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Safety and long-term outcomes of leadless vs. conventional lead-based pacemakers

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Abstract
Symptomatic bradycardia is a common clinical condition that may result in fatigue, syncope, or worsening heart failure, for which permanent pacemaker implantation remains the cornerstone of treatment. Leadless pacemakers (LPs) have emerged as alternatives to conventional transvenous pacemakers (TVPs), with the goal of reducing lead- and pocket-related complications. This systematic review evaluated the safety, efficacy, and intermediate- to long-term outcomes of LPs compared with TVPs in adults with symptomatic bradycardia, based on a PubMed literature search from 2020 to 2025 that identified observational and cohort studies reporting clinical outcomes. Study quality was assessed using the Newcastle-Ottawa Scale, and pooled hazard ratios with 95% confidence intervals were estimated using a random-effects model to account for potential heterogeneity between studies. Quantitative meta-analysis of two high-quality observational studies demonstrated a numerical trend toward lower rates of device-related complications with leadless pacemakers; however, the pooled estimate did not reach statistical significance. This pooled analysis should be interpreted as exploratory and hypothesis-generating, given the limited number of eligible studies. Across individual studies, LPs—especially the Micra™ AV system—were associated with lower rates of complications such as lead dislodgement, infection, and device-related pain, as well as fewer re-interventions, compared with TVPs. Although higher all-cause mortality was observed in some LP cohorts, this appeared to be largely attributable to greater baseline comorbidity burden rather than device-related causes, and device upgrades or removals were uncommon. Overall, current evidence suggests that LPs may offer a favorable safety profile compared with TVPs in selected clinical scenarios, with the Micra™ AV system showing promise in reducing lead-related risks; however, randomized controlled trials and longer-term follow-up are needed to establish durability, effectiveness, and generalizability across broader patient populations. Such a Bayesian adaptive, randomized, controlled trial comparing AV-synchronous leadless pacing vs dual-chamber transvenous pacing, with pre-specified response-adaptive randomization and sample-size re-estimation is proposed.

Keywords
Leadless pacemaker, Transvenous pacemaker, Symptomatic bradycardia, Cardiac pacing, Device complications, Re-intervention rates, Long-term outcomes, Micra™ pacemaker, Pacemaker safety, Bradycardia treatment

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1. Introduction

Bradycardia, characterized by a heart rate of 50 to 60 beats per minute or less, is one of the most frequently encountered types of arrhythmias and a common reason for cardiology referrals (1). While it may be a normal finding in young, physically fit individuals, it can also be associated with aging or underlying health conditions. Although many individuals with bradycardia remain asymptomatic, some may experience a range of clinical symptoms such as fatigue, dizziness, light headedness, reduced exercise capacity, episodes of syncope or near-syncope, exacerbation of angina or heart failure, and even cognitive decline (2). For those with symptomatic bradycardia, the primary and most reliable form of treatment is the implantation of a permanent pacemaker, which helps restore adequate heart rhythm and prevents further complications (3).

Temporary transvenous pacing involves threading a pacing electrode catheter into the right ventricle to deliver electrical impulses that restore effective cardiac depolarization and contraction, thereby supporting adequate heart rate and output (4). In contrast, leadless pacemakers (LPs) are compact, self-contained devices implanted directly within the heart, providing an alternative pacing strategy that eliminates the need for transvenous leads and subcutaneous pockets (5).

LPs, such as the Micra™ Transcatheter Pacemaker System, have been developed to reduce complications linked with conventional transvenous pacemakers (TVPs), including lead dislodgement and infection (6). Their design offers particular benefits for younger adults, who may face higher risks of lead-related issues due to their longer life expectancy and active lifestyles (7). Comparative studies have demonstrated that LPs are associated with lower complication rates and comparable efficacy when compared to TVPs (8).

2. Objective

The objective of this systematic review was to critically evaluate and compare the clinical safety, efficacy, and intermediate to long-term outcomes of leadless pacemakers (LPs) with those of conventional transvenous pacemakers (TVPs) in patients requiring permanent pacemaker implantation. This review aimed to synthesize existing evidence to assess complication rates, device performance, and patient-specific benefits, thereby informing clinical decision-making and guiding future research in cardiac pacing technologies.

3. Methods

3.1 Study inclusion and analytical framework

Four studies met the inclusion criteria and were included in this systematic review. Of these, two studies (10,15) reported compatible hazard ratios with corresponding confidence intervals and were therefore included in the quantitative meta-analysis. All quantitative results reported in this manuscript are derived exclusively from these two studies.

The remaining two studies (11,14) were included in the systematic review but were analyzed descriptively only, as they did not report hazard ratios, confidence intervals, or uniform denominators required for statistical pooling. These descriptive studies, along with external registry studies and prior meta-analyses, are referenced for contextual comparison only and were not included in the pooled meta-analysis.

3.2 Search strategy

A comprehensive literature search was performed using PubMed to identify studies published from 2020 up to 2025 that reported on the clinical outcomes of LPs versus TVPs. The exact search strings used were (leadless[tiab] OR wireless[tiab] OR Micra[tiab] OR Nanostim[tiab]) AND (transvenous[tiab] OR traditional[tiab] OR conventional[tiab] OR lead-based[tiab] OR "lead based"[tiab]) AND (pacemaker*[tiab] OR pacing[tiab]) AND (bradycardia[tiab] OR bradyarrhythmia*[tiab] OR bradyarrhythmic[tiab])

Article type filters included: Clinical Study, Clinical Trial (Phase I–IV), Comparative Study, Observational Study, Randomized Controlled Trial, Validation Study.

Although systematic reviews ideally incorporate multiple bibliographic databases, this review utilized PubMed as the primary data source due to its comprehensive indexing of cardiovascular and device-related literature and the focused nature of the research question. Recognizing the potential limitations of a single-database search, reference lists of all included studies were manually screened to identify additional relevant publications.

3.3 Inclusion and exclusion criteria

Adult patients (≥18 years) diagnosed with bradycardia, who required pacemaker implantation were included. Inclusion criteria encompassed studies evaluating intermediate to long-term safety, complication rates (e.g., infection, thrombosis, lead dislodgement), re-intervention rates, pacing performance, and quality of life. Exclusion criteria included studies involving pediatric populations, epicardial or experimental pacemakers, or those lacking clinical outcome data. The primary outcomes assessed were safety, re-intervention rates, and all-cause mortality.

3.4 Quality assessment

The quality of each study was assessed using Newcastle-Ottawa Scale (NOS) (9). Scores ranged from 0 to 9, related to study selection, participants, and assessment of outcomes. Studies with a score > 6 were considered to be of high quality.

3.5 Statistical analysis

Pooled effect estimates were calculated with 95% confidence intervals. Between-study heterogeneity was assessed using Cochran's Q test and the I^2 statistic. A fixed-effects model was prespecified for outcomes demonstrating low heterogeneity ($I^2 < 25\%$). Since the heterogeneity for all key primary outcomes, including the all-cause mortality analysis ($I^2 = 29.8\%$), exceeded this threshold, all pooled estimates were generated using a random-effects model. Given the limited number of eligible studies and the observational nature of the data, the meta-analysis was conducted as an exploratory synthesis to evaluate consistency of effect direction rather than to establish definitive comparative efficacy. Unless otherwise specified, statistical significance was defined as a two-sided p-value < 0.05.

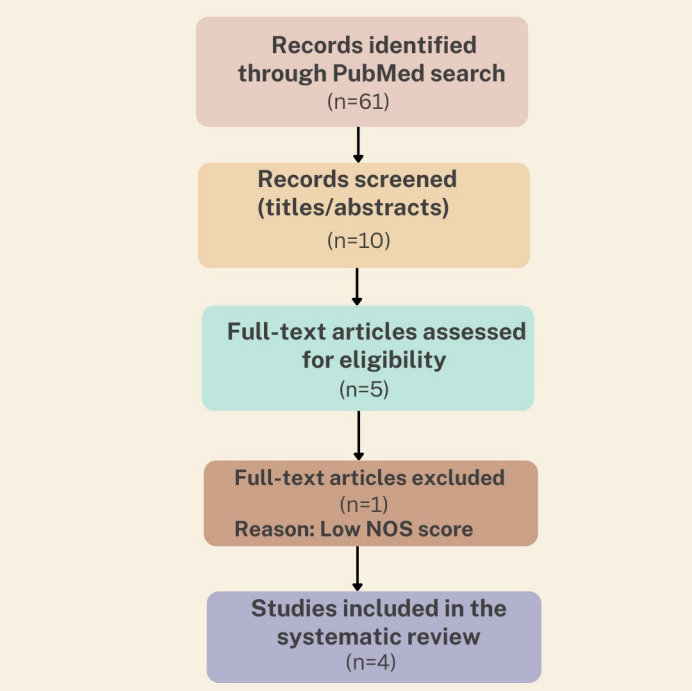

Figure 1. Flow chart of the study selection process

4. Results

4.1 Study selection and characteristics of included studies

All quantitative results reported in this manuscript are derived exclusively from the two studies included in the meta-analysis (10,15), while the remaining studies are presented descriptively only. Four studies met the inclusion criteria for this systematic review, comprising two studies eligible for quantitative meta-analysis and two studies included for descriptive analysis only (10,11,14,15). Study designs included large observational cohorts and an early-stage feasibility study. Sample sizes ranged from small first-in-human cohorts to registries of over 1,000 patients, with follow-up durations between 3 and 24 months. Based on the Newcastle–Ottawa Scale, two studies were rated as high quality, one as moderate quality, and one as low quality; the low-quality study was excluded from quantitative synthesis.

4.2 Results of studies included in the quantitative meta-analysis

4.2.1 *Study characteristics*

Two studies met the eligibility criteria for inclusion in the quantitative meta-analysis (10,15). Both were large observational cohort studies comparing the Micra™ AV leadless pacemaker with conventional dual-chamber transvenous pacemaker (DC-TV) systems. In both studies, recipients of leadless pacemakers were generally older and had a higher burden of baseline comorbidities compared with transvenous pacemaker recipients. Follow-up durations ranged from 18 to 24 months. Based on the Newcastle–Ottawa Scale (NOS), both studies were rated as high quality (8 stars).

Table 1. Characteristics of included studies

Study	Design & N	Population	Device Comparison	Complication Rate	Re-intervention	Mortality	Upgrade / Removal	Adjusted HR	Follow-up	Key Insight	NOS
El Chami 2024 (10)	Observational cohort; N NR	Micra™ AV recipients older, more comorbid	Micra™ AV vs dual-chamber TV	↓46 % chronic; ↓83 % dislodgement; ↓96 % infection; ↓74 % pain	↓38 % overall; ↓94 % revisions	34 % (MAV) vs 23.8 % (TV) at 24 mo	↓83 % removals; upgrades 1.4 %	0.54	24 mo	Lower complications; higher mortality reflects baseline risk	8
Garweg 2024 (15)	Registry; N NR	Older, more renal dysfunction, less CAD	Micra™ AV vs historical dual-chamber TV	3.7 % vs 8.8 % (58 %↓); 0 infection/dislodgement	1.5 % vs 5.5 %	9.9 % at 12 mo; 16.1 % at 18 mo	5 explants (all successful); 7 CRT upgrades	0.37	18 mo	High implant success; stable AV synchrony	8
Yu 2025 (11)	Single-centre comparative; N NR	More comorbidities in leadless group	Leadless vs transvenous TV	4.0 % vs 7.4 %; 0 % dislodgement with LP	4.0 % vs 6.6 %	5.5 % vs 3.8 %	No LP removals; 1 TV removal	—	6 mo	Leadless pacing safer despite baseline differences	7
Libbus 2024 (14)	Early feasibility; N = 13	First-in-human pilot	Subxiphoid novel vs none	7.7 % (1 dislodge-ment) no acute issues	1 case (7.7 %)	0%	None	—	3–6 mo	Early promise; larger trials needed	5

4.2.2 *Complications and re-intervention*

Across the two studies included in the quantitative meta-analysis (10,15), leadless pacemakers, particularly the Micra™ AV system, were consistently associated with lower device-related complication and re-intervention rates compared with DC-TV systems. In El-Chami et al. (10), lead dislodgement was reduced by 83%, device-related infections by 96%, and overall system revisions by 94% in the Micra™ AV cohort. Garweg et al. (15) similarly reported no lead dislodgement or device-related infections in the leadless pacemaker group.

Pooled analysis across these two cohorts demonstrated a numerical reduction in device-related complications with Micra™ AV compared with transvenous pacing, with a pooled hazard ratio of 0.51 (95% CI 0.14–1.84; p = 0.23), corresponding to a 49% relative risk reduction, although statistical significance was not reached (Figure 2).

4.2.3 *Mortality outcomes*

Both studies included in the quantitative meta-analysis reported higher all-cause mortality in the leadless pacemaker cohorts compared with transvenous pacemaker recipients (10,15). El-Chami et al. (10) reported all-cause mortality of 34.0% at 24 months in the Micra™ AV group compared with 23.8% in the DC-TV group. Garweg et al. (15) reported mortality rates of 9.9% at 12 months and 16.1% at 18 months in the leadless pacemaker cohort. In both studies, these differences were attributed to baseline comorbidities rather than to device-related causes.

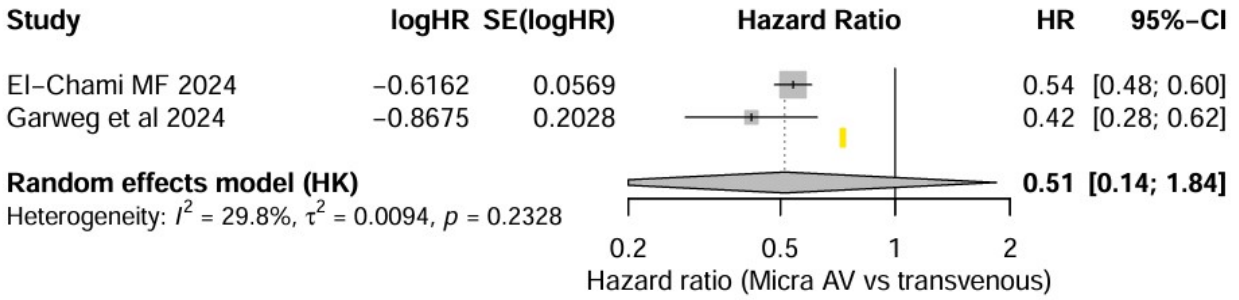

Figure 2. Forest plot of the association between complication rate and pacemaker

4.3 Results of studies included in the descriptive systematic review

4.3.1 *Study characteristics*

Two additional studies met inclusion criteria for the systematic review but were not eligible for quantitative meta-analysis due to the absence of hazard ratios, confidence intervals, or standardized denominators (11,14). Yu et al. (11) was a single-centre comparative observational study with six months of follow-up, while Libbus et al. (14) was an early-stage, first-in-human feasibility study with a small sample size and short-term follow-up.

4.3.2 *Reported complications and safety signals*

Yu et al. (11) reported lower overall complication and re-intervention rates in leadless pacemaker recipients compared with transvenous systems, with no lead dislodgement events observed in the leadless group during six months of follow-up. Libbus et al. (14) documented one device dislodgement requiring intervention (7.7%) but reported no device-related infections or deaths during short-term follow-up. These findings were derived from descriptive analyses and were not included in pooled statistical estimates.

4.4 TVP comparator results

All four studies in Table 1 were included in the systematic review. However, only El-Chami et al. (10) and Garweg et al. (15) provided compatible hazard Ratios for statistical meta-analysis. The TVP comparator data from the remaining studies are presented qualitatively in Table 2 because they lacked the uniform denominators or confidence intervals required for mathematical pooling. Garweg et al. (15) reported LP all-cause mortality of 9.9% at 12 months and 16.1% at 18 months; TVP-specific major complication and revision rates reported in the manuscript were 8.8% and 5.5% at 12 months, respectively (95% CIs not reported). Garweg et al. reported median AV synchrony for the LP cohort (79.4%, IQR 65.2–86.4); TVP AV synchrony was not numerically reported. El-Chami et al. (10) reported LP all-cause mortality of 34.0% at 24 months; TVP all-cause mortality in that cohort was 23.8% at 24 months (95% CIs not reported). El-Chami et al. reported TVP event counts for pericardial effusion (1 case, 0.06%), cardiac tamponade (6 cases, 0.33%), pacemaker syndrome (7 cases, 0.44%) and ventricular dyssynchrony (1 case, 0.06%). Because denominators and 95% CIs were not consistently reported across studies, we present author-reported counts/percentages and note missing CIs in Table 2.

4.5 Transvenous pacemaker comparator results

All studies included in Table 1 reported transvenous pacemaker comparator outcomes; however, only El-Chami et al. (10) and Garweg et al. (15) provided compatible hazard ratios for statistical pooling. Comparator outcomes from the remaining studies are presented qualitatively due to inconsistent reporting of denominators or confidence intervals.

Garweg et al. (15) reported leadless pacemaker all-cause mortality rates of 9.9% at 12 months and 16.1% at 18 months. Transvenous pacemaker complication and revision rates were reported as 8.8% and 5.5% at 12 months, respectively, without accompanying confidence intervals. Median AV synchrony for the leadless cohort was 79.4% (IQR 65.2–86.4); corresponding transvenous AV synchrony values were not reported.

El-Chami et al. (10) reported all-cause mortality of 34.0% in the leadless pacemaker cohort and 23.8% in the transvenous cohort at 24 months. Reported transvenous event counts included pericardial effusion (0.06%), cardiac tamponade (0.33%), pacemaker syndrome (0.44%), and ventricular dyssynchrony (0.06%). Due to inconsistent reporting, author-reported counts and percentages are summarized in Table 2.

Table 2. Transvenous Pacemaker comparator results from meta-analysis–eligible studies

Study	Outcome	LP Result	TVP Result	Notes
Garweg 2024 (15)	All-cause mortality	9.9% (12 mo); 16.1% (18 mo)	Not reported	CI not reported
Garweg 2024 (15)	Pericardial effusion	1.4% (n=5)	Not reported	—
Garweg 2024 (15)	AV synchrony	79.4% (IQR 65.2–86.4)	Not reported	No TVP AV-sync data
Garweg 2024 (15)	Complication HR	HR 0.25	Reference = TVP	95% CI 0.13–0.47
El-Chami 2024(10)	All-cause mortality	34.0% (24 mo)	23.8% (24 mo)	CI not reported
El-Chami 2024(10)	Pericardial effusion	—	1 case (0.06%)	Raw count
El-Chami 2024(10)	Cardiac tamponade	—	6 cases (0.33%)	Raw count
El-Chami 2024(10)	Pacemaker syndrome	—	7 cases (0.44%)	Surrogate for dyssynchrony
El-Chami 2024(10)	Ventricular dyssynchrony	—	1 case (0.06%)	Raw count
El-Chami 2024(10)	Major complications HR	HR 0.47	Reference = TVP	95% CI 0.36–0.61

4.6 Meta-analysis

Across the two cohorts included in the quantitative meta-analysis, Micra™ AV implantation was associated with a numerical reduction in device-related complications compared with DC-TV pacing, with a pooled hazard ratio of 0.51 (95% CI 0.14–1.84) (10,15). Heterogeneity in follow-up duration and patient characteristics was noted. Leave-one-out sensitivity analysis was not performed because only two studies contributed data, and removal of either study would yield an uninterpretable estimate (16).

4.7 Atrioventricular synchrony with leadless versus transvenous pacemakers

Atrioventricular synchrony was quantitatively reported for Micra™ AV leadless pacemakers; however, none of the included transvenous comparator cohorts reported numerical AV synchrony values, precluding direct pooled comparison. A prior systematic review and

meta-analysis reported a pooled AV synchrony rate of 78.9% in Micra™ AV recipients (17). This was consistent with real-world post-approval registry data demonstrating sustained AV synchrony performance at 12 months (15). Although comparative studies reported similar clinical outcomes between leadless and transvenous systems, the absence of quantitative AV synchrony data for transvenous pacemakers limits direct numerical comparison (10,11).

5. Discussion

This systematic review indicates that leadless pacemakers (LPs), particularly the Micra™ AV system, are associated with lower rates of device-related complications and procedural re-interventions compared with conventional transvenous pacemakers (TVPs). In studies reporting formal statistical comparisons, LPs showed statistically significant reductions in infection ($p < 0.05$) (10,15), lead dislodgement, and device-related pain. These benefits are plausibly attributable to the self-contained design of LPs and the absence of transvenous leads, which eliminates several common sources of lead-related complications. These design advantages have been linked to lower periprocedural risk and shorter hospital stays in real-world cohorts (8). In real-world registry data, 796 Micra™ AV recipients (mean age 74 years) compared with 2,667 historical dual-chamber TVP controls demonstrated 12-month major complication rates of 3.7% versus 8.8% (hazard ratio 0.42) and system revision rates of 1.5% versus 5.5% (hazard ratio 0.25), supporting a favorable safety profile for Micra™ AV in older, comorbid populations.

Our meta-analysis showed a numerical reduction in device-related complications with Micra™ AV implantation compared with transvenous dual-chamber pacing (HR 0.51, 95% CI 0.14–1.84; $p = 0.23$). These findings are directionally consistent with those of Piccini et al. (2024), who reported reductions in major complications in a matched cohort analysis of Micra™ versus transvenous systems (18). In addition, recent meta-analyses report similar safety trends; however, the meta-analyses by Ngo et al. (19) and Wu et al. (17) represented for contextual comparison only and were not included in our pooled hazard Ratio calculation to avoid double-counting patient data. Ngo et al. (19) reported that Micra™ recipients experienced a 51% reduction in major complications compared with transvenous systems (OR 0.49; 95% CI 0.34–0.70) across a pooled population exceeding 4,000 patients. Wu et al. (17) estimated pooled atrioventricular synchrony of 78.9% across eight Micra™ AV studies, with variability related to programming and optimization strategies.Real-world registry data align with these trends, with El-Chami et al. (10) documenting stable AV synchrony and major complication rates below 4% at 12 months. Although historical literature suggests atrioventricular synchrony rates of approximately 82–85% with transvenous systems, the studies included in this review did not report numerical TVP synchrony values, precluding direct quantitative comparison. However, long-term outcomes beyond two years remain sparsely reported, limiting assessment of durability and sustained performance.

A statistically non-significant increase in all-cause mortality observed in some LP cohorts, including those reported by El-Chami et al. (10), appeared to be associated with baseline patient characteristics such as renal disease and frailty rather than device-related causes (8). This

observation underscores the importance of careful patient selection and individualized risk stratification to optimize outcomes. Accordingly, large-scale, multicenter randomized controlled trials with extended follow-up are essential to validate long-term efficacy, device durability, cost-effectiveness, and generalizability across diverse patient populations. Registry-based real-world data should continue to complement randomized trials and inform evidence-based pacing strategies for symptomatic bradycardia (20).

5.1 Potential influence of LPs on atrial arrhythmogenesis

Leadless pacemakers (LPs), particularly single-chamber ventricular devices such as the Micra™ VR, lack direct atrial sensing and pacing, which may contribute to atrioventricular (AV) desynchrony and altered atrial hemodynamics that have been associated with atrial arrhythmias (21). A propensity-matched study found that patients with VVI-mode LPs had higher heart failure hospitalization rates than those with dual-chamber transvenous pacemakers, suggesting that absent coordinated atrial activity may contribute to maladaptive electrical and structural remodeling, key factors in atrial arrhythmogenesis (22). Newer devices such as the Micra™ AV are designed to restore AV synchrony through accelerometer-based atrial sensing; however, registry data demonstrate variable success, suggesting that some degree of atrial desynchronization may persist in certain patients (23). Additionally, in patients undergoing atrioventricular node ablation, leadless ventricular pacing effectively controls ventricular rate but does not address ongoing atrial electrical instability, which may persist in the absence of atrial pacing (24).

5.2 Critical gaps and future research directions

Despite encouraging safety and procedural outcomes, the current evidence base is derived predominantly from short-term observational studies, limiting insight into long-term results such as AV synchrony durability, retrieval feasibility, and the evolution of pacing thresholds over time (19). Although the Micra™ AV post-approval registry demonstrates acceptable short-term atrioventricular synchrony, with median values of approximately 79.4%, these estimates may change over time as right ventricular remodeling and fibrosis evolve (15). Economic evaluations remain largely confined to high-income health-care settings, limiting generalizability across systems with differing reimbursement structures, procedural volumes, and resource availability (25,26). Accordingly, there is a need for cost-effectiveness analyses in lower- and middle-income populations, particularly among older adults and patients with complex comorbid conditions (27). Anatomical and structural consequences also warrant further clarification, as emerging data suggest subtle but potentially progressive effects on tricuspid valve function and right-heart geometry following leadless pacemaker implantation, even in the absence of overt mechanical interference, possibly mediated by chronic device–tissue interaction (15,28).Taken together, these limitations underscore persistent uncertainties regarding device durability, economic impact, and cardiac remodeling that cannot be fully addressed within current follow-up horizons.

Accordingly, future research should prioritize multicenter randomized controlled trials directly comparing AV-synchronous LPs (e.g., Micra™ AV) with dual-chamber TVPs across diverse

patient populations—including those with heart failure, renal impairment, and conduction disorders—with follow-up extending beyond three years and standardized assessment of clinical outcomes, cost-effectiveness, quality of life, and cardiac remodeling (15,19,25,27). In parallel, technological evaluations are needed; preliminary data on dual-chamber and biventricular leadless pacing suggest feasibility but require rigorous longitudinal testing to establish reliability, battery consumption, and retrieval safety, as well as the development of fully retrievable systems capable of atrioventricular or resynchronization therapy (29,30). The role of LPs in atrial arrhythmogenesis remains under-investigated, with preliminary signals suggesting that atrial fibrillation incidence may differ from transvenous pacing, although comparative evidence remains limited (31). Prospective priorities include harmonized programming and optimization protocols, prespecified imaging of right-sided cardiac structure and valvular function, and incorporation of health-economic outcomes across varied care settings to inform contemporary pacing algorithms.

5.3 Proposed clinical trial

As described earlier, despite multivariable adjustment, the observed mortality differences between LPs and TVPs are likely influenced by residual confounding, since leadless pacemakers are preferentially implanted in older, more comorbid, and frailer patients—factors that are incompletely captured in administrative and registry datasets. Therefore, a Bayesian adaptive, randomized, controlled trial comparing AV-synchronous leadless pacing vs dual-chamber transvenous pacing, with pre-specified response-adaptive randomization and sample-size re-estimation could be conducted. An adaptive design is preferred because true clinical equipoise exists, heterogeneous treatment effects (such as age, frailty, CKD, pacing burden) are expected. There is a strong rationale for subgroup learning and because AV synchrony and valve effects evolve over time, endpoints are event driven. Such a study design would enable stronger causal inference than observational studies while preserving trial integrity.

The sample size can be estimated based on TVP and LP complication rates of 9% and 4.5% respectively. Assuming a statistical power of 80% and a one-sided $\alpha = 0.025$, the required sample size is calculated as 1400 patients (700 per arm). Recruitment of 1540 patients is targeted assuming an attrition rate of 10%. A Bayesian posterior probability framework prevents α inflation. Posterior probability thresholds could be set at $P(HR < 1.30) \geq 95\%$ for noninferiority and $P(HR < 1.00) \geq 97.5\%$ for superiority (exploratory). Missing data would be handled via joint modeling. Interim analyses can be performed at 500, 800 and 1200 patients. The adaptive rules will allow early stopping for noninferiority, expansion if event rates are lower than expected and stopping for futility if noninferiority probability is < 20%. To decouple device safety from patient risk, the primary estimand could be device-related major complications at 24 months. Secondary estimands could include all cause mortality (descriptive), AV synchrony durability and Tricuspid regurgitation progression. Pre-specified locked adaptation rules, blinded endpoint adjudication, DSMB oversight and no allowable outcome-driven protocol changes can safeguard against bias.

Initial burn-in would be the first 250 patients

randomized 1:1. Thereafter, randomization probabilities would be updated every 100 patients. The arm with the lower posterior probability of major complications would be favored. Randomization could be capped at 40-60% per arm to prevent imbalance and to preserve interpretability. If interim data show a clear benefit in ≥2 prespecified subgroups, then enrollment may be restricted to those subgroups with DSMB approval. An example of a trial with four subgroups could be age >80, CKD (eGFR <45), baseline HF and ventricular pacing burden > 80%. These particular sub-groups are confounder-heavy and repeatedly implicated in observational bias. No subgroup-specific claims of efficacy are permitted, thereby minimizing the risk of multiplicity-driven false-positive findings.

Overall, this adaptive randomized design would directly address residual confounding while reducing patient exposure to inferior strategies, should any emerge, making it particularly attractive for frail and high-risk populations.

6. Limitations

While this review provides clinically relevant insights, several important limitations should be acknowledged. The reliance on PubMed as the sole database and the use of article-type filters, including "clinical trial," may have resulted in the exclusion of relevant studies indexed differently or published outside this database. Additionally, the small number of high-quality, meta-analysis–eligible studies limited the scope of quantitative synthesis, and the relative paucity of long-term outcome data restricts conclusions regarding the sustained efficacy of leadless pacemakers. Assessment of publication bias using funnel plots, Egger's tests, or leave-one-out sensitivity analyses was not performed because the small number of included studies (n < 10) renders such methods statistically unreliable and potentially misleading (32). Furthermore, the long-term durability of leadless pacemaker systems remains incompletely characterized. Most notably, the predominance of observational study designs, the absence of randomized controlled trials, and relatively short follow-up durations limit the ability to robustly assess longitudinal outcomes such as battery longevity (33), cost-effectiveness, and device-related structural or valvular changes.

In addition, patients receiving leadless pacemakers in the included studies were often older and had a higher burden of comorbid conditions than transvenous pacemaker recipients, introducing residual confounding and limiting causal inference despite statistical adjustment.Heterogeneity in comparator transvenous pacemaker systems, outcome definitions, and reporting standards across studies further limits direct quantitative comparison and contributes to between-study variability. Finally, most included studies were conducted in high-income health-care systems with established leadless pacing expertise, potentially limiting the generalizability of findings to lower-resource settings or centers with limited procedural experience.

7. Conclusion

The findings of this review indicate that leadless pacemakers, particularly atrioventricular synchronous systems such as Micra™ AV, represent a promising alternative to transvenous pacemakers in carefully selected patients. Their lead- and pocket-free design, together with the potential for atrioventricular synchrony, makes them particularly suitable for patients with

venous access limitations or a history of device-related infection (15). However, clinical decision-making should continue to account for individual rhythm characteristics, cardiac anatomy, and the anticipated need for sustained dual-chamber pacing. In addition, long-term monitoring of valvular integrity and arrhythmic risk remains essential in recipients of leadless pacemakers (15). Future fully retrievable, dual-chamber leadless systems may further expand clinical indications and potentially influence future standards of care.

Leadless pacemakers, with the Micra™ AV system as the most extensively studied platform, have demonstrated lower rates of device-related complications and re-interventions compared with traditional transvenous pacemakers in observational studies (11). While short- to mid-term safety outcomes appear favorable, long-term durability, cost-effectiveness, and generalizability across diverse patient populations remain under investigation. Notably, five-year post-approval registry data for the Micra™ system reported a sustained reduction in major complications and no infection-related device removals (12). Accordingly, multicenter randomized controlled trials with extended follow-up are needed to confirm intermediate to long-term durability, clarify cost-effectiveness, and refine patient selection criteria. To address these gaps, a Bayesian adaptive, randomized, controlled trial comparing atrioventricular-synchronous leadless pacing with dual-chamber transvenous pacing, incorporating prespecified response-adaptive randomization and sample-size re-estimation, is proposed. Data from such trials may help resolve residual confounding that limits causal inference in current observational and descriptive studies. Until such data are available, leadless pacing systems remain a developing but promising alternative that may complement existing pacing strategies in carefully selected patients (34).

8. Conflict of interest

The author declares no conflicts of interest. The author has no financial, professional, or personal relationships with Medtronic or any manufacturer or distributor of Micra™ AV or related leadless pacemaker technologies.

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