Clinical outcome for heart failure hospitalizations in patients with leadless pacemaker

Tomonori Katsuki MD | Michio Nagashima MD | Hiroyuki Kono MD | Yohei Sadohara MD | Jun Hirokami MD | Rei Kuji MD | Kengo Korai MD | Masato Fukunaga MD | Kenichi Hiroshima MD | Kenji Ando MD

Department of Cardiology, Kokura Memorial Hospital, Kitakyushu, Japan

Correspondence
Tomonori Katsuki, MD, Department of Cardiology, Kokura Memorial Hospital, Kitakyushu, Japan.
Email: t.k.moon12@gmail.com

Abstract
Introduction: The long-term performance of leadless pacemaker (LPM) has not been well evaluated.

Methods: Between September 2017 and January 2021, 929 consecutive patients who underwent pacemaker implantation were grouped according to the types of pacemakers: LPM (LPM group, n = 368) and conventional pacemaker (PM group, n = 561).

Results: The median follow-up duration was 1.7 years (interquartile range 0.8–2.6 years). Hospitalization rate for heart failure in the LPM group was 9.3%, 15.6%, and 21.6% at 1, 2, 3 years, respectively. The LPM group had a significantly higher adjusted heart failure hospitalization risk than the PM group [hazard ratio (HR) 1.70, 95% confidence interval (CI) 1.09–2.64, \( p = .01 \)]. More patients with symptomatic bradycardia caused by sinus node dysfunction (SND) in the LPM group (n = 150) were admitted to the hospital for heart failure compared to those in the PM group (n = 219) (HR 2.02, 95%CI 1.04–3.90, \( p = .03 \)), whereas no significant difference was observed between the two groups in the patients with bradycardia caused by atrial fibrillation (LPM group, n = 71; PM group, n = 18) or atrioventricular block (LPM group, n = 147; PM group, n = 324).

Conclusions: Patients who received LPM implantation had greater hospitalization risk for heart failure, compared to those who received conventional pacemaker implantation. The increased risk was mainly attributed to patients with SND.

KEYWORDS
heart failure hospitalization, leadless pacemaker

1 INTRODUCTION

Leadless pacemakers (LPMs) have been associated with lower risk of complications such as infections, pneumothorax, and skin erosion,\(^1\)-\(^3\) and they have been considered as a good option for elderly patients.\(^4\) Ventricular pacing has been shown to induce ventricular desynchronization, which can cause heart failure.\(^5\)-\(^7\) A recent study reported LPM therapy was associated with increased tricuspid valve dysfunction.\(^8\) Although the results suggested an increased risk of heart failure, the incidence of heart failure in patients with LPM has
not been well evaluated. Therefore, the present study aimed to investigate the association between hospitalization due to heart failure and LPM implantation.

2 | METHODS

2.1 | Study population

This single-center, retrospective, and observational study was conducted between September 2017 and January 2021, and it included 929 consecutive patients who underwent pacemaker implantation at Kokura Memorial Hospital, Kitakyushu, Japan. Among the identified patients, 368 underwent LPM implantation (Micra VR™, Medtronic, Inc, Minneapolis, Minnesota). In accordance with the Japanese guideline focused update,5 LPM implantation was performed when venous access should be preserved or when venous occlusion or stenosis was identified. Furthermore, for patients with sinus node dysfunction (SND) and atrioventricular block (AVB), LPM implantation was considered when it was thought to be more beneficial outperforming the limitations of VVI therapy, whereas the indication for hospitalization due to heart failure and bradycardic atrial fibrillation (AF). Cumulative incidences of clinical outcomes were estimated using Kaplan–Meier curves. Crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CI) were calculated using univariate and multivariable Cox regression models. The following clinically relevant explanatory variables were included in the multivariable models to adjust for baseline characteristics: age, sex, body mass index, diabetes, hypertension, dyslipidemia, history of hospitalization for heart failure, left ventricular ejection fraction. All analyses were performed using the JMP statistical software (version 14.2.0; SAS Institute, Cary, NC, USA), with two-sided p < .05 indicating statistical significance.

3 | RESULTS

3.1 | Baseline characteristics

Patient characteristics are summarized in Table 1. The mean age of the study population was 80.1 ± 9.4 years (range: 31–101 years) and 49% were male. Majority of patients had preserved left ventricular ejection fraction (61.1% ± 9.8%), and 67% of the patients were categorized as class I, based on New York Heart Association (NYHA) functional classification. Meanwhile, one-fifth of patients had a history of hospitalization for heart failure. Pacing indications included SND (40%), AVB (50%), and bradycardic AF (10%).

Patients were divided into two groups according to the types of implanted pacemakers: the LPM group, which included 368 patients (40%), and the PM group, which included 561 patients (60%). Compared to the PM group, the LPM group were older and had lesser incidence rates of AVB but had higher incidence rates of bradycardic AF. Additionally, more patients in the LPM group were administered heart failure medication (diuretics, angiotensin converting enzyme, and β-blockers) compared to those in the PM group.

To evaluate the interaction of age, we divided the patients into two groups according to median age (median 82 years, interquartile range 75–87 years: ≥82 years, n = 468; <82 years, n = 461). A total of 265 patients older than 82 years underwent LPM implantation, while a total of 103 patients younger than 82 years underwent LPM implantation (Tables S1 and S2).

Patient characteristics according to background disease are detailed in Tables S3–S5. In each subgroup, patients in the LPM group were relative older compared to those in the PM group. More AVB patients in the LPM group received diuretics and β-blockers than those in the PM group. Moreover, half of the bradycardic AF patients in the PM group were categorized as New York Heart Association class III, whereas 72% had history of hospitalization for heart failure.

3.2 | Clinical outcomes

The median follow-up duration was 1.7 years (interquartile range 0.8–2.6 years). During the follow-up period, 47 and 41 patients in the
LPM and PM groups were hospitalized for heart failure, respectively. Hospitalization rates for heart failure were significantly higher in the LPM group than in the PM group (log-rank \( p < .0001 \); Figure 1), with the difference between both groups being significant both before (crude HR 2.37, 95%CI 1.55–3.61, \( p < .001 \)) and after adjusting for baseline characteristics (adjusted HR 1.69, 95%CI 1.08–2.62, \( p = .02 \), Table 2). A total of 88 patients were hospitalized for heart failure during the follow-up period. The causes of worsening heart failure are summarized in Figure 2. Poor adherence and infection were the main causes of worsening heart failure, accounting for 66% in each group. Notably, desynchronization due to non-physiological pacing or worsening tricuspid regurgitation due to the pacemaker leads was considered as a possible cause for worsening heart failure in 9% and 10% of the patients in the LPM and PM groups, respectively.

A significant interaction was observed between the two groups established according to median age (\( p \) for the interaction .002).

Among the \( \geq 82 \) years patients, significantly more patients in the LPM group were hospitalized for heart failure than those in the PM group (adjusted HR 2.13, 95%CI 1.21–3.77, \( p = .008 \)), whereas there was no similar significant difference in the <82 years patients (adjusted HR 1.36, 95%CI 0.61–3.02, \( p = .44 \)).

Among patients with SND, the crude and adjusted risks of hospitalization for heart failure were significantly greater in the LPM group than in the PM group (crude HR 2.50, 95%CI 1.37–4.57, \( p = .002 \); adjusted HR 2.01, 95%CI 1.04–3.90, \( p = .03 \), Figure S1A and Table S6). Meanwhile, no significant differences were observed between the two groups among AVB patients (crude HR 1.68, 95%CI 0.79–3.56, \( p = .17 \); adjusted HR 1.30, 95%CI 0.58–2.91, \( p = .51 \), Figure S1B and Table S7), and among bradycardic AF patients (crude HR 1.51, 95%CI 0.42–5.42, \( p = .52 \); adjusted HR 2.14, 95%CI 0.43–10.65, \( p = .35 \), Figure S1C and Table S8). As shown in Figure S2A–C, poor adherence or infection in each subgroup caused majority of

| Table 1 Patient characteristics |
|---------------------------------|
| Overall (n = 929) | LPM group (n = 368) | PM group (n = 561) | p value |
| Age, years | 80.1 ± 9.4 | 84.7 ± 7.1 | 77.0 ± 9.5 | <.0001 |
| Male | 454 (49%) | 176 (48%) | 278 (50%) | .61 |
| Body mass index, kg/m² | 22.6 ± 3.5 | 21.8 ± 3.6 | 23.2 ± 3.4 | <.0001 |

### NYHA functional classification

|        | Overall (n = 929) | LPM group (n = 368) | PM group (n = 561) |
|--------|------------------|---------------------|-------------------|
| I      | 627 (67%)        | 254 (69%)           | 373 (66%)         | .42 |
| II     | 224 (24%)        | 83 (23%)            | 141 (25%)         | .37 |
| III    | 68 (7%)          | 27 (7%)             | 41 (7%)           | .99 |
| IV     | 10 (1%)          | 4 (1%)              | 6 (1%)            | .98 |

### Diabetes

|        | Overall (n = 929) | LPM group (n = 368) | PM group (n = 561) |
|--------|------------------|---------------------|-------------------|
|        | 139 (15%)        | 53 (14%)            | 86 (15%)          | .70 |

### Hypertension

|        | Overall (n = 929) | LPM group (n = 368) | PM group (n = 561) |
|--------|------------------|---------------------|-------------------|
|        | 616 (66%)        | 241 (65%)           | 375 (67%)         | .67 |

### Dyslipidemia

|        | Overall (n = 929) | LPM group (n = 368) | PM group (n = 561) |
|--------|------------------|---------------------|-------------------|
|        | 303 (33%)        | 103 (28%)           | 200 (36%)         | .01 |

### Coronary artery disease

|        | Overall (n = 929) | LPM group (n = 368) | PM group (n = 561) |
|--------|------------------|---------------------|-------------------|
|        | 156 (17%)        | 53 (14%)            | 103 (18%)         | .11 |

### Cardiomyopathy

|        | Overall (n = 929) | LPM group (n = 368) | PM group (n = 561) |
|--------|------------------|---------------------|-------------------|
|        | 42 (5%)          | 14 (4%)             | 28 (5%)           | .39 |

### History of hospitalization for heart failure

|        | Overall (n = 929) | LPM group (n = 368) | PM group (n = 561) |
|--------|------------------|---------------------|-------------------|
|        | 188 (20%)        | 84 (23%)            | 104 (19%)         | .11 |

### Left ventricular ejection fraction, %

|        | Overall (n = 929) | LPM group (n = 368) | PM group (n = 561) |
|--------|------------------|---------------------|-------------------|
|        | 61.1 ± 9.8       | 60.0 ± 11.2         | 61.9 ± 8.7        | .99 |

### Pacing indications

|                    | Overall (n = 929) | LPM group (n = 368) | PM group (n = 561) |
|--------------------|------------------|---------------------|-------------------|
| Sinus node dysfunction | 369 (40%) | 150 (41%)           | 219 (39%)         | .60 |
| Atrioventricular block | 471 (50%) | 147 (40%)           | 324 (58%)         | <.0001 |
| Atrial fibrillation | 89 (10%)        | 71 (19%)            | 18 (3%)           | <.0001 |

### Medication

|                    | Overall (n = 929) | LPM group (n = 368) | PM group (n = 561) |
|--------------------|------------------|---------------------|-------------------|
| Diuretic | 247 (27%)        | 128 (35%)           | 119 (21%)         | <.0001 |
| ACE inhibitor | 97 (10%) | 49 (13%)            | 48 (9%)           | .02 |
| ARB | 281 (30%)        | 100 (27%)           | 181 (32%)         | .10 |
| Mineralocorticoid receptor antagonist | 138 (15%) | 63 (17%)           | 75 (13%)         | .12 |
| β-blocker | 205 (22%) | 96 (26%)            | 109 (19%)         | .01 |
| Calcium channel blocker | 389 (42%) | 141 (38%)           | 248 (44%)         | .08 |
| Antiarrhythmic drugs | 32 (3%) | 12 (3%)            | 20 (4%)           | .80 |

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; NYHA, New York Heart Association.
the patients to be hospitalized for heart failure. Among patients
with SND indicated for pacing, the pacemaker-related causes such
as desynchronization due to non-physiological pacing or worsening
tricuspid regurgitation due to the pacemaker leads were observed in
13% and 10% of patients in the LPM and PM groups, respectively,
whereas among patients with AVB for which pacing was indicated,
the foretokened events were observed in 9% and 11% of patients in
the LPM and PM groups, respectively. Obvious pacemaker-related
causes were not observed in patients with bradycardic AF for which
pacing was indicated. Tachycardia, including atrial tachycardia and
fibrillation, occurred in seven patients who were hospitalized for
heart failure; of these, six were those with SND and one was an AF
patient with bradycardia.

4 | DISCUSSION

The salient findings of the present study were as follows: Hospitalization
risk of heart failure was 1.69 times higher in patients who underwent
LPM implantation than in those who underwent PM implantation. The
main causes of worsening heart failure were poor adherence and in-
fection, whereas approximately 10% of the causes were pacemaker-
related, irrespective of the types of pacemakers. Regarding the clinical
endpoint, older patients (≥82 years) showed a trend similar to that in the
overall population, though significant differences were not observed in
younger patients (<82 years). According to disease background, hos-
pitalization rates for heart failure were significantly higher in patients
who underwent LPM implantation owing to SND compared to those
who underwent PM implantation. Notably, no differences between
the two devices were observed among patients who underwent pace-
maker implantation owing to AVB and bradycardic AF. Tachycardia
caused by worsening heart failure mainly occurred in SND patients.

Ventricular desynchronization caused by ventricular pacing in-
creases the risk of hospitalization for heart failure. In particular,
more than 40% cumulative ventricular pacing was a strong pre-
dictor of hospitalization due to heart failure in SND patients.\(^6,7\)

In the current study, clinical outcomes were mainly driven by
SND. Among SND patients, the risk of hospitalization for heart
failure was significantly higher in those with more than 40% cu-
mulative ventricular pacing than in those with less than 40% cu-
mulative ventricular pacing (Figure 5). As shown in Table S9, the
LPM group had significantly more SND patients with more than
40% cumulative ventricular pacing after pacemaker implantation
compared to the PM group, up to 2 years. Generally, SND patients
need only atrial pacing. PMs fulfill the demand by atrial pacing,
whereas LPMs fulfill the demand by ventricular pacing. The dif-
ferences in ventricular pacing rates and in the responses between
the two devices could affect the clinical outcomes. SND patients
after pacemaker implantation often suffered from AF, with the ev-
idence showing an increased risk of AF after ventricular pacing.\(^6,7\)

In the current study, supraventricular tachycardia accounted for

![Kaplan–Meier curves for heart failure hospitalization.](image)

**FIGURE 1** Kaplan–Meier curves for heart failure hospitalization.

**TABLE 2** Univariate and multivariable cox Hazard models for heart failure hospitalization

|                | Univariate | Multivariable |
|----------------|------------|--------------|
|                | HR (95% CI) | \( p \) value | HR (95% CI) | \( p \) value |
| LPM group      | 2.37 (1.55–3.61) | <.001 | 1.69 (1.08–2.62) | .02 |
| Age (80 ≥ years old) | 2.42 (1.51–3.88) | <.001 | 2.60 (1.56–4.33) | <.001 |
| Male           | 0.85 (0.56–1.30) | .46 | 1.01 (0.65–1.56) | .96 |
| Body mass index (22 ≥ kg/m\(^2\)) | 0.79 (0.52–1.21) | .28 | 0.92 (0.60–1.42) | .72 |
| Diabetes       | 1.66 (1.01–2.71) | .04 | 1.70 (1.02–2.84) | .04 |
| Hypertension   | 0.95 (0.61–1.47) | .81 | 0.69 (0.44–1.09) | .11 |
| Dyslipidemia   | 1.30 (0.84–2.01) | .22 | 1.49 (0.95–2.33) | .07 |
| History of hospitalization for heart failure | 3.63 (2.38–5.52) | <.001 | 3.14 (2.01–4.91) | <.001 |
| Left ventricular ejection fraction (50 < %) | 3.95 (2.42–6.46) | <.001 | 2.79 (1.66–4.70) | <.001 |

Abbreviation: LPM, leadless pacemaker.
14% of the cases of worsening heart failure among SND patients. In the patients with PMs, AF is easily detected by checking the pacemaker, and the immediate treatment, such as anti-tachycardia pacing, catheter ablation, and medication is possible. While the detection of supraventricular arrhythmia would be delayed in the patients with LPMs. The administration of antiarrhythmic drugs, including β-blockers, is needed for AF management, whereas the administration of the drugs for SND patients with LPMs could worsen bradycardia and increase desynchronization due to non-physiological ventricular pacing. Based on these findings, dual-chamber pacemakers with atrial anti-tachycardia pacing function would be a better option than LPMs for SND patients.

In the current study, LPMs were implanted for relative elderly and low body mass index patients; however, such patients often have a poor general condition and prognoses. Our analysis on the interaction of age showed that those ≥82 years were more likely to have undergone LPM implantation, with such patients also having significantly higher hospitalization rates due to heart failure. The quantitative interaction of age could be induced by factors that are not listed in the baseline characteristics, such as frailty, dementia, and other co-morbidities. Thus, elderly patients who underwent LPM implantation would need more careful treatment to prevent the occurrence of heart failure. Given the increasing risk of hospitalization due to heart failure among the elderly, leadless dual-chamber pacing devices could be a better option for patients with a high risk for complications.

5 | CONCLUSIONS

Hospitalization risk for heart failure was higher in patients who underwent LPM implantation than in those who underwent PM implantation. The increased risk was mainly attributed to patients ≥82 years old, and those with SND for which pacing indication.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

ETHICS APPROVAL STATEMENT

The study protocol was approved by the institutional review board of Kokura Memorial Hospital, and the study was conducted in accordance with the Declaration of Helsinki.

PATIENT CONSENT STATEMENT

We obtained informed written or verbal consent from all participants.
CLINICAL TRIAL REGISTRATION
This study was approved by the institutional review board of Kokura Memorial Hospital. (Permission number: 21101301).

ORCID
Tomonori Katsuki https://orcid.org/0000-0003-1178-3832
Masato Fukunaga https://orcid.org/0000-0002-0230-4556

REFERENCES
1. Udo EO, Zoithoff NPA, Van Hemel NM, De Cock CC, Hendriks T, Doevedans PA, et al. Incidence and predictors of short- and long-term complications in pacemaker therapy: the FOLLOWPACE study. Heart Rhythm. 2012;9:728–35.
2. Duray GZ, Ritter P, El-Chami M, Narasimhan C, Omar R, Tolosana JM, et al. Long-term performance of a transcatheter pacing system: 12-month results from the Micra transcatheter pacing study. Heart Rhythm. 2017;14:702–9.
3. 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 from the Micra postapproval registry. J Cardiovasc Electrophysiol. 2019;30:569–74.
4. Pagan E, Gabriels J, Khodak A, Chang D, Beldner S, Epstein LM, et al. Safety of leadless pacemaker implantation in the very elderly. Heart Rhythm. 2020;17:2023–8.
5. Tops LF, Schalij MJ, Bax JJ. The effects of right ventricular apical pacing on ventricular function and Dyssynchrony. J Am Coll Cardiol. 2009;54:764–76.
6. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with Normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation. 2003;107:2932–7.
7. Lamas GA, Lee KL, Sweeney MO, Silverman R, Leon A, Yee R, et al. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. New England Journal of Medicine. 2002;346:1854–62.
8. Beurskens NEG, Tjong FVY, De Bruin-Bon RHA, Dasselaar KJ, Kuitt WJ, Wilde AAM, et al. Impact of leadless pacemaker therapy on cardiac and atrioventricular valve function through 12 months of follow-up. Circ Arrhythm Electrophysiol. 2019;12:e007124.
9. Nogami A, Kurita T, Kusano K, Goya M, Shoda M, Tada H, et al. JCS/JHRS 2021 guideline focused update on non-pharmacotherapy of cardiac arrhythmias. J Arrhythm. 2022;38:1–30.
10. Padeletti L, Pürerfellner H, Mont L, Tukkie R, Manolis AS, Ricci R, et al. New-generation atrial antitachycardia pacing (reactive ATP) is associated with reduced risk of persistent or permanent atrial fibrillation in patients with bradycardia: results from the MINERVA randomized multicenter international trial. Heart Rhythm. 2015;12:1717–25.
11. Xu L, Zhang J, Shen S, Hong X, Zeng X, Yang Y, et al. Association between body composition and frailty in elderly inpatients. Clin Interv Aging. 2020;15:313–20.
12. Seko Y, Kato T, Morimoto T, Yaku H, Inuzuka Y, Tamaki Y, et al. Association between body mass index and prognosis of patients hospitalized with heart failure. Sci Rep. 2020;10:16663.
13. Bereuter L, Gysin M, Kueffer T, Kucera M, Niederhauser T, Fuhrer J, et al. Leadless dual-chamber pacing. JACC: Basic to Translational Science. 2018;3:813–23.

SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Katsuki T, Nagashima M, Kono H, Sadohara Y, Hirokami J & Kuji R et al. Clinical outcome for heart failure hospitalizations in patients with leadless pacemaker. J Arrhythmia. 2022;38:730–735. https://doi.org/10.1002/joa3.12761