NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of leadless cardiac pacemaker implantation for bradyarrhythmias

Bradyarrhythmias (abnormal heart rhythms) can cause a slow heartbeat, usually because of a problem with the electrical system of the heart. In this procedure, a leadless cardiac pacemaker is inserted into the heart using a thin tube (catheter) through a large blood vessel in the groin (at the top of the leg). It is attached directly to the heart wall where it stimulates the heart to beat more quickly. This avoids the need for a pacemaker box under the skin with leads passing into the heart. The aim is to help the heart beat at a normal rate and reduce symptoms such as dizziness, shortness of breath, tiredness and fainting.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in January 2018 and updated in July 2018.

Procedure name

- Leadless cardiac pacemaker implantation for bradyarrhythmias

Specialist societies

- British Heart Rhythm Society (BHRS)
- British Cardiovascular Society
- Royal College of Physicians.

Description of the procedure

Indications and current treatment

Bradyarrhythmias are abnormal heart rhythms that can result in a slow heart rate (bradycardia), usually defined as less than 60 beats per minute. There are a range of causes including diseases such as sick sinus syndrome or atrioventricular block. The most common causes are the natural ageing process, ischaemic heart disease, heart valve disorders and heart failure. If untreated, bradycardia may lead to fatigue, fainting, palpitations, dizziness, heart failure and an increased risk of death.

Bradyarrhythmias are managed with pacemakers as described in NICE technology appraisal guidance. Dual-chamber pacing is recommended for symptomatic bradycardia caused by sick sinus syndrome, atrioventricular block, or a combination of sick sinus syndrome and/or atrioventricular block, and also for sick sinus syndrome in people without atrioventricular block. Single-chamber ventricular pacemakers may be used for atrioventricular block alone or with sick

sinus syndrome in people with continuous atrial fibrillation, or people who have specific factors such as frailty or comorbidities that influence the balance of risks and benefits in favour of single-chamber pacing.

What the procedure involves

The aim of implanting a leadless cardiac pacemaker is to detect cardiac bradyarrhythmias and deliver electric pulses to the heart to increase the heart rate. The leadless pacemaker has a built-in pulse generator, battery and electrodes. The procedure is done under local anaesthesia, with or without sedation, in a cardiac catheterisation laboratory. Under fluoroscopic guidance, the proximal end of the pacemaker is attached to a deflectable bespoke delivery catheter system and inserted percutaneously through the femoral vein using a dedicated introducer sheath. It is then advanced into the right atrium through the tricuspid valve, into the right ventricle and positioned near the apex or lower septum. Contrast may be injected into the right ventricle to visualise the desired location. Once positioned, the pacemaker is deployed and securely implanted into the endocardial wall using a fixation mechanism (a screw-in helix or nitinol tines). An electrode at the distal end of the pacemaker delivers electrical impulses that pace the heart. Electrical measurements are taken and, if satisfactory, the pacemaker is released from the catheter and the catheter is removed. If the position is suboptimal, the pacemaker can be detached from the endocardium and repositioned prior to final release of the delivery catheter.

The pacemaker is programmed using an external programmer that transmits signals to it. The pacemaker can be retrieved using a catheter retrieval system, if device dislodgement is discovered at follow-up.

The device can only detect and pace the right ventricle (single chamber) in contrast to some conventional pacemakers that can provide dual-chamber (right atrium and right ventricle) detection and pacing. It is therefore suitable for people who only need single-chamber ventricular pacing.

Efficacy summary

Implantation outcomes

In a case series of 33 patients implanted with leadless cardiac pacemakers (LCP), the implant success rate was 97% (32/33). The mean procedure duration was 28±17 minutes and average time to discharge was 31±20 hours. Repositioning after initial deployment was needed because of inadequate electrical measurements in 29% (9/33) of patients. More than 1 device was

implanted during the procedure in 15% (5/33) of patients because of inadvertent placement of the device in the left ventricle (n=1), malfunction of the release knob (n=1), delivery catheter damage related to tortuosity of the venous vasculature (n=1), damage to the device helix during insertion (n=1) and difficulty with the wire deflection mechanism of the delivery catheter (n=1).[1]

In a case series of 526 patients, the LCP was successfully implanted in 96% (504/526) of patients who needed permanent single-chamber ventricular pacing. The mean procedure duration was 28.6±17.8 minutes and average time to discharge was 1.1±1.7 days. Repositioning after initial deployment was needed in 30% (150/504) of patients.[2]

In a case series of 725 patients, the leadless transcatheter pacing system (TPS) was successfully implanted in 99% (719/725) of patients. Unsuccessful implantations (3 patients with cardiac perforations, 1 patient with pericardial effusion, 1 patient with tortuous venous anatomy, and 1 patient in whom pacing threshold could not be achieved) were reported in less than 1% (6/725) of patients. The mean procedure duration was 23.0±15.3 minutes (range 11 to 74 minutes).[4]

In a case series of 795 patients, the TPS was successfully implanted in 97% (792/795) of patients. 77% of implantations needed 2 or more attempts of deployment.[6]

Pacing performance

In the case series of 33 patients implanted with LCP, the measures of pacing performance (sensing, impedance and pacing threshold) either improved or were stably within accepted range at 3, 6, 12 and 36 months follow-up (mean pacing threshold [at a 0.4-ms pulse width] 0.46 V, 0.40±0.26 V, 0.43±0.30 V and 0.47V; mean R-wave amplitude 10.6 mV, 10.6±2.6 mV, 10.3±2.2 mV and 10.8 mV; and mean impedance 627 ohms, 625±205 ohms, 627±209 ohms and 614 ohms)[1]. Rate–response sensor was activated in 61% (19/31) of patients at 12-month follow-up, 42% at 24 and 39% at 36 months follow-up.[1]

In the case series of 526 patients with LCP, the measures of pacing performance improved statistically significantly from pacemaker implantation to 12 months (mean pacing threshold (at a 0.4-ms pulse width) from 0.82±0.69 V to 0.58±0.31V, $p<0.01$; mean R-wave amplitude from 7.8±2.9 mV to 9.2±2.9 mV, $p<0.01$; mean impedance from 700±295 ohms to 456±111 ohms, $p<0.01$). The intention to treat primary efficacy point (acceptable pacing performance at 6 months) was achieved in 90% [270/300] of the primary cohort (95% confidence interval [CI] 86% to 93.2%, $p=0.007$).[2]

In the case series of 725 patients with TPS, acceptable pacing performance was achieved in 93% (292/297) of the patients with paired 6-month data (95% CI, 96.1% to 99.5%; p<0.001) compared with the efficacy performance goal of 80% (based on historical transvenous control data).[4] The measures of pacing performance improved statistically significantly from pacemaker implantation (n=725) to 24 months (n=58) (mean pacing threshold (at a 0.24-ms pulse width) from 0.63 V to 0.53±0.23 V; mean R-wave amplitude from11.2 mV to 15.5 mV; mean pacing impedance from 724 ohms to 596 ohms).[4]

In a retrospective matched case control study comparing pacing thresholds at implant and subsequent follow-up (0 to 6 months) between 711 patients with TPS with threshold data at 0.24 ms and 538 patients with transvenous leads at 0.4 ms, pacing thresholds in patients with elevated thresholds at implant (high more than 1.0 V or very high thresholds more than 1.5 V) decreased statistically significantly in both groups (TPS group: more than 1.0 V (n=45) : pacing threshold 87% decrease [1.28 to 0.78], p<0.001; more than 1.5 (n=27) pacing threshold 85% decrease [2.22 to 1.38], p<0.001; transvenous group more than 1.0 V (n=26) pacing threshold 80% decrease [1.31 to 0.85], p<0.001; more than 1.5V (n=19) pacing threshold 100% decrease [2.23 to 0.84], p<0.001).[5]

In the case series of 795 patients with TPS, the measures of electrical performance were low and stable. Average pacing thresholds at implant (n=701), 3 months (n=39) and 6 months (n=25) were 0.6±0.5 V, 0.5±0.3 V and 0.6±0.3 V respectively. Average impedance was 721±181 ohms, 634±143 ohms, and 572±115 ohms.[6]

In a retrospective comparative case series of 127 patients, acceptable sensing (R wave >5.0 mV) and pacing thresholds (<2.0 V at 0.4 ms) were reported in 95% (57/60) of patients in the LCP group and 97% (65/67) of patients in the CTP group (p=0.66).[10]

Safety summary

Overall complication rate

In the case series of 33 patients with LCP, the overall complication-free rate was 94% (31/33) at 90-day follow-up and 90% (30/33) at 36-month follow-up.[1]

In the case series of 725 patients with TPS, the overall device or procedure-related major complication-free rate was 96% at 12 months (95% confidence interval [CI] 94.2 to 97.2%; p<0.001) compared with the safety performance goal of 83% (based on historical transvenous control data).[4]

In a propensity-matched analysis of 440 patients comparing LCP (n=220) and conventional transvenous pacemakers (CTP), device-related complication rate at 800-day follow-up was 0.9% (2/220) in the LCP group and 4.7% (10/220) in the CTP group when excluding pacemaker advisory related revisions (p=0.02). When including the pacemaker advisory revisions, device-related complication rate increased to 6.3% (14/220) in the LCP group and 4.7% (10/220) in the CTP group (p=0.063).[11]

Device- or procedure-related serious adverse events

Forty device- or procedure-related serious adverse events were reported in 6.5% (34/526) of patients in the case series of 526 patients with LCP at a mean follow-up of 6.9 months[2]. In the primary cohort, 22 device-related serious adverse events were reported in 7% (20/300) patients at 6-month follow-up and 93% (280/300) of patients were free from these events and it exceeded the prespecified performance goal of 86% (p<0.001) (based on historical transvenous control data).[2]

Serious adverse device effects (SADEs) were reported in 5.9% (20/339) of patients in the primary cohort (including after the study was paused) of the post-market observational study of 470 patients with LCP at a mean follow-up of 19.5 months. 94.6% of patients were free from these events and demonstrated non-inferiority to a prespecified goal of 86% (p<0.001). The most frequently occurring events were cardiac perforation (1.5%), device dislodgement (0.3%), and vascular complications (1.5%). In the total cohort, 53 SADEs were observed in 10.6% (50/470) of patients. After stratifying the results in relation to the study pause, there was a statistically significant difference in the final LCP location (septum compared with apex; p<0.0001) and the number of repositioning attempts (<2 compared with >2; p=0.05) and a decreasing trend in the rates of cardiac perforation and device dislodgement.[8]

Thirty-two device- or procedure-related major complications (defined as events resulting in death, permanent loss of device function as a result of mechanical or electrical dysfunction, hospitalisation, prolongation of hospitalisation by at least 48 hours, or system revision) were reported in 4% (29/726) of patients in the case series of 725 patients with TPS. All resulted in hospitalisation.[4] The risk of major complications for patients with TPS was 48% lower than for historical control group patients with transvenous systems through 12 months' post-implant (hazard ratio 0.52; 95% CI 0.35 to 0.77; p=0.001). A risk reduction of 47% reduction was seen for hospitalisations and 82% risk reduction in system revisions. Across different subgroups of age, sex and comorbidities TPS reduced the risk of major complications compared with transvenous systems.[4]

Thirteen device-related major complications (defined as events resulting in death, permanent loss of device function as a result of mechanical or electrical

dysfunction, hospitalisation, prolongation of hospitalisation by at least 48 hours, or system revision) were reported in 1.5% (12/795) of patients in the case series (registry) of 795 patients with TPS. All resulted in hospitalisation.[6] When compared these early safety results with another TPS investigational study (n=726)[4] the rates of major complications were lower (odds ratio 0.58, 95% CI 0.27 to 1.25, p=0.0691).[6]

Major adverse events (loss of pacing and sensing) were reported in 2% (1/60) of patients in the LCP group and 3% (2/67) of patients (lead dislodgements) in the CTP group in the retrospective comparative case series of 127 patients (p=1.00). There was no difference in the rate of minor adverse events (10% [6/60] in the LCP group compared with 4.3% [3/67] in the CTP group, p=0.30).[10]

Perforation and cardiac tamponade

Right ventricular perforation leading to cardiac tamponade with haemodynamic collapse occurred during successful LCP implantation and repositioning in 1 patient in the case series of 33 patients. The patient had a massive ischaemic stroke 5 days later and eventually died after 2 weeks.[1]

Cardiac perforations were reported in 1.6% (8/526) of patients (cardiac tamponade with intervention in 5 patients, cardiac perforation with intervention in 1 patient and pericardial effusion with no intervention in 8 patients) in the case series of 526 patients with LCP at a mean follow-up of 6.9 months.[2]

Cardiac perforations or effusion occurred within 30 days in 1.6% (11/725) patients in the case series of 725 patients with TPS. Of these, 1 event occurred between 30 days to 6 months. All patients needed hospitalisation.[4]

Cardiac perforation or effusion within 30 days was reported in 1 patient in the case series of 795 patients with TPS. Patient needed pericardiocentesis on the day of implantation and this was resolved.[6] Non-serious cardiac perfusion or perforations were reported in 4 other patients in the same study within 30 days. Two patients needed drainage or pericardial puncture or both and 2 other patients needed no intervention.[6]

Vascular complications

Vascular complications were reported in 1.2% (6/526) of patients (bleeding in 2 patients, arteriovenous fistula in 1 patient, pseudoaneurysm in 2 patients and failure of vascular closure device needing intervention in 1 patient) in the case series of 526 patients with LCP at a mean follow-up of 6.9 months.[2]

Vascular complications at groin puncture site occurred within 30 days in fewer than 1% (5/725) of patients (atrioventricular fistula in 4 patients and

pseudoaneurysm 1 patient) in the case series of 725 patients. All patients needed hospitalisation.[4]

Vascular complications within 30 days were reported in less than 1% (6/795) of patients (arteriovenous fistula in 1, hematoma in 2, incision site haemorrhage in 1, persistent lymphatic fistula in 1 and vascular pseudoaneurysm in 1) in the case series of 795 patients with TPS.[6]

Venous thromboembolism

Deep vein thrombosis (in 1) and pulmonary thromboembolism (in 1) occurred within 30 days in less than 1% (2/725) of patients in the case series of 725 patients with TPS. Both patients needed hospitalisation.[4]

Deep vein thrombosis within 30 days was reported in 1 patient in the case series of 795 patients with TPS.[6]

Device dislodgement and migration

Device dislodgement at a mean 8 days (range 1 to 14 days) was reported in 1% (6/526) of patients in the case series of 526 patients with LCP at a mean follow-up of 6.9 months. Four leadless pacemakers dislodged to the pulmonary artery and 2 dislodged to the right femoral vein within 2 weeks after implantation. All devices were retrieved percutaneously and new LCPs were implanted.[2]

Device dislodgement (as a result of tines not embedded properly) was reported in 1 patient 2 days post-implant in the case series of 795 patients with TPS. The device was successfully repositioned at 50 days post-implant, with normal pacing thresholds.[6]

Device migration during implantation owing to inadequate fixation was reported in less than 1% (2/526) of patients in the case series of 526 patients with LCP at a mean follow-up of 6.9 months.[2]

Elevated pacing threshold needing device retrieval and replacement

Elevated pacing threshold needing percutaneous retrieval and new device replacement at a median 100 days (range 1 to 413 days) was reported in less than 1% (4/526) of patients in the case series of 526 patients with LCP at a mean follow-up of 6.9 months.[2]

Elevated pacing thresholds were reported in less than 1% (2/725) of patients within 30 days in the case series of 725 patients with TPS. Both patients were hospitalised and loss of device function was noted in 1 patient. System revisions were done in both.[4]

Elevated pacing threshold was reported in 1 patient (within 30 days) in the case series of 795 patients with TPS.[6]

Battery failures

Battery failures (occurring at 2.9±0.4 years) with no instances of associated patient injury were reported in 2.3% (34/1423) of patients in a case series of 1,423 patients implanted with LCPs. 28 of these were asymptomatic and 6 were related to bradycardia. The mean time from last follow-up to detection of battery failure was 140±70 days (range 31 to 353 days). Limited analysis of these batteries revealed an increase in battery resistance caused by insufficient electrolyte availability at the cathode or anode interface and lack of adequate current needed for device. 8 of these devices were retrieved and re-implanted with another new LCP (n=6) or transvenous pacemakers (n=2). Eighteen devices were abandoned and revision was done with new LCPs (n=7) or new transvenous pacemakers (n=16) and close monitoring without revision was done in 8 patients.[3]

Device retrieval and revisions

Device retrievals were reported in 9% (3/33) of patients in the case series of 33 patients implanted with LCPs. In 1 patient the device was inadvertently implanted in the apex of heart with acceptable pacing performance but it was retrieved and a new LCP implanted in the right ventricle. In another patient, the device was retrieved and a single-chamber transvenous implantable cardioverter defibrillator was implanted but the patient developed ventricular tachycardia after 5 days and was readmitted 2 weeks later for implantable cardioverter defibrillator (ICD) shocks. In another patient, a malfunctioning device (caused by a battery problem, leading to an abrupt loss of communication) was retrieved and replaced with a new LCP.[1]

Device retrievals and revisions were reported in 13% (181/1,423) of patients at a mean 1.7 years (range 0.2 to 4 years) in a case series of 1,423 patients implanted with LCPs. Indications for retrieval attempts included elevated pacing thresholds (n=8), need for device upgrade to defibrillator or biventricular pacemaker (n=9), elective explant (n=2), battery failure (n=8) and prophylactic explant based on battery failure advisory by the company (n=46). 37% (66/181) of the retrievals were successful and either new LCPs (n=29) or transvenous pacemakers (n=36) were re-implanted or no device was inserted (n=1). A total of 63% (115/181) of retrievals were unsuccessful (n=7) or abandoned with no retrieval (n=108). In 7 unsuccessful attempts (the LCP proximal button was inaccessible in 5 patients, docking button was in subvalvular apparatus and could not be snared in 1 and locking button detached from LCP during retrieval in1) new LCPs were implanted in 3 patients and transvenous pacemakers in 4 patients. In 108 abandoned patients, new LCPs were implanted in 5 and

transvenous pacemakers in 103. No adverse device-to-device interactions were identified.[3]

System revisions were performed in less than 1% (5/725) of patients in the case series of 725 patients with TPS at 12-month follow-up. In 3 patients percutaneous retrieval attempt was done (1 was successfully retrieved and a new TPS implanted 16 days post-implant; 1 was unsuccessful because of inability to extract device at 259 days post-implant, and 1 was aborted because of fluoroscopy failure 229 days post-implant). In 2 other patients with loss of device function (because of pacemaker syndrome and elevated pacing threshold) the device was turned off without a retrieval attempt and concomitant transvenous pacemaker was implanted 32 and 44 days post-implant.[4]

In a retrospective matched case control study comparing TPS (n=989) with transvenous pacemakers (historical control n=2,667), the risk of system revision through 24 months post-implant was 1.4% for patients with TPS (11 revisions in 10 patients), 75% lower than the 5.3% rate (95% confidence interval [CI] 4.4%–6.4%) for patients with transvenous pacemakers (123 revisions in 117 patients; hazard ratio 0.25; 95% CI 0.13–0.47; p<0.001) with 107 (87%) occurring within 12 months. TPS revisions occurred between 5 to 430 days post-implant for elevated pacing thresholds (n=3), pacemaker syndrome (n=2), need for alternative therapy (n=2), cardiac failure (n=1), battery depletion (=1) and prosthetic valve endocarditis (n=1). Devices were disabled and left in situ in 7 patients, 3 were retrieved percutaneously (between 9 to 406 days post-implant) and 1 was surgically removed.[7]

Cardiopulmonary arrest during implantation

Cardiopulmonary arrest during implantation was reported in 1 patient in the case series of 526 patients with LCPs.[2]

Arrhythmia during implantation

Arrhythmia during implantation was reported in less than 1% (3/526) of patients (asystole in 1 and ventricular tachycardia or ventricular fibrillation in 2) in the case series of 526 patients with LCPs.[2]

Other procedure-related serious adverse events

Other procedure-related adverse events reported in 1 patient each in the case series of 526 patients with LCPS included haemothorax, angina pectoris, acute confusion and expressive aphasia, dysarthria and lethargy, contrast induced nephropathy, orthostatic hypotension with weakness, left leg weakness during implantation, pulmonary embolism, and ischaemic stroke.[2]

Other serious adverse events reported in the case series of 725 patients with TPS included cardiac failure in (n=6), acute myocardial infarction in (n=1), metabolic acidosis (n=1), pacemaker syndrome (n=2) and syncope or presyncope (n=2).[4]

Other serious adverse events reported in the case series of 795 patients with TPS included pulmonary oedema (n=1), chest pain (n=1) and sepsis within 48 hours which was successfully treated using intravenous antibiotics (n=1).[6]

Death

Deaths were reported in 5.3% (28/526) of patients in the case series of 526 patients with LCPs. Of these, 68% (19/526) occurred within 6 months and 29% (8/526) between 6 and 12 months and 4% (1/526) after 12 months. None of these were device related, but less than 1% (2/526) were reported as procedure related. The cause of these deaths was classified as cardiac related in 4 patients, non-cardiac in 14 patients and unknown in 10 patients.[2]

Deaths were reported in 11% (78/725) the case series of 725 patients with TPS at a mean follow-up of 16.4 months. These were because of sudden cardiac death (n=10), non-sudden cardiac death (n=22), non-cardiac death (n=43) and unknown reasons (n=2). 1 death was reported as procedure related (because of metabolic acidosis in a patient with end stage renal failure who had concomitant atrioventricular nodal ablation during pacemaker implantation). [4a, 4b]

Deaths were reported in 3% (22/795) of patients within 30 days in the case series of 795 patients with TPS. 1 death was reported as procedure related (because of pulmonary oedema and cardiac arrest).[6]

Non-device or procedure-related serious adverse events

Thirty-six non-device-related serious adverse events were reported in 5.5% (29/526) of patients at a mean follow-up of 6.9 months in the case series of 526 patients with LCPs. Of these 22 events were reported within 6 months in 6.3% (19/300) of patients in the primary cohort.[2]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed the following anecdotal adverse event: infection. They considered that the

following were theoretical adverse events: device-device interaction and inability to communicate with programmer.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to leadless cardiac pacemaker implantation for bradyarrhythmias. The following databases were searched, covering the period from their start to 28.11.2017: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with bradyarrhythmias
Intervention/test	Leadless cardiac pacemaker implantation
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on about 6,000 patients who had leadless cardiac pacemaker implantation from 7 case series[1-4,6,8,10], 3 retrospective matched comparative studies[5,7,11] and 1 registry[9]. Data were extracted from 5 studies for 2 of the case series, which were reported in separate phases. There is an overlap of patients in the included studies.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on leadless cardiac pacemaker implantation for bradyarrhythmias

Study 1 Reddy VY [2014][1a], Knops RE (2015)[1b], Tjong FVY (2018)[1c]

Details

Study type	**Case series (LEADLESS trial NCT 01700244)**
Country	The Netherlands, Germany, Prague (3 centres)
Recruitment period	December 2012-April 2013
Study population and number	n=**33** patients with clinical indication for single-chamber pacing (VVIR)
Age and sex	Mean age 77±8 years and 67% (22/33) male
Patient selection criteria	Patients older than 18 years, with a clinical indication for single-chamber (right ventricular) pacing (VVIR): permanent atrial fibrillation with atrioventricular block (67% [22/33]), normal sinus rhythm with 2nd or 3rd degree AV block with a low level of physical activity or short expected life span (18%, 6/33) or sinus bradycardia with infrequent pauses or unexplained syncope with electrophysiology findings (prolonged HV interval) (15%, 5/33) were included. Patients were excluded if pacemaker dependent, had a mechanical tricuspid valve prosthesis, pulmonary hypertension, pre-existing pacemaker or defibrillation leads or an inferior vena cava filter.
Technique	Implantation of a self-contained leadless cardiac pacemaker (Nanostim Inc). Programming of the device was left to the discretion of the implanting physician. Pacing mode programmed to VVIR. Follow-up was done at pre-discharge, 2, 6 and 12 weeks post implantation.
Follow-up	**90 days (n=33)[1a], mean 1.2 years (n=31)[1b], median 38 months (range 21 to 41 months)[1c]**
Conflict of interest/source of funding	Study funded by Nanostim Inc. 2 authors have received grant support from Nanostim, 1 received stock options, and 2 authors are employees of the company.

Analysis

Follow-up issues: Patients were retrospectively analysed in the intermediate follow-up (1 year) study. In the retrospective analysis, 2 patients from the initial study cohort were excluded. No patients were lost at final follow-up.

Study design issues: small prospective multicentre study, primary safety endpoint was complication free rate (defined as serious adverse device effects) at 90 days and 40 months follow-up. Secondary endpoints included implant success (percentage of patients with an implanted and functioning LCP device), time, and measures of device performance.

Additionally LCP performance was assessed during magnet testing and 6 minute walk tests. An independent data and safety monitoring board reviewed the data.

Data from medical records of 31 patients were retrospectively analysed in the intermediate follow-up (1 year) study (Knops 2015).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **33**

Implantation outcomes

Implant success rate	97% (32/33)
Repositioning needed because of inadequate electrical measurements	29% (9/33)
More than 1 LCP during the procedure (range 1-3)	15% (5/33)*
Implantation duration, minutes	28±17 (range 11-74)
Average time to hospital discharge, hours	31±20 (range 17-113)

*1 because of inadvertent placement of device in the left ventricle, 1 malfunction of the release knob, 1 delivery catheter damage related to tortuosity of the venous vasculature, 1 damage to the LCP helix during insertion and 1 difficulty with the wire deflection mechanism of the delivery catheter.

Pacing performance

	12 weeks n=32	**6 months n=32**	**12 months n=31**	**36 months**
Mean pacing threshold (at a 0.4-ms pulse width)	0.46±0.31	0.40±0.26V	0.43±0.30v	0.47±0.19
Mean R-wave amplitude	10.6±2.3	10.6±2.6mV	10.3±2.2 mV	10.8±2.3 mV
Mean impedance	627±199	625±205 ohms	627±209 ohms	614±199 ohms

Rate response sensor was activated in 61% (19/31) of patients at 12 months follow-up, and an adequate rate response was seen in all patients.

Survival

At 3 year follow-up, 74% (23/31) patients were alive.

Safety

Complications

At 90 days follow-up	**% (n=33)**
Complication free rate	94 (31/33)
Right ventricular perforation leading to cardiac tamponade with haemodynamic collapse during LCP implantation and repositioning (operated successfully but had a massive ischemic stroke 5 days later and eventually died after 2 weeks).	1
Device-related complications	0
Device retrievals	**2**
LCP inadvertently implanted in the apex of heart with acceptable pacing performance (device was retrieved and new LCP implanted in the right ventricle)	1
LCP was retrieved and a single chamber transvenous ICD implanted after 5 days (because of VT but readmitted 2 weeks later for ICD shocks because of VT)	1
Rehospitalisation (1 for an elevated INR, 1 for an acute exacerbation of COPD, and 1 for VT)	9 (3/33)
At 1 year follow-up	**n=31**
Device-related events	0
Rehospitalisation (not related to procedure or pacemaker function)	19 (6/31)
At 3-year follow-up	**n=33**
Freedom from SADEs	89.9 % (30/33)
Device malfunction presenting an abrupt loss of communication and pacing attributable to battery malfunction at 37 months (LCP retrieved and replaced with a new LCP).	1

Abbreviations used: COPD, chronic obstructive pulmonary disease; INR, international normalised ratio; LCP, leadless cardiac pacemaker; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia.

Study 2 Reddy VY (2015)[2]

Details

Study type	**Case series (LEADLESS II pacemaker IDE study NCT 02030418)**
Country	US, Canada and Australia (56 centres)
Recruitment period	February 2014 to June 2015
Study population and number	n=**526** patients who needed permanent single-chamber ventricular pacing
Age and sex	Mean 75±8 years; 62% (325/526) male
Patient selection criteria	patients with indications for permanent single-chamber ventricular pacing, including chronic atrial fibrillation with atrioventricular or bifascicular bundle-branch block (n=294), sinus rhythm with second-degree or third-degree atrioventricular block (n=46) and a low level of physical activity or a shortened expected life span, or sinus bradycardia with infrequent pauses or unexplained syncope with an abnormal electrophysiological study (n=186). Patients were excluded if they had a mechanical tricuspid-valve prosthesis, pulmonary arterial hypertension, pre-existing endocardial pacing or defibrillation leads, or an inferior vena cava filter or if they had had cardiovascular or peripheral vascular surgery within 30 days before enrolment.
Technique	Implantation of a self-contained leadless cardiac pacemaker (Nanostim LP). Programming of the device was left to the discretion of the implanting physician. Pacing mode programmed to VVIR. Follow-up assessments done at 2, 4, 12 weeks and 6 months and thereafter every 6 months.
Follow-up	**Primary cohort: minimum 6 months (n=300); total cohort: mean 6.9±4.2 months (n=526)**
Conflict of interest/source of funding	This premarket study was funded by St. Jude Medical and approved by FDA.

Analysis

Study design issues: interim analysis of a large ongoing prospective multicentre study in 3 countries. Data collection and analysis was done by sponsor. The primary efficacy end point was both an acceptable pacing threshold (≤2.0 V at 0.4 ms) and an acceptable sensing amplitude (R wave ≥5.0 mV, or a value equal to or greater than the value at implantation) at 6 months. The primary safety end point was freedom from device-related serious adverse events at 6 months. Analysis was performed on data from the first 300 patients who completed 6 months of follow-up and additional outcomes (operator experience, device-related and non-device-related adverse events) were reported for all patients who were enrolled. The rates of the efficacy end point and safety end point were compared with performance goals (based on historical data from recipients of conventional transvenous pacemakers) of 85% and 86%, respectively. The study used the standard definition of serious adverse events.

Study population issues: varied group of patients.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **526**

Implantation outcomes

Implant success rate	95.8% (504/526)
No device repositioning needed	70.2% (354/504)
Repositioning needed because of inadequate electrical measurements (range 1-3)	29.8% (150/504)
Implantation duration, minutes	28.6±17.8 (range 11-74)
Average time to hospital discharge, days	1.1±1.7 (range 0-33)

Pacing performance in 90% [270/300] of primary cohort (95% CI, 86.0 to 93.2, p = 0.007)

	Baseline	**12 months**	**P value**
Mean pacing threshold (at a 0.4-ms pulse width)	0.82±0.69 V	0.58±0.31 V	<0.01
Mean R-wave amplitude	7.8±2.9 mV	9.2±2.9 mV	<0.01
Mean impedance	700±295 ohms	456±111 ohms	<0.01

Safety

Complications

	Primary cohort % (n=300)	**Total cohort % (n=526)**
Complication free rate	93.3 (280/300) 95% CI, 89.9 to 95.9; p<0.001	
Device-related serious adverse events	6.7 (20/300) 22 events	6.5 (34/526) 40 events
Cardiac perforation	1.3 (4/300) (tamponade 1, perforation1-with interventions; 2 pericardial effusions with no intervention)	1.6 (8/526) (tamponade 5, perforation 1-with interventions; pericardial effusion with no intervention 2)
Arrhythmia during implantation	0.6 (2/300) (asystole 1,VT or VF 1)	0.6 (3/526) (asystole 1, VT or VF 1)
Cardiopulmonary arrest during implantation	0	0.1 (1/526)
Vascular complications	1.3 (4/300) Bleeding 2, arteriovenous fistula 1, pseudoaneurysm 1)	1.2 (6/526) (Bleeding 2,arteriovenous fistula 1, pseudoaneurysm 2, failure of vascular closure device needing intervention 1)
Device dislodgement with retrieval (at 8 days, range 1-14)	1.7 (5/300)	1.1 (6/526) (4 LCPs dislodged to the pulmonary artery and 2 dislodged to the right femoral vein within 2 weeks after implantation, all were removed and new LCPs implanted)
Device migration during implantation	0	0.2 (2/526)
Elevated pacing thresholds needing device retrieval and replacement (median 100, range 1-413 days)	1.3 (4/300)	0.8 (4/526)
Non-device-related serious adverse events (2 with worsening heart failure needed device retrieval and cardiac resynchronisation therapy)	6.3% (19/300) 22 events	5.5 (29/526) 36 events
Deaths*		5.3 (28/526)

	Other device-related serious adverse events reported in 1 patient each included haemothorax, angina pectoris, acute confusion and expressive aphasia, dysarthria and lethargy, contrast induced nephropathy, orthostatic hypotension with weakness, left leg weakness during implantation, pulmonary embolism, and ischaemic stroke. *68% (19/526) occurred in 6 months and 29% (8/526) between 6 and 12 months and 4% (1/526) after 12 months. None were device related, but 0.4% (2/526) were procedure related. Only 4 deaths were cardiac related. **Influence of operator-experience- on device-related adverse events** The rate of device-related serious adverse events was 6.8% for the initial 10 cases versus 3.6% for the subsequent implants (p = 0.56).
Abbreviations used: CI, confidence interval; LCP, leadless cardiac pacemaker; VT, ventricular tachycardia; VF, ventricular fibrillation.	

Study 3 Lakkireddy D (2017)[3]

Details

Study type	**Case series**
Country	Worldwide (32 centres in Europe, US, Canada, and Australia)
Recruitment period	2012-2016 (data from 3 trials NCT02051972, NCT02030418, NCT01700244)
Study population and number	n=**1423 patients who had a leadless pacemaker (Nanostim)**
Age and sex	Not reported
Patient selection criteria	Data from patients who had a right ventricular active fixation leadless pacemaker within 3 multicentre clinical trials (NCT02051972, NCT02030418, NCT01700244). Inclusion criteria as described in studies above.
Technique	Leadless cardiac pacemaker (Nanostim) implanted (technique is described in procedure description above)
Follow-up	**Follow-up until March 2017 (4 years 3 months)**
Conflict of interest/source of funding	Study was funded by St. Jude Medical and approved by FDA; 2 authors were consultants to the manufacturer and received honorarium. Clinical trials included in this study were funded by St. Jude Medical.

Analysis

Study design issues: large retrospective study; data on incidence of battery failures and acute and chronic retrieval of leadless pacemakers were collected and assessed from 3 multicentre clinical studies worldwide. Patient management in clinical trials was based on the recommendations included in the battery advisory issued by the company (in October 2016) after 7 cases of battery malfunction leading to loss of pacing and communication were reported. Enrolment in these studies was suspended.

In retrieval attempts, adverse events related to the procedure and reason for retrieval were also collected. 3 retrievals conducted outside studies are also included here.

Key efficacy and safety findings

Safety

Number of patients analysed: **1423**

LCP battery failures

	% (n)
Battery failures (occurring at 2.9±0.4 years [range 2.3 -4 years] with no instances of associated patient harm or injury)	**2.3 (34/1423)** (30 in Europe, 3 in US, and 1 in Australia).
Asymptomatic	n=28
Symptomatic related to bradycardia	n=6
LCP retrieved	n=8 (re-implanted another new LCP in 6, TV pacemaker in 2)
LCP abandoned and revised	n=18 (re-implanted new LCP in 7 and new TV pacemaker in16)
No revision and close monitoring	n=8

The mean time from last follow-up to detection of battery failure is 140±70 days (range 31-353 days).

Limited analysis did not reveal clear predictors of failure. Failures were attributed to reduced electrolyte in the battery leading to an increased battery resistance, and lack of adequate current needed for device.

LCP retrievals and revisions

	% (n)
All LCP revisions	**12.7 (181/1423)**
Retrieval attempts	N=73 (20 before advisory and 53 after advisory) (Indications for retrieval: elevated pacing thresholds (n=8), need for device upgrade to defibrillator or biventricular pacemaker (n=9), elective explant (n=2), battery failure (n=8) and prophylactic explant based on advisory (n=46)).
LCP retrieval successful (implant duration mean 1.7 years; range 0.2-4 years)	37 (66/181) before advisory in 19 and after advisory in 47 (re-implanted with another LCP in 29, with TV pacemaker in 36, no device placed in 1)
LCP retrieval unsuccessful or abandoned	63 (115/181) 1. **unsuccessful retrieval attempts in 7 – re-implanted with another LCP in 4 and TV pacemaker in 3 2. LCPs abandoned with no retrieval attempt in 108- re-implanted with new LCP in 5 and TV pacemaker in 103 (no adverse device-to-device interactions identified)

**the LCP proximal button was inaccessible in 5 patients because of proximal button could not be accessed, docking button was in subvalvular apparatus and could not be snared, locking button detached from LCP during retrieval.

There was no statistically significant difference in retrieval success rates over time (0-1 year 86% [n=22], 1-2 years 93% [n=30], more than 2 years 90% [n=21]), p>0.05).

LCP retrieval-related adverse events

SADEs	**N**
Arteriovenous fistula (related to prophylactic replacement of device based on the advisory)	1
Docking button detached and LCP migrated to the pulmonary artery during retrieval attempt, button was not retrieved (related to prophylactic replacement of device based on the advisory)	1
Non-SADEs	
Tricuspid valve damage with trivial or moderate regurgitation(no long term sequelae)	2
Atrial flutter (had an ablation procedure)	1

Deaths =41

4 occurred after 2.6 years from implantation and 37 occurred at 0.7 years after implantation. No signs of battery problems were seen at visit before death (mean 64.4±53.8 days). 4 devices analysed by the manufacturer were found to be working properly.

Abbreviations used: LCP, leadless cardiac pacemaker; SADE, serious adverse device effects; TV, transvenous.

Study 4 Reynolds D (2016)[4a]; Duray GZ (2017)[4b]

Details

Study type	**Prospective case series (FDA IDE Micra TPS trial NCT02004873)**
Country	Worldwide (56 centres in 19 countries: US, Europe, Asia, Australia and Africa)
Recruitment period	2013-15
Study population and number	n=**725** patients with class I or II guideline indications for right ventricular pacing **posthoc analysis** **725** transcatheter pacing system (TPS) **versus 2667** transvenous pacemakers in the historical control cohort
Age and sex	Mean 75.9 years; 58.8% (426/725) male
Patient selection criteria	Patients who met class I or II guideline-based indications for de novo right ventricular pacing (i.e., for bradycardia because of atrial tachyarrhythmia (64%), sinus node dysfunction (17.5%), atrioventricular node dysfunction (14.8%), or other causes (3.7%)) were considered to be suitable candidates for single-chamber ventricular demand (VVI) pacing, were not prevented from participating as a result of coexisting conditions were included. Patients with an existing pacemaker or implantable cardioverter–defibrillator were not included in the study.
Technique	The Micra transcatheter pacemaker, a single chamber ventricular pacemaker was implanted by 94 physicians. Implant technique is described in procedure description. Follow-up assessments were done at 1, 3 and 6 months and thereafter biannually for at least 12 months.
Follow-up	**6 months (Reynolds D 2016); mean 16.4 ± 4.9 months (Duray GZ 2017)**
Conflict of interest/source of funding	Study funded by Medtronic; sponsor assisted in data analyses and publication. Most authors received consulting fees or grants from Medtronic.

Analysis

Follow-up issues: large study with longer follow-up. No patients were followed beyond 2 years.

Study design issues: large multicentre prospective study, Reynold D 2016 is a planned early performance interim analysis. The primary safety end point was freedom from system-related or procedure-related major complications. The primary efficacy end point was the percentage of patients with low and stable pacing capture thresholds at 6 months (≤2.0 V at a pulse width of 0.24 ms and an increase of ≤1.5 V from the time of implantation). Duray 2017 assessed long-term safety (at 12 months) and electrical performance (at 24 months). The safety and efficacy end points were evaluated against performance goals (based on historical data from recipients of conventional transvenous pacemakers for which individual patient level data was available) of 83% and 80%, respectively. The analysis of the primary end points began when 300 patients reached 6 months of follow-up. A post hoc analysis comparing the rates of major complications with those in a predefined historical control group of 2,667 patients with transvenous pacemakers from 6 previously published studies was also performed. Safety events were reviewed by an independent clinical events committee.

Study population issues: There were statistically significant differences between the study patients and the control patients with regard to baseline characteristics. Study patients were older and had more comorbidities. One additional successful implant occurred after the early performance analysis. 36% of patients were without persistent atrial arrhythmia at baseline.

Other issues: study used a self-defined safety end point.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **725 study group versus 2667 historical control group**

Implantation outcomes

Implant success rate	99.2% (719/725)
Unsuccessful implantations*	0.8% (6/725)
Implantation duration	23.0±15.3 minutes (range 11-74 minutes)

*3 with cardiac perforations, 1 with pericardial effusion, 1 with tortuous venous anatomy, and 1 in whom pacing threshold could not be achieved.

Evaluation of efficacy against the performance goal of 80% (based on historical data)

The rate of the primary efficacy end point was 98.3% (95% CI, 96.1 to 99.5; P<0.001) among 292 of 297 patients with paired 6-month data.

	At implantation (n=725)	**6 months (n=300)**	**12 months (n=630)**	**24 months (n=58)**
Mean pacing threshold (at a 0.24-ms pulse width)	0.63 V	0.54 V	0.60 ± 0.38 V	0.53 ± 0.23 V
Mean R-wave amplitude	11.2 mV	15.3 mV	15.1 mV	15.5 mV
Mean pacing impedance	724 ohms	627 ohms	596 ohms	596 ohms

The projected battery longevity was 12.1 years.

Safety

Evaluation of safety against the performance goal of 83% (based on historical data)

The Kaplan– Meier estimate of the rate of the primary safety end point at 6 months was 96.0% (95% CI, 93.9 to 97.3; P<0.001).

The long-term safety objective was achieved with a freedom from major complication rate of 96.0% at 12 months (95% confidence interval 94.2%–97.2%; P <0 .0001).

Complications

	Within 30 days (n=725)	**6 months % (n=725)**	**>6 months % (n=726)**	**Total % (n=726)**
Procedure-related death (because of metabolic acidosis in patient with end stage renal failure who had concomitant atrioventricular nodal ablation during TPS implantation)	0	1	0	1
Device-related deaths				0
Systemic-related deaths				77
Device- and procedure-related major complications* (all resulted in hospitalisation)	**2.89 (21/725) 24 events**	**0.8 (6/725) 6 events**	**0.2 (2/726) 2 events**	**3.99% (29/726) 32 events**
Cardiac perforations or effusion	10	1	0	1.6 (11/725)
Vascular complications (atrioventricular fistula 4 or pseudoaneurysm 1)	5	0	0	0.7 (5/726)
Venous thromboembolism (DVT, pulmonary embolism)	2	0	0	0.3 (2/726)
Elevated pacing threshold	2	0	0	0.2 (2/726)
Other events	5	5	2	1.4 (12/726)
Acute myocardial infarction	1	0	0	0.1 (1/726)
Cardiac failure	0	4	2	0.8 (6/726)
Metabolic acidosis	1	0	0	0.1 (1/726)
Pacemaker syndrome	1	1	0	0.2 (2/726)
Syncope or presyncope	2	0	0	0.2 (2/726)
Device dislodgements	0	0	0	0
Device- or procedure-related infections				0
Systemic infections				26

Revisions				**5**
Device was turned off without retrieval and TV pacemaker implanted in patients with loss of device function (because of pacemaker syndrome and elevated pacing threshold)		2		2
Device retrievals (in 1 with loss of capture, the device was retrieved and a new TPS implanted 16 days post-implant; 1 was unsuccessful because of inability to extract device at 259 days post-implant, 1 was aborted because of fluoroscopy failure 229 days post-implant)		3		3

* Major complications were defined as events resulting in death, permanent loss of device function as a result of mechanical or electrical dysfunction, hospitalisation, prolongation of hospitalisation by at least 48 hours, or system revision.

Major complications at 12 months between study and historical control patients

	Study group % (n=726)	**Historical control group % (n=2667)**	**Relative risk reduction (95% CI)**
Major complications	4.0 (2.8 to 5.8%)	7.6 (6.6 to 8.7%)	48% (23 to 65%) hazard ratio 0.52; 95% CI 0.35–0.77; p <0.001
Death	0.1 (0 to 1.0%)	0%	NE
Hospitalisations	2.3 (1.4 to 3.7%)	4.1 (3.4 to 5.0%)	47 (11 to 69%)
Prolonged hospitalisations	2.2 (1.4 to 3.6%)	2.4 (1.9 to 3.1%)	9 (-57 to 47%)
System revisions	0.7 (0.3 to 1.7%)	3.8 (3.1 to 4.6%)	82 (55 to 93%)
Loss of device function	0.3 (0.1 to 1.1%)	0	NE

The rates of fixation-related events (device or lead dislodgements) were statistically significantly higher in the historical control cohort than in the study cohort. The rates of access-site events, pacing issues, and cardiac injury events did not differ statistically significantly between the cohorts.

Across subgroups of age, sex, and comorbidities, TPS was associated with a reduced risk of major complications compared with TV systems.

Abbreviations used: CI, confidence interval; DVT, deep vein thrombosis; NE, not estimable; TV, transvenous; TPS, transcatheter pacing system.

Study 5 Piccini JP (2017)

Details

Study type	**Retrospective matched case control study (FDA IDE Micra TPS trial NCT02004873 versus Capture study)**
Country	TPS study -Worldwide (56 centres in 19 countries: US, Europe, Asia, Australia and Africa)
Recruitment period	TPS study 2013-15
Study population and number	**711** patients with transcatheter pacing system (TPS) with threshold data (at 0.24ms) at implant [83 with high pacing threshold >1.0V at 0.24 ms and 628 with low pacing threshold] **versus** **538** patients with transvenous pacemakers at 0.4ms (Capture study) [50 with high pacing threshold >1.0V at 0.40 ms and 488 with low pacing threshold]
Age and sex	Patients with elevated pacing threshold: TPS mean age 76 years; Capture cohort 72 years TPS 63% male; Capture cohort 50% male
Patient selection criteria	Patients who met class I or II guideline-based indications for de novo right ventricular pacing (i.e., for bradycardia because of atrial tachyarrhythmia (64%), sinus node dysfunction (17.5%), atrioventricular node dysfunction (14.8%), or other causes (3.7%)) were considered to be suitable candidates for single-chamber ventricular demand (VVI) pacing and were not prevented from participating as a result of coexisting conditions were enrolled in MICRA IDE study. Capture study patients who had their right ventricular lead and pulse generator implanted on the same day and had a ventricular pacing threshold measured at 0.40ms at implant were included as the comparator group (n=538).
Technique	The Micra transcatheter pacemaker, a single-chamber ventricular pacemaker was implanted by 94 physicians. Implant technique is described in procedure description. Follow-up assessments were done at 1, 3 and 6 months and thereafter biannually for at least 12 months. Capture study: EnPulse dual-chamber devices implanted, both atrial and ventricular pacing thresholds analysed. Follow-up capture thresholds were taken from capture management testing performed during clinic visits. Pacing electrodes were implanted mainly in the apical location in both studies.
Follow-up	**6 months**
Conflict of interest/source of funding	Dr Piccini received consulting fees or grants from Medtronic and other organisations, 2 authors are employees of Medtronic and 2 authors served as consultants to Medtronic.

Analysis

Follow-up issues: 87% (72/83) of TPS high pacing group were included in the analysis. 1 patient died at 3 months, 8 were awaiting their 6-month visit, and 2 missed their 6-month visit at the time of analysis. 90% (45/50) of Capture cohort high pacing group who had 6 months data were included in the analysis.

Study design issues: this is a retrospective matched case control study comparing pacing threshold progression relative to transvenous pacemakers and may be subject to confounding. The pulse duration in the transvenous Capture cohort study was longer and the pacing threshold in the TPS study was lower. In both cohorts, high pacing thresholds were defined as >1.0V and very high as >1.5V. Change in pacing threshold (0-6 months) with high (1.0 to<1.5V) or very high (>1.5v) thresholds were compared using the Wilcoxon signed-rank test.

Study population issues: all patients implanted successfully with TPS and pacing threshold data measured at a pulse duration of 0.24ms at implant (n=711) were included. There were no statistically significant differences in patient characteristics between those with and without an implant threshold of >1.0V. Prevalence of atrial fibrillation was much higher in the TPS cohort (73% versus 30%; p<0.001).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **83 TPS study cohort versus 50 Capture study patients with TV pacemakers**

Changes in pacing threshold after implantation

Study	HIGH PCT category	Follow-up visit	No of patients	Mean±SD	% decrease	P value vs implant	P value comparison
TPS cohort	>1 to 1.5 V	Implant	45	1.28±o.13			
		Discharge	38	1.02±0.42	68.4	<0.001	
		1 month	42	0.81±0.49	85.7	<0.001	0.786
		6 months	45	0.78±0.42	86.7	<0.001	0.418
	>1.5V	Implant	27	2.22±0.66			
		Discharge	23	1.93±1.26	60.9	0.107	
		1 month	22	1.64±1.30	81.8	0.008	0.004
		6 months	27	1.38±1.03	85.2	<0.001	0.032
Capture cohort	>1 to 1.5V	Implant	26	1.31±0.16			
		1 month	26	0.85±0.27	88.5	<0.001	
		6 month	26	0.85±0.29	80.8	<0.001	
	>1.5V	Implant	19	2.23±0.38			
		1 month	19	0.84±0.58	89.5	<0.001	
		6 months	19	0.84±0.40	100	<0.001	

Thresholds were measured at a pulse duration of 0.4ms for Capture patients and 0.24ms for TPS patients.

Among TPS cohort when the PCT was >2V, only 18% had a threshold of <1V at 6 months and 45.5% had a threshold of >2V.

Predictors of elevated thresholds

Multivariate logistic regression identified the number of device deployments as the factor associated with elevated implant thresholds (odds ratio 1.38; 95% CI 1.19 to 1.61, p<0.001 and apical location (OR 1.76; 95% CI 0.99 to 3.12; p=0.53).

Abbreviations used: CI, confidence interval; PCT, pacing capture threshold; SD, standard deviation; TPS, transcatheter pacing system; TV, transvenous.

Study 6 Roberts PR (2017)

Details

Study type	**Prospective case series (TPS ongoing post-approval registry)**
Country	Worldwide (96 centres in 20 countries: US, Europe, Asia, Australia and Africa)
Recruitment period	2015-17
Study population and number	n=**795** patients implanted with a transcatheter pacing system (TPS)
Age and sex	Mean 75.1 years; 62% (426/725) male
Patient selection criteria	Indications for implantation were bradyarrhythmia associated with permanent or persistent atrial tachyarrhythmia (57.7%), atrioventricular block (14.7%), syncope (14.1%), sinus node dysfunction (8.0%), other indications without permanent or persistent atrial tachyarrhythmia (3.4%) and reasons not specified (2.1%).
Technique	The Micra transcatheter pacemaker, a single chamber ventricular pacemaker was implanted by 149 physicians. Implant technique is described in procedure description. Patients were followed in accordance with the standard care practices of their provider. Follow-up assessments were done at 1 month and thereafter planned annually for at least 9 years. 86.6% physicians did not have previous experience.
Follow-up	**1.8 ± 2.9 months (range, 0–14.9 months)**
Conflict of interest/source of funding	Study funded by Medtronic; sponsor assisted in data analyses and publication. Most authors received consulting fees or grants from Medtronic.

Analysis

Follow-up issues: limited follow-up, including patients who had not yet been followed for 30 days. 54 patients had follow-up electrical data.

Study design issues: interim analysis of a prospective registry, Safety events were reviewed by an independent clinical events committee. System or procedure-related major complications through 30 days post implant, electric performance at implant or discharge were assessed. Safety events were defined using the same criteria as in the TPS IDE study. Early safety events between the investigational device exemption (IDE) (n=725) and the registry cohorts (n=795) were compared.

Study population issues: 104 patients (13.1%) had a previously implanted cardiac electronic implantable device. Types of previously implanted devices were transvenous pacemaker systems (73 patients), transvenous implantable cardioverter-defibrillators (13), epicardial systems (11), TPSs (1), and implantable cardiac monitors (6). In addition, 166 patients (20.9%) had >1 condition that precluded the use of a transvenous pacing system, including compromised venous access (72 patients), history of or risk of infection (70), need to preserve veins for haemodialysis (38), thrombosis (24), cancer (23), valvular issues/ prosthetic valve (8), and other (13). Compared with IDE study, the mean left ventricular ejection fraction was statistically significantly lower among patients in the Post-Approval Registry, and statistically significantly more patients in the registry had no venous access for a transvenous pacemaker or had a previously implanted cardiac device, as the latter was an exclusion criterion in the IDE study.

Compared with patients from the IDE study, statistically significantly fewer patients in the Post-Approval Registry had congestive heart failure, coronary artery disease, hypertension, chronic obstructive pulmonary disease, or atrial fibrillation.

Other issues: study used a self-defined safety end point.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **795**

Implantation outcomes

Implant success rate	99.6% (792/795)
More than 1 attempt during the procedure	77.3%

Electric performance

	At implantation (n=701)	**3 months (n=36)**	**6 months (n=25)**
Mean pacing threshold (at a 0.24-ms pulse width)	mean 0.6 ± 0.5 V	0.5 ± 0.3 V	0.6± 0.3 V
Mean R-wave amplitude	11.4 ± 5.3 mV	NR	NR
Mean pacing impedance	721±181 ohms	634±143 ohms	572±115 ohms

Based on 54 participants who had a minimum of 180 days of pacing data, the projected median battery longevity is 14.9 years

Safety

Complications at 30 days

	Total % (n=795)
Device-related major complications* (all resulted in hospitalisation)	**1.5% (12/795) 13 events**
Cardiac perforations or effusion (needed pericardiocentesis on the day of implantation and resolved)	0.1 (1/795)
Vascular complications (arteriovenous fistula 1, hematoma 2, incision site haemorrhage 1, persistent lymphatic fistula 1, vascular pseudoaneurysm 1)	0.8 (6/795)
Venous thromboembolism (DVT)	0.1 (1/795)
Elevated pacing threshold	0.1 (1/795)
Device dislodgement (on day 2 noted tines not embedded, successfully repositioned at 50 days post-implant, with normal pacing thresholds)	0.1 (1/795)
Other events	0.3 (3/795)
Pulmonary oedema	0.1 (1/795)
Chest pain	0.1 (1/795)
Sepsis (within 48 hours, successfully treated using intravenous antibiotics)	0.1 (1/795)
Deaths (1 procedure-related: patient developed pulmonary oedema, had cardiac arrest and could not be resuscitated.)	2.76 (22/795)
Non serious	
Cardiac perfusion/perforations (2 needed no intervention, 2 needed drainage or pericardial puncture or both)	0.4(4/795)

* defined as events resulting in death, permanent loss of device function as a result of mechanical or electrical dysfunction, hospitalisation, prolongation of hospitalisation by at least 48 hours, or system revision.

Major complications between study and IDE study patients (30 day rate)

	Study group % (n=795)	**IDE study group % (n=726)**	**Odds ratio (95%CI)**
Major complications	1.5% (12/795) 13 events	2.89% (21/726) 24 events	0.58 (0.27 to 1.25) P = 0.0691),
Death	0.1% (1/795)	0.1 (1/726)	0.91 (0.06 to 14.66)
Hospitalisations	0.5 (4/795)	1.1 (8/726)	0.45 (0.14 to 1.51)
Prolonged hospitalisations	1.01 (8/795)	1.9 (14/726)	0.52 (0.22 to 1.24)
System revisions	0.2 (2/795)	0.4 (3/726)	0.61 (0.10 to 3.65)
Loss of device function	0	0.28 (2/726)	NE

Abbreviations used: CI, confidence interval; DVT, deep vein thrombosis; IDE, investigational device exemption; NE, not estimable.

Study 7 Grubman E (2017)

Details

Study type	**Retrospective matched case control study**
Country	Worldwide
Recruitment period	Not reported
Study population and number	n**=989 patients with transcatheter pacing system (TPS) implantation** versus **2,667 patients with transvenous pacemakers**
Age and sex	Not reported
Patient selection criteria	Patients were included from the pre-market Micra Transcatheter Pacing Study NCT02004873 (n=720) and the Micra Pacing System Continued access study NCT02488681 (n=269. conducted in the same centres) sponsored by the company. Enrolled patients met class I or II guideline recommendations for ventricular pacing and there were no comorbidity restrictions. Control group: an individual patient level data set of 2,667 de novo patients with pacemaker from 6 recent Medtronic trials of dual-chamber pacing with transvenous leads was included.
Technique	The Micra single-chamber TPS implanted in study patients.
Follow-up	**Mean 12.6 ± 7.6 months** (16.4 ± 4.9 months in the initial trial and 2.4 ± 2.4 months in the continued access study).
Conflict of interest/source of funding	Study was supported my Medtronic. Authors received either consulting fees or research grants and 4 of them are employees of Medtronic.

Analysis

Follow-up issues: limited follow-up period.

Study design issues: a large cohort of patients with TPS pacemakers were included in this retrospective analysis of system revisions. TPS system revision rates were compared with the revision rate of transvenous pacemakers using a predefined historical control data set. Revisions included TPS retrieval or explant, repositioning, replacement, or electrical deactivation (with or without prior attempt at retrieval), generally followed by transvenous implantation for any reason. Kaplan Meier revision rates were calculated for varying follow-up periods and were compared between the TPS and historical control groups using a Fine-Gray risk model.

Study population issues: system revision events related to the right atrial lead were excluded from the historical control group.

Key efficacy and safety findings

Safety

Number of patients analysed: **10 (11 system revisions) TPS system revision**

Of the 10 patients needing TPS system revision, 4 were women and the mean age was 71.1 ± 14.6 years (range 43–92 years)

Reason for revision	n	Outcome*
Early revisions (5-104 days post implant		
Elevated pacing capture threshold (because of device dislocation in 1)	3	Devices removed percutaneously and new TPS implanted in 2 (at 5 and 16 days post-implant) , device turned off and transvenous pacing system implanted in 2 (1 at 9 days after new TPS was implanted and 1 at 32 days post-implant);
Pacemaker syndrome	2	Device programmed to VVI 40 beats/min and transvenous BiV pacing system implanted in 1 (at 44 days); percutaneous retrieval attempt was unsuccessful because of inability to dislodge device so device was turned off and transvenous pacing system implanted (at 229 days).
Need for BiV therapy	2	Device was turned off and transvenous BiV system implanted at 104 days in 1.
Late revisions (229 -430 days post implant)		
Need for BiV therapy (1 with cardiac failure)		Percutaneous device removal was abandoned after fluoroscopy failure and turned off, a transvenous BiV system implanted in another patient at 259 days post-implant.
Cardiac failure	1	Device turned off and BiV system implanted (at 296 days post-implant).
Battery depletion because of elevated pacing threshold	1	Device removed percutaneously and transvenous system implanted at 406 days post-implant
Prosthetic valve endocarditis	1	Device removed surgically during aortic valve surgery and patient died at 430 days post-implant (because of infection and surgical removal of the valve).

*Device was disabled and left in situ in 7 patients, 3 were retrieved percutaneously (range 9 to 406 days post-implant) and 1 was surgically removed.

There were no complications associated with revisions, or no reported interactions between devices when a system was implanted in the presence of an abandoned TPS.

Comparison with historical control

In the historical control population with transvenous pacemakers, there were 123 revisions in 117 patients through 24 months of follow-up (actuarial rate 5.3% [95% CI 4.4%–6.4%]), with 107 (87.0%) occurring within 12 months.

The risk of system revision through 24 months post-implant was 1.4% for patients with the transcatheter pacing system (11 revisions in 10 patients), 75% lower relative to control patients with transvenous pacemakers (hazard ratio 0.25; 95% CI 0.13–0.47; P <0.001)

After propensity score matching to adjust for differences in patient characteristics, a similar reduction in system revisions was seen with TPS (hazard ratio 0.27; 95% CI 0.14–0.54; p<.001).

Abbreviations used: CI, confidence interval; BiV, biventricular; TPS, transcatheter pacing system.

Study 8 Sperzel J (2018)

Details

Study type	**Prospective case series (NCT02051972)**
Country	Europe (32 sites: Germany, UK, the Netherlands, Italy, Spain, France, Czech Republic)
Recruitment period	2013-17
Study population and number	n=**470 (300 primary cohort)** patients with an indication for single-chamber pacemaker implantation. **Indications:** included chronic and/or permanent atrial fibrillation with 2/3° atrioventricular (AV) or bifascicular bundle branch (BBB) block (46.4%), sinus bradycardia with infrequent pauses or unexplained syncope with electrophysiology findings (29.1%) and normal sinus rhythm with 2/3° AV or BBB block and either had a low level of physical activity or a short expected lifespan (24.5%).
Age and sex	75.8 ± 13.1 years, 62.8% male
Patient selection criteria	Adult patients (18 and above) with clinical indications for single-chamber pacing, a life expectancy of at least 1 year, and suitable based on overall health and well-being were included in the study. Patients with a mechanical tricuspid valve prosthesis, pre-existing pulmonary arterial hypertension, an implanted vena cava filter, evidence of thrombosis in 1 of the veins to be used for access, cardiovascular or peripheral vascular surgery/intervention within 30 days of enrolment, or the presence of leads or devices from previous implants or system revisions were excluded.
Technique	Leadless pacemaker (Nanostim)
Follow-up	**mean 19.5± 11.5 months**
Conflict of interest/source of funding	The study was funded by St Jude Medical. Authors received consulting, speakers' fee and research grants from industry.

Analysis

Follow-up issues: patients were followed up at pre-discharge and at 90 days, 180 days, and every 6 months for the assessment of adverse events.

Study design issues: multi-centre post-market observational study. The study was paused in 2014 because of 2 cardiac perforations that lead to death. The primary cohort (n=300, used for approval requirements in Europe) consisted of patients who were enrolled after the study pause and who completed 6 months follow-up. The adverse events were adjudicated by an independent Clinical Events Committee. The primary end point was freedom from serious adverse device effects (defined as device or procedure related adverse events that resulted in death, life-threatening illness or injury, permanent impairment of a body structure or function, inpatient or prolonged hospitalisation or intervention to prevent conditions previously listed) at 180 days in the primary cohort. Rate of freedom from SADEs was calculated using the Kaplan–Meier method. Different protocol versions were used before and after the study pause. Results of the total cohort of 470 subjects enrolled as of 2017 were also analysed.

Study population issues: 9.8% patients had myocardial infarction and 8.9% patients had a medical history of congestive heart failure.

Other issues: study eligibility criteria were revised during the pause phase to be more consistent with the Leadless II IDE trial, so some patients with pre-existing conditions were excluded. The sponsor issued an advisory and stopped all worldwide implants after reports of battery failures, leading to loss of pacing output and communication with the LP, in 2016. There is some overlap of patients with study 1.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **470**

Implantation outcomes

Implant success	96.6 % (451/467)
LP placement	
RV apical septum	56.8%
RV apex	35.9%
Repositioning (1 or no attempts)	96.5%
Repositioning (2 or more attempts)	3.5 (16/451)
Failure/unsuccessful implants	3.4% (16/467)

Device measurements in successful patients [mean SD (n)]

	Pacing threshold (V) at 0.4ms	**R-wave amplitude (mV)**	**Impedance (ohms)**
Implantation	0.80±0.59 (446)	7.2±2.8 (400)	737.9±303.2 (450)
Pre-discharge	0.56±0.50 (441)	8.8 ± 2.9 (433)	664.8 ± 218.6 (446)
90 days	0.56 ± 0.42 (418)	9.5 ± 2.8 (407)	532.9 ± 158.7 (427)
6 months	0.54 ± 0.47 (390)	9.6 ± 2.8 (375)	516.5 ± 148.2 (395)

Freedom from SADEs at 6 months follow-up

The rate of freedom from SADEs, in 300 patients (analysed post-pause in the primary cohort) was 94.6% (95% CI 91.0–97.2%) and demonstrated non-inferiority to a performance goal of 86% (p<0.0001).

After stratifying the results in relation to the study pause, there was a statistically significant difference in the final LP location (septum compared with apex; p<0.0001) and the number of repositioning attempts (<2 compared with 2 or more; p=0.05) and a decreasing trend in the rates of cardiac perforation and device dislodgement.

Safety

Event	**Pre-pause % (n=131)**	**Post-pause % (n=339)**	**Total % (n=470)**
Perforation details	**4.6 (6)**	**1.5 (5)**	**2.3 (11)**
Cardiac perforation	0.8 (1)	0.3 (1)	2 (0.4)
Cardiac tamponade	3.1 (4)	0.9 (3)	1.5 (7)
Pericardial effusion	0.8 (1)	0.3 (1)	0.4 (2)
Device dislodgement	**0.8 (1)**	**0.3 (1)**	**0.4 (1)**
Vascular complications	**0**	**1.5 (5)**	**1.1 (5)**
AV fistula	0	0.9 (3)	0.6 (3)
Access site bleeding	0	0.3 (1)	0.2 (1)
Pain in the groin	0	0.3 (1)	0.2 (1)
Cardiac arrhythmias/AV block	**0.8 (1)**	**0.9 (3)**	**0.9 (3)**
Failure to /loss of capture	**0**	**0.6 (2)**	**0.4 (2)**
Battery failures*	**14.5 (19)**	**0**	**4.0 (19)**
Inability to interrogate or program due to programmer or device malfunction	12.2 (16)	0	3.4 (16)
Loss of device function due to battery failure or component malfunction	2.3 (3)	0	0.6 (3)
Inadequate device fixation or inadvertent release leading to device migration during implantation	1.5 (2)	0.6 (2)	0.9 (4)
Other	**1.5 (2)**	**0.9 (3)**	**1.1 (5)**
Hematoma formation, including retroperitoneal hematoma/haemorrhage	0.8 (1)	0	0.2 (1)
Pacemaker syndrome	0.8 (1)	0	0.2 (1)
Progression of congestive heart failure	0	0.3 (1)	0.2 (1)
Syncope	0	0.3 (1)	0.2 (1)
Thrombosis	0	0.3 (1)	0.2 (1)
Death	0	0.3 (1)	0.2 (1)
Total patients (events)	**22.9 (30/131) 31 events**	**5.9 (20/339) 22 events**	**10.6 (50/470) 53 events**

*5 devices were retrieved and implanted with either a conventional pacemaker or another leadless pacemaker, 14 were abandoned and implanted with 11 conventional pacemakers and 3 leadless pacemakers.

Some of these events occurred in the primary cohort.

Abbreviations used: AV, atrioventricular; CI, confidence interval; LP, leadless cardiac pacemaker; SADEs, serious adverse device effects; SD, standard deviation.

Study 9 Garweg C (2017)

Details

Study type	**Prospective registry**
Country	Belgium
Recruitment period	2015-17
Study population and number	n=**66** patients with a de novo class I or II indication for ventricular pacing**.**
Age and sex	Mean 79.1±9.7 years; 70% (46/66) male
Patient selection criteria	Indications included third degree atrioventricular block (30.3% [20/66]), second degree atrioventricular block (3% [2/66]), sinus node dysfunction (21.2%[14/66]), or permanent atrial fibrillation with bradycardia (45.5% [30/66]).
Technique	The MICRA leadless transcatheter pacemaker system (TPS) was implanted under general or local anaesthesia. Implanted at the apex in 22 patients, mid-ventricular septum in 34 patients, and at the basis of outflow tract in 9 patients.
Follow-up	**Mean 10.4±6.1 months (range 1 to 23 months)**
Conflict of interest/source of funding	The primary author is a proctor for the Micra TPS and all authors have received speaker and consultancy fees from different manufacturers.

Analysis

Follow-up issues: limited follow-up period.

Study design issues: small observational study in a single centre.

Study population issues: 22 patients were considered as challenging cases because of acquired or congenital cardiovascular abnormalities (n=15), pervious tricuspid valve surgery (n=4), cardiac transplantation (n=2), after pacemaker extraction (n=7), and cardiac amyloidosis (n=1). 13 had no option for implantation of a conventional pacing system.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **30**

Implantation outcomes

Implant success rate	98.5% (65/66)
Abandoned (after unsatisfactory repositioning)	2.5 % (1/66)
Mean deployments	2.00±1.46

Sensing and pacing parameters

Electric measurements	At implantation (Mean ±SD)	At last follow-up (mean 10.4±6.1 months) (Mean ±SD)
Pacing threshold (at 0.24 ms)	0.59±0.30 V	0.57±0.32 V
Ventricular sensing (mV)	9.0±4.7 mV	10.6±4.3 mV
Ventricular pacing impedance (ohms)	753±249 ohms	580±103 ohms

Safety

Complications

Major complication	**% (n=66)**
Pre-syncope related to intermittent loss of capture due to micro-dislodgement.(device was repositioned successfully)	1
Minor complications	**65 (4/66)**
Episode of asystole (treated by cardiac massage and atropine injection)	1
Symptomatic arteriovenous fistula at puncture site (healing spontaneously within 4 weeks)	1
Partial dislocation of the device after incomplete removal of the tether (delivery catheter removed and tether was recovered and the same device implanted at the right ventricular apex)	1
Deep venous thrombosis within 2 weeks	1
Death (unrelated to procedure at 6 months)	1

Abbreviations used: SD, standard deviation.

Study 10 Yarlagadda B (2018)

Details

Study type	**Retrospective comparative case series**
Country	US, Canada, Australia
Recruitment period	2014-16
Study population and number	n=**127** patients with atrial fibrillation (AF) undergoing atrioventricular node (AVN) ablation. **60 leadless cardiac pacemaker (LCP) compared with 67 conventional transvenous pacemaker (CTP)**
Age and sex	Mean 74±9 years; LCP versus CTP (48% versus 24% male)
Patient selection criteria	Patients who had LCP implantation as part of LEADLESS II trial (NCT02030418) in 56 centres were compared with patients who underwent AVN ablation and had a single chamber conventional transvenous pacemaker at the same period. Indications for AVN ablation included symptomatic AF refractory to medications and catheter ablation. Patients were excluded if less than 18 years, with pre-existing CTP, implantable or sub-cutaneous cardioverter defibrillator, cardiac resynchronisation therapy device, another implantable LCP, implantable vena cava filter, pacemaker syndrome, mechanical tricuspid valve prosthesis, pulmonary arterial hypertension, thrombosis, and those needing dual chamber pacing and right sided CTP
Technique	Leadless pacemaker implantation (Nanostim) compared with conventional transvenous pacemaker implantation. Standard techniques used for AVN ablation.
Follow-up	**Median 12 months (range 12 to 18 months)**
Conflict of interest/source of funding	Authors are investigators of the Leadless II study and have consulting agreement with the manufacturer.

Analysis

Follow-up issues: limited follow-up period.

Study design issues: small multicentre observational study in a single centre.

Study population issues: there is no significant difference in age, comorbid conditions or medications between the 2 groups.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **60 LCP compared with 67 CTP**

Implantation outcomes

Implant success rate	100%

Efficacy outcomes at 12 months follow-up

	LCP (n=60)	CTP (n=67)	P value
Acceptable sensing (R wave > 5.0 mV) and pacing thresholds (<2.0 V at 0.4 ms)	95% (57/60)	97% (65/67)	0.66
Loss of pacing	5% (3/60)	3% (2/67)	

Sensing and pacing parameters at 12 months follow-up

	LCP (n=60)	CTP (N=67)
Pacing (<2.0 V at 0.4ms)	0.94±0.48	0.63±0.45
Sensing (R wave >5.0mV)	8.9±2.48	9.8±3.28
Impedance (<1200 ohms	540±106.9	470±94.4

Safety

Complications

Adverse events	LCP (n=60)	CTP (N=67)	P value
Device malfunction requiring emergency intervention	**1.6% (1/60)**	**2.9 (2/67)**	**1.00**
Loss of telemetry and pacing	1	0	0.47
Lead/device dislodgement	0	2	0.49
Device malfunction requiring non-emergency intervention (Increasing right ventricular pacing threshold)	2	0	0.22
Other events			
Pocket haematoma	0	1	1.00
Vascular related complications	**5% (3/60)**	**2.9 (2/67)**	**0.66**
Pseudo aneurysm	2	1	0.60
Groin haematoma	1	1	1.00
Pericardial effusion not needing intervention	1	0	0.47
Cardiac death	1	1	

Abbreviations used: CTP, conventional transvenous pacemaker; LCP, leadless cardiac pacemaker.

Study 11 Tjong FVY (2018)

Details

Study type	**Propensity matched study**
Country	The Netherlands, US, Czech Republic
Recruitment period	2015-16
Study population and number	n=**440** patients with an indication for single-chamber pacemaker implantation. 220 leadless cardiac pacemaker (LCP) compared with 220 conventional transvenous pacemakers (CTP).
Age and sex	Median 78 years; 67% (20/30) male
Patient selection criteria	All patients who were implanted with LCP between 2012-16 were included in the analysis. Patients participated in 3 LCP trials (LEADLESS trial [NCT01700244], LEADLESS observational study [NCT02051972], LEADLESS II Pacemaker IDE study [NCT020030418] and The MICRA Transcatheter Pacing System [NCT02536118]). Patients who did not provide informed consent to use their data were excluded. Data for the CTP cohort (2003-2007) were obtained from the prospective FOLLOWPACE study in 23 centres in Netherlands [NCT00135174]. Only VVI-R patients were selected for the analysis.
Technique	Leadless cardiac pacemaker implantation compared with transvenous single-chamber pacemaker implantation. LCPs were implanted by 5 different physicians at 3 centres. 70% had Nanostim LCP and 30% had a MICRA Transcatheter Pacing System [TPS]. CTP were implanted in 23 hospitals in the Netherlands with implanters of variable levels of expertise.
Follow-up	**Median 599 days (range 802 to 1932 days)**
Conflict of interest/source of funding	Study was supported by a Czech Republic government scientific grant. Authors received consulting fees, research grants and speaker fee from the manufacturer.

Analysis

Follow-up issues: no patients were lost to follow-up; and 1 patient withdrew consent after 1 month.

Study design issues: propensity matched analysis; patients from 3 centres with LCPs (Nanostim and the MICRA Transcatheter Pacing System) were propensity matched to VVI-R patients from a prospective multicentre transvenous pacemaker registry. Data was collected retrospectively. 13 patients were excluded from the analysis.

Study population issues: indications for implantation were AF with slow ventricular rate or atrioventricular block (56%) and with various comorbidities. In the cohort, leadless cases (n=220) were similar to the CTP (n=220).

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 220 LCP compared with 220 CTP
Survival
The mortality rate in the matched cohort at 800-day follow-up was comparable in both groups: 17.9% in LCP group (95% CI 9.4% to 25.7%) compared with 16.4% (95% CI 11.4% to 21.2%) in the CTP group (p=0.56).</td><td>Complications at 800-day follow-up
<table>
<tr><th>Adverse event</th><th>LCP % (n=200)</th><th>CTP % (n=200)</th></tr>
<tr><td colspan="3">Device related adverse events</td></tr>
<tr><td>Lead complications</td><td>0</td><td>2.8 (7/220)</td></tr>
<tr><td>Lead dislocation</td><td>0</td><td>2.3 (5/220)</td></tr>
<tr><td>Lead fracture</td><td>0</td><td>0.5 (1/220)</td></tr>
<tr><td>Tricuspid valve damage by lead</td><td>0</td><td>0.5 (1/220)</td></tr>
<tr><td colspan="3">Other device related adverse events</td></tr>
<tr><td>Elevated pacing threshold</td><td>0.9 (2/220)</td><td>0</td></tr>
<tr><td>Pacing threshold issue</td><td>0</td><td>3.2 (3/330)</td></tr>
<tr><td>Pocket issue</td><td>0</td><td>0.5 (1/220)</td></tr>
<tr><td>Pocket revision</td><td>0</td><td>0.5 (1/220)</td></tr>
<tr><td>Pocket infection</td><td>0</td><td>0.5 (1/220)</td></tr>
<tr><td>Pocket erosion</td><td>0</td><td>0.5 (1/220)</td></tr>
<tr><td>Generator issue</td><td>0</td><td>0.5 (1/220)</td></tr>
<tr><td>Pacemaker revision due to advisory (to an LCP or CTP)</td><td>9.4 (12/220)</td><td>0</td></tr>
<tr><td colspan="3">Procedure related adverse events</td></tr>
<tr><td>Cardiac perforation (no tamponade)</td><td>0</td><td>0.9 (2/220)</td></tr>
<tr><td>Pericardial effusion</td><td>0.5 (1/220)</td><td>0.5 (1/220)</td></tr>
<tr><td>Pneumothorax</td><td>0</td><td>0.9 (2/220)</td></tr>
<tr><td>Haemothorax</td><td>0</td><td>0.5 (1/220)</td></tr>
<tr><td>Pseudo aneurysm</td><td>0</td><td>0.5 (1/220)</td></tr>
<tr><td>Groin hematoma</td><td>0</td><td>0.5 (1/220)</td></tr>
<tr><td>Access site bleeding</td><td>0</td><td>2.9 (3/220)</td></tr>
<tr><td>Ventricular arrhythmia during the procedure</td><td>0</td><td>0.5 (1/220)</td></tr>
<tr><td>Total adverse events</td><td>9.5 (21/220)</td><td>9.5 (21/220)</td></tr>
<tr><td>Device related adverse events excluding pacemaker advisory revisions</td><td>0.9 (2/220)</td><td>4.7 (10/220), p=0.02</td></tr>
<tr><td>Device related adverse events including pacemaker advisory revisions</td><td>6.3% (14/220)</td><td>4.7% (10/220)
p=0.063</td></tr>
</table></td></tr>
<tr><td colspan="2">Abbreviations used: CTP, conventional transvenous pacemaker; LCP, leadless cardiac pacemaker.</td></tr>
</table>

Validity and generalisability of the studies

- Leadless pacemakers are only suitable for patients with a single-chamber pacing indication and not suitable for dual-chamber pacing. There are 3 devices classified as leadless cardiac pacemakers: the Nanostim leadless pacemaker system, by St Jude Medical, Inc, the Micra transcatheter pacing system (TPS), by Medtronic Inc and the Boston Scientific prototype leadless pacemaker. They are different in their design, delivery mechanism, fixation method, battery and pacing mechanism. Therefore, it is difficult to compare these systems directly.
- There are no randomised controlled trails comparing leadless pacemakers with conventional pacing systems.
- There are only case series with short term follow-up. No long term performance and safety data are yet available.

Existing assessments of this procedure

An MHRA expert advisory group guidance document on leadless cardiac pacemakers aimed at manufacturers and notified bodies has issued the following initial guidelines for the adoption of leadless pacing[12].

2 Initial recommendations for adoption of leadless cardiac pacing therapy

2.1. Requirements for selection of patients and centres

2.1.1. Leadless pacing should be considered in patients with a clear indication for bradycardia pacing or cardiac resynchronization.

2.1.2. The following should be considered minimum resources for leadless pacemaker implantation:

a. cardiac catheter laboratory, with high quality fixed image intensifier with digital acquisition for review and ability to image in all conventional angles

b. trained clinical personnel with full resuscitation facilities including defibrillator/external pacing system

c. trained clinical personnel with immediate access to echocardiography and equipment for pericardiocentesis

2.1.3. Given the very limited intermediate and long-term evidence base for leadless pacing therapy, especially compared to conventional pacing, each patient should have a clear and explicit reason documented for this choice of device over a conventional pacemaker.

2.1.4. Careful attention should be paid to contraindications for leadless pacing, such as patient habitus and venous abnormalities likely to result in difficulties/complications from the large sheaths required for device delivery.

2.1.5. Patient consent should, in addition to referencing intended benefits of the treatment, explicitly state that early experience with leadless pacing technology has shown a small but significant incidence of serious acute adverse events, including tamponade requiring emergency thoracotomy, device displacement, vascular access issues, etc.

2.1.6. 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, leadless pacemakers should be implanted in centres with on-site cardiac surgery until there are robust data to confirm that the adverse event rate requiring surgery is as low as that associated with conventional pacing (0.1-0.5%).

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

2.2.1. In order to concentrate experience at this early stage, each centre should have a maximum of two operators and both should be encouraged to participate in all procedures. Each should be appropriately trained and proctored, in accordance with the manufacturers' protocols.

2.2.2. Operators should be cardiac specialists (consultant cardiologists or cardiac surgeons) with extensive experience of the use of intracardiac catheters and/or leads and the implantation of complex cardiac implantable electronic devices. They should have experience of vascular access using large bore catheters (12F and above) and of manipulation of deflectable catheters in the heart.

2.3. Implant surveillance

2.3.1. As well as being recorded in the British Heart Rhythm Society (BHRS) national audit for CRM devices (held by NICOR), all leadless pacemaker implants should be entered into a comprehensive registry or post-market clinical follow-up (PMCF[1]) study, held and funded by the relevant manufacturers and maintained to the standards of good clinical practice. Following CE-marking of the device,

implants should not take place outside the registry or PMCF study until at least half the target number of patients has been enrolled and a comprehensive clinical analysis of the safety and performance of the device including one-year patient follow-up has demonstrated a favourable outcome (see section 3 for further details on registry/PMCF study design). The analysis should be done by the manufacturer and reviewed by the notified body with independent clinical input as appropriate to these organisations. It should be made available to MHRA on request.

2.3.2. The PMCF study or registry should include, but not be limited to, collection of information on:
a. relevant patient demographics
b. indication(s) for pacemaker/CRT therapy
c. rationale for the choice of leadless approach
d. acute implant outcomes
e. implant location within heart (apex, mid-septum etc.)
f. in-hospital, 30-day and 1-year device performance, adverse events and all-cause mortality
g. MR scans (static field strength and body site scanned) and any adverse events arising affecting the device or patient.
h. interaction with/from other implanted or external devices
i. device explant or deactivation
j. long-term device/battery performance and late complications

2.3.3. Information held in the PMCF study or registry should be reported publically at pre-specified intervals (either of time or recruitment numbers) and made available at all times on request to MHRA.

2.3.4. The manufacturer's broader post-market surveillance strategy should ensure that information on the safety and performance of the leadless device is collected for the lifetime of the implant. This will enable an assessment to be made of the risks associated with either explanting the device or leaving it in situ, when it reaches end of life. It is important that information is captured on any mechanical or electrical interactions between an abandoned leadless device and the replacement pacing system.

2.3.5. Adverse incidents should be assessed for reportability to regulatory authorities according to the requirements set out in the applicable MEDDEV reporting guidelines [1].

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Laser sheath removal of pacing leads. NICE interventional procedure guidance 63 (2004). Available from https://www.nice.org.uk/Guidance/IPG63

Technology appraisals

- Dual chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome without atrioventricular block (part review of technology appraisal guidance 88). NICE technology appraisal guidance TA324 (2014). Available from https://www.nice.org.uk/guidance/ta324
- Dual-chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block. NICE technology appraisal guidance 88 (2005) available from https://www.nice.org.uk/Guidance/TA88

NICE guidelines

- Atrial fibrillation: the management of atrial fibrillation. NICE guidelines CG180 (2014). Available from https://www.nice.org.uk/guidance/CG180
- Chronic Heart Failure in adults: management. NICE guidelines CG108 (2010). Available from https://www.nice.org.uk/Guidance/CG108

Quality standard

- Atrial fibrillation (2015) NICE Quality standard 93

Related NICE pathways

- Atrial fibrillation
- Heart rhythm conditions
- Chronic Heart Failure

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed

questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. 3 Specialist Advisor Questionnaires for leadless cardiac pacemaker implantation for bradyarrhythmias were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme sent 20 questionnaires to 1 NHS trust for distribution to patients who had the procedure (or their carers). NICE received 7 completed questionnaires.

Patient organisation submissions

Three submissions were received from patient organisations and were discussed by the committee.

Company engagement

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received 2 completed submissions. These was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- Micra transcatheter pacing system is the only leadless pacemaker that received FDA approval in 2016. It is smaller than Nanostim device, about the size of a large capsule and is MRI compatible.
- Nanostim® has a CE mark but is currently not marketed and recruitment into clinical trials has been paused because of battery depletion problems in 2.4% (34/1423) patients worldwide. The devices lost telemetry and pacing capabilities 29 to 37 months after implantation. A new battery is under development.
- Ongoing studies
  - NCT02051972 **The LEADLESS Observational Study (post market clinical follow-up study).** Title: ***Nanostim study for a Leadless cardiac***

pacemaker system; study design: cohort study; indication: for a VVI(R) pacemaker; estimated enrolment: 1000; primary outcome: complication free-rate; Location: Czech Republic, Germany, Spain, Netherlands; study start date: December 2013; primary completion date: June 2017, completion date: March 2022; Status: suspended in January 2015 because of several reports of serious adverse events (6 perforations that led to 2 patient deaths). Trial suspension has led to tightening of the inclusion criteria and the study has been restarted and is currently recruiting participants.

- The National Audit of Cardiac Rhythm Management (CRM) managed by National Institute for Cardiovascular Outcomes Research (NICOR) collects information about all leadless pacemakers and other implanted cardiac devices for management of cardiac rhythm disorders in the UK. IPAC may wish to consider whether to recommend data submission to this database.

References

1. Reddy VY, Knops RE, Sperzel J, et al (2014). Permanent leadless cardiac pacing: results of the LEADLESS trial Circulation 129 (14): 1466-71.

   Knops RE, Tjong FV, Neuzil P, et al. (2015) Chronic performance of a leadless cardiac pacemaker: 1-year follow-up of the LEADLESS trial Journal of the American College of Cardiology 65 (15): 1497-504.

   Tjong FVY, Knops RE et al 92018). midterm safety and performance of a leadless cardiac pacemaker: 3 year follow-up to the leadless trial (Nanostim safety and performance trial of a leadless cardiac pacemaker system). Circulation 137:633-35.

2. Reddy VY, Exner DV, Cantillon DJ, et al. (2015) Percutaneous Implantation of an Entirely Intracardiac Leadless Pacemaker New England Journal of Medicine 373 (12): 1125-35.

3. Lakkireddy D, Knops R, Atwater B, et al. (2017) A worldwide experience of the management of battery failures and chronic device retrieval of the Nanostim leadless pacemaker Heart Rhythm.

4. Reynolds D, Duray GZ, Omar R, et al. (2016) A Leadless Intracardiac Transcatheter Pacing System New England Journal of Medicine 374 (6): 533-41.

   Duray GZ, Ritter P, El-Chami M, et al. (2017) Long-term performance of a transcatheter pacing system: 12-Month results from the Micra Transcatheter Pacing Study Heart Rhythm 14 (5): 702-709.

5. Piccini JP, Stromberg K, Jackson KP, et al (2017). Long-term outcomes in leadless Micra transcatheter pacemakers with elevated thresholds at implantation: Results from the Micra Transcatheter Pacing System Global Clinical Trial Heart Rhythm 14 (5): 685-691.

6. Roberts PR, Clementy N, Al Samadi F, et al. (1375) A leadless pacemaker in the real-world setting: The Micra Transcatheter Pacing System Post-Approval Registry Heart Rhythm 14 (9): 1375-1379.

7. Grubman E, Ritter P, Ellis CR, et al (2017). To retrieve, or not to retrieve: System revisions with the micra transcatheter pacemaker. Heart Rhythm 14:1801-1806.

8. Sperzel J, Defaye P, Delnoy PP, et al. (2018) Primary safety results from the LEADLESS Observational Study Europace 19: 19

9. Garweg C, Ector J, Voros G et al (2017). Monocentric experience of leadless pacing with focus on challenging cases for conventional pacemaker Acta Cardiologica: 1-10.

10. Yarlagadda B, Turagam MK et.al (2018). Safety and feasibility of leadless pacemaker in patients undergoing atrioventricular node ablation for atrial fibrillation. Heart Rhythm 2018, Mar 1.

11. Tjong FVY, Neuzil P et.al (2018). Leadless pacemaker versus transvenous single chamber pacemaker therapy: a propensity matched analysis. Heart Rhythm, 2018, April 27.

12. Leadless cardiac pacemaker therapy: design of pre and post-market clinical studies. Initial recommendations from MHRA Expert Advisory Group (March 2017). Medicines & Healthcare products Regulatory Agency (MHRA).

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	24/04/18	Issue 4 of 12, April 2018
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	24/04/18	Issue 4 of 12, April 2018
HTA database (Cochrane Library)	24/04/18	Issue 4 of 12, April 2018
MEDLINE (Ovid)	24/04/18	1946 to Present with Daily Update
MEDLINE In-Process (Ovid) &	24/04/18	April 23, 2018
Medline ePub ahead (Ovid)	24/04/18	April 23, 2018
EMBASE (Ovid)	24/04/18	1980 to 2018 Week 17

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 "Endovascular Procedures"/
2 *Electrodes, Implanted/
3 *Defibrillators, Implantable/
4 (Transvenous* or trans-venous*).tw.
5 ((Percutaneous* or transcather* or trans-cather*) adj4 implant*).tw.
6 or/1-5
7 *Cardiac Pacing, Artificial/ or *Pacemaker, Artificial/
8 ((leadless or artific*) adj4 (pacemaker* or pacing*)).tw.
9 (Single* chamber adj4 (pacemaker* or pacing*)).tw.
10 LPMS.tw.
11 or/7-10
12 *arrhythmias, cardiac/ or *bradycardia/ or *heart block/ or *atrioventricular block/ or *bundle-branch block/ or *sick sinus syndrome/
13 (bradycardia* or bradyarrhythmia*).tw.
14 ((cardiac* or heart* or atrioventricular*) adj2 (arrhythmia* or block*)).tw.
15 bundle* branch* block*.tw.
16 bifascicular* bundle* branch*.tw.
17 ((sinus* or sinotrial*) adj2 (syndrome or dysfunction* or disease*)).tw.

18 (BBB or SSS or SND).tw. (16069)
19 ((slow* or reduc* or low*) adj2 (heart* or cardiac*) adj2 (rate* or beat* or rhythm*)).tw
20 or/12-19
21 6 and 11 and 20
22 NanoStim*.tw.
23 (Micra and (pacemaker or pacing)).tw.
24 Micra LP.tw.
25 (St Jude and (pacemaker or pacing)).tw.
26 (Boston scientific and (pacemaker or pacing)).tw.
27 New Cardiac Pacemaker.tw.
28 or/21-27
29 limit 28 to yr="2007 -Current"
30 Animals/ not Humans/
31 29 not 30
32 limit 31 to ed=20171101-20180430

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Afzal MR, Ackers J, Hummel JD, et al (2017). Safety of Implantation of a Leadless Pacemaker via Femoral Approach in the Presence of an Inferior Vena Cava Filter Pacing & Clinical Electrophysiology 40 (8): 975-976.	Case report A 61-year-old woman with symptomatic complete heart block was referred for permanent pacemaker. The presence of a left-sided arteriovenous fistula and right-sided mastectomy with lymph node dissection precluded the implantation of a transvenous pacemaker, and therefore, a leadless pacemaker was recommended. The patient also had an inferior vena cava (IVC) filter.	The passage of a 27-French introducer sheath housing the leadless pacemaker through IVC filter was carefully visualised under fluoroscopy and advanced to the right ventricle without any compromise to the filter. This case report shows the safety of passage of large sheaths via the IVC filter.	Larger studies included in table 2
Afzal MR, Daoud EG, Cunnane R, et al. (2018) Techniques for successful early retrieval of the Micra transcatheter pacing system: A worldwide experience Heart Rhythm 08:08.	Retrospective analysis Retrieval of the Micra transcatheter pacing system (TPS).	Data from the manufacturer consisted of 40 successful retrievals of the Micra TPS. Operators for 29 retrievals (73%) provided the consent and procedural details. Of the 29 retrievals, 11 patients underwent retrieval during the initial procedure (immediate retrieval); the other 18 patients underwent retrieval during a separate procedure (delayed retrieval). Median duration before delayed retrieval was 46 days (range 1-95 days). The most common reason for immediate retrieval was elevated pacing threshold after tether removal. The most	Worldwide experience with successful retrieval of the Micra TPS.

		common reasons for delayed retrieval included elevated pacing threshold at follow-up, endovascular infection, and need for transvenous device. Mean procedure duration was 63.11±56 minutes. All retrievals involved snaring via a Micra TPS delivery catheter or steerable sheath. No serious complications occurred during the reported retrievals.	
Bernard ML (2016). Pacing Without Wires: Leadless Cardiac Pacing Ochsner Journal 16 (3): 238-42.	Review We discuss the 2 leadless cardiac pacemakers (LCPs), the Nanostim Leadless Pacemaker and Micra Transcatheter Pacing System, and the 1 ultrasound-powered device, the WiCS-LV, that have been studied in humans.	Initial studies of both the Nanostim and Micra LCPs show favourable efficacy and safety results compared with transvenous pacemakers. Pending US Food and Drug Administration approval, these devices will transform our ability to provide pacing for patients with bradyarrhythmias	Review
Borgquist R, Ljungstrom E, Koul B, et al (2016).Leadless Medtronic Micra pacemaker almost completely endothelialized already after 4 months: first clinical experience from an explanted heart European Heart Journal 37 (31): 2503.	Case report 43-year-old man with congenital heart disease and previous DDD pacemaker, device infections, progressive heart failure, epicardial pacing system placement, eventually infected and insufficient heart rhythm had MICRA leadless pacemaker implantation and 4 months thereafter had orthotopic heart transplant.	In the explanted native heart, the leadless pacemaker was found to be embedded within the RV cardiac wall and nearly completely endothelialised. Two of the 4 pacemaker tines were embedded entirely within the cardiac wall and the remaining 2 were nearly covered by endothelial tissue.	Larger studies included in table 2.
Use of leadless pacemakers in Europe: results of the European Heart Rhythm Association survey. Boveda et.al. Europace 2018, Mar 1.	Online survey		Survey
El-Chami MF, Merchant FM and Leon AR (2017). Leadless	Review	In this review we summarise the results of the 2 investigational	Review

Pacemakers American Journal of Cardiology 119 (1): 145-148.		device exemption trials and compare the pros and cons of these devices to traditional transvenous pacemakers.	
Da Costa A, Axiotis A, Romeyer-Bouchard C, et al (2017). Transcatheter leadless cardiac pacing: The new alternative solution International Journal of Cardiology 227: 122-126.	Case series N=14 patients with limited venous access or conventional pacemaker (PM) contraindication: indications f were atrioventricular (AV) block in 10/14 patients (71%), bradyarrhythmia in 1 (7%), and uncontrolled atrial fibrillation (AFib) requiring AV-node ablation in 3 (21.5%). TPS implanted. Follow-up: 3 months	All procedures were successful (100%) and electrical parameters remained stable over time. No direct pacemaker-related adverse events were reported, including mechanical complications, except for 1 ventricular fibrillation 1 day post-implantation under very specific conditions. This series demonstrated very stable performance and reassuring safety results during mid-term follow-up in a very fragile population requiring a PM. The Micra LPM constitutes an excellent alternative to the epicardial surgical approach in this very fragile population.	Larger studies included in table 2.
Dowdall M (2014).Milestone in pacemaker history: first postapproval implantation of NanostimTM in UK Future Cardiology 10 (2): 162.	Case report Nanostim leadless pacemaker in a 77 year old female.	Successfully implanted device in 8 minutes.	Larger studies included in table 2.
Essandoh M (2017). Perioperative Management of the Micra Leadless Pacemaker Journal of Cardiothoracic and Vascular Anesthesia.	Case report Patient with a leadless pacemaker MICRA who had non-cardiac surgery.	Surgery was completed successfully using a bipolar electrosurgical unit to minimise pacer therapy inhibition by electromagnetic interference.	Larger studies included in table 2.
El-Chami M, Kowal RC, Soejima K, et al (2017). Impact of operator experience and training strategy on procedural outcomes with leadless pacing: Insights from the Micra Transcatheter Pacing Study Pacing &	726 patients had implant attempt with the Micra transcatheter pacing system by 94 operators trained in a teaching laboratory using a simulator, cadaver, and large animal models (lab	The Micra TPS procedure was successful in 99.2% of attempts and did not differ between the 55 operators trained in the lab setting and the 39 operators trained locally at the hospital (P =	Operator experience and training.

Clinical Electrophysiology 40 (7): 834-842.	training) or locally at the hospital with simulator/demo model and proctorship (hospital training).	0.189). Implant case number was also not a determinant of procedural success (P = 0.456). Each operator performed between 1 and 55 procedures. Procedure time and fluoroscopy duration decreased by 2.0% (P = 0.002) and 3.2% (P < 0.001) compared with the previous case. Major complication rate and pericardial effusion rate were not associated with case number (P = 0.755 and P = 0.620, respectively). There were no differences in the safety outcomes by training method. Among a large group of operators, implantation success was high regardless of experience. While procedure duration and fluoroscopy times decreased with implant number, complications were low and not associated with case number. Procedure and safety outcomes were similar between distinct training methodologies.	
Holm N, A MU and Zbinden R (2017). Complications with the MICRA TPS Pacemaker System: Persistent Complete Heart Block and Late Capture Failure PACE Pacing and Clinical Electrophysiology 40 (4): 455-456.	Case report A Medtronic MICRA transcatheter pacing system (Medtronic, Minneapolis, MN, US) was implanted in an 86-year-old patient with sick sinus syndrome and left bundle branch block after transfemoral aortic valve implantation	During implantation she developed a persistent complete heart block because of manipulation with the large-bore delivery catheter. Two weeks later, acute pacemaker dysfunction occurred because of massive increase of pacing threshold and impedance without obvious pacemaker dislocation or myocardial perforation. Recurrent capture failure was seen with pacing output set at 5 V/1.0 ms. Hence, microdislocation or	Larger studies included in table 2.

		fixation of the tines in the right ventricular trabeculae has to be assumed.	
Karjalainen PP, Nammas W and Paana T (2016). Transcatheter leadless pacemaker implantation in a patient with a transvenous dual-chamber pacemaker already in place. Journal of Electrocardiology 49 (4): 554-6.	Case report 83-year-old lady with DDDR pacemaker developed atrial fibrillation and pacemaker was switched to VVIR mode and presented for elective battery replacement after 2 years.	After successful battery replacement, the ventricular lead threshold remained high; therefore, a MICRA leadless transcatheter pacemaker, via femoral vein access, using a dedicated catheter delivery system was implanted. Implantation was successful with satisfactory electrical measurements and no in-hospital complications.	DDDR pacemaker plus MICRA
Karim S, Abdelmessih M, Marieb M, et al (2016). Extraction of a Micra Transcatheter Pacing System: First-in-human experience. HeartRhythm Case Reports 2 (1): 60-62.	Case report 61 year old had MICRA transcatheter leadless pacemaker implantation, as part of the Micra TCP study. The implantation was uncomplicated and he was discharged from the hospital with stable pacing. He returned 15 days later, noting a several-day history of dizziness and fatigue.	An electrocardiogram demonstrated atrial fibrillation with a slow ventricular response as well as non-captured pacing impulses. An elevated capture threshold was noted. Plan was to place a second device and use to delivery system to remove the first one.it was difficult to remove and find a suitable RV site, so after a number of attempts the approach was abandoned and delivery system removed. So device was extracted using a multilobed snare 3 weeks after initial device implantation.	Larger studies included in table 2.
Kiehl EL and Cantillon DJ (2016). Leadless cardiac pacing: What primary care providers and non-EP cardiologists should know Cleveland Clinic Journal of Medicine 83 (11 Suppl 2): S24-S34.	Review	Leadless cardiac pacing has shown promise, eliminating pocket-related complications. Other advantages include postprocedural shoulder mobility and the ability to drive, shower, and bathe. Current devices are limited to single-	Review

		chamber ventricular pacing.	
Kolek MJ, Crossley GH and Ellis CR (2017). Implantation of a MICRA Leadless Pacemaker Via Right Internal Jugular Vein. JACC: Clinical Electrophysiology. (article in press)	Case report MICRA implantation via a right internal jugular (RIJ) vein approach in a patient with an inferior vena cava (IVC) filter (contraindication for a femoral approach because of the concerns of the manufacturer about strong lateral forces distorting the IVC filter).	MICRA can be safely implanted via a superior approach from the RIJ vein, thus avoiding potential complications of IVC filter dislodgement. because of increased axial forces with the RIJ approach, and concerns about advancing a large sheath through the relatively small RIJ, the femoral approach should remain standard for most MICRA implantations.	Larger studies included in table 2.
Kypta A, Blessberger H, Lichtenauer M, et al (2016). Temporary leadless pacing in a patient with severe device infection. BMJ Case Reports 17: 17.	Case report A 64-year-old patient had implantation of a transcatheter pacing systems (MICRA TPS) for severe device infection (lead endocarditis) and unstable rhythm.	The patient with a dual chamber pacemaker experienced fever after a dental procedure. Lead infection was noted and the device was removed and a temporary pacing lead was implanted. New infection was noted on the temporary pacing lead, so it was removed We used a TPS as a bridging device, followed by implantation of a resynchronisation system, and explantation of the TPS. After the Micra TPS was implanted, the patient recovered noticeably, without any complications. All inflammation parameters were negative and an additional (18)F-fluorodeoxyglucose-positron emission tomography/CT imaging also proved to be negative. So a CRT-D device was then implanted, and the TCP was removed. During a follow-up of 6 weeks patient styed free of infection and recovered totally.	Larger studies included in table 2.

Lloyd M, Reynolds D, Sheldon T, et al (2017). Rate adaptive pacing in an intracardiac pacemaker Heart Rhythm 14 (2): 200-205.	Assess system's performance during treadmill tests to maximum exertion in a subset of patients within the Micra Transcatheter Pacing Study. N=42 Patients had 69 treadmill tests at 3 or 6 months postimplant (TPS MICRA) with algorithm programming at physician discretion	30 tests from 20 patients who completed >=4 stages with an average slope of 0.86 (90% confidence interval 0.77-0.96) confirmed proportionality to workload. On an individual test basis, 25 of 30 point estimates (83.3%) had a normalised slope within the defined tolerance range (range 0.46-1.08). Accelerometer-based rate adaptive pacing was proportional to workload, thus confirming rate adaptive pacing commensurate to workload is achievable with an entirely intracardiac pacing system.	Device performance testing.
Marai I, Diab S, Ben-Avi R, et al. (2017) Intraoperative Implantation of Micra Leadless Pacemaker During Valve Surgery Annals of Thoracic Surgery 29: 29.	Case report Micra TPS implanted during valve surgery.	We present a case of a patient in whom a Micra leadless pacemaker was implanted during valve surgery.	Leadless pacemaker implanted during valve surgery
Martinez-Sande JL, Pena-Gil C, Garcia-Seara J, et al (2017).Usefulness of Three-dimensional Transthoracic Echocardiograhy in the Localization of the Micra Leadless Pacemaker Revista Espanola de Cardiologia 70 (8): 670-671.	Case report N=3 MICRA TPS implantations.	MICRA systems should be associated with correct characterisation of the implantation site. A protocol based examination including 3D TEE should be included.	Large studies included in table 2.
McCauley BD and Chu AF (2017). Leadless Cardiac Pacemakers: The Next Evolution in Pacemaker Technology Rhode Island Medicine 100 (11): 31-34.	Review	In this review, we will discuss single-component leadless cardiac pacemaker technology, provide an overview of the 2 approved devices, and discuss their benefits as well as their limitations.	Review
Miller MA, Neuzil P, Dukkipati SR, et al	Review	This review summarises the current evidence	Review

(2015). Leadless Cardiac Pacemakers: Back to the Future Journal of the American College of Cardiology 66 (10): 1179-89.		and potential benefits of leadless pacing systems, which are either commercially available (in Europe) or under clinical investigation.	
Mountfort K, Knops R, Sperzel J, et al (2014). The Promise of Leadless Pacing: Based on Presentations at Nanostim Sponsored Symposium Held at the European Society of Cardiology Congress 2013, Amsterdam, The Netherlands, 2 September 2013 Arrhythmia & Electrophysiology Review 3 (1): 51-5.	Review	A completely self-contained leadless pacemaker has recently been developed, and its key characteristics are discussed, along with the results of an efficacy and safety trial in an animal model. The results of the LEADLESS study, the first human trial to look at safety and feasibility of the leadless device, are discussed and the possible implications for future clinical practice examined.	Review
Nihr H (2014). Micra? Transcatheter Pacing System for atrial fibrillation and bradycardia (Structured abstract) Health Technology Assessment Database (4).	Micra™ Transcatheter Pacing System (TPS),		Technology alert
Nihr H (2014). Nanostim Leadless Pacemaker for atrial fibrillation and bradycardia (Structured abstract) Health Technology Assessment Database (4).	Nanostim Leadless Pacemaker system		Technology alert
Nihr H (2014). Wireless Cardiac Stimulation System for chronic heart failure (Structured abstract) Health Technology Assessment Database (4).			Technology alert
Okabe T, El-Chami MF, Lloyd MS, et al. (2018). Leadless pacemaker implantation and concurrent atrioventricular junction	Retrospective case series N=21 patients with atrial fibrillation that failed AF catheter ablation and/or pharmacotherapy who	At 12 months follow-up there was no device dislodgement or malfunction. Electrical performance data were available in 14 patients	Concurrent Micra leadless transcatheter pacemaker implantation and AVJ ablation

ablation in patients with atrial fibrillation. Pacing & Clinical Electrophysiology 24:24.	had Micra implantation and concurrent AVJ ablation. Follow-up: 12 months	(67%). Among patients with the complete data set, median pacing thresholds at implant and at 1, 3, 6, and 12 months were 0.5 V (range 0.25-0.88), 0.44 V (range 0.25-2.0), 0.5 V (range 0.25-1.63), 0.5 V (range 0.25-1.13), and 0.5 V (range 0.25-1.13) at a pulse width of 0.24 msec, respectively. Two patients died due to noncardiac causes. There were no patients with major device-related complications.	
Reddy V, Miller M, Knops R, et al (2016). Retrieval of the Leadless Cardiac Pacemaker: a Multicenter Experience Circulation: arrhythmia and electrophysiology 9 (12) (no pagination).	Retrospective case series N=16 patients enrolled in 3 multicentre trials, who had a leadless cardiac pacemaker implant and who subsequently had a device removal attempt.	The overall leadless pacemaker retrieval success rate was 94%: for patients whose leadless cardiac pacemaker had been implanted for <6 weeks (acute retrieval cohort), complete retrieval was achieved in 100% (n=5/5); for those implanted for > 6 weeks (chronic retrieval cohort), retrieval was achieved in 91% (n=10/11) of patients. The mean duration of time from implant to retrieval attempt was 346 days (range, 88-1188 days) in the chronic retrieval cohort, and nearly two thirds (n=7; 63%) had been implanted for >6 months before the retrieval attempt. There were no procedure-related adverse events at 30 days post retrieval procedure.	Larger studies included in table 2.
Richter S, Doring M, Ebert M, et al. (2018). Battery Malfunction of a Leadless Cardiac Pacemaker - A Worrisome Single-Center Experience. Circulation 14:14.	Case series (prospective study in single centre) N=14 Leadless cardiac pacemaker (LCP) Nanostim TM	Study analyses the long-term pacemaker performance and rate of battery malfunction of the Nanostim TM LCP. 43% (6/14) had battery malfunction, mean time to device failure was 39.0 months. No	Worldwide experience on battery malfunction already reported in table 2.

	Mean follow-up: 29.5 months	patients died or suffered severe injuries related to anti-bradycardia pacing failure. 11 patients received conventional pacemaker after mean time of 30.2 months from LCP implant: 5 for battery malfunction, 6 for safety reasons. 1 patient underwent LCP removal. Further analysis of retrieved devices revealed reduced electrolyte within the lithium carbon monoflouride battery resulting in high internal battery resistance, which impacts the current available to power the device electronics and results in loss of device functionality.	
Ritter P, Duray GZ, Steinwender C, et al (2015). Early performance of a miniaturized leadless cardiac pacemaker: the Micra Transcatheter Pacing Study European Heart Journal 36 (37): 2510-9.	Case series N=140 patients having Class I or II indication for VVI pacing had implantation of a Micra transcatheter pacing system. NCT02004873 Follow-up: mean 1.9 months	The safety endpoint was met with no unanticipated serious adverse device events. 30 adverse events related to the system or procedure occurred, mostly because of transient dysrhythmias or femoral access complications. 1 pericardial effusion without tamponade occurred after 18 device deployments. In 60 patients followed to 3 months, mean pacing threshold was 0.51 +/- 0.22 V, and no threshold was >=2 V, meeting the efficacy endpoint (P < 0.001). Average R-wave was 16.1 +/- 5.2 mV and impedance was 650.7 +/- 130 ohms.	Larger and longer follow-up studies included in table 2.
Ritter P, Duray GZ, Zhang S, et al (2015).The rationale and design of the Micra Transcatheter Pacing Study: safety and	Case series N=720 Micra Transcatheter Pacing Study nct02004873.	Approximately 720 patients will be implanted at up to 70 centres around the world. The study is designed to have a	Study design and protocol only.

efficacy of a novel miniaturized pacemaker Europace 17 (5): 807-13.		continuously growing body of evidence and data analyses are planned at various time points.	
Rutzen-Lopen H et al (2016). Leadless cardiac devices: pacemakers and implantable cardioverter defibrillators. Current treatment options in cardiovascular medicine.18 (8), 1-13.	Review	Despite the remarkable advantages of leadless pacing systems, the data are still quite limited and broad implementation of these technologies need to occur in a cautious and deliberate fashion as the periprocedural risks remains high. Two of the 3 systems, Nanostim™ (St. Jude Medical) and Micra Transcatheter Pacing System (Medtronic Inc.), have shown the greatest applicability, although they are currently only limited to single chamber pacing and procedural risks are modest.	Review
Salaun E, Tovmassian L, Simonnet B, et al. (2017). Right ventricular and tricuspid valve function in patients chronically implanted with leadless pacemakers. Europace 28:28.	Case series N=23 patients implanted with a leadless pacemaker (Nanostim LCP in 14 and Micra TPS in 9).	Indications for pacing were paroxysmal atrio-ventricular block in 12 patients, intermittent sinus bradycardia in 5, unexplained syncope in 3, and atrial fibrillation with slow ventricular rate in the remaining 3. The pacing percentage was 34±42% at the last visit. Most devices were implanted in the septo-apical or mid-septal region. There were no significant changes in echocardiographic parameters observed. One patient developed significantly increased tricuspid valve regurgitation, without abnormal leaflet motion or tricuspid valve annulus size changes, suggesting it to be due to right ventricle pressure changes. There were no significant changes in	Larger studies included in table 2.

		heart structure and function observed, especially concerning the right ventricle and tricuspid valve.	
Soejima K, Edmonson J, Ellingson ML, et al (2016). Safety evaluation of a leadless transcatheter pacemaker for magnetic resonance imaging use Heart Rhythm 13 (10): 2056-63.	Interactions of MRI with the Micra transcatheter pacemaker system were evaluated.	Compared with traditional MRI conditional pacemakers, the overall risk with Micra was greatly reduced because of the small size of the device and the absence of a lead. The modelling results predicted that the non-perfused temperature rise of the device would be less than 0.4degreeC at 1.5 T and 0.5degreeC at 3 T and that the risk of device heating with multiple device implants was not increased as compared with a single device. The MRI safety assessment tests conducted for the Micra pacemaker demonstrate that patients with a single device or multiple devices can safely have MRI scans in both 1.5- and 3-T MRI scanners. The clinical case study revealed no MRI-related complications.	Interactions with MRI-safety assessment.
Sperzel J, Burri H, Gras D, et al (2015). State of the art of leadless pacing Europace 17 (10): 1508-13.	Review	Recently, two miniaturised leadless pacemakers, NanostimTM (St. Jude Medical) and MicraTM (Medtronic), which can be completely implanted inside the right ventricle using steerable delivery systems, entered clinical application. leadless pacing systems may have the potential to overcome some complications of conventional pacing. However, acute and long-term complications still remains to be determined, as well as	Review

		the feasibility of device explantation years after device placement.	
Sideris S et al (2017). Leadless cardiac pacemakers: current status of a modern approach in pacing. Hellenic Society of Cardiology (2017) xx, 1-8 (in press)	Review	Recently, leadless pacing systems have emerged as a therapeutic alternative to conventional pacing systems that provide therapy for patients with bradyarrhythmias, while eliminating potential transvenous lead and pacemaker pocket-related complications. Initial studies have demonstrated favourable efficacy and safety of currently developed leadless pacing systems, compared with transvenous pacemakers. In the present paper, we review the current evidence and highlight the advantages and disadvantages of this novel technology.	Review
Seriwala HM et al (2016). Leadless pacemakers: A new era in cardiac pacing. Journal of Cardiology 67 (2016) 1–5	Review	Reviews the evidence from animal studies and the technological advancements that have ushered in the era of use in humans. Also discusses different leadless pacemakers currently under investigation, along with limitations and future developments of this innovative concept.	Review
Sterlinski M, Demkow M, Plaskota K, et al. (2017). Leadless Micra pacemaker percutaneous extraction from pulmonary artery in complex congenital heart disease and complete heart block patient. Eurointervention 26:26.	Case report of a 30 year old male with congenital corrected transposition of great arteries, ventricular septal defect, pulmonary stenosis and dextrocardia and with permanent complete atrioventricular block. Micra leadless pacemaker was implanted.	Micra uncontrollable dislodgement to pulmonary artery with subsequent percutaneous docking and retrieval. The device was deployed on inferior wall in sub-pulmonary ventricle, Micra changed slightly in position and	Larger studies included in table 2.

		repositioning was attempted. The device was released and it floated into right pulmonary artery branch. The device was withdrawn and pulled out and the same venous access was used to re-implant a new device in apical position without any complications.	
Tjong F and Reddy V (2017). Permanent Leadless Cardiac Pacemaker Therapy: a Comprehensive Review Circulation 135 (15): 1458-1470	Review Leadless pacemaker therapy	Early results with leadless devices are compared with historical results with conventional single-chamber pacing. Both presently manufactured leadless pacemakers show similar complications, which are mostly related to the implant procedure: cardiac perforation, device dislocation, and femoral vascular access site complications. In comparison with conventional transvenous single-chamber pacemakers, slightly higher short-term complication rates have been seen: 4.8% for leadless pacemakers versus 4.1% for conventional pacemakers. The complication rate of the leadless pacemakers is influenced by the implanter learning curve for this new procedure. No long-term outcome data are yet available for the leadless pacemakers. Larger leadless pacing trials, with long-term follow-up and direct randomised comparison with conventional pacing systems, will be required to define the proper clinical role of these leadless systems.	Review

		Although current leadless pacemakers are limited to right ventricular pacing, future advanced, communicating, multicomponent systems are expected to expand the potential benefits of leadless therapy to a larger patient population	
Tse G, Liu T, Li G, et al (2017). Implantation of the Micra leadless pacemaker in a patient with a low body mass index of 16 Oxford Medical Case Reports 2017 (9): omx051.	Case report A 71-year-old female patient has a history of complete heart block and recurrent pacemaker site infection requiring multiple pacemaker explanations.	A leadless pacemaker using passive fixation was inserted into the right ventricular apex via transvenous approach without complications. This case illustrates the feasibility of implanting a leadless pacemaker system in a small-sized adult with a low body mass index of 16 which may have potential application in elderly Asian subjects.	Larger studies included in table 2.
Vamos M, Honold J, Duray GZ, et al (2016).MICRA Leadless Pacemaker on Autopsy. JACC: Clinical Electrophysiology 2 (5): 636-637.	Case report N=68 year old man with newly developed third degree atrioventricular block and atrial fibrillation had a leadless pacemaker (MICRA TCS) implantation in an apical septal right ventricular location.	After 4 months of clinically stable conditions, the patient was rehospitalised with severe acute on-chronic renal failure, which led to his death 2 weeks later. On autopsy, the MICRA pacemaker was found in the apical region of the right ventricle. All 4 nitinol fixation tines of the device were totally embedded in myocardial tissue. The distance between the tip of the MICRA device and the epicardium was 5 mm. Approximately two-thirds of the device was completely covered with endocardial/myocardial tissue. On autopsy of the current case, a stable position of the MICRA device with satisfying security distance from epicardial	Larger studies included in table 2.

		site of the heart was seen. However, the fact that the MICRA device was deeply encapsulated raises doubts concerning removability of the device after longer periods of time.	
Wiles BM and Roberts PR (2017). Lead or be led: an update on leadless cardiac devices for general physicians Clinical Medicine 17 (1): 33-36.	Review	Leadless devices have become a reality and represent the future of device therapy. The absence of a transvenous lead offers a statistically significant clinical advantage because of many well established issues related to lead complications. The leadless pacemaker and subcutaneous ICD are significant new products that are currently not well recognised or understood by general physicians.	Review