St. Jude Medical
Nanostim Leadless Pacemaker

Presentation to the
Circulatory System Devices Panel

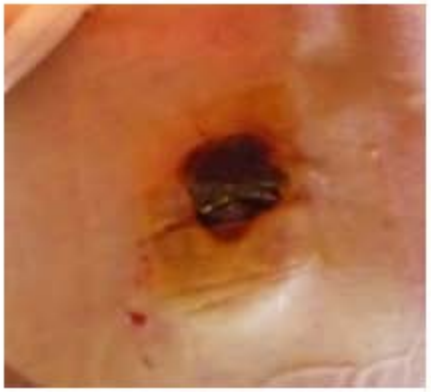
February 18, 2016

Introduction

Mark Carlson, MD
Chief Medical Officer and VP Global Clinical Affairs, St. Jude Medical
Adjunct Professor
Case Western Reserve University

Leadless Pacemaker Rationale for Development: Eliminate Issues with Pacemaker Pockets

- Discomfort (1.9%)[1]
- Cosmetic concerns
- Hematomas (3.0%)[1]
- Infections (2.7%)[1]

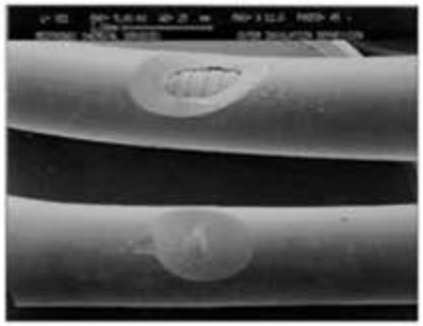
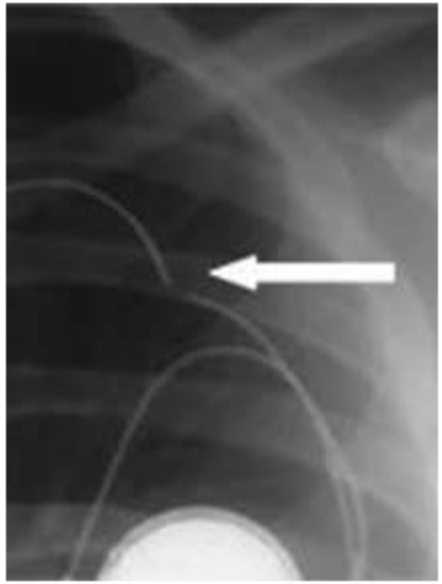
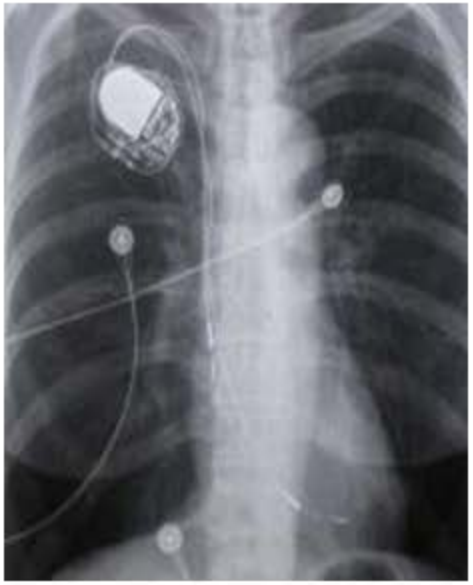



[1] Udo et al, *Heart Rhythm* 9:728–735 (2012)

Leadless Pacemaker Rationale for Development: Eliminate Issues with Pacemaker Leads

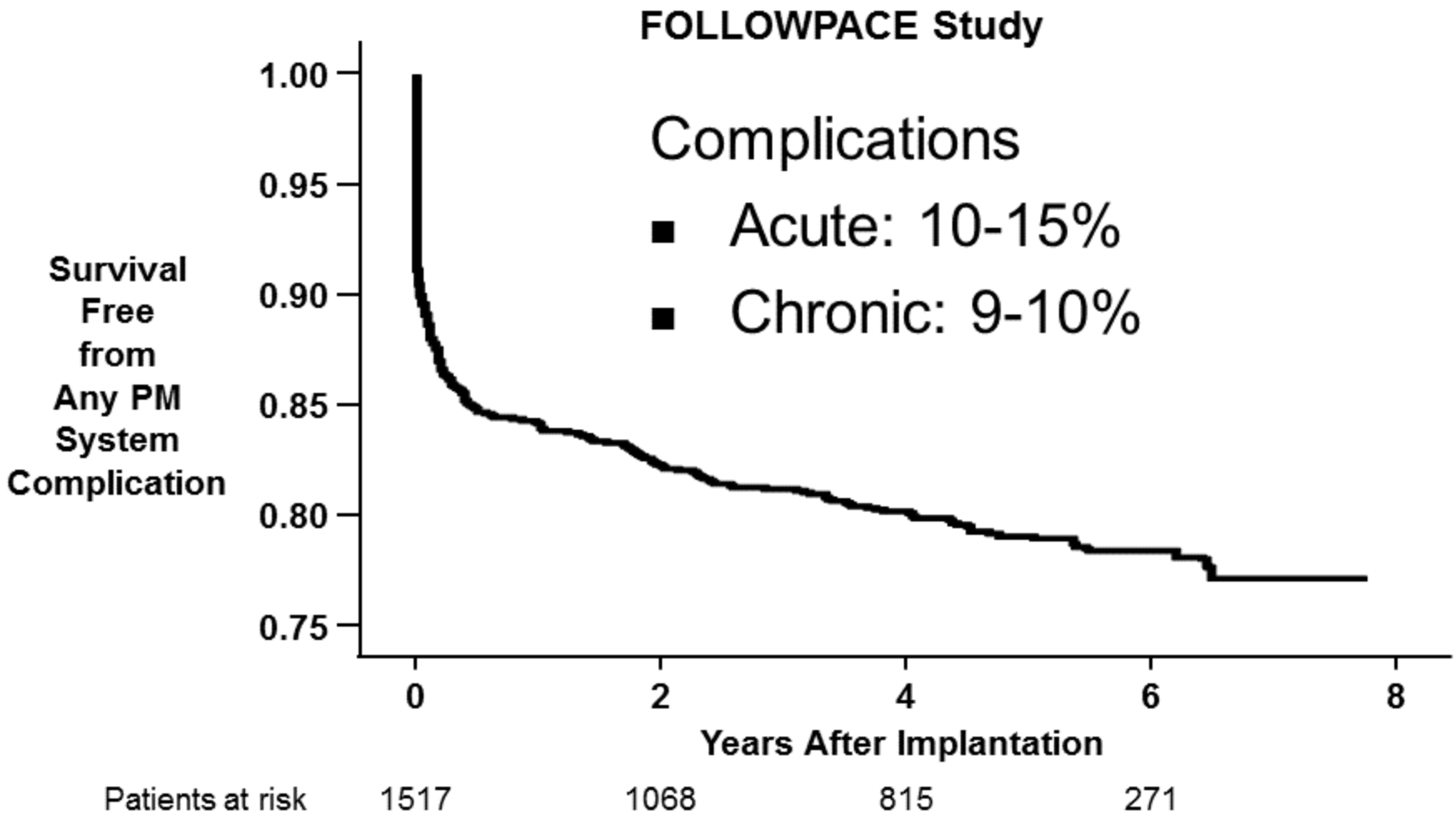
- Mechanical failures (1.5%) [1]
- Infections (0.2%) [1]
- Mobility restrictions



[1] Udo et al, *Heart Rhythm* 9:728–735 (2012)

Substantial Incidence of Acute and Chronic Complications with Standard Pacemakers



Udo et al, *Heart Rhythm* 9:728–735 (2012)
Note: Includes both single and dual chamber pacemakers

Description of Device and Procedure

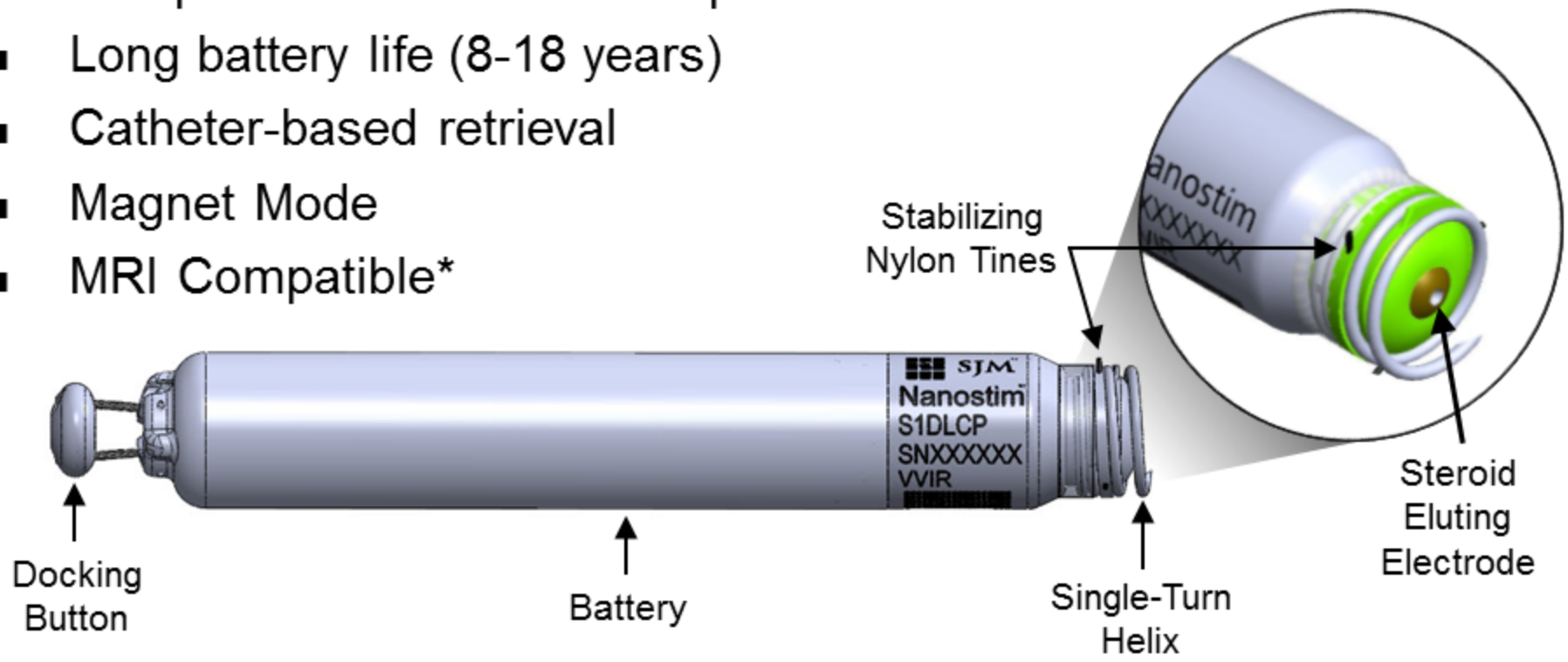
Today's Leadless Pacemaker System The Nanostim Device

- 42 mm (~1 $^{2}/_{3}$") long
- 6 mm (~$^{1}/_{4}$") wide
- Percutaneous femoral vein delivery
  - 18F introducer
  - Steerable catheter
- Self-contained in ventricle
  - No lead or surgical pocket
- Provides traditional single chamber pacing therapy in patients clinically indicated for VVI(R) pacemaker therapy

FDA Question Q4

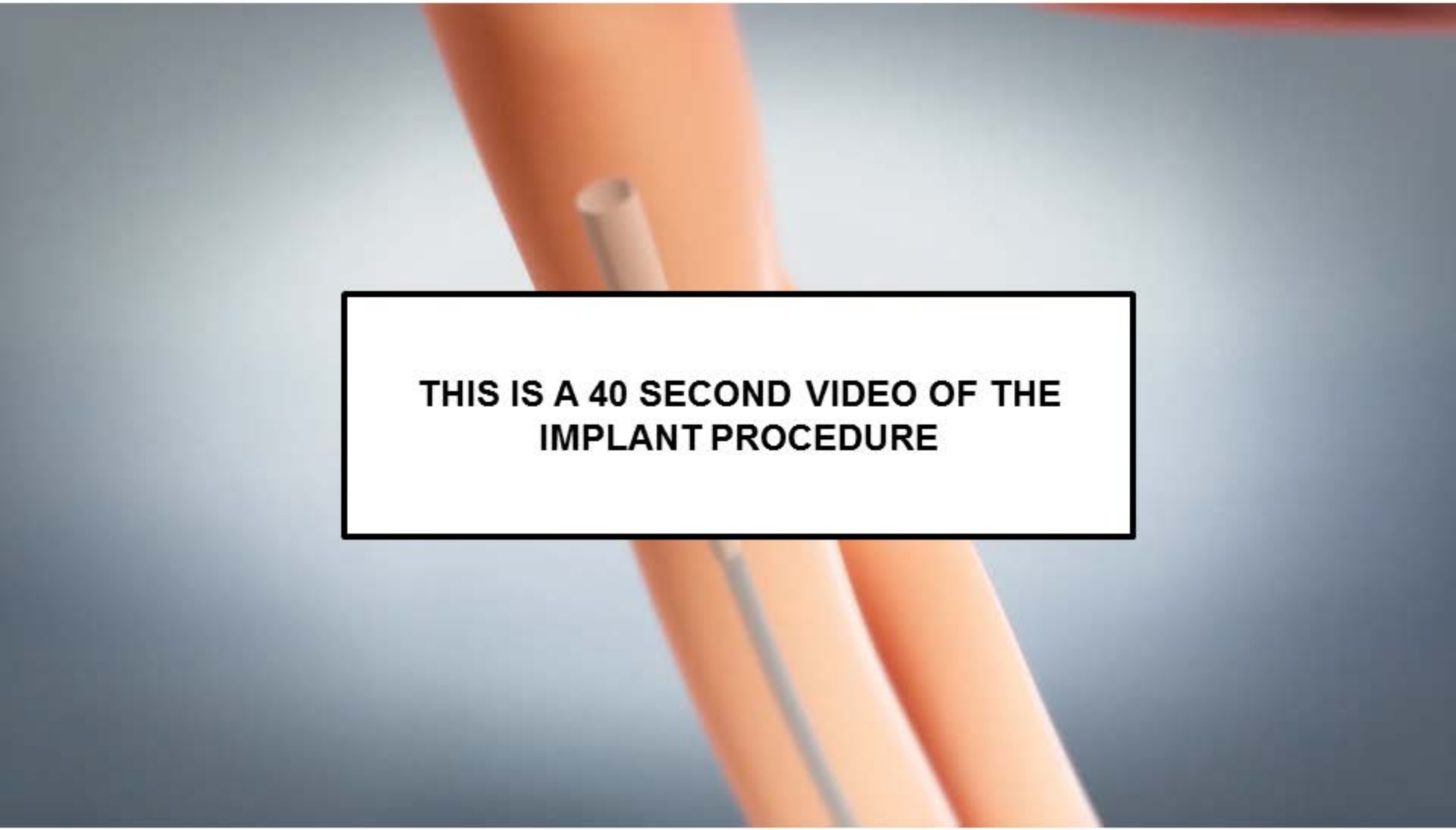
Today's Leadless Pacemaker System
The Nanostim Device

- Single-turn helix and short stabilizing nylon tines secure fixation
- Steroid eluting electrode
- Temperature-based rate response
- Long battery life (8-18 years)
- Catheter-based retrieval
- Magnet Mode
- MRI Compatible*



* MRI compatibility test results submitted in PMA

Leadless Pacemaker System Implantation Procedure



Agenda

Safety and Effectiveness for Leadless II Study	**Vivek Reddy, MD** Professor of Medicine and Cardiology Mount Sinai Hospital, New York
Nanostim Leadless EU Post Market Study **US Post Approval Study** **Training Program**	**Mark Carlson, MD** Chief Medical Officer St. Jude Medical Adjunct Professor Case Western Reserve University

Additional Experts

Dr. Paul Friedman, MD	Director – Implantable Device Lab Professor, Medicine Mayo Clinic, Minnesota
Dr. Joshua Cooper, MD	Director – Cardiac Electrophysiology Professor, Medicine Temple University, Pennsylvania
Barathi Sethuraman, Ph.D	Vice President – Clinical Science St. Jude Medical
Chris Hubbard	Vice President – Nanostim Technology St. Jude Medical

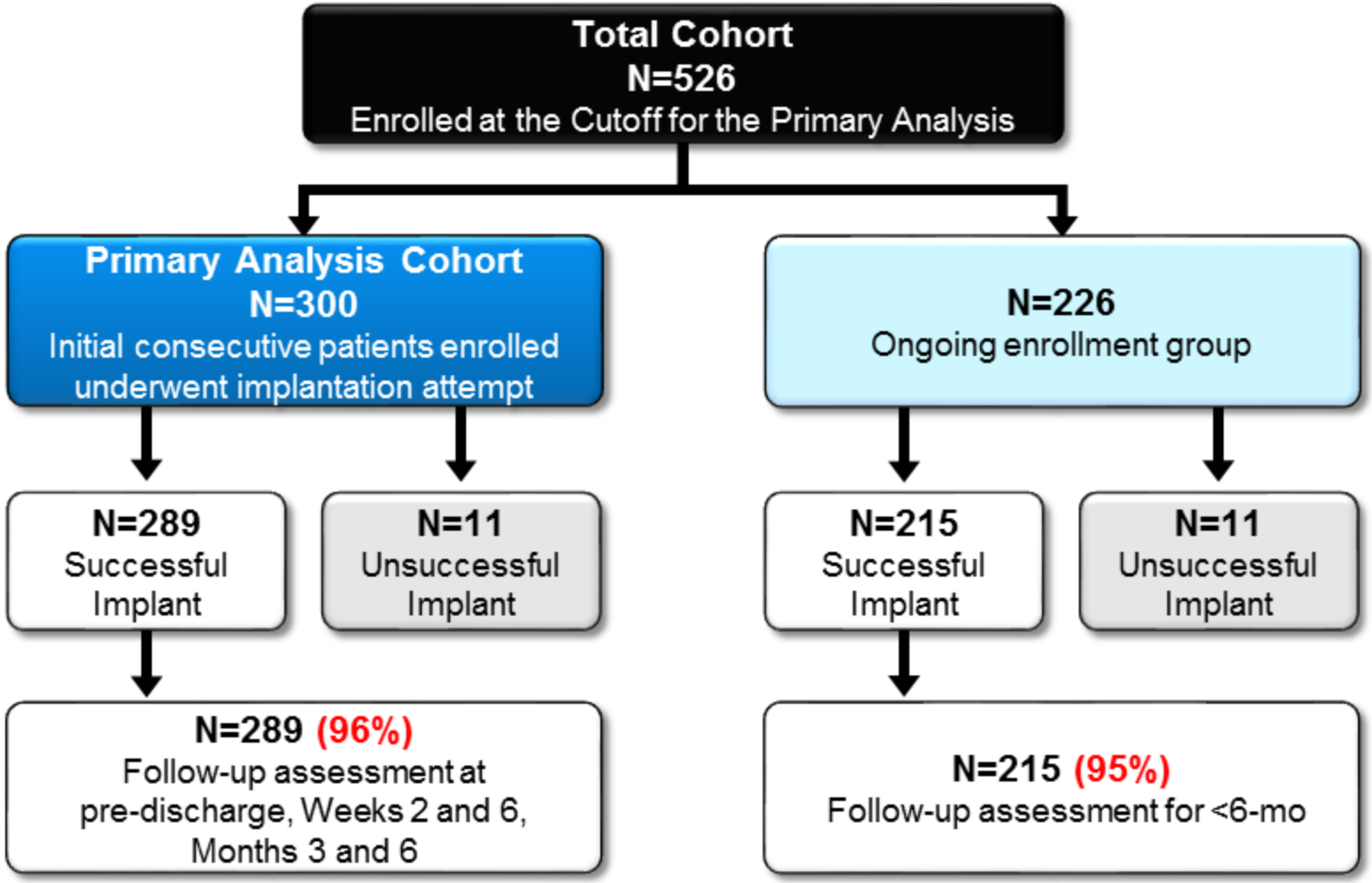
Safety and Effectiveness of a Leadless Pacemaker: Leadless II Clinical Trial Results

Vivek Reddy, MD
Professor of Medicine and Cardiology
Mount Sinai Hospital, New York

Leadless II Clinical Trial Overview

- Prospective, non-randomized
- Single chamber right ventricular pacing in clinically-indicated patients for traditional systems
- 56 Centers in US, Canada and Australia
  - 100 Operators
- N=667
- N=300 for pre-specified primary analysis

Leadless II Clinical Trial Patient Disposition



Demographics Reflect Elderly Population With Significant Comorbidities

Demographic Variable	Primary Analysis Cohort (N=300)	Total Cohort (N=526)
Mean Age (years)± SD	75.7 ± 11.6	75.8 ± 12.1
Sex - Female	35.7	38.2
Coronary Artery Disease	40.3	38.2
Hypertension	84.0	79.8
Diabetes Mellitus	27.3	27.3
Anticoagulants	60.0	58.9
Antiplatelets	47.7	47.0

Key Procedural Characteristics

Procedural Characteristics	Primary Analysis Cohort (N=300)	Total Cohort (N=526)
Successful implantation - n (%)	289 (96.3%)	504 (95.8%)
Device Repositioning		
None	68.9%	70.2%
1	18.3%	17.7%
2	8.3%	7.7%
>2	4.5%	4.4%
Final Device Position in Right Ventricle		
Apical	48.4%	38.1%
Septum	51.6%	60.7%
Other	0	1.2%

Primary Effectiveness and Safety Endpoints Achieved

	Population	P-Value
Effectiveness:		
Acceptable pacing capture threshold	**ITT**	**0.007**
AND		
Therapeutically acceptable sensing amplitude at 6 months	**Implanted**	**<0.001**
Safety:		
Freedom from Serious Adverse Device Effects through 6 months	**ITT**	**<0.001**

Primary Analysis Cohort (N=300)

Serious Adverse Device Effects

Serious Adverse Device Effect	Primary Analysis Cohort (N=300)		Total Cohort (N=526)	
	n	%	n	%
Total Patients	20	6.7	34	6.5
Cardiac perforation	4	1.3	8	1.5
Vascular complications	4	1.3	6	1.1
Device dislodgement	5	1.7	6	1.1
Pacing threshold elevation	4	1.3	4	0.8
Other	4	1.3	13	2.5

Other Events included: Arrhythmia during device implantation, Intra-procedural device migration, Orthostatic hypotension with weakness, Pericarditis, presumed Pulmonary embolism, Hemothorax, Angina pectoris, Acute confusion and expressive aphasia, Dysarthria and lethargy after implantation, Contrast-induced nephropathy, Left-leg weakness during implantation, Ischemic stroke

Events of Interest: Cardiac Perforation and Vascular Complications

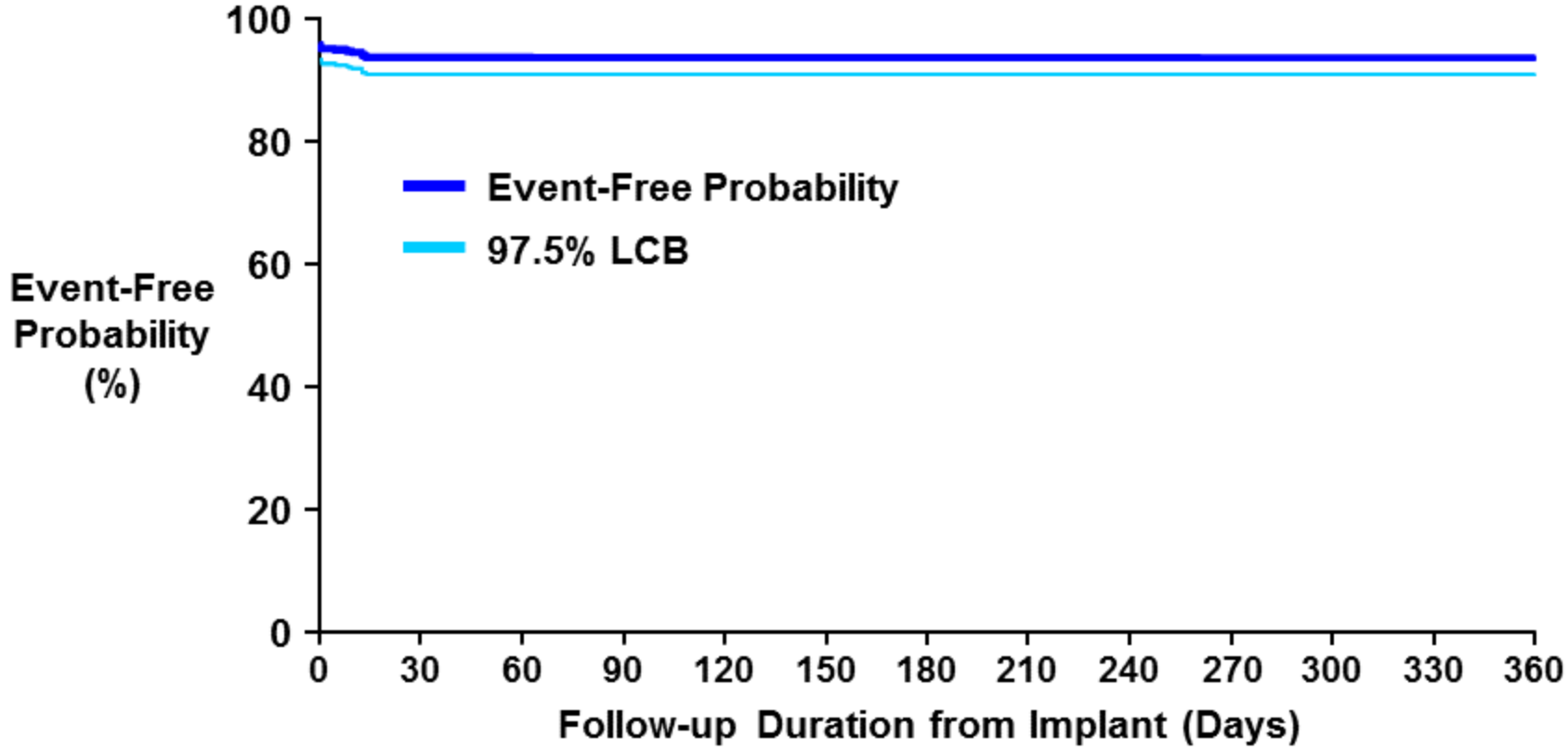
- Cardiac perforation (N=8)
  - 3 with surgical intervention
  - 2 with percutaneous intervention
  - 3 no intervention
    - 1 received traditional pacemaker
- Vascular complications (N=6)
  - 2 Access Site Hematoma
  - 2 Pseudoaneurysms
  - 1 AV Fistula
  - 1 Vascular Closure Malfunction

Total Cohort (N=526)

Events of Interest: Dislodgement and Retrieval

- Device dislodgement (N=6)
  - All reported in early post-op period (1 - 14 days)
  - All devices retrieved without issue
- Pacing threshold elevation with retrieval and new implantation (N=4)
  - All devices retrieved without issue

Freedom from SADEs: SADEs Occurred Within First Few Weeks of Procedure. No late SADEs.



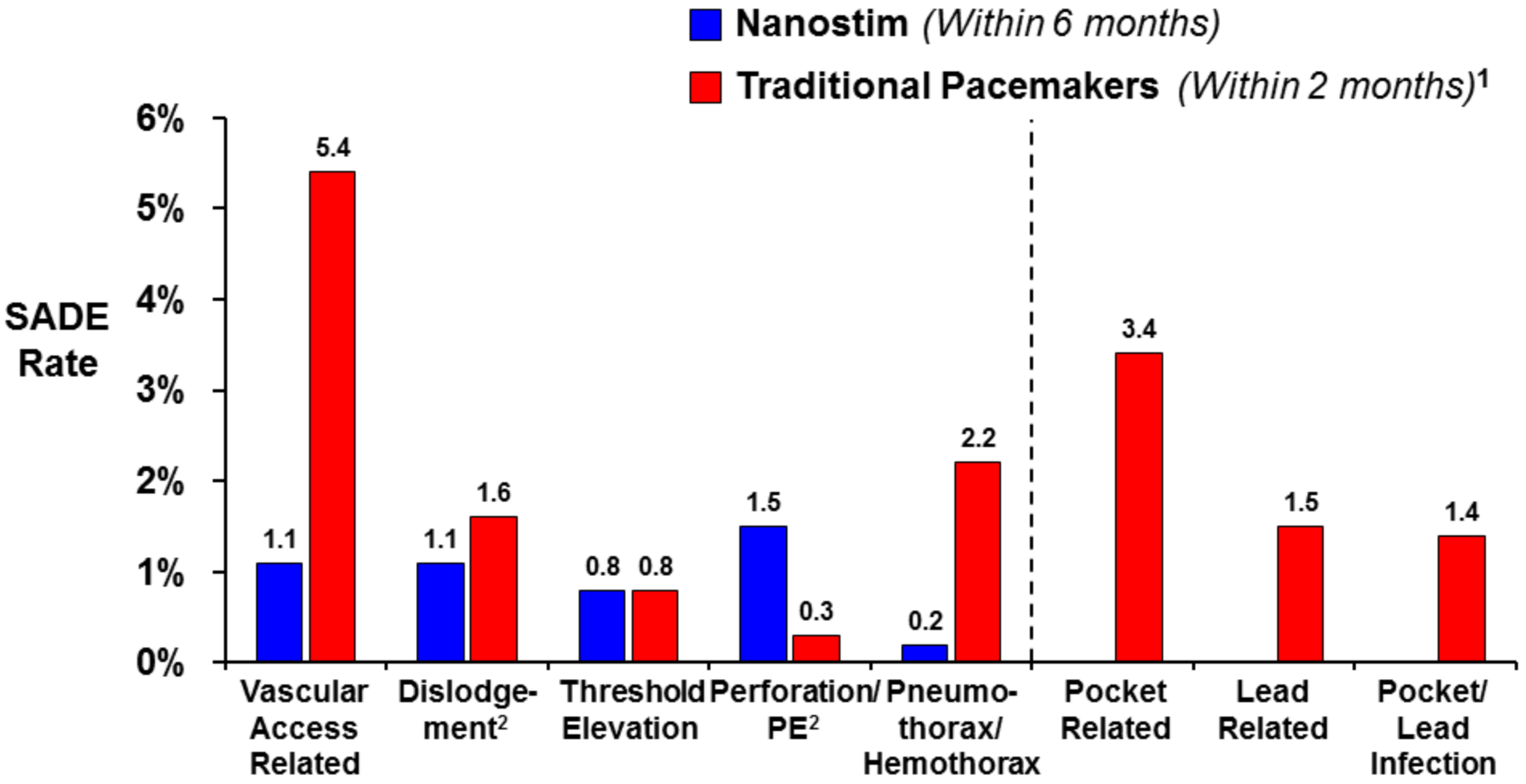
At Risk	526	479	430	381	334	308	279	70
Event	23	34	34	34	34	34	34	34
Success	95.6%	93.5%	93.5%	93.5%	93.5%	93.5%	93.5%	93.5%
97.5 LCB	93.5%	91.1	91.1	91.1	91.1	91.1	91.1%	91.1%

Total Cohort (N=526)

Reddy et al, *N Eng J Med* 373:1125-35 (2015)

FDA Question Q1.A

Comparison of SADE Rates Nanostim vs. Traditional Pacemakers



[1] Udo et al, *Heart Rhythm* 9:728 –735 (2012)

[2] Perforation and dislodgement for VVI pacemakers only; other data include single and dual chamber pacemakers

Procedure Related Mortality Adjudicated by Independent CEC

- No intraprocedural deaths
- 3 deaths (0.6%) adjudicated as procedure related
  1. 71 y.o. with cancer, respiratory arrest during implant (abandoned), required tracheotomy, made DNR, expired ~2 weeks later
  2. 89 y.o., successful implant, right groin hematoma, discharged home, expired ~ 2 weeks later
  3. 74 y.o., right atrial perforation, implant abandoned, large MCA stroke 2 days later and expired

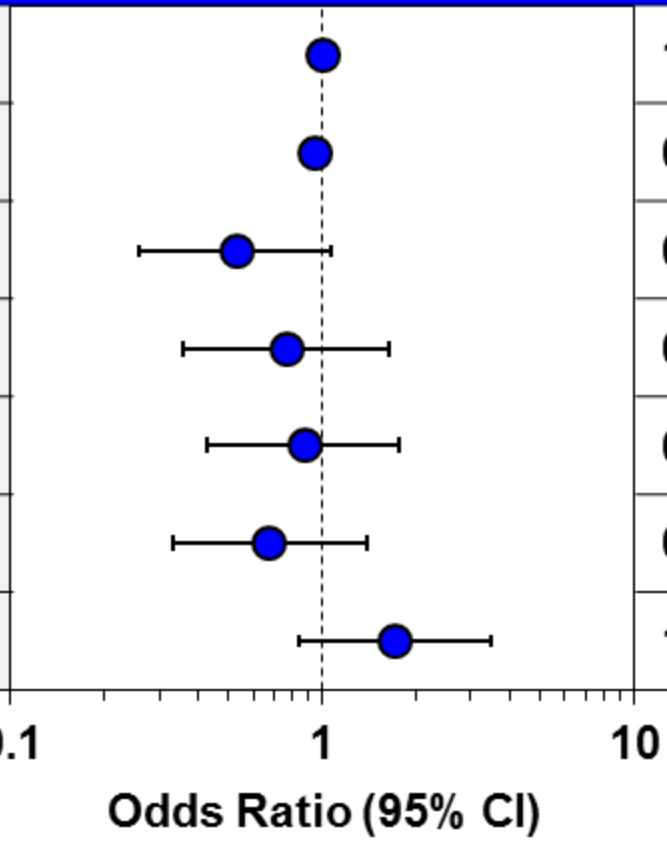
SCC = Squamous Cell Carcinoma

Total Cohort (N=526)

FDA Question Q1.B

No Significant Predictors of SADEs

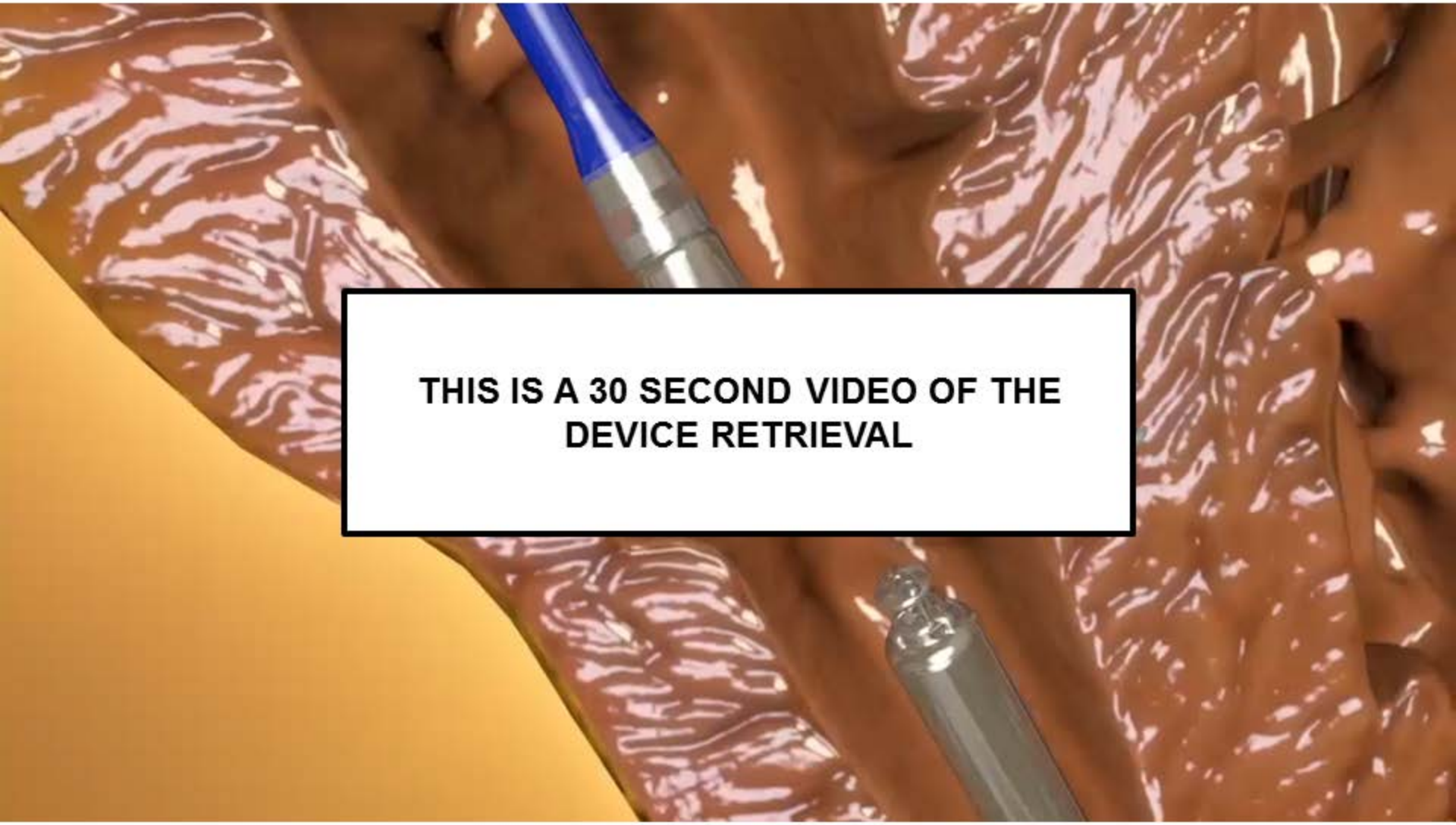
Variables Assessed	Odds Ratio (95% CI)	p-value
Age	**1.01** (0.98, 1.04)	**0.592**
BMI	**0.95** (0.89, 1.01)	**0.098**
Sex - Male	**0.53** (0.26, 1.06)	**0.072**
Prior cardiac intervention	**0.77** (0.36, 1.64)	**0.497**
Use of anticoagulant	**0.88** (0.43, 1.76)	**0.708**
Use of antiplatelet	**0.68** (0.33, 1.39)	**0.295**
Repositioning (Y/N)	**1.71** (0.84, 3.48)	**0.139**



Based on univariate logistic regression modelling

Total Cohort (N=526)

Retrieval Animation



Retrieval of Implanted Devices: 7 Retrievals, 100% Success Without SADEs

- Retrieval an important capability
- Time from implant to retrieval
  - Average 160 ± 180 days (Median = 100)
  - Range 1 - 413 days
- Reasons for retrieval
  - Elevated pacing thresholds (n=4)
  - CRT implantation (n=2)
  - Elective explant (n=1)

Total Cohort (N=526)

Leadless II Clinical Trial Summary

- Successfully implanted in ~96% of patients
- Trial met pre-specified Safety and Effectiveness endpoints
- Complication rate similar to conventional pacemakers
- Device is retrievable

Nanostim Leadless EU Post Market Study US Post Approval Study Training Program

Mark Carlson, MD
Chief Medical Officer and VP Global Clinical Affairs, St. Jude Medical
Adjunct Professor
Case Western Reserve University

Learnings and Enhancements from the EU Post Market Study

- Enhanced patient selection criteria
- Required high resolution fluoroscopy
- Recommended septal rather than apical implants
- Enhanced training program

EU SADE Rate Decreased After Changes From Key Learnings Were Implemented

	EU Post Market Study			
	Pre-Learnings (N=147)		Post-Learnings (N=93)	
	%	%	n	%
Cardiac perforation or pericardial effusion	6	4.1	2	2.2
Device dislodgement	2	1.4	0	0.0

U.S. Post Approval Study

U.S. Post Approval Study Overview (1 of 2)

- Prospective
- Non-randomized
- Multi-center
- Acute and long term safety including
  - Complications and success rate of removal/extraction
- Primary endpoint:
  - Freedom from Complication

FDA Question Q2.C.iii

FDA Question Q2.B.ii

U.S. Post Approval Study Overview (2 of 2)

- Data collected at:
  - Implant
  - Pre-discharge
  - Two weeks and
  - Semi-annually for 7 years
- Patient management at time of device replacement or deactivation
  - 30 day post replacement with traditional pacemaker
  - Continued follow up if replaced with Nanostim

FDA Questions
Q2.A.i
Q2.B.iv

FDA Questions
Q2.B.i
Q2.C.i
Q2.C.ii

Post Approval Study Overview Sample Size

FDA Questions
Q2.A.i
Q2.B.i
Q2.B.ii
Q2.B.iii
Q2.C.i

- 1,700 patients
- Design allows for early and late AEs to be estimated to within a 90% CI width of 1%
- Study to include Leadless II and newly enrolled patients clinically indicated for single chamber pacing therapy

Mandatory Nanostim Physician Training Program

Prerequisite Requirements

- Qualified for pacemaker implantation
- An established practice affiliation with institution that has:
  - Resources to support implantation
  - High resolution fluoroscopy equipment
  - Proper emergency facilities for cardioversion, defibrillation, pericardiocentesis and cardio-pulmonary resuscitation

7-Module Training Program Comprehensive Content

- Didactic Training / Patient Selection (Module 1)
- Hands-on Training
  - Implant Demonstration (Module 2)
  - Animal Lab Training (Module 3) or Virtual Reality Training (Module 5)
- Video Compendium Review (Module 4)
- Site-Training and onboarding, Case Observation, Technical and Implant Support and In-case Training provided by SJM certified personnel (Modules 6 and 7)

FDA Question Q3

Virtual Reality
Reinforcing Correct Technique

- Benefits over animal lab
- Virtual reality demonstrates:
  - Catheter handle operations
  - Procedural steps
  - Best and worst practices
  - How to avoid complications
- Provides real-time critical warning messages and feedback

7-Module Training Program Comprehensive Content

- Didactic Training / Patient Selection (Module 1)
- Hands-on Training
  - Implant Demonstration (Module 2)
  - Animal Lab Training (Module 3) or Virtual Reality Training (Module 5)
- Video Compendium Review (Module 4)
- Site-Training and onboarding, Case Observation, Technical and Implant Support and In-case Training provided by SJM certified personnel (Modules 6 and 7)

Physician Certification Contingent on Completion of Training Program

- Physician Certification received after successful completion of
  - All modules
  - 10 procedures with technical and implant support and in-case training provided by SJM certified personnel

Summary

- Complication rates similar to alternative therapies
- Absence of longer-term SADEs
- Absence of certain complications associated with standard pacemakers
- Robust training program will support safe use
- Event rates will continue to be monitored in post-approval study

St. Jude Medical
Nanostim Leadless Pacemaker

Presentation to the
Circulatory System Devices Panel

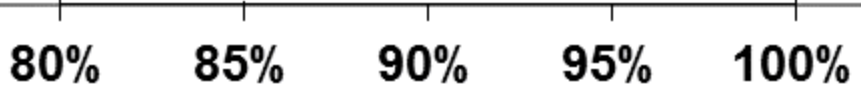
February 18, 2016

Changes to Transfer Nanostim Learnings

Lessons Learned	Action Taken
Nanostim used as device of last resort	Align inclusion/exclusion criteria with IDE study. Stress care during patient selection by SJM field personnel
All perforations were associated with RV apical implants	Placement in lower septum
Quick rotation may cause catheter to torque and over-rotate	Slowly rotate catheter with pauses, 1-1 ¼ turns rather than 1¼
Pressure on the endocardium increases if protective sleeve is not fully retracted and if the catheter buckles	Fully pull back protective sleeve before engaging endocardium and apply forward pressure gently so the device is moving with the cardiac cycle
COI associated with active fixation leads, associated with higher initial thresholds	Wait up to 20 mins for COI to resolve
Suboptimal imaging equipment contributed to at least one cardiac perforation	Sites were required to use high resolution fluoroscopy equipment for implantation
Presence of an existing perforation before device implant was observed in at least one case	IFU warning added to not implant device in presence of an existing perforation

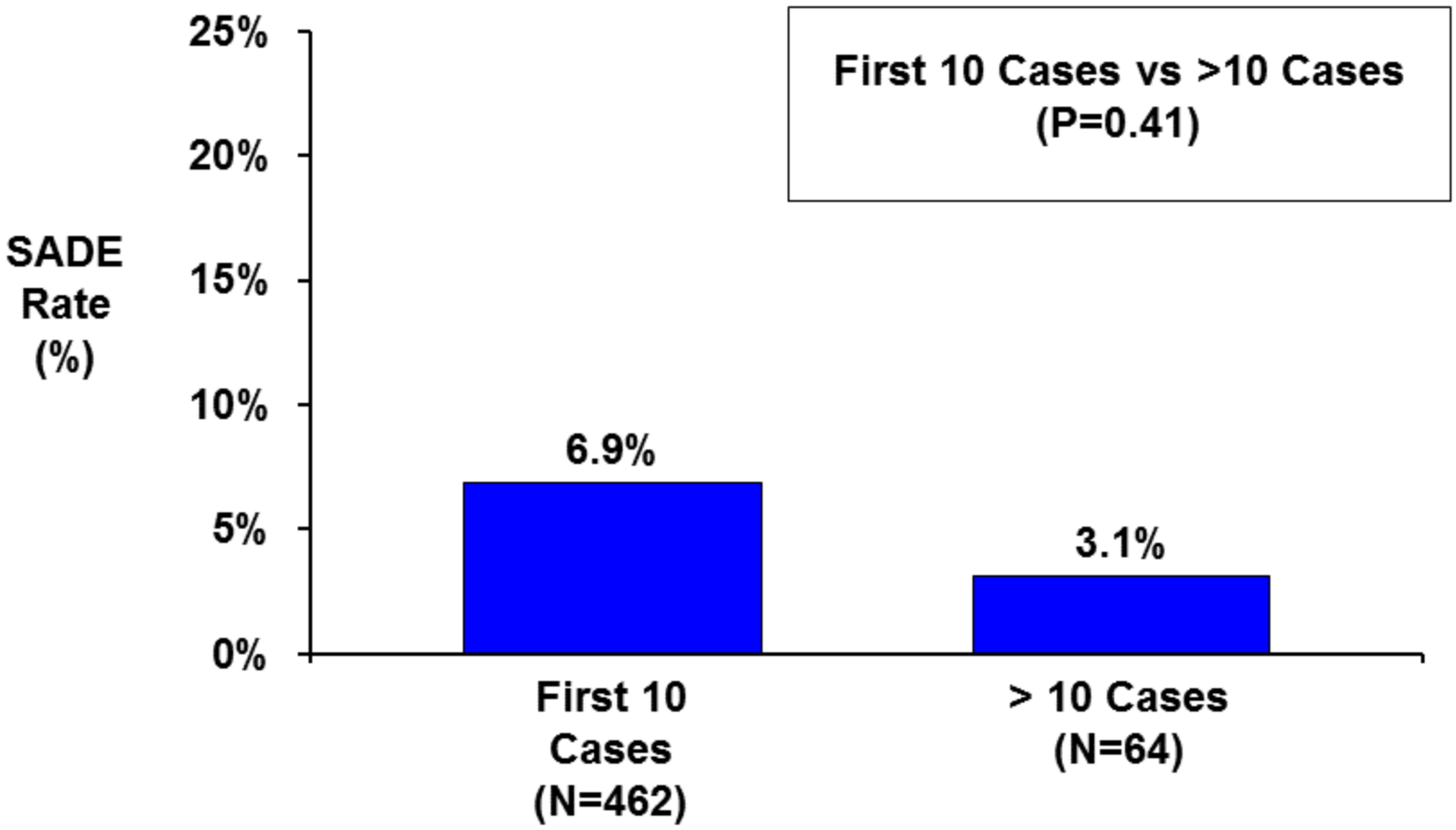
Primary Effectiveness Endpoint Surpassed the Performance Goal

	n / N	Performance Goal	Success Rate (95% CI)	P
ITT	270 / 300		90% (86%, 93%)	0.007
Successful Implant	270 / 289		93% (90%, 96%)	<0.001



Percent Achieving Primary Effectiveness Endpoint

SADE Rate
First 10 Cases vs >10 Cases



Threshold Elevation (N=4)

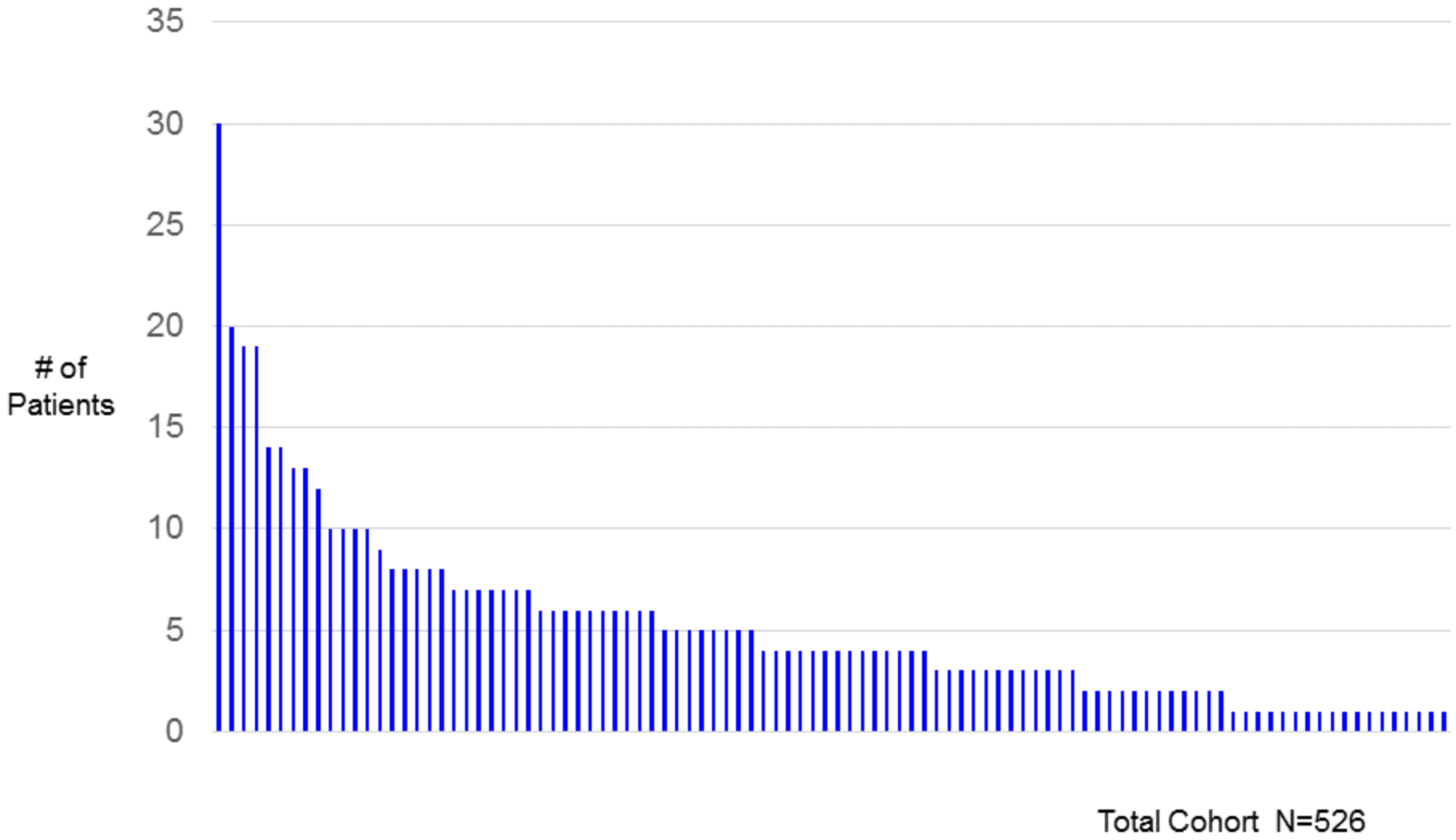
- Patient #1
  - Elevated Pacing Threshold at Implant
  - 2-week visit (Device reprogrammed)
  - 100 days post implant-LP retrieved and replaced with another LP
- Patient #2
  - Elevated Pacing Threshold at implant
  - The next day- LP retrieved and replaced with another LP
- Patient #3
  - Elevated Pacing Threshold at implant
  - The next day- LP retrieved and replaced with another LP
- Patient #4
  - Elevated Pacing Threshold- 72 hrs. post implant
  - Device Reprogrammed/Temporary pacer placed the following day
  - 23 days post implant-LP retrieved and replaced with transvenous ppm

Table 3-10: Deaths Classified by CEC Adjudication in Total Cohort

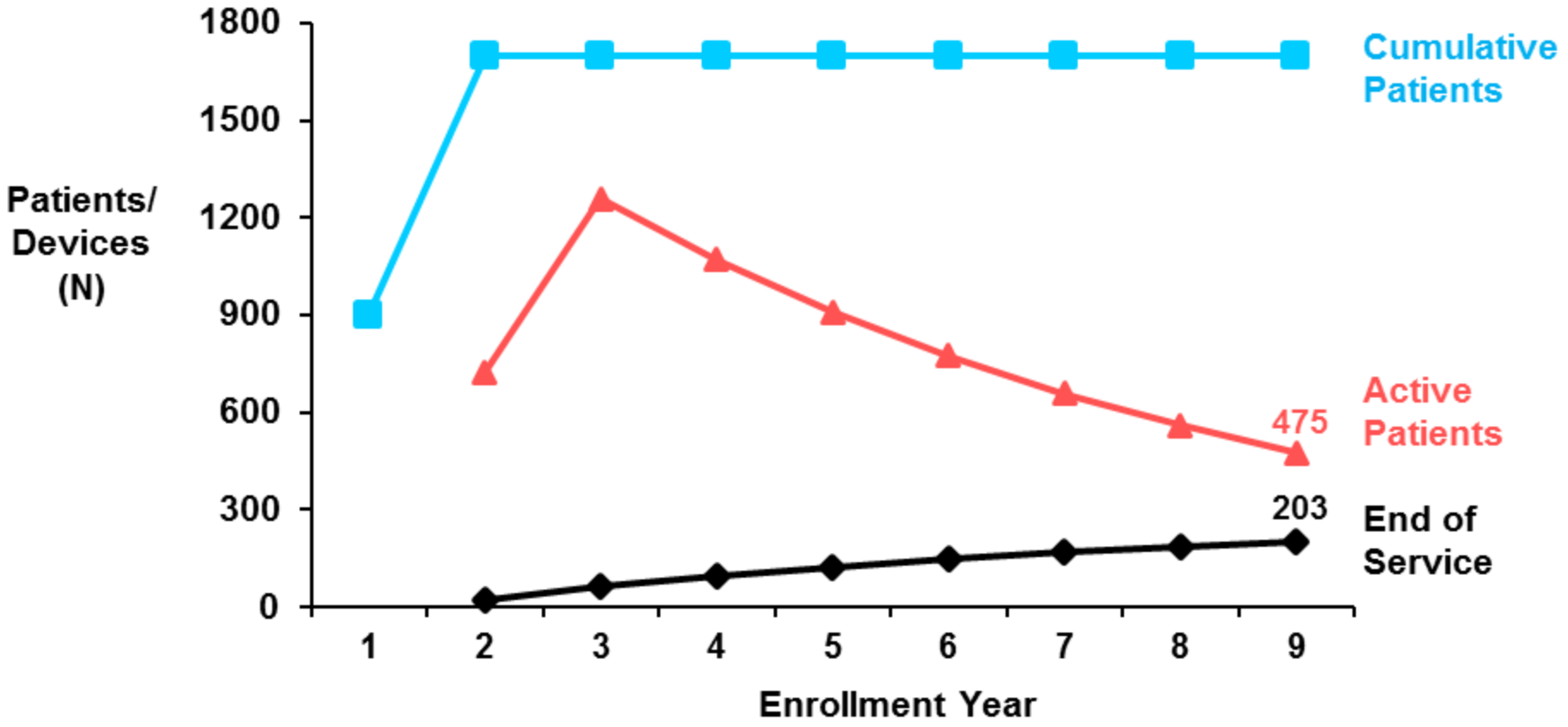
Cause of Death	Number of Patients	Relation to Device or Procedure	Number of Days Post-Implant
Cardiac			
Arrhythmic	2	Not Related (1); Procedure (1)	18, 100
Heart failure	1	Not Related (1)	99
Unknown	1	Procedure/ Introducer (1)	14
Non-cardiac			
Accidental gunshot wound	1	Not Related (1)	47
Renal or liver failure	5	Not Related (5)	73, 82, 89, 135, 320
Respiratory failure	3	Procedure (1) Not Related (2)	10, 103, 182
Multiple organ failure	2	Not Related (2)	34, 38
Ischemic bowel/small bowel obstruction	2	Not Related (2)	185, 270
Mixed respiratory and metabolic acidosis	1	Not Related (1)	176
Unknown*			
Death- Sudden with antecedent worsening heart failure	1	Not Related (1)	267
Death- Sudden without antecedent worsening heart failure	1	Not Related (1)	274
Death- Non-sudden with antecedent worsening heart failure	2	Not Related (2)	18, 42
Death- Non-sudden with antecedent worsening heart failure status unknown	1	Not Related (1)	281
Death-Unknown (presumed sudden) with no antecedent worsening heart failure	3	Not Related (2) Unknown (1)	5, 69, 126
Death-Unknown (presumed sudden) with antecedent worsening heart failure status unknown	1	Not Related (1)	219
Death- Unknown temporal cause and antecedent worsening heart failure status unknown	1	Not Related (1)	409
Total	**28**		

* Sudden death: death ≤1 hour after onset of symptoms
Non-sudden death: death > 1 hour after onset of symptoms
Death Unknown (presumed sudden): documentation of patient's condition by a witness within 24hours
Death Unknown: death where onset of symptoms cannot be determined

Enrollment By Operator



PAS - Projection of Patient Enrollment and Device End of Service



Assumes 15% attrition per year and 2.7% end of service per year