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FASTTRACK CLINICAL RESEARCH
Arrhythmias

Leadless vs. transvenous single-chamber ventricular pacing in the Micra CED study: 2-year follow-up

Mikhael F. El-Chami[1]*, Lindsay Bockstedt[2], Colleen Longacre[2], Lucas Higuera[2], Kurt Stromberg[2], George Crossley[3], Robert C. Kowal[2], and Jonathan P. Piccini [4]

[1]Emory University School of Medicine, 550 W Peachtree St NE, Atlanta, GA 30308, USA; [2]Medtronic, Inc, 710 Medtronoc PKW NE, Minneapolis, MN 55432, USA; [3]Vanderbilt University Medical Center, 1161 21ST Ave S, Nashville, TN 37232, USA; and [4]Duke University Medical Center & Duke Clinical Research Institute, 40 Duke Medicine Circle Clinic 2F/2 G, Durham, NC 27710, USA

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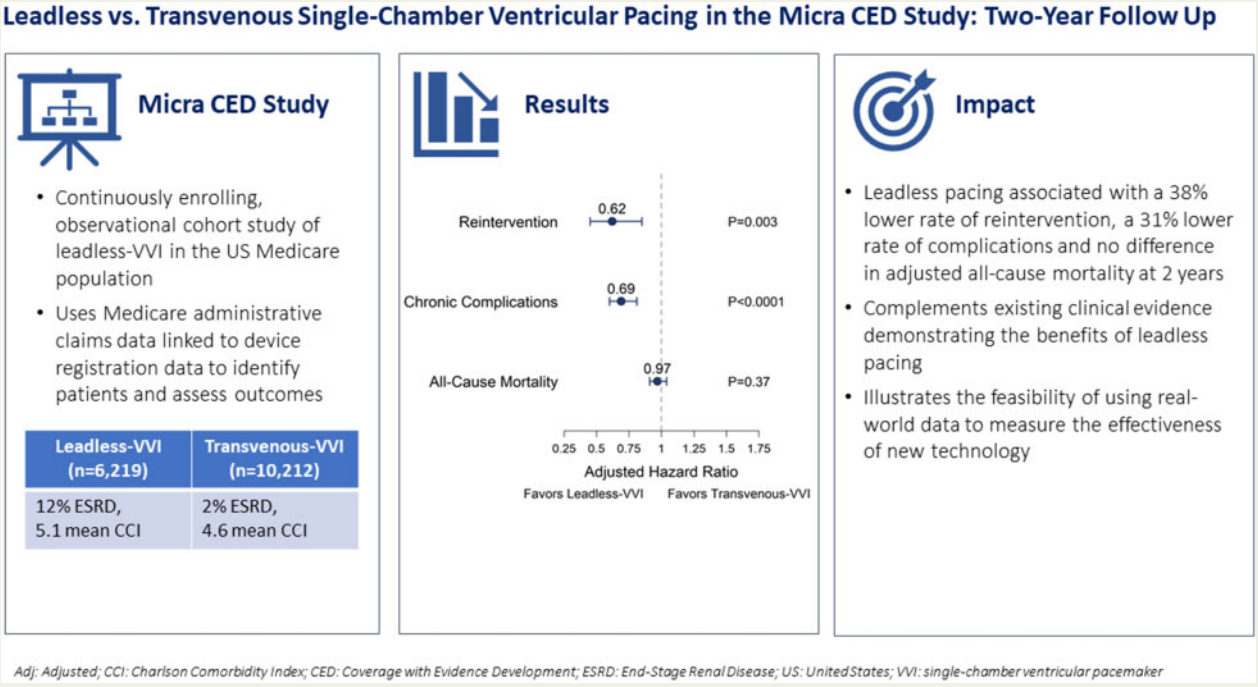
Aims Clinical trials have demonstrated the safety and efficacy of the Micra leadless VVI pacemaker; however, longer-term outcomes in a large, real-world population with a contemporaneous comparison to transvenous VVI pacemakers have not been examined. We compared reinterventions, chronic complications, and all-cause mortality at 2 years between leadless VVI and transvenous VVI implanted patients.

Methods and results The Micra Coverage with Evidence Development study is a continuously enrolling, observational, cohort study of leadless VVI pacemakers in the US Medicare fee-for-service population. Patients implanted with a leadless VVI pacemaker between March 9, 2017, and December 31, 2018, were identified using Medicare claims data linked to manufacturer device registration data ($n = 6219$). All transvenous VVI patients from facilities with leadless VVI implants during the study period were obtained directly from Medicare claims ($n = 10\,212$). Cox models were used to compare 2-year outcomes between groups. Compared to transvenous VVI, patients with leadless VVI had more end-stage renal disease (12.0% vs. 2.3%) and a higher Charlson comorbidity index (5.1 vs. 4.6). Leadless VVI patients had significantly fewer reinterventions [adjusted hazard ratio (HR) 0.62, 95% confidence interval (CI) 0.45–0.85, $P = 0.003$] and chronic complications (adjusted HR 0.69, 95% CI 0.60–0.81, $P < 0.0001$) compared with transvenous VVI patients. Adjusted all-cause mortality at 2 years was not different between the two groups (adjusted HR 0.97, 95% CI 0.91–1.04, $P = 0.37$).

Conclusion In a real-world study of US Medicare patients, the Micra leadless VVI pacemaker was associated with a 38% lower adjusted rate of reinterventions and a 31% lower adjusted rate of chronic complications compared with transvenous VVI pacing. There was no difference in adjusted all-cause mortality at 2 years.

* Corresponding author. Tel: +1 404 686 2504, Fax: +1 404 686 4826, Email: melcham@emory.edu

Graphical Abstract



Keywords Leadless pacemakers • Transvenous pacemakers • System reintervention • Complications • Survival

Introduction

Leadless pacemakers are an available pacing option for patients with bradycardia. These pacemakers are capsule-like devices that are completely intracardiac, positioned in the right ventricle, and typically placed at the interventricular septum. By virtue of their design, these pacemakers have the potential to reduce lead and pocket-related complications, two major drawbacks of traditional transvenous pacemakers. Currently, the Micra™ Transcatheter Pacing System is the only leadless pacemaker available on the global market, with regulatory approval in geographies including the European Union, the UK, Asia Pacific, and the USA. The pivotal Micra Investigational Device Exemption (IDE) study showed that this device can be successfully and safely implanted in patients with bradyarrhythmias.[1] In the IDE study, Micra was associated with a 48% reduction in major complications when compared to a historical cohort of transvenous pacemaker patients.[2] Most notable in this study were the absence of device dislodgment and device or procedure-related infection. These results were confirmed in the Micra Post-Approval Registry (PAR) that enrolled >1800 patients with pacing indications.[3]

Following Food and Drug Administration approval in 2016, the Center for Medicare and Medicaid Services (CMS) issued a National Coverage Determination (NCD) for leadless pacemakers in January 2017. This NCD requires Coverage with Evidence Development (CED) that mandates all Medicare beneficiaries receiving a leadless pacemaker to be enrolled in a CMS-approved CED study.[4] The Micra CED study relies on administrative claims data to assess the complications encountered with Micra leadless VVI devices as compared to a contemporaneous comparator cohort of patients implanted with a transvenous single-chamber ventricular pacemaker. This unique and novel study allows CMS to provide coverage for leadless pacemakers while constantly monitoring the performance of this new technology as it is widely implemented. It is also a continuously enrolling study until CMS determines that there is enough evidence to support or negate national coverage.

Acute and 6-month outcomes of the Micra CED study have been previously reported.[5] Leadless VVI pacemaker implants were associated with higher rates of pericardial effusion, but lower rates of other device-related complications and need for system revision at 6 months. The objective of this analysis is to evaluate and compare device reinterventions, chronic complications, and all-cause mortality at 2 years between leadless VVI and transvenous VVI pacemakers.

Methods

Study design and population

The design of the Micra CED study has been described previously.[5,6] The CED study is a continuously enrolling cohort study designed to evaluate

complications, utilization, and outcomes of the leadless-VVI pacing system in the US Medicare population. The study uses administrative claims data to enrol patients, ascertain patient characteristics, identify comorbidities, and measure outcomes. In addition, patients receiving a transvenous VVI pacemaker, regardless of manufacturer, during the study period were included as a contemporaneous control group. The study was approved by the Western Institutional Review Board with a waiver of informed consent and is registered on ClinicalTrials.gov (NCT03039712).

Database

We used Medicare claims and enrollment data from March 9, 2017, to December 31, 2018, and linked it to manufacturer device registration information to identify Medicare beneficiaries implanted with a Micra leadless pacemaker (Model MC1VR01, Medtronic, Inc), employing a previously described methodology.[6] We identified patients implanted with a transvenous VVI pacemaker using the International Classification of Diseases, 10th Revision, Procedure Coding System for implants occurring in the inpatient hospital setting and Current Procedural Terminology for implants occurring in the outpatient hospital setting, as defined in Supplementary material online, *Table S1*. We also limited transvenous VVI patients to hospitals that implanted leadless VVI pacemakers during the study period. This selective inclusion criteria potentially could minimize selection bias based on the assumption that patients implanted in these hospitals have the chance to receive either system.

The index date for outcomes ascertainment was the date of first observed pacemaker implant procedure during the study period. We excluded patients with <12 months of continuous enrolment in Medicare fee-for-service (FFS) prior to implant and patients with a prior cardiac implantable electronic device (CIED) to compare patients with *de novo* pacemaker implants.

Baseline comorbidities and encounter characteristics

Diagnosis and procedure codes present on any encounter during a 12-month lookback period, as defined in Supplementary material online, *Table S2*, were used to determine baseline patient comorbidities. This included end-stage renal disease (ESRD), renal dysfunction, coronary artery disease, peripheral vascular disease, tricuspid valve disease, atrial fibrillation, left bundle branch block, supraventricular tachycardia, ventricular arrythmia, steroid use, diabetes, heart failure, chronic obstructive pulmonary disease, hyperlipidaemia, and hypertension. History of any cardiovascular events and procedures (acute myocardial infarction, coronary artery bypass graft, transcatheter aortic valve, and percutaneous coronary intervention) and concomitant transcatheter aortic valve replacement and atrial fibrillation ablation were also included. In addition, the Charlson comorbidity index was calculated for each patient.[7] Age, sex, and US region were identified in the CMS enrolment file. Hospital presentation characteristics were also noted: inpatient or outpatient hospital setting, admission through an emergency department, admission during the weekend, and the number of days from hospital admission to implant procedure.

Study objectives

The primary aims of the overall Micra CED study were to determine acute (30-day) complications and 2-year survival rate in patients implanted with the Micra transcatheter pacing system (TPS) vs. transvenous VVI pacemakers. The secondary objectives of this study were to compare acute and chronic complications including requirements for system revisions between leadless VVI and transvenous VVI devices. Acute results have previously been reported.[5]

Outcomes

The present analysis focuses on a comparative analysis of device reinterventions, chronic complications, and mortality at 2 years between leadless VVI and transvenous VVI patients. Device reinterventions were identified using the relevant procedure codes and were defined as system revision, lead revision or replacement, system replacement (e.g. replacing a leadless VVI with a leadless VVI), system removal, switch to the alternative type of system (switch from leadless VVI to transvenous VVI or transvenous VVI to leadless VVI), upgrade to a dual-chamber system, or upgrade to a cardiac resynchronization therapy (CRT) device (Supplementary material online, *Table S1*). Chronic complications were prospectively defined as those most likely attributable to the device implant or the device itself that may continue to occur outside the acute period and included embolism, thrombosis, device-related complications, including device breakdown, dislodgment, infection, and pocket complications, pericarditis, and hemothorax (Supplementary material online, *Table S2*). Billing claims were available through December 31, 2019; patients without an event were censored on that date.

Statistical analysis

T-tests and Chi-square tests were used to compare continuous and categorical baseline and encounter characteristics, respectively. Standardized mean differences were also used to quantify imbalance between groups with values exceeding 0.1 suggesting imbalance.[8]

Propensity score overlap weights[9] were used to account for differences in baseline and encounter characteristics between the leadless VVI and transvenous VVI cohorts. A logistic regression model that included patient baseline and encounter characteristics was used to compute the propensity (i.e. probability) for each patient to be implanted with a leadless VVI pacemaker. These scores were used to construct an overlap weight for each patient and used as weights in the analyses described below. Overlap weights estimate the probability of receiving therapy with the opposing treatment based on characteristics used to construct the propensity score and place the most weight on patients considered the most exchangeable and the least emphasis on patients who are least likely to receive the opposing therapy. An advantage of using overlap weights as opposed to other weighting techniques is that they are bounded by zero and one and thus avoid arbitrary trimming or extreme weights.[10]

Unadjusted and overlap-weight adjusted 2-year reintervention rates were estimated using the cumulative incidence function. Fine–Gray competing risk models were used to compare the unadjusted and adjusted risk for 2-year device-related reinterventions and chronic complications between study groups, given that the competing risk of death may preclude these events. Unadjusted and overlap-weighted Cox proportional hazards models were used to compare all-cause mortality through 2 years. Standard error was correlated at the hospital level in unadjusted and adjusted models to account for within-hospital correlation. Events occurring between one and 10 patients were suppressed to protect beneficiary privacy as required by CMS.[11] All statistical analyses were conducted in SAS version 9.4 (SAS Institute).

Results

Cohort formation and baseline characteristics

Overall, there were 6219 leadless VVI and 10 212 transvenous VVI *de novo* implant procedures identified during the study period contributing to the analysis cohort (*Figure 1*). Patient baseline characteristics are detailed in *Table 1*. Compared with transvenous VVI patients,

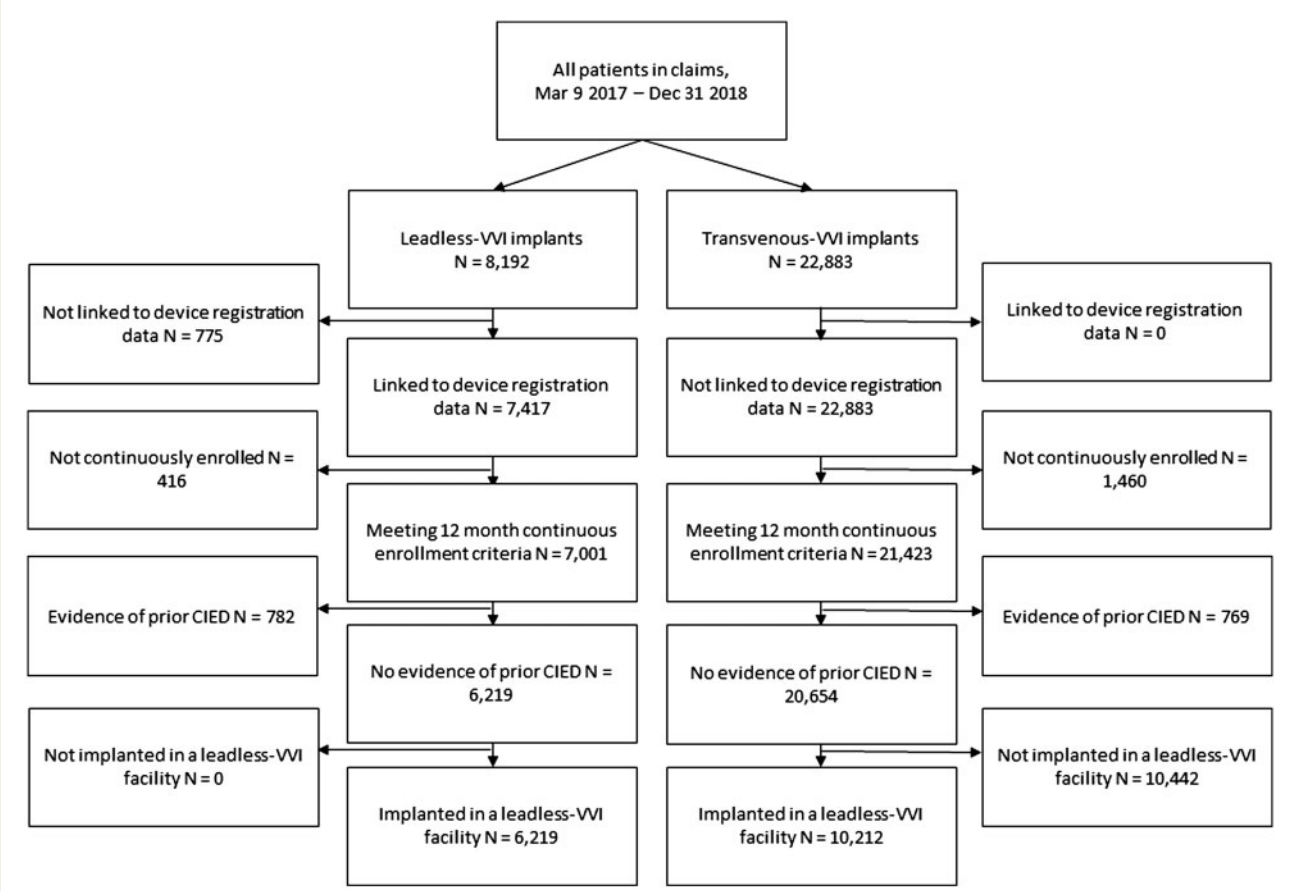


Figure 1 Cohort formation flow chart. Chart showing patient selection and exclusion criteria and the numbers of patients excluded/included at each step. CIED, cardiac implantable electronic device.

leadless VVI patients were more likely to have ESRD (12.0% vs. 2.3%, $P < 0.0001$), renal dysfunction (48.8% vs. 42.1%, $P < 0.0001$), and a higher mean Charlson comorbidity index score (5.1 ± 3.4 vs. 4.6 ± 3.0, $P < 0.0001$). The mean follow-up time for leadless VVI patients was 477 days, compared to 518 days for transvenous VVI patients ($P < 0.001$). After weighting, all measured baseline and encounter characteristics were well balanced with all standardized mean differences near zero (Supplementary material online, *Figure S1*). The study included all centres implanting Micra VR from 2017 to 2018, which comprised 941 providers. Across all centres, 38% of implants were leadless and 62% were transvenous single chamber. The proportion of leadless/transvenous systems at individual centres ranged from 3% leadless to 96% leadless (median: 34%, interquartile range: 20–50%).

Reinterventions

Table 2 shows the adjusted reintervention rates observed for leadless VVI and transvenous VVI patients. Both the unadjusted and adjusted overall reintervention rates were significantly lower in the leadless VVI patients compared with the transvenous VVI patients (unadjusted 3.0% vs. 4.8%, $P = 0.006$; adjusted 3.1% vs. 4.9%, $P = 0.003$). System revisions, removals, and upgrades to CRT were significantly lower in the leadless VVI patients compared with the transvenous VVI patients, while same device replacements were significantly higher among leadless patients (unadjusted 1.1% vs. 0.4%, $P = 0.002$; adjusted 1.1% vs. 0.4%, $P = 0.002$). The rate of lead-related reintervention among transvenous VVI patients was 0.7%. In the time-to-event Fine–Gray competing risks model, patients implanted with a leadless VVI pacemaker had a lower rate of reintervention compared with patients implanted with a transvenous VVI pacemaker [unadjusted hazard ratio (HR) 0.63; 95% confidence interval (CI) 0.45–0.88; adjusted HR 0.62; 95% CI 0.45–0.85; *Figure 2A*). Unadjusted reintervention rates are shown in Supplementary material online, *Table S3*.

Chronic complications

Table 3 details the adjusted rates for chronic complications. Both the unadjusted and adjusted overall chronic complication rate was significantly lower in the leadless VVI patients compared with the transvenous VVI patients (unadjusted 4.9% vs. 6.5%, $P = 0.0001$; adjusted 4.6% vs. 6.5%, $P < 0.0001$). Patients implanted with a leadless VVI pacemaker had significantly fewer overall chronic complications at 2 years compared with patients implanted with a transvenous VVI pacemaker (*Figure 2B*; unadjusted HR 0.75; 95% CI 0.65–0.87, $P = 0.0001$; adjusted HR 0.69; 95% CI 0.60–0.81, $P < 0.0001$). Leadless

Table 1 Baseline characteristics of patients undergoing *de novo* implantation with a leadless VVI pacemaker vs. a transvenous VVI pacemaker

Patient characteristics	Leadless VVI ($n = 6219$)	Transvenous VVI ($n = 10\,212$)	SMD[b]	*P*-Value
Demographic characteristics				
Age	79.5 ± 9.5	82.0 ± 8.1	0.29	<0.0001
Female sex	2741 (44.1%)	4412 (43.2%)	0.02	0.275
Midwest	1351 (21.7%)	2191 (21.5%)	0.01	0.685
South	2506 (40.3%)	3904 (38.2%)	0.04	0.008
Northeast	1051 (16.9%)	2266 (22.2%)	0.13	<0.0001
Encounter characteristics				
Inpatient implant	3309 (53.2%)	5790 (56.7%)	0.07	<0.0001
Days to implant	2.5 ± 5.3	1.9 ± 3.6	0.12	<0.0001
Weekend implant	163 (2.6%)	353 (3.5%)	0.05	0.003
Admission through the ED	745 (12.0%)	1105 (10.8%)	0.04	0.022
Clinical characteristics				
ESRD	744 (12.0%)	238 (2.3%)	0.38	<0.0001
Diabetes	2805 (45.1%)	4222 (41.3%)	0.08	<0.0001
Atrial fibrillation	5066 (81.5%)	9088 (89.0%)	0.21	<0.0001
Congestive heart failure	3282 (52.8%)	5391 (52.8%)	0.0003	0.983
Chronic obstructive pulmonary disease	1931 (31.1%)	2975 (29.1%)	0.04	0.009
Chronic steroid use	246 (4.0%)	327 (3.2%)	0.04	0.011
Coronary artery disease	3489 (56.1%)	5447 (53.3%)	0.06	0.001
Supraventricular tachycardia	476 (7.7%)	534 (5.2%)	0.10	<0.0001
Ventricular arrythmia	979 (15.7%)	1403 (13.7%)	0.06	0.0004
Hyperlipidaemia	4770 (76.7%)	7578 (74.2%)	0.06	0.0003
Left bundle branch block	334 (5.4%)	543 (5.3%)	0.002	0.883
Peripheral vascular disease	1685 (27.1%)	2736 (26.8%)	0.01	0.672
Prior coronary artery bypass graft	929 (14.9%)	1460 (14.3%)	0.02	0.258
Prior acute myocardial infarction	1242 (20.0%)	1680 (16.5%)	0.09	<0.0001
Prior percutaneous coronary intervention	979 (15.7%)	1416 (13.9%)	0.05	0.001
Renal dysfunction	3034 (48.8%)	4294 (42.1%)	0.14	<0.0001
Tricuspid valve disease	1795 (28.9%)	2945 (28.8%)	0.001	0.973
Transcatheter aortic valve replacement	106 (1.7%)	154 (1.5%)	0.02	0.328
Concomitant atrial[a] ablation	861 (13.8%)	1125 (11.0%)	0.09	<0.0001
Concomitant TAVR	170 (2.7%)	474 (4.6%)	0.10	<0.0001
Charlson comorbidity index	5.1 ± 3.4	4.6 ± 3.0	0.16	<0.0001

ED, emergency department; ESRD, end-stage renal disease; SMD, standardized mean difference; TAVR, transcatheter aortic valve replacement.
[a]Concomitant procedures are defined as those occurring during the implant encounter. Atrial ablation includes CPT codes 93650, 93653, 93656, 93657, 02583ZZ with diagnosis of atrial fibrillation and may include atrial fibrillation as well as atrio-ventricular node ablation (see Supplementary material online, *Table S2*).
[b]SMD > 0.10 are considered imbalanced (see Supplementary material online, *Figure S1* for values after weighting).

VVI patients experienced significantly fewer device-related complications than transvenous VVI patients (unadjusted 2.5% vs. 4.9%, $P < 0.0001$; adjusted 2.4% vs. 4.8%, $P < 0.0001$), though significantly more other complications, driven by higher rates of pericarditis in the leadless VVI group (unadjusted 1.7% vs. 0.8%, $P < 0.0001$; adjusted 1.6% vs. 0.8%, $P < 0.0001$). Unadjusted chronic complication rates are shown in Supplementary material online, *Table S4*.

Survival

The 30-day all-cause mortality rate was not significantly different between leadless VVI and transvenous VVI patients (unadjusted 4.4% vs. 3.8%, $P = 0.10$; adjusted 4.0% vs. 4.1%, $P = 0.60$). At 2 years of follow-up, there were 1807 observed deaths in the leadless VVI arm and 2865 observed deaths in the transvenous VVI arm. The unadjusted 2-year all-cause mortality rate was significantly greater in the leadless VVI patients compared with the transvenous VVI patients (cumulative rate 34.0% vs. 31.6%; HR 1.10; 95% CI 1.04–1.17, $P = 0.002$) (Supplementary material online, *Figure S2*); however, there was no difference in the adjusted 2-year all-cause mortality rate between leadless VVI and transvenous VVI patients (cumulative rate 31.4% vs. 32.5%; HR 0.97; 95% CI 0.91–1.04; *Figure 2C*).

Discussion

In this nationwide comparative evaluation of 6219 leadless VVI vs. 10 212 transvenous VVI *de novo* pacemaker implants, there are three

Table 2 Adjusted reintervention rates at 2 years in leadless VVI vs. transvenous VVI pacemaker patients

Reintervention type	Leadless VVI (*N* = 6219)		Transvenous VVI (*N* = 10 212)		Leadless VVI vs. transvenous VVI	
	Observed events (%[a])	2-Year weighted CIF estimates (95% CI)	Observed events (%[a])	2-Year weighted CIF estimates (95% CI)	Relative risk reduction (95% CI)	*P*-Value
Any reintervention	169 (2.7%)	3.1% (2.8–3.4%)	494 (4.4%)	4.9% (4.5–5.4%)	38% (15–55%)	0.003
System reinterventions						
Revisions	[b]	[b]	56 (0.6%)	0.6% (0.4–0.8%)	80% (50 to 92%)	0.001
Lead-related reinterventions	N/A	N/A	65 (0.6%)	0.7% (0.5–0.9%)	N/A	N/A
Replacement	68 (1.1%)	1.1% (0.9–1.3%)	44 (0.4%)	0.4% (0.3–0.6%)	-150% (-346 to 40%)	0.002
System switch (replacement with opposite type of device)	18 (0.3%)	0.4% (0.2–0.5%)	26 (0.3%)	0.3% (0.2–0.4%)	to 28% (-150 to 34%)	0.463
Removal	[b]	[b]	75 (0.7%)	0.8% (0.7–1.1%)	95% (80 to 99%)	<0.0001
Upgrades						
Dual-chamber	22 (0.4%)	0.4% (0.3–0.6%)	66 (0.7%)	0.8% (0.6–1.0%)	42% (-2 to 67%)	0.06
CRT	57 (0.9%)	1.2% (1.0–1.4%)	140 (1.4%)	1.7% (1.4–1.9%)	30% (4 to 49%)	0.025

CI, confidence interval; CIF, cumulative Incidence Function; CRT, cardiac resynchronization therapy; N/A, not applicable.
[a]Raw percentage defined as number of events divided by number of patients.
[b]Cell value between 1 and 10.

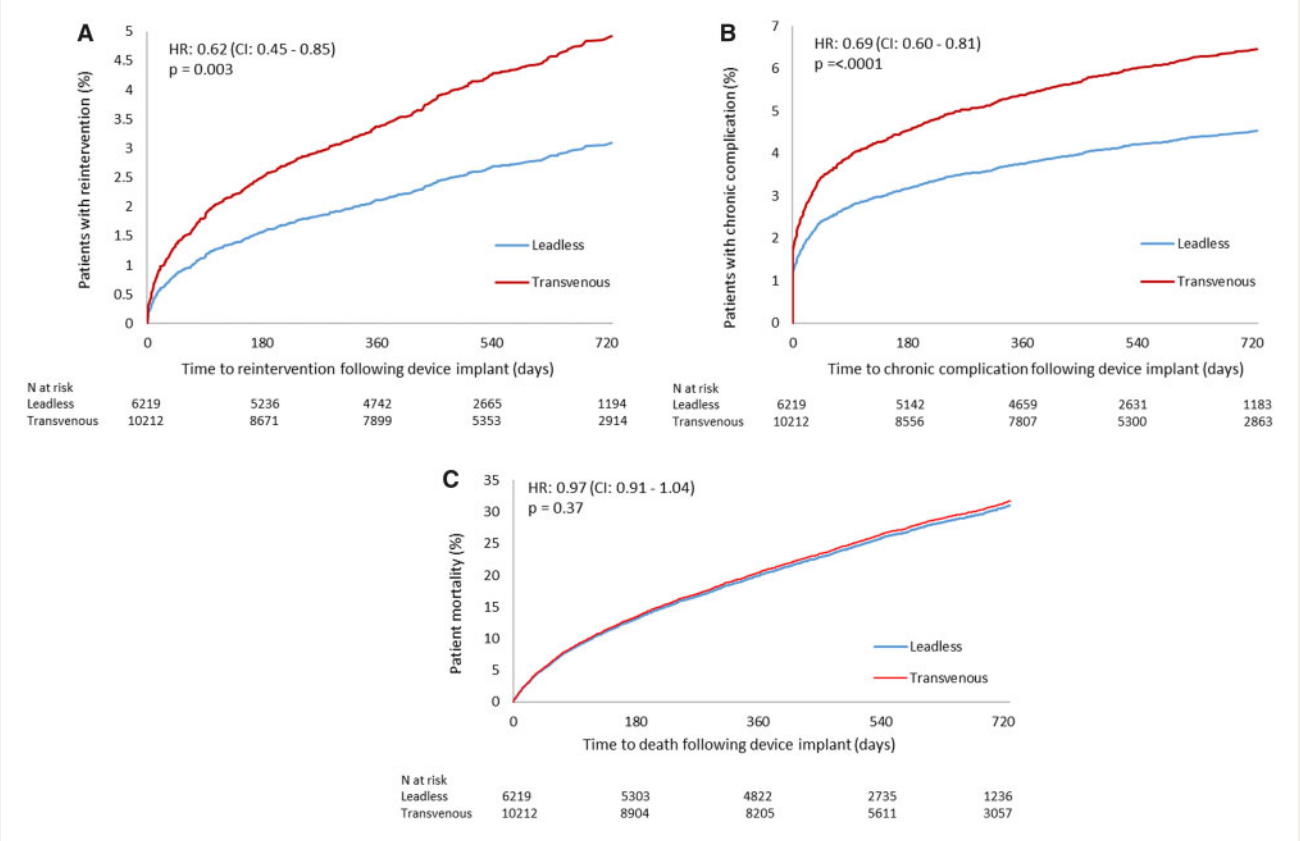


Figure 2 Adjusted time to event plots for device reinterventions, chronic complications and mortality out to 2 years of follow-up in patients treated with leadless VVI vs. transvenous VVI pacing. (*A*) Hazard ratio and cumulative incidence function for 2-year device reintervention based on the Fine–Gray competing risk model. (*B*) Hazard ratio and cumulative incidence function for 2-year chronic complications based on the Fine–Gray competing risk model. (*C*) Hazard ratio and patient mortality rates based on the Cox proportional hazards model. CI, confidence interval.

Table 3 Adjusted rates of device-related complication at 2 years of in leadless VVI vs. transvenous VVI pacemaker patients

Complication type	Leadless VVI (*N* = 6219)		Transvenous VVI (*N* = 10 212)		Leadless VVI vs. transvenous VVI	
	Observed events (%[a])	2-Year weighted CIF estimates (95% CI)	Observed events (%[a])	2-Year weighted CIF estimates (95% CI)	Relative risk reduction (95% CI)	*P*-Value
Overall complications	285 (4.6%)	4.6% (4.2–4.9%)	631 (6.2%)	6.5% (6.1–6.9%)	31% (19% to 40%)	<.0001
Embolism and thrombosis	[c]	[c]	23 (0.2%)	0.2% (0.2–0.2%)	46% (-17% to 75%)	0.12
Thrombosis due to cardiac device	[c]	[c]	[c]	[c]	51% (-19% to 80%)	0.12
Embolism due to cardiac device	[c]	[c]	[c]	[c]	14% (-402% to 85%)	0.87
Device-related complications[b]	155 (2.5%)	2.4% (2.2–2.5%)	500 (4.9%)	4.8% (4.7–5.0%)	52% (42% to 60%)	<.0001
Other complications	141 (2.3%)	2.1% (2.0–2.3%)	142 (1.4%)	1.4% (1.3–1.6%)	-48% (-91% to -15%)	0.002
Pericarditis	100 (1.6%)	1.6% (1.4–1.9%)	76 (0.7%)	0.8% (0.7–0.9%)	-105% (-180% to -50%)	<.0001
Haemothorax	43 (0.7%)	0.6% (0.5–0.8%)	71 (0.7%)	0.7% (0.6–0.9%)	13% (-33% to 43%)	0.51

CI, confidence interval; CIF, cumulative incidence function.
[a]Raw percentage defined as number of events divided by number of patients.
[b]Includes complications related to the mechanical integrity of the device or codes explicitly stating device relatedness (e.g. device dislodgement, device infection, device pocket complication).
[c]Cell value between 1 and 10.

major findings at 2-year follow-up. First, leadless VVI pacemakers were associated with a 38% reduction in the rate of system revisions. Second, patients with leadless VVI pacemakers experienced 31% fewer chronic complications than patients with transvenous VVI pacemakers. Finally, and most importantly, there was no significant difference in all-cause mortality at 2 years with leadless vs. transvenous VVI pacemaker implantation after adjustment for clinical characteristics (*Graphical abstract*).

The results of this current study build off of recently published results of shorter-term (30-day and 6-month) outcomes of the Micra CED study,[5] which found patients implanted with a leadless VVI pacemaker had higher rates of pericardial effusion and/or perforation, but lower rates of other device-related complications and need for system revisions, with no difference in the adjusted overall rate of acute (30-day) complications. These results are similar to a 2017 review by Tjong and Reddy,[12] which found slightly higher rates of short-term complications in leadless patients. This current analysis is the first to our knowledge to provide longer-term comparative outcome data on leadless vs. transvenous VVI pacing.

Leadless pacemakers have several advantages, including the avoidance of transvenous leads that have been associated with risks of vascular occlusion, infection, and interference with the tricuspid apparatus. However, this same advantage (avoidance of transvenous leads) is also a limitation as leadless pacemakers are less adaptable to modular system revision (e.g. addition of a CRT lead). There are also concerns that frequent right ventricular pacing can result in the development of pacemaker-induced cardiomyopathy requiring system revision.[13–15] Sanchez and colleagues recently reported a substantially lower rate of pacemaker-induced cardiomyopathy among a single-centre cohort of pacemaker-dependent patients receiving leadless VVI devices (3%) compared to those receiving transvenous pacemakers (13.7%).[16] Whether rates of device system revision in longer-term follow-up are different between leadless and transvenous VVI pacemakers is an important clinical question. After adjustment for baseline clinical risk, leadless VVI pacemakers were associated with a 38% lower rate of reintervention at 2 years. It is important to note that rates of system revision are not only determined by post-implant adverse events like pacing-induced cardiomyopathy but are also influenced by patient selection. The lower rates of reintervention observed in the leadless VVI patients likely reflect not only a low rate of adverse pacing complications but also careful patient selection among those undergoing leadless VVI pacemaker implantation [e.g. low rates of left bundle branch block (<5.4%) and presence of atrial fibrillation in the vast majority of patients (81.5%)].

Registry data suggest that as many as 1 in 8 patients receiving a transvenous VVI pacemaker experience a complication.[17] A lower risk of complications has been consistently observed with leadless VVI pacing when compared with transvenous VVI pacing. In the pivotal IDE study, the Micra leadless pacemaker was associated with a 48% reduction in major complications when compared with a historical cohort of transvenous VVI patients.[2] In the PAR, outcomes in international practice remained consistent with previously reported data: complications were infrequent and occurred 63% less often compared to transvenous systems.[3] In this analysis of >16 000 *de novo* pacemaker implants, there were 31% fewer chronic complications with leadlessbVVI pacemakers at 2 years of follow-up, both extending and confirming prior observations. In totality, there is consistent evidence of lower rates of complications both in acute and longer-term follow-up with leadless VVI pacemakers. Moreover, the lower rate of complications has been observed in both carefully controlled trials and general clinical practice.

While the risk of pericardial effusion following leadless VVI implantation has decreased over time, recent evaluations in the MAUDE database identified higher rates of *reported* severe adverse events due to pericardial effusion with the Micra leadless pacemaker compared with the CapSureFix transvenous lead. Nonetheless, the estimated incidence was low (<1%).[18] MAUDE reports also suggested a potentially higher rate of mortality following perforation

with leadless VVI pacemakers compared with transvenous VVI devices. While analyses of MAUDE are limited by the lack of a denominator, scant clinical data, and potential for ascertainment bias, individual cases do inform potential risks with medical devices and the leadless pacemaker is no exception. In the context of concerns over the safety of leadless VVI pacemaker implantation, it is very reassuring to see no evidence of increased mortality in nationwide US clinical practice in patients 65 years of age and older.

Inherent to the evaluation of any new device is an understanding of the advantages and disadvantages in both safety and effectiveness. In this regard, data from formal IDE approval studies as well as data from post-market observational registries can provide important and complimentary clinical insights. Post-market device data linked to CMS claims data have now served to provide important insight into multiple new device technologies, including transcatheter mitral repair[19] and now leadless VVI pacing.[5] Studies relying solely on CMS FFS claims data cannot supplant a holistic approach to post-market evaluation; however, CMS data can provide essential insights into utilization, safety, and outcomes in general US practice that cannot be provided in a traditional disease-specific registry platform. Notably, the Micra CED study illustrates the feasibility of utilizing real-world data to generate evidence measuring the effectiveness of new technology and can serve as a potential model for coverage of new medical technologies in other healthcare systems.

Limitations

There are several limitations that should be kept in mind when considering the data from this study. First, Medicare administrative claims data are a secondary database used primarily for billing purposes, not for clinical research purposes; therefore, traditional clinical adjudication is not conducted. It is possible that reinterventions, complications, or comorbidities could be missed, improperly coded, or inadequately documented in administrative claims. However, our prior analyses suggest that this probability is low.[6] Another limitation of using administrative claims is that we are not able to obtain device interrogation data and thus are unable to assess variables such as programmed lower rates, pacing thresholds, and battery longevity. Third, as with any observational study, the possibility of residual confounding or selection bias cannot be completely eliminated. In addition, this analysis was performed in a Medicare FFS population, which primarily consists of patients ≥65 years, disabled, or with ESRD. Medicare Advantage patients (a Medicare program by which Medicare-eligible patients enrol in commercial insurance plans) are not included in the CED study analyses due to unavailability of their claims data for research. Thus, the results may not be generalizable to populations outside the US Medicare FFS population, particularly younger populations. Finally, due to the 12- to 18-month lag in the availability of finalized Medicare claims files for research, this analysis does not include patients implanted beyond December 31, 2018, and outcomes beyond December 31, 2019.

Conclusions

In a real-world study of US Medicare patients, the leadless VVI pacemaker was associated with a 38% lower rate of reinterventions and a 31% lower rate of chronic complications at 2 years compared with transvenous VVI pacing. Despite the leadless VVI patients having more comorbidities than transvenous VVI patients, there was no difference in adjusted all-cause mortality at 2 years compared to the transvenous comparator population. Notably, the Micra CED study illustrates the feasibility of utilizing real-world data to generate evidence measuring the effectiveness of new technology and can serve as a potential model for coverage of new medical technologies in other healthcare systems.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

The authors are not owners of the dataset (dataset is owned by the Centers for Medicare and Medicaid Services) and do not have the right to share the data.

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