Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Reynolds D, Duray GZ, Omar R, et al. A leadless intracardiac transcatheter pacing system. N Engl J Med. DOI: 10.1056/NEJMoa1511643

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A Leadless Intracardiac Transcatheter Pacing System

Supplementary Appendix

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METHODS

Fixation Method

The primary requirements for the transcatheter pacemaker's fixation are that the potential for dislodgement must be minimized, the device must be safely and easily deployable and repositionable, and that the interface between the pacing cathode and the myocardium must be stable and contribute to low pacing thresholds. To meet those requirements, the fixation mechanism for the transcatheter pacemaker was designed with four electrically isolated nitinol tines, spaced far from the pacing cathode, that self-expand into the myocardium when an outer sheath of the transcatheter pacemaker delivery system is retracted. Nitinol is a shape memory metal, and in this design that characteristic is exploited by retracting the transcatheter pacemaker device and fixation into a cup on the end of the transcatheter pacemaker delivery system prior to deployment, then releasing the tine's shape memory spring energy to accomplish fixation to the myocardium. Recapture of the device during implant is accomplished by the reverse: extending the outer sheath over the device body and tines to disengage from the myocardium. The tines method of engaging the myocardium is substantially orthogonal to cardiac contractile motion, contributing to a low potential for dislodgement and to chronically stable thresholds. While promoting stable fixation, the tines were also designed with the intent that longitudinal tension on the device, as would be encountered during repositioning or extraction, would allow safe disengagement from the tissue. Further details of the transcatheter pacemaker's fixation, along with how the fixation was evaluated for safety have been previously reported.[1]

Derivation of the Performance Goal for the Primary Safety Endpoint

Due to limited rigorous clinical trial data available on single chamber pacemaker performance in recent years, dual-chamber pacemaker studies were used to set the transcatheter pacemaker

performance expectation. Specifically, as described previously[2], a single chamber dataset was approximated by excluding events related only to the right atrial lead from six recent Medtronic studies of dual chamber pacing. The six studies were: 3830[3], 5076[4], EnRhythm[5], EnRhythm MRI[6], Advisa MRI[7], and SAVEPACe[8]. The full data set (n=2667) was used to establish a historical control to provide a comparison of the transcatheter pacemaker to traditional transvenous pacemakers. The subset of patients with atrial fibrillation (n=977) were used as the data source to derive the primary safety performance goal since at the design stage of the study it was expected that most patients receiving VVI pacing in the transcatheter pacemaker study would have atrial fibrillation (Figure S1). When combining the data from these six studies, the combined freedom from major complications at 6-months was 91.6% (95% CI: 89.7% - 93.2%), which was comparable to the 89.3% (95% CI: 87.7% – 90.9%) freedom from complications at 2-months post-implant within the recent FOLLOWPACE[9] study when events indicated as related to the atrial lead were excluded. Since the performance goal is based on the lower confidence limit of the eventual rate that would be observed in the study, a performance goal of 83% was established to best reflect the uncertainty in the estimate of freedom from major complications at 6 months and the variability observed between each of the individual previous studies (of which two had point estimates lower than 89%).

Derivation of the Performance Goal for the Primary Efficacy Endpoint

To derive the performance goal for the efficacy objective the following analysis of Medtronic's CareLink® database was performed. Specifically, pacing threshold data stored by Medtronic pacemakers with the capture management feature was obtained from a query of the CareLink® database. The implanted pacing systems ("systems") selected required that the capture management feature be enabled so thresholds would be available for analysis, the lead be a non-

defibrillation pacing lead placed in the RV, and the RV lead be implanted on the same day as the pulse generator. There were no other selection criteria. This query resulted in 1,673 systems. Most current pulse generators evaluate pacing thresholds at a pulse duration of 0.4 milliseconds whereas the transcatheter pacemaker pacing capture threshold uses a 0.24 milliseconds pulse duration. Thus, to determine what the pacing capture threshold for current pulse generators would be at 0.24 milliseconds, data from 134 patients implanted with the model 4074 lead with pacing capture data available at two pacing thresholds were used from the CAPTURE study[10] to derive the strength duration curve using the Lapique equation. The 4074 lead was selected since it has the same electrode configuration as the transcatheter pacemaker system. Based on the resulting strength duration curve, the pacing threshold increased by a factor of 1.32 (32% increase) when the pulse duration was decreased from 0.4 milliseconds to 0.24 milliseconds. This factor was then applied to the daily pacing thresholds obtained from CareLink® and resulting transformed threshold rounded up to the nearest 0.125 Volt increment to account for resolution at which the transcatheter pacemaker measures pacing threshold.

Of the 1,673 systems queried, there were 322 systems with a transformed pacing capture threshold available within 30 days of implant and after 180 days of implant for evaluation. Of these 322 systems, 93% (95% CI: 89.8% - 95.7%) of implant and 6-month pacing capture thresholds met the primary efficacy endpoint of the transcatheter pacemaker system (Figure S2). Since the CareLink® database include data from different devices, leads, and programming and may be biased upwards since patients with system revisions for high thresholds would not be included, we felt the true percentage of transcatheter pacemaker patients that would meet the primary efficacy endpoint would be approximately 89%. Accounting for the uncertainty in this estimate, we opted to set our efficacy performance goal at 80%.

Post-Hoc Comparison to Traditional Transvenous Pacemakers (Historical Control)

Due to limited data available on single chamber performance in recent years, the same 6 dual-chamber studies referenced above were used to approximate a single chamber dataset by excluding events related only to the right atrial lead.[2] A post-hoc analysis was performed to compare rates of major complications between the transcatheter pacemaker and the historical control group (n=2667).

To compare performance to transvenous systems, the Fine-Gray[11] competing risk model was used to assess the risk of major complication, through 6-months, between transcatheter pacemaker patients and the historical control group. Comparisons of categorical groupings of major complications between the transcatheter pacemaker and historical control were made by comparing 6-month Kaplan-Meier rates using a chi-square test.[12] No multiplicity adjustments were made for these comparative analyses.

Propensity score matching was used to substantiate the comparison of major complication rates at 6-months post-implant between the transcatheter pacemaker and the historical control. Propensity scores for each patient were derived from age, sex, coronary artery disease history, congestive heart failure history, atrial fibrillation history, hypertension history, valvular disease history, and all pairwise interactions. Greedy nearest neighbor matching on the logit scale was used to identify 725 matched patients from the historical control. Absolute standardized differences in the variables used to construct the propensity score were all less than 0.2, suggesting improved balance in these parameters after matching (Table S7). The Fine-Gray model was then fit to this dataset of 725 transcatheter pacemaker patients and 725 matched historical control patients. The matching algorithm was implemented using the MatchIt[13]

package in R. All analyses were conducted using SAS software version 9.4 (SAS® Institute) or R.[14]

RESULTS

Cardiac Injuries and Deaths

There were 13 total cardiac injuries reported and adjudicated as related to the system or procedure; none resulted in death. No intervention was required in 4, pericardiocentesis was conducted in 7, and surgical repair was required in 2. Of the 13 events, 11 met the pre-defined criterion for major complication (Table 2). Characteristics of the 13 patients who experienced cardiac injury are described in Table S4.

There were 29 deaths; a full listing of causes of death for all 29 deaths in the study is shown in Table S5. There was one death that was adjudicated as related to the transcatheter pacemaker implantation procedure. A 77 year old female patient had a concomitant procedure (AV nodal ablation) performed during the transcatheter pacemaker implantation, which resulted in prolonged procedure time. Of note, the patient had end stage renal disease and was scheduled for dialysis that day (it had been 3 days since the last dialysis session). No arterial blood gases were monitored during the procedure and no autopsy was conducted; however, the Investigator felt the most likely cause of death was metabolic acidosis due to prolonged procedure time with underlying end stage renal disease. There was no perforation but the patient became hypotensive post procedure.

Table S1: Inclusion and exclusion criteria

Inclusion Criteria
Patients with Class I or II indication for pacing (for bradycardia due to atrial tachyarrhythmia, sinus node dysfunction, atrioventricular node dysfunction, or other causes) were considered suitable candidates for single-chamber ventricular demand (VVI) pacing
Able to undergo the study requirements
18 years of age (or older, if required by local law)
Exclusion Criteria
Entirely pacemaker dependent** (defined as escape rhythm ≤30 bpm).
Existing or prior pacemaker, ICD or CRT device implant
Unstable angina pectoris, acute myocardial infarction within 30d
Current implantation of neurostimulator or any other *chronically* implanted device which uses electrical current
Mechanical tricuspid valve, implanted vena cava filter, or left ventricular assist device
Morbidly obese where telemetry communication of 12.5 cm cannot be obtained with programmer
Femoral venous anatomy unable to accommodate a 23 French introducer sheath or implant on the right side of the heart
Unable to tolerate urgent sternotomy
Known intolerance to Nickel-Titanium (Nitinol) Alloy
Contraindication for single dose of 1.0mg dexamethasone acetate
Life expectancy <12-months
Enrollment in concurrent confounding study
Pregnant or breastfeeding women

** Restriction was removed after device reliability was verified.

Table S2: Historical Control study descriptions

Study	Study Description	Study Cohort Size, total n=2667	Median Follow-up Months (IQR)	Date Study Completed
EnRhythm	Pre-market study evaluating the safety and clinical performance of the EnRhythm system	150	6.0 (5.6 – 6.6)	2005
3830	Pre-market study evaluating the safety and effectiveness of the model 3830 lead	361	24.4 (5.7 – 29.9)	2005
5076	Pre-market study comparing the safety and effectiveness of the model 5076 lead to the 5068 lead	351	10.9 (6.9 – 12.6)	2000
EnRhythm MRI	Pre-market study evaluating the safety and effectiveness of the EnRhythm MRI in the MRI environment	469	30.9 (27.1– 36.1)	2008
Advisa MRI	Pre-market study evaluating the safety and effectiveness of the Advisa MRI in the MRI environment	266	6.0 (5.6 – 6.6)	2012
SAVEPACe	Post-market study comparing standard dual chamber and dual chamber minimal ventricular pacing algorithms	1070	23.6 (11.7 – 30.1)	2007

Table S3: Transcatheter pacemaker implant information

Implant Characteristics (N, %)	Successfully Implanted (N = 719)
Device Location	
RV – apex	474 (65.9%)
RV – septum	171 (23.8%)
RV – mid-septum	56 (7.8%)
RV – outflow tract	4 (0.6%)
RV – free-wall	0 (0.0%)
Other	14 (1.9%)[1]
Introducer In/Out Time (min)*	
Mean ± Standard Deviation	34.8 ± 24.1
Median	28.0
25th Percentile - 75th Percentile	21 - 41
Minimum - Maximum	7 - 280
Subjects With Measure Available (N,%)	719 (100.0%)
Delivery System In/Out Time (min)	
Mean ± Standard Deviation	23.0 ± 15.3
Median	18.0
25th Percentile - 75th Percentile	13 - 28
Minimum - Maximum	4 - 143
Subjects With Measure Available (N,%)	719 (100.0%)
Total Fluoroscopy Time (min)*	
Mean ± Standard Deviation	8.9 ± 16.6
Median	6.0
25th Percentile - 75th Percentile	4 - 10
Minimum - Maximum	1 - 387
Subjects With Measure Available (N,%)	713 (99.2%)
Closure method	
Manual pressure only	59 (8.2%)
Suture method only	223 (31.0%)
Manual pressure + suture	390 (54.2%)
Vascular closure device (+/- pressure or suture)	47 (6.5%)

*Includes 48 transcatheter pacemaker implants where a concomitant procedure was performed such as an AV nodal ablation or implantable cardiac monitor was implanted or removed.

[1]Includes apical septum (8), low septum (3), RV high septum (1), RV apex and RV septum (1), and juncture of anterior infundibulum RV proper (1).

[2]Includes local anesthesia and conscious sedation (53), local anesthesia (44), monitored anesthesia care (18), total intravenous anesthesia (1).

Table S4: Comparison of transcatheter pacemaker patients with and without cardiac injury

Subject Characteristics	No Cardiac Injury (N = 712)	Yes Cardiac Injury (N = 13)	p-value
Age (years)			
Mean ± Standard Deviation	75.8 ± 11.0	81.7 ± 8.6	0.053
Median	78.0	85.0	
25^{th} Percentile - 75^{th} Percentile	72.0 - 83.0	77.0 - 88.0	
Minimum - Maximum	19.0 - 94.0	64.0 - 91.0	
Number of Subjects With Measure Available (N,%)	712 (100.0%)	13 (100.0%)	
BMI			
Mean ± Standard Deviation	27.6 ± 5.3	24.5 ± 4.0	0.032
Median	26.8	24.8	
25^{th} Percentile - 75^{th} Percentile	24.2 - 30.7	22.1 - 27.9	
Minimum - Maximum	14.2 - 56.9	18.3 - 30.9	
Number of Subjects With Measure Available (N,%)	710 (99.7%)	13 (100.0%)	
Sex			
Male n (%)	422 (59.3%)	4 (30.8%)	0.048
Female n (%)	290 (40.7%)	9 (69.2%)	
Primary Pacing Indication n (%)			
Symptomatic sinus node dysfunction	308 (43.3%)	6 (46.2%)	0.83
AV Blocks	346 (48.6%)	7 (53.8%)	
Other Indications	58 (8.1%)	0 (0.0%)	
Cardiovascular Disease History n (%)			
Cardiomyopathy	76 (10.7%)	1 (7.7%)	1.00
Congestive heart failure	119 (16.7%)	4 (30.8%)	0.25
Coronary artery disease	199 (27.9%)	4 (30.8%)	0.76
Hypertension	561 (78.8%)	9 (69.2%)	0.49
Myocardial infarction	72 (10.1%)	4 (30.8%)	0.038
Pulmonary hypertension	77 (10.8%)	3 (23.1%)	0.16
Tricuspid valve dysfunction	176 (24.7%)	6 (46.2%)	0.10
Coronary artery intervention	108 (15.2%)	4 (30.8%)	0.13
Other Comorbidities n (%)			
COPD	85 (11.9%)	5 (38.5%)	0.015
Chronic lung disease	203 (28.5%)	8 (61.5%)	0.025
Diabetes	203 (28.5%)	4 (30.8%)	1.00
Renal dysfunction	143 (20.1%)	2 (15.4%)	1.00

Table S5: Causes of death in the total cohort

Cause	No.
Cardiac	**7**
Cardiac arrest	1
Cardiac failure	5
Pulseless electrical activity	1
Non-cardiac	**22**
Abdominal injury	1
Respiratory failure/respiratory arrest	2
Bladder cancer	1
Chronic kidney disease	2
Chronic obstructive pulmonary disease	1
Dementia	1
Gastrointestinal hemorrhage/intestinal ischemia	2
Metabolic acidosis	1
Multi-organ failure	2
Pleural effusion	1
Pneumonia	3
Pulmonary embolism	2
Sepsis	2
Subdural hemorrhage	1
Total	**29**

Table S6: Comparison of demographics and key medical history between transcatheter pacemaker subjects and historical control subjects

Subject Characteristics	Patients with Attempted Implant (N = 725)	Historical Control (N = 2667)	P-value[1]
Age (years)			
Mean ± Standard Deviation	75.9 ± 10.9	71.1 ± 12.1	<0.001
Minimum – Maximum	19.0 - 94.0	9.0 - 99.9	
Number of Subjects With Measure Available (N,%)	725 (100.0%)	2667 (100.0%)	
Sex n(%)			
Male	426 (58.8%)	1469 (55.1%)	0.08
Female	299 (41.2%)	1198 (44.9%)	
LVEF (%)			
Mean ± Standard Deviation	58.8 ± 8.8	58.1 ± 10.0	0.18
Minimum – Maximum	25.0 - 91.0	15.0 - 86.0	
Number of Subjects With Measure Available (N,%)	613 (84.6%)	804 (30.1%)	
Diabetes n(%)	207 (28.6%)	395 (21.9%)	<0.001
Number of Subjects With Measure Available	725 (100.0%)	1805 (67.7%)	
COPD n(%)	90 (12.4%)	53 (7.2%)	0.001
Number of Subjects With Measure Available	725 (100.0%)	735 (27.6%)	
Renal Dysfunction n(%)	145 (20.0%)	26 (9.8%)	<0.001
Number of Subjects With Measure Available	725 (100.0%)	266 (10.0%)	
LBBB n(%)	98 (13.5%)	191 (12.0%)	0.31
Number of Subjects With Measure Available	725 (100.0%)	1597 (59.9%)	
Vascular Disease n(%)	53 (7.3%)	170 (10.1%)	0.032
Number of Subjects With Measure Available	725 (100.0%)	1689 (63.3%)	
Other Co-morbidities n(%)			
CAD	203 (28.0%)	1025 (38.4%)	<0.001
AF	526 (72.6%)	977 (36.6%)	<0.001
CHF	123 (17.0%)	400 (15.0%)	0.20
Hypertension	570 (78.6%)	1792 (67.2%)	<0.001
Valvular Disease	306 (42.2%)	512 (19.2%)	<0.001

[1]P-value from from T-test (continuous variables) or Fisher's Exact test (categorical variables).
Abbreviations: LVEF: Left Ventricular Ejection Fraction; COPD: Chronic Obstructive Pulmonary Disease; LBBB: Left Bundle Branch Block; CAD: Coronary Artery Disease; AF: Atrial Fibrillation; CHF: Congestive Heart Failure

Table S7: Comparison of demographics and key medical history between transcatheter pacemaker and propensity matched historical control subjects

Subject Characteristics	Patients with Attempted Implant (N = 725)	Propensity Matched Historical Control (N = 725)	Standardized Mean Difference[1]
Age (years)			
Mean ± Standard Deviation	75.9 ± 10.9	74.8 ± 10.6	0.10
Minimum – Maximum	19 - 94	13 – 99	
Number of Subjects With Measure Available (N,%)	725 (100.0%)	725 (100.0%)	
Sex n(%)			
Male	426 (58.8%)	403 (55.6%)	0.06
Female	299 (41.2%)	322 (44.4%)	
Co-morbidities n(%)			
CAD	203 (28.0%)	206 (28.4%)	-0.01
AF	526 (72.6%)	514 (70.9%)	0.04
CHF	123 (17.0%)	102 (14.1%)	0.08
Hypertension	570 (78.6%)	562 (77.5%)	0.03
Valvular Disease	306 (42.2%)	265 (36.5%)	0.11

[1]Standardized mean difference is the difference in group means divided by the control standard deviation. Absolute values less than 0.2 suggest balance between propensity matched groups.
Abbreviations: CAD: Coronary Artery Disease; AF: Atrial Fibrillation; CHF: Congestive Heart Failure

Table S8: Major complication rates through 6-Months by endpoint criterion

	Patients with Attempted Implant (n=725)	**Historical Control (n=2667)**	
Major Complication[1] Criterion	**6-Month KM Estimates (95% CI)**	**6-Month KM Estimates (95% CI)**	**Relative Risk Reduction[2] (95% CI)**
Death	0.1% (0.0%-1.0%)	0.0% (NE)	NE
Hospitalization	2.3% (1.2%-4.1%)	3.9% (3.3%-4.8%)	54% (16%-75%)
Prolonged Hospitalization	2.6% (1.5%-4.3%)	2.4% (1.9%-3.1%)	6% (-62%-46%)
System Revision	0.4% (0.1%-1.4%)	3.5% (2.8%-4.2%)	87% (58%-96%)
Loss of Device Function	0.1% (0.0%-1.0%)	0.0% (NE)	NE

[1]Major complication endpoint criteria are not mutually exclusive. For example an event resulting in a system revision may also result in a hospitalization.
[2]Relative risk reduction computed from Cox regression model using events and follow-up through 6-months (183 days) post-implant.
NE = not estimable

Table S9: Events leading to major complication designation by technology

	Patients with Attempted Implant (n=725)		Historical Control (n=2667)		
Adverse Event Keyterm	**Events (Subjects, %)**	**183 Day KM Estimates (95% CI)**	**Events (Subjects, %)**	**183 Day KM Estimates (95% CI)**	**P-value[1]**
TOTAL MAJOR COMPLICATIONS	**28 (25, 3.45%)**	**4.0% (2.7%-6.1%)**	**243 (209, 7.84%)**	**7.4% (6.4%-8.4%)**	**0.006[1]**
TOTAL MAJOR COMPLICATIONS	28 (25, 3.45%)	4.0% (2.7%-6.1%)	243 (209, 7.84%)	7.4% (6.4%-8.4%)	--
CARDIAC ARRHYTHMIAS	**0 (0, 0.00%)**	**0.0% (0.0%-1.2%)[3]**	**20 (20, 0.75%)**	**0.7% (0.5%-1.1%)**	**0.156[2]**
ATRIAL FIBRILLATION	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	16 (16, 0.60%)	0.6% (0.4%-1.0%)	--
ATRIAL FLUTTER	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
PACEMAKER GENERATED ARRHYTHMIA	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	2 (2, 0.07%)	0.0% (0.0%-0.3%)	--
SUPRAVENTRICULAR TACHYCARDIA	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
EMBOLISM AND THROMBOSIS	**2 (2, 0.28%)**	**0.3% (0.1%-1.1%)**	**10 (10, 0.37%)**	**0.4% (0.2%-0.7%)**	**0.775[1]**
DEEP VEIN THROMBOSIS	1 (1, 0.14%)	0.1% (0.0%-1.0%)	0 (0, 0.00%)	0.0% (0.0%-0.2%)[3]	--
PULMONARY THROMBOEMBOLISM	1 (1, 0.14%)	0.1% (0.0%-1.0%)	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
THROMBOSIS	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	2 (2, 0.07%)	0.0% (0.0%-0.3%)	--
TRANSIENT ISCHEMIC ATTACK	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	2 (2, 0.07%)	0.1% (0.0%-0.3%)	--
VENOUS THROMBOSIS	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	5 (5, 0.19%)	0.2% (0.1%-0.5%)	--
ACCESS SITE	**5 (5, 0.69%)**	**0.7% (0.3%-1.7%)**	**49 (48, 1.80%)**	**1.6% (1.2%-2.2%)**	**0.074[1]**
ARTERIOVENOUS FISTULA	4 (4, 0.55%)	0.6% (0.2%-1.5%)	0 (0, 0.00%)	0.0% (0.0%-0.2%)[3]	--
DEVICE EXTRUSION	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
IMPLANT SITE HEMATOMA	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	5 (5, 0.19%)	0.2% (0.1%-0.5%)	--
IMPLANT SITE INFECTION	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	7 (6, 0.22%)	0.2% (0.1%-0.4%)	--
IMPLANT SITE PAIN	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	2 (2, 0.07%)	0.0% (0.0%-0.2%)[3]	--
MEDICAL DEVICE SITE REACTION	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
PNEUMOTHORAX	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	32 (32, 1.20%)	1.2% (0.9%-1.7%)	--
POCKET EROSION	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.2%)[3]	--
VASCULAR PSEUDOANEURYSM	1 (1, 0.14%)	0.1% (0.0%-1.0%)	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
TRAUMATIC CARDIAC INJURY	**11 (11, 1.52%)**	**1.6% (0.9%-2.8%)**	**32 (28, 1.05%)**	**1.1% (0.7%-1.5%)**	**0.288[1]**
CARDIAC PERFORATION	3 (3, 0.41%)	0.4% (0.1%-1.3%)	11 (11, 0.41%)	0.4% (0.2%-0.7%)	--
CARDIAC TAMPONADE	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	4 (4, 0.15%)	0.1% (0.1%-0.4%)	--
PERICARDIAL EFFUSION	8 (8, 1.10%)	1.1% (0.6%-2.3%)	14 (13, 0.49%)	0.5% (0.3%-0.9%)	--
PLEURAL EFFUSION	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	3 (3, 0.11%)	0.1% (0.0%-0.4%)	--

	Patients with Attempted Implant (n=725)		Historical Control (n=2667)		
Adverse Event Keyterm	**Events (Subjects, %)**	**183 Day KM Estimates (95% CI)**	**Events (Subjects, %)**	**183 Day KM Estimates (95% CI)**	**P-value[1]**
PACING ISSUES	**2 (2, 0.28%)**	**0.3% (0.1%-1.1%)**	**33 (31, 1.16%)**	**1.1% (0.8%-1.6%)**	**0.060[1]**
DEVICE CAPTURING ISSUE	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	12 (12, 0.45%)	0.4% (0.2%-0.8%)	--
DEVICE PACING ISSUE	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	14 (14, 0.52%)	0.5% (0.3%-0.8%)	--
DEVICE STIMULATION ISSUE	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	4 (3, 0.11%)	0.1% (0.0%-0.4%)	--
ELEVATED THRESHOLDS	2 (2, 0.28%)	0.3% (0.1%-1.1%)	0 (0, 0.00%)	0.0% (0.0%-0.2%)[3]	--
UNDERSENSING	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	3 (3, 0.11%)	0.1% (0.0%-0.4%)	--
MECHANICAL INTEGRITY	**0 (0, 0.00%)**	**0.0% (0.0%-1.2%)[3]**	**5 (5, 0.19%)**	**0.1% (0.0%-0.4%)**	**1.000[2]**
DEVICE CONNECTION ISSUE	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	3 (3, 0.11%)	0.1% (0.0%-0.4%)	--
DEVICE LEAD DAMAGE	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	2 (2, 0.07%)	0.0% (0.0%-0.2%)[3]	--
FIXATION	**0 (0, 0.00%)**	**0.0% (0.0%-1.2%)[3]**	**42 (42, 1.57%)**	**1.5% (1.1%-2.1%)**	**0.011[2]**
DEVICE DISLOCATION	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	42 (42, 1.57%)	1.5% (1.1%-2.1%)	--
OTHER	**8 (8, 1.10%)**	**1.7% (0.8%-3.5%)**	**52 (45, 1.69%)**	**1.6% (1.2%-2.1%)**	**0.890[1]**
ACUTE MYOCARDIAL INFARCTION	1 (1, 0.14%)	0.1% (0.0%-1.0%)	0 (0, 0.00%)	0.0% (0.0%-0.2%)[3]	--
BASILAR MIGRAINE	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
CARDIAC FAILURE	3 (3, 0.41%)	0.9% (0.3%-2.9%)	1 (1, 0.04%)	0.0% (0.0%-0.2%)[3]	--
CARDIAC FAILURE CONGESTIVE	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	11 (9, 0.34%)	0.3% (0.2%-0.6%)	--
CARDIOMYOPATHY	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
CHEST DISCOMFORT	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
CHEST PAIN	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	3 (3, 0.11%)	0.1% (0.0%-0.4%)	--
CORONARY ARTERY DISEASE	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	5 (5, 0.19%)	0.2% (0.1%-0.5%)	--
DEVICE COMPUTER ISSUE	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
DRESSLER'S SYNDROME	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
EJECTION FRACTION DECREASED	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.2%)[3]	--
ENDOCARDITIS	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.2%)[3]	--
FATIGUE	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
HYPERTENSION	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
INFECTION	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	2 (2, 0.07%)	0.1% (0.0%-0.3%)	--
LOSS OF CONSCIOUSNESS	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
METABOLIC ACIDOSIS	1 (1, 0.14%)	0.1% (0.0%-1.0%)	0 (0, 0.00%)	0.0% (0.0%-0.2%)[3]	--
MUSCULOSKELETAL PAIN	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
MYOCARDIAL INFARCTION	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
ORTHOSTATIC HYPOTENSION	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
PACEMAKER SYNDROME	1 (1, 0.14%)	0.2% (0.0%-1.1%)	0 (0, 0.00%)	0.0% (0.0%-0.2%)[3]	--
PAIN IN EXTREMITY	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
PALPITATIONS	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	3 (3, 0.11%)	0.1% (0.0%-0.4%)	--
PERICARDITIS	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	4 (4, 0.15%)	0.2% (0.1%-0.4%)	--
PNEUMONIA	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	2 (2, 0.07%)	0.1% (0.0%-0.3%)	--
PRESYNCOPE	1 (1, 0.14%)	0.1% (0.0%-1.0%)	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--

	Patients with Attempted Implant (n=725)		Historical Control (n=2667)		
Adverse Event Keyterm	**Events (Subjects, %)**	**183 Day KM Estimates (95% CI)**	**Events (Subjects, %)**	**183 Day KM Estimates (95% CI)**	**P-value[1]**
PULMONARY EDEMA	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
RENAL FAILURE	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
RESTLESSNESS	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
SYNCOPE	1 (1, 0.14%)	0.1% (0.0%-1.0%)	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--
VIRAL INFECTION	0 (0, 0.00%)	0.0% (0.0%-1.2%)[3]	1 (1, 0.04%)	0.0% (0.0%-0.3%)	--

[1]P-value from comparison of K-M rates at 183 days post-implant.
[2] P-value based on Fisher Exact Test.
[3] Confidence interval based on exact binomial distribution.

Figure S1: Freedom from major system or procedure complications at 6-month post-implant among patients reporting AF at baseline in previous pacing studies. Note: n below study label reflects number of patients with history of AF with an implant attempt. n above the upper 95% confidence interval reflects the number of patients remaining at risk 6-months post-implant.

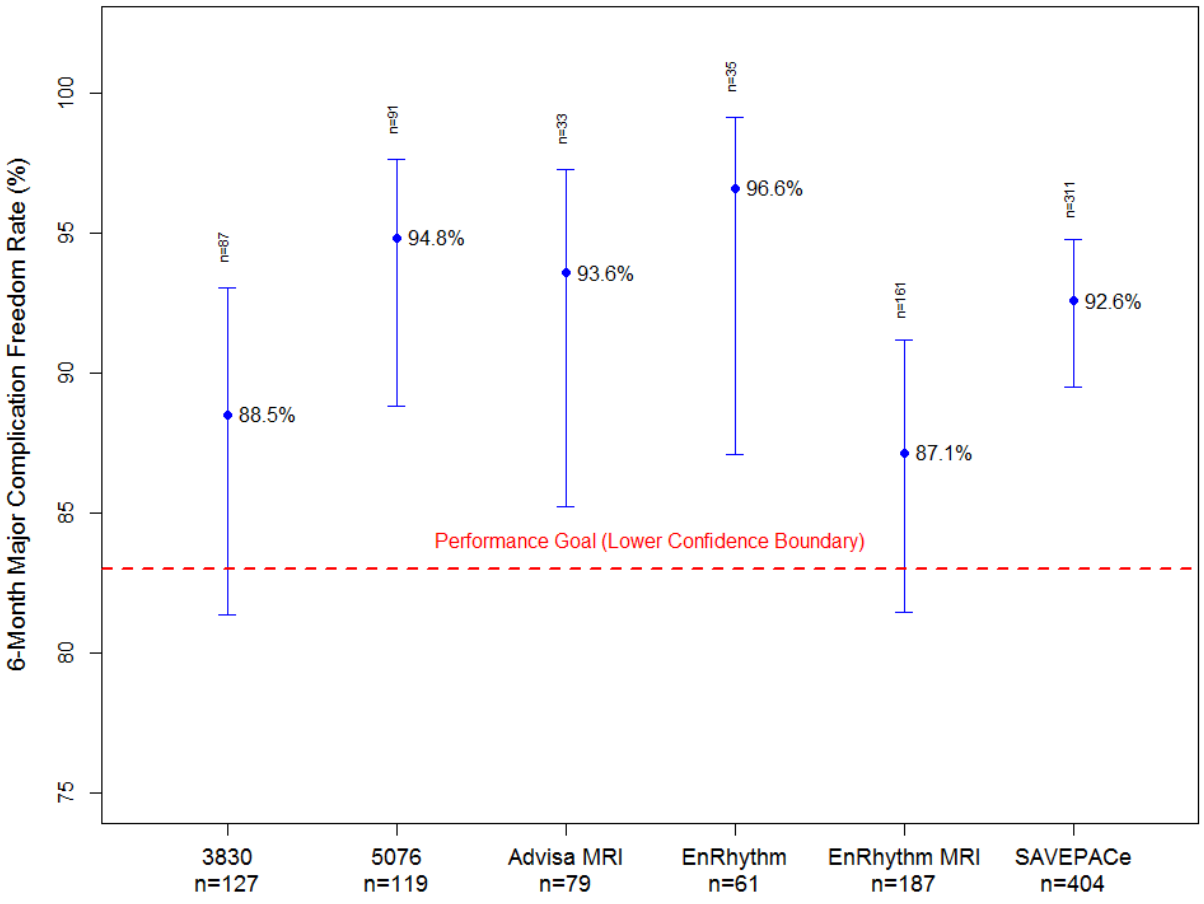


Figure S2: Distribution of 6-month and implant pacing thresholds for 322 pacing systems from the CareLink® network when normalized to a pulse duration of 0.24 milliseconds.

The plotting symbols are jittered to display the distributional density.

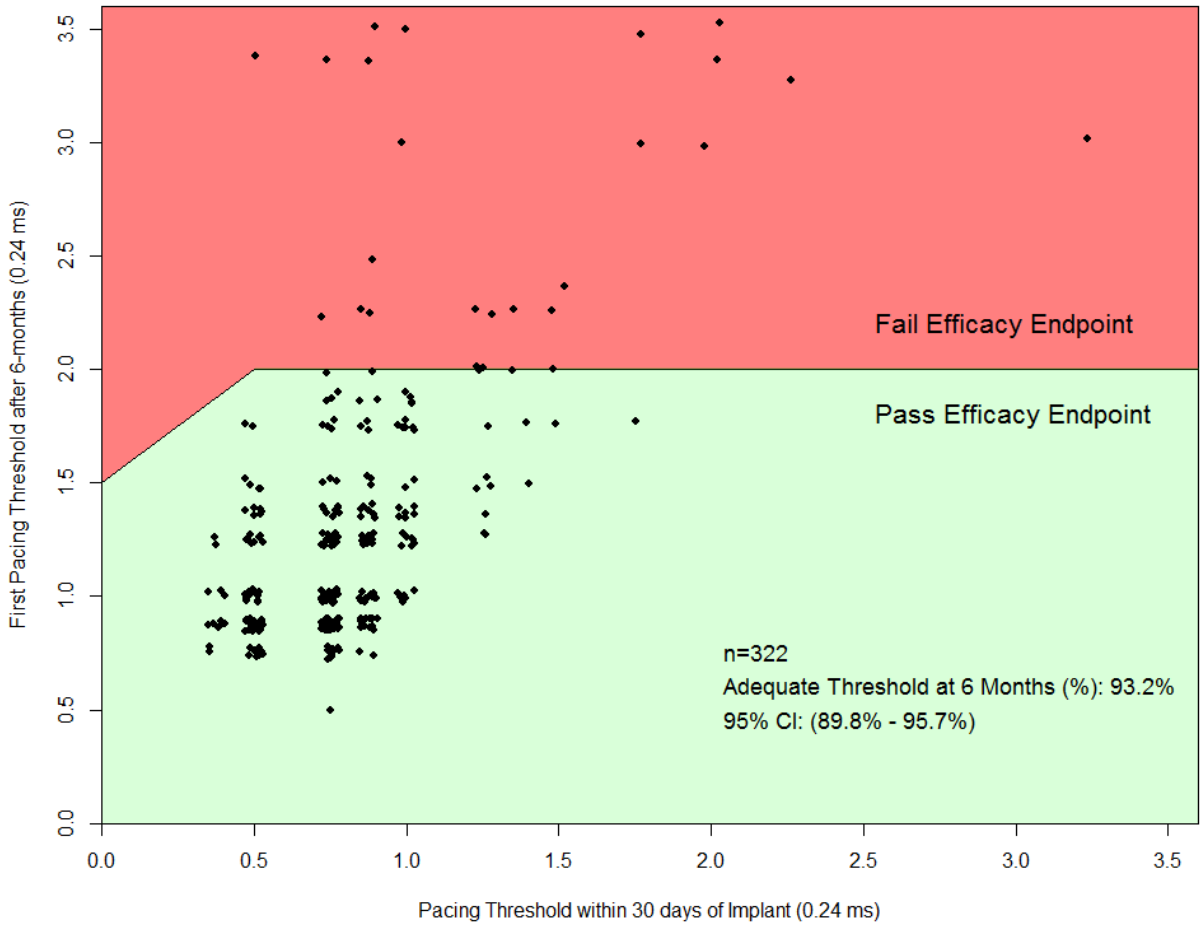


Figure S3: Patient flow diagram

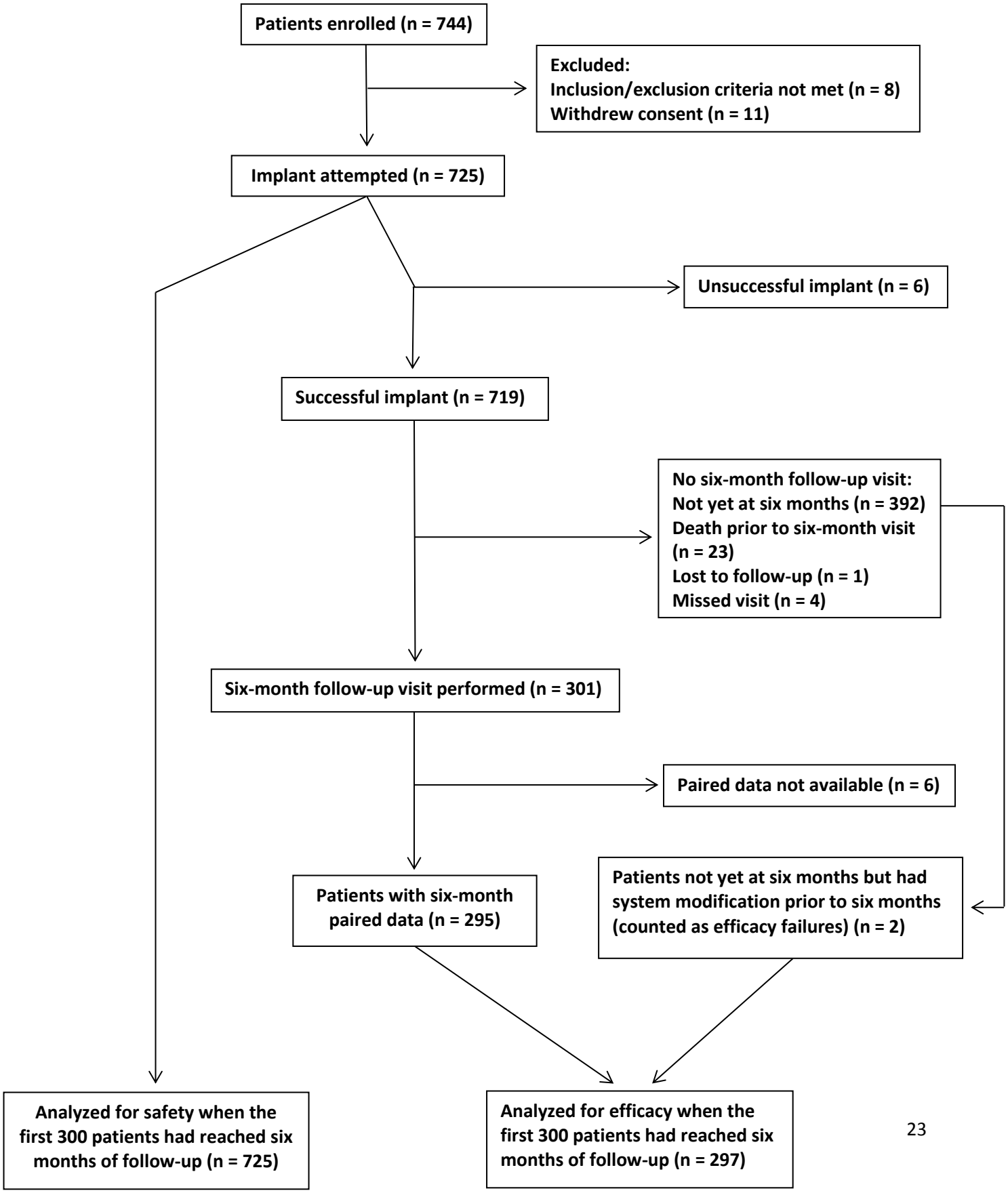


Figure S4: Major complication rate for the transcatheter pacemaker and historical control patients through 12 months post implant. Subdistributional hazard ratio derived from data through 182 days post implant for each cohort by comparing the cumulative incidence functions to the left of the dashed line.

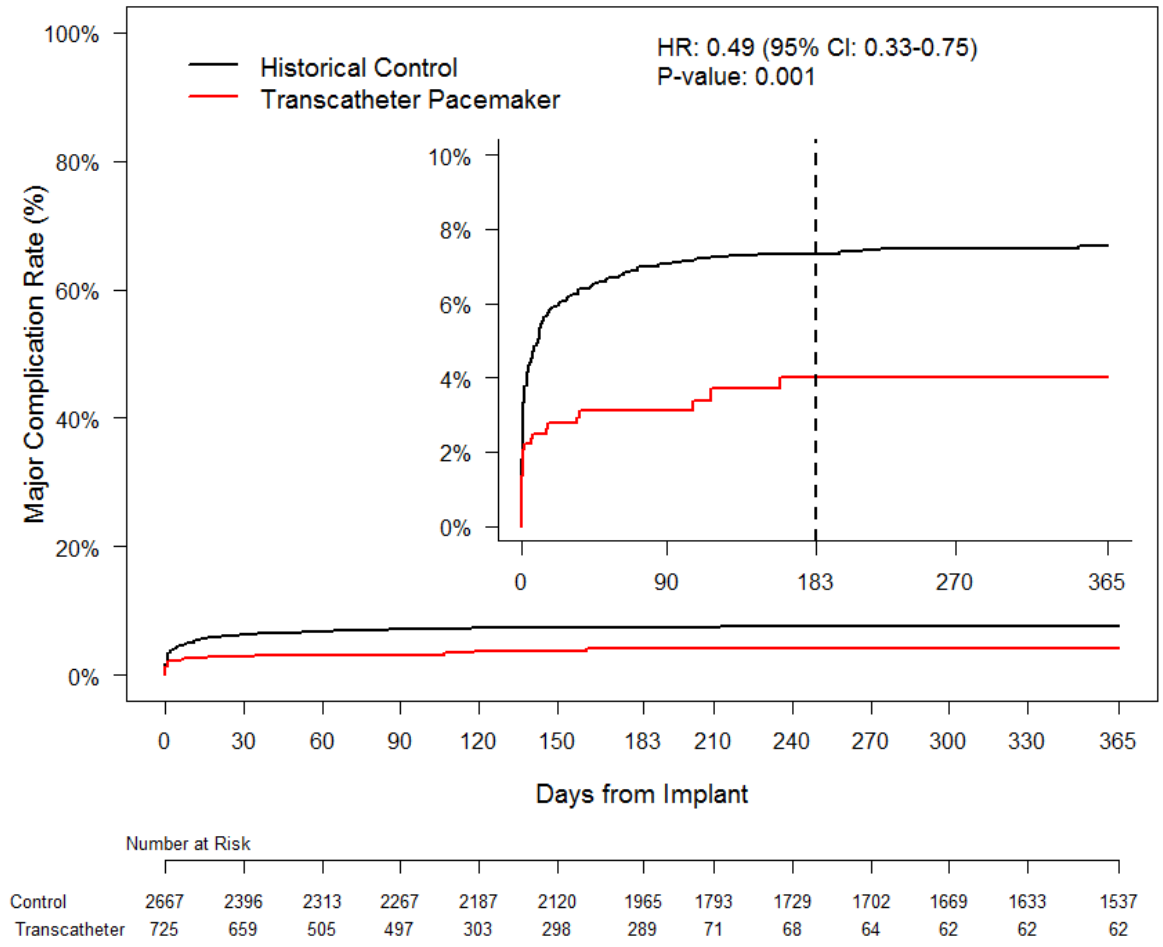
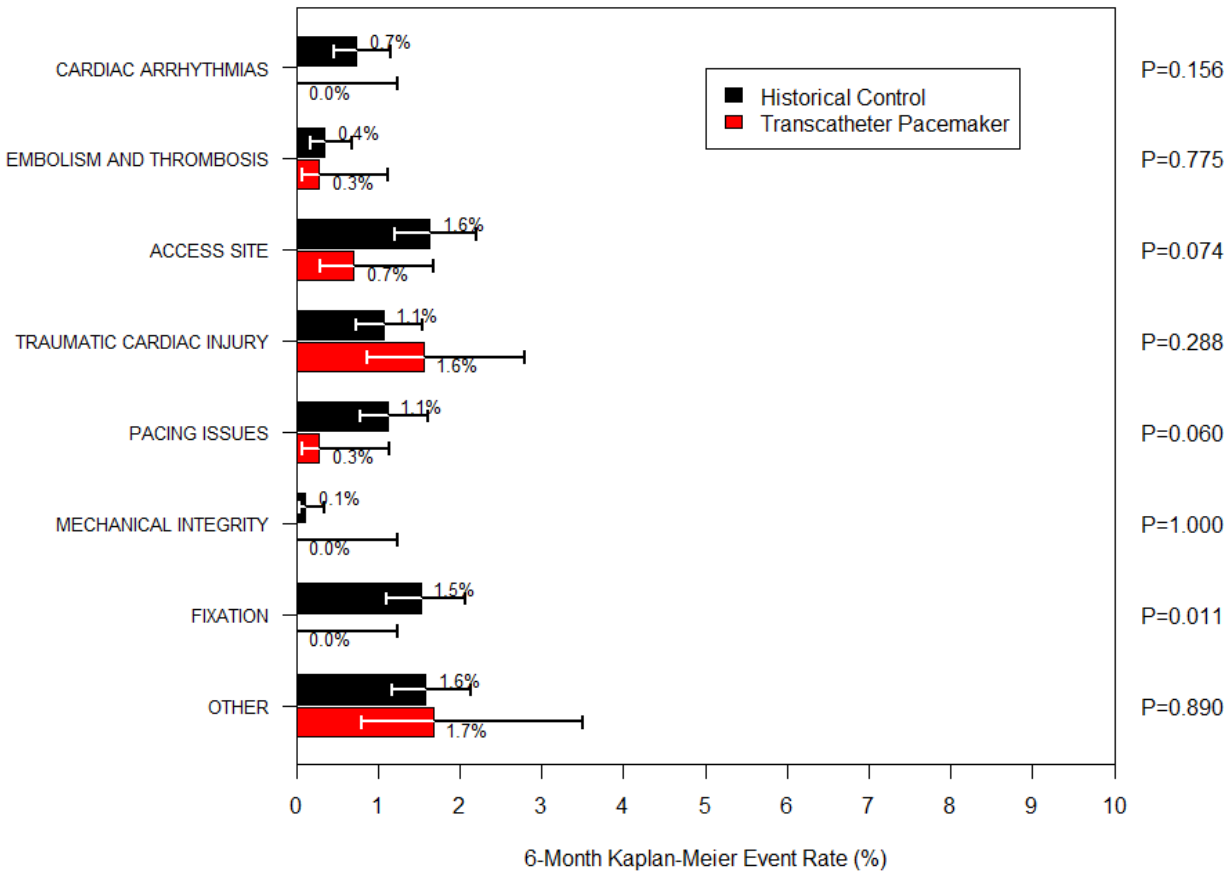


Figure S5: Categories of major complications (Historical Control vs. Transcatheter Pacemaker). 6-month Kaplan-Meier estimate of major complication rate by major complication category. Error bars represent 95% confidence intervals based on the log-log transformation of the Kaplan-Meier event rate except in cases where one group had zero events (mechanical integrity and fixation) where they are based on the binomial distribution. P-value based on comparison of Kaplan-Meier estimates at 183 days post-implant except in cases where zero events were observed in one group. In these cases the P-value is from Fisher's exact test.



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