Norwegian Medical Products Agency

Single Technology Re-Assessment

A leadless pacemaker, MicraTM Transcatheter Pacing System, in sub-groups of patients with indication for single-chamber ventricular pacing

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Executive summary

Introduction

Bradycardia is an abnormally slow heartbeat caused by issues in the heart's electrical conduction, often in the sinus or atrioventricular nodes. Symptoms include fatigue, dizziness, fainting, chest pain, and palpitations, affecting quality of life. Pacemaker therapy, which delivers electrical impulses to maintain a normal heart rhythm, is the primary treatment for symptomatic, non-reversible bradycardia. This therapy can improve and sometimes prolong life. Regular follow-ups are crucial to monitor and adjust the pacemaker.
In 2020, 3,779 new pacemakers were implanted in Norway, with the majority being dual chamber devices. Most were inserted following diagnoses of syncope, near syncope, bradycardia, or cardiac arrest. The largest age group receiving pacemakers were patients aged 61-80 years. The submitter, Medtronic Norge AS, estimates that about 70 patients annually would be eligible for Micra™ implantation in Norway, primarily in larger hospitals.
The Micra™ Transcatheter Pacemaker System (Micra™) is a class III medical device designed to treat symptomatic bradycardia. It received CE Mark approval in April 2015 and approval from the US Food and Drug Administration in April 2016. Micra™ is a leadless device implanted directly into the right ventricle, aimed at reducing complications associated with leads and subcutaneous pockets. The device is miniaturized, with an active fixation mechanism and automated pacing capture threshold management to maximize battery longevity. Micra™ is delivered via the femoral or jugular veins using a specialized introducer and delivery system. The device can be repositioned or retrieved, if necessary. At the end of its battery life, Micra™ can be turned off and additional devices can be implanted if needed.

Objective

The submitter presented the Micra™ device for consideration previously in 2016. This second assessment considers whether the submitter has provided adequate evidence to show that the Micra™ has the following benefits, compared with conventional transvenous pacemakers (TVPM):

- Equal or superior technical performance, patient-relevant effectiveness, and safety
- Equal or reduced impact on health care resources
- Is cost-effective

The submitter claims that Micra™ has benefits, compared with conventional pacemakers in terms of minimal infection risk, higher quality of life, and elimination of all lead and pocket complications. The submitter claims that the Micra™ offers expanded access for high-risk subgroups of patients (i.e. patients with end stage renal disease (ESRD), high risk of infection or with limited venous access) precluded from receiving a conventional transvenous pacemaker.

Methods

Literature search: NOMA evaluated the submitter's literature search and selection process to ensure all relevant studies were identified. We believe there is a non-negligible risk that the evidence base provided by the submitter is not complete.

Clinical effectiveness: NOMA evaluated the effectiveness of Micra™ by critiquing the quantification of the effect of the technology versus a transvenous pacemaker (TVPM) on 26 outcome measures presented in the submission. NOMA used data provided by the submitter complemented by own data extraction from original studies when necessary. NOMA conducted meta-analyses for outcomes where possible, following standard methods.

Health economics: the submitter’s analysis used a Markov model with a lifetime horizon to compare Micra™ vs. TVPM in three high-risk patient groups: (1) ESRD, (2) history of infection, and (3) patients requiring epicardial leads. NOMA’s main analysis adjusted the base case to calculate a weighted average of the incremental cost-effectiveness ratio (ICERs), assessing cost-effectiveness. The primary driver of the model was the probability of infection.

Results

The clinical and safety effectiveness evidence comes from 3 systematic reviews of quality ranging from poor (2) to fair quality (1), one small randomized controlled trial, 7 prospective and 10 retrospective non-randomized studies. Studies reported follow-up to a maximum of 36 months. Technical performance (pacing threshold, pacing impedance, and R-wave) results did not provide a clear picture in favor of Micra™. Micra™ appears comparable to TVPM in terms of mortality mid to long-term. Some studies have reported higher short term or in-hospital mortality rates for Micra™. This difference could be attributed to patients’ selection and referral patterns rather than an inherent risk associated with Micra™. Two studies' results suggest potential improvements in quality of life at 6 months. Also, two small studies indicated overall satisfaction among patients receiving Micra™ vs. TVPM at three and six months. The data available for Micra™ on safety are mixed. Both pacemakers have risks, while Micra™ complications may be more prominent short term (e.g. pericardial effusion or perforation during implantation) TVPM complications are often faced long-term (leads dislodgement, infections, etc.). NOMA’s meta-analysis of prospective studies for any complications shows comparable results between Micra™ vs. TVPM, but retrospective studies suggest individuals receiving Micra™ have a lower risk of any complications compared with TVPM. Studies suggest a potential advantage of Micra™ mitigating the risk of valvular regurgitation compared to TVPM, particularly tricuspid regurgitation.

Health economics: NOMA’s main analysis using the weighted ICER (across all 3 subgroups), Micra™ generated 0.1 additional QALYs compared with TVPM (3.59 versus 3.49), at a total cost of about NOK 156,000 for Micra™ compared with NOK 125,000 for TVPM (Δ ≈ NOK 31,000). While Micra™ was more costly, it was found to provide incremental health benefits with an ICER of around NOK 329,000 per QALY. The health benefit was primarily caused by a reduction in the probability of infection (as documented by the Micra CED study), which was a major concern in the high-risk subgroups evaluated. The most favorable scenario, assuming a reduction in Micra™ long term risk of infection, resulted in the lowest ICER of ≈ NOK 327,000 per QALY gained. In contrast, the scenario assuming no difference in probability of infection between Micra™ and TVPM led to the highest ICER, ≈ NOK 645,000 per QALY gained. Sensitivity analysis revealed that the risk of infection had the greatest impact on the ICER due to variations in infection odds ratio between Micra™ and TVPM. Higher Micra™ device costs raised the ICER, and improved battery performance, and enhanced cost-effectiveness. The weighted absolute shortfall was found to be 4.0 QALYs that corresponds to severity group 2. Adopting Micra™ for all eligible patients in the high-risk subgroups results in a budget impact of NOK 10.3 million, by year 5, with most costs driven by the initial implantation.

Discussion

Most submitter’s evidence for clinical effectiveness did not specifically focus on high-risk patients but rather on individuals eligible for single-chamber ventricular pacing. Regarding health economics, there were two main issues. First, except for the pivotal study, the evidence is derived from studies other than those used to assess clinical effectiveness. Second, the studies included in the model used any cardiac implantable electronic device as an intervention rather than single-chamber, leadless pacemakers, i.e. Micra™.

The clinical evidence is mostly based on non-randomized studies using data from individuals eligible for single-chamber ventricular implantation. NOMA suggests the clinical data provided do not match the submitter's claim. This is important as the submission presented clinical aggregated data rather than data specific for the high-risk subgroups for whom a leadless pacemaker may be the only treatment option. The discrepancy between the clinical effectiveness data provided and the submitter's claims makes it hard to determine the true impact of Micra™ compared to TVPM. Further trials are needed to confirm these findings focusing on the sub-groups of interest. Many sources rely on administrative claims data, which can be inaccurate or incomplete. The sources often lack long-term data, so it is difficult to assess the performance of Micra™ over extended periods.
NOMA was unable to present overall results for technology performance because of study heterogeneity. The mortality and infections data provided in the non-randomized studies show that Micra™ is comparable to TVPM at all available follow-up times. However, these results will be very dependent on the selection of patients. There were some benefits in quality of life at 6 months, but study participants may have had significant baseline limitations both physically and mentally. Overall, NOMA's assessment does not indicate that Micra™ is superior to TVPM technically, that it provides higher quality of life or reduces mortality and infections for the populations claimed.

The Micra™ incurs higher costs than TVPM but offers incremental health benefits by reducing infection-related complications in high-risk groups. This is especially relevant for patients with a history of infection, comorbidities, or those needing epicardial leads. However, the results are informed by a Micra Coverage with Evidence Development (CED) study and adjusted for subgroup-specific risks. While not included in the health economic model, clinical experts suggest that Micra™ may also benefit patients with limited venous access or those requiring temporary pacing due to endocarditis. However, significant uncertainties remain, particularly concerning long-term risks, as well as the generalizability of the cardiac implantable electronic devices (CIED) studies used in the model to proxy the intended Micra™ subgroups. The absence of RCTs and lack of documented evidence for high-risk groups in meta-analysis complicates the assessment of Micra™'s effectiveness and safety, particularly for these groups.

Conclusion

The current evidence base is heterogeneous and mostly composed of non-randomized studies with often small sample sizes and short follow-up periods. The literature search was probably not optimal. The overall certainty of evidence was rated as low or very low, with high risk of bias in many studies. A critical issue is the extrapolation of aggregated clinical data to high-risk subgroups for which benefits are claimed.

While Micra™ appears likely to be non-inferior to TVPM for most outcomes, higher quality evidence is needed to strengthen certainty in the findings. Clinical experts suggest that careful patient selection and operator expertise appear crucial for optimal outcomes.
The weighted ICER results in the main analysis, suggest Micra™ may be beneficial for high-risk groups, particularly those who are unable to use traditional pacing due to history of infection, comorbidities, or the need for epicardial leads. Although uncertainty exists due to limited evidence in high-risk subgroups, the challenges of conducting further studies should be considered when evaluating Micra™'s cost-effectiveness and safety.

Sammendrag (Norwegian summary)

Innledning

Bradykardi er en unormalt langsom hjerterytme forårsaket av problemer i hjertets elektriske ledningsevne, ofte i sinus eller atrioventrikulærknuter. Symptomer inkluderer tretthet, svimmelhet, besvimelse, brystsmerter og hjertebank, noe som påvirker livskvaliteten. Pacemakerterapi, som leverer elektriske impulser for å opprettholde en normal hjerterytme, er den primære behandlingen for symptomatisk, ikke-reversibel bradykardi. Denne terapien kan forbedre og noen ganger forlenge livet. Regelmessige oppfølginger er avgjørende for å overvåke og justere pacemakeren.
I 2020 ble det i Norge implantert 3 779 nye pacemakere, hvor de fleste var to-kammer pacemakere. De fleste pacemakere ble satt inn etter diagnoser av synkope, nesten synkope, bradykardi eller hjertestans. Den største aldersgruppen som fikk pacemakere var pasienter i alderen 61-80 år. Den årlige implantasjonsraten anslås av innsenderen (Medtronic Norge AS) til å være rundt 70 pasienter, primært ved større sykehus.
Micra™ Transcatheter Pacemaker System (Micra™) er en klasse III medisinsk utstyr utviklet for å behandle symptomatisk bradykardi. Den fikk CE-merkegodkjenning i april 2015 og godkjenning fra US Food and Drug Administration i april 2016. Micra™ er en ledningsfri enhet implantert direkte i høyre ventrikkel, og skal redusere komplikasjoner forbundet med ledninger og subkutane lommer. Enheten er miniatyrisert, med en aktiv fikseringsmekanisme og automatisert styring av pace-terskel for å maksimere batteriets levetid. Micra™ leveres via lår- eller halsvener ved hjelp av et spesialisert innførings- og leveringssystem. Enheten kan relokeres eller ekstraheres, om nødvendig. På slutten av batterilevetiden kan Micra™ slås av og ytterligere enheter kan implanteres om nødvendig.

Hensikt

Innsender, Medtronic Norge AS, presenterte Micra™ tidligere for vurdering i 2016. Denne revurderingen vurderer om innsenderen har fremlagt tilstrekkelig dokumentasjon for å vise at Micra™ har følgende fordeler sammenlignet med konvensjonelle transvenøse pacemakere:
• Lik eller bedre teknisk ytelse, pasientrelevant effekt og sikkerhet
• Lik eller redusert innvirkning på helsevesenets ressurser
• Er kostnadseffektiv
Innsenderen hevder at Micra™ har følgende fordeler sammenlignet med konvensjonelle pacemakere:
• Minimal infeksjonsrisiko, høyere livskvalitet; og eliminering av alle lednings- og lommekomplikasjoner. Innsenderen hevder at Micra tilbyr utvidet tilgang for høyrisikopasientgrupper (f.eks. pasienter med nyresykdom i sluttstadium (ESRD), høy infeksjonsrisiko og med begrenset venøs tilgang) som ikke kan få en konvensjonell transvenøs pacemaker.

Metode

Litteratursøk: DMP evaluerte innsenderens litteratursøk og utvalgsprosess for å sikre at alle relevante studier ble identifisert. Vi mener det er en ikke ubetydelig risiko for at dokumentasjonsgrunnlaget levert av innsender ikke er fullstendig.

Klinisk effekt: DMP evaluerte effekten til Micra™ ved å kritisk vurdere kvantifiseringen av effekten av teknologien og de relevante komparatorene på 26 utfallsmål presentert i dokumentasjonspakken. NOMA brukte data levert av innsender supplert med egne datauttrekk fra originale studier ved behov. NOMA gjennomførte metaanalyser for utfall der det var mulig, etter standardmetoder.

Helseøkonomi: Avsenderens analyse brukte en Markov-modell med en livstidshorisont for å sammenligne Micra™ med konvensjonelle transvenøse pacemakere (TVPM) i tre høyrisikogrupper: (1) ESRD, (2) tidligere infeksjon, og (3) pasienter med behov for epikardielle elektroder. NOMA's hovedanalyse justerte base-case ved å bruke en vektet ICER-tilnærming for pasientgruppene i hovedanalysen, for å beregne Micra™'s kostnadseffektivitet. Den primære driveren for modellen var sannsynligheten for infeksjon.

Resultater

Klinisk effektivitet: Dokumentasjonen for effekt og sikkerhet kommer fra 3 systematiske oversikter som varierer mellom dårlig (2) til middels kvalitet (1), én liten RCT, 7 prospektive og 10 retrospektive ikke-randomiserte studier. Studier rapporterte oppfølging til maksimalt 36 måneder. Teknisk ytelse (pacingterskel, pacing-impedans og R-bølge) ga ikke et klart bilde til fordel for Micra™. Micra™ ser ut til å være sammenlignbar med TVPM når det gjelder dødelighet på mellomlang og lang sikt. Noen studier har rapportert høyere korttids og sykehusdødelighet for Micra. Denne forskjellen kan bli tilskrevet pasientseleksjon og henvisningsmønstre heller enn en iboende risiko ved Micra™. To studier tyder på potensielle forbedringer i livskvalitet etter 6 måneder. To små studier antyder også større tilfredshet med Micra™ vs. TVPM ved 3 og 6 måneder. Dataene som er tilgjengelige for Micra™ angående sikkerhet er blandede. Begge typer av pacemakere er forbundet med risiko, men Micra™ kan ha mer komplikasjoner på kort sikt (f.eks. perikardial effusjon eller perforasjon ved implantasjon) mens TVPM komplikasjoner kommer mer på lang sikt (ledningsforflytning, infeksjoner, etc.). NOMA's metaanalyse av prospektive studier viser sammenliknbare resultater for alle komplikasjoner for Micra™ vs. TVPM, mens retrospektive studier viser en lavere risiko for komplikasjoner for Micra™. Studier tyder på en potensiell fordel for Micra™ ved å redusere risikoen for klaffelekkasje sammenliknet med TVPM, særlig trikuspidalklafflekkasje.

Helseøkonomi: I hovedanalysen (med vektet ICER for alle tre subgruppene) genererte Micra™ 0,1 ekstra QALYs sammenlignet med TVPM (3,59 mot 3,49), til en total kostnad på ca. NOK 156 000 for Micra™ mot NOK 125 000 for TVPM (Δ ≈ NOK 31 000). Mens Micra™ var dyrere, ble det funnet å gi økte helsegevinster med en ICER på rundt NOK 329 000 per QALY, primært gjennom en reduksjon i infeksjonsraten, som var en stor bekymring i de høyrisikopasientgruppene som ble evaluert. Det mest gunstige scenarioet, forutsatt en reduksjon i Micra™ infeksjonsrisiko, resulterte i den laveste ICER på ≈ NOK 327 000 per QALY. Derimot førte scenarioet som antok ingen forskjell i infeksjonsrater mellom Micra™ og TVPM til den høyeste ICER, ≈ NOK 645 000 per oppnådd QALY. Sensitivitetsanalyse viste at infeksjonsrater hadde størst innvirkning på ICER, med variasjoner i odds for infeksjon mellom Micra™ og TVPM som i betydelig grad påvirket kostnadseffektiviteten. Høyere enhetskostnader økte ICER, forbedret batteriytelse, og økte kostnadseffektiviteten. Det vektede absolutte helsetapet (AS) ble funnet å være 4.0 QALYs (alvorlighetsgruppe 2). Å ta i bruk Micra™ for alle kvalifiserte pasienter i høyrisiko-undergruppene resulterer i en budsjetteffekt på NOK 10,3 millioner innen år 5, med de fleste kostnadene drevet av den første implantasjonen.

Diskusjon

Det meste av den innsendte dokumentasjonen for klinisk effekt gjaldt individer som er aktuelle for énkammer ventrikkelpacemaker og ikke spesifikt høyrisikopasienter. Det var to hovedutfordringer i den helseøkonomiske delen av dokumentasjonspakken. For det første: bortsett fra den sentrale studien, var data hentet fra andre studier enn de som ble brukt for klinisk effekt. For det andre: intervensjonen i studiene inkludert i den økonomiske modellen var ikke avgrenset til Micra™ Transcatheter Pacing System, (énkammer, ventrikkelpacemaker uten ledning), men kunne være alle typer pacemakere og implanterbare hjertestartere.

Den kliniske dokumentasjonen er for det meste basert på ikke-randomiserte studier basert på data for individer som er aktuelle for énkammer ventrikkelpacemaker.

NOMA foreslår at de oppgitte kliniske dataene ikke samsvarer med innsenderens krav. Dette er viktig ettersom innsenderen presenterte aggregerte data i stedet for data som er spesifikke for høyrisikoundergruppene for hvem en trådløs pacemaker kan være det eneste behandlingsalternativet. Dette gjør det vanskelig å bestemme den faktiske effekten av Micra™ vs. TVPM. Flere studier er nødvendig for å bekrefte disse funnene i de aktuelle subgruppene. Mange av studiene er basert på registerdata som kan være unøyaktige og ufullstendige. Kildene mangler ofte langtidsoppfølging, noe som gjør det vanskelig å undersøke langtidseffekter av Micra™.
NOMA var ikke i stand til å presentere overordnede resultater for teknologiytelse på grunn av studienes heterogenitet. Dataene om dødelighet og infeksjoner gitt i de ikke-randomiserte studiene viser at Micra™ er sammenlignbar med TVPM på alle tilgjengelige oppfølgingstidspunkter. Imidlertid vil disse utfallsresultatene være svært avhengig av valg av pasienter. Det var noen fordeler med hensyn til livskvalitet etter 6 måneder, men studiedeltakerne kan ha hatt betydelige baselinebegrensninger både fysisk og mentalt. Samlet sett indikerer ikke NOMAs vurdering at Micra™ er overlegen TVPM teknisk sett, gir høyere livskvalitet eller reduserer dødelighet og infeksjoner.
Micra™ pådrar seg høyere kostnader enn TVPM, men kan gi inkrementelle helsefordeler ved å redusere infeksjonsrelaterte komplikasjoner, spesielt viktig for pasienter med infeksjonshistorikk, komorbiditeter eller behov for epikardiale elektroder.

Men resultatene kommer fra Micra Coverage with Evidence Development (CED) studien justert for subgruppespesifikk risiko. Selv om det ikke er inkludert i den helseøkonomiske modellen, så antyder rekrutterte kliniske eksperter at Micra™ også kan være nyttig for pasienter med begrenset venetilgang eller som trenger midlertidig pacing ved endokarditt. Det gjenstår imidlertid betydelige usikkerhetsmomenter, spesielt når det gjelder langsiktige risikoer, samt generaliserbarheten av Cardiac Implantable Electronic Devices studiene (CIED-studiene) som brukes i modellen til de tiltenkte Micra™ undergruppene. Fraværet av RCTer kompliserer vurderingen av Micra™s effektivitet og sikkerhet, spesielt i høyrisikogrupper.

Konklusjon

Det nåværende dokumentasjonsgrunnlaget er heterogent og hovedsakelig sammensatt av ikke-randomiserte studier med små utvalgsstørrelser og korte oppfølgingsperioder. Litteratursøket var sannsynligvis ikke optimalt. Den generelle tilliten til dokumentasjonen ble vurdert som dårlig til svært dårlig, med høy risiko for skjevhet i mange studier. Et kritisk problem er ekstrapolering av aggregerte kliniske data til høyrisikoundergrupper som innsenderen hevder har fordeler av behandlingen.

Selv om Micra™ sannsynligvis ikke er dårligere enn TVPM for de fleste utfall, er det nødvendig med dokumentasjon av høyere kvalitet for å styrke tilliten til funnene. Kliniske eksperter antyder at nøye utvelgelse av pasienter og operatørs implantatekspertise fremstår som avgjørende for best mulige resultater.
Den vektede ICER-analysen basert på hovedanalysen tyder på at Micra™ kan være gunstig for høyrisikopasienter, spesielt de som ikke kan bruke tradisjonell pacing på grunn av infeksjonsrisiko, komorbiditeter eller behov for epikardiale elektroder. Selv om det fortsatt er usikkerhet på grunn av begrenset dokumentasjon i høyrisikopopulasjoner, bør utfordringene ved videre studier vurderes når man evaluerer Micra™'s effektivitet og sikkerhet.

Preface

The Division of Health Economics and Analysis at the Norwegian Medical Products Agency (NOMA) was commissioned in June 2023 to perform a single technology assessment (STA) of the Micra™ TPS, leadless pacemaker. The commissioners are the National System for Managed Introduction of New Methods in the specialist health care service in Norway (Nye metoder).

In a STA, the technology (a medical device) is appraised based on documentation submitted by the manufacturer owning the technology, or their representatives ("the submitter"). The submitter in this assessment is Medtronic Norge AS.
A progress log that details the communication and progress is provided in Appendix 1.

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NOMA is solely responsible for the content of this report.

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Abbreviation List

AS	absolute shortfall
AV	atrioventricular
AV fistula	atriovenous fistula
BIM	budget impact model
CE	"conformité européenne", European conformity
CEA	cost-effectiveness analysis
CI	confidence interval
CIED	cardiovascular implantable electronic device
CKD	chronic kidney disease
CRT-P	cardiac resynchronization therapy pacemaker
DMP	Direktoratet for medisinske produkter (Norwegian for NOMA)
DRG	diagnosis-related group
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQoL 5 dimensions
ESRD	end-stage renal disease
EVPI	expected value of perfect information
FDA	Food and Drug Administration
GFR	glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	hazard ratio
HRQoL	Health-related Quality of Life
HTA	health technology assessment
ICD	implantable cardioverter-defibrillator
ICER	incremental cost-effectiveness ratio
ITT	Intention to treat
LHL	Norwegian organization working for patients with cardiovascular or respiratory disease and their next of kin
LPM	(or L-PM) leadless pacemaker
LVEF	left ventricular ejection fraction
MCID	minimal important clinically difference
MD	mean difference
Micra CDE	Micra Coverage with Evidence Development study
Micra IDE	Micra Investigational Device Exemption study
Micra PAR	Micra Transcatheter Pacing System Post-Approval Registry
Micra TP	Micra Transcatheter Pacing Study
MR	mitral regurgitation
ms	millisecond
mV	millivolts
NA	non available
NHLBI	National Heart, Lung, and Blood Institute
NOK	Norwegian kroner
NOMA	Norwegian Medical Products Agency
NR	not reported

OR	odds ratio
PICOS	Population, Intervention, Comparator, Outcomes, Study designs
PM	pacemaker
PMID	PubMed unique identifier
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-years
RCT	randomized controlled trial
RR	risk ratio
RV	right ventricular
R-wave	first positive (upward) deflection after the p-wave in the QRS complex
SC-PM	single chamber (transvenous) pacemaker
SD	standard deviation
SF-36	Short Form (36) health survey
STA	single technology assessment
T	tesla
TM	trademark
TPS	transcatheter pacing system
TR	tricuspid valve regurgitation
TVPM	transvenous pacemaker
US	United States
V	Volts
VoI	value of information
VR	ventricular rate
Vs.	versus
VVI	V (Ventricular pacing): The pacemaker delivers electrical impulses to the ventricle(s) of the heart. V (Ventricular sensing): The pacemaker monitors the electrical activity of the ventricle(s). I (Inhibition): If the pacemaker senses a natural heartbeat, it inhibits itself from delivering an impulse.
VVIR	V (Ventricular pacing). V (Ventricular sensing). I (Inhibition). R (Rate modulation): The pacemaker can adjust the pacing rate based on the patient's physical activity or metabolic needs.

1. Background

1.1 Bradycardia

A normal heartbeat starts as an electrical signal, typically originating from the sinus node, which travels along a conduction pathway. The atrioventricular (AV) node regulates the timing between the upper (atrial) and lower (ventricular) chambers of the heart. Parts of this conduction pathway can malfunction, resulting in an abnormally slow heartbeat known as bradycardia.

The two most common forms of abnormal bradycardia relate to the dysfunction of the sinus node the AV node. Sinus node dysfunction, also known as sick sinus syndrome, occurs when heart disease causes a delay or prevention of the initial electrical impulse that leads to a normal heartbeat. AV block occurs when the conduction of an electrical impulse from the atrium to the ventricles is impaired.

Bradycardia symptoms include fatigue, dizziness, confusion, fainting, chest pain, and palpitations. Patients with untreated bradycardia have a reduced quality of life compared with the general population of similar age. Their quality of life scores are similar to those of patients entering cardiac rehabilitation programmes after a heart attack, heart failure, angioplasty, or cardiac surgery (1).

For symptomatic and non-reversible bradycardia, the only effective treatment is pacemaker therapy. Pacemakers reduce symptoms by maintaining a normal heart rhythm when the heart's rhythm becomes too slow. By delivering an electrical stimulus to the heart muscle or myocardium, the pacemaker initiates a localized depolarization process that propagates as a wavefront of contraction. For the pacemaker's electrical pulse to stimulate (capture) the myocardium, it must be applied with sufficient amplitude and duration (output). Therapy efficacy is mainly assessed by the pacemaker's ability to deliver such pulses on demand. The minimum required pacing output needed to capture the myocardium is called the pacing threshold. A pacemaker system's threshold values can be measured with a simple test using a pacemaker programmer. In clinical practice, healthcare professionals measure efficacy or device performance during regular follow-up visits or patients report the recurrence or onset of bradycardia symptoms.

Pacemaker therapy has been shown to significantly improve quality of life, both in the short and long term, and in some instances can prolong life (1-3). Pacemaker treatment for bradycardia is common; more than one million people worldwide receive a pacemaker each year (4).

In Norway, 3,779 new pacemakers (representing 674 pacemakers per one million inhabitants) were inserted in 2022 including conventional transvenous single chamber pacemakers (n=570) and intracardiac (leadless) pacemakers (n=15) (5). Around 90% of pacemakers were inserted following a diagnosis of syncope/near syncope/bradycardia or cardiac arrest. Patients aged 61-80 years are the largest age group receiving pacemakers, followed by those aged 81-90 years and those aged 91-100 years (5). This age distribution has remained stable in Norway over the years. The breakdown of pacemaker types varies by implantation center.

The submitter estimates that the annual implant rate for Norway would be approximately 70 patients and that the use would be restricted to larger, likely university, hospitals due to the submitter’s strict requirement on training and operator implanting frequency.

1.2 Description of the technology

The technology under consideration is the Micra™ Transcatheter Pacemaker System (Micra™), a class III medical device to treat symptomatic bradycardia. Micra™ received CE Mark approval in 2015 (6;7) and was approved by the US Food and Drug Administration (FDA) on April 6, 2016 (8). Similar devices include Nanostim™ (Abbott), which was approved by the FDA in 2013 but discontinued in 2017, Aveir™ single chamber, which received US FDA approval in 2022, Empower (Boston Scientific) and WiSE-CRT (EBR Systems) (9).

The Nanostim™ leadless pacemaker system has received several advisories due to safety concerns. On February 18, 2016, the FDA's circulatory system devices panel discussed the device's effectiveness and safety outcomes. Later in April 2018 Abbott issued an update regarding the Nanostim™ leadless pacemaker, highlighting issues. Nanostim™ was removed from the market in October 2017 due to battery and docking button issues, which had caused device failures and the need for surgical interventions to remove or replace the pacemakers.

Conventional transvenous pacing systems consist of a pacemaker device implanted into a subcutaneous pocket in the chest, with one or two leads threaded through veins into the heart. Although this is generally effective, approximately one in eight patients (12.5%) experience complications, frequently related to the lead or subcutaneous pocket. Pocket complications include infections, hematomas, and erosions. Lead complications comprise infections, pneumothoraces, hemothoraces, dislodgments, fractures, and insulation breaches. Leads are the most vulnerable component because they are prone to fractures, insulation defects, connector issues, and infections. In the FOLLOWPACE study, lead complications such as dislodgement, fractures, and cardiac injuries reached 11% at 5 years, while pocket complications (infection, erosion, hematoma) were estimated at 8% over the same period (3).

Leadless pacemakers such as the Micra™ have built-in batteries and electrodes that have been developed to be implanted within the right ventricle of the heart. These types of pacemakers do not need a subcutaneous pocket and transvenous lead and hence reduce their related complications.

The Micra™ includes a delivery system, an introducer, and a pacemaker device. The implantable device, the Micra™ Model MC1VR01, is a miniaturized (2.8mm in diameter and 25.9mm long), single chamber transcatheter pacemaker that provides bipolar sensing and rate responsive pacing in the right ventricle. It offers automated pacing capture threshold management to maximize battery longevity. The device has an active fixation mechanism of 4 electrically inactive tines designed to anchor it in the cardiac tissue at the implant location in the right ventricle. Patients with an implanted Micra™ are able to receive magnetic resonance imaging scans if required for diagnostic purposes, allowing for full body scans at 1.5T and 3T (Figure 1).

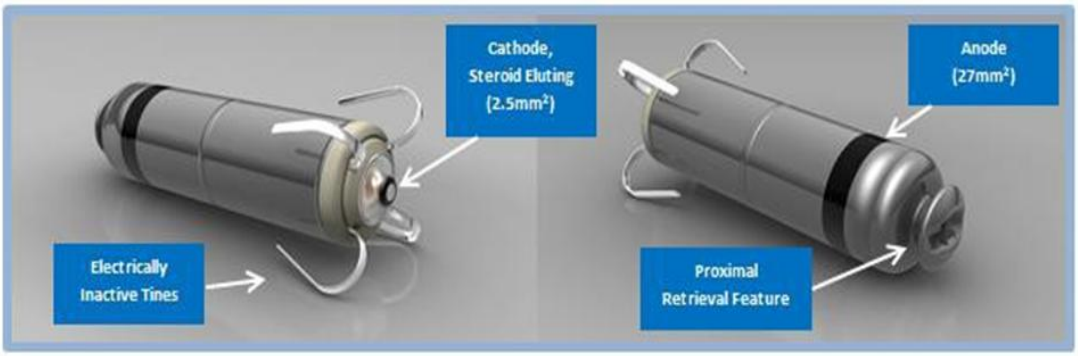


Figure 1. Micra Implantable Device
Source Medtronic submission.

The Micra™ is delivered to the heart via the femoral or jugular vein, or upper thorax using the introducer and delivery tool (Figure 2). The Micra™ Introducer is a single-use, disposable hydrophilic coated sheath system consisting of a dilator with a 0.89 mm guide wire and a coil-reinforced introducer sheath. It provides a flexible and haemostatic conduit for inserting the Micra™ device. The sheath features a radiopaque marker at the distal tip, a rigid seal housing with a haemostatic valve assembly, a side port extension with a 3-way valve, and a suture loop for attaching it to the patient.

Figure 2. Micra introducer
Source Medtronic submission.

The single-use Micra™ transfemoral catheter (Figure 3) delivery system is designed to deliver, deploy, and test the placement of the Micra™ device. It has two braided shaft assemblies attached to a handle, with an articulating distal end controlled by a button on the handle. The Micra™ device sits in a cup at the distal end and is deployed by a button on the handle. It is tethered through the shafts to the handle, allowing locking/releasing via a button. The delivery system works in conjunction with the introducer sheath.

Figure 3. Transfemoral delivery catheter
Source Medtronic submission

The Micra™ implanted device can be retrieved or repositioned using the three sterile components: the Micra™ Introducer, the Micra™ Model MC1VR01 transcatheter pacing system, and a 175 cm or longer retrieval snare with ≤4 French outer diameter. If repositioning is needed after tether removal during initial implantation, the original introducer and delivery system can be used.

Micra™ does not typically need to be explanted as it can be turned off and additional Micra™ devices or upgrades can be implanted. At the end of its battery life, Micra™ is

permanently programmed “off”. Micra™ occupies <1% of the right ventricle volume, which means the right ventricle can likely accommodate at least 3 devices. Considering the average pacemaker patient is 75 years old and that the Micra™ has a projected life of 13.7 years, the submission suggests that most patients will not outlive 3 Micra™ devices, avoiding the need for extraction at the end of service.

Acute retrieval of Micra™ is possible using the proximal retrieval feature, primarily for cases of threshold increase post-tether removal before encapsulation occurs. Long-term retrieval depends on the degree of encapsulation that has occurred. The submission reports that a successful retrieval has been made at 430 days (one patient). The submission reports that encapsulation varies by patient and while full encapsulation is generally beneficial (by eliminating blood contact to reduce infections and the risk of deep vein thrombosis) it can complicate late retrieval.

1.3 Objective and research question

The submitter presented the Micra™ TPS device for consideration in 2016. The Norwegian Institute of Public Health published the results in 2018 (10). Since then, the submitter claims that a substantial body of research evidence has been published to support a re-submission.

This re-assessment considers whether the submitter has provided adequate evidence to show that the Micra™ has the following benefits, compared with conventional transvenous pacing systems:

- Equal or superior technical performance
- Equal or superior patient-relevant effectiveness
- Equal or superior safety
- Equal or reduced impact on health care resources
- Is cost-effective

Specifically, the submitter claims that the Micra™ has the following benefits, compared with conventional pacemakers:

- Minimal infection risk
- Expanded access for patients precluded from receiving a conventional transvenous pacemaker
- Higher quality of life
- Elimination of all lead and pocket complications

1.4 How this report was developed

Literature search

A comprehensive search is crucial for the credibility of the assessment results. Therefore, the team evaluated whether the submitter’s literature searches and selection process, as reported in the submission, were likely to have identified all studies and publications that met the predefined selection criteria. We checked whether all articles included in the dossier could be retrieved from the relevant sources by the reported search strategy. NOMA's team investigated whether we, with minimal resources, could identify relevant publications beyond those included in the submission. We used two approaches. First, we checked whether publications included in the three systematic reviews referenced in the submission (11-13) were all accounted for as either included or on the submission list of excluded studies. Second, we ran a search in the bibliographic databases Embase and MEDLINE (Ovid) using clinical trial numbers from clinicaltrials.gov and other trial registries used in the submission.

This search retrieved journal articles that report results from or are otherwise related to these studies/trials. We assessed the record titles and abstracts for relevance and whether we would expect to find them either as included or on the submission list of excluded publications (see Appendix 2). We did not read the full text.

To supplement the safety information provided in the submission, in July 2024 NOMA searched the European database on medical devices, EUDAMED, the website of Medicines and Healthcare Products Regulatory Agency (MHRA, UK) and the US Food and Drug Administration MAUDE database (Manufacturer and User Facility Device Experience). We repeated the MAUDE search in November 2024 and also looked at data for the relevant Micra Model (MC1VR01 Micra VR) in the CRM Product Performance eSource and Product Performance Report. Results are reported in the results section under any serious adverse events.

Clinical effectiveness

This appraisal analysis aimed to get estimates of the clinical effectiveness of Micra™ versus conventional pacemakers. The submitter was required to consider and present all relevant studies in the assessment of clinical effectiveness, taking into account the range of typical patients, normal clinical circumstances, and clinically relevant outcomes.

NOMA evaluated the effectiveness of Micra™ by critiquing the quantification of the effect of the technology and the relevant comparator on appropriate outcome measures presented in the submission, using data from systematic reviews, a randomized controlled trial (RCT), non-randomized studies and ongoing studies.

- NOMA presents the results numerically or narratively by study design following a hierarchy of evidence where high quality systematic reviews are at the top of the hierarchy, followed by RCTs, prospective non-randomized controlled trials, and finally retrospective non-randomized controlled trials.
- The systematic reviews included in the submission compared “leadless pacemakers” to transvenous pacemakers. NOMA excluded poor quality systematic reviews included by the submitter as there were many methodological issues that could lead to skewed conclusions (see sections 3.2.1).
- NOMA reviewed data from the submission and also reviewed data from original studies when necessary.
- Two studies (14;15) included Micra™ and Nanostim™. When data were presented independently for Micra™, we used those data, otherwise, we used the data for all leadless pacing systems.
- NOMA contacted the authors of two studies (16;17) regarding the type of device included, but no response was obtained. Thus, NOMA cannot guarantee the intervention is only Micra™. We noticed that neither of the two studies has been included in the systematic reviews referenced in the submission. Attempts to contact authors for that and other reasons were recorded and responses are presented in Appendix 3.
- The submitter included 38 outcomes. However, upon reading the submission NOMA did not find data for 12 of them. For pragmatic reasons NOMA combined some outcomes. Battery life, and battery failure were combined, as were device revision, retrieval and replacement.
- When two or more studies reported the same outcome and NOMA assessed that the interventions were sufficiently homogeneous, NOMA pooled the data (meta-analysis). The meta-analyses are presented grouped by study design (RCTs, prospective studies, and retrospective studies). We included studies in the meta-analyses regardless of their individual risk of bias rating. We used a random-effects model for all meta-analyses (18).

    - For continuous data, we used group post-test mean and standard deviations to calculate effect sizes. We expressed effect sizes preferentially in the form of mean differences and 95% confidence intervals (95% CIs). We analysed dichotomous data as risk ratios (RRs) and 95% CIs.
    - We used RevMan web software (version 8.7.0) (19) to generate forest plots to display the results.
    - To assess heterogeneity, NOMA followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (18), interpreting an I^2 value from 0% to 40% as 'might not be important', a value from 30% to 60% as representing 'moderate' heterogeneity, a value from 50% to 90% as representing 'substantial' heterogeneity, and a value from 75% to 100% as representing 'considerable' heterogeneity. NOMA explored cases of statistical heterogeneity where the I^2 fell between 50% and 60%. The exploration started with visually inspecting the forest plot and was followed by a sensitivity analysis. In addition, we assessed clinical and methodological diversity in terms of participants, interventions, outcomes, and study characteristics to determine whether a meta-analysis was appropriate. No other sensitivity analyses were conducted.
    - In cases where a meta-analysis was not possible, results are displayed in a forest plot but suppressing the pooled estimate.
    - When the submitter provided hazard ratios, odds ratios, or narrative information on a particular outcome, or the study presented additional follow up times to what was entered in the meta-analysis, NOMA presents these narratively as “data not included in the meta-analysis.”
- NOMA used the GRADE framework (20) to present the certainty of evidence. As the risk of bias was not presented by outcome, a narrative synthesis is presented.
    - NOMA searched for the minimal important clinical difference (MICD) for health related quality of life and cardiology. MICD is defined as the smallest change that patients perceive as beneficial. MICD is also crucial for interpreting patient-reported outcomes and assessing treatment effectiveness.

Health Economics

NOMA reviewed the submitter’s Markov model. NOMA adjusted the base-case analysis for a weighted incremental cost-effectiveness ratio (ICER) approach to account for the distribution of patient subgroups, offering a more comprehensive view of the cost-effectiveness of LPM across different high-risk populations. The detailed methods are presented in section 6.1

Input from clinical experts and patients

Clinicians, appointed by the Norwegian commissioner for their clinical expertise, acted as peer reviewers, to enhance the assessment’s scientific rigor and relevance. Their insights provided real-world insight and context relevant to the clinical evidence and provided the Norwegian perspective on the technology’s effectiveness and safety. The report incorporates the valuable feedback provided by these clinicians. Additionally, a patient organization, serving as a liaison with the patient community, was engaged to offer feedback from the patients’ perspective. This feedback, presented in Section 5, enriches the HTA by highlighting the technology’s real-world impacts and aligning the evaluation with patients’ needs and values.

Following NOMA's policies, the clinical experts and the patient organization were asked to submit written disclosures of potential conflicts of interest that might affect, or might reasonably be perceived to affect, their objectivity and independence about the subject matter of the submission. No conflicts of interest were found.

Input from the submitter
NOMA shared a revised draft STA report with the submitter for their feedback. This step was a fact check for any additional insights or corrections needed before the report's final submission to the Norwegian commissioner.

2. Literature search and study selection

2.1 Inclusion criteria

The Micra™ submission file included studies investigating adult patients with bradycardia suitable for single-chamber ventricular pacemaker implantation.
The submitter compared the performance of the Micra™ leadless pacemaker to conventional pacemakers. Eligible study designs included randomized and non-randomized studies, including registry studies, systematic reviews and meta-analyses. Table 1 shows the submitter's selection criteria for the literature review. A wide range of outcomes were assessed considering different aspects of technical performance, patient-relevant effectiveness outcomes, safety outcomes and impact on health care resources. Comparative studies were eligible if they had at least 20 patients in each treatment arm. Any length of follow-up was eligible. The submitter placed no limits on date of publication or language.

Table 1. Research question (PICOS) specified by Medtronic relating to the effects, quality of life, safety and resource use of Micra™.

PICO element	Description
Population	Adult patients indicated for single-chamber ventricular pacemaker implantation.
Intervention	Micra™ Transcatheter Pacing System, Medtronic Inc.
Comparator	Conventional single chamber transvenous (VVI or VVIR) pacing
Outcomes	Technical performance • Pacing performance (sensing, impedance, pacing threshold) • Battery life • Adaptability (rate response) Patient-relevant effectiveness outcomes • Mortality (all-cause and cardiovascular) • Exercise capacity • Change of medication • Progression or recurrence of cardiac arrhythmias • Switch to an alternative device (pre-syncope or syncope) • Quality of life • Patient satisfaction Safety outcomes • Major procedure-related complications (infections, pericardial effusion, cardiac tamponade/perforation, thromboembolism, vascular complications (bleeding, arteriovenous/atrioventricular fistula, pseudoaneurysm, hematoma)) • Right ventricular dysfunction • Atrioventricular (AV-tricuspid and mitral) valve regurgitation • Pacemaker syndrome • Major device-related complications (device dislodgement, device malfunction, battery failure, device infection, pacemaker-induced arrhythmia) Health care resources • Procedure duration

	• Implant success rate • Time to hospital discharge
Follow-up	Any length
Years considered	All
Language	No exclusions
Study types	Controlled randomized clinical trials; non-randomized studies (N>20 in each treatment arm) including registry studies. Systematic reviews. HTAs were included in section 6.2 of the dossier.
Publication status	Published. Records from clinical trial registries that were not published were also examined for inclusion

Key: AV: atrioventricular; HTA: health technology assessment; VVI: ventricular pacing-ventricular sensing-inhibition; VVIR: ventricular pacing-ventricular sensing-inhibition rate modulation.

Animal studies, studies in vitro and studies using cadavers were excluded along with studies published only as abstracts, individual case studies, editorials and opinion pieces. Note that while studies including Nanostim™ or Aveir™ should not have been included (or should have been discounted) in primary studies, the systematic reviews included Nanostim and Averi studies.

2.2 Literature search and selection of studies in the submission

The submitter carried out searches of the following databases and resources in November 2021 with updates in November 2023:

- Embase and MEDLINE combined (Embase.com, Elsevier),
- MEDLINE In-process and Other Non-Indexed Citations (PubMed, National Library of Medicine),
- Cochrane Central Register of Controlled Trials (platform not specified),
- International HTA database (The International Network of Agencies for Health Technology Assessment),
- US National Library of Medicine Clinicaltrials.gov database,
- WHO International Clinical Trials Registry Platform.

The search strategies combined two concepts – the intervention and the comparator using the Boolean operator "AND". Within each concept, search terms were combined with the Boolean "OR" operator.

The searches identified a total of 790 records and following deduplication and study selection, 22 unique studies were eligible (19 clinical trials and 3 systematic reviews) reported in 28 documents (see PRISMA flow diagram in Appendix 4).

2.3 NOMA's comments on the submitted literature search and study selection

The literature searches performed by the submitter followed NIPH 2021 submission guidelines (21). The submitter provided the complete search strategies, a PRISMA flow

diagram, and a list of publications excluded following full text review enabling NOMA to conduct an appraisal of the search and selection process.

NOMA did not repeat or update the literature searches performed by the submitter. However, to investigate whether the search and screening might have missed relevant study reports we did some cross-checking to examine the following questions:

1. Was the search strategy in the main bibliographic databases (MEDLINE and Embase) able to retrieve all the included articles indexed in these databases?
2. Are all publications included in Darlington 2022, Gangannapalle 2023, and Shtembari 2023 (the systematic reviews referenced in the submission) accounted for as either included in the submission or on the submission list of studies excluded after full text screening?
3. Is it likely that all reports of included studies (i.e. all publications connected to a given study) fulfilling the selection criteria are either included or on the list of publications excluded after full text screening?

Our first step was to adapt the submitter's search strategy from Embase.com (Elsevier) to Ovid syntax (see Appendix 5). Next, we collected the PubMed identifiers (PMID) of all journal articles included in the submission. The PMIDs were put together in a search string and were run against the adapted search strategy in Ovid MEDLINE and Embase.

We found that all 28 articles included in the submission are indexed in MEDLINE. All included publications are also indexed in Embase, except for one of the systematic reviews (12). However, the search strategies missed three of the 28 included publications that could all have been retrieved, assuming the abstracts and indexing for the Embase records are the same across the Elsevier and Ovid platforms. The submitter clarified to us how these three articles were found: Garweg 2023 was found via their PubMed search (22), Marschall 2022 by reference checking (17) and Ritter 2015 (23) was known by the submitter in advance. Changing the search strategy for the comparator concept to also capture "conventional" pacemakers/ "pacing", would have retrieved Garweg 2023 and Ritter 2015. We have not investigated whether such an amendment would identify further relevant publications that should be added to the evidence base.

Regarding the second question, we assessed the abstracts of 20 articles not accounted for as included or excluded in the submission against the selection criteria. We found six that we would expect to see on the submission list of excluded publications. The remaining 14 articles did not meet the submitter's PICOS (see Figure 4).

Since September 2004, the International Committee of Medical Journal Editors (ICJME) "[..] has recommended that all medical journal editors require registration of clinical trials in a public trials registry at or before the time of first patient enrolment as a condition of consideration for publication" (24). It is reasonable to assume that clinical trial numbers often appear in the metadata or abstracts of journal articles reporting study results. Embase has a separate search field dedicated for clinical trial numbers associated with the database record for a journal article. Although searching for clinical trial numbers in MEDLINE and Embase is not likely to provide a complete list of references to journal articles reporting results from the studies, we regarded this procedure as a useful proxy to answer the third question. The search string of clinical trial numbers retrieved 22 unique records. We assessed the abstracts of the 22 records against the PICO framework criteria. We would expect to see two of the 22 on the submission list of excluded publications. The rest did not meet the PICO framework criteria (see Figure 5).

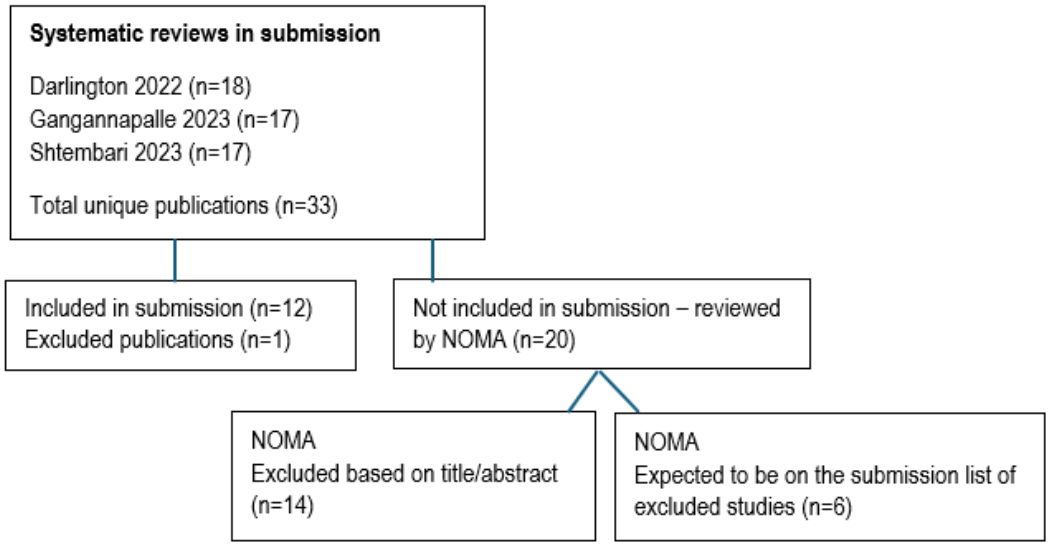


Figure 4. Tracing publications included in systematic reviews used in submissions

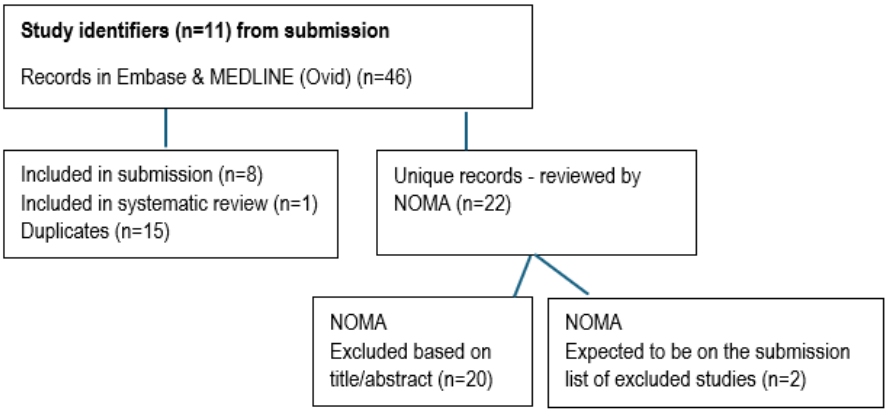


Figure 5. Tracing publications related to clinical trial numbers in the dossier

Looking at the submitted list of articles excluded after step two screening, we agree on all the exclusions. We were however surprised that as many as 23/31 of the references to publications excluded at full text screening were conference abstracts.
As described above, our cross-checking efforts identified eight publications that we would expect to find on the submission list of excluded publications after full text screening. We did not assess the full text of these publications. Overall, NOMA is concerned the submitter's information retrieval (literature search and selection) risked missing studies.

3. Evaluation of clinical effectiveness

3.1 Description of included studies

Evidence was available from three systematic reviews (see Table 2 and Sections 3.1.1 to 3.1.4), 20 primary studies and three trial registry records. The primary studies included in the submission were one randomized controlled trial (see Section 3.1.5 to 3.1.7), seven prospective non-randomized comparative studies published in 12 publications (see Sections 3.1.8 to 3.1.10) and eleven retrospective studies (see Sections 3.1.11 to 3.1.13). Data from some prospective studies were also likely to have been used in some retrospective studies.

The primary studies' characteristics are listed in Table 4, Table 5 and 6. Ongoing trials are presented in Table 7. The submitter clarified during email communication that no data were presented on some safety outcomes outlined in the PICO criteria as they were not reported in any of the included studies.

3.1.1 Populations in the systematic reviews

All three systematic reviews focused on patients receiving "leadless" pacemakers (i.e. Micra™, Nanostim™, and Aveir™) (11-13). The systematic reviews did not include the RCT (22), two of the Micra™ CED studies (25;26) or Micra™ TP (27) study, and did not include seven of the retrospective studies (14;16;17;28-31), likely because some of these studies were published after the reviews had completed their searches (i.e. the Darlington review search date was Nov 2020, the Gangannapalle search date was Aug 2023, and the Shtembari search date was April 2022).

Table 2. Details of the populations, study designs, comparator and outcomes reviewed in the submitter's eligible systematic reviews

Review author/year Number of studies Language	Population	Study designs	Comparator	Outcomes included in the reviews
Darlington 2022(11) Total 18 studies; included in meta-analysis Language: NR	Adult patients with an indication for single chamber right ventricular pacing who subsequently underwent leadless pacemaker Includes 4 studies with Nanostim™	All study types	Conventional pacemaker or none	Pacing threshold, mortality, any complications, infections, endocarditis, pericardial effusion, cardiac tamponade, hematoma, embolism or thrombosis, device dislodgement, device related complications, device revision/malfunction, reposition attempts, implant success rate
Gangannapalle 2023 (12) Total 17 studies; included in meta-analysis Limited to English	Leadless PM eligible patients Includes studies with Nanostim™ (1), Aveir™ (2), 'leadless' (1), dual chamber (3)	RCTs and non-RCTs	Conventional pacemaker	Mortality, overall complications, endocarditis, pericardial effusion, hemothorax, pneumothorax hematoma, device malfunction, revisions, re-intervention, retrieval.
Shtembari 2023 (13) Total 17 studies; included in meta-analysis English and English translations included	Patients undergoing leadless implantation Includes studies with Nanostim™ (2) and Aveir™ (2).	RCTs and non-RCTs	Conventional pacemaker	Pacing threshold, mortality, overall complications, endocarditis, pericarditis, pericardial effusion, cardiac tamponade, thrombosis and embolism, hemothorax, pneumothorax, AV fistula, device dislodgement, re-intervention, pseudoaneurysm, length of stay.

Key: AV, arterial venous; NR, not reported; PM, pacemaker; RCT, randomized controlled trials.

3.1.2 Systematic reviews overlap

The graphical representation of overlap for overviews (GROOVE) tool (32) is designed to improve overlap assessment by calculating the Corrected Covered Area metric for all systematic review pairs. The overlap of the included systematic reviews ranged from 16.7 to 70%. (see Figure 6 and Table 3). Figure 6 shows three “nodes” or each possible pair of systematic reviews with a representation of the results.

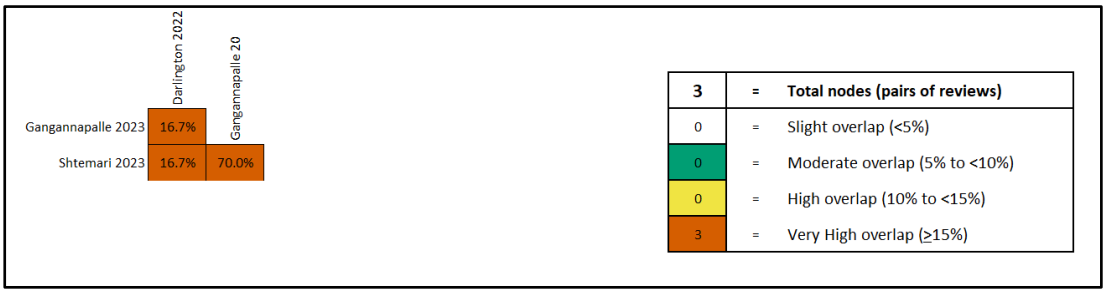


Figure 6. Graphical representation of the percentage of study overlap across the three systematic reviews

Table 3. Number of overlapping studies in the three included systematic reviews

Systematic review	Darlington 2022	Gangannapalle 2023	Shtembari 2023
	Number of studies =18	Number of studies =17	Number of studies =17
Darlington 2022 (11)		5 studies	5 studies
Gangannapalle 2023 (12)	5 studies		14 studies
Shtembari 2023 (13)	5 studies	14 studies	

3.1.3 Outcomes in the included systematic reviews

There is some overlap in the outcomes assessed in the three systematic reviews. The three reviews assessed overall complications, infections, pericardial effusion, and the need for revisions/re-intervention/retrieval. Two systematic reviews assessed hemothorax/pneumothorax, and device dislodgement. The following outcomes were assessed in only one of the reviews: mortality, cardiac tamponade, thromboembolism, hematoma, atrioventricular/arteriovenous fistula, and hospital discharge.

The submission suggests that Darlington 2022 has the most appropriate analyses and that the meta-analysis in Gangannapalle 2023 may have included studies that double count patients. The Darlington 2022 meta-analysis combines prospective and retrospective studies which can introduce challenges and potentially compromise the validity of the findings. Given the poor reporting in Gangannapalle 2023, NOMA is unable to ascertain whether the authors have double counted patients.

The submitter appraised the quality of the three systematic reviews and graded two as poor quality due to significant methodological flaws (11;12). Consequently, NOMA has excluded these reviews from the results section below. The Shtembari 2023 review was graded as fair quality and its findings are presented in the results section below, but they do not contribute to the overall assessment in this STA.

3.1.4 Interventions and comparators in the systematic reviews

In five studies included in the reviews, the intervention was Nanostim™ alone (33-36) or in combination with Micra™ (15). Two studies included Micra™ and Aveir™ pacemakers (37;38). All the other studies included only Micra™. Where comparisons were available these were reported as single or dual chamber transvenous pacemakers, different age groups of patients (e.g., ≥ 90 years vs. < 90 years), or different pacemaker heart locations (e.g., apical vs. non-apical lead placements). Details for each included study for each review are available in Appendix 6. Gangannapalle (12) explicitly focused on studies in English, Shtembari (13) included all languages, and Darlington (11) did not specify the eligible languages.

Darlington 2022 included four studies with Nanostim™, Gangannapalle 2023 included one study with Nanostim™ and one with Aveir™, and Shtembari 2023 included two studies with Nanostim™ and two with Aveir™. The submission states that only Darlington 2022 conducted a meta-analysis of studies with Micra™ leadless pacemaker patients separately from Nanostim™ studies and suggests that these pooled results are most applicable to the dossier. Darlington's review (11) quality was graded as poor by the submitter.

3.1.5 Populations in the included RCT

The submission includes one randomized open-label controlled non-inferiority trial (22). A summary of the study characteristics is presented in Table 4 . The study population included 51 adults aged 18 years and older with a class I or II indication for a single chamber transvenous pacemaker (TVPM) according to the 2013 European Society of Cardiology Guidelines (39). The submission states that patients had a mean age of 82.5 (standard deviation 4.6) years and 60.8% were male. The two groups had comparable baseline clinical characteristics and pacing indications. The trial was conducted in Belgium and enrolled patients between May 2018 and November 2020.

The submission reported that patients were excluded if they had previously received implanted cardiac devices or mechanical valves, if their echocardiography images were poor at baseline, if they had a left ventricular ejection fraction (LVEF) ≤ 40% at baseline, if they had a pre-existing condition that challenged or precluded the implant of a conventional pacemaker or if they refused or could not provide informed consent. The enrolment diagram shows that patients were also excluded because of COVID pandemic restrictions and because they had very short life expectancy because of comorbidities.

Table 4. Characteristics of the included randomized controlled trial

Study Trial registry number	**Study design** **Follow-up**	**Intervention (Number of patients)**	**Comparator (Number of patients)**	**Outcome(s) relevant to the PICO question**
Garweg 2023 (22) NCT06100757 (40)	Randomized controlled trial (non-inferiority open-label) 12 months	Micra™ (27)	Transvenous pacemaker (24)	Evolution of tricuspid valve and mitral valve function, pacemaker performance, and procedural and long-term complications

3.1.6 Intervention and comparator in the included RCT

Garweg 2023 randomized patients to Micra™ (n=27) or TVPM (n=24). The TVPM models were Medtronic Advisa ADSR03 or Azure XT VR. The trial was sponsored by Medtronic.

3.1.7 Outcomes in the included RCT

Garweg 2023 reported primary outcomes for heart function in terms of change in LVEF and global longitudinal strain at the end of the 12-month follow-up period (not included in this report). Secondary endpoints were (1) evolution of the right ventricular, tricuspid valve and mitral valve functions (2) evolution of N-terminal-pro hormone B-type natriuretic peptide (NT-pro-BNP) levels (not included in this report) (3) evolution of pacemaker performance and (4) occurrence of procedural and long-term complications.

Forty-seven patients had complete follow-up data and 48 patients were analysed at the 12-month follow-up point. Two patients who received the conventional pacemaker missed the control at 6 months because of the COVID pandemic. Three patients (one in the Micra™ group and two in the conventional pacemaker group) died at 9 months, 9 months, and 11 months follow-up from a non-cardiac cause (two patients died of cancer and one died following a pulmonary infection).

3.1.8 Populations in the prospective comparative studies

Seven prospective studies (reported in 12 publications) were included (see Table 5). The population age range in the prospective studies varied from 78-79 years to 81-82 years. The indications for pacemaker treatment were guidelines-based (n=4), following local practice (n=1), presenting with specific conditions (n=1), presenting as urgent cases (n=1) or not described (n=2). Some populations were focused on patients with less challenging issues (41;42) or who had not received pacemakers previously (25;27;42). The study populations varied in size from 106 patients (43) to 16431 patients (25).

Table 5. Characteristics of the seven included prospective non-randomized trials

Study	Study design Follow-up (FU)	Intervention (Number of patients)	Comparator (Number of patients)	Outcome(s) relevant to the PICO question
Bertelli 2022 (44)	Non-randomized, consecutive patients. FU: 2-3 weeks, 6 months and twice yearly thereafter.	Micra™ (72)	Transvenous pacemaker (272)	Periprocedural and long-term complications, survival, device, performance, hospital admissions
Cabanas-Grandio 2020 (43)	Non-randomized, consecutive patients FU: 6 months	Micra™ (42)	Transvenous pacemaker (64)	Quality of life and questionnaire related to the implant procedure
Martinez-Sande 2021 (45)	Prospective cohort	Micra™ (198)	Transvenous pacemaker (245)	Device related complications, mortality (minor or major)

	FU: Micra TPS 1, 3, 6, and 12 months and yearly if uneventful.			
Micra Coverage with Evidence Development (CED) study Crossley 2023 (25) Boveda 2023 (46) El Chami 2022 (47) Piccini 2021 (26)	Non-randomized, FU: 3 years	Micra™ (6219)	Transvenous pacemaker (10212)	Acute complication rate, survival, chronic complication rate, device-related reintervention rates
Micra transcatheter pacing study Duray 2017 (early performance) (27) Reynolds 2016 (48) Ritter 2015 (23)	Prospective single-arm, non-randomized study with historical control. Historical controls were collected from six published studies of patients receiving dual chamber pacemakers FU: 6, 12 and 24 months	Micra™ (726)	Transvenous pacemaker (2667)	Short and long term safety and electrical performance, mortality, infections, electrical performance, complications
Palmisano 2021 (41)	Non-randomized, FU: 1 week, 3 weeks after discharge and 6 months, and 12-months intervals.	Micra™ (91)	Transvenous pacemaker (152)	Procedure duration, electrical parameters, complications, hospitalization, patient acceptance, quality of life
Zuchelli 2021 (42)	Non-randomized cohort with matching controls FU: 1, 6 and 12 months and annually thereafter.	Micra™ (100)	Transvenous pacemaker (100)	Electrical parameters (including pacing capture thresholds, impedance, R wave amplitude), acute/chronic complications, mortality

3.1.9 Interventions and comparators in the included prospective comparative studies

All seven prospective studies compared Micra™ pacemakers to transvenous pacemakers.

3.1.10 Outcomes in the included prospective comparative studies

The seven prospective studies captured a range of outcomes including both acute peri-procedural outcomes and long-term outcomes at the follow-up points.

Four studies captured technical performance outcomes such as pacing threshold and impedance (41;42;44;45) and three reported R-wave (42;44;45). Two studies captured battery life (27;42). Six studies captured mortality (25;27;41;42;44;45). One study reported patient acceptance (41) and two studies reported quality of life (41;43). One study reported on the switch to another device (25).

Complications were reported by 10 studies, infections (including pericarditis and endocarditis) by three studies, pericardial effusion by one study (42), and tamponade by one study (25). Six studies reported vascular complications such as hematoma.

Device related complications: six studies reported dislodgement (25;42;44;45;48;49), two reported device malfunction (25;27), and four reported revisions, re-interventions, and retrievals (25;27;42;44).

Process duration (41;42) process success rate (41;42), and hospital hospitalization (27;41) were reported by two studies each.

3.1.11 Populations in the retrospective studies

The populations in the retrospective studies were adult patients aged 18 years and older in three studies (16;28;50), aged 75 years and over in one study (17), aged 85 years or older in two studies (49;51) and with a median age of 78 years (IQR 70-84) in one study (14) (see Table 6). Two studies did not report the minimum age of the population (30;31). The mean age of the study populations varied from ~75 years (29) to 90 years (30).

One study (29) included a post hoc retrospective analysis of patients from three prospective studies: Micra™ IDE, Micra™ CA and Micra™ PAR; given the risk of double counting participants, this study has not been used in this STA. Two studies used data from the (US) National Inpatient Sample (NIS) (28;31) and one study analysed patient data from the French hospital in-patient database (50). Patients in the Tjong study had mostly been involved in one of five prospective studies, including Micra™ IDE and Micra™ PAR (14). Five studies reported data collected from patients treated in one (16;30;51) or three specific hospitals or hospital systems (14;15). Most studies focused on first single chamber pacemaker insertion and excluded patients who had received reinsertions.

3.1.12 Interventions and comparators in the retrospective studies

Eleven retrospective studies compared records for patients who received leadless pacemakers to those who received conventional transvenous pacemakers. Three studies did not specify whether the intervention was Micra™ (16;17;28). These studies might have used Micra™, Nanostim™, Aveir™, or a combination of these leadless pacemakers available in the market. In a post hoc analysis, one study compared data for patients from three Micra™ trials to data from patients in the submitter’s register of Micra™ recipients (29).

Table 6. Characteristics of the eleven included retrospective studies

Study	Study design Follow-up (FU)	Intervention (Number of patients)	Comparator (Number of patients)	Key outcome(s) relevant to the PICO question
Alhuarrat 2023 (28)	Cohort study using propensity score matched/adjusted FU: In hospital	Leadless – Unclear if Micra™ implantation (7305)	Transvenous PM (7305)	Myocardial injury, pericardial complication, device thrombus, cardiovascular implantable electronic device revision, venous thromboembolism, vascular complications, bleeding complications, all cause in-hospital mortality.
Bodin 2022 (50)	Cohort study using propensity score matched/adjusted. FU: in hospital	Micra™ (1394)	Transvenous PM (1344)	All cause death, cardiovascular death, infective endocarditis, mode of death (cardiovascular or non-cardiovascular, major bleeding).
Garg 2020 (29) ClinicalTrials.gov identifier: NCT02536118 (52) NCT02488681 (53) NCT02004873 (54) NCT01524276 (55)	Post hoc study. Retrospective cohort studies with historical controls FU: Micra™ 23.5 ± 14.7 months Historical cohort 32.3 ± 25.6 months	Micra™ (2817)	Transvenous PM (515)	All-cause mortality.
Mararenko 2023 (16)	Cohort study FU: Micra™ 1, 3, 6, and 12 months and every year thereafter if uneventful. Patients with TVPM visits at 3 months after the procedure and yearly thereafter.	Leadless – Unclear if Micra™ (4105)	Transvenous PM (17677)	30-day readmission, inpatient mortality, length of stay, total cost, procedural complication rates, and trends in implantation.
Marschall 2022 (17)	Non-randomized, consecutive enrolment study of elderly and very elderly patients - urgent setting FU: mean 11 months	Leadless – Unclear if Micra™ (25)	Transvenous PM (53)	Pacing thresholds, R wave and impedance, complication rate and all-cause mortality.
Pagan 2020 (49)	Cohort study – in hospital FU: In hospital - within 24 hours of implantation	Micra™ (183)	Transvenous PM (119)	Procedure-related complications.
Sasaki 2023 (30)	Non-randomized study FU: in-hospital, 1, 6, 12 months	Micra™ (58/110)	Conventional pacemaker (58/83)	Worsening tricuspid and mitral regurgitation, defined as at least one-grade aggravation in severity
Tachibana 2020 (51)	Non-randomized study	Micra™	Transvenous PM	Complications, survival rate, electrical parameters,

	Very old patients aged 85 years and over FU: 6 months	(27)	(35)	procedure duration, time to hospital discharge.
Tjong 2018 (14) NCT01700244 (56) NCT02051972 (57) NCT02030418 (58) NCT02004873 (54) NCT02536118 (52) FOLLOWPACE NCT00135174 (59)	Non-randomized, propensity score matched study. FU: median 1.6 years leadless - 4.1 years TVPM	Leadless PM Implantation (220/254) includes some Nanostim™ PM	Transvenous PM (220/381)	Adverse events, (implant or procedure) complications (device related AE requiring invasive intervention)
Vaidya 2019 (15)	Non-randomized, with matched controls FU: 1,3,6 and 12 months	Mixed leadless (73 Micra™ and 17 Nanostim™)	Transvenous PM (90)	Procedure-related complications
Vincent 2022 (31)	Cohort study using case-control matching FU: in hospital	Micra™ implantation (3084)	Transvenous PM (3084)	Primary in-hospital all-cause mortality, pooled complication rate, and total duration of hospitalization, vascular complications rate, infectious, pericardial requirement of pericardiocentesis, and device retrieval or replacement.

Key: AE: adverse events: FU, follow up; PM, pacemaker; RCT, Randomized controlled trial; TVPM, transvenous pacemaker.

3.1.13 Outcomes in the included retrospective comparative studies

Three retrospective studies reported on technical performance pacing threshold (14;49;51) and two reported on impedance and R-wave sensing (49;51). Three studies reported on battery life (15;27;42).

Eight retrospective studies reported mortality (14-16;28;29;31;49;50) and one study reported survival rates (51). Six studies reported a variety of complications (14;15;17;31;49;51). Seven studies reported infections including pericarditis and endocarditis (14-16;28;31;50;51). Two studies reported pericardial effusion (15;49) and two studies reported thromboembolisms (17;28). Three studies reported cardiac tamponade (16;30;50).

Five studies reported hematoma (14;30;31;49;51), three studies reported pneumothorax/hemothorax (14;30;31), two studies reported dislodgement (49;51), and two studies reported revision/re-intervention/retrieval (15;31). One study each reported bleeding (28), AV fistula (30), device malfunctioning (14), and AV tricuspid valve regurgitation (15).

One study reported readmission rates (16), three studies reported length of stay (16;31;51) and one study reported costs (16).

3.1.14 Ongoing studies

The submitter identified three studies that have the potential to meet the inclusion criteria, but were either recruiting, not yet complete or had no publications (Table 7).

Table 7. Ongoing studies: trial identifier, sponsor, study name and design

Study identifier **[status]** ***Study sponsor***	**Study name** ***Summary***
NCT05327101 [completed] (60) *Abbott Medical Devices*	Patient preferences for leadless pacemakers *Prospective, non-randomized, multi-center study designed to quantify patient preferences pertaining to risks and features of conventional transvenous pacemakers and leadless pacemakers*
NCT05958836 [not yet recruiting] (61) *Shanghai Zhongshan Hospital*	Quality of life in patients treated with leadless pacemakers *The study aims to carry out a domestic multi-center, prospective, non-randomized, non-blinded post-approval study to assess health-related quality of life between Micra™ TPS and conventional pacemaker implantation. Pocket and leads-related complications would also be evaluated between these two strategies. The study uses EQ-5D-5L tool for data collection.*
ChiCTR2300077648 [completed and pre-print available (62)] (63) Department of Cardiology, Tangdu Hospital, Air Force Medical University, Xiâan, China	Comparison of the efficacy of leadless pacemaker and conventional single-chamber pacemaker *Comparison of clinical and life quality outcomes between leadless versus conventional transvenous pacemaker in treating patients with bradycardiac arrhythmia: a multi-center and propensity score-matched research. The study used the SF-36 tool for data collection*

Key: transcatheter pacing study

3.2 Methodological quality

The submitter assessed risk of bias (RoB) using three tools:

- Three systematic reviews using AMSTAR 2 (64).
- One RCT using the ROB 2 tool (65).
- 18 non-randomized studies using the NHLBI Tool (66).

3.2.1 Methodological quality of systematic reviews

Two of the reviews were graded as poor quality (11;12) and one review was graded as fair quality (13) according to the submitter's evaluation using the AMSTAR-2 tool.

3.2.2 RCT risk of bias

Figure 7 shows the submitter's judgment about the RCT RoB. According to the Cochrane Handbook if one of the domains is rated as "some concerns", the overall assessment of the trial is "some concerns". In addition to the submitter's judgement, NOMA appraised the information and found the submission indicates that the study probably used an intention-to-treat (ITT) analysis. However, NOMA could not find explicit confirmation of ITT usage; i.e. authors analyzed 48 out of 51 patients. The submission also states a low risk of bias for domain 2 (deviations from the intended intervention), but NOMA suggests that there could be some concerns in this area.

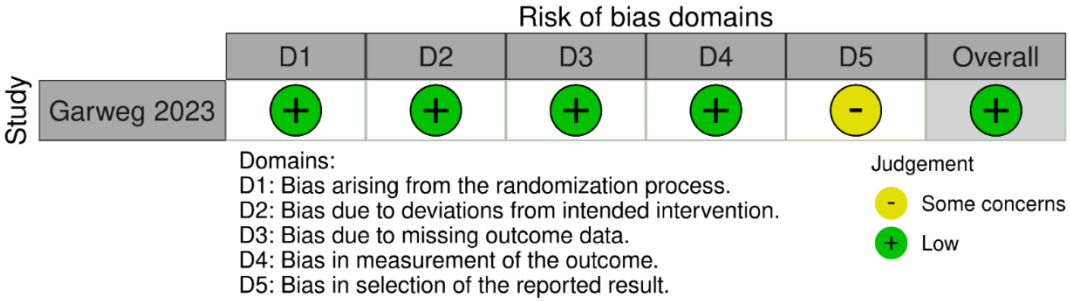


Figure 7. Risk of bias summary: Submitter's judgments about the risk of bias domains for the included RCT

3.2.3 Non-randomized studies risk of bias

The submitter used the National Heart, Lung, and Blood Institute (NHLBI) Study Quality Assessment Tool to review the internal validity of the non-randomized studies (66).

The non-randomized studies varied in quality, with most being rated as 'Poor' (n=10) or 'Fair' (n=8). Only 1 study achieved a 'Good' rating. Common issues leading to 'Poor' ratings included small sample sizes, risk of selection bias, lack of adjustments for confounding factors, and short follow-up periods. Studies rated as 'Fair' often had larger sample sizes and used propensity score matching to reduce bias but still faced challenges including potential selection bias and retrospective designs. The single 'Good' study stood out due to its large sample size, long follow-up, and statistical adjustments. Overall, readers should be cautious of biases, unadjusted confounding factors, and the design limitations of these studies when interpreting their findings. Larger sample sizes and longer follow-up periods generally provide more reliable evidence (see Table 8).

Table 8. Non-randomized studies: quality assessment summary using the National Heart, Lung, and Blood Institute (NHLBI) Study Quality Assessment Tool

Study	Quality	Additional Comments	Max score out of 11 and %
Alhuarrat 2023 (28)	Fair	Propensity score matched large cohort study; focus of the study was in-hospital complications and mortality so acute follow-up was appropriate.	8 73%
Bertelli 2022 (44)	Fair	Prospective, consecutive enrolment, with almost 2 years mean follow-up; Only a 'fair' rating given the high chance of selection bias.	8 73%
Bodin 2022 (50)	Fair	Propensity score matched large study of nationwide cohort; follow-up at mean 6 months; selection bias possible due to retrospective nature.	8 73%
Cabanas-Grandio 2020 (43)	Poor	Small study population (n=106); 8 'Yes' of 11 possible (omitting not applicable), however, given likely selection bias and differences in baseline characteristics that may confound results and no adjustment for these differences were made, the overall assessment is 'poor'.	8 73%
Garg 2020 (29)	Poor	The study relies on a historical control to Micra™, with Micra™ patients obtained from multiple studies; 50% of patients in the transvenous pacemaker historical cohort	7 64%

		were enrolled after their implantation, which may underestimate the acute mortality rate in this group; risk of selection bias and no adjustments made to analyses renders this study 'poor'.	
Mararenko 2023 (16)	Poor	Acute follow-up of clinical outcomes and healthcare utilization; No matching was used but regression analysis and adjusted hazard ratios were reported.	7 64%
Marschall 2022 (17)	Poor	Presented as a letter: single center; small sample size (n=78); possible selection bias and no adjustments to outcomes assessment to mitigate confounding renders this 'poor'.	6 55%
Martinez-Sande 2021 (45)	Fair	Choice of pacemaker based on patients' clinical condition hence risk of selection bias; however, analyses were adjusted mitigating potential for confounding, hence 'fair'.	8 73%
MICRA™ CED Study Crossley 2023 (25) Boveda 2023 (46) El Chami 2022 (47) Piccini 2021 (26)	Good	Complications could be missed or inadequately documented in administrative claims; An overlap weight propensity score matching was performed to adjust for differences in baseline characteristics and comorbidities, the large sample size (>15,000) and the reasonably long follow up (2 years) renders the study 'good' in the context of being a real world evidence study.	10 91%
Micra™ TPS Duray 2017 (27) Reynolds 2016 (48) Ritter 2015 (23)	Fair	Large cohort study with >12 months follow-up for most patients; not rated 'good' due to limitations with comparator arm.	9 82%
Pagan 2020 (49)	Poor	Possibility of selection bias; complications are limited to the index hospitalization, and no adjustments for potential confounders renders this study 'poor'.	6 55%
Palmisano 2021 (41)	Fair	This is a single centre study with 6 months follow-up, assessing quality of life of leadless pacemakers versus transvenous pacemakers; risk of selection bias. However, the analyses were performed on a propensity matched cohort, therefore limiting the risk of confounding, hence considered 'fair' in the context of non-randomized study.	8 73%
Sasaki 2023 (30)	Poor	Small retrospective study; selection bias acknowledged; large number of patients included initially due to having incomplete follow-up data.	7 64%
Tachibana 2020 (51)	Poor	Single center; small sample size (n=62); short follow-up; possible selection bias and no adjustments to outcomes assessment to mitigate confounding renders this study ‘poor'.	6 55%
Tjong 2018 (14)	Fair	Propensity score matched large cohort study; longer-term follow-up; separation of complications by leadless pacemaker type.	8 73%
Vaidya 2019 (15)	Poor	Possibility of selection bias; no adjustments made for differences in baseline characteristics renders the study 'poor'.	6 55%
Vincent 2022 (31)	Poor	Large leadless pacemaker cohort study,yet included a small single-chamber comparator without matching - leading to down grading and ‘Poor’ rating.	7 64%

Zucchelli 2021 (42)	Poor	A propensity score-matched analysis was not realized due the limited number of transvenous single-chamber ventricular pacemakers, thus introducing a potential bias in the selection of the control cases; single center; low reproducibility.	7 64%

Key: CED Micra Coverage with Evidence Development study; TPS: transcatheter pacing system

3.3 Results

3.3.1 Technical performance: pacing performance (sensing, impedance, pacing threshold)

Pacing threshold (volts (V) per millisecond (ms), lower is better)

Definition: The dossier states that the threshold achieved is the minimum power required to initiate a heartbeat.

One RCT (22), four prospective studies (41;42;44;45), and three retrospective studies (14;49;51) provided data for this outcome. Of these, five studies were included in a meta-analysis. The analysis revealed substantial heterogeneity and thus no totals are presented in Figure 8. The values are distributed on both sides of the forest plot. Notably, the RCT favours Micra™ (22). Of the two prospective studies, one favours TVPM (41) and the other (42) crosses the line of no effect. In contrast, the two retrospective studies favoured TVPM.

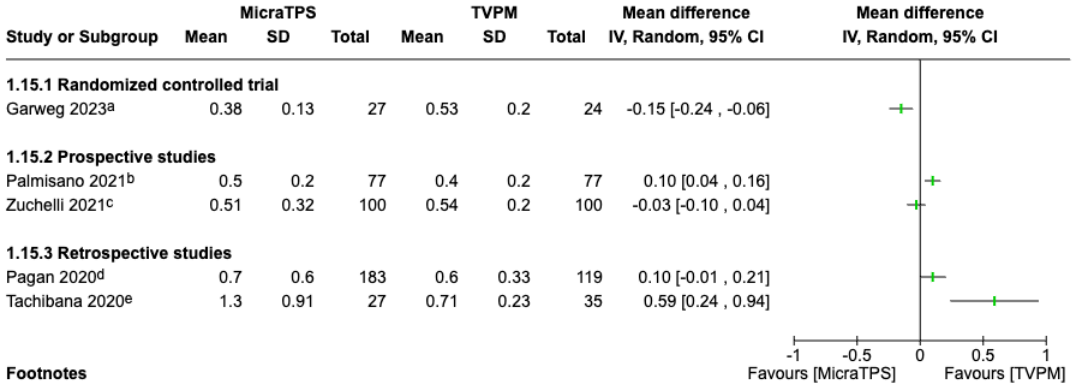


Figure 8. Micra™ vs. TVPM: Pacing threshold

Data not included above:

- The RCT reported a significantly lower pacing threshold in the Micra™ group compared with the TVPM group at implant (shown in forest plot) but also at discharge, at day 10, and at months 1, 6 and 12 follow-up times ($p<0.001$) (22).
- One small prospective study (44) involving two hospitals in Italy (n=344) reported that 2-3 weeks after implantation, there was no significant difference between Micra™ and TVPM ($p=0.79$) for pacing threshold (V@0.4ms). However, at follow-up (~25 months) there was a significant difference in favour of Micra™ ($p=0.005$). Five patients (2.2%) had required lead repositioning and one patient had an additional lead following high pacing threshold.

- One small (n=443) prospective study in one hospital in Spain did not provide a comparison of electrical parameters for Micra™ versus TVPM, but noted that the pacing capture threshold (V @ 0.24ms) in patients with leadless PM was stable during follow-up (at time of implant: 0.55; at 3-months post-implant: 0.51; at 12 months post-implant: 0.56; at 36 months post implant: 0.61) (45). Although these data are not comparative, NOMA presents the data because, in this study, Micra™ was encouraged in those patients who were at a higher risk of infection or who had difficult vascular access or abandoned electrodes.
- A small (440 patients used in propensity matching) retrospective study compared leadless PM and TVPM in a matched cohort design, using patients who had been previously enrolled in larger leadless PM studies as well as TVPM patients from a nationwide cohort in the Netherlands (14). After 800 days, there were pacing threshold issues in the TVPM group (n=3 (3.2%), Kaplan-Meier estimate) but none in the leadless PM group. An elevated pacing threshold was reported in 2 patients (0.9%) receiving leadless PM compared with 0% in the TVPM group.
- A small (n=62) retrospective study conducted at a single heart center in Japan and comprising very elderly patients (aged over 85 years) reported that at implantation and one-month follow-up, the pacing threshold was significantly higher in the Micra™ group compared with the TVPM group (implantation shown in the forest plot). However, over the first three- and six-months post-implantation, the pacing threshold in the Micra™ group gradually improved but did not reach statistical significance (month 3, 1.05 ± 1.02 V vs. 0.82 ± 0.20 V, p=0.16 and month 6, 1.19 ± 1.17 V vs. 0.78 ± 0.21 V, p=0.12) (51).

Pacing impedance (Ohm (Ω))

Definition: The dossier states that pacing impedance provides insight into the status of the tissue-pacemaker interface or fixation and is measured by Ohm (Ω).

One RCT (22), four prospective studies (41;42;44;45), and two retrospective studies (49;51) provided data for this outcome. Six studies were included in NOMA's analyses, but given the substantial heterogeneity, no totals are presented (Figure 9). The mixed results and variability need to be carefully considered when drawing conclusions from the forest plot.

Data not included in the forest plot:

- Bertelli et al. (44) (n=344) reported that at implantation there was no significant difference in impedance between groups. However, at follow-up (~25 months) there was a significant difference in favour of Micra™ (636 ± 18 vs. 606 ± 14, p=0.009) (shown in the meta-analysis).
- The Tachibana retrospective study (n=62) comprising patients aged over 85 years reported that at implantation, the pacing impedance was not significantly different between Micra™ group and the TVPM group (shown in forest plot), but there was a significant difference for Micra™ group at one, three and six months (month 1: 478.64 ± 73.31 vs. 553.10 ± 104.59, p=0.01; month 3: 458.23 ± 49.53 vs. 524.8 ± 94.78, p= 0.01; and month 6: 460.00 ± 55.10 vs. 512.2 ± 100.91, p=0.05) (51).
- The Martinez-Sande prospective study (n=443) noted that the pacing impedance in patients with Micra™ was stable. The average impedance at implant was 779.8 ± 211, and it was 584 ± 102 at 12 months, 580.5 ± 91 at 24 months, and 538.8 ± 91 at 36-months follow-up (45). No comparative data were provided. NOMA presents the data because in this study, Micra™ was encouraged in those patients who were at a higher risk of infection or who had difficult vascular access or abandoned electrodes.

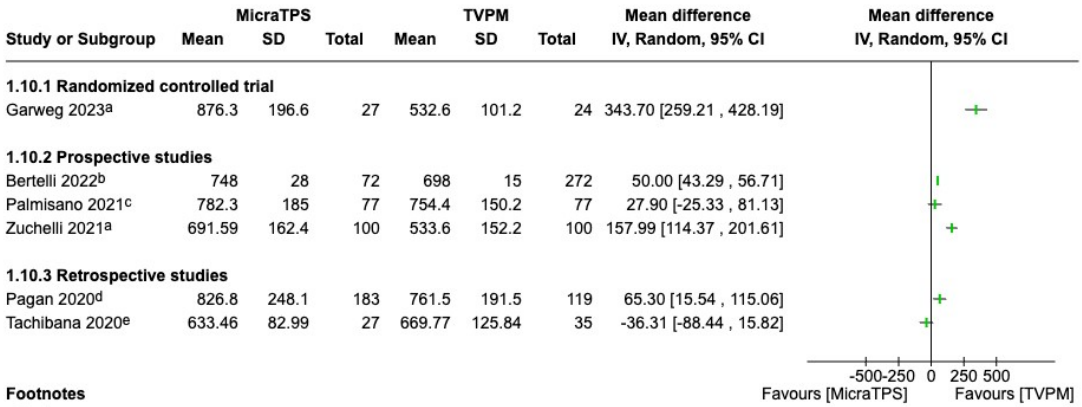


Figure 9. Micra™ vs. TVPM: Impedance

R-wave or R-wave sensing (mV, higher is better)

Definition: the R wave is the amplitude of the electrical signal provided by the heart.

Data for this outcome were provided by one RCT (22), three prospective studies (42;44;45), and two retrospective studies (49;51). Five of these studies were included in NOMA's analyses (Figure 10), but the analysis revealed substantial heterogeneity and so the overall effect sizes are not presented. The mixed results and variability need to be carefully considered when drawing conclusions from the forest plot.

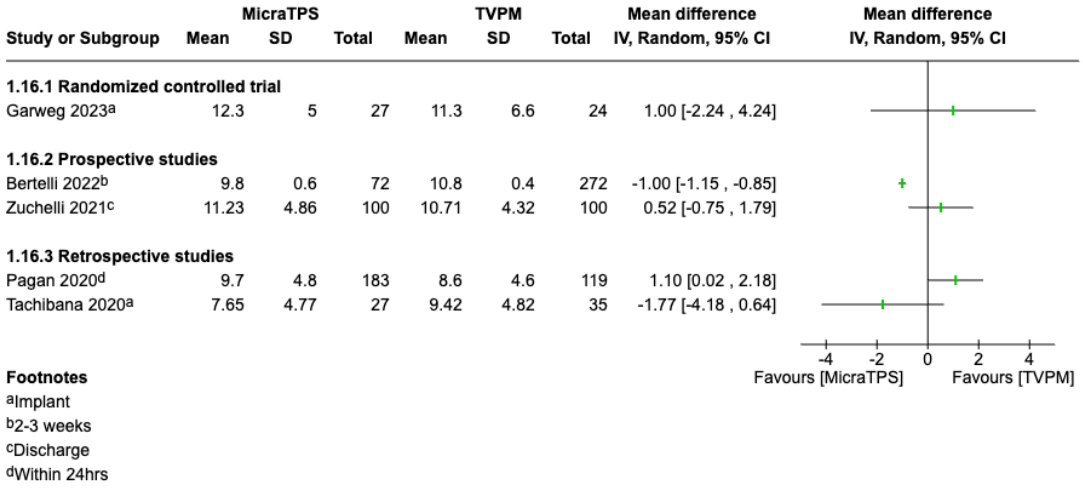


Figure 10. Micra™ vs. TVPM: R-wave

Data not included above:

- The RCT reported that R-wave sensing increased slightly over time in the Micra™ group, but remained stable in the TVPM group (22). Results were non-statistically significantly different at implant (included in the forest plot), discharge and day 10, but TVPM showed significantly higher voltages at 1, 6, and 12 months (Month 1: 1.2 ± 5.2 mV vs. 14.1 ± 4.4 mV. p=0.04; Month 6: 10.9 ± 4.8 mV vs. 14.6 ± 4.7 mV, p=0.01; Month 12: 10.4 ± 5.2 mV vs. 14.2 ± 4.7 mV, p=0.02).

- The Bertelli prospective study (n=344) reported no significant difference in sensing amplitude at implantation or at follow-up between Micra™ and TVPM (2-3 weeks included in the forest plot, and ~25 months, 11.6 ± 0.5 vs. 12.0 ± 0.4, p=0.86) (44).
- A small (n=200) prospective study reported that there was no significant difference in the R wave amplitude of the Micra™ group compared with the TVPM group at discharge (included in the forest plot) or at follow-up (data NR) (42).
- A small (n=62) retrospective study of very elderly patients (51) reported that the R wave amplitude was not significantly different between Micra™ and TVPM at any time point after the operation (implant included in the forest plot; Month 1: 9.85 ± 5.47 vs. 11.25 ± 4.31, p=0.41; Month 3: 10.58 ± 6.10 vs. 11.30 ± 4.62, p=0.9; Month 6: 11.45 ± 5.56 vs. 11.85 ± 5.11, p=0.9).
- One small (n=443) prospective study in one hospital in Spain did not provide a comparison of electrical parameters for Micra™ versus TVPM but noted that the sensing in patients with Micra™ was stable during follow-up. The average R amplitude at implant was 10.7 mV (± 4.6), 13.5 mV (± 4.6) at 12 months, 14.5 mV (± 4.9) at 24 months, and 12.9 mV (±5.2) at 36 months (45). NOMA presents the data because in this study Micra™ was encouraged in those patients who were at a higher risk of infection or who had difficult vascular access or abandoned electrodes.

Battery life (device interrogation)

- The Micra TPS prospective non-randomized study by Duray et al (27) including 726 patients with Micra™ with 2667 historical controls, reported the estimated battery longevity for Micra™ was 12.1 years based on use conditions at 12 months. No comparative data against the historical control are provided.
- A small (n=200) prospective study conducted in a single centre in Italy reported that there was a longer estimated battery life in the Micra™ group compared with the TVPM group (42). The authors reported mean delivered energy at threshold which they derive from threshold values squared x stimulation time. The threshold values in the two groups were similar (0.51V and 0.54V) meaning stimulation time or pulse width (given the reported values of 0.14 ± 0.21 vs. 0.26 ± 0.22 μJ p<0.001) would be longer in the TVPM group. All this should translate into a theoretically longer battery life (assuming the batteries in the two options are fully comparable) in the leadless pacemaker.
- A small (n=180) retrospective study in the Mayo Clinic, USA reported that estimated battery life was significantly greater for the leadless PM group (median 12.0 vs 10.0 years, p<0.0001) compared with the TVPM group (15). Patients included in the study may have also been included in either the Micra™ leadless pacemaker IDE and Product Surveillance Registry and the Nanostim™ studies.

Adaptability (rate response)

The submission did not present results for this outcome.

3.3.2 Patient-relevant effectiveness outcomes:

Mortality (all-cause and cardiovascular)

Data for this outcome were provided by five prospective studies reported in 6 publications (25;27;41;42;44;45), and nine retrospective studies (14-16;28;29;31;49-51). Twelve of these studies were included in NOMA's analysis (Figure 11) and were grouped by study design and follow-up time. The analysis revealed substantial heterogeneity.

The prospective analyses show the following:

- Mortality at ~12 months (2 studies): no statistically significant results.
- Mortality at ~22 months: participants using Micra™ had a 49% lower chance of dying compared with TVPM (RR 0.51 95% CI 0.30-0.85, 443 participants, 1 study).
- Mortality at 36 months (1 study): no statistically significant results.
- Mortality in a study with an unclear follow-up period: no statistically significant results.

Among the retrospective studies the findings were:

- In-hospital: mortality risk is 91% higher for the TVPM group compared with the Micra™ group (RR 1.91 95% CI 1.71-2.29, 41900 participants, 3 studies, p=0.00001, I^2=0%).
- From hospital discharge to 11 months follow-up; mortality risk was 40% lower for the Micra™ group compared with TVPM (RR 0.60, 95% CI 0.49-0.75, 3003 participants, 3 studies of which 1 had three arms, p=0.00001, I^2=0%).
- No study provided data for a period longer than 36 months.

Data not included in Figure 11:

Prospective studies

- One large (n=16431) prospective non-randomized study with a contemporaneous controls (Micra™ CED) reported no significant difference in the adjusted 3-year all-cause mortality rate between Micra™ and TVPM patients (HR 0.97, 95% CI 0.92-1.003, p=0.32) after accounting for differences in baseline characteristics (25).
- The small Bertelli prospective study (n=344) reported no significant difference in all-cause mortality between leadless PM and TVPM (HR 0.92, 95% CI 0.42-2.04, p=0.85) (44).
- One small (n=443) study in one hospital in Spain reported *in the abstract* that there was no significant difference in the mortality rates for Micra™ recipients compared with TVPM recipients (45). The article (Table 3) shows total mortality was 18 (9.1%) vs. 44 (17.9%) (p=0.007). NOMA contacted the author(s) for clarification but received no response.

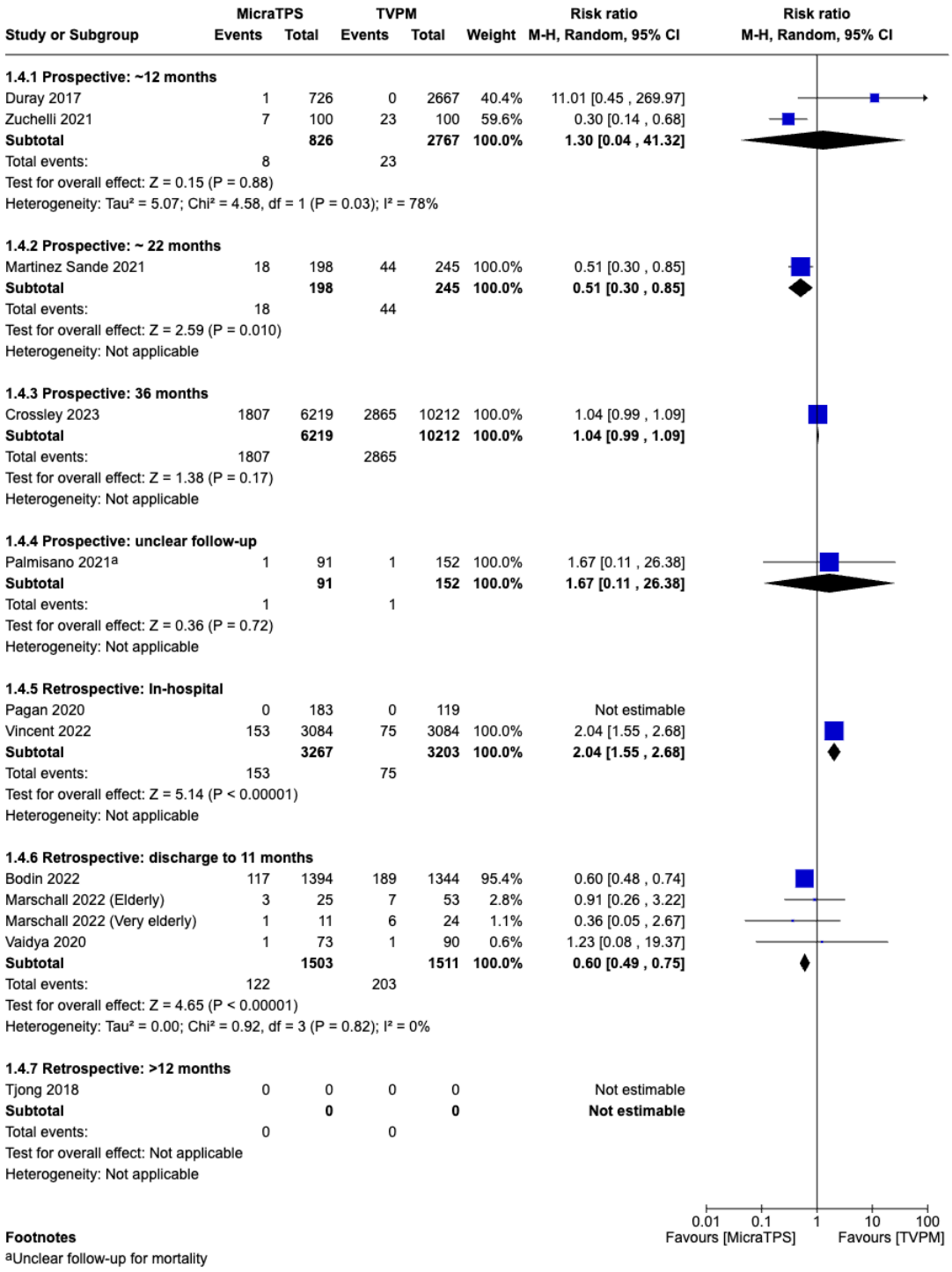


Figure 11. Micra™ vs TVPM: mortality (all cause and cardiovascular) at various timepoints

Retrospective studies:

- One large (n=21782) retrospective analysis of US hospital administrative data reported no statistical difference in inpatient mortality (HR 1.36, 95% CI 0.71-2.62, p=0.35) (16).
- One large (35430) retrospective analysis of the US National Inpatient Sample database reported that adjusted in-hospital mortality. Death was 1.63 times more likely to occur in patients undergoing leadless PM implantation compared with TVPM (adjusted OR 1.63, 96% CI 1.29-2.05, p< 0.001) (28).

- A retrospective matched control analysis of French hospital data reported that patients with Micra™ (n=1487) had a significantly lower rate of all-cause mortality and cardiovascular mortality than patients with TVPM (50) in the 30 days following implantation (matched cohort all-cause OR 0.58, 95% CI 0.45-0.74, p<0.0001; cardiovascular OR 0.41, 95% CI 0.27-0.62, p<0.0001). The submission states that after matching on all baseline characteristics including comorbidities (mean follow-up 6.2± 8.7 months), all-cause death (HR 1.17, 95% CI 0.95-1.45, p=0.13) and cardiovascular death (HR 0.78, 95% CI 0.55-1.11, p=0.17) were not statistically different between the two groups (50).

Exercise capacity

The submission did not present results for this outcome.

Change of medication

The submission did not present results for this outcome.

Progression or recurrence of cardiac arrhythmias

The submission did not present results for this outcome.

Switch to an alternative device (a different pacemaker or defibrillator)

One large (n=16431) prospective non-randomized study with a contemporaneous control reported a system switch at 3-years follow-up (replacement with the opposite type of device). There was no significant difference between leadless PM and TVPM groups (relative risk reduction RRR –36%, 95% CI –145% to 25%; p=0.31) (25).

Symptoms of cardiac arrhythmias (pre-syncope or syncope)

The submission did not present results for this outcome.

Health-related quality of life

Two studies reported quality of life using the Medical Outcomes Study 36-Item Short-Form (SF-36) General Health Survey at three and six months follow-up and were included in a meta-analysis. Results are presented as mean differences (MD) and standard deviations (SD).

The results for the mental component:

- At 3 months: there was no significant difference between Micra™ and TVPM (MD 3.54, 95% CI -0.23-7.31, p=0.18, I^2=44%, 349 participants, 2 studies).
- At 6 months: individuals receiving Micra™ rated their mental component 4.15 higher than individuals in the TVPM group (MD 4.15, 95% CI 0.58-7.73, p=0.19, I^2=41%, 349 participants, 2 studies) (see Figure 12).

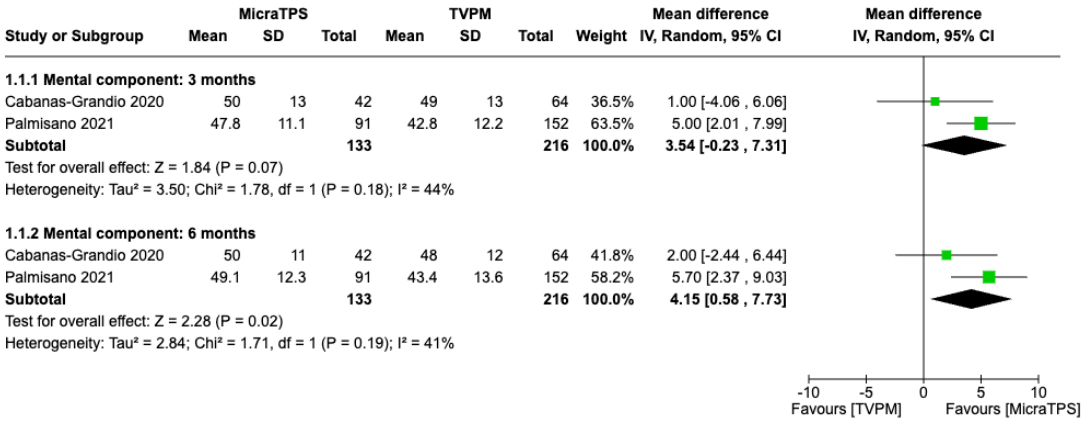


Figure 12. Micra™ vs. TVPM: SF-36 mental component at 3 months and 6 months

The results for the SF-36 physical component:

- At 3 months: there were significant differences between Micra™ and TVPM groups (in favour of Micra™) (MD 4.96, 95% CI 1.94-7.97, p=0.09, I²=65%, 349 participants, 2 studies).
- 6-months: this significant difference was maintained at the six-month follow-up (MD 3.86, 95% CI 1.53-6.18, p=0.20, I²=40%, 349 participants, 2 studies) (see Figure 13).

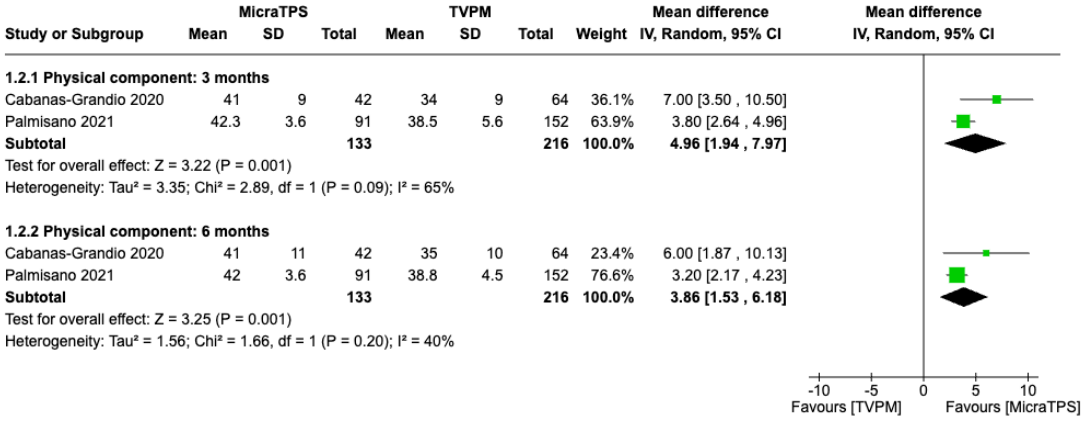


Figure 13. Micra™ vs. TVPM: SF-36 physical component

Data not included in the meta-analysis:

- The Palmisano prospective study (n=243) reported statistically significant differences in favour of Micra™ patients compared with TVPM at each time point (1 week, 3 months, and up to six months) for the physical and the mental aggregate scores of SF-36. The submission notes that there was no sign of convergence of curves over time, suggesting that the quality of life benefits of Micra™ in the physical and mental domains are likely to continue beyond 6 months (41) (see Table 9).
- The small Cabanas-Grandio (n=106) prospective multicentre study reported that at six months follow-up, recipients of Micra™ scored significantly higher than recipients of TVPM on the SF-36 v2 domains of physical function (mean change 19.7±4.5 vs. 1.1±3.5; p<0.001), role physical (mean change 40.8±6.9 vs. 12.7±8.3; p=0.01), and mental health (mean change 13.9±3.6 vs. 2.8±2.9, p=0.02) (43). There were significant differences in baseline characteristics between the two groups in terms of age (Micra™ 77.3±10 years vs. TVPM 81.5±7 years, p=0.012) and diabetes

(Micra™ 17% vs. TVPM 38%, p=0.021). However, the groups had no differences in baseline quality of life.

Table 9. SF-36 scores for physical and mental components at baseline, 1 week, 3 months and six months (41).

SF-36 (higher scores indicate better health-related quality of life)	Baseline Micra™ vs.TVPM Mean (±SD), p-value	1 week Micra™ vs.TVPM Mean (±SD), p-value	3 months Micra™ vs.TVPM Mean (±SD), p-value	6 months Micra™ vs.TVPM Mean (±SD), p-value
Physical component	36.1 ± 9.3 vs. 36.4 ± 11.0, p=0.855	39.0 ± 7.5 vs. 33.1 ± 8.0, p≤0.001	42.3 ± 3.6 vs. 38.5 ± 5.6, p≤0.001	42.0 ± 3.6 vs. 38.8 ± 4.5, p≤0.001
Mental component	45.6 ± 14.8 vs. 46.0 ± 15.1, p=0.868	46.3 ± 11.6 vs. 41.3 ± 12.0, p=0.009	47.8 ± 11.1 vs. 42.8 ± 12.2, p=0.008	49.2 ± 12.3 vs. 43.4 ± 13.6, p=0.006

Key SD, standard deviation; TVPM, transvenous pacemaker

Patient satisfaction

A small (n=243) prospective study reported that Micra™ was associated with greater patient acceptance measured using the disease-specific Florida Patient Acceptance Survey (higher score means better) at 3 months follow-up than TVPM (mean score 58.7±7.1 vs. 40.5±4.1; p<0.05) (41).

A small (n=106) prospective multicenter study reported the results of an author-designed questionnaire related to the implant procedure at one- and six-months follow-up. At one month follow-up, patient satisfaction was significantly higher in the Micra™ group than the TVPM group, except for chest discomfort (41% vs. 52%, p=0.38) and depression (18% vs. 28%, p=0.36). At six-months follow-up, recipients of Micra™ reported statistically significantly higher satisfaction in six out of 10 areas than recipients of TVPM. The four areas where patient satisfaction was not statistically significantly different were restriction in daily activities due to discomfort in the area of the intervention (8% vs. 20%, p=0.10), restriction in physical activities due to concern over complications (13% vs. 2 7%, p=0.10), restriction in physical activities due to discomfort in the area of the intervention (8% vs. 22%, p=0.067) and depression (11% vs. 22%, p=0.136) (43).

3.3.3 Safety outcomes (procedure-related):

Any complications

Several studies provided data for this outcome. One RCT (22), six prospective studies (25-27;42-45), and six retrospective studies (14;15;17;30;31;49) were included in a meta-analysis. Since the analysis of prospective studies revealed substantial heterogeneity (I^2=82%), we conducted a sensitivity analysis and removed data provided by Piccini (25). The RCT showed a non-statistically significant risk ratio with very wide confidence intervals (RR 0.30 95% CI 0.01-6.98, 51 participants, p=0.45). The results from the prospective studies before and after the sensitivity analysis indicated a non-significant difference between Micra™ and TVPM (Table 10). The six retrospective studies (one study has two arms) showed a statistically significant risk ratio suggesting that individuals receiving Micra™ had a 48% lower risk of any complications compared with TVPM (RR 0.52, 95% CI 0.40-0.68, p=0.00001, I^2=5%, 7148 participants, 6 studies) (Figure 14).

Table 10. Sensitivity analysis: outcome ‘any complications

Outcome	Before sensitivity analysis	After sensitivity analysis
Any complications	RR 0.80, 95% CI 0.54-1.19, p=<0.00001, I²=85%, 32932 participants, 6 studies	RR 0.65, 95% CI 0.37-1.12, p=0.14, I²=42%, 17575 participants, 5 studies

Key: CI: confidence interval; RR relative risk.

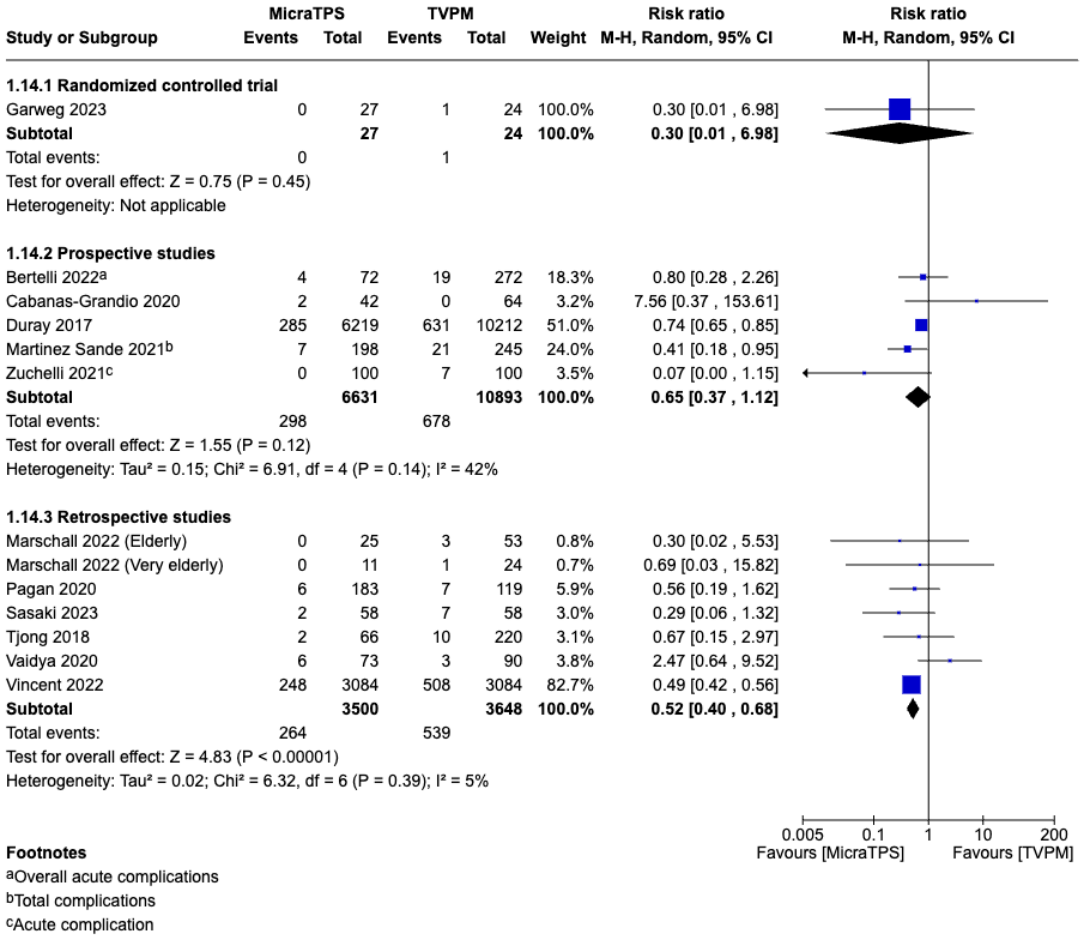


Figure 14. Micra™ vs TVPM: any complication

Data not included in the analyses:

- A fair quality systematic review (13) provided pooled results that showed 42% lower odds of occurrence of complications in leadless PM recipients compared with TVPM recipients (OR 0.58, 95% CI 0.42-0.80, I^2=53%, p=0.001) (11 studies, n=23348). This meta-analysis includes prospective and retrospective studies and includes not only Micra™ but also Aveir™ (37;38) and Nanostim™ (15) pacemakers.
- The RCT (22) reported that the complication rate at twelve months for both groups was zero.
- A small (n=243) prospective study reported zero complications within 24 hours of the implantation procedure for Micra™ compared with complications for 2 patients (1.3%) receiving TVPM (p=NR) (41). Long term (period unclear) complications were zero for both groups.
- Piccini et al. reported a large prospective non-randomized study (n=15408) with a contemporaneous control with the acute complication rate (≤ 30 days) for Micra™ vs. TVPM at six months (26). The acute overall complication rate was a composite

measure of separate elements: embolism and thrombosis, events at puncture site, cardiac effusion and perforation, and device-related complications. The adjusted acute complication rates show no difference at 30 days (7.7% vs. 7.4%, p=0.49), but favour Micra™ at 6 months (HR 0.77, 95% CI 0.62-0.96, p=0.02). The two-year complication rates were 4.6% for Micra™ compared with 6.2% for TVPM (p<0.0001), yielding a relative risk reduction in overall complication rates at 2 years of 31% (95% CI 19%-40%, p<0.0001) (47).

- One prospective study (n=344) reported that at a mean of 22.8 months, the Micra™ group had a complication rate of zero and at a mean of 23.7 months the TVPM group had a complication rate of 1.9% (p=0.25) indicating no significant difference between the two groups over the longer term (44).
- One prospective non-randomized study with historical controls reported that at 6 months, the Micra™ group had significantly fewer complications than historical controls (HR 0.49, 4.0% vs. 7.4%; 95% CI 0.33-0.75, p=0.001) (48). A separate publication of the same study reported that major complications were defined as events resulting in death, permanent loss of device function because of mechanical or electrical dysfunction, hospitalization, prolongation of hospitalization by at least 48 hours, or system revision. The risk of major complications for patients with Micra™ post-implant was 48% lower than that for patients with TVPM at 12 months follow-up (HR 0.4; 95% CI 0.30-0.72, p=0.001). The submission states that Micra™ reduced the risk of major complications compared with TVPM for subgroups based on age, sex and co-morbidities (27). However, NOMA was not able to appraise this information as no data were provided for these subgroups.
- A small (n=200) prospective study reported that no acute or chronic procedure-related complications were observed in the Micra™ recipients, (data included in the meta-analysis) and long-term complications (12 months) in three TVPM patients (3%, p=0.24) (42).
- One small (n=443) prospective study reported that at a mean of 22.3 months following implantation the Micra™ group presented significantly fewer total complications than the TVPM group (HR 0.39, 95% CI 0.15-0.98, p= 0.01), but the groups were not significantly different in terms of major complications (3% LPM vs. 5.6% TVPM, p=0.17) and minor complications (0.5% vs. 2.8%, p=0.06) (45).
- One large (n=16,431) prospective non-randomized study with historical controls reported that after three years Micra™ recipients' complication rates were significantly lower than those of patients who received TVPM (5% vs. 6.8%, p<0.0001) (25). Micra™ was associated with a relative risk reduction in overall complication rates at 3 years of 32% (95% CI 22%-41%, p<0.0001).
- A small (n=62) retrospective study including very elderly patients (aged over 85 years) reported that the complication-free rate was not significantly different in the Micra™ group compared with the TVPM group (88.6% vs. 92.6%, p=0.68) (51). The total complication rate within one week of implantation was 7.4% for Micra™ compared with 5.7% for TVPM (p=NR). The complication rate up to 6 months was zero for Micra™ and 5.7% for TVPM (p=NR).

Infections

This outcome includes endocarditis, pericarditis, any infection site, or pocket infection. The outcome may have also been included as part of "any complication" presented above. Figure 15 shows the results of studies that presented data in a way that could be included in the meta-analysis grouped by study design and follow-up time. Note the RCT did not provided data for this outcome.

The results for prospective studies were as follows for Micra™ compared with TVPM:

- 6 to 12 months; endocarditis: non-statistically significant difference.

- 6 to 12 months; implant site infection: non-statistically significant difference.
- 6 to 12 months; 'infection': non-statistically significant difference.
- 36 months: pericarditis (1 study): Micra™ is associated with a significantly higher risk of pericarditis than TVPM. The analysis shows the risk of developing pericarditis at 36 months is 103% higher for the Micra™ group compared with the TVPM group (RR 2.03, 95% CI 1.53-2.71, p<0.00001,16,431 participants).

The results for retrospective studies comparing Micra™ with TVPM were as follows:

- In-hospital: infection non-statistically significant difference.
- 1 to 4 months: endocarditis and pocket infection: non-statistically significant difference.
- > 24 months: pocket infection: non-statistically significant difference.
- Time unclear: any infection (1 study): non-statistically significant difference.
- Time unclear: endocarditis (1 study): non-statistically significant difference.

No studies provided data for periods longer than 36 months.

Data not included in the analyses:

- (data not included in the submission) A fair quality systematic review (13) pooled results for endocarditis and pericarditis. Pooled data for endocarditis showed 83% lower odds of endocarditis in the leadless PM group compared with the TVPM group (OR 0.17, 95% CI 0.06-0.54, I^2=0%, p=0.002, 7 studies, n=6455). However, two pooled studies reported that the odds of pericarditis were 2.1 times higher in the leadless PM group compared with the TVPM group (OR 2.12, 95% CI 1.58-2.85; I^2 = 20%, p=0.00001, 2 studies, n=19,823). The studies in this meta-analysis are the Micra TP study (48) and Micra CED study (47).
- A small (n=200) prospective study reported no significant difference in device endocarditis between Micra™ recipients and TVPM recipients after twelve months (0 vs. 1, p=1) (42).
- One large (n=16431) prospective non-randomized study with a contemporaneous control reported that after three years Micra™ recipients' device-related infection rate was significantly lower than that of patients who received TVPM (<0.2% vs. 0.7%, p<0.0001) (25) (not included in the submission).
- One large (n=35430) retrospective analysis reported a (pre-cohort matched) significantly higher likelihood of in-hospital infection following the implantation of leadless PM (<0.15%) compared with TVPM (<0.04%) (OR 4.47, 95% CI 1.75-1.42, p=0.002) (28).
- One large (n=21782) retrospective analysis reported a post-procedural infection rate of 0.09% for TVPM patients, but could not provide the same data for leadless PM patients due to database use agreement (i.e. restrictions sharing details to protect confidentiality) (p=0.47) (16).
- Bodin et al report a retrospective matched control analysis of French hospital data and found that after matching on all baseline characteristics including comorbidities (mean follow-up 6.2 ± 8.7 months, n=2721), cumulative incidence rates of infective endocarditis were not significantly different in groups receiving Micra™ compared with TVPM (HR 1.54, 95% CI 0.64-3.70, p=0.33) (50).
- A small (n=180) retrospective study reported no significant differences in infections in recipients of leadless (Micra™ and Nanostim™) PM compared with TVPM recipients (2% vs. 3%, p=0.69) (15). Device endocarditis was significantly more common in the TVPM group compared with the leadless PM group (0% vs. 3%, p=0.04).

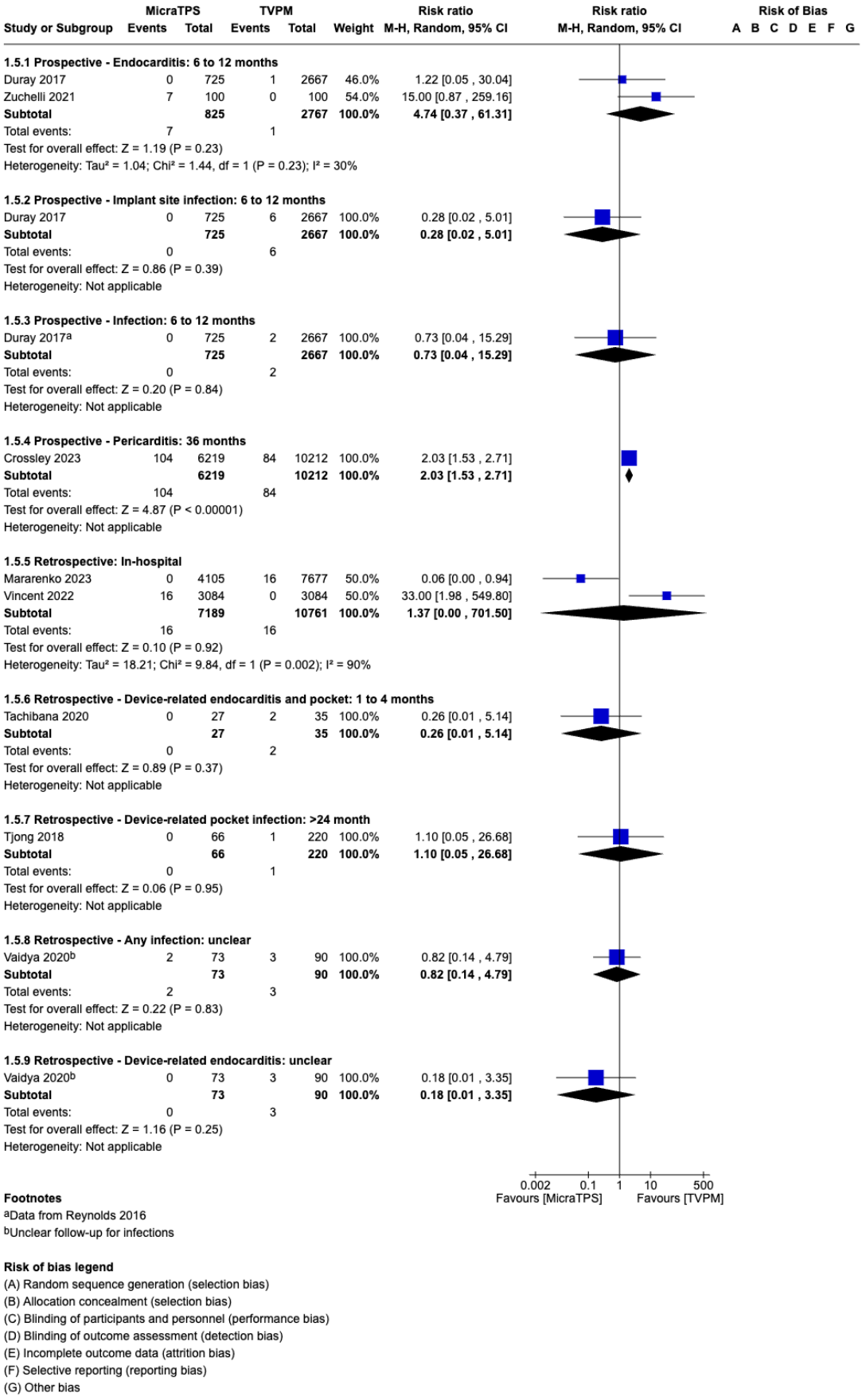


Figure 15. Micra™ vs TVPM: infections

Pericardial effusion

Data for this outcome were provided by one prospective study (42) and two retrospective studies (15;49). All three studies were included in the analysis. The prospective study forest plot showed a non-statistically significant risk ratio with very wide confidence intervals (RR 0.33, 95% CI 0.01-8.09, 200 participants). Similarly, results from the retrospective studies meta-analysis indicated a non-significant difference between Micra™ and TVPM (RR 1.20, 95% CI 0.05-32.01, p=0.91, I²=55%, 465 participants, 2 studies) (Figure 16).

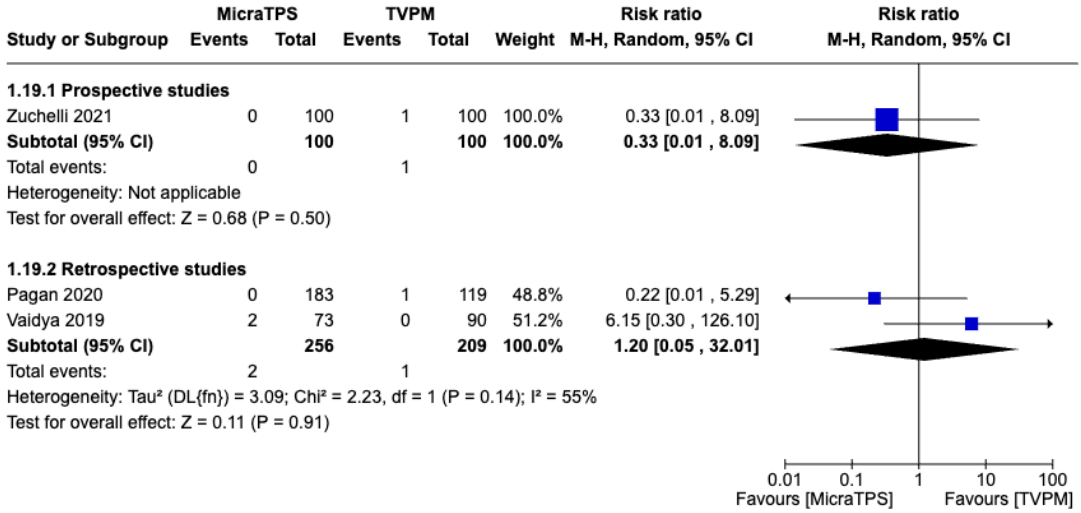


Figure 16. Micra™ vs. TVPM: pericardial effusion

Data not included in the analyses:

- A fair quality systematic review (13) reported that leadless PM recipients had 2.65 times higher odds of pericardial effusion compared with TVPM recipients (OR 2.65, 95% CI 1.49–4.70, I^2 0%, p=0.75, n= 6996, 8 studies). This meta-analysis includes 2 studies with Aveir as the intervention contributing 27.4% weight to the meta-analysis (37;38).

Cardiac Tamponade

(data not included in the submission) The fair quality systematic review (13) conducted a meta-analysis of four studies (n=6182) and reported that patients with leadless PM had a not statistically significant higher odds of cardiac tamponade than recipients of TVPM (OR 2.66, 95% CI 0.91-7.75, I^2=0%, p=0.07, 4 studies, 6182 participants). One of the studies in the meta-analysis includes the Aveir™ PM.

One large (n=21782) retrospective analysis reported statistically significant differences for in-patient cardiac tamponade with a greater incidence in the leadless PM group (0.76% vs. 0.18%, p=<0.001) compared with the TVPM group (16).

One small (n=205) retrospective study of newly implanted individuals reported zero cases of in-hospital tamponade (LPM 0 vs. TVPM 0, p=NR) (30).

A retrospective matched control analysis of French hospital data reported no significant differences in the incidence of tamponade between Micra™ and TVPM groups within the 30 days following implantation (OR 1, 95% CI 0.06-16.004, p=1, matched cohort n=1344) (50).

Thromboembolism

A fair quality systematic review (13) provided pooled results for thrombosis and embolism. Results showed that the likelihood of thromboembolism is lower in individuals in the Micra™ group compared with TVPM, but the difference was not statistically significant (OR 0.46, 95% CI 0.03-6.35; I^2=71%, 3 studies, n=19885). The three studies were also included individually in the submission.

One large (n=16431) prospective non-randomized study with a contemporaneous control reported that after three years Micra™ recipients had an adjusted relative risk reduction of 56% (95% CI 6%-79%, p=0.03) for all-cause thrombosis or embolism compared with TVPM patients (25). There were no significant differences at three years follow up between the two groups in terms of thrombosis or embolism due to the cardiac device (thrombosis due to cardiac device RRR 57%, 95% CI –2%-82%, p=0.06; embolism due to cardiac device RRR 16%, 95% CI -397%-86%, p=0.85).

One large (n=35,430) retrospective analysis reported higher likelihood of in-patient venous thromboembolism, cardiac-related complications, device thrombus formation, and vascular complications following the implantation of leadless PM compared with TVPM. In-hospital results show venous thromboembolism was 2.74 more likely to occur in the leadless PM group (OR 2.74, 95% CI 1.84-4.10, p≤0.01). After propensity matching venous thromboembolisms (lower extremity deep venous thrombosis and pulmonary embolism) were significantly more likely to occur in the leadless PM group (p≤0.01) (28).

One large (n=21782) retrospective analysis reported no device embolization was associated with either leadless PM or TVPM during procedures (16).

Vascular complications

This outcome includes hematoma, bleeding, arteriovenous/atrioventricular fistula, and pseudoaneurysm.

Hematoma

Data for this outcome were provided by one RCT (22), and six prospective studies (26;41;42;44;45;48), and five retrospective studies (14;30;31;49;51). All studies were included in the meta-analysis.

The RCT evaluated device-specific hematoma; results showed a non-statistically significant risk ratio of 0.30 (95% CI 0.01-6.98; 51 participants). This result is not surprising given that Micra™ is implanted directly into the heart via a catheter inserted through a vein in the leg or neck avoiding the need for a surgical pocket under the skin. This reduces the risk of bleeding and hematoma formation at the implantation site.

For prospective studies reporting '*hematoma*' the results are not statistically significant indicating the possibility of both reduced and increased risk (RR 1.41, 95% CI 0.62-3.20, p=0.41, I^2=25%, n=20611, 4 studies). Four prospective studies specified hematoma was '*device specific'* and their results show individuals with Micra™ had an 82% lower risk of developing device-specific hematoma compared with those receiving TVPM (RR 0.18, 95% CI 0.04-0.79, p=0.02, I^2=0%, 937 participants, 3 studies).

Five retrospective studies reported this outcome, either as hematoma or groin hematoma. While the results are not significantly different between Micra™ and TVPM, the effect sizes indicate a higher risk for individuals with Micra™ of developing hematoma (24%) or groin hematoma (890%) (hematoma RR 1.24, 95% CI 0.47-3.25, p=0.66, I^2=38%, 6640

participants, 4 studies; groin hematoma RR 9.90, 95% CI 0.41-240.09, 286 participants, 1 study) (Figure 17).

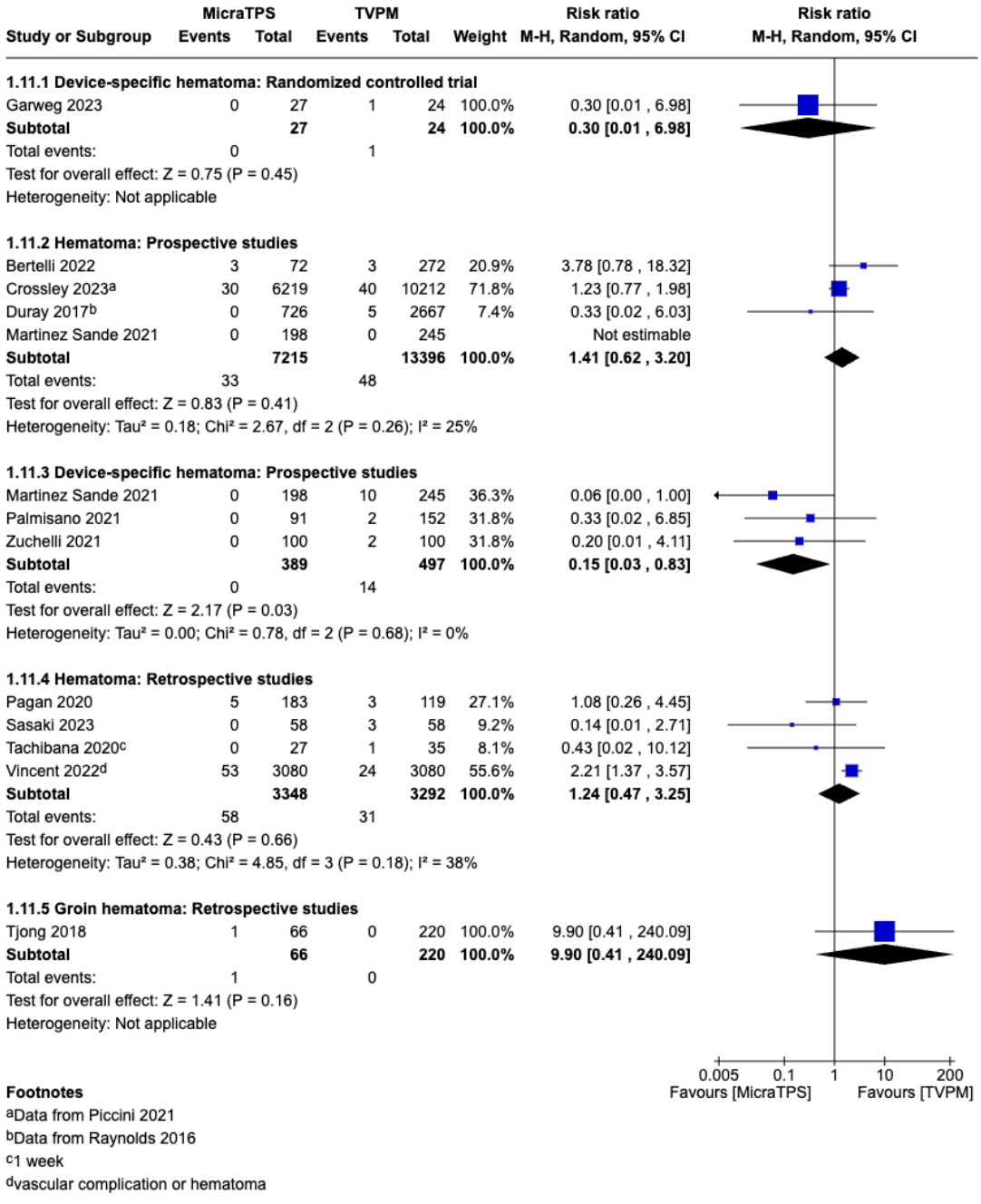


Figure 17. Micra™ vs. TVPM: hematoma

Bleeding

One large (n=35,430) retrospective analysis reported a significantly higher likelihood of needing blood transfusions following the implantation of leadless PM compared with TVPM (OR 1.54, 95% CI 1.14-2.07, p=0.005) (28).

Pneumothorax/hemothorax

Three retrospective studies (14;30;31) provided data for this outcome and NOMA included them in a forest plot. The results from the retrospective studies indicated a substantial heterogeneity (I^2=80%), so the overall effect size is not presented. Of the two studies that

could be estimated, one (14) crosses the line of no effect, while the other (31) favours Micra™ (Figure 18).

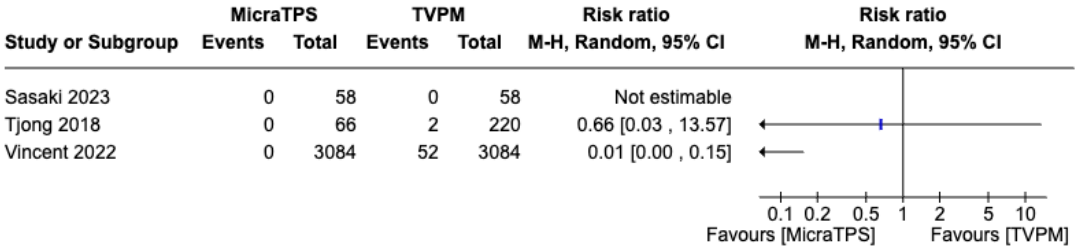


Figure 18. Micra™ vs. TVPM: pneumothorax/hemothorax

Data not included above:

- A fair quality systematic review (13) reported a pneumothorax meta-analysis (5 studies, n=4261) and shows that leadless PM recipients had 87% lower odds of pneumothorax compared with TVPM recipients (OR 0.13, 95% CI 0.03–0.57, p=0.007, I^2=0%). A further meta-analysis of hemothorax (3 studies, n=17067) shows no difference between leadless PM and TVPM groups (OR 0.98, 95% CI 0.67-1.43, p=0.92, I^2=0%). The primary studies in these meta-analyses were included in the submission but their data were not reported.

Arterial-venous fistula
A fair quality systematic review (13) reported the odds of recurrence of arterial venous fistula in a meta-analysis. Results indicate a higher risk of recurrence of AV fistula formation with the Micra™ PM compared with TVPM (OR 10.82, 95% CI 1.99-58.92, I^2=0%, p=0.006, 3 studies, n=4028). The three studies in the meta-analysis were also included individually in the submission.

One small (n=205) retrospective study of newly implanted individuals reported in hospital AV fistula results of 2 for Micra™ patients compared with zero for TVPM patients (p=NR) (30).

Right ventricular dysfunction
The submission did not present results for this outcome.

Atrioventricular (AV -tricuspid & mitral) valve regurgitation
The RCT (22) reported no significant change in tricuspid (p=0.19) or mitral (p=0.46) valve function at 12-month follow-up in the Micra™ group compared with the TVPM group. Tricuspid and mitral valve function worsened significantly in the TVPM group (p=0.001 and p=0.017, respectively). When comparing both groups, evolution of valve function was only significantly different for the tricuspid valve (p=0.009), but was not statistically significantly different for the mitral valve function (p=0.304). No interaction between the Micra™ and the tricuspid valve function was observed in any of the patients.

A small retrospective study of 205 patients who received Micra™ or TVPM in a single Japanese center reported tricuspid regurgitation (TR), mitral regurgitation (MR) and left ventricular ejection fraction (LVEF) (30). The Micra™ group experienced significantly more worsening TR than the TVPM group (33% vs. 20%, p=0.04), but there was no significant difference between the two groups with respect to worsening MR (26% vs. 18%, p=0.18) or LVEF change (-2±10% vs. -3±8%, p=0.40).

The Micra™ group had significantly higher estimated glomerular filtration rate (eGFR) values than the TVPM group (60±28 mL/min/1.73 m^2 vs. 51±22 mL/min/1.73 m^2, p=0.01) and the implantation center seemed to have a selection bias precluding Micra™ implantation for patients with low eGFR.

A small (n=180) retrospective study reported an increase in severity of tricuspid valve regurgitation by ≥2 grades in none of the leadless PM patients but in 19% of the TVPM patients (p=0.017) (15). Patients included in the study may have also been included in either the Micra™ leadless pacemaker IDE and Product Surveillance Registry or the Nanostim™ studies.

3.3.4 Pacemaker syndrome

The submission did not present results for this outcome.

3.3.5 Safety outcomes (device-related complications)

This includes device dislodgement, device malfunction, battery failure, device infection, pacemaker-induced arrhythmia.

Dislodgement

Five prospective (25;42;44;45;48) and three retrospective non randomized studies (14;49;51) provided data for dislodgement and NOMA included them in a meta-analysis. The prospective studies showed a non-statistically significant difference between Micra™ and TVPM (RR 0.30, 95% CI 0.08-1.13, p=0.12, I²=46%, 20.811 participants, 5 studies). Similarly, the retrospective studies show a non-statistically significant difference for dislodgement (RR 0.36, 95% CI 0.07-1.84, p=0.11, I²=0%, 650 participants, 3 studies) (see Figure 19).

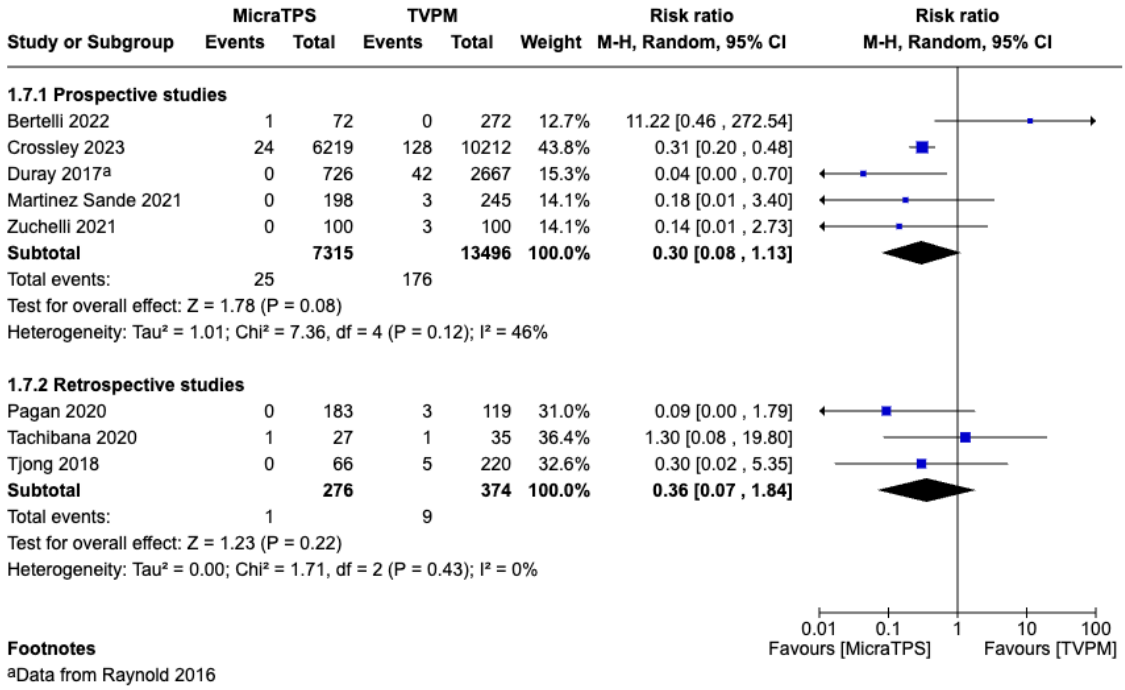


Figure 19. Micra™ vs TVPM: dislodgement

Data not included in the meta-analyses:

- A systematic review of fair quality (13) reports device dislodgement including 10 studies in the meta-analysis (3 of which were not included in the submission). Leadless PM was associated with 70% lower odds of dislodgement compared with TVPM (OR 0.30, 95% CI 0.21 to 0.43; p=<0.00001, I^2 = 0%, n=23348). This meta-analysis pooled prospective and retrospective studies which can introduce issues that may affect the validity and reliability of the results.
- One small (n=443) prospective study reported zero cases of dislodgement in Micra™ patients compared with 3 cases of dislodgement (1.2%) in TVPM patients (0 (0%) vs. 3 (1.2%), p=NR)(45).

Device Malfunction

One prospective non-randomized study with historical controls (n=726 Micra™ and 2667 historical controls) reported that at six months, loss of device function was 0.1% in the Micra™ group and 0% in the TVPM group (p=not estimatable (NE)) (48). A follow-up study reports loss of device function at a mean 16.4 ± 4.9 months (27) with estimates showing 0.3% for the LPM group compared with 0% for the TVPM group (p=NE).

One large (n=16431) prospective non-randomized study with a contemporaneous control reported that, after three years, Micra™ recipients had a relative risk reduction of 34% (95% CI 14%-50%, p=0.002) for device breakdown compared with TVPM recipients and a non-significant relative risk reduction of 26% for other mechanical failures (95% CI −3%-47%, p=0.08) (25). At 3 years, Micra™ recipients experienced significantly fewer device-related complications (including complications related to mechanical integrity of the device or codes like device dislodgement, device infection, device pocket complication) than TVPM recipients (adjusted cumulative incidence function: 2.6% vs. 5.2%, p<0.0001), with a relative risk reduction of 51% (95% CI 41%−59%; p<0.0001) (25).

A small (n=440 matched) retrospective study compared leadless PM and TVPM in a matched cohort design, using patients who had been previously enrolled in larger leadless PM studies as well as TVPM patients from a nationwide cohort in the Netherlands (14). After 800 days, there were more occurrences of lead fracture (leadless PM 0% vs. TVPM 0.45%), pocket issues/erosion (0% vs. 0.9%) and generator issues (0% vs. 0.45%) in the TVPM group compared with the leadless PM group (p=NR).

Battery failure

See battery life above

Device Infection

See infection above.

Device revision, retrieval, replacement, explantation

Five prospective studies (25;27;42;44;48) and two retrospective studies (15;31) provided data for this outcome. Only the data from three prospective and two retrospective studies were deemed appropriate for inclusion in the meta-analysis. The prospective studies demonstrated the risk of system revision, re-intervention and retrieval is 91% lower in the Micra™ group compared with the TVPM group (RR 0.09, 95% CI 0.04-0.21, p=0.00001, I^2=0%, n=16975 participants, 3 studies). Similarly, the retrospective studies showed a 70% lower risk of system revision, re-intervention and retrieval (RR 0.30, 95% CI 0.24-0.38,

p=0.00001, I²=0%, 6331 participants, 2 studies) in the Micra™ group compared with TVPM group (see Figure 20).

Data not included in the meta-analysis:

- A systematic review of fair quality (13) provided pooled results for re-intervention (4 studies, n=17009) and showed 46% lower odds of device/lead re-intervention (OR 0.54, 95% CI 0.45-0.64, I^2=0%, p=<0.0001) for recipients of leadless PM compared with recipients of TVPM. Three of the four studies were included in the submission and one may have included Nanostim™.
- A prospective non-randomized study with historical controls reported that at six months system revision due to complications was 0.4% (95% CI 0.1%-1.4%) in the Micra™ group compared with 3.5% (2.8%-4.2%) in the TVPM group (RRR 87%, 95% CI 58%-96%, p=NR) (48).
- One small prospective study (n=344) reported no significant difference at a mean of 22.8 months (Micra™ recipients) and 23.7 months (TVPM recipients) for pacing system repositioning (0% vs 1.9%, p=0.2) (44). At follow-up, no system revisions were needed in the Micra™ group whereas six patients (2.2%) in the TVPM group required either lead repositioning (5 cases) or addition (1 case).
- One large (n= 16,431) prospective non-randomized study with a contemporaneous control reported that after three years Micra™ recipients had a relative risk reduction of 70% for system revisions (95% CI 40%-85%, p=0.0007). System replacement rates were 1.2% for Micra™ compared with 0.5% for TVPM (RRR -124%, 95% CI 290%- -28%, p=0.005) (25).

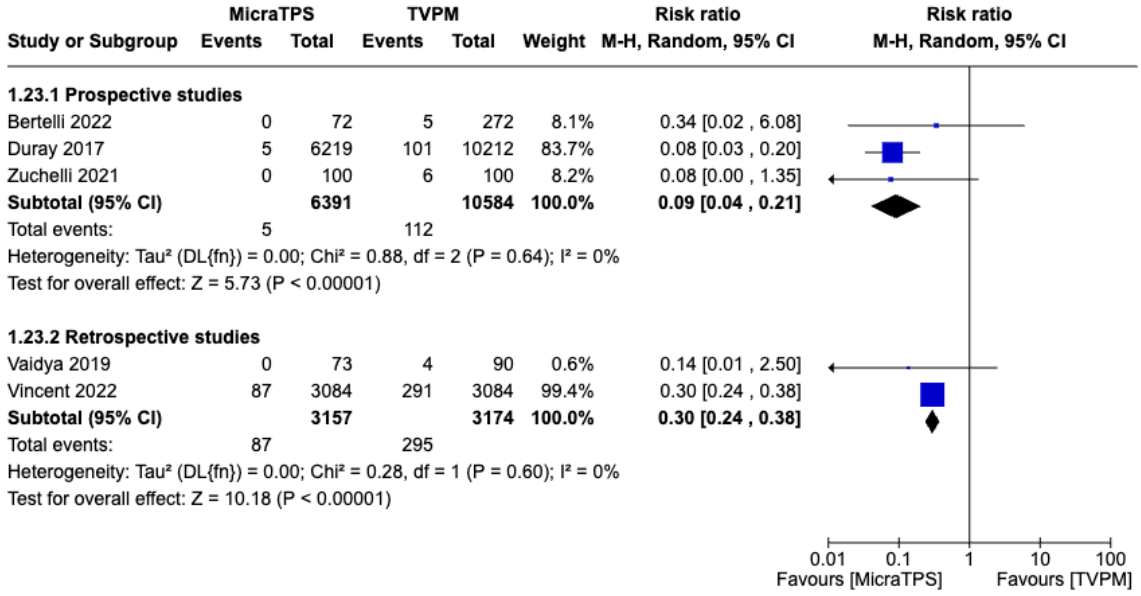


Figure 20. Micra™ vs TVPM: revision, retrieval, replacement

3.3.6 Any serious adverse event

For data from the submitter, see above under other safety outcomes.

The Medtronic CRM Product Performance eSource (67) reports day of implant and acute observations (first month, day of implant excluded) for registered USA implants of Micra™ model MC1VR01 for five complications/event types (see Table 11).

Table 11. Day of implant and acute observations from Medtronic CRM Product Performance Source.

	Day of implant (n=71898)	Acute (day 2-30) (n=71898)
Cardiac perforation	291	21
Dislodgement	178	22
Elevated pacing threshold	268	165
Failure to capture	131	83
Failure to sense	72	19

Referencing two publications not included in the submission, the eSource states that "The rate of perforation for commercially released Micra devices continues to perform acceptably within levels observed within the post-approval clinical study registry. Overall, clinical studies have demonstrated a reduction in the risk of major complications of 63% through 12 months and 57% through 36 months relative to transvenous pacing systems." (67) Patient outcomes are not specified in the eSource.

Per October 31 2024 the US Food and Drug Administration MAUDE database (68) (Manufacturer and User Facility Device Experience) has since 2016 received 199 medical device reports for Micra™ model MC1VR01 classified in the event category "death". NOMA assumes most of them are related to cardiac perforations reported above. The US FDA MAUDE database contains medical device reports (MDR) of adverse events. NOMA acknowledges that the submission of a medical device report itself does not necessarily demonstrate that the device caused or even contributed to the reported adverse outcome or event.

The Medicines and Healthcare products Regulatory Agency (MHRA, United Kingdom) issues safety notices for devices.
NOMA found two Urgent Field Safety Notices for Micra™ in the Alerts, recalls and safety information: drugs and medical devices section of MHRA. One is dated August 2019, the other one in May 2019 (broken link at MHRA, retrieved from Saudi Food & Drug Authority).

EUDAMED
We looked for Micra™ in the results list, sorted alphabetically by trade name, from a search in the EUDAMED segment Search Devices and System or Procedure Packs, with active search fields Risk class (Class III) and Applicable regulation (MDR (regulation (EU) 2017/745 on medical devices)). No information was found because the Micra™ device is not yet registered in EUDAMED.

3.3.7 Health care resources

Procedure duration (minutes)

Data for this outcome were provided by one RCT (22), two prospective studies (41;42) and two retrospective studies (49;51) which NOMA included in the analyses. As Figure 21 shows, there was no significant difference in procedure duration in the RCT (MD 2.7, 95% CI –6.44- 11.84, 51 participants) or prospective studies (MD –0.56, 95% CI –27.82- 26.71, I^2 =98%, 354 participants, 2 studies) between recipients of Micra™ and TVPM. The retrospective studies consistently show a reduction in procedure duration favouring Micra™ compared with TVPM (MD –27.61, 95% CI –33.44-21.75, I^2=0%, 364 participants, 2 studies).

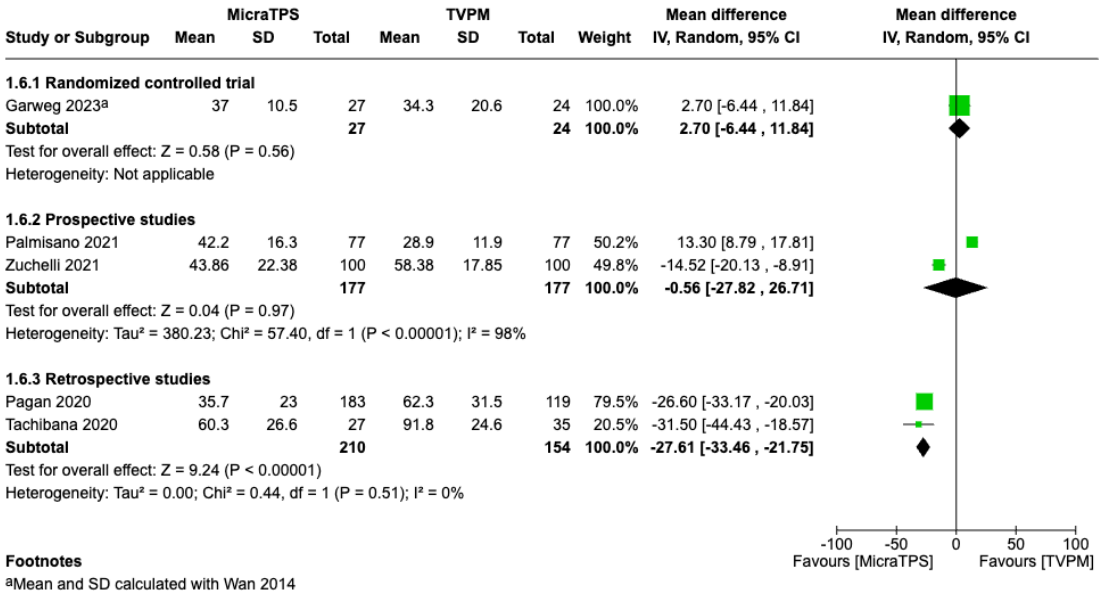


Figure 21. Micra™ vs. TVPM: procedure duration

Data not in the analyses:

- The RCT reported a non-significant difference in total implant procedure duration between groups (22). The submission notes that the median time from femoral venous puncture to Micra™ implant or from skin incision to lead in vessel ("venous time") was significantly longer in the Micra™ group than in the TVPM group (17.0 minutes 95% CI 14.0–19.0 vs. 7.0, 95% CI 6.00–14.0 minutes p≤0.001). The submission stated that the difference was partly related to the systematic acquisition of a right ventricular angiogram and the placement of a temporary pacing guide wire in 18 patients during the Micra™ implant procedure.

Implant success rate

One RCT (22) two prospective studies (41;42) and three retrospective studies (15;49;51) provided data for implant success rate. NOMA included three studies in the meta-analyses, while the remaining two are shown in the forest plot. The analysis showed no significant difference in implant success rates between the Micra™ and TVPM groups across both prospective and retrospective studies (Figure 22).

Data not included in the analysis:

- A small (n=243) prospective study conducted in a single Italian hospital reported an implantation success rate of 97.8% (91/93) for Micra™compared with 100% (152/152) for TVPM implantation (41). These numbers are in the general population and not the propensity score matched group and thus were not used in NOMA's meta-analysis

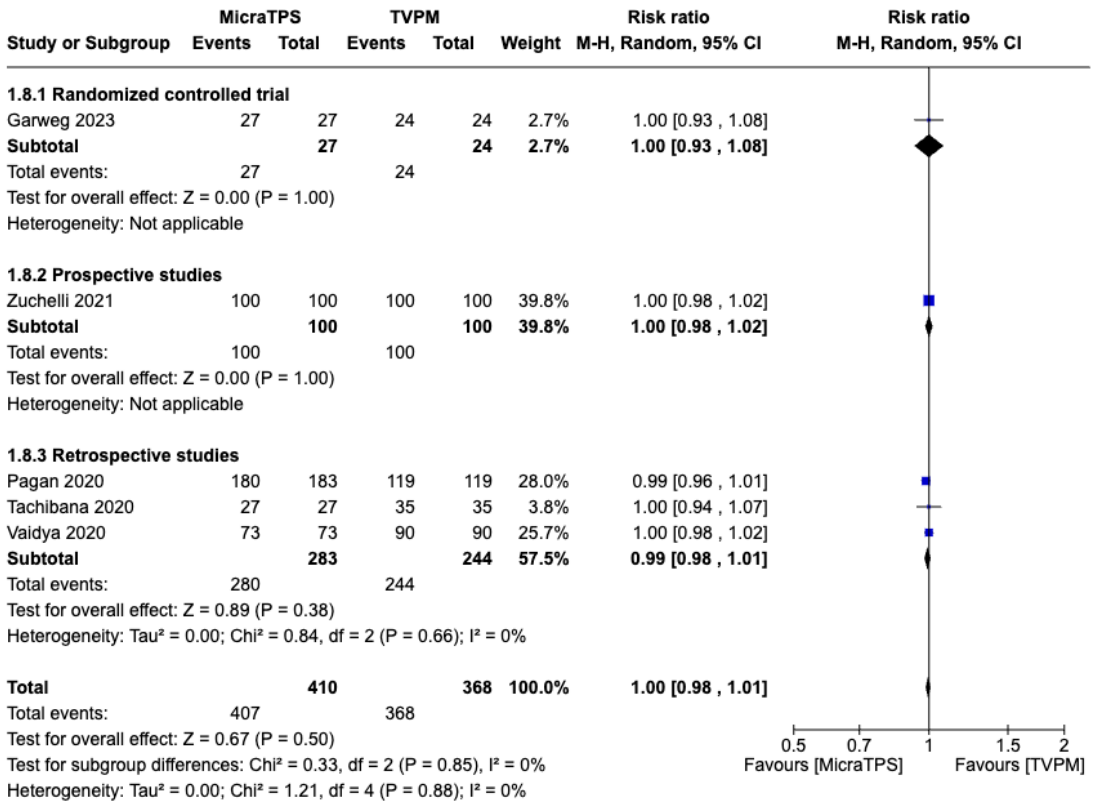


Figure 22. Micra™ vs. TVPM: implant success rate

Time to hospital discharge

One prospective study (41) and two retrospective studies (16;31) provided data for this outcome and NOMA conducted a meta-analysis of these studies. However, due to substantial heterogeneity, NOMA chose not to present the overall results (Figure 23). The forest plot indicates no difference in length of stay for participants in Mararenko's study.

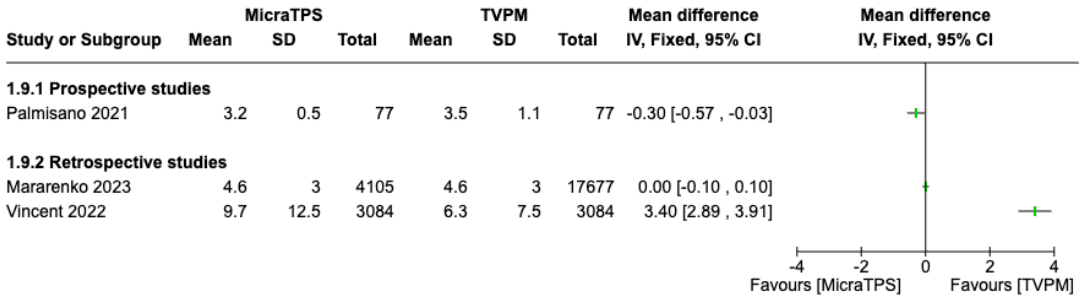


Figure 23. Micra™ vs. TVPM: length of stay

Data not included above:

- A fair quality systematic review (13) reported a shorter length of hospital stay in the leadless PM group in comparison with the TVPM group (3 studies, n=279). Individuals receiving a Micra™ stayed a mean 1.5 fewer days than individuals receiving a TVPM (95% CI -2.40 to -0.60, p=0.001, I^2 = 0%). One of the three studies in this meta-analysis was not included in the submission (69). That study included individuals receiving a concomitant transcatheter aortic valve implantation (TAVI). A pacemaker indication includes dual chamber.

- A small (n=62) retrospective study reported that there was no significant difference between the time to hospital discharge for Micra™ compared with TVPM (9.7 ± 6.8 vs. 12.5 ± 4.5, p=0.08) (51).

3.3.8 Results for subgroups

One large (n=16431) prospective non-randomized study with a contemporaneous control carried out a subgroup analysis of high-risk patients (25). The sub-group did not match the subgroups specified in the submission.

Patients who need pacing, but who had to have their conventional pacemaker explanted due to infection.
The submission did not present results for this subgroup.

Patients with end stage renal disease or on dialysis.
The submission states that four studies provided data for subgroups with end stage renal disease (ESRD), chronic kidney disease (CKD) or renal failure (16;31;44;46).

Baseline characteristics
Baseline data provided by the submitter suggest that patients receiving Micra™ in these studies might have had different characteristics or risk factors related to their kidney function even before the procedure:

- The Crossley 3-year Micra™ CED study, which builds on the Boveda 2023 CED study above, reported that patients implanted with Micra™ were significantly more likely to have ESRD (12.0% vs. 2.3%, p<0.001) and renal dysfunction (48.8% vs. 42.1%, p<0.001) than patients who received TVPM (25).

- One small prospective study involving two hospitals in Italy included 26/72 patients with CKD who received Micra™ and 157/272 patients with CKD who received TVPM (chronic kidney disease defined as GFR < 60 mL/min/1.73 m^2). There was a statistically significant baseline difference between groups (p≤0.01) (44).

- One large retrospective analysis of US hospital administrative data included 1652 (21.1%) Micra™ recipients and 6153 (78.8%) TVPM recipients with renal failure (p= <0.001). (16)

- A large retrospective analysis of the US National Inpatient Sample database for 2017 to 2019 included 2160 (12.8%) patients receiving Micra™with ESRD and 60 (4.8%) patients with ESRD in the TVPM group (p≤0.001) (31).

Results
The Boveda 2023 2-year Micra™ CED study included 1522 patients with Micra™ and 510 patients with TVPM with ESRD and 1368 patients with Micra™ and 1109 TVPM with chronic kidney disease stages 4 and 5 (46). At 30 days and 2-year follow-up, all cause mortality after adjusting for patients' characteristics, was not statistically different between the Micra™ and TVPM treatment groups.

The results are not statistically significantly different for ESRD or CKD stages 4 and t, ESRD, CKD stages 4 and 5 for 30-day acute complications, all chronic complications, or device related complications. (46).

The Bertelli 2022 (44) study analyzed all-cause mortality at long term follow up (22.8 ± 2.6 months vs. 23.7 ± 1.1 months, p = 0.31) and results indicate no statistically significant difference between groups (OR 0.62, 95% CI 0.32-1.20, p=0.82)

Results from Mararenko et al. (16) suggest no significant difference between the subgroups for in-patient mortality (HR 1.02, 95% CI 0.61-1.70, p=0.94), that Micra™ has no significant difference from the comparator in terms of 30-day readmissions (HR 1.13, 95% CI, 0.93–1.37, p=0.23) and length of stay (regression coefficient: -0.26, 95% CI -0.54 - 0.01, p=0.062) (16). Note: NOMA was unable to confirm this study used Micra™ as an intervention.

Vincent 2022 (31) reported a large retrospective analysis of the US National Inpatient Sample database for 2017 to 2019 that included 9065 patients in the Micra™group and 485 patients in the TVPM group with ESRD or CKD and presents pooled procedural complications and in hospital all-cause mortality for patients with ESRD.

There was no significant difference between the in-hospital all-cause mortality rates for the two groups (adjusted OR 1.00, 95% CI 0.77-1.29, p=0.99), but there were 21% higher odds of procedural complications associated with Micra™ compared with TVPM (adjusted OR 1.21, 95% CI 1.01-1.44, p=0.04) (31). The submitter indicates some dual chamber pacemakers were included in the TVPM group.

Patients with compromised venous access cause, for example by thrombosis and an occluded subclavian vein

One post hoc analysis (29) presents findings analyzing mortality predictors in patients precluded from transvenous pacing. The study includes data from the Micra IDE study, Micra CA study, and Micra PAR study, and found a significantly higher mortality rate among patients precluded from TVPM implantation compared with those who were not.
The authors used univariate and multivariable Cox models to assess the association between various patient characteristics (age, gender, BMI, comorbidities, etc.) and mortality.

The most common reason for preclusion was issues related to venous access (42.5%) including patients with venous thrombosis or occlusions, abnormal venous anatomy, renal dysfunction requiring hemodialysis where preserving venous access was prioritized. The second most common reason was a history of infection or bacteremia (38.8%) highlighting the risk associated with repeat device implantation in patients with prior infections. Other reasons for preclusion included cancer, prior complications with TVPM system, lifestyles, valve-related issues or other reasons.

The results suggest that these factors are important considerations in predicting mortality in this patient population.

The submission presents data for a malignancy subgroup which were not specified in the PICO (see p155 of the submission).

3.4 NOMA's certainty in the evidence

NOMA uses the Grading of Recommendations Assessment, Development and Evaluation) (GRADE) framework to interpret the overall certainty of this body of evidence and the strength of the recommendation (70). Grading the strength of the body of evidence incorporates judgments of study quality, but also includes how confident one is that a finding is true. Certainty of evidence is categorized as very low, low, moderate or high (Figure 24.

GRADE certainty rating and interpretation of symbols). The GRADE approach to rating confidence in estimates begins with identifying the study type (RCT or non-randomized) and then systematically considers criteria to rate the certainty of evidence up or down per outcome.

Certainty in the evidence	Definition
High (⊕⊕⊕⊕)	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate (⊕⊕⊕◯)	Further research is likely to have an important impact on our confidence in the effect and may change the estimate.
Low (⊕⊕◯◯)	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low (⊕◯◯◯)	Any estimate of effect is very uncertain.

Figure 24. GRADE certainty rating and interpretation of symbols

Source: GRADE handbook reference (20)

The submitter's body of evidence (systematic reviews, a small RCT, and prospective and retrospective non-randomized studies) presents a challenge to integrate and present optimally. First, the risk of bias is not available per outcome but per study. Second, there is scarce empirical guidance on grading the certainty of the evidence of RCTs and non-randomized studies (prospective and retrospective) (70).

It is important to note that in the presence of poor and fair-quality systematic reviews, and 1 small RCT, which were unable to answer the PICO question, non-randomized studies provided the best available evidence for decision-making. Non-randomized studies offer advantages in examining long-term outcomes and may be conducted by accessing large datasets from medical records, but have major design challenges for establishing causality. Even with careful planning, controlling confounding factors might affect the outcomes. Some non-randomized studies rely on existing data, which may be incomplete, inaccurate, or inconsistent.

NOMA has some concerns with the internal validity of the submitter's studies. The risk of bias was rated as 'Poor' due to significant methodological limitations such as small sample sizes, selection bias, and lack of adjustments for confounding factors. These issues reduce confidence in the results and suggest that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Studies rated as 'Fair' showed better methodological rigor but still had notable limitations, such as potential selection bias and the need for adjustment for confounding factors. The single 'Good' study (which was funded by the submitter) provides more reliable evidence, but it is an outlier. Overall, while some valuable insights can be drawn from the evidence, the evidence should be interpreted with caution. Higher-quality studies are needed to strengthen the certainty of the findings.

NOMA deemed that the overall certainty of evidence was 'low' to 'very low'. The reasons for this assessment are explained below. NOMA notes the limitations in the clinical evidence but suggests that Micra™ was not inferior and for some outcomes superior (where data were provided) compared with TVPM. The subgroup population data provided were not enough to arrive at any conclusions for the effectiveness of Micra™ for specific subgroups.

GRADE criteria and certainty of evidence

- RoB: The RCT has an overall RoB of ‘some concerns.’ Owing to the type of intervention, masking is not possible (raising concerns for performance and detection bias). The certainty in results from non-randomized studies are lowered because the non-randomized design inherently causes risk of bias.
- Imprecision: in general, point estimates vary widely across studies with wide confidence around the estimate of the effect creating uncertainty about the results.
- Inconsistency: For some outcomes there was considerable unexplained inconsistency (widely differing estimates of the treatment effect).
- Indirectness: For the intervention, this is not a concern. In most studies the intervention was Micra™. The systematic reviews and two primary studies included other pacemaker brands, but the intervention was always a leadless pacemaker. However, in some studies the comparator group included double chamber pacemakers. Regarding population, the studies mostly report data from individuals eligible for single-chamber ventricular implantation. This may be an indirectness issue if high-risk groups are the primary population.
- Publication bias: “Publication bias is a systematic under-estimation or an over-estimation of the underlying beneficial or harmful effect due to the selective publication of studies.” NOMA neither was able to assess publication bias nor has reasons to suspect publication bias is present, but cannot be absolutely confident that there is none.

4. Health economic assessment

4.1 Methods

Methods for evaluating submitted cost-effectiveness models

The aim of any economic evaluation is to identify, measure and compare costs and consequences of the alternatives under consideration. This is done in an incremental analysis in which the differences in costs between an intervention and its comparator are compared with differences in consequences. This economic evaluation supports decision making by informing the three criteria for priority setting in the Norwegian health care sector: 1) the benefit criterion, 2) the resource criterion, and 3) the severity criterion (71).

The primary objectives of health economic modelling are to provide a mechanism to determine the relative cost-effectiveness of the specified health intervention(s) compared with standard practice using the best available evidence, and to assess the most important sources of uncertainty surrounding the results. To make comparisons across different treatment or test strategies and multiple health outcomes, economic models typically measure health outcomes in terms of quality-adjusted life-years (QALYs). This is a variable designed to capture both life extension and health improvement. QALYs, by definition, take on a value of 1 for perfect health and 0 at death. The output of a cost-effectiveness model is expressed as an incremental cost-effectiveness ratio (ICER), which can be thought of as the extra cost of obtaining an extra life-year in perfect health. The ICER is defined as:

$$(Cost_{Intervention} - Cost_{Comparator}) \,/\, (QALY_{Intervention} - QALY_{Comparator})$$

There is no single correct way to build economic models estimating the cost-effectiveness of a specific health intervention. Modelling requires consulting with clinical experts to gain an understanding of expected disease progression, and to determine the relevant treatment population, comparators, health outcomes and adverse events connected to the treatment alternatives. This information informs the model structure and determines which clinical effect data are most important to retrieve in the systematic literature search. Once the model structure is in place, systematic searches and evidence grading are used to assess the model input parameters and relevant cost and quality of life data that are needed for cost-effectiveness calculations.

A model is rarely meant to capture every potential detail of the treatment landscape; rather the goal is to include sufficient details to provide a realistic view of the most significant pathways in disease progression, given the research question(s) one is trying to answer. Appraisal of a health economic model is primarily about determining whether the choices made by the submitter regarding model structure and treatment comparator are reasonable; whether the baseline epidemiological data reflect the population in which the analysis is being performed; whether the clinical effect data used in the model are of adequate quality; whether resource use and costs reflect the conditions of the healthcare system in question; whether there has been sufficient sensitivity and scenario analyses to determine the degree and sources of uncertainty in the model results; and whether the model displays external and internal validity.

In this report, NOMA first discusses the health economic model, and the parameters used for patients receiving Micra™ intervention compared with TVPM from the submitter. We analyzed the model's pathway and parameters according to NOMA's guidelines for single technology assessment, considering the choice of model and health states as stated below (72). Based on the assumptions and results related to efficacy and safety, we adjusted the

base-case analysis submitted to NOMA using the available evidence from NOMA's meta-analysis where appropriate. The model assumptions were further modified for subgroups based on the evidence, if needed, and we refer to this adjusted analysis as the main analysis.

We conducted scenario analyses to present the range of the ICERs and assess the variability considering uncertainty. Furthermore, we commented on the health economic results derived from the Micra™ CED study (25;26;47) and the outcomes relevant to the economic model. Finally, we discussed findings from other HTAs in different settings and the implications of these results in the discussion section of the report.

4.1.1 Cost-effectiveness model structure provided by the submitter

The economic model was developed in Microsoft Excel and evaluates the cost-effectiveness and budget impact of single-chamber transvenous pacemakers (TVPM) versus Micra™ in Norway, using a Markov structure over a 20-year horizon with 6-month cycles. The first model cycle is divided into 1 month and 5 months, to account for short-term complication rates.

The model, incorporating local cost data and patient-reported outcomes, calculates total mean costs and QALYs to derive the ICERs for different high-risk patient subgroups: ESRD, prior infection and epicardial leads. It includes health states of 'alive' (with and without infection) to reflect quality of life variations due to infections, and a 'dead' state.

The description of each health state is as follows:

- **Alive (without infection):** This is a starting health state for the cohort. This health state includes all patients that are not experiencing any infections but includes patients receiving revisions and re-intervention, device replacement and upgrades after adjusting for their respective mortality risk. This is a recurring health state.
- **Alive (with infection):** This health state includes all patients experiencing new infections adjusted for their respective mortality with infection. The patients transition back to the Alive (without infection) health state after the event has occurred, therefore this health state is a non-recurring health state, and only new infections are being considered each cycle.
- **Dead:** This includes all patients that experienced mortality with respect to their baseline mortality risk and mortality risk with infection.

4.1.2 NOMA's comments on the model structure

NOMA's model assessment suggest it lacked a clear overview of the model transitions, particularly concerning the extended health states related to infections, revisions, and upgrades, as well as their associated mortality risks. To address this, we conducted a thorough review of the submitter's model to describe the possible clinical pathway for patients undergoing pacemaker implantations. This assessment aimed to clarify how transitions occur between states, including infection and revision-related health states, and impact overall mortality risk, and also to provide a more comprehensive understanding of the model's dynamics.

The submitter's model structure compromised a Markov state-transition model for highlighting the different pathways associated with the patients undergoing pacemaker implantation. The comparator (TVPM) and the intervention (Micra™) followed a similar clinical pathway and allowed for the appropriate transitions for patients with and without

infections. The submission initially described the starting health states, but only after further evaluation was NOMA able to differentiate between the health states associated with infections, revisions, or replacements used in the model. These states were separately modelled to account for device-related complications, capturing revisions or upgrades to dual-chamber pacemakers or cardiac re-synchronization therapy pacemaker (CRT-P). Each health state had its own transition probabilities and incorporated mortality risk adjustments accordingly, reflecting the specific risks associated with each scenario.

Figure 25 shows the model schematic representing the model transitions between health states.

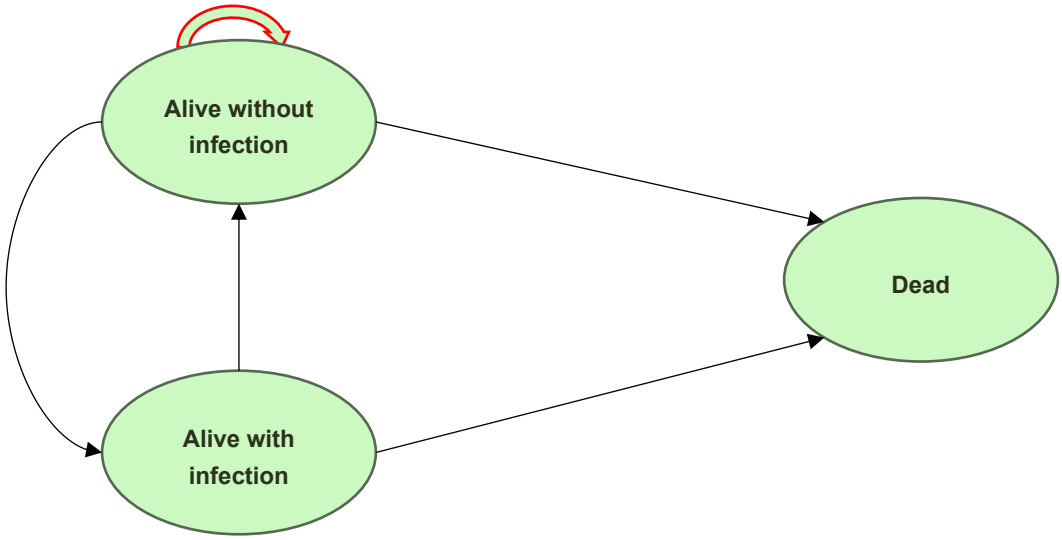


Figure 25. Model schematic showing model transitions between health states

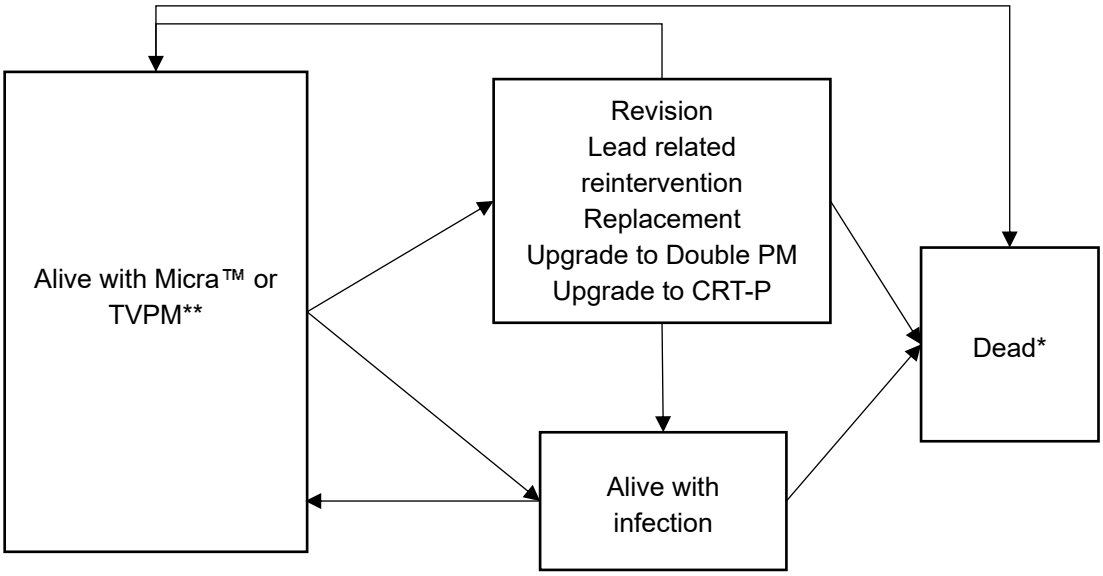
In NOMA's evaluation of the Markov model, the following health states and transitions are outlined Figure 26.

NOMA's health states identified from the model:

- **Alive with TVPM or Micra™ (without infection):** This is starting health state each cycle that includes all patients without infections, patients in this state have no infection and face potential transitions to other states. They can transition to the following health states below:
- **Alive with Infection (new infections)**: if new infections develop, based on baseline and relative risk adjustments for device replacement and short-term infection risk.
- **Reintervention** Health States: such as Revision, Lead Reintervention, Device Replacement, Upgrade to Double Chamber Pacemaker, or Upgrade to CRT-P, each with its own transition probabilities (capitalization as per the model).
- **Death**: Due to baseline mortality risk.

Patients remain in the **Alive without infection** state if no infections or complications arise.

NOMA's highlighted model transitions for the submitted model:



Key: CRT-P, Cardiac resynchronization therapy pacemaker; PM, Pacemaker; TVPM, Transvenous pacemaker; *Absorbing health state; **Recurring health state

Figure 26. Revised model schematic showing model transitions between health states form Micra™ vs TVPM

According to the health states in the submitted Markov model Figure 26, patients in the **Alive with Infection** state are those who have developed a new infection either from baseline risk or complications. These patients may transition back to the **Alive without infection** state once the infection is non-fatal and resolved. Alternatively, they may move to the **Death** state if the infection results in an increased mortality risk, which is determined by their specific subgroup characteristics. This state acts as an absorbing health state, accounting for all-cause mortality by incorporating both natural background mortality rates and any increased risks of death from specific conditions, such as infections or other complications, within the model's framework.

NOMA's evaluation reveals that patients who die after an infection will transition to the **Death state**, while those who survive the infection will be treated and transition back to the **Alive without infection** state. In this state, patients face a probability of experiencing another infection based on baseline infection risk for each arm. This risk is adjusted for both short-term and long-term infection risks, particularly for patients who experience acute and chronic complications, as detailed later in the submission.

Additionally, the **Reintervention** health states include **Revision, Lead Reintervention, Device Replacement, Upgrade to Double Chamber Pacemaker**, and **Upgrade to CRT-P**. Transitions to these states occur from the **Alive without infection** state due to complications, with each type of intervention having its own associated probability. Patients in these **Reintervention** health states may experience an infection and thus transition to the **Alive with Infection** state due to increased infection risk following reintervention. Alternatively, they may transition to the **Death** state due to mortality risks associated with the subgroup-adjusted relative risk. However, patients in the reintervention states cannot return to the **Alive without infection** state as they have already experienced a significant event, which adjusts their risk profile for baseline mortality risk.

Infections are recorded each cycle for the **Alive with Infection** state, applying relative risks for short-term, long-term, and replacement associated infection risks. Long-term infection risks are only considered for patients who have not experienced reinterventions or upgrades among those in the **Alive without infection** state each cycle. Infections are divided into short-term and long-term categories, with adjustments based on baseline infection risk and the cycle length: 1-6 months, 6-12 months, and beyond 12 months. The 6-month cycle incorporates the transition occurring within the year for the time point that is relevant to the clinical data. In addition, the initial cycle includes implantation costs related to Micra™ and TVPM.

Finally, the **Death** state is an absorbing state, meaning once patients enter this state, they cannot transition to any other state. Patients may enter the **Death** state from the **Alive without infection** state due to baseline mortality, from the **Alive with infection** state due to post infection-related mortality, or from any of the **Reintervention** health states due to mortality risks. Mortality is adjusted according to Norwegian life tables, with relative risks applied for high-risk populations such as those with end-stage kidney disease, prior infections, and patients using epicardial leads for temporary cardiac pacing. Additionally, the mortality relative risk (6 months) post-infection is applied to the base line mortality risk for infection each subgroup. After applying this relative risk of post infection, the mortality risk with infection reaches 100% in both the intervention and comparator arms by 30 months for ESRD, 10 years for prior infection and 19 years for epicardial leads for both the intervention and comparator arms. We further evaluate the odds of infection risk based on the subgroups of interest and the mortality relative risk later in the STA.

Overall, NOMA's evaluation is that the submitted model has appropriate parameters, formulas, transitions and Markov states relevant to the high-risk patient subgroups for the internal validity of the cost and effects. The generated outcomes are in accordance with the change in these parameter values for face validity.

4.1.3 Patient population and time horizon in the submitted model

The economic model is primarily based on the Medtronic CED study (25;26;47), a non-randomized study involving 16,431 patients designed to assess 30-day and 6-month complications in patients receiving Micra™ compared with TVPM. The CED study is reported in 4 publications Piccini 2021 (26), El Chami 2022 (47), Boveda 2023 (46) and Crossley 2023 (25). The study included a broad population of patients with symptomatic bradycardia requiring single-chamber ventricular pacing, including those with comorbidities, without specifically focusing on high-risk patients. The CED study was selected for the economic analysis due to its large patient cohort and the availability of long-term complication data (up to 3 years). In the study, 43.5% of the study population were female and the mean age of the population was 81 years.

Additionally, the El Chami and Piccini studies (26;47) were used to support the transition probabilities, including infection rates and reintervention rates, further informing the economic model. These studies provide the evidence base for assessing infection, reintervention, and long-term complication outcomes, helping to guide the cost-effectiveness analysis across subgroups**.**

Focus on high-risk subgroups

The model specifically focuses on three subgroups of patients who are at an elevated risk of device infection and for whom Micra™ offers the most potential benefits:

1. **Patients with ESRD:**

- Defined as stage 5 chronic kidney disease.
- A separate analysis was conducted for this subgroup, indicating a “younger” mean age of 72.3 years. This age was applied to the ESRD subgroup to provide a more accurate estimation of survival outcomes (46).

2. **Patients with prior infection:**
    - Includes patients with a history of cardiac device infection.
    - The mean age of 81 years, as derived from the broader CED study population, was applied to this subgroup.

3. **Patients with epicardial leads:**
    - Patients with epicardial leads, who are at increased risk of infection. Leadless pacing offers an alternative for patients with vascular access issues, such as compromised veins, thrombosis, or a need for vein preservation, who would otherwise require complex pacing with epicardial leads (73).
    - As with the prior infection subgroup, the mean age of 81 years was also used for these patients.

The economic analysis was performed from the perspective of the Norwegian healthcare system. The model captured the economic burden on the healthcare system of treating pacemaker complications. A 20-year time horizon was applied in the economic model to capture long-term health outcomes and costs, and to cover the period in which device replacements are expected to occur. This approach can therefore be considered a lifetime horizon. In line with Norwegian guidelines for economic analyses, discount rates of 4% per year were applied to both costs and health outcomes (72).

4.1.4 NOMA’s comments on the included patient population

NOMA notes that the model includes patient subgroups emphasized by other health technology assessment (HTA) agencies. NOMAs evaluation of the Micra™ model, incorporating insights from these HTAs, underscores its significant benefits for targeted subgroups, such as patients with ESRD, those needing epicardial leads for temporary pacing, and individuals with a history of infections (74-78).

The submitter has discussed the inclusion of these subgroups due to the policy recommendations provided by the HTAs conducted in other settings. Other HTAs suggest that the high-risk subgroups identified often face increased risks and complications when using TVPM, making them ideal candidates for Micra™. Evaluations from agencies such as the Haute Autorité de Santé (HAS) in France and the Medical Services Advisory Committee (MSAC) in Australia underscore the substantial clinical benefits that the agencies suggest Micra™ offers, particularly in terms of improved outcomes and reduced procedural risks for these vulnerable populations (Haute Autorité de Santé, 2023; MSAC, 2022). A fair quality systematic review included in the submission (13) indicates a 42% lower odds of occurrence of overall complications in the leadless group (note the meta-analysis included Aveir™, Nanostim™, and prospective and retrospective study designs). NOMA also notes that Shtembari et al., did not conduct subgroup analysis (i.e. for patients with compromised venous access, on dialysis, or with a history of infection) so results should be interpreted with caution.

NICE’s 2018 guidance (77) recommended leadless pacemakers for patients who cannot have transvenous devices due to venous access issues, infection risks, or thrombosis.

NICE's guidance is currently under re-evaluation with an expected publications date of November 2025.

NOMA considers that while the use of subgroups may have certain benefits in terms of the cost-effectiveness of Micra™ compared with TVPM there are certain factors that should be considered for a robust assessment of Micra™.

NOMA is critical regarding the submitter's use of studies that included patients receiving a cardiovascular implantable electronic device (CIED) because the populations might not accurately reflect the characteristics of patients suitable for Micra™ (79-81). Although Micra™ has been on the market since 2015, the submission presents very little data that could define parameters influencing outcomes in the relevant subgroups, a concern further discussed in other sections evaluating the modelling assumptions. The chosen population with CIED may not accurately represent Micra™ users due to significant differences in device technology, patient characteristics, and clinical indications. Micra™ is acknowledged by the HTA agencies as a viable alternative for patients with specific needs, such as those facing venous access challenges or heightened infection risks, thereby providing effective pacing solutions for a diverse array of individuals requiring long-term therapy (26;82). However, while the Medtronic CED study demonstrated that Micra™ can offer both safety and efficacy in the short term and through long-term follow-up (up to 3 years), it evaluated the total population of patients who are candidates for traditional transvenous devices, encompassing diverse patient groups with varying clinical characteristics (25). The studies were not specifically designed to identify sub-group differences. In particular, the study design did not focus on high-risk patients, and the high-risk patients' outcomes were assessed in the model using relative risks from CIED studies.

In this context, the European Society of Cardiology emphasizes the importance of leadless pacing technologies for patients who are not suitable candidates for standard transvenous devices.

The ESC guidelines provide a class IIa recommendation (level of evidence B) for leadless pacing as an alternative to transvenous pacing in selected patients with upper extremity venous access or pocket issues, as well as in those at a high risk of device pocket infection (e.g., patients undergoing haemodialysis). Additionally, a class IIb recommendation (level of evidence C) is made for its use as an alternative to standard single-chamber ventricular pacing in the broader population, taking into account factors such as life expectancy and the principles of shared decision-making (83). Nonetheless, further multicenter randomized controlled trials with extended follow-up are recommended by the ESC to substantiate these findings (82;83). However, conducting such clinical studies is challenging and may not be practical, as suggested by Norwegian clinical experts.

This underscores the need of caution when extrapolating results from studies involving individuals who received CIEDs to those receiving Micra™ which address a unique set of clinical needs and demographic factors.

NOMA highlights the need for long-term outcomes data to capture the safety and efficacy of Micra™, particularly in complex patient populations. There is a lack of comparative effectiveness studies evaluating Micra™ against various TVPM across different subgroups, as well as a broader representation of patient populations to enhance generalizability. In the absence of such data for Micra™, insights from CIED studies can provide some context regarding the relative risk of infection for patients, which is critical for assessing leadless PM like Micra™, as noted by other HTAs. However, these findings raise potential concerns about Micra's™ safety profile, especially among high-risk patients with similar comorbidities.

NOMA has not fullly evaluated the clinical and safety implications of CIED studies, as they do not meet the PICO criteria. Thus, it is essential to approach these extrapolations with caution, as the patient populations and clinical scenarios in CIED studies may not accurately reflect those of Micra™ recipients, thereby limiting the applicability of these insights for informing infection risk and management strategies effectively.

4.1.5 Model Parameters

Submitted clinical efficacy data
The model input parameters consist of acute complications in each treatment group for the period of less than 30 days, chronic complication rates beyond 30 days (per 6 months), short-term and long-term infection risk, baseline mortality, relative risks associated with subgroup specific mortality and infection, demographics, utility and disutility weights and costs.

This section focuses on presenting the most important inputs used in the model such as the calculation and assumptions regarding the complication rates, infection risk and mortality. Other sections provide details regarding utility and cost data applied in the economic model.

The critical clinical data used in the economic model focused on the rate of complications for each treatment group, based on data from the Micra™ CED study. These complication rates were categorized into two time periods: acute (<30 days) and chronic (>30 days).

Acute (short-term) complications
Acute complications were applied for the first 30 days post-implantation (Table 12). These were mainly procedural complications and events occurring shortly after the implant, such as infections, pocket issues (related to the implant site), Other complications within this period, such as hemorrhage, stenosis, and cardiac effusion, were not included in the model. It was assumed that the costs of these complications would be covered by the implant procedure's diagnosis-related group (DRG) payment. The acute complications were applied in the first month cycle of the model.

Table 12. Acute complication probabilities (<30 days) used in the Markov model

Complication Type	Probability – TVPM	Probability – Micra™	Source
Mechanical breakdown of device	0.00927	0.00753	(26)
Device dislodgement / displacement	0.00703	0.00239	
Other mechanical complication	0.00423	0.00483	

Key TVPM, Transvenous pacemaker.

NOMA's comments on acute short-term complications

NOMA assessed the acute complications based on the results of NOMA's meta-analysis included in the economic model to adjust the confidence intervals for complications used in the model for each subgroup. The probabilities of these complications, presented in Table 12

for both Micra™ and TVPM, were sourced from Piccini et al. (26). NOMA's (meta) analysis, included data from the RCT (22), six prospective (25;27;42-45), and six retrospective studies (one study provided two groups) (14;17;30;31;49). The RCT showed a non-statistically significant risk ratio with very wide confidence intervals (RR 0.30 95% CI 0.01-6.98, 51 participants, p=0.45, n=48). The results from the prospective studies in the NOMAs meta-analysis indicated a non-significant difference between Micra™ and TVPM (RR 0.65, 95% CI 0.37-1.12, p=0.14, I^2=42%, 17575 participants, 5 studies). NOMA's meta-analysis results for retrospective studies showed a statistically significant risk ratio suggesting individuals receiving Micra™ had a 48% lower risk of any complications compared with TVPM (RR 0.52, 95% CI 0.40-0.68, p=0.00001, I^2=5%, 7148 participants, 6 studies) (Figure 10). Additionally, a systematic review highlighted that leadless PM (13), including Micra™, Aveir™ and Nanostim™, showed a statistically significant 42% reduction in the odds of complications compared with TVPMs (OR 0.58, 95% CI 0.42-0.80). Shtembari's (13) meta-analysis did not include the RCT and combined prospective and retrospective studies together.

NOMA acknowledges that while the submitted model incorporates short-term complication data and while only the results of NOMA's meta-analysis from the retrospective studies suggest reduced risk of complications, this limits NOMAs evaluation to validate the short-term complications results based on prospective studies. Moreover, NOMA's meta-analysis results are not subgroup-specific. For example, the model uses data from Piccini et al., to account for short-term probabilities such as mechanical breakdown (0.00753 for Micra™ vs. 0.00927 for TVPM), but the evidence for short-term outcomes is less well-established, particularly for Micra™. The model estimates complication risks using probabilities from various studies. For mechanical breakdown, it shows a probability of 0.00753 for leadless PM and 0.00927 for TVPM, yielding a relative risk of 0.81, indicating a 19% lower risk for Micra™. For device dislodgement, the probabilities are 0.00239 for Micra™ and 0.00703 for TVPM, resulting in an RR of 0.34, signifying a 66% lower risk in Micra™. This conservative approach relies on estimated probabilities, which may overlook clinical nuances. Although retrospective studies suggest a reduced risk of acute complications with Micra™ (RR 0.52, 95% CI 0.40-0.68), the lack of subgroup-specific studies must be considered.

In conclusion, while the model analysis offers conservative estimates of complication risks associated with Micra™, it may not fully reflect the long-term outcomes highlighted in clinical studies. Balancing these insights is essential for a comprehensive understanding of Micra's™ safety and effectiveness. However, NOMA believes that using a conservative approach avoids overestimating the clinical benefit of Micra™ with regards to short-term acute complications. NOMA does not make any changes to the acute short-term complications and applies the same probabilities from Piccini et al. (26) in the main analysis, but adjusts the confidence interval for sensitivity analyses based on combining the mid-points from the study to estimate an aggregate confidence interval for the sensitivity analysis in its main analysis.

Chronic (long-term) complications

Chronic complications were applied for the period beyond 30 days post-implantation (Table 13). These complications were focused on the ongoing infection risk, including an elevated risk at the time of device replacement, revision, or upgrade. It also included re-interventions, such as repositioning the device or replacing a component. Upgrades to other device types, particularly dual-chamber pacemakers and cardiac resynchronization therapy were also included.

Table 13. Chronic complication probabilities beyond 30 days (per 6 months) in the Markov model

Complication Type	Probability – TVPM	Probability – Micra™	Source
Re-intervention (revision)	0.001	0.0003	(25)
Re-intervention (lead-related)	0.0011	N/A	
Re-intervention (replacement)	0.0009	0.002	
Upgrade to dual-chamber pacemaker	0.0014	0.0007	
Upgrade to CRT-P	0.0032	0.002	

Key: CRT-P, Cardiac resynchronization therapy pacemaker; N/A, not applicable; TVPM, Transvenous pacemaker

NOMA's comments on chronic complications

NOMA accepts the model's approach regarding the chronic complication rates, which tend to be higher for replacing Micra™ over long-term follow-up. Moreover, the reduction in re-intervention and revision risks strongly favours Micra™ in terms of cost-effectiveness and in line with the findings of clinical effectiveness. Battery longevity is a key factor when assessing the need for device reinterventions, as the device's lifespan can directly impact the frequency of replacements required (25). Additionally, the longevity of the pacemaker can influence overall costs, particularly when considering the need for battery replacements, therefore, the battery life and absence of leads with Micra™ may reduce the need for device revisions, which can also be a source of infection in patients receiving TVPM. However, clinical evidence beyond 3-years is lacking.

Infection risk

The infection risk was divided into short-term and long-term periods to accurately reflect the varying levels of risk over time. Unlike other complications, infection risk was modelled differently to ensure that both the timing of costs and the impact on quality of life (disutility) were appropriately captured at the time the infection occurred. The Kaplan-Meier data from the CED study were used to break down the infection risk into specific time periods for the TVPM, allowing for a more precise representation of when these infections were likely to occur.

The reported risks of infection at different points from the Kaplan-Meier data for TVPM were as follows:

- 30 days: 0.1095%
- 6 months: 0.4302%
- 12 months: 0.5302%
- 24 months: 0.6306%

In the Micra™ group, an equivalent Kaplan-Meier curve could not be produced due to insufficient infection events. Piccini et al., reported no infections in the first 30 days post-implant amongst Micra™ patients, (26) while due to the conditions of the data use agreement with the Centers for Medicare and Medicaid in the United States, the 3-year

analysis could not fully report the number of infections amongst Micra™ patients. For this reason, Crossley et al. (25) reported the number of infections as '<11', and although the reported relative risk reduction of 96% suggests an infection rate of around 0.028% amongst patients with Micra™, the submitter has conservatively assumed that 5 infections occurred amongst the 6,219 patients who received Micra™ (equivalent to a 3-year risk of 0.08%) (25).This risk was then divided evenly across the period from 30 days to 3 years, such that the probability in the period from 1 month to 6 months was 0.00011 (0.011%), and the 6-monthly probability thereafter was 0.00014 (0.014%). Baseline infection probabilities over time are summarised in Table 14.

Table 14. Infection probabilities by time period used in the Markov model

Time Period	Probability of Infection – TVPM	Source	Probability of Infection – Micra™	Source
< 30 days	0.11%	(47)	0%	(25)
31 days – 6 months	0.32%		0.011%	
6 months – 12 months	0.10%		0.014%	
Per 6 months beyond 12m	0.05%		0.014%	

Key: TVPM: Transvenous pacemaker.

NOMA's comments on infection probabilities

NOMA notes that the conservative assumption regarding infections seems reasonable given the constraints of the available data. The 3-year infection risk estimate of 0.08%, based on five assumed infections, is reasonable and aligns with the reported relative risk reduction of 96%. Dividing the total estimated infections evenly across the 35 months following the first 30 days is a conservative approach. While this method may not reflect the actual risk distribution (as infection risks typically diminish over time after the initial period), it provides a reasonable estimate for ongoing infection probabilities, especially considering that Piccini et al. (26) reported no infections within the first 30 days post-implantation.

One limitation is that the Kaplan-Meier curve was not produced due to insufficient infection events reported in the submitted data, which precludes accounting for the short-term infection risk in patients with Micra™. Upon further evaluation, NOMA notes that the 6-month probability by using a 35-month period, excluding the first month, is included to ensure an even distribution of infections. While short-term data up to 6 months is more robust, long-term data is less frequently available.

The clinical effect of Micra™ compared with TVPM indicates no statistically significant differences in infection rates across several studies, including prospective and retrospective studies over different time periods up to 36 months, while the number of events is likely to be lower in Micra™ compared with TVPM. Given these findings, it is reasonable to assume a very low infection risk beyond 6 months for Micra™, in line with conservative estimates such as those from Crossley et al. (25). NOMA believes that the impact of long-term infection risks in Micra™ can be evaluated through a scenario analysis. Further details regarding the infection by time are provided in the clinical effect and safety results. However, the long-term risks, particularly for complications like pericarditis are a potential area of concern regarding the long-term outcomes of Micra™ with regards to the economic model that are based on subgroup specific population. This has been excluded from the model and there were no specific data to evaluate whether infection-based pericarditis or non-infectious pericarditis

would be modelled in the same way as cardiac effusion, pain or stenosis with no impact on the costs or effects of the model. The Norwegian clinical experts suggested pericarditis to be an insignificant and minor complication. Therefore, NOMA assumes this will have no significant impact on the results.

Adjustments to baseline infection probabilities

Risk factors for cardiac implantable electronic device infection

The systematic review and meta-analysis by Polyzos et al. (79). identified key risk factors for CIED infections, including host-related factors like diabetes, renal disease, and prior infections, as well as procedure-related risks such as post-operative hematoma and lack of antibiotic prophylaxis. Addressing these factors can inform better infection control strategies and risk assessments for high-risk patients undergoing device management or revisions. In addition, Olsen et al. (84) assessed long-term device-related infections in a Danish CIED cohort, finding a low infection risk for pacemakers but higher rates for CRT systems and reinterventions.

Subgroup based infection probabilities in the model

The baseline infection risks for both the TVPM and Micra™ groups were adjusted according to high-risk patient subgroups using odds ratios from a published meta-analysis (79). The study compared a high-risk group of patients with specific factors such as device replacements or comorbidities against a normal group without these risk factors to assess their likelihood of developing CIED-related infections. This comparison, expressed through odds ratios, highlighted how much more vulnerable the high-risk group was to such complications.

The subgroups included patients with ESRD, a history of prior infection, and those with epicardial leads. These subgroups were found to have a significantly higher risk of infection. However, due to the short follow-up periods (typically 6-12 months) in the studies used to calculate these odds ratios, it was conservatively assumed that the increased risk would apply only within the first 12 months post-implant. The odds ratios are presented in Table 15.

Beyond 12 months, the long-term infection risk for these subgroups was assumed to be equivalent to that of the general PM population. However, if further surgery occurred, such as device replacement, revision, or upgrade, the model assumed an increased infection risk during the 6-month cycle in which the event occurred. Additionally, at the time of device replacement, a relative risk adjustment was applied to reflect an even higher infection risk (Table 16).However, this is not expected to substantially impact the results given the age of patients at baseline (81.05 years) and the expected battery longevity of each device (~12 years).

Table 15. Odds ratios to adjust baseline infection risk in the Markov model

Patient Sub-Group	Odds Ratio	Assumed Risk Period	RR Micra™	RR TVPM	Source
End-Stage Renal Disease	8.73	First 6 months post-implant	8.73*	8.66*	(79)
Prior Infection	7.84	First 6 months post-implant	7.84*	7.78*	
Epicardial Leads	8.09	First 6 months post-implant	8.09*	8.03*	

Key: RR, Relative risk

*Calculated from baseline infection risk of for each treatment arm and odds ratio for selected patient group

Table 16. Relative risk of infection at the time of device replacement in the Markov Model

Event	Relative Risk Applied	Assumed Risk Period	Source
Device Replacement*	4.93	6-month cycle in which the event occurs	(84)

*Elevated risk for probability of infection at time of device replacement

NOMA's comments on baseline risks of infection

NOMA notes that the economic model submitted by the company uses infection risk data and relative risk adjustments derived from CIED studies such as Polyzos and Olsen (79;84) to estimate complications for both Micra™ and TVPM. These studies were not included in the effectiveness section. Specifically, the model assumes a short-term infection risk of zero for Micra™, based on findings from Piccini 2021 (26), while assigning a 0.11% probability of infection for TVPM based on other data from El Chami (47). These infection probabilities are further adjusted using odds ratios from CIED populations to reflect subgroup-specific infection risks, such as for patients with ESRD, prior infections, and epicardial leads. The ORs used in the model are provided in Table 15. Additionally, a relative risk of 4.93 based on data from Olsen (84) is applied for infection risk during a 6-month cycle in which device replacement occurs.

However, a limitation in the model arises from the reliance on CIED-based infection risks for both the Micra™ and TVPM groups. While Micra™ has a leadless design that theoretically reduces infection risk, the model applies the same odds ratios across both arms. This may not fully reflect the lower infection risk associated with Micra™, particularly in high-risk groups such as individuals with ESRD. Furthermore, while studies like Boveda et al. and Crossley et al. (25;46) highlight the increased proportion of patients with ESRD receiving Micra™, they lack specific infection data for these subgroups, adding uncertainty to the model's assumptions. The clinical effects analysis of Micra™ vs. TVPM showed mixed results, with many outcomes not reaching statistical significance. Bertelli et al. (44) and the CED study (25) reported no significant difference in all-cause mortality at 2 and 3-years, respectively between Micra™ and TVPM. However, Vincent et al. in a retrospective matched case control study (31) observed a higher in-hospital mortality rate for Micra™, suggesting that patient population differences may impact outcomes. These findings indicate that while Micra™ is a promising alternative, mortality benefits remain inconclusive across various studies.

The submitter claims that the relative risk for infection, calculated from the odds ratio of infection for each subgroup (Table 15), was applied as a short-term relative risk in the economic model for the first 12 months, depending on the subgroup, and that no long-term relative risk was assumed for TVPM and Micra™. However, NOMA's evaluation reveals an inconsistency in this claim. NOMA's assessment finds that the model currently assumes a short-term risk of infection (Table 15) for subgroups of Micra™ and TVPM during the first 6 months. Therefore, no relative risk for long-term infection (RR = 1) is assumed for either treatment arm starting at 12 months and onwards. Crossley et al. (25) identified a significant risk of pericarditis at 36 months in the Micra™ group compared with TVPM but subgroup specific data are not available. Therefore, this pericarditis risk (relative risk 2.03) may be considered as part of the short-term infection risks for Micra™. By introducing this increased risk for pericarditis, the model can adjust for the excluded risks to more accurately reflect the clinical outcomes for Micra™, particularly for the short-term period where the current relative risk is calculated using the odds ratio from CIED studies for each subgroup (which adjusts the base-line infection risk in both arms). However, our clinical expert feedback indicates among possible PM complications such as a lead infection, that a pericarditis can be considered a minor complication. Therefore, NOMA notes that this would not impact the model results substantially and does not adjust for it in the model.

In summary, while the model appropriately uses CIED odds ratios to adjust infection risks in the short term, the model does not account for the pericarditis risk for Micra™. Applying CIED data equally to both arms may not capture the full benefits or risks associated with Micra™. Given this data constraint, NOMA does not include pericarditis risk as a short-term or long-term risk in the model. However, a scenario analysis is conducted to assess the impact of a decrease in long-term infection risk for the Micra™ arm beyond 12 months on the ICER. This scenario analysis explores the effect of a reduced long-term infection risk for Micra™ compared to TVPM, while maintaining other infection risks as modeled. NOMA does not include a scenario for an increase in long-term infection risk, based on clinical expert feedback suggesting that no infections were recorded in the 18-20 Micra™ pacemakers implanted since 2017 in Norway. However, NOMA did not receive information regarding the patient selection for Micra™ implantation for these patients.

Mortality

Baseline mortality was modelled using Norwegian life-tables (85), matched for the mean age (81.05 years) and gender distribution (43.5% female) of patients in the CED study (26). An the exception to this was made for the ESRD subgroup, in which patients enrolled in the Micra™ CED study were significantly younger. For this subgroup, NOMA therefore used a mean age of 72.3 years, based on the calculated mean age amongst patients with ESRD in the CED study (26).

Subgroup-specific mortality was adjusted using RR applied to the baseline mortality risk. For patients with epicardial leads, no increased mortality risk was found, so the RR was set to 1 (equivalent to the general population risk). Patients with prior infection had an RR of 2.1 based on long-term data on mortality after CIED infection (80). For patients with ESRD, the RR was calibrated to match the CED study survival data, which showed a 57-61% mortality rate within 2 years (46). Additionally, a temporary RR of 5.02 was applied for 6 months following any new infection during the model horizon. The summary of these relative risk ratios is presented in Table 17.

Table 17. Summary of mortality data used in the Markov model

Subgroup	Mean Age	Relative Risk Applied	Comment
General Population	81.05 years	Baseline (using Norwegian life tables)	Matched to the age and gender distribution of the Micra™ CED study population
Patients with end stage renal disease	72.3 years	Calibrated to match survival data (57-61% mortality within 2 years) RR= 16.5 (46)	Based on younger age and higher mortality risk in this group
Epicardial Leads	81.05 years	RR = 1 [Assumption]	No increased mortality risk identified
Prior Infection	81.05 years	RR = 2.1 (80)	Based on studies showing increased mortality after CIED infection
New Infection (all groups)	Varies during the model horizon	RR = 5.02 (for 6 months post-infection) or 1 model cycle post infection. (81)	Applied to reflect the severity of infections in high-risk patients

Key; CIED: cardiac implantable electronic device: ESRD, End-stage renal disease; RR, relative risk, TVPM, Transvenous pacemaker.

NOMA's comments on mortality

NOMA notes that the mortality results from the clinical effect data cannot be directly applied to Micra™ in the model due to the complexities of the subgroup analyses. In the economic model, relative risks and infection-related mortality adjustments are derived from CIED studies, which include broader populations and are not specific to leadless PM. These studies, such as those by Rizwan Sohail et al., (80) and Shariff et al. (81), provide generalized data on mortality after infection, particularly for high-risk groups like patients with ESRD or prior infections. The model applies these relative risks uniformly to both Micra™ and TVPM arms, however there is a lack of clinical evidence regarding the long-term risk of Micra™ as compared to TVPM to adequately reflect the differences between both arms for the relative risks.

However, the Micra™ CED publications (i.e., Crossley et al., 2023, Boveda et al, 2023, El-Chami et al., 2022, Piccini et al., 2021) lack subgroup-specific infection and mortality data making it challenging to adjust the mortality risk solely based on Micra™ outcomes. This results in the assumption that post-infection mortality risks, and thus mortality risks, are the same across both device types in the model. Due to the absence of Micra™-specific subgroup data, the model uses infection risks derived from broader CIED populations to estimate infection risk across different time periods. While this provides a general understanding of infection-related risks, it may not fully capture the unique risks associated with Micra™ patients. The model primarily relies on infection probabilities from the CED study, to estimate the cost effectiveness.

This limitation restricts the model from fully capturing the potential mortality impact and creates some uncertainty in assessing Micra™ cost-effectiveness. There are no long-term data as outlined by the clinical effectiveness results beyond 36 months and most studies report statistically non-significant differences between Micra™ and TVPM. Considering the data constraints and the framework of the current economic model, applying the relative risk of post-infection mortality beyond six months ensures consistency in overall survival outcomes for patients with infections or specific comorbidities. A high mortality risk from infections adversely affects the overall survival of patients equally across both the intervention (Micra™) and comparator (TVPM) arms. Thus, the primary factor influencing overall mortality in the model for patients experiencing infections is based on the differences in infection probability between Micra™ and transvenous pacemakers (TVPM).

Therefore, NOMA provides a scenario analysis to explore how different assumptions regarding mortality risk, particularly for Micra™ or TVPM, might affect the overall model outcomes and the ICER with regards to the weighted average approach to generate the ICER in the main analysis across all subgroups.

4.1.6 NOMA's comments on the efficacy input in the model

In conclusion, NOMA has validated the model using clinical effectiveness studies comparing Micra™ and TVPM. While the model's conservative approach to infection risks and mortality is reasonable given the data constraints, the uniform application of relative risks from broader CIED studies may not fully capture the infection rates and mortality risks of Micra™ in the long-term and other complications for the high-risk population (such as those with ESRD, prior infection or requiring epicardial leads). Based on clinicians' feedback, pericarditis is generally considered a minor, less significant complication in this context, with minimal impact compared to infections, which are more serious and costly. This distinction should be taken into account, as it would not influence the cost-effectiveness results. Therefore, NOMA conducted a sensitivity or scenario analysis for critical variables, especially long-term infection risks. NOMA's main analysis provides deterministic weighted average results for ICER across all high-risk subgroups based on the prevalence of these patients in each subgroup, as provided in the submission. However, the lack of data specific to Micra™ for the subgroup infection risk and post-infection mortality risks does not add value for presenting probabilistic sensitivity results or expected value of perfect information (EVPI) as this can only be explored when long term data or risks are available and relevant to Micra™ specifically.

Health-related quality of life
QALYs were used as the main health outcome metric in the model. Patients' quality of life was incorporated via a baseline utility weight to which treatment- and event-specific disutilities were applied (Table 18). A short-term (6-month) disutility was applied to patients in the TVPM group based on submitter assumption to reflect restrictions to patient activity, the effect of any infections, and aesthetic issues associated with the pocket. This disutility was then assumed to taper over the following 18 months so that utility in the two groups would be equal from 2 years onwards. Beyond 6 months, a further disutility was applied to any patients suffering an infection. This baseline utility in both treatment groups was fixed at 0.73 based on the NICE Technology Appraisal No. 314 of implantable cardioverter defibrillators and cardiac resynchronization therapy (86).

Table 18. Baseline utilities and disutility

Utility/Disutility	TVPM	Micra™	Source
Baseline Utility	0.73	0.73	NICE Technology Appraisal No. 314 (86)
6-Month Disutility	Applied	None	Refer to Table 20
Post-Infection Disutility	Applied	Applied	Refer to Table 20

Key TVPM, Transvenous pacemaker

To capture the short-term impact of the implantation of a TVPM, data from a study comparing TVPM and Micra™ was used to apply a disutility in the first 6 months of the model (41). This study used propensity scores to match patients with TVPM and Micra™ and evaluate their quality of life in the six months post-implant. It evaluated quality of life using the SF-36 questionnaire, which was administered at baseline (prior to implantation), 1 week, 3 months and 6 months (see Table 19 and Table 20). The submitter used the baseline and 6-month SF-36 sub-scale scores in each group and mapped these to the EuroQol 5-dimension (EQ-5D) utility weights to obtain a separate utility for TVPM and Micra™ at each visit (87) (Table 20).

Table 19. Mapped utility weights by treatment visit used in the Markov model

Treatment group	Baseline utility	6-month utility
Transvenous pacemaker	0.68	0.652
Micra™	0.663	0.695

Patients receiving TVPM experienced a decline in quality of life over the first 6 months, while those with Micra™ showed improvement based on mapped utility weights by the submitter (14) (41). A disutility of 0.061 was calculated for TVPM patients, leading to a utility weight of 0.669 for this period. This disutility was applied for the first 6 months of the model, reflecting the data collection period. From 6 to 24 months, the disutility was assumed to decrease linearly, with the quality of life difference between TVPM and Micra™ patients returning to zero by 24 months. This tapering effect used by the submitter was based on evidence from Tjong (2018) justifying showing that quality of life improvements observed at 3 months in Micra™ patients were sustained at 12 months (88). Beyond 24 months, no difference in utility was applied between the groups, except for patients with an infection or those requiring a device revision or upgrade (to CRT-P or ICD). In these cases, the same disutility of 0.061 was applied for a 6-month period at the time of the event.

Serious device infections can greatly reduce patients' quality of life, so a disutility was applied to patients experiencing infections after 6 months. The impact of infections within the first 6 months was considered to be covered by the short-term effects previously described. Disutility values were derived from the WRAP-IT study (89) which collected utility data at the point of infection diagnosis and at 1-, 3-, and 6-months post-infection. To estimate the disutility over the 6-month period, it was assumed that patients transitioned between utility levels midway through each period (e.g., from "infection diagnosis" to "1-month post-infection" disutility after 0.5 months). Table 21 shows the disutilities at each time point in the WRAP-IT study, along with the total disutility calculated based on these timing assumptions.

Table 20. Utility weights and disutilities for patients with TVPM and Micra™ used in the Markov model

Time Period	Event	TVPM Utility Weight	Disutility for TVPM	Micra™Utility Weight*	Notes	Source
First 6 months	Baseline	0.669	0.061	0.73	Decline in TVPM quality of life Utility	SF-36 Utility (41) Mapping to EQ-5D (87)
6 to 24 months	Tapering effect	Increases linearly to 0.73	Declines linearly	0.73	Quality of life difference converges	NICE (90) Assumption of tapering effect for 24 months, improvement for Micra™ (88)
Beyond 24 months	No specific event	0.73	No disutility	0.73	Equal utility for both groups	NICE (90)
At revision/ upgrade	Device revision/upgrade (TVPM)	0.669 for 6 months	Disutility of 0.061 for 6 months	Disutility of 0.061 for 6 months	Disutility applied at time of event	Disutility weight calculated from (41;87)
Beyond 6 months	Infection	Adjusted as per event	Additional disutility of 0.076	Additional disutility of 0.076	Applied only in infection cases	WRAP-IT study (89)

Key; TVPM, Transvenous pacemaker

A disutility of 0.076 was applied for all infections occurring beyond 6 months, lasting for 6 months (one model cycle) in each case. Age-specific utilities from the Norwegian population were also considered (91), ensuring that the utility for patients with pacemaker did not exceed the general population's utility of 0.786 for those aged 71 (ESRD) years, 81 (prior infection, epicardial leads) years and older. However, no adjustment was necessary as the utility weight for the pacemaker was lower than age-matched general population.

Table 21. Calculation of infection related disutility obtained from the WRAP-IT study

Time	Mean disutility vs. baseline	Disutility, assuming mid-way utility change
Infection diagnosis	-0.11	-0.005
1 month post-infection	-0.14	-0.018
3 months post-infection	-0.1	-0.021
6 months post-infection	0.04	0.005
Total disutility over 6 months		**-0.076**

4.1.7 NOMA's comments on the utility values in the model

The evaluation of HRQoL in the submitter's health economic model, based on QALYs, considers disutilities for various complications, including infections and reinterventions. The model incorporates baseline utility values from NICE's 2018 appraisal and incorporates other event-specific disutilities to simulate the patient journey over time, particularly for the TVPM group compared with the Micra™ group. Overall, the HRQoL model inputs are well supported by the clinical data, particularly the SF-36 studies that show patients receiving Micra™ experience better physical and mental health outcomes, although not reaching a minimal important clinical difference. NOMA notes that the evaluation of Micra™ leadless pacemakers should consider patients' baseline health, reflected in SF-36 scores. A baseline physical score of 36 indicates significant limitations, and a mental health score of 45-46 is below the general population average (92;93). Despite these challenges, NOMA assumes QALY improvements in health economic models for Micra™ show some gains for only 6 months and use of a tapering effect is assumed for a neutral approach so the QALY gains are not overestimated for the patients from 6-18 months, even though some results may not meet the MCID and these may be due to patient selection.

The disutility applied to TVPM in the short term, as well as the tapering effect, are only applicable for 24 months and there is no difference in QALYs after this time between Micra™ and TVPM. Lastly, incorporating infection disutility and reinterventions for both device types by using an approach to map the SF-36 scores to EQ-5D utility values has also been considered in other settings (94). NOMA does not suggest any changes should be made to assumptions with respect to disutilities in the main analysis or utilities used in the base-case of the submission. However, NOMA conducted a sensitivity analysis for the disutility applied in the model for the first six months and its tapering effect based on (41), to assess its impact on the cost-effectiveness of Micra™.

4.1.8 Costs and resource use input in the submitted health economic model

The model's cost analysis had three main categories: device acquisition and implantation; complication management; and replacement/upgrade of devices. Costs were modelled from a payer perspective and were largely based on the Norwegian diagnosis-related group (DRG) tariffs from 2024 (95). In some cases, alternative data were used where tariffs did not exist or where there was a strong rationale to apply a different cost.

Device acquisition and implantation

For the TVPM group, the cost of acquisition and implantation is covered by the DRG tariff of NOK 86,418, which includes both the device and the lead and other costs of the procedure. In contrast, the Micra™ group incurs a total cost of NOK [redacted], which encompasses the current price of NOK [redacted] for the Micra™ and the remaining costs of the procedure. The summary of the acquisition and implantation cost and their description is provided in Table 22.

Infection management cost

The cost of managing infections is crucial for assessing cost-effectiveness. Typically, managing an infection involves device explantation, a hospital stay for infection treatment, and implantation of a new device. The current DRG tariff for infectious endocarditis, which includes device extraction, is NOK 239,602 (DRG code 126) (96). However, the submitter claims that this tariff might not fully capture the higher costs associated with high-risk patients who have co-morbidities and might require extended hospitalization and temporary pacing. No clinical data were provided for device explantation (95).

Table 22. Device acquisition and implantation costs used in the Markov Model

	TVPM	Micra™	Source
Implantation Cost	NOK 86,418 (DRG code 115B) [redacted]	NOK [redacted] (NOK [redacted])	(Medtronic submission (95))

Key DRG, Diagnostic related group; HTA, Health technology assessment; TVPM, Transvenous pacemaker

To estimate these costs more accurately, the submitter used data from Frausing et al. (96), which reported a mean infection management cost of €40,765 for patients with CRT-P. Converted to Norwegian kroner, this amounts to NOK 468,021 (96). This cost estimate was applied to infections in the TVPM group. For the Micra™ group, the infection cost was adjusted by subtracting the cost of a TVPM and lead from the infection cost and adding the cost of a Micra™, resulting in a total estimated infection cost of NOK [redacted] (96). This adjustment accounts for the increased expense of replacing a leadless device. Additionally, as argued by the submitter Medicare data shows that treating pacemaker infections is more than twice as expensive for patients with chronic kidney disease compared with those without CKD (97). Table 23 provides an overview of these included costs.

Table 23. Infection management costs used in the Markov model

	TVPM	Micra™	Notes and sources
Infection Cost*	NOK 468,021	NOK [redacted]*	[redacted]

Key DRG, Diagnostic related group, TVPM, Transvenous pacemaker

*[redacted]

Management of non-infection complications

The costs of managing non-infection complications were divided into acute and chronic complications for each treatment group, based on DRG payments.

For acute complications, the TVPM group faced costs related to the device issues, such as mechanical breakdown, device dislodgement, and other mechanical complications. These were assigned a cost of NOK 122,469 per event, which is based on the DRG code 115A, covering device extraction and implantation of a new device (26;95) (see Table 24). In contrast, the Micra™ group incurred a higher cost of NOK [redacted] per acute complication. [redacted] (26;95).

Chronic complications, occurring more than 30 days after implantation, were similarly managed with DRG tariffs. For the TVPM group, revisions were assigned a cost of NOK 122,469 under DRG code 115A (26;95). Full device replacement or repositioning / replacement of the lead also used DRG code 115A or DRG code 115B (NOK 86,418), if only the device (generator) was replaced (26;95). In the Micra™ group, revisions were similarly assigned a cost of NOK 122,469 under DRG code 115A (26;95). Device replacement was priced at NOK [redacted], based on DRG code [redacted], adjusted for the cost of the leadless

device (26;95). Lead re-positioning or replacement was not applicable to the Micra™ group (26;95).
Device longevity was estimated at 13.7 years for TVPM devices and 13.3 years for leadless PM (98;99) . Upgrades to dual-chamber pacemakers or cardiac resynchronization therapy were assumed to cost NOK 86,418 and NOK [redacted], respectively, with these costs including the new device (26).

Table 24. Cost of complications used in the Markov model

Complication Type	TVPM Costs	Micra™ Costs	Details
Acute Complications	NOK 122,469 per event	NOK [redacted] per event	TVPM**:** Based on DRG code 115A (device extraction) (26;95).
			Micra™**:** Adjusted cost from DRG code 115B ([redacted] (26;95).
Mechanical Breakdown	NOK 122,469	NOK [redacted]	-
Device Dislodgement/Displacement	NOK 122,469	NOK [redacted]	(95)
Other Mechanical Complications	NOK 122,469	NOK [redacted]	(95)
Chronic Complications			
Revisions	NOK 122,469	NOK [redacted]	DRG code 115A for both groups (26;95).
Full Device Replacement/Re-positioning/Replacement of Lead	NOK 122,469 or NOK 86,418 (if only device replaced)	NOK [redacted]	TVPM: DRG code 115A (full replacement) or DRG code 115B (NOK 86,418 if only generator replaced) (26;95).
			Micra™**:** DRG code 115B [redacted] (26;95).
Device Longevity	13.7 years*	13.3 years*	Based on settings (98;99).
Upgrades	NOK 86,418 (dual-chamber)	NOK [redacted] (CRT-P)	Costs include new device (26;95).

* With an average implant age of 75 for pacemaker patients and the median projected battery longevity of the Micra™ estimated at 13.7 years (47) patients will unlikely survive past 3 Micra TPS devices.
Key CRT-P, Cardiac Resynchronization Therapy Pacemaker; DRG, Diagnostic related group; TVPM, Transvenous pacemaker.

Cost of other inputs

Device replacements due to battery depletion were assumed to occur at 13.5-year intervals for both device types for simplicity and to align with the model's cycle length. Thus, all patients still alive at each 13.5-year interval were assumed to incur the cost of a new implantation procedure (plus the cost of the device, in the Micra™ group). The cost of device replacement was therefore NOK 86,418 (DRG code 115B) and NOK [redacted] for the TVPM and Micra™ groups,

respectively. No further disease management costs were included in the model, as these were assumed to be equivalent between the two PM groups.

NOMA's comments on cost and resource use
In evaluating the health economic model, particularly the impact of procedure duration, NOMA note that there is variability in the reported times between Micra™ and TVPM implantation. Prospective studies, such as Garweg and Palmisano (22;41), show no significant difference in procedure duration between Micra™ and TVPM, while retrospective studies, like Pagan and Tachibana (49;51), suggest that Micra™ may have a shorter procedure time (see Figure 21). This inconsistency reflects potential differences in real-world practice, including health practitioner training, or settings.

Clinical experts in Norway emphasize that pacemaker infections can have severe consequences, both for patients and the healthcare system. A single infection often results in prolonged hospital stays, typically lasting several weeks, during which the patient requires intravenous antibiotics. These infections are not only physically and emotionally taxing for patients but also impose significant financial burdens on the healthcare system, with real costs exceeding NOK 500,000 per case. This perspective supports the submitter's approach of applying a higher cost estimate for infections compared to the DRG 126 classification.

NOMA considers the use of relevant DRGs as a standard approach for allocating costs based on the prospective studies, however, to evaluate the impact of procedure duration in the economic model, NOMA assesses this in a sensitivity analysis for the cost of implantation as reasonable approach. By creating a cost range that accounts for the possibility of shorter or longer procedure times, it can be understood how variation in procedure duration affects overall cost-effectiveness. The prospective studies, which typically provide more reliable data due to their design, suggest no difference in duration. However, the retrospective studies lean toward Micra™ having a shorter procedure duration. In terms of implant success rates, all studies showed no significant difference between Micra™ and TVPM based on the findings from NOMA's meta-analysis. Thus, the DRG application in the model appears appropriate here, as success rates are consistently high across studies.

NOMA's sensitivity analysis:

NOMA set the following bounds:

- Lower bound (best-case scenario): Assuming Micra™ has a shorter procedure time (e.g., 10% reduction in procedural costs).
- Upper bound (worst-case scenario): Assuming Micra™ has a longer procedure time, leading to increased costs (e.g., 20% increase in procedural costs).

Calculation of severity – absolute shortfall
A separate analysis calculated the QALY shortfall for each patient subgroup, considering their age differences (ESRD patients ~72 years vs. prior infection or epicardial leads patients ~81 years) (26)]. The proportion of females was fixed at 43.5% across all subgroups (26). Expected QALYs were derived from national life tables and age-specific utility weights (0.786) (91). Shortfalls were calculated by comparing undiscounted QALYs from the model (including mortality effects) with unadjusted QALY predictions (excluding mortality effects).

The submitter estimated absolute shortfall (AS) based on projections about life expectancies. The AS calculation follows the NOMA guidelines outlined in the guidelines for the dossier of documentation STA of medical devices and diagnostic interventions (72).

These guidelines are based on the White Paper on Priority Setting, as well as a Norwegian life table and age-adjusted HRQoL data from a general Swedish population (21;71;85).

AS represents the difference between quality-adjusted life expectancies at a specific age *(A)* without the presence of the disease ($QALYs_A$), and the prognosis with the disease while receiving the current standard of care (P_A).

$$AS = QALYs_A - P_A$$

For the calculations, method employed undiscounted numbers for $QALYs_A$ and P_A as indicators of prognosis. P_A represents the remaining quality-adjusted life years for patients receiving the standard of care (TVPM), considering the average age at diagnosis. $QALYs_A$ refers to the overall quantity of remaining quality-adjusted life years for a healthy population at the average age at diagnosis.

4.1.9 One-way sensitivity analysis by the submitter

For each subgroup, a series of one-way sensitivity analyses (OWSA) has been performed by the submitter, varying each input parameter between a specified upper and lower range. This range was defined using the reported 95% confidence interval (wherever available), and otherwise by specifying a confidence interval based on 20% variation either side of the mean value. The model was re-run for each parameter in turn, using the lower and upper values, with the ICER re-calculated in each case. The submitter then used the results to generate a tornado diagram to highlight the parameters for which uncertainty had the greatest impact on the ICER.

4.1.10 Probabilistic sensitivity analysis by the submitter

Finally, a full probabilistic sensitivity analysis (PSA) was performed by the submitter to assess the effect of joint uncertainty in all model parameters. A statistical distribution was assigned to each input parameter using the reported confidence interval or standard error (where available), or by creating a distribution with an assumed 95% confidence interval based on 20% variation on either side of the mean. Some DRG tariffs were used as part of cost calculations for different elements of care (e.g., the implant tariff was also used in the cost of infection management). In such cases, uncertainty in the tariff was not modelled separately for each application, but instead was sampled once and applied to all linked parameters.

The method of moments was used to estimate distributional parameters where necessary (100). Appropriate distributions were assigned to different parameter types to ensure plausibility of the sampled values. For example, gamma distributions were used for cost parameters to avoid sampling negative values, with beta distributions used for probability parameters to ensure values bounded by 0 and 1. In the PSA, 10,000 samples of these distributions were generated, with the costs and QALYs in each group re-calculated each time. Scatter plots and cost-effectiveness acceptability curves (CEACs) were then generated for each subgroup to show the overall uncertainty in the ICER.

4.1.11 Value of information analysis

A value of information (VoI) analysis was undertaken for each subgroup by the submitted, using the results of the PSA. In each case, the expected value of perfect information (EVPI) was calculated on a per-patient basis, using the 10,000 sampled estimates of the costs and QALYs for Micra™ and TVPM. The following formula was used to generate the EVPI:

$$\text{EVPI} = E_\theta\{\max_d NB(d,\theta)\} - \max_d\{E_\theta\, NB(d,\theta)\}$$

where,

$E_\theta\{\max_d NB(d,\theta)\}$ = expected net benefit given full information

$\max_d\{E_\theta\, NB(d,\theta)\}$ = expected net benefit given current information

For the purposes of this analysis, and in the absence of an official willingness-to-pay threshold, a threshold of NOK 400,000 per QALY gained was applied to enable calculation of the expected net benefit by the submitter.

4.1.12 Budget impact Analysis

In addition to the cost-effectiveness analysis (CEA), a budget impact model (BIM) was developed to determine expected budget impact for each patient subgroup. The BIM compared a scenario in which all high-risk patients are implanted with single-chamber devices with one in which all patients would receive a leadless PM. A 5-year time horizon was used to model expected additional costs through the adoption of Micra™, with a new cohort of patients being implanted each year. The number of new implants per year was assumed to be constant over the 5-year period. For the purposes of the BIM, the discount rate for costs was set to 0% per year.

The cost inputs and outputs from the CEA model in conjunction with data on the expected number of pacemaker implants in each subgroup (ESRD n=22, prior infection n=38 and epicardial leads n=8). The annual number of patients implanted within each subgroup was estimated as follows by the submitter. Public data from Medtech Europe (but specific to Norway) was used as the basis for the number of single-chamber pacemaker implants per year (n=715) (101). For ESRD, this number of implants was multiplied by the proportion of patients expected to have ESRD (3%), to give a total of 22 patients per year (102). For the prior infection subgroup, the submitter began by considering the active number of patients with a pacemaker in Norway (n=37,730), using data from the Norwegian pacemaker registry (5). Using Medtech Europe public data once again (101), the submitter calculated that 16% of pacemakers sold are single-chamber devices producing a total of 6,037 active single-chamber devices (37,730 * 16%). Lastly, the submitter applied an infection rate amongst these patients of 0.14% per year, using data from the Micra™ CED study and adjusted to an annual probability (47). Thus, for the prior infection subgroup, submitter assumed the number of implants to be 8 per year (6,037 * 0.14%). Finally, the number of new implants in the epicardial leads subgroup was estimated using Medtronic sales data (54 epicardial leads sold in 2023) (103). However, since some patients require two leads, the submitter used data from the Swedish ICD & Pacemaker Registry to estimate a mean of 1.43 epicardial leads per patient (104). The number of leads sold (54) was divided by the mean number of leads per patient (1.43) to estimate 38 patients per year. Across the three subgroups, the submitter assumed a total of 68 new implants.

NOMA's comments on the method of the budget impact analysis

NOMA does not propose any changes to BIM estimates for the budget impact of Micra™ leadless PMs in Norway using local data and relevant clinical studies. However, NOMA incorporates the use of high-risk patient subgroups' prevalence as a method for estimating a

weighted average ICER for its main analysis, to ensure a comprehensive representation of the high-risk patients.

4.2 Results

4.2.1 Deterministic results (base-case) from the submission

Table 25 shows the main deterministic results of the cost-effectiveness model for each subgroup, using a 20-year time horizon and a 4% discount rate for discounting costs and health outcomes. For each subgroup the mean costs and QALYs are presented.

Table 25. Discounted cost-effectiveness results (base-case)

Subgroup	Costs (NOK)			QALYs		ICERs (NOK)	
	TVPM	Micra™	Incremental Costs Δ	TVPM	Micra™	Incremental QALYs Δ	ICER (NOK per QALY)
ESRD	114,412	144,671	30,259	1.469	1.564	0.095	319,295
Prior infection	119,247	149,365	30,118	3.130	3.224	0.095	318,502
Epicardial leads	132,490	164,022	31,532	4.744	4.837	0.094	336,908

Key ESRD, end-stage renal disease; ICER, Incremental cost effectiveness ratio; QALYs, quality-adjusted life-years; TVPM, Transvenous pacemaker.

The above results lead to the following ICERs for each subgroup: NOK 319,295 per QALY (ESRD); NOK 318,502 per QALY (prior infection); NOK 336,908 per QALY (epicardial leads).

4.2.2 NOMA (main analysis) using weighted average

The discounted main analysis results for Micra™ versus TVPM, derived using a weighted average approach across all high-risk subgroups, are shown in Table 26.

The weighted average for all subgroups was calculated based on the number of patients in each subgroup (ESRD = 22, Prior Infection = 8, and Epicardial Leads = 38), as detailed in section 4.1.12. Consequently, the weighted average results represent an overall ICER that is proportionally adjusted based on the number of patients in each subgroup for a total of 68 patients in all subgroups. The weights for each subgroup, based on patient numbers, are ESRD: 32.35%, Prior Infection: 11.76%, and Epicardial Leads: 55.88%.

The ICER for all subgroups using this weighted average approach is estimated to be about NOK 329,000 per QALY. The total QALYs for Micra™ were estimated at 3.59, compared with 3.49 for TVPM for the weighted average approach.

Micra™ incurred a higher total cost of NOK 156,037, compared with NOK 125,083 for TVPM for the weighted average approach. While Micra™ was more costly, it also generated additional QALYs compared with TVPM.

Table 26. Discounted cost-effectiveness results (main analysis)

Subgroup (Number of patients; % weight)*	Costs (NOK)			QALYs			ICER
	TVPM	Micra™	Incremental Costs Δ	TVPM	Micra™	Incremental QALYs Δ	ICER (NOK per QALY)
ESRD (22; 32.35%)	37,016	46,805	9,790	0.48	0.51	0.03	-
Prior infection (8; 11.76%)	14029	17572	3,543	0.37	0.38	0.01	-
Epicardial leads (38; 55.88%)	74,038	91,659	17,621	2.65	2.70	0.05	-
Weighted Costs (All subgroups)	125,083	156,037	30,954	3.49	3.59	0.09	328,992

Key ESRD, end-stage renal disease; ICER, Incremental cost effectiveness ratio; QALYs, quality-adjusted life-years; TVPM, Transvenous pacemaker.

*Weight calculation: k_i, number of patients in the subgroup = k_i / total patients in all subgroups), total patients are estimated to be 68.

4.2.3 NOMA's scenario analysis results

The scenario analysis in Table 27 shows that the cost-effectiveness of Micra™ implantation is sensitive to infection probability, post-infection mortality, and implantation procedure costs (excluding the cost of the device). In the base case, the ICER is about NOK 329,000 per QALY. Including pericarditis as a long-term infection risk slightly raises the ICER to about NOK 340,000, while assuming no difference in infection probabilities between Micra™ and TVPM increases it significantly to about NOK 645,000 per QALY. Lowering post-infection mortality also increases the ICER to about NOK 402,000 per QALY, while reducing long-term infection risk for Micra™ improves cost-effectiveness (ICER of about NOK 327,000 per QALY). Changes in implantation costs (excluding the cost of the Micra™ device) have a major impact: a 20% increase raises the ICER to about NOK 514,000 per QALY, while a 10% decrease lowers it to about NOK 236,000 per QALY. Overall, in the scenario analysis, cost-effectiveness is most sensitive to infection probability between Micra™ and TVPM, and implantation costs.

Table 27. Scenario analysis results

Scenario	Value in Main Analysis	Value Used in Scenario	ICER (NOK per QALY)
Main case (weighted average)	All values set to Base-case submitted for each subgroup	NA	329,000
Including Pericarditis as long-term risk of infection in Micra™ (RR of infection (Micra™) - long-term)	1	2.03	340,000
Post Infection Mortality with (RR of 2.5 vs 5.02 in main analysis)	5.02	2.5	402,000
No difference in Infection probability (1-6 month and 6 months beyond) Micra™ vs TVPM	0.011%, 0.014%	0.32%, 0.05%	645,000
Long term infection risk Micra™ (RR: 0.8 vs 1 in mainanalysis)	1	0.8	327,000
20% higher implantation cost for Micra™ implantation procedure	79,777	[redacted]	514,000
10% lower cost for Micra™ implantation procedure	79,777	[redacted]	236,000
Assuming average mortality risk for all subgroups	Different for each subgroup	6.53	337,000
Average OR and average mortality risk	Different for each subgroup	8.22	338,000

Key: ICER, incremental cost-effectiveness ratio: OR: Odds ratio; QALY, quality-adjusted life year; RR, Relative risk; TVPM, Transvenous pacemaker.
All ICER results are rounded to the nearest thousand.

4.2.4 NOMA one-way sensitivity analysis for main analysis

Figure 27 illustrates the sensitivity of the ICER to different factors influencing the cost-effectiveness of Micra™. The extremity of each red bar denotes the ICER when the 'upper' range value was applied, while the extremities of the blue bars are based on using the 'lower' range for the parameter of interest. The most significant factor is the odds ratio of infection across all subgroups, showing that changes in infection rates substantially impact the ICER. Following this, the cost of Micra™ device also plays a major role, with both higher and lower device costs significantly affecting the ICER. Battery longevity has a moderate effect, improving cost-effectiveness slightly by reducing long-term replacement costs. The utility decrement at 6 months for conventional pacemakers shows a smaller influence, while reductions in the risk of mechanical issues and device displacement have the least impact on the ICER. The results correspond with the results of all subgroups in their one-way sensitivity analysis for the most impactful variables on the ICER (from the submission).

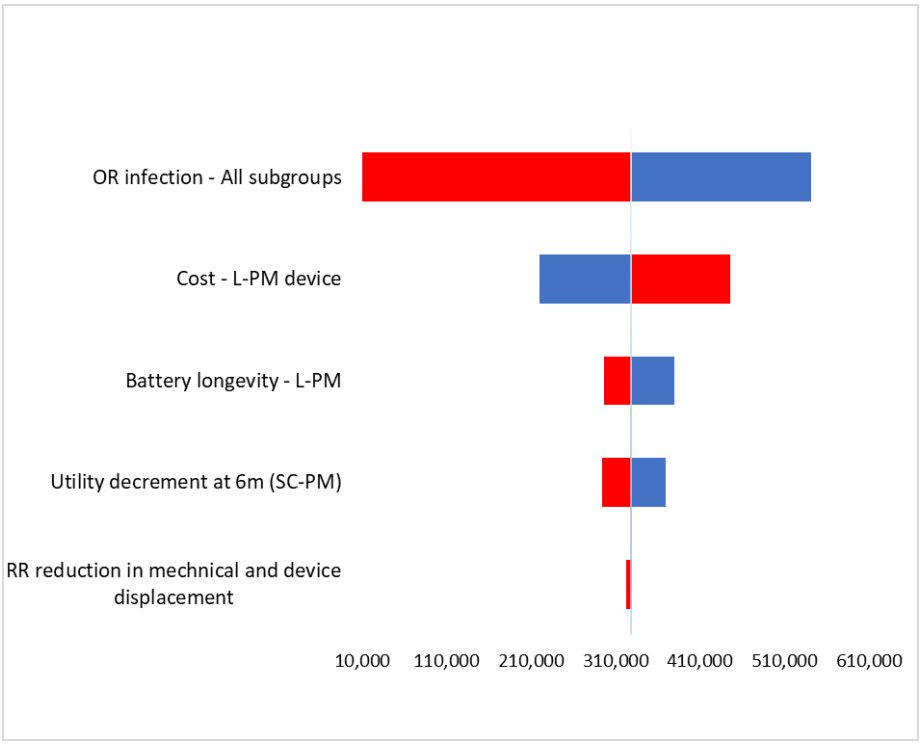


Figure 27. Tornado diagram for most imperative variables including all subgroups

Key: L-PM, Leadless pacemaker; OR, Odds ratio; RR, relative risk; SC-PM, Single chamber transvenous pacemaker

NOMA's comment on overall uncertainty (OWS and Scenario)
Based on the results of the one-way sensitivity analysis and scenario analysis for the weighted average approach compromising of all subgroups, NOMA concludes that most of the uncertainty is driven by the probability of infection between the treatment arms (Micra™ vs. TVPM). While the odds ratio of infection applied in the model for the first 6 months to calculate the relative risk for infection in short-term also affects the ICER, its impact is less significant than the probability of infection. Additionally, the cost of implantation has a greater impact on the ICER than the cost of the Micra™ device itself.

4.2.5 One-way sensitivity analysis from the submission

The following three figures show the tornado diagram for each subgroup by the submitter, with the most influential parameters towards the top of the graph in each case. The extremity of each red bar denotes the ICER when the 'upper' range value was applied, while the extremities of the blue bars are based on using the 'lower' range for the parameter of interest.

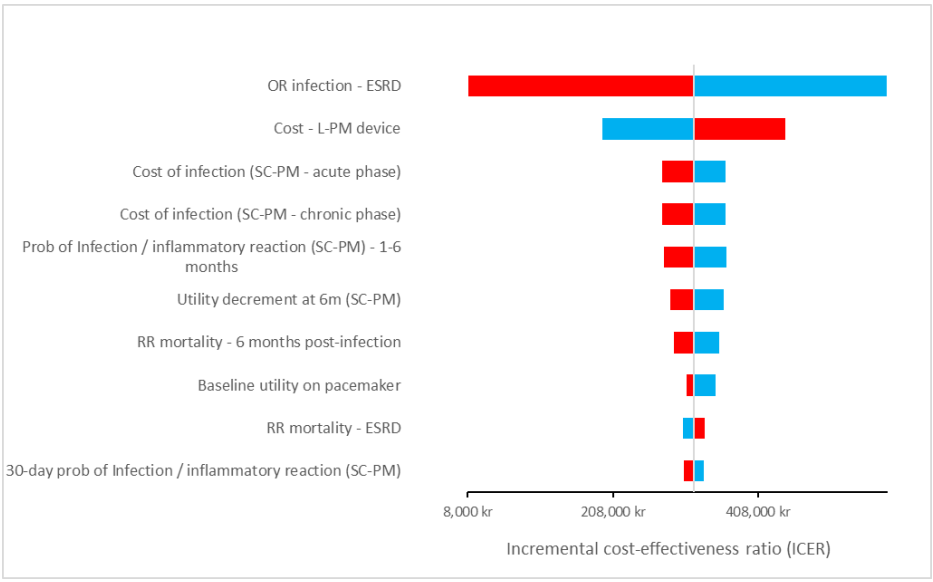


Figure 28. Tornado diagram for end-stage renal disease

Key: ESRD, end-stage renal disease, L-PM, Leadless pacemaker; OR, Odds ratio; RR, relative risk; SC-PM, Single chamber transvenous pacemaker

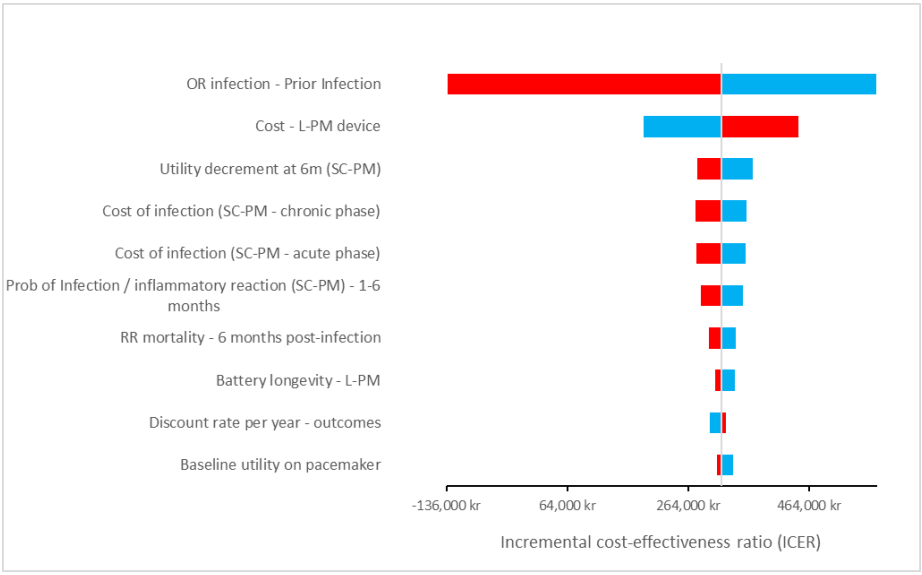


Figure 29. Tornado diagram for prior infection

Key: L-PM, Leadless pacemaker; OR, Odds ratio; RR, relative risk; SC-PM, Single chamber transvenous pacemaker

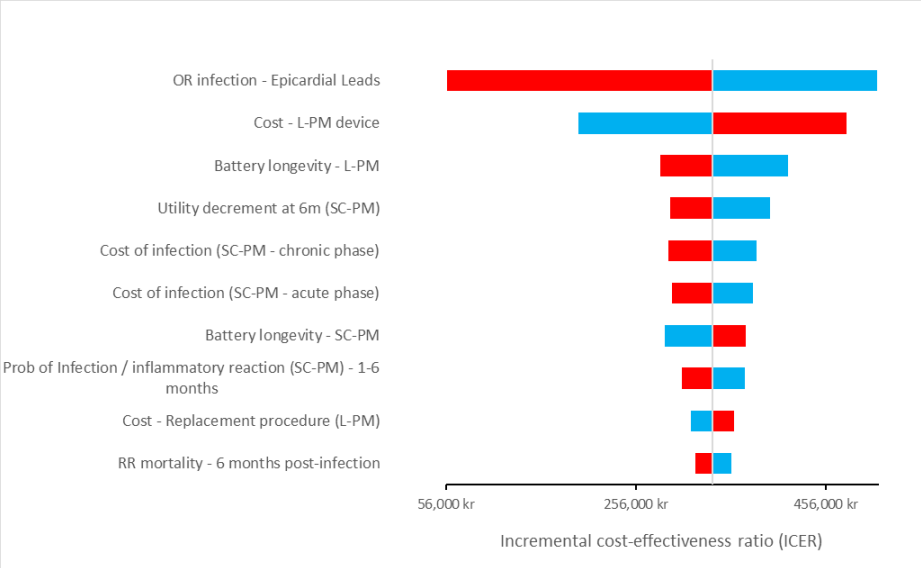


Figure 30. Tornado diagram for epicardial leads

Key: L-PM, Leadless pacemaker; OR, Odds ratio; RR, relative risk; SC-PM, Single chamber transvenous pacemaker

Consistent results are observed for each subgroup, with the key driver of uncertainty being the odds ratio of infection for the subgroup. This effect is seen because of the wide confidence limits reported in the meta-analysis by Polyzos (79). Micra™'s cost-effectiveness was not affected in most scenarios tested by the submitter, except when the odds ratio of infection was reduced or the price of Micra™ was increased, both of which led to the ICER exceeding NOK 400,000. Battery longevity had a greater impact in the 'epicardial leads' subgroup because these patients were predicted to live longer than those in the other two subgroups (and thus a greater proportion of patients incurred the cost of a replacement device).

4.2.6 Probabilistic sensitivity analysis provided by the submitter

Figure 31and Figure 32 show the cost-effectiveness scatter plots and cost-effectiveness acceptability curves (CEAC), respectively, for the ESRD subgroup. The orange dot near the centre of the cloud of points represents the deterministic incremental costs and QALYs or the mean ICER.

The PSA predicted, in the ESRD sub-group, that Micra™ was always more effective than TVPM, and cost-saving in 2.8% of replications. Micra™ was predicted to be the more cost-effective option at willingness-to-pay thresholds above NOK 320,000 per QALY gained. Equivalent graphs for the 'prior infection' sub-group are in Figure 33 and Figure 34.

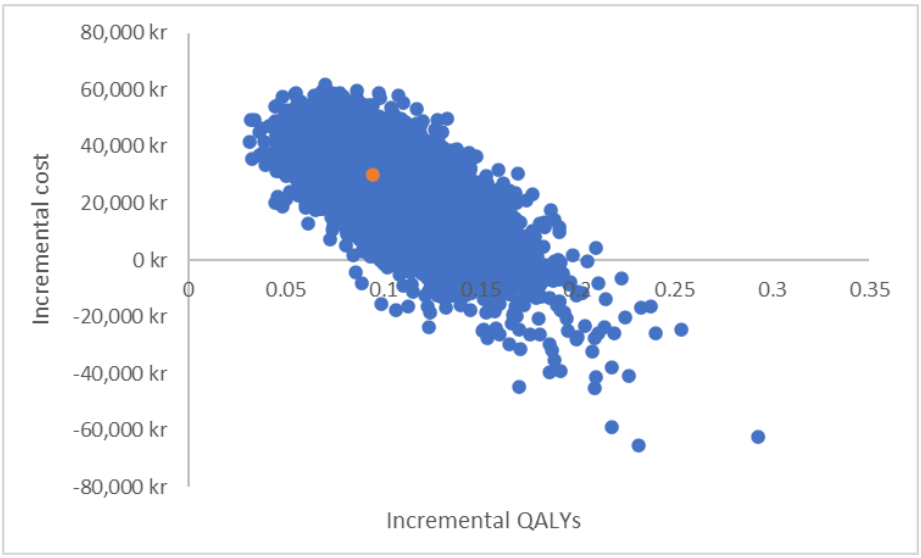


Figure 31. Cost-effectiveness scatter plot for the end-stage renal disease subgroup

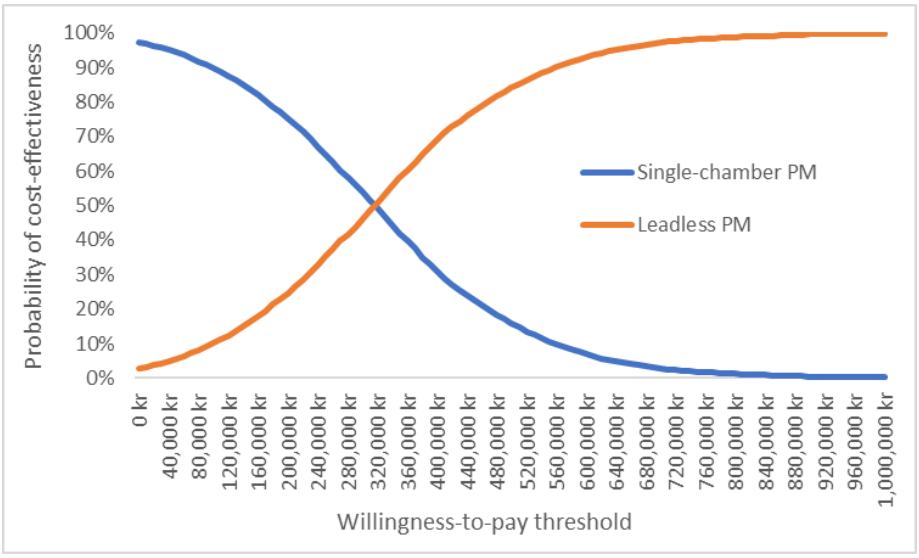


Figure 32. Cost-effectiveness acceptability curve for the end-stage renal disease sub-group

In the prior infection subgroup, similar results were observed, with Micra™ predicted to generate greater QALYs than TVPM and with cost savings in 8.8% of replications. Micra™ was predicted to be the more cost-effective intervention at thresholds above NOK 310,000 per QALY gained for this subgroup.

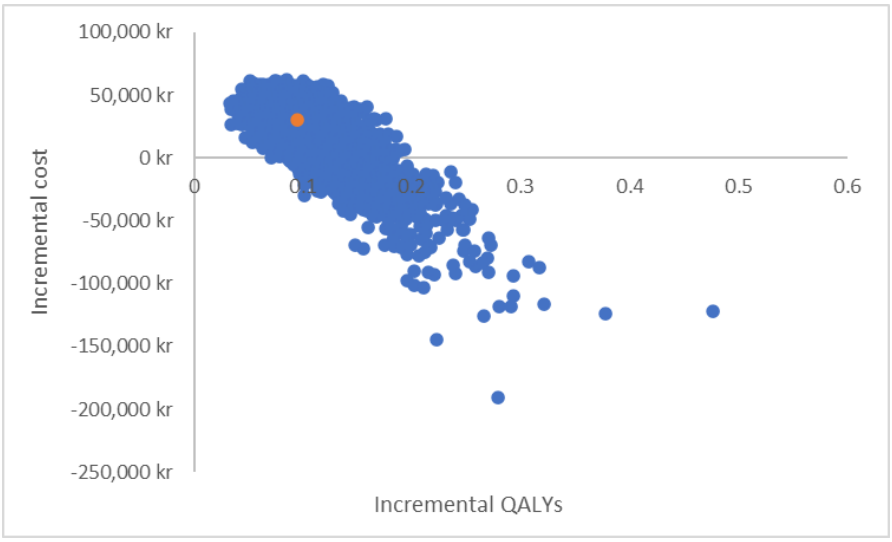


Figure 33. Cost-effectiveness scatter plot for the prior infection subgroup

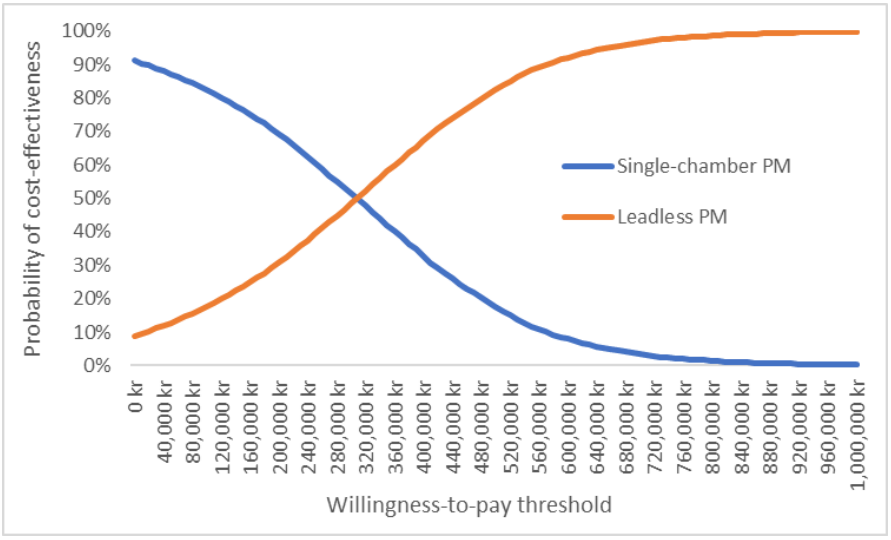


Figure 34. Cost-effectiveness acceptability curve for the prior infection subgroup

Figure 35 and Figure 36 show the corresponding results in the ‘epicardial leads’ subgroup. In all 10,000 model replications for the epicardial leads subgroup, Micra™ was predicted to generate additional QALYs, with cost savings in 1.5% of cases. Micra™ was the most cost-effective treatment option at thresholds above NOK 330,000 per QALY gained.

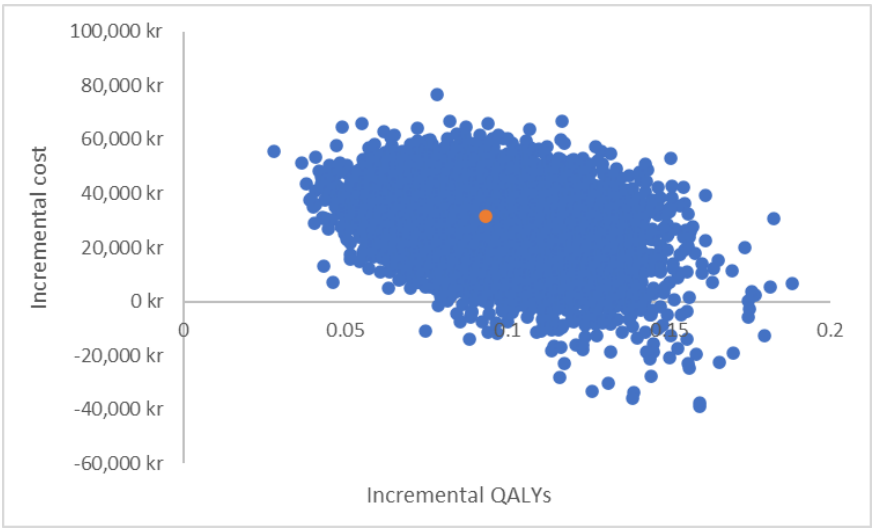


Figure 35. Cost-effectiveness scatter plot for the epicardial leads subgroup

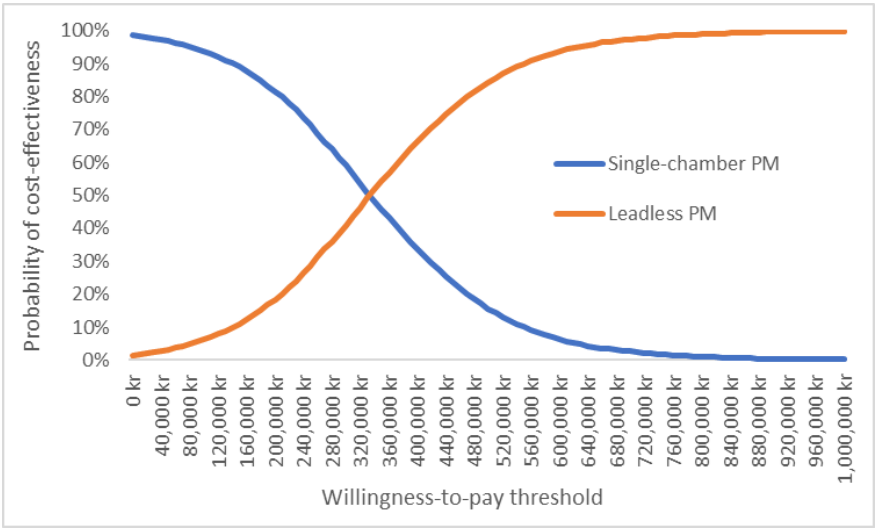


Figure 36. Cost-effectiveness acceptability curve for the epicardial leads subgroup

Severity calculation – absolute shortfall

In the submitted economic model, patients are assumed to enter the model at the age of 72 and 81 depending upon the choice of subgroup. At this age, the expected quality-adjusted life expectancy for the general population is presented in Table 28. Absolute shortfall values for the end-stage renal disease, prior infection and epicardial leads subgroups. The disease prognosis, the expected QALYs for patients receiving conventional pacemaker for each sub-group is also presented in Table 26. The absolute shortfall is then calculated for each sub-group separately with and without mortality effect of each sub-group.

As outlined in the Report to the Government White Paper on priority-setting (71), the cost-effectiveness threshold should be adjusted based on the severity categories proposed by the Norheim and Magnussen commissions. These categories suggest that diseases with an absolute shortfall value below 4 belong to the least severe group, while those exceeding 20 QALYs are considered among the most severe. The absolute shortfall for patients receiving conventional pacemaker is 9.78 for patients with ESRD, 2.93 for patients with prior infection and 0.73 for epicardial leads.

Table 28. Absolute shortfall values for the end-stage renal disease, prior infection and epicardial leads subgroups

	End-stage renal disease	Prior infection	Epicardial leads
Mean age of diagnosis used for prognosis	72	81	81
% female	43.5%	43.5%	43.5%
Population utility	0.786	0.786	0.786
Expected survival of general population (years)	14.45	8.27	8.27
Expected QALYs (general population)	11.36	6.50	6.50
Expected QALYs (model output with mortality effect of sub-group)	1.58	3.57	5.76
Expected QALYs (model output without mortality effect of sub-group)	9.85	5.76	5.76
QALY shortfall (including mortality effect)	9.78	2.93	0.73
QALY shortfall (excluding mortality effect)	1.51	0.73	0.73

Key: QALY, Quality adjusted life year.

NOMA's comment on absolute shortfall and submitted probabilistic analysis
Based on the subgroup analysis the average shortfall was calculated to be 4.5 including mortality and 0.99 excluding mortality. The weighted average absolute shortfall based on proportion of patients for each subgroup was estimated to be 4 with mortality and 1 without mortality. NOMA's calculation of absolute shortfall corresponds to the severity group 2 if mortality is included for the submitted model. Whereas the severity group would be 1 if mortality is excluded from the model submitted. The aggregate absolute shortfall with mortality (without weights) across all subgroups was estimated to be 13.5
NOMA believes that including the effect of mortality is more relevant when assessing the absolute shortfall and considers the weighted absolute shortfall (4) to be of relevance with regards to weighted ICER approach.

NOMA did not conduct a probabilistic sensitivity analysis for the weighted ICER approach, which combines results from all subgroups, due to differences in key parameters across these subgroups. However, based on the submitter's results for each subgroup, NOMA notes that all subgroups demonstrated a probability of more than 50% for Micra™ to be a cost-effective option of treatment at thresholds above NOK 330,000 per QALY gained.

4.2.7 Value of information analysis

Table 29 below shows the expected value of perfect information per patient for each subgroup of interest conducted by the submitter.

Table 29. Expected value of perfect information by subgroup

Patient sub-group	Expected value of perfect information (per patient)
End-stage renal disease	NOK 268,854
Prior infection	NOK 449,472
Epicardial leads	NOK 264,773

4.2.8 NOMA's comments on the value of information analysis

NOMA considers that the VOI analysis can be more valuable in instances where the odds ratio for infection risk regarding each subgroup are available for Micra™ and are not based on patients receiving CIED. Therefore, it is evident that because of data unavailability, the odds ratio for estimating relative risk for Micra™ and TVPM in the short term proves to be the most impactful on the ICER of each subgroup presented by the submitter and may have the highest expected value of perfect parameter information. NOMA does not make a comment regarding the current VOI results due to limitations expressed earlier.

4.2.9 Budget impact

Table 30 shows the total eligible patients for the budget impact analysis in each subgroup based on the adoption rate over the 5-year period. Table 31 shows the results of the budget impact analysis, comparing a 'current' scenario (in which all eligible patients in the three high-risk subgroups are implanted with a single-chamber device) with an 'alternative' scenario (in which all patients are implanted with a leadless device). The expected (undiscounted) budget impact is then calculated over a 5-year period.

The predicted budget impact of switching from TVPM to Micra™ across these three subgroups (over a 5-year period) is approximately NOK 10.3 million. The year-by-year costs remain relatively constant, reflecting the fact that most of the cost is incurred at the time of implantation. The predicted budget impact assumes all eligible patients receiving Micra™ with 100% probability each year, over 5 years.

Table 30. Number of patients expected to be treated over next 5 years with intervention

	Year 1	Year 2	Year 3	Year 4	Year 5
Market share of Micra™ by year	100%	100%	100%	100%	100%
Intervention	Year 1	Year 2	Year 3	Year 4	Year 5
Baseline eligible patients-ESRD	22	22	22	22	22
Micra™ (baseline - new patients) - ESRD	22	22	22	22	22
Baseline eligible patients-Prior infection	8	8	8	8	8
Micra™ (baseline - new patients) – Prior infection	8	8	8	8	8

Baseline eligible patients- Epicardial leads	38	38	38	38	38
Micra™ (baseline - new patients) – Epicardial leads	38	38	38	38	38
Total Micra™ New patients All subgroups	68	68	68	68	68

Key ESRD, End-stage renal disease

Table 31. Budget impact analysis comparing a TVPM with Micra™ scenario in all subgroups in Norwegian kroner

Sub-group	Device type	Year 1	Year 2	Year 3	Year 4	Year 5	Total (years 1-5)
ESRD (n=22)	TVPM	2,445,000	2,476,000	2,497,000	2,511,000	2,519,000	12,447,000
	Micra™	3,127,000	3,149,000	3,165,000	3,176,000	3,182,000	15,799,000
Prior infection (n=8)	TVPM	879,000	895,000	909,000	921,000	931,000	4,536,000
	Micra™	1,137,000	1,148,000	1,157,000	1,165,000	1,172,000	5,781,000
Epicardial leads (n=38)	TVPM	4,207,000	4,292,000	4,372,000	4,446,000	4,514,000	21,833,000
	Micra™	5,404,000	5,459,000	5,511,000	5,559,000	5,604,000	27,537,000
All sub-groups (n=68)	TVPM	7,531,000	7,663,000	7,778,000	7,878,000	7,965,000	38,816,000
	Micra™	9,668,000	9,756,000	9,833,000	9,900,000	9,958,000	49,117,000
Total budget impact*		**2,137,000**	**2,093,000**	**2,055,000**	**2,022,000**	**1,993,000**	**10,301,000**

Key ESRD, End-stage renal disease; TVPM, transvenous pacemaker, *All results are rounded to the nearest thousand.

4.2.10 NOMA's comments on the budget impact analysis

NOMA does not suggest changes to the submitted budget impact analysis. Micra™ present significant upfront costs, particularly in larger subgroups like epicardial leads, and the budget impact remains relatively constant over the five-year period. This suggests that while Micra™ may require more investment, they could potentially offer long-term benefits, such as fewer complications or reinterventions. However, these long-term benefits would need to be evaluated against the short-term budget increase seen here.

5. Patient perspective

NOMA invited a user representative to provide input on the patient perspective on the technology under assessment. LHL (previously known as Landsforeningen for Hjerte- og Lungesyke) has 54000 members and represents and works for people with cardiovascular or respiratory disease, allergies, stroke, aphasia, and the families of these patients. The LHL representative liaising with NOMA has a professional background that makes her particularly well-suited to help us incorporate the patient perspective in this STA. We asked the representative a few questions based on a questionnaire developed by Health Technology Assessment International (105). The questions were related to how the condition affects the daily lives of patients and their families, experiences with current treatment of the condition, and experiences with or expectations for the method being evaluated. The representative sought contributions directly from users and gathered further information from the organization's advisory service and relevant Facebook- and LHL-interest groups.

Impact of condition

The symptoms of bradycardia and atrial fibrillation make it difficult for many to participate in activities they wish to engage in, both social and work-related. Palpitations, dizziness, fatigue, shortness of breath, and chest pain reduce physical capacity and affect the ability to care for oneself and others, maintain employment, and participate in leisure activities. Symptoms of anxiety and depression are common. Many individuals with bradycardia and atrial fibrillation experience lower self-esteem and social isolation. Comorbidities are common, which can further reduce their quality of life.

Practical and other support from relatives is often crucial for the quality of life and mental health of patients in need of a pacemaker. The role of a caregiver is often demanding and may lead to stress, emotional reactions, and poorer health. Significant caregiving responsibilities can lead to isolation and loneliness by limiting social activities and the ability to participate in the workforce as much as desired. The latter can also result in lost income and financial burden.

Benefit of leadless compared with conventional pacemakers

According to the user representative, individuals with high risk of infection, such as patients in dialysis, and those whose veins into the heart do not allow for implantation of a conventional pacemaker, could particularly benefit from an intracardiac pacemaker like Micra™. The user representative also mentioned a patient had stated he/she hopes for further research and development to enable leadless pacemakers with an integrated cardioverter-defibrillator (ICD) for patients who have had to remove their conventional pacemaker with ICD due to infection.

The user representative further points out that it can be especially challenging for individuals with dementia or certain mental disorders to adhere to postoperative restrictions after the insertion of a conventional pacemaker. Specifically, limitations on how the patients can use their arms in the first few weeks after surgery and the importance of keeping the surgical wound clean are highlighted as challenging. For some of these patients, a leadless pacemaker might be a suitable treatment alternative.

6. Discussion

Most submitter's evidence for clinical effectiveness did not specifically focus on high-risk patients but rather on individuals eligible for single-chamber ventricular pacing. Regarding health economics, there were two main issues. First, except for the pivotal study, the evidence is derived from studies other than those used to assess clinical effectiveness. Second, the studies included in the model used any cardiac implantable electronic device as an intervention rather than single-chamber, leadless pacemakers, i.e. Micra™.

6.1 Discussion – clinical effectiveness

This STA re-evaluated the cost-effectiveness of the Micra™ pacemaker. The submission included systematic reviews of poor (2) and fair quality (1), one RCT, seven prospective (in 12 publications) and 10 retrospective non-randomized comparative studies. In addition, the submitter included 3 ongoing studies. The longest follow-up was 36 months (25). The submitter provided data for 26 of the 38 outcomes of interest (as defined by the inclusion criteria). The outcomes evaluated technical performance, patient-relevant effectiveness outcomes, safety, and health care resources against the conventional transvenous pacemaker.

6.1.1 Key findings

Population
NOMA noticed a discrepancy between what the submitter claims the patient groups/conditions to be helped using Micra™ are, that is patients precluded from a conventional transvenous pacemaker device, and the population included in the PICO framework (i.e. adult patients indicated for single-chamber ventricular pacemaker implantation). The PICO framework chosen means that the publications included in the submission do not support the submitter's claim but show the effect and safety profile of Micra™ in individuals eligible for single-chamber implantation. Only two of the included studies specifically indicate in their inclusion criteria that individuals in the high-risk subgroups have been selected. A study by Bertelli and colleagues (44) suggests Micra™ was favoured in the presence of ongoing or expected chronic haemodialysis, superior venous access issues or need to preserve venous access. A second study by Zuchelli et al. (42) described high risk of infection, superior venous access issues and patient and operator's preferences as inclusion criteria. None of the remaining studies specified high-risk sub-groups in their inclusion criteria. The submitter included information on four studies' sub-group analyses (16;31;44;46) which are valuable for understanding the results of Micra™ for different population segments. It is however important to mention that subgroup analyses have limitations and are generally considered hypothesis-generating analyses. This means subgroup analyses should be interpreted with caution and not as definitive conclusions (106).

As the primary studies were not specifically designed to address the high-risk population, one can only cautiously extrapolate their conclusions to those populations. It is essential to recognize that assuming the findings from a population eligible for single-chamber ventricular implantation can be generalised directly to high-risk groups may lead to erroneous assumptions, as the unique clinical characteristics and needs of high-risk group could differ significantly from those individuals.

In the submitted evidence, it was common to find that the decision between leadless PM vs. TVPM rested with the attending physician (e.g., was made "following the decision of the attending physician"). This suggests that after many years of Micra™ being in the market, the

patient's history and physical examination of the patient remain pivotal factors when choosing the pacing technology. Reliance on the clinician's judgment may lead to variability in patient selection as different physicians might have varying levels of access, familiarity and comfort with leadless PM technology. Although decisions should be guided by high-quality evidence, to date there are no published guidance available to inform the choice between leadless PM and TVPM (107). A report by the Andalusian Health Technology Assessment Department (AETSA) (76) presents the development of criteria for the implantation of leadless pacemakers in patients with atrial fibrillation or in sinus rhythm. AETSA concluded that leadless pacing is appropriate in cases where there is a significant or complete limitation of vascular access through the superior vena cava. AETSA emphasize that the criteria should be considered as a decision aid in conjunction with other scientific information in the context of the individual patient-physician relationship.

Despite limitations on the clinical evidence for high risk sub-groups, expert opinion (including Norwegian experts) and the international guidance from several cardiological societies (108-112) suggest that the indications for implanting a leadless PM are:

- Patients with a history of significant risk of infections including systemic endocarditis inflammation or immunocompromised individuals (e.g. those with end-stage renal failure, immunosuppressive therapy) or the presence of 2 or more risk factors for infection such as diabetes, dialysis, chronic use of corticosteroids, fragility.
- Patients with absent or difficult venous access or other anatomical constraints to the use of TVPM. This may include occluded subclavian veins, and certain congenital heart diseases.
- Patients with a history of previous TVPM complications such as lead dislodgement, lead fracture, or tricuspid valve damage.
- Patients with lifestyle factors (for example, people who are involved in sporting activities requiring use of shoulders) and who are older.

Important caveats noted in the publications are the limited long-term data on device longevity and management strategies, and how to extract the device safely. The sources advocate for national registries to track usage, outcomes and long-term performance of leadless PMs. These data will be crucial for refining patient selection criteria and optimizing device management strategies.

Technology performance

NOMA was unable to present overall results for technology performance because of study heterogeneity. Generally, Micra™ provides lower pacing thresholds that may be due to its direct myocardial contact. One study found that the pacing threshold may be higher immediately after implantation but stabilizes over time (47). For R wave sensing and impedance values, the point estimates varied widely and some of the confidence intervals do not overlap. The efficacy of a pacemaker is reliant on battery performance, which is intrinsic to the device. Only 3 studies provided information on battery life for Micra™, but no comparative data were available. Adaptability is a feature of pacemakers that allows rate responsiveness to increased exertion and it is therefore a feature of device efficacy. No data were provided for this outcome. Information beyond 3 years on electrical performance was lacking leaving uncertainty about the longevity of the device performance. While Micra™ technical performance may be encouraging, long-term data on pacing parameters and battery longevity are still emerging.

Patient important outcomes

Mortality data suggests comparable mid to long term mortality rates for Micra™ and TVPM. Some studies have reported higher short term or in-hospital mortality rates for patients receiving Micra™. This difference could be attributed to patients' selection and referral

patterns rather than an inherent risk associated with Micra™ . The prospective studies and retrospective in-hospital mortality data show Micra™ is comparable to TVPM at all available follow-up times. Only two studies found Micra™ had significantly lower mortality than TVPM. At 22 months, results from 1 small study favoured Micra™ and a retrospective study of the period from discharge to 11-month showed Micra™ was superior to TVPM.

Device switching is an important outcome to patients and a single study found Micra™ was comparable to TVPM.

An important reason for pacemaker implantation, beyond treating the clinical disturbances is to improve the individual's quality of life. NOMA's meta-analysis shows the physical component summary for Micra™ is superior to TVPM at 3 and 6 months follow up. For the mental component, there was no significant difference between Micra™ and TVPM. At the six-month follow-up, individuals receiving Micra™ rated their mental component significantly higher than TVPM. It is important to consider that both sources are single-centre studies and the sample sizes are small.
NOMA's results agree with the broader pacemaker literature, which supports that pacemaker implantation generally improves a patient's quality of life, particularly in domains of health and functional status (113). The literature indicates however, that research on psychosocial and quality of life outcomes for pacemakers is limited and inconsistent (113;114) and several factors may need to be considered at the cross-section between quality of life and pacemaker implantation such as gender, age, and marital status (19;115;116).

The interpretation of NOMA's results should be contextualized using a minimal important clinically difference (MICD). An MICD refers to the smallest change at which a patient feels that an improvement or decline in their condition is meaningful. While NOMA did not identify studies specifically involving pacemakers and MICD, we identified relevant research by Blokzijl (92) on surgical aortic valve replacement which utilized the SF-12 and SF-36 tools. In their study, a >5 point difference was established as the MCID. Additionally, Masterson (93) reported MICDs following coronary artery bypass grafting noting that for the SF-36 mental component score at 5 years, the MICD anchored to the New York Heart Association functional class was 14 (95% CI: 14-17), and 12 (95% CI: 13-15) when anchored to the Canadian Cardiovascular Society scale. For the SF-36 physical component score at 5 years, the MICD was 17 (95% CI: 17-20) and 15 (95% CI: 15-17), for the New Yor Heart Association and Canadian Cardiovascular Society scale respectively. Although these studies provide indirect evidence, applying the >5 point threshold set by Blokzijl et al. suggests that NOMA's results do not meet the MICD. The submitter's claim that Micra™ implantation improves patients' quality of life is not supported by our results.

The SF-36 scores range from 0 to 100, with higher scores representing better health. As shown by Palmisano's baseline values, individuals may have significant limitations in physical activities and overall physical health. A baseline value of 36 for the physical component indicates a relatively low level of physical functioning. Similarly, a baseline value of 45-46 indicates that the individual's mental health status is slightly below the average for the general population. In the context of the SF-36 a score of 50 is considered the average for the general population. Given the baseline values and the status from which the patients started, it is not surprising that there were improvements in HRQoL. Published literature supports this observation (117). Long term data will be essential to confirm the sustainability of the benefits over time.

Two small studies indicated overall satisfaction among patients receiving Micra™ vs. TVPM at three and six months. One of the studies noted differences in certain areas related to daily activities, restriction in physical activities, and depression. These studies suggest higher

satisfaction is due to the less invasive nature of the leadless pacemaker, coupled with the absence of a subcutaneous pocket and leads, which contributes to a more positive patient experience.

Safety

Norway's first evaluation of Micra™ (10) indicated the major complications following a Micra™ implantation were compared with safety data from a historical control using a dual-chamber pacemaker implant – this study was also included in this STA (27). The certainty of evidence for this result was rated as very low because of the study design and the choice of a historical control.

Both pacemakers have inherent risks, while leadless complications may be more prominent short term (e.g. pericardial effusion or perforation during implantation) TVPM complications are faced long-term (leads dislodgement, infections, etc.). NOMA's meta-analysis of prospective studies for any complications shows comparable results for the two types of device, but retrospective studies suggest individuals receiving Micra™ have a lower risk of any complications compared with TVPM. NOMA's results are partially supported by the literature, for example a review by Cui et al (118) suggests that leadless pacemakers (note the review included Micra™ and other devices) when compared to traditional pacemakers have a significantly decreased risk of major complications. Of note, the review authors defined major complications as system and procedure-related events resulting in death, permanent loss of device function, hospitalization, hospitalization prolonged by 48 hours or system revision. This is important to note as "any complications" or "complications" have been described and interpreted differently yielding heterogeneous results. Other researchers have noted that data on longer follow up periods are needed (119)

Infections

A complex interplay of risk factors and procedural differences needs to be taken into consideration when discussing infection profiles or Micra™ and TVPM. The evidence suggests a shift from the peri-procedural period for Micra™ to the long term for TVPM. Micra™ carries a higher initial risk of pericardial complications due to its intracardiac placement. However, the absence of leads and pocket translates to a lower risk of infection in the long term. TVPM becomes more susceptible to infection over time due to the presence of leads and pocket components. It is important to note that the study designs and follow-up durations vary across the sources, making direct comparisons challenging. Moreover, infection rates can be influenced by numerous factors, including patient characteristics, operator experience, and institutional protocols. Further research with standardized definitions and longer follow-up periods is needed to definitively establish the long-term infection risks associated with each pacing modality. While the submitter claims the risk of infection is lower in individuals with certain risk factors (e.g. diabetes, immunosuppression, previous history of infections), no data for these sub-groups were provided for NOMA to appraise. NOMA's meta-analysis results showed that at 36 months individuals receiving Micra™ had a higher risk of pericarditis, but no other results can confirm the submitter's claim.

Pericardial effusion

The studies providing data for this outcome emphasize pericardial effusion represents a notable risk associated with Micra™ given the intracardiac placement of the pacemaker. This risk is most pronounced during the initial in-hospital period. NOMA's meta-analysis results for this outcome show Micra™ is comparable to TVPM. This finding is not supported by the literature. Three systematic reviews by Shtembari, Oliveira and Cui (13;118;120) reported that leadless PM recipients had higher odds of pericardial effusion than TVPM recipients. It worth noting the systematic reviews are not high quality, include 'leadless' pacemakers, and

their analyses combine prospective and retrospective designs. It is important to recognize that these findings are derived from studies with varying designs and follow-up durations, making direct comparisons challenging.

Regurgitation
Studies suggest a potential advantage of Micra™ mitigating the risk of valvular regurgitation compared to TVPM, particularly tricuspid regurgitation. While TVPM leads may interfere with the tricuspid valve's normal function, leadless PM should cause less mechanical interference. NOMA's meta-analysis shows no significant change in tricuspid or mitral valve function at 12 months follow up (22). A retrospective study shows the Micra™ group experienced significantly more worsening TR than the TVPM group (33% vs. 20%, p=0.04), but there was no significant difference between the two groups with respect to worsening MR (26% vs. 18%, p=0.18). A third study provided data for this outcome but the study included Nanostim™ pacemakers. Haeberlin (121) conducted a meta-analysis that supports the RCT results and showed no difference in TR after implementing leadless PM.

Device dislodgement, malfunction, revision, retrieval replacement
The elimination of vulnerabilities associated with leads and subcutaneous pocket provides an inherent advantage to Micra™ over TVPM. NOMA's analysis of 8 studies (prospective and retrospective) on dislodgement found Micra™ is comparable to TVPM. This is surprising given the elimination of leads, as a common source of dislodgement in TVPM, NOMA results are not supported by the included systematic review (13) which found 70% lower odds of dislodgement with leadless PM compared with TVPM. Dislodgement, device malfunction, revisions, retrieval and replacement are often included as "any complications". For example, Cui (118) reported device revision or extraction, and loss of device function under major complications and concluded that compared to traditional pacemakers, leadless PM decreased these risks. Oliviera (120) included dislodgement as a complication and concluded that leadless PM have a relatively low complication rate. The studies provided by the submitter report minimal, if any, instances of device revisions or retrievals during follow-up periods ranging from 12 months to 3 years (25;27;42).

More data are also needed about the long-term management of Micra™ such as pacemaker retrieval and how additional devices are implanted when Micra™ reaches the end of battery life.

Human resources
NOMA's results showed that Micra™ has a comparable successful implant rate to TVPM. This is supported by the literature which has shown high implant success rates, ranging from 96% to 99.6% across multiple studies. Norwegian experts agree that training and having the capacity to practice regularly (5-10 procedures per year) is an important component of implant success. NOMA's finding for process duration (36 to 60 minutes reported in Pagan et al., 2020 and Tachibana et al., 2020) from retrospective non-randomized studies is similar to the 29 to 74 minutes reported previously (122;123). The included RCT showed no difference between Micra™ and TVPM groups. The variations reported in procedure times across studies likely stem from several factors including operator experience (e.g. a learning curve associated with Micra™ implantation), implantation location (e.g. right ventricular septum or apex) or patient characteristics (e.g. patient-specific factors such as anatomical variations and comorbidities). As leadless technology and operator experience continue to advance, procedure times may further decrease.

Length of stay varied among the studies in NOMA's analysis. While the literature indicates the minimally invasive nature of the procedure will allow for quicker recovery, NOMA's results were too heterogeneous to be meta-analysed. Patient factors, such as frailty are

found to be a strong predictor of longer hospital stays (124). Other factors influencing length of stay are procedural complexity and complications (e.g. bleeding or infections), post-procedure monitoring and rehabilitation, or hospital protocols and discharge criteria (e.g., shorter vs longer observation periods). One of the studies (51) reported length of hospital stay was 2.8 days shorter for Micra™ compared to TVPM. While results were not statistically significantly different (p=0.08), the authors note this is relevant because even a few days of hospitalization is enough to weaken leg muscles in very elderly patients, impacting their return to daily life.

The submission did not include data for several outcomes. NOMA is not able to comment on the effect and safety of the following outcomes:

- Technology performance: adaptability,
- Patient relevant effectiveness outcomes: exercise capacity, change of medication, progression or recurrence of cardiac arrhythmias,
- Safety (procedure & device related): right ventricular dysfunction, pacemaker syndrome, pseudoaneurysm, battery failure, pacemaker induced arrhythmia.

Limitations: methodological and content considerations
There are several limitations to interpreting the results. Methodologically, the evidence in this STA is predominantly based on non-randomized data of population needing pacing. Non-randomized studies are susceptible to selection bias and confounding variables. Thus, it is difficult to isolate the true impact of Micra™ as patient characteristics and other factors could influence the observed outcomes. The reliance on administrative claims data, as seen in several sources, introduces limitations related to coding accuracy and the potential for missing or misclassified information. Content-wise, the sources often lack data on long-term outcomes, limiting the ability to assess the durability and performance of Micra™ over extended periods. This limited long term perspective hampers the ability to draw definitive conclusions about the overall benefits and risk of Micra™ compared with TVPM. There is a huge variety in how safety and clinical outcomes are reported making the pooling of information challenging. Despite the above, the available data show Micra™ is not inferior to TVPM; future trials are needed to confirm these findings focusing on the sub-groups of interest.

Information retrieval
In relation to the completeness of the evidence submitted, NOMA is concerned that relevant studies and publications could be missing for reasons detailed in section 2.3. The submitter's search strategies in the main database, Embase.com (MEDLINE and Embase combined) failed to retrieve three of the 28 included publications. Using a search strategy that cannot retrieve known relevant records may indicate a suboptimal search strategy and raises the question what else might be missing.

With a modest effort, by cross-checking articles included in systematic reviews used in the submission and publications related to study identifiers in the submission, we identified eight potentially relevant articles that were not included nor were present in the submission's list of excluded articles. We would have assessed those in full text had we completed the search and selection processes ourselves. We cannot rule out that some of them should have been included in the analyses of this STA. Results from these articles might have moved effect estimates on important outcomes in either direction. Taken together this indicates to NOMA that the study identification and selection process has potential for improvement.

Patient perspective
The patient organization highlighted that individuals with dementia or certain mental disorders often face significant challenges adhering to postoperative restrictions after the

insertion of a conventional pacemaker. The patient organization argues that for these patients (and their caregivers), a leadless pacemaker might be a more suitable treatment alternative. Although the literature is limited, a few preliminary studies support the patient organization's views. For instance, a case report (125) describes a 97-year-old female with severe dementia who developed a pocket infection. The authors noted the potential difficulties for such a patient to stay in the hospital for an extended period with a temporary pacing catheter after pacemaker lead removal. This temporary solution, which maintains heart rhythm until a permanent pacemaker can be implanted, requires close monitoring and can be uncomfortable. In that instance, a leadless pacemaker addressed these challenges. Similarly, in another case (126) clinicians decided to proceed with Micra™ implantation (dual chamber) for an elderly man with gait instability and dementia after device interrogation. Tachibana (51), a study in the submission, included Japanese patients over 85 years old, some with dementia, and concluded that Micra™ appears to be safe for those with small body sizes and dementia. Specific considerations for pacemaker implantation are found in the literature which acknowledges the complex interplay between cognitive status, age, and cardiac device implantation, emphasizing the need for careful consideration of risks and benefits when making treatment decisions for patients with cognitive impairment or frailty. This underscores the potential benefits of leadless pacemakers for patients with dementia or other mental disorders, because although we do not yet have published evidence, they may offer a less invasive and more manageable option.

The patient organization mentioned the caregivers' burden, a fact that is widely supported by the literature (127;128). Caregivers may experience physical exhaustion, stress, depression and reduced quality of life. There is a complex relation between caregiver burden, and chronic illnesses like dementia and bradyarrhythmias, emphasizing the need for tailored patient and caregiver care when managing these conditions. Again, although we do not yet have published evidence, there may be potential benefits of leadless pacemakers for caregivers.

6.2 Discussion – health economic evaluation

6.2.1 Key findings

The cost-effectiveness analysis comparing Micra™ to TVPM shows that across high-risk subgroups in the base-case submitted by the company, Micra™ results in higher costs but also provides incremental QALYs. NOMA's result in its main analysis for the ICER was based on the weighted average across all subgroups.

For patients with ESRD, Micra™ incurs an additional NOK 30,259 with a QALY gain of 0.095, leading to an ICER of about NOK 31,900 per QALY. In the prior infection subgroup, the incremental cost of Micra™ is NOK 30,118, with a QALY gain of 0.095 and an ICER of about NOK 319,000. The epicardial leads subgroup saw the highest incremental cost of NOK 31,532 and a QALY gain of 0.094, resulting in an ICER of about NOK 337,000 per QALY.

Overall, the weighted average ICER for all high-risk subgroups (based on the proportion of patients eligible for Micra™ in each subgroup) in the main analysis was estimated to be approximately NOK 329,000 per QALY with an additional cost of NOK 30,954 and total QALY gain of 0.09 for Micra™ compared with TVPM. These results rely on the generalizability of CIED studies to estimate relative infection risks across high-risk patient subgroups, supplemented by data from Piccini et al., 2021. Due to the lack of Micra™-specific data for infection risks within subgroups, NOMA's meta-analysis found no statistically

significant difference in infection rates between TVPM and Micra™, although these results were not subgroup-specific. Therefore, assuming an extreme scenario with no difference in infection probability between both treatment arms (Micra™ vs TVPM), the ICER is estimated at approximately NOK 645,000 per QALY.

The scenario analyses for the weighted average results revealed that including long-term risk for Micra™ (12 months and onwards) raised the ICER to about NOK 340,000 per QALY, while reducing post-infection mortality increased the ICER to about NOK 402,000 per QALY. When long-term infection risk for Micra™ was lowered, the ICER dropped to NOK 327,000 per QALY. Adjusting the implantation costs by 20% higher increased the ICER to NOK 514,000 per QALY, while a 10% lower cost reduced it significantly to NOK 236,000 per QALY. These results suggest that Micra™ generally provides incremental health benefits over TVPM, though the cost-effectiveness varies depending on specific clinical scenarios.

Lastly, the sensitivity analysis revealed that the odds ratio of infection across all subgroups was the most impactful parameter, significantly affecting the ICER. This underscores the importance of ICER's sensitivity to variations in relative risk within high-risk patient groups, rather than across the entire pacemaker population. Variations in the cost of the Micra™ device also notably influenced the ICER, with higher costs leading to an increased ICER values. Conversely, improvements in battery longevity contributed positively by reducing the ICER, indicating improved cost-effectiveness of Micra™.

The adoption of Micra™, assuming hundred percent eligibility of patients in the high-risk subgroups, leads to a projected budget impact of NOK 10.3 million by year 5. The majority of costs are incurred at the time of implantation, with annual expenditures remaining relatively stable in subsequent years.

6.2.2 Limitations and uncertainties

There are significant limitations and uncertainties in the analysis. First, the use of CIED-based relative risks for mortality in subgroups presents a challenge, as the clinical data for Micra™ do not provide subgroup-specific RRs for post-infection mortality. Additionally, long-term data beyond the initial years (up to 36 months) for Micra™ are lacking, limiting the ability to accurately project outcomes beyond this period. High-risk groups, including those with elevated infection risk, limited venous access, or endocarditis and comorbidities were not included in the NOMA meta-analysis.

The inclusion of studies such as those by Rizwan Sohail et al. (80) and Shariff (81), which were based on broader CIED populations and are not Micra™-specific, introduces uncertainties when applying the findings to Micra™ subgroups. This is particularly relevant for subgroups such as ESRD and prior infection, where assumptions on infection risks and mortality are based on generalized CIED data, not specific to leadless technology. The GRADE criteria applied to the available evidence indicate low certainty, with much of the evidence coming from non-randomized studies. Additionally, while Micra CED (25) reported lower infection rates for Micra™ compared with TVPMs, it is important to note that the study is not randomized, which limits the strength of the evidence. While the study presents evidence in favor of lower infection risks with Micra™, the overall body of clinical evidence does not strongly support a consistent or statistically significant advantage in terms of infection rates. The lack of specific data on high-risk patients, particularly those with limited venous access means that CIED studies serve as indirect evidence for the high-risk subgroups included in the analysis. This introduces uncertainty into the cost-effectiveness model, as the probability of infection for Micra™ may differ from TVPMs in high-risk population as diverse group of patients are included in this single study. This highlights a

need for caution when interpreting the infection-related benefits of Micra™ and incorporating these assumptions into economic modeling.

The notable variability in incremental cost-effectiveness ratios (ICER) from the scenario analysis, which ranges from NOK 236,000 to 645,000, highlights the impact of existing clinical evidence gaps, particularly concerning long-term infection risks and subgroup-specific outcomes. While Micra™ demonstrates potential benefits, many of these outcomes lack statistical significance, which ultimately affects the reliability of the CEA results. The uncertainty surrounding these factors.

Similarly, the odds ratios for infection risks in the model are derived from the broader CIED studies, which may not fully reflect the infection rates observed with Micra™. The conservative assumption that Micra™ shares similar infection risks and mortality to TVPM introduces a potential bias. Studies, including those by Bertelli and Crossley (25;44), found no significant difference in mortality rates between Micra™ and TVPM. This emphasizes the critical need for more robust, subgroup-specific data to accurately assess the effectiveness and safety of leadless pacemakers in various patient populations.

Additionally, complications like pericarditis, which could impact long-term outcomes, are excluded from the model, along with other early complications such as cardiac effusion, pain, stenosis, and hemorrhage. These are all relevant but were not modeled due to their occurrence in the first cycle.

Overall, these limitations suggest that the current model might not capture the full extent of the long-term benefits or costs on the cost-effectiveness of Micra™, particularly with respect to infection and mortality risks specific to the chosen subgroups of interest.
Lastly, the application of a weighted average to the ICERs from each subgroup introduces limitations in accurately reflecting the unique profiles of each subgroup. However, the model accounts for differences in mortality and infection risks based on CIED data for each subgroup in the base-case submitted, the primary source of uncertainty lies in the generalizability of CIED studies to the high-risk subgroups, rather than the weighted ICER approach itself. The weighted ICER approach reduces the risk of bias that may arise from focusing on individual subgroups, where small sample sizes may lead to misleading conclusions. Despite these challenges, the weighted ICER provides valuable insight into cost-effectiveness by considering all subgroups collectively, based on the distribution of patients in each subgroup. While this method may not fully capture specific clinical nuances or the economic impact of other comorbidities in high-risk patients, the relatively similar ICERs across subgroups in the submission support the use of the weighted ICER as a reasonable estimate for the broader high-risk population such as those with prior infection, ESRD and those requiring epicardial leads.

6.3 Consistency with other literature reviews and studies

The findings of the cost-effectiveness of Micra™ in other settings align with the results presented in this analysis, although direct comparisons may be limited by variations in costs and the prevalence of specific patient populations across different regions. The cost-effectiveness outcomes can vary based on local healthcare systems, costs associated with device implantation, and the demographic characteristics of the patient cohorts considered.

The Australian HTA concluded that Micra™ was likely to provide a cost-effective alternative for managing patients with bradycardia and atrial fibrillation (94). They noted that, given the serious complications associated with infections, such as increased mortality and morbidity,

adopting a leadless pacemaker may be particularly beneficial for high-risk patients. Furthermore, Micra™ offered advantages related to improved quality of life due to the absence of lead restrictions and the reduced visibility of the device (94).

In the UK, NICE has also reviewed Micra™ and acknowledged its potential advantages over conventional pacemakers, especially in terms of reducing infection rates and enhancing patient satisfaction (77).

Similarly, HTAs from other countries, such as France (75) and Austria (78), have recognized the potential benefits of Micra™ in specific patient populations, The Austrian Ludwig Boltzmann Institute recommended Micra™ for patients contraindicated for conventional pacemakers, emphasizing the need for thorough risk assessments and registry documentation before broad use. They suggested a re-evaluation in 2027 when long-term data would be available, reflecting caution in adopting new technologies without comprehensive evidence (78).

In France, the Haute Autorité de Santé (HAS) recognized substantial benefits of Micra™ for specific subgroups, such as those with occluded venous access or prior infections. However, the HAS highlighted the importance of robust clinical evidence for reimbursement, using a rating system that significantly impacts access to new treatments (75).

HTA evaluations underscore the challenges in demonstrating the value of Micra™ in different healthcare systems, stressing the need for robust data to support clinical decisions. In our analysis, the incorporation of a weighted average ICER approach across various high-risk subgroups emphasizes the influence of these regional differences and the need for localized studies to better understand the economic impact of leadless pacemakers like Micra™ in different healthcare settings. Our comprehensive evaluation suggests that Micra™ has potential to reduce complications and enhance overall quality of life for patients aligning with broader conclusions found in international HTAs, but requires further research to demonstrate benefits in the subgroups of interest.

6.4 Implications of the findings for practice

This analysis employs a weighted average ICER approach across various high-risk patient subgroups to provide a comprehensive overview of the cost-effectiveness of Micra™.

By capturing all high-risk patient cohorts in a single analysis, this evaluation highlights Micra's™ potential to reduce complications and improve overall quality of life for the patients. These results are consistent with broader conclusions found in international HTAs, which advocate for the adoption of leadless pacemakers as a beneficial option for specific high-risk patients. The limitations related to the reliance on CIED data for mortality and infection risks, as well as the lack of long-term data specific to Micra™, may introduce some uncertainty regarding the robustness of the findings in our analysis.

The clinical experts in Norway emphasize that the current results from studies on Micra™ leadless pacemakers do not fully capture its likely value for high-risk patient sub-groups, particularly those with increased infection risk and limited venous access. The clinical experts suggest that these sub-groups, which are often underrepresented in RCTs can benefit significantly from Micra™ due to its ability to avoid the risks associated with transvenous leads, such as infection and complications from venous access. As stated previously, Norwegian experts suggest Micra™ is particularly useful for patients who cannot undergo traditional pacemaker implantation due to challenges with venous access, as well as for patients who require temporary pacing in cases of endocarditis. In these situations,

Micra™ provides a safer, effective and perhaps the only alternative, allowing patients to receive treatment while an infection is managed. Experts also note that using Micra™ as a temporary solution for endocarditis patients is more efficient, as it avoids prolonged hospital stays and external pacemaker use, which are often required with traditional devices.

Further, the experts emphasize the importance of high procedural volumes for achieving optimal outcomes with leadless pacemakers. Expertise in the implantation procedure is critical, and centres with experience in performing 5-10 procedures annually are more likely to achieve favourable results. This factor is crucial when evaluating the cost-effectiveness of Micra™ in the current analysis, as lower procedural volumes may lead to higher complication rates, potentially skewing cost-effectiveness models. Thus, while NOMA's meta-analyses offer useful insights, they may not adequately reflect the true clinical value of Micra™ in high-risk sub-groups, that is included in the economic evaluation, despite the use of CIED studies. Real-world experience from high-volume centres as highlighted by one of the clinical experts, reinforces the device's potential for improving patient outcomes and supports its broader use in specific high-risk patient sub-groups.

Therefore, while Micra™ may offer significant advantages in terms of patient outcomes and overall healthcare costs, a careful consideration of the existing evidence, clinicians feedback and potential uncertainties is essential for informed decision-making in clinical practice for selected high-risk patient groups, including those with comorbidities such as ESRD, epicardial leads or a history of prior infections.

6.5 Need for further research

Further research is essential to strengthen the evidence base for more informed cost-effectiveness analyses of Micra™ in high-risk patient groups. However, experts caution that conducting these studies is challenging, as infection rates are expected to be significantly higher in the TVPM group compared to Micra™, which may complicate direct comparisons.

While RCTs are necessary to better understand Micra™-specific mortality, infection rates, and post-infection complications, this type of research is difficult to execute in high-risk populations. Additionally, studies need to focus on subgroups like patients with end-stage ESRD, limited venous access, epicardial leads, those with a history of prior infections or increased risk of infections. These insights are valuable, but their applicability may be limited due to the challenges associated with conducting such RCTs due to practical and ethical considerations.

7. Conclusion

7.1 Effects and safety

The current evidence base is heterogeneous and of low quality, primarily composed of non-randomized studies with small sample sizes and short follow-up periods (maximum 36 months). Only one small RCT was included, and systematic reviews were of poor to fair quality. There is some concern that the submitter's literature search and selection process may not have been optimal. The overall quality of evidence was rated as poor to very poor, with high risk of bias in many studies. The evidence is sparse for the subgroups who are suggested would benefit most from Micra™.

Technical performance results did not provide a clear picture in favour of Micra™. Micra™ appears comparable to TVPM in terms of mortality, with some limited evidence suggesting potential improvements in quality of life. The data available for Micra™ on safety are mixed, with some studies indicating a lower risk of complications and infections for Micra™ recipients, while others show no clear difference or potential increased risks for certain complications (e.g., pericardial effusion, cardiac tamponade). For some key safety outcomes, no data were presented. Several important outcomes lack sufficient data, including long-term effectiveness and safety beyond 36 months. There is little evidence on quality of life and patient and caregiver satisfaction.

While Micra™ appears to be non-inferior to TVPM for most outcomes in eligible individuals for single-chamber ventricular implantation, higher quality evidence and evidence in high-risk sub-groups is needed to strengthen certainty in the findings. Careful patient selection and analysis providing data for the submitter claims (i.e. high-risk subgroups) is needed. Operator's expertise appears to be crucial for optimal outcomes.

7.2 Health economics

The cost-effectiveness of Micra™ was assessed, suggesting there may be potential benefits compared with TVPM, particularly in reducing complications or infections associated with leads and the device visibility in high-risk patient subgroups. Despite the current analysis reflecting higher costs for Micra™ compared with TVPM, the weighted average approach provides valuable insights into the overall impact across various high-risk patient groups. Micra™ was shown to generate more QALYs, highlighting its potential to offer additional health benefits over TVPM, particularly in specific high-risk **subgroups** such as those with prior infection, ESRD and those requiring epicardial leads.

Due to the lack of documented evidence specific to the high-risk population from NOMA's meta-analysis, the CEA results based on the Micra CED study—adjusted for subgroup-specific infection risks from CIED studies—suggest that Micra™ may be a beneficial option for high-risk patients, such as those with a history of prior infection, ESRD, or those requiring epicardial leads due to anatomical or clinical factors. However, this has to be understood in the context of limited knowledge (uncertainty) coming from the clinical and cost-effectiveness analyses presented. The challenges of conducting additional studies and RCTs must be taken into account when evaluating Micra™'s cost-effectiveness and safety. As such, ensuring careful selection of the right high-risk patients is essential to guarantee that the findings are both relevant and applicable to those who would most benefit from the device.

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115. Barros RT, Carvalho SM, Silva MA, Borges JB. Evaluation of patients' quality of life aspects after cardiac pacemaker implantation. Rev Bras Cir Cardiovasc 2014;29(1):37-44. DOI: 10.5935/1678-9741.20140009
116. Willy K, Ellermann C, Reinke F, Rath B, Wolfes J, Eckardt L, et al. The Impact of Cardiac Devices on Patients' Quality of Life: A Systematic Review and Meta-Analysis. J Cardiovasc Dev Dis 2022;9(8):257. DOI: 10.3390/jcdd9080257
117. Udo EO, van Hemel NM, Zuithoff NP, Nijboer H, Taks W, Doevendans PA, et al. Long term quality-of-life in patients with bradycardia pacemaker implantation. Int J Cardiol 2013;168(3):2159-63. DOI: 10.1016/j.ijcard.2013.01.253
118. Cui D, Liao Y, Du J, Chen Y. A Meta-analysis of Major Complications between Traditional Pacemakers and Leadless Pacemakers. Cardiovascular Innovations and Applications 2021;5(3):145-53. DOI: 10.15212/CVIA.2019.0596
119. Oliveira SF, Carvalho MM, Adao L, Nunes JP. Clinical outcomes of leadless pacemaker: a systematic review. Minerva cardiology and angiology 2021;69(3):346-57. DOI: 10.23736/S2724-5683.20.05244-5
120. Oliveira VMR, Rivera A, Oliveira IC, de Sousa AM, Nishikubo MEP, Serpa F, et al. The Effectiveness and Safety of Leadless Pacemakers: An Updated Meta-Analysis. Curr Cardiol Rep 2024;26(8):789-99. DOI: 10.1007/s11886-024-02079-6
121. Haeberlin A, Bartkowiak J, Brugger N, Tanner H, Wan E, Baldinger SH, et al. Evolution of tricuspid valve regurgitation after implantation of a leadless pacemaker: A single center experience, systematic review, and meta-analysis. J Cardiovasc Electrophysiol 2022;33(7):1617-27. DOI: 10.1111/jce.15565
122. Denman RA, Lee AC, Mengel C, Townsend S, Betts J, Bovey N, et al. Leadless Permanent Pacing: A Single Centre Australian Experience. Heart Lung and Circulation 2019;28(11):1677-82. DOI: 10.1016/j.hlc.2018.09.014
123. Tolve S, Zucchelli G, Barletta V, Parollo M, Di Cori A, Della Tommasina V, et al. P1470 Outcome of leadless pacemaker implantation in a referral centre for lead extraction: a comparison with transvenous pacemaker. EP Europace 2020;22(Supplement_1):euaa162.31. DOI: 10.1093/europace/euaa162.131
124. Diaz-Arocutipa C, Calderon-Ramirez PM, Mayta-Tovalino F, Torres-Valencia J. Association between frailty and in-hospital outcomes in patients undergoing leadless pacemaker implantation: A nationwide analysis. Heart Rhythm O2 2024;5(2):85-94. DOI: 10.1016/j.hroo.2023.12.007
125. Matsumura M, Minamiguchi H, Mori N, Ichibori Y, Hayashi T, Makino N, et al. A Case of Pacemaker Pocket Infection in the Elderly Who Underwent Simultaneous Percutaneous Lead Extraction and Leadless Pacemaker Implantation. [Japanese]. Therapeutic Research 2022;43(3):206-8.
126. Nona P, Altawil M, Khan E, Maskoun W. Dual-chamber pacing using a hybrid transvenous and leadless pacing approach. PACE - Pacing and Clinical Electrophysiology 2021;44(4):751-4. DOI: 10.1111/pace.14190
127. Adelman RD, Tmanova LL, Delgado D, Dion S, Lachs MS. Caregiver burden: a clinical review. JAMA 2014;311(10):1052-60. DOI: 10.1001/jama.2014.304
128. Coleman CI, Coleman SM, Vanderpoel J, Nelson W, Colby JA, Scholle JM, et al. Factors associated with 'caregiver burden' for atrial fibrillation patients. Int J Clin Pract 2012;66(10):984-90. DOI: 10.1111/j.1742-1241.2012.02996.x

Appendix 1: Progress log/time-line (reverse order)

Date (DD.MM.YYYY)	Milestone
18.12.2024	Report finalised

31.05.2024	NOMA accepted the submission (project start)
28.05.2024	NOMA received the requested clarifications and revised documentation from submitter.
24.05.2024	Patient representative recruited
15.05.2024	Feedback from NOMA's initial assessment of documentation (pdf) file sent to the submitter.
29.04.2024	NOMA received first submission file
01.03.2024	Last clinical expert recruited (three in all)
19.06.2023	Single Technology Assessment commissioned

NOMA, Norwegian Medical Products Agency

Appendix 2: Publications screened by NOMA, not included in the submission

References to publications included in systematic reviews - Darlington 2022, Gangannapalle 2023, Shtembri 2023 - not mentioned in the submission (n=20)

(6/20 expected to be on the submission list of excluded studies)

No.	Study citation	Action (i.e. expected on the exclusion list, excluded at title and abstract (T/A)
1	Beurskens NEG, Tjong FVY, De Bruin-Bon RHA, Dasselaar KJ, Kuijt WJ, Wilde AAM, et al. Impact of Leadless Pacemaker Therapy on Cardiac and Atrioventricular Valve Function Through 12 Months of Follow-Up. Circulation: Arrhythmia and Electrophysiology 2019;12(5):e007124. DOI: 10.1161/CIRCEP.118.007124	Expected on exclusion list
2	Bongiorni MG, Della Tommasina V, Barletta V, Di Cori A, Rogani S, Viani S, et al. Feasibility and long-term effectiveness of a non-apical Micra pacemaker implantation in a referral centre for lead extraction. Europace 2019;21(1):114-20. DOI: 10.1093/europace/euy116	Exclude at T/A
3	Cantillon DJ, Dukkipati SR, Ip JH, Exner DV, Niazi IK, Banker RS, et al. Comparative study of acute and mid-term complications with leadless and transvenous cardiac pacemakers. Heart Rhythm 2018;15(7):1023-30. DOI: 10.1016/j.hrthm.2018.04.022	Exclude at T/A
4	Denman RA, Lee AC, Mengel C, Townsend S, Betts J, Bovey N, et al. Leadless Permanent Pacing: A Single Centre Australian Experience. Heart Lung and Circulation 2019;28(11):1677-82. DOI: 10.1016/j.hlc.2018.09.014	Exclude at T/A
5	El Amrani A, Campos B, Alonso-Martin C, Guerra-Ramos JM, Rodriguez-Font E, Moreno-Weidmann Z, et al. Performance of the Micra cardiac pacemaker in nonagenarians. Revista espanola de cardiologia (English ed) 2020;73(4):307-12. DOI: 10.1016/j.rec.2019.06.001	Exclude at T/A
6	El-Chami MF, Al-Samadi F, Clementy N, Garweg C, Martinez-Sande JL, Piccini JP, et al. Updated performance of the Micra transcatheter pacemaker in the real-world setting: A comparison to the investigational study and a transvenous	Expected on exclusion list

	historical control. Heart Rhythm 2018;15(12):1800-7. DOI: 10.1016/j.hrthm.2018.08.005	
7	Haeberlin A, Kozhuharov N, Knecht S, Tanner H, Schaer B, Noti F, et al. Leadless pacemaker implantation quality: Importance of the operator's experience. Europace 2020;22(6):939-46. DOI: 10.1093/europace/euaa097	Exclude at T/A
8	Hai JJ, Fang J, Tam CC, Wong CK, Un KC, Siu CW, et al. Safety and feasibility of a midseptal implantation technique of a leadless pacemaker. Heart Rhythm 2019;16(6):896-902. DOI: 10.1016/j.hrthm.2018.12.007	Exclude at T/A
9	Martinez-Sande JL, Garcia-Seara J, Rodriguez-Manero M, Fernandez-Lopez XA, Gonzalez-Melchor L, Redondo-Dieguez A, et al. The Micra Leadless Transcatheter Pacemaker. Implantation and Mid-term Follow-up Results in a Single Center. Revista espanola de cardiologia (English ed) 2017;70(4):275-81. DOI: 10.1016/j.rec.2016.11.027	Exclude at T/A
10	Moore SKL, Chau KH, Chaudhary S, Rubin G, Bayne J, Avula UMR, et al. Leadless pacemaker implantation: A feasible and reasonable option in transcatheter heart valve replacement patients. PACE - Pacing and Clinical Electrophysiology 2019;42(5):542-7. DOI: 10.1111/pace.13648	Exclude at T/A Mentioned p. 108 - not in reference list
11	Okuyama K, Izumo M, Sasaki K, Kuwata S, Kaihara T, Watanabe M, et al. Comparison in clinical outcomes between leadless and conventional transvenous pacemaker following transcatheter aortic valve implantation. J Invasive Cardiol 2020;32(10):400-4.	Exclude at T/A
12	Piccini JP, Stromberg K, Jackson KP, Laager V, Duray GZ, El-Chami M, et al. Long-term outcomes in leadless Micra transcatheter pacemakers with elevated thresholds at implantation: Results from the Micra Transcatheter Pacing System Global Clinical Trial. Heart Rhythm 2017;14(5):685-91. DOI: 10.1016/j.hrthm.2017.01.026	Expected on exclusion list
13	Reddy VY, Knops RE, Sperzel J, Miller MA, Petru J, Simon J, Sediva L, de Groot JR, Tjong FV, Jacobson P, Ostrosff A, Dukkipati SR, Koruth JS, Wilde AA, Kautzner J, Neuzil P. Permanent leadless cardiac pacing: results of the LEADLESS trial. Circulation. 2014 Apr 8;129(14):1466-71. doi: 10.1161/CIRCULATIONAHA.113.006987	Exclude at T/A
14	Reddy VY, Exner DV, Cantillon DJ, Doshi R, Bunch TJ, Tomassoni GF, et al. Percutaneous implantation of an entirely intracardiac leadless pacemaker. N Engl J Med 2015;373(12):1125-35. DOI: 10.1056/NEJMoa1507192	Exclude at T/A
15	Sanchez R, Nadkarni A, Buck B, Daoud G, Koppert T, Okabe T, et al. Incidence of pacing-induced cardiomyopathy in pacemaker-dependent patients is lower with leadless pacemakers compared to transvenous pacemakers. J Cardiovasc Electrophysiol 2021;32(2):477-83. DOI: 10.1111/jce.14814	Expected on exclusion list
16	Sasaki K, Togashi D, Nakajima I, Suchi T, Nakayama Y, Harada T, et al. Clinical Outcomes of Non-Atrial Fibrillation Bradyarrhythmias Treated With a Ventricular Demand Leadless Pacemaker Compared With an Atrioventricular Synchronous Transvenous Pacemaker - A Propensity Score-Matched Analysis. Circ J 2022;86(8):1283-91. DOI: 10.1253/circj.CJ-21-0889	Expected on exclusion list
17	Sperzel J, Defaye P, Delnoy PP, Garcia Guerrero JJ, Knops RE, Tondo C, Deharo JC, Wong T, Neuzil P. Primary safety results from the LEADLESS Observational Study. Europace. 2018;20(9):1491-1497. doi: 10.1093/europace/eux359	Exclude at T/A
18	Tolosana JM, Guasch E, San Antonio R, Apolo J, Pujol-Lopez M, Chipa-Ccasani F, et al. Very high pacing thresholds during long-term follow-up predicted by a combination of implant pacing threshold and impedance in leadless transcatheter	Exclude at T/A

	pacemakers. J Cardiovasc Electrophysiol 2020;31(4):868-74. DOI: 10.1111/jce.14360	
19	Valiton V, Graf D, Pruvot E, Carroz P, Fromer M, Bisch L, et al. Leadless pacing using the transcatheter pacing system (Micra TPS) in the real world: Initial Swiss experience from the romandie region. Europace 2019;21(2):275-80. DOI: 10.1093/europace/euy195	Exclude at T/A
20	Yarlagadda B, Turagam MK, Dar T, Janagam P, Veerapaneni V, Atkins D, et al. Safety and feasibility of leadless pacemaker in patients undergoing atrioventricular node ablation for atrial fibrillation. Heart Rhythm 2018;15(7):994-1000. DOI: 10.1016/j.hrthm.2018.02.025	Excluded on exclusion list Mentioned p. 108 - not in reference list
References to study ID-related articles not in submission (n=22) **(2/22 expected to be on the submission list of excluded studies)**		
1	Bari Z, Vamos M, Bogyi P, Reynolds D, Sheldon T, Fagan DH, et al. Physical activity detection in patients with intracardiac leadless pacemaker. J Cardiovasc Electrophysiol 2018;29(12):1690-6. DOI: 10.1111/jce.13729	Exclude at T/A
2	Chinitz LA, El-Chami MF, Sagi V, Garcia H, Hackett FK, Leal M, et al. Ambulatory atrioventricular synchronous pacing over time using a leadless ventricular pacemaker: Primary results from the AccelAV study. Heart Rhythm 2023;20(1):46-54. DOI: 10.1016/j.hrthm.2022.08.033	Exclude at T/A
3	Clementy N, Coelho R, Veltmann C, Marijon E, Tolosana J, Galand V, et al. Leadless pacemakers in critically ill patients requiring prolonged cardiac pacing: A multicenter international study. J Cardiovasc Electrophysiol 2021;32(9):2522-7. DOI: 10.1111/jce.15175	Exclude at T/A
4	Cook J, Richardson TD. Leadless pacing with mechanical atrial sensing and variable AV conduction. J Cardiovasc Electrophysiol 2021;32(7):1958-60. DOI: 10.1111/jce.15056	Exclude at T/A
5	Crossley GH, Longacre C, Higuera L, Stromberg K, Cheng A, Piccini JP, et al. Outcomes of patients implanted with an atrioventricular synchronous leadless ventricular pacemaker in the Medicare population. Heart Rhythm 2024;21(1):66-73. DOI: 10.1016/j.hrthm.2023.09.017	Exclude at T/A
6	Della Tommasina V, Zucchelli G, Barletta V, Rogani S, De Lucia R, Paperini L, et al. Feasibility and effectiveness of a non-apical site of implantation of Micra transcatheter pacing system: Results from a referral centre for pacemaker lead extraction. Europace 2018;20(Supplement 1):i74. DOI: 10.1093/europace/euy015	Exclude at T/A
7	El-Chami M, Kowal RC, Soejima K, Ritter P, Duray GZ, Neuzil P, et al. Impact of operator experience and training strategy on procedural outcomes with leadless pacing: Insights from the Micra Transcatheter Pacing Study. PACE - Pacing and Clinical Electrophysiology 2017;40(7):834-42. DOI: 10.1111/pace.13094	Exclude at T/A
8	El-Chami MF, Clementy N, Garweg C, Omar R, Duray GZ, Gornick CC, et al. Leadless Pacemaker Implantation in Hemodialysis Patients: Experience With the Micra Transcatheter Pacemaker. JACC: Clinical Electrophysiology 2019;5(2):162-70. DOI: 10.1016/j.jacep.2018.12.008	Exclude at T/A In submission reference list
9	El-Chami MF, Garweg C, Iacopino S, Al-Samadi F, Martinez-Sande JL, Tondo C, et al. Leadless pacemaker implant, anticoagulation status, and outcomes: Results from the Micra Transcatheter Pacing System Post-Approval Registry. Heart Rhythm 2022;19(2):228-34. DOI: 10.1016/j.hrthm.2021.10.023	Exclude at T/A
10	El-Chami MF, Johansen JB, Zaidi A, Faerestrand S, Reynolds D, Garcia-Seara J, et al. Leadless pacemaker implant in patients with pre-existing infections: Results	Excluded at T/A

	from the Micra postapproval registry. J Cardiovasc Electrophysiol 2019;30(4):569-74. DOI: 10.1111/jce.13851	In submission reference list
11	El-Chami MF, Shinn T, Bansal S, Martinez-Sande JL, Clementy N, Augostini R, et al. Leadless pacemaker implant with concomitant atrioventricular node ablation: Experience with the Micra transcatheter pacemaker. J Cardiovasc Electrophysiol 2021;32(3):832-41. DOI: 10.1111/jce.14881	Exclude at T/A
12	El-Chami MF, Soejima K, Piccini JP, Reynolds D, Ritter P, Okabe T, et al. Incidence and outcomes of systemic infections in patients with leadless pacemakers: Data from the Micra IDE study. PACE - Pacing and Clinical Electrophysiology 2019;42(8):1105-10. DOI: 10.1111/pace.13752	Exclude at T/A In submission reference list
13	Grubman E, Ritter P, Ellis CR, Giocondo M, Augostini R, Neuzil P, et al. To retrieve, or not to retrieve: System revisions with the Micra transcatheter pacemaker. Heart Rhythm 2017;14(12):1801-6. DOI: 10.1016/j.hrthm.2017.07.015	Expected on exclusion list
14	Lloyd M, Reynolds D, Sheldon T, Stromberg K, Hudnall JH, Demmer WM, et al. Rate adaptive pacing in an intracardiac pacemaker. Heart Rhythm 2017;14(2):200-5. DOI: 10.1016/j.hrthm.2016.11.016	Exclude at T/A
15	McCune C, McKavanagh P, Menown IBA. A Review of the Key Clinical Trials of 2015: Results and Implications. Cardiology and Therapy 2016;5(2):109-32. DOI: 10.1007/s40119-016-0063-5	Exclude at T/A
16	Okabe T, El-Chami MF, Lloyd MS, Buck B, Gornick CC, Moore JC, et al. Leadless pacemaker implantation and concurrent atrioventricular junction ablation in patients with atrial fibrillation. PACE - Pacing and Clinical Electrophysiology 2018;41(5):504-10. DOI: 10.1111/pace.13312	Exclude at T/A
17	Piccini JP, Cunnane R, Steffel J, El-Chami MF, Reynolds D, Roberts PR, et al. Development and validation of a risk score for predicting pericardial effusion in patients undergoing leadless pacemaker implantation: experience with the Micra transcatheter pacemaker. Europace 2022;24(7):1119-26. DOI: 10.1093/europace/euab315	Exclude at T/A In submission reference list
18	Piccini JP, Stromberg K, Jackson KP, Kowal RC, Duray GZ, El-Chami MF, et al. Patient selection, pacing indications, and subsequent outcomes with de novo leadless single-chamber VVI pacing. Europace 2019;21(11):1686-93. DOI: 10.1093/europace/euz230	Exclude at T/A
19	Ritter P, Duray GZ, Zhang S, Narasimhan C, Soejima K, Omar R, et al. The rationale and design of the Micra Transcatheter Pacing Study: Safety and efficacy of a novel miniaturized pacemaker. Europace 2015;17(5):807-13. DOI: 10.1093/europace/euv026	Exclude at T/A
20	Soejima K, Asano T, Ishikawa T, Kusano K, Sato T, Okamura H, et al. Performance of leadless pacemaker in japanese patients vs. Rest of the world: Results from a global clinical trial. Circ J 2017;81(11):1589-95. DOI: 10.1253/circj.CJ-17-0259	Exclude at T/A
21	Tjong FVY, Beurskens NEG, de Groot JR, Waweru C, Liu S, Ritter P, et al. Health-related quality of life impact of a transcatheter pacing system. J Cardiovasc Electrophysiol 2018;29(12):1697-704. DOI: 10.1111/jce.13726	Expected on exclusion list
22	Wilson DG, Yue A, Roberts PR, Morgan JM. Leadless pacing: The old with the new. Int J Cardiol 2016;203:407-8. DOI: 10.1016/j.ijcard.2015.10.103	Exclude at T/A

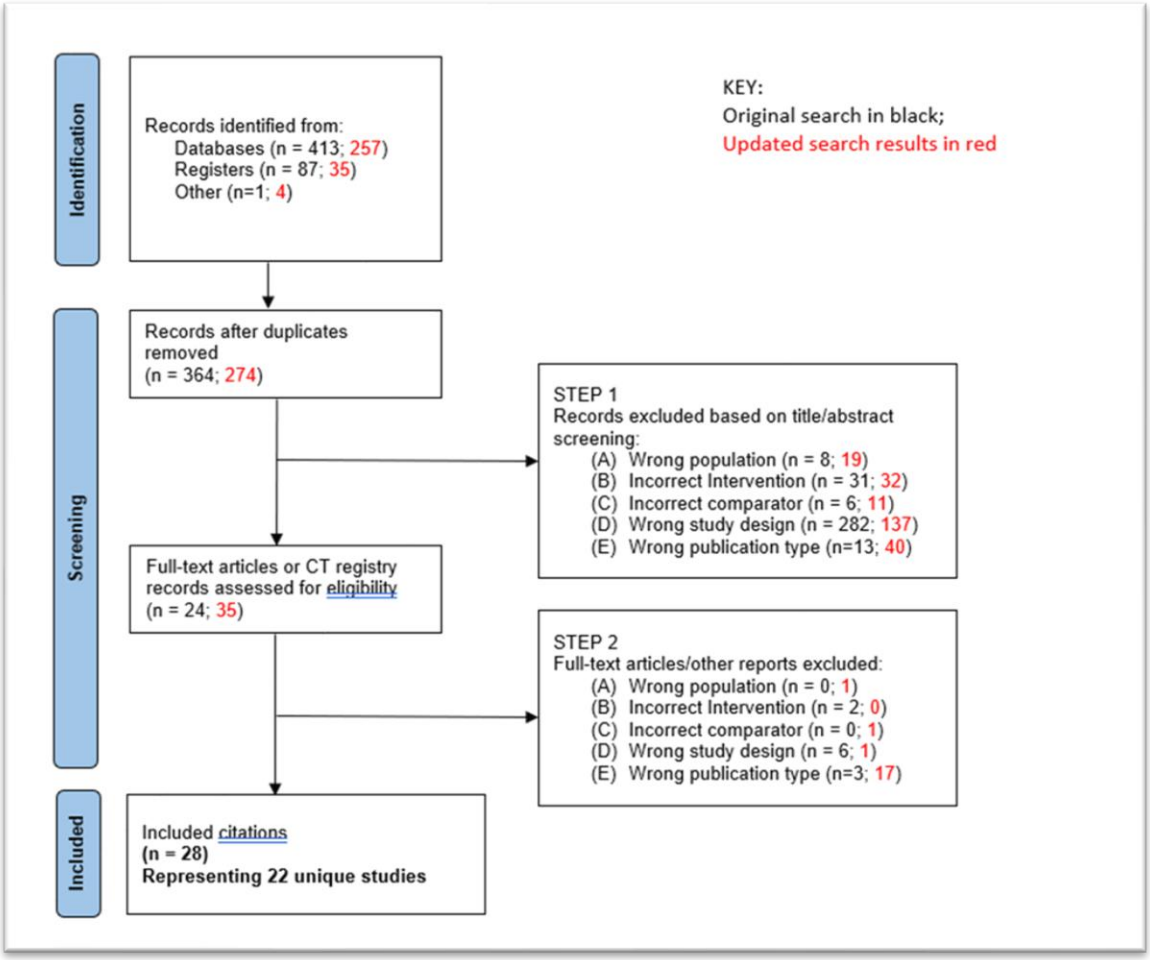
Key: T/A title and abstract screening

Appendix 3: Authors contacted and responses

Date contacted	Message	Response
20.08.2024	Contacted Banba because there was no response from **Tachibana**.	No response
20.08.2024	Contacted **Pannu** because there was no response from **Heaton (Mararenko paper)**	No response
20.08.2024	Contacted **Carnivali** because there was no response from **Marschall**.	No response
20.08.2024	Contacted Dr. Nicolas **Clementy** (on Research Gate) because there was no response from Bodin	01.10.2024: The type of leadless pacemaker was Micra™
20.08.2024	Tried to find email address for the other authors of the Palmisano article. Did not find any.	
20.08.2024	Contacted **Martinez-Sande** because there was no response from **Gonzalez-Melchior**	No response
13.08.2024	Contacted **Gonzalez-Melchor** regarding the statement of no mortality differences in the abstract and a significant difference in Table 3.	No response
13.08.2024	Contacted **Palmisano** regarding the follow-up time for the pacing impedance. Geir	No response
13.08.2024	Contacted **Bodin** regarding type of leadless pacemaker. Geir	(From Clementy) 01.10.2024: The type of leadless pacemaker was Micra™
13.08.2024	Contacted Alexander **Marschall** regarding the type of leadless PM and whether the study was prospective or retrospective. Geir	No response
12.08.2024	Contacted author of **Mararenko** 2023 (**Heaton)** about type of leadless PM. Geir	No response
12.08.2024	Contacted first author of **Tachibana** 2020 about volt by millisecond. Geir	No response
27.07.2024	Contacted Fleur **Tjong** regarding access to supplementary information *Julia	No response

Appendix 4: Submitter PRISMA flow diagram

PRISMA flowchart for literature search on the use of Micra™ TPS vs. standard single-chamber transvenous pacemaker – figure 5 copied from the submission file



Appendix 5: Search strategies

NOMA strategy

The submitter strategy in Embase.com (Elsevier) adapted to Ovid syntax by NOMA (lines 1-17) + testing retrieval against NOMA questions, section 7.3, (lines 17-29)

Embase <1974 to 2024 August 14> Ovid MEDLINE(R) ALL <1946 to August 14, 2024> Advanced search		
1	Micra/ use oemezd	280
2	micra.ti,ab,kf,dv.	2852
3	leadless pacemaker/ use oemezd	1576
4	(leadless adj5 pacemaker*).ti,ab,kf.	2787
5	(leadless adj5 cardiac).ti,ab,kf.	543

6	(leadless transcatheter pacing system* or tps).ti,ab,kf.	23631
7	1 or 2 or 3 or 4 or 5 or 6	28069
8	single chamber pacemaker/ use oemezd	782
9	(single chamber pacemaker* or single-chamber pacemaker*).ti,ab,kf.	595
10	(single chamber pulse generator* or single-chamber pulse generator*).ti,ab,kf.	13
11	exp transvenous pacemaker electrode/ use oemezd	224
12	transvenous pacemaker electrode*.ti,ab,kf.	96
13	(transvenous adj5 pacemaker*).ti,ab,kf.	3184
14	(wire* adj5 pacemaker*).ti,ab,kf.	751
15	(lead adj5 pacemaker*).ti,ab,kf.	5563
16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	9875
17	7 and 16	931
18	("37957879" or "36807378" or "36757859" or "34788416" or "34319383" or "37904603" or "37196728" or "37712644" or "35430342" or "36294401" or "36983448" or "34506348" or "35929449" or "33888044" or "33418071" or "32712901" or "31840881" or "32763431" or "32454218" or "32134134" or "30632622" or "29709576" or "28192207" or "26551877" or "26045305" or "37842352" or "37106267" or "34922032").pm. or ("2022294414" or "2019799860" or "2010671239" or "2016504366" or "606365120").an. use oemezd [Question 1: PMIDs or Embase accession numbers of articles included in submission. 27/28 publications in Embase. Gangannapalle 2023 not indexed in Embase]	27
19	("37957879" or "36807378" or "36757859" or "34788416" or "34319383" or "37904603" or "37196728" or "37712644" or "35430342" or "36294401" or "36983448" or "34506348" or "35929449" or "33888044" or "33418071" or "32712901" or "31840881" or "32763431" or "32454218" or "32134134" or "30632622" or "29709576" or "28192207" or "26551877" or "26045305" or "37842352" or "37106267" or "34922032").an. use medall [Question 1: PMIDs articles included in submission - 28/28 publications in MEDLINE]	28
20	18 not 17 [Garweg 2023; Marschall 2022; Ritter 2015 - not retrieved in Embase by submitters strategy]	3
21	19 not 17 [Garweg 2023; Marschall 2022; Ritter 2015 - not retrieved in MEDLINE by submitters strategy]	3
22	(NCT06100757 or NCT02004873 or NCT02488681 or NCT02536118 or NCT04051814 or NCT04235491 or NCT04253184 or NCT04245345 or NCT03039712 or NL6542 or NTR6730).af. [Question 3: records tagged with or mentioning relevant studyIDs from submission]	46

Submitter's strategy

Search of Embase.com (Embase & Medline Combined)

No.	SEARCH STRING	15-NOV-23 RESULTS
#1	'micra'/exp	256
#2	'micra:ti,ab,kw,dn	1674
#3	'leadless pacemaker'/exp	1279
#4	(leadless NEAR/5 pacemaker*):ti,ab,kw	1466
#5	(leadless NEAR/5 cardiac):ti,ab,kw	283
#6	'leadless transcatheter pacing system*':ti,ab,kw OR tps:ti,ab,kw	14342
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	16742
#8	'single chamber pacemaker'/exp	721
#9	'single chamber pacemaker*':ti,ab,kw OR 'single-chamber pacemaker*':ti,ab,kw	376
#10	'single chamber pulse generator*':ti,ab,kw OR 'single-chamber pulse generator*':ti,ab,kw	5
#11	'transvenous pacemaker electrode'/exp	202
#12	'transvenous pacemaker electrode*':ti,ab,kw	59
#13	(transvenous NEAR/5 pacemaker*):ti,ab,kw	1860
#14	(wire* NEAR/5 pacemaker*):ti,ab,kw	446
#15	(lead NEAR/5 pacemaker*):ti,ab,kw	3186
#16	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	5956
#17	#7 AND #16	542
#18	comment:de,it,ti OR editorial:de,it,ti OR letter:de,it,ti OR note:de,it,ti	3166031
#19	#17 NOT #18	516
#20	#17 NOT #18 AND [10-11-2021]/sd**;[limiting to citations from 10-NOV 21 to 15-NOV 23]***	201

(Table 4 in submission)

*The original search conducted on 10th November 2021 identified 324 citations. This search from 10-NOV 21 to 15-NOV 23 identified a further 201 citations.

Appendix 6: The submitter's systematic reviews included studies

Author/year	Trial registration ID	*	Comparator or other issues	D	G	S
Beurskens 2019			**Nanostim** (28) Micra (25) vs TVPM DDD			x
Bodin 2022		I	cohort matched control – Micra		X	
Bongiorni 2018			single arm, apical vs non-apical Micra	x		
Boveda 2023	NCT03039712	I	Micra vs TVPM in high-risk subgroup - 2yr		X	
Cabanas-Grandio 2020		I	Micra vs TVPM			x
Cantillon 2018	NCT04559945		**Aveir** trial (no FT)		X	X
Denman 2018			single arm? (no FT)	x		

El Amrani 2020			Comparison is ≥ 90 and < 90 years	x		
El-Chami 2018	NCT02004873		single arm + historical control	x		
El-Chami 2022	NCT02536118	I	Micra vs TVPM		x	X
Haeberlin 2020			Learning curves x procedure	x		
Hai 2018			Safety of septal implant – single arm?	x		
Martinez-Sande 2017			Single arm? (30 patients)	x		
Martinez-Sande 2021		I	Micra vs TVPM		x	X
Moore 2019			Patients with THVRS - LPM (10) vs TVPM (23) (no FT)		x	X
Okuyama 2020			Concomitant TAVI – Micra (10) vs TVPM (24)		X	X
Pagan 2020		I	Micra vs TVPM	x	X	X
Palmisano 2021		I	Micra vs TVPM		X	X
Palmisano 2023			Micra vs TVPM (**DDD**)		X	
Piccini 2017	NCT02536118		Micra single arm			X
Reddy 2014	NCT01700244 (LEADLESS)		Single arm **Nanostim**	X		
Reddy 2015	NCT02030418 (LEADLESS II)		Single arm **Nanostim**	X		
Reynolds 2016	NCT02004873	I	Micra single arm vs historical control TVPM	x	X	X
Ritter 2015	NCT02004873	I	Single arm	x		
Sanchez 2021			Micra (67) vs TVPM (131) (single and **dual chamber**)		x	X
Sasaki 2022			Micra (58) vs TVPM **DDD** (58)		X	X
Sperzel 2018	NCT02051972		**Nanostim**	X		
Tachibana 2020		I	Micra vs TVPM	X	X	X
Tolosana 2020			Micra single arm? (no FT)	X		
Vaidya 2019		I	Micra and **Nanostim** vs TVPM	X	x	X
Valiton 2018			Micra single arm	X		
Yarlagadda 2018	NCT02030418 (LEADLESS II)		**Aveir** Leadless vs TVPM in patients undergoing AVN ablation (no FT)		x	X
Zucchelli 2021		I	Micra vs TVPM	x	x	X

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Key:* included in the STA; D Darlington: DDD dual chamber; FT: full text; G: Gangannapalle; LPM leadless pacemaker; S: Shtembari; TAVI; Transcatheter Aortic Valve Implantation; THVRS: Transcatheter Heart Valve Replacement; TVPM transvenous pacemaker.