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Leadless cardiac pacemakers

3. Update 2025
Systematic Review

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

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Content

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List of abbreviations

ACC ..... American College of Cardiology
ADE ..... Adverse device effects
AF ..... Atrial fibrillation
AHA ..... American Heart Association
AHRQ ..... Agency for Healthcare Research and Quality
AMI ..... Acute myocardial infarction
AV ..... Atrioventricular
AVB ..... Atrioventricular block
CABG ..... Coronary artery bypass graft
CAD ..... Coronary artery disease
CED ..... Coverage with Evidence Development
CI ..... Confidence interval
CIED ..... Cardiac implantable electronic device
CIF ..... Cumulative incidence function
COPD ..... Chronic obstructive pulmonary disease
C-PM ..... Conventional cardiac pacemaker
CPT ..... Current Procedural Terminology;
CRT ..... Cardiac Resynchronization Therapy
CRT-D ..... Cardiac Resynchronization Therapy-Defibrillator
CRT-P ..... Cardiac Resynchronization Therapy-Pacemaker
CSP ..... Conduction System Pacing
DC-TV ..... Dual chamber transvenous
DARE ..... Database of Abstracts of Reviews of Effects
EC ..... European Commission
EQ-5D-5L ..... European Quality of Life 5 Dimensions 5 Level Version
ESC ..... European Society of Cardiology
ESRD ..... Endstage renal disease
FFS ..... Fee-for-service
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
INAHTA ..... International Network of Agencies for Health Technology Assessment
ICD ..... Implantable cardioverter defibrillator
ICD-10 ..... International Classification of Diseases, Tenth Revision
ICE ..... International Statistical Classification of Diseases and Related Health Problems
IEC ..... Institutional Ethics Committee
IHE ..... Institute of Health Economics
IRB ..... Institutional Review Board
IUD ..... Intrauterine Device
LBI-HTA ..... Ludwig Boltzmann Institute of Health Technology Assessments
LCP ..... Leadless Cardiac Pacemaker
L-PM ..... Leadless pacemaker
LVAD ..... Left ventricular assist device
LVEF ..... Left ventricular ejection fraction
MoH ..... Ministry of Health
NA ..... Not applicable
NR ..... Not reported
NS ..... Not significant
NYHA ..... New York Heart Association
ODI ..... Oswestry Disability Index
PCI ..... Percutaneous coronary intervention
PM ..... Pacemaker
RCT ..... Randomized controlled trial
RD ..... Risk difference;
RRR ..... Relative risk reduction
SADE ..... Serious adverse device effects
SAE ..... Serious adverse events
SD ..... Standard deviation
SF-36 ..... Short form-36 health survey
SIE ..... Serious infectious events
SND ..... Sinus node dysfunction
SR ..... Sinus rhytm
TAVI ..... Transcatheter aortic valve replacement
TPS ..... Transcatheter Pacing System
USA ..... United States of America
VVI ..... Single chamber ventricular pacing

Executive Summary

Introduction

This report is the third update of the systematic review on "Leadless Pacemakers for Right Ventricle Pacing" initially prepared in 2016 and updated in 2017 and 2020.

3rd Update

Health Problem

In the scope of this assessment are cardiac arrhythmias in adults for which single- or dual chamber ventricular pacing is indicated. This included patients with bradycardic and persistent atrial fibrillation, where VVI pacemakers are implanted to bridge bradycardic phases. Patients with bradycardia due to sick sinus syndrome or atrioventricular (AV) block may also be indicated for a VVI pacemaker if other pacing systems are not suitable. With the new leadless pacemakers (VDD or DDD pacemakers), the indications can be expanded to include patients with high-degree or complete AV block and normal sinus node function, who may also benefit from leadless pacemakers. The goal of pacemaker therapy is to stabilize the heart rhythm, thereby restoring effective circulation and normal hemodynamics, which are impaired by bradycardia. This aims to reduce symptoms associated with bradyarrhythmias (e.g., dizziness, fainting, fatigue, low exercise capacity) and increase the quality of life of affected patients. In some indications it may also lower the risk of heart failure and cardiac death.

adults with cardiac arrhythmias

indications for single- or dual chamber pacing

Description of Technology

Leadless pacemakers (L-PM) are self-contained devices that perform the same functions as conventional pacemakers (C-PM), but are miniaturized and can be implanted entirely inside the right ventricle (VR) or the right atrium (AR) 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 focuses on leadless single chamber pacemakers for right ventricle pacing and leadless single chamber pacemakers for AV synchronous pacing as well as dual chamber L-PM.

leadless pacemakers (L-PM)

Methods

This update report assesses the effectiveness and safety of leadless cardiac pacemakers (single- or dual chamber) in comparison to conventional cardiac pacemakers in patients with relevant indications (e.g., cardiac arrhythmias with bradycardia, sinus node dysfunction, AV block).

A systematic literature search for primary studies was conducted in four databases (Medline, Embase, Cochrane Library, INAHTA) and three clinical trial registries (ClinicalTrials.gov, WHO-ICTRP, and EU Clinical Trials). Randomized and non-randomized comparative studies between L-PM and C-PM were primarily included. If no comparative studies were identified for one of the leadless systems under investigation, the inclusion criteria were expanded to include uncontrolled studies. The selection of relevant studies, data extraction, and assessment of methodological quality were performed independently by two authors. No meta-analyses were conducted. The presentation, summary, and comparison of study results were descriptive and sepa-

systematic search for primary studies in 4 databases and 3 trial registries

certainty of evidence according to GRADE

rated by the individual systems under investigation. For the rating of the certainty of evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used.

Domain effectiveness

effectiveness outcomes

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

Domain safety

safety outcomes

The following safety-related outcomes were used as evidence to derive a recommendation: serious adverse events (SAEs), severe complications (i.e., severe product- or intervention-related adverse events), and overall complications (i.e., all product- or intervention-related adverse events).

Results

Available evidence

single chamber L-PM VR: 1 RCT and 7 cohort studies

For the comparison of single chamber L-PM for right ventricular pacing (L-PM VR) versus conventional single chamber pacemakers, one randomized controlled trial (RCT) with 51 patients and seven cohort studies with a total of 18,664 patients were included. All included studies investigated the Micra™ VR TPS. The primary indication for a pacemaker in these studies was atrial fibrillation with severe bradycardia or impaired sinus node function. The mean age of study participants ranged from 70 to 84 years, with 42% to 72% being male. Most participants also had comorbidities. The follow-up period of the individual studies ranged from three to 39 months. For the second single chamber L-PM VR currently available on the market, the Aveir™ VR L-PM, no studies were be identified.

single chamber L-PM AV: 1 cohort study

For the comparison of single chamber L-PM for AV synchronous pacing (L-PM AV) versus conventional dual chamber pacemakers, one cohort study with a total of 118,110 patients investigating the Micra™ AV TPS was included. The primary indication for a pacemaker in this study was AV block. The mean age of study participants was 79 years, with 53% being male. Most participants also had comorbidities. The follow-up period of the study was two years.

For the single chamber LP-M for atrial pacing, no studies were identified in the literature search.

dual chamber L-PM: 1 case series

For the dual chamber L-PM system (Aveir™ DR), no comparative studies with C-PM were found. Only one uncontrolled case series with 452 analyzed participants was included. The primary indications for a pacemaker in this study were AV block and sinus node dysfunction. The mean age of study participants was 69 years, with 62% being male. Most participants also had comorbidities. The follow-up period of the study was up to two years.

Clinical effectiveness

single chamber L-PM VR vs single chamber C-PM: no difference in mortality

improvement in HrQoL and physical function

Regarding overall mortality, four studies (including one RCT) showed no difference between single chamber L-PM VR (Micra™ VR TPS) and conventional single chamber pacemakers over a period of six to 36 months. In two other studies, the overall mortality rates over 18 and 22 months were statistically significantly lower in patients with Micra™ VR TPS compared to those with conventional single chamber pacemakers. Cardiac mortality rates were re-

ported in four studies, with no difference between the pacemaker systems under investigation. In two cohort studies, HRQoL was assessed three and six months after pacemaker implantation. Both studies showed statistically significantly better HRQoL scores with Micra™ VR TPS compared to conventional single chamber pacemakers. In the only RCT, exercise capacity was assessed using a 6-minute walking test after 12 months, with no difference reported between patients with Micra™ VR TPS and those with conventional single chamber pacemakers.

single chamber L-PM AV vs dual chamber C-PM: higher mortality rates

no results for HrQoL and physical function

In the only included cohort study comparing single chamber L-PM AV (Micra™ AV TPS) with conventional dual chamber pacemakers, overall mortality rate after two years of follow-up was statistically significantly higher with the single chamber L-PM AV. The study authors attributed this to differences in comorbidities and patient characteristics between the two study groups. However, adjustments in the analysis did not change the statistical significance of the result. No results were reported for the other key effectiveness endpoints of cardiac mortality, HRQoL, or exercise capacity.

dual chamber L-PM: mortality rate: 3.5%

no results for HrQoL and physical function

In the uncontrolled case series for the dual chamber L-PM (Aveir™ DR), four deaths (1.3%) occurred within three months, two of which were due to cardiac causes. During the further follow-up of 12 months, 3.5% of study participants died. No information on the cause of death was provided. No results were reported for the other key effectiveness endpoints of HRQoL or exercise capacity.

Safety

single chamber L-PM VR vs single chamber C-PM: lower complication rates

no results for SAE

None of the included studies reported results on SAEs. Severe complications related to the procedure or the implant were reported in the included RCT and two cohort studies comparing single chamber L-PM VR (Micra™ VR TPS) with conventional single chamber pacemakers. No difference was observed between the groups over a period of six to 22 months. Results on overall complication rates related to the procedure or the implant were reported in six cohort studies. Acute complications occurred in 0% to 7.7% of patients with Micra™ VR TPS and 0.5% to 21.4% of patients with conventional single chamber pacemakers, with rates being statistically significantly lower Micra™ VR TPS in two studies. The rates of further complications during follow-up of 18 to 39 months ranged from 0% to 4.9% with Micra™ VR TPS and 1.4% to 8.6% with conventional single chamber pacemakers, with rates being statistically significantly lower with Micra™ VR TPS in three studies. One cohort study also reported complications solely attributable to the pacemaker system, showing statistically significantly lower rates with Micra™ VR TPS at all four assessment time points (30 days, 6, 24, and 36 months post-implantation) compared to conventional single chamber pacemakers.

single chamber L-PM AV vs dual chamber C-PM: lower complication rates

no results for SAE

In the included study comparing single chamber L-PM AV (Micra™ AV TPS) with conventional dual chamber pacemakers, no results on SAEs or severe complications related to the procedure or the implant were reported. Results on overall complication rates related to the procedure or the implant were reported at 30 days (acute) and 24 months. Acute complications occurred statistically significantly less frequently in patients with Micra™ AV TPS (8.6%) than in those with conventional dual chamber pacemakers (11%). The rate of complications during further follow-up (24 months) was also statistically significantly lower with Micra™ AV TPS (5.3%) compared to conventional dual chamber pacemakers (9.6%). The study also reported complications solely attributable to the pacemaker system, showing statistically significantly lower rates with Micra™ AV TPS at both 30 days (1.4% vs. 4.1%) and 24 months (2.2% vs. 5.9%) compared to conventional dual chamber pacemakers.

In the uncontrolled case series for the dual chamber L-PM (Aveir™ DR), SAEs occurred in 44.7% of study participants over a period of up to 24 months. The most common SAEs were cardiac arrhythmias, heart failure, and infections. Severe complications related to the procedure or the implant occurred in 9.7% of patients within the first three months. Additionally, at 12 months post-implantation, the rate of patients without severe complications related to the procedure or the implant was 88.6%. No results were reported on overall complications.

dual chamber L-PM: high SAE rates (45%)

no results for complications

Certainty of evidence

The quality of the included studies was generally rated as good. However, since only cohort studies, with the exception of one small RCT, were available for single chamber L-PMs, the certainty of the evidence according to GRADE is rated as low at best. For dual chamber L-PM, no results from comparative studies were found; only an uncontrolled case series exists. The certainty of the evidence is therefore rated as very low and thus insufficient.

certainty of evidence low for single chamber L-PM

very low for dual chamber L-PM

Upcoming evidence

Three ongoing RCTs comparing single chamber L-PM for AV synchronous pacing with C-PM are listed in the trial registers. The follow-up periods of these RCTs range from three to 12 months, with primary endpoints including complication rates, HRQoL, or exercise capacity. The planned study completion dates are between August 2025 and December 2027. Additionally, there are three ongoing case-control studies investigating different single chamber L-PM systems ad one ongoing case-control study investigating the dual chamber L-PM. These studies are expected to conclude between October 2025 and January 2031.

3 ongoing RCTs for single chamber L-PM AV

Conclusion

Although no sufficient evidence from RCTs is available, several large prospective cohort studies with long follow-up periods suggest that the evaluated technology, single chamber L-PM for right ventricular pacing, is equally effective and safer than a conventional single chamber pacemaker.

additional benefit only for L-PM VR, but based on less robust evidence

Based on the results of a large cohort study, the current evidence regarding the effectiveness and safety of single chamber L-PM for AV synchronous pacing is inconclusive. The evidence suggests that single chamber L-PM for AV synchronous pacing tends to be safer but less effective than conventional dual chamber pacemakers.

The evidence for a dual chamber L-PM is currently insufficient for a definitive assessment of effectiveness and safety. No published study results are available for L-PM for right atrial pacing at the time of writing this update report.

Therefore, the current evidence supports an additional benefit only for single chamber L-PM for right ventricular pacing, but based on less robust evidence.

Given that results from three RCTs comparing a single chamber L-PM for AV synchronous pacing with conventional pacemakers are expected by the end of 2027, a further update is suggested in 2028.

re-evaluation in 2028 recommended

Zusammenfassung

Einleitung

3. Update

Der vorliegende Bericht ist das dritte Update des erstmals im März 2016 erstellten systematischen Reviews „Leadless pacemakers for right ventricle pacing“, der 2017 bzw. 2020 ein Update erhielt. Er erfasst neu verfügbare Informationen aus publizierten Dokumenten. Da seit dem letzten Bericht von 2020 neue sondenlose Herzschrittmacher auf den Markt gekommen sind, die auch für Patient:innen mit Indikationen für Zweikammer-Herzschrittmacher geeignet sind, wurde die Fragestellung auf „Leadless Cardiac Pacemakers“ erweitert.

Indikation und therapeutisches Ziel

Indikation: kardiale Arrhythmien

Gegenstand der Untersuchung sind kardiale Arrhythmien, die eine Indikation für einen Ein- oder Zweikammerschrittmacher darstellen. Dabei handelt es sich einerseits um Patient:innen mit bradykardem, permanenten Vorhofflimmern, bei denen VVI-Schrittmacher zur Überbrückung der bradykarden Phasen implantiert werden. Andererseits kann auch bei Patient:innen mit Bradykardie aufgrund eines Sick-Sinus-Syndroms oder atrioventrikulärem (AV) Blocks ein VVI-Schrittmacher indiziert sein, wenn andere Schrittmachersysteme nicht in Frage kommen. Durch die neuen sondenlosen Schrittmacher (VDD- bzw. DDD-Schrittmacher) können die Indikationen dahingehend erweitert werden, dass z. B. auch Patient:innen mit höhergradigem oder vollständigem AV-Block und normaler Sinusknotenfunktion für einen sondenlosen Schrittmacher 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 sowie die Lebensqualität der betroffenen Personen gesteigert werden. Darüber hinaus können sie auch das Risiko der kardialen Mortalität senken.

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. Ein potenzieller Vorteil liegt darin, 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 mit sondenlosen Schrittmachern im Vergleich zu konventionellen Schrittmachern. Aktuell sind fünf unterschiedliche sondenlose Herzschrittmacher-Systeme am Markt verfügbar. Als Einkammer-Schrittmacher, der Micra™ VR sowie der Aveir™ VR für eine rechtsventrikuläre Stimulation, das Micra™ AV für eine AV-synchrone Stimulation, sowie der Aveir™ AR für eine atriale Stimulation. Als Zweikammer-Schrittmacher, der Aveir™ DR, welcher Aveir™ VR und Aveir™ AR kombiniert. Alle inkludierten Geräte sind für den US-amerikanischen Markt zugelassen und verfügen auch über eine europäische CE-Zertifizierung.

Methoden

Dieses Update vergleicht die Wirksamkeit und Sicherheit einer Implantation eines sondenlosen Herzschrittmachers (Ein- oder Zweikammern-Schrittmacher) mit der Implantation eines konventionellen Ein- oder Zweikammer-Schrittmachers bei Patient:innen mit entsprechenden Indikationen (z. B. kardiale Arrhythmien mir Bradykardie, gestörter Sinuskotenfunktion, AV-Block).

systematische Recherche nach Primärstudien in 4 Datenbanken und 3 Studienregistern

Eine systematische Literatursuche nach Primärstudien wurde in vier Datenbanken (Medline, Embase, Cochrane Library, INAHTA) und drei Registern für klinische Studien (ClinicalTrial.gov, WHO-ICTRP und EU Clinical Trials) durchgeführt. Inkludiert wurden in erster Linie randomisierte und nichtrandomisierte Vergleichsstudien zwischen sondenlosen und konventionellen Schrittmachern. Falls für eines der untersuchten sondenlosen Systeme keine Vergleichsstudien identifiziert werden konnten, wurden die Einschlusskriterien auf unkontrollierte Studien erweitert. Die Selektion relevanter Studien, die Datenextraktion und die Bewertung der methodischen Qualität der Studien wurden von zwei Autor:innen unabhängig voneinander durchgeführt. Es wurden keine Meta-Analysen durchgeführt. Die Darstellung, Zusammenfassung und Gegenüberstellung der Studienergebnisse erfolgten deskriptiv, getrennt für die einzelnen untersuchten Systeme. Für die Bewertung der Vertrauenswürdigkeit der Evidenz wurde das GRADE-System (Grading of Recommendations Assessment, Development and Evaluation) verwendet.

Einschluss von Vergleichsstudien

Bewertung der Evidenz nach GRADE

Klinische Wirksamkeit

Endpunkte Wirksamkeit

Für die Bewertung der klinischen Wirksamkeit wurden folgende Endpunkte herangezogen: Gesamtmortalität und kardiale Mortalität, gesundheitsbezogene Lebensqualität (LQ), körperliche Funktionsfähigkeit.

Sicherheit

Endpunkte Sicherheit

Für die Bewertung der Sicherheit wurden folgende Endpunkte herangezogen: Schwerwiegende unerwünschte Ereignisse (SUE), schwere Komplikationen (d. h. schwere produkt- oder interventionsbezogene unerwünschte Ereignisse) sowie Komplikationen insgesamt (d. h. produkt- oder interventionsbezogene unerwünschte Ereignisse insgesamt).

Ergebnisse

Verfügbare Evidenz

L-PM VR: 1 RCT und 7 Kohortenstudien

Für den Vergleich sondenlose Einkammer-Herzschrittmacher mit rechtsventrikulärer Stimulation versus konventionelle Einkammer-Herzschrittmacher konnten eine RCT mit 51 Patient:innen sowie sieben Kohortenstudien mit insgesamt 18.664 Patient:innen eingeschlossen werden. Alle eingeschlossenen Studien untersuchten dabei den Micra™ VR. Die Hauptindikation für einen Herzschrittmacher in den Studien war Vorhofflimmern mit schwerer Bradykardie oder gestörter Sinusknotenfunktion. Das mittlere Alter der Studienteilnehmer:innen lag bei 70 bis 84 Jahren. 42 % bis 72 % der Teilnehmenden waren männlich. Bei der Mehrzahl lagen auch Begleiterkrankungen vor. Die Beobachtungsdauer der einzelnen Studien lag bei drei bis 39 Monaten. Zum zweiten derzeit am Markt befindlichen sondenlosen Einkammer-Herzschrittmacher mit VR-Stimulation, dem Aveir™ VR, konnte aktuell keine Studie identifiziert werden.

L-PM AV: 1 Kohortenstudie

Für den Vergleich eines sondenlosen Einkammer-Herzschrittmachers für eine synchrone AV-Stimulation (Micra™ AV) versus konventionelle Zweikammer-Herzschrittmacher konnte eine Kohortenstudie mit insgesamt 118.110 Patient:innen eingeschlossen werden. Die Hauptindikation für einen Herzschrittmacher in der Studie war ein AV-Block. Das mittlere Alter der Studienteilnehmer:innen lag bei 79 Jahren. 53 % der Teilnehmenden waren männlich. Bei der Mehrzahl lagen auch Begleiterkrankungen vor. Die Beobachtungsdauer der Studie lag bei zwei Jahren.

Für den sondenlosen Herzschrittmacher für eine atriale Stimulation (Aveir™ AR) konnte in der Literaturrecherche keine Studie identifiziert werden.

Zweikammer-L-PM: keine Vergleichsstudie, nur 1 Fallserie

Für das sondenlose Zweikammer-Herzschrittmacher System (Aveir™ DR) fand sich keine Vergleichsstudie zu konventionellen Herzschrittmachern. Es konnte lediglich eine unkontrollierte Fallserie mit 452 analysierten Teilnehmer:innen eingeschlossen werden. Die Hauptindikationen für einen Herzschrittmacher in der Studie war ein AV-Block bzw. eine gestörte Sinusknotenfunktion. Das mittlere Alter der Studienteilnehmer:innen lag bei 69 Jahren. 62 % der Teilnehmenden waren männlich. Bei der Mehrzahl lagen auch Begleiterkrankungen vor. Die Beobachtungsdauer der Studie lag bei bis zu zwei Jahren.

Klinische Wirksamkeit

L-PM VR vs C-PM: vergleichbare Mortalitätsraten

Vorteil bei LQ und körperlicher Funktion

Hinsichtlich der Gesamtmortalität zeigte sich in vier Studien (darunter eine RCT) kein Unterschied zwischen dem sondenlosen Einkammer-Herzschrittmacher zur rechtsventrikulären Stimulation (Micra™ VR) und konventionellem Einkammer-Herzschrittmacher im Zeitraum von sechs bis 36 Monaten. In zwei weiteren Studien war die Sterblichkeit im Zeitraum von 18 bzw. 22 Monaten bei Patient:innen mit dem Micra™ VR statistisch signifikant geringer als bei Patient:innen mit konventionellem Einkammer-Herzschrittmacher. Kardiale Mortalitätsraten wurden in vier Studien berichtet, wobei jeweils kein Unterschied zwischen den untersuchten Herzschrittmachersystemen vorlag. In zwei Kohortenstudien wurde die LQ drei bzw. sechs Monate nach der Implantation eines Schrittmachers untersucht. Dabei zeigten sich in beiden Studien statistisch signifikant bessere LQ-Werte in der Interventionsgruppe mit Micra™ VR im Vergleich zu einem konventionellen Einkammer-Herzschrittmacher. In der einzigen RCT wurde die körperliche Funktion nach 12 Monaten anhand eines 6-Minuten-Gehtests ermittelt. Dabei wurde kein Unterschied zwischen Patient:innen mit Micra™ VR und jenen mit konventionellem Einkammer-Herzschrittmacher berichtet.

L-PM AV vs C-PM: höhere Mortalitätsraten

keine Ergebnisse zu LQ und körperlicher Funktion

In der einzigen inkludierten Kohortenstudie zum Vergleich eines sondenlosen Einkammer-Herzschrittmachers mit synchroner AV-Stimulation (Micra™ AV) und einem konventionellem Zweikammer-Herzschrittmacher zeigte sich hinsichtlich der Gesamtmortalität nach zwei Jahren Follow-up eine statistisch signifikante höhere Mortalitätsrate mit Micra™ AV. Von den Studienautor:innen wurde dies mit den unterschiedlichen Begleiterkrankungen und Charakteristika der Patient:innen in den beiden Studiengruppen begründet. Entsprechende Adjustierungen in der Analyse führen jedoch zu keiner Änderung in der statistischen Signifikanz des Ergebnisses. Zu den übrigen wesentlichen Wirksamkeitsendpunkten kardiale Mortalität, LQ sowie körperliche Funktionsfähigkeit liegen aus der Studie keine Ergebnisse vor.

Zweikammer-L-PM: Mortalitätsrate: 3,5 %

In der unkontrollierten Fallserie zum Zweikammer-Herzschrittmacher System (Aveir™ DR) kam es im Zeitraum von drei Monaten zu vier Todesfällen (1,3 %), wobei zwei dieser Todesfälle kardiale Ursachen hatten. Während des

weiteren Follow-ups von 12 Monaten verstarben 3,5 % der Studienteilnehmer:innen. Es wurden dabei keine Angaben zur Todesursache gemacht. Zu den übrigen wesentlichen Wirksamkeitsendpunkten LQ und körperliche Funktionsfähigkeit liegen aus der Studie keine Ergebnisse vor.

keine Ergebnisse zu LQ und körperlicher Funktion

Sicherheit

In keiner der eingeschlossenen Studien wurden Ergebnisse zu SUE berichtet. Schwere Komplikationen im Zusammenhang mit dem Eingriff oder dem Implantat wurden in der inkludierten RCT sowie in zwei Kohortenstudien für den Vergleich sondenlose Einkammer-Herzschrittmacher zur rechtsventrikulären Stimulation (Micra™ VR) versus konventionelle Einkammer-Herzschrittmacher erhoben. Dabei zeigte sich im Zeitraum von sechs bis 22 Monaten kein Unterschied zwischen den Vergleichsgruppen. Ergebnisse zu Komplikationsraten im Zusammenhang mit dem Eingriff oder dem Implantat insgesamt wurden in insgesamt sechs Kohortenstudien berichtet. Akute Komplikationen traten bei 0 bis 7,7 % der Patient:innen mit Micra™ VR und 0,5 % bis 21,4 % der Patient:innen mit konventionellem Einkammer-Herzschrittmacher auf, wobei die Raten in zwei Studien statistisch signifikant geringer in der Interventionsgruppe waren. Die Raten an weiteren Komplikationen im Laufe eines Follow-ups von 18 bis 39 Monaten lagen bei 0 bis 4,9 % mit Micra™ VR und 1,4 % bis 8,6 % bei konventionellem Einkammer-Herzschrittmacher. Hier war die Raten in drei Studien statistisch signifikant geringer mit Micra™ VR. In einer Kohortenstudien wurden auch jene Komplikationen erhoben die ausschließlich auf das Herzschrittmachersystem zurückzuführen waren. Dabei zeigten sich zu allen vier Erhebungszeitpunkten (30 Tage, 6, 24 bzw. 36 Monate nach Implantation) statistisch signifikant geringere Raten mit Micra™ VR im Vergleich zu konventionellen Einkammer-Herzschrittmachern.

L-PM VR vs C-PM: geringere akute und spätere Komplikationsraten

keine Ergebnisse zu SUE

In der eingeschlossenen Studie zum Vergleich sondenlosen Einkammer-Herzschrittmacher für eine synchrone AV-Stimulation (Micra™ AV) versus konventionellem Zweikammer-Herzschrittmacher wurden keine Ergebnisse zu SUE bzw. zu schweren Komplikationen im Zusammenhang mit dem Eingriff oder dem Implantat berichtet. Ergebnisse zu Komplikationsraten im Zusammenhang mit dem Eingriff oder dem Implantat insgesamt wurden nach 30 Tagen (akut) bzw. 24 Monaten erhoben. Akute Komplikationen traten bei Patient:innen mit Micra™ AV (8,6 %) statistisch signifikant seltener auf als bei Patient:innen mit konventionellem Zweikammer-Herzschrittmacher (11 %). Auch die Rate an Komplikationen im weiteren Studienverlauf (24 Monate Follow-up) war mit Micra™ AV (5,3 %) statistisch signifikant geringer als bei konventionellen Zweikammer-Herzschrittmachern (9,6 %). Es wurden in der Studie auch jene Komplikationen erhoben, die ausschließlich auf das Herzschrittmachersystem zurückzuführen waren. Dabei zeigten sich sowohl nach 30 Tagen (1,4 % versus 4,1 %) als auch nach 24 Monaten (2,2 % versus 5,9 %) statistisch signifikant geringere Raten in der Interventionsgruppe im Vergleich zu konventionellen Zweikammer-Herzschrittmachern.

L-PM AV vs C-PM: geringere akute und spätere Komplikationsraten

keine Ergebnisse zu SUE

In der unkontrollierten Fallserie zum sondenlosen Zweikammer-Herzschrittmacher System Aveir™ DR kam es im Zeitraum von bis zu 24 Monaten bei 44,7 % der Studienteilnehmer:innen zu SUE. Die häufigsten SUE waren dabei kardiale Arrhythmien, Herzinsuffizienz und Infektionen. Schwere Komplikationen im Zusammenhang mit dem Eingriff oder dem Implantat traten in den ersten drei Monaten bei 9,7 % der Patient:innen auf. Zum Zeitpunkt 12 Monate nach Implantation lag die Rate an Patient:innen ohne schwere Komplikationen bei 88,6 %. Daten zu Komplikationsraten insgesamt im Zusammenhang mit dem Eingriff oder dem Implantat wurden in der Studie nicht berichtet.

Zweikammer-L-PM: SUE bei 45 % der Patient:innen

keine Angaben zu Komplikationsraten

Vertrauenswürdigkeit der Evidenz

Vertrauenwürdigkeit der Evidenz gering für Einkammer-L-PM und sehr gering für Zweikammer-L-PM

Die Qualität der inkludierten Studien wird insgesamt als gut bewertet. Da jedoch, mit Ausnahme einer kleinen RCT, für sondenlosen Einkammer-Herzschrittmacher lediglich Kohortenstudien inkludiert werden konnten, wird die Vertrauenswürdigkeit der Evidenz nach GRADE bestenfalls als gering eingeschätzt. Für das sondenlose Zweikammer-Herzschrittmacher System liegen keine Ergebnisse aus Vergleichsstudien, sondern lediglich aus einer unkontrollierten Fallserie vor. Die Vertrauenswürdigkeit der Evidenz wird hier als sehr gering und somit als unzureichend bewertet.

Laufende Studien

3 laufende RCTs zu L-PM AV

In den Studienregistern sind derzeit drei laufende RCTs zum sondenlosen Einkammer-Herzschrittmacher für eine synchrone AV-Stimulation im Vergleich zu konventionellen Herzschrittmachern aufgeführt. Die Beobachtungsdauer der RCTS liegt bei drei bis 12 Monaten. Als primäre Endpunkte werden Komplikationsraten, LQ oder Belastungsfähigkeit untersucht. Das geplante Studienende der RCTs liegt zwischen August 2025 und Dezember 2027. Darüber hinaus finden sich in den Studienregistern zwei laufende Fall-Kontrollstudien zu den sondenlosen Herzschrittmachersystemen für rechtsventrikuläre Stimulation sowie jeweils eine Fall-Kontrollstudie zum sondenlosen Herzschrittmacher für atriale Stimulation und zum Zweikammer-Herzschrittmacher System. Das geplante Studienende dieser Studien liegt zwischen Oktober 2025 und Jänner 2031.

Schlussfolgerung

L-PM VR gleich wirksam aber sicherer

Obwohl keine ausreichende Evidenz auf Basis von RCTs vorliegt, deuten mehrere große prospektive Kohortenstudien mit langer Beobachtungsdauer darauf hin, dass der sondenlose Einkammer-Herzschrittmacher zur rechtsventrikulären Stimulation gleich wirksam und zugleich sicherer ist als ein herkömmlicher Einkammer-Herzschrittmacher.

L-PM AV: tendenziell sicherer aber eventuell weniger wirksam

Auf Basis der Ergebnisse einer großen Kohortenstudie ist die derzeitige Evidenzlage in Bezug auf die Wirksamkeit und Sicherheit des sondenlosen Einkammer-Herzschrittmacher für eine synchrone AV-Stimulation nicht eindeutig. Die derzeitige Evidenz deutet darauf hin, dass die bewertete Technologie des sondenlosen Einkammer-Herzschrittmacher für eine synchrone AV-Stimulation tendenziell sicherer, aber möglicherweise weniger wirksam ist als konventionelle Zweikammer-Herzschrittmacher.

Zweikammer-L-PM: Evidenz derzeit unzureichend

Die Evidenzbasis für sondenlose Zweikammer-Herzschrittmacher ist derzeit unzureichend, um eine abschließende Beurteilung der Wirksamkeit und Sicherheit vorzunehmen. Für sondenlose Herzschrittmacher zur atrialen Stimulation liegen derzeit keine publizierten Studienergebnisse vor.

Hinweis auf zusätzlichen Nutzen nur für L-PM VR, aber wenig robuste Evidenz

Die derzeitige Evidenz weist ausschließlich für sondenlose Einkammer-Herzschrittmacher zur rechtsventrikulären Stimulation auf einen zusätzlichen Nutzen hin, jedoch auf Grundlage wenig robuster Evidenz.

Re-Evaluierung 2028 empfohlen

Da die Ergebnisse von drei RCTs zum Vergleich eines sondenlosen Einkammer-Herzschrittmacher für eine synchrone AV-Stimulation mit konventionellen Herzschrittmachern Ende 2027 vorliegen sollen, wird eine neuerliche Evaluierung im Jahr 2028 vorgeschlagen.

Summary of previous assessment 2020

2. Update 2020

Commissioned by the Austrian Ministry of Health (MoH), the HTA-report "Lead-less pacemakers for right ventricle pacing" was initially prepared by the Ludwig Boltzmann Institute of Health Technology Assessments (LBI-HTA) in March 2016 [1] and twice updated in 2017 [2] and 2020 [2]. The following paragraphs summarize the results and the recommendation of the last 2020 update report.

Scope

PIKO-Frage 2020

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

Inclusion criteria for relevant studies are summarised in Table 1.

Table 1: Inclusion criteria

Population	First-line treatment of patients with indications for single chamber ventricular pacemakers: ■ 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) 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
Intervention	Leadless self-contained and fully implantable VVI(R) pacemaker Setting: Vascular Surgery, Interventional Cardiology; specialist hospital, general hospital Product: Micra™ TPS, Medtronic Inc (available in Austria)
Control	Conventional VVI(R) pacemaker
Outcomes	
Effectiveness	■ Overall mortality ■ Cardiovascular mortality ■ Cardiovascular morbidity ■ Patient-related quality of life ■ Exercise capacity ■ Pacing performance
Safety	■ Serious adverse events ■ Overall adverse events ■ Complication rate

Study design	
Effectiveness	■ Randomized controlled trials (Non-inferiority)[1] ■ Prospective non-Randomized controlled trials
Safety	■ Randomized controlled trials ■ Prospective non-Randomized controlled trials ■ Prospective case series or registries with at least 50 patients

Abbreviations: AF: Atrial fibrillation; AV: Atrioventricular; ICD: International Classification of Diseases; SND: Sinus node dysfunction; TPS: Transcatheter pacing system; VVIR: Single chamber ventricular pacing with response modulation

entscheidungsrelevante Endpunkte

The following outcomes were defined as crucial to derive a recommendation in the report 2020.

Clinical effectiveness:

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

Safety:

- Complication rates
  - Serious Adverse Effect (SAE)
  - Adverse device effect (ADE)
  - Serious adverse device effect (SADE)

Results

Available evidence

keine RCTs oder non-RCTs

3 prospective Einarmstudien, 1 Fall-Kontroll-Studie und 5 Fallserien

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

For the 2020 update-report, no randomized or non-randomized controlled trials assessing leadless cardiac pacemakers versus conventional pacemakers were available. 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 investigating the only market-available device – Micra™ VR TPS – were identified. In addition, a propensity score-matched analysis comparing L-PM to C-PM was included. The total number of patients analysed for effectiveness 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 one month to a maximum of 24 months. Four publications focussed on specific subgroups within the included studies. These

[1] Randomized 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 sham-controlled trials would be unethical due to the availability of an effective treatment.

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

sehr wenige Todesfälle mit Bezug zu Eingriff oder Implantant

LQ: Verbesserung nach 12 Monaten

Overall 233 of 2,915 patients with successful Micra™ VR 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 effectiveness 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 six months beneficial effects in HRQoL in Micra™ VR TPS patients compared to patients with conventional single chamber pacemakers were reported.

Safety

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

SAEs 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™ VR 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.

Certainty of evidence

Vertrauenswürdigkeit der Evidenz: niedrig

Overall, the certainty of evidence for the effectiveness and safety of leadless pacemakers in comparison to conventional pacemakers was low to very low according to GRADE scheme.

Upcoming evidence

1 laufende RCT zu L-PM VR

A search in clinical trial registries found one ongoing 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™ VR TPS and two further ongoing observational studies on another leadless pacemaker system developed in India were registered.

Discussion

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™ VR 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 effectiveness and safety is possible. Nevertheless, the Micra™ VR TPS might have the potential for being a treatment for patients with contra-indications for conventional pacemaker implantation or with increased complication risk.

L-PM VR: Behandlungsoption für spezifische Patientengruppen

Conclusion

In 2020 the evidence was not sufficient to determine whether the leadless pacemaker Micra™ VR 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™ VR TPS seems to be advantageous. Therefore, the inclusion of the technology in the catalogue of benefits was recommended with restrictions only to well-defined patient groups after careful risk assessment und under extensive documentation.

Wirksamkeit: Evidenz unzureichend; Sicherheit: möglicher Vorteil

UPDATE 2025

1 Objectives and Scope

1.1 PICO question

Since the last report update in 2020, new leadless pacemaker systems with AV synchronous ventricular pacing as well as dual chamber pacing have been developed. Therefore, for the 2025 update the PICO question was extended to patients with indication for right ventricular and atrial pacing. The present PICO question is as follows:

PIKO-Frage 2025

Are leadless pacemakers in comparison to conventional pacemakers in patients with indications for right ventricular or atrial 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

Inclusion criteria for relevant studies are summarized in Table 1-1. **Einschlusskriterien 2025**

Table 1-1: Inclusion criteria

Population	First-line treatment of adult patients with indications for single chamber or dual chamber cardiac pacemakers: ■ 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) ■ Patients with sick sinus syndrome (ICD-10 I. 49.5) ■ Patients with chronic, symptomatic second- and third-degree AV block (ICD-10 I.44) ■ Recurrent Adams-Stokes syndrome (intermittent high-grade block or arrhythmia that results in cerebral hypoperfusion) (ICD-10 I. 45.9) ■ Symptomatic bilateral bundle-branch block when tachyarrhythmia and other causes have been excluded. (ICD-10 I. 45.10) ■ Sinus node dysfunction and normal AV and intraventricular conduction systems **Contraindications:** ■ Patients requiring long-term pacing exceeding estimated device longevity (NB. children) ■ Patients with indications for cardiac resynchronisation therapy

Intervention	Leadless self-contained and fully implantable VVI(R) or VDD pacemaker **Setting:** Vascular Surgery, Interventional Cardiology; specialist hospital, general hospital **Products:** ■ Micra™ VR TPS, Medtronic Inc (available in Austria) ■ Mirca™ AV TPS, Medtronic Inc (available in Austria) ■ Aveir™ VR Leadless Pacemaker, Abbott Lab. (available in Austria) ■ Aveir™ AR Leadless Pacemaker, Abbott Lab. (available in Austria) ■ Aveir™ DR Leadless Pacemaker, Abbott Lab. (available in Austria)
Control	Conventional cardiac pacemaker systems
Outcomes	
Effectiveness	■ Overall mortality ■ Cardiovascular mortality ■ Cardiovascular morbidity ■ Health-related quality of life ■ Physical function ■ Pacing performance
Safety	■ Serious adverse events ■ Overall adverse events ■ Complication rates
Study design	■ Randomized controlled trials[2] ■ Prospective non-Randomized controlled trials

Abbreviations: AF: Atrial fibrillation; AV: Atrioventricular; ICD: International Classification of Diseases; SND: Sinus node dysfunction; TPS: Transcatheter pacing system; VVIR: Single chamber ventricular pacing with response modulation

[2] Randomized 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 sham-controlled trials would be unethical due to the availability of an effective treatment.

2 Methods

This systematic review was conducted in accordance with Austrian Institute for Health Technology Assessment (AIHTA) methods for the assessment of new medical procedures in the MoH catalogue of procedure [3].

Assessment elements from the European Network for Health Technology Assessment (EUnetHTA) Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customized to the specific objectives of this assessment [4].

2.1 Description of the technology and health problem and current use

Quellen für Beschreibung der Technologien und der Indikationen

The sources used to describe the health problem, and the technologies of the L-PM and C-PM are provided by the results of a manual literature search (hand search). This search identified key background publications that provide a detailed understanding of the technology and its development as well as the indications for use. In addition, current clinical practice guidelines reflecting the current state of medical practice and recommendations were identified.

2.2 Clinical effectiveness and safety

2.2.1 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on the 23.12.2024 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- International Network of Agencies for Health Technology Assessment (INAHTA)

The systematic search was limited to the years 2020 to 2024. After deduplication, overall 1,173 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 Register (EudraCT)) was conducted on the 13.01.2025 resulting in 62 hits.

By hand-search, no additional records were found.

2.2.2 Flow chart of study selection

Overall 2,076 hits were identified. After deduplication, 1,234 references were screened by two independent researchers (CK, NB, TS) and in case of disagreement a third researcher (CK, NB, TS) was involved to solve the differences. The selection process is displayed in Figure 2-1.

Literaturauswahl: insgesamt 1.234 Referenzen

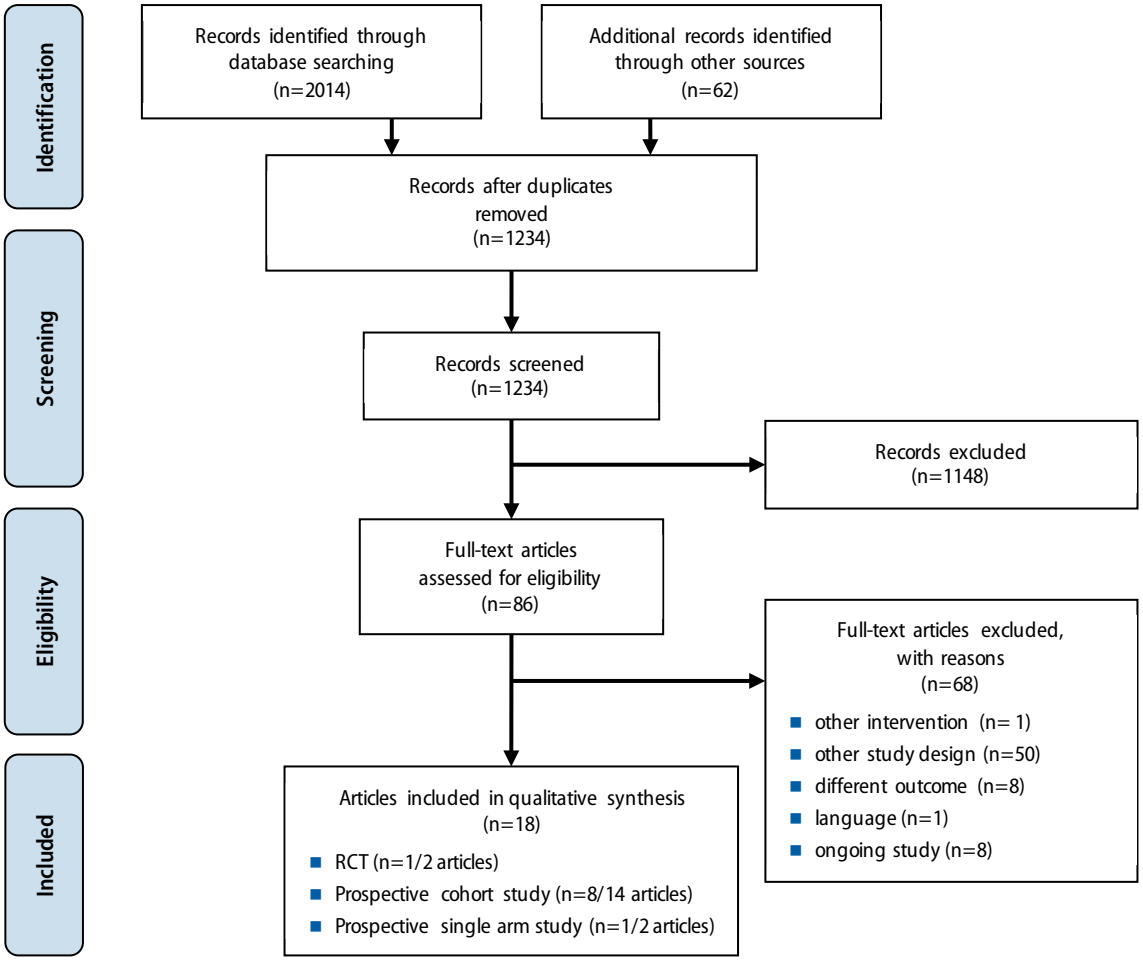

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

Overall, 18 publications were included in this updated report, comprising one RCT [5] and eight prospective cohort studies [6-16] comparing leadless single chamber pacemaker systems to conventional cardiac pacemakers. Additionally, we included one prospective single-arm study on a dual chamber pacemaker [17].

insgesamt 1 RCT, 8 Kohortenstudien und 1 unkontrollierte Studie inkludiert

2.2.3 Analysis

Datenextraktion

Relevant information was retrieved from the sources identified. Data from included primary studies were extracted into piloted data extraction tables based on the study design and research question (see Appendix Table A-1 to Table A-5). An independent second reviewer (CK or TS) validated the data for accuracy. Due to the small number of included studies, a meta-analysis was not performed.

Risk of Bias: Cochrane RoB 2, Ottawa Newcastle Scale und IHE Checkliste

Two researchers (CK, TS) conducted risk of bias assessments independently. Differences were resolved by consensus. The risk of bias (RoB) of the included RCTs was evaluated using the Cochrane RoB v.2 tool [18] (see Appendix Table A-7). We used the Ottawa Newcastle Scale for the quality assessment of prospective cohort studies [19] (see Appendix Table A-8). The quality of the included single-arm studies was assessed using the Institute of Health Economics (IHE) checklist for case series [20] (see Appendix Table A-9).

2.2.4 Synthesis

qualitative Synthese der Evidenz mithilfe von GRADE

Based on the piloted data-extraction-tables (see Appendix Table A-1 to Table A-5), data on each selected outcome were synthesized. Certainty of evidence was assessed across studies for each outcome according to GRADE (Grading of Recommendations Assessment, Development and Evaluation [21]). The research questions were answered in plain text format with reference to GRADE evidence tables that are included in Appendix, results were summarized in Table 6-1 to Table 6-3.

3 Description and technical characteristics of technology

3.1 Features of the technology and comparators[3, 4, 5, 6]

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 [22]. 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 [22].

konventionelle Schrittmacher: Pulsgeber + Sonden

mögliche schwere Komplikationen

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 [22]. 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 [23, 24].

sondenlose Schrittmacher (L-PM): 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 [25]. First generation L-PM have been developed for single chamber pacing. They could only provide right ventricular pacing (L-PM VR) and lack AV synchrony, increasing the risk of pacemaker syndrome [26]. To address this issue, a single chamber L-PM for AV synchronous ventricular pacing was developed that can detect atrial contractions using an internal 3-axis accelerometer (L-PM AV) [26]. In order to accommodate all pacing indications – including atrial pacing – the first dual chamber L-PM system was developed and approved in 2023. It is a modular system consisting of two separate L-PM, one implanted into the right ventricle and a second implanted into the right atrium [26].

[3] **B0001** – What is a leadless pacemaker and a conventional pacemaker?

[4] **A0020** – For which indications has the leadless pacemaker received marketing authorization or CE marking?

[5] **B0002** – What is the claimed benefit of leadless pacemakers in relation to conventional single chamber pacemakers?

[6] **B0003** – What is the phase of development and implementation of leadless pacemakers and conventional single chamber pacemakers?

Vorteile des L-PM: keine Implantation eines externen Pulsgenerators und keine Sonden

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 [27].

aktuell 5 unterschiedliche L-PM verfügbar

There are different leadless pacing systems that have been clinically tested: the Nanostim™ leadless cardiac pacemaker developed and manufactured by St. Jude Medical (later Abbott Inc., USA), the Micra™ transcatheter pacing system (TPS) by Medtronic Inc., USA, including the Micra™ VR L-PM for ventricular pacing only and the Micra™ AV L-PM for AV synchronous ventricular pacing, the Aveir™ VR L-PM for single chamber ventricular pacing, the Aveir™ AR L-PM for single chamber atrial pacing and the Aveir™ DR L-PM for dual chamber pacing, all three by Abbott Inc., USA.

The Nanostim™ was withdrawn from the market in 2016 after battery malfunctions in serval patients [27]. Later, the Nanostim™ was redesigned into the Aveir™ L-PM system [26].

Indikation L-PM VR

The first Micra™ VR L-PM received CE marking (CE: 0123) in April 2015 [28] and Food and Drug Administration (FDA)-approval in April 2016 [29] for the use in patients with indications for single chamber right-ventricular pacing. The second generation of the Micra™ VR L-PM – the Micra™ VR2 – received FDA approval in May 2023, and European CE Mark approval in January 2024 [30].

Indications for VR/VR2 L-PM include [31]:

- 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

zusätzliche Indikationen L-PM AV

The Micra™ AV L-PM received CE marking and FDA-approval in January 2020. In addition to the indication listed above, it is also indicated for VDD pacing in patients with adequate sinus rates who may benefit from maintenance of AV synchrony. The second generation of the Micra™ AV L-PM – the Micra™ AV2 – received FDA approval in May 2023, and European CE Mark approval in January 2024 [30]. The Micra™ AV2 is indicated for use in patients who have experienced one of the following [31]:

- Paroxysmal or permanent high-grade AV block in the absence of AF
- Paroxysmal or permanent high-grade AV block in the presence of paroxysmal AF
- Paroxysmal or permanent high-grade AV block in the presence of persistent AF when attempts at restoring sinus rhythm are still planned

Kontraindikationen für Einkammer-L-PM

The Micra™ VR and AV L-PM systems are contraindicated for patients with morbid obesity that prevents the implanted device from obtaining telemetry communication within ≤12.5 cm, femoral venous anatomy unable to accom-

modate a 7.8 mm introducer sheath or implant on the right side of the heart, known material intolerance or with implanted medical devices that would interfere with the pacemaker systems [31].

The Aveir™ VR single chamber pacing system received FDA approval in April 2022 [32] and European CE marking in September 2023 [33]. It is indicated for patients with significant bradycardia and [34]:

- Normal sinus rhythm with rare episodes of AV block or sinus arrest
- Chronic atrial fibrillation
- Severe physical disability

Indikationen Zweikammer-L-PM

The Aveir™ DR dual chamber pacing system received FDA approval in July 2023 and European CE marking in June 2024. It is a modular system consisting of an Aveir™ VR L-PM, implanted into the right ventricle, and an Aveir™ AR L-PM, implanted into the right atrium [26]. The Aveir™ DR is indicated for patients with [35]:

- Sick sinus syndrome; chronic
- Symptomatic second- and third-degree AV block
- Recurrent Adams-Stokes syndrome
- Symptomatic bilateral bundle-branch block when tachyarrhythmia and other causes have been ruled out

In addition, it is indicated for atrial pacing in patients with sinus node dysfunction and normal AV and intraventricular conduction systems.

Kontraindikationen für Zweikammer-L-PM

The Aveir™ L-PM systems are contraindicated for patients with a co-implanted ICD, implanted vena cava filter or mechanical tricuspid valve, and for patients with known history of allergies to any of the components of the devices. The Aveir™ VR single chamber pacing system is also contraindicated for patients who have demonstrated pacemaker syndrome, have retrograde ventriculoatrial conduction, or suffer a drop in arterial blood pressure with the onset of ventricular pacing [35].

3.2 Administration, Investments, personnel and tools required to use the technology and the comparator(s)[7, 8, 9]

L-PM: beschränkt auf speziell geschulte Teams

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

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

[8] **B0008** – What kind of special premises are needed to use leadless pacemakers and conventional single chamber pacemakers?

[9] **B0009** – What supplies are needed to use leadless pacemakers and conventional single chamber pacemakers?

using a dedicated introducer sheath. 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.

3.3 Regulatory & reimbursement status[10]

L-PM: derzeit nicht im Leistungskatalog

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

[10] **A0021** – What is the reimbursement status of leadless pacemakers?

4 Health Problem and Current Use

4.1 Overview of the disease or health condition[11, 12, 13]

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 [36]. 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 [37, 38]. 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

Indikationen laut Leitlinien: Bradykardie mit Symptomen

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) [39] and by the European Society of Cardiology (ESC) [36]. 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 [36]. 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 [36]. 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 [36].

VVI bevorzugt bei Patient*innen mit chronischer AF

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)

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 [40].

[11] **A0001** – For which health conditions, and for what purposes are leadless pacemakers used?

[12] **A0002** – What is the disease or health condition in the scope of this assessment?

[13] **A0003** – What are the known risk factors for bradyarrhythmia?

4.2 Target population[14, 15]

Patients with indications for cardiac pacing:

Indikationen für Herzschrittmacher

- 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)
- Patients with sick sinus syndrome (ICD-10 I. 49.5)
- Patients with chronic, symptomatic second- and third-degree AV block (ICD-10 I.44)
- Recurrent Adams-Stokes syndrome (intermittent high-grade block or arrhythmia that results in cerebral hypoperfusion) (ICD-10 I. 45.9)
- Symptomatic bilateral bundle-branch block when tachyarrhythmia and other causes have been excluded (ICD-10 I. 45.10)
- Sinus node dysfunction and normal AV and intraventricular conduction systems

Österreich 2019: 120.000 Personen mit kardialen Arrythmien

In Austria, over 120,000 patients with cardiac arrhythmias were recorded in 2019 [41]. In 2023, a total of 5,491 individuals underwent pacemaker implantation in Austria, including 3,263 males and 2,228 females [42].

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

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

5 Results: Clinical effectiveness and Safety

5.1 Outcomes

5.1.1 Outcomes effectiveness

entscheidungsrelevante Endpunkte – Wirksamkeit: Mortalität, Lebensqualität, körperliche Funktionsfähigkeit

The implantation of pacemakers serves the primary purpose to alleviate symptoms associated with a slow heart rhythm, such as fatigue, dizziness, or short of breath. The assessment of quality of life and physical functioning is paramount in determining a patient's clinical condition, offering a comprehensive evaluation of treatment effectiveness [36]. The most common indications for pacemaker therapy are high-degree AV-block and SND. For patients diagnosed with SND, there is no evidence supporting the effectiveness of pacemaker therapy in enhancing overall survival outcomes. Conversely, patients with high-grade AV block who undergo pacemaker implantation demonstrate a marked improvement in survival when compared to patients who receive conservative treatment [36]. Pacemaker therapy has been demonstrated to have a substantial impact on quality of life, both in the immediate short term and over extended periods. In certain cases, the therapy can also lead to a prolonged life span [24, 36, 43].

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

- Overall mortality
  - Cardiac mortality
- Physical function
- Health-related quality of life (HRQoL)

Mortality is considered a highly patient-relevant outcome measure. Mortality was reported as overall mortality rates and as cardiac mortality rates in the included studies.

Patient-reported outcomes like physical function or HRQoL are taken into account if they were assessed by validated tests, e.g. 6-minutes' walking distance test, or recorded using valid measurement instruments, e.g. validated scales like Oswestry Disability Index (ODI), Short Form 36 (SF-36) questionnaire, or the European Quality of Life–5 Dimensions (EQ-D) questionnaire.

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

5.1.2 Outcomes safety

entscheidungsrelevante Endpunkte – Sicherheit: SUE, 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 con-

cern 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.

- Serious Adverse Effect (SAE)
- Complication rates
  - Serious adverse device effect (SADE)
  - Adverse device effect (ADE)

In accordance with the European Commission guidelines on serious adverse event reporting of medical devices[16] 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 including the implantation procedure. 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

5.2 Included studies

5.2.1 Included studies effectiveness

Single chamber L-PM for right ventricular pacing

Evidenz L-PM VR: 1 RCT, 7 Kohortenstudien

In our update search, we identified 10 journal articles [5-14] and two clinical trial registry entries [44, 45] on eight studies comparing leadless single chamber right ventricular pacemaker (L-PM VR) to conventional cardiac pacemaker. This includes one RCT, published in 2023, and seven prospective cohort studies, published between 2021 and 2023. All included studies investigated the same L-PM VR, the Micra™ VR TPS. No publications were found reporting effectiveness or safety results for the Aveir™ VR L-PM.

RCT: 51 Patient:innen

Ø Alter: 82 Jahre

The RCT [5] was conducted in Belgium and included 51 adult patients with Class I or II indication for single chamber ventricular pacing, according to the 2013 European Society of Cardiology guidelines. The mean age of the study participants was 82 years. 61% were male. The indications for pacing were AF + severe bradycardia or SND (48.1% vs. 78.0%) or sinus rhythm + high

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

degree AV block (51.9% vs. 25.0%). The most frequent comorbidity was hypertension (78%). Other frequent comorbidities were valve disease (37%), coronary artery disease (CAD) (27%), and diabetes mellitus (22%). The follow-up of the RCT was 12 months.

12 Monate Follow-up

The US-American Micra CED study [7, 8, 12], an ongoing prospective cohort study, enrolling 37,000 Medicare patients with indications for leadless or conventional single chamber ventricular pacemaker implantation. Interim results were published after six months including 15,408 patients [12], two years including 16,431 patients [8], and three years follow-up again including 16,431 patients [7]. The mean age of the study participants was about 80 years. 56% of the patients were male. There is no information about the main pacing indications. The most frequent comorbidities were hyperlipidaemia (75%), CAD (55%), heart failure (53%), diabetes mellitus (43%), and renal dysfunction (45%).

große Kohortenstudie: 37.000 Patient:innen

Ø Alter: ~80 Jahre

3 Jahre Follow-up

Four Italian prospective cohort studies enrolled 200 [14], 243 [11], 344 [6], and 2,669 patients [10] with indications for leadless or conventional single chamber ventricular pacemaker implantation. The mean follow-up of the studies was six [11], 18 [14], 23 [6], and 39 months [10], respectively. The mean age of the participants ranged from 73 to 84 years. 60% to 72% of the participants were male. Pacing indications were reported in two studies. These were bradycardia with persistent or permanent atrial tachyarrhythmia (45% vs. 80%) or AV block (30% vs. 15%) in one study [14], and bradycardia with permanent atrial tachyarrhythmia (74% vs. 69%) or sinus rhythm + AV block (11% vs. 23%) in the other study [11].

6 kleiner Kohortenstudien: insgesamt 4.018 Patient:innen

Ø Alter: 73-84 Jahre

Follow-up: 6 bis 39 Monate

The remaining two prospective cohort studies were conducted in Spain [9] and China [13], respectively. They included 443 [9] and 119 patients [13] with indications for a single chamber pacemaker implant. The mean age of the included participants was 82 and 70 years, respectively. 42% and 62% were male. Pacing indications were not reported for these two studies. The most frequent comorbidities were hypertension (71% and 66%) and diabetes mellitus (30% and 39%). The mean follow-up of the two studies was 22 months and three months, respectively.

Single chamber L-PM for AV synchronous ventricular pacing

For the comparison of single chamber L-PM with AV synchronous ventricular pacing (L-PM AV) to conventional cardiac pacemaker, we found two journal publications [15, 16] and one clinical trial registry entry [46] on one prospective cohort study. No RCT was identified investigating this type of L-PM. The investigated L-PM AV in this study was the Micra™ AV TPS, which is currently the only L-PM AV available on the market.

Evidenz L-PM AV: 1 Kohortenstudie

The US-American Micra AV study [15, 16], an ongoing prospective cohort study, enrolling Medicare patients with indications for single chamber L-PM AV or conventional dual chamber ventricular pacemaker implantation. Interim results were published after 30 days and six months follow-up including 115,271 patients [15] and after two years follow-up including 118,110 patients [16]. The mean age of the study participants was 79 years. 53% of the patients were male. The pacing indication was AV block in 74% of the patients with leadless AV pacemaker and in 48% of the patients with conventional dual chamber pacemaker. Other pacing indications were not reported. The most frequent comorbidities were hypertension (90%), hyperlipidaemia (77%), CAD (49%), diabetes mellitus (39%), renal dysfunction (35%), and heart failure (31%).

große Kohortenstudie: über 115.000 Patient:innen

Ø Alter: ~80 Jahre

2 Jahre Follow-Up

Dual chamber L-PM

Currently the only dual chamber L-PM available on the market is the Aveir™ DR L-PM system.

Evidenz Zweikammer-L-PM: keine Vergleichsstudie, nur 1 Fallserie

No RCTs or non-randomized comparative studies were identified for this dual chamber L-PM system. In our literature search, we found one journal publication [17] and one clinical trial registry entry with study results [47] on one single-arm trial investigating this type of L-PM.

The identified Aveir DR i2i study [17, 47] is a prospective, multi-centre, international, single-arm study. Results were reported after three [17] and 12 months follow-up [47] including 300 patients. The mean age of the study participants was 69 years. 62% of the patients were male. The primary pacing indication was SND in 63% and AV block in 33% of the participants. The most frequent comorbidities were hypertension (67%), hyperlipidaemia (61%), CAD (34%), and diabetes mellitus (25%).

Fallserie: 300 Patient:innen

Ø Alter: 69 Jahre

12 Monate Follow-Up

Table 5-1 presents an overview of all included and the corresponding sources.

Study characteristics and results of included studies are displayed in Table A-1 to Table A-6, and in the evidence profile in Table A-10 to Table A-12.

Table 5-1: Study pool: Sources of included studies comparing L-PM to C-PM

Study	Study design	Journal publication	Clinical trial registry ID	Results reported in clinical trial registry
Single chamber L-PM VR				
Garweg 2023	RCT	[5]	NCT06100757 [45]	No
Micra CED study	cohort study	[7, 8, 12]	NCT03039712 [44]	No
Bertelli 2022	cohort study	[6]	-	No
Martinez-Sande 2021	cohort study	[9]	-	No
Palmisano 2021	cohort study	[11]	-	No
Pamisano 2023	cohort study	[10]	-	No
Yu 2023	cohort study	[13]	-	No
Zucchelli 2021	cohort study	[14]	-	No
Single chamber L-PM AV				
Micra AV CED study	cohort study	[15, 16]	NCT04235491 [46]	No
Dual chamber L-PM				
Aveir DR i2i study	single-arm study	[17]	NCT05252702 [47]	Yes

Abbreviations: AV: AV synchronous ventricular pacing; CED: Coverage with Evidence Development; L-PM: Leadless pacemaker; RCT: Randomized controlled trial; VR: Right ventricular pacing.

5.2.2 Additional included studies safety

Results from the studies included for effectiveness outcomes were also included in the safety analyses. No additional studies were included.

5.3 Results

5.3.1 Single chamber L-PM for right ventricular pacing

Mortality[17,18]

L-PM VR vs C-PM

Data on overall mortality were reported in one RCT and five prospective cohort studies, comparing the L-PM VR Micra™ VR TPS to conventional single chamber pacemakers.

Gesamtmortalität. kein Unterschied in RCT

In the RCT by Garweg et al. 2023 [5], three patients died during 12 months follow-up. One in the Micra™ VR TPS group and two in the conventional pacemaker group. All deaths were from non-cardiac cause.

Gesamtmortalität: kein Gruppenunterschied in 3 Kohortenstudien; stat. signifikanter Vorteil für L-PM VR in 2 Studien

In the US-American Micra CED study there were overall mortality rates of 3.9% versus 4.1% in the first 30 days [12] and 31.4% versus 32.5% after two years follow-up (HR 0.97 [95% CI 0.91-1.04]) [8]. Also after three years follow-up, there was no statistically significant difference between patients with Micra™ VR TPS and conventional single chamber pacemaker (HR 0.97 [95% CI 0.92-1.03]) [7]. No information was provided concerning the underlying cause of death.

ingesamt geringe Raten als kardialer Mortalität

In three other cohort studies, overall mortality rates were 1.1% versus 0.7% after six months (p=0.72) [11], 7% versus 23% after 18 months (p=0.003) [14], and 9.1% versus 17.9% after 22 months (p=0.0075) [9]. In a fourth cohort study, the hazard ratio for overall mortality after 23 months follow up was 0.93 [95% CI 0.42-2.04]; p=0.85 [6]. Three of these studies also reported results on cardiac mortality, with only few events. There were no difference between Micra™ VR TPS and conventional single chamber pacemaker in two studies (6 months: 0 vs 0 events [11]; 22 months: 0.5% vs 0.8% [9], and statistically significant less cardiac death with Micra™ VR TPS in the third study (18 months: 0% vs 8% [14]. One of these eight death was classified as device related.

Morbidity[19,20]

keine Evidenz zur Wirksamkeit in Bezug auf Arrhythmien

No evidence was found to answer this research questions.

[17] **D0001** – What is effect of single chamber L-PM VR versus conventional cardiac pacemakers on mortality?

[18] **D0003** – What is the effect of single chamber L-PM VR versus conventional cardiac pacemakers on the mortality due to causes other than the target disease?

[19] **D0005** – How does the single chamber L-PM VR in comparison to conventional cardiac pacemakers affect symptoms and findings (severity, frequency) of cardiac arrhythmias?

[20] **D0006** – How does the single chamber L-PM VR in comparison to conventional cardiac pacemakers affect progression (or recurrence) of cardiac arrhythmias?

Health-related quality of life[21,22]

LQ: signifikant besser mit L-PM VR in 2 Kohortenstudien nach 3 bzw. 6 Monaten

Two cohort studies investigated the impact of Micra™ VR TPS or conventional single chamber pacemakers on generic HRQoL [11, 13], both using the SF-36 questionnaire.

Yu et al. 2023 reported HRQoL results after three months follow-up [13]. There were statically significant better scores in both SF-36 subscales ($p<0.001$) and seven out of eight SF-36 domains.

In the cohort study by Palmisano et al. 2021 [11], both SF-36 subscales were statistically significant better in the Micra™ VR TPS group compared to the conventional single chamber pacemaker group after six months follow-up ($p<0.001$ for physical component scale; $p=0.006$ for mental component scale). In addition, patients in the Micra™ VR TPS group had significantly higher scores in seven of the eight SF-36 domains.

No results were reported on disease-specific quality of life.

Function[23, 24]

körp. Funktion: kein Gruppenunterschied beim 6-Minuten Gehtest in RCT nach 12 Monaten

Results from a 6-minutes' walk distance test were reported at baseline and after 12 months follow-up in the included RCT [5]. There were no differences in the walking distance in both groups between baseline and 12 months follow-up ($p=0.577$). At 12 months follow-up there was also no difference in the walking distance between the Micra™ VR TPS group and the conventional single chamber pacemaker group ($p=0.088$).

Patient satisfaction[25]

keine Evidenz zu Patientenzufriedenheit

No evidence was found to answer this research questions.

Patient safety[26, 27, 28, 29]

Serious adverse events (SAE)

keine Ergebnisse zu SUE

There were no results concerning SAE for the comparison of single chamber L-PM VR versus conventional single chamber pacemakers.

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[21] **D0012** – What is the effect of single chamber L-PM VR versus conventional cardiac pacemakers on generic health-related quality of life?

[22] **D0013** – What is the effect of single chamber L-PM VR versus conventional cardiac pacemakers on disease-specific quality of life?

[23] **D0011** – What is the effect of single chamber L-PM VR versus conventional cardiac pacemakers on patients' body functions?

[24] **D0016** – How does the use of the single chamber L-PM VR affect activities of daily living in comparison to conventional cardiac pacemakers?

[25] **D0017** – Was the use of the single chamber L-PM VR worthwhile in comparison to conventional cardiac pacemakers?

[26] **C0008** – How safe is the single chamber L-PM VR in comparison to conventional cardiac pacemakers?

[27] **C0004** – How does the frequency or severity of harms change over time or in different settings?

[28] **C0005** – What are the susceptible patient groups that are more likely to be harmed through the use of the single chamber L-PM VR?

[29] **C0007** – Are the single chamber L-PM VR and conventional cardiac pacemakers associated with user-dependent harms?

Serious device or procedure-related adverse events (SADE)

schwere Komplikationen selten

Major complications related to device or procedure were reported in one RCT and two prospective cohort studies comparing Micra™ VR TPS to conventional single chamber pacemakers.

kein Gruppenunterschied in 1 RCT und 2 Kohortenstudien

In the RCT by Garweg et al. 2023, no acute major complications occurred in the Micra™ VR TPS group. In the conventional pacemaker group one patient developed a pocket hematoma the day following implantation, requiring prolonged hospitalization [5]. There was no device failure related to elevated pacing threshold or loss of capture during 12 months follow-up in both groups. No results on other major complications during follow-up were reported [5].

In the cohort study Palmisano et al. 2021, no major complications occurred in the Micra™ VR TPS group during six months follow up. In the conventional pacemaker group two patients developed a pocket hematoma the day following implantation, requiring prolonged hospitalization. No further major complications occurred in the conventional pacemaker group during follow-up [11]. In the cohort study Martinez-Sande et al. 2021, 22-months major complication rates were 3% with Micra™ VR TPS and 5.6% with conventional single chamber pacemakers (p=0.1761) [9].

All adverse events

keine Ergebnisse zu UE insgesamt

There were no results concerning all adverse events for the comparison of single chamber L-PM VR versus conventional single chamber pacemakers.

All device or procedure-related adverse events

Overall device- or procedure-related adverse events (i.e. overall complications), were reported in six prospective cohort studies comparing Micra™ VR TPS to conventional single chamber pacemakers.

akute Komplikationen: kein Gruppenunterschied in 3 Kohortenstudien; stat. signifikanter weniger mit L-PM VR in 2 Studien

In the US-American Micra CED study, acute device or procedure-related adverse events were reported in 7.7% of the patients with Micra™ VR TPS, and 7.4% of the patients with conventional single chamber pacemakers [12]. Acute complications directly related to the device were reported in 1.4% of the patients with Micra™ VR TPS, and 2.5% of the patients with conventional single chamber pacemakers (p<0.001) [12]. In four other prospective cohort studies, acute device or procedure-related adverse events ranged from 0 to 5.6% in the Micra™ VR TPS groups compared to 0.5% to 21.4% in the conventional single chamber pacemaker groups. There were no group differences in two studies [10, 14], and statically significant lower rates with Micra™ VR TPS in the other two studies [6, 13].

Although, cardiac effusion/perforation rates were generally low, they were statistically significantly higher with Micra™ VR TPS compared to conventional single chamber pacemakers (0.8% vs. 0.4%; p=0.004) in the Micra CED study [12]. In two other studies, there were no differences in cardiac effusion/perforation rates between Micra™ VR TPS and conventional single chamber pacemakers [9, 10].

Komplikationen während Follow-up: kein Gruppenunterschied in 2 Kohortenstudien …

In the Micra CED study adjusted device or procedure-related complications were statistically significant lower with Micra™ VR TPS compared to conventional single chamber pacemakers after six months (3.2% vs. 4.1%; p<0.0001) [12], after 24 months (4.6% vs. 6.5%; p<0.0001) [8], and after 36 months (4.9% vs. 7.1%; p<0.0001) follow-up [7]. The rates of complications directly related to the device were also statistically significant lower with Micra™ VR TPS

compared to conventional single chamber pacemakers after six months (1.7% vs. 3.3%) [12], after 24 months (2.4% vs. 4.8%; p<0.0001) [8], and after 36 months (2.6% vs. 5.2%; p<0.0001) [7].

… stat. signifikanter weniger mit L-PM VR in 3 Studien nach 3 bis 39 Monaten

In four other cohort studies, device or procedure-related complications during three to 39 months follow-up occurred in 0 to 3.5% of the patients with Micra™ VR TPS and 1.4 to 3.6% with conventional single chamber pacemakers. There were no group differences in two of these studies [6, 14], and statically significant lower rates with Micra™ VR TPS in the other two studies [10, 13].

Device dislodgements and loss of device function were reported after 36 months follow-up [7]. Both rates were statistically significant lower with Micra™ VR TPS compared to conventional single chamber pacemakers (device dislodgement: 0.4% vs. 1.3%, p<0.0001; loss of device function: 1.5% vs. 2.4%, p=0.002).

Overall, no results were available from the included study whether there are patient subgroups that are more or less likely to be harmed through the use of the single chamber L-PM VR. Also, no information on the influence of operator experience on procedural and safety outcomes was available.

Detailed results from included studies for leadless single chamber L-PM VR are displayed in Table A-1 to Table A-4.

5.3.2 Single chamber L-PM for AV synchronous ventricular pacing

Mortality[30,31]

L-PM AV vs C-PM

Gesamtmortalität: stat. signifikant höhere Rate mit L-PM AV in 1 Kohortenstudie nach 24 Monaten

In the US-American Micra CED AV study, overall mortality rates were reported after six months and 24 months follow-up. The mortality rates were statistically significant higher with Micra™ AV TPS compared to conventional dual chamber pacemakers. After six months, 6% of the patients died in the Micra™ AV TPS group, and 3.5% of the patients died in the conventional dual chamber pacemaker group (HR 1.69 [95% CI 1.57-1.83]; p<0.0001) [15]. After 24 months there was an overall mortality rate of 34% with Micra™ AV TPS, and 23.8% with conventional dual chamber pacemakers (adjusted HR 1.53 [95% CI 1.44-1.62]; p<0.0001) [16].

The study publications did not include any results concerning cardiac mortality.

Morbidity[32,33]

keine Evidenz zur Wirksamkeit in Bezug auf Arrhythmien

No evidence was found to answer this research questions.

[30] **D0001** – What is effect of single chamber L-PM AV versus conventional cardiac pacemakers on mortality?

[31] **D0003** – What is the effect of single chamber L-PM AV versus conventional cardiac pacemakers on the mortality due to causes other than the target disease?

[32] **D0005** – How does the single chamber L-PM AV in comparison to conventional cardiac pacemakers affect symptoms and findings (severity, frequency) of cardiac arrhythmias?

[33] **D0006** – How does the single chamber L-PM AV in comparison to conventional cardiac pacemakers affect progression (or recurrence) of cardiac arrhythmias?

Health-related quality of life[34,35]

No evidence was found to answer this research questions.

keine Evidenz zu LQ

Function[36, 37]

No evidence was found to answer this research questions.

keine Evidenz zu körperlicher Funktion

Patient satisfaction[38]

No evidence was found to answer this research question.

keine Evidenz zu Patientenzufriedenheit

Patient safety[39, 40, 41, 42]

Serious adverse events (SAE)

No evidence was found to answer this research questions.

keine Evidenz zu SUE

Serious device or procedure-related adverse events (SADE)

No evidence was found to answer this research questions.

keine Evidenz zu schweren Komplikationen

All adverse events

No evidence was found to answer this research questions.

keine Evidenz zu UE insgesamt

All device or procedure-related adverse events

Device or procedure-related adverse events and only device-related complications were reported after the first 30 days (acute events), and after six months [15] and 24 months [16], respectively.

Acute device or procedure-related adverse events were reported in 8.6% of the patients with Micra™ AV TPS, and 11% of the patients with conventional dual chamber pacemakers ($p<0.0001$) [15]. Acute complications related directly to the device were reported in 1.4% of the patients with Micra™ AV TPS, and 4.1% of the patients with conventional dual chamber pacemakers ($p<0.0001$) [15].

akute Komplikationen: stat. signifikanter weniger mit L-PM AV

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[34] **D0012** – What is the effect of single chamber L-PM AV versus conventional cardiac pacemakers on generic health-related quality of life?

[35] **D0013** – What is the effect of single chamber L-PM AV versus conventional cardiac pacemakers on disease-specific quality of life?

[36] **D0011** – What is the effect of single chamber L-PM AV versus conventional cardiac pacemakers on patients' body functions?

[37] **D0016** – How does the use of the single chamber L-PM AV affect activities of daily living in comparison to conventional cardiac pacemakers?

[38] **D0017** – Was the use of the single chamber L-PM AV worthwhile in comparison to conventional cardiac pacemakers?

[39] **C0008** – How safe is the single chamber L-PM AV in comparison to conventional cardiac pacemakers?

[40] **C0004** – How does the frequency or severity of harms change over time or in different settings?

[41] **C0005** – What are the susceptible patient groups that are more likely to be harmed through the use of the single chamber L-PM AV?

[42] **C0007** – Are single chamber L-PM AV and conventional cardiac pacemakers associated with user-dependent harms?

Although, cardiac effusion/perforation rates were generally low, they were statistically significant higher with Micra™ AV TPS compared to conventional dual chamber pacemakers (1.4% vs. 0.8%; p<0.0001) [15].

Komplikationen während Follow-up: stat. signifikanter weniger mit L-PM AV nach 24 Monaten

Also after six months (3.5% vs. 7.0%; p<0.0001) [15] and after 24 months (5.3% vs. 9.6%; p<0.0001) [16] device or procedure-related adverse events were statistically significant lower with Micra™ AV TPS compared to conventional dual chamber pacemakers. Again, the rates for acute complications related directly were also statistically significant lower with Micra™ AV TPS compared to conventional dual chamber pacemakers after six months (2.2% vs. 5.9%; p<0.0001) [15] and after 24 months (2.9% vs. 6.8%; p<0.0001) [16].

Device dislodgement was reported after six months and 24 months follow-up. In both timeframes, rates were statistically significant lower with Micra™ AV TPS compared to conventional dual chamber pacemakers (six months: 0.4% vs. 2.5%; p<0.0001; 24 months: 0.5% vs 2.8%; p<0.0001) [15,16]. Loss of device function was only reported after 24 months follow-up, with statistically significant lower rates in the Micra™ AV TPS group compared to the conventional dual chamber pacemaker group (1.8% vs. 3.0%; p<0.0001) [16].

Overall, no results were available from the included study whether there are patient subgroups that are more or less likely to be harmed through the use of the single chamber L-PM AV. Also, no information on the influence of operator experience on procedural and safety outcomes was available.

Detailed results from the included study for single chamber L-PM AV are displayed in Table A-5.

5.3.3 Dual chamber leadless pacemaker

Mortality[43,44]

Zweikammer-L-PM

Gesamtmortalität: 3,5 % nach 12 Monaten

In the Aveir DR i2i single-arm study there was an overall mortality rate of 1.3% (4 of 300 patients) after three months follow-up [17]. Two of these deaths were attributed to cardiac causes. None of the deaths were classified as device- or procedure related [17]. After 12 months follow-up the overall mortality rate was 3.54% (16 of 452 patients). Cause of death or relationship to device- or procedure were not reported [47].

Morbidity[45,46]

AF nach 24 Monaten bei 9,1 %

Knops et al. 2023 reported nine cases of AF (3%), one case of transient complete atrioventricular block (0.3%), and one case of heart failure (0.3%) during three months follow-up after Aveir™ DR L-PM system implantation [17]. In the time-frame up to 24 months follow-up, 41 cases of atrial fibrillation (9.1%), 18 cases of heart failure (4.0%), 11 cases of supraventricular arrhythmia (2.4%), four myocardial infarctions (0.9%), and three cases of transient ischemic attack (0.7%) occurred [47].

[43] **D0001** – What is effect of the dual chamber leadless pacemaker on mortality?

[44] **D0003** – What is the effect of dual chamber leadless pacemaker on the mortality due to causes other than the target disease?

[45] **D0005** – How does the dual chamber leadless pacemaker affect symptoms and findings (severity, frequency) of cardiac arrhythmias?

[46] **D0006** – How does the dual chamber leadless pacemaker affect progression (or recurrence) of cardiac arrhythmias?

Health-related quality of life[47,48]

No evidence was found to answer this research questions.

keine Evidenz zu LQ

Function[49, 50]

No evidence was found to answer this research questions.

keine Evidenz zu körperlicher Funktion

Patient satisfaction[51]

No evidence was found to answer this research question.

keine Evidenz zu Patientenzufriedenheit

Patient safety[52, 53, 54, 55]

Serious adverse events (SAE)

In the Aveir DR i2i single-arm study, SAE were reported after three months follow-up including 300 patients and up to 24 months follow-up including 452 patients. After three months, the rate of SAE not related to device or procedure was 11.7% (35 of 300 patients). Most common SAEs were cardiac arrhythmia (2.6%), heart failure (1.3%), infections (1.3%), and pain (1.0%) [17]. During follow-up up to 24 months, SAE (including both device and non-device related events) occurred in 202 of 452 patients (44.7%). Here, the most common SAEs were cardiac arrhythmia (11.5%), heart failure (3.98%), and infections (2.2%) [47].

SUE nach 24 Monaten bei 44,7 %

Serious device or procedure-related adverse events (SADE)

Acute SADE were reported in the Aveir DR i2i single-arm study after three months follow-up. There were 35 SADE in 29 of 300 patients, including cardiac arrhythmia (10 patients), device dislodgement (10 patients), pericardial effusion (two patients), and capture threshold issues (two patients) [17].

akute schwere Komplikationen bei 9,7 %

In addition, the percentage of patients free from SADE, and the percentage of patients free from major complications related to the atrial L-PM (Aveir™ AR) after three and 12 months follow-up were reported [47]. The percentage of patients free from SADE was 90.3% (95% CI 87.0-93.7) after three months follow-up, and 88.6% (95% CI 84.5-91.8) after 12 months follow-up. After three

88,6 % ohne schwere Komplikationen nach 12 Monaten

[47] **D0012** – What is the effect of dual chamber leadless pacemaker on generic health-related quality of life?

[48] **D0013** – What is the effect of dual chamber leadless pacemaker on disease-specific quality of life?

[49] **D0011** – What is the effect of dual chamber leadless pacemaker on patients' body functions?

[50] **D0016** – How does the use of the dual chamber leadless pacemaker affect activities of daily living?

[51] **D0017** – Was the use of dual chamber leadless pacemaker worthwhile?

[52] **C0008** – How safe is the dual chamber leadless pacemaker?

[53] **C0004** – How does the frequency or severity of harms change over time or in different settings?

[54] **C0005** – What are the susceptible patient groups that are more likely to be harmed through the use of the dual chamber leadless pacemaker?

[55] **C0007** – Is the dual chamber leadless pacemaker associated with user-dependent harms?

months, 91.3% (95% CI 88.1-94.5), and after 12 months 91.0% (95% CI 87.1-93.7) were free of major complications related to the Aveir™ AR L-PM [47].

All adverse events

In the Aveir DR i2i single-arm study, all non-serious AEs were reported after a follow-up up to 24 months including 452 patients. Non-serious AEs were reported in 366 patients (81%) [47].

UE nach 24 Monaten bei 81 %

All device or procedure-related adverse events

No results were reported for this outcome in the included study.

keine Ergebnisse zu Komplikationen insgesamt

Overall, no results were available from the included study whether there are patient subgroups that are more or less likely to be harmed through the use of the dual chamber L-PM. Also, no information on the influence of operator experience on procedural and safety outcomes was available.

Detailed results from the included study for dual chamber L-PM are displayed in Table A-6.

6 Certainty of evidence

Rob: Cochrane RoB 2, Ottawa Newcastle Scale und IHE

RoB for individual studies was assessed with the Cochrane RoB v.2 tool for RCTs [18] and the Ottawa Newcastle Scale for prospective cohort studies [19] and is presented in Table A-7 and Table A-8 in the Appendix. The quality of the included single-arm studies was assessed using the IHE checklist for case series [20] (see Appendix Table A-9).

RoB moderat in 1 RCT

gute Studienqualität bei Kohortenstudien, aber Einschränkungen durch Studiendesign

RoB of the single included RCT investigating single chamber L-PM VR was judged as moderate. The main reasons for the moderate RoB were some concerns regarding the selection of reported results. Since trial registration was done after study start and randomization, it is unclear, whether all reported outcomes were predefined. The seven prospective cohort studies investigating single chamber L-PM VR pacemakers, the prospective cohort study investigating single chamber L-PM AV, and the uncontrolled studies investigating the dual chamber L-PM system were adjudged to demonstrate adequate study quality in their entirety. Nonetheless, cohort studies are subject to certain inherent limitations with respect to their informative value. On the one hand, these limitations stem from an increased risk of selection bias and attrition bias. On the other hand, variables (so called confounders) that are not part of the investigated intervention may be associated with the outcome, thereby modulating the effects of the intervention and contributing to a false association. Given that cohort studies are observational, individuals are not randomly assigned to either the intervention or control group, and matching both groups by certain variables, such as sex, age, or other (especially unknown) confounders, is not always feasible [48].

Vertrauenswürdigkeit der Evidenz nach GRADE

The certainty of evidence was rated according to GRADE [21] 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 [21].

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 tables below (see Table 6-1 to Table 6-3) and in the evidence profile in Appendix Table A-10 to Table A-12.

Einkammer-L-PM: Vertrauenswürdigkeit insgesamt niedrig; Zweikammer-L-PM: Vertrauenswürdigkeit sehr niedrig

Overall, the certainty of evidence is mainly low for the effectiveness and safety of the investigated single chamber L-PM VR (Micra™ VR TPS) and the investigated single chamber L-PM AV (Micra™ AV TPS) in comparison to conventional pacemakers, The certainty of evidence for the effectiveness and safety of the only available dual chamber L-PM system (Aveir™ DR) is very low.

Table 6-1: Summary of findings table of single chamber L-PM VR compared to conventional cardiac pacemakers

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with C-PM	Risk with L-PM				
Effectiveness						
Overall mortality	see comment		-	51 (1 RCT) 17,651 (5 cohort studies)	⨁⨁◯◯ Low	Overall mortality rates were 1.1% to 31.4% with L-PM and 0.7% to 32.5% with C-PM. No statistically significant between-group difference in four studies (including one RCT), significant lower rates with L-PM in two studies. Mean follow-up six to 36 months.
Cardiac mortality	see comment		-	51 (1 RCT) 1,020 (3 cohort studies)	⨁⨁◯◯ Low	Cardiac mortality rates were generally low, with 0 to 0.5% with L-PM and 0 to 8% with C-PM. No statistically significant between-group difference in all studies. Mean follow-up six to 22 months.
Health related quality of life	see comment		-	273 (2 cohort studies)	⨁⨁◯◯ Low	HRQoL SF-36 mental and physical health subscores statistically significant better with L-PM in both studies. Statistically significant better scores with L-PM in seven of eight SF-36 domains. Three to six months follow-up
Physical function	Δ 6 min walk: -5.0 (-28.5 to 30.0) vs. 8.0 (-37.8 to 47.8), p=0.577		-	51 (1 RCT)	⨁◯◯◯ Very low	6 minutes walk distance test at 12 months post implantation.
Safety						
Serious adverse events	No results					
Serious adverse device effect (i.e. major complications)	see comment		-	51 (1 RCT) 243 (2 cohort studies)	⨁⨁◯◯ Low	No major complications with L-PM in two studies (including one RCT). Major complications in 3% with L-PM and 5.6% with C-PM. No statistically significant between-group difference in all studies. Mean follow-up six to 22 months.
Adverse device effect (i.e. overall complications)	see comment		-	17,978 (5 cohort studies)	⨁⨁◯◯ Low	**Acute overall complication rates** were 0 to 7.7% with L-PM and 0.5% to 21.4% with C-PM. No statistically significant between-group difference in three studies, significant lower rates with L-PM in two studies.
	see comment		-	18,302 (5 cohort studies)	⨁⨁◯◯ Low	**Long-term complications rates** rates were 0 to 4.9% with L-PM and 1.4% to 8.6% with C-PM. No statistically significant between-group difference in two studies, significant lower rates with L-PM in three studies. Mean follow-up 18 to 39 months.

** The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: Confidence interval; C-PM: Conventional pacemaker; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; HRQoL: Health-related quality of life; L-PM: Leadless pacemaker; RCT: Randomized controlled trial; SF-36: Short form 36 questionnaire.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table 6-2: Summary of findings table of single chamber L-PM AV compared to conventional cardiac pacemakers

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with C-PM	Risk with L-PM				
Effectiveness						
Overall mortality	238 per 1,000	340 per 1,000 (324 to 356)	HR 1.53 (1.44 to 1.62); p<0.0001	118,110 (1 cohort study)	⨁⨁◯◯ Low	24 months follow-up
Cardiac mortality	No results					
Health related quality of life	No results					
Physical function	No results					
Safety						
Serious adverse events	No results					
Serious adverse device effect (i.e. major complications)	No results					
Adverse device effect (i.e. overall complications)	110 per 1,000	87 per 1,000 (80 to 92)	RR 0.79 (0.73 to 0.84)	115,271 (1 cohort study)	⨁⨁◯◯ Low	Acute overall complications
	96 per 1,000	53 per 1,000 (48 to 60)	HR 0.54 (0.49 to 0.61)	118,110 (1 cohort study)	⨁⨁◯◯ Low	Long term overall complications; 24 months follow-up

** The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: Confidence interval; C-PM: Conventional pacemaker; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; HR: Hazard ratio; L-PM: Leadless pacemaker; RR: Risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table 6-3: Summary of findings table of dual chamber leadless pacemaker

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with C-PM	Risk with L-PM				
Effectiveness						
Overall mortality	-	13 per 1,000	-	452 (1 single-arm study)	⨁⨁◯◯ Very low	Single-arm observational studies, no control group; 12 months follow-up
Cardiac mortality	No results					
Health related quality of life	No results					
Physical function	No results					
Safety						
Serious adverse events	-	447 per 1,000	-	452 (1 single-arm study)	⨁⨁◯◯ Very low	Single-arm observational studies, no control group; 24 months follow-up
Serious adverse device effect (i.e. major complications)	-	113 per 1,000	-	300 (1 single-arm study)	⨁⨁◯◯ Very low	Single-arm observational studies, no control group; 12 months follow-up
Adverse device effect (i.e. overall complications)	No results					

** The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: CI: confidence interval; C-PM: Conventional pacemaker; L-PM: Leadless pacemaker; GRADE: Grading of Recommendations, Assessment, Development and Evaluation.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

7 Discussion

Summary of findings

1 RCT und 8 prospektive Kohortenstudien zu Einkammer-L-PMs

1 Fallserie zu Zweikammer-L-PM

The 2020 report exclusively examined the effectiveness and safety of the Micra™ VR TPS, which was the sole L-PM available on the market at the time. In this report, no comparative studies investigating L-PM versus C-PM could be included. Results up to 24 months from uncontrolled studies showed low overall mortality and device- or procedure-related mortality and complications rates in patients with successful single chamber L-PM VR implantation. Indirect comparisons resulted in statistically lower complication rates with Micra™ VR TPS to C-PM within 800 days of follow-up.

For the current 2025 report, in addition to the Micra™ VR TPS, other L-PM systems available on the market were identified. Overall, we could identify one RCT and seven prospective cohort studies comparing leadless single chamber for right ventricular pacing to C-PM. In addition, one large prospective cohort study comparing leadless single chamber for AV synchronous ventricular pacing to C-PM was included. Additionally, we included one uncontrolled case series investigating the dual chamber leadless pacemaker system Aveir™ DR in this report update. No studies were identified for leadless pacemakers implanted into the right atrium.

L-PM VR vs C-PM: kein Unterschied bei Mortalität, bessere LQ, weniger Komplikationen

For the single chamber L-PM VR, the results on effectiveness and safety in comparison to single chamber C-PM, focusing on critical outcomes can be summarized as follows:

- Results from comparative studies are only available for the Micra™ VR TPS.
- No studies were identified for the Aveir™ VR L-PM.
- Compared to C-PM, Micra™ VR TPS showed no statistically significant difference in overall mortality rates over a follow-up period of up to three years. Cardiac mortality rates were very low, again with no difference between Micra™ VR TPS and C-PM.
- Patients treated with Micra™ VR TPS seem to have a better HRQoL compared to patients treated with C-PM after three to six months.
- It appears that there has been no statistically significant difference in the physical function of patients implanted with the Micra™ VR TPS compared with those implanted with the C-PM, 12 months following their respective implantations.
- Compared to single chamber C-PM, the Micra™ VR TPS showed lower acute and long-term (up to 39 months) overall complication rates. Major complication rates were rarely reported, with no statistically significant differences observed between Micra™ VR TPS and C-PM.
- No results on SAE were reported in the included studies.

L-PM AV: höhere Mortalität, aber weniger Komplikationen;

keine Ergebnisse zu LQ

For the single chamber L-PM AV, the results on effectiveness and safety in comparison to dual chamber C-PM, focusing on critical outcomes can be summarized as follows:

- All results refer to the Micra™ AV TPS, which is currently the only market-available single chamber L-PM with AV synchronous ventricular pacing.

- Compared to C-PM, the Micra™ AV TPS showed a statistically significant higher overall mortality rate over a follow-up period of two years. Cardiac mortality rates were not reported in the included study. Although higher overall mortality rates might result from more comorbidities and differences in patient characteristics in the Micra™ AV TPS group compared to the C-PM group, adjustments for patients' baseline characteristics did not change the results.
- No results on the effectiveness outcomes HRQoL and physical function were reported in the included study.
- Compared to C-PM, the Micra™ AV TPS showed lower acute and long-term (up to two years) overall complication rates.
- No results on SAE or major complications were reported in the included study.

The observed higher overall mortality rate (HR 1.53) in patients L-PM AV despite lower complication rates appears paradoxical. The authors of the Micra CED AV study posit that patients in the Micra™ AV TPS group were considerably sicker at the time of implantation than those in the control group with conventional dual chamber pacemakers. This discrepancy could not be mitigated by statistical adjustments based on comorbidities and patient characteristics, as the analyses were based on U.S. Medicare data and the patient characteristics may not have been fully available [15]. Potential other explanations for this phenomenon might be the relevance of true atrial pacing in conventional dual chamber pacing compared to pure AV synchronization with the L-PM AV device, or the potential limitations of accelerometer-based AV synchronization in certain hemodynamic situations. These hypotheses should be specifically investigated in future (randomized) controlled trials.

Zweikammer-L-PM: geringe Sterblichkeit, aber hohe Rate an SUE

keine Ergebnisse zu LQ

For the dual chamber L-PM, the results on effectiveness and safety focusing on critical outcomes can be summarized as follows:

- All results refer to the Aveir™ DR L-PM system, which is currently the only market-available dual chamber L-PM.
- There are studies comparing dual chamber L-PM to dual chamber C-PM.
- Overall mortality rates were low with dual chamber L-PM within 12 months follow-up (13 per 1000).
- No results on the effectiveness outcomes cardiac mortality, HRQoL and physical function were reported in the included single-arm study.
- SAE were frequent in the included single-arm study (about 50% of the study participants within 12 months).
- Major complications occurred in about 10% of the study participants with a follow-up period of up to 24 months.
- No results on overall complications were reported in the included single-arm study.

Internal validity

interne Validität: Studienqualität insgesamt gut, aber nur 1 kleine RCT

große prospektive Kohortenstudien mit mehrjährigem Follow-up zu L-PM VR und L-PM AV

Although the Micra™ VR TPS is available on the market since 2015, currently only one small RCT with 51 patients and 12 months follow-up comparing the L-PM to conventional single chamber pacemakers could be identified. In addition, there is no ongoing RCT on single chamber L-PM for right ventricular pacing listed in the clinical trial registries. Therefore, the current evidence mainly relies on several prospective cohort studies investigating a total of 7,382 patients with L-PM VR and 13,069 patients with C-PM over a follow-up period of up to 39 months. For the single chamber L-PM with AV synchronous ventricular pacing no results from RCTs are currently available. The only relevant study identified is a large prospective cohort studies comparing the Micra™ AV TPS to conventional dual chamber pacemakers. The trial investigated 118,110 patients over a follow-up period of up to two years. The overall quality of these included studies for both single chamber L-PM devices is good, but possible prognostic imbalance threatens the validity of all observational studies. This leads to a certainty of evidence according to GRADE not better than low for all outcomes.

keine Studien mit Kontrollgruppe zu Zweikammer-L-PM

No comparative studies could be identified for most recently available dual chamber L-PM system, Aveir™ DR L-PM. We could only identify one single uncontrolled study investigating the dual chamber leadless pacemaker system. Therefore, in the absence of randomized or non-randomized controlled trials or at least case-control-studies, the current evidence is not adequate to assess the effectiveness or safety of dual chamber L-PMs, which leads to a certainty of evidence according to GRADE of very low for all outcomes.

External validity

externe Validität: weitgehende Übereinstimmung mit 4 anderen rezenten systematischen Reviews

For external validity, there are no limitations in terms of applicability of the study results in terms of study population, intervention or setting (see Appendix Table A-13).

There are several systematic reviews on the topic of leadless pacemakers. The systematic review of Dai et al. 2024 [49] systematically compared postoperative outcomes between L-PM and C-PM, incorporating data from 24 observational studies with a total of 78.938 patients, of whom 24.191 (30.7%) received L-PM. The results indicated that L-PM was associated with a significantly lower incidence of lead or device dislodgment (OR 3.32, 95% CI: 1.91-5.77, $p<0.01$), infective endocarditis (OR 3.62, 95% CI: 3.10-4.24, $p<0.01$), and infection (OR 3.93, 95% CI: 1.67-9.24, $p<0.01$). The incidence of pocket-related complications were higher in patients pacing with C-PM (OR 0.01, 95% CI: 1%-2%, $p<0.01$). However, L-PM implantation carried a higher risk of puncture site complications (OR 0.24, 95% CI: 0.19-0.32, $p<0.01$) and pericardial effusion or perforation (OR 0.33, 95% CI: 0.28-0.39, $p<0.01$). A limitation of this study is that most data came from retrospective studies, which may introduce many biases [49].

Oliveira et al. 2024 [50] included 21 studies (eight prospective, 13 retrospective) involving 47.229 patients, with 12.199 (25.8%) receiving L-PM. The authors found that L-PM was significantly associated with a lower risk of overall complications (OR 0.61, 95% CI 0.45-0.81; $p<0.01$), dislodgement (OR 0.34, 95% CI 0.20-0.56; $p<0.01$), and pneumothorax (OR 0.27, 95% CI 0.16-0.46; $p<0.01$) compared to traditional pacemakers. No significant differences were found in all-cause mortality (OR 1.43, 95% CI 0.65-3.15; $p=0.35$), both in unadjusted and multivariate-adjusted analyses. However, L-PM implanta-

tion was associated with a higher risk of pericardial effusion (OR 2.47, 95% CI 1.39-4.38; p<0.01) and cardiac tamponade (OR 3.75, 95% CI 2.41-5.83; p<0.01). L-PM was also associated with a lower pacing capture threshold (MD -0.19 V, 95% CI [-0.23 V]-[-0.16 V]; p<0.01), although no significant difference in impedance was observed. The studies used different L-PM devices, with Micra™ system being the most commonly used [50].

The systematic review carried out from Wu et al. 2023 [51] included eight single-arm studies involving 464 patients, all of whom received single chamber L-PM AV. The studies were predominantly prospective observational designs, and the primary safety outcome was related to major complications associated with the procedure and device algorithm. The overall incidence of complications was low (approximately 6.3%), with major complications related to the algorithm being rare, highlighting the strong safety profile of the L-PM AV device [51].

Gangannapalle et al. 2023 [52] included 17 studies, primarily retrospective cohort studies, comparing L-PM with C-PM. The results showed that L-PM was associated with a lower risk of total complications, device-related complications, pneumothorax, and infective endocarditis. The risk of re-intervention was also significantly lower in the L-PM group. However, compared to C-PM, the risk of pericardial effusion was higher in the L-PM group. While the risk of all-cause mortality was slightly lower in the L-PM group, the difference was not statistically significant (RR 0.80, 95% CI: 0.63-1.03). A notable finding was the significant heterogeneity among the study results, indicating variability in outcomes across different settings [52].

Ergebnisse aus systematischen Reviews: weniger produktbezogene Komplikationen, aber höheres Risiko für Herztamponade bei Einkammer-L-PM

In summary, the findings across these reviews suggest that L-PM is generally associated with a lower risk of device-related complications, pneumothorax, infective endocarditis, infection, and device dislodgment compared to C-PM. However, they are associated with higher risks of pericardial effusion, cardiac tamponade, and puncture site complications. No significant difference in all-cause mortality has been observed between L-PM and C-PM. The Micra™ AV device, in particular, has shown a strong safety profile with minimal major complications. While the results are promising, the studies highlight the need for further prospective, randomized trials to better understand the long-term outcomes and refine patient selection criteria.

keine verlässliche Evidenz für Zweikammer-L-PM

It is important to note that no relevant studies, such as RCTs or large observational studies, were found regarding the effectiveness and safety of the dual chamber L-PM in adult patients. This gap in the literature highlights the need for further research to evaluate the performance and safety profile of this newer device in comparison to conventional pacemakers.

Limitations of the report

Limitationen: nur Vergleichsstudien

nur publizierte Daten

This report is mainly limited to controlled studies for effectiveness and safety outcomes. Therefore, uncontrolled registries and single-arm studies were excluded. As a result, not the full body of evidence was considered, especially for the leadless single chamber pacemaker devices. In order to draw conclusions about intervention effects, it is essential that the results from intervention groups are always related to the results of a comparison group. Conventional pacemakers represent the current gold standard in the treatment of cardiac arrhythmias. Studies that lack a comparison group with conventional pacemakers are therefore not suitable for adequately assessing the effectiveness and safety of L-PM. The excluded studies would therefore not have changed the interpretation and the drawn conclusion of the report.

Only published study data were used for this report; unpublished raw data from the included trials and individual patient data were not available.

This report includes only studies published in English or German language. There is a possibility that additional studies may be available in other languages which have not been taken into account in this report.

nur Publikationen in englischer und deutscher Sprache

Ongoing studies

3 laufende RCTs zu L-PM AV

A closer review of clinical trial registries identified several ongoing studies investigating the effectiveness of leadless pacemakers in comparison to conventional pacing methods. Three RCTs are currently evaluating the effectiveness and safety of single chamber L-PMs with AV synchronous ventricular pacing: The COMPAREPACE trial (NCT06690333) compares Micra™ AV TPS to transvenous pacemakers with left bundle pacing, focusing on procedural success, freedom from complications, and heart failure outcomes at one year. The LEAVE DDD trial (NCT05498376) compares the Micra™ AV TPS to conventional DDD pacemakers, with the primary outcome being exercise capacity at three months. The DANVERS trial (NCT05856799) compares the Micra™ AV TPS to a transvenous dual chamber pacemaker, with quality of life as the primary outcome at seven months. The estimated completion date for the aforementioned RCTs ranges from August 2025 to December 2027.

For single chamber L-PMs with right ventricular pacing two ongoing comparative studies were identified. One case-control study investigates the Micra™ VR TPS in comparison to conventional dual or single chamber pacemakers, focusing on health-related quality of life (NCT05958836). Another case-control study compares the Aveir™ VR L-PM to conventional single chamber pacemakers using data from Medicare beneficiaries in the USA. Primary outcomes are acute device related complication and two-year survival rates (NCT05336877).

Furthermore, one ongoing case-control study (NCT06100770) investigates the single chamber L-PM for right atrial pacing (Aveir™ AR L-PM) and another ongoing case-control study (NCT05932602) investigates the dual chamber L-PM system (Aveir™ DR L-PM). Both studies, involving Medicare beneficiaries in the USA, assess acute device related complication and two-year survival rates.

Details on all ongoing comparative studies can be found in Appendix Table A-14.

8 Evidence-based conclusion

Schlussfolgerung

In Table 8-1 to Table 8-3 the schemes for the evidence-based conclusion concerning leadless single chamber VR pacemakers, leadless single chamber AV pacemaker, and leadless dual chamber pacemaker system are displayed and the according choice are highlighted.

Table 8-1: Evidence-based conclusion for single chamber L-PM for ventricular pacing

	1	Strong evidence for added benefit in routine use.
	2a	Evidence indicates added benefit only in specific indications.
X	2b	**Less robust evidence indicating an added benefit in routine use or in specific indications.**
	3	No evidence or inconclusive evidence available to demonstrate an additional benefit of the intervention of interest.
	4	Strong evidence indicates that intervention is ineffective and or harmful.

Table 8-2: Evidence-based conclusion for single chamber L-PM for AV synchronous ventricular pacing

	1	Strong evidence for added benefit in routine use.
	2a	Evidence indicates added benefit only in specific indications.
	2b	Less robust evidence indicating an added benefit in routine use or in specific indications.
X	3	**No evidence or inconclusive evidence available to demonstrate an additional benefit of the intervention of interest.**[1]
	4	Strong evidence indicates that intervention is ineffective and or harmful.

[1] *Current evidence remains inconclusive, though evidence indicates a lower complication rate alongside a higher overall mortality rate*

Table 8-3: Evidence-based conclusion for dual chamber L-PM

	1	Strong evidence for added benefit in routine use.
	2a	Evidence indicates added benefit only in specific indications.
	2b	Less robust evidence indicating an added benefit in routine use or in specific indications.
X	3	**No evidence or inconclusive evidence available to demonstrate an additional benefit of the intervention of interest.**[2]
	4	Strong evidence indicates that intervention is ineffective and or harmful.

[2] *No sufficient evidence available*

Reasoning:

Although no sufficient evidence from RCTs is available, several large cohort studies with long term follow-up indicate that a single chamber L-PM for right ventricular pacing[56] is equally effective and safer than the comparator of a conventional single chamber ventricular pacemaker.

L-PM VR: möglicher Zusatznutzen aber wenig robuste Evidenz

Based on the results of one large cohort study, the current evidence is inconclusive regarding the effectiveness and safety of the single chamber L-PM for AV synchronous pacing. The current evidence indicates that, L-PM AV tends to be safer but less effective than the comparator of a conventional dual chamber pacemaker. New study results will potentially influence the effect estimate considerably.

L-PM AV: Ergebnisse widersprüchlich

For dual chamber L-PM, the evidence base does not appear sufficient for a conclusive judgement of the effectiveness and safety. New study results will potentially influence the effect estimate considerably.

Zweikammer-L-PM: Evidenz unzureichend

For single chamber atrial L-PM no published study results are currently available.

Since results from three RCTs comparing single chamber L-PM for AV synchronous pacing to C-PM should be available in the end of 2027, a re-evaluation is recommended in 2028.

Re-Evaluierung 2028

[56] All of the included studies evaluated the same L-PM system, the Micra™ VR TPS. For the second L-PM system for right ventricular pacing that is currently available on the market, no studies could be identified.

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Single chamber L-PM VR: Results from RCTs

Study (acronym, ID no.), Reference	Garweg 2023 (NCT06100757) [5]
Study description	
Country	Belgium
Sponsor	Medtronic Inc.
Intervention/Product	Leadless Micra™ VR TPS (L-PM)
Comparator	Conventional VVI pacing system (Medtronic, Advisa ADSR03) with a ventricular pacing lead (Medtronic, 5076-58) in the right ventricle (C-PM)
Study design	Prospective, un-blinded, randomized, non-inferiority, single centre study
Duration of the study	May 2018 – November 2020
Randomisation method	1:1 randomisation using sealed envelope system
Blinding method (investigator, patient, outcomes assessor)	Open label
Number of patients – Intervention (n)	*Enrolled: 27* *Implantation attempt: NR* *Analyzed: 27*
Number of patients – Control (n)	*Enrolled*: 24 *Implantation attempt*: NR *Analyzed*: 24
Population	Patients with Class I or II indication for single chamber ventricular PM
Inclusion criteria	■ ≥ 18 years old ■ Class I or II indication for single chamber ventricular PM
Exclusion criteria	■ patients with previously implanted cardiac devices/mechanical valves that would interfere with the echocardiographic measurements ■ patients with inadequate image quality at baseline that prohibited the assessment of myocardial mechanics using echocardiography ■ patients with a left ventricular ejection fraction (LVEF) ≤40% at baseline ■ patients considered to have a pre-existing condition challenging/precluding the implant of a conventional pacemaker ■ patients who refused or were not able to provide written informed consent
Primary outcome (including measurement tools and measurement times)	change in LVEF and global longitudinal strain during a 12-month follow up period
Secondary outcome (including measurement tools and measurement times)	■ evolution of the right ventricular, tricuspid valve and mitral valve function ■ evolution of NT-pro-BNP (N-terminal-pro hormone B-type natriuretic peptide) levels; ■ evolution of pacemaker performance; and ■ occurrence of procedural and long-term complications
Follow-up (months)	10 days, 1, 6, and 12 months
Loss to follow-up, n (%)	NR
Population characteristics (L-PM vs C-PM)	
Age (mean), y	81.9 (4.6) vs 83.2 (4.5)
Male, n (%)	18 (66.7) vs 13 (54.2)
Pacing indication, n (%)	■ AF + severe bradycardia/SND: 13 (48.1) vs 18 (75.0), p=ns ■ SR + high degree AVB: 14 (51.9) vs 6 (25.0), p=NR

Study (acronym, ID no.), Reference	Garweg 2023 (NCT06100757) [5]
Comorbidities, n (%)	■ Previous history of AF: 16 (59.3) vs 15 (62.5), p=ns ■ Hypertension: 21 (77.8) vs 19 (79.2), p=ns ■ Diabetes mellitus: 6 (22.2) vs 5 (20.8), p=ns ■ CHA2DS2-VASc score: 3.0 (3.0–4.0) vs 4.0 (3.0–4.0), p=ns ■ CAD: 8 (29.6) vs 6 (25.0), p=ns ■ Valve disease: 8 (29.6) vs 11 (45.8), p=ns ■ Previous valve surgery: 1 (3.7) vs 0 (0), p=ns ■ COPD/fibrosis: 3 (11.1) vs 1 (4.2), p=ns ■ Oral anticoagulation: 15 (55.6) vs 17 (70.8), p=ns ■ Anti-aggregation therapy: 8 (29.6) vs 4 (16.7), p=ns ■ Renal function (eGFR, ml/min): 58.9 ± 18.8 vs 61.0 ± 13.3, p=ns
Outcomes (L-PM vs C-PM)	
Effectiveness	
Implant success rate, n/N (%)	27/27 (100) vs 24/24 (100)
Adequad pacing performance (pacing threshold ≤ 1.0 V at 0.24ms)	27/27 (100) vs 24/24 (100)
Overall mortality, n/N %	1/27 (3.7) vs 2/24 (8.3)
Cardiac mortality, n/N (%)	0/27 vs 0/24
Procedure-related mortality, n/N (%)	NR
Cardiac morbidity, n/N (%)	NR
Health related quality of life [SF-36]; mean score (SD)	NR
Physical function; mean score (SD)	***6-min walk test*** 392.5 (305.5-442.5) vs 322 (228.5-413.0) Change to baseline: 8.0 (-37.8-47.8) vs -5.0 (-28.5-30.0); p=0.577
Patient satisfaction; %	NR
Safety	
Serious adverse events, n/N (%)	NR
Overall Adverse events, n/N (%)	NR
Serious adverse events related to device or procedure (SADE = major complications), n/N (%)	*Acute major complications:* 0/27 vs 1/24 (4.2)
Overall adverse device or procedure-related effects (ADE), n/N (%)	NR
Total pericardial perforation/effusion, n/N (%)	NR
Major pericardial perforation/effusion, n/N (%)	NR
Serious infectious events (SIE), n/N (%)	NR
Major infections– device or procedure related, n/N (%)	NR
Loss of device function, n/N (%)	0/27 vs 0/24
Device dislodgement, n/N (%)	NR
Device revisions, n/N (%)	NR
Elevated pacing thresholds requiring retrieval/replacement, n/N (%)	NR
New hospitalization, n/N (%)	NR
Prolonged hospitalization, n/N (%)	0/27 vs 1/24 (4.2)

Abbreviations: ADE: Adverse device or procedure-related effects; AF: Atrial fibrillation; AVB: Atrioventricular block; C-PM: Conventional pacemaker; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; L-PM: Leadless pacemaker; LVEF: Left ventricular ejection fraction; NR: Not reported; ns: Not significant; PM: Pacemaker; SADE: Serious adverse events related to device or procedure; SD: Standard deviation; SF-36: Short form-36 health survey; SND: Sinus node dysfunction; SR: Sinus rhythm; TPS: Transcatheter pacing system.

Table A-2: Single chamber L-PM VR: Results from observational studies – part 1

Study (acronym, ID no.)	Micra CED study (NCT03039712)		
Subsample, Reference	**Follow-up: 30-days and 6-months [12]**	**Follow-up: 2-years [8]**	**Follow-up: 3-years [7]**
Study description			
Country	USA		
Sponsor	Medtronic Inc.		
Intervention/Product	Implantation of a leadless cardiac pacemaker/Micra™ VR TPS (model MC1VR01) (L-PM)		
Comparator	Implantation of a transvenous single chamber ventricular pacemaker, regardless of manufacturer (C-PM)		
Study design	Prospective cohort safety/efficacy study		
Duration of the study	March 2017 – December 2018		
Number of patients – Intervention (n)	*Enrolled*: 5746 *Implantation attempt*: NR *Analyzed*: 30 days: 5746 6 months: 3726	*Enrolled*: 6219 *Implantation attempt*: NR *Analyzed*: 6219	*Enrolled*: 6219 *Implantation attempt*: NR *Analyzed*: 6219
Number of patients – Control (n)	*Enrolled*: 9662 *Implantation attempt*: NR *Analyzed*: 30 days: 9662 6 months: 7256	*Enrolled*: 10212 *Implantation attempt*: NR *Analyzed*: 10212	*Enrolled*: 10212 *Implantation attempt*: NR *Analyzed*: 10212
Population	Patients indicated for leadless (L-PM) or transvenous VVI pacing (C-PM)		
Inclusion criteria	■ Medicare beneficiaries implanted with a leadless VVI pacemaker (CPT 0387T or 33274 or ICD-10 PCS 02HK3NZ), or ■ Medicare beneficiaries with implanted with a full system single chamber ventricular transvenous pacemaker (CPT 33207 or ICD-10 PCS 0JH605Z or 0JH604Z and 02HK3JZ). Patients with transvenous VVI pacemakers were identified with International Classification of Diseases, 10th Revision, Procedure Coding System codes for implants occurring in the inpatient hospital setting and Current Procedural Terminology codes for implants occurring in the outpatient hospital setting. Transvenous VVI patients were also limited to hospitals that implanted leadless VVI pacemakers during the study period.		
Exclusion criteria	■ Patients with <12 months of continuous enrolment in Medicare fee-for-service prior to implant and patients with a prior cardiac implantable electronic device to compare patients with de novo pacemaker implants.		
Primary outcome (including measurement tools and measurement times)	■ acute complication rate (within 30 days) ■ 6-month complication rate ■ device-related complications ■ all-cause-mortality	■ device re-interventions ■ chronic complications ■ all-cause mortality at 2 years	■ device re-interventions ■ chronic complications ■ heart failure-related hospitalizations ■ all-cause mortality at 3 years
Secondary outcome (including measurement tools and measurement times)	NR	NR	NR
Follow-up (months)	30 days, 6 months	2 years	3 years
Loss to follow-up, n (%)	0	0	0

Study (acronym, ID no.)	Micra CED study (NCT03039712)		
Subsample, Reference	**Follow-up: 30-days and 6-months [12]**	**Follow-up: 2-years [8]**	**Follow-up: 3-years [7]**
Population characteristics (L-PM vs C-PM)			
Age (mean), y	79.4 (9.5) vs 82 (8.1), p<0.001	79.5 (9.5) vs 82 (8.1), p<0.0001	
Male, n (%)	3237 (56.3) vs 5470 (56.6), p=ns	3478 (55.9) vs 5800 (56.8), p=ns	
Pacing indication, n (%)	NR	NR	
Comorbidities, n (%)	■ End-stage kidney disease: 690 (12) vs 226 (2.3), p<0.001 ■ Diabetes mellitus: 2597 (45.2) vs 3994 (41.3), p<0.001 ■ Atrial fibrillation: 4679 (81.4) vs 8609 (89.1), p<0.001 ■ Congestive heart failure: 3023 (52.6) vs 5111 (52.9), p=ns ■ COPD: 1778 (30.9) vs 2824 (29.2), p<0.02 ■ Chronic steroid use: 230 (4.0) vs 311 (3.2), p<0.01 ■ Coronary artery disease: 3215 (56.0) 5161 (53.4), p<0.002 ■ Supraventricular tachycardia: 436 (7.6) vs 513 (5.3), p<0.001 ■ Ventricular arrythmia: 895 (15.6) vs 1333 (13.8), p<0.002 ■ Hyperlipidemia: 4410 (76.8) vs 7163 (74.1), p<0.001 ■ Left bundle branch block: 302 (5.3) vs 520 (5.4), p=ns ■ Peripheral vascular disease: 1558 (27.1) vs 2583 (26.7), p=ns ■ Prior coronary artery bypass graft: 857 (14.9) vs 1380 (14.3), p=ns ■ Prior acute myocardial infarction: 1141 (19.9) vs 1589 (16.5), p<0.001 ■ Prior percutaneous coronary intervention: 903 (15.7) vs 1325 (13.7), p<0.001 ■ Kidney dysfunction: 2792 (48.6) vs 4057 (42.0), p<0.001 ■ Tricuspid valve disease: 1660 (28.9) vs 2803 (29.0), p=ns ■ Transcatheter aortic valve replacement: 101 (1.8) vs 147 (1.5), p=ns ■ Concomitant atrial ablation: 793 (13.8) vs 1069 (11.1), p<0.001 ■ Concomitant transcatheter aortic valve replacement: ■ 151 (2.6) vs 449 (4.7), p<0.001 ■ Charlson Comorbidity Index score: ■ 5.1 (3.4) vs 4.6 (3.0), p<0.001	■ End-stage kidney disease: 744 (12) vs 238 (2.3), p<0.0001 ■ Diabetes mellitus: 2805 (45.1) vs 4222 (41.3), p<0.0001 ■ Atrial fibrillation: 5066 (81.5) vs 9088 (89), p<0.001 ■ Congestive heart failure: 3282 (52.8) vs 5391 (52.8), p=ns ■ COPD: 1931 (31.1) vs 2975 (29.1), p=0.009 ■ Chronic steroid use: 246 (4) vs 327 (3.2), p=0.011 ■ Coronary artery disease: 3489 (56.1) vs 5447 (53.3), p=0.001 ■ Supraventricular tachycardia: 476 (7.7) vs 534 (5.2), p<0.0001 ■ Ventricular arrhythmia: 979 (15.7) vs 1403 (13.7), p=0.0004 ■ Hyperlipidaemia: 4770 (76.7) vs 7578 (74.2), p=0.0003 ■ Left bundle branch block: 334 (5.4) vs 543 (5.3), p=ns ■ Peripheral vascular disease: 1685 (27.1) vs 2736 (26.8), p=ns ■ Prior coronary artery bypass graft: 929 (14.9) vs 1460 (14.3), p=ns ■ Prior acute myocardial infarction: 1242 (20) vs 1680 (16.5), p<0.0001 ■ Prior percutaneous coronary intervention: 979 (15.7) vs 1416 (13.9), p=0.001 ■ Renal dysfunction: 3034 (48.8) vs 4294 (42.1), p<0.0001 ■ Tricuspid valve disease: 1795 (28.9) vs 2945 (28.8), p=ns ■ Transcatheter aortic valve replacement: 106 (1.7) vs 154 (1.5), p=ns ■ Concomitant atrial ablation: 861 (13.8) vs 1125 (11), p<0.0001 ■ Concomitant transcatheter aortic valve replacement: 170 (2.7) vs 474 (4.6), p<0.0001 ■ Charlson comorbidity index: 5.1 (3.4) vs 4.6 (3.0), p<0.0001	
Outcomes (L-PM vs C-PM)			
Effectiveness			
Implant success rate, n/N (%)	NR	NR	NR
Adequate pacing performance (pacing threshold ≤ 1.0 V at 0.24ms)	NR	NR	NR

Study (acronym, ID no.)	Micra CED study (NCT03039712)		
Subsample, Reference	**Follow-up: 30-days and 6-months [12]**	**Follow-up: 2-years [8]**	**Follow-up: 3-years [7]**
Overall mortality, n/N (%)	*30 days:* 3.9% vs 4.1%; adjusted RD -0.2% (-0.8 to 0.5, 95% CI), p=ns *6 months*: adjusted HR 1.0 (0.89 to 1.12, 95% CI), p=ns	31.4% vs. 32.5%; HR 0.97 (0.91 to 1.04, 95% CI), p=ns	HR 0.97 (0.92 to 1.03, 95% CI), p=ns
Cardiac mortality, n/N (%)	NR	NR	NR
Procedure-related mortality, n/N (%)	NR	NR	NR
Cardiac morbidity, n/N (%)	NR	NR	NR
Health related quality of life [SF-36]; mean score (SD)	NR	NR	NR
Physical function; mean score (SD)	NR	NR	NR
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 device or procedure (SADE = major complications), n/N (%)	NR	NR	NR
Overall adverse device or procedure-related effects (ADE), n/N (%)	***Device or procedure-related complications:*** **30-days – adjusted rates:** 7.7% vs 7.4%; RD 0.3% (-0.6 to 1.3, 95% CI), p=ns **6 months – adjusted rates:** **weighted CIF estimates (95% CI):** 3.2% (2.9 to 3.6) vs 4.1% (3.8 to 4.6) RRR (95% CI): 23% (4 to 38), p=NR HR 0.77 (0.62 to 0.96, 95% CI), p=0.02 ***Device-related complications:*** **30-days – adjusted rates:** 1.4% vs 2.5%; RD -1.1% (-1.5 to -0.6, 95% CI), p<0.001[1] **6 months – adjusted rates:** **weighted CIF estimates (95% CI):** 1.7% (1.5 to 1.9) vs 3.3% (3.0 to 3.7) RRR (95% CI): 49% (33 to 61), p=NR[1]	***Device or procedure-related complications:*** 285/6219 (4.6) vs 631/10212 (6.2) **weighted CIF estimates (95% CI):** 4.6% (4.2 to 4.9) vs 6.5% (6.1 to 6.9) RRR (95% CI): 31% (19 to 40), p<0.0001 HR 0.69 (0.60 to 0.81, 95% CI), p<0.0001 ***Device-related complications:*** 155/6219 (2.5) vs 500/10212 (4.9) **weighted CIF estimates (95% CI):** 2.4% (2.2 to 2.5) vs 4.8% (4.7 to 5) RRR (95% CI): 52% (42 to 60), p<0.0001	***Device or procedure-related complications:*** 310/6219 (5) vs 699/10212 (6.8) **weighted CIF estimates (95% CI):** 4.9% (4.6 to 5.2) vs 7.1% (6.7 to 7.6) RRR (95% CI): 32% (22 to 41), p<0.0001 HR 0.68 (0.59 to 0.78, 95% CI), p<0.0001 ***Device-related complications:*** 172/6219 (2.8) vs 538/10212 (5.3) **weighted CIF estimates (95% CI):** 2.6% (2.5 to 2.7) vs 5.2% (5.1 to 5.3) RRR (95% CI): 51% (41 to 59), p<0.0001
Total pericardial perforation/effusion, n/N (%)	**30 days – adjusted rates:** 0.8% vs 0.4%; RD 0.4% (0.1 to 0.7, 95% CI), p=0.004	NR	NR

Study (acronym, ID no.)	Micra CED study (NCT03039712)		
Subsample, Reference	**Follow-up: 30-days and 6-months [12]**	**Follow-up: 2-years [8]**	**Follow-up: 3-years [7]**
Major pericardial perforation/effusion, n/N (%)	NR	NR	NR
Serious infectious events (SIE), n/N (%)	***Pericarditis:*** 0.8% vs 0.3%; RD 0.6% (0.3 to 0.9), p<0.001	NR	NR
Major infections–device or procedure related, n/N (%)	NR	NR	NR
Loss of device function, n/N (%)	NR	NR	91/6219 (1.5) vs 218/10212 (2.1) **weighted CIF estimates (95% CI):** 1.5% (1.4 to 1.8) vs 2.4 (2.1 to 2.7) RRR (95% CI): 34% (14 to 50), p=0.002
Device dislodgement, n/N (%)	NR	NR	24/6219 (0.4) vs 128/10212 (1.3) **weighted CIF estimates (95% CI):** 0.4% (0.3 to 0.5) vs 1.3% (1.2 to 1.6) RRR (95% CI): 71% (53 to 82), p<0.0001
Elevated pacing thresholds requiring retrieval/replacement, n/N (%)	NR	NR	NR
Device revisions, n/N (%)	*6-months revision:* HR 0.63 (0.36 to 1.12, 95% CI), p=ns	*Any re-intervention:* 169/6219 (2.7) vs 494/10212 (4.4) **2-year weighted CIF estimates (95% CI):** 3.1% (2.8 to 3.4) vs 4.9% (4.5 to 5.4) RRR (95% CI): 38% (15-55), p=0.003 *System re-interventions:* ***Revisions:*** 1-10/6219 vs 56/10212 (0.6) **2-year weighted CIF estimates (95% CI):** 1-10 vs 0.6% (0.4 to 0.8) RRR (95% CI): 80% (50 to 92), p=0.001 ***Replacement:*** 68/6219 (1.1) vs 44/10212 (0.4) **2-year weighted CIF estimates (95% CI):** 1.1% (0.9 to 1.3) vs 0.4% (0.3 to 0.6) RRR (95% CI): -150% (-346 to 40), p=0.002 ***System switch (replacement with opposite type of device):*** 18/6219 (0.3) vs 26/10212 (0.3) **2-year weighted CIF estimates (95% CI):** 0.4% (0.2 to 0.5) vs 0.3% (0.2 to 0.4) RRR (95% CI): to 28% (-150 to 34), p=ns	*Any re-intervention:* 199/6219 (3.2) vs 548/10212 (5.4) **3-year weighted CIF estimates (95% CI):** 3.6% (3.2 to 3.9) vs 6% (5.5 to 6.5) RRR (95% CI): 41% (22 to 56), p=0.0002 *System re-interventions*: Revisions: 11/6219 (0.2) vs 59/10212 (0.6) **3-year weighted CIF estimated (95% CI):** 0.2% (0.1 to 0.3) vs 0.6% (0.5 to 0.8) RRR (95% CI): 70% (40 to 85), p=0.0007 ***Replacement:*** 74/6219 (1.2) vs 53/10212 (0.5) **3-year weighted CIF estimates (95% CI):** 1.2% (1.0 to 1.5) vs 0.5% (0.4 to 0.7) RRR (95% CI): -124% (-290 to -28), p=0.005 ***System switch (replacement with opposite type of device):*** 24/6219 (0.4) vs 31/10212 (0.3) **3-year weighted CIF estimates (95% CI):** 0.5% (0.4 to 0.7) vs 0.4% (0.3 to 0.5) RRR (95% CI): -36% (-145 to 25), p=ns

Study (acronym, ID no.)	Micra CED study (NCT03039712)		
Subsample, Reference	**Follow-up: 30-days and 6-months [12]**	**Follow-up: 2-years [8]**	**Follow-up: 3-years [7]**
Device revisions, n/N (%) *(continuation)*		***Removal:*** 1-10 vs 75/10212 (0.7) **2-year weighted CIF estimates (95% CI):** 1-10 vs 0.8% (0.6 to 1.0) RRR (95% CI): 95% (80 to 99), p<0.0001	***Removal:*** 1-10 vs 88/10212 (0.9) **3-year weighted CIF estimates (95% CI):** 1-10 vs 1.0% (0.8 to 1.2) RRR (95% CI): 98% (83 to 100), p=0.0002
New hospitalization, n/N (%)	NR	NR	*Heart-failure hospitalizations*: 19.9% vs 22%; HR 0.90 (0.83 to 0.97, 95% CI), p=0.005[2] 11.2% vs 13.6%; HR 0.81 (0.71 to 0,93, 95% CI), p=0.003[3] HR 0.91 (0.84 to 0.99, 95% CI), p=0.02[4]
Prolonged hospitalization, n/N (%)	NR	NR	NR

Abbreviations: ADE: Adverse device or procedure-related effects; CED: Coverage with Evidence Development; CI: Confidence interval; CIF: Cumulative incidence function; COPD: Chronic obstructive pulmonary disease; C-PM: Conventional pacemaker; CPT: Current Procedural Terminology; HR: Hazard ratio; ICD: International Classification of Diseases; L-PM: Leadless pacemaker; NR: Not reported; ns: Not significant; RD: Risk difference; RRR: Relative risk reduction; SADE: Serious adverse events related to device or procedure; SD: Standard deviation; SF-36: Short form-36 health survey; SIE: Serious infectious events; TPS: Transcatheter pacing system.

Comments:

[1] *device related complication includes complications related to the mechanical integrity of the device or codes explicitly stating device relatedness (e.g. device dislodgement, device infection, device pocket complication)*

[2] *Overall patient cohort*

[3] *Patients without prior history of heart failure*

[4] *Patients with atrial fibrillation*

Table A-3: Single chamber L-PM VR: Results from observational studies – part 2

Study (acronym, ID no.), Reference	Palmisano 2021 [11]	Bertelli 2022 [6]	Zucchelli 2021 [14]
Study description			
Country	Italy	Italy	Italy
Sponsor	None	None	NR
Intervention/Product	Leadless Micra™ VR TPS	Leadless Micra™ VR TPS	Leadless Micra™ VR TPS
Comparator	Conventional transvenous pacemaker	Conventional transvenous single chamber ventricular pacemaker, regardless of manufacturer	Implantation of a transvenous single chamber ventricular pacemaker, regardless of manufacturer
Study design	Prospective, single-centre, propensity-matched cohort study	Prospective multicentre cohort safety/efficacy study	Prospective single centre cohort safety/efficacy study
Duration of the study	February 2016 – May 2020	June 2015 – May 2021	May 2014 – April 2019
Number of patients – Intervention (n)	*Enrolled*: 93 *Implantation attempt*: 93 *Analyzed*: 91 Propensity Score Matched: 77	*Enrolled*: 72 *Implantation attempt*: NR *Analyzed*: 72	*Enrolled: 100* *Implantation attempt: 100* *Analyzed: 100*
Number of patients – Control (n)	*Enrolled*: 152 *Implantation attempt*: NR *Analyzed*: 152 Propensity Score Matched: 77	*Enrolled*: 272 *Implantation attempt*: NR *Analyzed*: 272	*Enrolled*: 100 *Implantation attempt*: 100 *Analyzed*: 100
Population	Patients undergoing single chamber PM implantation (L-PM or C-PM)	Patients indicated for leadless (L-PM) or transvenous VVI pacing (C-PM)	Patients indicated for leadless (L-PM) or transvenous VVI pacing (C-PM)
Inclusion criteria	■ Patients who met class I or II guideline recommendations for de novo ventricular pacing ■ L-PM was preferentially implanted in patients aged >65 years with a reasonable expectation of survival with good functional status >1 year, in patients at high risk of infection, and in patients with difficult or unavailable venous access for C-PM implantation	■ Indications for VVIR pacing included "slow conducted" AF, atrio-ventricular block with comorbid AF (either permanent or accepted as "destination rhythm") or, in a minority of cases, with sinus rhythm in bedridden cognitively impaired patients.	■ Previously undergone transvenous lead extraction ■ High risk of infection, superior venous access issues and patient and operator's preference
Exclusion criteria	■ Patients underwent L-PM implantation after the extraction of a conventional PM, and those underwent T-PM implantation after an unsuccessful attempt to implant an L-PM	NR	■ Age < 18 years, hemodynamic instability, mechanical tricuspid valve prosthesis or inferior vena cava filter, morbid obesity that could impair remote Micra control, femoral venous occlusion, allergy to Micra™ TPS components, < 12 months life expectancy and risk of interference with any other electronic device

Study (acronym, ID no.), Reference	Palmisano 2021 [11]	Bertelli 2022 [6]	Zucchelli 2021 [14]
Primary outcome (including measurement tools and measurement times)	■ intra- and post-procedural data of duration of the procedure ■ final position of C-PM or L-PM ■ electrical parameters ■ intra- and postprocedural complications ■ number of patients requiring analgesic drugs in post-operative period ■ total duration of hospitalization ■ QoL ■ Patient Acceptance	■ periprocedural and long-term complications	■ long-term clinical outcomes and electrical performance
Secondary outcome (including measurement tools and measurement times)	NR	NR	NR
Follow-up (months)	1 week, 3-, 6 months	22.8 (2.6) vs 23.7 (1.1), p=ns	17.33 (17.98) vs 19.01 (17.8) months, p=ns
Loss to follow-up, n (%)	0 vs 0	0	0
Population characteristics (L-PM vs C-PM)			
Age (mean), y	77.5 (8.2) vs 78.3 (5.9), p=ns	79.5 (2.5) vs 85.0 (1.0), p<0.01	77.46 (9.58) vs 78.78 (9.78), p=ns
Male, n (%)	55 (71.4) vs 49 (63.6), p=ns	46 (64) vs 161 (59), p=ns	77 (77) vs 67 (67), p=ns
Pacing indication, n (%)	*Propensity Score Matched:* ■ Sinus node disease: 2 (2.6) 1 (1.3), p=ns ■ SR with AVB: 9 (11.7) vs 11 (14.3), p=ns ■ SR with paroxysmal II or III degree AVB: 9 (11.7) vs 11 (14.3), p=ns ■ SR with persistent II or III degree AVB: 0 vs 0 ■ Unexplained syncope and chronic bifascicular block: 4 (5.2) vs 5 (6.5), p=ns ■ Bradycardia associated to permanent atrial tachyarrhythmia: 62 (80.5) vs 60 (77.9), p=ns ■ Neuromediated syncope: 0 vs 0	NR	■ Bradycardia with persistent or permanent atrial tachyarrhythmia: 45 (45) vs 80 (80), p<0.0001 ■ Atrioventricular block: 30 (30) vs 15 (15), p=0.018 ■ Sinus-node dysfunction: 19 (19) vs 3(3), p<0.001 ■ Syncope with bi-fascicular bundle branch block: 3 (3) vs 2 (2), p=ns ■ Carotid sinus syndrome: 2 (2) vs 0, p=ns ■ Syncope with suspected bradycardia but no definite diagnosis: 1 (1) vs 0, p=ns
Comorbidities, n (%)	*Propensity Score Matched:* ■ Hypertension on therapy: 58 (75.3) vs 64 (83.1), p=ns ■ Diabetes mellitus: 19 (24.7) vs 20 (26), p=ns ■ Dyslipidaemia: 19 (24.7) vs 27 (35.1), p=ns ■ Chronic renal failure: 13 (16.9) vs 21 (27.3), p=ns ■ Pre-dialysis chronic renal failure: 14 (16.9) vs 21 (27.3), p=ns ■ Chronic dialysis: 0 vs 0	■ Diabetes mellitus: 19 (26.4) vs 49 (18), p<0.01 ■ Hypertension: 51 (70.8) vs 212 (77.9), p=ns ■ Ejection fraction, median: 57% (3) vs 59% (2), p=ns ■ Permanent atrial fibrillation: 58 (80.6) vs 262 (96.3), p<0.01 ■ Ischaemic heart disease: 14 (19.4) vs 83 (30.5), p=ns	■ Coronary artery disease: 22 (22) vs 17 (17), p=ns ■ Hypertension: 72 (72) vs 64 (64), p=ns ■ Diabetes mellitus: 22 (22) vs 23 (23), p=ns ■ Renal impairment: 17 (17 vs 16 (16), p=ns ■ Obstructive pulmonary disease: 15 (15) vs 22 (22), p=ns

Study (acronym, ID no.), Reference	Palmisano 2021 [11]	Bertelli 2022 [6]	Zucchelli 2021 [14]
Comorbidities, n (%) *(continuation)*	■ Previous TIA/stroke: 3 (3.9) vs 6 (7.8), p=ns ■ COPD: 8 (10.4) 14 vs (18.2), p=ns ■ Atrial fibrillation: 60 (77.9) vs 58 (75.3), p=ns ■ Persistent/paroxysmal: 3 (3.9) vs 2 (2.6), p=ns ■ Permanent: 57 (74.0) vs 56 (72.7), p=ns ■ CAD: 16 (20.8) vs 23 (29.9), p=ns ■ Valvulopathy: 10 (13) vs 11 (14.3), p=ns Heart failure: 7 (9.1) vs 12 (15.6), p=ns	■ Previous CIED extraction: 7 (9.7) vs 272 (0.7), p<0.01 ■ Surgical or percutaneous treatment of valvular disease: 20 (27.8) vs 82 (30.1), p=ns ■ Chronic kidney disease (GFR < 60 mL/min): 26 (36.1) vs 157 (57.7), p<0.01 ■ Chronic haemodialysis: 5 (6.9) vs 2 (0.7), p<0.01 ■ Bedridden/cognitive impairment: 0 vs 3 (1.1), p=ns	
Outcomes (L-PM vs C-PM)			
Effectiveness			
Implant success rate, n/N (%)	91/93 (97.8) vs 152/152 (100)	NR	100/100 (100) vs 100/100 (100)
Adequate pacing performance (pacing threshold ≤ 1.0 V at 0.24ms)	0.5 (0.2) vs 0.4 (0.2)	70/72 (97.2) vs 253/262 (96.6)[2]	*High pacing threshold (1-1.5 V/0.24 ms):*7 (7) vs NR *Very high pacing threshold (1.5-2 V/0.24 ms)*: 2 (2) vs NR *Mean pacing threshold:* 0.51 (0.32) vs 0.54 (0.2), p=ns
Overall mortality, n/N %	*General population*: 1/91 (1.1) vs 1/152 (0.7)	Kaplan-Meier estimates [95% CI]: ~24.7% (55.6% vs 30.9%), p=0.03 [3] HR 0.93 (0.42 to 2.04, 95% CI), p=0.85	7/100 (7) vs 23/100 (23), p=0.003
Cardiac mortality, n/N (%)	0/91 vs 0/152	Kaplan-Meier estimates [95% CI]: ~18% (98.1% vs 80.1%), p=0.04 [3]	0 vs 8/100 (8); p=NR
Procedure-related mortality, n/N (%)	NR	NR	0/100 (0) vs 1/100 (1), p=ns
Cardiac morbidity, n/N (%)	NR	NR	NR
Health related quality of life [SF-36]; mean score (SD)	*Propensity Score Matched:* ■ Physical Functioning: Baseline: 57.0 ± 11.0 vs 59.7 ± 14.0, p=ns 1 week: 63.3 ± 7.6 vs 57.2 ± 10.5, p<0.001 3 months: 63.1 ± 9.5 vs 59.6 ± 9.8, p=0.026 6 months: 62.8 ± 9.3 vs 59.4 ± 10.5, p=0.035 ■ Social Function: Baseline: 66.0 ± 11.2 vs 64.2 ± 14.6, p=ns 1 week: 64.7 ± 14.4 vs 54.2 ± 14.6, p<0.001 3 months: 65.4 ± 11.9 vs 58.9 ± 12.4, p=0.001 6 months: 73.3 ± 11.2 vs 60.8 ± 10.2, p<0.001	NR	NR

Study (acronym, ID no.), Reference	Palmisano 2021 [11]	Bertelli 2022 [6]	Zucchelli 2021 [14]
Health related quality of life [SF-36]; mean score (SD) *(continuation)*	■ Role Physical: Baseline: 40.0 ± 16.3 vs 38.9 ± 14.3, p=ns 1 week: 55.6 ± 10.9 vs 38.9 ± 12.1, p<0.001 3 months: 58.9 ± 9.8 vs 50.3 ± 10.1, p<0.001 6 months: 57.8 ± 9.2 vs 52.1 ± 12.3, p<0.001 ■ Role Emotional: Baseline: 59.9 ± 8.9 vs 61.5 ± 8.2, p=ns 1 week: 59.7 ± 5.8 vs 48.5 ± 8.2, p<0.001 3 months: 64.4 ± 9.6 vs 55.4 ± 9.9, p<0.001 6 months: 64.7 ± 10.1 vs 58.4 ± 9.8, p<0.001 ■ Mental Health: BL: 68.7 ± 9.6 vs 70.9 ± 14.8, p=ns 1 week: 73.6 ± 12.5 vs 70.0 ± 14.1, p=ns 3 months: 75.8 ± 9.2 vs 71.1 ± 9.6, p=0.002 6 months: 75.9 ± 10.9 vs 71.2 ± 9.7, p=0.005 ■ Bodily Pain: Baseline: 58.2 ± 6.4 vs 59.3 ± 7.7, p=ns 1 week: 47.2 ± 7.5 vs 42.5 ± 6.1, p<0.001 3 months: 55.4 ± 7.7 vs 55.3 ± 8.5, p=ns 6 months: 54.6 ± 7.8 vs 53.4 ± 9.8, p=ns ■ Vitality: Baseline: 36.3 ± 4.5 35.7 ± 9.7, p=ns 1 week: 42.7 ± 8.4 vs 34.7 ± 9.7, p<0.001 3 months: 47.7 ± 12.0 vs 45.3 ± 11.1, p=ns 6 months: 49.8 ± 7.8 vs 46.2 ± 9.9, p=0.013 ■ General Health: Baseline: 43.6 ± 5.5 vs 42.5 ± 6.9, p=ns 1 week: 48.3 ± 7.6 vs 43.3 ± 7.5, p<0.001 3 months: 55.5 ± 8.8 vs 46.8 ± 8.9, p<0.001 6 months: 56.1 ± 8.9 vs 48.7 ± 7.8, p<0.001 ■ Physical Component Scale: Baseline: 36.1 ± 9.3 36.4 ± 11.0, p=ns 1 week: 39.0 ± 7.5 vs 33.1 ± 8.0, p<0.001 3 months: 42.3 ± 3.6 vs 38.5 ± 5.6, p<0.001 6 months: 42.0 ± 3.6 vs 38.8 ± 4.5, p<0.001 ■ Mental Component Scale: Baseline: 45.6 ± 14.8 vs 46.0 ± 15.1, p=ns 1 week: 46.3 ± 11.6 vs 41.3 ± 12.0, p=0.009 3 months: 47.8 ± 11.1 vs 42.8 ± 12.2, p=0.008 6 months: 49.2 ± 12.3 vs 43.4 ± 13.6, p=0.006		
Physical function; mean score (SD)	NR	NR	NR
Patient satisfaction; %	NR	NR	NR

Study (acronym, ID no.), Reference	Palmisano 2021 [11]	Bertelli 2022 [6]	Zucchelli 2021 [14]
Safety			
Serious adverse events, n/N (%)	NR	NR	NR
Overall Adverse events, n/N (%)	NR	NR	NR
Serious adverse events related to device or procedure (SADE = mayor complications), n/N (%)	0/91 vs 2/152 (1.3)[1]	NR	NR
Overall adverse device or procedure-related effects (ADE), n/N (%)	NR	*Acute complications*: 5.6% vs 5.1%, p=ns *Long-term complications*: 0/72 vs 5/272 (1.9), p=0.25	0/100 vs 10/100 (10), p=0.004 *Acute complications*[1]: 0/100 vs 7/100 (7), p=0.02 *Long-term complications*[2]: 0/100 vs 3/100 (3), p=0.24
Total pericardial perforation/effusion, n/N (%)	NR	NR	NR
Major pericardial perforation/effusion, n/N (%)	NR	NR	NR
Serious infectious events (SIE), n/N (%)	NR	NR	NR
Major infections– device or procedure related, n/N (%)	NR	*Superficial suture infection*: 0/72 vs 3/272 (1.1), p=ns *Infection requiring surgical revision*: 0/72 vs 2/272 (0.8), p=ns	NR
Loss of device function, n/N (%)	NR	NR	NR
Device dislodgement, n/N (%)	NR	NR	0/100 vs 3/100 (3), p=ns
Device revisions, n/N (%)	NR	NR	NR
Elevated pacing thresholds requiring retrieval/replacement, n/N (%)	NR	*Repositioning*: 0/72 vs 5/272 (1.9), p=ns *Lead addition*: 0/72 vs 1/272 (0.4), p=ns	*Overall device revisions*: 0/100 vs 6/100 (6), p=0.038
New hospitalization, n/N (%)	NR	NR	NR
Prolonged hospitalization, n/N (%)	0/91 vs 2/152 (1.3)	NR	NR

Abbreviations: ADE: Adverse device or procedure-related effects; AF: Atrial fibrillation; AVB: Atrioventricular block; CAD: Coronary artery disease; CI: Confidence Interval; CIED: Cardiac implantable electronic devices; COPD: Chronic obstructive pulmonary disease; C-PM: Conventional pacemaker; HR: Hazard ratio; L-PM: Leadless pacemaker; NR: Not reported; ns: Not significant; SADE: Serious adverse events related to device or procedure; SD: Standard deviation; SF-36: Short form-36 health survey; SIE: Serious infectious events; SR: Sinus rhythm; TPS: Transcatheter pacing system.

Comments:

[1] *Pocket hematoma*

[2] *Mean capture threshold increase > 1V at follow-up*

[3] *The difference in survival rates was calculated based on Kaplan-Meier estimates derived from own calculations, using data from Figure 2 in the cited publication [6]*

Table A-4: Single chamber L-PM VR: Results from observational studies – part 3

Study (acronym, ID no.), Reference	Martinez-Sande 2021 [9]	Palmisano 2023 [10]	Yu 2023 [13]
Study description			
Country	Spain	Italy	China
Sponsor	NR	NR	National Key Research and Development Program of China (2017YFC 0908800) Beijing Municipal Administration of Hospitals' Mission Plan (SML20180601)
Intervention/Product	Leadless Micra™ VR TPS	Leadless Micra™ VR TPS	Leadless pacemaker
Comparator	Conventional single chamber pacemaker	Conventional transvenous-permanent single- or dual chamber pacemaker	Conventional single- or dual chamber pacemaker
Study design	Prospective, observational, single-center study	Prospective, multicentre, observational study	Single-centre observational study
Duration of the study	June 2015 – December 2019	May 2016 – December 2019	January 2020 – March 2022
Number of patients – Intervention (n)	*Enrolled*: 198 *Implantation attempt*: NR *Analyzed*: 198	*Enrolled*: 665 *Implantation attempt*: NR *Analyzed*: 665 *Propensity score matched:* 442	*Enrolled*: 35 *Implantation attempt*: NR *Analyzed*: 35
Number of patients – Control (n)	*Enrolled*: 245 *Implantation attempt*: NR *Analyzed*: 245	*Enrolled*: 2004 *Implantation attempt*: NR *Analyzed*: 2004 *Propensity score matched:* 442	*Enrolled*: 84 *Implantation attempt*: NR *Analyzed*: 84
Population	Patients with an indication for a single chamber pacemaker implant	Patients undergoing de novo PM implantation at participating centres	Patients who received pacemaker implantation at the 12th ward of Beijing Anzhen Hospital
Inclusion criteria	■ Patients with an indication for a single chamber pacemaker implant, according to the current guidelines	■ Class I or II guideline recommendations for permanent pacing	■ Indication of pacemaker implantation ■ No cognitive disorder, and signed informed consent to complete the SF-36 quality of life questionnaire
Exclusion criteria	NR	■ Patients receiving a biventricular PM were excluded	■ Surgical intervention or invasive treatment 3 months before the pacemaker implantation ■ Other indications for surgical intervention at the time of pacemaker implantation
Primary outcome (including measurement tools and measurement times)	■ clinical characteristics ■ electrical performance ■ device-related complications	■ device-related complications	■ QoL
Secondary outcome (including measurement tools and measurement times)	NR	NR	■ discomfort in surgical area (chest/groin) ■ restricted in daily activities by discomfort in the region of the intervention

Study (acronym, ID no.), Reference	Martinez-Sande 2021 [9]	Palmisano 2023 [10]	Yu 2023 [13]
Secondary outcome (including measurement tools and measurement times) *(continuation)*			■ concerned about heart condition and general health since pacemaker implantation ■ depressed since pacemaker implantation
Follow-up (months)	mean: 22.3 (15.9) months	mean: 39 months	1, 3 months
Loss to follow-up, n (%)	NR	NR	NR
Population characteristics (L-PM vs C-PM)			
Age (mean), y	83.6 (NR) vs 79.2 (NR), p<0.00001	73.9 (13.8) vs 72.5 (13.3), p = 0.013	76.17 (7.92) vs 67.92 (9.49), p<0.001
Male, n (%)	67 (27.3) vs 123 (62.1), p<0.00001	462 (69.5) vs 1224 (61.1), p<0.001	23 (65.7) vs 51 (60.7), p=ns
Pacing indication, n (%)	■ Atrial fibrillation: 388 (87.6) ■ Slow ventricular response: 253 (57.2) ■ Atrioventricular block: 101 (22.8) ■ Fast ventricular response: 34 (7.7) ■ Left atrial flutter: 15 (3.4)	■ NR	■ Atrial fibrillation: 20 (57.1) vs 34 (40.5), p=ns ■ Others: 15 (42.9) vs 50 (59.5), p=ns
Comorbidities, n (%)	■ Hypertension: 155 (63.3) vs 160 (80.8), p<0.00001 ■ Diabetes mellitus: 63 (25.7) vs 69 (34.8), p=ns ■ COPD: 33 (13.5) vs 34 (17.1), p=ns ■ Renal disease: (35.1) vs 36 (18.2), p=0.00007 ■ Cardiomyopathy: 68 (27.7) vs 95 (48) p=0.00001 ■ Ischemic cardiopathy: 39 (15.9) vs 43 (21.7), p=ns ■ Heart failure: 67 (27.3) vs 46 (23.2), p=ns ■ LVEF: 56.9 (8.6) vs 59.8 (7.9), p=0.000262 ■ Peripheral arteriopathy: 16 (6.5) vs 12 (6.1), p=ns ■ Valvular disease: 80 (32.6) vs 87 (43.9), p=0.0148	■ Hypertension on therapy: 496 (74.7) vs 1252 (62.5), p<0.001 ■ Diabetes mellitus: 163 (24.4) vs 413 (20.6), p=ns ■ Left bundle-branch block: 43 (6.4) vs 116 (5.8), p=ns ■ Congestive heart failure: 119 (17.9) vs 292 (14.6), p=ns ■ Ischemic cardiopathy: 56 (8.4) vs 40 (2.0), p<0.001 ■ Atrial fibrillation: 445 (67.0) vs 870 (43.4), p<0.001 ■ History of TIA/stroke: 62 (9.5) vs 156 (7.8), p=ns ■ Renal dysfunction: 133 (20.4) vs 233 (11.7), p<0.001 ■ COPD: 115 (17.4) vs 168 (8.4), p<0.001 ■ Oral anticoagulant therapy: 416 (62.6) vs 754 (37.6), p<0.001 ■ Oral antiplatelet drug therapy: 151 (22.7) vs 683 (34.1), p<0.001	■ Hypertension: 21 (60) vs 58 (69), p=ns ■ Diabetes mellitus: 13 (37.1) vs 34 (40.5), p=ns ■ Structural heart disease: 6 (17.1) vs 29 (34.5), p=ns ■ Renal insufficiency: 7 (20) vs 10 (11.9), p=ns ■ Coronary heart disease: 9 (25.7) vs 22 (26.2), p=ns ■ Heart failure class III or IV: 4 (11.4) vs 7 (8.3), p=ns ■ Cerebrovascular disease: 6 (17.1) vs 10 (11.9), p=ns ■ Oral anticoagulant therapy: 21 (60.0) vs 30 (35.7), p=0.015 ■ Oral antiplatelet drug therapy: 11 (31.4) vs 25 (29.8), p=ns ■ Atrial fibrillation: 20 (57.1) vs 34 (40.5), p=ns ■ Others: 15 (42.9) vs 50 (59.5), p=ns
Outcomes (L-PM vs C-PM)			
Effectiveness			
Implant success rate, n/N (%)	NR	NR	NR
Adequate pacing performance (pacing threshold ≤ 1.0 V at 0.24ms)	NR	*1-year follow-up:* 612/665 (92) vs 1826/2004 (91.1), p=ns	NR
Overall mortality, n/N (%)	18/198 (9.1) vs 44/245 (17.9), p=0.0075	NR	NR
Cardiac mortality, n/N (%)	1/198 (0.5) vs 2/245 (0.8), p=ns	NR	NR

Study (acronym, ID no.), Reference	Martinez-Sande 2021 [9]	Palmisano 2023 [10]	Yu 2023 [13]
Procedure-related mortality, n/N (%)	NR	NR	NR
Cardiac morbidity, n/N (%)	NR	NR	NR
Health related quality of life [SF-36]; mean score (SD)	NR	NR	*1 month follow up:* Physical function: 56.51 ± 13.03 vs 42.9 ± 8.33, p<0.001 Role physical: 52.63 ± 14.61 vs 24.80 ± 8.33, p<0.001 Bodily pain: 59.91 ± 12.01 vs 54.50 ± 13.47, p=0.042 General health: 55.11 ± 10.97 vs 45.48 ± 7.91, p<0.001 Vitality: 54.26 ± 13.00 vs 45.29 ± 8.73 p<0.001 Social function: 74.20 ± 14.65 vs 69.42 ± 11.20, p=0.055 Role emotional: 71.06 ± 11.20 vs 62.15 ± 9.18, p<0.001 Mental health: 70.97 ± 10.75 vs 67.57 ± 9.61, p=0.092 Physical component: 56.05 ± 10.15 vs 41.92 ± 5.87, p<0.001 Mental component summary: 67.62 ± 9.45 vs 61.12 ± 6.72, p<0.001 *3 month follow up:* Physical function: 63.63 ± 9.97 vs 47.50 ± 7.94, p<0.001 Role physical: 60.20 ± 10.73 vs 40.23 ± 9.43, p<0.001 Bodily pain: 65.57 ± 9.52 vs 61.69 ± 9.35, p=0.042 General health: 55.60 ± 12.56 vs 52.37 ± 9.13, p=0.175 Vitality: 56.26 ± 10.84 vs 49.57 ± 9.17, p<0.001 Social function: 80.14 ± 10.83 vs 74.70 ± 8.64, p=0.004 Role emotional: 76.14 ± 10.28 vs 71.42 ± 6.34, p=0.015 Mental health: 75.46 ± 10.27 vs 68.18 ± 9.99, p<0.001 Physical component: 61.25 ± 8.17 vs 50.57 ± 5.98, p<0.001 Mental component summary: 72.00 ± 6.42 vs 65.97 ± 5.65, p<0.001
Physical function; mean score (SD)	NR	NR	NR
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 device or procedure (SADE = mayor complications), n/N (%)	6/198 (3) vs 14/245 (5.6), p=ns[1]	NR	NR
Overall adverse device or procedure-related effects (ADE), n/N (%)	7/198 (3.5) vs 21/245 (8.6), p=0.030 HR = 0.39 (0.15 to 0.98, 95% CI), p=0.013 *Minor complications:* 1/198 (0.5) vs 7/245 (2.8), p=ns[2]	3/442 (0.7) vs 8/442 (1.8), p=ns *Acute complications:* 3/442 (0.7) vs 2/442 (0.5), p=ns *Late complications:* 0/442 vs 6/442 (1.4), p=0.014	*Acute complications:* 0/35 vs 18/84 (21.4), p<0.001

Study (acronym, ID no.), Reference	Martinez-Sande 2021 [9]	Palmisano 2023 [10]	Yu 2023 [13]
Major pericardial perforation/effusion, n/N (%)	NR	0/442 vs 0/442	NR
Total pericardial perforation/effusion, n/N (%)	2/198 (1) vs 0/245, p=ns	0/442 vs 0/442	NR
Serious infectious events (SIE), n/N (%)	NR	NR	NR
Major infections– device or procedure related, n/N (%)	NR	Device: 0/442 vs 2/442 (0.5), p=ns Systemic: 0/442 vs 1/442 (0.2), p=ns Local: 0/442 vs 1/442 (0.2), p=ns	NR
Loss of device function, n/N (%)	NR	Device malfunction: 1/442 (0.2) vs 0/442, p=ns Premature battery depletion: 0/442 vs 0/442	NR
Device dislodgement, n/N (%)	0/198 vs 3/245 (1.2), p=ns	NR	NR
Elevated pacing thresholds requiring retrieval/replacement, n/N (%)	Threshold elevation (retrieval/replacement not mentioned): 1/198 (0.5) vs 0/245, p=ns	NR	NR
New hospitalization, n/N (%)	NR	NR	NR
Prolonged hospitalization, n/N (%)	NR	NR	NR

Abbreviation: ADE: Adverse device or procedure-related effects; COPD: Chronic obstructive pulmonary disease; C-PM: Conventional pacemaker; HR: Hazard ratio, L-PM: Leadless pacemaker; LVEF: Left ventricular ejection fraction; NR: Not reported, ns: Not significant; SADE: Serious adverse events related to device or procedure; SD: Standard deviation; SF-36: Short form-36 health survey; SIE: Serious infectious events; TPS: Transcatheter pacemaker system.

Comments:

[1] *Major complications included the following:*

i) severe deterioration of clinical status; and/or

ii) a life threatening event that required intervention that prolonged hospitalization or death;

iii) vascular (aneurysm, pseudoaneurysm, arteriovenous fistula, hematoma and/or hemorrhage);

iv) thoracic complications (pneumothorax);

v) pericardial effusion and/or tamponade;

vi) stimulation related failures (capture failure, electrode dislodgment); and

vii) complications from the pacemaker pocket (infection or hematoma)

[2] *Device-related complications were classified as minor or major.*

Table A-5: Single chamber L-PM AV: Results from observational studies

Study (acronym, ID no.)	Micra AV CED study (NCT04235491)	
Subsample, Reference	**Follow up: 2 years [16]**	**Follow up: 6 months [15]**
Study description		
Country	USA	
Sponsor	Medtronic Inc.	
Intervention/Product	Leadless Micra™ AV TPS (Model MC1AVR1, Medtronic, Inc.)	
Comparator	Conventional dual chamber transvenous pacemaker	
Study design	Prospective cohort safety/efficacy study	
Duration of the study	February 2020 – December 2021	
Number of patients – Intervention (n)	*Enrolled*: 7,552 *Implantation attempt*: NR *Analyzed*: 7,552	*Enrolled*: 7,471 *Implantation attempt*: NR *Analyzed*: 7,471
Number of patients – Control (n)	*Enrolled*: 110,558 *Implantation attempt*: NR *Analyzed*: 110,558	*Enrolled*: 107,800 *Implantation attempt*: NR *Analyzed*: 107,800
Population	Patients implanted with a Micra™ AV leadless pacemaker or a DC-TV pacemaker	
Inclusion criteria	NR	■ Patients implanted with a Micra™ AV leadless pacemaker (model MC1AVR1, Medtronic, Inc, Minneapolis, MN) ■ Patients implanted with a dual chamber transvenous pacemaker from any manufacturer identified directly from Medicare claims and regardless of pacing indication
Exclusion criteria	■ Dual chamber transvenous patients implanted in a hospital or clinic without Micra™ AV patients ■ Patients with evidence of a prior cardiovascular implantable electronic device or without at least 12 months of pre-implant continuous enrolment in Medicare FFS	NR
Primary outcome (including measurement tools and measurement times)	■ Pre-specified chronic complications ■ Device-related re-interventions ■ All-cause mortality 2 years after implant	■ Acute (30-day) complication rate ■ Complications, re-interventions, and all-cause mortality through 6 months
Secondary outcome (including measurement tools and measurement times)	NR	NR
Follow-up (months)	24 months	30 days, 6 months
Loss to follow-up, n (%)	NR	NR

Study (acronym, ID no.)	Micra AV CED study (NCT04235491)	
Subsample, Reference	**Follow up: 2 years [16]**	**Follow up: 6 months [15]**
Population characteristics (L-PM vs C-PM)		
Age (mean), y	79 (10.2) vs 78.7 (8.0), p=0.015	79 (10.2) vs 78.7 (8.0), p=0.012
Male, n (%)	3,917 (51.9) vs 58,908 (53.3)	3,865 (51.7) vs 57,418 (53.2)
Pacing indication, n (%)	AV Block: 5,607 (74.2) vs 52,652 (47.6), p<0.0001	NR
Comorbidities, n (%)	■ Atrial fibrillation: 3,050 (40.4) vs 49,823 (45.1), p<0.0001 ■ End-stage renal disease: 1,126 (14.9) vs 2,191 (2.0), p<0.0001 ■ Renal dysfunction: 3,621 (47.9) vs 37,852 (34.2), p<0.0001 ■ Coronary artery disease: 3,750 (49.7) vs 53,761 (48.6), p=p=ns ■ Peripheral vascular disease: 1,927 (25.5) vs 21,824 (19.7), p<0.0001 ■ Tricuspid valve disease: 1,572 (20.8) vs 21,971 (19.9), p=0.047 ■ Left bundle branch block: 682 (9) vs 8,056 (7.3), p<0.0001 ■ Supraventricular tachycardia: 624 (8.3) vs 12,164 (11), p<0.0001 ■ Ventricular arrhythmia: 1,043 (13.8) vs 18,034 (16.3,) p<0.0001 ■ Prior acute myocardial infarction: 1,274 (16.9) vs 15,494 (14.0), p<0.0001 ■ Prior coronary artery bypass graft: 796 (10.5) vs 12,515 (11.3), p=0.038 ■ Prior transcatheter aortic valve replacement: 206 (2.7) vs 1,910 (1.7), p<0.0001 ■ Prior percutaneous coronary intervention: 1,023 (13.5) vs 15,339 (13.9), p=ns ■ Diabetes mellitus: 3,487 (46.2) vs 42,323 (38.3), p<0.0001 ■ Congestive heart failure: 3,127 (41.4) vs 33,784 (30.6), p<0.0001 ■ COPD: 1,867 (24.7) vs 22,882 (20.7), p<0.0001 ■ Hyperlipidaemia: 5,598 (74.1) vs 84,927 (76.8), p<0.0001 ■ Hypertension: 6778 (89.8) vs 99,075 (89.6),p=ns ■ COVID-19: 631 (8.4) vs 5,855 (5.3), p<0.0001 ■ Charlson Comorbidity Index, mean ± SD (range): 5.0 ± 3.4 (0–20) vs 3.9 ± 3.0 (0–21), p<0.0001	■ Atrial fibrillation: 3,011 (40.3) vs 48,576 (45.1), p<0.0001 ■ End-stage renal disease: 1,116 (14.9) vs 2,163 (2.0), p<0.0001 ■ Renal dysfunction: 3,588 (48) vs 37,072 (34.4), p<0.0001 ■ Coronary artery disease: 3,698 (49.5) vs 52,407 (48.6), p=ns ■ Peripheral vascular disease: 1,901 (25.5) vs 21,297 (19.8), p=<0.0001 ■ Tricuspid valve disease: 1,556 (20.8) vs 21,446 (19.9), p=p=ns ■ Left bundle branch block: 672 (9.0) vs 7,855 (7.3), p<0.0001 ■ Supraventricular tachycardia: 617 (8.3) vs 11,849 (11.0,) p<0.0001 ■ Ventricular arrhythmia: 1,032 (13.8) vs 17,551 (16.3), p<0.0001 ■ Prior acute myocardial infarction: 1,255 (16.8) vs 15,122 (14.0), p<0.0001 ■ Prior coronary artery bypass graft: 787 (10.5) vs 12,219 (11.3), p=0.034 ■ Prior transcatheter aortic valve replacement: 204 (2.7) vs 1,862 (1.7), p<0.0001 ■ Prior percutaneous coronary intervention: 1,008 (13.5) vs 14,962 (13.9), p= ns ■ Diabetes mellitus: 3,450 (46.2) vs 41,323 (38.3), p<0.0001 ■ Congestive heart failure: 3,093 (41.4) vs 32,947 (30.6), p<0.0001 ■ COPD: 1,848 (24.7) vs 22,332 (20.7), p<0.0001 ■ Hyperlipidaemia: 5,536 (74.1) vs 82,764 (76.8), p<0.0001 ■ Hypertension: 6,703 (89.8) vs 96,593 (89.6), p=ns ■ COVID-19: 621 (8.3) vs 5,616 (5.2), p<0.0001 ■ Charlson Comorbidity Index, mean ± SD (range): 4.9 ± 3.4 vs 3.9 ± 3.0 p<0.0001
Outcomes (L-PM vs C-PM)		
Effectiveness		
Implant success rate, n/N (%)	NR	NR
Adequate pacing performance (pacing threshold ≤ 1.0 V at 0.24ms)	NR	NR
Overall mortality, n/N %	***weighted CIF estimates (95% CI):*** 34% (33.3 to 34.7) vs 23.8% (23.2 to 24.4) RRR: −53% (−62 to 44%), p<0.0001 ***Adjusted HR:*** 1.53 (1.44 to 1.62, 95% CI), p<0.0001	*30 days:* 6% vs 3.5%, p<0.0001 *6 months:* HR 1.69 (1.57 to 1.83, 95% CI), p<0.0001

Study (acronym, ID no.)	Micra AV CED study (NCT04235491)	
Subsample, Reference	**Follow up: 2 years [16]**	**Follow up: 6 months [15]**
Cardiac mortality, n/N (%)	NR	NR
Procedure-related mortality, n/N (%)	NR	NR
Cardiac morbidity, n/N (%)	NR	NR
Health related quality of life [SF-36]; mean score (SD)	NR	NR
Physical function; mean score (SD)	NR	NR
Patient satisfaction; %	NR	NR
Safety		
Serious adverse events, n/N (%)	NR	NR
Overall Adverse events, n/N (%)	NR	NR
Serious adverse events related to device or procedure (SADE = mayor complications), n/N (%)	NR	NR
Overall adverse device or procedure-related effects (ADE), n/N (%)	*Device or procedure-related complications:* ***Weighted CIF estimates(95% CI):*** 5.3% (5.1 to 5.5) vs 9.6% (9.3 to 9.9) RRR: 46% (40 to 51, 95% CI), p<0.0001 adjusted HR: 0.544 [95% CI 0.488-0.605] *Device-related complications:* ***Weighted CIF estimates (95% CI):*** 2.9% (2.8 to 2.9) vs 6.8% (6.7 to 6.9) RRR: 59% [95% CI 53 to 64], p<0.0001	*Device or procedure-related complications:* *30 days:* 8.6% vs 11%, p<0.0001 adjusted RR: 0.79 [95% CI 0.73-0.84][1] *6 months:* ***Weighted CIF (95% CI):*** 3.5% (3.4 to 3.7) vs 7.0% (6.7 to 7.3); adjusted HR 0.5 (0.43 to 0.57, 95% CI), p<0.0001 *Device-related complications:* *30 days:* 1.4% vs 4.1%, p<0.0001 *6 months:* ***Weighted CIF (95% CI):*** 2.2% (2.2 to 2.3) vs 5.9% (5.8 to 5.9) RRR: 62% (56 to 68, 95% CI), p<0.0001
Total pericardial perforation/effusion, n/N (%)	NR	*30 days:* 1.4% vs 0.8%, p<0.0001[2]
Major pericardial perforation/effusion, n/N (%)	NR	NR
Serious infectious events (SIE), n/N (%)	NR	NR
Major infections– device or procedure related, n/N (%)	NR	NR
Loss of device function, n/N (%)	***Weighted CIF estimates:*** 1.8% (1.6 to 1.9) vs 3% (2.8 to 3.2) RRR: 41% (29 to 51, 95% CI), p<0.0001	NR

Study (acronym, ID no.)	Micra AV CED study (NCT04235491)	
Subsample, Reference	**Follow up: 2 years [16]**	**Follow up: 6 months [15]**
Device dislodgement, n/N (%)	***Weighted CIF estimates:*** 0.5% (0.5 to 0.5) vs 2.8% (2.7 to 2.9) RRR: 83% (76 to 88, 95% CI), p<0.0001	*6 months:* ***Weight CIF (95% CI):*** 0.4% (0.4 to 0.4) vs 2.5% (2.4 to 2.6) RRR: 84% (77 to 89, 95% CI), p<0.0001
Device revisions, n/N (%)	***Weighted CIF estimates:*** 3.5% (3.3 to 3.7) vs 5.6% (5.2 to 5.9) RRR 38% (28 to 46, 95% CI), p<0.0001	*6 months:* HR 0.46 (0.36 to 0.58, 95% CI), p<0.0001
Elevated pacing thresholds requiring retrieval/replacement, n/N (%)	*Removal:* 1-10 vs 0.7% (0.6 to 0.8) RRR: 83% (66 to 91), p<0.0001 *Replacement:* 0.5% (0.4 to 0.6) vs 0.6% (0.6 to 0.7) RRR 22% (-29 to 53), p=ns	NR
New hospitalization, n/N (%)	NR	NR
Prolonged hospitalization, n/N (%)	NR	NR

Abbreviations: ADE: Adverse device or procedure-related effects; AV: Atrioventricular; CED: Coverage with Evidence Development; CI: Confidence interval; CIF: Cumulative incidence function; COPD: Chronic obstructive pulmonary disease; C-PM: Conventional pacemaker; DC-TV: Dual chamber transvenous; FFS: Fee-for-service; HR: Hazard ratio; L-PM: Leadless pacemaker; NR: Not reported; ns: Not significant; RRR: Relative risk reduction; SADE: Serious adverse events related to device or procedure; SD: Standard deviation; SF-36: Short form-36 health survey; SIE: Serious infectious events; TPS: Transcatheter pacing system.

Comments:

[1] *Own calculation*

[2] *Cardiac perforation*

Table A-6: Dual chamber leadless pacemaker system: Results from observational studies

Study (acronym, ID no.)	**Aveir DR i2i study 2023 (NCT05252702)**	
Subsample, Reference	**90 days follow-up [17]**	**up to 24 months follow-up [47]**
Study description		
Country	USA, Canada, Europe	
Sponsor	Abbott Medical	
Intervention/Product	Leadless Aveir™ DR pacemaker system	
Comparator	None	
Study design	Prospective, multicentre, single-group efficacy/safety study	
Duration of the study	February 2022 – August 2022	February 2022 – February 2023
Number of patients – Intervention (n)	*Enrolled*: 300 *Implantation attempt*: 298 (both atrial and ventricular) 2 (ventricular only) *Analyzed*: 300	*Enrolled*: 464 *Implantation attempt*: 452 *Analyzed*: 300 (Effectiveness) 452 (mortality and adverse events)
Number of patients – Control (n)	NA	
Population	Patients indicated for atrial and ventricular leadless pacemaker	
Inclusion criteria	■ Subject must have at least one of the clinical indications for device implant in adherence with ACC/AHA/HRS/ESC dual chamber pacing guidelines ■ Subject is ≥ 18 years of age or age of legal consent, whichever age is greater ■ Subject has a life expectancy of at least one year ■ Subject is willing to comply with clinical investigation procedures and agrees to return to clinic for all required follow-up visits, tests, and exams ■ Subject has been informed of the nature of the clinical investigation, agrees to its provisions and has provided a signed written informed consent, approved by the IRB/EC	
Exclusion criteria	■ Subject is currently participating in another clinical investigation that may confound the results of this study as determined by the Sponsor ■ Subject is pregnant or nursing and those who plan pregnancy during the clinical investigation follow-up period ■ Subject has presence of anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could confound the assessment of the investigational device and/or implant procedure, limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements of the clinical investigation results ■ Subject has a known allergy or hypersensitivity to < 1 mg of dexamethasone sodium phosphate or any blood or tissue contacting material listed in the Instructions for Use ■ Subject has an implanted vena cava filter or mechanical tricuspid valve prosthesis ■ Subject has pre-existing, permanent endocardial pacing or defibrillation leads (does not include lead fragments) ■ Subject has current implantation of either conventional or subcutaneous implantable cardioverter defibrillator or cardiac resynchronization therapy device ■ Subject has an implanted leadless cardiac pacemaker (except for an Aveir™ ventricular leadless pacemaker) ■ Subject is implanted with an electrically-active implantable medical device with stimulation capabilities (such as neurological or cardiac stimulators) ■ Subject is unable to read or write	

Study (acronym, ID no.)	Aveir DR i2i study 2023 (NCT05252702)	
Subsample, Reference	**90 days follow-up [17]**	**up to 24 months follow-up [47]**
Primary outcome (including measurement tools and measurement times)	■ device-or-procedure-related serious adverse event after 3 months ■ composite success rate of acceptable atrial pacing thresholds and P-wave amplitudes in de novo subjects after 3 months ■ AV synchrony success rate at rest while seated in de novo subjects after 3 months	
Secondary outcome (including measurement tools and measurement times)	■ complication free rate in de novo subjects based on Clinical Events Committee adjudication of adverse events after 3 months ■ appropriate and proportional rate response of the atrial leadless pacemaker in de novo subjects during graded exercise testing	
Follow-up (months)	3 months	up to 24 months
Loss to follow-up, n (%)	0 (0)	19 (4.1)[6]
Population characteristics		
Age (mean), y	69.2 (13.5)	69.8 (13.3)[7]
Male, n (%)	187 (62.3)	278 (61.5)[7]
Pacing indication, n (%)	■ Sinus-node dysfunction: 190 (63.3) ■ AV block: 100 (33.3)	NR
Comorbidities, n (%)	■ Conduction disorder with 1:1 atrioventricular conduction: 4 (1.3) ■ Vasovagal (reflex) syncope: 6 (2.0) ■ Congestive heart failure: 37 (12.3) ■ Left ventricular ejection fraction: 59.6 ± 6.9 (226) ■ History of tobacco use: 107 (35.7) ■ Hypertension: 201 (67) ■ Diabetes mellitus: 75 (25) ■ Hyperlipidemia: 184 (61.3) ■ Peripheral vascular disease: 39 (13) ■ Coronary artery disease: 102 (34.0) ■ Myocardial infarction: 35 (11.7) ■ Unstable angina: 17 (5.7) ■ Transcatheter aortic valve replacement: 7 (2.3) ■ Mitral valve replacement or repair: 8 (2.7) ■ Tricuspid valve intervention: 3 (1.0) ■ Percutaneous coronary intervention: 49 (16.3) ■ Left atrial appendage closure: 11 (3.7) ■ Peripheral vascular intervention of femoral veins: 7 (2.3) ■ Coronary artery bypass graft surgery: 31 (10.3) ■ Heart transplant: 1 (0.3) ■ Ventricular assist device: 1 (0.3) ■ Aortic valve replacement: 14 (4.7)	NR

Study (acronym, ID no.)	Aveir DR i2i study 2023 (NCT05252702)	
Subsample, Reference	**90 days follow-up [17]**	**up to 24 months follow-up [47]**
Comorbidities, n (%) *(continuation)*	■ Atrial septal defect or patent foramen ovale closure: 1 (0.3) ■ Right atrial tissue modification: 20 (6.7) ■ Uncorrected atrial septal defect: 1 (0.3)	
Outcomes		
Effectiveness		
Implant success rate, n/N (%)	295/300 (98.3) [1]	NR
Adequate pacing performance (pacing threshold ≤ 1.0 V at 0.24ms)	0.82 (0.7) V at 0.4 ms [2]	*3 months (n=297):* 90.8% (87.5-94.1) *12 months (n=292):* 92.8% (89.7-95.8)
Overall mortality, n/N (%)	4/300 (1.3)[3]	*up to 24 months follow-up:* 16/452 (3.54)
Cardiac mortality, n/N (%)	2/300 (0.7)[4]	NR
Procedure-related mortality, n/N (%)	0/300	NR
Cardiac morbidity, n/N (%)	■ Atrial fibrillation: 9/300 (3) ■ Transient complete atrioventricular block: 1/300 (0.3) ■ Heart failure: 1/300 (0.3)	*up to 24 months follow-up:*[8] ■ Cardiac arrhythmia – atrial fibrillation: 41/452 (9.07) ■ Cardiac arrhythmia – supraventricular arrhythmia: 11/452 (2.43) ■ Heart failure: 18/452 (3.98) ■ Myocardial infarction: 4/452 (0.88) ■ Transient ischemic attack: 3/452 (0.66)
Health related quality of life [SF-36]; mean score (SD)	NR	NR
Physical function; mean score (MD)	NR	NR
Patient satisfaction; %	NR	NR
Safety		
Serious adverse events, n/N (%)	35/300 (11.9) (not SADE)	*up to 24 months follow-up:* 202/452 (44.69)
Overall Adverse events, n/N (%)	NR	*up to 24 months follow-up:* 366/452 (80.97)[9]
Serious adverse events related to device or procedure (SADE = major complications), n/N (%)	29/300 (9.7)[5]	*Patient free from Aveir™ DR system-related complications:* 3 months: 90.3% (87.0-93.7) 12 months: 88.6% (84.5-91.8) *Patient free from Aveir™ AV L-PM-related complications:* 3 months: 91.3% (88.1-94.5) 12 months: 91.0% (87.1-93.7)

Study (acronym, ID no.)	Aveir DR i2i study 2023 (NCT05252702)	
Subsample, Reference	**90 days follow-up [17]**	**up to 24 months follow-up [47]**
Overall adverse device or procedure-related effects (ADE), n/N (%)	NR	NR
Total pericardial perforation/effusion, n/N (%)	2/300 (0.7)	12/452 (2.65)
Major pericardial perforation/effusion, n/N (%)	NR	7/452 (1.55)
Serious infectious events (SIE), n/N (%)	NR	*up to 24 months follow-up:* 10/452 (2.21)
Major infections– device or procedure related, n/N (%)	NR	NR
Loss of device function, n/N (%)	1/300 (0.3)	NR
Device dislodgement, n/N (%)	Intraprocedural dislodgement: 6/300 (2) Postprocedural dislodgement: 5/300 (1.7)	Mechanical device dislodgement: 3/452 (0.66) Device dislodgement: 12/452 (2.65)
Elevated pacing thresholds requiring retrieval/replacement, n/N (%)	Intraprocedural repositioning of the atrial device: once: 72/300 (24.2) more than one: 31/300 (10.4) Intraprocedural repositioning of the ventricular device: once: 40/300 (13.4) more than one: 6/300 (2)	NR
Device revisions, n/N (%)	8/300 (2.7)	NR
New hospitalization, n/N (%)	NR	NR
Prolonged hospitalization, n/N (%)	NR	NR

Abbreviations: ACC: American College of Cardiology; ADE: Adverse device or procedure-related effects; AHA: American Heart Association; HRS: Heart Rhythm Society; ESC: European Society of Cardiology; IRB/IEC: Institutional review board/ethics committee; NR: Not reported; ns: Not significant; SADE: Serious adverse events related to device or procedure; SD: Standard deviation; SF-36: Short form-36 health survey; SIE: Serious infectious events; TAVR: Transcatheter aortic valve replacement.

Comments:

[1] *Two patients left an attempted procedure without an atrial leadless pacemaker implanted. Three patients left the procedure without established i2i communication.*

[2] *299 patients analyzed; success rate: 90.2%, p<0.001 (conservative approach: all unsuccessful device implants imputed as failures).*

[3] *Four deaths occurred during follow-up, between 46 and 86 days after implantation.*

[4] *Two deaths occurred after cardiac arrest.*

[5] *Events were classified as device- or procedure-related if they were considered by the clinical events committee to be possibly, probably, or causally related to any investigational device or procedure.*

[6] *No attempted implant, subjects withdrawn (n=12); system explant (n=5); lost to follow-up (n=1); withdrawn by investigator (n=1).*

[7] *Baseline characteristics for patients with implantation attempt (n=452).*

[8] *Reported as serious adverse events.*

[9] *Other adverse events, not including serious adverse events*

Risk of bias tables and GRADE evidence profile

Table A-7: Risk of bias – outcome level (randomized studies), see [18]

Trial	Outcome	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Garweg 2023 [5, 45]	Mortality	Low	Low	Low	Low	Some concerns[3]	Some concerns
	Physical function[1]						
	Safety[2]						

Comments:
[1] *6 minute walk distance test*
[2] *Device effects, loss of device function, device dislodgement, prolonged hospitalization*
[3] *Since trial registration was done after study start and randomization, it is unclear, whether all reported outcomes were predefined.*

Table A-8: Risk of bias – study level (cohort studies) – single chamber L-PM VR, see [19]

Trial	Domains			Overall score[1]
	Selection	Comparability	Exposure	
Single chamber L-PM VR				
Micra CED study [7, 8, 12, 44]	4 of 4 points	2 of 2 points	3 of 3 points	good
Bertelli 2022 [6]	3 of 4 points	1 of 2 points	2 of 3 points	good
Martinez-Sande 2021 [9]	4 of 4 points	1 of 2 points	3 of 3 points	good
Yu 2023 [13]	4 of 4 points	1 of 2 points	2 of 3 points	good
Palmisano 2023 [10]	4 of 4 points	1 of 2 points	3 of 3 points	good
Palmisano 2021 [11]	4 of 4 points	1 of 2 points	3 of 3 points	good
Zucchelli 2021 [14]	3 of 4 points	2 of 2 points	3 of 3 points	good
Single chamber L-PM AV				
Mirca AV CED study [15, 16, 46]	4 of 4 points	2 of 2 points	3 of 3 points	good

Comments:
[1] *Converting the Newcastle Ottawa Scale (NOS) to Agency for Healthcare Research and Quality (AHRQ) standards (good, fair, poor)*

Table A-9: Risk of bias – study level (case series), see [20]

Study	Aveir DR i2i study 2023 [17, 47]
Study objective	
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes
Study design	
2. Was the study conducted prospectively?	Yes
3. Were the cases collected in more than one centre?	Yes
4. Were participants recruited consecutively?	Yes
Study population	
5. Were the characteristics of the patients included in the study described?	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes
7. Did participants enter the study at similar point in the disease?	Yes
Intervention and co-intervention	
8. Was the intervention of interest clearly described?	Yes
9. Were additional interventions (co-interventions) clearly reported?	No
Outcome measures	
10. Were relevant outcome measures established a priori?	Yes
11. Were outcome assessors blinded to the intervention that patients received?	Yes
12. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes
13. Were the relevant outcomes measures made before and after intervention?	No
Statistical Analysis	
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes
Results and Conclusions	
15. Was follow-up long enough for important events and outcomes to occur?	Yes
16. Were losses to follow-up reported?	Yes
17. Did the study provided estimates of the random variability in the data analysis of relevant outcomes?	Yes
18. Were the adverse events reported?	Yes
19. Were the conclusions of the study supported by results?	Yes
Competing interest and source of support	
20. Were both competing interest and source of support for the study reported?	Partial
Overall Risk of bias	**Low**

Table A-10: Evidence profile: effectiveness and safety of single chamber L-PM for right ventricular pacing in patients with indications for cardiac pacing

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	C-PM	L-PM	Relative (95% CI)	Absolute (95% CI)	
Overall mortality											
1 5	RCT cohort studies	serious [1]	not serious	not serious	not serious	none	24 (RCT) 10,981 (cohort studies	27 (RCT) 6,707 (cohort studies)	-	1.1% to 31.4% vs. 0.7% to 32.5%	⊕⊕◯◯ Low
Cardiac mortality											
1 3	RCT cohort studies	serious [1]	not serious	not serious	not serious	none	24 (RCT) 497 (cohort studies	27 (RCT) 389 (cohort studies)	-	0 to 0.5% vs. 0 to 8%	⊕⊕◯◯ Low
HRQoL											
2	cohort studies	serious [1]	not serious	not serious	not serious	none	161	112	-	HRQoL SF-36 mental and physical health subscores statistically significant better with L-PM in both studies.	⊕⊕◯◯ Low
Physical function											
1	RCT	not serious	not serious	not serious	very serious [2]	none	27	24	-	Δ 6 min walk: -5.0 (-28.5 to 30.0) vs. 8.0 (-37.8 to 47.8), p=0.577	⊕◯◯◯ Very low
Serious adverse events											
No results available											
Serious adverse device effect (i.e. major complications)											
1 2	RCT cohort studies	serious [1]	not serious	not serious	not serious	none	24 (RCT) 397 (cohort studies	27 (RCT) 289 (cohort studies)	-	0 to 5.6%% vs. 0 to 3%	⊕⊕◯◯ Low
Adverse device effect (i.e. overall complications) – acute											
5	cohort studies	serious [1]	not serious	not serious	not serious	none	11,110	6,868	-	0.5% to 21.4% vs. 0 to 7.7%	⊕⊕◯◯ Low
Adverse device effect (i.e. overall complications) – long term											
5	cohort studies	serious [1]	not serious	not serious	not serious	none	11,271	7,031	-	1.4% to 8.6% vs. 0 to 4.9%	⊕⊕◯◯ Low

Abbreviations: CI: Confidence interval; C-PM: Conventional pacemaker; HRQoL: Health-related quality of life; L-PM: Leadless pacemaker; RCT: Randomized controlled trial; SF-36: Short form 36 questionnaire

Comments:

[1] Mainly non-randomized studies [2] Very low number of studies and participants

Table A-11: Evidence profile: effectiveness and safety of single chamber L-PM with AV synchronous pacing in patients with indications for cardiac pacing

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	C-PM	L-PM	Relative (95% CI)	Absolute (95% CI)	
Overall mortality											
1	cohort study	serious [1]	not serious	not serious	not serious	none	110,558	7,552	HR 1.53 (1.44 to 1.62)	102 more (86 to 118)	⨁⨁◯◯ Low
Cardiac mortality											
No results available											
HRQoL											
No results available											
Physical function											
No results available											
Serious adverse events											
No results available											
Serious adverse device effect (i.e. major complications)											
No results available											
Adverse device effect (i.e. overall complications) – acute											
1	cohort study	serious [1]	not serious	not serious	not serious	none	107,800	7,471	RR 0.79 (0.73 to 0.84)	23 fewer (18 to 30)	⨁⨁◯◯ Low
Adverse device effect (i.e. overall complications) – long term											
1	cohort study	serious [1]	not serious	not serious	not serious	none	110,558	7,552	HR 0.54 (0.49 to 0.61)	43 fewer (36 to 48)	⨁⨁◯◯ Low

Abbreviations: *CI: Confidence interval; C-PM: Conventional pacemaker; HR: Hazard ratio; HRQoL: Health-related quality of life; L-PM: Leadless pacemaker; RR: Risk ratio*

Comments:

[1] *Non-randomized study*

Table A-12: Evidence profile: effectiveness and safety of dual chamber leadless pacemaker system in patients with indications for cardiac pacing

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	C-PM	L-PM	Relative (95% CI)	Absolute (95% CI)	
Overall mortality											
1	single-arm study	very serious [1]	not serious	not serious	not serious	none	-	452	-	13 per 1,000	⨁⨁◯◯ Low
Cardiac mortality											
No results available											
HRQoL											
No results available											
Physical function											
No results available											
Serious adverse events											
1	single-arm study	very serious [1]	not serious	not serious	not serious	none	-	452	-	447 per 1,000	⨁⨁◯◯ Low
Serious adverse device effect (i.e. major complications)											
1	single-arm study	very serious [1]	not serious	not serious	not serious	none	-	300	-	113 per 1,000	⨁⨁◯◯ Low
Adverse device effect (i.e. overall complications)											
No results available											

Abbreviations: CI: Confidence interval; C-PM: Conventional pacemaker; HRQoL: Health-related quality of life; L-PM: Leadless pacemaker

Comments:

[1] *Single-arm study, no control*

Applicability table

Table A-13: Summary table characterizing the applicability of a body of studies

Domain	Description of applicability of evidence
Population	All studies investigated patients with indication for cardiac pacing. Specific pacing indications were reported in seven of 10 included studies. The majority of study participants had chronic atrial fibrillation with severe bradycardia or sinus node dysfunction. A substantial number of participants had a pacemaker indication due to AV block. It is unclear if the selection of patients for cardiac pacing in Austria results in comparable frequencies of the respective indication groups.
Intervention	In the studies, the intervention was the transcatheter implantation of three different L-PM systems, the Micra™ VR TPS, the Micra™ AV TPS, and the Aveir™ DR L-PM system. All products currently available on the market and correspond to the products used in Austria. For two other products, currently available on the market, the Aveir™ VR L-PM for right ventricular pacing, and the Aveir™ AR L-PM for right atrial pacing, no studies could be identified.
Comparators	In the studies investigating the single chamber L-PM for right ventricular pacing, conventional single chamber pacemakers used for right ventricle pacing were used as compator. In the study investigating the single chamber L-PM for AV synchronous pacing, conventional dual chamber pacemakers were used for as compator. These correspond to the standard therapies for patients with pacing indications. In the study investigating the dual chamber L-PM system, there was no comparator.
Outcomes	The main outcomes reported in the studies were pacing performance for effectiveness and complication rates for safety. Mortality and health-related quality of life were clinically relevant effectiveness 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.

Abbreviations: CI: Confidence interval; C-PM: Conventional pacemaker; HRQoL: Health-related quality of life; L-PM: Leadless pacemaker

List of ongoing comparative studies

Table A-14: List of ongoing studies of leadless pacemaker implantation

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Estimated study completion date	Sponsor
RCT						
NCT06690333/ COMPAREPACE	*Inclusion criteria:* ■ Age > 18 ■ Planned for permanent pacemaker implantation for AV node disease (first, second or third degree) ■ Preserved ejection fraction > 50% ■ Preserved sinus node function ■ Willingness to adhere to study restrictions and comply with all post-procedural follow-up requirements ■ Life expectancy > 1 year ■ Female subject of childbearing potential is not pregnant, not breast feeding, does not plan to be pregnant during the course of the study, and agrees to use a highly effective contraceptive method (i.e. IUD, birth control, vasectomized partner, sexual abstinence, etc.) during the course of the study. ■ Subject has been informed of the nature of the study, agrees to its provision and has provided written informed consent, approved by the IRB *Exclusion criteria:* ■ Sinus node dysfunction, anticipating atrial pacing or atrial fibrillation ■ Anatomical restriction for either Micra™ or transvenous pacing such as ■ Access vein occlusion or thrombosis ■ Previous radiation therapy at insertion site ■ Inferior vena cava filter ■ Endstage renal disease (ESRD)/on dialysis ■ Dementia (inability to give consent) ■ Moderate to Severe Tricuspid valve regurgitation ■ Moderate to Severe Mitral valve regurgitation ■ History of mitral or tricuspid valve surgery ■ Preexisting implanted pacemaker or ICD or lead ■ Subject is allergic to titanium ■ Life expectancy < 1 year ■ Recurrent or high risk of infections ■ Active malignancy requiring systemic chemotherapy or local chest radiation	Leadless pacemaker Micra™ AV	Transvenous pacemaker with left bundle area pacing	The composite of: ■ procedural success ■ freedom from serious device-related complications at one year ■ freedom from heart failure or drop in ejection fraction below 50%. at 12 months.	February 2026	NCH Healthcare System, Inc. dba Naples Comprehensive Health and dba NCH

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Estimated study completion date	Sponsor
NCT06690333/ COMPAREPACE *(continuation)*	■ Subject has myocardial infarction, unstable angina, cerebrovascular accident, or heart failure admission within 3 months of the baseline visit ■ CABG, valve surgery or PCI within the last 3 months ■ Other major cardiac surgery within the last 6 months ■ Persistent and permanent atrial fibrillation diagnosed by a healthcare provider ■ NYHA class 3 or 4 Heart Failure					
NCT05498376/ LEAVE DDD	*Inclusion criteria:* ■ Patients (≥70y) undergoing a de-novo pacemaker implantation due to intermittent or permanent AV block, qualifying for a conventional or leadless pacemaker ■ Written informed consent *Exclusion criteria:* ■ Permanent atrial fibrillation or atrial standstill ■ Evidence of sinus node disease and need for right atrial pacing (not possible with Micra™ AV) ■ LVEF <50% and permanent high-degree or total AVB (requiring CRT/His-Bundle/CSP pacing) ■ Preoperative E/A ratio >1.5 in the echocardiography ■ Any co-existing ICD indications (no leadless ICD systems available) ■ Hemodialysis ■ Presence of a mechanical tricuspid valve prosthesis ■ Unwilling or unable to comply fully with study procedures and follow-up	Leadless pacemaker Micra™ AV	Conventional pacemaker DDD	Exercise capacity (VO_2 at anaerobic threshold) at 3 months	December 2027	Insel Gruppe AG, University Hospital Bern
NCT05856799/ DANVERS	*Inclusion criteria:* ■ First time pacemaker implantation on class I or II ESC recommendations for AVB with an expected amount of right ventricular pacing >80% of the time, ■ Age 75 years or older ■ Intact sinus node function ■ Expected survival more than 12 months based on clinical evaluation ■ Able to provide informed consent *Exclusion Criteria:* ■ Persistent or previous cardiac implantable electronic device i.e., pacemaker, ICD, or CRT. ■ Persistent, or chronic atrial fibrillation ■ Reversible AVB ■ Transient AVB due to ongoing ischemia ■ Heart failure NYHA class III-IV	Leadless pacemaker Micra™ AV	Transvenous Azure XT DR dual chamber pacemaker	Quality of Life by SF-36 at 7 months	August 2025	University of Aarhus

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Estimated study completion date	Sponsor
NCT05856799/ DANVERS *(continuation)*	■ Heart failure with branch block and indication for CRT implantation, irrespective of NYHA class ■ Indication for primary or secondary prophylactic ICD implantation ■ Acute myocardial infarction (AMI) within 3 months ■ Severe chronic pulmonary disease with pulmonal hypertension limiting exercise capacity ■ Expected survival < 12 months based on clinical evaluation ■ Performing high intensity sport ■ Participation in another trial with experimental treatment ■ Contraindication against device implantation (e.g., concurrent infection)					
Case-Control study						
NCT05932602/ Aveir DR CED	*Inclusion criteria:* ■ Medicare beneficiaries implanted with an Aveir™ DR leadless pacemaker on or after the study start date (i.e., the date of Aveir™ DR market approval) OR ■ Medicare beneficiaries implanted with a full system (e.g. lead and generator) dual chamber transvenous pacemaker on or after the study start date *Exclusion Criteria:* ■ None	Aveir™ DR Leadless Pacemaker System	Dual Chamber Transvenous Pacemaker	■ Acute device related complication rate (30 days) ■ Two-year survival rate	October 2025	Abbott Medical Devices
NCT05336877/ Aveir VR CED	*Inclusion criteria:* ■ Medicare beneficiaries implanted with an Aveir VR leadless pacemaker on or after the study start date (i.e., the date of Aveir VR market approval) OR ■ Medicare beneficiaries implanted with a full system (e.g. lead and generator) single chamber ventricular transvenous pacemaker on or after the study start date *Exclusion Criteria:* ■ None	Aveir™ VR Leadless Pacemaker System	Single chamber Transvenous Pacemaker	■ Acute device related complication rate (30 days) ■ Two-year survival rate	January 2028	Abbott Medical Devices
NCT06100770/ ARRIVE	*Inclusion criteria:* ■ Medicare beneficiaries implanted with an Aveir AR leadless pacemaker on or after the study start date (i.e., the date of Aveir VR market approval) OR ■ Medicare beneficiaries implanted with a full system (e.g. lead and generator) single chamber atrial transvenous pacemaker on or after the study start date *Exclusion Criteria:* ■ None	Aveir™ AR Leadless Pacemaker System	Single chamber atrial transvenous pacemaker	■ Acute device related complication rate (30 days) ■ Two-year survival rate	January 2031	Abbott Medical Devices

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Estimated study completion date	Sponsor
NCT05958836	*Inclusion criteria:* ■ With an age arranged from 18 to 80 years old; ■ Conforming to indication of a pacemaker implantation; ■ Life expectancy>1 year; ■ Normal cardiac function with preserved LVEF; ■ Adequate self-care ability or self-help skills before pacemaker implantation; ■ Mentally healthy so as to participate in the quality-of-life assessments; ■ Willing to participate in study through consent and willing to undergo study specific required procedures with expectancy of geographically stable for follow up duration. *Exclusion Criteria:* ■ Subject with indication for ICD/CRT-P/CRT-D; ■ Subject with persistent symptomatic sinus bradycardia; ■ Subject has an existing or prior pacemaker, ICD or CRT device implant; ■ Subject has unstable angina pectoris or has an acute myocardial infarction (AMI) in the 30 days prior to eligibility assessment; ■ Subjects with a mechanical tricuspid valve, implanted vena cava filter, or left ventricular assist device (LVAD); ■ Subjects with a life expectancy of less than 12-months; ■ Subjects with medical condition which precludes patient from participation in the opinion of the investigator, such as arthritis, lung disease or previous stroke, renal dysfunction, recent major surgery within six months, clinically overt congestive heart failure; ■ Pregnant women or breastfeeding women, or women of child bearing potential and who are not on a reliable form of birth regulation method or abstinence; ■ Psychological disorders unable to participate in the quality-of-life assessments.	Leadless pacemaker Micra™ VR	Traditional pacemaker	■ Health-related quality of life measured by EQ-5D-5L (6 months) ■ Health-related quality of life measured by NHP (Nottingham Health Profile (6 months)	July 2026	Shanghai Zhongshan Hospital

Abbreviations: AMI: Acute myocardial infarction; AV: Atrioventricular; AVB: Atrioventricular block; CABG: Coronary artery bypass graft; CRT: Cardiac Resynchronization Therapy; CRT-D: Cardiac Resynchronization Therapy-Defibrillator; CRT-P: Cardiac Resynchronization Therapy-Pacemaker; CSP: Conduction System Pacing; EQ-5D-5L: European Quality of Life 5 Dimensions 5 Level Version; ESC: European Society of Cardiology; ESRD: Endstage renal disease; ICD: Implantable cardioverter defibrillator; IRB: Institutional Review Board; IUD: Intrauterine Device; LVAD: Left ventricular assist device; LVEF: Left ventricular ejection fraction; NCH: Naples Comprehensive Health; NHP: Nottingham Health Profile; NYHA: New York Heart Association; PCI: Percutaneous coronary intervention

Research questions

Table A-15: Health problem and Current Use

Element ID	Research question
A0001	For which health conditions, and for what purposes is the technology used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?

Table A-16: Description of the technology

Element ID	Research question
B0001	What is the technology and the comparator(s)?
A0020	For which indications has the technology received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the technology in relation to the comparators?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
B0004	Who administers the technology and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology?

Table A-17: Clinical Effectiveness

Element ID	Research question
D0001	What is the expected beneficial effect of the technology on mortality?
D0003	What is the effect of the technology on the mortality due to causes other than the target disease?
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of the technology on patients' body functions?
D0016	How does the use of technology affect activities of daily living?
D0012	What is the effect of the technology on generic health-related quality of life?
D0013	What is the effect of the technology on disease-specific quality of life?
D0017	Was the use of the technology worthwhile?

Table A-18: Safety

Element ID	Research question
C0008	How safe is the technology in comparison to the comparator(s)?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?
C0007	Are the technology and comparator(s) associated with user-dependent harms?

Literature search strategies

Search strategy Medline

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2020 to December 20, 2024>, Ovid MEDLINE(R) <1946 to December Week 2 2024>	
Search date: 23.12.2024	
ID	Search
1	exp Pacemaker, Artificial/ (34285)
2	exp Cardiac Pacing, Artificial/ (31376)
3	pacemaker*.mp. (63150)
4	1 or 2 or 3 (84943)
5	leadless.mp. (1858)
6	((leadless or transcatheter*) adj5 pacing).mp. (811)
7	5 or 6 (2010)
8	4 and 7 (1854)
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. (75)
10	8 not 9 (1789)
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 "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. (91)
12	10 not 11 (1698)
13	("31930621" or "31478304" or "31429191" or "31808227" or "31907831" or "31868084" or "31866598" or "31863250" or "31858200" or "31840881" or "31839660" or "31831404" or "31728873" or "31709982" or "31610949" or "31556951" or "31380741" or "31395499" or "31208898" or "31145671" or "31122719" or "30251546" or "30155871" or "30572227" or "31512298" or "31355937" or "31310416" or "31284049" or "31222756" or "31890573" or "31890568" or "31232461" or "31180481" or "30915451" or "31576502" or "31097335" or "31813504" or "31803374" or "30710216" or "30758053" or "31125672" or "31283461" or "31087624" or "30661279" or "31483168" or "31687066" or "31681964" or "31624520" or "31425571" or "30392985" or "31114859" or "30552694" or "31373521" or "31537341" or "31280132" or "31226509" or "31486925" or "31463061" or "31463060" or "31453314" or "31453094" or "31453088" or "31410240" or "31045296" or "31045294" or "31320021" or "31146075" or "31160054" or "31285989" or "30976654" or "30413293" or "31236319" or "31193668" or "31193201" or "31191144" or "31111100" or "30870634" or "30639936" or "30576877" or "30550834" or "31136402" or "31122389" or "28491633" or "28491798" or "30279895" or "29531727" or "29915709" or "29951156" or "28491609" or "28928978" or "28491630" or "28491710" or "28491727" or "29915713" or "29988242" or "29487683" or "29250275" or "29881575" or "29876290" or "30228959" or "30210877" or "28491705" or "31060372" or "31060371" or "31020236" or "31007801" or "30698786" or "30805056" or "30805055" or "30581734" or "30581731" or "30555612" or "30479947" or "30784685" or "30452615" or "30452610" or "30202950" or "29018521" or "30623141" or "28496929" or "30340063" or "30329040" or "30129440" or "30059962" or "29986008" or "29893837" or "30532859" or "31657945" or "29915613" or "29856150" or "29807136" or "29780151" or "29674842" or "29274799" or "29269168" or "29250229" or "29110935" or "28765766" or "28707043" or "29759585" or "28491667" or "28401869" or "29759410" or "29759322" or "27932427" or "29993502" or "30839003" or "30288752" or "30653690" or "30829416" or "30687931" or "30632622" or "29779988" or "28165125" or "29314625" or "28799709" or "30638213" or "29992205" or "29877203" or "30176097" or "30168233" or "30203520" or "29987119" or "30441181" or "30089573" or "30441125" or "30025684" or "30497729" or "29600780" or "29488177" or "30130999" or "29796785" or "29795543" or "30378719" or "29143810" or "29993450" or

	"29189109" or "30105398" or "31099767" or "31070324" or "28608114" or "29335839" or "30341813" or "30255304" or "30456580" or "30406825" or "30382341" or "30367235" or "30341551" or "30306303" or "29761338" or "29759846" or "29759829" or "28943497" or "29759633" or "30530338" or "28707515" or "28733765" or "28188515" or "30221378" or "29540439" or "29462311" or "30066363" or "30516083" or "29637013" or "28449773" or "29291376" or "30855732" or "30788024" or "30792165" or "29985798" or "29868887" or "29365073" or "29697182" or "29873937" or "29431664" or "29300871" or "30717848" or "30103071" or "28572238" or "27577107" or "29973228" or "29792384" or "29538139" or "29476660" or "29758405" or "29709576" or "30468062" or "30396572" or "28472387" or "30054186" or "30105428" or "29552930" or "29957188" or "29217253" or "29427820" or "29496606" or "29346109" or "29428139" or "29194683" or "30544594" or "29360974" or "29016827" or "30091710" or "29779297" or "28594061" or "28449772" or "28733677" or "28688703" or "27537740" or "30376685" or "30348615" or "30106456" or "29551369" or "28666317" or "28148576" or "28396380" or "28936891" or "29951805" or "29905373" or "29520466" or "29519702" or "29453212" or "29260369" or "29229522" or "29221628" or "29126950" or "29045345" or "29016787" or "28941981" or "28882363" or "28826669" or "28818562" or "28696087" or "28528890" or "28419218" or "29185614" or "29088572" or "29021417" or "28965962" or "28957879" or "28754393" or "28713024" or "28705736" or "28666931" or "28645719" or "28643850" or "28627451" or "28606633" or "28595994" or "28588092" or "28583688" or "28566657" or "28529181" or "28502871" or "28489502" or "28443966" or "28439940" or "28383712" or "28365650" or "28342501" or "28342500" or "28321573" or "28295442" or "28213895" or "28192209" or "28192207" or "28117279" or "28111349" or "28089328" or "28081830" or "28081829" or "28040461" or "27996100" or "27943488" or "27925339" or "27908571" or "27889044" or "27871854" or "27855290" or "27836644" or "27756706" or "27371661" or "27344513" or "28043451" or "28011844" or "27861115" or "27849261" or "27799257" or "27726912" or "27704685" or "27616697" or "27600684" or "27591908" or "27445025" or "27392946" or "27374239" or "27351174" or "27323664" or "27296508" or "27236278" or "27236275" or "27083173" or "27055811" or "27038713" or "27017442" or "26941338" or "26927858" or "26896468" or "26875055" or "26851812" or "26851811" or "26851809" or "26830889" or "26685334" or CN-01887455 or CN-01988868).ui. (379)
14	12 not 13 (1375)
15	remove duplicates from 14 (857)
Total hits: 857	

Search strategy Embase

Search Name: Leadless Pacemakers (Update 2024)		
Search date: 23.12.2024		
No.	Query Results	Results
#1	'leadless pacemaker'/exp	1,692
#2	'heart pacing'/exp	54,527
#3	'artificial heart pacemaker'/exp	50,622
#4	pacemaker*:ti,ab,de,kw	96,897
#5	peacemaker*:ti,ab,de,kw	98
#6	'pace-maker':ti,ab,de,kw	929
#7	'pace-makers':ti,ab,de,kw	153
#8	'peace-maker':ti,ab,de,kw	12
#9	'peace-makers':ti,ab,de,kw	1
#10	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	137,256
#11	leadless:ti,ab,de,kw	2,526
#12	((leadless OR transcatheter*) NEAR/4 pacing):ti,ab,de,kw	913
#13	#11 OR #12	2,675
#14	#10 AND #13	2,488
#15	#1 OR #14	2,488
#16	micra:dn	619
#17	nanostim:dn	137
#18	aveir:dn	60
#19	#15 OR #16 OR #17 OR #18	2,537
#20	#19 AND [15-01-2020]/sd NOT [24-12-2024]/sd	1,702
#21	#20 AND 'Conference Abstract'/it	560
#22	#20 NOT #21	1,142
Total hits: 1,142		

Search strategy Cochrane Library

Search Name: Leadless Pacemakers (Update 2024)	
Search date: 23.12.2024	
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 pace?maker*) (Word variations have been searched)
#10	#8 OR #9 with Cochrane Library publication date Between Jan 2020 and Dec 2024
#11	(#8 OR #9) with Publication Year from 2020 to 2024, in Trials
#12	#10 OR #11
#13	(conference proceeding):pt
#14	(abstract):so
#15	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#16	#13 OR #14 OR #15
#17	#12 NOT #16
Total hits: 10	

Search strategy INAHTA

Search Name: Leadless Pacemakers (Update 2024)	
Search date: 23.12.2024	
ID	Search
1	"Pacemaker Artificial"[mhe],"68","2024-12-23T16:04:07.000000Z"
2	"Cardiac Pacing Artificial"[mhe],"62","2024-12-23T16:04:39.000000Z"
3	pacemaker*,"81","2024-12-23T16:05:09.000000Z"
4	(pacemaker*) OR ("Cardiac Pacing Artificial"[mhe]) OR ("Pacemaker Artificial"[mhe]),"132","2024-12-23T16:05:15.000000Z"
5	leadless,"10","2024-12-23T16:05:34.000000Z"
6	transcatheter*,"92","2024-12-23T16:05:48.000000Z"
7	(transcatheter*) OR (leadless),"98","2024-12-23T16:05:58.000000Z"
8	((transcatheter*) OR (leadless)) AND ((pacemaker*) OR ("Cardiac Pacing Artificial"[mhe]) OR ("Pacemaker Artificial"[mhe])),"19","2024-12-23T16:06:06.000000Z"
9	(((transcatheter*) OR (leadless)) AND ((pacemaker*) OR ("Cardiac Pacing Artificial"[mhe]) OR ("Pacemaker Artificial"[mhe]))) FROM 2020 TO 2024,"5","2024-12-23T16:06:19.000000Z"
Total hits: 1	

Search strategy in clinical trial registries

Search date: 13.02.2025

ClinicalTrials.gov (Expert search)

Leadless pacemaker OR leadless pacemaker* OR leadless pace-maker* OR leadless pacing OR transcatheter pacing OR trans-catheter pacing OR MICRA OR AVEIR OR Nanostim in Intervention/treatment

Last update posted from 02/03/2021-01/13/2025

57 Studies identified

WHO-ICTRP (Advanced search)

"leadless pacemaker" OR leadless pacemaker* OR leadless pace-maker* OR leadless pacing OR transcatheter pacing OR trans-catheter pacing OR MICRA OR AVEIR OR Nanostim in Title

[Date of registration is between 03/02/2021 and 13/01/2025]

26 (5 additional) studies identified

EU Clinical Trials Register (EudraCT) (Basic search)

"leadless pacemaker" OR "leadless pace-maker" OR "leadless pacing" OR "transcatheter pacing" OR "trans-catheter pacing" OR MICRA OR AVEIR OR Nanostim

No studies identified

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH