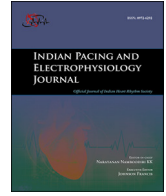




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## Leadless cardiac pacing

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### 1. Introduction

Transvenous cardiac pacemakers definitely improve quality of life and reduce mortality in at-risk patients, but they are associated with several potential device-related complications. Approximately 10% of patients experience complications related to transvenous implantation of the pacemaker. These may be attributable to either the pulse generator (hematoma, skin breakdown, pocket infection) or venous access and lead implantation (pneumothorax, cardiac tamponade, lead dislodgement) [1]. Pacemaker leads continue to be the “Achilles’ heel” of the pacing and defibrillation systems. In the long term, transvenous leads, often considered the weakest link of the cardiac pacing system, can cause venous obstruction and are prone to insulation breaks, conductor fractures, and infections [1–3].

### 2. Permanent leadless cardiac pacing

#### Results of the LEADLESS trial

Reddy et al. [4] in a prospective nonrandomized study showed the safety and feasibility of a novel, completely self-contained leadless cardiac pacemaker (LCP) in 33 patients. The primary safety end point was freedom from complications at 90 days. Secondary performance end points included implant success rate, implant time, and measures of device performance (pacing/sensing thresholds and rate-responsive performance). The most common indication for cardiac pacing was permanent atrial fibrillation with atrioventricular block. The implant success rate was 97%. Five patients (15%) required the use of >1 leadless cardiac pacemaker during the procedure. One patient developed right ventricular perforation and cardiac tamponade during the implant procedure,

and eventually died as the result of a stroke. The overall complication-free rate was 94% (31/33). After 3 months of follow-up, the measures of pacing performance (sensing, impedance, and pacing threshold) either improved or were stable within the accepted range [4].

#### 2.2. Chronic performance of a leadless cardiac pacemaker

##### Year follow-up of the LEADLESS trial

Knops and colleagues [5], retrospectively assessed intermediate-term follow-up data for 31 of 33 patients from the LEADLESS trial cohort who had an indication for single-chamber pacing. Between 3 and 12 months of follow-up, there were no pacemaker-related adverse events reported. The pacing performance results at 6- and 12-month follow-up were, respectively, as follows: mean pacing threshold (at a 0.4-ms pulsewidth), 0.40 V and 0.43 V; R-wave amplitude 10.6 mV and 10.3 mV; and impedance 625 U and 627 U. At the 12-month follow-up in 61% of the patients (n 19 of 31), the rate response sensor was activated, and an adequate rate response was observed in all patients. This study demonstrates very stable performance and reassuring safety results during intermediate-term follow-up of leadless pacemaker.

#### 2.3. Percutaneous implantation of an entirely intracardiac leadless pacemaker

LEADLESS II study [6] was a prospective, nonrandomized, multicenter trial which examined the clinical safety and efficacy of the Nanostim leadless cardiac pacemaker in patients who require permanent ventricular pacing. Reddy et al. [6] reported the interim analysis, which includes the primary analysis of efficacy and safety in the initial 300 patients who were followed for 6 months (the primary cohort) and outcomes for all 526 patients who were enrolled as of June 2015 (the total cohort). The primary efficacy end point was both an acceptable pacing threshold ( $\leq 2.0$  V at 0.4 msec) and an acceptable sensing amplitude (R wave  $\geq 5.0$  mV, or a value equal to or greater than the value at implantation) through 6 months. The primary safety end point was freedom from device-related serious adverse events through 6 months. The rates of the efficacy end point and safety end point were compared with performance goals (based on historical data) of 85% and 86%, respectively. The leadless pacemaker was successfully implanted in 504 of

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**Table 1**  
Comparison of leadless pacemakers.

Device	Size (cm <sup>3</sup> )	Means of fixation	No. of patients	Successful implantation (%)	Major complication (%)	Perforation or effusion (%)	Device dislodgement	Adequate pacing parameters at 6 months (%)
Nanostim	1.0	Helical wire screw	526	95.8	6.5	1.5	1.1	90
Micra	0.8	Tines	725	99.2	4	1.6	0	98.3

the 526 patients in the total cohort (95.8%). The intention-to-treat primary efficacy end point was met in 270 of the 300 patients in the primary cohort (90.0%; 95% confidence interval [CI], 86.0 to 93.2,  $p = 0.007$ ), and the primary safety end point was met in 280 of the 300 patients (93.3%; 95% CI, 89.9 to 95.9;  $P < 0.001$ ). The mean pacing threshold and sensing values at 6 months were similar to those observed with conventional transvenous leads [7] and these values were stable over time. At 6 months, device-related serious adverse events were observed in 6.7% (approximately 1 in 15) of the patients; events included device dislodgement with percutaneous retrieval (in 1.7%), cardiac perforation (in 1.3%), and pacing-threshold elevation requiring percutaneous retrieval and device replacement (in 1.3%).

#### 2.4. A leadless intracardiac transcatheter pacing system

Micra Transcatheter Pacing Study [8] is a prospective, non-randomized, single-study-group, multisite, international clinical study to evaluate the safety and efficacy of the Micra Pacemaker System (Medtronic). The analysis of the primary end points began when 300 patients reached 6 months of follow-up. 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 ( $\leq 2.0$  V at a pulse width of 0.24 msec and an increase of  $\leq 1.5$  V from the time of implantation). They also did a post hoc analysis in which the rates of major complications were compared with those in a control cohort of 2667 patients with transvenous pacemakers from six previously published studies. The device was successfully implanted in 719 of 725 patients (99.2%). The Kaplan–Meier estimate of the rate of the primary safety end point was 96.0% (95% confidence interval [CI], 93.9 to 97.3;  $P < 0.001$  for the comparison with the safety performance goal of 83%); there were 28 major complications in 25 of 725 patients, and no dislodgements. The rate of the primary efficacy end point was 98.3% (95% CI, 96.1 to 99.5;  $p < 0.001$  for the comparison with the efficacy performance goal of 80%) among 292 of 297 patients with paired 6-month data. Although there were 28 major complications in 25 patients, patients with transcatheter pacemakers had significantly fewer major complications than did the control patients (hazard ratio, 0.49; 95% CI, 0.33 to 0.75;  $p = 0.001$ ). In this historical comparison study, the transcatheter pacemaker met the pre-specified safety and efficacy goals; it had a safety profile similar to that of a transvenous system while providing low and stable pacing thresholds [8].

An editorial [9] compared (Table 1) these two nonrandomized,

industry-sponsored studies of leadless pacemakers (the Nanostim device from St. Jude Medical and Micra device from Medtronic).

These studies demonstrate that leadless pacing is feasible and relatively safe, at least in the short term. Whether the long-term results will show that these devices remain safe and effective over time and that these leadless devices are as durable as transvenous pacemakers remains to be seen. To date, these newer devices can be used only for single-chamber ventricular pacing, a procedure generally reserved for patients with atrial fibrillation and bradycardia or in patients thought to need infrequent pacing. These leadless pacemakers will have limited usefulness in the treatment of the majority of pacemaker recipients, including patients with sinus-node dysfunction or heart block, and they will have no role in the treatment of patients with heart failure who need left-ventricular resynchronization to improve cardiac output.

In spite of these concerns, these studies have encouraging short-term results that show the promise of leadless pacing; they are likely to generate substantial interest in leadless pacing and defibrillation technology. Importantly, the results of these studies suggest the potential value of the next generation of leadless devices, which will include atrial-based systems and left ventricular resynchronization systems that are more widely applicable [9].

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