta-analyzed to identify important clinical risk factors. A total of 28 studies comprising 60,744 patients undergoing conventional PM implantation were analyzed. The incidence of lead perforation ranged from 0 % to 6.37 % (mean of 0.82 %, weighted mean of 0.31 %, median of 0.40 %). There was no significant difference in perforation risk between atrial and ventricular electrodes (prevalence odds ratio [POR] 0.72, 95 % CI: 0.28 to 1.87, p = 0.50) and between MRI conditional and conventional leads (POR 5.93, 95 % CI: 0.72 to 48.76, p = 0.10). The use of active fixation leads (POR 4.25, 95 % CI: 1.00 to 17.95, p = 0.05) and utilization of DDD versus VVI PM systems (POR 3.50, 95 % CI: 1.48 to 8.28, p < 0.01) were associated with higher rates of perforation. In the 2 leadless PM studies, the incidence of cardiac perforation was 1.52 % for each. The authors concluded that PM lead perforation rates varied in individual studies with an overall low incidence; leadless PMs appeared to be associated with a slightly higher perforation risk, most likely reflecting a learning curve effect of this novel technology.

Zucchelli and co-workers (2018) stated that LP technology was recently developed and introduced for clinical purpose as an alternative to traditional systems in order to reduce leads and pocket-related complications. Currently, 2 self-contained
right ventricular pacemaker implanted by using a femoral percutaneous approach have been developed and initial results appear promising. Although the clinical use is still limited to the right ventricular pacing, the LP currently represents an alternative solution in several settings, when the standard pacemaker cannot be used or its use is associated with higher risk of complications. Implementation of particular pacing algorithms in the near future will allow for a VDD (ventricular pacing with atrial tracking) pacing mode with only a single ventricular component, whereas the next evolution of technology will lead to develop multi-component, communicating leadless systems capable to perform a dual-chamber pacing or even a cardiac resynchronization. The management after battery depletion is still controversial and experience on retrievability is anecdotic. The authors concluded that long term data from registry are needed to reinforce the reliability of these systems in the real life and randomized trials comparing LPs with traditional pacemaker are essential to better understand if the LP can become a new paradigm in cardiac pacing.

Furthermore, an UpToDate review on "Permanent cardiac pacing: Overview of devices and indications" (Hayes, 2017) states that "Leadless cardiac pacing systems have been approved for use in Europe since 2013, and in April 2016, the first leadless cardiac pacing system was approved for use in the United States. As of December 2016, two leadless pacemaker systems are commercially available, with slightly different sizes and implantation requirements:

- Nanostim (St. Jude Medical), which measures 4.2 x 0.6 cm and requires an 18-French sheath
- Micra (Medtronic), which measures 2.6 x 0.7 cm and requires a 23-French introducer sheath
Leadless cardiac pacing holds promise as a long-term permanent cardiac pacing option for patients requiring single ventricle (RV only) pacing. However, longer-term follow-up is needed to assess the safety and efficacy of these devices. The potential for and incidence of long-term deleterious effects of pacing only the RV will also need to be assessed.

Additional studies are necessary to evaluate the safety, efficacy and stability of leadless pacemakers.

Beurskens and co-workers (2017) stated that the optimal end-of-life (EOL) strategy of leadless pacemakers is undefined. Suggested strategies comprise of placing an additional leadless device adjacent to the leadless pacemaker, or retrieving the non-functioning leadless pacemaker and subsequently implanting a new device. Although initial studies demonstrate promising results, early experience of acute and mid-term retrieval feasibility and safety remains mixed. These investigators suggested that the approach of leadless pacemaker retrieval is more appealing to limit the amount of non-functioning intra-cardiac hardware. In addition, potential risks for device-device interference, and unknown long-term complications associated with multiple intra-cardiac devices are prevented. The authors concluded that the potential inability to retrieve chronically implanted leadless pacemakers limited the application of this novel technology. Thus, long-term prospective analysis is needed to define the most optimal EOL strategy.

Gonzalez Villegas and associates (2018) noted that leadless pacemaker can be considered as a technical revolution in cardiac pacing devices, with clear advantages over conventional pacemakers in overcoming all lead-related complications. However, the management of these devices once they reach the EOL of the battery is still controversial. In the next years, there will be an increase in the need to define a clear strategy in the management of leadless PM once they reach their EOL. Safe extraction of these devices will define in
a great manner this strategy. These investigators performed the extraction of 3 functioning Nanostim leadless pacemaker prophylactically in 2 females and 1 male patients as part of the Nanostim battery depletion field action recommendation. All patients had a prior transesophageal 3D echocardiography to determine the device intra-cardiac mobility and the extent of possible endothelialization. For the extractions, these investigators used the Nanostim Retrieval Catheter S1RSIN (St. Jude Medical, St. Paul, MN), which is a proprietary catheter provided by the manufacturing company based on a lasso. Complete extraction of the devices was achieved in all patients using a relatively short fluoroscopic time (16, 19, and 12 minutes). The authors concluded that the extraction of leadless pacemakers could be considered a safe and feasible procedure using the tools provided by the manufacturer and designed for the extraction. However, a very low threshold must be maintained to avoid any risk to the patients. They stated that their extraction time ranged between 983 and 1,070 days, nevertheless it is necessary to gather more long-term data to assess the feasibility and safety of these procedures.

Cantillon and colleagues (2018) noted that LCPs aim to mitigate lead- and pocket-related complications seen with trans-venous pacemakers (TVPs). These investigators compared complications between the LCP cohort from the LEADLESS Pacemaker IDE Study (Leadless II) trial and a propensity score-matched real-world TVP cohort. The multi-center LEADLESS II trial evaluated the safety and efficacy of the Nanostim LCP (Abbott, Abbott Park, IL) using structured follow-up, with serious adverse device effects independently adjudicated; TVP data were obtained from Truven Health MarketScan claims databases for patients implanted with single-chamber TVPs between April 1, 2010 and March 31, 2014 and more than 1 year of pre-implant enrollment data. Co-morbidities and complications were identified via International Classification of Diseases, Ninth Revision and Current Procedural Terminology codes. Short-term (less than or equal to 1 months) and mid-term (greater than 1 to 18
months) complications were compared between the LCP cohort and a propensity score-matched subset of the TVP cohort. Among 718 patients with LCPs (mean age of 75.6 ± 11.9 years; 62 % men) and 1,436 patients with TVPs (mean age of 76.1 ± 12.3 years; 63 % men), patients with LCPs experienced fewer complications (HR 0.44; 95 % CI: 0.32 to 0.60; p < 0.001), including short-term (5.8 % versus 9.4 %; p = 0.01) and mid-term (0.56 % versus 4.9 %; p < 0.001) events. In the short-term time frame, patients with LCPs had more pericardial effusions (1.53 % versus 0.35 %; p = 0.005); similar rates of vascular events (1.11 % versus 0.42 %; p = 0.085), dislodgments (0.97 % versus 1.39 %; p = 0.54), and generator complications (0.70 % versus 0.28 %; p = 0.17); and no thoracic trauma compared to patients with TVPs (rate of thoracic trauma 3.27 %). In short- and mid-term time frames, TVP events absent from the LCP group included lead-related, pocket-related, and infectious complications. The authors concluded that patients with LCPs experienced fewer overall short- and mid-term complications, including infectious and lead- and pocket-related events, but more pericardial effusions, which were uncommon but serious.

Tjong and associates (2018) stated that the recent introduction of leadless PMs was aimed to eliminate trans-venous lead- and pocket-related complications. While the initial results with the leadless PMs appeared promising, the non-randomized nature, limited implant experience of operators, and short follow-up period of these studies precluded a simple comparison to TVPs. These researchers provided a balanced comparison of leadless and trans-venous single-chamber PM therapies through a propensity score-matched analysis. Leadless patients from 3 experienced leadless implant centers were propensity score-matched to ventricular rate responsive demand (VVIR) patients from a contemporary prospective multi-center trans-venous PM registry. The primary outcome was device-related complications that required invasive intervention during mid-term follow-up. Separate analyses including and excluding PM advisory-related complications
were performed. A total of 635 patients were match-eligible (leadless: n = 254; trans-venous: n = 381), of whom 440 patients (median age of 78 years; inter-quartile range [IQR] 70 to 84 years; 61 % men) were successfully matched (leadless: n = 220 versus trans-venous: n = 220). The complication rate at 800 days of follow-up was 0.9 % (95 % CI: 0 % to 2.2 %) in the leadless group versus 4.7 % (95 % CI: 1.8 % to 7.6 %) in the trans-venous group when excluding PM advisory-related complications (p = 0.02). When including these PM advisory-related complications, the complication rate at 800 days increased to 10.9 % (95 % CI: 4.8 % to 16.5 %) in the leadless group versus 4.7 % (95 % CI: 1.8 % to 7.6 %) in the trans-venous group (p = 0.063). The authors concluded that the findings of this study revealed favorable complication rates for leadless compared to trans-venous single-chamber pacing therapy at mid-term follow-up in a propensity score-matched cohort; however, when including PM advisory-related complications, this advantage was no longer observed.

Bhatia and El-Chami (2018) stated that leadless pacemakers have shown both safety and efficacy in the short-term and intermediate follow-up as an alternative to trans-venous pacemakers. This technology showed promise in the field of cardiac pacing. The authors concluded that as this technology continues to mature, randomized clinical trials comparing this technology to traditional TVPs are needed to confirm or refute the perceived advantage of this technology. In addition, an approach to end of service management and retrieval of chronically implanted devices still need to be addressed.

Boveda and co-workers (2018) stated that the purpose of the European Heart Rhythm Association (EHRA) survey was to provide an overview of the current use of leadless pacemakers (LLPM) across a broad range of European centers. An online questionnaire was sent to centers participating in the EHRA Electrophysiology Research Network. Questions dealt with standards of care and policies used for patient management, indications, and techniques of implantation of LLPM. In total,
52 centers participated in the survey. Most (86%) reported using LLPM, although 82% of these centers implanted less than 30 LLPM devices during the last 12 months. Non-availability (36%), lack of reimbursement (55%), and cost of the device (91%) were factors limiting the use of LLPM. The most commonly reported indications for LLPM were permanent AF (83%), a history of complicated conventional pacemaker (87%), or an anticipated difficult vascular access (91%). Implantation of LLPM was perceived as an easy-to-do and safe procedure by most implanters (64%), while difficult or risky in 28%, and comparable to conventional pacemakers by only a few (8%). Local vascular complications were the most frequently reported major problems (28%), but a significant number of respondents (36%) had never encountered any issue after LLPM implantation. The authors concluded that the use of this device is influenced by cost issues and lack of reimbursement, which currently limit its uptake in clinical practice; most respondents (72%) anticipated a significant increase in device utilization within next 2 years.

The authors stated that his survey had several drawbacks. First, because it was fully based on a voluntary participation, it was non-exhaustive. Second, because questions had a limited number of options to be chosen, some situations may have not been completely covered. Third, this questionnaire was launched before Abbott paused the distribution of the Nanostim LLPM. Finally, because purely declarative, it may not be entirely representative of the whole activity or decisions of the responding centers. However, the purpose of this survey was reached by providing an overview of the current use of LLPMs across a broad range of the European centers. Oliveira and colleagues (2020) noted that transvenous pacemakers are associated with a significant amount of complications; LPs are emerging as an alternative to conventional devices. In a systematic review, these investigators provided patient eligibility, safety and clinical outcomes of the LP devices. They carried out a systematic search for articles describing the use of LP. Out of 2 data-
bases, 24 articles were included in the qualitative analysis. These articles comprised a total of 4,739 patients, with follow-up times of 1 to 38 months; further information was obtained from 10 more studies. From a population of 4,739 patients included in the qualitative analysis, 4,670 LP were implanted with success (98.5%). A total of 248 complications were described (5.23%) during the follow-up. The most common were pacing issues such as elevated thresholds, dislodgements or battery failure (68 patients), events at the femoral access site such as hemorrhage, hematoma or pseudoaneurysms (64 patients) and procedure related cardiac injuries such as cardiac perforation, tamponade or pericardial effusion (47 patients). There were 360 deaths during the follow-up and 11 were described as procedure- or device-related; 4 studies presented the strategy of using a combined approach of atrio-ventricular node ablation (AVNA) and LP implantation. The authors concluded that leadless pacemakers appeared to have a relatively low complication rate. These devices may be a good option in patients with an indication for single-chamber pacing, in patients with conditions precluding conventional transvenous pacemaker implantations. Moreover, these researchers stated that studies directly comparing LP and transvenous pacemakers and data on longer follow-up periods are needed.

Rordorf and associates (2020) stated that approximately 4.5% to 20% of patients after heart transplant require PM implantation. The high infective risk profile and the low probability of pacing dependency make heart-transplanted patients the ideal candidates for a leadless single-chamber PM. These investigators reported the first multi-center experience of leadless PM implantation in a series of heart-transplanted patients with a long-term follow-up. The results confirmed the feasibility and acceptable safety of leadless device in this group of patients, despite implantation appeared to be slightly more challenging when compared with non-transplanted patients. The authors concluded that although
more data are needed, a leadless single-chamber surveillance PM appeared to be a viable option for heart-transplanted patients.

Lenarczyk and co-workers (2020) noted that the objective of the prospective European Heart Rhythm Association (EHRA) snapshot survey was to examine procedural settings, safety measures, and short-term outcomes associated with implantation of LLPM, across a broad range of tertiary European electrophysiology centers. An Internet-based electronic questionnaire (30 questions) concerning implantation settings, peri-procedural routines, complications, and in-hospital patient outcomes was circulated to centers routinely implanting both LLPMs and transvenous pacemakers (TV-PM). The centers were requested to prospectively include consecutive patients implanted with either LLPMs or TV-PMs during the 10-week enrolment period. Overall, 21 centers from 4 countries (France, Italy, Netherlands, and Spain) enrolled 825 consecutive patients between November 2018 and January 2019, including 69 (9 %) implanted with LLPMs. Leadless pacemakers were implanted mainly under local anesthesia (69 %), by an electrophysiologist (60 %), in the electrophysiology laboratory (71 %); 95 % of patients received prophylactic antibiotics prior to implantation. Most patients on chronic oral anti-coagulation were operated on-drug (35 %), or during short-term (to 48 hours) drug withdrawal (54 %). Implantation was successful in 98 % of patients and the only in-hospital procedure-related complication was groyne hematoma in 1 patient. The authors concluded that this EHRA snapshot survey provided important insights into LLPM implantation routines and patient outcomes. These researchers stated that these findings suggested that despite the unfavorable clinical profile of pacemaker recipients (they were more likely to have AF and a high anticipated risk of infection), LLPM implantation was associated with relatively low risk of complications and good short-term outcomes.
In a different publication by the same group of investigators on the EHRA snapshot survey, Boveda et al (2020) stated that this prospective, observational study had several drawbacks. First, this survey included a voluntary participation of the centers; thus, the survey was not exhaustive and the center selection process could have been biased. Second, the multiple-choice questions in the survey’s electronic questionnaire could have not completely covered all relevant options. Finally, owing to the declarative description of the reasons for choosing specific treatment options, the survey may not be entirely representative of the treatment decision-making process in the participating centers.

Breatnach et al (2020) stated that the development of leadless cardiac pacemakers avoids the inherent complications that may occur secondary to lead insertion. A large number of devices have been inserted in adult patients although data in pediatric patients are lacking. These investigators described their experience with the leadless device in the pediatric population. They carried out a retrospective study on all pediatric patients who underwent insertion of a leadless pacemaker in their center. Data were collected for demographic, procedural, and outcome variables; 9 patients with a median (IQR) age and weight of 13 (12 to 14) years and 37 (31 to 50) kg, respectively, were enrolled. The median (IQR) procedural time was 62 (60 to 65) mins with insertion thresholds of 0.5 (0.35 to 1) Volts at 0.24 ms. All devices were successfully inserted without complication; 1 device was replaced with a single-lead endocardial pacemaker at 1 year for increased thresholds. The authors concluded that leadless pacemaker device insertion is feasible in pediatric patients. Moreover, these researchers stated that further studies and long-term follow-up are needed to determine device longevity and complication rates.
Furthermore, an UpToDate review on "Permanent cardiac pacing: Overview of devices and indications" (Link, 2020) states that "Leadless pacing systems are now available and hold significant promise for the future".

**Combined Leadless Pacemaker and Subcutaneous Implantable Cardioverter Defibrillators**

Tjong and colleagues (2016) stated that S-ICD and leadless pacemaker (LP) are evolving technologies that do not require intra-cardiac leads. However, interactions between these 2 devices are unexplored. These researchers examined the feasibility, safety, and performance of combined LP and S-ICD therapy, considering (i) simultaneous device-programmer communication, (ii) S-ICD rhythm discrimination during LP communication and pacing, and (iii) post-shock LP performance. The study consists of 2 parts: (i) Animal experiments: 2 sheep were implanted with both an S-ICD and LP (Nanostim, St Jude Medical, St Paul, MN), and the objectives above were tested, and (ii) Human experience: Follow-up of 1 S-ICD patient with bilateral subclavian occlusion who received an LP and 2 LP (all Nanostim) patients (without S-ICD) who received electrical cardioversion (ECV) were presented. Animal experiments: Simultaneous device-programmer communication was successful, but LP-programmer communication telemetry was temporarily lost (2 ± 2 s) during ventricular fibrillation (VF) induction and 4/54 shocks; LP communication and pacing did not interfere with S-ICD rhythm discrimination. Additionally, all VF episodes (n = 12/12), including during simultaneous LP pacing, were detected and treated by the S-ICD. Post-shock LP performance was unaltered, and no post-shock device resets or dislodgements were observed (24 S-ICD and 30 external shocks). Human experience: The S-ICD/LP patient showed adequate S-ICD sensing during intrinsic rhythm, nominal, and high-output LP pacing; 2 LP patients (without S-ICD) received ECV during follow-up, and no impact on performance or LP dislodgements were observed. The
authors concluded that combined LP and S-ICD therapy appeared feasible in all animal experiments \((n = 2)\) and in 1 human subject. No interference in sensing and pacing during intrinsic and paced rhythm was noted in both animal and human subjects. However, induced arrhythmia testing was not performed in the patient. They stated that defibrillation therapy did not appear to affect LP function; more data on safety and performance are needed.

Ahmed and associates (2017) noted that S-ICDs provide effective defibrillation, while also reducing the risk of long-term lead problems. However, S-ICDs do not offer bradycardia or anti-tachycardia pacing and therefore use has been limited. Combined implantation of an S-ICD with a LP has been proposed to overcome this limitation. Although a handful of combined S-ICD/LP implantations have been reported for the Nanostim as well as the Micra LP systems, none had documented delivery of appropriate shock therapies for spontaneous ventricular tachycardia (VT). These investigators reported the 1st case of effective defibrillation for spontaneous VT in a patient with combined Micra LP and S-ICD.

Tjong and colleagues (2017) examined the acute and 3-month performance of the modular anti-tachycardia pacing (ATP) -enabled LP and S-ICD system, particularly device-device communication and ATP delivery. The combined modular cardiac rhythm management therapy system of the LP and S-ICD prototypes was evaluated in 3 animal models (ovine, porcine, and canine) both in acute and chronic (90 days) experiments; LP performance, S-ICD to LP communication, S-ICD and LP rhythm discrimination, and ATP delivery triggered by the S-ICD were tested. The LP and S-ICD were successfully implanted in 98% of the animals (39 of 40). Of the 39 animals, 23 were followed-up for 90 days post-implant; LP performance was adequate and exhibited appropriate VVI behavior (VVI mode denotes that it paces and senses the ventricle and is inhibited by a sensed ventricular event) during the 90 days of follow-up in all tested animals. Uni-directional
communication between the S-ICD and LP was successful in 99% (398 of 401) of attempts, resulting in 100% ATP delivery by the LP (10 beats at 81% of the coupling interval). Adequate S-ICD sensing was observed during normal sinus rhythm, LP pacing, and ventricular tachycardia/ventricular fibrillation. The authors concluded that this study presented the pre-clinical acute and chronic performance of the combined function of an ATP-enabled LP and S-ICD. Appropriate VVI functionality, successful wireless device-device communication, and ATP delivery were demonstrated by the LP; clinical studies on safety and performance are needed.

**Leadless Pacemaker in Patients Undergoing Atrioventricular Node Ablation for Atrial Fibrillation**

Yarlagadda and colleagues (2018) stated that atrio-ventricular node (AVN) ablation and permanent pacing is an established strategy for rate control in the management of symptomatic AF; LPs can overcome some of the short-term and long-term limitations of conventional trans-venous pacemakers (CTPs). These researchers compared the feasibility and safety of LP with those of single-chamber CTP in patients with AF undergoing AVN ablation. They conducted a multi-center observational study of patients undergoing AVN ablation and pacemaker implantation (LP versus single-chamber CTP) between February 1, 2014 and November 15, 2016. The primary efficacy end-points were acceptable sensing (R wave amplitude greater than or equal to 5.0 mV) and pacing thresholds (less than or equal to 2.0 V at 0.4 ms) at follow-up. Safety end-points included device-related major and minor (early less than 1 month, late greater than 1 month) adverse events (AEs). A total of 127 patients with LP (n = 60) and CTP (n = 67) were studied. The median follow-up was 12 months (IQR 12 to 18 months); 95% of the LP group and 97% of the CTP group met the primary efficacy end-point at follow-up (57 of 60 versus 65 of 67; p = 0.66). There was 1 major AE (loss of pacing and sensing) in the LP group and 2 (lead
dislodgement) in the CTP group (1 of 60 [1.7 %] versus 2 of 67 [3 %]; p = 1.00). There were 6 minor AEs (5 early and 1 late) in the LP group and 3 (early) in the CTP group (6 of 60 [10 %] versus 3 of 67 [4.5 %]; p = 0.30). The authors concluded that these findings demonstrated the feasibility and safety of LP compared with CTP in patients undergoing AVN ablation for AF. This was a feasibility/safety study; further investigation is needed to determine the health outcomes of this approach.

Okabe and associates (2018) evaluated the feasibility and safety of concurrent Micra leadless trans-catheter pacemaker implantation and AV junctional (AVJ) ablation. These investigators retrospectively assessed patients who underwent Micra implantation and concurrent AVJ ablation at 3 institutions between August 2014 and March 2016. All patients and devices were followed at baseline and at 1, 3, 6, and 12 months post-implantation. A total of 21 patients with permanent AF (median age of 77 [range of 62 to 88], women 15 [71.4 %]) underwent successful Micra implantation followed by concurrent AVJ ablation. There was no device dislodgement or malfunction during the 12-month follow-up. Complete 12-month electrical performance data were available in 14 patients (67 %). Among patients with the complete data set, median pacing thresholds at implant and at 1, 3, 6, and 12 months were 0.5 V (range of 0.25 to 0.88), 0.44 V (range of 0.25 to 2.0), 0.5 V (range of 0.25 to 1.63), 0.5 V (range of 0.25 to 1.13), and 0.5 V (range of 0.25 to 1.13) at a pulse width of 0.24 msec, respectively; 2 patients died due to non-cardiac causes during follow-up. There were no patients with major device-related complications. The authors concluded that concurrent Micra implantation and AVJ ablation was feasible and appeared safe. There was no device dislodgement, malfunction, or significant pacing threshold rise requiring device re-implantation during the 12-month follow-up. This was a small (n = 21) study with relatively short-term follow-up (12 months). These preliminary findings need to be validated by well-designed studies.
Combined Leadless Pacemaker and Atrioventricular Nodal Ablation for Atrial Fibrillation

Chieng and colleagues (2020) stated that AVNA with permanent pacemaker (PPM) insertion is indicated for rate control in patients with AF who remain unresponsive to rate or rhythm control strategies. The leadless PPM (Micra Transcatheter Pacing System [TPS], Medtronic, Minneapolis, MN) has the advantage of eliminating transvenous lead and pacemaker pocket-related complications. In a retrospective, case-series study, these researchers examined the outcomes of patients who had undergone combined Micra TPS and AVNA, performed via a single femoral approach. They carried out a review on patients who had undergone concurrent procedures, across 2 major hospitals in Perth, Western Australia. Procedural details were obtained from a cardiac devices data-base whilst patient demographics and clinical information were determined from medical records. A total of 14 patients underwent concurrent Micra TPS insertion and AVNA for symptomatic AF. The average age was 73 ± 9.2 years, and 43 % of them were men. There was no acute procedural/device-related complication. Over a median follow-up duration of 9 months (36 % completing 12-month follow-up), there was no incidence of device complications, in particular device dislodgement, malfunction or infection; 1 patient had a resuscitated VF arrest event with new onset cardiomyopathy during follow-up and needed Micra TPS removal; 1 patient died at 33 days post-procedure from a non-cardiac cause. Device performance was excellent with stable sensing and pacing thresholds during the follow-up period. The authors concluded that the findings of this study showed that combined leadless PPM (Micra TPS) implantation and AVNA using a single femoral approach was feasible, with good safety and efficacy profile in the short-medium term. Moreover, these researchers stated that long-term data involving larger cohorts is needed to confirm these preliminary findings and ascertain the clinical usefulness of this combined approach.
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<th>Code</th>
<th>Code Description</th>
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<td>33270</td>
<td>Insertion or replacement of permanent subcutaneous implantable defibrillator system, with subcutaneous electrode, including defibrillation threshold evaluation, induction of arrhythmia, evaluation of sensing for arrhythmia termination, and programming or reprogramming of sensing or therapeutic parameters, when performed [use of combined leadless pacemaker and subcutaneous implantable cardioverter defibrillators]</td>
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<tr>
<td>33271</td>
<td>Insertion of subcutaneous implantable defibrillator electrode [use of combined leadless pacemaker and subcutaneous implantable cardioverter defibrillators]</td>
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<td>33274</td>
<td>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</td>
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<td>33275</td>
<td>Transcatheter removal of permanent leadless pacemaker, right ventricular</td>
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<td>93650</td>
<td>Intracardiac catheter ablation of atrioventricular node function, atrioventricular conduction for creation of complete heart block, with or without temporary pacemaker placement</td>
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The above policy is based on the following references:


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0893 Leadless Cardiac Pacemaker

There are no amendments for Medicaid.

revised 12/11/2020