Leadless Pacemakers for Right Ventricle Pacing

2. Update 2020

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

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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
ADE .....Adverse device effects
AF.....Atrial fibrillation
AHA .....American Heart Association
AV.....Atrioventricular
CAD .....Coronary artery disease
CHF .....Congestive heart failure
CIED.....Cardiac implantable electronic device
CI.....Confidence interval
C-PM.....Conventional cardiac pacemaker
CRD .....Centre for reviews and dissemination
DARE.....Database of Abstracts of Reviews of Effects
EC.....European Commission
ESC .....European Society of Cardiology
EU .....European Union
FDA.....Food and Drug Administration
GRADE.....Grading of Recommendations Assessment, Development and Evaluation
HAS.....Haute Autorité de Santé
HR.....Hazard ratio
HRQoL .....Health-related quality of life

HRS.....Heart Rhythm Society
HTA .....Health technology assessment
ICE .....International Statistical Classification of Diseases and Related Health Problems
ICER .....Incremental cost-effectiveness ratio
IHE.....Institute of Health Economics
LCP .....Leadless Pacemaker System
L-PM .....Leadless cardiac pacemaker
NA .....Not applicable
NHS-EED.....National Health Service Economic Evaluation Database
NICE.....National Institute for Health and Care Excellence
NIPH.....Norwegian Institute of Public Health
NR .....Not reported
OR .....Odds ratio
RCT.....Randomized controlled trial
SADE .....Serious adverse device effects
SAE.....Serious adverse events
SAPACT .....South Australian Policy Advisory Committee on Technology
SND.....Sinus node disease
TAVI .....Transcatheter aortic valve replacement
TPS.....Transcatheter Pacing System
USA .....United States of America
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 second update of the systematic review on "Leadless pacemakers for right ventricle pacing" initially prepared in March 2016 and first updated in 2017. It comprises all new information from published and unpublished documents.

Health Problem

indication: cardiac arrhythmias

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 (AF) who require a pacemaker due to slow ventricular response, but also patients with bradycardia due to atrioventricular block (AV-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 re-establish effective circulation and more normal haemodynamic 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 pacemakers: miniaturized, entirely implantable cardiac pacemakers

only available system: Micra™ TPS

Leadless cardiac pacemakers (L-PM) are self-contained intracardiac devices that are designed to have the same function as conventional cardiac pacemakers (C-PM), 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. This update focusses on Medtronics Micra™ Transcatheter Pacing System (TPS) since this is the only system currently available on the market.

Methods

systematic search in bibliographic databases

quality of the evidence according to GRADE

We assessed whether leadless cardiac pacemakers in comparison to conventional cardiac 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 four different bibliographic databases and three clinical trials registries was conducted. Furthermore, the manufacturer of the relevant device was 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 independently from each other. For the rating of the quality of evidence the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system was used.

Domain effectiveness

efficacy: mortality HRQoL and exercise capacity

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

Domain safety

safety: serious adverse events and complication rate

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).

Results

Available evidence

no RCTs or non-RCTs

3 prospective single-arm studies, 1 case-control study and 5 case series

1 propensity score-matched analysis comparing L-PM to C-PM

For this update-report, still, no randomized or non-randomized controlled trials assessing leadless cardiac pacemakers versus conventional pacemakers were available. We identified 16 new relevant documents on three ongoing prospective multi-centre single arm studies, one small multi-centre case-control study and five additional small single-centre case series. In addition, a recently published propensity score-matched analysis comparing L-PM to C-PM was included. The total number of patients analysed for efficacy and safety endpoints were 2,976. Atrial fibrillation with or without AV block was the major indication for pacing in the included studies. Mean age of the study participants ranged from 75 to 87 years, and co-morbidities were frequent. The follow-up in the included studies ranged from 1 month to a maximum of 24 months. Four publications focussed on specific subgroups within the included studies. These were patients with previous cardiac implantable electronic device (CIED) infections, patients with history of atrial fibrillation, patients on haemodialysis and Japanese patients, respectively.

Clinical effectiveness

Device- or procedure-related death: 0.2%

HrQoL: sustained improvement after 12 months

Overall 233 of 2915 patients with successful Micra™ TPS implant in seven studies died during follow-up of up to 24 months. Device- or procedure-related death ware rare with six in 2,915 patients (0.2%). None of the included studies reported efficacy results associated with cardiac arrhythmias or results for exercise capacity. For HRQoL, 12-months results in one prospective single-arm study and 6-months results in one case-control study showed statistically significant improvements from baseline in SF-36 scores. After 6 months beneficial effects in HRQoL in Micra™ TPS patients compared to patients with conventional single-chamber pacemakers were reported.

Safety

SAE: 32.2% and 9,8%

major device- or procedure-related complications: 2.5%

indirect comparison: lower complication rates with L-PM compared to C-PM

SAE were only reported in two studies with event rates of 32.2% and 9.8%, respectively. Nevertheless, major device- or procedure-related complications occurred in 75 of 2,976 patients with successful Micra™ TPS implant (2.5%). There were 28 pericardial effusions/perforations, 16 major infection and two device dislodgement reported in the included studies. A propensity score-matched analysis comparing data from L-PM studies to one large single-chamber C-PM cohort study data showed statistically significant lower complication rates for the L-PM within 800 days post implantation.

Subgroup analyses for patients with an increased risk for complications like patients with prior cardiac device infections or patients on haemodialysis showed no increased complication rates compared to all other patients included in the studies.

Upcoming evidence

one ongoing RCT

There is only one ongoing randomized controlled trial (RCT) comparing leadless pacemaker implantation to conventional pacemaker implantation in 210 transcatheter aortic valve replacement (TAVI) patients. The expected completion date of the study is at the end of 2020. Four ongoing observational studies on the Micra™ TPS and two further ongoing observational studies on another leadless pacemaker system developed in India are registered.

Discussion

low mortality and complication rates with Micra™ TPS, but no evidence from direct comparisons to C-LP

treatment option for well-defined patient groups

New mid-term results up to 24 months showed low overall mortality and device- or procedure-related mortality and complications rates in patients with successful Micra™ TPS implantation. Indirect comparisons resulted in statistically lower complication rates with L-PM to C-PM within 800 days of follow-up. However, since no controlled trials with direct comparisons of leadless pacemakers and conventional single-chamber pacemakers are available, no reliable judgement of the efficacy and safety is possible. Nevertheless, the Micra™ TPS might have the potential for being a treatment for patients with contra-indications for conventional pacemaker implantation or with increased complication risk.

Conclusion

current evidence insufficient to conclude about comparative effectiveness;
safety profile potentially advantageous

The current evidence is not sufficient to determine whether the leadless pacemaker Micra™ TPS is equal or more effective than single-chamber C-PM. Based on the evidence of indirect comparison to C-PM, the safety profile of the Micra™ TPS seems to be advantageous. Therefore, the inclusion of the technology in the catalogue of benefits is recommended with restrictions only to well-defined patient groups after careful risk assessment und under extensive documentation.

Zusammenfassung

Einleitung

Der vorliegende Bericht ist das zweite Update des erstmals im März 2016 erstellten und 2017 upgedateten 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 Bradykardie aufgrund eines Sick-Sinus-Syndroms oder atriventrikulärem 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 subkutanen Hauttasche und den transvenösen Sonden für die Impulsübertragung, die bei konventionellen Herzschrittmachern notwendig sind, vermieden werden. Das vorliegende Update befasst sich dabei ausschließlich mit dem Micra™ Transkatheter Pacing System (TPS) der Firma Medtronic Inc., da es derzeit das einzige am Markt verfügbare sondenlose Herzschrittmachersystem darstellt. Das Nanostim™ Leadless Pacemaker System (LCP) von Abbott Inc., das in den bisherigen Berichten 2016 und 2017 ebenfalls inkludiert war, wurde im Jahr 2016 vom Hersteller gestoppt, da es zu frühzeitigen Batterie-Fehlfunktionen gekommen war. Das Produkt ist daher derzeit nicht verfügbar und auch die CE-Zertifizierung wurde ruhend gestellt.

Micra™ TPS derzeit das einzige verfügbare Produkt

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 vier verschiedenen bibliografischen Datenbanken (Medline, Embase, Cochrane library, CRD) sowie in drei Studienregistern durchgeführt. Zusätzlich wurden der Hersteller des Medizinprodukts im Hinblick auf weitere publi-

Qualität der Evidenz mit GRADE

zierte und nicht publizierte Studienergebnisse kontaktiert. Die Studienauswahl, Datenextraktion sowie die Bewertung der methodischen Qualität der Studie wurde unabhängig voneinander von zwei ReviewerInnen 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: Mortalität, gesundheitsbezogene Lebensqualität (HRQoL), Belastungsfähigkeit.

Wirksamkeit: Mortalität, HRQoL und Belastungsfähigkeit

Sicherheit

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

Sicherheit: Schwere unerwünschte Ereignisse, Komplikationsraten

Ergebnisse

Verfügbare Evidenz

Es konnten nach wie vor keine randomisiert oder nicht-randomisiert klinischen Studien identifiziert werden, die sondenlose Herzschrittmacher im Vergleich zu konventionellen Herzschrittmachern untersuchten. Insgesamt konnten für das vorliegende Update 16 neue relevante Dokumente zu drei laufenden prospektiven multizentrischen Einzelarmstudien, zwei davon bereits im Update 2017 inkludiert, zu einer multizentrischen Fall-Kontroll-Studie und zu weiteren fünf kleinen monozentrischen Fallserien eingeschlossen werden. Zusätzlich wurde eine kürzlich veröffentliche Propensity score-mached Analyse zum Vergleich sondenloser Herzschrittmacher versus konventioneller Einkammernschrittmacher als relevant identifiziert. Die Gesamtzahl der in den neuen Studien untersuchen PatientInnen betrug 2.976 Personen. Die Hauptindikation für einen Herzschrittmacher in den Studien war Vorhofflimmern mit oder ohne AV Block. Das mittlere Alter der StudienteilnehmerInnen lag zwischen 75 und 87 Jahren, wobei eine Fallserie nur PatientInnen im Alter ab 70 Jahren einschloss. Bei der Mehrzahl lagen auch Begleiterkrankungen vor. Die Beobachtungsdauer der einzelnen Studien betrug 30 Tage bis zu maximal 24 Monate. Vier der inkludierten aktuellen Publikationen befassen sich mit Wirksamkeit und vor allem Sicherheit des Micra™ TPS in spezifischen PatientInnensubgruppen aus den inkludierten Studien, wie z. B. PatientInnen mit Infektionen auf Grund von früheren kardialen Implantaten oder PatientInnen mit erhöhtem Komplikationsrisiko (PatientInnen mit Hämodialysebehandlungen).

keine RCTs oder non-RCTs

3 prospektive Einzelarmstudien, 1 Fall-Kontroll Studie und 5 Fallserien

1 Propensity score-matched Analyse zum Vergleich L-PM versus C-PM

Klinische Wirksamkeit

Mortalität mit Bezug zu Eingriff oder Implantat: 0,2 %

HrQoL: Nachhaltige Verbesserung nach 12 Monaten

Insgesamt kam es in sieben der inkludierten Studien mit 2915 PatientInnen mit einer erfolgreichen Implantation eines sondenlosen Schrittmachers im Rahmen eines Follow-ups von bis zu 24 Monaten zu 233 Todesfällen (8,0 %). Sechs dieser Todesfälle (0,2 %) wurden dabei als ursächlich auf den Eingriff oder das Implantat zurückzuführend beurteilt. Ergebnisse zur Wirksamkeit im Hinblick auf kardiale Arrhythmien oder zur Belastungsfähigkeit lagen in den Studien weiterhin nicht vor. Eine Befragung der PatientInnen im Hinblick auf die gesundheitsbezogene Lebensqualität wurde in zwei Studien vorgenommen. So zeigte sich in einer der multizentrischen Beobachtungsstudien bei 635 befragten PatientInnen nach 12 Monaten eine signifikante Verbesserung der Lebensqualität in allen Domänen des SF-36 Fragebogens im Vergleich zum Zeitpunkt vor der Implantation. In einer Fall-Kontroll-Studie wurde die Veränderung der Lebensqualität bei PatientInnen mit einem sondenlosen Schrittmacher im Vergleich zu einem konventionellen Einkammer-Schrittmacher nach 6 Monaten untersucht. Dabei zeigte sich in allen Domänen des SF-36 Fragebogens ein Vorteil zu Gunsten des sondenlosen Schrittmachers, welcher in 4 Fällen auch statistisch signifikant war.

Sicherheit

SAE: 32,2 % bzw. 9,8 %

schwere Komplikationen mit Bezug zum Eingriff oder Implantat: 2,5 %

indirekter Vergleich: signifikant geringere Komplikationsraten mit L-PM im Vergleich zu C-PM

Schwerwiegende unerwünschte Ereignisse wurden nur in zwei der neun inkludierten Studien berichtet, wobei die Ereignisraten bei 32,2 % bzw. 9,8 % lagen. Schwere Komplikationen im Zusammenhang mit dem Eingriff oder dem Implantat traten im Zeitraum bis zu 24 Monaten in 75 von 2976 PatientInnen auf (2,5 %), darunter waren 28 Fälle von Perikardperforation bzw. –erguss, 16 schwere Infektionen und zwei Ablösungen des Implantats. Eine kürzlich publizierte Propensity score-matched Analyse zum Vergleich sondenlose Schrittmacher versus konventioneller Einkammernschrittmacher ergab statistisch signifikant geringere Komplikationsraten innerhalb von 800 Tagen nach Implantation für die Gruppe mit sondenlosen Schrittmachern.

Die Subgruppenauswertungen mit Personen mit einem erhöhten Komplikationsrisiko ergaben keine signifikanten Unterschiede in den Sicherheitsparametern im Vergleich zu den übrigen PatientInnen in den Studien.

Laufende Studien

1 laufender RCT

Es konnte ein laufender RCT identifiziert werden, in dem die Implantation eines sondenlosen Herzschrittmachers im Vergleich zu einem konventionellen Schrittmacher bei Personen mit perkutane Aortenklappenersatz untersucht wird. Das vorläufige Studienende ist für Dezember 2020 festgelegt. Darüber hinaus finden sich in den Studienregistern vier laufende Beobachtungsstudien zum Micra™ TPS sowie zwei laufende Beobachtungsstudien zu einem weiteren sondenlosen Herzschrittmacher der in Indien entwickelt wurde.

Diskussion

geringe Mortalitäts- und Komplikationsraten mit Micra™ TPS, jedoch nach wie vor keine Evidenz aus direkten Vergleichen zu C-PM

Neue mittelfristige Ergebnisse (Follow-up bis 24 Monate) aus mehreren prospektiven Beobachtungsstudien zeigen für PatientInnen nach erfolgreicher Implantation eines sondenlosen Herzschrittmachers (Micra™ TPS) insgesamt niedrige Mortalitäts- und Komplikationsraten. Allerdings wurden nach wie vor keine randomisierten oder nicht-randomisierten kontrollierten Studien durchgeführt, die einen direkten Vergleich zwischen sondenlosen Herzschrittmachern und den etablierten konventionellen Einkammernschrittmachern erlauben. Eine verlässliche Beurteilung der Wirksamkeit und Sicherheit der sondenlosen Herzschrittmacher ist daher nicht möglich. Dennoch scheint der Micra™ TPS auf Basis der verfügbaren Evidenz das Potenzial für eine Behandlungsalternative, besonders für PatientInnen mit Indikationen für VVI-Schrittmacher bei denen eine Kontraindikation für konventionelle Schrittmachern oder ein erhöhtes Komplikationsrisiko vorliegt, zu haben.

gegebenenfalls Behandlungsoption für eine eingeschränkte PatientInnengruppe

Empfehlung

verfügbare Evidenz ist für die Bewertung der Wirksamkeit nicht ausreichend; möglicherweise vorteilhaftes Sicherheitsprofil

Die derzeitige Evidenz ist immer noch nicht ausreichend, um den Micra™ TPS im Hinblick auf die Wirksamkeit im Vergleich zu konventionellen Herzschrittmachern verlässlich beurteilen zu können. Im Hinblick auf Sicherheitsaspekte scheint Micra™ TPS jedoch gewisse Vorteile zu haben. Daher wird eine Aufnahme in den Leistungskatalog mit Einschränkungen ausschließlich auf ausgewählte PatientInnengruppen nach einem sorgfältigen Risiko-Assessment und unter umfangreicher Dokumentation (Register) empfohlen.

Summary of the previous assessments 2016 and 2017

Commissioned by the Austrian Ministry of Health, the HTA-report "Leadless pacemakers for right ventricle pacing" was initially prepared by the Ludwig Boltzmann Institute of Health Technology Assessments (LBI-HTA) in March 2016 [1]. In 2017, the report was updated for the first time [2]. The following paragraphs summarize the results and the recommendation of the 2016 and 2017 reports.

systematischer Review 2016, 1. Update 2017

Scope

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 2016 und 2017

Inclusion criteria for relevant studies are summarised in Table 1.

Table 1: Inclusion criteria

Population	First-line treatment of patients with indications for single-chamber ventricular pacemakers [3, 4] • 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]
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

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

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

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 reports 2016 and 2017.

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)

Results

Report 2016

2016: keine Vergleichsstudien, 3 prospektive Einzelarmstudien

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 [1]. Two studies investigated the Nanostim™ LCP and one study the Micra™ TPS. All of the studies were sponsored by the device manufacturers.

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 1,284 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% and 1%, respectively.

[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.

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.

schwere produktbezogene Ereignisse: 4-6.5 %

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

sehr niedrige Evidenzstärke

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

Update report 2017

For the update-report [2], still, no comparative studies assessing leadless cardiac pacemakers versus conventional pacemakers were available. Twelve new relevant documents on three ongoing prospective multi-centre single arm studies and four small single-centre case series were identified in the literature search. The total number of patients analysed for efficacy and safety endpoints respectively were 1,391 and 1,581. Atrial fibrillation with AV block was the major indication for pacing in the included studies. Six of the seven studies investigated the Micra™ TPS, only one publication reported results on the Nanostim™ LCP.

2017: weiterhin keine Vergleichsstudie, 3 prospektive Einzelarmstudien und 4 Fallserien

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.

HRQoL: Verbesserung nach 3 Monaten

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.

Mortalität: 10,3 % nach 12 Monaten

Recommendation

The evidence included in the reports 2016 and 2017 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.

Evidenz 2016 und 2017 nicht ausreichend für Empfehlung

UPDATE 2020

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, 4] • 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]
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) MESH term: Pacemaker, Artificial [E07.305.250.750]
Control	Conventional VVI(R) pacemaker MESH term: Pacemaker, Artificial [E07.305.250.750]

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

Outcomes	
Efficacy	❁ Overall mortality ❁ Cardiovascular mortality ❁ Cardiovascular morbidity ❁ Patient-related quality of life ❁ Exercise capacity ❁ Pacing performance
Safety	❁ Serious adverse events ❁ Overall adverse events ❁ Complication rates
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 with at least 50 patients

[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

Description of the technology	
Element ID	**Research question**
B0001	What is a leadless pacemaker and a conventional pacemaker?
A0020	For which indications has the leadless pacemaker received marketing authorisation or CE marking?
B0002	What is the claimed benefit of leadless pacemakers in relation to conventional single-chamber pacemakers?
B0003	What is the phase of development and implementation of leadless pacemakers and conventional single-chamber pacemakers?
B0004	Who administers leadless pacemakers and conventional single-chamber 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 pacemakers?
B0009	What supplies are needed to use leadless pacemakers and conventional single-chamber 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 bradyarrhythmia?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?

Clinical Effectiveness	
Element ID	**Research question**
D0001	What is the expected beneficial effect of leadless pacemakers on mortality?
D0005	How do leadless pacemakers affect symptoms and findings (severity, frequency) of cardiac arrhythmias?
D0006	How do leadless pacemakers affect progression (or recurrence) of cardiac arrhythmias?
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
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

- Background publications identified in hand search
- Clinical practice guidelines identified in hand search
- Documentation provided by the manufacturer

Health problem and Current Use

- Background publications identified in hand search
- Clinical practice guidelines identified in hand search

2.3 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on the 15.01.2020 in the following databases:

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

The systematic search was limited to the years 2017 to 2020. After deduplication, overall 691 citations were included. The specific search strategy employed can be found in the Appendix Literature search strategies.

Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 03.02.2020 resulting in 17 potential relevant hits.

insgesamt 709 Publikationen identifiziert

The manufacturer from the only available product (Medtronic Inc., USA) was contacted and submitted 28 publications of which two additional citations were identified.

By hand-search, no additional were found.

2.4 Flow chart of study selection

Literaturauswahl

Overall 1047 hits were identified. After deduplication, 709 references were screened by two independent researchers (TS, CZ, CL) and in case of disagreement a third researcher was (TS, CZ, CL) involved to solve the differences. The selection process is displayed in Figure 2-1.

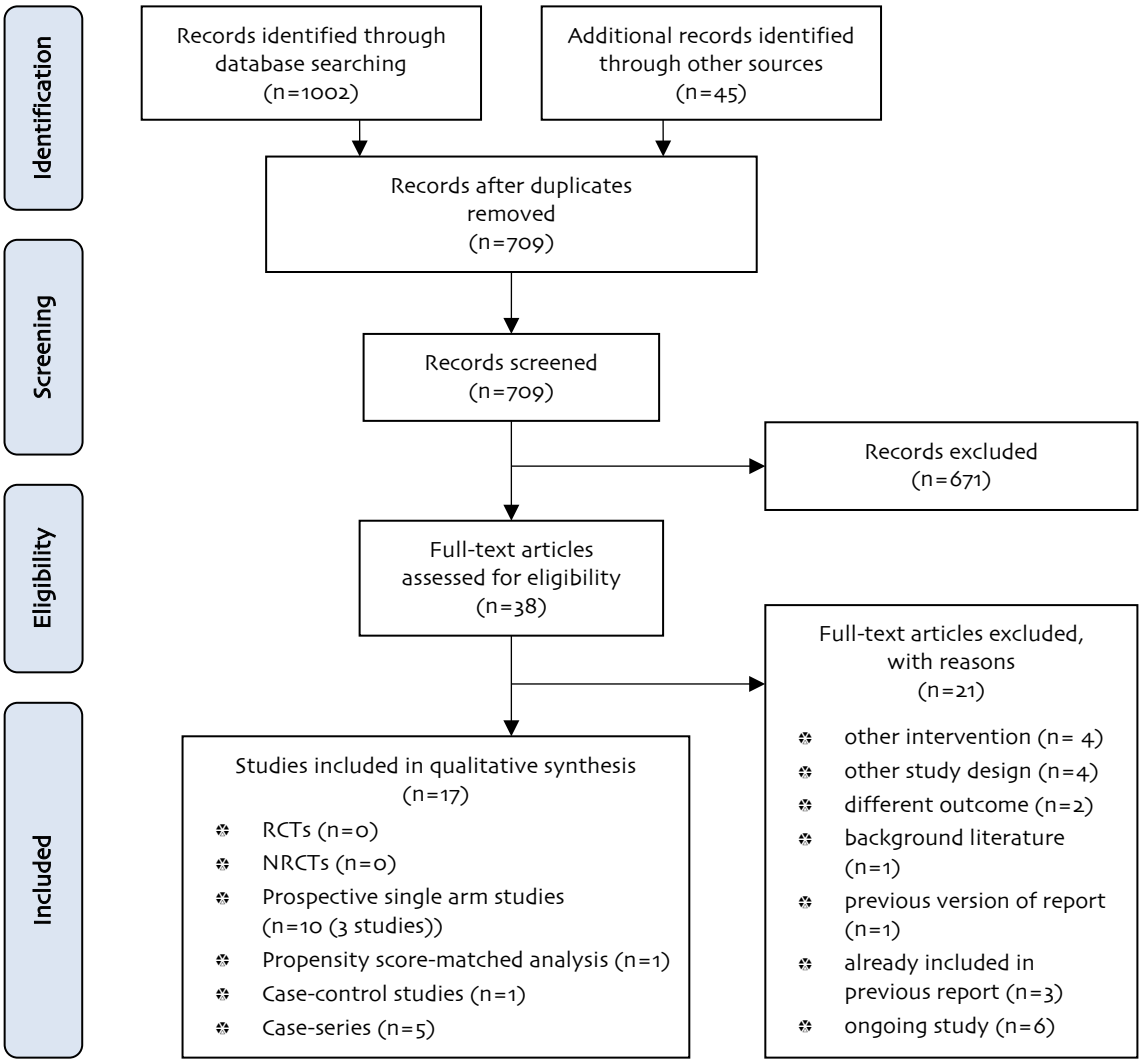

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.5 Analysis

Datenextraktion in Tabellen

Relevant information was retrieved from the sources identified. Data from included studies were extracted into data extraction tables based on the study design and research question (see Appendix Table A-1). An independent second reviewer (TS) validated the data for accuracy. No meta-analysis was performed.

Risk of Bias Bewertung mit IHE Checkliste

Two researchers (CZ, CL) conducted risk of bias assessments independently. Differences were resolved by consensus. The quality of the included single-arm studies was assessed using the Institute of Health Economics (IHE) checklist for case series [5] (see Table A-2).

2.6 Synthesis

Zusammenfassung der Ergebnisse

Bewertung der Qualität der Evidenz mit GRADE

Based on the data-extraction-table (see Appendix Table A-1), data on each selected outcome were synthesized. Quality of evidence was assessed across studies for each outcome according to GRADE (Grading of Recommendations Assessment, Development and Evaluation [6]).The research questions were answered in plain text format with reference to GRADE evidence tables that are included in Appendix Table A-3, results were summarized in Table 7-1.

3 Description and technical characteristics of technolgy

Features of the technology and comparators

B0001 – What is a leadless pacemaker and a conventional pacemaker?

Herzschrittmacher zur Behandlung kardialer Arrhythmien eingesetzt

Pacemakers are developed for the treatment of a variety of cardiac arrhythmias. By providing an appropriate heart rate and heart rate response, cardiac pacing can re-establish effective circulation and more normal hemodynamics that are compromised by a slow heart rate [7]. For patients with symptomatic bradycardia caused by sick sinus syndrome, atrioventricular block (AV block) or a combination of this conditions, dual-chamber pacing is recommended. Single-chamber ventricular pacemakers may be considered for patients with AV block alone or with sick sinus syndrome in people with continuous atrial fibrillation, or people who have specific factors such as frailty or comorbidities that influence the balance of risks and benefits in favour of single-chamber pacing [7].

Konventionelle Schrittmacher: Pulsgeber + Sonden

schwere Komplikationen: Reinterventionen aufgrund von Sondendefekten oder Sonden-/Generator-problemen, Infektionen, Herzperforationen, etc.

Conventional cardiac pacemakers (C-PM) consist of a pulse generator, which provides the electrical impulse for myocardial stimulation and one or more leads, which deliver the electrical impulse to the myocardium. The pulse generator is implanted in the infraclavicular region of the anterior chest wall. Usually the impulses generated are transmitted to the myocardium via transvenous leads [7]. Major complications associated with the implantation of a conventional 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 [8, 9].

Sondenlose Schrittmacher: miniaturisierte, vollständig implantierbare Herzschrittmacher

Leadless cardiac pacemakers (L-PM) have been developed as alternatives for C-PM. They are self-contained intra-cardiac devices that include both the pulse generator and the electrode within a single unit. They are designed to have the same function as C-PM, but are miniaturized and can be implanted entirely inside the right ventricle of the heart via a steerable catheter [10]. Single-unit L-PM have been developed for single-chamber pacing, specifically right ventricular pacing [11].

Micra™ TPS derzeit einzig verfügbares Produkt

Nanostim™ LCP nach Batterieproblemen gestoppt

There are two leadless pacing systems that have been clinically tested: the Nanostim™ leadless cardiac pacemaker developed and manufactured by St. Jude Medical (later Abbott Inc., USA) and the Micra™ transcatheter pacing system (TPS) by Medtronic Inc., USA. Currently the Micra™ TPS is the only commercially available system, since the Nanostim™ was withdrawn from the market in 2016 after battery malfunctions in serval patients [12].

A0020 – For which indications has the leadless pacemaker received marketing authorisation or CE marking?

Indikation: Patienten, die aufgrund von Arrhythmien unter Belastungsintoleranz oder Belastungsbeschränkungen leiden

The Micra™ TPS received CE marking (CE: 0123) in April 2015 [13] and Food and Drug Administration (FDA)-approval in April 2016 [14] for the use in patients with indications for single-chamber right-ventricular pacing. These include following conditions [15]:

- Paroxysmal or permanent high-grade AV block in the presence of atrial fibrillation (AF)
- Paroxysmal or permanent high-grade AV block in the absence of AF, as an alternative to dual chamber pacing, when a dual-chamber transvenous pacing system is considered difficult, high risk, or not deemed necessary for effective therapy
- Symptomatic bradycardia-tachycardia syndrome or sinus node dysfunction (sinus bradycardia or sinus pauses), as an alternative to atrial or dual chamber pacing, when a dual-chamber transvenous pacing system is considered difficult, high risk, or not deemed necessary for effective therapy

The Micra™ TPS is contraindicated for patients with morbid obesity, femoral venous anatomy unable to accommodate a 7.8 mm introducer sheath or implant on the right side of the heart, Micra™ TPS material intolerance or with implanted medical devices that would interfere with the L-PM [15].

B0002 – What is the claimed benefit of leadless pacemakers in relation to conventional single-chamber pacemakers?

Vorteile des L-PM: keine Implatation eines externen Pulsgenerators und keine Sonden, dadurch Vermeidung entsprechender Komplikationen

In contrast to traditional pacemakers, L-PM 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 to achieve the same pacing results as a C-PM avoiding complications, such as problems with lead placement and reduction in risk of infections, associated with these two components of C-PM implantation [12].

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

Micra™ TPS: CE-Zertifizierung 2015 und FDA Zulassung 2016

L-PM were first implanted in human patients in 2012 [12]. In 2013 the Nanostim™ received CE marking, while the Micra™ TPS was CE market approved in 2015 and FDA approved in 2016. Late 2016 the manufacturer stopped the implantation of the Nanostim™ pacemaker and the CE market approval was suspended later on. The use of the remaining Micra™ TPS in clinical practice is constantly increasing [12].

Konventionelle Schrittmacher: seit über 60 Jahren implantiert; Wirksamkeit mehrfach in großen Studien gezeigt

The first implantation of cardiac pacemakers occurred in 1958. After that, several large studies showed an improvement of severity and frequency of bradycardia symptoms and of mortality in patients with higher-grade AV block. Therefore, the implantation of C-PM today is recommended in various international guidelines as standard intervention for the treatment of bradyarrhythmias [12].

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

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

C-PM and L-PM are implanted by a cardiologist or a cardiac surgeon experienced in implanting these devices. In Austria, L-PM implantation is restricted to specialist teams, who have undergone an extensive training programme and are certified and regularly re-certified.

Erfahrene/r Kardiologe/In oder HerzchirurgIn; L-PM: beschränkt auf speziell geschulte Teams

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

C-PM and L-PM are usually implanted at a cardiac catheterisation laboratory or in an operating theater. In contrast to C-PM implantation, L-PM are implanted under fluoroscopic guidance via catheter-based delivery through the femoral vein using a dedicated introducer sheath.

Herzkatheterlabor oder Operationssaal

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

For both C-PM and L-PM implantation, patients are monitored by an anaesthesiologist and usually receive regional anaesthesia. The implantation procedure is performed under sterile conditions. The implanting physician is supported by specialized trained assistance/nurses.

Implantation unter Regionalanästhesie

Regulatory & reimbursement status

A0021 – What is the reimbursement status of leadless pacemakers?

The L-PM does not yet have its own settlement rate and is currently being billed as a conventional single-chamber pacemaker.

L-PM: derzeit nicht im Leistungskatalog abgebildet

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?

kardiale Arrhythmien

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 conduction. 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 [16, 17]. 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.

AV Block: erhöhtes Sterberisiko aufgrund von Herzversagen

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) [4] and by the European Society of Cardiology (ESC) [3]. In patients with sinus node disease as well as in patients with AF, 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].

Indikationen laut Leitlinien: Bradykardie mit Symptomen

VVI bevorzugt bei PatientInnen mit chronischer AF

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

Patients with indications for right ventricle pacing:

Patienten mit Indikation für VVI

- Patients with chronic atrial fibrillation (AF; ICD-10 I.48) who require a pacemaker for persistent or intermittent bradycardia due to slow ventricular response (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)

A0003 – What are the known risk factors for bradyarrhythmia?

Risikofaktoren: Alter, Schädigung des Herzgewebes durch Herzerkrankungen

The major risk factor for cardiac bradyarrhythmia is age. Heart problems, which are often associated with bradyarrhythmias, are more common in older adults. In addition, bradyarrhythmia is often associated heart tissue damage from certain types of heart diseases, which themselves are associated with e.g. hypertension, smoking or alcohol misuse [18].

Target population

A0007 – What is the target population in this assessment?

Chronische oder persitierende kardiale Arrhythmien

Patients with indications for right ventricle pacing:

- Patients with chronic atrial fibrillation (AF; ICD-10 I.48) who require a pacemaker for persistent or intermittent bradycardia due to slow ventricular response (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)

A0023 – How many people belong to the target population?

Österreich: 116.000 Personen mit kardialen Arrythmien

In Austria, over 116,000 patients with cardiac arrhythmias were recorded in 2011 [19].

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 itself does not treat AF, the main indication for single chamber ventricular pacing. Recent reports indicate that prognosis of bradycardia pacemaker recipients are mainly determined by comorbidities and a bradycardia pacing indication as such does not influence survival [1].

entscheidungsrelevante Endpunkte – Wirksamkeit: Mortalität, Lebensqualität, Beslastungsfähigkeit

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

- Overall mortality
- Device- or procedure-related mortality
- Exercise capacity
- Health-related quality of life (HRQoL)

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.

5.2 Included studies

As in the 2017 report, there are still no RCTs or non-RCTs available to assess the effectiveness of leadless pacemakers. In our update search, we identified 16 documents [20-35] on nine studies addressing our research question. This includes two prospective multi-centre single arm studies, which have already been included in the 2017 report and a third prospective multi-centre single arm study. The three prospective multi-centre single arm studies were the Micra Transcatheter Pacing study [28, 33], the Micra Transcatheter Pacing System Post-Approval registry [30, 34] and the Micra Transcatheter Pacing System Continued Access study [35], and included 2,819 patients. All three studies were sponsored by the device manufacturer. In addition, we included one multi-centre case-control study with 106 patients [20] and five single-centre case series including a total of 390 patients [21, 23, 25, 27, 29]. One case series was sponsored by the manufacturer and other two were sponsored by public grants. In the remaining three studies the sponsor was not reported.

immer noch keine RCTs oder non-RCTs

seit Update 2017: neue Ergebnisse aus 17 Publikationen; 3 prospektive Einzelarm-Studien mit insgesamt 2.819 PatientInnen, 1 Fall-Kontroll-Studie und 5 Fallserien;

The mean follow-up of the three large studies of the Micra Transcatheter Pacing study program was 12 months for the Micra Transcatheter Pacing study [28, 33] and the Micra Transcatheter Pacing System Continued Access study [35], and 6.8 months for the Micra Transcatheter Pacing System Post-Approval Registry [30, 34], respectively. The follow-up in the included case series ranged from 1 month to a maximum of 24 months.

Follow-up bis zu 24 Monaten

verschiedene Indikationen für VVI Schrittmacher

hohes Alter

All studies included patients with indications for VVI pacing. The main indications for pacing were permanent, uncontrolled AF (range 15-96%), AV block (range 12-70%) and sinus node dysfunction (range 3-24%). Eight of the nine studies included patients aged 18 and older, with a mean age of 76 to 80 years. One case series included only patients older than 70 years of age (mean 87 years) [21]. The study populations were predominantly male (range 50-70%).

zahlreiche Begleiterkrankungen

Comorbidities were reported in seven of the included studies. The most frequent comorbidity was hypertension (60-84%). Other frequent comorbidities were diabetes mellitus (17-29%), coronary artery disease (CAD) (12-32%) and heart failure (6-39%).

Subgruppenanalysen zu PatientInnengruppen mit erhöhtem Komplikationsrisiko

Three recent publications reported subgroup results from one or more of the Micra Transcatheter Pacing System study program. These included subgroup analyses for patients with previous cardiac implantable electronic device (CIED) infections [24], patients on haemodialysis [26] and Japanese patients [31], respectively.

Study characteristics and results of included studies are displayed in Table A-1 and in the evidence profile in Table A-3

5.3 Results

Mortality

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

Gesamtmortalität: 8 % in 24 Monaten

Overall mortality was reported in seven of the included trials [23, 25, 27-30, 33, 34]. Altogether, there were 233 death in 2,915 patients (8%) during a follow-up from one to 24 months.

In the Micra Transcatheter Pacing study there was an overall mortality rate of 10.3% (77 of 745 patients) after 12 months follow-up [33], while in the Micra Transcatheter Pacing System Post-Approval registry 144 of 1,817 patients (7.9%) died after a mean follow-up of 6.8 months (range 0–30 months) [30].

In four case series with a follow-up of one to 24 months, the overall mortality rate ranged from zero [23] to 6% [25]. In one case series, including only patients aged 70 year or older, 29 of 129 persons (22.4%) died during 12 months of follow-up [21].

kardiale Mortalität: 1-4 %

Results on cardiac mortality were reported in five studies and were generally low [23, 25, 27, 30, 33]. In two case series including 104 patients, there were no cardiac death during follow-up [23, 27]. In three other studies, the cardiac death rate ranged from 1.3% [25] to 4.3% [33] after 12 to 24 months.

6 Todesfälle mit Bezug zu Eingriff oder Implantant in 2.915 PatientInnen

From the 233 death in 2,915 patients (8%), only six were classified as related to the procedure or the device.

Five of them were reported in the Micra Transcatheter Pacing System Post-Approval registry [30] and one in the Micra Transcatheter Pacing study [33]. Two of these deaths were related to cardiac perforations, one patient died of pulmonary edema in the setting of severe aortic valve disease and another

from retroperitoneal bleeding. The fifth death was presumed to be due to right ventricular failure, possibly from acute infarct during the implantation process, while the sixth patient died from metabolic acidosis due to a prolonged procedure time. There was no procedure or the device-related death in any of the included case series.

Morbidity

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

No evidence was found to answer this research question.

keine Ergebnisse zur Wirksamkeit in Bezug auf Arrhythmien

D0006 – How do leadless pacemakers affect progression (or recurrence) of cardiac arrhythmias?

No evidence was found to answer this research question.

Function

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

No evidence was found to answer this research question.

keine Ergebnisse zur Körperfunktion

D0016 – How does the use of leadless pacemakers affect activities of daily living?

In one case-control study comparing the implantation of a L-PM with the implantation of a C-PM the 106 study participants were asked to complete a 10-item questionnaire on discomfort and physical restriction 30 days and 6 months after intervention [20].

Aktivitäten des täglichen Lebens: Fall-Kontroll-Studie zu L-PM versus C-PM

At 1-month follow-up there was no statistically significant difference in the percentage of patients with chest discomfort between the two study groups (41% in L-PM-group vs 52% in C-PM-group; p=0.385), while after 6 months there were significant less patients in the L-PM-group reporting chest discomfort (18% vs 39%; p=0.032). Restrictions in physical activity and in daily living due to chest discomfort were significant lower in the L-PM-group compared to the C-PM-group at 1 month (23% vs 54%; p=0.014; 18% vs 54%; p=0.005) and 6-months follow-up (11% vs 37%; p=0.004; 13% vs 32%; p=0.034) [20].

Einschränkungen im täglichen Leben geringer in L-PM Gruppe vs C-PM nach 6 Monaten

Restrictions in physical activity due to fear of complications were lower one month after implantation (32% vs 61%; p=0.025), but not at 6-months follow-up (13% vs 27%; p=0.103), while restrictions in daily living due to fear of complications were lower in the L-PM-group at both times (23% vs 65%; p=0.001; 3% vs. 29%; p=0.001) [20].

Health-related quality of life

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

One recent publication of the Micra Transcatheter Pacing study reported HRQoL results [28]. HRQoL was measured at baseline before implantation and at 3-months and 12-months follow-up, using the SF-36 generic instrument. 681 and 635 patients completed the questionnaire at 3 and 12 months,

HRQoL: nachhaltige Verbesserung nach 12 Monaten

respectively. The results at 3 months showed a significant improvement of the HRQoL scores in each of the eight SF-36 domains. At baseline, the mean composed physical component summary score was 36.9 ± 9.0 points and improved 3 months post-implant to 38.7 ± 9.1 points ($p<0.001$). In the same period, the mean mental component summary score improved from 47.3 ± 12.5 to 50.9 ± 11.6 points ($p<0.001$). This increase was sustained through 12 months of follow-up (38.6 ± 9.4 for physical summary score and 50.7 ± 12.2 for mental summary score). In addition, the scores in all eight SF-36 domains were significantly higher at 3- and 12-months follow-up compared to baseline [28].

Fall-Kontroll-Studie: signifikant bessere HRQoL Werte in L-PM Gruppe vs C-PM nach 6 Monaten

In one case-control study with 106 patients, that compared leadless pacemaker to conventional pacemaker for right ventricle pacing HRQoL was also assessed with the SF-36 questionnaire [20]. Compared to baseline, there was a significant improvement after 6 months in five of eight domains and in the physical component summary score in the L-PM group but only in one domain (bodily pain) and in none of the summary scores in the C-PM group. Between group differences after 6 months follow-up showed significant advantages from leadless pacemakers in the domains physical function, role physical and mental health, and in the physical component summary score [20].

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

keine Ergebnisse zur krankheitsspezifischen QoL

No evidence was found to answer this research question.

Patient satisfaction

D0017 – Was the use of leadless pacemakers worthwhile?

PatientInnen-zufriedenheit: PatientInnen mehrheitlich zufrieden nach 3 Monaten

In the HRQoL publication of the Micra Transcatheter Pacing study results on patient satisfaction were reported [28]. To assess patient satisfaction, a nonvalidated questionnaire with three domains (recovery, aesthetic appearance and level of activity) was used. After 3 months of follow-up 693 of the 720 patients with successful Micra™ TPS implantation completed the questionnaire. 91%, 96% and 74% of the patients were either satisfied or very satisfied with their recovery, their aesthetic appearance, and their level of activity after implant, respectively [28].

6 Safety

6.1 Outcomes

entscheidungsrelevante Endpunkte – Sicherheit: Unerwünschte Ereignisse, Komplikationsraten

The claimed benefit of L-PM in comparison to C-PM 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 L-PM. The implantation of L-PM uses a different approach than that used for transvenous leads and requires substantially larger venous access tools.

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)

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

6.2 Included Studies

Ergebnisse aus gleichen Studien wie zur Wirksamkeit + 1 propensity score-matched Analyse zum Vergleich L-Pm vs C-PM

As for the efficacy results, there were no RCTs or non-RCTs assessing the safety of leadless pacemakers. The nine included studies (one case-control study, three prospective multicentre single-arm trials and five single-centre case series) already described in the efficacy section of this update report also reported results on safety outcomes. In addition, one recent publication reporting safety results from a propensity score-matched analysis comparing L-PM to C-PM was included. Study characteristics and results of included studies are displayed in Table A-1 and in the evidence profile in Table A-3.

6.3 Results

Patient safety

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

SAE in 2 Studien: 31,2 % bzw. 9,8 %

SAE were only reported in the Micra Transcatheter Pacing study [33] and the Micra Transcatheter Pacing System Continued Access study [35]. In the Micra Transcatheter Pacing study the SAE rate was 31.2% at 6 months follow-up. Most common SAE categories were cardiac disorders (16%), infections and infestations (8%), nervous system disorders (4%), and vascular disorders (4%), respectively. In the Micra Transcatheter Pacing System Continued Access study the SAE rate was 9.8% after up to 12 months of follow-up. In both studies, the rate for SAE related to the device or procedure was 4.0%.

All adverse events were reported in the Micra Transcatheter Pacing System Continued Access study [35], with events in 43 of 276 patients (15.6%) after 12 months and in one small case series with events in two of 79 patients (2.5%) after 24 months of follow-up.

schwere Komplikationen mit Bezug zu Eingriff oder Implantat in 4 % der PatientInnen

Eight of the nine included studies reported on serious device or procedure-related adverse events (i.e. major complications). The overall major complication rate was 2.5% (75/2,976 patients) during one to 24 months of follow-up. In the three prospective multi-centre trials of the Micra Transcatheter Pacing study program, serious device or procedure-related adverse events occurred in 4.0% of the patients after 6 months [33], in 2.3% after 6.8 months [30] and in 4.0% after up to 12 months [35], respectively.

L-PM vs C-PM: Risiko für schwere Komplakationen:

Vergleich mit historischer Kontrolle: 2,7 % vs 7,6 % nach 12 Monaten

Propensity score-mached Analyse: 0,9 % vs 4,7 % nach 800 Tagen

One recent publication compared major complication rates reported from the Micra Transcatheter Pacing System Post-Approval registry to those from a transvenous historical control [30]. Through 12 months post implantation, the risk for major complications was 2.7% in patients from the Micra Transcatheter Pacing System Post-Approval registry compared to 7.6% in patients from the historical control. In a second publication, complication rates in leadless pacemaker studies (including Micra™ TPS and Nanostim™ LCP) and conventional single-chamber pacemaker studies were compared in a propensity score-matched analysis [36]. After excluding premature battery failures related only to the Nanostim™ pacemaker, the analysis including 440 patients showed a statistically significant lower 800 days complication rate in the L-PM group (0.9% [95%CI 0 to 2.2] vs 4.7% [95%CI 1.8 to 7.6]; p=0.02).

In two case series no major complication occurred during 13 or 24 months of follow-up [25, 27], while in the remaining three case-series the major complication rates ranged from 0.9% (1 of 107 patients; 30 days follow-up) [23] to 2.0% (3 of 129 patients; 12 months follow-up) [21].

häufigste Komplikation: kardiale Verletzungen

Most common major complications reported in the included studies were pericardial effusion/perforation (28/2,795 patients; 1.0%), elevated pacing thresholds (13/2,672 patients; 0.48%) and loss of device function (11/2,622 patients).

schwere Infektionen: 2,2 % in 18 Monaten

One recent publication on the Micra Transcatheter Pacing study focussed on the occurrence of major infections after leadless pacemaker implantation [22]. During a mean of 18-months follow-up 16 patients developed major infections among the 720 patients with successful implantation (2.2%). All of them were adjudicated as unrelated to the device or the procedure.

During a mean of 6.8 months of follow-up, there were three of 1817 patients with major infections related to the device in the Micra Transcatheter Pacing System Post-Approval registry [30]. In three case-series, no device- or procedure-related infections occurred during 6 to 24 months of follow-up [21, 25, 29].

2 Implantatsablösungen

Altogether, there were two device dislodgements in 2,817 patients from five studies.

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

Subgruppenanalysen zu PatientInnen mit erhöhtem Komplikationsrisiko

Two recent publications on the Micra Transcatheter Pacing study program focussed on safety results for different patient subgroups, who were on extended risk for complications after pacemaker implant [24, 26].

PatientInnen mit CIED Infektionen: schwere Komplikationen bei 3,8 %

In the Micra Transcatheter Pacing System Post-Approval registry, a total of 105 patients with prior CIED infections underwent Micra implant attempt [24]. The device was successfully implanted in 104 of the 105 patients. During a mean of 8.5 months of follow up, 10 patients died, two of them from sepsis. None of the deaths was adjudicated to be related to the device or the implant procedure. Six major complications related to the device or procedure occurred in four of 105 patients (3.8%). These included two pacemaker syndromes, one cardiac perforation/effusion, one elevated pacing threshold, one abdominal wall infection and one complication of device removal, respectively. There were no recurrent infections requiring leadless pacemaker removal during the follow-up period [24].

Hämodialyse-PatientInnen: kein signifikanter Unterschied bei schweren Komplikationen zu nicht-dialyse PatientInnen

A second publication compared results for haemodialysis patients, who have a high infection risk, with those for nondialysis patients from all three studies of the Micra Transcatheter Pacing study program [26]. Across the three studies, 201 dialysis patients and 2,615 nondialysis patients underwent leadless pacemaker implant attempt. Dialysis patients were younger and less likely to have a history of atrial arrhythmia, but they tended to have more comorbidities. During an average follow-up of 6.2 months, the major complication rate was 4.5% in the dialysis patients compared to 2.6% in the nondialysis patients. To compare the risk for major complication through 12 months between dialysis patients and nondialysis patients, the Cox proportional hazard model and Fine-Grey competing risk model were used. Both models showed an elevated risk for major complication among patients on dialysis, but without statistical significance (Cox model: HR 1.8 [95% CI 0.9 to 3.7]; p=0.088; Fine-Gray model: HR 1.8 [95% CI 0.9 to 3.6]; p=0.100). There were there

device- or procedure-related death among the 105 dialysis patients during follow-up. There were also three reported procedure-related deaths in 2615 patients of the nondialysis group. Major infections related to device or procedure occurred in one of the dialysis patients and two of the nondialysis patients [26].

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

L-PM and C-PM pacemakers are associated with user-dependent harms due to the risk of SAE related to the implantation procedure.

nach entsprechender Schulung der Anwender: kein Zusammenhang zwischen Komplikationsrate und Anzahl der durchgeführten Eingriffe

In one study the influence of operator experience on procedural and safety outcomes was evaluated [32]. A total of 726 patients underwent a leadless pacemaker implantation attempt by 94 operators. All operators had prior experience gaining femoral access with large-bore catheters and with the implant of cardiac electronic devices, but had no prior experience implanting a leadless pacemaker. Operators were trained either at training labs or locally at their hospital. There was no significant association between implant number and major complication rate at 30 days after implantation (OR 0.99 with each additional procedure [95% CI 0.95 to 1.04]; p=0.755). There was also no significant association between operator experience and pericardial effusion rate on a per implant (OR 1.01 with each additional procedure [95% CI 0.96 to 1.07]; p=0.620) [32].

7 Quality of evidence

Qualität der Evidenz nach GRADE: niedrig

The quality of the included single-arm studies was assessed using the IHE checklist for case series [5] (see Appendix Table A-2).

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme [6] 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 [6].

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 the summary of findings table below (Table 7-1) and in the evidence profile in Appendix Table A-3.

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

Table 7-1: Summary of findings table of L-PM (Micra™ TPS) in patients with indications for right ventricle pacing

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with C-PM	Risk with L-PM (Micra™ TPS)				
Overall mortality	NA	80 per 1000	-	2915 (7 studies)	Low	Single-arm observational studies, no control group
Device- or procedure-related mortality	NA	2 per 1000	-	2915 (7 studies)	Low	Single-arm observational studies, no control group
Exercise capacity	No data					
Health related quality of life	Significant improvement in SF-36 scores in Micra™ TPS patients, no improvent in C-PM patients		-	741 (2 studies)	Very low	One single-arm observational study without control + one case-control study with high risk of bias; low number of studies and participants
Serious adverse events	NA	312 per 1000	-	735 (2 studies)	Very low	Single-arm observational studies, no control group; low number of studies and participants
Major complications	NA	25 per 1000	-	2976 (8 studies)	Low	Single-arm observational studies, no control group
Major complications (indirect comparision)	47 per 1000 (18 to 76)	9 per 1000 (0 to 22)	0.9 (0 to 2.2) vs 4.7 (1.8 to 7.6)	440 (1 study)	Very low	Propensity score-matched analysis of patient data from single-arm observational studies; Indirectness

Abbreviations: CI *– confidence interval;* ***C-PM*** *– conventional cardiac pacemaker;* ***L-PM*** *– Leadless cardiac pacemaker;* ***TPS*** *– Transcatheter pacing system;* ***vs*** *– versus*

8 Discussion

Since the implantation of Abbot's Nanostim™ pacemaker was stopped in 2016, this second update report focusses on the currently only available L-PM, the Micra™ TPS by Medtronic. It comprises new information from recent publications of three large prospective multi-centre single-arm studies [28, 30, 33-35], from one small multi-centre case-control study [20] and from five additional small single-centre case series [21, 23, 25, 27, 29]. As in the initial report 2016 [1] and in last update report in 2017 [2], 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 available on the effect of leadless cardiac pacemakers on symptoms or progression of cardiac arrhythmias. The new evidence from the Transcatheter Pacing study program focusses 12 months HRQoL results [28] and on feasibility and safety of the Micra™ TPS implantation in specific subpopulations, such as patients with prior CIED infections [24] or haemodialysis patients [26]. Short- to mid-term results safety results were available from the included case series.

2. Update mit Fokus auf neuen Publikationen

Nanostim nicht mehr verfügbar, daher Fokus auf Micra™ TPS

Neue Ergebnisse vorallem zu HRQoL und zu Subgruppen mit erhöhtem Komplikationsrisiko

Current evidence, based on data from nearly 3,000 patients in the nine included studies, indicate that the Micra™ TPS can be successfully implanted in more than 98% of the patients and sustain a low pacing threshold (<1.0 V at 0.24ms) for up to 24 months. Overall mortality rates during follow-up periods of up to 24 months were generally low (8%), with less than 1% of mortality rates being judged as procedure- or device related. Results from the Micra Transcatheter Pacing study [28] including 635 patients showed a sustainable improvement in HRQoL 12 months after implementation in all SF-36 domains and subscales. In addition, one small Spanish case-control study, in which L-PM were compared to C-PM, significant advantages in HRQoL improvement 6-months after implementation were reported for the L-PM group [20].

fast 3.000 PatientInnen in 9 Studien: erfolgreiche Implantation in 98 %

geringe Mortalitätsrate

SAE were frequent in the Micra Transcatheter Pacing study, with one third of the patients experiencing at least one SAE within six months, but lower in the consecutive Micra Transcatheter Pacing System Continued Access study (SAE rate 10% within up to 12 months). Nevertheless, major complication rates associated with the implantation procedure or the device were rare in all included studies (mean 2.5%; range: 0-4.0%). An indirect comparison with historical data from previous studies with C-PM, which was provided in the Micra Transcatheter Pacing System Post-Approval registry [30], resulted in a 63% risk reduction for L-PM (HR 0.37 [95% CI 0.27 to 0.52]; p<0.0001) for major complications through 12 months post implantation. However, 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 [30]. In addition, one recent publication reported results from a propensity score-matched analysis of L-PM and single-Chamber C-PM including 440 patients [36]. For the L-PM group, this analysis included data from Micra™ TPS and Nanostim™ studies. When excluding complications related to the PM advisory, which was related to the Nanostim™ malfunction, the analysis showed a 0.9% [95% CI 0 to 2.2] complication rate at 26 months of follow-up in the L-PM group compared to 4.7% [95% CI 1.8 to 7.6] in the C-PM group (p=0.02) [36].

SAE in der 1. Studie bei einem Drittel der PatientInnen, aber nur 4 % mit Bezug zur Intervention

Indirekte Vergleiche mit C-PM zeigen signifikant geringere Komplikationsraten für Micra™ TPS

There were two cases of device dislodgement in 2817 patients with successful Micra™ TPS implantation. Major infections occurred in 16 of 720 patients (2.2%) during a maximum of 18 months of follow-up. Device- or procedure related major infections occurred in three of 2811 patients.

mögliche Therapieoption für Patienten mit Kontraindikationen für C-PM oder erhöhtem Komplikationsrisiko

L-PM might represent a treatment alternative in patients, for whom an implantation of a transvenous pacemaker system is precluded or of high risk. This includes patients with a compromised venous access, with a history of device infection or patients with increased infection risk. A recent publication reported results from a subgroup analysis of the Micra Transcatheter Pacing System Post-Approval registry [24] with 104 patients with prior CIED infections. Even in this subgroup, as in the overall patient cohort, rates of major complication, especially major infections, were very low. A second analysis comparing haemodialysis patients, a patient group with an increased risk for infections, compared to nondialysis patients showed no significant difference in the risk of major complications (HR 1.8 [95% CI 0.9 to 3.7]; p=0.088) after 12 months.

kein Hinweis auf Batterieprobleme bei Micra™ TPS

One issue concerning pacemakers that was raised in the 2017 update report [2] is battery longevity. Based on the available data it was estimated at 15.0 years for the Nanostim™ pacemaker and 12.5 years for the Micra™ TPS [37]. However, these expectations did not come true for the Nanostim™ pacemaker, since it was withdrawn after a few years due battery malfunctions. For the Micra™ TPS there is currently no evidence of similar battery issues [37].

erfolgreiche Rückholungen des Micra™ TPS berichtet

Another important feature for L-PM is their retrievability. Normally, the Micra™ TPS is not intended to be removed at the end of battery life [38] and no retrieval system is available [37]. Instead, the turned-off Micra™ TPS is abandoned in the right ventricle and another device is added. Nevertheless, there might be situations, where a retrieval of the Micra™ TPS is necessary. Some retrospective analyses of Micra™ TPS retrievals, with data obtained from the manufacturer, were conducted. In total, 40 retrievals of the Micra™ TPS were attempted due to inadequate pacing threshold with a median time until extraction of 46 days. The success rate of Micra™ TPS retrieval was 100 % with no major complications [39, 40]. Another publication reported, that Micra™ TPS retrieval was successful in two of two patients between 5-104 days post implantation (early revision cases). In late revisions cases (229-430 days post implantation) percutaneous retrieval was successful in one of three patients. In the two unsuccessful cases, the device was snared but retrieval was not successful [41]. Furthermore, case studies report on successful Micra TPS™ retrieval at different time points. Two studies report successful retrieval during implantation [42, 43], two other studies after 1 and 2 months [44, 45] and two studies after 2 and 4 years post implantation [46, 47].

mittelfristige Ergebnisse aus 3 prospektiven Einzelarmstudien, 1 Fall-Kontroll-Studie und 5 Fallserien

keine RCTs oder non-RCTs

In summary, the new mid-term results from three large uncontrolled prospective multicentre trials, one case-control study and some small single-centre case series comprising data from nearly 3,000 patients indicate, that the Micra™ TPS has the potential for being a treatment option for patients with indication for right ventricle pacing, especially for patients with contraindications for C-PM implantation. Nevertheless, the evidence is still limited, since there are still no RCTs or non-RCTs with direct comparisons of L-PM with well-established single-chamber C-PM.

Applicability of included studies is summarized in Table A-4.

Andere HTA-Berichte:

Micra™ TPS stellt mögliche Alternative für ausgewählte PatientInnengruppen dar

There are four other health technology assessment (HTA) reports [48-51], which investigated the Micra™ TPS leadless pacemaker device. All of them found sufficient evidence to prove that the Micra™ TPS is beneficial compared to C-PM. However, the Micra™ TPS might have an advantageous safety profile, especially in patients with high risk for complications. Based on this evidence, the French Haute Autorité de Santé (HAS) recognized, that Micra™ TPS may be an alternative for patients with high risk for complications or with contraindications for C-PM [51]. In 2018, the Norwegian Institute of Public Health (NIPH) concluded, that budget impact analyses for all patients indicated for single chamber pacing and patients with high risk of complications resulted in ICER that were considered not to be cost-effective for Norway [49]. In the same year, the South Australian Policy Advisory Committee on Technology (SAPACT) also concluded that there is a lack of evidence on clinical-effectiveness of the Micra™ TPS and it would not replace C-PM. A restricted recommendation was made for select patients who need single-chamber ventricular VVI or VVIR pacing and in whom a conventional transvenous or epicardial cardiac pacemaker implantation is not feasible or are contraindicated following a careful risk assessment [48]. The British National Institute for Health and Care Excellence (NICE) stated that for people who can have C-PM implantation, L-PM should only be used in the context of research, while for people with contraindication for C-PM, following a careful risk assessment by a multidisciplinary team, L-PM should only be used with special arrangements for clinical governance, consent and audit or research [50].

laufende Studien:
1 RCT und
4 Beobachtungsstudien zu Micra™ TPS

Having a look on clinical trials registries, we could identify only one ongoing RCT comparing L-PM implantation to C-PM implantation in 210 transcatheter aortic valve replacement (TAVI) patients. The expected completion date of the study is at the end of 2020 (see Table A-5). No other ongoing or planned RCT or clinical controlled trial investigating the Micra™ TPS or any other leadless pacemaker was identified. Beside the Micra Transcatheter Pacing System Post-Approval registry (NCT02536118), whose interim results are presented in this update report and which should be completed in 2026, we found three other ongoing observational studies on the Micra™ TPS (NCT03624504, NCT03039712, UMIN000035117) and two further ongoing observational studies on another leadless pacemaker system developed in India (CTRI020173, CTRI021603).

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 **inclusion** in the catalogue of benefits is **recommended**.
X	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
	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 determine whether the leadless pacemaker Micra™ TPS is equal or more effective than single-chamber C-PM. Based on the available evidence from prospective single-arm studies, overall mortality rates and device- or procedure-related complications rates were low in patients after successful Micra™ TPS implantation. Based on the evidence of two indirect comparisons to C-PM, the safety profile of the Micra™ TPS seems to be advantageous. Therefore, the Micra™ TPS may be a possible treatment option only for patients with contraindications for C-PM or with high risk for complications following a careful risk assessment and under extensive documentation (registry). The procedure should only be done by clinicians with specific training on L-PM implantation.

verfügbare Evidenz ist für die Bewertung der Wirksamkeit nicht ausreichend; möglicherweise vorteilhaftes Sicherheitsprofil

eingeschränkte Empfehlung für ausgewählte PatientInnengruppen

Nevertheless, RCTs that allow direct comparisons of L-PM to C-PM are needed to assess efficacy and safety.

New study results will potentially influence the effect estimate considerably. The re-evaluation is recommended in 2027, when long-term safety results from the Micra Transcatheter Pacing System Post-Approval registry might be available.

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: L-PM (Micra™ TPS): Results from observational studies (part 1)

Study (acronym, ID no.)	**Micra Transcatheter Pacing study (NCT02004873)**		
Reference	**[22, 28, 33]**	**[32]**	**[31]**
Subsample	**-**	**Influence of operators experience**	**Japanese subgroup**
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		Japan
Sponsor	Medtronic		
Intervention/Product	Implantation of a leadless cardiac pacemaker/Micra™ TPS		
Comparator	NA		
Study design	Prospective multicenter single cohort safety/efficacy study		
Duration of the study	November 2013 – May 2017		
Randomisation method	None		
Blinding method (investigator, patient, outcomes assessor)	Open label		
Intervention (n)	Enrolled: 745 Implantation attempt: 726 Analyzed: 720		Enrolled (Japan): 38 Analyzed: (Japan): 36
Control (n)	0		0
Population	Patients with class I or II guideline indication for VVI(R) pacing		Patients with class I or II guideline indication 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)		
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		

Study (acronym, ID no.)	Micra Transcatheter Pacing study (NCT02004873)		
Reference	**[22, 28, 33]**	**[32]**	**[31]**
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))		
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		
Follow-up (months)	HRQoL: 12 months Patient satisfaction: 3 months Infections: mean 17.9 ± 9.9 months	30 days	12 months
Loss to follow-up, n (%)	85 (12%) **Reasons:** death (n=52); study discontinuation (n=7); no HRQoL data (n=26)	0	2 (38%) **Reasons:** did not meet eligibility criteria (relocate durng the follow-up, narrow femoral vein)
Population characteristics			
Age (mean), y	75.8±11.0		78.2±10.0 8
Male, n (%)	425 (59)		24 (66.7)
Pacing indication, n (%)	✿ Bradyarrhythmia with AF, 460 (63.9) ✿ Sinus node dysfunction, 125 (17.4) ✿ AV block, 108 (15.0) ✿ Syncope, 16 (2.2) ✿ Other reasons, 11 (1.5)		✿ Bradyarrhythmia with AF, 15 (41.7) ✿ Sinus node dysfunction, 15 (41.7) ✿ AV block, 5 (13.9) ✿ Trifascicular block with presyncope, 1 (2.8)
Comorbidities, n (%)	✿ Cardiomyophathy, 79 (11.0) ✿ CHF, 129 (17.9) ✿ CAD, 201 (27.9) ✿ Hypertension, 565 (78.5) ✿ Myocardial infarction, 76 (10.6) ✿ Pulmonary hypertension, 79 (11.0) ✿ Tricuspid valve dysfunction, 187 (26.0) ✿ Diabetes, 205 (28.5) ✿ COPD, 91 (12.6) ✿ Renal dysfunction, 147 (20.4) ✿ Chronic lung disease, 212 (29.4)		✿ Cardiomyopathy, 0 (0) ✿ CHF, 14 (38.9) ✿ CAD, 4 (11.1) ✿ Hypertension, 25 (69.4) ✿ Myocardial infarction, 3 (8.3) ✿ Pulmonary hypertension, 1 (2.8) ✿ Tricuspid valve dysfunction, 7 (19.4) ✿ COPD, 3 (8.3) ✿ Diabetes, 9 (25.0) ✿ Renal dysfunction, 11 (30.6) ✿ Chronic lung disease, 12 (33.3)
Outcomes			
Efficacy			
Implant success rate, n/N (%)	720/726 (99.2)	Influence of operator´s experience (number of implant cases): OR=0.98 [95% CI 0.93 – 1.03]; p=0.456	36/36 (100)

Study (acronym, ID no.)	Micra Transcatheter Pacing study (NCT02004873)		
Reference	**[22, 28, 33]**	**[32]**	**[31]**
Adaequad pacing performance (pacing threshold ≤ 1.0 V at 0.24ms)	NR	NR	35/36 (97)
Overall mortality, n/N (%)	77/745 (10.3)	NR	0/36 (0)
Cardiac mortality, n/N (%)	32/745 (4.3)	NR	0/36 (0)
Procedure-related mortality, n/N (%)	1/745 (0.1)	NR	0/36 (0)
Cardiac morbidity, n/N (%)	NR	NR	NR
Health related quality of life [SF-36]; mean score (SD)	n=635; 3 and 12 months results	NR	NR
Pysical component summary	pre-implant (baseline): 36.3±9.0 3 months: 38.7±9.1 12 months: 38.6±9.4; p<0.001		
Mental component summary	pre-implant (baseline): 47.3±12.5 3 months: 51.9±11.6 12 months: 50.7±12.2; p<0.001		
Bodily pain	pre-implant (baseline): 40.4±11.7 3 months: 42.2±11.3 12 months: 41.7±11.3; p<0.001		
General health	pre-implant (baseline): 56.4±20.3 3 months: 61.9±21.2 12 months: 60.8±9.4; p<0.001		
Physical functioning	pre-implant (baseline): 51.6±29.4 3 months: 57.8±29.5 12 months: 57.5±30.5; p<0.001		
Role physical	pre-implant (baseline): 49.1±30.1 3 months: 60.4±30.5 12 months: 60.3±30.8; p<0.001		
Mental health	pre-implant (baseline): 68.9±20.9 3 months: 73.6±19.7 12 months: 73.1±20.1; p<0.001		
Role emotional	pre-implant (baseline): 67.7±30.7 3 months: 74.8±28.3 12 months: 75.0±28.6; p<0.001		
Social functioning	pre-implant (baseline): 67.7±29.4 3 months: 77.4±26.2 12 months: 75.6±27.9; p<0.001		
Vitality	pre-implant (baseline): 48.4±23.2 3 months: 56.3±22.4 12 months: 56.7±22.5; p<0.001		

Study (acronym, ID no.)	Micra Transcatheter Pacing study (NCT02004873)		
Reference	**[22, 28, 33]**	**[32]**	**[31]**
Patient satisfaction; %	n=693; 3 months results	NR	n=35; 3 months results
Level of activity	Very satisfied: 38.0% Satisfied: 36.1% Neutral: 20.6% (Very) dissatisfied: 5.3%		(Very) satisfied/60.0% Neutral: 34.3% (Very) dissatisfied: 5.7%
Aesthetic appearence	Very satisfied: 75.5% Satisfied: 20.5% Neutral: 3.6% (Very) dissatisfied: 0.4%		(Very) satisfied/91.4% Neutral: 8.9% (Very) dissatisfied: 0%
Recovery	Very satisfied: 57.3% Satisfied: 33.6% Neutral: 5.9% (Very) dissatisfied: 3.2%		(Very) satisfied/74.3% Neutral: 20.0% (Very) dissatisfied: 5.7%
Safety			
Serious adverse events, n/N (%)	226/726 (31.2)	NR	NR
Overall adverse events, n/N (%)	NR	NR	NR
Serious adverse events related to divice or procedure (SADE = major complications), n/N (%)	29/726 (4.0)	Overall: 29/726 (4.0) Within 30 days: 21/726 (2.9) ***Influence of operator´s experience (number of implant cases):*** OR = 0.99 [95% CI 0.95 -1.04]; p=0.755	0/36 (0)
Overall adverse device effects (ADE), n/N (%)	NR	NR	5/36 (14)
Total pericardial perforation/effusion, n/N (%)	NR	13/726 (1.8) ***Influence of operator´s experience (number of implant cases):*** OR = 1.01 [95% CI 0.96 -1.07]; p=0.620	1/36 (3)
Major pericardial perforation/effusion, n/N (%)	NR	NR	NR
Major infection, n/N (%)	Total: 16/720 (2.2) Device-related: 0/720 (0) Death due infection: 2/720 (0.3)	NR	NR
Major infections – device or procedure related, n/N (%)	0/726 (0)	NR	NR
Loss of device function, n/N (%)	2/726 (0.3)	NR	0/36 (0)
Device dislodgement, n/N (%)	0/726 (0)	NR	0/36 (0)
Elevated pacing thresholds requiring retrieval/ replacement, n/N (%)	2/726 (0.3%)	NR	NR

Study (acronym, ID no.)	Micra Transcatheter Pacing study (NCT02004873)		
Reference	**[22, 28, 33]**	**[32]**	**[31]**
New hospitalization, n/N (%)	17/726 (2.3)	NR	0/36 (0)
Prolonged hospitalization, n/N (%)	18/726 (2.2)	NR	0/36 (0)

Abbreviations: ***ADE*** *– Adverse device effect;* ***AF*** *– Atrial fibrillation;* ***AV*** *– Atrioventricular;* ***CAD*** *– Coronary artery disease;* ***CHF*** *– Congestive heart failure;* ***CI*** *– Confidence interval;* ***COPD*** *– Chronic obstructive pulmonary disease;* ***E*** *– Efficacy;* ***ECG*** *– Electrocardiogram;* ***HRQoL*** *– Health-related quality of life;* ***NA*** *– Not applicable;* ***NR*** *– Not reported;* ***S*** *– Safety;* ***SADE*** *– Serious adverse device effect;* ***TPS*** *– Transcatheter pacing system;* ***VVI(R)*** *– Single-chamber ventricular pacing (with response modulation)*

Table A-1: L-PM (Micra™ TPS): Results from observational studies (part 2)

Study (acronym, ID no.)	Micra Transcatheter Pacing System Post-Approval registry (NCT02536118)		Micra Transcatheter Pacing System Continued Access study (NCT02488681)
Reference	**[30]**	**[24]**	**[35]**
Subsample	**-**	**Patients with prior CIED infection**	
Study description			
Country	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		USA
Sponsor	Medtronic		Medtronic
Intervention/Product	Implantation of a leadless cardiac pacemaker/Micra™ TPS		Implantation of a leadless cardiac pacemaker/Micra™ TPS
Comparator	NA		NA
Study design	Prospective single cohort safety/efficacy registry		Prospective, non-randomized, multi-center, study
Duration of the study	July 2015 – ongoing (planed competion date: 08/2026)		June 2015 – July 2016
Randomisation method	None		None
Blinding method (investigator, patient, outcomes assessor)	Open label		Open label
Intervention (n)	Estimanted enrollment: 3,100 Analysed: 1,817	Subgroup-analysis of patients with prior CIED infection: 105	276
Control (n)	Historical control: 2,667		0
Population	Patients indicated for VVI(R) pacing	Subgroup of patients with prior CIED infection	Patients indicated for VVI(R) pacing
Inclusion criteria	❁ Patient is intended to receive or be treated with a Micra Transcatheter Pacing System and must be enrolled prior to the TPS implant procedure		❁ Class I or II indication for implantation of single chamber ventricular pacemaker and is intended to be implanted with a Micra System ❁ At least 18 years of age

Study (acronym, ID no.)	Micra Transcatheter Pacing System Post-Approval registry (NCT02536118)		Micra Transcatheter Pacing System Continued Access study (NCT02488681)
Reference	**[30]**	**[24]**	**[35]**
Exclusion criteria	✿ 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		✿ Acute myocardial infraction within 30 days of implant ✿ Implantation of neurostimulator or any other chronically implanted device which uses current in the body ✿ Mechanical tricuspid valve, implanted vena cava filter, or left ventricular assist device ✿ Morbid obesity and physician believes telemetry communication of ≤5 inches (12.5 cm) could not be obtained with programmer head ✿ Femoral venous anatomy is unable to accommodate a 23 French introducer sheath or implant on the right side of the heart (for example due to obstructions or sever tortuosity) in the opinion of the implanter ✿ Known intolerance to Nickel-Titanium (Nitinol) Alloy ✿ Contraindication for single dose of 1.0 mg dexamethasone acetate ✿ Life expectancy less than 12-months
Primary outcome (including measurement tools and measurement times)	✿ S: Acute complication rate (within 30 days); ✿ S: Long-term complication free survival (up to 9 years)		✿ S: Micra system and/or procedure-related complication rate (3 months post last follow up)
Secondary outcome (including measurement tools and measurement times)	✿ 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)		NR
Follow-up (months)	Mean: 6.8±6.9 months	Mean: 8.5±7.1 months	Up to 12 months
Loss to follow-up, n (%)	0	0	0
Population characteristics			
Age (mean), y	75.6±13.5	72.7±14.7	76.1±11.9
Male, n (%)	1,111 (61.1)	69 (65.7)	155 (56.2)
Pacing indication, n (%)	✿ Bradyarrhythmia with AF, 1,127 (62.0) ✿ AV block, 211 (11.6) ✿ Syncope, 243 (13.4) ✿ Sinus node dysfunction, 177 (9.7) ✿ Other reasons, 50 (2.8) ✿ Not reported, 9 (0.5)	✿ Bradyarrhythmia with AF, 52 (49.5) ✿ AV block, 23 (21.9) ✿ Syncope, 12 (11.4) ✿ Sinus node dysfunction, 11 (10.5) ✿ Other reasons, 6 (5.7) ✿ Not reported, 1 (1.0)	NR

Study (acronym, ID no.)	Micra Transcatheter Pacing System Post-Approval registry (NCT02536118)		Micra Transcatheter Pacing System Continued Access study (NCT02488681)
Reference	**[30]**	**[24]**	**[35]**
Comorbidities, n (%)	✿ Diabetes, 480 (26.4) ✿ COPD, 176 (9.7) ✿ CAD, 402 (22.1) ✿ Atrial arrhythmia, 1,370 (75.4) ✿ CHF, 134 (12.9) ✿ Hypertension, 1,165 (64.1) ✿ Conditions that precludes the use of a transvenous pacemaker, 435 (13.4) ✿ Previous implanted CIED, 265 (14.6)	✿ Diabetes, 34 (32.4) ✿ COPD, 17 (16.2) ✿ CAD, 26 (24.8) ✿ Atrial arrhythmia, 60 (57.1) ✿ CHF, 16 (15.2) ✿ Hypertension, 51 (48.6) ✿ Previous implanted CIED, 105 (100)	NR
Outcomes			
Efficacy			
Implant success rate, n/N (%)	1801/1817 (99.1)	104/105 (99.0)	269/276 (97.4)
Adaequad pacing performance (pacing threshold ≤ 1.0 V at 0.24ms)	549/566 (97) (12 M0)	NR	NR
Overall mortality, n/N (%)	144/1817 (7.9)	10/105 (9.5)	NR
Cardiac mortality, n/N (%)	48/1817 (2.6)	NR	NR
Procedure- or divice-related mortality, n/N (%)	5/1817 (0.3) vs 0/2667 (0) *12-mo Kaplan-Meier estimates [95%CI]:* 0.3 [0.1 to 0.8] vs 0.0 [0 to 0]; p=0.0109	0/105 (0)	NR
Cardiac morbidity, n/N (%)	NR	NR	14/276 (5.1)
Health related quality of life	NR	NR	NR
Patient satisfaction; %	NR	NR	NR
Safety			
Serious adverse events, n/N (%)	NR	NR	27/276 (9.8)
Overall adverse events, n/N (%)	NR	NR	43/276 (15.6)
Serious adverse events related to divice or procedure (SADE = major complications), n/N (%)	41/1817 (2.26) vs 196/2667 (7.35) *12-mo Kaplan-Meier estimates [95%CI]:* 2.7 [2.0 to 3.7] vs 7.6 [6.6 to 8.7]; p<0.0001	4/105 (3.81)	11/276 (4.0)
Overall adverse device effects (ADE), n/N (%)	NR	NR	NR
Total pericardial perforation/effusion, n/N (%)	14/1817 (0.77)	1/105 (0.95)	4/276 (1.4)
Major pericardial perforation/effusion, n/N (%)	8/1817 (0.44)	1/105 (0.95)	4/276 (1.4)

Study (acronym, ID no.)	Micra Transcatheter Pacing System Post-Approval registry (NCT02536118)		Micra Transcatheter Pacing System Continued Access study (NCT02488681)
Reference	**[30]**	**[24]**	**[35]**
Major infection, n/N (%)	NR	NR	NR
Major infections – device or procedure related, n/N (%)	3/1817 (0.17)	1/105 (0.95)	NR
Loss of device function, n/N (%)	9/1817 (0.50) vs 0/2667 (0) *12-mo Kaplan-Meier estimates [95%CI]:* 0.7 [0.4 to 1.3] vs 0.0 [0 to 0]; p=0.0003	NR	NR
Device dislodgement, n/N (%)	1/1817 (0.06)	NR	NR
Elevated pacing thresholds requiring retrieval/ replacement, n/N (%)	11/1817 (0.61)	1/105 (0.95)	NR
New hospitalization, n/N (%)	16/1817 (0.88) vs 106/2667 (3.97) *12-mo Kaplan-Meier estimates [95%CI]:* 1.3 [0.8 to 2.1] vs 4.1 [3.4 to 5.0]; p<0.0001	NR	NR
Prolonged hospitalization, n/N (%)	29/1817 (1.60) vs 64/2667 (2.4) *12-mo Kaplan-Meier estimates [95%CI]:* 1.9 [1.3 to 2.7] vs 2.4 [1.9 to 3.1]; p=0.2278	NR	NR

Abbreviations: ***ADE*** *– Adverse device effect;* ***AF*** *– Atrial fibrillation;* ***AV*** *– Atrioventricular;* ***CAD*** *– Coronary artery disease;* ***CHF*** *– Congestive heart failure;* ***CIED*** *– Cardiac implantable electronic device;* ***COPD*** *– Chronic obstructive pulmonary disease;* ***E*** *– Efficacy;* ***NA*** *– Not applicable;* ***NR*** *– Not reported;* ***S*** *– Safety;* ***SADE*** *– Serious adverse device effect;* ***TPS*** *– Transcatheter pacing system;* ***VVI(R)*** *– Single-chamber ventricular pacing (with response modulation)*

Table A-1: L-PM (Micra™ TPS): Results from observational studies (part 3)

Study (acronym, ID no.)	Micra TPS (NCT02004873), Micra CA (NCT02488681) and Micra PAR (NCT02536118) [26]	Tjong 2018 [36]	Cabanas-Grandio 2019 [20]
Subsample	**Comparison of haemodialysis patients versus nondialysis patients**		
Study description			
Country	Australia, Austria, Belgium, Canada, Czech Republic, China, Denmark, France, Germany, Greece, Hungary, Iceland, India, Israel, Italy, Japan, Kuwait, Malaysia, Netherlands, New Zealand, Norway, Poland, Portugal, Russian Federation, Saudi Arabia, Serbia, Slovenia, South Africa, Spain, Sweden, Switzerland, United Arab Emirates, United Kingdom, USA	Netherlands, Czech Republic and USA	Spain
Sponsor	Medtronic	Netherlands Heart Institute Research Fellowship; Czech Republic governmental scientific grant	NR

Study (acronym, ID no.)	Micra TPS (NCT02004873), Micra CA (NCT02488681) and Micra PAR (NCT02536118) [26]	Tjong 2018 [36]	Cabanas-Grandio 2019 [20]
Intervention/Product	Medtronic's Micra transcatheter pacing system (M-TPS)	Leadless cardiac pacemaker system (Micra™ TPS and Nanostim LCP)	Medtronic's Micra transcatheter pacing system (M-TPS)
Comparator	NA	Conventional VVI-R cardiac pacemakers	Conventional pacemakers
Study design	Prospective cohort study	Propensity score-matched analysis	Multicenter observational study
Duration of the study	NA	NA	from December 2016 to March 2018
Randomisation method	NA	Propensity score matching was performed using the following 10 baseline variables: age, sex, body mass index, PM indication, hypertension,AF, CAD/myocardial infarction, diabetes mellitus, (congestive) heart failure, and cardiac surgery. Patients were 1:1 greedy matched using the nearest-neighbor method.The caliper for the propensity score match was set at 0.2.[1]	NA
Blinding method (investigator, patient, outcomes assessor)	NA	NA	NA
Intervention (n)	Dialysis patients: 201 Nondialysis patients: 2615	220	Enrolled: 42 Analyzed: 38
Control (n)	0	220	Enrolled: 64 Analyzed: 58
Population	Patients with a history of renal dysfunction requiring dialysis and indications for single-chamber ventricular pacemakers (VVI (R))	Patients with indications for single-chamber ventricular pacemakers (VVI (R))	Patients with indications for single-chamber ventricular pacemakers (VVI (R))
Inclusion criteria	✪ Patients that met class I or II guideline recommendations for ventricular pacing with no comorbidity restrictions	✪ Patients participating in one of five leadless pacemaker studies or a transvenous single-chamber pacemaker cohort study	✪ Age ≤ 18 years with an indication for implantation of a single-chamcer pacemaker according to local clinical practice; ✪ Absence of cognitive impairment and ability to complete the SF-36 questionaire; ✪ Ability to provide written informed consent
Exclusion criteria	✪ Patients with an existing pacemaker or implantable cardioverter-defibrillator (only excluded from the Micra IDE study, but were allowed to participate in the Micra CA and PAR studies)	NA	✪ Surgical intervention or invasive treatment 3 months before the single-chamber pacemaker implant; ✪ Indication for any other surgical intervention at the moment of implantation
Primary outcome (including measurement tools and measurement times)	✪ Events related to the Micra TPS device or implantation procedure and resulting in death; permanent loss of device function, hospitalization; prolonged hospitalization (by 48 h or more); ✪ System revision	✪ Adverse events ✪ Complications	✪ Quality of life (SF-36)

Study (acronym, ID no.)	Micra TPS (NCT02004873), Micra CA (NCT02488681) and Micra PAR (NCT02536118) [26]	Tjong 2018 [36]	Cabanas-Grandio 2019 [20]
Secondary outcome (including measurement tools and measurement times)	NR	NR	NR
Follow-up (months)	12 months	L-PM: median 599 days (IQR 375-831) C-PM: median 1486 days (IQR 802-1932)	6 months (in two centers an additional follow-up at 1 month)
Loss to follow-up, n (%)	NR	0	6 months: 10 (9.4)
Population characteristics			
Age (mean), y	Dialysis patients: 70.5 ± 13.5 No dialysis patients: 76.1 ± 12.6	78 (70-84) vs 77 (69-82)	79.8 ± 9
Male, n (%)	Dialysis patients: 119 (59.2) No dialysis patients: 1,574 (60.2)	134 (60.9) vs 133 (60.5)	74 (70)
Pacing indication, n (%)	*Dialysis patients vs nondialysis patients:* ✿ Bradyarrhythmia with AF, 91 (45.3) vs 1,680 (64.2) ✿ Sinus node dysfunction, 35 (17.4) vs 300 (11.5) ✿ AV-block: 51 (25.4) vs 292 (11.2) ✿ Syncope, 17 (8.5) vs 277 (10.6) ✿ Other, 6 (3.0) vs 59 (2.3) ✿ Not reported, 1 (0.5) vs 7 (0.3)	✿ High degree AV block, 39 (17.7) vs 44 (20.0) ✿ Sinus bradycardia, 47 (21.4) vs 46 (20.9) ✿ AF with slow ventricular rate, 134 (60.9) vs 130 (59.1)	✿ Atrial fibrillation, 85 (80) ✿ Other, 21 (20)
Comorbidities, n (%)	*Dialysis patients vs nondialysis patients:* ✿ CHF, 54 (26.9) vs 385 (14.7) ✿ Cardiomyopathy, 43 (21.4) vs 388 (14.8) ✿ COPD, 22 (10.9) vs 297 (11.4) ✿ CAD, 78 (38.8) vs 631 (24.1) ✿ Myocardial infarction, 20 (10.0) vs 230 (8.8) ✿ Pulmonary hypertension, 16 (8.0) vs 205 (7.8) ✿ Coronary artery intervention, 54 (26.9) vs 361 (13.8) ✿ Hypertension: 161 (80.1) vs 1792 (68.5) ✿ Diabetes, 123 (61.2) vs 649 (24.8) ✿ Prior Cardiac implantable electronic device, 30 (14.9) vs 280 (10.7) ✿ Preclusion for transvenous system, 144 (71.6) vs 403 (15.4)	✿ Diabetes Mellitus, 40 (18.2) vs 40 (18.2) ✿ AF, 161 (73.2) vs 153 (69.5) ✿ Hypertension, 145 (65.9) vs 146 (66.4) ✿ CAD/MI, 22 (10.0) vs 22 (10.0) ✿ Cardiac Surgery, 31 (14.1) vs 38 (17.3) ✿ CHF, 22 (10.0) vs 21 (9.5)	✿ Hypertension, 88 (83) ✿ Diabetes, 31 (29) ✿ Structural Heart Disease, 34 (32) ✿ Heart failure, 6 (6) ✿ COPD, 13 (12) ✿ Stroke, 12 (11) ✿ Peripheral artery disease, 3 (3) ✿ Renal dysfunction,14 (13) ✿ Malignancy, 10 (9)

Study (acronym, ID no.)	Micra TPS (NCT02004873), Micra CA (NCT02488681) and Micra PAR (NCT02536118) [26]	Tjong 2018 [36]	Cabanas-Grandio 2019 [20]
Outcomes			
Efficacy			
Implant success rate, n/N (%)	*Dialysis patients:* 197/201 (98)	NR	NR
Adaequad pacing performance (pacing threshold ≤ 1.0 V at 0.24ms)	NR	NR	NR
Overall mortality, n/N (%)	NR	NR	3/106 (2.8)[2]
Cardiac mortality, n/N (%)	NR	NR	3/106 (2.8)[2]
Procedure-related mortality, n/N (%)	*Dialysis patients:* 3/201 (1.5)	NR	NR
Cardiac morbidity, n/N (%)	NR	NR	NR
Health related quality of life [SF-36]; mean score (SD)	NR	NR	*6 months change to baseline (L-PM vs C-PM):*
Pysical component summary			8.0 ± 1 vs 2.9 ± 1.4 p=0.029
Mental component summary			3.6 ± 2.6 vs 0.3 ± 1.8; p=0.705
Bodily pain			18.1 ± 4.8 vs 8.4 ± 3.8; p=0.115
General health			5.2 ± 2.7 vs 3.6 ± 2.9; p=0.704
Physical functioning			19.7 ± 4.5 vs 1.1 ± 3.5; p=0.001
Role physical			40.8 ± 6.9 vs 12.7 ± 8.3; p=0.011
Mental health			13.9 ± 3.6 vs 2.8 ± 2.9; p=0.020
Role emotional			13.2 ± 10.3 vs 2.3 ± 6.9; p=0.365
Social functioning			8.9 ± 4.6 vs 4.2 ± 3.6; p=0.425
Vitality			12.4 ± 2.9 vs 4.2 ± 3.4; p=0.070
Patient satisfaction; %	NR	NR	NR
Safety			
Serious adverse events, n/N (%)	NR	NR	NR
Overall adverse events, n/N (%)	NR	NR	NR
Serious adverse events related to divice or procedure (SADE = major complications), n/N (%)	*Major complications (dialysis patients vs nondialysis patients):* 11 events, 9/201 (4.5) vs 76 events, 69/2,615 (2.6) *Major complication rate at 12 months (Kaplan-Meier):* 4.9 (95%CI 2.6 to 9.5) vs 3.2 (95%CI 2.5 to 4.0) *HR (dialysis vs nondalysis patients):* 1.8 (95%CI 0.9 to 3.6); p=0.088[3]	*800 days major complication rate [95%CI]:* 0.9% [0 to 2.2] vs 4.7% [1.8 to 7.6]; p=0.02[4] 10.9% [4.8 to 16.5] vs 4.7% [1.8 to 7.6]; p=0.06[5]	NR

Study (acronym, ID no.)	Micra TPS (NCT02004873), Micra CA (NCT02488681) and Micra PAR (NCT02536118) [26]	Tjong 2018 [36]	Cabanas-Grandio 2019 [20]
Overall adverse device effects (ADE), n/N (%)	NR	*800 days complication rate [95%CI]:* 4.1% [1.4 to 6.7] vs 9.5% [5.4 to 14.1]; p=0.03[4] 13.4% [7.3 to 19.1] vs 9.5% [5.4 to 14.1]; p=0.39[5]	2/42 (5.0) vs 0/64 (0); p=0.159
Total pericardial perforation/effusion, n/N (%)	*Dialysis patients vs nondialysis patients:* 2 events 2/201 (1.0) vs 21 events, 21/2615 (0.8)	3 (1.4) vs 1 (0.5)	NR
Major pericardial perforation/effusion, n/N (%)	NR	NR	NR
Major infection, n/N (%)	NR	NR	NR
Major infections – device or procedure related, n/N (%)	*Dialysis patients vs nondialysis patients:* 1 event, 1/201 (0.5) vs 0 events, 0/2615 (0)	NR	NR
Loss of device function, n/N (%)	NR	NR	NR
Device dislodgement, n/N (%)	*Dialysis patients vs nondialysis patients:* 1 event, 1/201 (0.5) vs 1 event, 1/2615 (0.04)	NR	NR
Elevated pacing thresholds requiring retrieval/ replacement, n/N (%)	NR	NR	NR
New hospitalization, n/N (%)	NR	NR	NR
Prolonged hospitalization, n/N (%)	NR	NR	NR

Abbreviations: ***ADE*** *– Adverse device effect;* ***AF*** *– Atrial fibrillation;* ***AV*** *– Atrioventricular;* ***CAD*** *– Coronary artery disease;* ***CHF*** *– Congestive heart failure;* ***CI*** *– Confidence interval;* ***COPD*** *– Chronic obstructive pulmonary disease;* ***E*** *– Efficacy;* ***ECG*** *– Electrocardiogram;* ***HR*** *– Hazard ratio;* ***HRQoL*** *– Health-related quality of life;* ***LPS*** *– Leadless pacemaker system;* ***MI*** *– Myocardial infarction;* ***NA*** *– Not applicable;* ***NR*** *– Not reported;* ***S*** *– Safety;* ***SADE*** *– Serious adverse device effect;* ***TPS*** *– Transcatheter pacing system;* ***VVI(R)*** *– Single-chamber ventricular pacing (with response modulation)*

Explanations:

[1] *Propensity score-matching method*

[2] *Unclear in which study group the deaths occurred*

[3] *Cox regression model*

[4] *After exclusion of premature battery failures of the Nanostim LCP*

[5] *Including premature battery failures of the Nanostim LCP*

Table A-1: L-PM (Micra™ TPS): Results from observational studies (part 4)

Study (acronym, ID no.)	San Antonio, 2019 [23]	Denman, 2019 [25]	El Amrani, 2019 [21]	Garweg, 2018 [29]	Bongiorni 2019 [27]
Study description					
Country	Spain	Australia	Spain	Belgium	Italy
Sponsor	European Union's Horizon 2020 Research and Innovation Programme	Queensland Health New Technology Grant	Medtronic	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	Medtronic's Micra trans-catheter pacing system (M-TPS)
Comparator	NA	NA	NA	NA	NA
Study design	Single-center observational study	Single-center study	Single-center observational study	Single-center observational study	Uncontrolled Singlecenter Trial
Duration of the study	February 2014 – September 2018	November 2015 – April 2018	June 2015 – NR	July 2015 – May 2017	2014 to 2017
Randomisation method	none	none	None	none	none
Blinding method (investigator, patient, outcomes assessor)	Open label	Open label	Open label	Open label	Open label
Intervention (n)	Analysed: 107	Analysed: 79	Analysed: 129 41 ≥ 90 years 88 < 90 years	Analysed: 66	Analysed:52
Control (n)	NA	NA	NA	NA	NA
Population	Patients with class I or II guideline indication for VVI(R) pacing	Patients indicated for VVI pacing	Patients aged > 70 years with a single-chamber ventricular pacing indication	All patients fulfilled standard criteria for de novo pacemaker implantation with Class I or II indications	Patients with indications for single-chamber ventricular pacemakers (VVI (R))
Inclusion criteria	All met class I or II guideline-based indications for de novo permanent VVI pacing	Consecutive patients undergoing leadless pacemaker (LP) implantation at The Prince Charles Hospital	NR	NR	Patients who met class indications for pacing and were suitable for single-chamber ventricular stimulation
Exclusion criteria	No exclusion criteria were applied	NR	✪ Age < 70 years ✪ Transvenous Pacemaker ✪ Previous PM Infection ✪ No upper vascular access	NR	✪ Age < 18 years ✪ Haemodynamic instability ✪ Mechanical tricuspid valve prosthesis or inferior vena cava filter ✪ Morbid obesity that could impair remote M-TPS control ✪ Femoral venous occlusions ✪ Allergy to M-TPS components ✪ < 12 months life expectancy ✪ Risk of interference with any other electronic device

Study (acronym, ID no.)	San Antonio, 2019 [23]	Denman, 2019 [25]	El Amrani, 2019 [21]	Garweg, 2018 [29]	Bongiorni 2019 [27]
Primary outcome (including measurement tools and measurement times)	✿ S: Incidence of bleeding, thromboembolic, and vascular events (evaluated at implantation, before hospital discharge, and 30 days postprocedure)	✿ S: All late complications related to the procedure	✿ S:Major complications at implantation and within 30-day after implantion ✿ E: Pacing threshold ≤ 1.0 V at 0.24 ms	✿ S: Major and minor complications ✿ E: Mean pacing capture threshold at 0.24 ms	✿ Adverse events ✿ Device function
Secondary outcome (including measurement tools and measurement times)	NR	NR	NR	NR	NR
Follow-up (months)	30 days	24 months	Total: 342 ± 279 days ≥ 90: 230 ± 233 < 90: 394 ± 285	6 months	13 ± 9 months
Loss to follow-up, n (%)	0	5 (6) **Reasons:** death (n=5) during follow-up from unrelated causes	NR	NR	0
Population characteristics					
Age (mean), y	78.1±10.9	78 (72–84)	≥ 90 years: 92.9 ±2.4 < 90 years: 83.9 ±4.1	79.1±9.7	76±11
Male, n (%)	54 (50.4)	52 (66)	≥ 90 years: n=18 (43.9) < 90 years: n=56 (63.6)	46 (69.7)	39 (75)
Pacing indication, n (%)	✿ Bradycardia associated with AF, 41 (38) ✿ Sinus node dysfunction, 20 (19) ✿ AV block, 24 (22) ✿ Other reasons, 22 (21)	✿ Permanent atrial fibrillation with slow VR or intermittent pauses, 61 (77) ✿ Permanent atrial fibrillation with CHB, 15 (19) ✿ Sinus rhythm with CHB, 1 (1) ✿ Sinus node dysfunction, 2 (3)	✿ AV block, ≥ 90: 29 (70.7) < 90: 61 (69.3) ✿ AF with slow ventricular response ≥ 90: 8 (19.5) < 90: 11 (12.5) ✿ Sinus node dysfunction ≥ 90: 4 (9.8) < 90: 16 (18.2)	✿ AV block III, 20 (30.3) ✿ AV block II, 2 (3.0) ✿ Sinus node dysfunction, 14 (21.2) ✿ AF, 30 (45.5)	✿ Symptomatic AF, 24 (46) ✿ Symptomatic sinus node dysfunction, 12 (24) ✿ 2nd degree AV block, 8 (15) ✿ 3rd degree AV block 8 (15)
Comorbidities, n (%)	✿ AF, 49 (46) ✿ CAD, 16 (15) ✿ Chronic kidney disease, 25 (24) ✿ Hypertension, 64 (60) ✿ Diabetes, 18 (17) ✿ Mechanical heart valve, 7 (6) ✿ Ischemic stroke, 7 (6)	NR	✿ Hypertension ≥90: 36 (87.8) <90: 73 (83) ✿ Diabetes mellitus ≥90: 9 (22) <90: 23 (33,3) ✿ Chronic kidney disease ≥90: 24 (58.5) <90: 31 (35,2)	✿ AF, 47 (71.2) ✿ CAD, 29 (43.9) ✿ Valvular disease, (36 (54.5) ✿ Hypertension, 48 (72.7) ✿ Diabetes, 16 (24.2) ✿ CHF, 14 (21.2) ✿ Renal dysfunction, 19 (28.7) ✿ COPD, 8 (12.1) ✿ Chronic corticoid therapy, 7 (10.6)	✿ CHF, 8 (15) ✿ Hypertension, 36 (69) ✿ Dyslipidaemia, 17 (33) ✿ Diabetes, 10 (19) ✿ Renal dysfunction, 10 (19) ✿ COPD, 9 (17) ✿ CAD, 6 (12)

Study (acronym, ID no.)	San Antonio, 2019 [23]	Denman, 2019 [25]	El Amrani, 2019 [21]	Garweg, 2018 [29]	Bongiorni 2019 [27]
Comorbidities, n (%) *(continuation)*	✪		✪ Cardiopathy ≥90: 14 (34,1) <90: 49 (55,7) ✪ CHF ≥90: 19 (46,3) <90: 31 (35,2) ✪ Atrial fibrillation ≥90:16 (39) <90: 43 (48,9) ✪ Stroke ≥90: 9 (22) <90: 9 (10.2) ✪ Peripheral vascular disease ≥90: 1 (2.4) <90: 10 (11.4)	✪	✪
Outcomes					
Efficacy					
Implant success rate, n/N (%)	Overall: 105/107 (98.1) On the first attempt: 82/107 (78)	76/79 (96)	≥90: 40 (97.6) <90: 87 (98.9)	65 (98.5%)	52/52 (100)
Adaequad pacing performance (pacing threshold ≤ 1.0 V at 0.24ms)	NR	74/79 (94)	≥90: 39 (97.5) <90: 83 (95.4)	NR	49/52 (94.2)
Overall mortality, n/N (%)	0/52 (0)	5/79 (6)	29/129 (22.4) *≥90 years:* 13 (31.7) *<90 years:* 16 (18.2)	1/66 (1.5)	2/52 (3.8)
Cardiac mortality, n/N (%)	0/52 (0)	1/79 (1.3)	NR		0/52 (0)
Procedure-related mortality, n/N (%)	0/52 (0)	0/79 (0)	0/129 (0)	0/66 (0)	0/52 (0)
Cardiac morbidity, n/N (%)	NR	NR	NR	NR	NR
Health related quality of life [SF-36]; mean score (SD)	NR	NR	NR	NR	NR
Patient satisfaction; %	NR	NR	NR	NR	NR
Safety					
Serious adverse events, n/N (%)	NR	NR	NR	NR	NR
Overall Adverse events, n/N (%)	NR	2/79 (2.5)	NR	NR	NR

Study (acronym, ID no.)	San Antonio, 2019 [23]	Denman, 2019 [25]	El Amrani, 2019 [21]	Garweg, 2018 [29]	Bongiorni 2019 [27]
Serious adverse events related to divice or procedure (SADE = mayor complications), n/N (%)	1/107 (0.9)	0/79 (0)	3/129 (2.0) *≥90 years:* 0/41 (0) *<90 years:* 3/88 (3.4)	1/66 (1.5)	0/52 (0)
Overall adverse device effects (ADE), n/N (%)	2/107 (1.9)	0/79 (0)	NR	5/66 (7.5)	0/52 (0)
Total pericardial perforation/effusion, n/N (%)	1/107 (0.9)	0/79 (0)	1/129 (0.1) *≥90 years:* 0/41 (0) *<90 years:* 1/88 (3.4)	0/66 (0)	NR
Major pericardial perforation/effusion, n/N (%)	NR	NR	NR	NR	NR
Serious infectious events (SIE), n/N (%)	NR	0/79 (0)	0/129 (0)	NR	NR
Major infections– device or procedure related, n/N (%)	NR	0/79 (0)	0/129 (0)	0/66 (0)	0/52 (0)
Loss of device function, n/N (%)	NR	0/79 (0)	NR	NR	NR
Device dislodgement, n/N (%)	NR	1/79 (1.3)	0/129 (0)	0/66 (0)	NR
Elevated pacing thresholds requiring retrieval/ replacement, n/N (%)	NR	NR	0/129 (0)	NR	NR
New hospitalization, n/N (%)	NR	0/79 (0)	NR	NR	2/52 (3.8)
Prolonged hospitalization, n/N (%)	NR	NR	NR	NR	NR

Abbreviations: ***ADE*** *– Adverse device effect;* ***AF*** *– Atrial fibrillation;* ***AV*** *– Atrioventricular;* ***CAD*** *– Coronary artery disease;* ***CHB*** *– complete heart block;* ***CHF*** *– Congestive heart failure;* ***CI*** *– Confidence interval;* ***COPD*** *– Chronic obstructive pulmonary disease;* ***E*** *– Efficacy;* ***ECG*** *– Electrocardiogram;* ***HR*** *– Hazard ratio;* ***HRQoL*** *– Health-related quality of life;* ***NA*** *– Not applicable;* ***NR*** *– Not reported;* ***S*** *– Safety;* ***SADE*** *– Serious adverse device effect;* ***TPS*** *– Transcatheter pacing system;* ***VVI(R)*** *– Single-chamber ventricular pacing (with response modulation)*

Risk of bias tables and GRADE evidence profile

Table A-2: Risk of bias – study level (case series) (part 1), see [5]

Study	Micra Transcatheter Pacing study (NCT02004873)	Micra Transcatheter Pacing System Post-Approval registry (NCT02536118)	Micra Transcatheter Pacing System Continued Access study (NCT02488681)
Study objective			
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes	Yes
Study population			
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?	Unclear	Unclear	Yes
6. Did participants enter the study at similar point in the disease?	No	No	No
Intervention and co-intervention			
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
Outcome measures			
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?	Yes	No	No
Statistical Analysis			
12. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes
Results and Conclusions			
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?	Yes	Yes	Yes
16. Are adverse events reported?	Yes	Yes	Yes
17. Are the conclusions of the study supported by results?	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
Overall Risk of bias	Low	Low	Low

Table A-2: Risk of bias – study level (case series) (part 2), see [5]

Study	Antonio, 2019	Denman, 2019	Bongiorni 2019	Garweg, 2018	Cabanas Grandío, 2020	El Amrani, 2019
Study objective						
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Partial	Partial	Yes	Yes	Partial
Study design						
2. Was the study conducted prospectively?	Unclear	Yes	Unclear	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	No	No	No	No	Yes	No
4. Were patients recruited consecutively?	Yes	Yes	Yes	Yes	Yes	Yes
Study population						
5. Were the characteristics of the patients included in the study described?	Yes	Partial	Yes	Yes	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Partial	Yes	Partial	Yes	Partial
7. Did patients enter the study at a similar point in the disease?	No	No	No	No	Unclear	Unclear
Intervention and co-intervention						
8. Was the intervention of interest clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	No	No	No	No	No	No
Outcome measures						
10. Were relevant outcome measures established a priori?	Yes	Yes	Partial	Partial	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	Unclear	Yes	Yes	Yes	Yes	Yes
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes	Yes	Partial	Yes
13. Were the made before relevant outcome measures and after the intervention?	Yes	Yes	Yes	Yes	Yes	Yes
Statistical Analysis						
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	Yes	Yes	Yes
Results and Conclusions						
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes	Yes	Yes	Yes
16. Were losses to follow-up reported?	Yes	Yes	Yes	No	Unclear	Unclear
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Yes	Partial	Yes	Yes	Partial	Partial
18. Were the adverse events reported?	Yes	Yes	Yes	Yes	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes	Yes	Yes	Yes
Competing interests and sources of support						
20. Were both competing interests and sources of support for the study reported?	Yes	Partial	Partial	Partial	Yes	Yes
Overall Risk of bias	High	High	High	High	High	High

Table A-3: Evidence profile: efficacy and safety of L-PM (Micra™ TPS) in patients with indications for right ventricle pacing

Quality assessment							Summary of findings				
							Number of patients		Effect		Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Impression	Other considerations	Micra™ TPS	C-PM	Relative (95% CI)	Absolute (95% CI)	
Overall mortality (up to 24 months)											
7	2 prospective single arm studies; 5 case series	Very serious[1]	Not serious	Not serious	Not serious	none	2915	NA	-	233 per 2915 (8%)	Low
Device- or procedure-related mortality (up to 24 months)											
7	2 prospective single arm studies; 5 case series	Very serious[1]	Not serious	Not serious	Not serious	none	2915	NA	-	6 per 2915 (0.2%)	Low
Exercise capacity											
No evidence available											
Health related quality of life (6 to 12 months)											
2	1 prospective single arm study; 1 case-control study	Serious[2]	Not serious	Not serious	Serious[3]	none	677	64	-	Significant improvement in SF-36 scores in Micra™ TPS patients, no improvent in C-PM patients	Very low
Serious adverse events (up to 24 months)											
2	2 prospective single arm studies	Very serious[1]	Not serious	Not serious	Serious[3]	none	725	NA	-	226 per 725 (31.2%)	Very low
Major complications (up to 24 months)											
8	3 prospective single arm studies; 5 case series	Very serious[1]	Not serious	Not serious	Not serious	none	2976	NA	-	75 per 2976 (2.5%)	Low
Major complications (indirect comparision C-PM; up to 800 days)											
1	1 propensity score-matched analysis	Very serious[1]	Not serious	Serious[4]	Not serious	none	220	220	0.9 (0 to 2.2) vs 4.7 (1.8 to 7.6)	9 per 1000 (0 to 22) vs 47 per 1000 (18 to 76)	Very low

Abbreviations: ***CI*** *– Confidence interval;* ***C-PM*** *– conventional pacemaker;* ***NA*** *– not applicable;* ***SF-36*** *– Short form 36;* ***TPS*** *– Transcatheter pacing system;* ***vs*** *– versus*

Comments:

[1] *Single-arm studies without control group*

[2] *One single arm study with low risk of bias and one small case control with high risk of bias*

[3] *Low number of studies and participants*

[4] *Indirect comparison*

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 the Micra™ TPS, which is the only product currently available on the market and corresponds to the product used in Austria.
Comparators	In one studies conventional pacemakers used for right ventricle pacing were used as compator, which corresponds to the standard therapy for patients with pacing indications. In all other included studies, there were no comparators.
Outcomes	The main outcomes reported in the studies were pacing performance for efficacy and complication rates for safety. Mortality and health-related quality of life were clinically relevant efficacy outcomes 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. No applicability issues are expected from the geographical setting of the included studies.

List of ongoing randomised controlled trials

Table A-5: List of ongoing randomised controlled trials of leadless pacemaker implantation

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NL6542 (NTR6730)/ Pace Now	Patients aged 18 years and older after transcatheter aortic valve implantation (TAVI) with indication for temporary pacing therapy	Implant of a leadless pacemaker	Implant of a conventional transvenous permanent pacemaker	Difference in intervention-related complications	12/2020	Academic Medical Center Amsterdam NL

Literature search strategies

Search strategy for Cochrane

Last Saved: 15/01/2020 16:06:21

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 (Word variations have been searched)
#5	(leadless or transcatheter*) near pacing (Word variations have been searched)
#6	leadless (Word variations have been searched)
#7	#5 or #6 (Word variations have been searched)
#8	#4 and #7 (Word variations have been searched)
#9	(leadless pacemaker*) (Word variations have been searched)
#10	#8 OR #9 with Cochrane Library publication date Between Apr 2017 and Jan 2020 (Word variations have been searched)
#11	(#8 OR #9) (Word variations have been searched) with Publication Year from 2017 to 2020, in Trials
#12	#10 OR #11

16 Hits

Search strategy for CRD

15.01.2020

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	(leadless pacemaker*)
10	(micra)
11	(nanostim)
12	#8 OR #9 OR #10 OR #11
13	(#12) WHERE LPD FROM 06/04/2017 TO 15/01/2020

2 Hits

Search strategy for Embase

15 Jan 2020

No.	Query	Results
#19.	(#15 OR #16 OR #17) AND [6-4-2017]/sd NOT [16-1-2020]/sd	628
#18	#15 OR #16 OR #17	886
#17.	nanostim:dn	86
#16.	micra:dn	199
#15.	#1 OR #14	852
#14.	#10 AND #13	852
#13.	#11 OR #12	970
#12.	((leadless OR transcatheter*) NEAR/4 pacing):ti,ab,de,kw	442
#11.	leadless:ti,ab,de,kw	869
#10.	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	108,189
#9.	'peace-makers':ti,ab,de,kw	2
#8.	'peace-maker':ti,ab,de,kw	9
#7.	'pace-makers':ti,ab,de,kw	140
#6.	'pace-maker':ti,ab,de,kw	799
#5.	peacemaker*:ti,ab,de,kw	71
#4.	pacemaker*:ti,ab,de,kw	77,021
#3.	'artificial heart pacemaker'/exp	39,442
#2.	'heart pacing'/exp	41,807
#1.	'leadless pacemaker'/exp	321

Search strategy for Medline

15.01.2020

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily - without Revisions <2015 to January 14, 2020>, Ovid MEDLINE(R) <1946 to January Week 1 2020>		
ID	Search	Hits
1	exp Pacemaker, Artificial	29,966
2	exp Cardiac Pacing, Artificial	27,586
3	pacemaker*.mp	52,022
4	1 or 2 or 3	71,676
5	leadless.mp.	712
6	((leadless or transcatheter*) adj5 pacing).mp.	360
7	5 or 6	801
8	4 and 7	708
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.	101
10	8 not 9	619

11	("26685334" or "26956500" or "28213895" or "27799257" or "27392946" or "26860611" or "27017442" or "25488281" or "27351174" or "27660571" or "26863366" or "27326221" or "27494362" or "27537740" or "27055811" or "26298308" or (170)"26851812" or "27355553" or "26830889" or "27855290" or "28342501" or "27038713" or "28192207" or "27889044" or "27600684" or "27078167" or "26896468" or "27996100" or "26794011" or "28011844" or "27371661" or "27323664" or "26105728" or "27861115" or "27588153" or "26060209" or "27296508" or "26927858" or "28165125" or "27062484" or "27190123" or "26994050" or "26493306" or "27220535" or "26842114" or "28365650" or "27083173" or "28342500" or "27871854" or "27726912" or "27849261" or "28081830" or "28040461" or "28089328" or "27277596" or "27078248" or "27591908" or "26835067" or "28081829" or "27943488" or "26710918" or "27344513" or "26856790" or "26875055" or "28111349" or "26863365" or "27932427" or "26970532" or "27355552" or "27091192" or "27287746" or "27157452" or "27957193" or "27374239" or "27836644" or "26851809" or "27577107" or "25873801" or "27616697" or "28117279" or "27012782" or "26941338" or "25926474" or "27445025" or "27925339" or "28188515" or "28148576" or "26882193" or "26863367" or "27756706" or "28295442" or CN-01108729).ui.	170
12	10 not 11	449
13	limit 10 to ed=20170406-20200115	411
14	12 or 13	555
15	remove duplicates from 14	356

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