Summary

- Leadless pacemakers may provide an alternative to traditional pacemakers for the treatment of patients with cardiac arrhythmias who require single-chamber ventricular pacing. Two leadless pacemakers, the Micra Transcatheter Pacing System (TPS) (Medtronic) and the Nanostim (St. Jude Medical), are currently in development. Each consists of a self-contained intracardiac device including the pacemaker, electronic circuits, battery, and leads.

- The less invasive and shorter implantation procedure of leadless pacemakers reduces recovery time and eliminates complications related to the transvenous leads and the subcutaneous pulse generator used in traditional pacemakers. In addition, there is no visible lump or scar, shoulder mobility is maintained, and patients are expected to experience a better quality of life.

- One prospective, non-randomized, single-arm, multi-centre study is evaluating the Micra Transcatheter Pacing System pacemaker for safety and long-term performance.

- 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.

Background

Slow heart rhythms are a type of cardiac arrhythmia; arrhythmia occurs when there is a failure of the intrinsic sinus, or there is a delay or interruption in the transmission of electrical impulses from the atria to the ventricles (atrioventricular [AV] conduction). Symptoms include dizziness, syncope, fatigue, shortness of breath, weakness, and poor exercise tolerance. Pacemakers are implanted in patients with slow heart rhythms to transmit electrical impulses to the heart that stimulate contraction. Traditional cardiac pacemakers consist of a pulse generator (containing the battery and the machinery for sensing and timing of electrical impulses) and the leads (insulated wires that deliver electrical impulses from the pulse generator to the heart). Pacemakers may be single- or dual-chambered. Single-chamber pacemakers have one lead that carries impulses to either the right atrium or the right ventricle. A dual-chamber pacemaker usually has one lead to the right atrium and one lead to the right ventricle to allow for synchronous AV conduction.
Although traditional cardiac pacemakers have been shown to reduce mortality and improve quality of life in patients with cardiac arrhythmias, they are associated with several procedure- and device-related complications. Traditional pacemakers require a surgical incision in the chest to create a subcutaneous pocket for the pulse generator. Complications arising from placement of the pulse generator in the chest pocket include hematoma (a large bruise caused by bleeding after surgery), skin breakdown, and pocket infection. In addition, up to six out of ten patients experience reduced mobility in the shoulder region where the pulse generator is implanted. In the long-term, the leads of traditional pacemakers are the main concern. Lead-related complications include venous obstruction, insulation breaks, lead dislodgement, electrical malfunction, lead fractures, and infection. Further problems may appear when lead extraction is required to treat infection—a procedure associated with a high risk of complications including trauma to the heart or a major blood vessel, which can cause fatal internal bleeding.

### The Technology

Two leadless cardiac pacemakers, the Nanostim leadless pacemaker (St. Jude Medical, St. Paul, Minnesota) and the Micra Transcatheter Pacing System (TPS) (Medtronic, Minneapolis, Minnesota), are currently in development for patients with cardiac arrhythmias who have an indication for single-chamber ventricular pacing. Both are self-contained intracardiac devices that include the pacemaker electronics, battery, and leads. The Nanostim pacemaker is less than 10% of the size of a traditional pacemaker, with a battery life ranging between 8.4 years and 12.4 years, depending on pacing parameters. A screw-in helix fixes the Nanostim pacemaker to the right ventricle. The Micra TPS pacemaker is 30% smaller than the Nanostim. Four tines (prongs) anchor the pacemaker to the right ventricle. The tines are designed to cause less trauma to the cardiac tissue if the device needs to be repositioned. The estimated battery life of the Micra TPS ranges from 10 to 15 years (Medtronic data on file).

Both devices are implanted in the same setting as traditional pacemakers (i.e., in a cardiac catheterization laboratory or operating room) using sedative medications and local anesthesia. However, the entire procedure for both mechanisms is faster (20 to 45 minutes, depending on the experience of the specialist) compared to the 60-minute procedure for the insertion of traditional pacemakers. After placing a sheath in the femoral vein in the groin, the pacemaker is delivered to the apex of the right ventricle using a steerable catheter. The procedure is guided by fluoroscopy (an X-ray imaging technique). If the position is suboptimal, both leadless pacemakers are repositionable and retrievable in the short-term using a specific catheter. After pacemaker implantation, a closing bandage is used for the access site in the groin. Generally, patients are observed over a 24-hour period before discharge. Patients are instructed to avoid heavy lifting or exercise for a week.

There are several anticipated benefits to using leadless pacemakers over traditional pacemakers owing to the less invasive implantation procedure and the absence of the transvenous leads and subcutaneous pulse generator. These include the elimination of complications related to the leads and pulse generator; shorter procedure and recovery times, and reduced fluoroscopy exposure for patients and staff. In addition, there is no visible lump or scar, and patients are expected to maintain their shoulder mobility and experience a better quality of life.

### Regulatory Status

The Nanostim and Micra TPS leadless pacemakers are not currently licensed for sale in Canada. In October 2013, St. Jude Medical received CE mark approval (for European commercialization) to market the Nanostim leadless pacemaker in the European Union (EU). Implants have occurred as part of a post-market study in the United Kingdom, Germany, Italy, the Czech Republic, France, Spain, and the Netherlands. A trial designed to investigate Nanostim for United States (US) Food and Drug Administration (FDA) approval was initiated in February 2014. Medtronic plans to submit an application for Micra TPS to Health Canada in 2015 once results are available from the ongoing clinical trial (Medtronic of Canada Ltd.: personal communication, 2015 Jan 9). Medtronic expects to receive the CE mark for Micra TPS in 2015, and US FDA approval is expected in 2017-2018.

### Patient Group

An estimated 200,000 Canadians are living with pacemakers. Approximately 20% to 30% of these patients are using single-chamber ventricular pacemakers. Data collected by the Canadian Institute for Health Information show that, between 2012 and 2013, a total of 12,342 procedures relating to the
implantation or removal of a pacemaker were performed in Canada at a total cost of $155 million dollars.28

**Current Practice**

Traditional pacemakers are usually implanted by cardiac electrophysiologists, cardiologists, or surgeons in a variety of settings in Canada including cardiac catheterization laboratories, electrophysiology laboratories, and operating rooms.29 The procedure is performed using sedative medications and local anesthesia. A one- to two-inch incision in the upper chest is used to create a pocket under the skin in which to place the pulse generator. The incision is sutured and a dressing is placed over the wound for a few days to protect it while it is healing. The leads are inserted through a central vein and guided to the right ventricle, right atrium, or both, where they are secured to the cardiac tissue using a screw-in helix. The position of the pacemaker leads is checked using fluoroscopy. The entire implantation procedure typically takes an hour. Some centres in Canada routinely discharge patients the same day of the procedure, while others keep patients overnight.29 Restrictions in patient activities are recommended for several weeks after implantation to reduce the risk of dislodgement or damage to the pacemaker leads. The battery in most traditional pacemakers lasts an average of six to eight years.2 Replacing the pulse generator usually requires a skin incision made over the old incision in the chest, the removal of the old generator, and the placement and connection of a new generator to the existing leads.30 Because of the high risk of complications associated with lead extraction, the pacemaker leads are usually used indefinitely unless a specific complication occurs, such as an infection.15-17

**Methods**

A peer-reviewed literature search was conducted using bibliographic databases to identify literature related to the assessment of leadless pacemakers, as follows: MEDLINE, PubMed, Embase, and the Cochrane Library (2014, Issue 12) were searched. Grey literature was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters). No methodological filters were applied. The search was limited to English language documents published between January 1, 2009 and December 11, 2014. Regular alerts were established to update the search until project completion. Peer-reviewed published studies and unpublished data from industry communications and conference presentations reporting the clinical efficacy and safety of leadless pacemakers for the treatment of cardiac arrhythmias were considered for inclusion in the evidence section of this bulletin. Case reports, editorials, letters, and literature reviews were excluded.

**The Evidence**

Clinical data to support the use of leadless pacemakers have been reported in the LEADLESS trial — a prospective, non-randomized, single-arm, multi-centre study in Europe.19,31 The safety and technical performance of the Nanostim pacemaker was tested in patients with a clinical indication for single-chamber right-ventricular pacing. Indications included permanent atrial fibrillation with AV block (which includes atrial fibrillation with a slow ventricular response); normal sinus rhythm with a high degree of AV block (with a low level of physical activity, or short expected lifespan); or sinus bradycardia (with infrequent pauses, or unexplained syncope with electrophysiology findings). Patients were excluded if they were pacemaker-dependent (i.e., at risk of suffering significant symptoms or cardiac arrest with the cessation of pacing), had a mechanical tricuspid valve prosthesis, had pulmonary hypertension, pre-existing pacemaker/defibrillator leads, or an inferior vena cava filter. The primary safety outcome was freedom from complications (complication-free rate), defined as not having serious device-related adverse effects at 90 days. Safety was measured by reporting the complication-free rate, based on subjects who completed their 90-day follow-up visit or who dropped out because of a complication. The secondary safety outcome was implant success rate, defined as the percentage of subjects leaving the implant procedure with an implanted and functioning leadless cardiac pacemaker device. The secondary performance outcomes were pacemaker performance characteristics including sensing, impedance, pacing threshold, and cumulative cell charge.

Thirty-three patients (mean age 76.5 ± 8.4 years, range 53 years to 91 years; 67% male) underwent implantation of the Nanostim leadless pacemaker. The mean procedure duration was 28 ± 17 minutes (range 11 minutes to 74 minutes). Ten patients (30%) required a repositioning of the leadless cardiac pacemaker after initial placement (1 repositioning [n = 4], 2 repositionings [n = 4], 3 repositionings [n = 2]). Five of these patients (15%) required the use of more than one
pacemaker during the procedure owing to either the inadvertent placement of the device in the left ventricle (n = 1), a malfunction of the release knob (n = 1), delivery catheter damage related to compromised venous access (n = 1), damage to the helix during insertion (n = 1), or difficulty with the wire deflection mechanism of the delivery catheter (n = 1). Implant success rate for patients completing the implant procedure successfully was reported to be 97% (n = 32). The average time to hospital discharge was 31 ± 20 hours (range 17 hours to 113 hours). The measures of pacing performance were stable within the accepted range over the three months. One year data from the study were reported at the Heart Rhythm Society 2014 Scientific Sessions. Results showed that the Nanostim leadless pacemaker continued to work as expected. Measures of pacing performance remained similar to those seen in the initial three months of follow-up.

Two additional prospective, single-arm, non-randomized studies are evaluating the Nanostim pacemaker for procedural and safety outcomes in patients indicated for single-chamber ventricular pacing. The LEADLESS Pacemaker Observational Study is a post-market study designed to build additional evidence to support the safety profile of the Nanostim pacemaker. It was designed to establish the long-term clinical performance and safety of the Nanostim leadless cardiac pacemaker within its intended use and according to current instructions for use. The primary outcome is a complication-free rate at 90 days. Complications at six months and five years will also be assessed. The study was expected to enroll approximately 1,000 patients in approximately 100 centres in Europe, with completion in 2020. The study was halted in January 2015 following several reports of serious device-related adverse events. The LEADLESS II trial is a multi-centre trial being conducted under an investigational device exemption (IDE) from the US FDA. An estimated 670 patients will be enrolled in 55 centres in the US, Canada, and Europe. Participating centres in Canada include the Foothills Medical Centre (Calgary, Alberta), the Southlake Regional Health Centre (Newmarket, Ontario), and the Vancouver General Hospital (Vancouver, British Columbia). The primary outcome is the complication-free rate and performance measures at six months. The estimated date for final data collection is June 2015. The study completion date has not been specified.

The Micra Transcatheter Pacing Study is a prospective, single-arm, non-randomized study evaluating the safety and long-term performance of the Micra TPS pacemaker for single-chamber ventricular pacing. The study will be conducted in up to 70 sites in the US, Canada, Europe, Malaysia, Australia, and Japan. Participating centres in Canada are the Montreal Heart Institute (Montreal, Quebec) and the Institut universitaire de cardiologie et de pneumologie de Québec (Quebec City, Quebec). Overall, an estimated 780 patients will be enrolled. The primary outcome is a device- or procedure-related major complication-free rate and pacing performance at six months post-implant. Study completion is expected in June 2018. The study also has a separate long-term safety objective that will provide additional long-term safety data following potential regulatory submissions. Preliminary results from the trial were released at the CARDIOSTIM/ EHRA EUROPACE 2014 World Congress in electrophysiology and device therapies. The Micra TPS pacemaker was successfully implanted in the first four patients (age range 74 to 83 years). There were no major complications at one and three months post-implant and the device performed as expected, with electrical values within normal ranges. The average procedure time was 43 minutes. Outcomes from the first 60 patients are expected to be published in the spring of 2015 (Medtronic of Canada Ltd.: personal communication, 2015 Jan 9).

### Adverse Events

One serious device-related adverse event was reported in the LEADLESS trial evaluating the Nanostim pacemaker. The patient developed right-ventricular perforation and acute pericardial effusion (a rapid buildup of fluid in the pericardium resulting in compression of the heart) during the implantation procedure, and eventually died as the result of stroke. Three patients were re-hospitalized within 90 days for reasons unrelated to the device. There were no instances of vascular injury (deep vein thrombosis, femoral hematoma, fistula, or pseudoaneurysm) requiring intervention for treatment, causing long-term disability, or resulting in a prolonged hospitalization. There were no additional adverse events (including device dislodgement, device migration, infection, mechanical failure, early battery depletion, or proarrhythmia) uncovered after following the 33 patients enrolled in the preliminary study for 12 months. Six more hospitalizations were reported, but none were device-related.
In July 2014, St. Jude Medical issued a letter describing a voluntary safety evaluation of the Nanostim pacemaker after observing perforation and pericardial effusion events in six (4.1%) patients during the implantation procedure in the post-market study, two of which resulted in death.\textsuperscript{18,33,39} A total of 147 patients had been enrolled up until that point. Other serious device-related adverse events included dislodgement in two (1.4%) patients and femoral hematoma in one (0.7%) patient. Patient selection and implantation techniques were identified to be the factors that led to these adverse events. The post-market study was halted in April 2014 and several revisions were made to the instructions for using the Nanostim pacemaker, including a revised contraindication, additional warnings, and clarification on implantation practices.\textsuperscript{39} The new instructions contraindicate the use of the device in patients with pre-existing pulmonary arterial hypertension or severe lung disease. Careful consideration is suggested for use in patients who are at a higher risk for perforation including those who have had cardiovascular or peripheral vascular surgery within the last 30 days. The study protocol was aligned with these revisions and additional training was provided for all implanting physicians on implantation steps and best practices. Following meetings with regulatory authorities and clinical investigators, which led to refining the inclusion criteria, the study was restarted in June 2014 with the new protocol.

In February 2015, St. Jude issued another letter instructing clinical investigators of the post-market study to discontinue implants of the Nanostim device due to two (2.2%) further incidents of pericardial effusion occurring in the 93 patients who enrolled after the study resumed.\textsuperscript{33} Failure to adequately pace the right ventricle was also noted in one (1.1%) patient. An additional five (1.6%) cases of pericardial effusion, six (1.9%) cases of device dislodgement, four (1.2%) cases of failure to pace the right ventricle, four (1.2%) cases of femoral hematoma, and one (0.3%) case of pulmonary embolism have been reported in the 322 patients enrolled since initiating the LEADLESS II trial.\textsuperscript{33} The suspension of the post-market study is stated to be a precautionary measure while the firm analyzes interim data from the Nanostim studies. These data will be reviewed by regulatory agencies and the resumption of the study will depend upon approval from these agencies.

### Cost

The manufacturers’ prices for the Nanostim and Micra TPS leadless pacemakers in Canada are not currently available. One source\textsuperscript{40} estimates that the cost for the Nanostim pacemaker in Canada would be approximately $10,000, which is three times more than the standard traditional pacemaker. In Europe, the estimated cost for the Nanostim pacemaker and implantation procedure is €11,500.\textsuperscript{18} The cost for the retrieval of the pacemaker (if necessary) shortly after implantation is €6,000.\textsuperscript{18}

### Concurrent Developments

The limited lifetime of pacemaker batteries and the risk of complications from replacement procedures have sparked interest in alternate methods of powering pacemakers.\textsuperscript{7} The approaches currently under investigation are in the early stages of development and have not been tested in humans.

### Harvesting Biologic Energy From Cardiac Motion

Various concepts have been proposed to harness the kinetic energy within the cardiovascular system to power a pacemaker.\textsuperscript{7} One such concept is piezoelectric systems that convert the vibrations of heartbeats into electrical energy, which can then be used to power a pacemaker. A research team from KAIST — the Korea Advanced Institute of Science and Technology — has developed a self-powered cardiac pacemaker that is operated semi-permanently by a flexible piezoelectric nanogenerator.\textsuperscript{41} Results from the team’s study in rats showed that the piezoelectric nanogenerator can directly stimulate the heart using electrical energy harnessed from small body movements. In December 2013, a collaborative project coordinated by the Tyndall National Institute at University College Cork in Ireland secured €6.1 million in funding to research new materials and devices that will facilitate the extraction and storage of energy from a beating heart to power a pacemaker.\textsuperscript{42} The project will target the development of perpetually self-powered electronic systems that can be implanted into the human body to eliminate the requirement for battery replacement.

### Biological Pacemakers

Biological pacemakers use a gene-based approach to convert heart muscle cells into pacemaker cells.\textsuperscript{7} Biological pacemakers are currently being investigated as a potential alternative or supplement to electronic pacemaker devices.\textsuperscript{7} A recent proof-of-concept study from the Cedars-Sinai Heart Institute in Los Angeles, California showed that injecting a human embryonic...
transcription factor called T-box 18 (TBX18) into ventricular muscle cells provided effective pacemaker activity for 14 days in a pig model, with complete AV conduction block. 43

All three studies evaluating leadless pacemakers are assessing procedural and safety outcomes in patients indicated for single-chamber ventricular pacing. 25,26,32 Further development of both leadless pacemakers for multi-chamber pacing may occur pending positive results from the ongoing studies. 18 However, the safety of the Nanostim pacemaker is currently under investigation following several incidents of perforation and pericardial effusion. 33,39 Further assessment of the risk of other serious, device-related complications including dislodgement and migration into the pulmonary vasculature (embolization) and mechanically induced arrhythmias is required. 7,19,44 Any differences in safety and pacing performance because of design differences in the two leadless pacemakers (e.g., tines versus helical screw fixation, size of the pacemaker sheath diameter) are currently unknown. 22

Implementation Issues

It is anticipated that leadless pacemakers will be more expensive than traditional pacemakers. 40 However, savings generated from the shorter procedure time and fewer health care resources used to manage lead and chest pocket complications could help offset the additional cost. Although the setting and staff required for leadless pacemaker implantations do not differ from traditional pacemaker procedures, some training will be required for clinicians to become familiar with the device and implantation practices. 18 The feasibility of device extraction in the case of battery depletion, device malfunction, or infection is currently unknown. Animal studies have shown that it is possible to retrieve the device six months after implantation, 21 but it is not known if it is possible to safely retrieve the device after it has been in place for years. It may be possible to place multiple devices within the cardiac chamber, but it is not yet known if this is feasible.

Further evaluation of leadless pacemakers for long-term pacing performance, complication rates, and cost-effectiveness compared with traditional pacemakers is required. If long-term efficacy, safety, and cost-effectiveness can be demonstrated, leadless pacemakers may provide an additional treatment option for select patients with cardiac arrhythmias.

References


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