Journal of the American Heart Association

ORIGINAL RESEARCH

Leadless or Conventional Transvenous Ventricular Permanent Pacemakers: A Nationwide Matched Control Study

Alexandre Bodin, MD; Nicolas Clementy, MD; Arnaud Bisson, MD; Bertrand Pierre, MD; Julien Herbert, MSc; Dominique Babuty, MD, PhD; Laurent Fauchier, MD, PhD

BACKGROUND: Leadless ventricular permanent pacemakers (leadless VVI or LPM) were designed to reduce lead-related complications of conventional VVI pacemakers (CPM). The aim of our study was to assess and compare real-life clinical outcomes within the first 30 days and during a midterm follow-up with the 2 techniques.

METHODS AND RESULTS: This French longitudinal cohort study was based on the national hospitalization database. All adults (age ≥18 years) hospitalized in French hospitals from January 1, 2017 to September 1, 2020, who underwent a first LPM or CPM were included. The study included 40 828 patients with CPM and 1487 with LPM. After propensity score matching 1344 patients with CPM were matched 1:1 with patients treated with LPM. Patients with LPM had a lower rate of all-cause and cardiovascular death within the 30 days after implantation. During subsequent follow-up (mean: 8.6±10.5 months), risk of all-cause death in the unmatched population was significantly higher in the LPM group than in the CPM group, whereas risk of cardiovascular death and of endocarditis was not significantly different. After matching on all baseline characteristics including comorbidities (mean follow-up 6.2±8.7 months), all-cause death, cardiovascular death, and infective endocarditis were not statistically different in the 2 groups.

CONCLUSIONS: Patients treated with leadless VVI pacemakers had better clinical outcomes in the first month compared with the patients treated with conventional VVI pacing. During a midterm follow-up, risk of all-cause death, cardiovascular death, and endocarditis in patients treated with leadless VVI pacemaker was not statistically different after propensity score matching.

Key Words: leadless ■ pacemakers ■ transvenous

Conventional transvenous ventricular permanent (VVI) pacemaker (CPM) implantation with a pacing lead placed permanently in the ventricle is associated with complications affecting 15% of patients within the first 3 years (pneumothorax or hemothorax, lead revision, infection, pocket complications, or pericardial effusion).[1–3] Leadless VVI pacemaker (LPM) was designed and proposed to reduce the risk of these lead- and pocket-related complications. The IDE (Investigational Device Exemption) Study showed a 4% rate of complications within 6 months following implantation.[4] In the PAR (Micra Post-Approval Registry), more consistent with a real-world setting, major complication rate at 12 months was 2.7% in the LPM group versus 7.6% in a CPM historical cohort. Most of the major complications in the LPM group were mainly driven by pericardial effusions, groin puncture site complications, and pacing threshold elevation. They occurred within the 30 days post implantation.[5,6]

However, exhaustive real-life data are lacking. The aim of our study was to assess clinical outcomes following LPM implantation, as compared with CPM, in an exhaustive nationwide matched cohort.

Correspondence to: Alexandre Bodin, MD, Service de Cardiologie, Centre Hospitalier Universitaire Trousseau, Tours, France. Email: alexandre.bodin@univ-tours.fr

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.025339

For Sources of Funding and Disclosures, see page 9.

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CLINICAL PERSPECTIVE

What Is New?

- Mortality is high among unselected patients implanted with ventricular permanent pacemakers, whether leadless or conventional pacemaker are used.
- Implantation of leadless pacemakers seems to be a safe procedure in this high-risk population, with better outcomes at 1 month.
- Midterm outcomes appear relatively similar in patients with leadless or conventional pacemaker.

What Are the Clinical Implications?

- In nonprecluded patients, an economic evaluation comparing both technologies may be interesting, as a lower complication rate and associated costs within the first month with leadless ventricular permanent pacemaker should be balanced with a higher device cost.

Nonstandard Abbreviations and Acronyms

CPM	conventional VVI pacemaker
LPM	leadless VVI pacemaker
PAR	Post-Approval Registry
PMSI	Programme de Médicalisation des Systèmes d'Information
VVI	ventricular permanent

METHODS

Data Access

The data and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Because this study used data from human subjects, the data and everything pertaining to the data are governed by the French Health Agencies and cannot be made available to other researchers.

Study Design

This longitudinal cohort study was based on the national hospitalization database covering hospital care from the entire French population. The data for all patients admitted in French hospitals in France were collected from the national administrative PMSI (Programme de Médicalisation des Systèmes d'Information) database as previously described.[7] In the PMSI system, identified diagnoses are coded according to the *International Classification of Diseases, Tenth Revision (ICD-10)*. All medical procedures are recorded according to the national nomenclature, Classification Commune des Actes Medicaux. The PMSI contains individual anonymized information on each hospitalization that are linked to create a longitudinal record of hospital stays and diagnoses for each patient. The reliability of PMSI data has already been assessed and this database has previously been used to study patients with cardiovascular conditions.[8–10]

The study was conducted retrospectively and, as patients were not involved in its conduct, there was no impact on their care. Ethical approval was not required, as all data were anonymized. The French Data Protection Authority granted access to the PMSI data. Procedures for data collection and management were approved by the *Commission Nationale de l'Informatique et des Libertés*, the independent National Ethical Committee protecting human rights in France, which ensures that all information is kept confidential and anonymous, in compliance with the Declaration of Helsinki (authorization number 1897139).

Study Population

All adults (age ≥18 years) hospitalized in French hospitals from January 1, 2017 to September 1, 2020, who underwent a first LPM or CPM implantation were included. Importantly, patients with dual chamber pacemaker were not included in our study and VDD leadless pacemaker was not available over the period of the study. Patient information (demographics, comorbidities, medical history, and events during hospitalization or follow-up) was described using data collected in the hospital records. For each hospital stay, combined diagnoses at discharge were obtained. Each variable was identified using *ICD-10* and Classification Commune des Actes Medicaux codes. Exclusion criteria were age <18 years. We used the Charlson Comorbidity Index and the Claims-based Frailty Index to assess patients' clinical status.[11] Based on the database, we were also able to estimate a proxy of the EuroSCORE II[12,13] (originally proposed to evaluate the risk of early death in case of cardiac surgery), which was used to indirectly evaluate the risk of early complications related to pacemaker implantation.

Outcomes

Patients were followed until September 1, 2020 for the occurrence of outcomes. The end points were evaluated with follow-up starting from the date of hospitalization with VVI pacemaker implantation until the date of each specific outcome or date of last news in the absence of the outcome. Information on outcomes during the follow-up was obtained by analyzing the PMSI codes for each patient. All-cause death,

cardiovascular death, recurrence of infective endocarditis, and outcomes of interest at day 30 were identified using their respective *ICD-10* or procedure codes. The mode of death (cardiovascular or noncardiovascular) was identified based on the main diagnosis during hospitalization resulting in death. We defined major bleeding using the Bleeding Academic Research Consortium definitions.[14] Major bleeding was defined as bleeding with a reduction in the hemoglobin level resulting in anemia, or with transfusion of at least 1 unit of blood, or symptomatic bleeding in a critical area or organ (eg, intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome) or bleeding that causes death.

Statistical Analysis

Qualitative variables are described as frequency and percentages and quantitative variable as means (SDs). Multivariable analyses for clinical outcomes during the whole follow-up in the groups of interests were performed using a Cox model with all baseline characteristics and reporting hazard ratio.

Owing to the nonrandomized nature of the study, and considering the significant differences in baseline characteristics, propensity-score matching was also used to control for potential confounders of the treatment outcome relationship. Propensity scores were calculated using logistic regression with LPM implantation as the dependent variable. The propensity score included the cardiovascular risk factors and noncardiovascular comorbidities from baseline characteristics listed in Table 1.

For each patient with LPM, a propensity score-matched patient with CPM was selected (1:1) using the 1-to-1 nearest neighbor method (with a caliper of 0.01 of the SD of the propensity score on the logit scale) and no replacement. We assessed the distributions of demographic data and comorbidities in the 2 cohorts with standardized differences, which were calculated as the difference in the means or proportions of a variable divided by a pooled estimate of the SD of that variable. A standardized difference of 5% or less indicated a marginal difference between means of the 2 cohorts (Figures S1 and S2).

A logistic regression model was used for all outcomes at 30 days and odds ratios (ORs) were reported. Incidence rates (%/year) for each outcome of interest during longer-term follow-up was estimated in both groups and were compared using hazard ratios (HRs). HRs and 2-sided 95% CIs were estimated using Cox proportional hazards model for death and the model by Fine and Gray for competing risks. All comparisons with a P value <0.05 were considered statistically significant. In addition, we checked that the Hosmer–Lemeshow goodness of fit test had nonsignificant P values, suggesting that the logistic regression models were accurate. We also checked the proportional hazard assumption by plotting the log–log Kaplan-Meier curves and scaled Schoenfeld residuals against time plots. The test of proportional-hazards assumption had P values ranging from 0.20 to 0.90 and plots for all outcomes displayed lines that were reasonably parallel (and did not cross), implying that the proportional-hazards assumption was not violated. Regarding the scaled Schoenfeld residuals against time plots, we saw no evidence of a trend in the effect of time for our models.

All analyses were performed using Enterprise Guide 7.1 (SAS Institute Inc., SAS Campus Drive, Cary, NC, USA) and STATA 12.0 (Stata Corp, College Station, TX, USA).

RESULTS

Of 42 315 patients included in the cohort, 40 828 patients (96%) had a CPM and 1487 had an LPM (Figure 1). Patients with CPM were more likely to have an older age, hypertension, heart failure, and atrial fibrillation/flutter and less likely to have diabetes, valve disease, or vascular disease. Patients with LPM had higher rates of prior endocarditis, chronic kidney disease or dialysis, liver diseases, obesity, and previous cancer. Patients with CPM had a lower Charlson comorbidity index but a higher frailty index (Table 1).

Using propensity score, 1344 patients with CPM were adequately matched in a 1:1 fashion with patients with LPM (Table 2 and Figures S1 and S2).

Clinical Outcomes at Day 30

In the unmatched population, within the 30 days after implantation, patients with LPM had a lower rate of all-cause mortality (OR, 0.635 [95% CI, 0.527–0.765], P<0.0001) and from a cardiovascular cause (OR, 0.568; [95% CI, 0.405–0.797], P=0.001). They also had lower rates of major bleeding and need for transfusion. There was no significant difference between groups regarding tamponade, pneumothorax, or hemothorax (Table 3). The same trends were found after adjustment on all risk factors described in Table 1 (Tables S1 and S2).

In the matched population, LPM implantation was still significantly associated with a lower rate of all-cause death (OR, 0.583 [95% CI, 0.456–0.744], P<0.0001), cardiovascular death (OR, 0.413 [95% CI, 0.271–0.629], P<0.0001), major bleeding (OR, 0.523 [95% CI, 0.348–0.786], P=0.002), or transfusion (OR, 0.481 [95% CI, 0.296–0.780], P<0.0001). However, tamponade, pneumothorax, and hemothorax were not significantly different between the 2 groups (Table 3).

Table 1. Baseline Characteristics of Patients

	Conventional VVI pacemaker (n=40 828)	Leadless VVI pacemaker (n=1487)	*P* value	Standardized difference, (%)	Total (n=42 315)
Age, y	83.4±9.1	70.7±18.4	<0.0001	−87.8	82.9±9.9
Sex (male)	24 586 (60.2)	861 (57.9)	0.07	−4.7	25 447 (60.1)
Hypertension	30 914 (75.7)	989 (66.5)	<0.0001	−20.4	31 903 (75.4)
Diabetes	10 562 (25.9)	445 (29.9)	0.0005	9.1	11 007 (26.0)
Heart failure	21 620 (53.0)	717 (48.2)	0.0003	−9.5	22 337 (52.8)
Valve disease	11 499 (28.2)	481 (32.3)	0.0004	9.1	11 980 (28.3)
Aortic stenosis	6287 (15.4)	273 (18.4)	0.002	7.9	6560 (15.5)
Aortic regurgitation	2093 (5.1)	92 (6.2)	0.07	4.6	2185 (5.2)
Mitral regurgitation	5177 (12.7)	205 (13.8)	0.21	3.3	5382 (12.7)
Previous endocarditis	321 (0.8)	77 (5.2)	<0.0001	26.0	398 (0.9)
Dilated cardiomyopathy	4673 (11.4)	156 (10.5)	0.26	−3.1	4829 (11.4)
Coronary artery disease	13 670 (33.5)	484 (32.5)	0.45	−2.0	14 154 (33.5)
Previous myocardial infarction	2597 (6.4)	106 (7.1)	0.23	3.1	2703 (6.4)
Previous percutaneous coronary intervention	3481 (8.5)	156 (10.5)	0.01	6.7	3637 (8.6)
Previous coronary artery bypass graft	665 (1.6)	33 (2.2)	0.08	4.3	698 (1.6)
Vascular disease	9594 (23.5)	422 (28.4)	<0.0001	11.2	10 016 (23.7)
Atrial fibrillation/flutter	32 376 (79.3)	767 (51.6)	<0.0001	−60.9	33 143 (78.3)
Sinus node disease	7870 (19.3)	187 (12.6)	<0.0001	−18.4	8057 (19.0)
Ischemic stroke	3136 (7.7)	117 (7.9)	0.79	0.7	3253 (7.7)
Intracranial bleeding	1305 (3.2)	52 (3.5)	0.52	1.7	1357 (3.2)
Smoker	2522 (6.2)	208 (14.0)	<0.0001	26.2	2730 (6.5)
Dyslipidemia	13 277 (32.5)	493 (33.2)	0.61	1.4	13 770 (32.5)
Obesity	9031 (22.1)	422 (28.4)	<0.0001	14.4	9453 (22.3)
Alcohol-related diagnoses	1953 (4.8)	105 (7.1)	0.0001	9.7	2058 (4.9)
Chronic kidney disease	6178 (15.1)	380 (25.6)	<0.0001	26.1	6558 (15.5)
Dialysis	833 (2.0)	253 (17.0)	<0.0001	52.7	1086 (2.6)
Lung disease	7281 (17.8)	301 (20.2)	0.02	6.1	7582 (17.9)
Sleep apnea syndrome	4340 (10.6)	184 (12.4)	0.03	5.5	4524 (10.7)
Chronic obstructive pulmonary disease	4325 (10.6)	182 (12.2)	0.04	5.2	4507 (10.7)
Liver disease	1857 (4.5)	117 (7.9)	<0.0001	13.8	1974 (4.7)
Thyroid diseases	5908 (14.5)	206 (13.9)	0.51	−1.8	6114 (14.4)
Inflammatory disease	4165 (10.2)	202 (13.6)	<0.0001	10.5	4367 (10.3)
Anemia	9090 (22.3)	497 (33.4)	<0.0001	25.1	9587 (22.7)
Previous cancer	7357 (18.0)	416 (28.0)	<0.0001	23.8	7773 (18.4)
Poor nutrition	6025 (14.8)	245 (16.5)	0.07	4.7	6270 (14.8)
Cognitive impairment	4892 (12.0)	90 (6.1)	<0.0001	−20.8	4982 (11.8)
Charlson comorbidity index	3.5±2.8	4.0±3.3	<0.0001	16.2	3.5±2.8
Frailty index	10.2±10.0	8.7±9.4	<0.0001	−17.8	10.1±10.0
EuroSCORE II	3.6±1.0	3.5±1.5	0.002	−20.5	3.5±1.1

Values are presented as n (%) or mean±SD.

Clinical Outcomes During Midterm Follow-Up

In the unmatched patients, mean follow-up was 8.6±10.5 months (median: 3.5 months, interquartile range: 0.2–14.8). Annual incidence of all-cause death was high in both groups and significantly higher in the LPM group than in CPM group (31%/year versus 20%/year, *P*<0.0001) with an HR of 1.519 (95% CI, 1.296–1.780) (Table 4 and Figure 2). Cardiovascular death was not significantly different between groups (Table 4, Figure 3). Infective endocarditis was higher in the LPM group than in the CPM group with an HR of

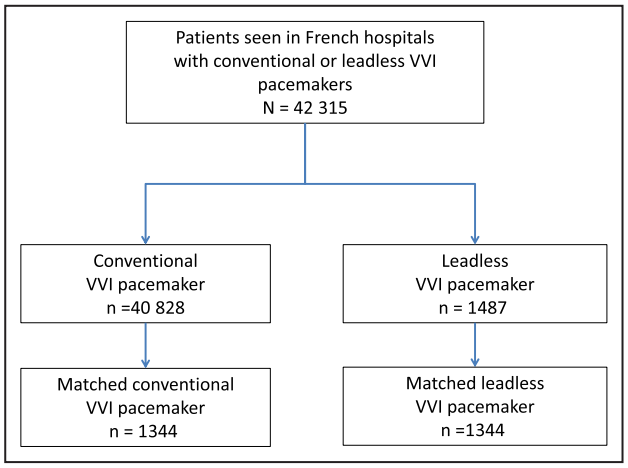

Figure 1. Flow chart of the study patients.
VVI indicates ventricular permanent pacemaker.

2.108 (95% CI, 1.119–3.973) (Table 4 and Figure 4). The same trends were found after adjustment on all risk factors described in Table 1 (Table S2).

An upgrade to cardiac resynchronization therapy during follow-up was needed for 6 patients (0.5%) in the LPM group and 12 patients (0.9%) in the CPM group (P=0.16).

In the matched patients, mean follow-up was 6.2±8.7 months (median: 1.9 months, interquartile range: 0.2–8.9 months). All-cause death, cardiovascular death, and infective endocarditis were not significantly different between groups (Table 4, Figures 2, 3, and 4).

DISCUSSION

We show on this exhaustive nationwide matched study that (1) mortality is high among unselected patients implanted with ventricular permanent pacemakers, whether leadless or conventional pacemaker are used; (2) implantation of leadless pacemakers seems to be a safe procedure in this high-risk population, with better outcomes at 1 month; (3) midterm outcomes appear relatively similar in patients with LPM and CPM, although the trends toward a marginally higher mortality with LPM need to be better evaluated in other large analyses.

Our study main strength is exhaustivity, as it included all patients implanted with an LPM in France and even in smaller centers who did not participate in any published registry.

Population Characteristics

Patients with LPM were younger but had more comorbidities compared with the CPM population. Mean age was 70.7 years but with more comorbidities: 17% of the patient were treated with hemodialysis and 28% had a history of cancer, which is consistent with the conditions of LPM reimbursement in France. Indeed, LPM is reimbursed in France for patients with high burden of comorbidities, that is, patients without suitable supracaval venous access, at high risk of lead-related complication (hemodialysis, chemotherapy via implantable chamber) or patients with previous endocarditis or sepsis.

Patients with CPM were older with fewer comorbidities. Mean age of recipients of CPM was 83.4 years with 53% of heart failure. Surprisingly, only 79% of patients had atrial fibrillation/flutter, which is a preferential indication for single-chamber ventricular pacemaker, suggesting a significant use for backup pacing.[15] Such rates were previously reported.[1] In the LPM group, 52% of patients had atrial fibrillation, which is lower than in the IDE and PAR studies but consistent with French reimbursement rules where indications are irrespective of atrial fibrillation status.

In both groups, mortality was high (31%/year and 20%/year for LPM and CPM groups, respectively). Our data are consistent with literature and similar yearly mortality rates with CPM were previously reported.[16] Such rates emphasize the frailty of both populations, which is confirmed by the high Charlson comorbidity index and frailty index scores. Frailty may play a significant role in deciding LPM implant in several health care systems. In our analysis, patients treated with LPM were younger than those treated with CPM before matching and had a low complication rate, which implies that LPMs can also be used in a younger cohort successfully and that frailty should not be the main driver for LPM implant.

Postoperative Complications

In the PAR of LPM, most of the complications appear within the first month. In our study, our patients had slightly lower tamponade rate (0.1% versus 0.4% in the PAR) but a higher major bleeding rate (2.8% versus 0.55% in the PAR).[6] This higher bleeding rate may be explained by our definition of major bleeding including device-related bleeding (groin hematoma, pocket hematoma, hemothorax) but also other bleeding (hemorrhagic stroke, gastrointestinal bleeding or significant bleeding that needed a transfusion).

There were no differences in pneumothorax between the 2 devices. Pneumothorax is unlikely to be related to leadless pacemaker implantation and we cannot be sure that the complications listed are a result of the procedures, or simply a coexisting diagnosis in the same patient. For example, some patients could have a CPM failure because of venous access difficulties resulting in pneumothorax and LPM implantation. The same concern may be true for other complications that may as well be attributed to possible pacemaker complications (eg, transfusion, major bleeding etc).

Table 2. Baseline Characteristics of Matched Patients

	Conventional VVI pacemaker (n=1344)	Leadless VVI pacemaker (n=1344)	*P* value	Standardized difference, (%)	Total (n=2688)
Age, y	73.5±17.2	73.5±15.2	0.99	−0.1	73.6±16.2
Sex (male)	803 (59.7)	787 (58.6)	0.53	−2.4	1590 (59.2)
Hypertension	951 (70.8)	927 (69.0)	0.31	−4.0	1878 (69.9)
Diabetes	430 (32.0)	408 (30.4)	0.36	−3.7	838 (31.2)
Heart failure	726 (54.0)	668 (49.7)	0.03	−8.6	1394 (51.9)
Valve disease	474 (35.3)	448 (33.3)	0.29	−4.2	922 (34.3)
Aortic stenosis	269 (20.0)	260 (19.3)	0.66	−1.8	529 (19.7)
Aortic regurgitation	87 (6.5)	79 (5.9)	0.52	−2.6	166 (6.2)
Mitral regurgitation	204 (15.2)	193 (14.4)	0.55	−2.4	397 (14.8)
Previous endocarditis	75 (5.6)	66 (4.9)	0.44	−4.0	141 (5.2)
Dilated cardiomyopathy	162 (12.1)	144 (10.7)	0.27	−4.3	306 (11.4)
Coronary artery disease	446 (33.2)	457 (34.0)	0.65	1.7	903 (33.6)
Previous myocardial infarction	110 (8.2)	99 (7.4)	0.43	−3.3	209 (7.8)
Previous percutaneous coronary intervention	139 (10.3)	147 (10.9)	0.62	2.0	286 (10.6)
Previous coronary artery bypass graft	31 (2.3)	29 (2.2)	0.79	−1.1	60 (2.2)
Vascular disease	395 (29.4)	386 (28.7)	0.7	−1.5	781 (29.1)
Atrial fibrillation/flutter	795 (59.2)	746 (55.5)	0.06	−8.0	1541 (57.4)
Sinus node disease	218 (16.2)	184 (13.7)	0.07	−6.9	402 (15.0)
Ischemic stroke	116 (8.6)	107 (8.0)	0.53	−2.5	223 (8.3)
Intracranial bleeding	49 (3.6)	44 (3.3)	0.6	−2.1	93 (3.5)
Smoker	187 (13.9)	174 (12.9)	0.46	−3.2	361 (13.4)
Dyslipidemia	484 (36.0)	460 (34.2)	0.33	−3.8	944 (35.1)
Obesity	401 (29.8)	387 (28.8)	0.55	−2.4	788 (29.3)
Alcohol-related diagnoses	106 (7.9)	92 (6.8)	0.3	−4.4	198 (7.4)
Chronic kidney disease	352 (26.2)	323 (24.0)	0.2	−5.4	675 (25.1)
Dialysis	224 (16.7)	190 (14.1)	0.07	−8.9	414 (15.4)
Lung disease	289 (21.5)	277 (20.6)	0.57	−2.3	566 (21.1)
Sleep apnea syndrome	176 (13.1)	166 (12.4)	0.56	−2.3	342 (12.7)
Chronic obstructive pulmonary disease	176 (13.1)	169 (12.6)	0.69	−1.6	345 (12.8)
Liver disease	111 (8.3)	103 (7.7)	0.57	−2.5	214 (8.0)
Thyroid diseases	184 (13.7)	189 (14.1)	0.78	1.1	373 (13.9)
Inflammatory disease	189 (14.1)	181 (13.5)	0.65	−1.8	370 (13.8)
Anemia	460 (34.2)	432 (32.1)	0.25	−4.7	892 (33.2)
Previous cancer	355 (26.4)	385 (28.6)	0.2	5.3	740 (27.6)
Poor nutrition	244 (18.2)	219 (16.3)	0.2	−5.1	463 (17.2)
Cognitive impairment	101 (7.5)	87 (6.5)	0.29	−3.7	188 (7.0)
Charlson comorbidity index	4.1±3.3	4.1±3.3	0.52	−2.6	4.1±3.3
Frailty index	9.6±10.1	8.9±9.4	0.06	−4.2	9.2±9.8
EuroSCORE II	3.6±1.5	3.5±1.5	0.82	−4.6	3.6±1.5

Values are presented as n (%) or mean±SD. VVI indicates ventricular permanent pacemaker.

Overall, our data from this nationwide cohort indicate that LPM as an alternative to CPM appears safe within the first month.

Midterm Outcomes

All-cause mortality was slightly higher in LPM than in the CPM group. However, after matching on baseline characteristics, all-cause and cardiovascular mortalities did not significantly differ. As described before, recipients of CPM were older, but patients with LPM had numerous comorbidities such as hemodialysis which is one of the preferential indication.[17] In the CED (Micra Coverage With Evidence Development) study, all-cause mortality was similar at 6 months between

Table 3. Clinical Outcomes and Complications at Day 30 in the Unmatched and Matched Cohort of Patients With Conventional or Leadless VVI Pacing

	Conventional VVI pacemaker	Leadless VVI pacemaker	OR (95% CI) for leadless vs conventional VVI	*P* for conventional vs leadless VVI
Unmatched patients	**(n=40 828)**	**(n=1487)**		
All-cause death	5115 (12.5)	124 (8.3)	0.635 (0.527–0.765)	<0.0001
Cardiovascular death	1663 (4.1)	35 (2.4)	0.568 (0.405–0.797)	0.001
Tamponade	18 (0.0)	1 (0.1)	1.526 (0.204–11.436)	0.68
Pneumothorax	41 (0.1)	2 (0.1)	1.340 (0.324–5.544)	0.69
Hemothorax	21 (0.1)	1 (0.1)	1.308 (0.176–9.728)	0.79
Major bleeding	2494 (6.1)	42 (2.8)	0.447 (0.328–0.609)	<0.0001
Transfusion	1899 (4.7)	30 (2.0)	0.422 (0.293–0.608)	<0.0001
Matched patients	**(n=1344)**	**(n=1344)**		
All-cause death	189 (14.1)	117 (8.7)	0.583 (0.456–0.744)	<0.0001
Cardiovascular death	75 (5.6)	32 (2.4)	0.413 (0.271–0.629)	<0.0001
Tamponade	1 (0.1)	1 (0.1)	1.000 (0.062–16.004)	1.00
Pneumothorax	1 (0.1)	2 (0.2)	2.001 (0.181–22.099)	0.57
Hemothorax	1 (0.1)	1 (0.1)	1.000 (0.062–16.004)	1.00
Major bleeding	69 (5.1)	37 (2.8)	0.523 (0.348–0.786)	0.002
Transfusion	51 (3.8)	25 (1.9)	0.481 (0.296–0.780)	0.003

Values are presented as n (%). OR indicates odds ratio; and VVI, ventricular permanent pacemaker.

the 2 groups.[18] However, French and US population of LPM were not similar. In CED, they were older, had more atrial fibrillation, but had less comorbidities such as chronic kidney disease. This might be explained by the specific patient selection in France related to the reimbursement conditions previously mentioned. Even if both studies cannot be directly compared, after propensity matching on baseline characteristics, similar results were obtained in our cohort, with no significant difference on all-cause mortality.

LPM was associated with a significant higher risk of all-cause death, which was significant in the multivariable Cox model and not significant in the propensity matched analysis. Interestingly, there were no significant differences on cardiovascular death between the 2 groups. First, one cannot exclude that this may be related to the device, which is unlikely considering numerous evidences in literature.[6,18,19] Second, even though multivariable adjustment and matching was done, it cannot fully eradicate the possible confounding variables between these groups and patients treated with LPM may be sicker on some aspects not captured by the baseline characteristics. Third, it is finally possible that these trends in a "real-world" analysis are more generally related to the health system. However, our study was not designed to answer such question and a randomized clinical trial comparing LPM and CPM would be interesting in the future.

In our study LPM was associated to a higher rate of endocarditis compared with patients with CPM. To our

Table 4. Incident Outcomes in Unmatched and Matched Patients With Conventional or Leadless VVI Pacing

	Conventional VVI pacemaker		Leadless VVI pacemaker		*P* for conventional vs leadless VVI	Hazard ratio (95% CI) associated with leadless VVI pacing (vs conventional VVI pacing)
	Person-time (patient.year)	Incidence, %/year (95% CI)	Person-time (patient.year)	Incidence, %/year (95% CI)		
Unmatched patients						
All-cause death	29 871	19.71 (19.21–20.22)	508	31.08 (26.60–36.33)	<0.0001	1.519 (1.296–1.780)
Cardiovascular death	29 871	7.27 (6.98–7.59)	508	10.23 (7.80–13.43)	0.24	1.179 (0.894–1.553)
Infective endocarditis	29 478	0.94 (0.83–1.05)	473	2.11 (1.14–3.93)	0.02	2.108 (1.119–3.973)
Matched patients						
All-cause death	915	23.93 (20.96–27.32)	466	32.19 (27.43–37.77)	0.13	1.178 (0.952–1.457)
Cardiovascular death	915	10.49 (8.59–12.81)	466	10.30 (7.76–13.67)	0.17	0.782 (0.550–1.112)
Infective endocarditis	850	1.29 (0.72–2.34)	437	2.29 (1.23–4.25)	0.33	1.543 (0.643–3.700)

OR indicates odds ratio; and VVI, ventricular permanent pacemaker.

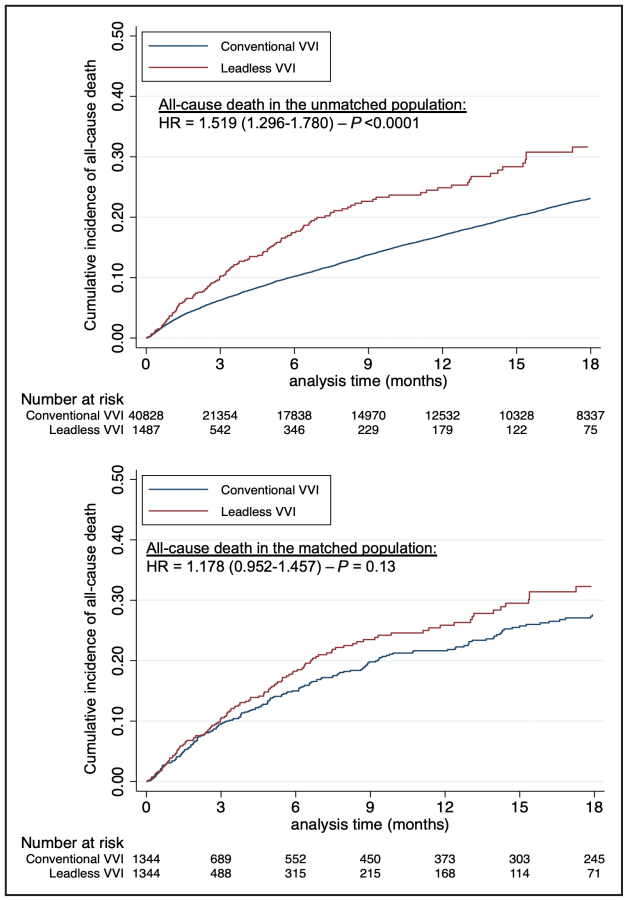

Figure 2. Cumulative incidences for all-cause death in unmatched (top panel) or matched (lower panel) patients during follow-up.
HR indicates hazard ratio; and VVI, ventricular permanent pacemaker.

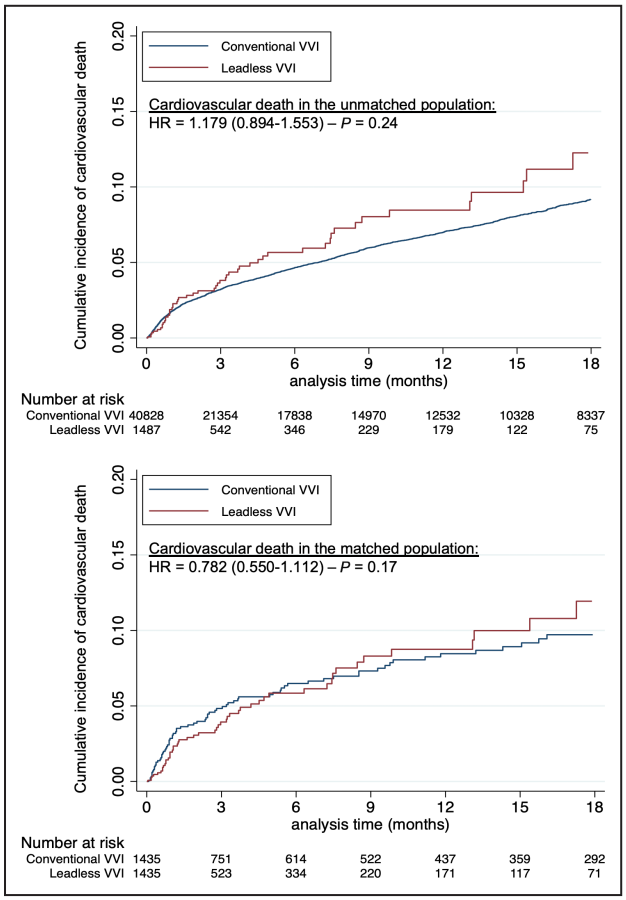

Figure 3. Cumulative incidences for cardiovascular death in unmatched (top panel) or matched (lower panel) patients during follow-up.
HR indicates hazard ratio; and VVI, ventricular permanent pacemaker.

knowledge, as in the leadless clinical trials, no device-related infections required removal of the leadless pacemaker during the follow-up.[20] Infective endocarditis cannot be defined t only o device-related endocarditis and also occurs on left-sided valves in recipients of pacemakers.[21] In our opinion, LPM implantation was associated with a higher rate of right- and left-sided endocarditis in the unmatched population again possibly owing to the specific reimbursement conditions (patients with previous endocarditis). Indeed, the LPM group had a higher rate of previous endocarditis rate (5.2% versus 0.8% of patients in the CPM group) and patients with prior endocarditis are at higher risk of recurrence.[22] This is emphasized by the nonsignificant differences observed in the multivariable and propensity-matched analyses.

As previously described,[23] LPM appears safe in patients where CPM cannot be implanted because of a difficult supracaval venous access or a high risk of lead-related complications for example. However, patients eligible for CPM remain fragile with high mortality rates, and an economic evaluation comparing both technologies may be warranted, as a lower complication rate and associated costs within the first month should be offset with a higher device cost.[1–3]

Study Limitations

The main limitation of this study was inherent to its retrospective observational nature. However, *ICD-10* is considered reliable in cardiovascular diseases and their risk factors.[7,24,25]

Data were based on the diagnostic codes registered for reimbursement purposes by a responsible physician and were not checked externally with a potential information bias. Events included were only in hospital, and we had no data on extra-hospital diagnoses. However, cardiac devices are almost exclusively managed in hospital facilities in our (as in most other) health care system. Further, the nonrandomized design of the analysis leaves a risk of residual confounding factors. Definite conclusions for comparisons between groups may not be fully appropriate

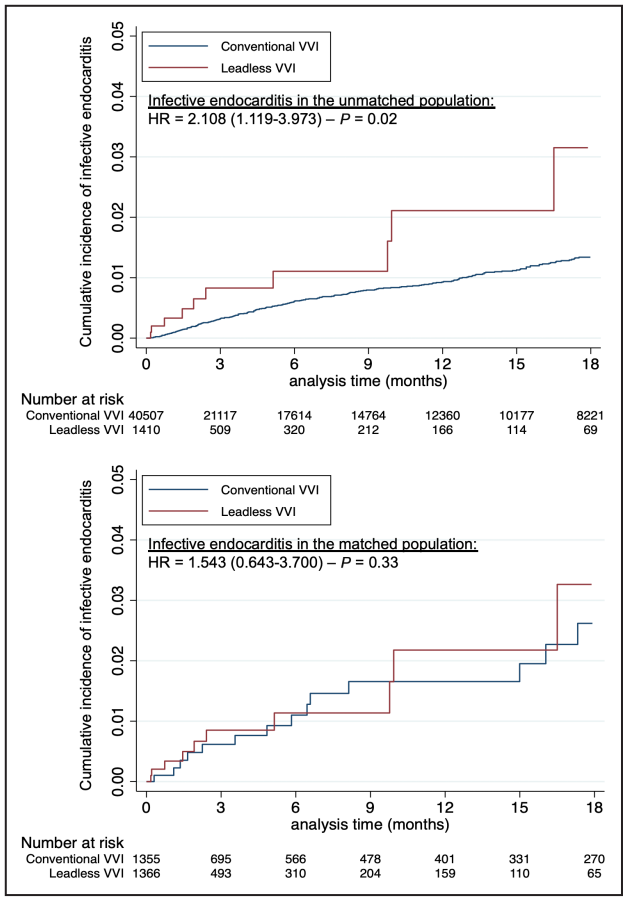

Figure 4. Cumulative incidences for first diagnosis of infective endocarditis in unmatched (top panel) or matched (lower panel) patients during follow-up.
HR indicates hazard ratio; and VVI, ventricular permanent pacemaker.

even though multivariable matching was done, as it cannot fully eradicate the possible confounding variables between these groups.

In our study, we mainly focused on shared complications with the 2 techniques, that is, tamponade and major bleeding. Then, we made the choice to focus on hard clinical outcomes as we were not able to confidently retrieve data on CPM's lead revision and device pocket complications or on LPM's embolization/dislodgement. Moreover, such data are already well described in the IDE and PAR studies.

Data on anticoagulation were not available in our database. Results on major bleeding must be analyzed with caution. However, results are similar before and after matching on baseline characteristics such as atrial fibrillation, which is one of the main reasons for anticoagulation among our population.

Device parameters at discharge or during follow-up were lacking because they are not available in this administrative nationwide database. However, the French health care system provides a routine follow-up by a cardiologist experienced in cardiac devices. We may consider that appropriate care was given when needed in both groups.

A referral center bias may also exist in our analysis. Indeed, some centers with appropriate patients for LPM selection may not have access to this modality or do not have the capacity to make an immediate referral and may prefer a CPM implantation.

CONCLUSIONS

Mortality is high among unselected patients implanted with ventricular permanent pacemakers, whether leadless or conventional pacemaker are used.

Patients treated with leadless VVI pacemakers had better clinical outcomes in the first month compared with the patients treated with conventional VVI pacing.

During a mid-erm follow-up, risk of all-cause death, cardiovascular death, and endocarditis in patients treated with leadless VVI pacemaker was not statistically different after propensity score matching.

ARTICLE INFORMATION

Received January 10, 2022; accepted June 17, 2022.

Affiliations

Service de Cardiologie, Centre Hospitalier Universitaire Trousseau (A.Bodin, N.C., A.Bisson, B.P., J.H., D.B., L.F.) and Service d'information médicale, d'épidémiologie et d'économie de la santé, Centre Hospitalier Universitaire et EA7505 (J.H.), Faculté de Médecine, Université François Rabelais, Tours, France.

Sources of Funding

None.

Disclosures

Nicolas Clementy reports consulting or speaking for Abbott, Biotronik, Medtronic, and Microport. Bertrand Pierre reports consulting or speaking for Abbott, Biotronik, Boston Scientific, and Microport. Dominique Babuty reports consulting or speaking for Biotronik, Boston Scientific, and Medtronic. Laurent Fauchier reports consulting or speaking for Bayer, BMS/Pfizer, Boehringer Ingelheim, Medtronic, and Novartis. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S2
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Odds ratio (95% CI) associated with leadless VVI pacing (vs conventional VVI pacing) for incident outcomes at day 30.

	Model A	Model B	Model C
All-cause death	0.635 (0.527-0.765)	0.679 (0.552-0.834)	0.583 (0.456-0.744)
Cardiovascular death	0.568 (0.405-0.797)	0.661 (0.463-0.942)	0.413 (0.271-0.629)
Tamponade	1.526 (0.204-11.436)	1.248 (0.131-11.883)	1.000 (0.062-16.004)
Pneumothorax	1.340 (0.324-5.544)	1.451 (0.322-6.544)	2.001 (0.181-22.099)
Hemothorax	1.308 (0.176-9.728)	1.013 (0.116-8.826)	1.000 (0.062-16.004)
Major bleeding	0.447 (0.328-0.609)	0.536 (0.388-0.739)	0.523 (0.348-0.786)
Transfusion	0.422 (0.293-1.194)	0.478 (0.328-0.697)	0.481 (0.296-0.780)

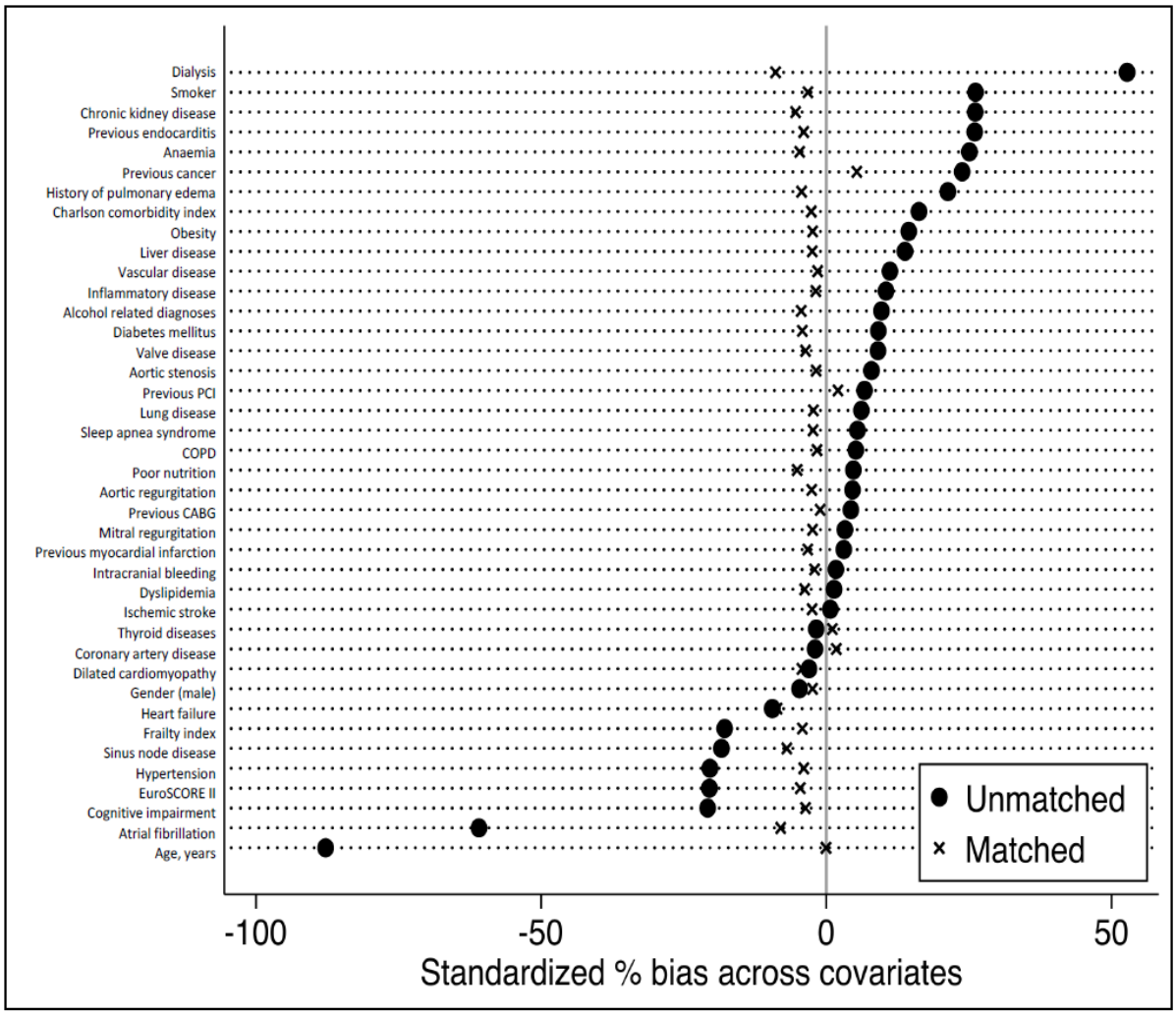
Model A: unadjusted.
Model B: adjusted on all risk factors from Table 1.
Model C: propensity score matched analysis.

Table S2. Hazard ratio (95% CI) associated with leadless VVI pacing (vs conventional VVI pacing) for incident outcomes.

	Model A	Model B	Model C
All-cause death	1.519 (1.296-1.780)	1.594 (1.350-1.881)	1.178 (0.952-1.457)
Cardiovascular death	1.179 (0.894-1.553)	1.308 (0.983-1.742)	0.782 (0.550-1.112)
Infective endocarditis	2.108 (1.119-3.973)	1.222 (0.620-2.406)	1.543 (0.643-3.700)

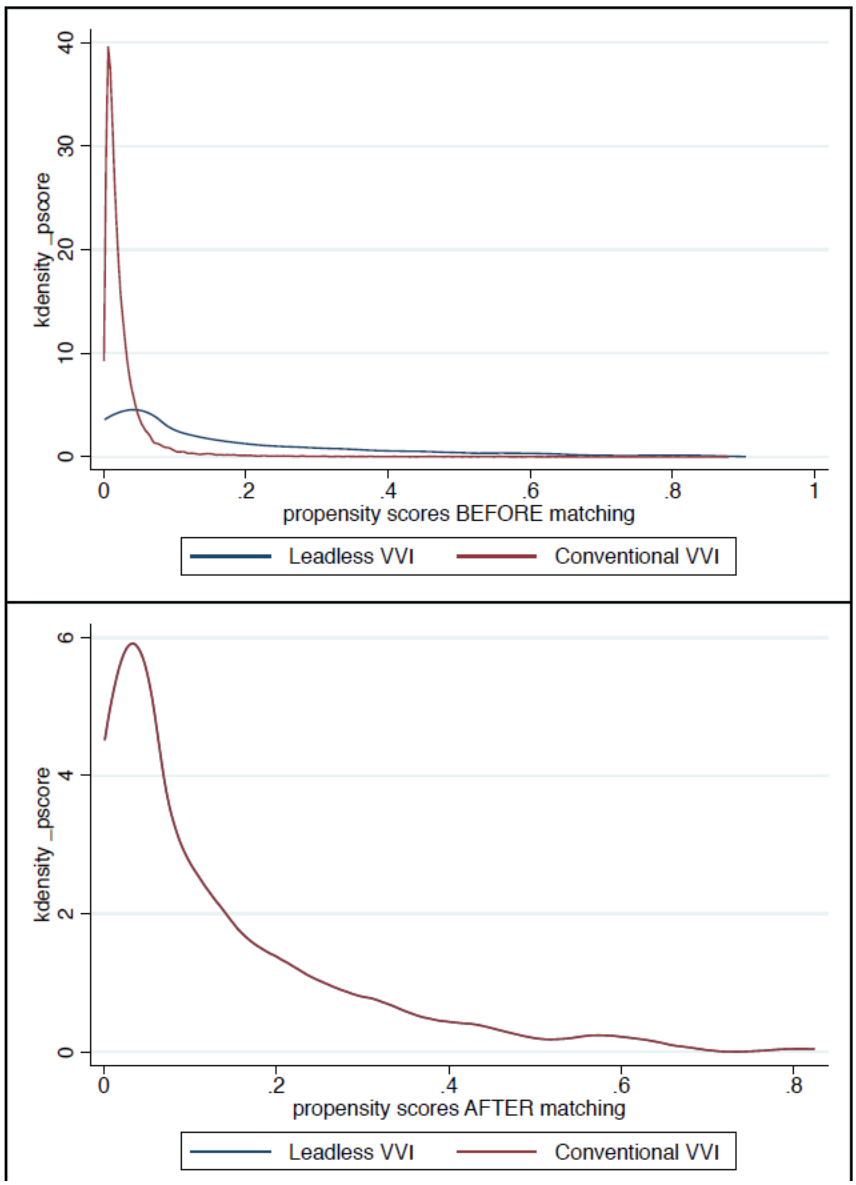
Model A: unadjusted.
Model B: adjusted on all risk factors from Table 1.
Model C: propensity score matched analysis.

Figure S1. Standardized percentages of bias across main baseline characteristics in unmatched and matched patients with conventional or leadless VVI pacing.



CABG: Coronary artery bypass graft, COPD: Chronic obstructive pulmonary disease, PCI: percutaneous coronary intervention, VVI: ventricular permanent pacemaker.

Figure S2. Propensity score distribution for unmatched and matched populations of patients with conventional or leadless VVI pacing.



VVI: ventricular permanent pacemaker.