THE NEXT GENERATION OF LEADLESS CARDIAC PACING: A REVIEW

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ABSTRACT

The next-generation wireless pacemakers first became commercially available in 2012. A wireless pacemaker is 90% smaller than a transvenous pacemaker. There is no need for a chest incision or a visible pacemaker pocket. A wireless pacemaker has advantages and disadvantages compared to traditional devices. More studies are needed to determine how this affect long-term electrical performance, valve function, and left ventricular systolic function. The price of these devices and the choice of the patient are decisive. We expect this wireless, lead-free technology to offer long-term benefits by avoiding the recurring problems associated with other devices. This is particularly true of the shortcomings of current approaches, especially for lead-related vascular problems. This assessment will provide UK regulatory guidance as well as a detailed description of the currently available leadless pacing system. Development of next-generation lead-free devices capable of dual-chamber pacing and communication with subcutaneous defibrillators, expanding the scope of wireless pacing beyond 2022.

KEYWORDS: Leadless pacemaker; Precautions and safety information; UK Guidance on Leadless Pacemaker; Marketed Leadless Pacemakers; Clinical study data.

INTRODUCTION

There has been a notable change in the way cardiac patients are monitored as a result of the quick development of telemedicine and the development of remote monitoring systems that communicate with cardiac devices. Early detection of a decompensated cardiac state and prompt implementation of a medical management plan are made possible by the use of continuous and virtually real-time hemodynamic and rhythm monitoring. Several regulatory organisations, notably the US Food and Drug Administration, have accepted these advancements [1]. Leadless cardiac pacing had been in a state of stagnation for nearly 20 years, but this has changed with the development of catheter-based delivery systems, miniaturised high-density energy sources, low-power electronics, novel packaging capabilities, and novel communication technologies, among other areas [2]. Leadless pacemakers were first made commercially available in 2012 with the release of the Nanostim Leadless Pacemaker System, and then soon after with the Micra leadless pacemaker and in 2022 with the Aveir^{TM} Leadless Pacemaker System [3]. The leadless pacemaker, which is 90% smaller than a transvenous pacemaker and is implanted directly into the right ventricle, is a self-contained generator and electrode system [4]. There is no need for a chest incision or subcutaneous generator pocket because the device is placed via a femoral vein transcatheter technique. Lead- or pocket-related issues that come with a traditional permanent transvenous pacemaker are intended to be lessened by leadless pacemakers. Despite these advancements, it is still necessary to consider problems and technical failures. The existence of a transvenous lead and/or subcutaneous pocket is often linked to short-term problems, which have been found to be up to 12% Pneumothorax, heart perforation, lead dislodgement, pocket infection, and hematoma are some of these problems. Long-term issues can also be caused by the pacing lead and subcutaneous pocket and can include insulation failure, tricuspid regurgitation, pocket infection, venous blockage, and lead fractures. Lead-related endocarditis is another major cause for concern, with fatality rates ranging from 12% to 31%. According to studies, lead failure is the primary cause of long-term problems and the weakest link in the existing pacing system. In this thorough study, we analyse the advantages and disadvantages of leadless implantable devices compared to conventional cardiac devices and highlight the various devices that are currently on the market [5].

Advantages

There has been a notable change in the way cardiac patients are monitored as a result of the quick development of telemedicine and the development of remote monitoring systems that communicate with cardiac devices. Early detection of a decompensated cardiac state and prompt implementation of a medical management plan are made possible by the use of continuous and virtually real-time

hemodynamic and rhythm monitoring. The primary benefit of a leadless pacemaker is the elimination of several complications related to transvenous pacemakers and leads, including lead fracture, hematoma, pocket infections, and lead dislodgment. The leadless pacemaker also has cosmetic appeal because there is no visible pacemaker pocket or chest incision. Implanting a device is substantially simpler. Battery life is similar to that of a transvenous pacemaker and is around 5-15 years for this very compact, self-contained device with an internal battery. A leadless pacemaker's battery life can be extended by switching it off and implanting a new leadless or conventional pacemaker. Magnetic resonance imaging (MRI) is compatible with leadless pacemakers. Patients are able to freely move their hands and engage in activities like swimming, exercise, etc., which prevents patients from accidentally tampering with their pacemaker on their chest, a condition known as twiddler's syndrome that could harm the device's functionality [6].

Disadvantages

High price. Uncommon abnormal haemorrhage. Leadless pacemakers are incapable of defibrillation and only offer single-chamber ventricular pacing [7]. Patients who require dual-chamber pacing, such as those with specific types of cardiac block or sinus node dysfunction, should not use leadless pacemakers. A leadless cardiac pacemaker, like a traditional pacemaker, may stop working if it becomes loose. For instance, groyne access and a bigger sheath are necessary during implantation; this may cause more bleeding, pseudoaneurysms, artery perforations, or hematomas. The best strategy for device management after battery depletion is not known. Operators who implant devices need to complete additional training [8].

Patient Target Group

Single-chamber pacing therapy is specifically recommended for: symptomatic patients with AV block who have chronic atrial fibrillation (AF) or other atrial tachyarrhythmias (AT), or when maintaining AV synchrony during pacing is not required [9]. Select patients with AV block who require permanent pacing and are unlikely to require frequent ventricular pacing or who have significant comorbidities that are likely to influence clinical outcomes and may limit the benefit of dual chamber pacing. Patients with sinus node dysfunction (SND) who have evidence of impaired AV conduction or are concerned about the development of AV block in the future, while maintaining AV synchrony during pacing is not required, Patients with SND who are symptomatic and do not require frequent ventricular pacing or who have significant comorbidities that would otherwise determine survival and clinical outcomes Patients with atrial fibrillation and AV block who have an LVEF between 36% and 50% are predicted to need

ventricular pacing less often than 40% of the time and do not require AV synchronisation during pacing [10].

PRECAUTIONS AND SAFETY INFORMATION

Environmental and Medical Therapy Hazards

The LPs are outfitted with special shielding and filters that significantly reduce the detrimental effects of electromagnetic interference (EMI) on the LP's operation. Patients should be advised to avoid strong electric or magnetic fields with reasonable caution. If the LP inhibits or switches to asynchronous operation while exposed to EMI, the patient should move away from the source or turn it off. Advise patients to seek medical advice before entering environments that could interfere with the operation of the LP, such as areas barred from entry by pacemaker patients.

Medical Procedures and Environments

Pacemaker patients, in general, should avoid hospital equipment that generates high electromagnetic field strength signals, such as diathermy machines and electrosurgical units. Exposure to devices that produce high levels of electric or magnetic interference (EMI) may result in LP resets, malfunctions, or damage [11].

External defibrillation. The LP's electronic circuitry protects against defibrillation discharges. However, do not place the defibrillator paddles directly on the LP. Check that the LP is working properly after defibrillation [12].

Therapeutic diathermy. Even if the LP is turned off, avoid diathermy because it can harm the tissue around the implanted electrodes or permanently damage the LP [13].

Electrosurgical cautery. This can result in ventricular arrhythmias and/or fibrillation, as well as asynchronous or inhibited LP function. If electrocautery is required, keep the current path and ground plate as far away from the LP as possible. The electrocautery axis should be perpendicular to the electrode axis. These effects may be mitigated by using a bipolar cauterizer. Conduct a thorough examination of the LP following electrocautery [14].

RF ablation. Intracardiac radiofrequency (RF) energy delivered during an RF ablation procedure in patients with a cardiac implantable electronic device may result in: Pacing above or below the

programmed rate Reversion to asynchronous operation LP's electrical reset Premature triggering of the recommended replacement (RRT) indicator Permanent LP malfunction and/or damage RF ablation risks may be minimised by programming an asynchronous, non-rate-responsive pacing mode prior to the RF ablation procedure. Avoiding direct contact between the ablation catheter tip and the LP Positioning the grounding patch or pad so that the current pathway does not pass through or near the LP (for example, placing the ground plate under the patient's buttocks or legs). Having a programming system readily
available Monitoring the patient during and immediately after the procedure Having external pacing or defibrillation equipment available [15].

Patient Environments. Advise patients to avoid strong electric or magnetic fields with reasonable caution. Exposure to these powerful electric or magnetic fields may cause a LP reset. If the LP inhibits or switches to asynchronous operation while exposed to electromagnetic interference (EMI), the patient should move away from the EMI source or turn it off. Advise patients to seek medical advice before entering environments that could interfere with the operation of the LP, such as areas barred from entry by pacemaker patients [16].

Cellular phones. In accordance with ISO 14117, the LP has been tested for compatibility with handheld wireless transmitters. The operating frequencies were tested (385 MHz-3 GHz). According to the findings of this testing, normal cellular phone operation should have no effect on the LP. If a patient is over the limit, advise them not to carry a cell phone in a breast pocket or any other location. Magnets may be found in some cell phone accessories, such as cases with magnetic clasps. Advice patients to keep cell phones and smart watches at least 15 centimetres (6 inches) away from the LP to avoid interference [17].

Portable electronic devices

Patients should be advised not to carry electronic portable devices such as e-cigarettes, key cards, credit cards, or other items with magnetic strips in their breast pocket or near their heart.

Advise patients not to carry earbuds or headphones in their breast pocket or close to their heart and not to allow earbuds or headphones to drape around their neck or hang on their chest. These devices may contain a magnet or magnetic material, or they may emit RF signals that can disrupt the LP [18].

Environmental conditions. Advise patients to avoid situations that could result in a sudden change in body temperature, which could affect rate response if sensor mode is activated.

The LP is built to withstand absolute ambient pressures ranging from 50 kPa (0.5 atm) to 304 kPa (3 atm). Advise patients to avoid situations where the LP may be exposed to atmospheric pressures outside of this range [19].

MRI Safety Information

A Magnetic Resonance Imaging (MRI) scanner is a large machine that can produce images of your body's soft tissues. This tool is extremely useful in diagnosing a variety of conditions. However, in order to create the MR image, the scanner must generate extremely strong magnetic forces, which can be extremely dangerous to almost all implanted devices, including your pacemaker. Magnetic fields can interfere with your pacemaker's tiny computer. However, the Leadless pacemaker was specifically designed to withstand the fields of most MRI scanners. You can have an MRI scan under certain conditions because it is an MR Conditional device. Before scheduling an MRI scan, consult with your doctor to see if you are a good candidate. A Before the MRI exam, notify the MRI site personnel that you have an implanted MR Conditional medical device [20].

Storage and Handling

Store the Leadless pacemaker at 25°C (77°F) room temperature. Excursions are permitted between the temperatures of 15°C and 30°C (59°F and 86°F). The Leadless pacemaker can be safely exposed to temperatures ranging from -20°C to 60°C (-4°F to 140°F) for up to 24 hours during transportation and handling. Storage outside of this range may cause the Leadless pacemaker to be reset. To avoid device damage, store the LP in a clean area away from magnets, magnet-containing kits, and sources of electromagnetic interference. Do not implant an LP that has been dropped from a height of more than 24 inches (61 cm) while inside its intact shelf package or from a height of more than that while outside of it. Under these circumstances, sterility, integrity, or function cannot be guaranteed. Keep the delivery catheter cool and dry. Do not expose to direct sunlight [21].

UK GUIDANCE ON LEADLESS PACEMAKER

The Device Expert Advisory Committee (DEAC) of the MHRA established the leadless devices Expert Advisory Group in 2015. The group's mandate was to assess the requirements for: Pre-market clinical evaluation of current and planned devices, including pre-market clinical trial design advice and post-market clinical evaluation of current and planned devices, as well as evaluation of post-market data

Market approval and dissemination of leadless pacing

A medical device's UKCA, CE UKNI, or CE marking denotes a manufacturer's certification of compliance with the standards outlined in the relevant legislation, as attested to, where appropriate, by an approved body or notified body. To legally promote the item in the UK, this is necessary [22].

The UK's regulatory body for medical devices, MHRA, has acknowledged that leadless pacing represents a significant change from traditional cardiac rhythm management (CRM) devices rather than a refinement of existing ones. Leadless pacemakers have so far received market approval based on a dearth of clinical data, both in terms of the number of patients involved in the studies and the length of time they were followed.

In order to ensure that this new technology is used properly and that the risk of patient harm is as low as possible, the MHRA wants to encourage innovation in medical technology. However, it would like to see clinical guidance on the use of leadless pacemakers combined with rigorous safety surveillance. The implementation of this potentially crucial technology might be greatly delayed by the tardy discovery of safety or training difficulties, thus doing this is obviously in the interests of patients, physicians, and industry.

Due to this, a British Heart Rhythm Society-recommended group of consultant cardiologists known as the Expert Advisory Group was established. The Association of British Healthcare Industries and TEAM-NB have both asked for feedback from the Notified Bodies (now renamed Approved Bodies were located in the UK), as well as from the medical device industry. The MHRA has released the initial guidelines for the use of leadless pacing based on the suggestions of this group [23].

Initial recommendations for adoption of leadless cardiac pacing therapy

Patients who have a strong reason for bradycardia pacing or cardiac resynchronization should be given the option of leadless pacing.

Some of the bare minimum for leadless pacemaker implantation includes, a) A cardiac catheter lab with a high-quality fixed image intensifier, digital acquisition for review, and the capability to image from all usual directions b) Trained clinical professionals with immediate access to echocardiography and pericardiocentesis equipment c) Trained clinical personnel with comprehensive resuscitation facilities, including defibrillator/external pacing device [24].

Each patient should have a specific and documented justification for choosing a leadless pacemaker over a conventional pacemaker given the extremely limited intermediate and long-term evidence base for leadless pacing therapy, especially when compared to conventional pacing. Contraindications for leadless pacing, such as patient habits and venous anomalies likely to cause problems with the large sheaths needed for device supply, should be carefully considered. The patient's consent form should

expressly mention that early experience with leadless pacing technology has revealed a tiny but significant incidence of serious acute adverse events, such as tamponade necessitating an emergency thoracotomy, device displacement, vascular access difficulties, etc. Leadless pacemakers should be implanted in centres with on-site cardiac surgery until there are reliable data to confirm that the device-specific adverse event rate requiring surgery is as low as that associated with conventional pacing (0.1-0.5%), in view of the incidence of tamponade and the fact that this has required emergency surgery in a higher proportion of cases than with other invasive procedures. Nevertheless, it is advised that leadless pacemakers be placed at high-volume facilities with the training and experience to handle any issues [25].

Minimum acceptable operator experience and training, to be specified in the manufacturer's study protocol and/or IFU

Each centre should have a maximum of two operators at first, and both should be encouraged to engage in all procedures, in order to concentrate experience at an early stage. The introduction of more operators may then occur, depending on the number of procedures. All operators should get the necessary training and supervision, in accordance with the manufacturer's guidelines. Each operator should be able to provide proof of continuous practises to show that they are maintaining their competence. The national CRM audit should keep track of procedure numbers and make them available. Operators should be cardiac specialists with considerable experience in the insertion of complicated cardiac implanted

electronic devices as well as the use of intracardiac catheters and/or leads. They ought to be familiar with manipulating deflectable catheters in the heart and with vascular access utilising large bore catheters (12F and higher). To retain competency and to emphasise advancements in patient selection and implant procedure, manufacturers should have processes in place to guarantee operators receive continual training [26].

Implant surveillance

All leadless pacemaker implants should be included in a thorough registry or post-market clinical follow-up (PMCF [1]) research, held and sponsored by the appropriate manufacturers and maintained to the norms of good clinical practise, following UKCA, CE UKNI, or CE registration of the device. Implants should wait until at least half the intended number of patients have signed up for the registry or PMCF trial and a thorough clinical examination of the device's performance and safety, including a one-year patient follow-up, has shown a positive outcome. The manufacturer should conduct the analysis, and the approved body or notified body should review it and provide independent clinical

feedback as appropriate to these organisations. It should also be included in the British Heart Rhythm Society's (BHRS) national audit for CRM devices and made available to the MHRA upon request (held by NICOR) [27].

The PMCF study or registry should include, but not be limited to, gather data on a) Important patient characteristics b) The rationale for using a pacemaker or CRT therapy c) Justification for selecting a lead-free strategy d) Immediate implant results e) The site of the cardiac implant (apex, mid-septum etc) f) Device performance, adverse events, and all-cause mortality at in-hospital, 30-day, and 1-year intervals. g) MR scans (static field strength and body location scanned), as well as any unfavourable outcomes that may harm the patient or the device. h) Communication with/from other external or implantable devices i) Deactivation or device removal j) Long-term performance of the device/battery and subsequent issues k) Data from the PMCF study or registry shall be made available to MHRA at all times upon request and reported to the public at predetermined intervals. l) Information on the performance and safety of the leadless device should be gathered during the duration of the implant thanks to the manufacturer's comprehensive post-market surveillance strategy. This will make it possible to evaluate the hazards involved with either removing the device or leaving it in place when it reaches the end of its useful life. m) Adverse incidents should be evaluated for reportability to regulatory authorities according to the requirements set out in the relevant MEDDEV reporting guidelines. It is crucial to record any mechanical or electrical interactions between an abandoned leadless device and the replacement pacing system [28].

Design of clinical studies for UK market approval and post-market follow-up of leadless cardiac pacing therapy

It is crucial that studies are created to address certain queries concerning the security and effectiveness of novel technologies that cannot be addressed by bench or animal testing. Wherever possible, the outcomes of clinical research should be contrasted with an appropriate "standard of care" approach [29].

Standard of care (transvenous pacing)

The condition's existing standard of care should be thoroughly explained, together with published evidence of its effectiveness, safety (rates of short-, medium-, and long-term adverse events), and (where available) cost-effectiveness. The relative qualities of the new treatment can then be evaluated using this.

Representative sampling

It is critical that the study participants represent the patients who will be cared for in actual practise. It is necessary for the therapeutic indications for which the device receives market approval to be supported by data from comparable patients who participated in the pre-market study. At the time of approval, approved patient indications should be unambiguously stated on the labelling of the device. A new pre-market clinical investigation should be conducted to examine any expansion of approved patient indications. The inclusion criteria must be precise and accurate representations of the target population. The exclusion criteria must clearly identify the patient populations for which the treatment is inappropriate.

Sample size and follow-up duration

The necessary sample size will be determined by a) The kind and gravity of the potential negative outcomes. Only adverse events that affect 5% of patients may be significant for some adverse events. A 1% (or less) rate for other unfavourable occurrences, such mortality, might be unacceptable. An appropriately powered comparison with published adverse event rates linked with treatment options should be possible given the number of patients. Adverse event rates must be pre-specified and chosen from approved statistics on 'standard of care treatment' defined in published literature in order to compare study outcomes. b) The type of study - pre-market (gathering data for approval) or post-market. the pre-market (data collection for approval) or post-market study kind. Wider confidence intervals and lower power may be acceptable for pre-market studies in order to strike a balance between ensuring an accurate assessment of the short- and medium-term device safety and preventing unwarranted delays in patient access to the novel treatment. Greater confidence in the correctness of the study results is crucial for PMCF studies or registries, necessitating the choice of a sample size that will produce results with smaller confidence intervals and higher power. c) Particular performance standards.

Grading of adverse events severity

The severity of adverse events should be rated using the following list of additional widely used scales.

Grade 1: Mild; no or little symptoms; merely clinical or diagnostic observations; no need for intervention.

Grade 2: Moderate; limited age-appropriate instrumental, ADL activity indicated; minimum, local or non-invasive intervention suggested (activities of daily living).

Grade 3: Limits ADL and is severe or medically significant but not immediately life-threatening; hospitalisation or continuation of hospitalisation is recommended;

Grade 4: Serious repercussions; indications of an urgent intervention.

Grade 5: Death connected to a negative incident in grade

Monitoring of adverse event rates

An impartial data monitoring group should examine each bad incident. To lessen the chance of a recurrence, the factors leading to each negative incident should be examined.

Based on predetermined criteria, interim safety studies should be carried out. A re-evaluation of the suggested treatment or its effectiveness may be suggested if, for instance, there are only three major (grade 4-5) adverse events in the first 59 patients, which suggests that there is a 95% confidence that the adverse event rate is less than 1%.

It may be wise to stop the study if the rate of adverse events is higher than anticipated, unless and until the causes have been found. To lessen the hazards, significant adjustments may be required to the device, implant method, or patient selection procedure. The safety information from the preliminary study should then be incorporated into a new research proposal or study modification. To guarantee that the influence of any changes can be quantified, the data collection for research modifications should be adequately segmented to permit both independent and combined analysis with respect to the original study data.

The purpose of this document is to offer manufacturers, approved bodies, and notified bodies with guidelines on leadless CIED evaluation and installation requirements. Additionally, it was created with doctors and other professionals working on the creation of these services in mind. The document was also developed to give manufacturers, approved bodies/notified bodies, and other parties advice on how to construct studies for leadless device market approval and post-market follow-up [30].

THE MARKETED LEADLESS PACEMAKER'S

The currently available leadless pacing systems are the Nanostim Leadless Cardiac Pacemaker, the Micra Transcatheter Pacing System, the Abbott Medical Aveir™ Leadless Pacemaker and the Aveir™ DR dual-chamber which is under investigation by Abbot.

NANOSTIM LEADLESS CARDIAC PACEMAKER- Nanostim LCP

Nanostim was the first self-contained intracardiac pacemaker to be implanted in a human patient. They are placed in the right ventricular septum after being implanted via the femoral pathway. They need an introducer with a huge bore of about 18 Fr. A helix-shaped screw serves as the nanostim's fixation

mechanism. 2013 saw the Nanostim earn the CE Mark. Between 2013 and 2016, 1423 Nanostim implants totalled the world, and three clinical trials were started. A significant recall was prompted by premature battery failure in a portion of these devices. Another factor keeping the hold on Nanostim implantation is the spontaneous separation of the docking button, which has been documented to impact this device [31].

MICRA TRANSCATHETER PACING SYSTEM- Micra TPS

Micra TPS are intracardiac implants that are positioned in the right ventricular septum after being inserted by the femoral channel. It is a leadless, fully functional, miniature (0.8 cc), single chamber ventricular pacemaker that is implanted immediately into the right ventricle. It needs an introducer system with a big bore and a size range of 23 Fr (Micra). It offers patients with Class I or Class II indications for bradycardia pacing therapy a treatment choice. A delivery system, an introducer, and the pacemaker device make up Micra TPS. The fixation tines of Micra are released from the delivery system and engage with the heart tissue. To enhance battery life, Micra offers rate responsive pacing in addition to automatic pacing capture threshold control. The MRI environment can be utilised with Micra, enabling complete body scans at 1.5T and 3T. The Micra pacemaker, which is significant, offers the possibility of being programmed to Device Off mode, permanently deactivating pacing and sensing, letting it to stay in the body after its useful life without improper interaction with concurrent device therapy. When percutaneous retrieval is required, Micra features a retrieval feature. The Micra single chamber ("VR") device received CE marking in 2015 and FDA approval in 2016. In 2020, the FDA authorised the Micra AV, a single chamber device with AV synchronisation capabilities18. While these devices reduce some of the hazards associated with conventional systems, they also have their own set of postoperative issues and long-term effects [32].

Characteristics of Nanostim and Micra Leadless Pacemakers

While the Micra TPS was CE-certified in 2015 and was authorised by the FDA in April 2016, the Nanostim LPS acquired a CE mark in October 2013 but is currently seeking FDA approval. There are various similarities and differences between the two self-contained leadless devices. The Nanostim LPS has a discrete volume of 1 **cm^3** compared to the Micra TPS's discrete volume of 0.8 **cm^3** (42mm x 5.99mm vs. 25.9mm x 6.7mm, respectively). While Micra uses a three-axis accelerometer, Nanostim's stimulation mode (VVI/R) is based on a temperature sensor and has an integrated algorithm for rate response modality. To check that the device is in the right ventricle, a little amount of contrast material is delivered via the sheath [33]. In case of retrievability of the device, both devices have proximal ends that are intended to recapture the system. A catheter made specifically for Nanostim features a single-loop snare mechanism. The success rate for nanostim recovery is high (up to 88%), and, in some circumstances, it is still high in older devices. A steerable sheath or the delivery system must be used to insert a goose-neck catheter for microscopic retrieval. There seems to be a 60‑80% success rate. Abandonment appears to be a recommended course of action because there are some reservations and inadequate documentation regarding the retrieval of older devices caused by early encapsulation. In magnetic resonance imaging (MRI), both devices have been shown to be safe between 1.5 and 3.0 T. The attachment mechanism for the Micra TPS uses flexible, curved nitinol tines, while the LPS uses a

non-retractable screw-in helix. The Nanostim uses conductive technology with five ECG surface electrodes to administer subliminal 250 kHz pulses as part of the communication system for interrogating and programming the leadless pacemaker, while the Micra uses conventional radiofrequency technology [34].

CLINICAL STUDY DATA

Nanostim LPS

The LEADLESS trial was the first prospective, nonrandomized, single-arm, multicenter study to assess the efficacy and safety of the Nanostim LPS. During the months of December 2012 and April 2013, 33 patients were enrolled. At 90 days, the absence of major adverse events was the main safety objective. The overall percentage of cases without complications was 94%, and there was just one significant adverse event documented. The success rate of implants, which was the second safety endpoint, was 97% in the patients (32 out of 33). During the three-month follow-up period, the electrical parameters improved and no adverse events necessitating the device's revision took place. In a 12-month follow-up period, complication incidence, electrical characteristics, and rate response characteristics were evaluated in 31 patients [35].

The Nanostim LPS confirmed good electrical performance and no adverse occurrences during this midterm follow-up. The FDA IDE Investigational Device Exemption trial, LEADLESS II, was a prospective, single-arm, multicenter study with 526 individuals. A satisfactory pacing threshold and R-wave amplitude, the key effectiveness endpoints, were attained by 270 of the initial cohort's 300 patients. The primary safety endpoint, which was determined by the standard ISO 14555:2003 3.36 definition of serious device adverse effect at 6 months of follow-up, included cardiac perforation (1,3%), device dislodgement (1,7%), elevated pacing threshold requiring replacement (1,3%), and vascular complications (1,3%).

It is noteworthy that the Nanostim LPS manufacturer issued a first battery advisory in 2016 (an abrupt battery depletion in about 5% of patients between 29- and 37-months post-implant) and that a second safety advisory was then raised for docking button detachments observed in 4 out of 1423 patients implanted up until April 2018. These factors led to the cessation of Nanostim implantation [36].

Micra TPS

The FDA IDE Micra Transcatheter Pacing Study enrolled 725 patients in a prospective, non-randomized, single-arm, multicenter study. At 6 months of follow-up, the primary efficacy outcome was an acceptable pacing threshold. It was met by 98.3% of the 297 patients who completed the 6-month follow-up.

The primary safety endpoint was the absence of adverse device and procedure events. There were 28 events in 25 patients, with one death due to metabolic acidosis caused by the prolonged procedure time (implant plus atrioventricular node ablation). There was no evidence of device dislodgement, and electrical parameters tended to improve over time. The Micra TPS Post-Approval Registry is an ongoing prospective, non-randomized, multicenter registry that aims to evaluate the safety and effectiveness of the TPS in a real-world setting. An interim analysis of the 705 patients enrolled so far revealed a high rate of successful implantation (99.6%). During the 30-day follow-up period, 13 serious adverse events occurred in 12 patients, the majority of which were related to the percutaneous access. There were five pericardial effusions or perforations in total, but only one met the criteria for a major complication. The Micra TPS was not responsible for any of the deaths reported. During a 12-month midterm follow-up period, comparable results were observed in another real-world setting of PAR. At 12 months, the risk of major complications was 63% lower than for transvenous conventional implantation [37].

Comparison of Micra Versus Nanostim

There is no direct comparison between the Micra and the Nanostim. The Micra and Nanostim both had similar rates of vascular injury and pericardial effusion (1.5%). The rate of pericardial effusion was lower in the Micra Post Approval Study, occurring in 5 of 795 patients (0.63%), with two requiring pericardiocentesis. Device dislodgment was greater in the Nanostim than in the Micra pacemaker. There were no device dislodges in the LEADLESS trial. In the LEADLESS II trial, however, there were six device dislocations: four in the pulmonary vein and two in the femoral vein, all of which were successfully retrieved. In comparison, there were no dislodgements in the Micra IDE trial (one was retrieved due to a rise in threshold, but there was no overt macro-dislodgment) and only one in the Micra Pacing Post Approval study. The difference in the fixation mechanism between the two devices could explain the higher rate of dislodgement in the Nanostim [38].

AVEIR™ VR LEADLESS SYSTEM

The Nanostim LP system was modified prior to market release and renamed the AveirTM Leadless Pacemaker (LP) system. Phase II of this IDE study confirmed the safety and effectiveness of these modifications in the Aveir LP system. The Aveir VR Leadless Pacemaker (Abbott, Chicago, IL) recently received FDA approval, joining the Micra (Medtronic, Minneapolis, MN) transcatheter pacing system in the category of non-trans venous cardiovascular implantable devices. The Aveir Leadless Pacemaker System is designed to treat slow (bradycardia) or irregular heart rhythms by generating electrical pulses

that stimulate the heart to beat normally. A leadless pacemaker, delivery catheter, and link module are all part of this system.

The AveirTM Leadless Pacemaker System is indicated for patients with significant bradycardia and:

a) Normal sinus rhythm with rare episodes of A-V block or sinus arrest
b) Chronic atrial fibrillation
c) Severe physical disability

Rate-modulated pacing is indicated for patients with chronotropic incompetence and for those who would benefit from increased stimulation rates concurrent with physical activity [39].

Components of The Aveir™ Leadless System

a) Aveir™ Leadless Pacemaker
b) Aveir™ Delivery Catheter
c) Aveir Link Module

Aveir Leadless Pacemaker (Model LSP112V)

The Nanostim LP system was modified prior to market release and renamed the AveirTM Leadless Pacemaker (LP) system. Phase II of this IDE study confirmed the safety and effectiveness of these modifications to the Aveir LP system.

The Avert Leadless Pacemaker System, a pulse generator with an integrated battery and electrodes for bradycardia pacing, is intended for implantation in the right ventricle. The Aveir Leadless Pacemaker is designed to detect intrinsic cardiac signals and deliver cardiac pacing therapy to the intended population.

It does not require a connector, pacing lead, or pulse generator pocket because it is leadless. The LP is attached to the endocardium by a distal, nonretractable helix. A single dose of dexamethasone sodium phosphate (DSP) is included in the tip electrode to reduce inflammation. Three additional features on the LP nosecone's exterior are intended to provide secondary fixation security. Pacing and sensing take place between a distal electrode near the helix and the LP's external can. The LP's proximal end has a docking feature for delivery and retrieval catheters, allowing for repositioning and retrieval.

Electrical signals conducted between the implanted LP's electrodes and skin electrodes applied to the patient's chest and connected to the programmer system allow the LP to communicate bidirectionally

with the programmer system. As a result, the LP transmits signals using pacing circuits and electrodes, with data encoded in pulses delivered during the ventricle's refractory period.

The LP detects right ventricular blood temperature and increases pacing rate in response to increased metabolic demand.

LEADLESS PACEMAKER

The components of the leadless pacemaker include a docking button and a helix. A single dose of dexamethasone sodium phosphate (DSP) is included in the tip electrode to reduce inflammation. The LP is contained within the loading tool. The loading tool consists of a chamber icon, LP inside the loading tool, a latch, a funnel, and curved wings.

Aveir Delivery Catheter (Model LSCD111)

The Aveir Delivery Catheter consists of a steerable delivery catheter, an integrated guiding catheter with a protective sleeve to shield the electrode and fixation helix of an attached LP, and a valve bypass tool to widen the 25-Fr introducer sheath haemostasis valve and advance the system into the femoral vein. The Aveir Delivery Catheter is designed to deliver and manipulate an LP in the peripheral vasculature and cardiovascular system. Implanting an LP within the target chamber of the heart is part of the delivery and manipulation process. The components of the delivery catheter include a catheter tip, a guide catheter with marker bands, flush or irrigation ports, a lock for the valve bypass tool, a guide catheter hub lock, and a delivery catheter handle.

During the implantation procedure, the delivery catheter allows you to attach and dock a separate LP that has been preloaded in the loading tool. Place the protective sleeve over the LP's fixation helix and secure it in place. Advance the LP through the femoral vein into the right ventricle from a groyne access site (using minimally invasive techniques). Hand injects contrast solution through the guide catheter flush port to its distal tip. Pull back the protective sleeve to expose the flexible section of the delivery catheter. Map the endocardium with the docked LP to determine implant site suitability. Position and rotate the LP to secure its fixation helix to the endocardium. Undock the LP from the delivery catheter, leaving it tethered to the delivery catheter to assess thresholds with minimal force transmission from the delivery catheter. Dock the delivery catheter again, unscrew, and reposition the LP as needed for acceptable thresholds. Disconnect the LP from the delivery catheter tethers, leaving the LP implanted in the endocardium. Aside from the docking mechanism, the delivery catheter and its control system (handle) operate in the same way as a conventional steerable catheter and control system.

Aveir Link Module (Model LSL02)

Through the patient cable and skin electrodes, the Aveir Link Module communicates with an implanted Aveir leadless pacemaker. To programme and interrogate the Aveir Leadless Pacemaker, safe, high-frequency electrical pulses are sent between the LP and programmer systems. The Link Module also acquires a patient's ECG waveform using the patient cable and skin electrodes. The Link Module is powered by the Merlin Patient Care System Model 3650's USB port.

CLINICAL STUDY DATA

The clinical study results demonstrate the safety and effectiveness of the Aveir VR Leadless System in a population indicated for a VVI-R pacemaker. In the clinical study, the confirmatory safety endpoint was met as the 6-week CFR among 200 enrolled subjects was 96.0%, of which the one-sided 97.5% lower confidence bound, 92.2%, exceeded the performance goal of 86% with statistical significance ($p<0.0001$).The confirmatory effectiveness endpoint was met as the 6-week composite success rate among 196 successfully implanted subjects was 95.9%, of which the one-sided 97.5% lower confidence bound, 92.1%, exceeded the performance goal of 85% with statistical significance (p 0.0001). The rate response assessment in the clinical study demonstrated an appropriate and proportional rate response during graded exercise testing. The mean slope of the normalised increase in sensor-indicated rate versus normalised CAEP workload for each subject among 17 analysable subjects was 0.93 0.29 with a 95% confidence interval (0.78, 1.08), which fell within the pre-specified success criterion of a 35% equivalence margin (0.65, 1.35), with statistical significance (p 0.0001). Finally, the 2-year estimated survival rate for Phase I subjects was 85.3%, of which the one-sided 97.5% lower bound, 82.7%, exceeded the performance goal of 80% with statistical significance (p 0.0001). The Leadless II Study– Phase 2 met the pre-specified performance goals for both the confirmatory safety (freedom from SADEs) and effectiveness (acceptable pacing and sensing) endpoints. The study also met both secondary endpoints. These results showed that the Aveir LP System is safe and effective for single-chamber pacing indications.

Clinical Advantages

The Aveir™ Leadless Pacemaker System provides all of the clinical advantages of traditional pacemakers:

detecting intrinsic heart signals and delivering cardiac pacing therapy. Long-term management of various forms of atrioventricular conduction anomalies and chronic symptomatic sinus bradycardia

Reduced morbidity and mortality, as well as improved health-related quality of life (QOL). When compared to a traditional single-chamber transvenous lead and IPG pacemaker, the Aveir™ Leadless Pacemaker system has no lead-related complications (such as infection, lead fracture, or insulation problems). There are no pocket-related complications (such as infection, skin erosion, or keloid formation). Elimination of pectoral scars and breast bulge. Improved health-related quality of life (QOL). When clinically necessary, the Aveir™ Leadless Pacemaker System also provides patients with the option of undergoing an MRI scan under defined conditions of use.

Sterilization

Before shipment, the contents of the package were sterilised with ethylene oxide. The LP and delivery catheter are only for single use and should not be resterilized.

Any attempt to resterilize and reuse this system may jeopardise its integrity. Adverse effects associated with component desterilization and reuse may include local and/or systemic infection, mechanical damage, and inaccurate functionality. And do not implant the LP if the sterility indicator within the inner package is purple, indicating that it has not been sterilised, or if the storage package has been pierced or altered, indicating that it has become non-sterile.

AVEIR™ DR DUAL-CHAMBER (Investigational device)

The Aveir™ DR dual-chamber pacemaker, which is under investigation by Abbott, is intended to offer synchronous, beat-by-beat pacing of the right atrium and right ventricle of the heart.

Proprietary implant-to-implant (i2iTM) device technology is used for communication between two implanted leadless pacemakers to regulate the heart rate.

The implant of Abbott's investigational Aveir™ dual-chamber leadless pacemaker within the pivotal study marks a significant technological advancement for leadless pacing technology.

Because synchronising two leadless pacemakers has proven to be quite challenging, the leadless pacing choices that are currently available are limited to single-chamber devices. Abbott overcame this challenge by developing the company's innovative "i2i technology," which allows for beat-by-beat communication between two leadless pacemakers, one in the right ventricle and one in the right atrium. This technology is intended to synchronise the heart rate between chambers and enable true dual-chamber leadless pacing.

The first-in-human implant of a dual-chamber leadless pacemaker is a significant clinical milestone that will open up new options for patients who require pacing assistance. Abbott has made significant investments in leadless pacing technology, which has the potential to improve care for more patients suffering from abnormal heart rhythms. The latest milestone for the Aveir DR leadless pacemaker comes on the heels of recent data showing that Abbott's investigational single-chamber leadless pacemaker, Aveir VR, met the pivotal trial's pre-specified primary endpoints.

According to studies, nearly 80% of people who receive a pacemaker require a dual-chamber option to pace both chambers on the right side of the heart. Aveir DR has been designed to meet a critical need for these patients.

It is also designed to be retrievable, allowing the system to be replaced or retrieved as therapy needs change. The Aveir DR system is intended to provide real-time mapping capability, allowing physicians to evaluate therapy delivery and reposition the device before implanting it during a patient's procedure.

THE AVEIR DR I2I STUDY

The Aveir DR i2i study is a prospective, multicentre, international, single-arm investigational study aimed at assessing the clinical efficacy and safety of the Aveir DR leadless pacemaker in patients who were indicated for a DDD(R) pacemaker, or dual-chamber bradycardia pacing pacemaker, which stimulates the appropriate chamber of the heart when clinically necessary. The study is expected to enrol up to 550 patients from as many as 80 sites in the United States, Canada, Europe, and Asia-Pacific. Each patient will be monitored for at least 12 months following implant placement.

In a global pivotal study, the Aveir DR i2i leadless pacemaker was identified as an investigational product that is currently not for sale on the market. The device design specifications are subject to change [40].

DISCUSSION

The potential for more widespread usage of this innovative technology is supported by the early experience with the first-generation leadless pacing systems. The development of smaller and less invasive delivery systems and devices will probably reduce the problems that come with conventional pacemakers. It will be much easier for a bigger population to use subcutaneous defibrillating systems (S-ICD) if leadless pacing technology is included in them to provide efficient bradycardia rate support and anti-tachycardia pacing. It is obvious that any evolving technology would require ongoing clinical

testing in larger populations to show the security and effectiveness of these more recent generations of systems. Leadless pacemakers have evolved from single-chamber pacing devices to those that can synchronise with the Micra AV device for atrioventricular pacing. Consistent AV synchrony remains elusive with the current generation of devices, but it is expected to improve with the introduction of dual-chamber leadless pacemakers, which are currently in clinical trials. Even though dual-chamber leadless pacemakers, which are now undergoing clinical testing, are projected to become more common, consistent AV synchronisation with the current generation of devices is still difficult to achieve. In the future, patients may receive the best physiological pacing possible while avoiding the disadvantages of transvenous pacing systems thanks to dual-chamber leadless pacemakers that may synchronously pace the atrial Bachman's bundle and the ventricular conduction system.

CONCLUSIONS

Leadless pacemakers are frequently used in elderly and comorbid populations, but they also have a high probability of implant success and a low risk of serious consequences. As the potential advantages, such as the lack of device infection, are understood, it is projected that the use of leadless pacemakers will rise. The field of cardiac pacing is one where this technology has promise. It will take more research to determine how they affect long-term electrical performance, valvular function, and left ventricular systolic function. These devices' cost and patient choice will be key determining factors in their widespread adoption. We anticipate that this wireless, leadless technology will provide long-lasting advantages while avoiding the frequent difficulties associated with other devices. This is especially true given the shortcomings of current approaches, particularly lead-related vascular issues. The next generation of leadless devices, capable of dual-chamber pacing and communication with subcutaneous defibrillators, is being developed and will extend the scope of leadless pacing past 2022.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation**.**

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Not applicable.

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