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PII: S1547-5271(23)02538-9

DOI: https://doi.org/10.1016/j.hrthm.2023.07.061

Reference: HRTHM 9952

To appear in: *Heart Rhythm*

Received Date: 15 May 2023

Revised Date: 13 July 2023

Accepted Date: 17 July 2023

Please cite this article as: Mitacchione G, Schiavone M, Gasperetti A, Arabia G, Tundo F, Breitenstein A, Montemerlo E, Monaco C, Gulletta S, Palmisano P, Hofer D, Rovaris G, Russo AD, Biffi M, Pisano ECL, Della Bella P, Di Biase L, Chierchia GB, Saguner AM, Tondo C, Curnis A, Forleo GB, Sex differences in leadless pacemaker implantation: a propensity matched analysis from i-LEAPER registry, *Heart Rhythm* (2023), doi: https://doi.org/10.1016/j.hrthm.2023.07.061.

Sex differences in leadless pacemaker implantation: a propensity matched analysis from i-LEAPER registry

Short title: Sex differences in leadless pacemaker

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WORD COUNT: 4932

DISCLOSURES: The authors report no disclosures.

FUNDING: This research did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abstract

Background: The impact of sex in clinical and procedural outcomes in leadless pacemakers (LPMs) patients has not been investigated yet.

Objective: To investigate sex-related differences in patients undergoing LPMs implantation.

Methods: Consecutive patients enrolled in the i-LEAPER registry were analyzed. Comparisons between sexes were performed within the overall cohort and using an adjusted analysis with 1:1 propensity-matching for age and comorbidities. The primary outcome was the comparison of major complication rates; sex-related differences regarding electrical performance and all-cause mortality during follow-up were deemed secondary outcomes.

Results: In the overall population (n=1179 patients; median age 80 years), 64.3% were men. After propensity-matching, 738 patients with no significant baseline differences among groups were identified. During a median follow-up of 25 (interquartile range [IQR] 24-39) months, female sex was not associated with LPM-related major complications (hazard ratio [HR] 2.03, 95% confidence interval [CI] 0.70-5.84, p=0.190) and with all-cause mortality (HR 0.98, 95% CI 0.40-2.42, p=0.960). LPM electrical performance resulting comparable between groups, excepting for a higher pacing impedance in women at implant and during follow-up (24-month: 670 [550-800] vs 616 [530-770] ohms, p=0.014), however remaining within normal limits.

Conclusions: In a real-world setting, we found differences in sex-related referral patterns for LPM implantation with an under-representation of women, although major complication rate, and LPM performances were comparable between sexes. Female patients showed higher impedance values, not showing any impact on the overall device performance. Electrical parameters remained within normal limits in both groups during the entirety of follow-up.

Keywords: leadless pacemaker; sex differences; Micra; CIED; device-related complications.

ClinicalTrial.gov identifier: NCT05528029

Introduction

Leadless pacemakers (LPMs) represent a significant advancement in the treatment of bradyarrhythmia and an attractive alternative to traditional transvenous pacemakers (TV-PMs), particularly for patients at high risk of infection or upper extremity venous occlusion.[1–3] The introduction of a second generation of LPMs, capable of providing atrioventricular (AV) synchrony with VDD pacing, has allowed clinical electrophysiologists to achieve satisfactory outcomes in patients with AV blocks as well.[4,5] In several cardiovascular disorders, sex plays an important role in pathophysiology, clinical presentation, and clinical outcomes. Sex-related differences may represent a challenge in the management of patients with cardiovascular diseases, with females often having a higher likelihood of complications following complex interventional procedures.[6,7] Some sex-related differences may be explained by discrepancies in the electrophysiological structure of the heart or hormonal effects.[8] Additionally, females with cardiovascular diseases are less likely to receive timely interventions and secondary prevention treatments.[9–12] Studies on cardiac implantable electronic devices (CIEDs) have reported sex-specific differences in clinical outcomes after TV-PM implantation, with females having a higher likelihood of complications in TV-pacing procedures[8,13,14]. However, only a few studies have adequately controlled for confounding comorbidities. Currently, limited data are available regarding sex differences in outcomes related to LPMs.[15,16] The aim of the present study is therefore to assess sex-related differences in patients undergoing LPM implantation in real-world clinical practice.

Methods

Registry population

The data for this study were obtained from the International LEAdless PacemakEr Registry (I-LEAPER - ClinicalTrial.gov identifier NCT05528029). This European, multicenter, open-label, independent, retrospective, and physician-initiated observational registry included consecutive patients who received LPM (Micra MC1VR01 or Micra AV MC1AVR1 Transcatheter Pacing System, Medtronic, Inc., Minneapolis, MN, USA) implants at 12 public and private healthcare institutions in three different European countries (Italy, Switzerland, and Belgium). All LPM procedures were carried out by experienced and certified cardiac electrophysiologists. The Micra Transcatheter Pacing System's design, technical specifications, and implantation procedure have been previously described in literature.[2,17,18] This study was conducted in accordance with the principles of the Helsinki Declaration on human research and approved by the local institutional review board.

Study population, follow-up, and outcomes

The aim of the study was to compare the clinical outcomes of two propensity-matched cohort LPM patients, stratified by sex. A 1:1 propensity matching was performed, addressing differences of clinicals characteristics potentially affecting the study outcomes: age, left ventricular ejection fraction (LVEF), coronary artery disease (CAD), chronic kidney disease (CKD) (defined as an estimated glomerular filtration rate-eGFR <60 mL/min/m^2, calculated with the CKD-EPI equation) and coronary artery bypass graft (CABG). **Figure 1** and **Supplementary Table 1** report the pre- and post-propensity matching differences and the inter-cohort bias reduction.

For each patient included in the final study cohort, demographic characteristics, patients' medical history, and LPM implantation procedures characteristics were extracted into a centralized de-identified spreadsheet, clearly defining each research item. Follow-up strategy was left to each center's policy, with most patients being evaluated at discharge, 1 month, 12 months and every 12 months thereafter. Adverse events were derived from electronic medical reports. Procedural

characteristics, electrical parameters (pacing impedance, R-wave sensing, and pacing threshold-PT) were obtained over the entirety of follow-up (during in-clinic device interrogation), as well as data on in-hospital readmissions due to device-related or unrelated causes. Data on overall and cardiovascular mortality were collected as well.

The primary outcomes of our study were the comparison of major complication rates across the two cohorts. Adopting the same criteria of the Micra Investigational Device Exemption study,[2] major complications were defined as system and procedure-related events resulting in death, permanent loss of device function, hospitalization, prolonged hospitalization >48 hours, or system revision. The overall all-cause mortality, the comparison of LPM-related electrical parameters (PT, pacing impedance, and R-wave sensing), across the 2 cohort at implant and during follow-up were deemed secondary outcomes. Additionally, the incidence and predictors of new-onset atrial fibrillation (AF) were investigated.

Statistical analysis

Continuous variables were expressed as mean±standard deviation (SD) or median and interquartile range (IQR) if not normally distributed according to the D'Agostino-Pearson test. Categorical data were expressed as absolute value and proportion. Propensity matching for prespecified variables was performed using the neighbor method without replacement, using common support and a caliper set at 0.005. Post-matching bias reduction was reported (**Figure 1**). The Student *t*-test for independent samples with a confidence interval (CI) of 95% was used for comparison of continuous variables with a normal distribution; otherwise, a nonparametric tests Mann-Whitney-U was used for comparisons. A X^2-test or a Fisher-exact-test was used to test for an association between categorical variables, as appropriate according to frequency distribution. Univariate logistic regression was used to assess the correlation between sex and outcomes; all variables with a p-value <0.1 on univariate analysis were considered for inclusion in a multivariate regression model. Hazard ratio (HR), 95% CI was reported. For all variable with a significance A 2-sided p-value <0.05 was considered significant across the

144 analysis. All statistical analyses were performed using SPSS Statistics version 26.0 (IBM
145 Corporation, Armonk, NY).

Results

Baseline characteristics before and after propensity score matching

From an overall registry population of 1179 patients, LPMs were more likely to be implanted in men (64.3%). A comparison of baseline characteristics for men and women (**Supplementary Table 1**) shows that there were significant differences between the two populations. Particularly, women were older (81 [IQR 74-85] vs 80 [IQR 73-84] years, p=0.017), and more affected by CKD (37.8% vs 20.3%, p<0.001). Coronary artery disease (CAD) (29.0% vs 19.1%, p<0.001) and previous coronary artery bypass graft (CABG) (10.2% vs 4.3%, p<0.001) were more frequent in men.

After 1:1 propensity matching, 369 patients for each group were identified. The two cohorts resulted comparable for age, CKD, CAD, CABG and median LVEF (**Figure 1**). Others baseline characteristics remained statistically balanced among groups (**Table 1**): median age was 80 years [IQR 74-85] (males 80 [IQR 75-85] vs females 80 [IQR 74-85] years, p=0.906), with 88.1% of the entire cohort being older than 65 years. Median BMI was comparable among groups (males=25.0 [23.5-27.7] vs females=24.7 [23-27] kg/m2, p=0.105), with the 11.9% of the entire cohort having a BMI ≥30 kg/m2.

Leadless pacemaker indications before and after propensity score matching

Data regarding baseline indications for LPM implantation have been summarized in **Supplementary Table 2**. Before propensity matching, most patients (52.1%) required a LPM due to AF with slow ventricular rate or intermittent/complete AV block, with no differences among groups. Women were implanted with a LPM due to a sinus node disease (SND) more frequently than men (17.6% vs 13.1%, p=0.039). The reason why a LPM was preferred over a traditional TV-PM was mostly represented by a high infective risk [66.9%; 251 males (68%) vs 243 females (65.9%), p=0.584], and then followed by vascular access concerns [16.5%; 55 males (14.9%) vs 67% females (18.2%), p=0.276], and patient's choice [6.8%; 26 males (7.9%) vs 24 females (6.5%), p=0.884], with no significant differences among groups for every characteristic of interest in this regard.

Procedural characteristics and outcomes

Peri-procedural features have been reported in **Table 2**. No significant differences were detected among groups. Specifically, similar median procedural duration (50 [IQR 40-67] vs 47 [IQR 39-65] mins, p=0.427), fluoroscopy times (6.1 [IQR 4.0-9.0] vs 6.0 [IQR 4.0-9.0] mins, p=0.184) and duration of in-hospital stay (3 [IQR 2-5] vs. 3 [IQR 2-5] days) were found. The overall number of LPM deployments and the location of LPM deployment (proximal septum vs distal septum vs RVOT vs apex) were similar between groups, with most LPMs deployed in the proximal septum (47.4% in the overall cohort). Regarding the primary outcome, after a median of 25 [24-39] months follow-up, major complication rate (men=3% vs. women=1.4%, HR=2.03; 95% CI 0.70-5.84, p=0.190) did not differ between groups. All-cause mortality rates (men=6.8% vs. women=6.8, HR=0.98; 95% CI 0.40-2.42, p=0.960) were balanced across groups as well.

Sex differences in LPM electrical performance

Median R-wave sensing amplitude, PT, and pacing impedance at discharge and during follow-up were reported in **Supplementary Table 3** and **Figure 2**. While PT and right ventricular sensing did not show any significant difference over the entirety of follow-up, pacing impedance resulted lower in women when compared to men from implantation to last follow-up (implantation: men=740 [IQR 640-850] vs women=760 [650-899] ohms, p=0.016; last follow-up 616 [IQR 530-770] vs 670 [550-800 ohms], p=0.014). As shown in **Figure 3**, no specific concerns regarding differences in high PT (HPT) and very high PT (VHPT) patients between groups were found at 24-month follow-up (males=1.8% vs females=0.4%, p=0.220).

Atrial fibrillation during follow-up

As reported in **Supplementary Figure 1,** an overall higher prevalence of AF patients was reported at 24-month follow-up (61.9% vs 54.1%) when compared to baseline, with new-onset AF detected in 33 patients (14.1%) that were in sinus rhythm at baseline (n=23 men and n=10 women). As shown in

198 **Supplementary Table 4**, among all variables associated to new-onset of AF during follow-up, male
199 sex (aHR=2.13, 95% CI 1.01-4.51, p=0.048), the use of Micra-VR (aHR=6.44 95% CI 1.49-27.79,
200 p=0.013), and a pre-existent AV-block (aHR=2.54, 95% CI 1.18-5.48, p=0.017), remained
201 significantly associated at multivariate logistic regression (**Supplementary Figure 2**).

Discussion

To the best of our knowledge, this is the first comprehensive multicenter study that compares the outcomes of LPMs regarding sex stratification across a consistent follow-up period. The study used data from the i-LEAPER registry and analyzed the implant and long-term post-operative safety and performance of LPMs in 738 propensity-matched patients, who were balanced for baseline clinical characteristics. The main findings of our study are as follows:

- Women constituted only 35.7% of the overall registry population, and this percentage was significantly lower than that of men.
- The safety profile of LPMs was similar in both men and women, with no statistically significant differences in terms of major complication rates (males 4.9% vs. females 4.3%, p=0.861) or overall mortality rates.
- The electrical performance of LPMs (pacing threshold and R-wave sensing) was overall comparable between the cohorts, remaining within normal range during the entirety of follow-up. However, women showed higher values of pacing impedance than men, which was noted at implantation and remained consistent throughout the follow-up, although not showing any impact on the overall device performance.

Safety of leadless pacemaker implantation: does sex matter?

In interventional cardiology, sex differences have become increasingly recognized as a factor that may influence outcomes. In our study, women made up 35.7% of the entire cohort, consistent with the Micra post-approval registry[1], where females represented 37.7%. The lower rate of women receiving LPM implantation in these studies may potentially reflect a sex-based bias towards a less complex invasive strategy in females, such as traditional TV-PM implantation. Although the reasons for this finding are not definitive, our report's strength lies in the extensive number of patients enrolled in a real-world registry, which may have at least mitigated some degree of selection bias.

Previous data have shown a higher rate of complications in women during TV-PM implantation, such as pneumothorax, pocket hematomas, and lead perforation, despite the procedure being perceived as simpler.[6,19] This higher risk of complications in women may be partly attributed to their lower BMI, as reported in the Danish pacemaker registry[19], as well as anatomic differences such as smaller vessels and cardiac chambers. A study by Mohamed et al. involving 1,179,742 women undergoing TV-PM and CRT-P implantations showed that the odds of adverse complications in the overall CIED cohort increased persistently in women over the study period[20], with similar odds of all-cause mortality across the sexes observed throughout the follow-up. Conversely, Riesenhuber et al.[21] demonstrated that women had significantly longer 10-year survival than men (HR 0.83, 95% CI 0.70-0.99) following TV-PM implantation, despite a markedly older age at implantation, with male sex as a predictor of increased mortality in long-term follow-up. However, these results were guided by cardiovascular comorbidities that significantly influenced PM implantations and sex differences leading to long-term outcome discrepancies, whose effect was mitigated in our study due to the propensity-matching.

Currently, there is a lack of data on the differences between traditional sex disparities in traditional TV-PMs and LPM implantations. LPMs have consistently demonstrated a remarkable safety profile, with major adverse events not exceeding 2.89% in real-world registries[1,22,23]. Compared to TV-PMs, LPMs have shown a reduction of approximately 63% in major complication rates during a 12-month follow-up (2.7% in Micra vs. 7.6% in TV-PM, HR 0.37; 95% CI 0.27–0.52; $p<0.001$).[23] In our study, we observed that LPMs maintain their safety profile in women, with 2.1% major adverse events associated with LPMs during a median follow-up of 25 [24-39] months, and no significant differences between sexes (3% in men vs. 1.4% in women, HR 2.03; 95% CI 0.70-5.84; $p=0.190$). The commonly perceived belief that LPM implantation may be more challenging in women due to their smaller body size and cardiac and vascular chambers does not seem to be supported by evidence of major complications related to mechanical injury during device implantation, such as

pericardial effusion and cardiac tamponade, which were similar in both groups, after controlling for baseline potentially significant confounders.

Additionally, we found no significant difference in all-cause mortality between men and women during follow-up. A non-randomized direct comparison between LPMs and TV-PMs found that female sex was not predictive of all-cause mortality, with no significant differences in the two cohorts[24]. Those findings are in contrast to what has been published by Riesenhuber et al.[21], who reported that women who received a TV-PM had longer 10-year survival than men. However, our study employed propensity matching to account for differences in cardiovascular risk factors and comorbidities, which may explain the lack of sex difference in mortality. Despite the relatively short follow-up period, our results show that male sex did not predict increased mortality in the mid-term (6.8% in men vs. 6.8% in women, HR=0.98; 95% CI 0.4-2.42, p=0.960), after adjusting for baseline confounders. Therefore, our data support the overall safety profile of LPM, which appears to be equally safe in women as well, a subgroup of patients who are often perceived as more fragile and prone to adverse events related to conventional pacing and complex interventional procedures.

Sex differences in LPM electrical performance

In our study, we found that the LPM's electrical features were generally normal at implantation and during follow-up. Both male and female patients showed similar electrical features, except for pacing impedance, which was slightly higher in female patients. This difference in pacing threshold did not affect the overall electrical performance of LPMs during the study analysis, that confirmed a favorable outcome in terms of pacing threshold and R-wave sensing. The higher pacing impedance in female patients, may be due to the higher pressure applied during LPM delivery in women, as the smaller heart chambers require a more pronounced transversal curvature to achieve a more solid interaction with the endocardial tissue, thereby leading to higher impedance.

Regarding PT, previous studies on LPMs have shown stable electrical performances at implantation and during follow-up, with several predictors associated with elevated PTs.[25,26] Recent

studies have also found that worse LPM electrical performances may occur in patients who underwent TLE when the LPM was implanted in the same cardiac site where the previous transvenous ventricular lead was removed.[22] However, our study did not find male sex to be a predictor of HPT in our cohort, unlike the report from Kiani et al.[15] The cumulative rate of HPT (9.8%) and VHPT (1.1%) after two-year follow-up in our study was consistent with historical data, as reported in other analyses from our group of authors.[1,22,25,26] Our data therefore suggest that LPMs are generally safe and effective in both male and female patients, and the overall electrical performance of LPMs is similar in both sexes.

Indication for a leadless pacemaker in both sexes

Among the indications for LPM implantation, we report that the most common reason was the risk of infection, which was observed by 66.9% of patients, with no significant differences between groups. Additionally, we did not observe any sex differences regarding vascular issues (16.5%), prior transvenous lead extraction (13.8%), or - interestingly - patient choice (6.8%). These findings suggest that female patients undergoing high-risk interventional procedures, such as TLE followed by LPM implantation, are treated similarly to male patients, despite being perceived as a more vulnerable group. It is worth nothing that in our series, women were more likely to receive LPM implants for sinus node disease (SND). This is in line with previous literature indicating that females have a lower incidence of AV block and a higher incidence of SND as the primary indication for pacing, in comparison to males.[6,27] Our results showed that male sex, VVI stimulation, and pre-existing AV block are independently associated with a higher risk of new-onset AF during follow-up, even after accounting for other potential confounders. These findings are consistent with previous literature[28], with VVI pacing mode proven to be a risk factor for AF occurrence in patients requiring atrio-ventricular synchrony (AV-block patients). The underlying reasons for men being more likely to develop AF remain unclear and goes beyond the pacing modality and type, being at least partially

explained by the effects of sex hormones on autonomic tone modification and electrophysiological properties of myocardial cells.[8,28]

Limitations

This study has several limitations. First, this is a non-randomized retrospective study showing inherent drawbacks due to its intrinsic design, such as a certain grade of data underreporting, potentially involving significant clinical outcomes. Second, due the relatively low number of procedural and post-procedural complications, it should be considered that this analysis might be, at least partially, underpowered to detect major complications differences among the two cohorts. However, this represents to date the largest multicenter independent registry, reflecting the real-world LPM current scenario. Third, all the institutions participating at this study are high expertise EP centers for LPM implantation, with all procedures being performed by experienced electrophysiologists, therefore our clinical outcomes may not reflect results achieved by less-experienced operators. Lastly, a direct propensity-matched comparing gender differences between LPM and TV-PM patients was not reported, being beyond the scope of this research protocol.

Conclusion

Despite being underrepresented in our study, females achieved comparable safety and efficacy outcomes to males, regarding LPM-related complications and electrical performance. Electrical parameters remained within normal limits in both groups; higher impedance values in females did not affect overall LPM efficacy. Male sex resulted independently associated to a higher prevalence of post-implantation AF during follow-up. Our finding suggests that LPMs are equally effective and safe in both sexes, despite females have been proven to be more likely to develop adverse events related to TV-PMs implantation and to complex invasive procedures. LPMs should be offered to female patients, whenever clinically appropriate, as to their male counterpart.

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Tables

Table 1. Baseline characteristics of the overall propensity-matched population and according to sex stratification. *BMI= body mass index; CAD=coronary artery disease; CABG=coronary artery bypass graft; LVEF=left ventricle ejection fraction; TLE=transvenous lead extraction; CIED=cardiac implantable electronic device.*

	Overall Matched N=738	**Men N=369**	**Women N=369**	***p-value***
Age (years), median [IQR]	80[74-85]	80[75-85]	80[74-85]	*0.906*
Older (years > 65 years), N (%)	650(88.1)	327(88.6)	323(87.5)	*0.733*
BMI (Kg/m^2)	25.0[23.1-27-5]	25.0[23.5-27.7]	24.7[23.0-27.0]	*0.105*
Obesity, (BMI ≥30 kg/m^2) N (%)	88(11.9%)	51(13.8)	37(10.0)	*0.139*
Diabetes, N (%)	176(23.8)	86(23.3)	90(24.4)	*0.796*
Hypertension, N (%)	435(58.9)	229(62.1)	206(55.8)	*0.100*
Chronic Kidney disease, N (%)	234(31.7)	121(32.8)	113(30.6)	*0.580*
CAD, N (%)	149(20.2)	76(20.6)	73(19.8)	*0.855*
Valvular disease, N (%)	192(26.1)	86(23.4)	106(28.7)	*0.111*
Cardiac surgery, N (%)	101(13.7)	52(14.2)	49(13.3)	*0.749*
CABG, N (%)	35(4.7)	19(5.1)	16(4.3)	*0.730*
LVEF (%), median [IQR]	56.0[53.0-60.0]	56.0[53.0-60.0]	55.0[53.0-60.0]	*0.870*
Previous TLE for CIED infection	165(14.0)	115 (15.2)	50(11.9)	0.136

Table 2. Leadless pacemaker implant features and outcomes in the overall propensity-matched population and according to sex stratification. *IQR=interquartile; LPM=leadless pacemaker; RVOT=right ventricle outflow tract.*

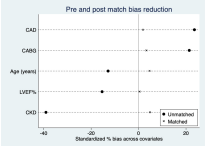
	Overall Matched N=738	**Men N=369**	**Women N=369**	***P-value***
Duration of procedure, min (median-IQR)	50(40-65)	50(40-67)	47(39-65)	0.427
Radiological time, min (median-IQR)	6.1(4-9)	6.1(4-9)	6.0(4-9)	0.184
In-hospital stay, days (median-IQR)	3(2-5)	3(2-5)	3(2-5)	0.713
Deployments, N(%)				
1	633(85.8)	319(86.4)	314(85.1)	0.674
2	86(11.7)	36(9.8)	50(13.6)	0.135
3	11(1.5)	9(2.4)	2(0.5)	0.063
≥4	8(1.1)	5(1.4)	3(0.8)	0.725
LPM final positioning, N(%)				
Proximal septum	349(47.4)	165(44.7)	184(50.1)	0.161
Distal septum	316(43.1)	169(46.2)	174(39.9)	0.101
RVOT	17(2.3)	8(2.2)	9(2.5)	0.811
Apex	58(8.0)	27(7.4)	31(8.6)	0.586
LPM related complications, N(%)	34(4.6)	18(4.9)	16(4.3)	0.861
Pericardial effusion	*4(0.5)*	*2(0.5)*	*2(0.5)*	*1.0*
Cardiac tamponade	*2(0.3)*	*1(0.3)*	*1(0.3)*	*1.0*
LPM dislodgement/embolization	*2(0.3)*	*2(0.5)*	*0*	*0.499*
Battery premature depletion	*2(0.3)*	*2(0.5)*	*0*	*0.499*
Peri-procedure stroke	*1(0.1)*	*0*	*1(0.3)*	*1.0*
Femoral artery injury	*9(1.2)*	*4(1.1)*	*5(1.4)*	*1.0*
Groin hematoma	*13(1.8)*	*6(1.6)*	*7(1.9)*	*1.0*
Systemic/LPM infection	*1(0.1)*	*1(0.3)*	*0*	*1.0*
Major complications, N(%)	16(2.2)	11(3.0)	5(1.4)	0.205
Minor complications, N(%)	18(2.4)	7(1.9)	11(3.0)	0.475
Intraprocedural, N(%)	16(2.2)	8(1.9)	8(2.2)	1.0
Early post-procedure, N(%)	16(2.2)	8(1.9)	8(1.9)	1.0
Late post-procedure, N(%)	2(0.3)	2(0.5)	0	0.499
All cause of death, N(%)	50(6.7)	25(6.8)	25(6.8)	1.0

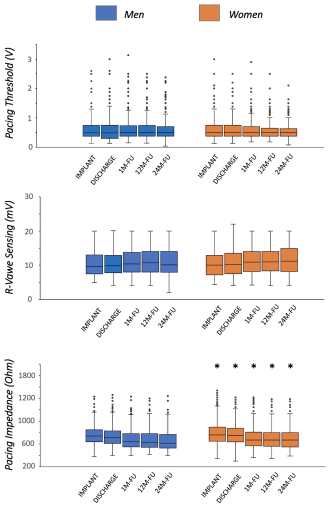
Figure legend:

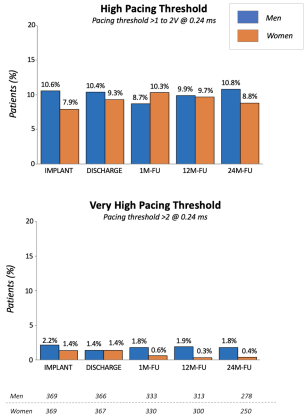
Figure 1. Propensity matching bias reduction of baseline characteristics according to sex stratification. *CAD=coronary artery disease; CABG=coronary bypass graft; LVEF=left ventricular ejection fraction; CKD= chronic kidney disease.*

Figure 2. Comparison of leadless pacemaker electrical performance at different time points between men and women. *1M-follow-up=1-month follow-up; 12M-follow-up=12-month follow-up; 24M-follow-up=24-month follow-up.* ***** *p<0.05 vs. same time-point of "Men" group*

Figure 3. Comparison of leadless pacemakers with high pacing threshold (>1 to 2V@0.24ms) and very high pacing threshold (>2V@0.24cm) at different time points between men and women.







Men	369	366	333	313	278
Women	369	367	330	300	250

Supplementary Table 1. Baseline characteristics of the study cohort according to sex stratification before and after propensity matching.

BMI=body mass index; CAD=coronary artery disease; CABG=coronary artery bypass graft; LVEF=left ventricle ejection fraction; TLE=transvenous lead extraction; CIED=cardiac implantable electronic device.

	Unmatched				*Matched*			
	Overall N=1179	**Men N=758**	**Women N=421**	***p-value***	**Overall N=738**	**Men N=369**	**Women N=369**	***p-value***
Age (years), median [IQR]	80 [74-85]	80 [73-84]	81 [74-85]	**0.017**	80 [74-85]	80 [75-85]	80 [74-85]	0.906
Older (years > 65 years), N (%)	1017 (86.2)	646 (85.2)	371 (88.1)	0.186	650 (88.1)	327 (88.6)	323 (87.5)	0.733
BMI (Kg/m^2)	25.0 [23.0-27.4]	25.0 [23.0-27.7]	24.6 [23.0-27]	0.095	25.0 [23.1-27-5]	25.0 [23.5-27.7]	24.7 [23.0-27.0]	0.105
Obesity, (BMI ≥30 kg/m^2) N (%)	124 (10.5)	84 (11.1)	40 (9.5)	0.429	88 (11.9%)	51 (13.8)	37 (10.0)	0.139
Diabetes, N (%)	280 (23.8)	178 (23.5)	102 (24.2)	0.775	176 (23.8)	86 (23.3)	90 (24.4)	0.796
Hypertension, N (%)	668 (56.7)	425 (56.2)	243 (57.9)	0.623	435 (58.9)	229 (62.1)	206 (55.8)	0.100
Chronic Kidney disease, N (%)	313 (26.5)	154 (20.3)	159 (37.8)	**< .001**	234 (31.7)	121 (32.8)	113 (30.6)	0.580
CAD, N (%)	298 (25.4)	218 (29)	80 (19.1)	**< .001**	149 (20.2)	76 (20.6)	73 (19.8)	0.855
Valvular disease, N (%)	288 (24.4)	174 (23.0)	114 (27.1)	0.119	192 (26.1)	86 (23.4)	106 (28.7)	0.111
Cardiac surgery, N (%)	169 (14.4)	116 (15.3)	53 (12.6)	0.225	101 (13.7)	52 (14.2)	49 (13.3)	0.749
CABG, N (%)	84 (7.1)	68 (9.0)	16 (3.8)	**< .001**	35 (4.7)	19 (5.1)	16 (4.3)	0.730
LVEF (%), median [IQR]	56.0 [51.0-60.0]	56.0 [50.3-60.0]	56.0 [53.0-61.0]	**0.046**	56.0 [53.0-60.0]	56.0 [53.0-60.0]	55.0 [53.0-60.0]	0.870
Previous TLE for CIED infection, N (%)	165 (14.0)	115 (15.2)	50 (11.9)	0.136	102 (13.8)	56 (15.2)	46 (12.5)	0.337

Supplementary Table 2. Indication for leadless pacemaker implantation the study cohort according to sex stratification before and after propensity matching. *AF=atrial fibrillation; AV=atrioventricular; SND=sinus node disease; LPM=leadless pacemaker.*

	Unmatched				*Matched*			
	Overall N=1179	**Men N=758**	**Women N=421**	***p-value***	**Overall Matched N=738**	**Men N=369**	**Women N=369**	***p-value***
Micra AV, N (%)	108 (9.1)	73 (9.6)	35 (8.3)	0.057	75 (10.2)	43 (11.7)	32 (8.7)	*0.223*
Pacemaker indication, N (%)								
AF with slow ventricular rate or intermittent/complete AV block	614 (52.1)	399 (52.6)	215 (51.1)	0.627	386 (52.3)	200 (54.2)	186 (50.4)	*0.302*
Sinus rhythm with intermittent/complete AV block	322 (27.3)	212 (28.0)	110 (26.1)	0.539	201 (27.2)	103 (27.9)	98 (26.6)	*0.741*
SND	173 (14.7)	99 (13.1)	74 (17.6)	**0.039**	108 (14.6)	43 (11.7)	65 (17.6)	***0.022***
Cardioinibitory Syncope	33 (2.8)	23 (3.0)	10 (2.4)	0.584	19 (2.6)	11 (3.0)	8 (2.2)	*0.486*
Ablate and pace	22 (1.9)	15 (2.0)	7 (1.7)	0.824	13 (1.8)	6 (1.6)	7 (1.9)	*0.780*
Other	15 (1.3)	10 (1.3)	5 (1.2)	1.0	11 (1.6)	6 (1.6)	5 (1.4)	*0.761*
LPM indication, N (%)								
Infective risk	786 (66.7)	514 (67.8)	149 (64.6)	0.273	494 (66.9)	251 (68)	243 (65.9)	*0.584*
Vascular access	184 (15.6)	107 (14.1)	77 (18.3)	0.065	122 (16.5)	55 (14.9)	67 (18.2)	*0.276*
Patient choice	95 (8.1)	71 (9.4)	24 (5.7)	**0.026**	50 (6.8)	26 (7.9)	24 (6.5)	*0.884*
Other	114 (9.7)	66 (8.7)	48 (11.4)	0.150	72 (9.8)	37 (10.0)	35 (9.5)	*0.901*

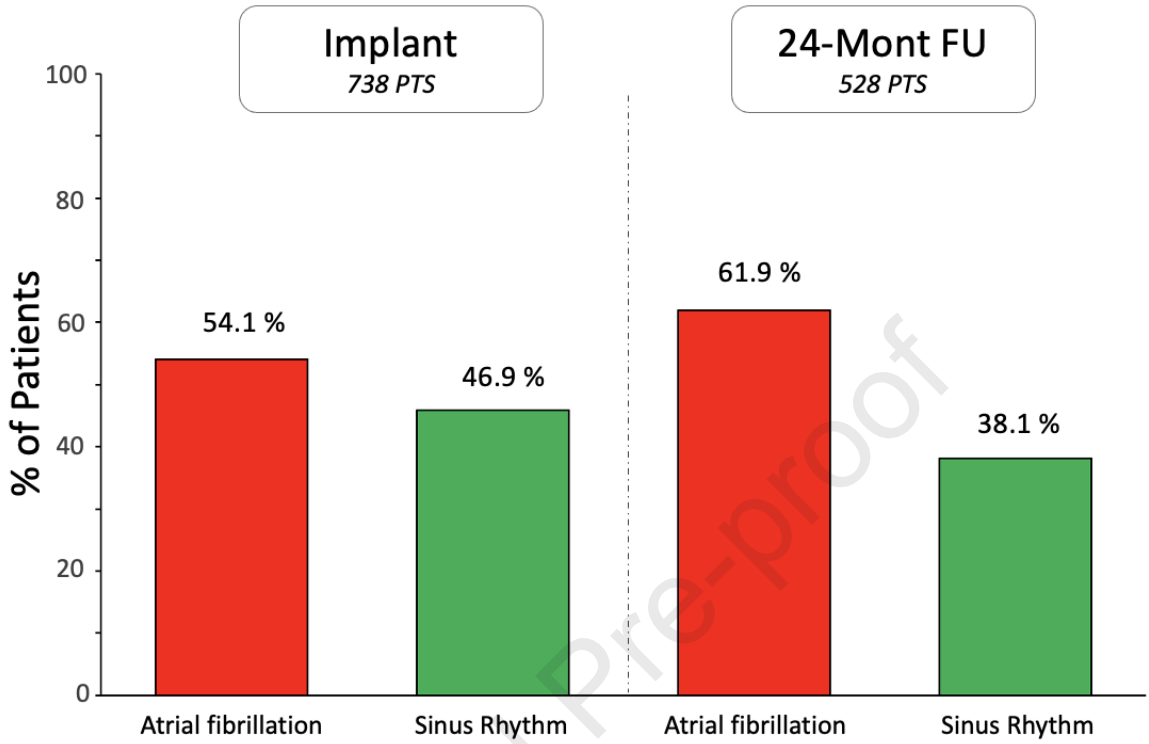
Supplement table 3 Comparison of leadless pacemaker electrical performance at different time points between men and women. *FU=follow-up*

Timepoint	Men	Women	*P-value*
	Pacing Threshold, V/0.24, median [IQR]		
Implant	0.50 [0.38-0.75]	0.50 [0.38-0.75]	*0.868*
Discharge	0.49 [0.30-0.75]	0.50 [0.38-0.75]	*0.257*
1-Month FU	0.50 [0.38-0.72]	0.50 [0.38-0.7]	*0.926*
12-Month FU	0.50 [0.38-0.74]	0.50 [0.38-0.64]	*0.658*
24-Month FU	0.50 [0.38-0.70]	0.50 [0.38-0.63]	*0.184*
	Sensing, mV, median [IQR]		
Implant	9.5 [7.5-12.9]	10 [7.2-12.8]	*0.345*
Discharge	9.8 [7.8-12.8]	10.2 [7.5-13.4]	*0.303*
1-Month FU	10.4 [8.0-13.7]	10.9 [8.1-14.0]	*0.490*
12-Month FU	10.7 [8.0-13.9]	11.0 [8.3-14.0]	*0.474*
24-Month FU	10.6 [8.0-14.0]	11.4 [8.2-15.2]	*0.116*
	Impedance, Ohm, median [IQR]		
Implant	740 [640-850]	760 [650-899]	***0.016***
Discharge	710 [610-825]	750 [645-880]	***0.034***
1-Month FU	645 [550-780]	670 [570-810]	***0.045***
12-Month FU	630 [540-780]	670 [560-800]	***0.024***
24-Month FU	616 [530-770]	670 [550-800]	***0.014***
	Pacing threshold >1 to 2V/0.24ms, N. (%)		
Implant	39 (10.6)	29 (7.9)	*0.252*
Discharge	38 (10.4)	34 (9.3)	*0.622*
1-Month FU	29 (8.7)	34 (10.3)	*0.510*
12-Month FU	31 (9.9)	29 (9.7)	*1.0*
24-Month FU	30 (10.8)	22 (8.8)	*0.468*
	Pacing threshold >2V/0.24ms, N. (%)		
Implant	8 (2.2)	5 (1.4)	*0.578*
Discharge	5 (1.4)	5 (1.4)	*1.0*
1-Month FU	6 (1.8)	2 (0.6)	*0.286*
12-Month FU	6 (1.9)	1 (0.3)	*0.123*
24-Month FU	5 (1.8)	1 (0.4)	*0.220*

Supplementary Table 4. Univariate and multivariate Cox regression analysis for new-onset atrial fibrillation at 24-month follow-up according to baseline characteristics. *24M-FU=24-mont follow-up; AF=atrial fibrillation; HR=hazard ratio; aHR=adjusted hazard ratio; CI=confidence interval; CKD=chronic kidney disease; CAD=coronary artery disease; CABG=coronary artery bypass graft; AV=atrioventricular; SND= sinus node disease*

Variables	Sinus rhythm at 24M-FU N=201	New-onset AF at 24M-FU N=33	**Univariate**			**Multivariate**		
			HR	95% CI	P	aHR	95% CI	P
Male, N (%)	101 (50.2)	23 (69.7)	1.98	0.94-4.15	**0.072**	2.13	1.01-4.51	**0.048**
Micra-VR, N (%)	157 (78.1)	31 (93.9)	3.73	0.89-15.59	**0.072**	6.44	1.49-27.79	**0.013**
Age>65 years, N (%)	150 (74.6)	25 (75.8)	1.13	0.51-2.52	0.759	-	-	-
Obesity, N (%)	34 (16.9)	2 (6.1)	0.38	0.09-1.60	0.189	-	-	-
CKD, N (%)	57 (28.4)	9 (27.3)	1.35	0.63-2.92	0.442	-	-	-
Hypertension, N (%)	102 (50.7)	21 (63.6)	1.65	0.81-3.35	0.166	-	-	-
Diabete, N (%)	43 (21.4)	4 (12.1)	0.64	0.23-1.84	0.411	-	-	-
CAD, N (%)	36 (17.9)	7 (21.2)	1.25	0.54-2.87	0.605	-	-	-
CABG, N (%)	8 (4.0)	3 (9.1)	2.92	0.89-9.65	**0.078**	2.47	0.74-8.22	0.139
Valvular disease, N (%)	39 (19.5)	4 (12.1)	0.57	0.20-1.63	0.294	-	-	-
Cardiac Surgery, N (%)	27 (13.6)	5 (15.2)	1.33	0.51-3.47	0.554	-	-	-
AV-block, N (%)	114 (56.7)	23 (69.7)	1.90	0.90-4.01	**0.092**	2.54	1.18-5.48	0.017
SND, N (%)	69 (34.3)	9 (27.3)	0.61	0.28-1.32	0.209	-	-	-
Sincope, N (%)	12 (6.0)	1 (3.0)	0.75	0.10-5.53	0.780	-	-	-
Other rhythm disorder, N (%)	6 (3.0)	0 (0)	0.00	0.00-Inf	0.997	-	-	-

Supplementary figure 1. Atrial Fibrillation and sinus rhythm patients at implant and comparison with 24-month follow-up in the matched population. *PTS=patients; FU=follow-up*



Supplementary figure 2. Forest plot of multivariate logistic regression model of new-onset atrial fibrillation at 24-mont follow-up according to variable significatively associated at univariate analysis. *AF=atrial fibrillation; CI=confidence interval; aHR=adjusted hazard ratio; CABG=coronary artery bypass graft; AV=atrioventricular*