Summary of findings

Evidence for the safety and effectiveness of LPs is limited. Only one small study in humans has been finalised and the other trials assessing procedural and safety outcomes in patients indicated for single chamber ventricular pacing are still ongoing. It is not known if there are differences in effectiveness and safety when comparing the two devices (Nanostim and Micra). Data on the long term effectiveness and risk of complications, e.g. spontaneous dislodgement and embolisation, is lacking and should be investigated.

HealthPACT Advice

HealthPACT noted that this technology has the potential to reduce side effects and adverse events compared to pacemakers currently in use. Leadless pacemakers are, however, significantly more expensive in comparison to conventional single chamber pacemakers ($16,000 vs $6,000), which may limit their potential diffusion and uptake in clinical practice in Australia and New Zealand. HealthPACT does not support investment in this technology in clinical practice at this time; however, it is recommended that the evidence be reviewed again in 24 months.
Technology, Company and Licensing

Register ID      WP 222
Technology name Leadless Pacemaker
Patient indication Symptomatic bradycardia and atrial fibrillation (AF)

Description of the technology

The leadless pacemaker (LP) is designed to have the same function as a standard cardiac pacemaker, but it requires no leads and it is placed completely inside the right ventricle of the heart (See Figure 1). Furthermore, it is around 10 per cent of the size of a traditional pacemaker. As it is placed using a steerable catheter and does not have a separate pulse generator, the pacemaker requires no surgical pocket. A traditional pacemaker placement procedure takes around 60 minutes, whereas the procedure for LP placement takes between 20 and 45 minutes. A sheath is placed in the femoral or jugular vein and this is used to deliver the device into the apex of the right ventricle using a steerable catheter. The LP then attaches using a fixation mechanism and the LP’s pacing and sensing system are tested while the LP is still connected to the catheter. Subsequently, the device is deployed and detached from the catheter. If the placement is suboptimal, the LP is repositionable and retrievable. Generally the patient is observed for 24 hours before discharge. The battery life of LPs ranges between 9.4 and 15 years, depending on pacing parameters.

Figure 1  Placement of the leadless (Nanostim) pacemaker in the heart and relative size of the pacemaker

Company or developer

Two different leadless pacing systems have been developed and are currently being implanted in humans:

1. The Nanostim leadless pacemaker by St. Jude Medical (St Paul, MN, USA);
2. The Medtronic Micra Transcatheter Pacing System by Medtronic, Inc (Minneapolis, MN, USA).

**Reason for assessment**

Leadless pacemakers are an innovative technology designed to reduce the complications of traditional pacemakers, and may reduce procedure times, hospital stays and resources spent on managing lead and chest pocket complications.  

**Stage of development in Australia**

- Yet to emerge
- Experimental
- Investigational\(^a\)
- Established
- Established but changed indication or modification of technique
- Should be taken out of use
- Nearly established

**Licensing, reimbursement and other approval**

The technology is not currently approved for use in Australia and is not listed on the Australian Register of Therapeutic Goods (ARTG). In the US, the LP is an investigational device and also not yet approved for commercial use, although FDA approval is expected in 2017-2018\(^2\). However, the Micra Transcatheter Pacing system and the Nanostim device received the CE (Conformité Européenne) mark in April 2015 and October 2013, respectively, which enables free movement and sale of the product throughout the European Economic Area.\(^8,9\)

**Australian Therapeutic Goods Administration approval**

- Yes
- No
- Not applicable

**Technology type**

- Device

**Technology use**

- Therapeutic

\(^a\) The LEADLESS pacemaker IDE study (NCT02030418) is being conducted in the United States, Australia and the UK, and the Micra Transcatheter pacing study (NCT02004873) is being conducted in the United States, Australia, Austria, Canada, Czech Republic, France, Greece, Hungary, Italy, Japan, Malaysia, Netherlands, Serbia, Spain, and the United Kingdom.
**Patient Indication and Setting**

**Disease description and associated mortality and morbidity**

**Atrial fibrillation**

Atrial fibrillation (AF) is the most common cardiac rhythm disorder in clinical practice; the prevalence is less than one per cent in people aged under 60 years but estimated to be 10 per cent or higher in people older than 80 years.\(^\text{10}\) AF means there is an irregular and often abnormally fast heart rate (may be over 140 beats a minute), caused by abnormal electrical impulses from the atria which override the heart’s natural pacemaker. The condition is associated with increased cardiovascular morbidity and mortality as it can lead to stroke and heart failure.\(^\text{11}\) Furthermore, it can affect quality of life through symptoms such as palpitations, dizziness, fatigue and dyspnoea. There are different classifications of AF: paroxysmal (self-terminating episodes that last <48 hours), persistent (>7 days or requiring cardioversion), longstanding persistent AF (>1 year), and permanent AF (refractory to cardioversion or when it is no longer attempted to establish a sinus rhythm).\(^\text{10}\)

**Symptomatic bradycardia**

Bradycardia is defined as a pulse rate below 60 beats per minute (in adults), which can cause fatigue, dizziness, fainting and chest pain, and can be caused by an atrioventricular (AV) block. Severe bradycardia can cause haemodynamic consequences of hypotension, altered conscious state, a limited perfusion and heart failure. Bradycardia is only treated if it causes compromised blood flow (haemodynamic compromise) with symptoms of decreased perfusion, such as hypotension, chest pain, syncope (fainting) and heart failure. Atropine can be used as an acute treatment. When atropine is ineffective and patients continue to suffer symptoms resulting from compromised blood flow due to the bradycardia, they should be referred for consideration of pacemaker implantation.\(^\text{12}\)

**Number of patients**

AF is estimated to affect between one and two per cent of the population in Australia.\(^\text{13}\) The prevalence is increasing due to the increasing age of the population. There are no good epidemiological data for bradycardia and the incidence and prevalence are unknown. However, it is known to occur in both sexes equally and is more common in older people.\(^\text{14}\) According to the Australian Bureau of Statistics (ABS), 1,319 people died of atrial fibrillation in 2008 (0.9% of all deaths). Deaths from stroke and heart failure numbered 11,987 and 2,758 in 2008, respectively. In 2013, 1,892 deaths from cardiac arrhythmias (group of conditions with irregular heartbeat, also including bradycardia) were reported by the ABS.\(^\text{15, 16}\) In New Zealand, 5,534 (65.4 per 100,000) and 1,285 (15.0 per 100,000) deaths were reported due to ischaemic heart disease and other forms of heart disease, respectively.\(^\text{17}\) AF affects around two per cent of the New Zealand population, where Maori had almost twice
the rate of AF as compared with the total population. Furthermore, Maori are reported to be affected at a younger age.\textsuperscript{18}

Between July 2013 and June 2014, 9,234 traditional pacemakers were implanted and claimed on Medicare in Australia.\textsuperscript{19} In 2012-2013, the National Hospital Morbidity Database reported 14,557 procedures involving insertion of a pacemaker generator in Australian private and public hospitals. According to The Australian and New Zealand Cardiac Pacemaker and Implantable Cardioverter-Defibrillator Survey, 4,131 atrial or ventricular single chamber pacemakers were sold in Australia in 2013 (both new and replacement, 22% of total), compared to 772 (37% of total) in New Zealand.\textsuperscript{20} The majority of these were single chamber ventricular pacemakers. The survey also reported that 15,203 pacemakers were sold as new implants in Australia in 2013, which translates to 652 implants per million people, compared to 1,641 pacemakers in New Zealand (367 implants per million people).

<table>
<thead>
<tr>
<th>Speciality</th>
<th>Cardiovascular disease and vascular surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technology setting</td>
<td>Specialist hospital, General hospital</td>
</tr>
</tbody>
</table>

**Impact**

**Alternative and/or complementary technology**

This technology would be a direct substitute for patients with class I or II indications, according to American College of Cardiology/American Heart Association/Heart Rhythm Society 2001 guidelines, for a single-chamber ventricular pacemaker (with leads), as it will only pace the right ventricle. Patients who require dual chamber pacing would still need the “traditional” dual-chamber pacemaker.\textsuperscript{21}

**Current technology**

There are numerous models of pacemaker and leads available in Australia and listed on the Prostheses List. The use of pacemakers to treat heart arrhythmias was pioneered in Australia and has been undertaken for many decades now.\textsuperscript{22} Traditional transvenous cardiac pacemakers are associated with several potential procedure and device-related complications. Around 10 per cent of patients experience complications related to the pacemaker. Complications typically happen with the leads or in the pocket where the pacemaker is implanted. Transvenous leads can cause venous obstruction, infection and are prone to insulation breaks.\textsuperscript{3, 23} Patients with a traditional pacemaker will have a scar and lump where the pacemaker is implanted, and the majority of patients (60%) experience shoulder-related problems in the shoulder where the pacemaker has been placed.\textsuperscript{24}

**Diffusion of technology in Australia**

Currently the technology has not been implemented in Australia. However, ongoing multi-centre studies include Australian sites. The technology has been approved for use in Europe.
and has been the subject of horizon scanning briefs in the UK, Canada and Italy.\textsuperscript{2, 7, 25} With Australian sites participating in ongoing trials, the technology is likely to emerge in Australia in the future.

### International utilisation

<table>
<thead>
<tr>
<th>Country</th>
<th>Trials underway or completed</th>
<th>Limited use</th>
<th>Widely diffused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe (Austria, Czech Republic, France, Greece, Hungary, Italy, Netherlands, Serbia, Spain, and the United Kingdom)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Japan, Malaysia</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

### Cost infrastructure and economic consequences

As yet there are no data available about the cost of these devices. Conventional single chamber pacemakers currently available in Australia are listed on the Australian Prostheses List at a price of $5,928, with leads varying in cost according to their features and priced between $1,248 and $6,240.\textsuperscript{26} In a Horizon Scanning report published by the Italian group AGENAS, the reported cost of the Nanostim device and implantation was €11,500 (approximately AUS$16,200), according to St Jude Medical, however costs were not available for the Micra device.\textsuperscript{25}

Given the novel implantation method for this device, additional training for medical specialists who implant pacemakers will be required.

### Ethical, cultural, access or religious considerations

No additional issues compared to the traditional pacemaker were identified; however, should LPs become available in Australia, it is likely that they will be more expensive than the current pacemakers, which could affect the accessibility of the technology depending on the funding mechanisms associated with it. Additionally, especially in the initial stages of implementation, there may be a shortage of medical specialists with adequate training and skill to implant the LPs.

### Evidence and Policy

#### Safety and effectiveness

The safety and effectiveness of the Nanostim device was studied in the non-comparative (level IV) LEADLESS trial, and it is the only published study to date with results in humans.\textsuperscript{3} Thirty-three patients underwent LP implantation in three different centres in three different countries (Czech Republic, Germany and the Netherlands). Indications included permanent
AF with AV block (n=22, 67%), normal sinus rhythm with second or third degree AV block with a low level of physical activity or short expected lifespan (n=6, 18%), or sinus bradycardia with infrequent pauses or unexplained fainting with electrophysiology findings (n=5, 15%). Other clinical characteristics are shown in Table 1.

Table 1  Safety and clinical performance of the Nanostim LP in the LEADLESS study.

<table>
<thead>
<tr>
<th>Reference and type of LP</th>
<th>Study design and follow up</th>
<th>Number of participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reddy et al. (2014)³</td>
<td>Multi centre single arm cohort study (level IV)</td>
<td>33 patients with a clinical indication for single-chamber, right-ventricular pacing. Mean age: 77±8 years (range 53-91) Male: 22/33</td>
<td>Implant success rate: 32/33 (97%) Requiring repositioning: 10/33 (30%) Require &gt;1 LP: 5/33 (15%) Procedure duration: 28±17 min Time to hospital discharge: 31±20 hours Complication-free rate: 31/33 (94%)</td>
</tr>
<tr>
<td>Nanostim Inc, Sunnyvale CA</td>
<td>Follow-up: 90 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LP= Leadless Pacemaker

The study reported that the implant success rate was 97 per cent (32/33), defined as the percentage of patients who left the implant procedure with a working LP device. However, 30 per cent required repositioning of the LP after initial deployment (10/33). Five patients (15%) required more than one device due to the inadvertent placement of the LP in the left ventricle, failure of the release mechanism, delivery catheter damage, damage to the LP helix during insertion, or difficulty with the catheter’s wire deflection mechanism.

The complication-free rate, defined as freedom from serious adverse events due to device defects at 90 days, was 94 per cent (31/33). One patient with persistent slow AF developed cardiac tamponade⁵ with haemodynamic collapse before final release of the LP. A perforation of the right ventricular apex was surgically repaired, however more complications occurred on day five, i.e. acute-onset left-sided hemiplegia attributable to a right-sided main cerebral artery ischaemic infarct and progressive cerebral oedema. The patient died 18 days after the procedure. Another patient, 86 years of age, returned two days after LP placement for recurrent syncope. Monomorphic ventricular tachycardia at 260 beats per minute (bpm) was observed and the LP had to be removed on day five. Three people were rehospitalised within 90 days: the 86 year old patient described above, one patient for an elevated international normalised ratio⁶ of 9.3, and one patient for an acute exacerbation of chronic obstructive pulmonary disease.

One year follow up data from the LEADLESS study (n=31) were reported at a scientific conference in 2014.²⁷ Between three and 12 months follow-up, there were no LP adverse

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⁵ accumulation of fluid in the pericardial space, resulting in reduced ventricular filling

⁶ International normalised ratio is a laboratory measurement of how long it takes for blood to form a clot. A high INR (>4.5) increases the risk of major haemorrhage.
events reported. In 61 per cent of the patients (n=19) the rate response sensor had been activated and in all patients an adequate rate response was observed.

Other than the published study, the only evidence in humans consists of five conference abstracts on LPs, as most studies are still ongoing. The results of only three abstracts are discussed below, as one abstract was on early results of the LEADLESS trial and another abstract was on the same patients as Tjong et al (2014), but with a shorter follow-up period. Eitel et al. (2014) reported the clinical experience of five patients (mean age 78.4±6 years) who underwent LP implantation (type of system/developer not specified). The device had to be repositioned in one patient due to impaired sensing values. There were two peri-procedural complications: one patient with pre-existing left bundle branch block experienced temporary complete AV block during manipulation with the LP system, and one patient suffered from a pseudoaneurysm of the right arteria femoralis profunda that was treated with thrombin. Good sensing and pacing values were seen in all patients at discharge. A second abstract reported on implantation of the Micra LP by Medtronic in four patients (age 74-83 years, 2 males). No unsuccessful implants or post procedural complications were reported, and the mean total procedure time was 47 (range 37-73) minutes. The third abstract reported the longest follow-up so far: 18 months with the Nanostim LP in a centre in Amsterdam (n=8, 82 ± 9 years, six males). The device was successfully implanted in all patients with a mean procedure time of 41 ± 17 minutes. One patient did not complete follow-up due to the need for implantable cardioverter defibrillator implantation and successful LP retrieval. No late complications were reported.

Economic evaluation
No studies on cost-effectiveness of LPs have been identified.

Ongoing research
Two prospective single-arm studies are currently evaluating the Nanostim device: the LEADLESS pacemaker Investigational Device Exemption (IDE) study (Leadless II), and the LEADLESS Observational Study. The Observational study (NCT02051972) aims to confirm clinical performance and safety of the Nanostim device in multiple centres in Europe. Complication-free rates at 90 days, six months and five years will be used as outcome measures. Approximately 1,000 patients are expected to be recruited and the study is due for completion 2020. The study was suspended in January 2015 due to several reports of serious adverse events (six perforations that led to two patient deaths). There were several media reports about the issue. Trial suspension led to tightening of the inclusion criteria and the study has since been restarted.

The Leadless II study (NCT02030418) is being conducted in the US, Australia and Canada. The aim of this study is to evaluate the safety and effectiveness of the LP (Nanostim) in
treating people with a slow heart rate or irregular heartbeats. An estimated 667 patients will be enrolled in the multicentre trial. Primary outcome measures are complication-free rate and pacing thresholds and R-wave amplitudes within the therapeutic range at six months, and secondary outcome measures are appropriate and proportional rate response during graded exercise testing. The estimated final data collection is set for June 2015, although the study completion date has not yet been provided.

One prospective single-arm study is currently evaluating the safety and efficacy of Micra LP (by Medtronic, NCT02004873). The study also aims to evaluate long term performance. It is being conducted in up to 70 centres of which up to 35 are in the United States, with the others in Australia, Austria, Canada, Czech Republic, France, Greece, Hungary, Italy, Japan, Malaysia, Netherlands, Serbia, Spain, and the United Kingdom. The expectation is to enrol up to 780 patients with 600 subjects to be followed at least six months post implant. The primary objectives are to investigate pacing capture threshold success and major complications related to the Micra system at six months follow-up, and study completion is expected in June 2018. Some preliminary results on the first four patients were presented in a conference abstract which is discussed in the safety and effectiveness section.

**Other issues**

LEADLESS trials are funded by St. Jude Medical (developer), and the Micra study is conducted and funded by Medtronic Cardiac Rhythm Disease Management.

**Number of studies included**

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

Total number of completed studies: 1

Total number of Level IV studies: 1

**Search criteria to be used (MeSH terms)**

MeSH: Pacemaker

Text: leadless pacemaker; leadless cardiac pacing; nanostim; micra; leadless pacing system
References


