Micra™ Transcatheter Pacing System (TPS)

Circulatory System Devices Panel

February 18, 2016

Medtronic

Introduction

David M. Steinhaus, MD

Medical Director, Vice President

Medtronic Cardiac Rhythm and Heart Failure

Presenters/Responders

Introduction to Technology	**David M. Steinhaus, MD** Medical Director, Vice President Medtronic Cardiac Rhythm and Heart Failure
Study Results	**Dwight W. Reynolds, MD** Regents Professor, Chief Cardiovascular Section University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma
Summary	**David M. Steinhaus, MD** Medical Director, Vice President Medtronic Cardiac Rhythm and Heart Failure
Additional Responders	**John D. Hummel, MD** Professor of Medicine, Director of Electrophysiology Research The Ohio State University Wexner Medical Center, Columbus, Ohio
	Robert C. Kowal, MD, PhD Co-Medical Director, Cardiac Electrophysiology Baylor Scott and White Health Care System, Dallas, Texas

Agenda

- Introduction to Micra
- Clinical Study Results
- FDA Questions
  1. AEs, subgroups, physician training
  2. Post-approval requirements
  3. Device end-of-life options
  4. Indications for Use
- Conclusion

Cardiac Pacing Milestones

External Pacemaker

1958

Implantable Pacemaker

1960

Rate Responsive Pacemaker

1986

MRI Conditional Pacemaker

2011

Intracardiac Pacemaker

Today

The Clinical Need for Micra

- 1 in 8 patients with traditional pacemaker may experience complication
  - Lead related 2.4 - 5.5%
  - Pocket related 0.4 - 4.8%
  - Pneumothorax 0.9 - 2.2%
  - Infection 0.3 - 0.8%

Udo, et al. *Heart Rhythm*. 2012;9:728-35. Kirkfeldt, et al. *Eur Heart J*. 2014;35:1186-94.

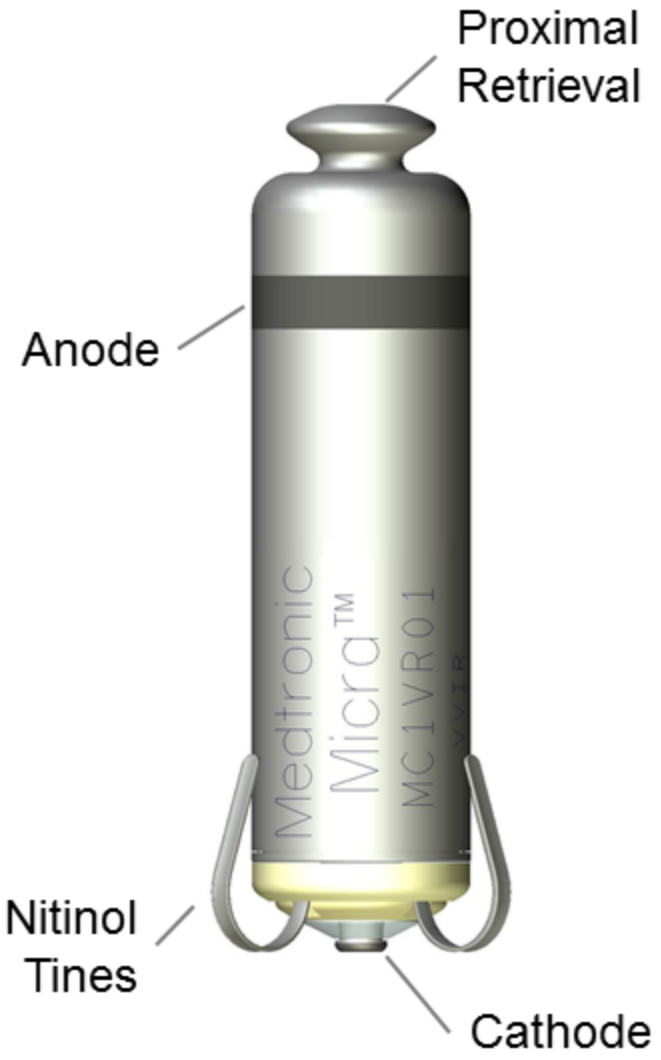
Micra: 93% Smaller than Traditional Pacemakers

Micra: Improvement in Every Component

	Average 12+ Year Longevity		15x Required Holding Force
Micra	Ultra, Low Power Circuit 	Significantly Smaller Battery 	Nitinol Tines 
Traditional			

Micra Capabilities

- Device-Off Mode
- MRI compatible (1.5 T or 3 T)
- Accelerometer-based rate response
- Capture Management™
- CareLink™ Remote Monitoring capability



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Study Results

Dwight W. Reynolds, MD

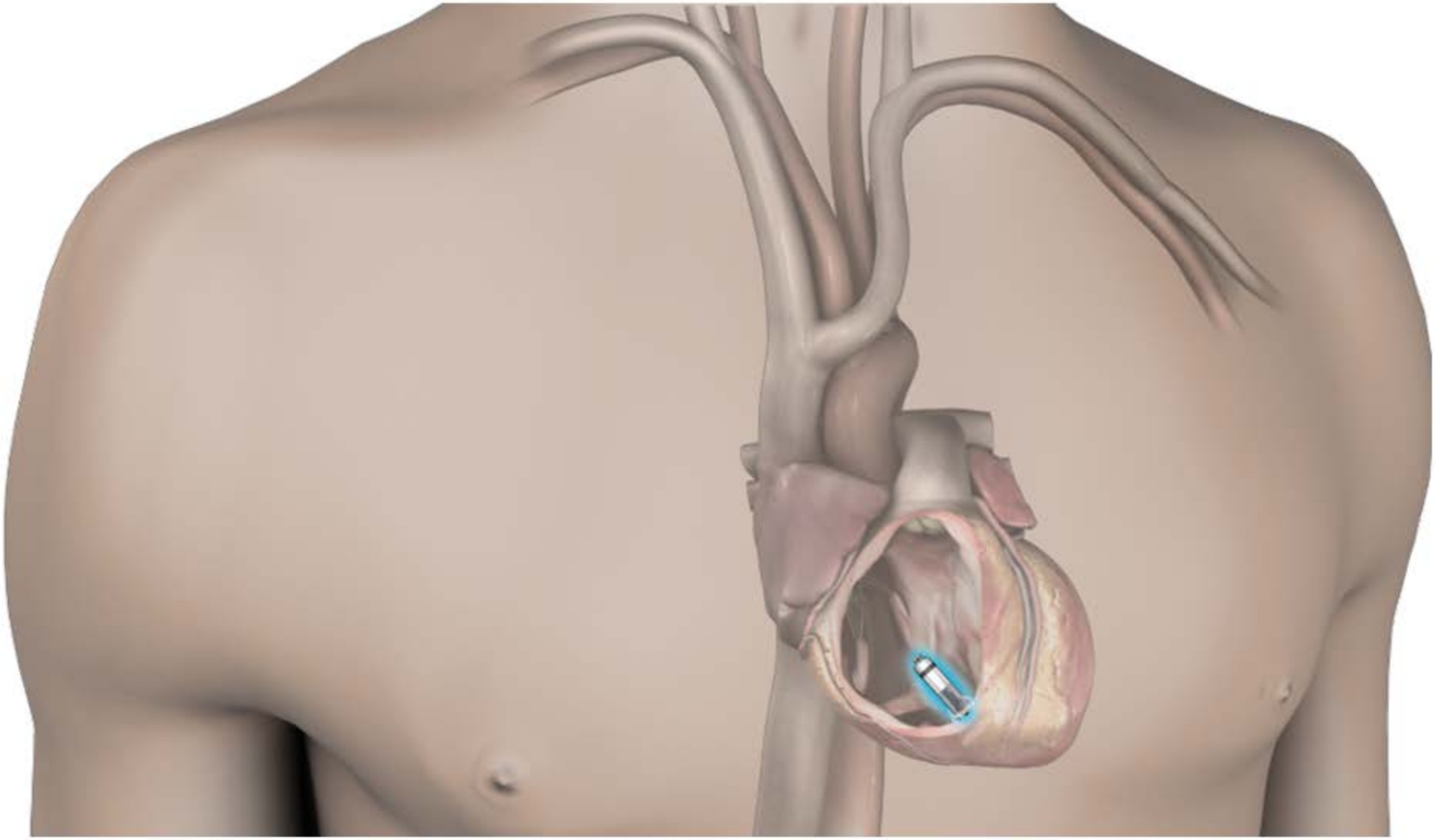
Regents Professor, Chief Cardiovascular Section

University of Oklahoma Health Sciences Centers, Oklahoma City, Oklahoma

Key Clinical Results/Overview

- 99.2% implant success
- Met primary efficacy and safety objectives
- Efficacy
  - 98.3% had low, stable pacing capture threshold at 6 months
- Safety
  - 96% freedom from device / procedure-related major complications at 6 months
  - 51% fewer major complications than traditional pacemakers
  - No dislodgements and no infections

Implant Procedure Video



Globally Diverse Patient Population with Robust Trial Design

- 725 patients, 94 implanters, 56 centers, 19 countries, 5 continents
  - North America, Europe, Asia, Australia, Africa
- VVIR patients: Class I or II guideline indication* for *de novo* ventricular pacing with no restriction by comorbidity (e.g. COPD)
- Pre-defined historical control group for comparison (2000-2012)

*Epstein et al., 2008; Zipes et al., 2006

Micra Patients Older, More Comorbidities: Baseline Characteristics

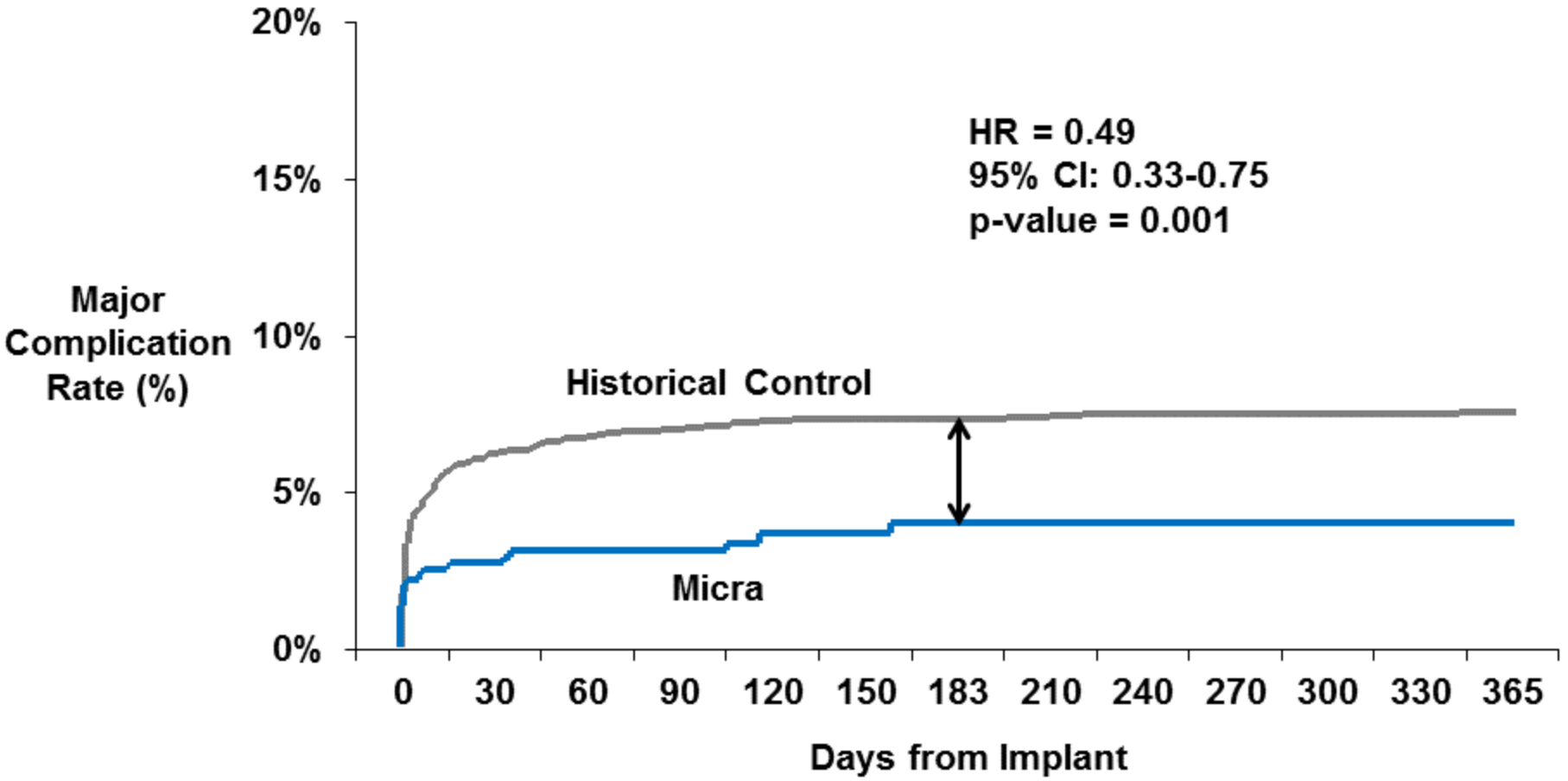
	Micra (N=725)	Historical Control (N=2667)	p-value*
Age (years)	75.9 ± 10.9	71.1 ± 12.1	<0.001
Female	41.2%	44.9%	0.08
Hypertension	78.6%	67.2%	<0.001
AF	72.6%	36.6%	<0.001
Valvular Disease	42.2%	19.2%	<0.001
Diabetes	28.6%	21.9%†	<0.001
CAD	28.0%	38.4%	<0.001
CHF	17.0%	15.0%	0.20
COPD	12.4%	7.2%†	0.001
Vascular Disease	7.3%	10.1%	0.032

*P-value from T-test (continuous variables) or Fisher's Exact test (categorical variables).
†Data parameter not collected across all 6 trials.

Micra Major Complications (N=725)

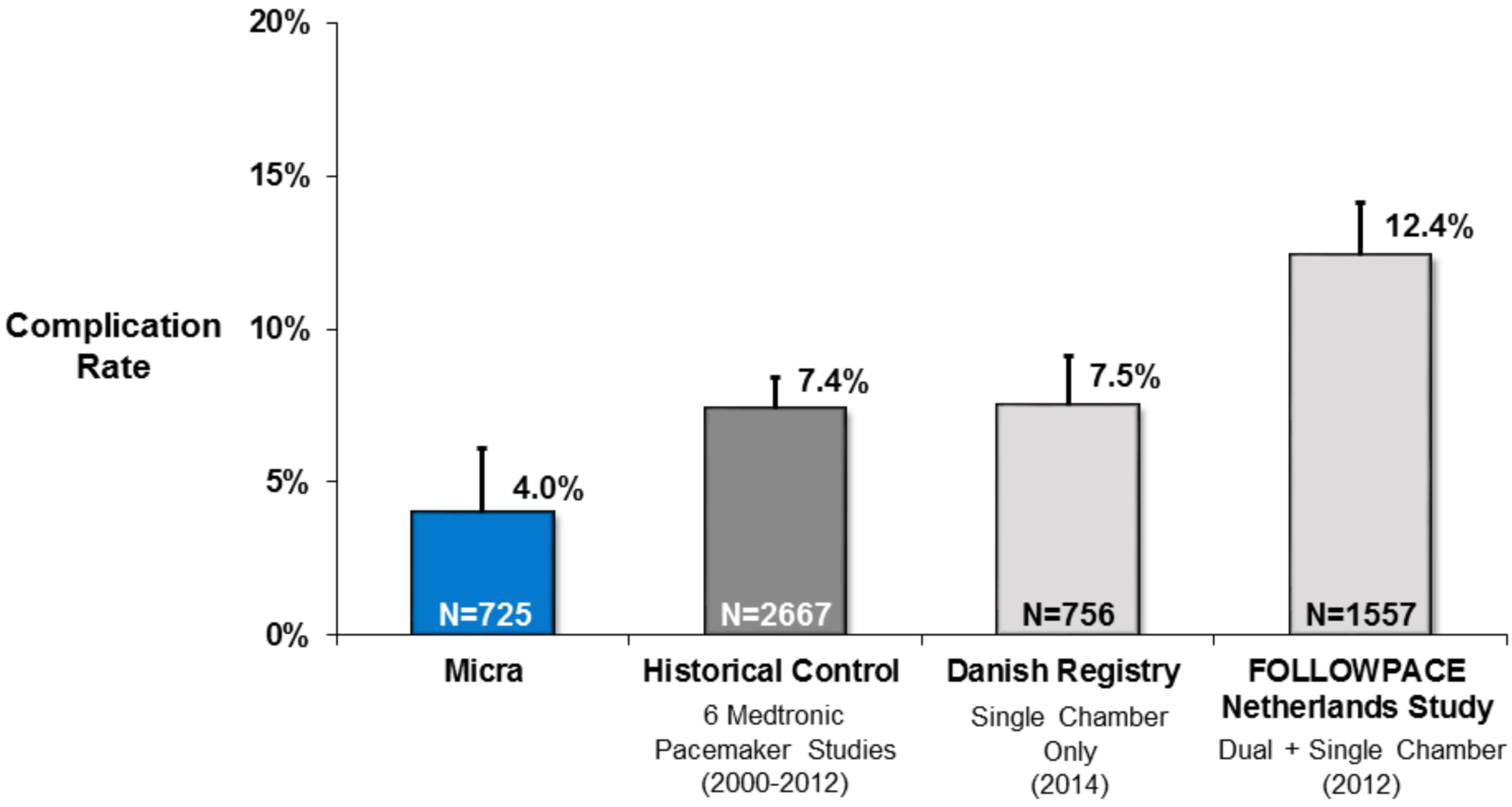
	Total Events	Patients (Kaplan-Meier at 6 Mos)
Total	28	25 (4.0%)
Deep Vein Thrombosis	1	1 (0.1%)
Pulmonary Embolism	1	1 (0.1%)
AV Fistula/Pseudoaneurysm	5	5 (0.7%)
Cardiac Perforation/Effusion	11	11 (1.6%)
Elevated Thresholds	2	2 (0.3%)
Acute MI	1	1 (0.1%)
Cardiac Failure	3	3 (0.9%)
Metabolic Acidosis	1	1 (0.1%)
Pacemaker Syndrome	1	1 (0.1%)
Presyncope	1	1 (0.1%)
Syncope	1	1 (0.1%)

51% Fewer Major Complications with Micra vs Transvenous Pacemakers



# at risk													
Control	2667	2396	2313	2267	2187	2120	1965	1793	1729	1702	1669	1633	1537
Micra	725	659	505	497	303	298	289	71	68	64	62	62	62

Micra Complication Rate Lower than Recently Published Data



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FDA Question #1A
Clinical Significance of AEs

- Please discuss the clinical significance and any concerns you might have for rate of occurrence of each of following AEs observed to occur at implant with leadless pacemaker devices as compared to traditional pacemakers.
  - Cardiac Perforation
  - Pericardial Effusion
  - Dislodgement
  - Embolization
  - Other events (e.g. stroke, arrhythmia)

Major Complication Rates Requested by FDA

6-Month Kaplan-Meier Estimates	Micra (N=725)	Historical Control (N=2667)	p-value
Cardiac Perforation/Pericardial Effusion	1.6%	1.1%	0.288
Dislodgement	0%	1.5%	0.011
Device Embolization	0%	Not applicable	Not estimable
Arrhythmias	0%	0.7%	0.156
Stroke *(Transient Ischemic Attack)*	0%	0.1%	1.000

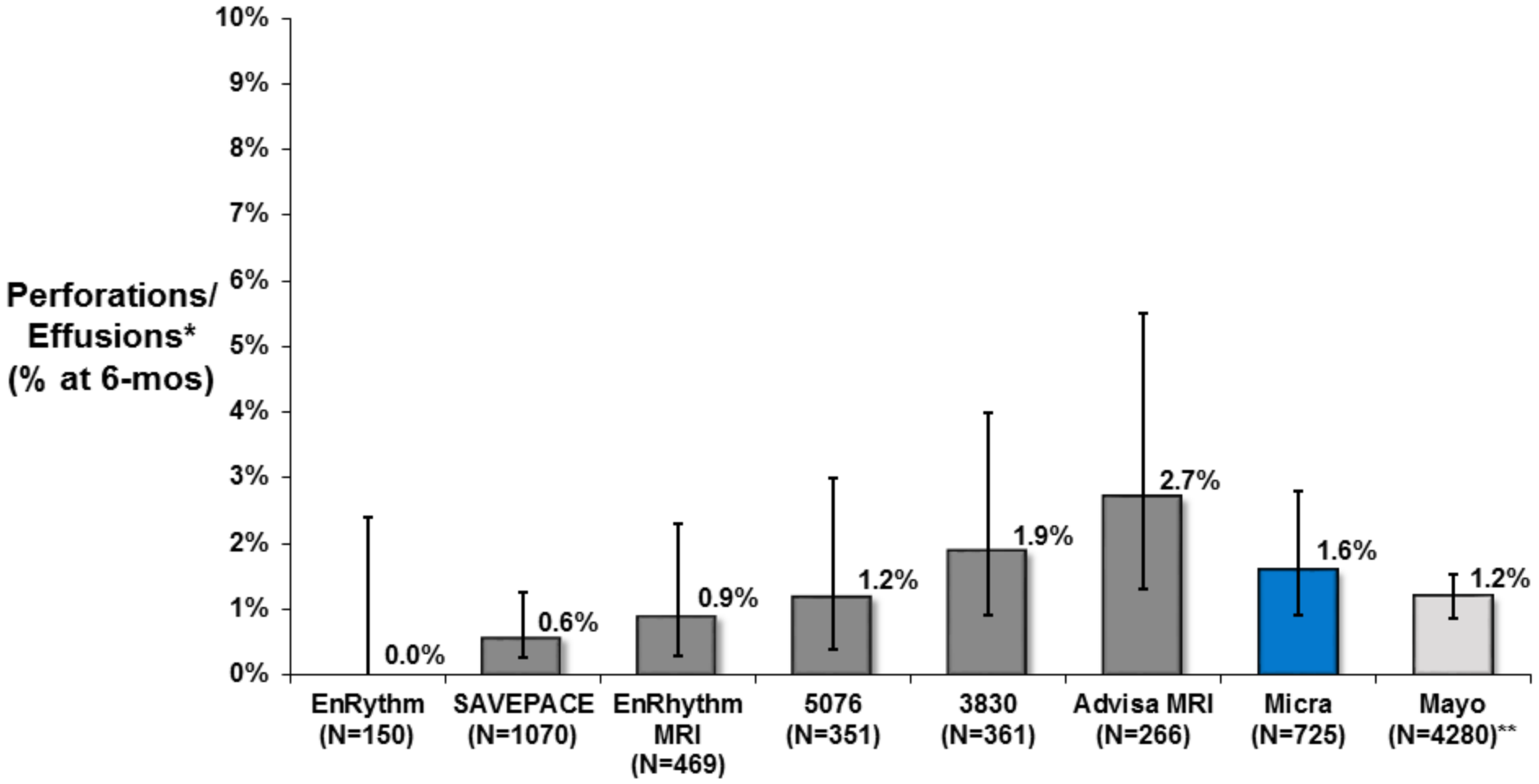
All Micra Patients with Perforations/ Effusions had ≥ 1 Risk Factor

- All are reported risk factors for transvenous lead complications*

Subject Characteristics	No Cardiac Effusion (n=712)	Yes Cardiac Effusion (n=13)	p-value
Age (years), Mean ± SD	75.8 ± 11.0	81.7 ± 8.6	0.053
BMI, Mean ± SD	27.6 ± 5.3	24.5 ± 4.0	0.032
Female, n (%)	290 (40.7%)	9 (69.2%)	0.048
COPD, n (%)	85 (11.9%)	5 (38.5%)	0.015
Chronic Lung Disease, n (%)	203 (28.5%)	8 (61.5%)	0.025

*Ellenbogen et al., 2003; Hsu et al., 2013; Mahapatra et al., 2005; Ohlow et al., 2013

Micra Perforation/Effusion Rate Similar to Traditional Pacing



* Meeting major complication endpoint criterion

** Clinical signs and symptoms of perforation from Mahapatra et al., 2005

Perforation/Effusion Intervention

Perforations/Enrollments n(%)	Micra (n=13*/725)	Historical Control (n=50/2667)	Mayo Clinic Data* (n=50/4280)	Zentralklinik, Germany† (n=20/968)
Surgical Repair *(w or w/o pericardiocentesis)*	2 (15%)	2 (4%)	0 (0%)	2 (10%)
Pericardiocentesis	7 (54%)	10 (20%)	35 (70%)	12 (60%)
Lead Revision	-	11 (22%)	4 (8%)	-
No Intervention	4 (31%)	27 (54%)	11 (22%)	6 (30%)
Death	-	-	-	2 (10%)

Includes 2 events not meeting major complication criteria

*Mahapatra et al. *Heart Rhythm* 2005. †Ohlow et al. *Circ J.* 2013.

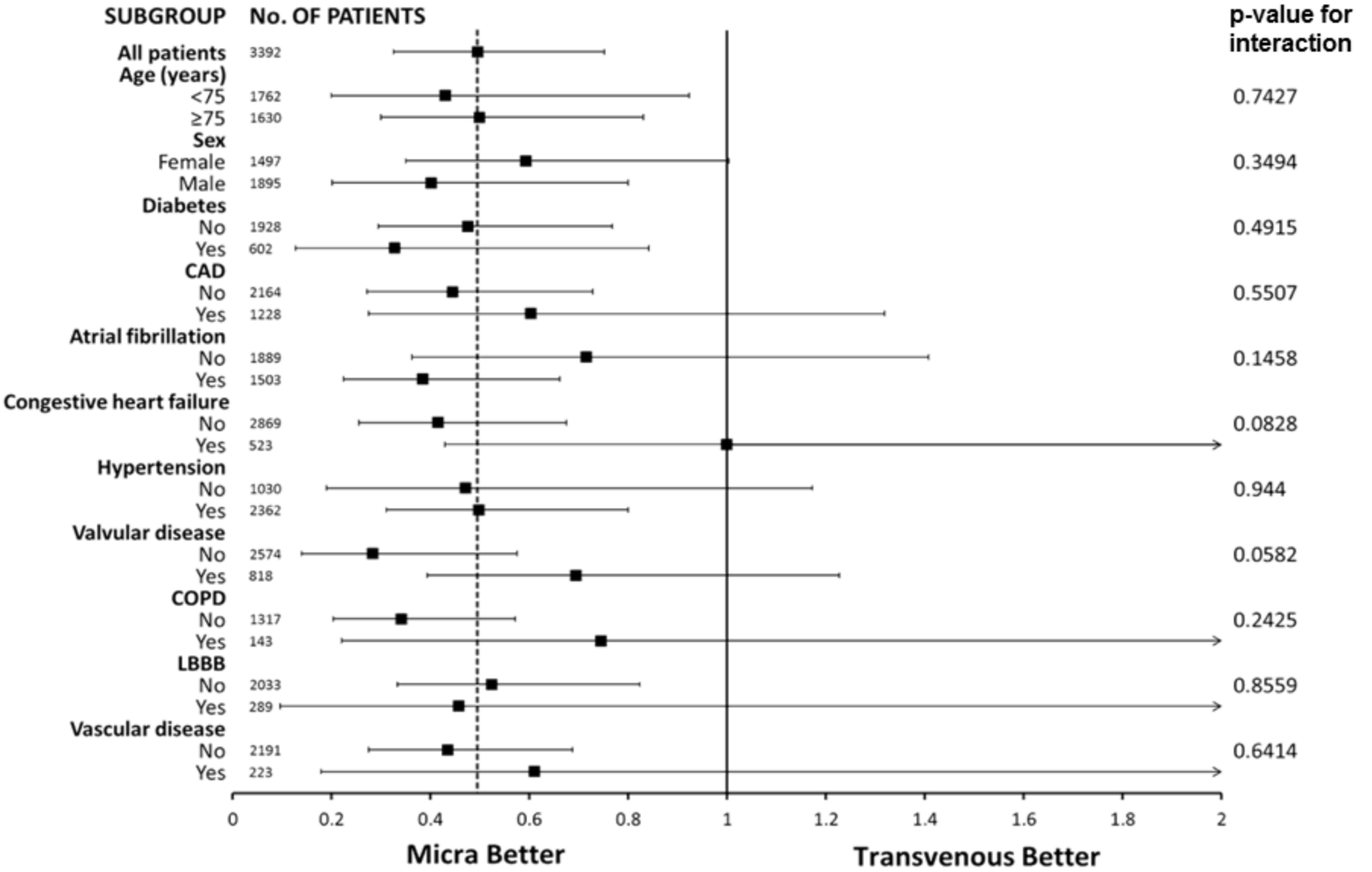
Micra Overall Safety Profile Favorable Vs. Traditional Pacemakers

- Perforation/effusion rate in-line with traditional pacemaker procedures
- Patients older and sicker
- Significant reduction in complications

FDA Question #1B
Patient Sub-Groups

- Please identify any subgroups of patients (e.g., based on anatomical characteristics, demographics, etc.) as having an increased risk based on AE rates associated with these devices.

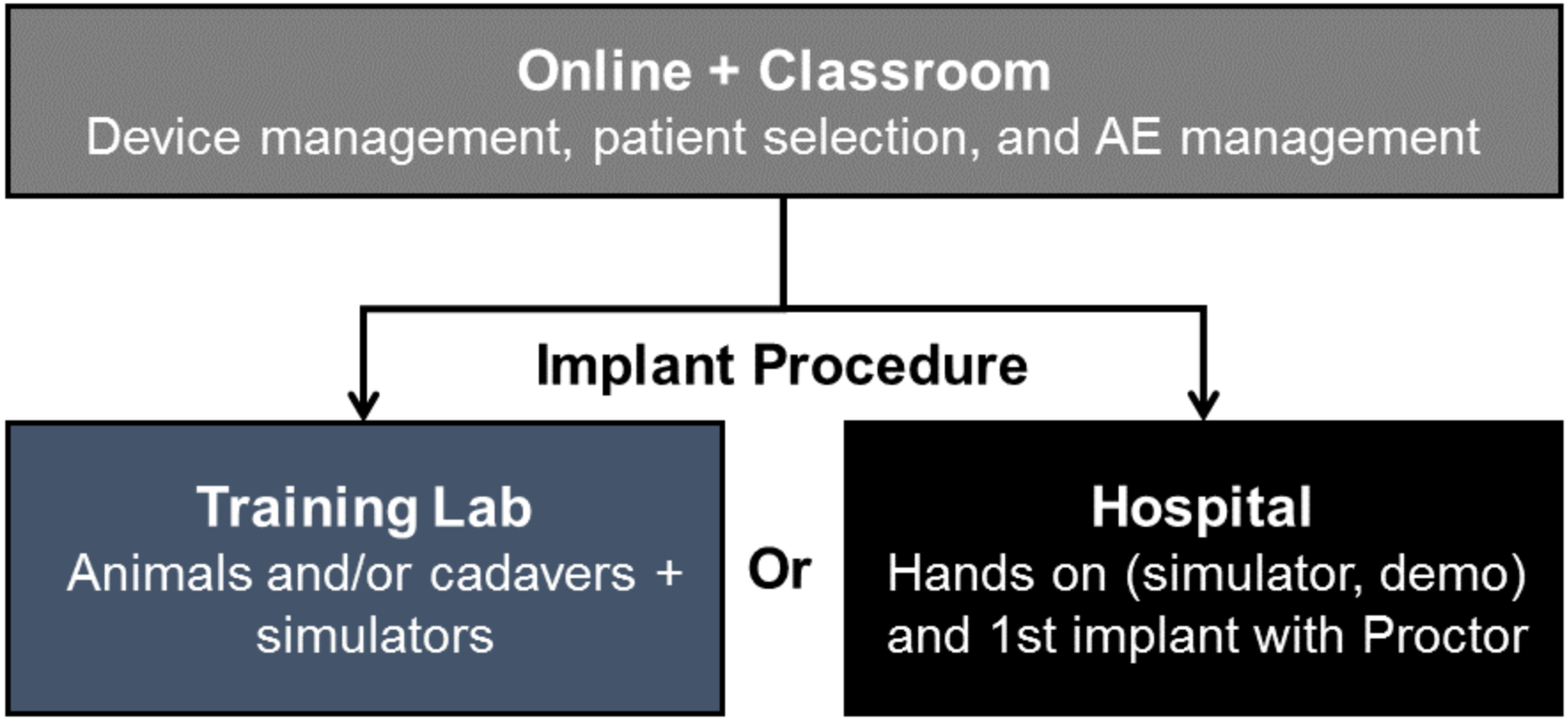
Most Sub-Groups Fared Better with Micra than Traditional Pacemakers



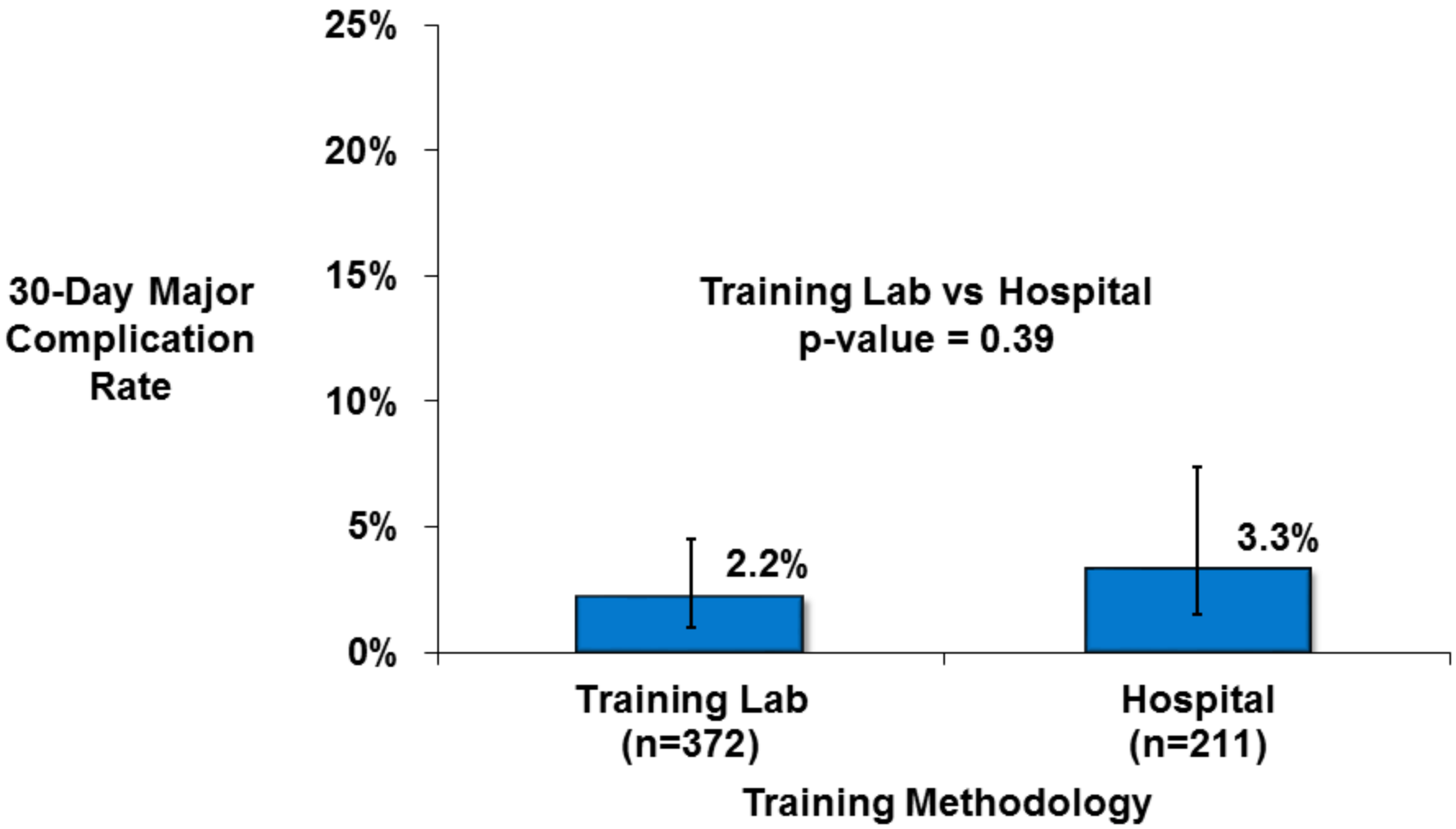
FDA Question #1C
Physician Training

- Please discuss what measures you would recommend to ensure implanting physicians are adequately trained/informed regarding potential occurrence of AEs and appropriate device and patient selection.

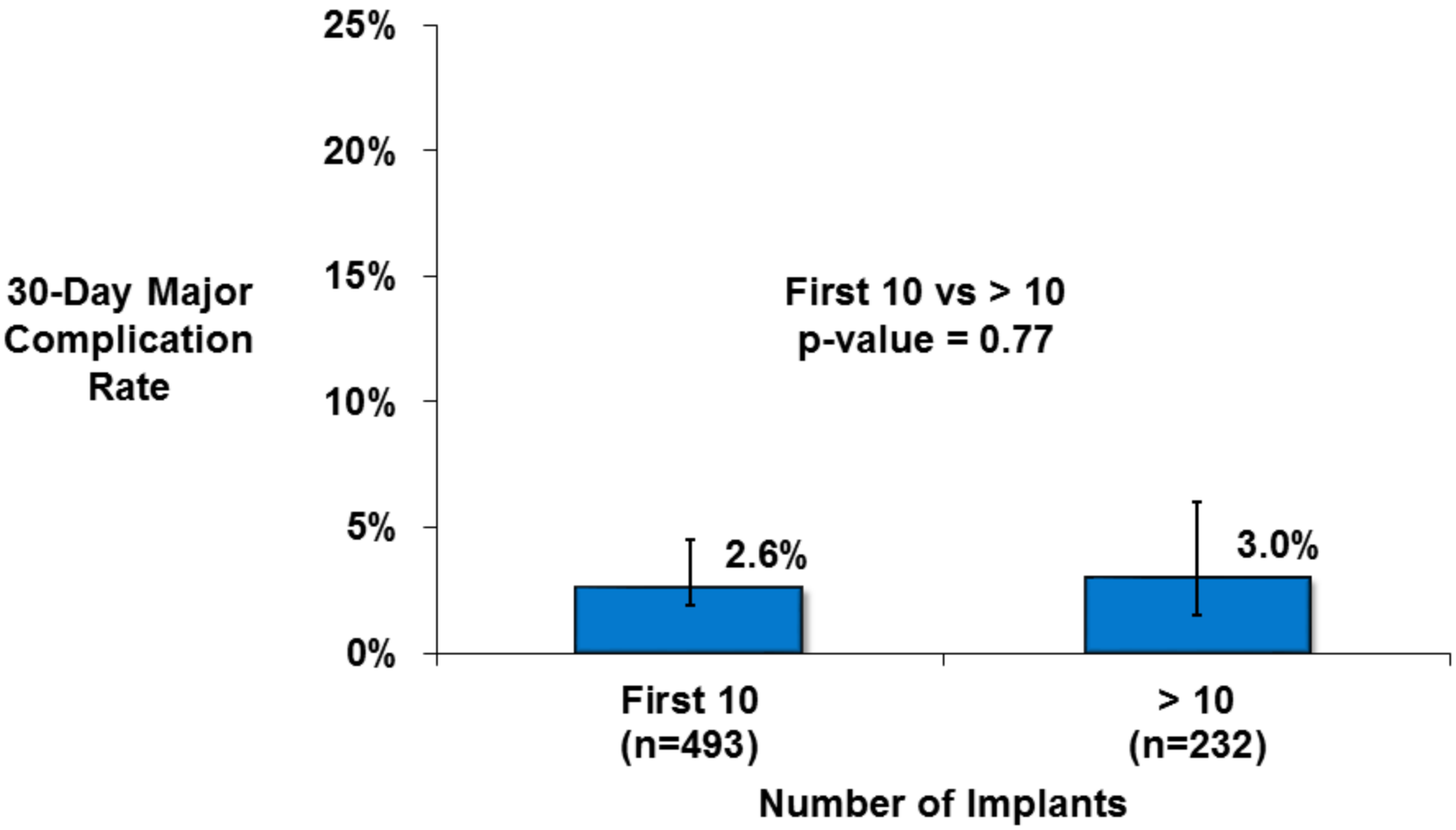
Medtronic Training Pathways: Similar to Clinical Trial



Low Major Complication Risk with Both Training Methodologies



No Learning Curve For Implanting Physicians



Transvenous Pacemaker Complications Mitigated by Micra

	Short-term	Long-term
Pocket	• Infection • Hematoma	• Infection • Twiddler's Syndrome
Lead	• Dislodgement • Loose header connection	• Venous thrombosis/ obstruction • Fracture • Insulation breach • Tricuspid valve injury
Access	• Pneumothorax	

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FDA Question #2a
Post-Approval Study

- How to collect data for acute performance
- Long-term performance
  - Expected late device failures
  - Appropriateness of complication-free-rate as endpoint
  - Ways to complete long-term study

Medtronic PAS Proposal: Prospective Study (N=1895)

- Provides precise estimates for individual failures at 1% rate (95% CI width ± 0.8%)
- Estimate acute complication rate at 30 days
- Estimate complication-free survival probability at 5 years
  - 1,000 patients at 5 years
  - 500-800 patients at 8 years
- Broad inclusion criteria

FDA Question #2b Post-Approval Study (End-of-Service/Deactivation)

- Please recommend an approach to evaluate device removal/extraction, i.e. how often it is attempted, success rates, and complications associated with removal/extraction.

Identify Revisions from U.S. Registration System

- Register all U.S. Micra patients
- Identify revisions by change in Micra status
- Request clinical data to characterize type of Micra revision
  - Number of extraction attempts, success rate, associated complications
- ~250 events within 5 years

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FDA Question #3
Labeling for End of Service Options

- In the absence of data on long term performance and end-of-life options for leadless pacemakers, please comment on content and points to address for appropriate labeling regarding extractions, replacements, and best practices at this time.

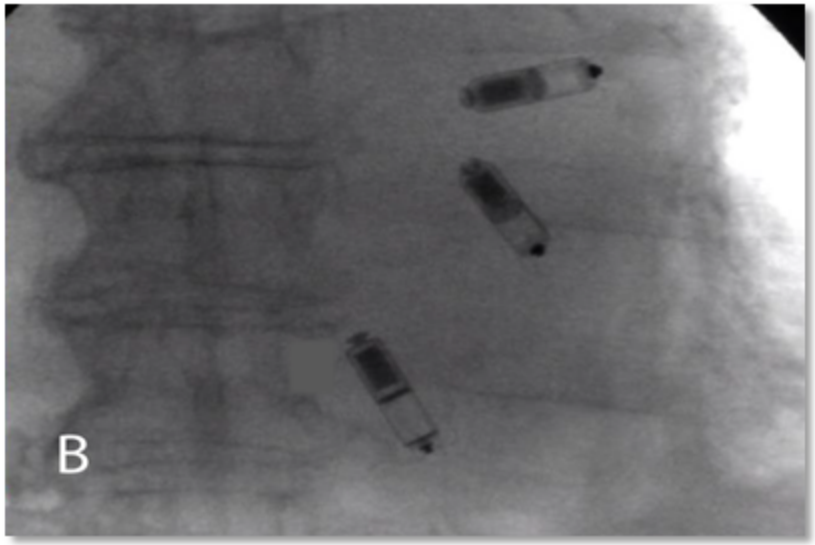
Best Practices/Labeling Recommendations

- One Micra sufficient for most patients
- Replacements (primary recommendation)
  - Leave Micra in place/Turn off
  - Implant new device
- Extractions
  - Performed by clinician with expertise in lead extraction

Rationale For Leaving Micra in Place and Turning Off

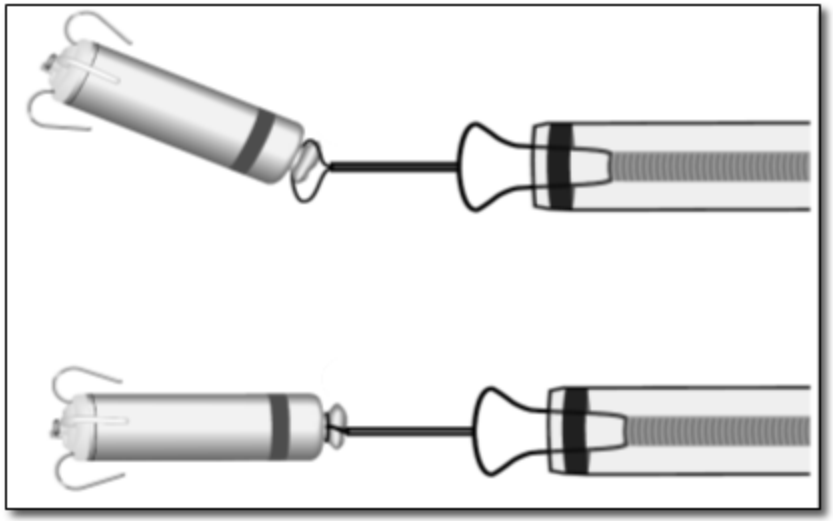
- Only takes up ~0.5% of right ventricle
- Complete encapsulation may protect against infection
- Other devices can be safely implanted
  - 5 cases concomitant device successfully placed

Example of 3 Micra devices placed in right ventricle of cadaver heart



Extractions: Micra Percutaneous Retrieval with Standard Tools

- Current experience (n=9)
  - All 7 within 6 months post implant successful
  - 2 attempts after 6 months
    - Micra left *in situ*, programmed off, new device successfully added



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FDA Question #4: Instructions for Use for VVIR Leadless Pacemakers

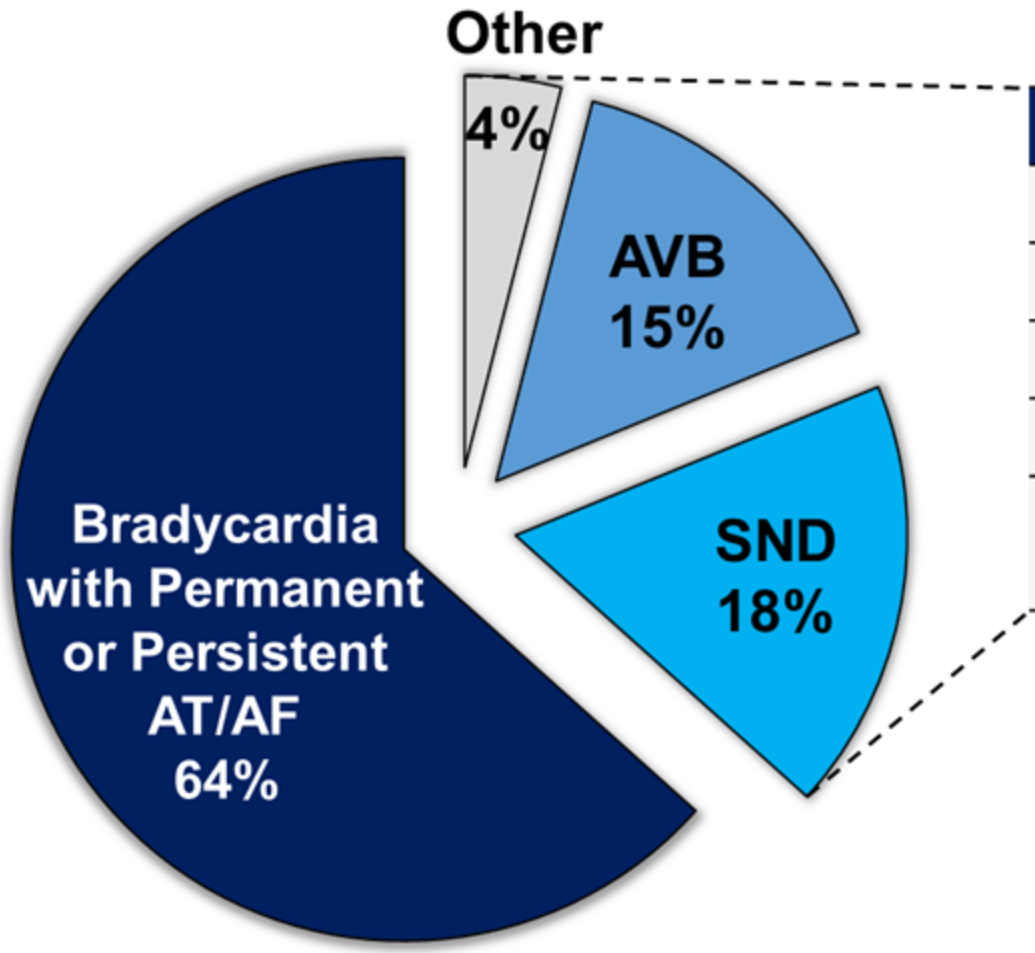
- Should the Leadless Pacemakers be indicated for all patients with symptomatic paroxysmal or permanent second or third degree AV block?
- Should the Leadless Pacemakers be indicated for all patients with paroxysmal or transient sinus node dysfunction?
- Should the Leadless Pacemakers be indicated for all patients with bradycardia-tachycardia syndrome or should it be recommended only if infrequent pacing is expected in a patient with advanced age, sedentary lifestyle, anatomical limitations or based on comorbidities.
- Should the Leadless Pacemakers be contraindicated in patients with pacemaker syndrome?
- If Leadless Pacemakers are reasonable to implant in patients with rare episode of AV block, should "rare“ be quantified in some way to minimize the possibility of implanting patients who will later develop pacemaker syndrome?

Micra Indications for Use Same as All Medtronic Pacemakers

Micra Model MC1VR01 is indicated for use in patients who may benefit from rate-responsive pacing to support cardiac output during varying levels of activity. This device is indicated for use in patients who have experienced one or more of the following conditions:

- Symptomatic paroxysmal or permanent 2nd- or 3rd-degree AV block
- Symptomatic bilateral bundle branch block
- Symptomatic paroxysmal or transient sinus node dysfunctions with or without associated AV conduction disorders
- Bradycardia-tachycardia syndrome

Physicians Consistent with Guidelines Indications for Pacing (N=725)



Reasons for selecting VVIR
Infrequent pacing expected
Advanced age
Sedentary lifestyle
Anatomical limitations
Co-morbidities increasing complication risk

Consistent with Guideline Recommendations for VVI Pacing*

*Gillis et al., 2012

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Conclusion

- Micra met efficacy, safety objectives by wide margins
- Reduced complications of traditional pacemakers
- Proven training program
- Medtronic committed to ongoing monitoring and refinement of post-marketing program

Micra: Transformation in Pacing Technology and Patient Experience

1958

2013

Micra™ Transcatheter Pacing System (TPS)

Circulatory System Devices Panel

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Medtronic

BACK-UP

Unsuccessful Retrievals (n=2)

- 1 retrieval attempted 229 days post implant
  - Micra was snared, but physician abandoned removal because he was concerned about applying too much tension
  - Micra was programmed OFF and a transvenous system was successfully implanted
- 1 retrieval attempted 259 days post implant
  - Equipment failure: Micra was snared, then fluoroscopy machine malfunctioned precluding any further attempted removal
  - Micra was programmed OFF and a transvenous system was successfully implanted

Device Upgrade Experience

- 4 IDE study patients
  - 2 bi-ventricular
  - 2 traditional transvenous
    - elevated threshold
- 2 continued access patient
  - 1 traditional transvenous
    - elevated threshold
  - 1 bi-ventricular
- 1 commercial release patient
  - Bi-ventricular

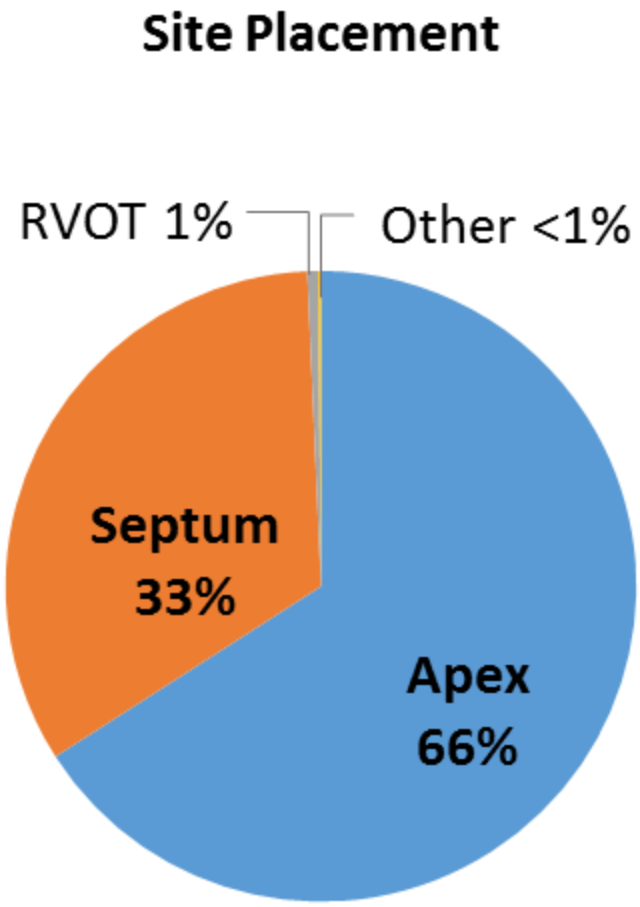
Table 8. Detailed Listing of Cardiac Effusions / Perforations

Age/ Sex/	BMI	# Repositions	# Risk Factors[1]	Final Micra Location	# for Implanter	Pericardio-centesis?	Surgical Repair?
Major Complications (n = 11)							
74/F	27.9	3	2	NA; traditional	21	Yes	Yes
91/F	20.7	2	3	NA; traditional	19	Yes	Yes
84/F	22.8	0	5	NA; traditional	10	Yes	No
88/M	23.5	1	4	Apex	4	Yes	No
83/F	24.8	0	4	Apex	28	Yes	No
85/F	25.2	0	3	Apex	4	Yes	No
88/M	26.9	2	1	NA; traditional	1	Yes	No
90/F	30.9	17	3	Apex	5	Yes	No
64/F	18.4	0	2	Apex	30	No	No
67/F	28.6	1	2	Septum	3	No	No
85/M	22.1	2	3	Apex	11	No	No
Minor Complication/Observation (n = 2)							
86/M	18.3	7	4	Mid-septum	2	Yes	No
77/F	28.0	0	2	Apex	5	No	No

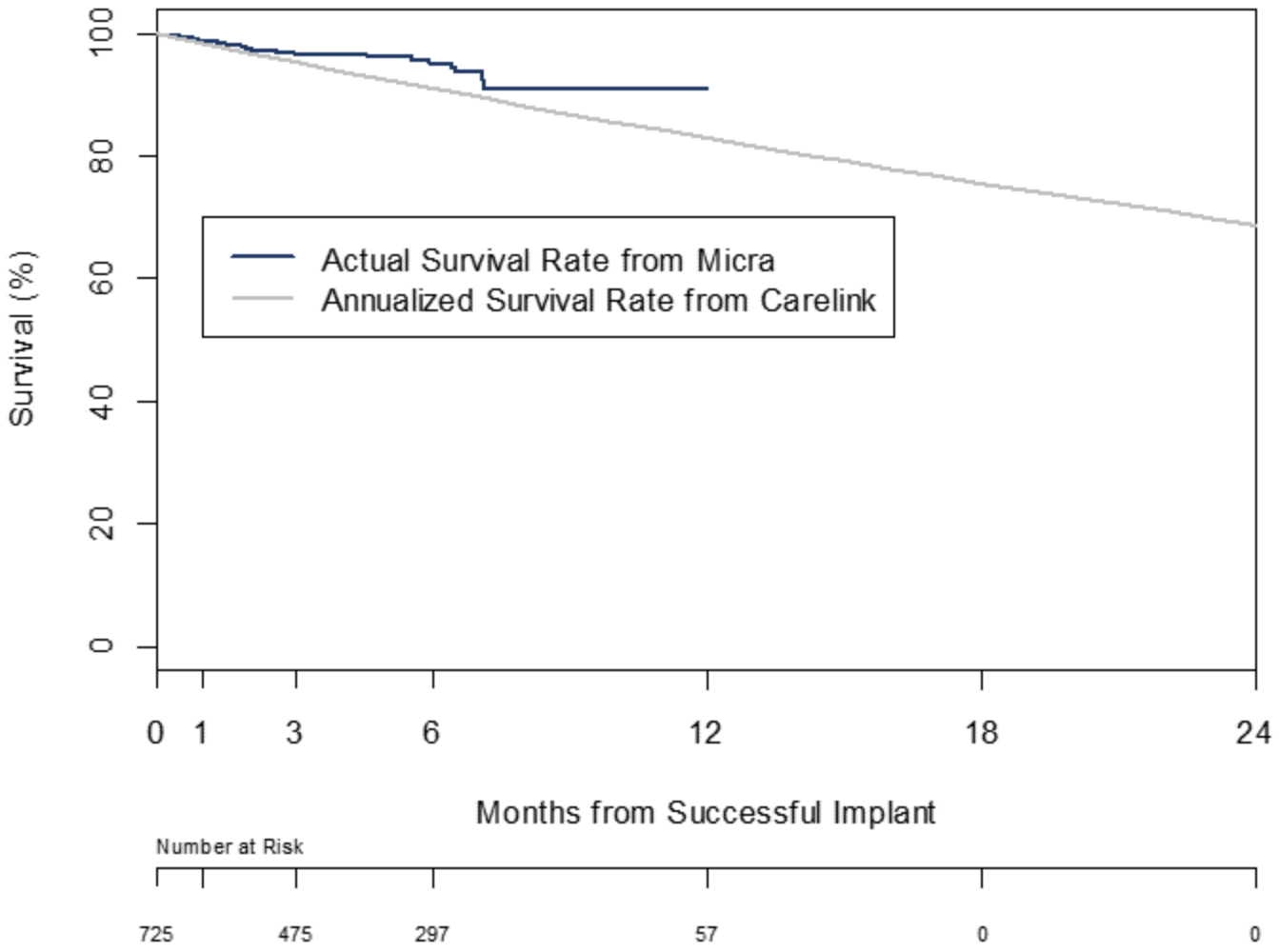
[1]*Risk factors: female, age >75 years, chronic lung disease, prior percutaneous artery intervention, and BMI <25.*

Micra TPS Implant

- 99.2% implant success (719 of 725 attempts) with 94 implanters
- Median implant time was 28 min introducer in to introducer out
  - 22 min after 1st 10 implants



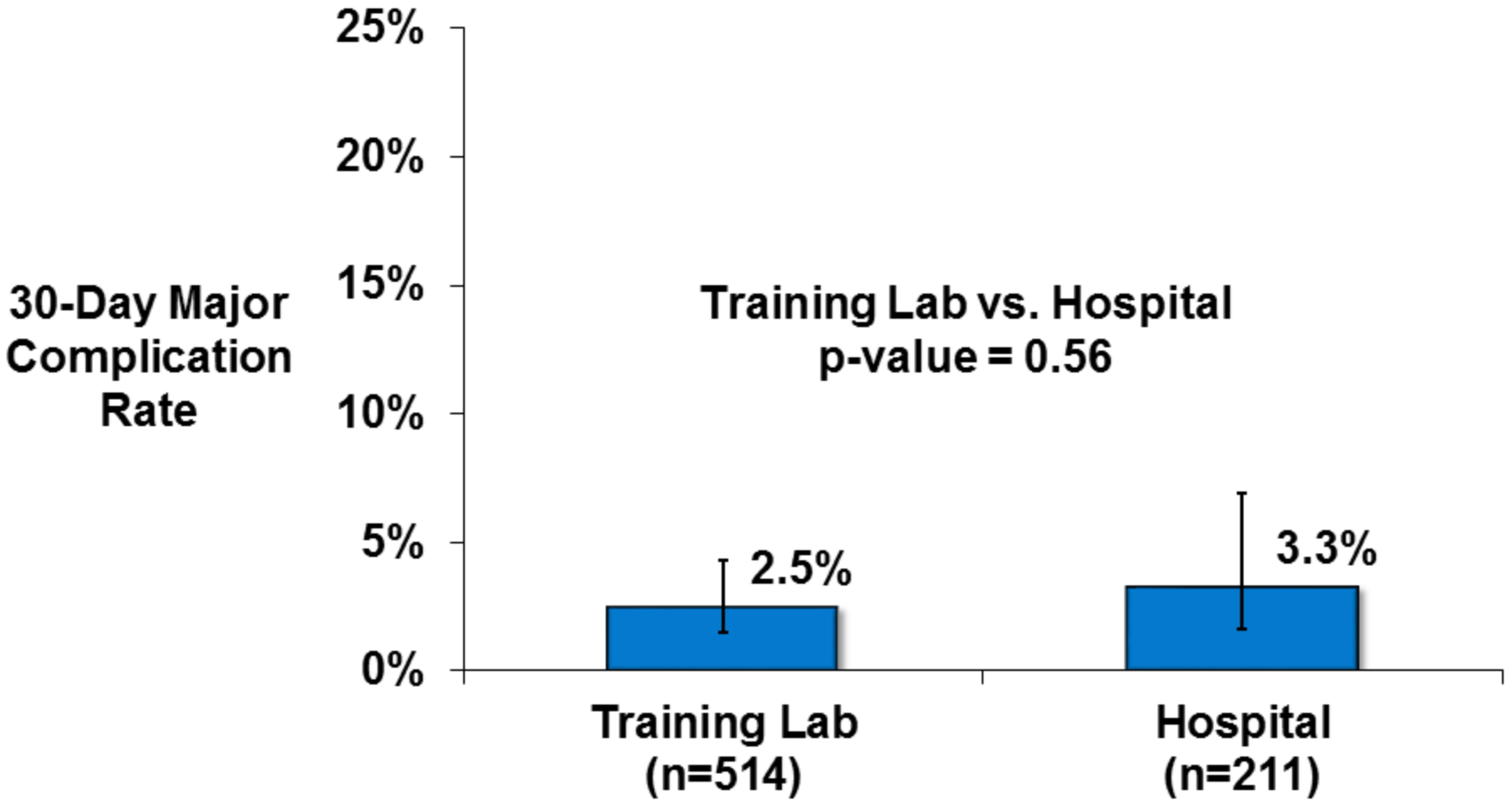
Micra Patient Survival Consistent with Traditional Single Chamber Pacemaker



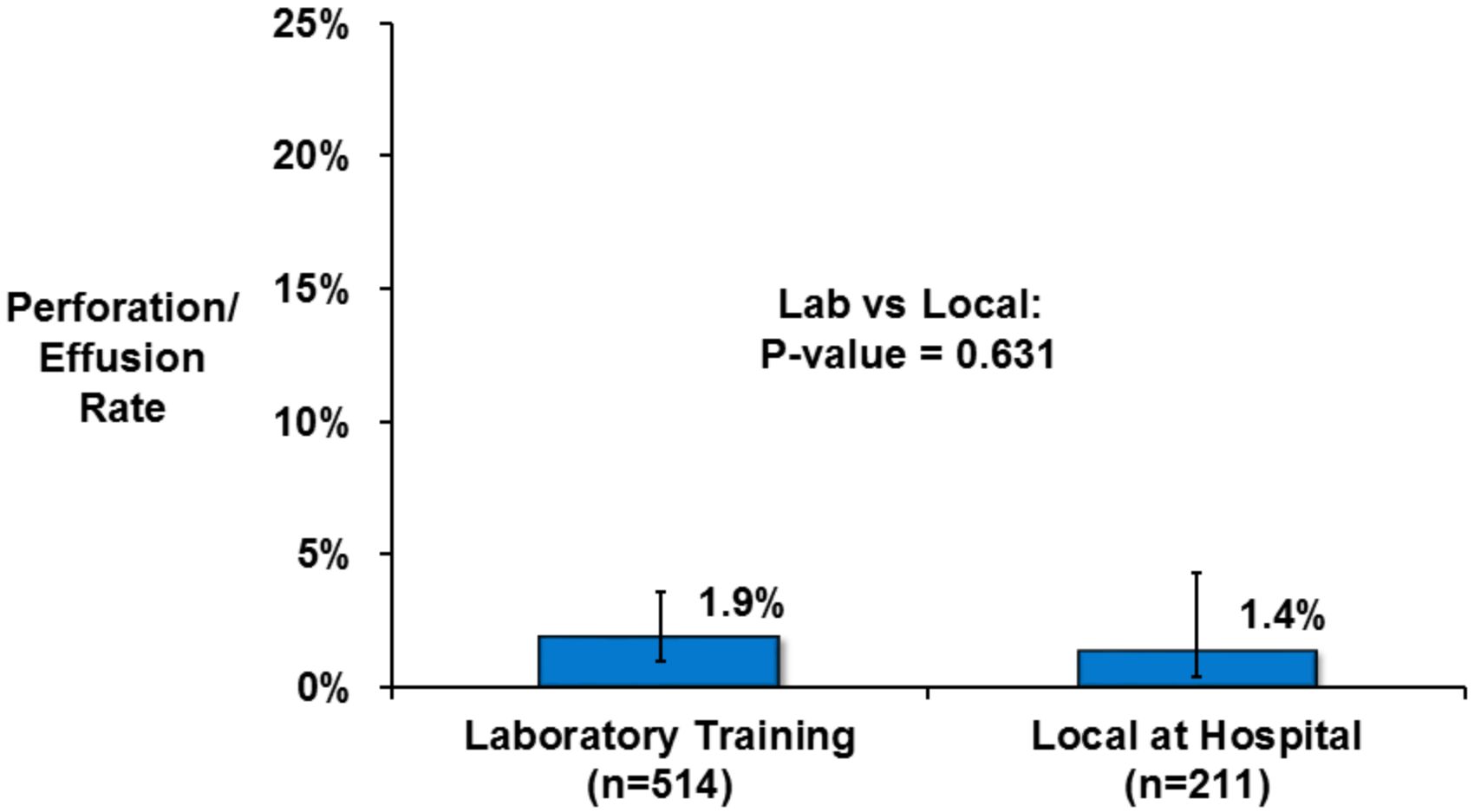
Primary Causes of Patient Deaths (n=29)

Total	29
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

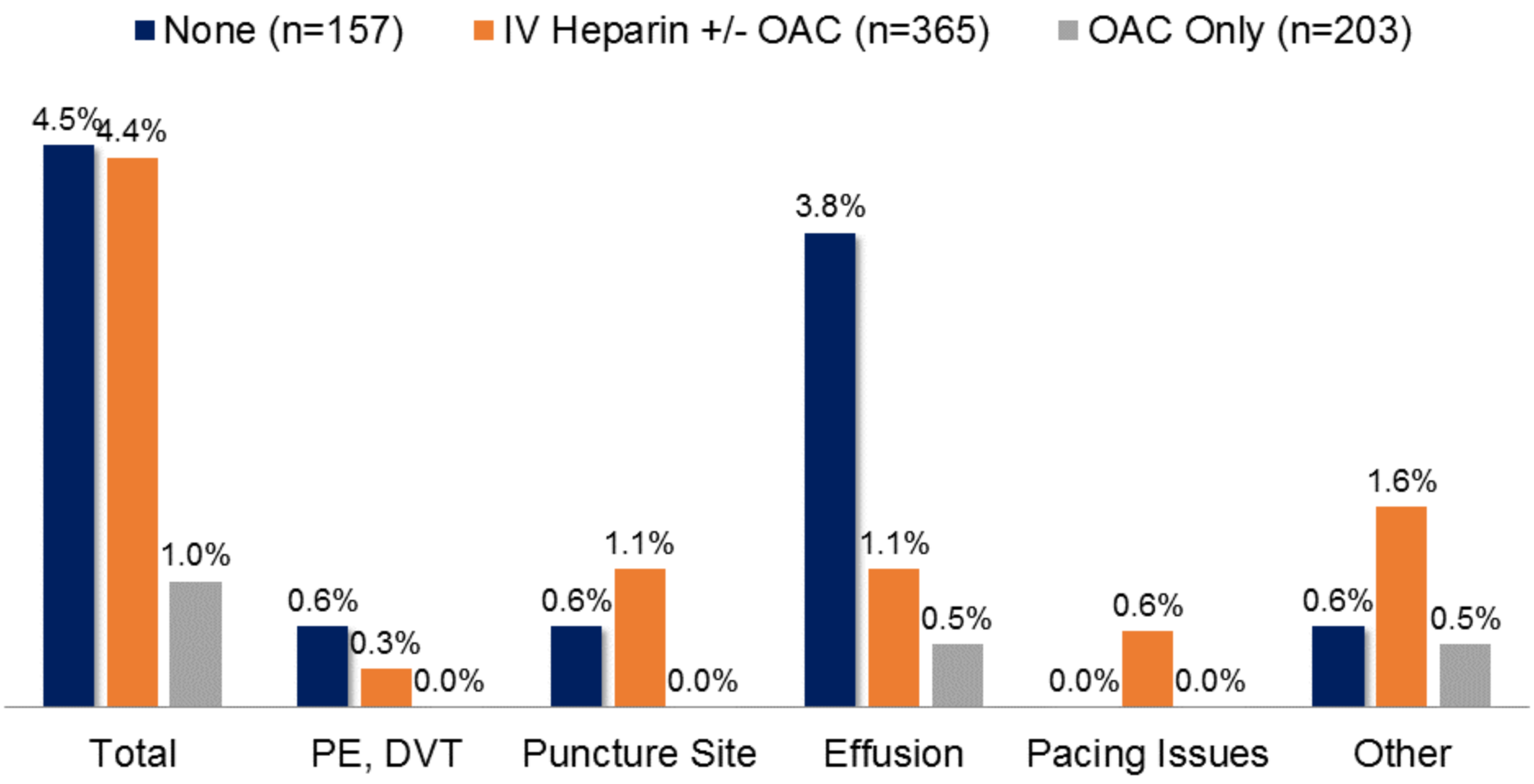
Low Major Complication Risk with Both Training Methodologies



Perforation/Effusion Risk Similar by Training Method



Major Complication Rates by Procedure Anticoagulation Strategy



Training to Minimize Risk of Effusion

- Ensure good visualization of location:
  - Consider small amount of contrast
  - Utilize multiple fluoroscopic views
- Correct catheter manipulation techniques
- Follow guidance on repositioning attempts
- Awareness of known patient risk factors for traditional pacemakers and Micra
  - Elderly, female, chronic lung disease, BMI <25, prior percutaneous coronary artery intervention

Guidance on Micra Repositioning (Proposed Labeling Addition)

- > 3-5 deployments:
  - Ensure adequate tip pressure
  - Remove tool and check for clots (consider adding heparin)
  - Consider higher septal position
  - Consider patient pacing/sensing/longevity needs
- >10 deployments:
  - Consider abandonment of system; revert to traditional transvenous approach

Diverse Implanter Population