



CJC Open ■ (2023) 1–9

Original Article

Clinical Predictors of Pacing Device Implantation in Implantable Cardiac Monitor Recipients for Unexplained Syncope

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ABSTRACT

Background: Implantable cardiac monitors (ICMs) help investigate the cause of unexplained syncope, but the probability and predictors of needing a pacing device thereafter remain unclear.

Methods: We retrospectively analyzed the data of patients who received ICM insertion for unexplained syncope with suspected arrhythmic etiology. The data were obtained from a nationwide database obtained between April 1, 2012 and March 31, 2020. Multivariable mixed-effects survival analysis was performed to identify predictors of pacing device implantation (PDI), and a risk score model was developed accordingly.

Results: In total, 2905 patients (age: 72 years [range: 60–78]) implanted with ICMs to investigate the cause of syncope were analyzed. During the median follow-up period of 128 days (range:

RÉSUMÉ

Contexte : Les moniteurs cardiaques implantables (MCI) aident à déterminer la cause d'une syncope inexpiquée, mais la probabilité et les facteurs prédictifs du besoin d'un dispositif de stimulation cardiaque par la suite demeurent incertains.

Méthodologie : Nous avons analysé de façon rétrospective les données de patients s'étant fait implanter un MCI après une syncope inexpiquée et chez lesquels une étiologie d'arythmie était soupçonnée. Les données proviennent d'une base de données nationale et s'étendent du 1^{er} avril 2012 au 31 mars 2020. Une analyse de survie multivariable à effets mixtes a été effectuée pour cibler les facteurs prédictifs de l'implantation d'un dispositif de stimulation cardiaque (IDSC), et un modèle de score de risque a été conçu en conséquence.

Received for publication October 21, 2022. Accepted December 19, 2022.

Ethics Statement: This study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Centre (approval number: R19066; October 6, 2019). The requirement for informed consent was waived, as personal information was not included in the database.

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See page 8 for disclosure information.

Syncope is common in the general population¹; however, in approximately 30% of patients with syncope, the underlying mechanism cannot be identified, despite extensive neurologic and cardiac workups.^{1–3} Efficacy of pacing for prevention of recurrent syncope has been demonstrated in randomized controlled trials among patients with syncope and bifascicular block, and those with reflux syncope with cardioinhibitory response.^{4–6} Based on these results, permanent pacing-device implantation (PDI) is recommended in these populations, as well as in patients with syncope due to bradycardia in Western countries,^{2,3} and Japanese guidelines make similar recommendations.⁷

<https://doi.org/10.1016/j.cjco.2022.12.007>

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68–209) days, 473 patients (16%) underwent PDI. Older age, history of atrial fibrillation, bundle branch block (BBB), and diabetes were independent predictors of PDI in multivariable analysis. A risk score model was developed with scores ranging from 0 to 32 points. When patients with the lowest quartile score (0–13 points) were used as a reference, those with higher quartiles had a higher risk of PDI (second quartile: 14–15 points, hazard ratio [HR]: 3.86, 95% confidence interval [CI]: 2.62–5.68; third quartile: 16–18 points, HR: 4.67, 95% CI: 3.14–6.94; fourth quartile: 19–32 points, HR: 6.59, 95% CI: 4.47–9.71).

Conclusions: The 4 identified predictors are easily assessed during the initial evaluation of patients with syncope. They may help identify patients with a higher risk of requiring permanent PDI.

Several studies involving long-term electrocardiogram (ECG) monitoring through implantable cardiac monitors (ICMs) have demonstrated an underlying etiology related to arrhythmia, predominantly bradyarrhythmia, in 32%–75% of patients with unexplained syncope.^{8,9} Although several reports have investigated the clinical predictors of PDI in patients with syncope who have undergone ICM insertion, the number of patients included in these studies was limited.^{10–12}

The objective of this study was to identify predictive factors for PDI and develop a risk-score model in patients who received ICMs for unexplained syncope with suspected arrhythmia-related etiology. We used the Japanese Registry of All Cardiac and Vascular Diseases-Diagnosis Procedure Combination (JROAD-DPC), a nationwide claims database that uses data from the Japanese Diagnosis Procedure Combination Per-Diem Payment System.¹³

Material and Methods

This study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center (approval number: R19066; October 6, 2019). The requirement for informed consent was waived, as personal information was not included in the database.

Data source

This retrospective, cross-sectional study used the JROAD-DPC database, which has been described in detail previously.¹³ The JROAD-DPC database includes the following patient information: age; sex; height; weight; Barthel index¹⁴; primary diagnoses/comorbidities/conditions arising after admission based on the International Classification of Diseases, 10th revision codes; received drugs; diagnostic and therapeutic procedures; and discharge status. In addition to these codes, detailed diagnosis names were listed, ensuring determination of conditions that could not be identified using the codes alone. These diagnoses recorded in the text were carefully reviewed to exclude vague diagnoses and increase diagnosis accuracy. Additionally, the JROAD-DPC database includes data regarding readmission and outpatient treatment

Résultats : Au total, les cas de 2905 patients (âge : 72 ans [écart interquartile (ÉI) : 60-78]) ayant reçu un MCI pour déterminer la cause de la syncope ont été analysés. Durant la période de suivi médiane de 128 jours (ÉI : 68-209), 473 patients (16 %) ont subi une IDSC. L'âge avancé, les antécédents de fibrillation auriculaire, le bloc de branche et le diabète étaient des facteurs prédictifs indépendants de l'IDSC dans l'analyse multivariable. Un modèle de score de risque a été conçu, les scores allant de 0 à 32 points. Lorsque les patients ayant un score dans le quartile inférieur (0 à 13 points) étaient utilisés à titre de référence, ceux ayant un score dans les quartiles supérieurs avaient un risque plus élevé d'IDSC (deuxième quartile : 14-15 points, rapport des risques instantanés [RRI] : 3,86, intervalle de confiance [IC] à 95 % de 2,62 à 5,68; troisième quartile : 16-18 points, RRI : 4,67, IC à 95 % de 3,14 à 6,94; quatrième quartile : 19-32 points, RRI : 6,59, IC à 95 % de 4,47 à 9,71).

Conclusions : Les quatre facteurs prédictifs ciblés sont faciles à évaluer durant l'évaluation initiale des patients ayant subi une syncope. Ils peuvent aider à repérer les patients présentant un risque plus élevé d'avoir besoin d'un dispositif de stimulation cardiaque permanent.

within the same year for each patient. As medical information for the next fiscal year was available for only patients admitted to the same hospital during the following year, only events within the same fiscal year were included in the present analysis. The procedures and diagnoses codes used in this study are shown in [Supplemental Table S1](#). If more than one possible diagnosis for pacing indication was listed at readmission for PDI (eg, sinus node dysfunction [SND], and atrioventricular block [AVB]), the primary diagnosis was considered the main reason for device implantation.

Inclusion/exclusion criteria

A flowchart of the study is shown in [Figure 1](#). We initially identified 4177 hospitalized patients between April 2012 and March 2020. The inclusion criteria were a diagnosis of syncope and hospitalization with ICM insertion. According to current guidelines,^{2,3,7} patients with syncope eligible for ICM insertion are those with unexplained syncope, justifying the need for a precise diagnosis after a negative initial workup. Moreover, Japanese physicians tend to follow the Japanese guidelines⁷; however, the recommendations for initial workup, ICM insertion, and PDIs for syncope are generally similar to those in the Western guidelines.^{2,3} The exclusion criteria were any one of the following: (i) age < 18 years (n = 85) or unknown (n = 34); (ii) implanted cardiac implantable electronic devices on admission (n = 7); (iii) death during the index hospitalization (n = 1); (iv) unavailability of follow-up data (n = 29); and (v) ICM insertion procedure date in the last 3 months of the fiscal year (n = 1116). Following patients across years was not possible using the JROAD-DPC database. As the Japanese fiscal year starts in April, discharges with ICM insertion between January and March, the last 3 months of each fiscal year, were excluded to maintain a follow-up period > 3 months.

Outcomes and follow-up

The primary outcome of this study was the implantation of cardiac pacing devices. Pacing devices were defined as conventional pacemakers, leadless pacemakers, transvenous

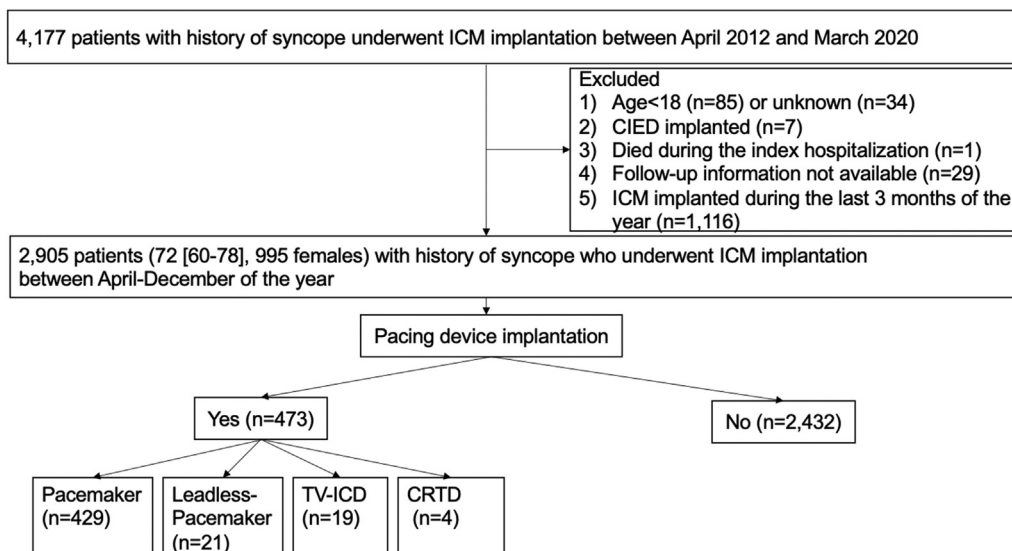


Figure 1. Flow chart of the study. A total of 2905 patients (median age 72 [range: 60-78]) were included in the study. CIED, cardiovascular implantable electronic device; CRTD, cardiac resynchronization defibrillator; ICM, implantable cardiac monitor; TV-ICD, transvenous implantable cardioverter-defibrillator.

implantable cardioverter-defibrillators (ICDs), or cardiac resynchronization therapy pacemakers or defibrillators (CRTDs). The secondary outcomes were the primary reasons for PDI, based on the International Classification of Diseases, 10th revision diagnosis code or the detailed diagnosis names.

In patients who underwent PDI, the duration from ICM insertion to PDI was considered the follow-up period in the survival analysis. In patients who did not undergo PDI, the follow-up period was the duration from ICM insertion to the earliest following date for either subcutaneous ICD (S-ICD) implantation, ICM removal, or the last outpatient visit or remote monitoring date. All follow-up durations were determined within the same fiscal year as that of the initial ICM insertion.

Definition of exposure or variables

The collected variables included age, sex, body mass index, Barthel index at admission, comorbidities (such as atrial fibrillation [AF], left BBB [LBBB], right BBB [RBBB], left anterior or posterior hemi-block, first-degree or second-degree AVB, nonsustained ventricular tachycardia [VT], heart failure, ischemic cardiomyopathy, nonischemic cardiomyopathies, long QT syndrome, Brugada syndrome, early repolarization syndrome, diabetes, hypertension, dyslipidemia, chronic kidney disease, chronic lung disease, stroke), and current treatment (including dialysis and beta-blockers). Bifascicular block was defined as complete LBBB or RBBB associated with left anterior or posterior hemi-block.

Statistical analysis

Categorical data are presented as frequencies and percentages; continuous data are presented as medians (interquartile ranges). The Wilcoxon rank-sum test was used to compare continuous data; the χ^2 test or Fisher exact test was used to

compare categorical data. The Cochran-Armitage trend test was performed.

Multivariable mixed-effects parametric survival analysis, using the institute as a random intercept, adjusted for characteristics with $P < 0.05$ in univariate analysis, was performed to estimate the hazard ratio (HR) and 95% confidence interval (CI) for PDI. To derive the risk score for each variable, coefficients were multiplied by a factor of 10 to allow for integer scores. The total score was calculated as the sum of the individual weighted scores. Mixed-effects parametric survival analysis was performed to estimate the HR and 95% CI for having higher quartiles of the risk score using patients with the lowest quartile as a reference. The Kaplan-Meier survival curves for PDI in patients within each quartile score were shown, and the log-rank test was performed. We evaluated the discriminatory ability of the risk models using concordance statistics (C-statistics). To explore the consistency of the risk model developed, the entire study cohort was divided randomly in a 7:3 ratio into derivation ($n = 2033$) and validation cohorts ($n = 872$). Using the derivation cohort, the risk score was similarly developed. Then, using the validation cohort, we evaluated the discriminatory ability of the risk models using C-statistics. All statistical comparisons were 2-sided, with statistical significance set at $P < 0.05$. All analyses were performed using Stata 16.0 (StataCorp, College Station, TX).

Results

Patient characteristics

A total of 2905 patients (median age: 72 years [range: 60-78]; 995 women [34%]) were included in the study. Patients who required PDI were older (75 years [range: 69-80] vs 71 years [range: 57-78]; $P < 0.001$) and more likely to have a history of AF (33% vs 23%; $P < 0.001$), BBB (4.4% vs 1.8%,

Table 1. Baseline characteristics of patients

Characteristic	Overall population	PDI (+)	PDI (-)	P
	N = 2905	n = 473	n = 2432	
Age, y	72 (60–78)	75 (69–80)	71 (57–78)	< 0.001
Female sex	995 (34)	169 (36)	826 (34)	0.46
Body mass index, kg/m ²	23.0 (20.8–25.4)	23.4 (21.1–25.7)	23.0 (20.8–25.3)	0.05
Barthel score < 100	354 (13)	53 (12)	301 (14)	0.40
Comorbidities				
Atrial fibrillation	726 (25)	158 (33)	568 (23)	< 0.001
Conduction disturbance				
First-degree AVB	25 (0.9)	7 (1.5)	18 (0.7)	0.17
Second-degree AVB	78 (2.7)	11 (2.3)	67 (2.8)	0.76
Bundle branch block	65 (2.2)	21 (4.4)	44 (1.8)	< 0.001
LBBB	29 (1.0)	11 (2.5)	18 (0.7)	0.002
RBBB	36 (1.2)	10 (2.1)	26 (1.1)	0.06
Left hemi-block	13 (0.4)	2 (0.4)	11 (0.5)	0.93
Bifascicular block	42 (1.5)	13 (2.8)	29 (1.2)	0.002
Nonsustained ventricular tachycardia	74 (2.6)	6 (1.3)	68 (2.8)	0.06
Heart failure	562 (19)	92 (20)	470 (19)	0.95
Ischemic cardiomyopathy	150 (5.2)	29 (6.1)	121 (5.0)	0.29
Nonischemic cardiomyopathy	119 (4.1)	12 (2.5)	107 (4.4)	0.06
Valvular disease	110 (3.8)	25 (5.3)	75 (3.1)	0.05
Long QT, Brugada, or early repolarization syndrome	76 (2.6)	3 (0.6)	73 (3.0)	0.001
Long QT syndrome	20 (0.7)	2 (0.4)	18 (0.7)	0.76
Brugada syndrome	54 (1.9)	1 (0.2)	53 (2.2)	0.001
Early repolarization syndrome	2 (0.1)	0 (0)	2 (0.1)	> 0.99
Diabetes	358 (12)	80 (17)	278 (11)	< 0.001
Hypertension	1598 (55)	277 (59)	1321 (54)	0.09
Dyslipidemia	872 (30)	159 (34)	713 (29)	0.06
Chronic kidney disease	105 (3.6)	18 (3.8)	87 (3.6)	0.81
Dialysis	46 (1.6)	11 (2.3)	34 (1.4)	0.07
Chronic lung disease	16 (0.6)	5 (1.1)	11 (0.5)	0.10
Stroke	87 (3.0)	15 (3.2)	72 (3.0)	0.81
Medication				
Beta-blocker	539 (19)	93 (20)	447 (18)	0.48

Values are median (interquartile ranges) or n (%), unless otherwise indicated.

AVB, atrioventricular block; LBBB, left bundle branch block; PDI, pacing-device implantation; RBBB, right bundle branch block.

$P < 0.001$), or diabetes (17% vs 11%; $P < 0.001$; Table 1). In contrast, the proportion of patients with either long QT, Brugada, or early repolarization syndrome was lower among those who required PDI (0.6% vs 3.0%; $P = 0.001$).

A total of 29, 36, and 13 patients, respectively, had complete LBBB, RBBB, and left hemi-block. All 13 patients with left hemi-block had concomitant RBBB, and no patient had left hemi-block alone. Therefore, the numbers of patients with bifascicular block and non-bifascicular block were 42 (29 patients with complete LBBB, and 13 patients with RBBB associated with left hemi-block) and 23, respectively.

The Kaplan-Meier curve for outcomes of PDI after ICM insertion is presented in Figure 2. During the median follow-up period of 128 days (range: 68–209), 473 patients (16%) required PDI. The incidence of PDI was 0.42 cases per person-year, and the median period between ICM insertion and PDI was 57 days (range: 28–111). Of the patients who required PDI, most ($n = 429$ [91%]) received conventional pacemakers; others received leadless pacemakers ($n = 21$ [4.4%]), ICDs ($n = 19$ [4.0%]), or CRTDs ($n = 4$ [0.8%]). No patients underwent cardiac resynchronization therapy pacemaker implantation. Of the patients who did not undergo PDI, S-ICD was implanted in one patient (0.04%) for ventricular fibrillation (VF), and ICMs were removed in 29 patients (1.2%). No patients died during the index admission after undergoing ICM insertion.

Predictors of PDI

In the multivariable mixed-effects parametric survival analysis, higher age (when age < 60 years was used as a reference; 60–69 years, HR: 3.80, 95% CI: 2.53–5.72; 70–79 years, HR: 4.34, 95% CI: 2.96–6.37; ≥ 80 years, HR: 4.73, 95% CI: 3.17–7.04), history of AF (HR: 1.43, 95% CI: 1.18–

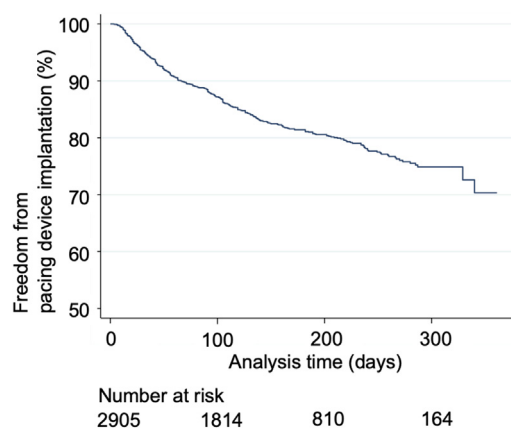


Figure 2. Kaplan–Meier curve for the outcome of pacing device implantation after implantable cardiac monitor insertion.

Table 2. Results of univariable and multivariable mixed-effects survival analysis

Characteristic	Univariable analysis			Multivariable analysis		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
Age, y						
< 60	1.0 (ref)			1.0 (ref)		
60–69	4.1	(2.72–6.14)	< 0.001	3.80	(2.53–5.72)	< 0.001
70–79	4.88	(3.34–7.12)	< 0.001	4.34	(2.96–6.37)	< 0.001
≥ 80	5.37	(3.62–7.96)	< 0.001	4.73	(3.17–7.04)	< 0.001
Female	1.04	(0.86–1.25)	0.71			
Body mass index, kg/m ²	1.02	(0.99–1.04)	0.16			
Barthel score < 100 points	0.91	(0.68–1.22)	0.53			
Atrial fibrillation	1.57	(1.29–1.91)	< 0.001	1.43	(1.18–1.75)	< 0.001
First-degree AVB	1.87	(0.95–3.69)	0.07			
Second-degree AVB	0.95	(0.51–1.74)	0.86			
Bundle branch block	2.59	(1.65–4.08)	< 0.001	2.54	(1.61–4.00)	< 0.001
Nonsustained ventricular tachycardia	0.50	(0.22–1.12)	0.09			
Heart failure	1.01	(0.80–1.27)	0.94			
Ischemic cardiomyopathy	1.16	(0.79–1.70)	0.45			
Nonischemic cardiomyopathy	0.56	(0.32–1.00)	0.05			
Valvular disease	1.39	(0.92–2.11)	0.12			
Long QT, Brugada, or early repolarization syndrome	0.24	(0.08–0.75)	0.01	0.52	(0.17–1.65)	0.27
Diabetes	1.42	(1.11–1.81)	0.005	1.29	(1.01–1.64)	0.045
Hypertension	1.12	(0.93–1.35)	0.24			
Dyslipidemia	1.18	(0.97–1.43)	0.10			
Chronic kidney disease	1.07	(0.66–1.72)	0.80			
Dialysis	1.69	(0.94–3.03)	0.08			
Chronic lung disease	1.84	(0.74–4.54)	0.19			
Stroke	1.13	(0.67–1.92)	0.64			
Beta-blocker	1.05	(0.83–1.32)	0.70			

AVB, atrioventricular block; CI, confidence interval; HR, hazard ratio; ref, reference.

1.75), BBB (HR: 2.54, 95% CI: 1.61–4.00), and diabetes (HR: 1.29, 95% CI: 1.01–1.64) were independently associated with PDI (Table 2).

When the presence of a non-bifascicular block was used as a reference, presence of the bifascicular block was not associated with an increased risk of PDI (age-adjusted HR: 0.72, 95% CI: 0.29–1.80; Supplemental Table S2). Additionally, when RBBB was used as a reference, presence of LBBB was not associated with an increased or decreased risk of PDI (age-adjusted HR: 1.34, 95% CI: 0.56–3.23).

The integer scores for each variable derived from coefficients in the multivariable models are listed in Table 3. Possible scores ranged from 0 to 32 points. The C-statistic value for the model was 0.65 (95% CI, 0.62–0.67). When patients with the lowest quartile score were used as a reference, those with higher quartile scores had a higher risk of PDI (second quartile, HR: 3.86, 95% CI: 2.62–5.68; third quartile, HR: 4.67, 95% CI: 3.14–6.94; fourth quartile, HR: 6.59, 95% CI: 4.47–9.71; Table 4). Kaplan-Meier curves for PDI in patients with each quartile score are shown in Figure 3. The incidence of PDI was 0.42 cases per person-year in the entire cohort, and 0.11, 0.42, 0.52, and 0.72, respectively, in patients with first, second, third, and fourth quartile scores.

The results of mixed-effects survival analysis in the derivation cohort (n = 2033) are presented in Supplemental Table S3. Supplemental Table S4 shows the coefficients and risk scores in the derivation cohort (n = 2033) of the model. The results were similar to those presented in Table 3. The C-statistic value for the model in the validation cohort was 0.63 (95% CI, 0.59–0.67).

Primary reason for PDI

A breakdown of the primary reasons for PDI is shown via stacked bar graphs in Figure 4. Among the 473 patients who underwent PDI, the primary reasons were as follows: (i) SND (n = 308 [65%]); (ii) advanced AVB (n = 120 [25%]); (iii) AF with slow ventricular response (n = 12 [2.5%]); and (iv) VT or VF (n = 13 [2.7%]). Patients with VT or VF underwent transvenous ICD or CRTD implantation.

In the age-specific analysis, the proportion of individuals who underwent PDI for SND or AVB did not show increasing or decreasing trends among older patients (SND, P for trend = 0.07; AVB, P for trend = 0.77). Conversely, the proportion of individuals who underwent PDI for VT or VF was greater among younger patients (P for trend < 0.001). The proportion of individuals who underwent PDI for SND was higher among patients with AF than it was among those without AF (79% vs 59%, P < 0.001), and advanced AVB was the major indication for PDI in patients with BBB,

Table 3. Coefficients of multivariable mixed-effects survival analysis and pacing device implantation risk points

Characteristic	Coefficient	Points
Age, y		
< 60	0	0
60–69	1.36	14
70–79	1.50	15
≥ 80	1.58	16
Atrial fibrillation	0.37	4
Bundle branch block	0.94	9
Diabetes	0.26	3

Table 4. Results of univariate mixed-effects survival analysis to estimate hazard ratios depending on quartiles of risk scores

Quartile (score)	Overall		HR	95% CI	P
	population N = 2905	PDI (+) n = 473			
First (0–13)	712	31 (4.4)	1.0 (ref)		
Second (14, 15)	958	161 (17)	3.86	(2.62–5.68)	< 0.001
Third (16–18)	618	121 (20)	4.67	(3.14–6.94)	< 0.001
Fourth (19–32)	617	160 (26)	6.59	(4.47–9.71)	< 0.001

CI, confidence interval; HR, hazard ratio; PDI, pacing-device implantation; ref, reference.

compared to those without it (74% vs 23%, $P < 0.001$). The proportion of patients who underwent PDI for SND and AVB was similar between patients with vs without a history of diabetes (SND: 61% vs 66%, $P = 0.43$; AVB: 26% vs 25%, $P = 0.84$).

Discussion

A strength of the present study is the large number of patients included. To our knowledge, this study is the largest conducted with patients who underwent ICM insertion for the investigation of unexplained syncope.

The major findings of the present study were as follows:

- Among patients who underwent ICM insertion for the investigation of unexplained syncope, the incidence of PDI was 0.42 cases per person-year within the same fiscal year of ICM insertion.
- Higher age, a history of AF, BBB, and diabetes were independent predictors of PDI. We developed a risk-score model and evaluated its discriminatory ability and consistency. A higher risk score was associated with a higher risk of need for a pacing device.
- Among patients with unexplained syncope and a history of AF, SND was the major indication for PDI. Conversely, advanced AVB was the major indication for PDI in patients with BBB, compared to those without BBB.

Usefulness of ICM in the investigation of unexplained syncope

The incidences of pacemaker and ICD implantation in this study were 15% and 0.8%, respectively, within the same fiscal year, which was similar to the incidences in previous reports on pacemakers (15.1%–21.3%) but slightly lower than those for ICDs (1.6%–6.0%).^{8,9} A final diagnosis was made in 503 patients (17%) who underwent either PDI/S-ICD implantation or ICM removal. The assumption was made that most patients who underwent ICM removal were those who did not require cardiac implantable electronic devices, as the monitoring results suggest that their symptoms were not arrhythmia-related. Our findings confirm the usefulness of ICM in the evaluation of patients with unexplained syncope.^{8,9}

Predictors of PDI

Using a large nationwide database, we identified higher age, a history of AF, BBB, and diabetes as independent

predictors of PDI. To our knowledge, history of diabetes has never been reported as a predictor of PDI after implantable loop recorder implantation for the investigation of unexplained syncope. The other 3 variables—advanced age, a history of AF, and the presence of BBB—have previously been reported as predictors.^{10–12} In addition, female sex and first-degree AVB have been reported as predictors of PDI after loop-recorder implantation for investigation of unexplained syncope, but they were not significant predictors in the present study.¹¹ Other reported predictors, such as a history of trauma secondary to syncope, detection of asymptomatic bradycardia during ECG monitoring, and the number of syncopal episodes, were not available in our database.^{10,12}

When patients with the lowest quartile score were used as a reference, those with risk scores in the second quartile had an almost 4-fold increase, whereas those with risk scores in the fourth quartile had a 6.6-fold increase in risk of requiring a permanent pacing device.

Advanced age was an independent predictor of PDI, consistent with previous reports.^{10,11} This finding can be explained by the fact that elderly patients demonstrate a heightened propensity to develop bradyarrhythmia requiring pacemaker implantation owing to age-related degenerative changes in both the sinus node and the atrioventricular conduction system. These changes include progressive fibrosis and changes in the properties of specific ion channels.

The second predictive factor was a history of AF, which has been reported as a risk factor for syncope.^{2,3} In patients with tachycardia-bradycardia syndrome (a type of SND), syncope can occur upon termination of AF when prolonged pauses are present. Tachycardia due to AF may be associated with suppression of sinus node automaticity as well as a sinus pause of variable duration when the tachycardia terminates. Aside from tachycardia-bradycardia syndrome, AF has recently been suggested as a risk factor for developing SND, likely through atrial remodeling, using Mendelian randomization analysis.^{4,5} Consistent with the aforementioned report, our data indicated that SND was a major reason for PDI in patients with AF.

The presence of BBB was the third independent predictor of PDI. AVB was the major reason for PDI among those with BBB, which can be explained by the successful detection of intermittent advanced AVB via ICM monitoring, as well as the exacerbation of conduction disturbance during the follow-up periods.^{13,16} In the Syncope: Pacing or Recording in the Later Years (SPRITELY) trial, empiric permanent pacing reduced major adverse events compared with ICM monitoring among patients aged ≥ 50 years with syncope and bifascicular block.¹⁷ Careful follow-up examination may be necessary for patients with unexplained syncope and BBB.

The fourth predictive factor was a history of diabetes mellitus, which has never been reported as a predictor for PDIs in patients with unexplained syncope. Although the mechanism of syncope in patients with diabetes is unknown, these patients may be less tolerant to bradycardia due to concomitant autonomic neuropathy. This autonomic neuropathy reduces sympathetic functions, such as vasoconstriction and increased cardiac output, to maintain cerebral circulation when bradycardia occurs.¹⁸ As the indication for permanent pacing is determined by an individual's symptoms

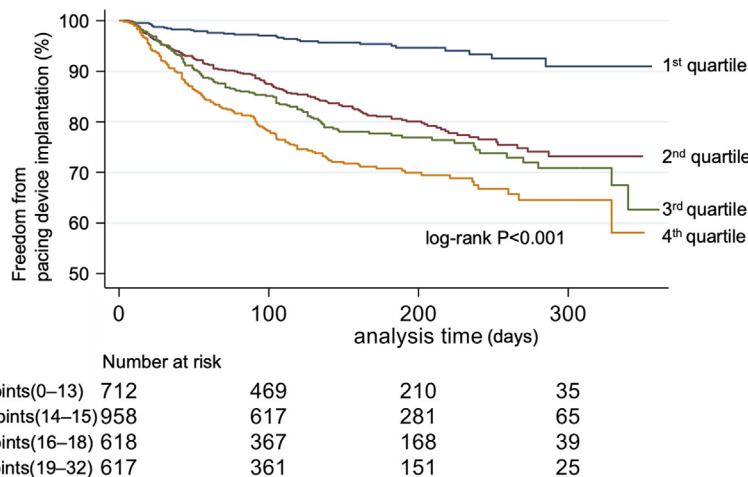


Figure 3. Kaplan–Meier curves for pacing device implantation in patients within each quartile score.

due to bradyarrhythmia,¹⁹ patients with diabetes may be more likely to require pacemaker implantation.

Comorbidities of structural heart disease, such as structural changes due to valvular disease, or ischemic/nonischemic cardiomyopathy, are known risk factors for cardiogenic syncope.^{20,21} However, none was a significant predictor of PDI in this study. This finding may be attributed to the fact that structural heart disease can cause syncope by mechanically decreasing cardiac output despite having no direct relationship with bradyarrhythmia, for which pacing is effective. For example, severe aortic stenosis/regurgitation causes a decrease in cardiac output, resulting in a decrease in cerebral blood flow and syncope, without affecting cardiac rhythm. Additionally, we were unable to determine whether congenital heart disease was a significant risk factor, as the number of patients with the disease was too small.

Although a history of inheritable arrhythmia syndrome was not associated with PDI, caution must be used in interpreting

the results. In patients with a diagnosis of long QT syndrome who experienced recurrent syncopal events while on beta-blocker therapy, ICD implantation is a class IIa recommendation according to the latest expert consensus.²² Therefore, patients with long QT syndrome and a history of syncope tend to be referred for ICD implantation directly, and few patients are likely to undergo ICM implantations. Only 2 patients in this study had early repolarization syndrome, so drawing conclusions regarding the association of syncope and a history of early repolarization with future PDI is difficult. Among 54 patients with Brugada syndrome, only one patient required PDI during the observation period. Further studies are needed to determine whether a history of Brugada syndrome is associated with a higher incidence of PDI when patients are observed over a longer period of time.

Although the present study included individuals in whom an ICM was inserted, likely a certain number of patients with unexplained syncope do not have an ICM inserted in actual

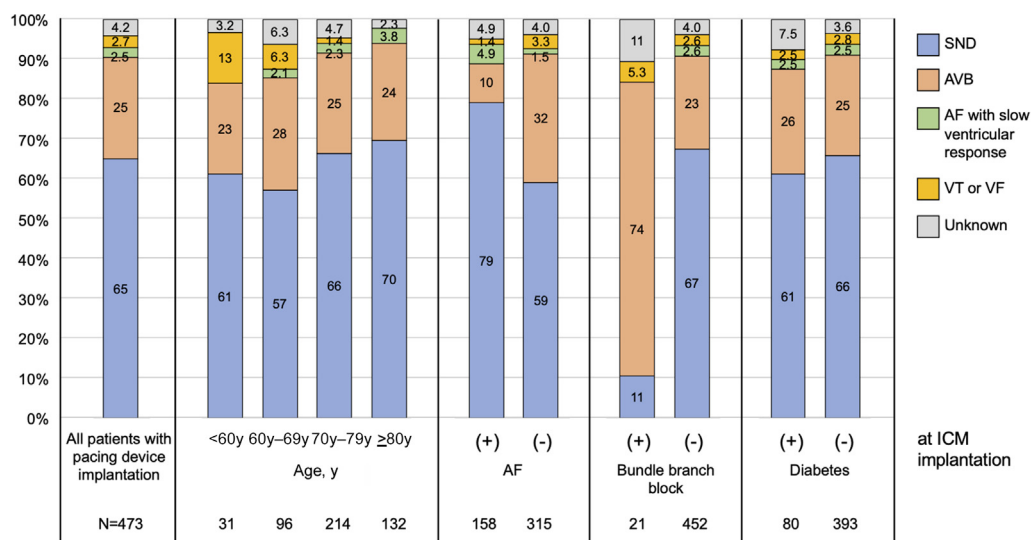


Figure 4. Primary reasons for pacing device implantation. Values along bottom are n. AF, atrial fibrillation; AVB, atrioventricular block; ICM, implantable cardiac monitor; SND, sinus node dysfunction; VF, ventricular fibrillation; VT, ventricular tachycardia.

clinical practice. Initial evaluation of syncope largely relies on the history of the events^{3,37}; however, judging whether the syncope is neurogenic, reflex, or cardiogenic is not always easy, especially in cases in which the patient is not good at recounting what occurred or in which no observers were present. Given the relative low risk of complications from ICM insertion, patients with multiple risks of requiring a pacing device in the future should be encouraged to undergo ICM insertions for further assessment, even if they are not immediate candidates for PDI. Aggressive monitoring using wearable devices or external loop recorders also might be effective. Whether the approach of having patients with higher risk directly undergo PDI to avoid delay from monitoring is reasonable is difficult to judge based on the findings of this study. Therefore, further investigation is warranted.

Study limitations

Our study has several limitations. First, the study design was both observational and retrospective. Second, as the DPC data are based on medical claims, data not directly related to the cost, such as diagnosis, were not completely validated. Nevertheless, previous studies have proven the validity of the diagnoses in the JROAD-DPC, compared with that in other nationwide databases or in-hospital registries.^{23,24} Third, we followed up on only events that occurred within the same fiscal year, as follow-up across years is nearly impossible, except for patients in special situations. Therefore, the follow-up period was relatively short, compared to those in previous reports, and an underestimation of the proportion of patients who require a permanent pacing device is possible. Despite that, by excluding patients who underwent ICM insertion during the last 3 months of each fiscal year, patients were followed up for a median of 128 days, which was longer than is realistically possible when using an external loop recorder (typically up to 1 month).²⁵ Fourth, some of the important clinical variables were not available, such as history of injury due to syncope, number of syncopal episodes before ICM implantation, history of asymptomatic pause, details of syncopal events, laboratory data, echocardiology results, ECGs, electrophysiology studies, actual waveforms recorded by ICMs, and death during the follow-up period. Fifth, although second-degree AVB is an important comorbidity related to the need for permanent PDI, we could not differentiate between the Wenckebach and Mobitz type AVBs. Sixth, we were unable to identify the recurrence of syncope and its timing after PDI because we used an inpatient database, and patients may have not been hospitalized after syncope if the characteristics of the syncope were not dangerous. Seventh, our study did not include patients who underwent ICM insertion at an outpatient clinic. However, many ICM implantations are performed in an inpatient setting in Japan. For example, between January and March 2020, of the 1136 implantations of ICM performed in Japan (both inpatient and outpatient settings),²⁶ this database includes 684 cases (60%), all of which were performed in inpatient settings. Considering that the JROAD-DPC database includes approximately 70% of inpatient cases at cardiology teaching hospitals, approximately 86% of the ICM implantations can be assumed to have been performed in inpatient settings.

Finally, the risk model was not externally validated, as no cohort was available for external validation.

Conclusions

ICMs were confirmed to be powerful tools for the evaluation of patients with unexplained syncope. Using a nationwide claims-based database, we identified advanced age, BBB, a history of AF, and diabetes as independent predictors of PDI in a population of patients who underwent ICM insertion for unexplained syncope. These 4 predictors are easily assessed during the initial evaluation of patients with syncope and may be useful for the identification of patients at high risk of developing adverse events requiring permanent PDI. Patients with unexplained syncope and these predictors should be encouraged to undergo ICM implantation for further assessment, if they are not immediate candidates for PDI.

Funding Sources

This study was supported by a research grant from JSPS KAKENHI (Grant Number JP22H03365), EP Cruise Inc. (to K.K.; No. 989-1) and an Intramural Research Fund (21-6-9) for cardiovascular diseases from the National Cerebral and Cardiovascular Centre.

Disclosures

Dr. Kusano has received speaker honoraria and research grants from Medtronic Japan.

References

1. Soteriades ES, Evans JC, Larson MG, et al. Incidence and prognosis of syncope. *N Engl J Med* 2002;347:878-85.
2. Shen WK, Sheldon RS, Benditt DG, et al. 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation* 2017;136:e60-122.
3. Brignole M, Moya A, de Lange FJ, et al. 2018 ESC guidelines for the diagnosis and management of syncope. *Eur Heart J* 2018;39:1883-948.
4. Santoni M, Castro A, Fiada F, et al. Prevention of syncope through permanent cardiac pacing in patients with bifascicular block and syncope of unexplained origin: The PRESS Study. *Circ Arrhythm Electrophysiol* 2013;6:101-7.
5. Brignole M, Menozzi C, Moya A, et al. Pacemaker therapy in patients with neurally mediated syncope and documented asystole: Third International Study on Syncope of Uncertain Etiology (ISSUE-3): a randomized trial. *Circulation* 2012;125:2566-71.
6. Baron-Esquivas G, Morillo CA, Moya-Mitjans A, et al. Dual-chamber pacing with closed loop stimulation in recurrent reflex vasovagal syncope: The SPAIN Study. *J Am Coll Cardiol* 2017;70:1720-8.
7. Nogami A, Kurita T, Kusano K, et al. JCS/JHRS 2019 guideline on non-pharmacotherapy of cardiac arrhythmias. *J Arrhythm* 2021;37:709-870.
8. Edvardsson N, Frykman V, van Mechelen R, et al. Use of an implantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry. *Europace* 2011;13:262-9.

9. Lacunza-Ruiz FJ, Moya-Mitjans A, Martínez-Alday J, et al. Implantable loop recorder allows an etiologic diagnosis in one-third of patients. Results of the Spanish Reveal Registry. *Circ J* 2013;77:2535-41.
10. Palmisano P, Accogli M, Zaccaria M, et al. Predictive factors for pacemaker implantation in patients receiving an implantable loop recorder for syncope remained unexplained after an extensive cardiac and neurological workup. *Int J Cardiol* 2013;168:3450-7.
11. Ahmed N, Frontera A, Carpenter A, et al. Clinical predictors of pacemaker implantation in patients with syncope receiving implantable loop recorder with or without ECG conduction abnormalities. *Pacing Clin Electrophysiol* 2015;38:934-41.
12. Miyazaki Y, Yamagata K, Ishibashi K, et al. Paroxysmal atrial fibrillation as a predictor of pacemaker implantation in patients with unexplained syncope. *J Cardiol* 2022;80:28-33.
13. Yasuda S, Nakao K, Nishimura K, et al. The current status of cardiovascular medicine in Japan—analysis of a large number of health records from a nationwide claim-based database. JROAD-DPC. *Circ J* 2016;80:2327-35.
14. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. *Md State Med J* 1965;14:61-5.
15. Thorolfsson RB, Sveinbjornsson G, Aegisdottir HM, et al. Genetic insight into sick sinus syndrome. *Eur Heart J* 2021;42:1959-71.
16. Moya A, García-Civera R, Croci F, et al. Diagnosis, management, and outcomes of patients with syncope and bundle branch block. *Eur Heart J* 2011;32:1535-41.
17. Sheldon R, Talajic M, Tang A, et al. Randomized Pragmatic Trial of Pacemaker Versus Implantable Cardiac Monitor in Syncope and Bifascicular Block. *JACC Clinical Electrophysiol* 2022;8:239-48.
18. Spallone V. Update on the impact, diagnosis and management of cardiovascular autonomic neuropathy in diabetes: what is defined, what is new, and what is unmet. *Diabetes Metab J* 2019;43:3-30.
19. Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. *Circulation* 2019;140:e333-81.
20. Costantino G, Perego F, Dipaola F, et al. Short- and long-term prognosis of syncope, risk factors, and role of hospital admission: results from the STePS (Short-Term Prognosis of Syncope) study. *J Am Coll Cardiol* 2008;51:276-83.
21. Del Rosso A, Ungar A, Maggi R, et al. Clinical predictors of cardiac syncope at initial evaluation in patients referred urgently to a general hospital: the EGSYS score. *Heart* 2008;94:1620-6.
22. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm* 2013;10:1932-63.
23. Nakai M, Iwanaga Y, Sumita Y, et al. Validation of acute myocardial infarction and heart failure diagnoses in hospitalized patients with the nationwide claim-based JROAD-DPC database. *Circ Rep* 2021;3:131-6.
24. Yokoyama Y, Miyamoto K, Nakai M, et al. Complications associated with catheter ablation in patients with atrial fibrillation: a report from the JROAD-DPC study. *J Am Heart Assoc* 2021;10:e019701.
25. Locati ET, Moya A, Oliveira M, et al. External prolonged electrocardiogram monitoring in unexplained syncope and palpitations: results of the SYNARR-Flash study. *Europace* 2016;18:1265-72.
26. Japan Arrhythmia Device Industry Association, Annual report of insertable cardiac monitor use in Japan [in Japanese]. Available at: <https://www.jadia.or.jp/>. Accessed February 28, 2023.

Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjopen.ca/> and at <https://doi.org/10.1016/j.cjco.2022.12.007>.