Leadless pacemakers for right ventricle pacing

Systematic Review
Update 2017

Ludwig Boltzmann Institut
Health Technology Assessment

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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.icmje.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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Content

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List of abbreviations

ACC ..... American College of Cardiology
ADE ..... Adverse Device Effects
AF ..... Atrial fibrillation
AHA ..... American Heart Association
AV ..... Atrioventricular
CRD ..... Centre for reviews and dissemination
DARE ..... Database of Abstracts of Reviews of Effects
ESC ..... European Society of Cardiology
EU ..... European Union
FDA ..... Food and Drug Administration
GRADE ..... Grading of Recommendations Assessment, Development and Evaluation
HRS ..... Heart Rhythm Society
HRQoL ..... Health-related quality of life
ICD ..... International Statistical Classification of Diseases and Related Health Problems
LCP ..... Leadless cardiac pacemakers
NHS-EED ..... NHS Economic Evaluation Database
PRISMA ..... Prevention and Recovery Information System for Monitoring and Analysis
SADE ..... Serious adverse device events
SAE ..... Serious adverse events
SND ..... Sinus node disease (Sick sinus syndrome)
TPS ..... Transcatheter pacing system
VVI ..... Single-chamber ventricular pacing
VVIR ..... Single-chamber ventricular pacing with response modulation
WHO-ICTRP ... World Health Organisation-International Clinical Trials Registry Platform

Executive Summary

Introduction

This report is the first update of the systematic review on "Leadless pacemakers for right ventricle pacing" prepared in March 2016 and comprises all new information from published and unpublished documents.

update 2017

Health Problem

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.

indication: cardiac arrhythmias

The purpose of cardiac pacing is to provide an appropriate heart rate and heart response to re-establish 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.

Description of Technology

Leadless cardiac pacemakers are self-contained intracardiac devices that are designed to have the same function as conventional 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.

leadless pacemakers: miniaturized, entirely implantable cardiac pacemakers

Methods

We assessed whether leadless cardiac 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 and mortality, and more effective and safe concerning health-related quality of life and complications rate. Therefore a systematic literature search in five different bibliographic databases and three clinical trials registries was conducted. Furthermore, the manufacturers of the relevant devices were contacted for additional published or unpublished study results. The study selection, data extraction and assessing the methodological quality of the studies was performed by two review authors (TS, NP) independently from each other.

systematic search in bibliographic databases

quality of the evidence according to GRADE

Domain effectiveness

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

efficacy: HRQoL and exercise capacity

Domain safety

safety: mortality and complication rate

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

Results

Available evidence

no comparative studies

3 prospective single-arm trials und 4 case series

For this update-report, still, no comparative studies assessing leadless cardiac pacemakers versus conventional pacemakers were available. We identified 12 new relevant documents on three ongoing prospective multi-centre single arm studies and four small single-centre case series. The total number of patients analysed for efficacy and safety endpoints respectively were 1391 and 1581. Atrial fibrillation with AV block was the major indication for pacing in the included studies. In three studies patients with contraindications for conventional pacemakers were included and analysed. Mean age of the study participants ranged from 75 to 79 years, and co-morbidities were frequent. Six of the seven studies investigated the Micra™ TPS, only one new publication reported results on the Nanostim™ LCP.

Clinical effectiveness

HRQoL: improvement after 3 mo

None of the studies reported efficacy results associated with cardiac arrhythmias or results for exercise capacity. For HRQoL, conference proceedings on 3-months interim analyses of the Micra Transcatheter Pacing Study and the LEADLESS II study reported statistically significant improvements from baseline in EQ-5D and SF-36 scores.

Safety

overall mortality: 10,3% after 12 mo

16 p. with cardiac injuries

1 device dislodgement, 1 major infection

Overall mortality was reported in five studies and ranged from no death in three case series to a 10.3% mortality rate in the 12 months analysis of a large prospective multi-centre single-arm trial. Overall, two patients died due to the implant procedure. There were 16 cardiac injuries, one device dislodgement and one major infection reported in the included Micra™ TPS studies. For Nanostim™ LCP, no new safety results were available since the report 2016.

Upcoming evidence

currently no ongoing controlled trials

There are no randomised or non-randomised controlled trials currently planned or ongoing. Five ongoing single-arm studies are registered, where safety endpoints and pacing thresholds are defined as primary endpoints.

Discussion

treatment option for well-defined patient groups

long-term issues not solved

Leadless pacemakers might have the potential for being a treatment option for patients with indication VVI pacing, especially for patients with contraindications for traditional transvenous pacemaker implantation. Major device or procedure related complications were rare, but only short term results are available so far. Long-term issues such as battery longevity and device retrieval after a prolonged implantation time are not yet resolved. Currently, the Micra™ TPS is the only clinical available device, since implantation of the Nanostim™ LCP was stopped in late 2016 due to battery malfunctions.

Available evidence is still very limited. There are no controlled trials – randomised or non-randomised – comparing leadless pacemaker systems to well established conventional single-chamber pacemakers. The overall number of patients analysed is rather small and long-term efficacy and safety results are missing.

evidence limited: no direct comparison to conventional pacemakers; no long-term results

Conclusion

Current evidence is still not sufficient to prove, that the assessed technology "Leadless pacemakers" is as effective but more safe than conventional VVI pacemakers. Therefore the inclusion of the technology in the catalogue of benefits is still not recommended.

evidence still not sufficient for recommendation

Zusammenfassung

Einleitung

Update 2017

Der vorliegende Bericht ist das erste Update des im März 2016 erstellten systematischen Reviews "Leadless pacemakers for right ventricle pacing" und erfasst verfügbare neue Informationen aus publizierten und nicht-publizierten Dokumenten zu diesem Thema.

Indikation und therapeutisches Ziel

Indikation: kardiale Arrhythmien

Gegenstand der Untersuchung 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 atri-ventrikulärem 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.

Beschreibung der Technologie

Sondenlose Herzschrittmacher: miniaturisierte, vollständig implantierbare Herzschrittmacher

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.

Methoden

Systematische Recherche in bibliografischen Datenbanken

Es wurde untersucht, ob sondenlose Herzschrittmacher im Vergleich zu konventionellen Herzschrittmachern in PatientInnen mit Indikationen für VVI-Schrittmacher ebenso wirksam und sicher hinsichtlich der Endpunkte Belastungsfähigkeit sowie kardialer Morbidität und Mortalität und wirksamer und sicherer hinsichtlich der Endpunkte gesundheitsbezogene Lebensqualität und Komplikationsrate sind. Dazu wurde eine systematische Literatursuche in

Qualität der Evidenz mit GRADE

fünf verschiedenen bibliografischen Datenbanken (Medline, PubMed, Embase, Cochrane library, CRD) sowie in drei Studienregistern durchgeführt. Zusätzlich wurden die Hersteller der Medizinprodukte im Hinblick auf weitere publizierte und nicht publizierte Studienergebnisse kontaktiert Die Studienauswahl, Datenextraktion sowie die Bewertung der methodischen Qualität der Studie wurde unabhängig voneinander von zwei ReviewerInnen (TS, NP) durchgeführt. Die Qualitätsbewertung der eingeschlossenen Studien erfolgte nach den Methoden der EUnetHTA. Die Gesamtbeurteilung der Qualität der Evidenz wurde mit der Grading Recommendations, Assessment, Development and Evaluation (GRADE)-Methode vorgenommen.

Klinische Wirksamkeit

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

Wirksamkeit: HRQoL und Belastungsfähigkeit

Sicherheit

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

Sicherheit: Mortalität, Komplikationsraten

Ergebnisse

Verfügbare Evidenz

Es konnten keine kontrollierten Studien, randomisiert oder nicht-randomisiert, identifiziert werden, die sondenlose Herzschrittmacher im Vergleich zu konventionellen Herzschrittmachern untersuchten. Insgesamt konnten für das Update 12 neue relevante Dokumente zu drei laufenden prospektiven multizentrischen Einzelarmstudien sowie vier kleinen monozentrischen Fallserien eingeschlossen werden. Die Gesamtzahl der untersuchen PatientInnen betrug für die Wirksamkeitsparameter 1391 und für die Sicherheitsparameter 1581 Personen. Die Hauptindikation für einen Herzschrittmacher in den Studien war Vorhofflimmern mit AV Block. In drei Studien wurden PatientInnen mit Kontraindikationen für konventionelle Schrittmacher eingeschlossen und ausgewertet. Das mittlere Alter der StudienteilnehmerInnen lag zwischen 75 und 79 Jahren, bei der Mehrzahl lagen auch Begleiterkrankungen vor. In sechs der sieben eingeschlossenen Studien wurde das Micra™ TPS verwendet, nur eine neue Publikation berichtete Ergebnisse zum Nanostim™ LCP.

Keine Vergleichsstudien

3 prospektive Einzelarmstudien und 4 Fallserien

Klinische Wirksamkeit

Keine der Studien berichtete Ergebnisse zur Wirksamkeit im Hinblick auf kardiale Arrhythmien oder zur Belastungsfähigkeit. In zwei Konferenz-Abstracts der Micra Transcatheter Pacing Study bzw. der LEADLESS II Studie wurden Ergebnisse zur gesundheitsbezogenen Lebensqualität nach 3 Monaten Follow-up berichtet. Dabei zeigten sich statistisch signifikante Verbesserungen in den EQ-5D und SF-36 Scores im Vergleich zu Studienbeginn.

HRQoL: Verbesserung nach 3 Mo

Sicherheit

Aus fünf Studien lagen Ergebnisse zur Gesamtmortalität vor. Dabei wurde in drei Fall Serien berichtet, dass kein/e StudienteilnehmerIn in Zeitraum bis maximal 3 Monate nach Implantation verstarb. In zwei prospektiven multizentrischen Einzelarmstudien lag die Mortalitätsrate bei 2.8 % in 30 Tagen bzw. 10,3 % in 12 Monaten. Insgesamt wurden in den eingeschlossenen Studien zwei prozedur-bezogene Todesfälle berichtet. Darüber hinaus traten in den Studien 16 kardiale Verletzungen, eine Implantatsablösung sowie eine schwere Infektion in den Micra™ TPS Studien auf. Für den Nanostim™ LCP fanden sich keine neuen Ergebnisse zu Sicherheitsparametern seit dem Bericht 2016.

Mortalität: 10,3% nach 12 Mo

16 P. mit kardialen Verletzungen

1 Implantatsablösung, 1 schwere Infektion

Laufende Studien

derzeit keine laufenden kontrollierten Studien

Es finden sich derzeit keine Informationen hinsichtlich laufender oder geplanter randomisierter oder nicht-randomisierter kontrollierter Studie. In den Studienregistern sind fünf laufende Einzelarmstudien registriert, in denen Sicherheitsparameter und Reizschwellenwert als primäre Endpunkte definiert sind.

Diskussion

mögliche Behandlungsoption für bestimmte Personengruppen

Langzeit-Fragen ungeklärt

Sondenlose Herzschrittmacher könnten Behandlungsoption für PatientInnen mit Indikationen für VVI-Schrittmacher darstellen, im Besondern für Personen bei denen eine Kontraindikation für konventionelle Schrittmachern vorliegt. Schwere prozedur- oder produktbezogene Komplikationen treten in den vorliegenden Studien selten auf, jedoch handelt es sich dabei lediglich um Kurzzeitergebnisse. Langfristige Fragen im Hinblick auf die Lebensdauer der Batterien oder die Explantation nach langer Implantationsdauer sind derzeit noch offen. Batterie-Fehlfunktionen waren es auch, die Ende 2016 zu einem Stopp der Implantationen des Nanostim™ LCP führten, weshalb das Micra™ TPS das derzeit einzige verfügbare System am Markt ist.

Evidenz sehr eingeschränkt: kein direkter Vergleich zu konventionellen VVI-Schrittmacher; keine Langzeitergebnisse

Insgesamt ist die derzeitige Evidenzlage immer noch sehr eingeschränkt. Es gibt keine Kontrollgruppenstudien, randomisiert oder nicht-randomisiert, die sondenlose Schrittmacher mit den etablierten konventionellen Schrittmachern vergleichen. Die Gesamtzahl der in den Studien untersuchten PatientInnen ist verhältnismäßig klein und Langzeitergebnisse zur Wirksamkeit und Sicherheit fehlen.

Empfehlung

Evidenz für Empfehlung weiterhin nicht ausreichend

Die derzeitige Evidenz ist immer noch nicht ausreichend, um die untersuchte Technologie „Sondenlose Herzschrittmacher“ im Hinblick auf eine gleichwertige Wirksamkeit und eine erhöhte Sicherheit im Vergleich zu konventionellen Schrittmachern beurteilen zu können. Daher wird eine Aufnahme in den Leistungskatalog weiterhin nicht empfohlen.

Summary of the assessment 2016

systematischer Review 2016

Commissioned by the Austrian Ministry of Health, the HTA-report "Leadless pacemakers for right ventricle pacing" was prepared by the Ludwig Boltzmann Institute of Health Technology Assessments (LBI-HTA) in March 2016 [1]. This report provides the basis for the current update. The following paragraphs summarize the description of the health problem, the characteristics of technology, the results and the recommendation of the 2016 report.

Health Problem and characteristics of the technology

Herzschrittmacher zur Behandlung kardialer Arrhythmien eingesetzt

In Ö: 116.000 Personen mit kardialen Arrhythmien

AV Block: erhöhtes Sterberisiko aufgrund von Herzversagen

SND: kein erhöhtes Sterberisiko

Pacemakers are developed for the treatment of a variety of cardiac arrhythmias. 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. In Austria, over 116,000 patients with cardiac arrhythmias were recorded in 2011 [2]. The natural history differs depending on the type of bradyarrhythmia. 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 [3]. On the other hand, 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 [4, 5]. 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.

Indikationen laut Leitlinien: Bradykardie mit Symptomen

VVI bevorzugt bei PatientInnen mit chronischer AF

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) [6] and by the European Society of Cardiology (ESC) [3]. 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 single-chamber ventricular (VVI) pacing [3]. 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 [3]. 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 [3].

schwere Komplikationen: Reinterventionen aufgrund von Sondendefekten oder Sonden-/Generatorproblemen, Infektionen; Herzperforationen; …

Major complications associated with the implantation of a single-chamber right-ventricular 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 [7, 8].

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. For single-chamber pacemakers, this risk is however significantly lower, with 3.3%

experiencing any major complication [8]. Especially the risk of lead complications is lower for single chamber right ventricular pacemakers compared to other pacemaker types [9].

LCP: miniaturisierte, vollständig implantierbare Herzschrittmacher

Leadless cardiac pacemakers (LCP) have been developed as alternatives for traditional permanent cardiac pacemakers. They 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 [10]. The current generation of single-unit leadless cardiac pacemakers can only be used for single-chamber pacing, specifically right ventricular pacing [11].

Zwei Produkte: Nanostim™ LCP und Micra ™ TPS

At the time of the report 2016 two leadless pacing systems were available: the Nanostim™ LCP developed and manufactured by St. Jude Medical, which received CE market approval for Europe in 2013 but has not yet been approved for Australia and North America, and Medtronic´s Micra™ transcatheter pacing system (TPS), which was approved for the European market in 2015 and for the USA in 2016. Both devices are approximately ten times smaller than conventional VVI pacemakers and have an estimated battery longevity of approximately ten years, which is comparable to conventional pacemakers [10, 11] 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.

Scope

PIKO-Frage 2016

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?

Inclusion criteria for relevant studies are summarised in Table 0-1.

Table 0-1: Inclusion criteria

Population	First-line treatment of patients with indications for single-chamber ventricular pacemakers [3, 6] • 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) • Patients with persistent or intermittent bradycardia due to AV block or symptomatic sinus node disease (SND, ICD-10 I.49.5)[1] Contraindications: • Patients requiring long-term pacing exceeding estimated device longevity (NB. children) • Patients with indications for atrial single-chamber pacemakers or dual-chamber pacemakers or with indications for cardiac resynchronisation therapy MESH term: Arrhythmias, Cardiac [C14.280.067] and Arrhythmias, Cardiac [C23.550.073]

[1] Only in specific instances, where other pacing modes (dual-pacing, atrial pacing) are not recommended

Intervention	Leadless self-contained and fully implantable VVI(R) pacemaker Setting: Vascular Surgery, Interventional Cardiology; specialist hospital, general hospital Products: Micra™ TPS, Medtronic Inc (available in Austria) Nanostim™, St. Jude Medical (available in Austria by end of 2016) MESH term: Pacemaker, Artificial [E07.305.250.750]
Control	Conventional VVI(R) pacemaker MESH term: Pacemaker, Artificial [E07.305.250.750]
Outcomes	
Efficacy	❁ Cardiovascular mortality ❁ Cardiovascular morbidity ❁ Patient-related quality of life ❁ Exercise capacity ❁ Pacing performance
Safety	Complication rate
Study design	
Efficacy	❁ Randomised controlled trials (Non-inferiority)[2] ❁ 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

entscheidungsrelevante Endpunkte: Wirksamkeit – Lebensqualität, Belastungsfähigkeit Sicherheit – Komplikationsrate, Mortalität

The following outcomes were defined as crucial to derive a recommendation in the report 2016.

Clinical effectiveness:

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

Safety:

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

[2] 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.

Results

keine Vergleichsstudien

No comparative studies to assess the effectiveness and safety of leadless pacemakers could be identified. Five references on three prospective multi-centre single arm studies were included in the report 2016. Two studies investigated the Nanostim™ LCP and one study the Micra™ TPS. All of the studies were sponsored by the device manufacturers.

3 prospektive Einzelarmstudien

keine Ergebnisse zu klinischer Wirksamkeit

Pacing performance was the primary efficacy endpoint in all of the included studies. However, none of the studies reported any of the clinical effectiveness outcomes defined as crucial to derive a recommendation.

Sicherheit: 3-5% Mortalität

Safety population of the three included studies comprises 1284 patients. Overall mortality was reported in all three studies and ranged from 3 to 5%. None of the death was classified as device related, but in total, four deaths in the three studies were related to the implantation procedure. Cardiac mortality was reported in two studies with 0.8% [12] and 1% [13, 14], respectively.

schwere produktbezogene Ereignisse: 4-6.5%

The rates of SADE ranged between 4% and 6.5% in the three studies. Cardiac injuries were reported in 20 patients, and device dislodgements in six patients, the latter all with the Nanostim™ LCP. Other SAE 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.

sehr niedrige Evidenzstärke

The strength of evidence for the effectiveness and safety of leadless pacemakers in comparison to conventional pacemakers was rated very low according to GRADE scheme.

A search in clinical trial registries found no planned or ongoing randomised or non-randomised controlled trials on leadless pacemakers. A total of five ongoing single-arm studies, that will analyse safety endpoints and pacing thresholds, were identified

Recommendation

Evidenz nicht ausreichend für Empfehlung

The evidence included in the report 2016 was not sufficient to prove, that the assessed technology Leadless Pacemakers is as effective but more safe than conventional VVI pacemakers. Therefore the inclusion of the technology in the catalogue of benefits was not recommended.

UPDATE 2017

1 Scope

1.1 PICO question

PIKO-Frage

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?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

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

Table 1-1: Inclusion criteria

Population	First-line treatment of patients with indications for single-chamber ventricular pacemakers [3, 6] • 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) • Patients with persistent or intermittent bradycardia due to AV block or symptomatic sinus node disease (SND, ICD-10 I.49.5)[3] Contraindications: • Patients requiring long-term pacing exceeding estimated device longevity (NB. children) • Patients with indications for atrial single-chamber pacemakers or dual-chamber pacemakers or with indications for cardiac resynchronisation therapy MESH term: Arrhythmias, Cardiac [C14.280.067] and Arrhythmias, Cardiac [C23.550.073]
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Control	Conventional VVI(R) pacemaker MESH term: Pacemaker, Artificial [E07.305.250.750]
Outcomes	
Efficacy	• Cardiovascular mortality • Cardiovascular morbidity • Patient-related quality of life • Exercise capacity • Pacing performance
Safety	Complication rate

[3] Only in specific instances, where other pacing modes (dual-pacing, atrial pacing) are not recommended

Study design	
Efficacy	❁ Randomised controlled trials (Non-inferiority)[4] ❁ Prospective non-randomised controlled trials
Safety	❁ Randomised controlled trials ❁ Prospective non-randomised controlled trials ❁ Prospective case series or registries

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

[4] 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

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?
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?
D0016	How does the use of leadless pacemakers affect activities of daily living?
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?
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?
C0008	How safe are leadless pacemakers in comparison to conventional single-chamber ventricular pacemakers?

2.2 Systematic literature search

systematische Literatursuche in 5 Datenbanken

The systematic literature search was conducted on the 06.04.2017 in the following databases:

- Medline via Ovid
- PubMed
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)

After deduplication, overall 168 citations were included. The specific search strategy employed can be found in the appendix.

insgesamt 185 Publikationen identifiziert

Manufacturers of the two available products (Medtronic, St. Jude Medical) were contacted and they submitted 20 documents of which 17 new citations were identified.

Furthermore, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 07.04.2017 resulting in 20 potential relevant hits.

No additional references were found by hand search.

2.3 Flow chart of study selection

Literaturauswahl

Overall 185 hits were identified. The references were screened by two independent researchers and in case of disagreement, a third researcher was involved to solve the differences. From the search in bibliographic databases eight new articles [15-22], published since the previous report 2016 [1], were identified, that met the predefined inclusion criteria. A further four documents with additional information on relevant outcomes were identified from documents submitted by the manufacturers [23-26]. Altogether, a total of 12 references [15-26] referring to seven studies were included in this update-report. The selection process is displayed in Figure 2-1.

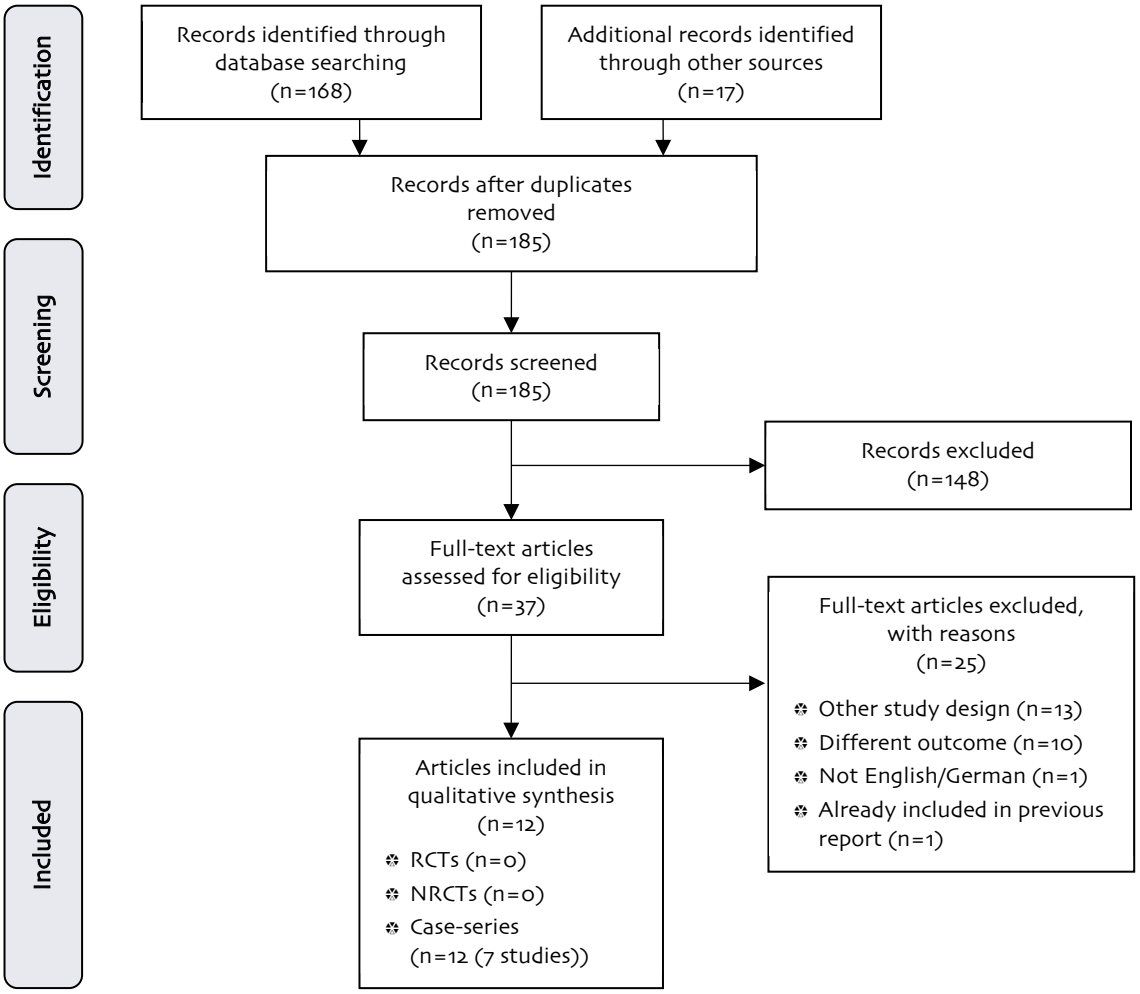

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

Among the 20 potentially relevant hits in the clinical trials registries, we identified one additional unpublished completed study and five ongoing trials. For details see Table A-5.

2.4 Analysis

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

Quality was assessed using the EUnetHTA checklist for case series [27] (see Table A-3).

2.5 Synthesis

The questions were answered in plain text format with reference to GRADE evidence tables [28] that are included in Table 5-1.

3 Clinical effectiveness

3.1 Outcomes

The implantation of pacemakers serves the primary purpose to alleviate symptoms associated with a slow heart rhythm. The pacemaker itself does not treat atrial fibrillation, the main indication for single chamber ventricular pacing. Recent reports indicate that prognosis of bradycardia pacemaker recipients are mainly determined by comorbitities and a bradycardia pacing indication as such does not influence survival [1].

entscheidungsrelevante Endpunkte – Wirksamkeit: Lebensqualität, Beslastungsfähigkeit

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

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

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.

3.2 Included studies

There are still no comparative studies to assess the effectiveness of leadless pacemakers. For this update-report we identified eight relevant documents on three ongoing prospective multi-centre single arm studies that reported interim results on the performance of leadless pacemakers [16, 17, 21-26] and four additional references to four small single-centre case series [15, 18-20]. The total number of patients included in the efficacy analyses (pacing performance) was 1,391. All three prospective multi-centre single arm studies were sponsored by device manufacturers, while the sponsor was not reported in the four case-series. In six of the included studies, the Medtronic Micra™ TPS was the investigated device [15-20, 22-26], while in one study the Nanostim™ LCP developed by St. Jude Medical was used [21].

immer noch keine Vergleichsstudien

seit Bericht 2016: neue Ergebnisse 7 Studien; insgesamt 1.391 PatientInnen

In two conference proceedings of the Micra Transcatheter Pacing Study [23] and the LEASLESS II study [21] results on HRQoL including 956 participants were reported. These were the only available results on one of the efficacy outcomes defined as crucial to derive a recommendation.

2 Konferenz-Abstracts zu mit Ergebnissen zu HRQoL

All seven studies included patients with indications for VVI pacing. In addition, one case series included only patients contraindicated for or unable to receive conventional endovenous pacemaker implantation [19], while another case series included only patients after lead extractions because of severe device infections [20]. The main indications for pacing were permanent, uncontrolled atrial fibrillation (range 21-70%), AV-block (range 10-100%) and sinus node dysfunction (range 8-17%). Mean age of the study participants was 75 to 79 years. The study populations were predominantly male (range 50-83%).

verschiedene Indikationen für VVI Schrittmacher

2 Fallserien mit PatientInnen mit Kontraindikationen für konventionelle Schrittmacher

hohes Alter, zahlreiche Begleiterkrankungen

Comorbidities were frequent, with 57-86% of the participants suffering from hypertension. For one study [16, 22], subgroup efficacy results for patients with elevated implant threshold (i.e. (> 1.0 V at 0.24ms) were reported.

Details on study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table 5-1.

3.3 Results

Morbidity

D0005 – How do leadless pacemakers affect symptoms and findings (severity, frequency) of cardiac arrhythmias?

keine Ergebnisse zur Wirksamkeit in Bezug auf Arrhythmien

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

D0006 – 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

D0011 – What is the effect of leadless pacemakers on patients' body functions?

keine Ergebnisse zur Belastungsfähigkeit

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

D0016 – 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

D0012 – What is the effect of leadless pacemakers on generic health-related quality of life?

Ergebnisse zur HRQoL aus 2 Studien: Bessere EQ-5D und SF-36 Scores nach 3 Monaten

HRQoL was reported in conference proceedings of the LEADLESS II study [21] and the Micra Transcatheter Pacing Study [23], respectively. In the LEASLESS II study [21] 468 patients completed the EuroQol EQ-5D questionnaire at pre-discharge, and at weeks 2, 6 and 12. EQ-5D is a standardized instrument for measuring generic health status. EQ-5D utility scales were calculated using the EuroQol US algorithm and ranged from 0.0 to 1.0. At pre-discharge the mean EQ-5D utility score was 0.81. This score increased to 0.84 in week 12. Compared to a baseline utility score of 0.73, which was obtained from a meta-analysis of single-chamber pacemaker studies in the US, the EQ-5D utility score increased by 14.7% ($p<0.001$). In the Micra Transcatheter Pacing Study [23], HRQoL was measured at baseline before implantation and at 3 months follow-up, using the SF-36 generic instrument. 488 patients were analysed. The results showed a significant improvement of the HRQoL scores in each of the eight SF-36 domains. At baseline, the mean composed physical

summary score was 36.9 points and improved 3 months post-implant to 38.7 points. In the same period, the mean mental component summary score improved from 47.8 to 51.4 points. Both differences were statistically significant.

D0013 – What is the effect of leadless pacemakers on disease-specific quality of life?

keine Ergebnisse zur krankheitsspezifischen QoL

None of the studies reported results on disease-specific quality of life.

Patient satisfaction

D0017 – Was the use of leadless pacemakers worthwhile?

Patientenzufriedenheit: Ergebnisse aus 1 Studie

In the HRQoL publication of the Micra Transcatheter Pacing Study [23] some results on patient satisfaction were reported. After 3 months of follow-up 90%, 96%, and 72% of patients were very satisfied or satisfied with their recovery, their aesthetic appearance, and their level of activity respectively, while 4% of the patients were dissatisfied with their recovery and 5% dissatisfied with their level of activity.

4 Safety

4.1 Outcomes

entscheidungsrelevante Endpunkte – Sicherheit: Komplikationsrate, Mortalität

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 haematoma, 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™ LCP trials in 2014 and 2015, due to reports of serious adverse events, including perforation of the heart and dislodgement of the device [29].

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[5] 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.

[5] http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_7_3_en.pdf

4.2 Included Studies

seit Bericht 2016: neue Ergebnisse 7 Studien; insgesamt 1.581 PatientInnen

As for the efficacy results, there were no comparative studies assessing the safety of leadless pacemakers. For this update-report we identified eight relevant documents on three ongoing prospective multi-centre single arm studies that reported interim results on the performance of leadless pacemakers [16, 17, 21-26] and four additional references to four small single-centre case series [15, 18-20] (see section 3.2). The total number of patients included in the safety analyses was 1,581. Details on study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table 5-1.

4.3 Results

Mortality

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

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

Gesamtmortalität – Prospektive Einzelarmstudie: 10,3 % in 12 Monaten

Fallserien: keine Todesfälle

Overall mortality was reported in five of the included trials [15-17, 19, 20, 22-26]. The 12 months interim analysis of the Micra Transcatheter Pacing Study [17] showed an overall mortality rate of 10.3% (77 of 745 patients), 32 of these were due to cardiac death. In the Micra Transcatheter Pacing System Post-Approval Registry [24-26] 22 of 795 patients died through 30 days post-implant (2.8%). In the three case series that reported on overall mortality, including 14 [19], 10 [15] and 6 patients [20], none of the patients died during follow-up. For the LEADLESS II study no new information on mortality was found in the included publication [21]. Safety results for this study can be found in the report 2016 [1].

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

2 Todesfälle im Zusammenhang mit dem Eingriff

Information on procedure-related mortality was found in five studies. While no procedure-related death was reported in the three case series [15, 19, 20], one patient died due to the implant procedure in the Micra Transcatheter Pacing Study [17] and one in the Micra Transcatheter Pacing System Post-Approval Registry [25], respectively. None of these deaths were classified as related to the device. In the Micra Transcatheter Pacing study [17], a 77 year old female patient with end-stage renal disease died from metabolic acidosis due to a prolonged procedure time. In Micra Transcatheter Pacing System Post-Approval Registry [25], a 96 year old male patient with aortic valvular disease developed pulmonary edema one day after implant and was unable to be resuscitated. For the LEADLESS II study, no new information on procedural mortality was found in the included publication [21]. Safety results for this study can be found in the report 2016 [1].

Patient safety

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

SAE were only reported in the Micra Transcatheter Pacing Study [16, 17, 22, 23], with 226 of 725 patients with events (31.2%) at 6 months follow-up. The number of overall adverse events was not reported in any of the included studies.

SAE:
31,2 % nach 6 Monaten

SADE were reported in three studies. While in a case series [15] no major complication occurred during 55 days of follow-up, the rates in the two prospective single-arm Micra studies ranged from 1.5% (12 of 795 patients; 30 days follow-up) [25] to 4.0% (29/726 patients; 12 months) [17]. There were 11 patients with cardiac injuries in the Micra Transcatheter Pacing Study [17] and five patients in the Micra Transcatheter Pacing System Post-Approval Registry [25]. Major device or procedure related cardiac events were reported in three studies [16-19, 22, 23]. Six patients with cardiac failure, two with pacemaker syndrome and one patient with acute myocardial infarction within 12 months of follow up in the Micra Transcatheter Pacing cohort [17], one patient with cardio-circulatory arrest related to a ventricular fibrillation one day after implantation in the case series of Da Costa 2017 [19] and one patient with moderate pericardial effusion in the case series of Martinez-Sande 2017 [18]. One case of device dislodgement and one major infection were reported within the six studies using the Micra ™ TPS. Other SAE hat were attributable either to the device or the procedure included elevated pacing thresholds requiring retrieval and implantation of a new device, loss of device function, events at groin puncture site and embolism or thrombosis. For the LEADLESS II study, no new information on SADE was found in the included publication [21]. Safety results for this study can be found in the report 2016 [1].

SADE: 1,5-4 %

16 PatientInnen mit kardialen Verletzungen

eine Implantatsablösung;

eine schwere Infektion

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.

keine Daten vorhanden

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 SAE related to the implantation procedure.

anwenderabhängige Schäden bei beiden Interventionen möglich

5 Quality of evidence

Qualität der Evidenz nach GRADE: immer noch sehr niedrig

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. 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].

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 5-1.

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

Table 5-1: 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
Efficacy							
Health related quality of life							
2/956	2 prospective single arm studies	+5% improvement in SF-36 physical health score after 3 months +8% improvent in SF-36 mental helath score afer 3 months +15% improvement in EQ-5D utility score after 3 months	-1[6]	0	0	0	Very low
Exercise capacity							
No data							
Safety							
Overall mortality							
5/1570	2 prospective single arm studies; 3 case series	Range: 0-10.3%	-1[6]	0	0	-1[7]	Very low
Cardiovascular mortality							
4/775	1 prospective single arm study; 3 case series	Range: 0-4.3%	-1[6]	0	0	-1[7]	Very low
Procedure-related mortality							
5/1570	2 prospective single arm studies; 3 case series	Range: 0-0.1%	-1[6]	0	0	-1[7]	Very low
Major complication rate (SADE)							
3/1531	2 prospective single arm studies; 1 case series	Range: 0-4,0%	-1[6]	0	0	-1[7]	Very low

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)

[6] No control group

[7] Imprecise data due to low number of events

6 Discussion

Update auf Basis des Berichts 2016 mit Fokus auf neuen Publikationen

weiterhin keine Vergleichsstudien

This update report comprises new information from interim analyses of three large ongoing prospective multi-centre single-arm studies [16, 17, 21-26] and publications of four small single-centre case series [15, 18-20] on LCP, available since the previous report published in March 2016 [1]. As in the report 2016, again no randomised or non-randomised controlled trials comparing leadless pacemaker systems to traditional single-chamber pacemakers could be identified. There are still no data on the effect of leadless cardiac pacemakers on symptoms or progression of cardiac arrhythmias available. As in previous publications, the new evidence focusses on the feasibility and safety of the leadless pacemaker implantation procedure. Short-term results on HRQoL were only reported in two conference abstracts [21, 23].

Mehrheit der neuen Ergebnisse zu Micra™ TPS

Nanostim™ LCP 2016 auf Grund von Funktionsstörung der Batterie gestoppt

The majority of the included studies (six of seven) in this update report assessed the implantation of the Micra™ TPS [15-20, 22-26], while only one new publication was available for the Nanostim™ LCP [21]. Therefore the results of this update mainly refer to the Micra™ TCP, which is currently the only device which is available on the market. For the Nanostim™ LCP, all further implantations were stopped by the manufacturer in late 2016 and recruitment for all ongoing trials has been suspended. Reasons for this stop were reports of lost telemetry and pacing due to battery malfunctions in seven patients [30].

erfolgreiche Implantation und anhaltend niedrige Stimulationamplitude

Verbesserung der Lebensqualität nach 3 Monaten, aber keine Vergleichsdaten zu herkömmlichen Schrittmachern

Current results indicate that leadless pacemaker can be successfully implanted in most of the patients – implantation rates ranged from 99.2 to 100% – and sustain a low pacing threshold (<1.0 V at 0.24ms) for up to 24 months. This low pacing threshold can also be achieved in patients with an elevated implant threshold [16, 22]. Interim results from the Micra Transcatheter Pacing Study [23] and the LEADLESS II study [21] showed an increase in HRQoL in the first 3 months after implantation. These results are not unexpected, since also studies on traditional pacemakers showed an increase in HRQoL in the first year after pacemaker implantation [31]. Thus, without comparative trials, it remains unclear whether the avoidance of lead/generator complications translates into a relevant HRQoL benefit for the patients or not.

Komplikationen der Implantation selten, ein Fall von Dislokation

12 Monats-Follow-Up Daten verfügbar:

keine Rückschlüsse auf Überlegenheit möglich, da keine Vergleichsstudien

Major complication rates associated with the implantation procedure or the device were rare in the studies (0-4.0%) and might even be improved by a learning curve and/or special training to develop proficiency specific for the leadless pacemaker implantation [32]. Only one case of device dislodgement was reported within the included studies for the Micra™ TPS. Long term safety data were now available from one study with a follow-up of 12 months [17]. Within this period, 77 of 745 patients died, 32 due to cardiac reasons. Systemic infections occurred in 26 patients, all of them unrelated to the device or procedure and none of them classified as major infections. But again, since no direct comparisons to contemporary single-chamber systems exist, no definitive conclusion can be drawn on the superiority or even non-inferiority of the new technology compared to standard therapy. An indirect comparison with historical data from previous pacemaker studies, which was provided in the Micra Transcatheter Pacing Study [17], resulted in a 48% lower rate of patients with major complications. Buts these results are of limited validity, since the historic control included patients with dual-chamber pacemakers, for which higher complications rates have to be considered [7-9]. In a most recently published review results from an indirect comparison between leadless and traditional single-chamber pacemakers were reported [32]. In this

analysis, the short-term complication rate (≤ 2 months) of conventional pacemakers (4.0%) appeared to be slightly lower compared to the leadless pacemakers (4.8%). For long-term outcomes, no comparison was drawn, since for leadless pacemakers not enough data were available.

mögliche Therapieoption für Patienten mit Kontraindikationen für konvetionelle Schrittmacher – Ergebnisse aus 3 Studien zeigen geringe Komplikationsraten; jedoch geringe PatientInnenzahl und keine Langzeitergebnisse

Leadless pacemakers might represent a treatment alternative in patients, for whom an implantation of a transvenous pacemaker system is precluded. This includes patients with a compromised venous access, with a history of device infection or patients with cancer. Three of the included studies reported results on those patient groups. A subgroup analysis of the Micra Transcatheter Pacing System Post-Approval Registry [26] analysing 104 patients with previously implanted cardiac implantable electronic devices, a case series with 14 patients with full or relative contraindications for traditional transvenous pacemaker implantation [19] and another case series with six patients with lead extraction after severe device infections [20]. In all studies there was a 100% successful implantation rate and the rates of major complication were very low. No device dislodgements or device infections occurred. Nevertheless, the number of patients investigated so far is very small and maximum follow-up was only 3 months. Therefore it remains unclear whether these patient groups are at increased risk for long-term complications, especially late infections or not.

Batterielebenszeit derzeit unklar

One issue concerning pacemakers is battery longevity. Based on the 6 months follow-up data it was estimated at 15.0 years for the Nanostim™ LCP and 12.5 years for the Micra™ TPS [32]. However, these estimations are based on short-term data and might be overestimated [33], in particular, since discrepancies between estimations and actual battery longevity were shown in studies on traditional pacemakers [33, 34]. In addition, as mentioned above, battery malfunctions already occurred in the Nanostim™ LCP. For the Micra™ TPS there is no evidence of similar battery issues [32].

erfolgreiche Rückholung des Nanostim™ LCP bei 15 von 16 Personen

Another important feature, especially for leadless pacemakers, is their retrievability. For the Nanostim™ LCP a steerable retrieval catheter was developed, while for the Micra™ TPS no such system is available [32]. However, the Micra™ TPS is not intended to be removed at the end of battery life [35]. Instead, the turned-off leadless pacemaker is abandoned in the right ventricle and another device is added. So far, there is no experience from human studies on the feasibility of the implantation of additional leadless pacemakers in the heart chamber. There is one publication on retrieval attempts after short- and mid-term implant time from three Nanostim™ LCP studies reporting successful retrieval in 15 of 16 patients with no related serious adverse events [36]. Retrievability of the leadless pacemaker after a prolonged implantation time has not been studied.

neue Ergebnisse aus 3 prospektiven Einzelarmstudien und 4 Fallserien

Evidenzstärke nach GRADE sehr gering

keine direkten Vergleiche zu konventionellen Schrittmachern

In summary, the results from uncontrolled prospective multicentre trials and small case series indicate, that leadless pacemakers might have the potential for being a treatment option for patients with indication VVI pacing, especially for patients with contraindications for traditional transvenous pacemaker implantation. Nevertheless, the evidence is still limited. First of all, there are no controlled trials – randomised or non-randomised – comparing leadless pacemaker systems to well established traditional single-chamber pacemakers. Second, relevant efficacy results (i.e. HRQoL) were only reported in conference proceedings, no full peer-reviewed journal publications on that outcome are currently available. Third, since the event rates in the relevant outcomes were rather small, the number of patients analysed so far is too small to reach the optimal information size and therefore the results are imprecise.

And fourth, no long-term data on the performance of the leadless systems or on safety are yet available. So, as already mentioned in the 2016 report [1], further evaluation of leadless pacemakers for long-term clinical efficacy and complication rates, especially from controlled trials comparing them to 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.

niedrige PatientInnenzahlen

keine Langzeitergebnisse

7 Recommendation

In Table 7-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 7-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is ***currently*** **not recommended.**
	The **inclusion in** the catalogue of benefits is **not recommended.**

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. This conclusion is mainly based on the fact, that still no controlled studies assessing leadless pacemakers in comparison to conventional pacemakers, the current well established standard interventions for the treatment of a variety of cardiac arrhythmias, are available. New study results will potentially influence the effect estimate considerably.

nach wie vor Evidenz nicht ausreichend für Empfehlung

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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 (part 1)

Study (acronym, ID no.)	Micra Transcatheter Pacing Study (NCT02004873)	The Micra Transcatheter Pacing System Post-Approval Registry (NCT02536118)	The LEADLESS II pacemaker IDE study (NCT02030418)
Reference	[16, 17, 22, 23]	[24-26]	[21]
Study description			
Country	USA, Australia, Austria, Canada, Czech Republic, China, Denmark, France, Greece, Hungary, India, Italy, Japan, Malaysia, Netherlands, Serbia, South Africa, Spain, United Kingdom	USA, Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Iceland, Israel, Italy, Kuwait, Netherlands, New Zealand, Norway, Poland, Portugal, Russian Federation, Saudi Arabia, Slovenia, Spain, Sweden, Switzerland, United Arab Emirates, United Kingdom	Australia, Canada, USA
Sponsor	Medtronic	Medtronic	St. JudeMedical
Intervention/Product	Implantation of a leadless cardiac pacemaker/Micra™ TPS	Implantation of a leadless cardiac pacemaker/Micra™ TPS	Implantation of a leadless cardiac pacemaker/Nanostim™ LCP
Comparator	NA	NA	NA
Study design	Single cohort safety/efficacy study (with historical control)	Prospective single cohort safety/efficacy registry	Single cohort safety/efficacy study
Duration of the study	November 2013 – ongoing	July 2015 – ongoing	February 2014 – ongoing
Randomisation method	None	None	None
Blinding method (investigator, patient, outcomes assessor)	Open label	Open label	Open label
Intervention (n=)	630 (Efficacy cohort – 12 months) 58 (Efficacy cohort – 24 months) 726 (Safety cohort) 504 (HRQoL cohort) *Subgroup analysis – patients with elevated implant threshold (> 1.0 V at 0.24ms):* 83	~ 1830 (Planned enrollment) 701 (Efficacy cohort – 30 days) 795 (Safety cohort – 30 days)	~ 1567 (Planned enrollment) 468 (HRQoL cohort)
Control (n=)	0	0	0

Study (acronym, ID no.)	Micra Transcatheter Pacing Study (NCT02004873)	The Micra Transcatheter Pacing System Post-Approval Registry (NCT02536118)	The LEADLESS II pacemaker IDE study (NCT02030418)
Population	Patients indicated for VVI(R) pacing	Patients indicated for VVI(R) pacing	Patients indicated for VVI(R) pacing
Inclusion criteria	Class I or II indication for pacing (bradycardia due to atrial tachyarrhythmia, sinus node dysfunction, atrioventricular node dysfunction, or other causes)	Patient is intended to receive or be treated with a Micra Transcatheter Pacing System and must be enrolled prior to the TPS implant procedure	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 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 sinus bradycardia with infrequent pauses or unexplained syncope with EP findings
Exclusion criteria	Entirely pacemaker dependent (escape rhythm <30 bpm)* (restriction was lifted following review of the Early Performance Assessment) Existing or prior pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy device implant; Unstable angina pectoris, acute myocardial infarction within 30d, Current implantation of neurostimulator or any other chronically implanted electronic device, mechanical tricuspid valve, implanted vena cava filter, or left ventricular assist device; Morbidly obese; Femoral venous anatomy unable for transcatheter procedure; intolerance to device material or hypersensitivity to <1mg dexamethasone; life-expectancy <12m; pregnant or breastfeeding women	Patient who is, or is expected to be inaccessible for follow-up; Patient with exclusion criteria required by local law; Patient is currently enrolled in or plans to enroll in any concurrent drug and/or device study that may confound results	Pacemaker syndrome, retrograde VA conduction or drop in arterial blood pressure with the onset of ventricular pacing; Pre-existing endocardial pacing or defibrillation leads; or Pre-existing pulmonary arterial hypertension or significant physiologically-impairing lung disease; Current implantation of either conventional or subcutaneous implantable cardioverter de-fibrillator or cardiac resynchronization therapy; Mechanical tricuspid valve prosthesis; Implanted vena cava filter; Implanted leadless cardiac pacemaker; Evidence of thrombosis in one of the veins used for access during the procedure; Recent cardiovascular or peripheral vascular surgery within 30 days of enrolment Allergic or hypersensitive to <1mg of dexamethasone sodium phosphate; life-expectancy <12m; pregnant or breastfeeding women
Primary outcome (including measurement tools and measurement times)	S: Freedom from major complications related to the Micra™ TPS and/or procedures at 6-month post-implant (within 183 days) E: Adequate pacing capture threshold at 6 months (≤ 2 V at a pulse width of 0.24 ms and stable (increase of ≤ 1.5 V))	S: Acute complication rate (within 30 days); S: Long-term complication free survival (up to 9 years)	S: Complication-free rate (freedom of SADE) at 6 months E: Therapeutically acceptable pacing capture threshold (≤ 2.0 V at 0.4 msec) and a therapeutically acceptable sensing amplitude (R wave ≥ 5.0 mV, or a value equal to or greater than the value at implantation) through 6 months

Study (acronym, ID no.)	Micra Transcatheter Pacing Study (NCT02004873)	The Micra Transcatheter Pacing System Post-Approval Registry (NCT02536118)	The LEADLESS II pacemaker IDE study (NCT02030418)
Secondary outcome (including measurement tools and measurement times)	E: Automated ventricular capture management 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	E: Pacing impedance and pacing threshold (up to 9 years) E: System longevity (up to 9 years) S: Complications stratified by implant type (up to 9 years) S: Micra system revision rate (including system explant, replacement, reposition) (up to 9 years)	S: Non–device-related SAE during 6 months of follow-up. S: SADE and Non-device-related SAE during follow-up (Full cohort)
Follow-up (months)	Efficacy: 12 and 24 months Safety: 6 and 12 months HRQoL: 3 months *Subgroup analysis – patients with elevated implant threshold (> 1.0 V at 0.24ms):* Efficacy: 6 months	30 days	12 weeks
Loss to follow-up, n (%)	0 *Subgroup analysis – patients with elevated implant threshold (> 1.0 V at 0.24ms):* 11 (13.3)	0	0
Population characteristics			
Age (mean), y	75.9±10.9 (Safety cohort) 77±11 (HRQoL cohort) *Subgroup analysis – patients with elevated implant threshold (> 1.0 V at 0.24ms):* 76.0±9.0	75.2±14.2 (Safety cohort)	75.0±12.0
Male, n (%)	426 (58.8) (Safety cohort) 300 (60) (HRQoL cohort) *Subgroup analysis – patients with elevated implant threshold (> 1.0 V at 0.24ms):* 52 (62.7)	495 (62.3) (Safety cohort)	292 (62.4)

Study (acronym, ID no.)	Micra Transcatheter Pacing Study (NCT02004873)	The Micra Transcatheter Pacing System Post-Approval Registry (NCT02536118)	The LEADLESS II pacemaker IDE study (NCT02030418)
Pacing indication, n (%)	*Safety cohort:* Bradycardia associated with persistent or permanent atrial tachyarrhythmia, 464 (64.0) Sinus node dysfunction, 127 (17.5) AV block, 107 (14.8) Other reasons, 27 (3.7)	Bradycardia associated with persistent or permanent atrial tachyarrhythmia, 459 (57.7) AV block, 117 (14.7) Syncope, 112 (14.1) Sinus node dysfunction, 64 (8.0) Other reasons, 44 (5.5)	NR[8]
Comorbidities, n (%)	*Safety cohort:* 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) *Subgroup analysis – patients with elevated implant threshold (> 1.0 V at 0.24ms):* Diabetes, 25 (30.1) COPD, 6 (7.2) Renal dysfunction, 18 (21.7) CAD, 22 (26.5) AF, 62 (74.7) CHF, 14 (16.9) Hypertension, 63 (75.9) Valvular Disease, 27 (32.5)	Diabetes, 196 (24.7) COPD, 67 (8.4) Renal dysfunction, 152 (19.1) CAD, 132 (16.6) AF, 532 (66.9) CHF, 46 (5.8) Hypertension, 454 (57.1) Conditions that precludes the use of a transvenous pacemaker, 166 (20.9) Previous implanted CIED, 115 (14.5)	Diabetes, 129 (27.6) CAD, 176 (37.6) CHF, 74 (15.8) Hypertension, 367 (78.4) Valvular Disease, 58 (12.4)
Outcomes			
Efficacy			
Adaequad Pacing performance (pacing threshold ≤ 1.0 V at 0.24ms)	12 months: 586/630 (93) 24 months: 56/58 (97) *Subgroup analysis – patients with elevated implant threshold (> 1.0 V at 0.24ms):* 6 months: 51/72 (71)	At implant: 611/701 (87.2)	NR[8]

[8] not reported within this publication; for efficacy and safety results see MEL-Report 2016 [1]

Study (acronym, ID no.)	Micra Transcatheter Pacing Study (NCT02004873)	The Micra Transcatheter Pacing System Post-Approval Registry (NCT02536118)	The LEADLESS II pacemaker IDE study (NCT02030418)
Health related quality of life	***SF-36 scores [mean];*** n=488 *Pysical component summary:* pre-implant (baseline): 36.9 3 months: 38.7 Δ: +5% (p<0.05) *Mental component summary:* pre-implant (baseline): 47.8 3 months: 51.4 Δ: +8% (p<0.05)	NR	***EuroQol EQ-5D 3L [mean utility];*** n=468 *baseline:* 0.73[9] *pre-discharge:* 0.805±0.222 *week 12:* 0.838±0.178; p<0.01
Safety			
Implant success rate, n/N (%)	720/726 (99.2)	792/795 (99.6)	NR[8]
Overall Mortality, n/N (%)	77/745 (10.3)	22/795 (2.8)	NR[8]
Procedure-related mortality, n/N (%)	1/745 (0.1)	1/795 (0.1)	NR[8]
Cardiac mortality, n/N (%)	32/745 (4.3)	NR	NR[8]
Cardiac morbidity, n/N (%)	NR	NR	NR[8]
Systemic infection, n/N (%)	26/726 (3.6)	NR	NR[8]
Overall Adverse Events, n/N (%)	NR	NR	NR[8]
Serious Adverse Events, n/N (%)	226/725 (31.2)[10]	NR	NR[8]
Non-device-related SAE, n/N (%)	NR	NR	NR[8]
Overall Adverse Device Effects (ADE), n/N (%)	NR	NR	NR[8]
Serious Adverse Device Effects (SADE), n/N (%)	29/726 (4.0)	12/795 (1.5)	NR[8]
New hospitalization, n/N (%)	17/726 (2.3)	4/795 (0.5)	NR[8]
Prolonged hospitalization, n/N (%)	18/726 (2.2)	9/795 (1.0)	NR[8]
Loss of device function, n/N (%)	2/726 (0.3)	0/795	NR[8]

[9] baseline utility obtained from a meta-analysis of single-chamber pacemaker studies in the US

[10] 6 months data

Study (acronym, ID no.)	Micra Transcatheter Pacing Study (NCT02004873)	The Micra Transcatheter Pacing System Post-Approval Registry (NCT02536118)	The LEADLESS II pacemaker IDE study (NCT02030418)
Cardiac morbidity – device or procedure related, n/N (%)	9/726 (1.2) [11]	NR	NR[8]
Cardiac injury, n/N (%)	11/726 (1.5)	5/795 (0.6)	NR[8]
Major infections– device or procedure related, n/N (%)	0/726	1/795 (0.1)	NR[8]
Device dislodgement, n/N (%)	0/726	1/795 (0.1)	NR[8]
Elevated pacing thresholds requiring retrieval/replacement, n/N (%)	2/726 (0.3%)	NR	NR[8]

ADE: Adverse device effect; AF: Atrial fibrillation; AV: Atrioventricular; BBB: Bundle branch block; CAD: Coronary artery disease; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease; E: Efficacy; ECG: Electrocardiogram; HRQoL: Health-related quality of life; LCP: Leadless cardiac pacemaker; NA: Not applicable; NR: Not reported; S: Safety; SADE: Serious adverse device effect; SAE: Serious adverse event; TPS: Transcatheter pacing system; VCM: Ventricular capture management; VVI(R): Single-chamber ventricular pacing (with response modulation)

Table A-2: Leadless pacemakers: Results from observational studies (part 2)

Study (acronym, ID no.)	Da Costa 2017	Kypta 2016	Martínez-Sande 2017	Pachon 2016
Reference	[19]	[20]	[18]	[15]
Study description				
Country	France	Austria	Spain	Spain
Sponsor	NR	NR	NR	NR
Intervention/Product	Implantation of a leadless cardiac pacemaker/Micra™ TPS	Implantation of a leadless cardiac pacemaker/Micra™ TPS	Implantation of a leadless cardiac pacemaker/Micra™ TPS	Implantation of a leadless cardiac pacemaker/Micra™ TPS
Comparator	NA	NA	NA	NA
Study design	Case series	Case series	Prospective observational study	Case series
Duration of the study	May 2015 – July 2016	September 2015 – May 2016	June 2015 – May 2016	NR
Randomisation method	None	None	None	None
Blinding method (investigator, patient, outcomes assessor)	Open label	Open label	Open label	Open label

[11] acute Myocardial infarction, cardiac failure or pacemaker syndrome

Study (acronym, ID no.)	Da Costa 2017	Kypta 2016	Martínez-Sande 2017	Pachon 2016
Intervention (n=)	14	6	30	10
Control (n=)	0	0	0	0
Population	Patients contraindicated for or unable to receive conventional endovenous PM implantation	Patients With Severe Device Infection	Patients indicated for VVI pacing	Patients indicated for VVI pacing
Inclusion criteria	Indication for pacemaker implantation; full or relative contraindications for traditional transvenous PM implantation	Pacemaker dependance; lead extraction due to severe device infection (class I indication)	Indication for single-chamber pacemaker placement; age ≥ 65 years;	Standard indication for a permanent pacemaker; clinical profile and indication for VVI pacing
Exclusion criteria	NR	NR	NR	Patients without own cardiac rhythm
Primary outcome (including measurement tools and measurement times)	Implant success rate; pacing performance	Ongoing infection (C-reactive protein, white blood count)	Electrical parameters at implantation and over follow-up	NR
Secondary outcome (including measurement tools and measurement times)	Absence of serious adverse events at 3 months	Ongoing infection or reinfection (PET scan); Major or minor complications	Complications related to the implantation procedure	NR
Follow-up (months)	3 months	3 months	1, 3, 6 and 12 months (mean 5.3±3.3)	mean 55±33 days
Loss to follow-up, n (%)	0	0	NR	0
Population characteristics				
Age (mean), y	75.0±10.0	78.3±11.9	79.4±6.4	77.1±5.1
Male, n (%)	7 (50)	5 (83.3)	20 (66.7)	6 (60)
Pacing indication, n (%)	AV block, 10 (71.4) Uncontrolled AF, 3 (21.4) Bradyarrhythmia, 1 (7.1)	AV block, 6 (100)	Slow AF, 28 (93.3) Trifascicular block and syncope, 1 (3.3) Recurrent episodes of rapid atrial tachycardia, 1 (3.3)	Permanent AF, 7 (70) Bradycardia-tachycardia syndrome, 2 (20) AV block, 1 (10)
Comorbidities, n (%)	Diabetes, 6 (42.8) COPD, 2 (14.3) Renal dysfunction, 9 (64.3) CAD, 3 (21.4) AF, 9 (64.3) CHF, 8 (57.1) Hypertension, 12 (85.7) Valvular Disease, 3 (21.4)	NR	Diabetes, 11 (36.6) COPD, 60 (20.0) Renal dysfunction, 2 (6.6) Peripheral arterial disease, 5 (16.6) AF, 28 (93.3) IHD, 6 (20.0) Hypertension, 25 (83.3) Valvular Disease, 8 (26.6)	Diabetes, 2 (20) COPD, 1 (10) Renal dysfunction, 2 (20) Hypertension, 8 (80) Dyslipidemia, 4 (40) Obstructive sleep apnea, 1 (10) AF, 8 (80)

Study (acronym, ID no.)	Da Costa 2017	Kypta 2016	Martínez-Sande 2017	Pachon 2016
Outcomes				
Efficacy				
Adaequad Pacing performance (pacing threshold ≤ 1.0 V at 0.24ms)	14/14 (100)	6/6 (100)	6 months: 16/16 (100) 12 months: 4/4 (100)	10/10 (100)
Health-related quality of life	NR	NR	NR	NR
Safety				
Implant success rate, n/N (%)	14/14 (100)	6/6 (100)	30/30 (100)	10/10 (100)
Overall Mortality, n/N (%)	0/14	0/6	NR	0/10
Procedure-related mortality, n/N (%)	0/14	0/6	NR	0/10
Cardiac mortality, n/N (%)	0/14	0/6	NR	0/10
Cardiac morbidity, n/N (%)	1/14 (7.1)	NR	NR	NR
Systemic infection, n/N (%)	NR	0/6	0/30	NR
Overall Adverse Events, n/N (%)	NR	NR	NR	NR
Serious Adverse Events, n/N (%)	NR	NR	NR	NR
Non-device-related SAE, n/N (%)	NR	NR	NR	NR
Overall Adverse Device Effects (ADE), n/N (%)	1/14 (7.1)	NR	NR	0/10
Serious Adverse Device Effects (SADE), n/N (%)	NR	NR	NR	0/10
New hospitalization, n/N (%)	NR	NR	NR	NR
Prolonged hospitalization, n/N (%)	NR	NR	NR	NR
Loss of device function, n/N (%)	0/14	NR	NR	NR
Cardiac morbidity – device or procedure related, n/N (%)	1/14 (7.1)	NR	1/30 (3.3)	0/10
Cardiac injury, n/N (%)	NR	NR	NR	NR
Major infections– device or procedure related, n/N (%)	NR	0/6	NR	0/10
Device dislodgement, n/N (%)	0/14	0/6	0/30	0/10
Elevated pacing thresholds requiring retrieval/replacement, n/N (%)	0/14	0/6	0/30	0/10

ADE: Adverse device effect; AF: Atrial fibrillation; CAD: Coronary artery disease; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease; IHD: Ischemic heart disease; NA: Not applicable; NR: Not reported; SADE: Serious adverse device effect; VVI(R): Single-chamber ventricular pacing (with response modulation)

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 [37] and in the Guidelines of EUnetHTA [38, 39].

Table A-3: Risk of bias – study level (case series), see [27]

Study	Micra Transcatheter Pacing Study (NCT02004873)	The Micra Transcatheter Pacing System Post-Approval Registry (NCT02536118)	The LEADLESS II pacemaker IDE study (NCT02030418)	Da Costa 2017	Kypta 2016	Martínez-Sande 2017	Pachon 2016
reference/ID	[16, 17, 22, 23]	[24-26]	[21]	[19]	[20]	[18]	[15]
Study objective							
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear
Study population							
2. Are the characteristics of the participants included in the study described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	Yes	Yes	Yes	No	No	No	No
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Yes	Yes	Yes	Partially	Partially	Partially	Partially
5. Were participants recruited consecutively?	Unclear	Unclear	Yes	Yes	Unclear	Yes	Unclear
6. Did participants enter the study at similar point in the disease?	No	No	No	No	Yes	No	No
Intervention and co-intervention							
7. Was the intervention clearly described in the study?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Were additional interventions (co-interventions) clearly reported in the study?	No	No	No	No	Partially	No	No

Study	Micra Transcatheter Pacing Study (NCT02004873)	The Micra Transcatheter Pacing System Post-Approval Registry (NCT02536118)	The LEADLESS II pacemaker IDE study (NCT02030418)	Da Costa 2017	Kypta 2016	Martínez-Sande 2017	Pachon 2016
Outcome measures							
9. Are the outcome measures clearly defined in the introduction or methods section?	Yes	Yes	Yes	Yes	Partially	Partially	No
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
11. Were outcomes measured before and after intervention?	No	No	No	No	No	No	No
Statistical Analysis							
12. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	Unclear	Unclear	Yes	Unclear
Results and Conclusions							
13. Was the length of follow-up reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14. Was the loss to follow-up reported?	Yes	Yes	Yes	No	No	No	Yes
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16. Are adverse events reported?	Yes	Yes	Yes	Partially	Partially	Partially	Partially
17. Are the conclusions of the study supported by results?	Yes	Yes	Yes	No	Yes	Yes	Yes
Competing interest and source of support							
18. Are both competing interest and source of support for the study reported?	Yes	Yes	Yes	Partially	Partially	Partially	Partially
Overall Risk of bias	Low	Low	Low	High	High	High	High

Applicability table

Table A-4: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	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.
Intervention	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.
Comparators	There were no comparators.
Outcomes	The main outcomes reported in the studies were pacing performance for efficacy and complication rates for safety. Health-related quality of life was the only clinically relevant efficacy outcome reported in the studies. For safety, the reported outcomes are clinically relevant.
Setting	In all studies, the intervention was performed in a clinical setting, corresponding to the utilisation setting in Austria. Four studies were led in Europe, one in Australia, Canada and the US and two were global studies with study centres in North America, Europe, Africa, Asia and Australia. No applicability issues are expected from the geographical setting.

List of ongoing randomised controlled trials

Table A-5: 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	September 2017	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 2026	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	Estimated Study Completion Date: May 2017 Primary Completion Date: May 2015	Medtronic Cardiac Rhythm and Heart Failure
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
NCT03039712 Longitudinal Coverage With Evidence Development Study on Micra Leadless Pacemakers (Micra CED)	Bradycardia	Device: Micra™ leadless pacemaker therapy	Single Chamber Transvenous pacemaker	Acute complication rate The 2-year survival rate of patients implanted with a Micra leadless pacemaker	June 2021	Medtronic

Literature search strategies

Search strategy for CRD

Search Name: Leadless Pacemakers_Update 2017 (TS)	
Search Date: 06.04.2017	
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
#9	* WHERE LPD FROM 09/12/2015 TO 06/04/2017
#10	#8 AND #9
Total: 1 Hit	

Search strategy for Embase

Search Name: Leadless Pacemakers_Update 2017 (TS)	
Search Date: 06.04.2017	
ID	Search
#1	'heart pacing'/exp
#2	'artificial heart pacemaker'/exp
#3	pacemaker*
#4	peacemaker*
#5	'pace-maker'
#6	'pace-makers'
#7	'peace-maker'
#8	'peace-makers'
#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'
#10	leadless
#11	(leadless OR transcatheter*) NEAR/4 pacing
#12	leadless OR (leadless OR transcatheter*) NEAR/4 pacing
#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)
#14	'heart pacing'/exp OR 'artificial heart 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) AND [9-12-2015]/sd
Total: 144 Hits	

Search strategy for Medline

Search Name: Leadless Pacemakers_Update 2017 (TS)	
Search Date: 06.04.2017	
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
#9	("26227982" or "26321198" or "25546862" or "25906000" or "24732365" or "25319956" or "25223835" or "25040838" or "25606637" or "25881931" or "25881930" or "25289391" or "24798955" or "24497573" or "24664277" or "24519117" or "22581741" or "23168008" or "23703364" or "23620339" or "23687235" or "23104398" or "23027843" or "22138425" or "22427074" or "21798878" or "21276495" or "21391322" or "21135811" or "20553288" or "20927783" or "20465717" or "20136603" or "19467502" or "19427274" or "19170906" or "16810701" or "12001828" or "10505390" or "3520168" or "26370553" or "26337997" or "26024918" or "26183288" or "26102353" or "26370476" or "26487626" or "26045305" or "26282468" or "26427291" or "26233700" or "26261157" or "25639949" or "25123732" or "25855677" or "25814425" or "25367066" or "25610802" or "26606963" or "26551877" or "26551666" or "26539965" or "26519678" or "26458791" or "26261298" or "26100053" or "21261667" or "24347317" or "23449923" or "21699827" or "22968177" or "21195583" or "26307459" or "24056152" or "15478788").ui.
#10	8 not 9
#11	remove duplicates from 10
Total: 91 Hits	

Search strategy for Pubmed

Search Name: MEL 2016: Leadless Pacemakers: Update 2017(ST)	
Search Date: 06.04.2017	
ID	Search
#1	(((Pacemaker, Artificial[MH] OR Cardiac Pacing, Artificial[MH] OR pacemaker*) AND (leadless OR leadless pac* OR transcatheter pac*))) AND ("2015/12/09"[Date – Entrez] : "3000"[Date – Entrez]) (((Pacemaker, Artificial[MH] OR Cardiac Pacing, Artificial[MH] OR pacemaker*) AND (leadless OR leadless pac* OR transcatheter pac*))) AND ("2015/12/09"[Date – Entrez] : "3000"[Date – Entrez])
Total: 77 Hits	

Search strategy for Cochrane

Search Name: Leadless Pacemakers (Update 2017)	
Search Date: 04.04.2017	
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 Publication Year from 2015 to 2017
Total: 9 Hits	

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