Horizon Scanning report No. 17

Transcathether implantable miniaturised leadless pacemakers

December 2014

Methods

Agenas is a public body. Its mission is to promote innovation and development within the Italian national healthcare service and provide an Early Awareness and Alert (EAA) service by Horizon Scanning (HS) activities in the field of new and emerging health technologies.
Agenas serves as a hub for RIHTA, the Italian network for Health Technology Assessment. Agenas develops EAA and HTA projects and initiatives together with RIHTA members (Regional departments, Autonomous Provinces, and Regional Public Health Agencies).
ASSR-RER is member of the RIHTA network and collaborates at the development of joint HTA projects.

A full description of the methods used for the production of the present HS report can be found at www.agenas.it

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Limitations

This report is based on information available when the searches were made and does not contain data on subsequent developments or improvements of the evaluated technology. The observations made on effectiveness, safety or cost-effectiveness of the technology evaluated in the report are to be considered temporary.

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Declaration of Conflict of Interest

The authors declare that they will not receive either benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.

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Name of the technology/procedure: **Transcathether implantable miniaturised leadless pacemakers**

Target population

The target population of transcathether implantable miniaturised leadless pacemakers is represented by patients with arrhythmia requiring single-chamber ventricular demand pacing. According to European Society of Cardiology (ESC) guidelines 2013 this kind of pacing is recommended as first choice in atrial fibrillation (AF) with atrioventricular (AV) block (with or without sinus node disease) and as third choice in AV block without AF. Among patients treated by permanent pacing, single-chamber ventricular demand pacing represents 21-32% of pacing modality in the registries of some European national pacing societies [Coma SR, 2011; Cunningham D 2010; Markewitz A, 2010; Proclemer A, 2010; Swedish 2010, Tuppin P, 2011].

Description of the procedure and technology

Conventional cardiac pacemakers are acknowledged to be safe and effective when used according to guidelines [European Society of Cardiology, 2013]. A traditional pacemaker (referred also as pacing system) consists of a pulse generator and one or more (up to three) pacing leads. The pulse generator contains the battery as well as all the sensing, timing, and output circuits, and is placed subcutaneously or sub muscularly in the chest wall. The leads, committed to the stimulation, are inserted transvenously and advanced to the right ventricle/atrium (or both), where they are secured to the tissue [DLA Piper Australia, 2013].
Several procedure and device-related complications have been reported in current practice. Short-term complications may be associated with both the pulse generator (e.g., hematoma, skin breakdown, pocket infection) and the leads implantation (pneumothorax, cardiac tamponade, lead dislodgement) [Udo EO, 2012]. Long-term complications mostly involve the leads that may be responsible of venous obstruction, insulation breaks, conductor fracture, and infection. Further criticalities may appear in the case of lead extraction, procedure associated with a high-risk profile [Borek P, 2008].
The firsts efforts toward the design of implantable pacing systems with no leads have been reported decades ago (in dogs) [Spickler JW, 1970] but only recently the technology reached the clinical market. The present Horizon Scanning (HS) report focuses on the implantable miniaturised leadless pacing systems.
The technology consists of a self-contained intracardiac device (extremely small in size) that includes the pacemaker electronics, battery, and leads. The pacing occurs on a single chamber. The device is implanted transvenously by a steerable catheter and secured to the heart tissue by means of different fixation approaches (e.g., metallic tines or screw-in helix). The device is fully retrievable and repositionable [Reddy VY, 2014].

Clinical importance and burden of disease

A cardiac arrhythmia is any rhythm that is not normal sinus rhythm with normal atrioventricular (AV) conduction. During sinus rhythm, the heart rate is in the normal range, the P waves are normal on the electrocardiogram, and the rate is stable [Levy S, 2014]. Arrhythmias requiring cardiac pacing can be caused by a variety of aetiologies and the early identification of a potentially reversible cause is the first step towards treatment. If a reversible cause of arrhythmia is not identified, a decision regarding permanent pacemaker insertion is driven by two main factors: the presence of symptoms associated with the arrhythmia and the possible worsening of the rhythm disturbance. Patients' symptoms comprise dizziness, light-headedness, syncope, fatigue, and poor exercise tolerance and the direct correlation between symptoms and arrhythmias increase the likelihood of recommending pacemaker placement [Hayes DL, 2014a].

The prevalence of arrhythmias requiring permanent cardiac pacing therapy is unknown, but in 2011 in Europe 938 pacemakers/1.000.000 inhabitants were implanted [ESC Guidelines 2013].

The most common indications for pacemaker implantation are persistent bradycardias - due to sinus node dysfunction or acquired type 2 AV block - and intermittent documented bradycardias - due to sinus node dysfunction or intermittent/paroxysmal AV block (including atrial fibrillation with slow ventricular conduction) [ESC Guidelines 2013; Hayes DL, 2014a]. Other indications are much less common and include symptomatic (unexplained syncope) bundle branch block, neurocardiogenic syncope and iatrogenic causes (eg, post-AV node ablation) [Hayes DL, 2014a].

Sinus bradycardia is a rhythm in which fewer than the normal number of impulses arise from the sinoatrial node. The normal heart rate has been considered to range from 60 to 100 beats per minute, with sinus bradycardia being defined as a sinus rhythm with a rate below 60 beats per minute [Ganz L, 2014]. Sinus bradycardia is caused by a primary sinus node dysfunction (sick sinus disease) or by other conditions (exaggerated vagal activity, acute myocardial infarction, obstructive sleep apnea, drugs, etc.) [Ganz L, 2014].

Atrioventricular (AV) block is defined as a delay or interruption in the transmission of an impulse, either transient or permanent, from the atria to the ventricles due to an anatomic or functional impairment in the conduction system. The conduction can be delayed, intermittent, or absent. The commonly used terminology includes first degree AV block (slowed conduction without missed beats), second degree AV block (missed beats, often in a regular pattern, eg. 2:1, 3:2, or higher degrees of block), and third degree or complete AV block [Sauer WH, 2014].

Once it has been established that bradycardia or a conduction disorder warrants permanent pacing, the most appropriate pacing mode for the patient must be selected. A variety of types of pacemakers have been developed to restore or sustain a regular heartbeat in different ways. Pacemakers for bradycardias may be single or dual chambered: single-chamber pacemakers have one lead to carry impulses to either the right atrium or right ventricle; a dual-chamber pacemaker usually has two leads, one to the right atrium and one to the right ventricle, which can allow a heart rhythm that more naturally resembles the normal activities of the heart. Moreover pacemakers are equipped with a lead for monitoring the heart's natural electrical activity, placed in atrium or in ventricle [Hayes DL, 2014b]. To facilitate the use and understanding of pacemakers, a standardized classification code - reported for clarification in Appendix 1 - has been developed: The Revised NASPE/BPEG Generic Code for Antibradycardia, Adaptive-Rate, and Multisite Pacing [Bernstein AD, 2002].

Short- and long-term complications of pacemaker therapy have been reported to be 12.4 and 9.2% [Udo EO, 2012] respectively. Overall complication rates increase sharply as individual and centre implantation volumes decrease. Lead complications are the main reason for re-operation after implantation of pacemaker. Lead complications are reported to occur in 3.6% of patients [Kirkfeldt RE, 2011]: 4.3% of all left ventricular leads, 2.3% of right atrial leads and 2.2% of right ventricular leads. The majority of the complications with

pacemakers occur in-hospital or during the first 6 months [Kirkfeldt RE, 2011, Udo EO, 2012] after implantation. Early complications (i.e. occurring after 6–8 weeks post-implantation) have been reported to range from 5.7% to 12.4% [Udo EO, 2012]. After this period, the complication rate decreases but is still substantial, being reported in 4.8% of cases at 30 days, 5.5% at 90 days and 7.5% at 3 years [Ellenbogen, KA, 2003]. Long term complication rates are reported in 15.6, 18.3 and 19.7% of patients at 1, 3 and 5 years, respectively [Udo EO, 2012]. Over 6 months of follow-up, device upgrade or revision is associated with a complication risk ranging from 4% of patients who had a generator replacement only, to 15.3% of patients who had a generator replacement or upgrade combined with one or more lead insertions [Poole JE, 2010]. More frequent adverse events are coronary sinus dissection or perforation, pericardial effusion or tamponade, pneumothorax and haemothorax, lead problems and infections. Peri-implantation deaths are reported to occur. Haematomas are very frequent (2.9–9.5% of the cases) and are usually managed conservatively. Pacemaker infection is one of the most worrying post-operative complications and range between 1.82 and 1.90 per 1000 device-years after the first implantation [Johansen JB, 2011].

Products, manufacturers, distributors and approval

Following the notification of the technology to Agenas we identified 2 systems classifiable as "implantable miniaturised leadless pacing system": the Micra Transcatheter Pacing System (TPS), manufactured by Medtronic, Inc., and the Nanostim Leadless Pacemaker system, manufactured by St. Jude Medical, Inc..
Both systems offer single-chamber pacing by a self-contained intracardiac device that is implanted by a specific transvenous catheter (delivery system) and secured into the right ventricle by atramautic metallic tines (Micra) or a single steroid-eluting helix (Nanostim). Both systems are fully repositionable and retrievable by a specific catheter (retrieval system). The Micra pacemaker weights 1.75 grams and has a volume of 0.8 cm3 (25.9 mm in length and maximum diameter of 6.7 mm) [Medtronic website]. The Nanostim pacemaker weights 2 grams and has a volume of 1 cm3 (42.3 mm in length and maximum diameter of 6 mm) [St. Jude Medical website]. St. Jude Medical also stated that a 18F introduced is recommended and expects a longevity of 9.8 years at 100% pacing at 2.5 V, 0.4 ms, 60 ppm.

- Medtronic expects to receive the CE mark for Micra TPS in 2015; manufacturer stated that FDA approval is expected in 2017-2018.
- Nanostim received the CE mark in 2013; in February 2014, the first implant in the USA has been performed within an Investigational Device Exemption (IDE) trial designed for FDA approval.

Regarding target population producers stated that:

- the leadless pacemaker "Nanostim" by St. Jude Medical, is proposed to treat patients with one of the following conditions:
    - chronic atrial fibrillation with 2 or 3 atrioventricular (AV) or bifascicular bundle branch block (BBB);
    - normal sinus rhythm with 2 or 3 AV or BBB block and a low level of physical activity or short expected lifespan;
    - sinus bradycardia with infrequent pauses or unexplained syncope with electrophysiologic findings [St. Jude 2014]
- the leadless pacemaker "Micra" by Medtronic, is proposed to treat patients indicated for "single chamber ventricular pacing or for pacemaker who may benefit from a minimally invasive approach" [communication by the producer].

Product name [Manufacturer]	Distributor	CE Mark RD	M FD	A
Micra™ Transcatheter Pacing System (TPS) [Medtronic, Inc.]	Medtronic Italia, S.p.A.	☐	☐	☐
Nanostim™ Leadless Pacemaker [St. Jude Medical, Inc.]	St. Jude Medical Italia, S.p.A.	☑	☑	☐

Setting

The implantable miniaturised leadless pacing systems are implanted in the same setting as the conventional pacemakers (i.e., cardiac catheterization laboratory or in an operating room). The implant is performed as in-patient procedure; sedative medications and local anaesthesia are administered to the patient that will remain awake during the procedure. Generally, a 24-hours observation stay is necessary.

☐ Home	☑ Hospital	☐ Outpatient
☐ Accident and Emergency	☐ Other:	

Roll out in Italy

Worldwide, Micra TPS is under investigational use only and is not currently available commercially. The launch on the Italian market is scheduled during 2015. Currently, one italian public hospital (Azienda Ospedaliera Universitaria Pisana, Pisa) is taking part to the Micra Transcatheter Pacing Study (information provided by Medtronic, Inc.).
Worldwide, Nanostim is currently only available within clinical trials. Commercialisation is expected in the second half of 2015, depending on the results from ongoing trials. Fourteen Italian hospitals are involved in the ongoing LEADLESS clinical trial: at time of writing, there have been 32 implants in Italy. Overall, more than 360 devices implanted in the world (information provided by St. Jude Medical, Inc.).

☑ Pre-marketing	☑ On the market for 1-6 months	☐ On the market for 7-12 months
☐ On the market for more than 12 months	☐ Not identified	

Comparators

The main comparator of these technology is any lead pacemaker capable of single-chamber ventricular demand pacing (ventricle paced, ventricle sensed, and pacemaker inhibited in response to a sensed beat: VVI-VVIR stimulation according to the Revised NASPE/BPEG Generic Code, Bernstein 2002, see Appendix 1 for details).

Effectiveness and safety

Literature search has been conducted in PubMed, Cochrane Library and Embase, looking for studies published up to June 2014 (further details in "Evidence searches" section). Studies have been included if they report safety, efficacy or effectiveness data (neither type of studies nor language restriction has been applied) about leadless peacemaker capable of VVI-VVIR stimulation. Abstract, commentary and animal/reanimated human heart studies have been excluded. We have been searched also in ClinicalTrial.gov looking for ongoing trial (further details in "Evidence searches" section).
After studies screening process (see "Evidence searches" section), one primary study [Reddy VY, 2014] and one Technology Alert by NIHR HSC [NIHR 2014a] have been included for Nanostim, and one Technology Alert by NIHR HSC [NIHR 2014b] has been included for Micra.
Evidence section in the first Technology Alert by NIHR HSC [NIHR 2014a] is based only on one conference communication abstract [Reddy VY, 2013] that does not match our inclusion/exclusion criteria, while in the other [NIHR 2014b] evidence section reports only company information.
The primary study included [Reddy 2014] is a prospective, nonrandomized, single-arm multicenter study on the safety and technical performance of a completely self-contained leadless cardiac pacemaker [Nanostim]. Patients with a clinical indication for single-chamber (right ventricular) pacing (VVIR) were eligible for the device. Indications included (1) permanent atrial fibrillation (AF) with atrioventricular (AV) block (which includes AF with a slow ventricular response), (2) normal sinus rhythm with second or third degree AV block with a low level of physical activity or short expected lifespan, or (3) sinus bradycardia with infrequent pauses or unexplained syncope with electrophysiology findings (eg, prolonged HV interval). Thirty-three patients (mean age 77 years, SD ±8, range 53–91; 22 males) underwent implantation of the leadless cardiac pacemaker and were followed up to 90 days. Indications for cardiac pacing were permanent AF with AV block (n=22, 67%), normal sinus rhythm with second or third degree AV block and with a low level of physical activity or short expected lifespan (n=6, 18%), sinus bradycardia with infrequent pauses or unexplained syncope with electrophysiological findings (n=5, 15%). The primary safety end point was freedom from complications (complication-free rate), defined as serious adverse device 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 drop out because of a complication. The secondary safety end point 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 end points were pacemaker performance characteristics including pacing threshold, pacing impedance, cell voltage, R-wave amplitude, pacing percentage, and cumulative cell charge.
Thirty per cent of patients (n.10) required a repositioning of the leadless cardiac pacemaker after its initial deployment (4 patients needed 1 repositioning, 4 patients 2 repositioning attempts, 2 patients 3 repositioning attempts). Among them 5 patients (15%) required the use of more than one leadless cardiac 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 tortuosity of the venous vasculature (n=1), damage to the LCP helix during insertion (n=1), or difficulty with the wire deflection mechanism of the delivery catheter (n=1). However the authors reports implant success rate, in terms of

patients completing the implant procedure successfully, to be 97% (n=32). Procedure mean duration was 28±17 minutes and average time to hospital discharge 31±20 hours. Three device related adverse events are reported. One serious adverse event: a 70-year-old man with persistent slow AF and previous embolic infarct of the kidney developed cardiac tamponade with hemodynamic collapse after repositioning of the leadless cardiac pacemaker and manipulation of the delivery catheter in the right ventricular apex. The patient underwent immediate reversal of anticoagulation, percutaneous pericardial drainage, and emergent median sternotomy on cardiopulmonary bypass with surgical repair of a perforation of the right ventricular apex. On post-procedural day 5, he developed acute-onset left-sided hemiplegia attributable to a right-sided main cerebral artery ischemic infarct with progressive cerebral edema. The patient died on post-procedure day 18. A second 86-year old patient, who had the leadless cardiac pacemaker implanted for sinus rhythm with second degree AV block, was readmitted 2 days later for recurrent syncope. Inpatient cardiac monitoring revealed monomorphic ventricular tachycardia at 260 bpm, accompanied by syncope. The leadless cardiac pacemaker was removed on post-implant day 5, and a subsequent workup revealed non-obstructive coronary artery disease and a focal area of scar in the basal posterior wall of the left ventricle. He subsequently underwent implantation of a single-chamber transvenous implantable cardioverter-defibrillator system, and was initiated on β-blocker therapy. He was readmitted ≈2 weeks later for appropriate implantable cardioverter-defibrillator shocks attributable to VT at 260 bpm. In a third patient, it was recognized that the device was in the left ventricle. The patient had a patent foramen ovale, through which the deflectable delivery sheath had inadvertently transited, thereby permitting access to the left ventricle. Although the patient did not experience any permanent clinical sequelae, it is possible that, had the event not been recognized, it could have led to an adverse outcome.

Three patients (9%) were re-hospitalized within 90 days, 1 patient for an elevated international normalized ratio (international normalized ratio=9.3, without bleeding), 1 patient for an acute exacerbation of chronic obstructive lung disease, and 1 patient for the aforementioned ventricular tachycardia. 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. Due to the short follow up of the study, some medium and long-term outcomes have not been evaluated: risk of dislodgment, feasibility of device extraction in case of infection/malfunction, etc. Therefore medium and long-term safety profile and post-implant device maintenance issues remain unexplored and unknown.

No clinical outcome on efficacy was evaluated by this study.

Three leadless pacemaker studies are ongoing (for further details see Table 1), one on Micra Transcatheter (Medtronic) device (NCT02004873) and two on Nanostim (St. Jude Medical) device (NCT02030418, NCT02051972). All three studies are not RCTs, do not have active comparators, enrol adult patients with indication for VVI pacemaker and are currently recruiting participants. Purpose of the three studies is claimed to be evaluation of safety and efficacy/effectiveness of leadless pacemaker, although the lack of comparison and of randomization will hinder any conclusion on efficacy/effectiveness. Completion date (when reported) vary from June 2018 to March 2020.

During this evaluation Saint Jude Medical sent to Italian MoH an “Important Medical Device Information” on NanostimTM Leadless Pacemaker & Delivery System Catheter, Model (2014 July 29) S1DLCP (see appendix 2). St. Jude Medical informed that it is performing a voluntary Field Safety Corrective Action "after observing a limited number of pericardial effusion adverse events in the Post Market clinical Follow up (PMCF) study” (The Leadless Observational Study, NCT02051972). Saint Jude Medical informed that factors that contributed to the pericardial effusion events during the implant procedure included patient selection and implant technique. For this reasons, the following three actions were being implemented: 1) Revision of the Instructions for Use (IFU) to include additional warnings, cautions and clarification on implant practices; 2) Amendment of the PMCF protocol to align with the revised IFU; and 3) Additional training of all implanting physicians and Saint Jude Medical personnel on implant steps and best practices and the revised PMCF

protocol. The PMCF study has been reinitiated with a new study protocol. In total, 161 subjects in 27 active centers have been enrolled so far out of 1000 enrolment target (information provided by St. Jude Medical, Inc).

Potential benefits to patients

Implantable miniaturised leadless pacing systems' anticipated benefits are: lower risk of complications, shorter procedure times, reduced hospital length of stay, reduced fluoroscopy exposure for patients and staff, as well as lack of a visible lump and scar, improved life style and improved quality of life in general. A reduction of the burden of the managing of lead and chest pocket complications and repeated procedures is also expected [NIHR HSC, 2014(a); NIHR HSC, 2014(b)].

☐ Mortality reduction or increased survival	☑ Reduction of the morbidity	☑ Improved quality of life (patient/users)
☐ Improved patient monitoring	☐ Other:	☐ Not identified

Cost of the technology/procedure

Transcathether implantable miniaturised leadless pacemakers are proposed as an alternatives to conventional pacemaker.
According to Medtronic:

- the Micra Transcatheter Pacing System is under investigational use only and is not currently available commercially. To date there are not economic evaluations on Micra. Medtronic will be comparing the cost of complications associated with Micra based on data from the single-arm clinical trial with costs of transvenous pacemaker complications.

According to Saint Jude Medical:

- to date there are not economic evaluation on Nanostim. The relevant items and cost for single procedure are:
  - N.1 Pacemaker and delivery system: € 11,500
  - N. 1 (retrieval system - not always necessary): € 6,000

Price of device will depend by local commercial agreements.
This new devices have not a According to MoH decree on DRG fees (12 oct 2012 "*Remunerazione prestazioni di assistenza ospedaliera per acuti, assistenza ospedaliera di riabilitazione e di lungodegenza post acuzie e di assistenza specialistica ambulatoriale*") the reimbursement for DRG 551 (Impianto di Pacemaker cardiaco permanente con diagnosi cardiovascolare maggiore o di defibrillatore automatico (AICD) o di generatore di impulsi) is €9,384 and € 4,756 for DRG 552 ("*Altro impianto di pacemaker cardiaco permanente senza diagnosi cardiovascolare maggiore*").

☑ Increased costs compared to alternative treatments	☐ Increased costs due to increased demand	☐ Increased costs due to the required investments
☐ New costs	☐ Other:	☐ Not identified

Potential structural and organisational impact

Structural impact

The transcatheter implantable miniaturised leadless pacemakers have structural requirements that are similar to the ones of the conventional pacemakers with the difference that the creation of a subcutaneous pocket (by sharp and blunt dissection) is not necessary.

☐ Increase in requirement of instruments	☑ Always be used	☐ Can be used only under specific circumstances
☑ Decrease in requirement of instruments	☐ Other:	☐ Not identified

Organisational impact

From an organisational point of view the staff involved during the procedure is similar to a traditional pacemaker implantation. Manufacturer provide training for all staff involved during the procedure.
Regarding to the learning curve of the implantation procedure data are expected from clinical trial and ongoing study.

☐ Increase in the number of procedures	☐ Re-organisation required	☑ Training required for users
☐ Reduction in the number of procedures	☐ Other:	☐ Not identified

Conclusions

Leadless pacemakers are intended for patients requiring single-chamber ventricular demand pacing (VVI-VVIR stimulation). Most of these patients are affected by AF with AV block. According to registries of European national pacing societies, this pacing modality is applied in 21-32% of patients requiring pacing. To date this technology is implanted only in research clinical contest.
Only one non-comparative single-arm study on Nanostim was found by the systematic search. It included 33 patients with a clinical indication for right ventricular pacing. No clinical outcome on efficacy was evaluated

and although the authors claimed an high implant success rate, it could however be underlined that within this study, procedural data show 5 patients that required the use of more than one leadless cardiac pacemaker.
Regarding safety, two patients had a serious device related adverse event, and in one case the patient died. Due to the short follow up of the study, medium and long-term safety profile and post-implant device maintenance issues remain unexplored and unknown.
No data are available on Micra.
Recently, amended NanostimTM Leadless Pacemaker System Post Market clinical Follow up study protocol, revising patient selection and implant technique, due to the occurrence of a number of pericardial effusion adverse events, emerged during one of the ongoing studies (NCT02051972).
The introduction of a registry of the use of these new technologies, held by an independent public body, is crucial for monitoring pacemakers implants in relation with its potential benefit to patients.

Future prospects

Both the manufacturers, Medtronic and St. Jude Medical, are currently developing strategies to provide dual-chamber pacing as an evolution of the current implantable miniaturised leadless pacing systems.
Three ongoing non-comparative single-arm studies were found (1 for Micra, 2 for Nanostim). These studies aim to assess only procedural and safety outcomes. The lack of comparison and of randomization will hinder any conclusion on efficacy/effectiveness.

Table 1: Summary of the registered studies on the leadless pacemaker identified on ClinicalTrials.gov.

Trial number: "Official title"	Device used	Condition	Purpose	Primary outcome	Intervention model	Arms		Enrolment [patients] / Location countries	Date (Start – Completion)	Status
						Experimental	Active comparators			
NCT02004873 Micra Transcatheter Pacing Study	Micra Pacemaker Implant	Class I or II Indication for Implantation of a Single Chamber Ventricular Pacemaker According to ACC/AHA/HRS 2001 Guidelines and Any National Guidelines	The purpose of this clinical study is to evaluate the safety and efficacy of the Micra Transcatheter Pacing System and to assess long term performance.	Micra system and/or procedure related major complication free rate 6-months post-implant Pacing capture threshold (PCT) at the 6-month post-implant visit where success is defined as PCT <=2 volts at 0.24 ms pulse width and the increase from implant is <=1.5 volts.	Single Group Assignment	Micra Pacemaker Implant	Not applicable	Estimated: 780 Gender: Both Ages: 18 Years and older United States, Austria, China, Czech Republic, Denmark, France, Germany, Hungary, India, Italy, Japan, Malaysia, Netherlands, Russian Federation, Serbia, Spain, United Kingdom	November 2013 June 2018	This study is currently recruiting participants

NCT02030418 "The LEADLESS II IDE"]* Safety and Effectiveness Trial for the Nanostim Leadless Pacemaker	Nanostim Leadless Pacemaker	Subjects Who Are Indicated for a VVI(R) Pacemaker	Prospective, non-randomized, single-arm, international multicenter, clinical safety and effectiveness investigation.	Complication-Free Rate (6 months) Pacing thresholds and R-wave amplitudes within the therapeutic range	Single Group Assignment	Leadless Pacemaker	Not applicable	Estimated: 667 Gender: Both Ages: 18 Years and older United States	February 2014 Not Provided (Estimated Primary Completion Date: June 2015)	This study is currently recruiting participants
NCT02051972 "The LEADLESS Observational Study1" Nanostim Study for a Leadless Cardiac Pacemaker System	Nanostim leadless pacemaker system	Indications for VVI(R) Pacemaker	The objective of the study is to confirm clinical performance and safety of the Nanostim leadless cardiac pacemaker system within its intended use and according to its instructions for use	90 day complication-free rate, where a complication is defined as a serious adverse device effect	(Observational Model): Cohort	Implanted with a Nanostim leadless pacemaker system	Not applicable	Estimated: 1000 Gender: Both Ages: 18 Years and older Czech Republic, Germany, Netherlands, Spain	December 2013 March 2020	This study is currently recruiting participants

* The LEADLESS Observational PMCF Study" (information provided by producer).

Evidence searches

Searches of the databases were carried out on June 2014 using the only keywords to indicate

- ***the technology of interest:*** *Cardiac Pacing; Wireless Technology, Transcatheter Pacing System, Leadless*

Studies have been included if they report safety, efficacy or effectiveness data (neither type of studies nor language restriction have been applied) about leadless peacemaker capable of VVI-VVIR stimulation. Abstract, commentary and animal/reanimated human heart studies have been excluded. Databases searches were carried out on June 2014 using the following strategies:

Pubmed

1. "Pacemaker, Artificial"[Mesh]
2. "Cardiac Pacing, Artificial"[Mesh])
3. 1 OR 2
4. “Wireless Technology"[Mesh]
5. 3 AND 4
6. wireless[ti/] AND (pacemaker[ti/] or pacing[ti/])
7. (leadless OR lead-free) AND (pacemaker OR pacing OR cardiac OR heart OR cardio*)
8. nanostim
9. “Transcatheter Pacing System”
10. Leadless
11. 5 OR 6 OR 7 OR 9 OR 10

Identified references: 60

Cochrane library

1. nanostim
2. "lead-less" or leadless or leadfree or "lead-free"
3. MeSH descriptor: [Wireless Technology] explode all trees
4. MeSH descriptor: [Pacemaker, Artificial] explode all trees
5. MeSH descriptor: [Cardiac Pacing, Artificial] explode all trees
6. (4 OR 5) AND 3
7. 6 OR 1 OR 2

Identified references: 9 (Central)

Embase

1. leadless
2. nanostim
3. 'wireless communication'/exp
4. 'artificial heart pacemaker'/exp OR 'heart pacing'/exp
5. 2 AND 3
6. 1 OR 2 OR 5

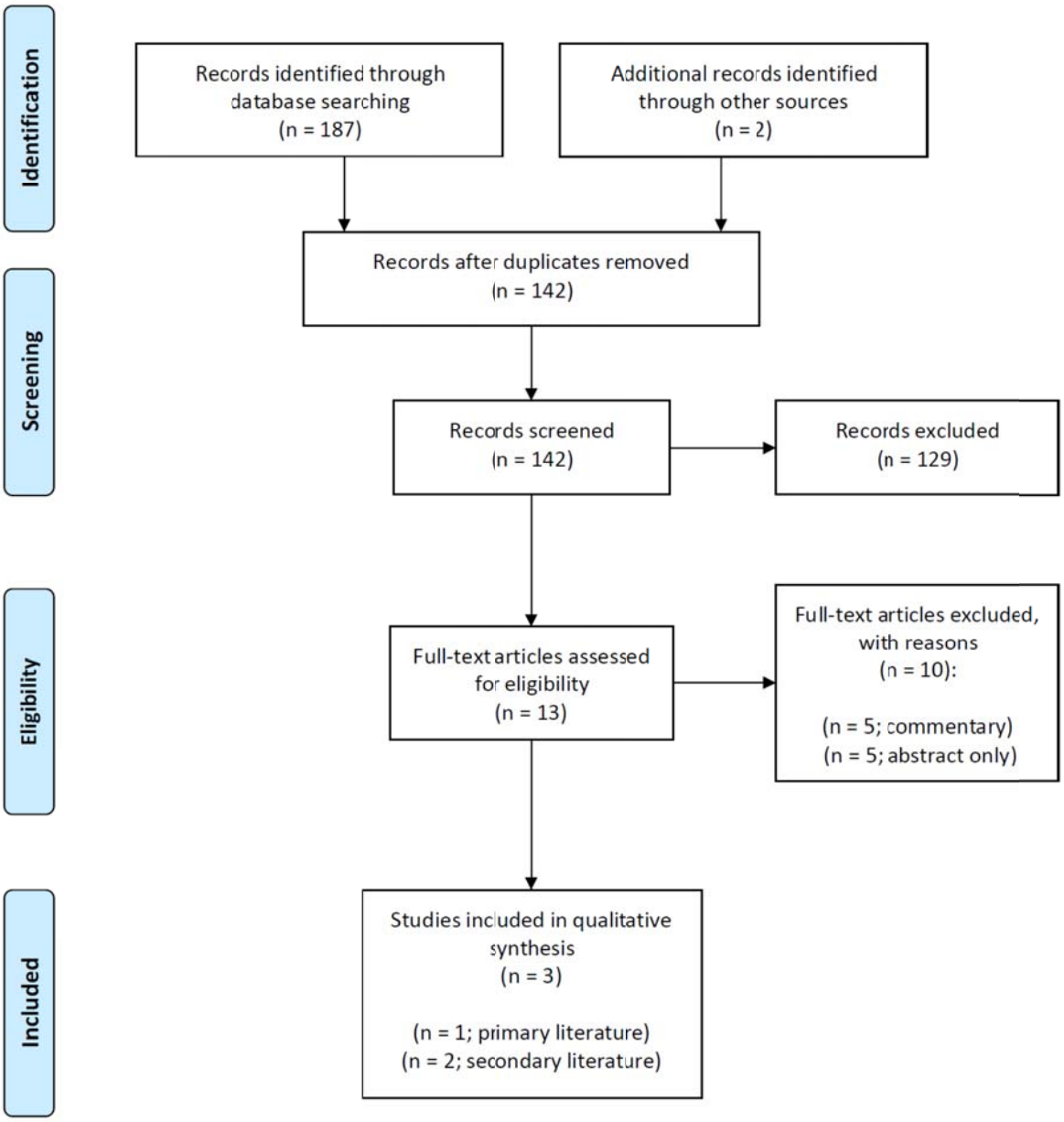
Identified references: 118

ClinicalTrial.gov

- Keywords: Leadless or nanostim or “Transcatheter Pacing System”

Identified references: 8
Included trials: 3

PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Glossary

AVB: *atrioventricolar block*

BBB: *bifascicular bundle-branch block*

FDA: Food and Drug Administration.

IDE: *Investigational Device Exemption*

RDM: Medical device Repertory (http://www.salute.gov.it/dispositivi/paginainternasf.jsp?id=499&menu=repertorio).

Appendix 1 - The Revised NASPE/BPEG Generic Code for Antibradycardia, Adaptive-Rate, and Multisite Pacing

A five-letter code (NBG code for pacing nomenclature, Bernstein 2002) describes the basic function of the various pacing systems (Hayes 2014b). Positions I and II indicate the chambers in which pacing and sensing occur. "A" indicates the atrium, "V" indicates the ventricle, and "D" means dual chamber (ie, both the atrium and the ventricle). Position III refers to how the pacemaker responds to a sensed event, i.e. the effect of each instance of sensing on the triggering or inhibition of subsequent pacing stimuli. "I" indicates that a sensed event inhibits the output pulse and causes the pacemaker to recycle for one or more timing cycles. "T" indicates that an output pulse is triggered in response to a sensed event. "D" indicates that there are dual modes of response. Position IV is used to indicate the presence ("R") or absence ("O") of an adaptive-rate mechanism (rate modulation). Position V is used to indicate whether multisite pacing, as described above, is present in none ("O") of the cardiac chambers, one or both of the atria ("A"), one or both of the ventricles ("V"), or any combination of A or V as just described ("D").

The Revised NASPE/BPEG Generic Code for Antibradycardia Pacing (adapted from Bernstein 2002)

Position	I	II	III	IV	V
Category	**Chamber(s) Paced**	**Chamber(s) Sensed**	**Response to Sensing**	**Rate Modulation**	**Multisite Pacing**
	O = None A = Atrium V =Ventricle D = Dual (A+V)	O = None A = Atrium V = Ventricle D = Dual (A+V)	O = None T = Triggered I = Inhibited D = Dual (T+I)	O = None R = Rate modulation	O = None A = Atrium V = Ventricle D = Dual (A+V)

Appendix 2 - Important Medical Device Information

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Important Medical Device Information

July 29, 2014

Subject: Nanostim™ Leadless Pacemaker & Delivery System Catheter, Model S1DLCP

Dear Doctor,

St. Jude Medical is performing a voluntary Field Safety Corrective Action related to the Nanostim™ Leadless Pacemaker System. St. Jude Medical became aware of a limited number of pericardial effusion adverse events during the implant procedure. Those events were observed during our Post Market clinical Follow up (PMCF) study. St. Jude Medical performed a comprehensive investigation into these events and the results were discussed with the PMCF Study Steering Committee. Factors that contributed to the pericardial effusion events during the implant procedure include patient selection and implant technique.

Please refrain from implanting the Nanostim™ Leadless Pacemaker until the below steps are completed.

The actions below are being implemented as part of the Field Safety Corrective Action:

- Revision of the Instructions for Use (IFU) (see change summary Table included in Annex) to include additional warnings, cautions and clarification on implant practices. This revision has been approved by the Notified Body
- Amendment of the PMCF protocol to align with the revised IFU
- Additional training of all implanting physicians and SJM personnel on implant steps and best practices and the revised PMCF protocol

The study will be reinitiated in the PMCF centers upon fulfillment of the following conditions:

- Amended PMCF protocol approved by local Ethics Committee and where appropriate by Competent Authorities
- Retraining of implanting physicians

There is no change to existing patient follow-up requirements.

A detailed description of the significant changes made to the Instructions for Use of the Nanostim™ Leadless Pacemaker and Nanostim™ Delivery System Catheter is provided in the Annex.

Please review this information with all members of your staff who need to be aware of the contents of this communication.

St. Jude Medical is committed to providing the highest quality products and support. This action has been communicated to the appropriate authorities and Ethics Committees.

If you need any further information or support concerning this issue, please contact your local St. Jude Medical Representative or Technical Support at +46 8 474 4147.

Sincerely,

Roland Gerard
VP, Quality and Regulatory Affairs
St. Jude Medical

Nanostim™ Leadless Pacemaker and Nanostim™ Delivery System Catheter **IFU SIGNIFICANT CHANGE SUMMARY**	
Old Instructions For Use	**Revised Instructions For Use**
Contraindications	
CONTRAINDICATION *Use of a leadless pacemaker could involve higher levels of risks, compared to those of conventional pacemakers, due to inadvertent pulmonary embolism of the pacemaker in patients also presenting with elevated right-ventricular pressure or reduced pulmonary reserve.*	***REVISED CONTRAINDICATION*** *The leadless pacemaker is contraindicated for use in patients with pre-existing pulmonary arterial (PA) hypertension (PA systolic pressure > 40 mmHg or RV systolic pressure > 40 mmHg) or significant physiologically-impairing lung disease.*
Warning	
	NEW WARNING *Careful consideration should be given to patients who have had cardiovascular or peripheral vascular surgery/intervention within the last 30 days because these patients may have a higher risk of complications.*
	NEW WARNING *Implant of a Nanostim leadless pacemaker should not be attempted in the presence of an active perforation. Implant sites where a previous clinical event such as perforation or lead extraction with myocardial tissue removal should be avoided as this may result in a higher rate of perforation.*
Room and Patient Preparation	
ROOM AND PATIENT PREPARATION *Implantation should be performed only when:* • *proper emergency facilities for cardioversion and/or defibrillation are available*.	***REVISED ROOM AND PATIENT PREPARATION*** *Implantation should be performed only when:* • *proper emergency facilities for cardioversion, defibrillation and cardio-pulmonary resuscitation are available.* • *proper equipment is available for high resolution fluoroscopy including the ability to record and save images, to zoom, and to obtain images in multiple projections.*
Insert the Nanostim™ Leadless Pacemaker and Nanostim™ Delivery System Catheter	
	NEW CAUTION *Do not independently advance the delivery catheter as this may advance the LP outside of the protective sleeve and leave the LP helix exposed and result in damage to the LP helix. Do not advance the device by pushing the device from the handle or delivery catheter.*

Position the Guide Catheter and Nanostim™Leadless Pacemaker	
CAUTION *If there is reason to believe the patient has an unusually thin wall at the apex of the right ventricle (for example, use of oral steroids, apical right ventricular infarction, history of ARVD), consider a lower septal site for placement of the Nanostim™ Leadless Pacemaker (LP).*	***CAUTION TO WARNING*** *To reduce risk of perforation, consider a lower septal site for placement of the Nanostim™ Leadless Pacemaker (LP), especially if there is reason to believe the patient has an unusually thin wall at the apex of the right ventricle (for example, use of oral steroids, right ventricular infarction, history of ARVD.*
CAUTION *If the awake patient feels a twinge of pain, this may be an early sign of perforation.*	***CAUTION DELETED***
	NEW WARNING *Do not apply excessive forward force to the delivery catheter, because perforation can occur.*
NOTE *Do not advance all the way to the apex with the protective sleeve covering the device (see the picture that follows), because this could result in perforation.*	***NOTE TO WARNING*** *Do not advance the LP to the endocardium until the protective sleeve, is fully retracted because this may result in perforation.*
CAUTION *Maintain LP position as you pull back the guide catheter protective sleeve, because movement could lead to perforation or entanglement.*	***CAUTION TO WARNING*** *Maintain the LP position by holding the delivery catheter handle on the patient table as you slowly pull back the guide catheter protective sleeve, because movement could lead to perforation or entanglement. Fix the delivery catheter handle on the patient table, without bending, so that relative movements can be made in a controlled manner. The protective sleeve should be fully retracted before advancing the LP to the endocardium.*
Affix the Nanostim™ Leadless Pacemaker in the Right Ventricular Area	
NOTE *Turns of the control knob will not necessarily match turns of the device during implantation.*	***NOTE*** *Turns of the control knob will not necessarily match turns of the device during implantation. Do not exceed 16 clicks of the control knob and do not exceed 1.25 turns of the LP device.*
5. Continue to turn the control knob slowly until you have visualized 1 1/4 turns of the device. Count approximately 12-16 total clicks of the control knob. *Do not exceed 16 clicks when affixing, because this may lead to perforation.*	*5. Continue to turn the control knob slowly until you have visualized a minimum of 1 turn and a maximum of 1.25 turns of the device radiopaque marker. Do not exceed 16 clicks of the control knob or rotation of the device radiopaque marker beyond 1.25 turns when affixing, because this may lead to perforation.*
Assess Pacing and Sensing Thresholds	
	NEW WARNING *If the device does not capture at maximum pulse amplitude and pulse width (6.01V/1.5ms) and the impedance is >2000 ohms, consider the possibility that perforation has occurred, leave the device in place, perform an echocardiogram and prepare for possible urgent pericardiocentesis.*