

# Leadless pacemakers for right ventricle pacing

Systematic Review  
Final



Ludwig Boltzmann Institut  
Health Technology Assessment

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### **Conflict of interest**

All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors ([www.imce.org](http://www.imce.org)).

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**Commissioned by the Austrian Ministry of Health**, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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**List of abbreviations**

ACC.....American College of Cardiology	NBG.....North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology Group (BPEG)
ADE.....Adverse Device Effects	
AF.....Atrial fibrillation	
AHA.....American Heart Association	NHS-EED.....NHS Economic Evaluation Database
AV.....Atrioventricular	
BBB.....Bundle branch block	POP.....Planned and Ongoing Projects
CAD.....Coronary artery disease	PM.....Pacemaker
CHF.....Congestive heart failure	PRISMA.....Prevention and Recovery Information System for Monitoring and Analysis
CRD.....Centre for reviews and dissemination	
DARE.....Database of Abstracts of Reviews of Effects	RCT.....Randomized controlled studies
ECG.....Electrocardiogram	SADE.....Serious adverse device events
EKG.....Elektrokardiogramm	SAE.....Serious adverse events
ESC.....European Society of Cardiology	SB.....Sinus bradycardia
EU.....European Union	SD.....Standard deviation
FDA.....Food and Drug Administration	SND.....Sinus node disease (Sick sinus syndrome)
GRADE.....Grading of Recommendations Assessment, Development and Evaluation	TGA.....Therapeutic Goods Administration
HRS.....Heart Rhythm Society	TPS.....Transcatheter pacing system
HRQoL.....Health-related quality of life	VCM.....Ventricular capture management
HSM.....Herzschrittmacher	VVI.....Single-chamber ventricular pacing
ICD.....International Statistical Classification of Diseases and Related Health Problems	VVIR.....Single-chamber ventricular pacing with response modulation
IDE.....Investigational device exemption	
LCP.....Leadless cardiac pacemakers	

# Summary

## Introduction

Leadless cardiac pacemakers (LCP) are self-contained intracardiac devices that are designed to have the same function as traditional cardiac pacemakers, but are miniaturized and can be implanted entirely inside the right ventricle of the heart. The expected benefit is the avoidance of complications associated with the placement of an external pulse generator in a surgical pocket in the chest and the transmission of impulses through transvenous leads required in conventional pacemakers.

In the scope of this assessment are cardiac arrhythmias in adults for which single-chamber ventricular pacing (VVI) is indicated. First and foremost, these are patients with atrial fibrillation who require a pacemaker due to slow ventricular response, but also patients with bradycardia due to atrioventricular block or sinus node disease might be considered if other pacing modes are not appropriate.

The purpose of cardiac pacing is to provide an appropriate heart rate and heart response to reestablish effective circulation and more normal haemodynamics that are compromised by a slow heart rate. Permanent pacemaker implantation is further considered to alleviate symptoms associated with a bradyarrhythmia (e.g. dizziness, light-headedness, syncope, fatigue, poor exercise tolerance) or to prevent the possible worsening of the rhythm disturbance.

## Methods

We assessed whether leadless pacemakers in comparison to conventional pacemakers in patients with indications for right ventricle pacing are as effective and safe concerning exercise capacity and cardiovascular morbidity-mortality, and more effective and safe concerning health-related quality of life and complications rate. Answering these research questions was based on a systematic literature search from different databases. The study selection, data extraction and assessing the methodological quality of the studies was performed by two review authors (AK, RE) independently from each other.

### Domain effectiveness

The following efficacy-related outcomes were used as evidence to derive a recommendation: health related quality of life (HRQoL), exercise capacity.

### Domain safety

The following safety-related outcomes were used as evidence to derive a recommendation: serious adverse device effects (SADE), adverse device effects (ADE) and serious adverse events (SAE).

**miniaturisierte,  
vollständig  
implantierbare  
Herzschrittmacher  
(HSM)**

**angegebener Nutzen:  
Vermeidung von  
Komplikationen  
verursacht durch  
externe Generatoren  
und Sonden**

**systematischer Review**

**entscheidende  
Endpunkte:  
Wirksamkeit: HRQoL  
und Belastungsfähigkeit**

**Sicherheit:  
Komplikationsraten**

<p>3 Einzelarmstudien/ 633 P. in Wirksamkeitskohorten, 1.284 P. in Sicherheitskohorten</p>	<p><b>Results</b></p> <p><b>Available evidence</b></p> <p>We identified three prospective multi-centre single-arm trials with a total of 633 participants analysed for efficacy endpoints and 1,284 participants analysed for safety endpoints. For the majority of the study participants, pacing was indicated due to atrial fibrillation with AV block. Other indications were sinus node dysfunction and AV block. Mean age of the study participants was 76 years in all three studies.</p>
<p>keine Ergebnisse zu klinischer Wirksamkeit</p>	<p><b>Clinical effectiveness</b></p> <p>None of the studies reported results on the outcomes defined as crucial to assess clinical effectiveness.</p>
<p>Sicherheit: 3-5 % Mortalität</p> <p>schwere produktbezogene Ereignisse in 4-6,5 %</p> <p>20 P. mit kardialen Verletzungen</p> <p>6 Implantatsablösungen (nur Nanostim™)</p>	<p><b>Safety</b></p> <p>Overall mortality ranged from 3 to 5%; cardiac mortality was reported in two studies with 0.8% and 1%. Four deaths were reported as procedure-related.</p> <p>The rates of serious adverse device effects ranged between 4% and 6.5% in the three case series. In total, 20 patients experienced a cardiac injury. Six device dislodgements were reported with the Nanostim™ device, but none with the Micra™ TPS system.</p> <p>Other serious adverse events that were attributable either to the device or the procedure included vascular complications, arrhythmia during device implantation and elevated pacing thresholds requiring retrieval and implantation of a new device.</p>
<p>aufkommende Technologie, keine Daten zu klinischer Wirksamkeit, Bedenken zu prozeduralen Komplikationen</p>	<p><b>Upcoming evidence</b></p> <p>There are no randomised controlled trials currently planned or ongoing. Five single-arm studies are registered, that will analyse safety endpoints and pacing thresholds.</p> <p><b>Discussion</b></p> <p>Leadless pacemakers are an emergent technology for which there are only preliminary results available. The results indicate that leadless pacemaker can be successfully implanted and sustain a low pacing threshold for several months. The complications associated with leads and generators can be avoided, but procedural morbidity and mortality is a concern. Whether acute complications can be improved by training remains to be proven. Long-term issues such as battery longevity and device retrieval are not yet resolved.</p>
<p>kein direkter Vergleich zu herkömmlichen HSM</p>	<p>The available studies are non-randomised and there is no direct comparison of the benefit of LCP over contemporary single-chamber systems, so no definitive conclusion can be drawn on the superiority or even non-inferiority of the new technology compared to standard therapy. There are no data on health-related quality of life of the patients.</p>
<p>Evidenz nicht ausreichend für Empfehlung</p>	<p><b>Conclusion</b></p> <p>The current evidence is not sufficient to prove, that the assessed technology Leadless pacemakers is as effective but more safe than conventional VVI pacemakers. New study results will potentially influence the effect estimate considerably.</p>

# Zusammenfassung

## Einleitung

Sondenlose Herzschrittmacher sind miniaturisierte, in sich geschlossene Herzschrittmacher, die dieselben Funktionen wie herkömmliche Herzschrittmacher erfüllen sollen, aber zur Gänze in die rechte Herzkammer implantiert werden können. Daraus erwartet man den Vorteil, dass Komplikationen im Zusammenhang mit dem externen Generator in einer subkutane Hauttasche und den transvenösen Sonden für die Impulsübertragung, die bei konventionellen Herzschrittmachern notwendig sind, vermieden werden.

Gegenstand dieses Berichts sind kardiale Arrhythmien, die eine Indikation für einen Einkammerschrittmacher in der rechten Herzkammer (VVI Schrittmacher) darstellen. Dabei handelt es sich in erster Linie um PatientInnen mit bradykardem, permanenten Vorhofflimmern, bei denen VVI-Schrittmacher zur Überbrückung der bradykarden Phasen implantiert werden. Auch bei PatientInnen mit Bradykardien aufgrund eines Sick-Sinus-Syndroms oder atrioventrikulärem Blocks kann ein VVI Schrittmacher indiziert sein, wenn andere Schrittmachersysteme nicht in Frage kommen.

Ziel der Schrittmachertherapie ist die Stabilisierung des Herzrhythmus und damit die Wiederherstellung eines effektiven Kreislaufs und normaler Hämodynamik, die durch die Bradykardie beeinträchtigt wurden. Damit sollen die Symptome, die mit Bradyarrhythmien einhergehen (z. B. Schwindel, Ohnmacht, Müdigkeit, niedrige Belastungsfähigkeit) verringert werden.

## Methoden

Wir untersuchten, ob sondenlose Herzschrittmacher im Vergleich zu konventionellen Herzschrittmachern in PatientInnen mit Indikationen für VVI HSM ebenso wirksam und sicher hinsichtlich der Endpunkte Belastungsfähigkeit und kardialer Morbimortalität und wirksamer und sicherer hinsichtlich der Endpunkte gesundheitsbezogene Lebensqualität und Komplikationsrate sind.

Um diese Forschungsfrage zu beantworten, wurde eine systematische Literatursuche in verschiedenen Datenbanken durchgeführt. Die Studienauswahl, Datenextraktion sowie die Bewertung der methodischen Qualität der Studie wurde unabhängig voneinander von zwei AutorInnen (AK, RE) durchgeführt.

## Wirksamkeit

Die folgenden Endpunkte wurden für die Bewertung der Wirksamkeit als entscheidend definiert: HRQoL, Belastungsfähigkeit.

## Sicherheit

Die folgenden Endpunkte wurden für die Bewertung der Sicherheit als entscheidend definiert: schwere produktbezogene unerwünschte Ereignisse (SADE), produktbezogene unerwünschte Ereignisse (ADE) und schwere unerwünschte Ereignisse (SAE).

**miniaturisierte, vollständig implantierbare Herzschrittmacher (HSM)**

**angegebener Nutzen: Vermeidung von Komplikationen verursacht durch externe Generatoren und Sonden**

**systematischer Review**

**entscheidende Endpunkte:**

**Wirksamkeit: HRQoL und Belastungsfähigkeit**

**Sicherheit: Komplikationsraten**

<p><b>3 Einzelarmstudien/ 633 P. in Wirksamkeitskohorten, 1.284 P. in Sicherheitskohorten</b></p>	<p><b>Ergebnisse</b></p> <p><b>Verfügbare Evidenz</b></p> <p>Wir identifizierten drei prospektive multizentrische Einzelarmstudien mit insgesamt 633 TeilnehmerInnen, die für Wirksamkeitsendpunkte analysiert wurden (Wirksamkeitskohorten) und insgesamt 1.284 TeilnehmerInnen, die für Sicherheitsendpunkte analysiert wurden. Bei der Mehrheit der TeilnehmerInnen war der Herzschrittmacher aufgrund von Vorhofflimmern mit AV Block indiziert. Andere Indikationen waren Sick-Sinus-Syndrom und AV Block. Das Durchschnittsalter lag bei 76 Jahren in allen drei Studien.</p>
<p><b>keine Ergebnisse zu klinischer Wirksamkeit</b></p>	<p><b>Wirksamkeit</b></p> <p>Keine der eingeschlossenen Studien berichtete Ergebnisse zu klinischen Wirksamkeitsendpunkten.</p>
<p><b>Sicherheit: 3-5 % Mortalität</b></p> <p><b>schwere produktbezogene Ereignisse in 4-6,5 %</b></p> <p><b>20 P. mit kardialen Verletzungen</b></p> <p><b>6 Implantatsablösungen (nur Nanostim™)</b></p>	<p><b>Sicherheit</b></p> <p>Die Gesamtmortalität lag bei 3 bis 5 %; die kardiale Mortalität bei 0,8 bzw. 1 % (Daten aus zwei Studien). Es wurden insgesamt vier Todesfälle berichtet, die als prozedur-bezogen eingestuft wurden.</p> <p>Schwere produktbezogenen Ereignisse wurden in 4 bis 6,5 % der TeilnehmerInnen berichtet. Insgesamt gab es 20 Fälle von Herzverletzungen. Nur in den Nanostim™ Studien wurden – insgesamt 6 – Implantatsablösungen berichtet.</p> <p>Andere schwere unerwünschte Ereignisse, die entweder im Zusammenhang mit der Prozedur oder dem Gerät auftraten, inkludierten vaskuläre Komplikationen, Arrhythmien während der Implantation und erhöhte pacing thresholds, die die Entfernung oder den Tausch des Geräts erforderten.</p>
<p><b>aufkommende Technologie, keine Daten zu klinischer Wirksamkeit, Bedenken zu prozeduralen Komplikationen</b></p>	<p><b>Laufende Studien</b></p> <p>Es sind keine randomisierten kontrollierten Studien geplant oder laufend. Es sind fünf Einzelarmstudien registriert, die Sicherheitsendpunkte und pacing thresholds als primäre Endpunkte analysieren werden.</p>
<p><b>kein direkter Vergleich zu herkömmlichen HSM</b></p>	<p><b>Diskussion</b></p> <p>Sondenlose Herzschrittmacher sind eine aufkommende Technologie, für die erst vorläufige Ergebnisse verfügbar sind. Die Studien zeigen, dass sondenlose Schrittmacher erfolgreich implantiert werden können und therapeutisch wirksame thresholds für mehrere Monate erhalten können. Zwar fallen generator- und sonden-assoziierte Komplikationen weg, es bestehen jedoch Bedenken hinsichtlich der prozeduralen Morbidität und Mortalität. Ob diese durch geplante Trainingsmaßnahmen reduziert werden können, bleibt noch zu beweisen. Längerfristige Probleme im Zusammenhang mit Batteriedauer und eventuell notwendiger Gerätexplantation sind vorerst ungeklärt.</p> <p>Die vorhandenen Studien sind nicht-randomisiert und es gibt keinen direkten Vergleich zwischen sondenlosen HSM und konventionellen Geräten. Wesentliche Endpunkte etwa zur Lebensqualität wurden noch gar nicht untersucht.</p>
<p><b>Evidenz nicht ausreichend für Empfehlung</b></p>	<p><b>Schlußfolgerung</b></p> <p>Eine abschließende Beurteilung ist aufgrund fehlender Daten zu wesentlichen Endpunkten nicht möglich.</p>

# 1 Scope

## 1.1 PICO question

Are leadless pacemakers in comparison to conventional pacemakers in patients with indications for right ventricle pacing as effective and safe concerning cardiovascular morbidity and mortality, exercise capacity, and more effective and safe concerning patient-related quality of life and complication rate?

**PIKO-Frage**

## 1.2 Inclusion criteria

Inclusion criteria for relevant studies are summarised in Table 1-1.

**Einschlusskriterien  
für relevante Studien**

Table 1-1: Inclusion criteria

Population	<p>First line treatment of patients with indications for single-chamber ventricular pacemakers [1, 2]</p> <ul style="list-style-type: none"> <li>✳ Patients with chronic atrial fibrillation (AF; ICD-10 I.48) who require a pacemaker for persistent or intermittent bradycardia due to slow ventricular response (atrioventricular (AV) block, ICD-10 I.44)</li> <li>✳ Patients with persistent or intermittent bradycardia due to AV block or symptomatic sinus node disease (SND, ICD-10 I.49.5)<sup>1</sup></li> </ul> <p>Contraindications:</p> <ul style="list-style-type: none"> <li>✳ Patients requiring long-term pacing exceeding estimated device longevity (NB. children)</li> <li>✳ Patients with indications for atrial single-chamber pacemakers or dual-chamber pacemakers or with indications for cardiac resynchronisation therapy</li> </ul> <p>MESH term: Arrhythmias, Cardiac [C14.280.067] and Arrhythmias, Cardiac [C23.550.073]</p>
Intervention	<p>Leadless self-contained and fully implantable VVI(R) pacemaker</p> <p>Setting: Vascular surgery, Interventional cardiology; specialist hospital, general hospital</p> <p>Products:</p> <p>Micra™ TPS, Medtronic Inc (available in Austria)</p> <p>Nanostim™, St. Jude Medical (available in Austria by end of 2016)</p> <p>MESH term: Pacemaker, Artificial [E07.305.250.750]</p>
Control	<p>Conventional VVI(R) pacemaker</p> <p>MESH term: Pacemaker, Artificial [E07.305.250.750]</p>
Outcomes	
Efficacy	<p>Cardiovascular mortality</p> <p>Cardiovascular morbidity</p> <p>Patient related quality of life</p> <p>Exercise capacity</p> <p>Pacing performance</p>
Safety	<p>Complication rate</p>

<sup>1</sup> Only in specific instances, where other pacing modes (dual-pacing, atrial pacing) are not recommended

<b>Study design</b>	
Efficacy	Randomised controlled trials (Non-inferiority) <sup>2</sup> Prospective non-randomised controlled trials
Safety	Randomised controlled trials Prospective non-randomised controlled trials Prospective case series or registries with >100 patients

*ESC – European Society of Cardiology; AV – atrioventricular; TPS – transcatheter pacing system;  
VVIR – Single-chamber ventricular pacing with response modulation*

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<sup>2</sup> Randomised controlled trials comparing leadless pacemakers with traditional pacemakers are desired, since they are appropriate (adequate number of patients, intervention not urgent) and ethical (clinical equipoise, patients able to give consent) and necessary due to small plausible effect sizes. Blinding of operators and patients however is not possible, and placebo-controlled trials would be unethical due to the availability of an effective treatment.

## 2 Methods

### 2.1 Research questions

Description of the technology	
Element ID	Research question
B0001	What are leadless pacemakers and conventional single-chamber ventricular pacemakers?
A0020	For which indications have leadless pacemakers received marketing authorisation or CE marking?
B0002	What is the claimed benefit of leadless pacemakers in relation to conventional single-chamber ventricular pacemakers?
B0003	What is the phase of development and implementation of leadless pacemakers and conventional single-chamber ventricular pacemakers?
B0004	Who administers leadless pacemakers and conventional single-chamber ventricular pacemakers and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use leadless pacemakers and conventional single-chamber ventricular pacemakers?
B0009	What supplies are needed to use leadless pacemakers and conventional single-chamber ventricular pacemakers?
A0020	What is the marketing authorisation status of leadless pacemakers?
A0021	What is the reimbursement status of leadless pacemakers?

Health problem and Current Use	
Element ID	Research question
A0001	For which health conditions, and for what purposes are leadless pacemakers used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for cardiac arrhythmias?
A0004	What is the natural course of cardiac arrhythmias?
A0005	What are the symptoms and the burden of disease for the patients with cardiac arrhythmias?
A0006	What are the consequences of cardiac arrhythmias for the society?
A0024	How are cardiac arrhythmias currently diagnosed according to published guidelines and in practice?
A0025	How are cardiac arrhythmias currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are leadless pacemakers utilised?

Clinical Effectiveness	
Element ID	Research question
D0005	How do leadless pacemakers affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How do leadless pacemakers affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of leadless pacemakers on patients' body functions?
D0016	How does the use of leadless pacemakers affect activities of daily living?
D0012	What is the effect of leadless pacemakers on generic health-related quality of life?
D0013	What is the effect of leadless pacemakers on disease-specific quality of life?
D0017	Was the use of leadless pacemakers worthwhile?

Safety	
Element ID	Research question
D0001	What is the expected beneficial effect of leadless pacemakers on mortality?
D0003	What is the effect of leadless pacemakers on the mortality due to causes other than the target disease?
C0008	How safe are leadless pacemakers in comparison to conventional single-chamber ventricular pacemakers?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?
C0007	Are leadless pacemakers and conventional single-chamber ventricular pacemakers associated with user-dependent harms?

## 2.2 Sources

### Description of the technology

#### Quellen

- ✿ Handsearch in the POP, AdHopHTA and CRD databases for Health Technology Assessments
- ✿ Background publications identified in database search: see Section 2.3
- ✿ Documentation provided by the manufacturers
- ✿ Questionnaire completed by the submitting hospitals

### Health problem and Current Use

- ✿ Handsearch in the POP, AdHopHTA and CRD databases for Health Technology Assessments
- ✿ Background publications identified in database search: see Section 2.3
- ✿ Documentation provided by the manufacturers
- ✿ Questionnaire completed by the submitting hospitals
- ✿ National registries (Statistik Austria)
- ✿ Handsearch for management guidelines

## 2.3 Systematic literature search

#### systematische Literatursuche in fünf Datenbanken

The systematic literature search was conducted on 09.12.2015 in the following databases:

- ✿ Medline via Ovid
- ✿ Embase
- ✿ Pubmed
- ✿ CRD (DARE, NHS-EED, HTA)
- ✿ Cochrane library

After deduplication, overall 144 citations were included. The specific search strategy employed can be found in the appendix.

Manufacturers from the two available products (Medtronic, St. JudeMedical) submitted 8 publications of which 0 new citations were identified.

**insgesamt  
144 Publikationen  
identifiziert**

No additional references were found by handsearch.

## 2.4 Flow chart of study selection

Overall 144 hits were identified. The references were screened by two independent researchers (AK, RE) and in case of disagreement a third researcher was involved to solve the differences. The selection process is displayed in Figure 2-1.

**Literaturauswahl**

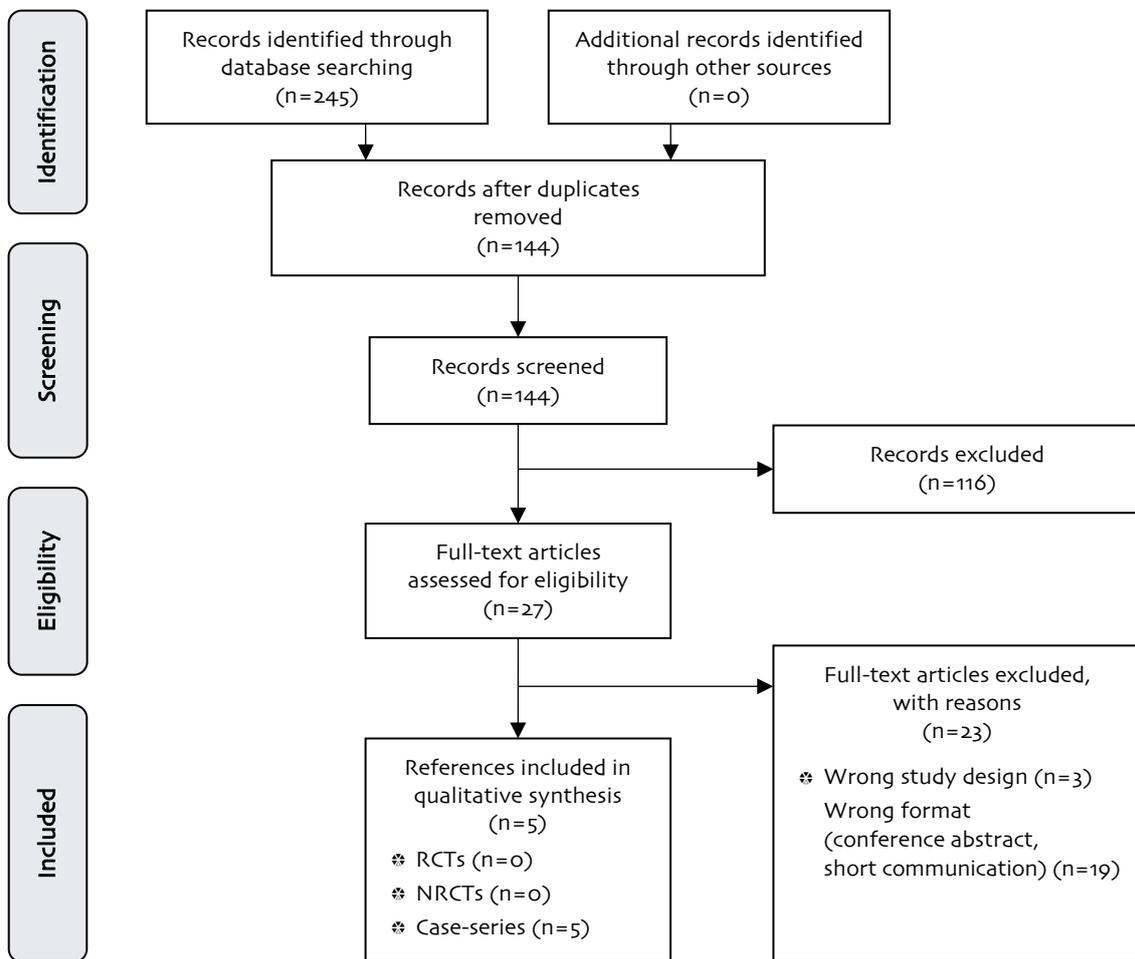


Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

## 2.5 Analysis

The information was retrieved from the sources identified. No further analysis was performed.

Quality was assessed using the EUnetHTA checklist for case series (see Table A-2).

## 2.6 Synthesis

The questions were answered in plain text format with reference to GRADE evidence tables that are included in Table 7-1.

### 3 Description and technical characteristics of technology

#### Features of the technology and comparators

##### B0001 – What are leadless pacemakers and conventional single-chamber ventricular pacemakers?

Leadless cardiac pacemakers (LCP) are self-contained intracardiac devices that are designed to have the same function as traditional cardiac pacemakers, but are miniaturized and can be implanted entirely inside the right ventricle of the heart via a steerable catheter [3]. In conventional pacemakers, a separate pulse generator containing the battery and the machinery for sensing and timing of the electrical impulses is placed in a (most commonly) pectoral subcutaneous pocket. The electrical impulses are delivered from the generator to the heart through one or more transvenous leads, depending on the desired pacing mode [4]. The majority of conventional pacemakers are capable of several pacing modes, such as single-chamber ventricular or atrial pacing, or dual chamber pacing. The current generation of single-unit LCP can only be used for single-chamber pacing, specifically right ventricular pacing [4]. Pacing modes are classified according to a standardised code (Table 3-1).

**miniaturisierte, vollständig implantierbare Herzschrittmacher (HSM)**

This limitation does not apply to multi-component leadless pacing systems using ultrasound or induction to deliver electrical impulses from a separate generator to the heart; these systems are however not the subject of the present report, which is restricted to fully self-contained leadless pacemakers.

Table 3-1: Revised NBG code for pacing nomenclature [5]

Position	I	II	III	IV	V
Category	Chamber(s) paced	Chamber(s) sensed	Response to sensing	Rate modulation	Multisite pacing
	o = None A = Atrium V = Ventricle D = Dual (A+V)	o = None A = Atrium V = Ventricle D = Dual (A+V)	o = None T = Triggered I = Inhibited D = Dual (T+I)	o = None R = Rate modulation	o = None A = Atrium V = Ventricle D = Dual (A+V)

#### Marketed products

Currently two leadless pacing systems are available: the Nanostim™ leadless cardiac pacemaker and the Micra™ transcatheter pacing system (TPS) (see Table 3-2 for a comparison of the specifications). Both have a volume of up to 1cm<sup>3</sup> and thus are approximately ten times smaller than conventional single-chamber ventricular (VVI) pacemakers [3, 4]. The devices have an estimated battery longevity of approximately ten years, which is comparable to conventional pacemakers [3, 4]. In theory, both systems offer a device retrieval option, allowing repositioning or retrieval of the devices following implantation [3, 4]. There are no data, however, on the removal of chronic implanted systems [3]. Main differences between the systems are related to the fixation mechanism: Nanostim™ LCP uses a screw-in helix and a secondary fixation mechanism of three nylon tines, whereas the Micra™ TPS uses four self-expanding nitinol tines [4].

**zwei Produkte: Nanostim™ leadless cardiac pacemaker und Micra™ transcatheter pacing system**

Table 3-2: Specifications of fully self-contained leadless cardiac pacemakers

	Nanostim™ leadless cardiac pacemaker	Micra™ transcatheter pacing system
Manufacturer	St. Jude Medical	Medtronic
Volume (cm <sup>3</sup> )	1	0.8
Size (h x w), maximum thickness, mm	42 x 5.99	25.9 x 6.7
Fixation mechanism	Screw-in helix (+ nylon tines)	Self-expanding nitinol tines
Pacing mode	VVI(R)	VVI(R)
Battery longevity (years)	9.8	10
Device retrieval option	Yes	Yes
CE mark	Yes, October 2013	Yes, April 2015
FDA approval	No, investigational device	No, investigational device

**Indikationen  
wie für Einkammer-  
schrittmacher**

According to the manufacturer's website [6] Nanostim™ leadless pacemaker is indicated for:

- ✦ Chronic atrial fibrillation with 2 or 3° atrioventricular block (AV) or bifascicular bundle branch block (BBB),
- ✦ Normal sinus rhythm with 2 or 3° AV or BBB block and a low level of physical activity or short expected lifespan, or
- ✦ Sinus bradycardia with infrequent pauses or unexplained syncope with electrophysiological findings.

According to the product manual [7] the Micra™ Transcatheter Pacing System is indicated for use to improve cardiac output, prevent symptoms, or protect against arrhythmias related to cardiac impulse formation or conduction disorders. The device is indicated for use in patients who are experiencing exercise intolerance or exercise restrictions related to an arrhythmia. The device is designed to be used only in the right ventricle.

**Boo02 – What is the claimed benefit of leadless pacemakers  
in relation to conventional single-chamber ventricular pacemakers?**

**angegebener Nutzen:  
Vermeidung von  
Komplikationen  
verursacht durch  
externe Generatoren  
und Sonden**

In contrast to traditional pacemakers, leadless pacemakers do not require the placement of an external pulse generator in a surgical pocket in the chest and the transmission of impulses through transvenous leads. The claimed benefit is accordingly the avoidance of complications associated with these two components of traditional pacemaker implantation. The subcutaneous pocket has a potential for local complications such as skin erosion, pocket haematoma and pocket infection. In up to six out of ten patients, it causes reduced mobility in the shoulder region where the pulse generator is placed [8]. Lead-related complications include venous obstructions, insulation breaks, lead dislodgements, electrical malfunction lead fractures and infection. Of particular concern are infections requiring lead extraction, as the procedure is associated with a high risk of complications [9, 10].

**kürzere  
Behandlungsdauer,  
verbesserte  
Lebensqualität**

Additional benefits are expected with regards to shorter procedure and recovery times and a better quality of life as a result of the maintenance of shoulder mobility and the absence of a lump or scar.

### **B0003 – What is the phase of development and implementation of leadless pacemakers and conventional single-chamber ventricular pacemakers?**

Conventional single-chamber ventricular pacemakers are a well-established standard technique [1].

Leadless pacemakers are an emerging technology, not yet established in use. The technology represents a modification of the existing pacemaker technology.

**konventionelle HSM gut etablierte, sondenlose HSM aufkommende Technologie**

### **Administration, Investments, personnel and tools required to use the technology and the comparator(s)**

#### **B0004 – Who administers leadless pacemakers and conventional single-chamber ventricular pacemakers and in what context and level of care are they provided?**

#### **B0008 – What kind of special premises are needed to use leadless pacemakers and conventional single-chamber ventricular pacemakers?**

#### **B0009 – What supplies are needed to use leadless pacemakers and conventional single-chamber ventricular pacemakers?**

Both LCP and traditional pacemakers are provided in specialised centres with interventional cardiology in the cardiac catheterization, laboratory sedative medication and local anaesthesia. LCP implantation further requires fluoroscopy to guide positioning of the device.

**Setting: interventionelle Kardiologie**

Setting and staff required for LCP implantation do not differ from traditional pacemaker procedures. However, given the novel implantation method for this device, additional training for medical specialists who implant LCP will be required.

**spezielles Training für LCP Implantation notwendig**

### **Regulatory & reimbursement status**

#### **A0020 – What is the marketing authorisation status of leadless pacemakers?**

#### **A0021 – what is the reimbursement status of leadless pacemakers?**

#### **Nanostim™ LCP**

Europe: In October 2013, St. Jude Medical received CE mark approval (for European commercialization) to market the Nanostim™ leadless pacemaker in the European Union (EU). According to the EU registry, the Leadless Observational Study (NCT02051972) is ongoing in Europe with sites in the United Kingdom, Germany, Italy, the Czech Republic, France, Spain, and the Netherlands with a planned enrolment of 1,000 patients and follow-up for 5 years. Data from 300 patients with 6 months of follow-up will be used to meet the post market clinical follow-up requirements for CE marking.

**Nanostim™:  
CE Mark seit  
Oktober 2013**

**FDA Zulassung  
für 2016 angestrebt**

The United States, Canada and Australia: A trial designed to investigate Nanostim™ for the United States Food and Drug Administration (FDA) approval was initiated in February 2014 (NCT02030418). Sites from the USA, Canada and Australia participated in the LEADLESS II study. The enrolments (667 patients) were completed in 2015 and the pre-specified safety/effectiveness endpoints were met. FDA has provided approval to enrol up to 900 additional patients in the continued access phase and enrolments are underway. The device has not yet been approved by FDA, Health Canada or TGA (Australia). FDA approval of the device is sought in 2016.

Japan: Enrolments in the Leadless Japan pre-market study are underway and the plan is to enrol 22 Japanese patients in the study to meet the primary end-point analysis. (Information on regulatory status was submitted by the manufacturer)

**Micra™ TPS**

**Micra™  
CE Mark seit 2015  
  
FDA Zulassung für  
2017-2018 angestrebt**

Medtronic received CE mark for Micra™ TPS in 2015, and the US FDA approval is sought in 2017-2018. An FDA approval study on Micra™ TPS was initiated in November 2013 (NCT02004873). (Information on regulatory status was submitted by the manufacturer)

Leadless pacemakers are currently reimbursed in Austria via the MEL code DE080 Implantation of a single-chamber pacemaker.

## 4 Health Problem and Current Use

### Overview of the disease or health condition

#### A0001 – For which health conditions, and for what purposes are leadless pacemakers used?

Leadless pacemakers are developed as alternatives for traditional permanent cardiac pacemakers for the treatment of a variety of cardiac arrhythmias. The natural pacemaker of the heart is the sinus node located in the right atrium. It generates around 70 regular electrical impulses per minute (at rest), that are conducted across the rest of the heart. This triggers contraction of the atriums followed by the contraction of the ventricles allowing the blood flow. Cardiac bradyarrhythmias are mainly due to either the incapacity of the sinus node to produce enough number of impulses per minute (sinus node disease) or the disturbance in atrioventricular (AV) conduction.

Atrial fibrillation is an abnormal heart rhythm characterized by rapid and irregular beating, but can be associated with bradycardia. The principal reason to place a pacemaker in a patient with atrial fibrillation (AF) is to treat symptomatic bradycardia. Pacing has not been shown to prevent the development of AF.

The purpose of cardiac pacing is to provide an appropriate heart rate and heart response to reestablish effective circulation and more normal haemodynamics that are compromised by a slow heart rate (bradycardia or bradyarrhythmia: <60 beats per minute). Permanent pacemaker implantation is further considered to alleviate symptoms associated with a bradyarrhythmia (e.g. dizziness, light-headedness, syncope, fatigue, poor exercise tolerance) or to prevent the possible worsening of the rhythm disturbance [11].

#### A0002 – What is the disease or health condition in the scope of this assessment?

In the scope of this assessment are cardiac arrhythmias in adults for which single-chamber ventricular pacing (VVI) is indicated. Guidelines for implantation of permanent pacemakers have been established by the American College of Cardiology, the American Heart Association and the Heart Rhythm Society (ACC/AHA/HRS) [2] and by the European Society of Cardiology (ESC) [1].

VVI pacing mode is the method of choice for patients with chronic atrial fibrillation (AF; ICD-10 I.44) who require a pacemaker due to slow ventricular response (atrioventricular (AV) block, Class I recommendation [1]).

This pacing mode may be considered for patients with AV block, even in the absence of AF, on an individual basis, but in general is not considered the first choice [1].

In patients with sinus node disease as well as in patients with atrial fibrillation, pacing is only indicated if bradycardia causes symptoms. Dual-chamber pacing is recommended over VVI pacing [1].

**LCP werden zur Behandlung kardialer Arrhythmien eingesetzt**

**Ursachen für Bradycardia:**  
- Störung des Sinusknoten  
- Blockierung der Erregungsüberleitung auf den AV-Knoten

**Fokus dieses Berichts: Indikationen für Einkammerschrittmacher**

**A0003 – What are the known risk factors for cardiac arrhythmias?**

**Bradyarrhythmien können eine Vielzahl an Ätiologien zugrunde liegen**

Bradyarrhythmias requiring cardiac pacing can be caused by a variety of aetiologies [1]. Intrinsic causes are:

- ✿ Idiopathic (ageing) degeneration
- ✿ Ischaemic heart disease
- ✿ Infiltrative diseases (e.g. sarcoidosis, amyloidosis, haemochromatosis)
- ✿ Collagen vascular diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis, scleroderma)
- ✿ Congenital diseases, including sinus node and AV node disease
- ✿ Infective diseases (e.g. Lyme disease)
- ✿ Rare genetic diseases
- ✿ Surgical trauma: valve replacement (including percutaneous aortic replacement), heart transplantation
- ✿ Intended or unintended AV block due to catheter ablation procedure

**Unterscheidung zwischen extrinsischen und intrinsischen Faktoren**

Extrinsic causes are:

- ✿ Physical training (sports)
- ✿ Vagal reflex: vasovagal, situational, carotid sinus syndrome
- ✿ Idiopathic paroxysmal AV block
- ✿ (Adverse) drug effects
- ✿ Cocaine abuse and other recreational drugs
- ✿ Electrolyte imbalance: hypokalaemia, hyperkalaemia
- ✿ Metabolic disorders: hypothyroidism, hypothermia, anorexia nervosa
- ✿ Neurological disorders
- ✿ Obstructive sleep apnoea

**A0004 – What is the natural course of cardiac arrhythmias?**

The natural history and the role of pacing differ depending on the type of bradyarrhythmia.

**AV Block: erhöhtes Sterberisiko aufgrund von Herzversagen**

In patients with untreated AV block, death can occur due to heart failure secondary to low cardiac output or to sudden cardiac death caused by prolonged asystole or bradycardia-triggered ventricular tachyarrhythmia. Several observational studies indicate that pacing prevents recurrence of syncope and improves survival [1].

**SND: kein erhöhtes Sterberisiko**

Total survival and the risk of sudden cardiac death of patients with sinus node disease (SND, also sick sinus syndrome) are similar to the general population [12, 13]. There is a strong consensus that patients with SND will benefit from cardiac pacing for symptom relief (only) [1].

## Effects of the disease or health condition on the individual and society

### A0005 – What is the burden of disease for patients with cardiac arrhythmias?

Symptoms are present if bradycardia is severe enough to compromise blood flow: they may comprise fatigue, dizziness, syncope (fainting), dyspnoea, chest pain, weakness and a reduced exercise capacity.

Major complications associated with the implantation of a single-chamber RV pacemaker include lead-related re-interventions, local infections requiring re-intervention, device-related systemic infections, endocarditis, pneumothorax requiring drainage, cardiac perforation, pocket revisions because of pain, generator-lead interface problems requiring re-intervention, haematomas requiring re-intervention, deep venous thrombosis, Twiddler's syndrome, wound revisions, stroke, myocardial infarctions, and procedure-related deaths. Minor complications include haematomas resulting in a prolonged hospital stay, hospital re-admissions, additional out-patient visits, wound infections treated with antibiotics, conservatively treated pneumothorax, and lead dislodgements without re-intervention [9, 14].

Up to 6% of patients experience major complications within the first six months following implantation of cardiac electronic devices (all types), with lead-related re-intervention being the single most common complication, followed by infections, pneumothorax and cardiac perforation. For single-chamber pacemakers, this risk is however significantly lower, with 3.3% experiencing any major complication [14]. Also the risk of lead complications is lower for single chamber right ventricular pacemakers compared to other pacemaker types [10].

### A0006 – What are the consequences of cardiac arrhythmias for the society?

The prevalence of indications requiring single-chamber pacemaker implantation in Austria is unclear. In 2011 over 116,000 patients with cardiac arrhythmias were recorded [15]. Each year there are about 6,000 pacemaker implantations in Austria, of which approximately one third are single-chamber pacemakers [16, 17].

Symptome bei eingeschränktem Blutfluss

schwere Komplikationen sind u. a. erforderliche Reinterventionen aufgrund von Sondendefekten oder Sonden-/Generatorproblemen, Infektionen; Herzperforation, Pneumothorax

ca. 6.000 Schrittmacherimplantationen pro Jahr in Ö

## Current clinical management of the disease or health condition

### A0024 – How are cardiac arrhythmias currently diagnosed according to published guidelines and in practice?

There is no defined heart rate below which treatment is indicated. When deciding on the need for cardiac pacing, the correlation between symptoms and bradyarrhythmia needs to be established. The diagnosis of bradyarrhythmia is usually made from a standard electrocardiogram (ECG) when persistent, and from a standard ECG or more prolonged ECG recordings (ambulatory monitoring or implantable loop recorder) when intermittent. Provocative testing or an electrophysiological study may be required when a bradycardia is suspected but not documented. This strategy is based on the assumption that provoked abnormalities will have the same mechanism as spontaneous episodes. (Long-term) ECG monitoring has the advantage of high diagnostic accuracy, whereas provocative testing is faster, but more prone to misdiagnosis [1].

Diagnose über Langzeit-EKG oder Stresstest

**A0025 – How are cardiac arrhythmias currently managed according to published guidelines and in practice?**

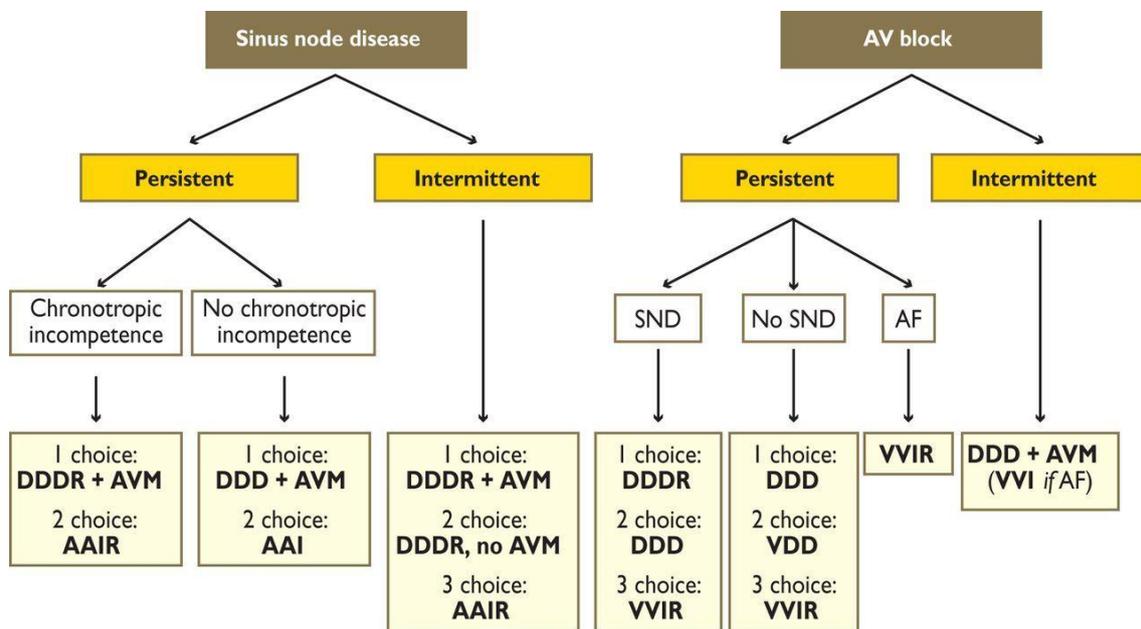
**A0007 – What is the target population in this assessment?**

**A0023 – How many people belong to the target population?**

**sondenlose  
Herzschrittmacher  
als Alternative zu  
herkömmlichen  
VVI Schrittmachern**

Leadless pacemakers are intended to be used as replacement for conventional single-chamber right ventricular pacemakers. The target population consists of the patients in which this pacing mode is indicated. There are no data available on the number of patients belonging to the target population. Approximately 2,000 patients receive a single-chamber pacemaker each year in Austria [16, 17].

The decision regarding pacemaker implantation and choice of pacing mode is based on three clinical factors: the location of the conduction abnormality, the presence of symptoms and their association with the bradyarrhythmia, and the absence of a reversible cause (Figure 4-1).



SND Sinus node disease; AV atrioventricular; AF Atrial fibrillation; AVM AV delay management. For nomenclature of pacing modes see Table 3-1: Revised NBG code for pacing nomenclature [5]

Figure 4-1: Choice of the pacing mode (ESC guidelines, [1])

**VVI Methode der Wahl für PatientInnen mit chronischem Vorhofflimmern und AV Block**

VVI pacing mode is the method of choice for patients with chronic atrial fibrillation (AF; ICD-10 I.44) who require a pacemaker due to slow ventricular response (atrioventricular (AV) block, Class I recommendation [1]).

Atrioventricular (AV) block is defined as a delay or interruption in the transmission of an impulse from the atria to the ventricles due to an anatomical or functional impairment in the conduction system. The conduction can be delayed, intermittent, or absent. The commonly used classification includes first degree (slowed conduction without loss of atrioventricular synchrony), second degree (intermittent loss of atrioventricular conduction, often in a regular pattern, e.g., 2:1, 3:2, or higher degrees of block), and third degree or complete AV block [11].

In patients with acquired AV block (but no AF) or sinus node disease (SND), the condition can be managed with either a single or dual chamber pacemaker. Dual-chamber pacing is recommended over single chamber ventricular pacing for avoiding pacemaker syndrome, lowering the risk of developing AF and improving quality of life (class IIa recommendation, [1]). However, the decision should take into account the increased complication risk and costs of dual-chamber pacing.

**nicht die erste Wahl für PatientInnen mit AV Block ohne Vorhofflimmern**

Sinus bradycardia (SB) is a rhythm in which fewer impulses than the normal number arise from the sinoatrial node. It is caused by a primary sinus node dysfunction or by other conditions (drugs, acute myocardial infarction, obstructive sleep apnoea, etc.). In general, SB is only an indication for pacing if bradycardia is symptomatic, if the symptoms can be attributed to SB and if a reversible cause can be excluded. Dual-chamber pacing is the pacing mode of first choice and unnecessary right ventricular pacing should be avoided since it may cause AF and deterioration of heart failure. In the subset of patients with SND in whom AV conduction is intact, single-chamber is feasible (AAI mode); atrial pacemakers are recommended over ventricular pacemakers [1].

**VVI nicht erste Wahl für SND ohne AV Block, sollte vermieden werden**

## Target population

### A0011 – How much are leadless pacemakers utilised?

Estimates of the expected yearly utilisation of leadless pacemaker vary from 270 to 2,400 implantations in Austria (information from the submitting hospitals).

**geschätzter Bedarf zwischen 270 und 2.400 Implantationen**



## 5 Clinical effectiveness

### 5.1 Outcomes

The implantation of pacemakers serves the primary purpose to alleviate symptoms associated with a slow heart rhythm. The pacemaker does not treat atrial fibrillation, the main indication for single chamber ventricular pacing, itself. Recent reports indicate that prognosis of bradycardia pacemaker recipients are mainly determined by comorbid diseases and a bradycardia pacing indication as such does not influence survival [18].

The following outcomes were therefore defined as *crucial* to derive a recommendation:

- ✧ Health related quality of life (HRQoL)
- ✧ Exercise capacity

For the assessment of HRQoL, Aquarel is a QoL questionnaire specifically designed for patients with PM, which must be used with the SF-36 generic questionnaire [19-21]. Aquarel consists of 20 questions divided into three domains: chest discomfort (corresponding to questions 1 to 6, about chest pain, and questions 11 and 12, about dyspnea at rest), arrhythmia (corresponding to questions 13 to 17), and dyspnea on exertion (corresponding to questions 7 to 10, about dyspnea on exertion, and questions 18 to 20, about fatigue).

Exercise capacity was chosen as a measure of functional capacity. The assessment is typically performed on a motorised treadmill or a stationary cycle ergometer and exercise duration, maximal exercise capacity and maximal oxygen uptake are measured [22].

Pacing performance was the primary efficacy endpoint in all studies identified, however this endpoint is not a clinical endpoint and hence was not defined as crucial to derive a recommendation.

**Wirksamkeit –  
entscheidungsrelevante  
Endpunkte:  
Lebensqualität,  
Belastungsfähigkeit**

### 5.2 Included studies

There are no comparative studies to assess the effectiveness of leadless pacemakers. We identified five references to three prospective multi-centre single arm studies that reported the performance of leadless pacemakers [23-27] in a total of 633 participants (efficacy cohorts). All studies were sponsored by device manufacturers. Study characteristics and results of included studies are displayed in Table A-1.

All three studies included patients with indications for VVI pacing, with a restriction on non-pacemaker dependent patients in one study [23, 25]. For the majority of the study participants, pacing was indicated due to atrial fibrillation with AV block (range 56-67%). Other indications were sinus node dysfunction (range 15-35%) and AV block (range 8.7-18%). For the latter two indications, reasons for the selection of VVI pacing mode were the expectation of only infrequent need for pacing, advanced age of the patient, patient preference, conditions that precluded implantation of a transvenous pacemaker system or significant comorbidities.

**3 prospektive  
Einzelarmstudien mit  
633 TeilnehmerInnen  
(Wirksamkeitskohorte)**

**verschiedene  
Indikationen für  
VVI Herzschrittmacher**

**hohes Alter, viele  
Begleiterkrankungen**

Mean age of the study participants was 76 years in all three studies. The study populations were predominantly male (range 59-67%). Comorbidities were frequent, with almost 80% of the participants suffering from hypertension.

However none reported any of the outcomes defined as crucial to derive a recommendation.

## 5.3 Results

### Morbidity

#### **Do005 – How do leadless pacemakers affect symptoms and findings (severity, frequency) of cardiac arrhythmias?**

None of the studies reported results on symptoms associated with cardiac arrhythmias.

#### **Do006 – How do leadless pacemakers affect progression (or recurrence) of cardiac arrhythmias?**

None of the studies reported results on progression of cardiac arrhythmias.

None of the studies reported pacing-induced arrhythmias.

### Function

#### **Do011 – What is the effect of leadless pacemakers on patients' body functions?**

None of the studies reported results on patient's body functions.

#### **Do016 – How does the use of leadless pacemakers affect activities of daily living?**

None of the studies reported results on exercise capacity.

### Health-related quality of life

#### **Do012 – What is the effect of leadless pacemakers on generic health-related quality of life?**

#### **Do013 – What is the effect of leadless pacemakers on disease-specific quality of life?**

None of the studies reported results on health-related quality of life.

### Patient satisfaction

#### **Do017 – Was the use of leadless pacemakers worthwhile?**

None of the studies reported results on patient satisfaction.

keine Ergebnisse  
zu klinischen  
Wirksamkeitsendpunkten

## 6 Safety

### 6.1 Outcomes

The claimed benefit of leadless pacemakers in comparison to conventional pacemakers is the avoidance of complications associated with the surgical generator pocket or with the leads. In particular local complications such as hematoma, skin breakdown or pocket infection, as well as lead failures and venous obstruction due to long term transvenous implantation can be ruled out using leadless pacemakers.

However complications related to the transvenous implantation procedure (cardiac tamponade, pneumothorax, device dislodgement) are a safety concern with leadless pacemakers. The implantation of leadless pacemakers uses a different approach than that used for transvenous leads and requires substantially larger venous access tools. There were two halts to the Nanostim™ trials in 2014 and 2015, due to reports of serious adverse events, including perforation of the heart and dislodgement of the device.

Therefore, the following outcomes were defined as *crucial* to derive a recommendation:

- ✧ Complication rates
  - ✧ Serious Adverse Effect (SAE)
  - ✧ Adverse device effect (ADE)
  - ✧ Serious adverse device effect (SADE)
- ✧ Mortality (Overall and procedure-related)

In accordance with the EC guidelines on serious adverse event reporting of medical devices<sup>3</sup> these outcomes are defined as follows:

*Serious Adverse Event (SAE)* is an adverse event that led to a death, to a serious deterioration in health of the subject, that either resulted in a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, or in-patient hospitalization or prolongation of existing hospitalization, or in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function. This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate.

*Adverse Device Effect (ADE)* is an adverse event related to the use of an investigational medical device. First, this includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. Second, this includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

*Serious Adverse Device Effect (SADE)* is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

**Sicherheit –  
entscheidungsrelevante  
Endpunkte:  
Komplikationsrate,  
Mortalität**

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<sup>3</sup> [http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2\\_7\\_3\\_en.pdf](http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_7_3_en.pdf)

## 6.2 Included Studies

3 prospektive Einzelarmstudien mit 1.284 TeilnehmerInnen (Sicherheitskohorte)

There are no comparative studies to assess the safety of leadless pacemakers. We identified five references to three prospective single arm studies (see Section 5.2) that assessed the safety of leadless pacemakers in a total of 1,284 participants [23-27]. Study characteristics and results of included studies are displayed in Table A-1 and in the evidence profile in Table 7-1.

## 6.3 Results

### Mortality

#### D0001 – What is the expected beneficial effect of leadless pacemakers on mortality?

Mortalität 3-5 %  
kardiale Mortalität  
0,8-1 %

Leadless pacemakers are not expected to have a beneficial effect on mortality compared to conventional VVI pacemakers.

Overall mortality ranged from 3 to 5%. Cardiac mortality was reported in two studies with 0.8% [24] and 1% [26, 27], respectively.

#### D0003 – What is the effect of leadless pacemakers on the mortality due to causes other than cardiac arrhythmia?

vier Todesfälle im Zusammenhang mit dem Eingriff

Procedural mortality was reported in all three studies. In LEADLESS I, one patient had a perforation during the implantation procedure, leading to cardiac tamponade. He died of a massive cerebral artery ischaemic infarct five days later [23, 25]. Two procedure-related (but classified as non-device-related) deaths were reported in the LEADLESS II cohort: in one patient LCP implantation was complicated by a large groin haematoma, the patient suffered fatal cardiac arrest 14 days later. The second subject underwent an unsuccessful LCP implant complicated by pericardial effusion, developed atrial fibrillation two days after the operation and died 8 days after the failed LCP implant [24]. In the Micra Transcatheter Pacemaker Study cohort, one death was adjudicated as related to the transcatheter implantation procedure: the patient had a prolonged procedure time due to a concomitant AV node ablation and end stage renal disease and the cause of death was perceived to be metabolic acidosis [26].

### Patient safety

#### C0008 – How safe are leadless pacemakers in comparison to conventional single-chamber ventricular pacemakers?

Komplikationsraten:  
4-6,5 %

The rates of serious adverse device effects ranged between 4% and 6.5% in the three case series.

There was one patient with cardiac injury in the LEADLESS I trial [25], eight in LEADLESS II [23, 24] and 11 cases in the Micra Transcatheter Pacemaker Study [26, 27].

Six dislodgements were reported with the Nanostim™ device [23, 24], but none with the Micra™ TPS system [26, 27]. Other serious adverse events that were attributable either to the device or the procedure included vascular complications, arrhythmia during device implantation and elevated pacing thresholds requiring retrieval and implantation of a new device.

**C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of the technology?**

There are not enough data to answer this question.

**C0007 – Are leadless pacemakers and conventional single-chamber ventricular pacemakers associated with user-dependent harms?**

Leadless pacemakers and conventional single-chamber ventricular pacemakers are associated with user-dependent harms due to the risk of serious adverse events related with the implantation procedure.



## 7 Quality of evidence

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme [28] for each endpoint individually. Each study was rated by two independent researchers (AK, RE). In case of disagreement a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [28].

**Qualität der Evidenz  
nach GRADE:  
sehr niedrig**

GRADE uses four categories to rank the strength of evidence:

- ❖ **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- ❖ **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- ❖ **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- ❖ **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in Table 7-1.

Overall the strength of evidence for the effectiveness and safety of leadless pacemakers in comparison to conventional pacemakers is very low.

Table 7-1: Evidence profile: efficacy and safety of Leadless pacemakers

No of studies/ patients	Study Design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
<b>Efficacy</b>							
<b>Health related quality of life</b>							
No data							
<b>Exercise capacity</b>							
No data							
<b>Safety</b>							
<b>Cardiovascular Mortality</b>							
2/1,251	Prospective single arm studies	Range: 0.8-1%	-1 <sup>4</sup>	o	o	o	Very low
<b>Procedure related Mortality</b>							
3/1,284	Prospective single arm studies	Range: 0.1-3%	-1 <sup>4</sup>	o	o	o	Very low
<b>Complication rate (SADE)</b>							
3/1,284	Prospective single arm studies	Range: 4-6.5%	-1 <sup>4</sup>	o	o	o	Very low

SADE Serious adverse device effects

**Nomenclature for GRADE table:**

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

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<sup>4</sup> No control group

## 8 Discussion

Leadless pacemakers are an emergent technology for which there are only preliminary results available. There are no data on the effect of leadless pacemakers on symptoms or progression of cardiac arrhythmias. Currently, available evidence focusses on the feasibility and safety of the leadless pacemaker implantation procedure.

The results indicate that leadless pacemaker can be successfully implanted and sustain a low pacing threshold for several months. The complications associated with leads and generators can be avoided, but procedural morbidity and mortality is still a concern, and led to two halts of the Nanostim™ trials [29]. The reported rates of serious adverse device effects range from 4 to 6.5% in the three studies [23-27]. Acute complications associated with the implantation procedure might be improved by a learning curve and/or special training to develop proficiency specific for the LCP implantation, in particular the handling of large venous sheaths and the intraprocedural positional integrity testing. Both manufacturers have proposed training programmes in their FDA submissions [30, 31]. However the extent to which the learning effect is able to significantly reduce acute complications remains to be demonstrated.

The two products differ in the rates of dislocations (6 with Nanostim™ LCP vs. 0 with the Micra™ TCP). The differences might be due to the different fixation technologies of the two products (see Table 3-2). It is recommended to re-assess the fixation technology of the Nanostim™ LCP.

The available studies are non-randomised and there is no direct comparison of the benefit of LCP over contemporary single-chamber systems, so no definitive conclusion can be drawn on the superiority or even non-inferiority of the new technology compared to standard therapy. Indirect comparisons with historical data from previous pacemaker studies are difficult, since most studies include patients with dual-chamber pacemakers or other implantable cardiac devices, for which complication rates are considerably higher than for single-chamber pacemakers [9, 10, 14]. There are no data on clinical efficacy endpoints and, in particular, HRQoL was not assessed in the studies. It is unclear, if the avoidance of lead/generator complications translates in a relevant benefit for the patients. In most patients receiving a traditional pacemaker, HRQoL increases in the first year after pacemaker implantation – the occurrence of an in-hospital adverse event however did not have any impact on how HRQoL was perceived 1 year after the pacemaker implantation [32].

In a number of patients, the implantation of a transvenous pacemaker system is precluded because of conditions such as compromised venous access, the need to preserve veins for haemodialysis, thrombosis, a history of infection, or the need for an indwelling venous catheter. While leadless pacemakers potentially represent the only treatment alternative in these patients, it remains to be demonstrated that these patients are not at increased risk for complications associated with the implantation procedure.

Finally, safety data are available only for 6 months follow-up. Battery longevity of leadless pacemakers was estimated to be up to ten years, but actual longevity has not been measured and might be overestimated [33]. So far, there is no definitive answer how pacemaker-dependent patients can be treated after the battery expires. Retrievability of the leadless pacemaker after a prolonged implantation time has not been studied at later timepoints and might

**keine Daten zur klinischen Wirksamkeit**

**LCP Implantation machbar, bei Komplikationsraten von 4 bis 6,5 %**

**kein direkter Vergleich mit herkömmlichen Schrittmachern**

**mögliche Therapieoption für Patienten mit Gegenanzeigen für herkömmliche Schrittmacher**

**verfügbare Daten nur für 6 Monats-Follow-Up**

be compromised by complete encapsulation of the devices observed in autopsies [34]. So far, there is no experience on the feasibility of the implantation of additional LCP in the heart chamber.

**Langzeitdaten und  
Daten zu klinischer  
Wirksamkeit  
erforderlich**

Further evaluation of leadless pacemakers for long-term clinical efficacy and complication rates, compared with traditional pacemakers is required. If long-term efficacy and safety can be demonstrated, leadless pacemakers may represent an alternative treatment option for a subset of patients with cardiac arrhythmias.

## 9 Recommendation

In Table 9-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 9-1: Evidence based recommendations

	The <b>inclusion</b> in the catalogue of benefits is <b>recommended</b> .
	The <b>inclusion</b> in the catalogue of benefits is <b>recommended with restrictions</b> .
<b>X</b>	The inclusion in the catalogue of benefits is <b>currently not recommended</b> .
	The <b>inclusion in</b> the catalogue of benefits is <b>not recommended</b> .

### Reasoning:

The current evidence is not sufficient to prove, that the assessed technology Leadless pacemakers is as effective but more safe than conventional VVI pacemakers. New study results will potentially influence the effect estimate considerably.

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# Appendix

## Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Leadless pacemakers: Results from observational studies

Study (acronym, ID no.)	LEADLESS I – Evaluation of a new cardiac pacemaker (NCT01700244)	The LEADLESS II pacemaker IDE study (NCT02030418)	Micra Transcatheter Pacing Study (NCT02004873)
Reference	[23, 25]	[24]	[26, 27]
<b>Study description</b>			
Country	Czech Republic; Germany; Netherlands	Australia; Canada; USA	USA, Australia, Austria, Canada, Czech Republic, China, Denmark, France, Greece, Hungary, India, Italy, Japan, Malaysia, Netherlands, Serbia, South Africa, Spain, United Kingdom
Sponsor	St. JudeMedical	St. JudeMedical	Medtronic
Intervention/Product	Implantation of a leadless cardiac pacemaker/Nanostim™ LCP	Implantation of a leadless cardiac pacemaker/Nanostim™ LCP	Implantation of a leadless cardiac pacemaker/Micra™ TPS
Comparator	NA	NA	Dual-chamber pacemaker
Study design	Single cohort feasibility trial	Single cohort safety/efficacy study.	Single cohort safety/efficacy study with historical control
Duration of the study	December 2012 – April 2013	February 2014 – September 2015	November 2013 – May 2015
Randomisation method	None	None	None
Blinding method (investigator, patient, outcomes assessor)	Open label	Open label	Open label
Intervention (n=)	33	300 (Primary cohort) 526 (Full cohort)	297 (Efficacy cohort) 725 (Safety cohort)
Control (n=)	0	0	0
Population	Patients indicated for VVI pacing who are not Pacemaker dependant	Patients indicated for VVI(R) pacing	Patients indicated for VVI(R) pacing

Study (acronym, ID no.)	LEADLESS I – Evaluation of a new cardiac pacemaker (NCT01700244)	The LEADLESS II pacemaker IDE study (NCT02030418)	Micra Transcatheter Pacing Study (NCT02004873)
Inclusion criteria	<p>Chronic atrial fibrillation with 2 or 3° AV or bifascicular bundle branch block (BBB block); or</p> <p>Normal sinus rhythm with 2 or 3° AV or BBB block and a low level of physical activity or short expected lifespan (but at least one year); or</p> <p>Sinus bradycardia with infrequent pauses or unexplained syncope with EP findings</p>	<p>Chronic and/or permanent atrial fibrillation with 2 or 3° AV or bifascicular bundle branch block (BBB block), including slow ventricular rates (with or without medication) associated with atrial fibrillation; or</p> <p>Normal sinus rhythm with 2 or 3° AV or BBB block and a low level of physical activity or short expected lifespan (but at least one year); or</p> <p>Sinus bradycardia with infrequent pauses or unexplained syncope with EP findings;</p>	<p>Class I or II indication for pacing (bradycardia due to atrial tachyarrhythmia, sinus node dysfunction, atrioventricular node dysfunction, or other causes)</p>
Exclusion criteria	<ul style="list-style-type: none"> <li>✳ Pacemaker dependent;</li> <li>✳ Known pacemaker syndrome, have retrograde VA conduction or suffer a drop in arterial blood pressure with the onset of ventricular pacing;</li> <li>✳ Pre-existing pacing or defibrillation leads;</li> <li>✳ Pre-existing pulmonary arterial (PA) hypertension or significant physiologically-impairing lung disease;</li> <li>✳ Current implantation of an implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT);</li> <li>✳ Mechanical tricuspid valve prosthesis;</li> <li>✳ Presence of implanted vena cava filter;</li> <li>✳ Presence of implanted leadless cardiac pacemaker;</li> <li>✳ Hypersensitivity to &lt;1mg of dexamethasone sodium phosphate;</li> <li>✳ life-expectancy &lt;12m; pregnant or breastfeeding women</li> </ul>	<ul style="list-style-type: none"> <li>✳ Pacemaker syndrome, retrograde VA conduction or drop in arterial blood pressure with the onset of ventricular pacing;</li> <li>✳ Pre-existing endocardial pacing or defibrillation leads; or</li> <li>✳ Pre-existing pulmonary arterial (PA) hypertension or significant physiologically-impairing lung disease;</li> <li>✳ Current implantation of either conventional or subcutaneous implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT);</li> <li>✳ Mechanical tricuspid valve prosthesis;</li> <li>✳ Implanted vena cava filter;</li> <li>✳ Implanted leadless cardiac pacemaker;</li> <li>✳ Evidence of thrombosis in one of the veins used for access during the procedure;</li> <li>✳ Recent cardiovascular or peripheral vascular surgery within 30 days of enrolment</li> <li>✳ Allergic or hypersensitive to &lt;1mg of dexamethasone sodium phosphate;</li> <li>✳ life-expectancy &lt;12m; pregnant or breastfeeding women</li> </ul>	<ul style="list-style-type: none"> <li>✳ Entirely pacemaker dependent (escape rhythm &lt;30 bpm)* (restriction was lifted following review of the Early Performance Assessment)</li> <li>✳ Existing or prior pacemaker, ICD or CRT device implant;</li> <li>✳ Unstable angina or pectoris, acute myocardial infarction within 30d,</li> <li>✳ Current implantation of neurostimulator or any other chronically implanted electronic device, mechanical tricuspid valve, implanted vena cava filter, or left ventricular assist device;</li> <li>✳ Morbidly obese;</li> <li>✳ Femoral venous anatomy unable for transcatheter procedure;</li> <li>✳ intolerance to device material or hypersensitivity to &lt;1mg dexamethasone;</li> <li>✳ life-expectancy &lt;12m; pregnant or breastfeeding women</li> </ul>
Primary outcome (including measurement tools and measurement times)	<p>S: Complication-free rate (freedom of SADE at 90 days)</p>	<p>S: Complication-free rate (freedom of SADE) at 6 months</p> <p>E: Therapeutically acceptable pacing capture threshold (<math>\leq 2.0</math> V at 0.4 msec) and a therapeutically acceptable sensing amplitude (R wave <math>\geq 5.0</math> mV, or a value equal to or greater than the value at implantation) through 6 months</p>	<p>S: Freedom from major complications related to the Micra™ TPS and/or procedures at 6-month post-implant (within 183 days)</p> <p>E: Adequate pacing capture threshold at 6 months (<math>\leq 2</math> V at a pulse width of 0.24 ms and stable (increase of <math>\leq 1.5</math> V))</p>

Study (acronym, ID no.)	LEADLESS I – Evaluation of a new cardiac pacemaker (NCT01700244)	The LEADLESS II pacemaker IDE study (NCT02030418)	Micra Transcatheter Pacing Study (NCT02004873)
Secondary outcome (including measurement tools and measurement times)	S: Implant success rate (% of subjects leaving the implant procedure with an implanted and functioning LCP device)  E: pacemaker performance characteristics, LCP performance during magnet testing (predischarge) and 6-minute walking test (at 2 weeks)	S: Non-device-related SAE during 6 months of follow-up.  S: SADE and Non-device-related SAE during follow-up (Full cohort)	E: Automated ventricular capture management (VCM) feature by comparing the percentage of subjects with a VCM within +0.5 V of pacing capture thresholds evaluated manually at 6 months  Rate response during treadmill testing in a subset of subjects  Micra™ TPS longevity estimates at 6 months, electrical performance, implant procedure ambulatory ECG monitoring, quality of life, and device orientation  S: Adverse Events  Freedom from SADE at 12 months
Follow-up (months)	12	6 (Primary cohort) Mean ( $\pm$ SD) of 6.9 $\pm$ 4.2 (Full cohort)	6
Loss to follow-up, n (%)	0	0	0
<b>Population characteristics</b>			
Age (mean), y	76.5 $\pm$ 8.4	75.7 $\pm$ 11.6 75.8 $\pm$ 12.1 (Full cohort)	75.9 $\pm$ 10.9 (Safety cohort) vs. 71.1 $\pm$ 12.1
Male, n (%)	22 (67)	193 (64.3) 325 (61.8) (Full cohort)	426 (58.8) (Safety cohort) vs. 1469 (55.1)
Pacing indication, n (%)	Permanent AF with AV block (including AF with slow ventricular response) 22 (67) Sinus rhythm with 2 <sup>nd</sup> /3 <sup>rd</sup> degree AV block and significant comorbidities 6 (18) Sinus bradycardia with infrequent pauses or unexplained syncope 5 (15)	AF with AV block 294 (55.9) Sinus rhythm with high-grade AV block 46 (8.7) Sinus bradycardia with infrequent pauses or syncope 186 (35.4) (Full cohort)	Bradycardia associated with persistent or permanent atrial tachyarrhythmia (64.0%) Sinus-node dysfunction (17.5%) AV block (14.8%) Other reasons (3.7%)
Comorbidities		Diabetes, 143 (27.2) CAD, 201 (38.2) CHF, 82 (15.6) Hypertension, 420 (79.8) Valvular Disease, 106 (20.2)	Diabetes, 207 (28.6) COPD, 90 (12.4) Renal dysfunction, 145 (20.0) CAD, 203 (28.0) AF, 526 (72.6) CHF, 123 (17.0) Hypertension, 570 (78.6) Valvular Disease, 306 (42.2)

Study (acronym, ID no.)	LEADLESS I – Evaluation of a new cardiac pacemaker (NCT01700244)	The LEADLESS II pacemaker IDE study (NCT02030418)	Micra Transcatheter Pacing Study (NCT02004873)
<b>Outcomes</b>			
<b>Efficacy</b>			
Pacing performance	N/A (no threshold defined)	270/300 (90%, 95% CI 86.0-93.2)	292/297 (98.3)
Quality of life	NR	NR	NR
<b>Safety</b>			
Implant success rate, n (%)	32 (97)	504/526 (95.8)	719/725 (99.2)
Overall Mortality, n (%)	1 (3)	28/526 (5.3)	29/725 (4)
Procedure-related mortality, n (%)	1 (3)	2/526 (0.4)	1/725 (0.1*)
Cardiac mortality, n (%)	NR	4/526 (0.8)	7/725 (1.0)
Cardiac morbidity, n (%)	NR	NR	NR
Overall Adverse Events, n (%)	NR	NR	NR
Serious Adverse Events, n (%)	NR	NR	NR
Non-device-related SAE, n (%)	NR	29/526 (5.5)	NR
Overall Adverse Device Effects (ADE), n (%)	NR	NR	NR
Serious Adverse Device Effects (SADE), n (%)	2 (6)	34/526 (6.5)	25/725 (4.0*)
Hospitalization, n (%)	9 (27)	NR	12/725 (2.3*)
Loss of device function, n (%)	NR	NR	1/725 (0.1*)
Cardiac injury, n (%)	1 (3)	8/526 (1.5)	11/725 (1.6*)
Device dislodgement, n (%)	0	6/526 (1.1)	0
Elevated pacing thresholds requiring retrieval/ replacement, n (%)	0	4/526 (0.8)	2/725 (0.3%*)

LCP – Leadless cardiac pacemaker, IDE – Investigational device exemption; TPS – Transcatheter pacing system; NA – not applicable; NR – not reported; SAE – Serious adverse events; VCM – Ventricular capture management; AF – Atrial fibrillation; AV – atrioventricular; COPD Chronic obstructive pulmonary diseases; CAD – Coronary artery disease; CHF – Congestive Heart failure; CI – Confidence interval; ADE – Adverse device events; SADE – Serious adverse device events

\* 183days Kaplan-Meier estimates

## Risk of bias tables

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA [35] and in the Guidelines of EUnetHTA [36-38].

Table A-2: Risk of bias – study level (case series), see [30]

Study	LEADLESS I – Evaluation of a new cardiac pacemaker (NCT01700244)	The LEADLESS II pacemaker IDE study (NCT02030418)	Micra Transcatheter Pacing Study (NCT02004873)
reference/ID	[23, 25]	[24]	[26, 27]
<b>Study objective</b>			
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes	Yes
<b>Study population</b>			
2. Are the characteristics of the participants included in the study described?	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	Yes	Yes	Yes
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Yes	Yes	Yes
5. Were participants recruited consecutively?	Yes	Yes	Unclear
6. Did participants enter the study at similar point in the disease?	No	No	No
<b>Intervention and co-intervention</b>			
7. Was the intervention clearly described in the study?	Yes	Yes	Yes
8. Were additional interventions (co-interventions) clearly reported in the study?	No	No	No
<b>Outcome measures</b>			
9. Are the outcome measures clearly defined in the introduction or methods section?	Yes	Yes	Yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	Yes	Yes
11. Were outcomes measured before and after intervention?	No	No	No
<b>Statistical Analysis</b>			
12. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes
<b>Results and Conclusions</b>			
13. Was the length of follow-up reported?	Yes	Yes	Yes
14. Was the loss to follow-up reported?	Yes	Yes	Yes
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	No	No	Yes
16. Are adverse events reported?	Yes	Yes	Yes
17. Are the conclusions of the study supported by results?	Yes	Yes	Yes
<b>Competing interest and source of support</b>			
18. Are both competing interest and source of support for the study reported?	Yes	Yes	Yes
Overall Risk of bias	Low	Low	Low

## Applicability table

Table A-3: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
<b>Population</b>	The majority of study participants had chronic atrial fibrillation with AV block. A substantial number of participants had a pacemaker indication due to SND or AV block without AF based on individual factors precluding dual-chamber pacing. It is unclear if the selection of patients for VVI pacing in Austria results in comparable frequencies of the respective indication groups.
<b>Intervention</b>	In the studies, the intervention was the transcatheter implantation of one of two marketed products (Nanostim™ LCP and Micra™ TPS), which corresponds to the products likely to be used in Austria.
<b>Comparators</b>	There were no comparators.
<b>Outcomes</b>	The main outcomes reported in the studies were pacing performance for efficacy and complication rates for safety. No clinical outcomes were reported on efficacy. For safety, the reported outcomes are clinically relevant.
<b>Setting</b>	In all studies, the intervention was performed in a clinical setting, corresponding to the utilisation setting in Austria. Two studies were led in Europe, one in Australia, Canada and the US. No applicability issues are expected from the geographical setting.

## List of ongoing studies

There are no randomised controlled trials on leadless pacemakers registered.

Table A-4: List of ongoing non-RCT studies on leadless pacemakers

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT02030418 The LEADLESS Pacemaker IDE Study (Leadless II)	Bradycardia	Device: Leadless Pacemaker	None	Complication-Free Rate Pacing thresholds and R-wave amplitudes within the therapeutic range	June 2015	St. Jude Medical
NCT02536118 Micra Transcatheter Pacing System Post-Approval Registry	Bradycardia	Device: Micra™ Transcatheter Pacing System	None	Acute complication rate Long-term complication free survival	August 2023	Medtronic
NCT02004873 Micra Transcatheter Pacing Study	Class I or II Indication for Implantation of a Single Chamber Ventricular Pacemaker According to ACC/AHA/HRS 2001 Guidelines and Any National Guidelines	Device: Micra™ Pacemaker Implant	None	Major Complications Pacing Capture Threshold Success	May 2015	Medtronic Cardiac Rhythm Disease Management
NCT02488681 Micra Transcatheter Pacing System Continued Access Study Protocol	Bradycardia	Device: Micra™ Pacemaker Implant	None	Adverse Events	November 2016	Medtronic
NCT02051972 The LEADLESS Observational Study	Indications for VVI(R) Pacemaker	Device: Implanted with a Nanostim™ leadless pacemaker system	None	Complication free-rate	June 2017	St. Jude Medical

## Literature search strategies

### Search strategy for CRD

Search Name: Leadless Pacemakers (MEL2016 AKis/ER)	
Search Date: 09.12.2015	
ID	Search
#1	MeSH DESCRIPTOR Pacemaker, Artificial EXPLODE ALL TREES
#2	MeSH DESCRIPTOR Cardiac Pacing, Artificial EXPLODE ALL TREES
#3	(pacemaker*)
#4	#1 OR #2 OR #3
#5	(leadless)
#6	((leadless OR transcatheter*) NEAR pacing)
#7	#5 OR #6
#8	#4 AND #7
Total: 2 Hits	

### Search strategy for Embase

Search Name: Leadless Pacemakers (MEL2016 AKis/ER)	
Search Date: 09.12.2015	
ID	Search
#13	`heart pacing'/exp OR `artificial pacemaker'/exp OR pacemaker* OR peacemaker* OR `pace-maker' OR `pace-makers' OR `peace-maker' OR `peace-makers' AND (leadless OR (leadless OR transcatheter*) NEAR/4 pacing)
#12	leadless OR (leadless OR transcatheter*) NEAR/4 pacing
#11	(leadless OR transcatheter*) NEAR/4 pacing
#10	leadless
#9	`heart pacing'/exp OR `artificial heart pacemaker'/exp OR pacemaker* OR peacemaker* OR `pace-maker' OR `pace-makers' OR `peace-maker' OR `peace-makers'
#8	`peace-makers'
#7	`peace-maker'
#6	`pace-makers'
#5	`pace-maker'
#4	peacemaker*
#3	pacemaker*
#2	`artificial heart pacemaker'/exp
#1	`heart pacing'/exp
Total: 128 Hits	

## Search strategy for Medline

Search Name: Leadless Pacemakers (MEL2016 AKis/ER)	
Search Date: 09.12.2015	
ID	Search
#1	exp Pacemaker, Artificial/
#2	exp Cardiac Pacing, Artificial/
#3	pacemaker*.mp.
#4	1 or 2 or 3
#5	leadless.mp.
#6	((leadless or transcatheter*) adj5 pacing).mp.
#7	5 or 6
#8	4 and 7
Total: 58 Hits	

## Search strategy for Pubmed

Search Name: Leadless Pacemakers (MEL2016 AKis/ER)	
Search Date: 09.12.2015	
ID	Search
#1	(Pacemaker, Artificial[MH] OR Cardiac Pacing, Artificial[MH] OR pacemaker*) AND (leadless OR leadless pac* OR transcatheter pac*)
Total: 55 Hits	

## Search strategy for Cochrane

Search Name: Leadless Pacemakers (MEL2016 (AK/RE)	
Search Date: 09.12.2015	
ID	Search
#1	MeSH descriptor: [Pacemaker, Artificial] explode all trees
#2	MeSH descriptor: [Cardiac Pacing, Artificial] explode all trees
#3	(pacemaker*) (Word variations have been searched)
#4	#1 OR #2 OR #3
#5	(leadless OR transcatheter*) near pacing (Word variations have been searched)
#6	leadless (Word variations have been searched)
#7	#5 or #6
#8	#4 and #7
Total: 2 Hits	