# Sentinel® Cerebral Protection System During TAVR

February 23, 2017

Claret Medical, Inc.

Circulatory System Devices Panel

# Introduction

**Thomas Engels**

Vice President of Clinical Affairs

Claret Medical, Inc.

# The Sentinel Cerebral Protection System

- Class 2 (proposed), temporary accessory device
- Placed prior to and removed after Transcatheter Aortic Valve Replacement (TAVR)
- TAVR associated with cerebrovascular events[1]
- Embolic Protection Devices (EPD) have been used in carotid stenting for >15 years
- No alternative option available for embolic protection in TAVR
- Sentinel investigational in US
- Sentinel CE Marked 2013
  - >3,000 TAVR procedure

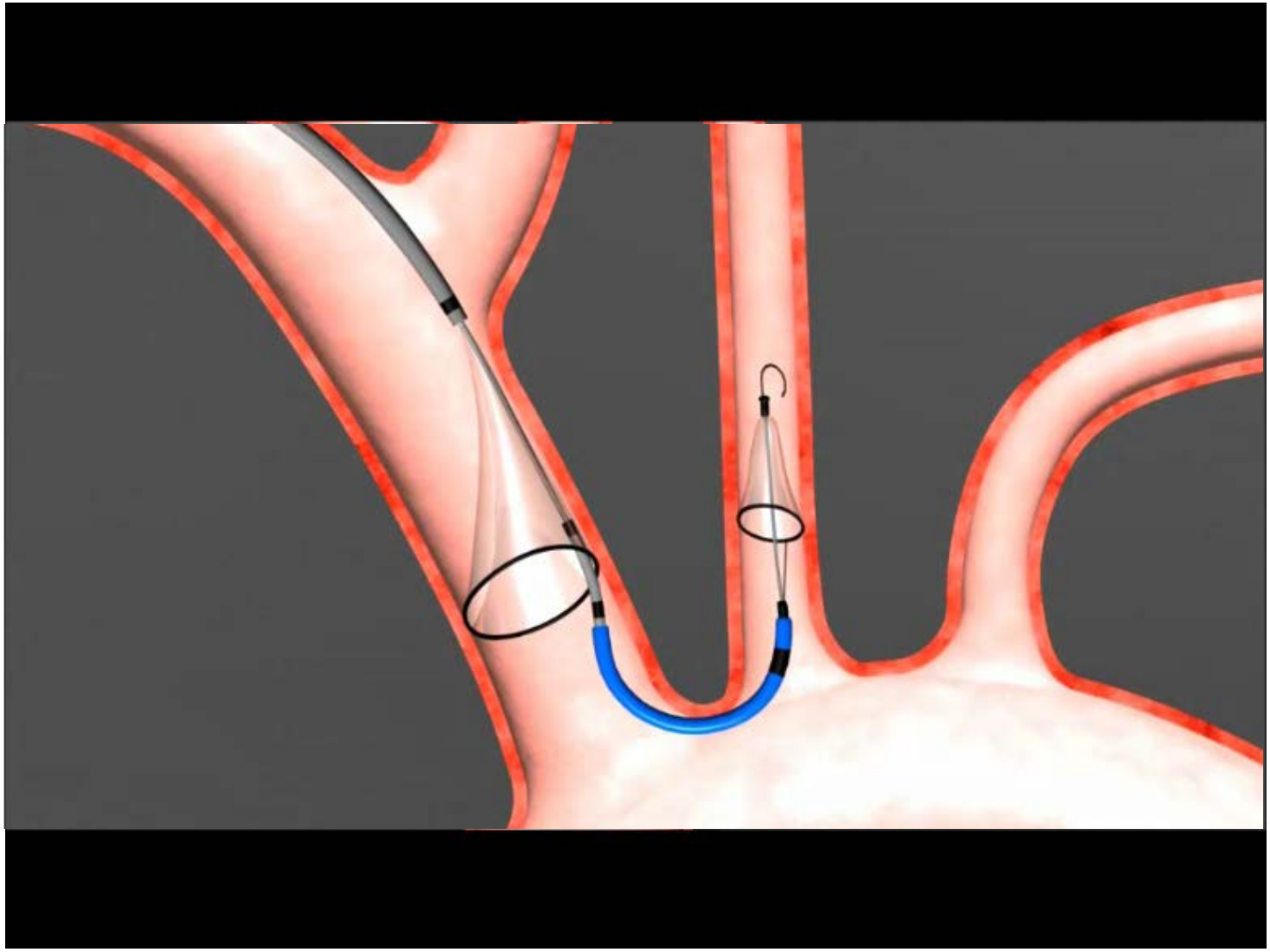
1 Smith, E., et al. "Cerebral Microinfarcts: The Invisible Lesions." Lancet Neurol. 2012; 11(3): 272–282

# Proposed Sentinel System Indication

***The Sentinel® Cerebral Protection System is indicated for use as a cerebral protection device to capture and remove embolic material while performing transcatheter aortic valve procedures in order to reduce peri-procedural ischemic brain injury.***

*The diameters of the arteries at the site of filter placement should be between 9 – 15 mm for the brachiocephalic and 6.5 mm – 10 mm for the left common carotid arteries.*

# Animation of the Sentinel System During TAVR



# Safety and Effectiveness Outcomes

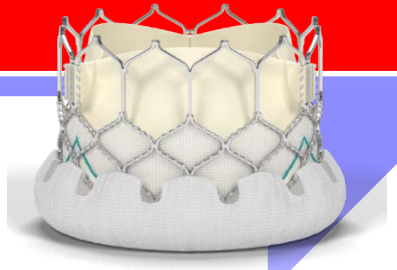
- Primary Safety
  - 30-Day MACCE vs. Performance Goal – Achieved
- Primary Effectiveness – Median New Lesion Volume (DW-MRI)
  - Observed treatment effect ≥ 30% – Achieved
  - Test vs. Control – Not achieved
- Other Relevant Study Outcomes
  - Sentinel system successfully delivered & retrieved in 94% of patients
  - Major Sentinel access-related complications were rare (N=1, 0.4%)
  - Embolic debris captured in 99% of patients

# US Medical Device Classification

**Class 1**
Lowest Risk
e.g. Surgical Gauze

**Class 2**
Medium Risk
e.g. BAV

**Class 3**
Highest risk
e.g. TAVR



- Medium risk, temporary accessory device
- *De Novo* pathway required due to lack of predicate cerebral protection device
- *De Novo* pathway risk/benefit balance on the basis of the totality of pre-market evidence and post market measures

# Presentation Agenda

**Background, Device Description, Trial Design, Safety and Effectiveness Data**

**Martin B. Leon, MD**
Professor of Medicine,
Columbia University Medical Center

**Histopathology**

**Renu Virmani, MD**
President, CVPath Institute, Inc.
Clinical Professor, George Washington University

**History of Neuroprotection**

**William A. Gray, MD**
System Chief of the Division of Cardiovascular Disease,
Lankenau Medical Center, Main Line Health

**Conclusion**

**Azin Parhizgar, PhD**
President and Chief Executive Officer
Claret Medical, Inc.

# Additional Experts

## Interventional Cardiology

**Samir Kapadia, MD**
Director, Cardiac Catheterization Laboratory
Cleveland Clinic

**Susheel Kodali, MD**
Director, Structural Heart & Valve Center
Columbia University Medical Center

**Axel Linke, MD**
Co-director, Department of Internal Medicine/ Cardiology
University of Leipzig Heart Center

**Roxana Mehran, MD**
Professor of Medicine, Cardiology
Mount Sinai, New York

## Neurology and Neurosurgery

**Maxim Mokin, MD, PhD**
Director of Neuro Interventional Surgery
University of South Florida Health

**Jesse Weinberger, MD**
Vascular Neurology Specialist
Mount Sinai Hospital

## MRI Neuroimaging

**Robert Zivadinov, MD, PhD**
Professor of Neurology,
Director, Buffalo Neuroimaging Analysis Center

**Michael Dwyer, PhD**
Director Of Technical Imaging
Buffalo Neuroimaging Analysis Center
Assistant Professor of Neurology
University of Buffalo

## Neurocognition

**Ronald Lazar, PhD**
Professor of Neuropsychology
Columbia University Medical Center

## Statistics

**Roseann White, MA**
Director, Pragmatic Clinical Trial Statistics
Duke Clinical Research Institute

# Background

**Martin B. Leon, MD**

Professor of Medicine

Columbia University Medical Center

# Strokes are Considered a Major Complication after TAVR

The NEW ENGLAND JOURNAL of MEDICINE

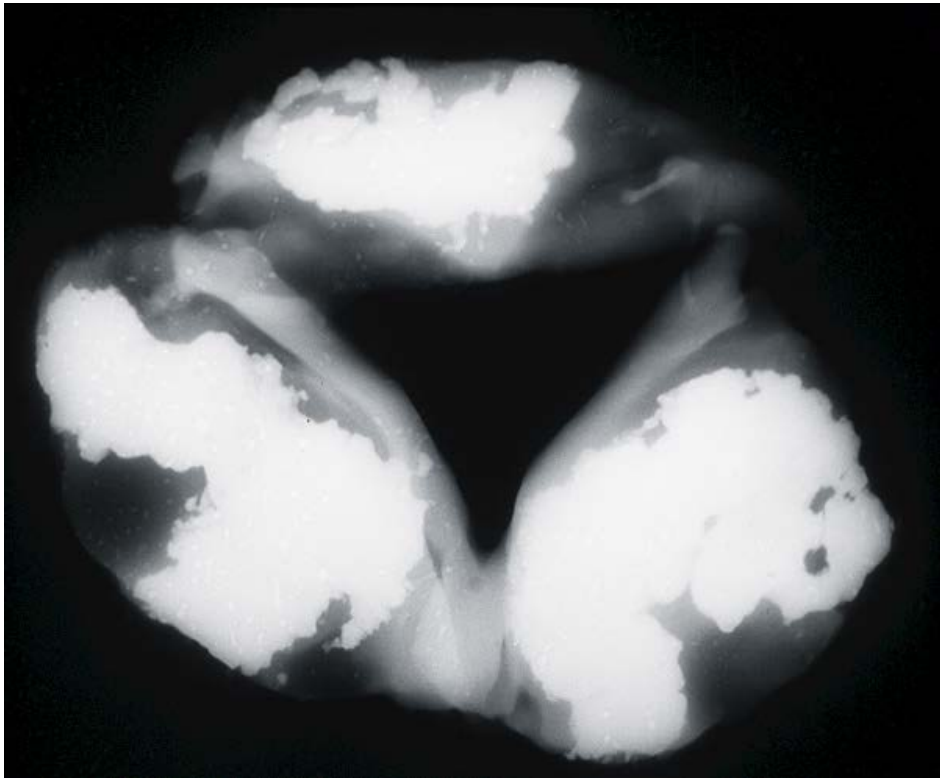
ESTABLISHED IN 1812 JUNE 9, 2011 VOL. 364 NO. 23

## Transcatheter and Surgical Aortic-Valve Replacement in High-Risk Patients

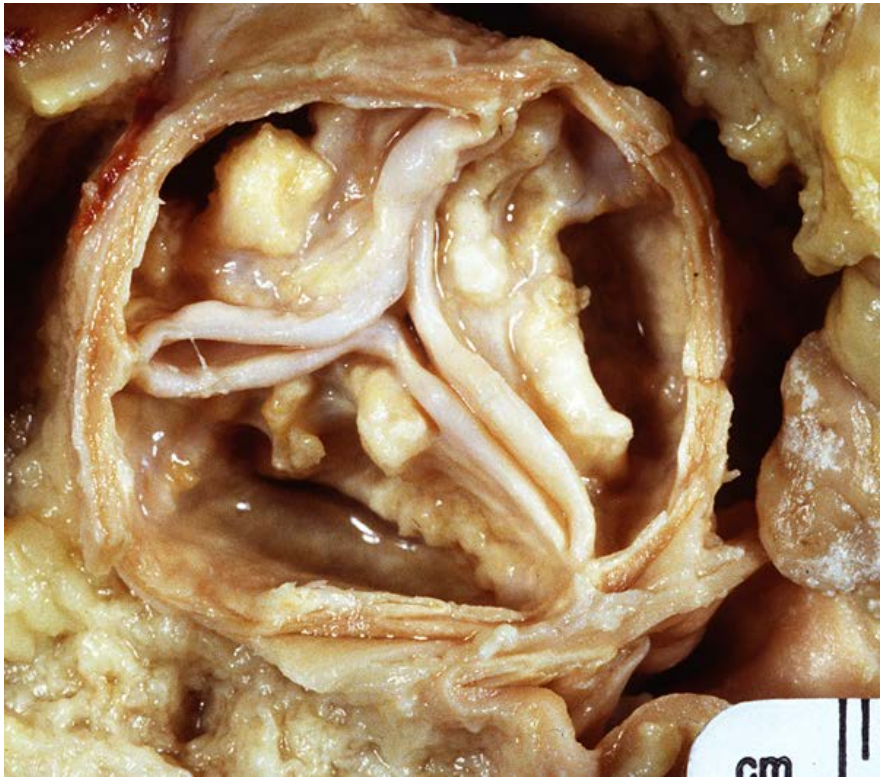
Craig R. Smith, M.D., Martin B. Leon, M.D., Michael J. Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., Mathew Williams, M.D., Todd Dewey, M.D., Samir Kapadia, M.D., Vasilis Babaliaros, M.D., Vinod H. Thourani, M.D., Paul Corso, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., and Stuart J. Pocock, Ph.D., for the PARTNER Trial Investigators*

**PARTNER 1A RCT (SAPIEN TAVR vs. Surgery); 699 high-risk patients with severe AS;**
**N Engl J Med 2011;364:2191-2202**

# Typical Examples of Heavily Calcified Aortic Valves

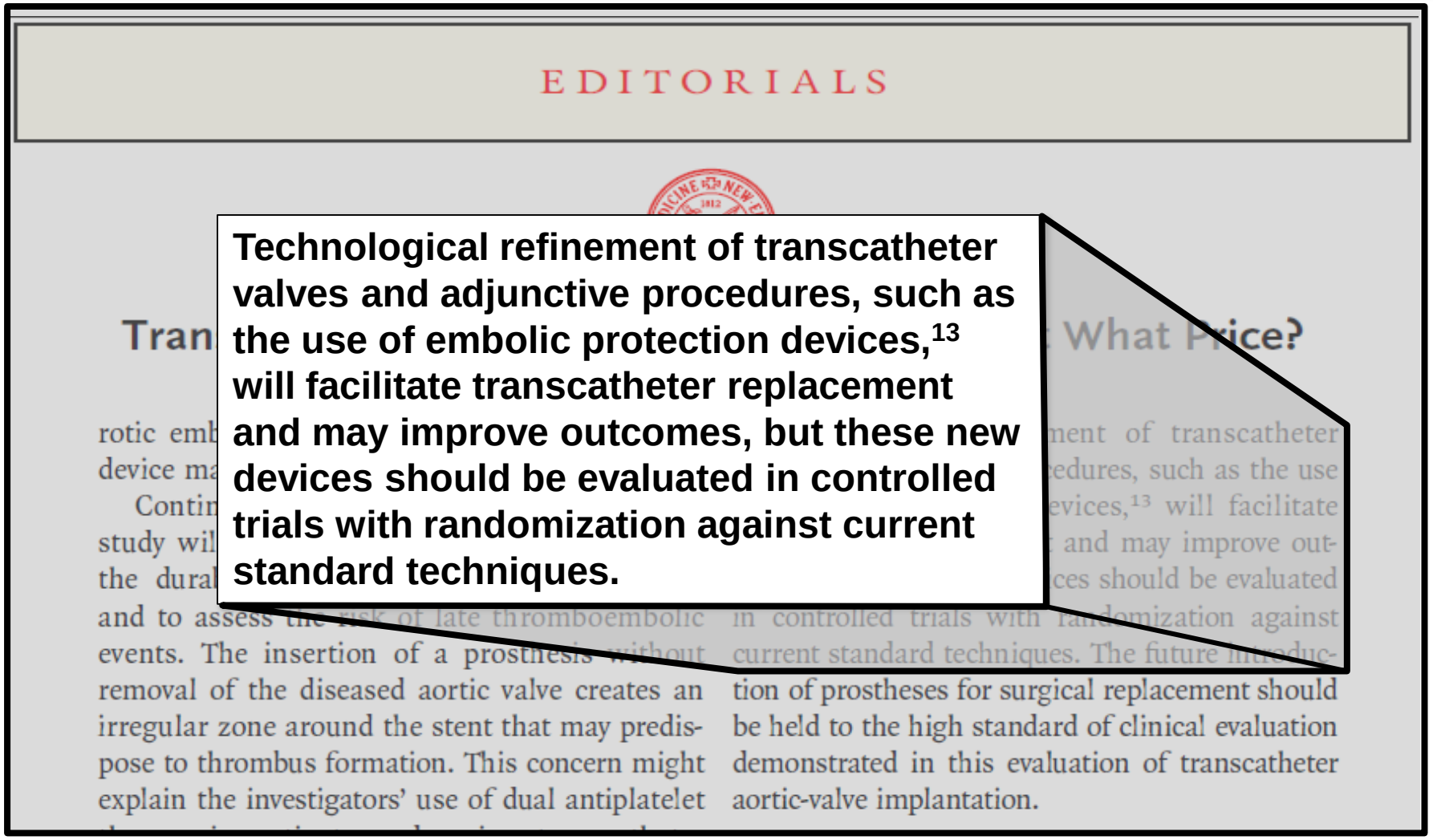


Radiograph of surgical specimen




Autopsy specimen

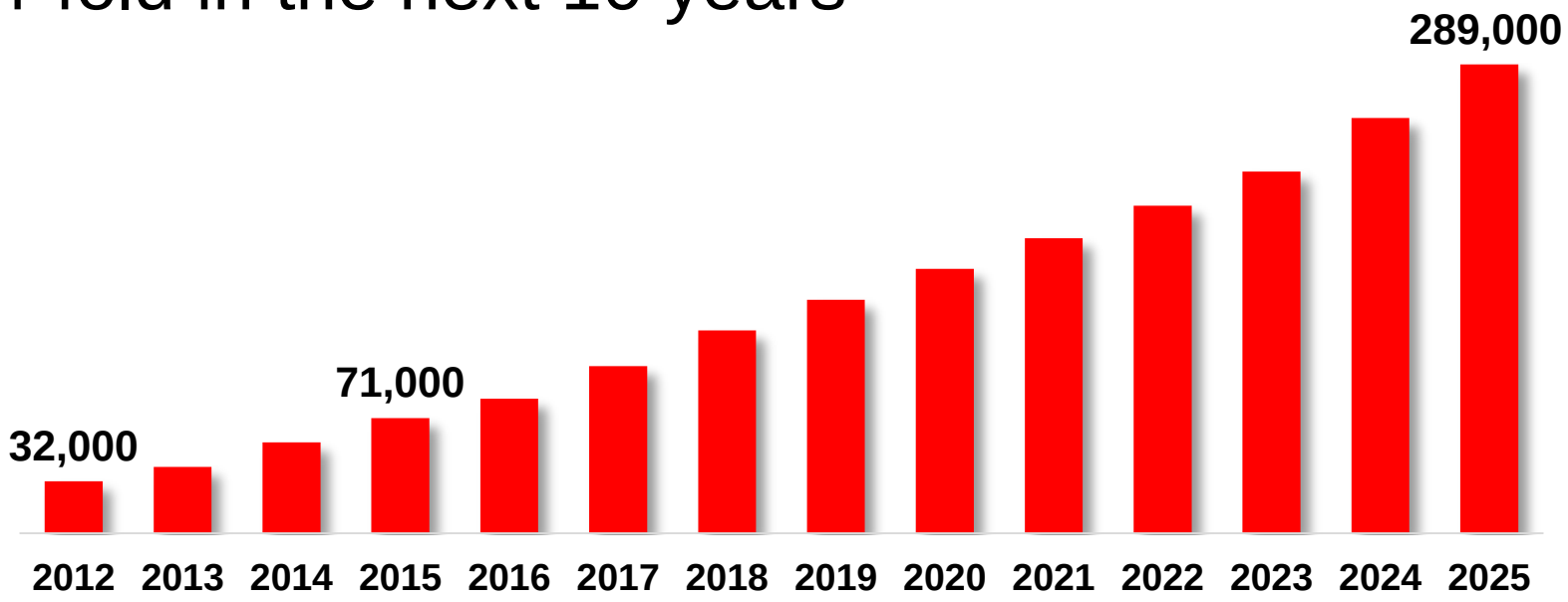
# Strokes are Considered a Major Complication after TAVR




N Engl J Med 2011;364:2191-2202

# TAVR is Projected to Grow in the Next Decade

- In 2015, TAVR accounted for 32% of all Medicare AV replacements in the US
- Globally, TAVR is expected to grow approximately 4-fold in the next 10 years




Courtesy of Dr M. Leon TVT 2016; Adapted from Credit Suisse TAVI Comment – January 2015

# Strokes After TAVR

- Approximately 3% to 7% at 30 days in high surgical risk patients (CEC adjudicated FDA studies)
- Up to 85% of strokes occur within 1 week of TAVR
- Associated with increased 1-year mortality and reduced quality-of-life
- Frequency is highly dependent on stroke definitions (e.g. VARC-2*) and ascertainment methods (e.g. w/wo neurology assessments)

*** VARC-2 = valve academic research consortium, standard definitions (JACC, 2012)**

# Strokes After TAVR

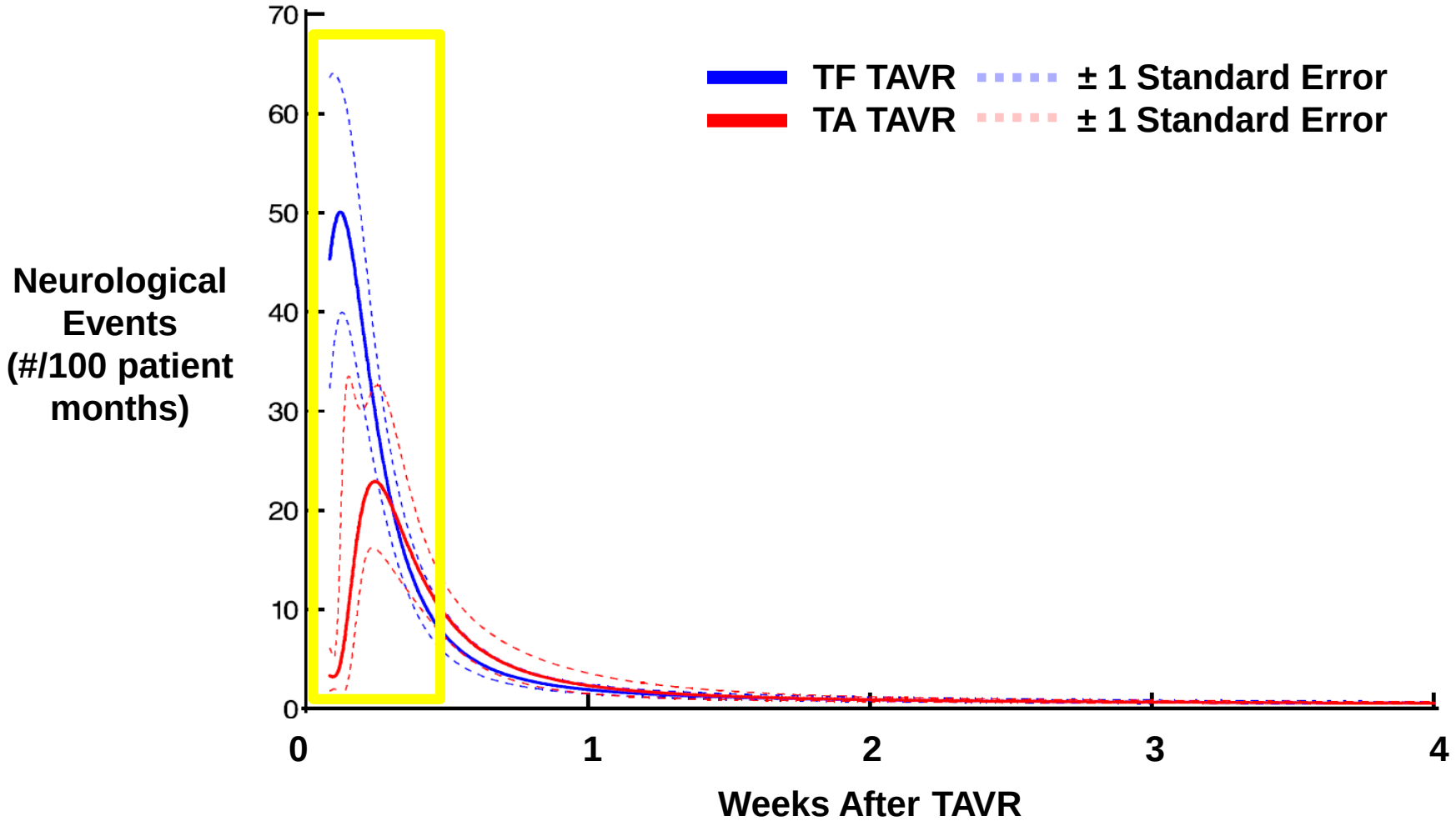
**Insights Into Timing, Risk Factors, and Outcomes of Stroke and Transient Ischemic Attack After Transcatheter Aortic Valve Replacement in the PARTNER Trial (Placement of Aortic Transcatheter Valves)**

Samir Kapadia, MD; Shikhar Agarwal, MD; D. Craig Miller, MD; John G. Webb, MD; Michael Mack, MD; Stephen Ellis, MD; Howard C. Herrmann, MD; Augusto D. Pichard, MD; E. Murat Tuzcu, MD; Lars G. Svensson, MD, PhD; Craig R. Smith, MD; Jeevanantham Rajeswaran, PhD; John Ehrlinger, PhD; Susheel Kodali, MD; Raj Makkar, MD; Vinod H. Thourani, MD; Eugene H. Blackstone, MD; Martin B. Leon, MD

- 2621 patients from PARTNER (high and extreme risk); CEC adjudication
- Acute-phase (peri-procedural) stroke risk peaked at 2 days, with a low constant risk of 0.8% per year

Kapadia S, et al. Circ Cardiovasc Interv 2016;9:e002981

# Strokes After TAVR (Acute Phase)




Kapadia S, et al. Circ Cardiovasc Interv 2016;9:e002981

# Spectrum of Brain Injury Caused by Embolic Material

- Clinical neurologic events
  - Strokes (disabling and non-disabling)
  - Transient ischemic attacks (TIA)
- Brain injury on neuro-imaging studies detected by DW-MRI
- Neuronal injury without overt symptoms[1] which may result in acute or chronic changes in neurocognitive function

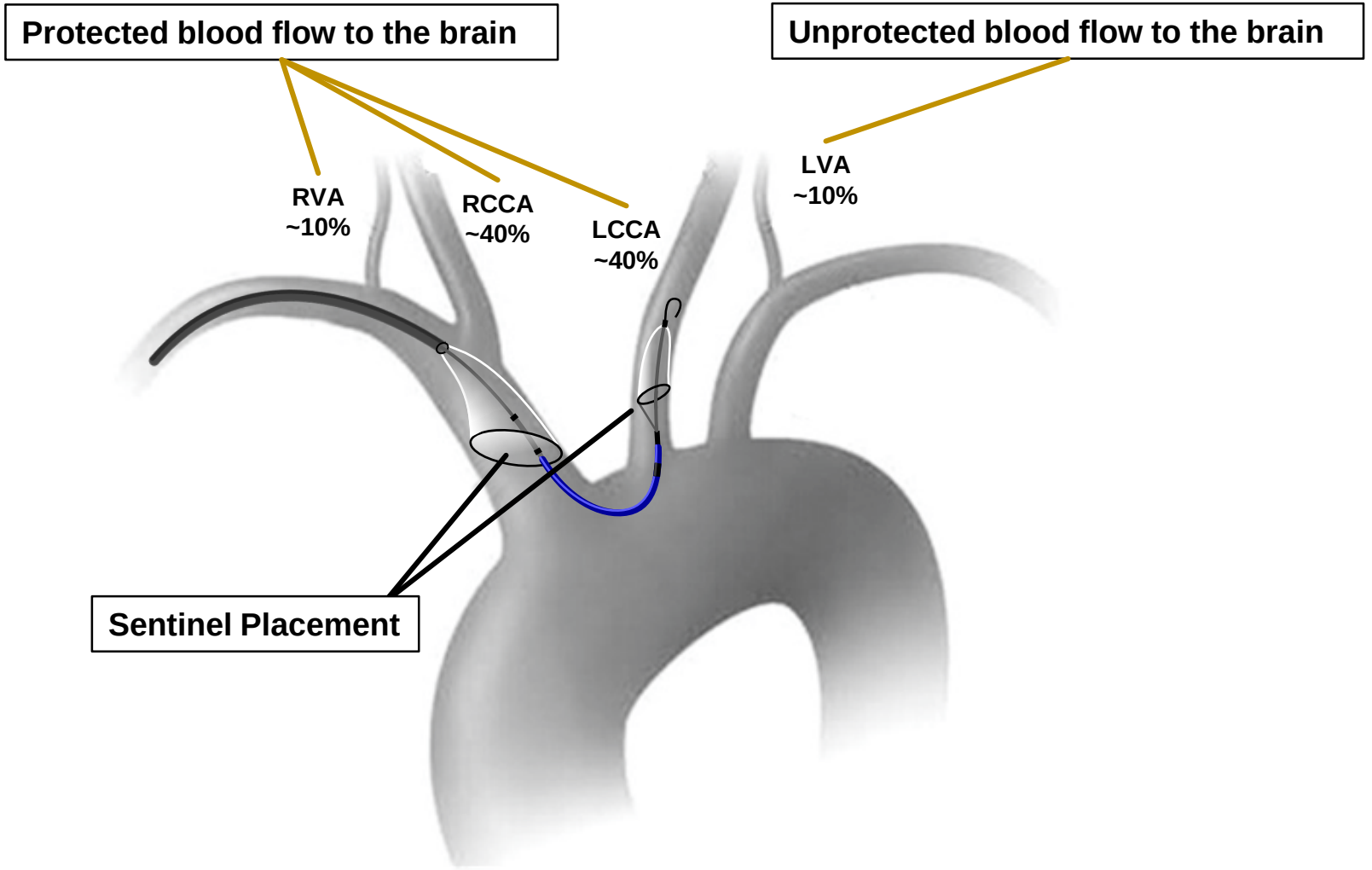
[1] **Lansky AJ et al; JACC, Vol 69, No.6, 2017**

# Brain Injury on Neuro-imaging (DW-MRI) after TAVR

- Frequent early DW-MRI abnormalities (68%-100% of patients) after TAVR from 9 studies
- Most patients have multiple infarcts which represent permanent ischemic brain damage
- SENTINEL trial based on results from predicate trial (CLEAN-TAVI)
  - Randomized, controlled study in 100 patients
  - Single TAVR system
  - Exact MRI methodology was used by the same core laboratory as is used in the current study

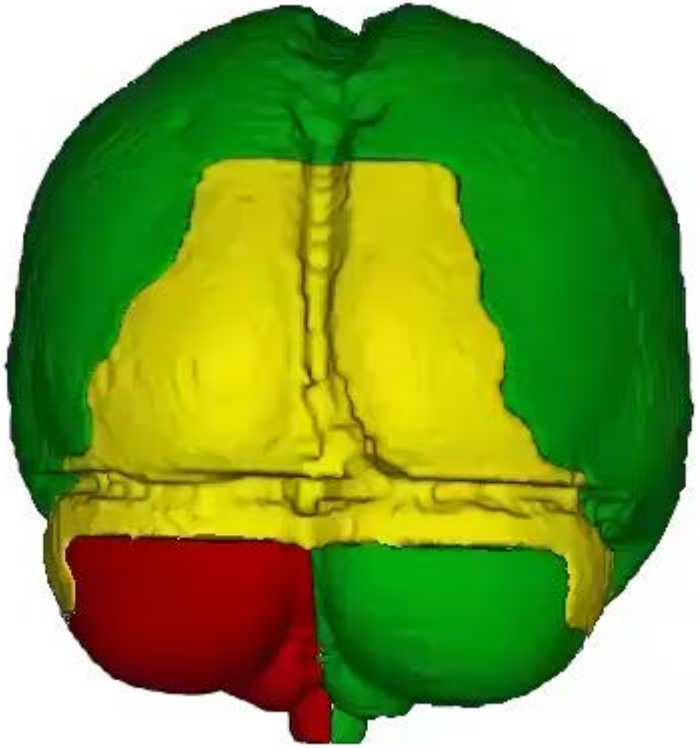
# Sentinel Cerebral Protection System: Device Description and Case

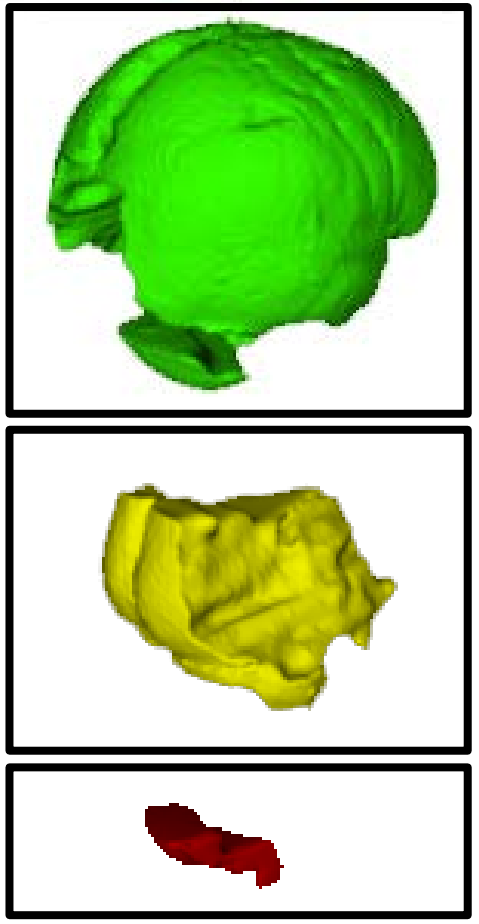
# Protected vs All Territories Intra-cerebral Vasculature




Zhao M, et al. Regional Cerebral Blood Flow Using Quantitative MR Angiography. AJNR 2007;28:1470-1473

# Protected and Unprotected Cerebral Vascular Territories





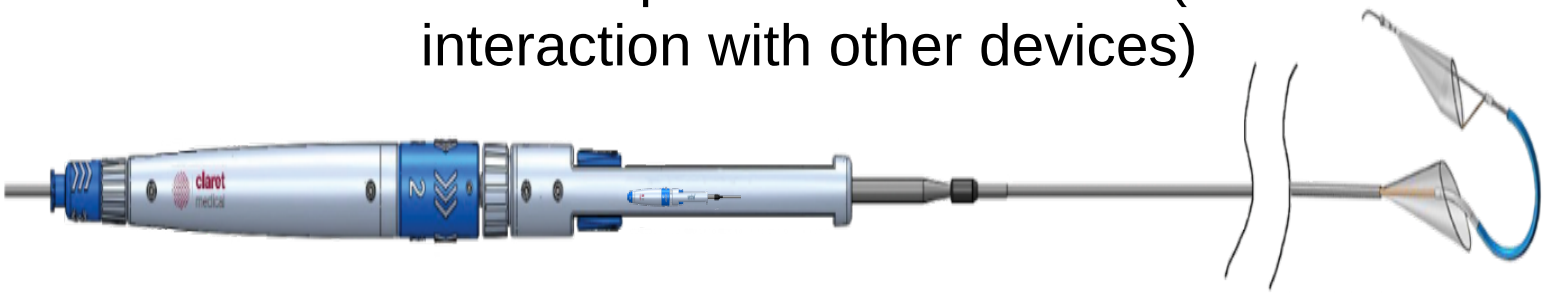
Protected
74% brain volume

Partially Protected
24% brain volume

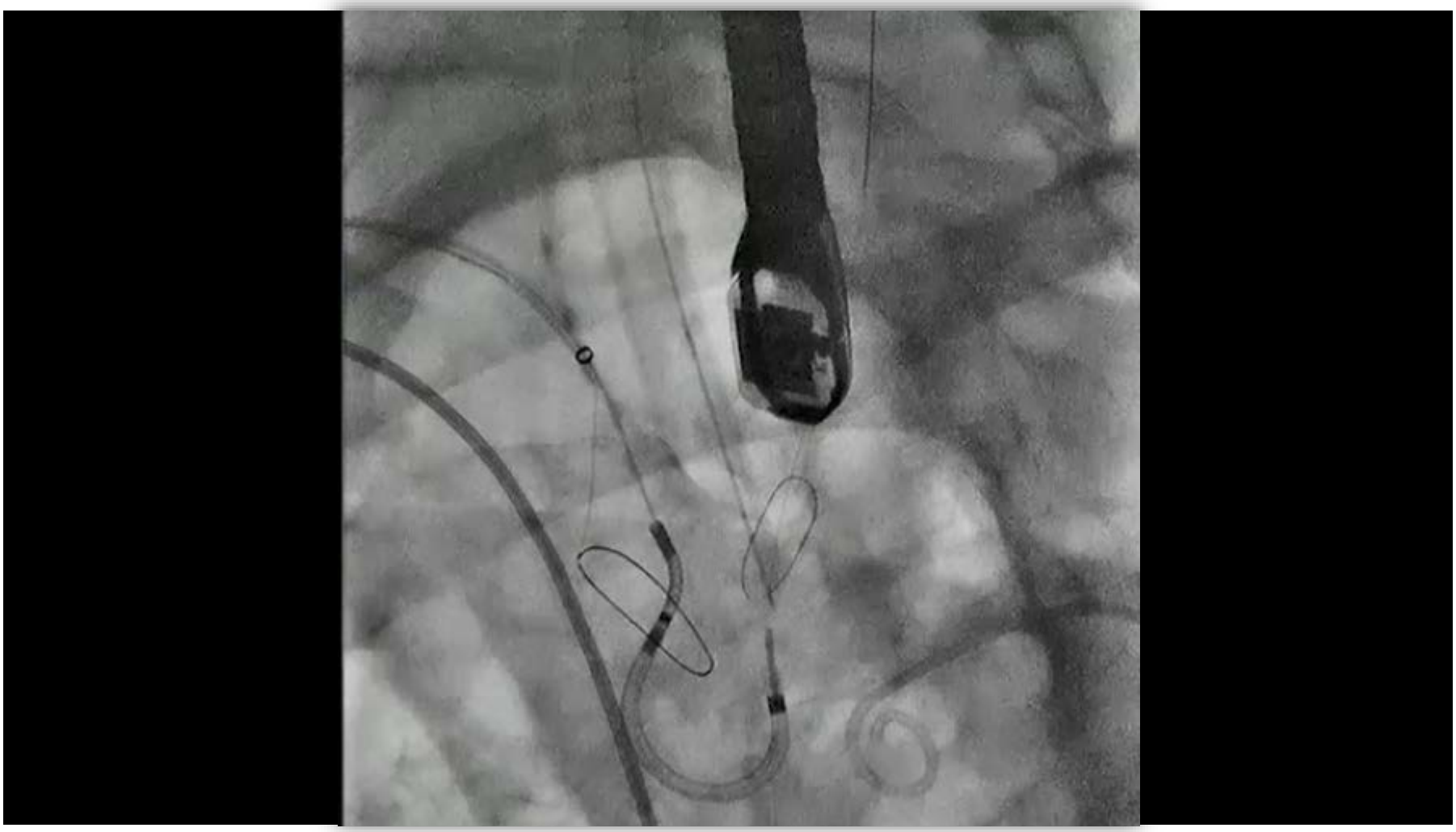
Unprotected
2% brain volume

# Sentinel Cerebral Protection System During TAVR

- Two independent filters capture & remove embolic material
- Polyurethane filter, pore size = 140 µm
- Standard R trans-radial sheath access (6F)
- One size accommodates most vessel sizes (brachiocephalic 9-15 mm and left common carotid [LCC] 6.5-10 mm)
- Deflectable compound-curve catheter facilitates cannulation of LCC
- Minimal profile in aortic arch (little interaction with other devices)

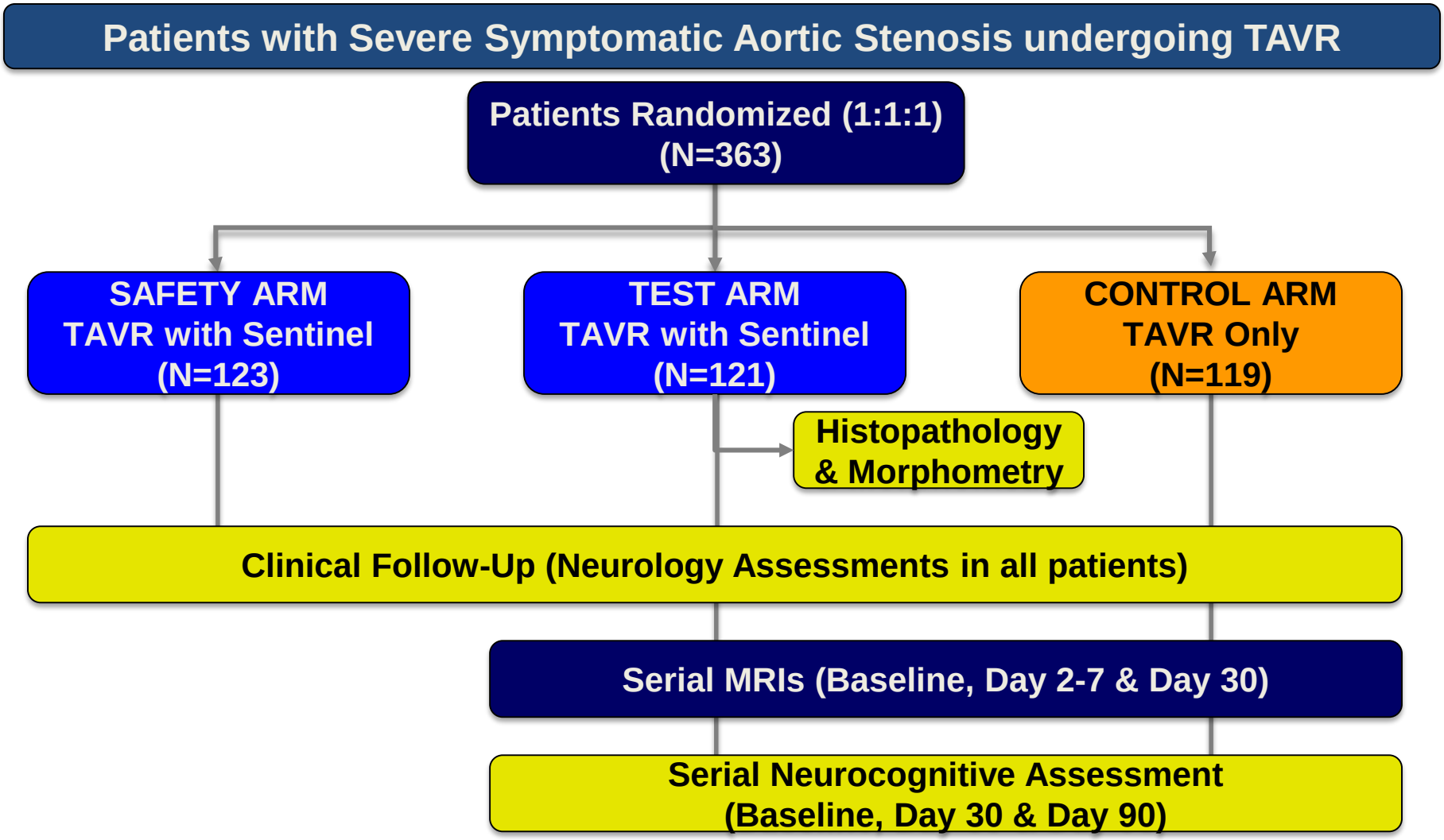


# Sentinel Cerebral Protection System During TAVR – Case



# SENTINEL Trial Overview

# SENTINEL Trial Design Overview



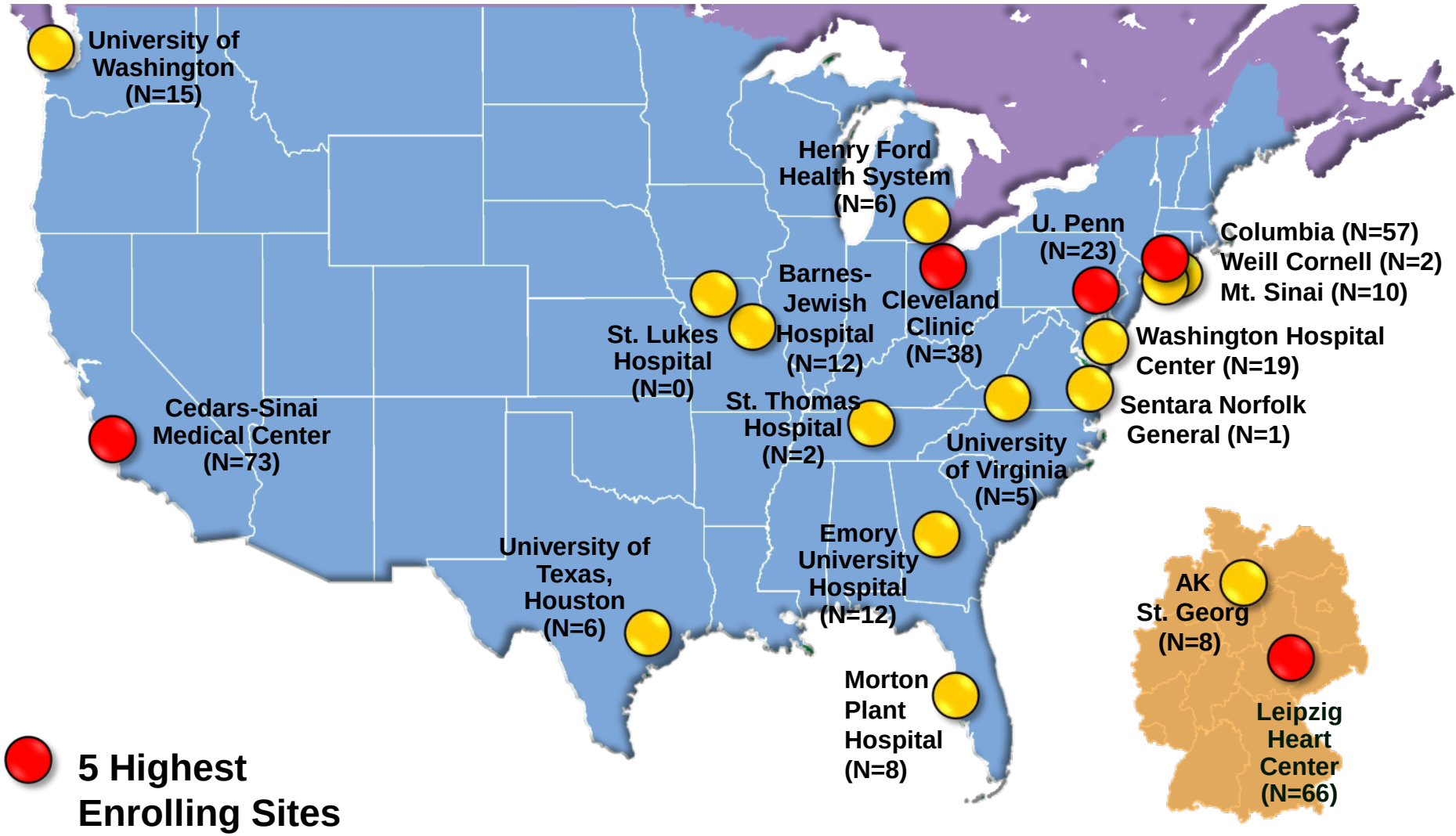
# Key Inclusion Criteria

- Patients with symptomatic severe aortic stenosis eligible for treatment with a US commercially approved TAVR system
  - 4 different TAVR systems used (not stratified during randomization)
- Acceptable aortic arch anatomy and vessel diameters without significant stenosis
  - Brachiocephalic diameter 9 -15 mm
  - Left common carotid diameter 6.5 -10 mm

# Key Exclusion Criteria

- Anatomic
  - Right extremity vasculature not suitable
  - Brachiocephalic, left carotid or aortic arch not suitable
- Clinical
  - CVA or TIA within 6 months
  - Neurological disease with persistent deficits
  - Carotid disease requiring treatment within 6 weeks
  - Contraindications to MRI
  - Renal insufficiency (CR >3.0 mg/dL or GFR <30 cc/min)
  - Severe LV dysfunction (EF <20%)
  - Balloon valvuloplasty (BAV) within 30 days

# Multicenter Trial: 363 Patients at 19 Sites



# Study Administration

**Co-Principal Investigators:**
**Susheel Kodali, MD**
Columbia University Medical Center

**Samir R. Kapadia, MD**
Cleveland Clinic

**Axel Linke, MD**
Co-director, Department of Internal Medicine/Cardiology
University of Leipzig Heart Center

**Clinical Steering Committee Chairman:**
**Martin B. Leon, MD**
Columbia University Medical Center

**Study Medical Monitor:**
**Roxana Mehran, MD**
Mount Sinai School of Medicine

**Clinical Events Committee:**
Cardiovascular Research Foundation
Chair: **Ozgen Dogan, MD**
Neurologists: **Jesse Weinberger, MD**
**Joshua Willey, MD**

**Data Safety Monitoring Board:**
Cardiovascular Research Foundation
Chair: **Blase A. Carabello, MD**

**Histopathology / Morphometry Core Laboratory:**
CV Path Institute
Chair: **Renu Virmani, MD**

**MRI Core Laboratory:**
Buffalo Neuroimaging Analysis Center, University of Buffalo
Chair: **Robert Zivadinov, MD, PhD**

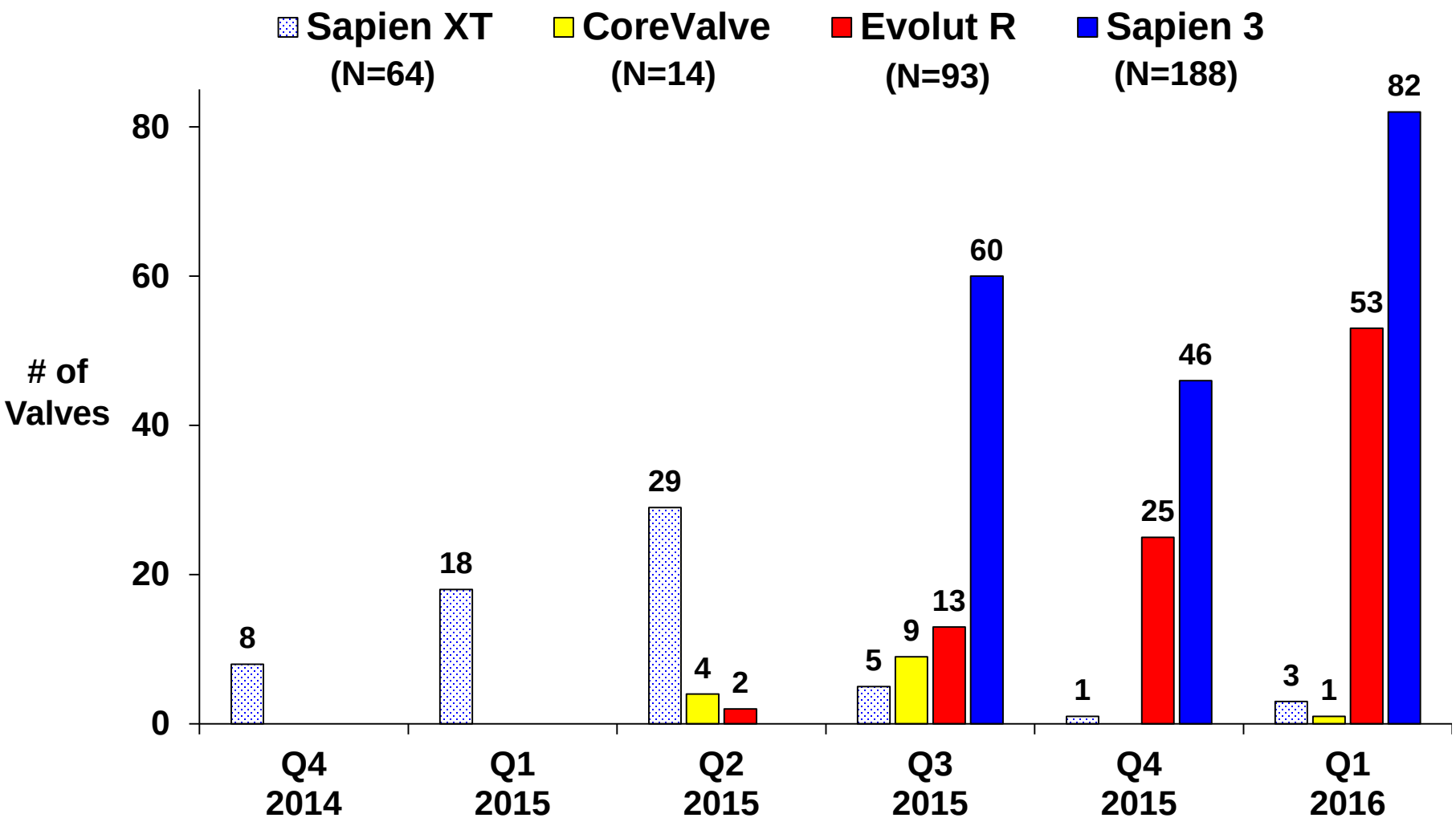
**Neurocognitive Core Laboratory:**
Tananbaum Stroke Center, Neurological Institute
Columbia University
Chair: **Ronald M. Lazar, PhD**

**Sentinel CT Planning Center:**
Cedars-Sinai Medical Center
Chair: **Hasan Jilaihawi, MD**

**Statistical Analysis**
Duke Clinical Research Institute
Project Director: **Roseann White, MA**

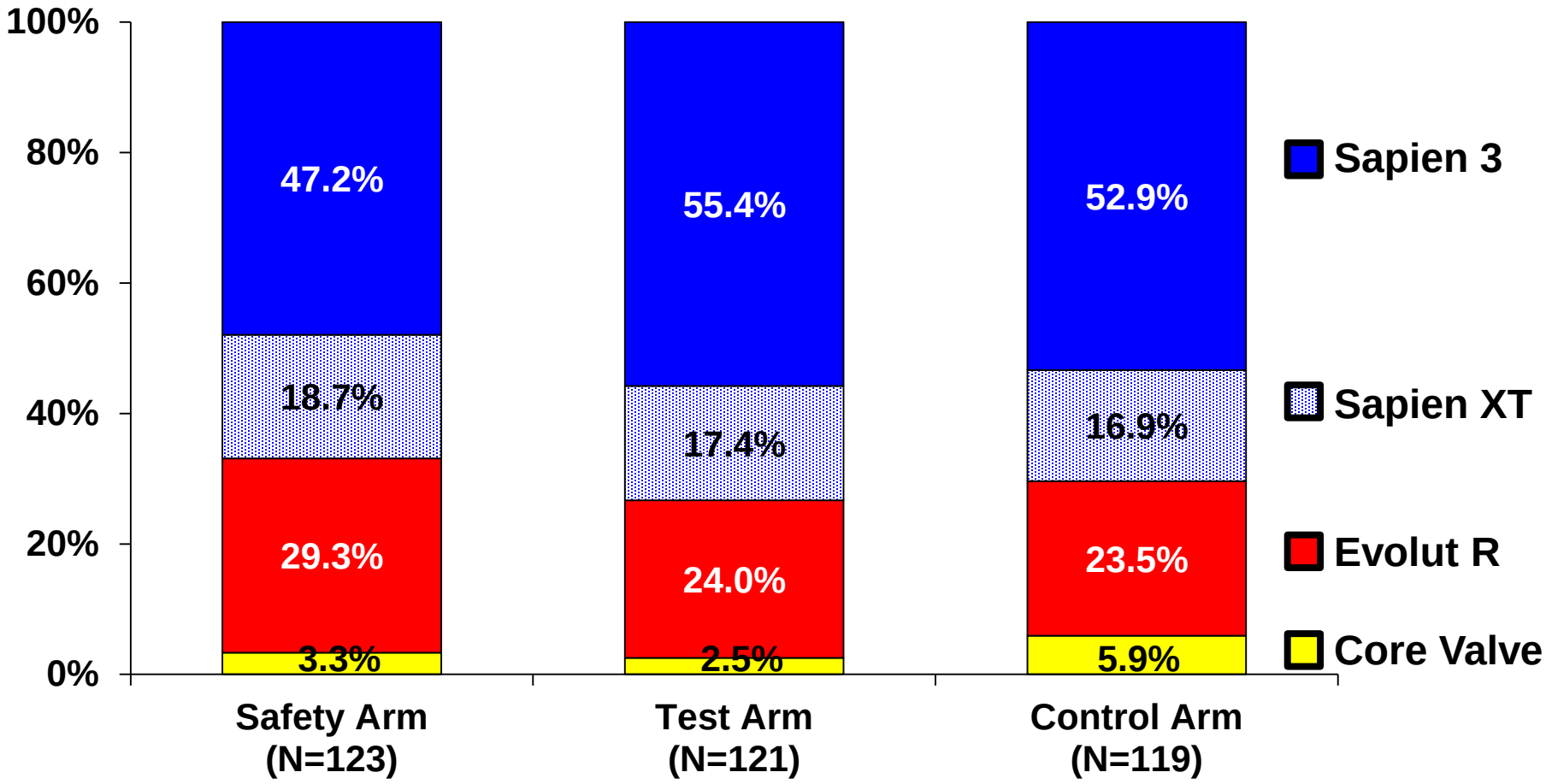
North American Science Associates, Inc (NAMSA)

# Valve Type Distribution Over Time



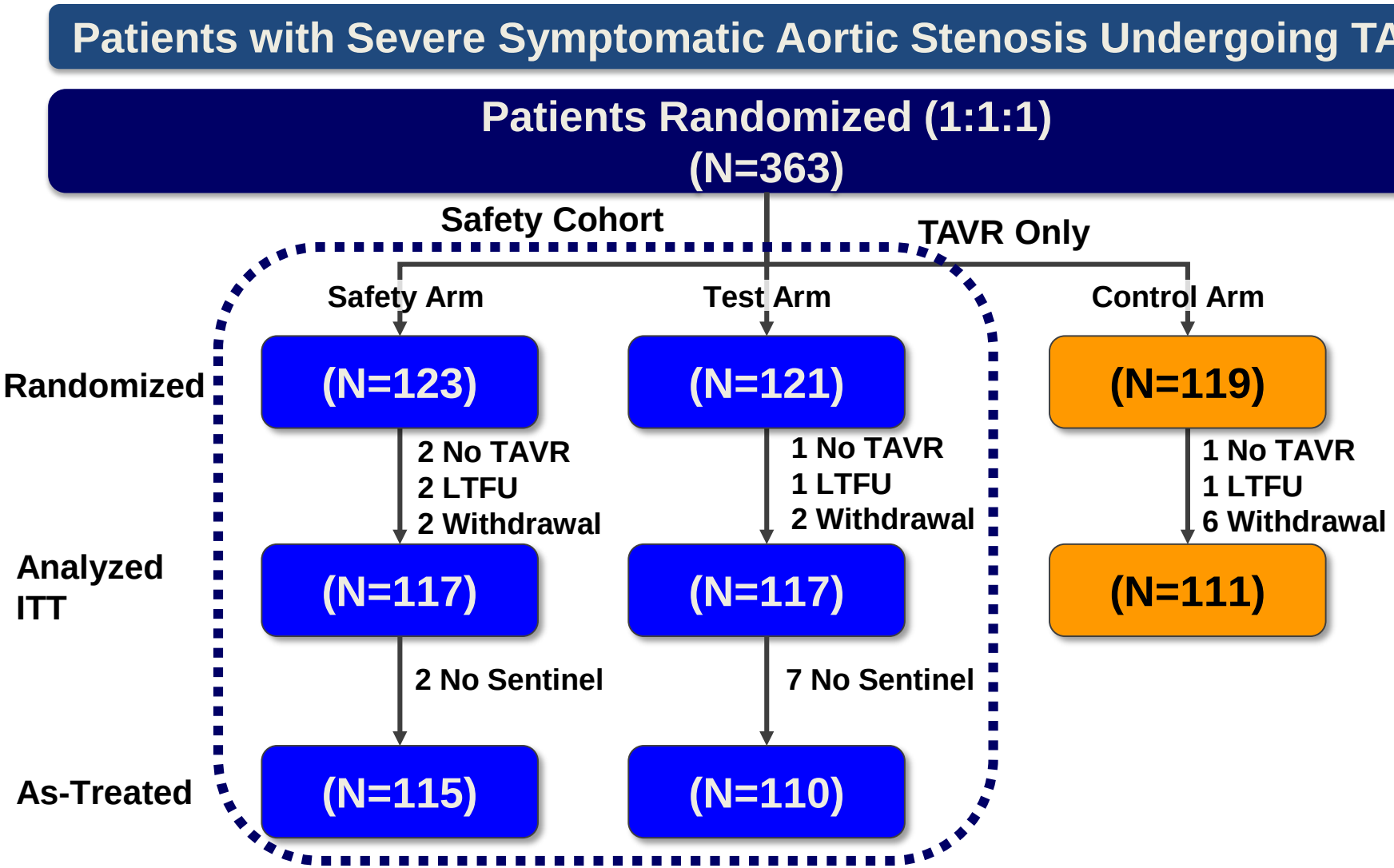
# Distribution of Valve Types Across Study Arms

**No Significant Differences in Valve-type Distribution (p = 0.71)**



# SENTINEL Trial
# Safety and Performance

# SENTINEL Safety Populations



# Primary Safety Endpoint

- Non hierarchical MACCE at 30 days
  - All-cause mortality
  - All strokes
  - Acute kidney injury (Stage 3) within 72 hours
- Historical MACCE performance goal
  - Weighted average of all FDA pivotal TAVR trials approved at time of SENTINEL trial initiation = 13.3%
- Upper-bound of one-sided 95% CI for MACCE derived from Safety Cohort (Safety Arm + Test Arm subjects) must be <18.3% (13.3% + 5% non-inferiority margin)
- Device cohort (Safety + Test arm) also compared to concurrent randomized Control arm

# Patient Demographics

| | Sentinel | | |
|---|---|---|---|
| | Safety Arm (N=123) | Imaging Arm (N=121) | Control Arm (N=119) |
| Age (mean, yrs) | 82 | 82 | 83 |
| Female (%) | 55 | 52 | 49 |
| STS PROM Score (mean, %) | 6.2 | 6.4 | 7.5 |
| Previous stroke (%) | 8 | 4 | 5 |
| Previous TIA (%) | 8 | 7 | 7 |
| Diabetes (%) | 27 | 41 | 38 |
| h/o atrial fibrillation (%) | 30 | 35 | 30 |
| Heavily calcified aorta (%) | 3 | 2 | 3 |
| h/o CAD (%) | 54 | 50 | 56 |
| h/o PVD (%) | 16 | 14 | 15 |
| NYHA III/IV (%) | 83 | 85 | 82 |
| Valve area ($cm^2$) | 0.7 ± 0.18 | 0.7 ± 0.17 | 0.7 ± 0.20 |
| Mean aortic valve gradient (mmHg) | 42 ± 15 | 44 ± 15 | 41 ± 14 |

# Sentinel Access and Device Success

**Reasons for No Sentinel (N=13, 5.6%)**
**No TAVR: 3**
**Inadequate vascular access: 6**
**Late screen failure: 3**
**Test patient treated as Control (protocol deviation): 1**

| | Sentinel (Safety + Test) |
|---|---|
| **Sentinel Access** | |
| **Radial** | **94.4%** |
| **Brachial** | **5.6%** |
| **Device Success** | |
| **Both Filters Deployed*** | **94.4%** |
| **≥ One Filter Deployed** | **99.6%** |

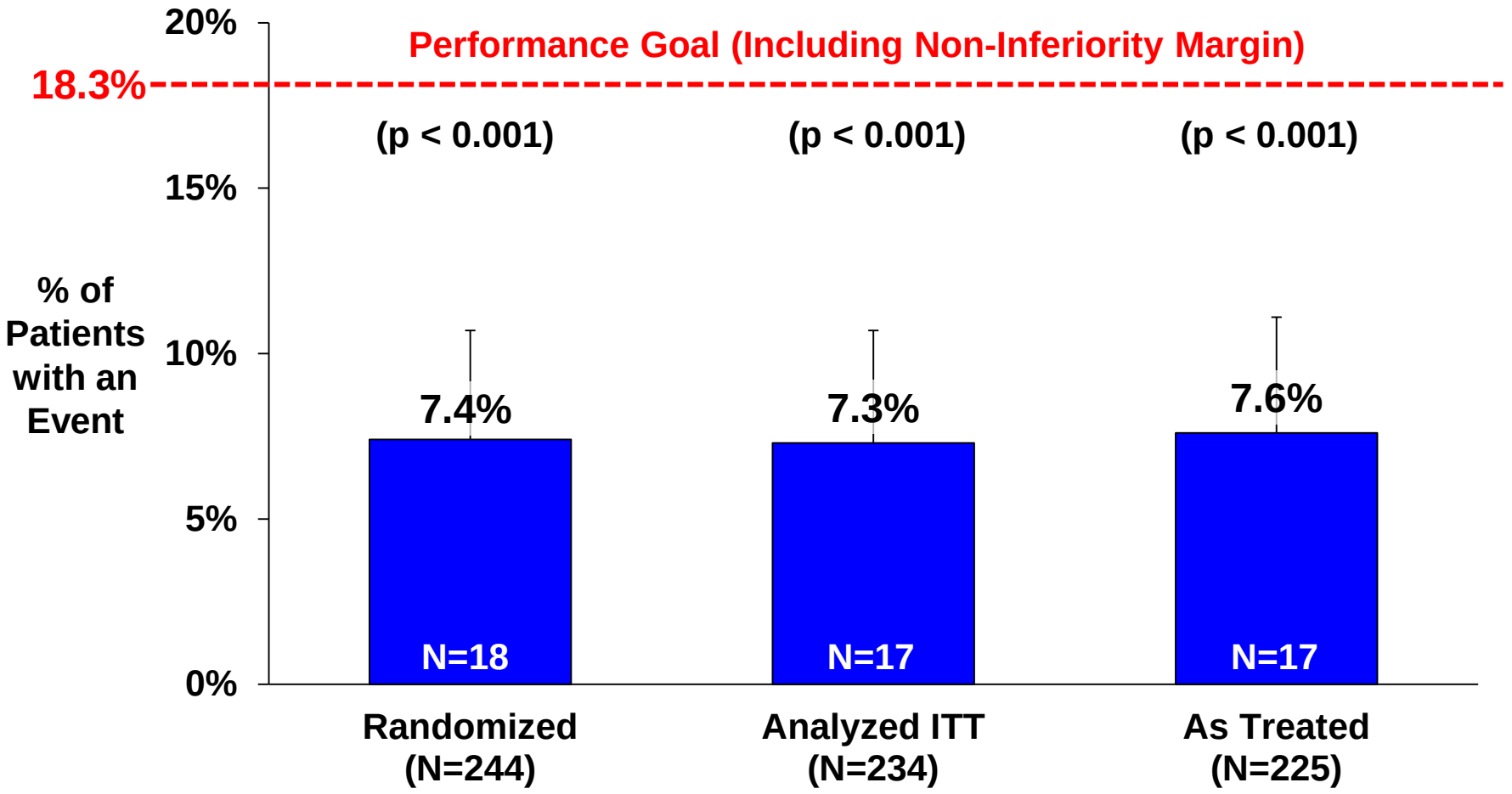
***Acute delivery and retrieval success:** Deployment and retrieval of the proximal and distal filters in accessible anatomies (not excessively tortuous or calcified)

# TAVR Procedural Factors in SENTINEL Study

| | Sentinel (Safety + Test) | Control | P-value |
|---|---|---|---|
| TAVR Procedure Time (Mean Minutes[1)] | 87 | 74 | 0.013 |
| TAVR Fluoroscopy Time (Mean Minutes[2]) | 19 | 17 | 0.073 |

[1] Time elapsed between first arterial access and removal of the last guide from the arterial access sheath
[2] Time elapsed use of fluoroscopy during TAVR Procedure

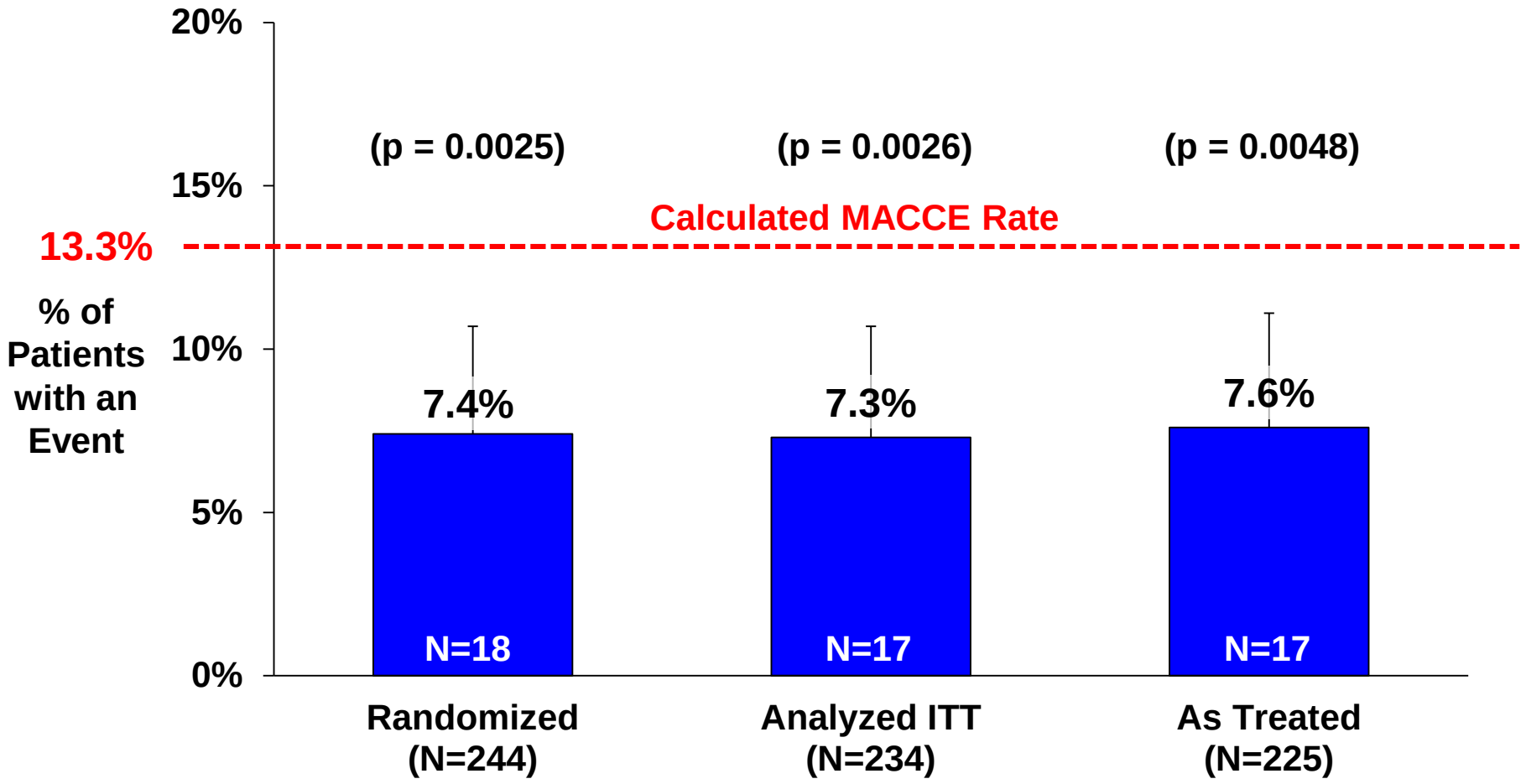
# Primary Safety Endpoint (30-Day MACCE)




Error bars represent upper bound of the one-sided 95% Upper CI

Imputation method based on the logistic regression method. Factors used in imputation algorithm: age, sex, BMI, history of diabetes, history of atrial fibrillation, previous stroke with permanent deficit, and geography

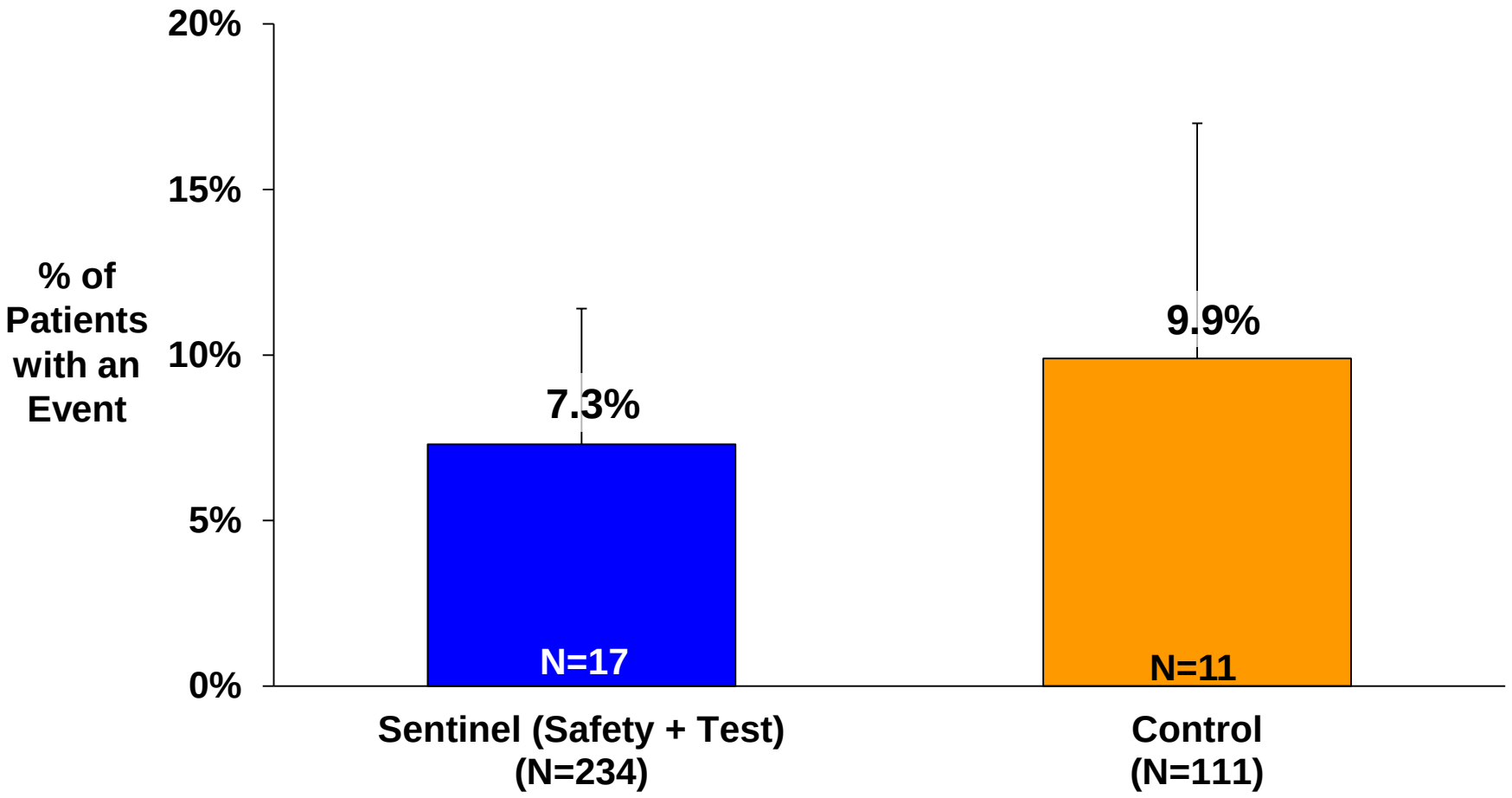
# Safety Endpoint Evaluation (Without Non-Inferiority Margin)




Error bars represent upper bound of the one-sided 95% Upper CI

Imputation method based on the logistic regression method. Factors used in imputation algorithm: age, sex, BMI, history of diabetes, history of atrial fibrillation, previous stroke with permanent deficit, and geography

# 30-Day MACCE Sentinel vs. Concurrent Control (Analyzed ITT)



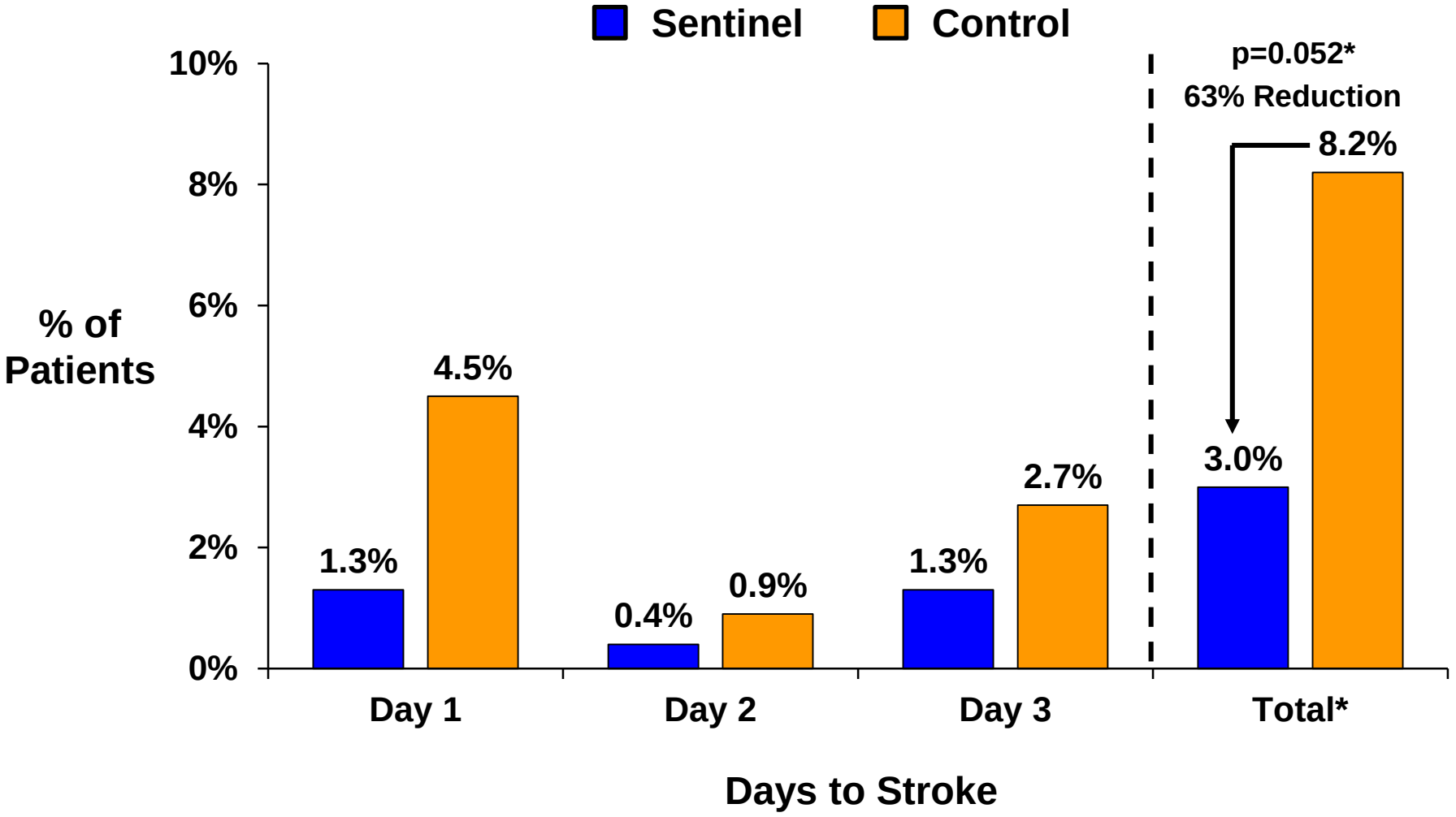

Error bars represent upper bound of the one-sided 95% Upper CI

# 30-Day Clinical Safety Results (Analyzed ITT)

| | Sentinel (Safety + Test) (N=234) | | Control (N=111) | | |
|---|---|---|---|---|---|
| | N | % | N | % | P-value |
| **Any MACCE† patients** | 17 | **7.3** | 11 | **9.9** | 0.40 |
| **Events** | | | | | |
| **Death (all-cause)** | 3 | **1.3** | 2 | **1.8** | 0.65 |
| **Stroke** | 13 | **5.6** | 10 | **9.1** | 0.25 |
| **Disabling** | 2 | **0.9** | 1 | **0.9** | 1.00 |
| **Non-disabling** | 11 | **4.8** | 9 | **8.2** | 0.22 |
| **AKI (Stage 3)** | 1 | **0.4** | 0 | **0** | 1.00 |
| **TIA** | 1 | **0.4** | 0 | **0** | 1.00 |
| **Sentinel-related complications[1]** | 1 | **0.4** | N/A | **N/A** | N/A |

[1]Late brachial artery pseudo-aneurysm treated with thrombin injection
†MACCE defined as Death (any cause), Stroke (any), Acute Kidney Injury (Stage 3).
Note: MACCE events adjudicated by independent Clinical Events Committee who were blinded to treatment arm

# Stroke Diagnosis ≤72 hours (Analyzed ITT)




*Fisher Exact Test

# Safety Summary

- Primary Safety Endpoint achieved
  - 30-day Sentinel MACCE vs. Performance Goal ($p < 0.001$)
- 30-Day MACCE
  - Sentinel 7.3% vs. Control 9.9%
- 30-Day stroke rate
  - Sentinel 5.6% vs. Control 9.1%
- Peri-procedural stroke rate (≤72 hours)
  - Sentinel 3.0% vs. Control 8.2%
- One (0.4%) Sentinel-related access site complication

# Histopathology

**Renu Virmani, MD**

President, CVPath Institute Inc.

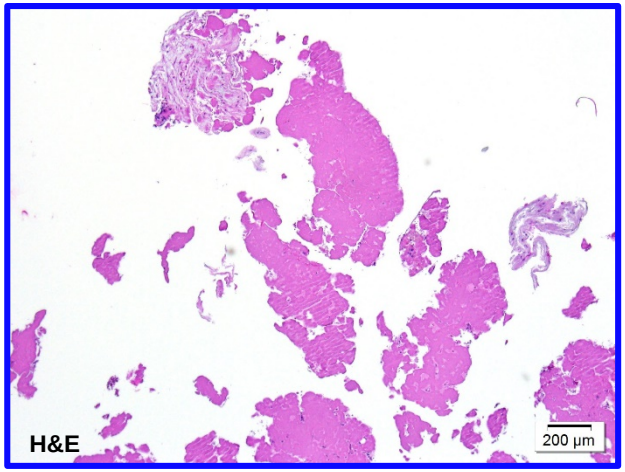
Clinical Professor
George Washington University

# Histopathologic Analysis of Filters: Proximal and Distal

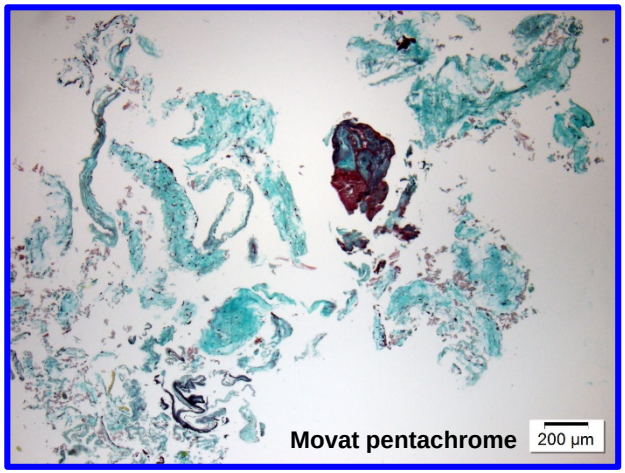
- 105 patients with 210 evaluable filters
- Filters processed and embedded in paraffin and sectioned
- Slides classified by thrombus and tissue type
  - Thrombus (acute and chronic)
  - Valve tissue
  - Calcium nodules
  - Arterial wall (intima or media including necrotic core)
  - Myocardium
  - Foreign material

# Type of Tissue Identified

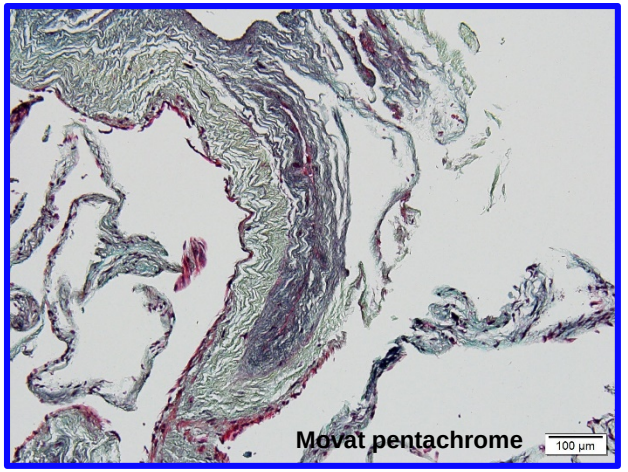
Acute + organizing thrombus



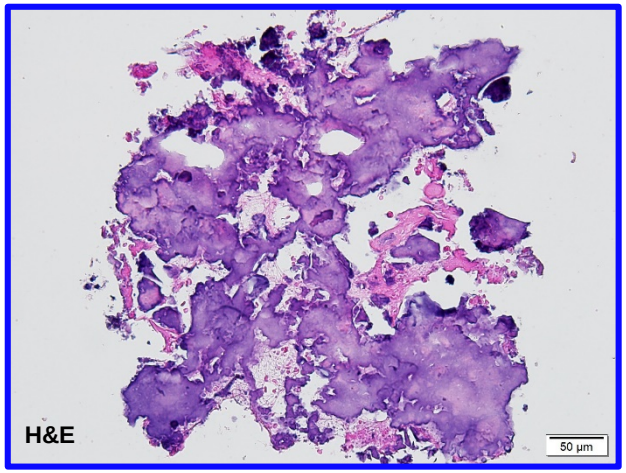

Arterial wall + thrombus



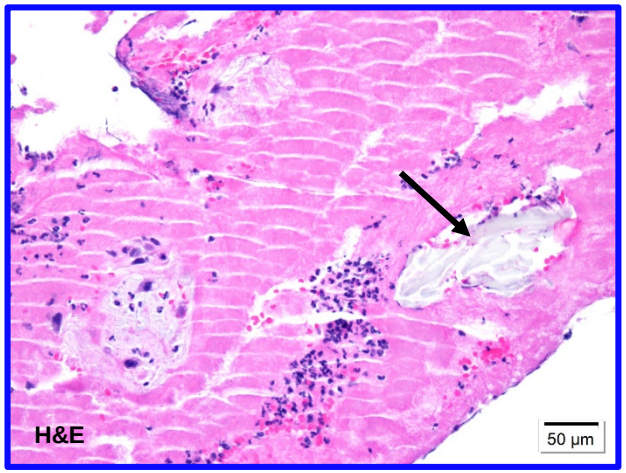

Valve tissue



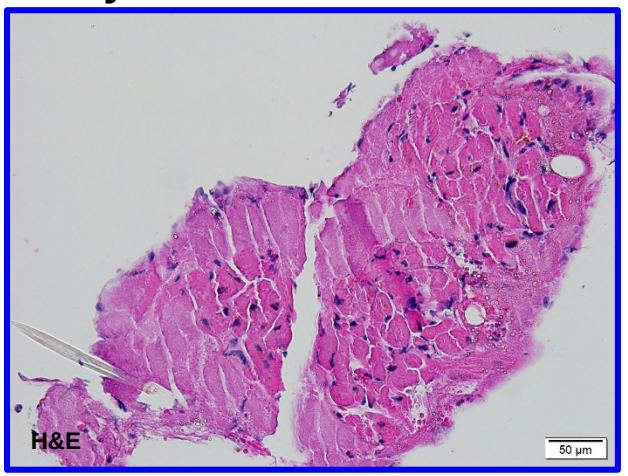

Calcium nodules




Foreign material + thrombus



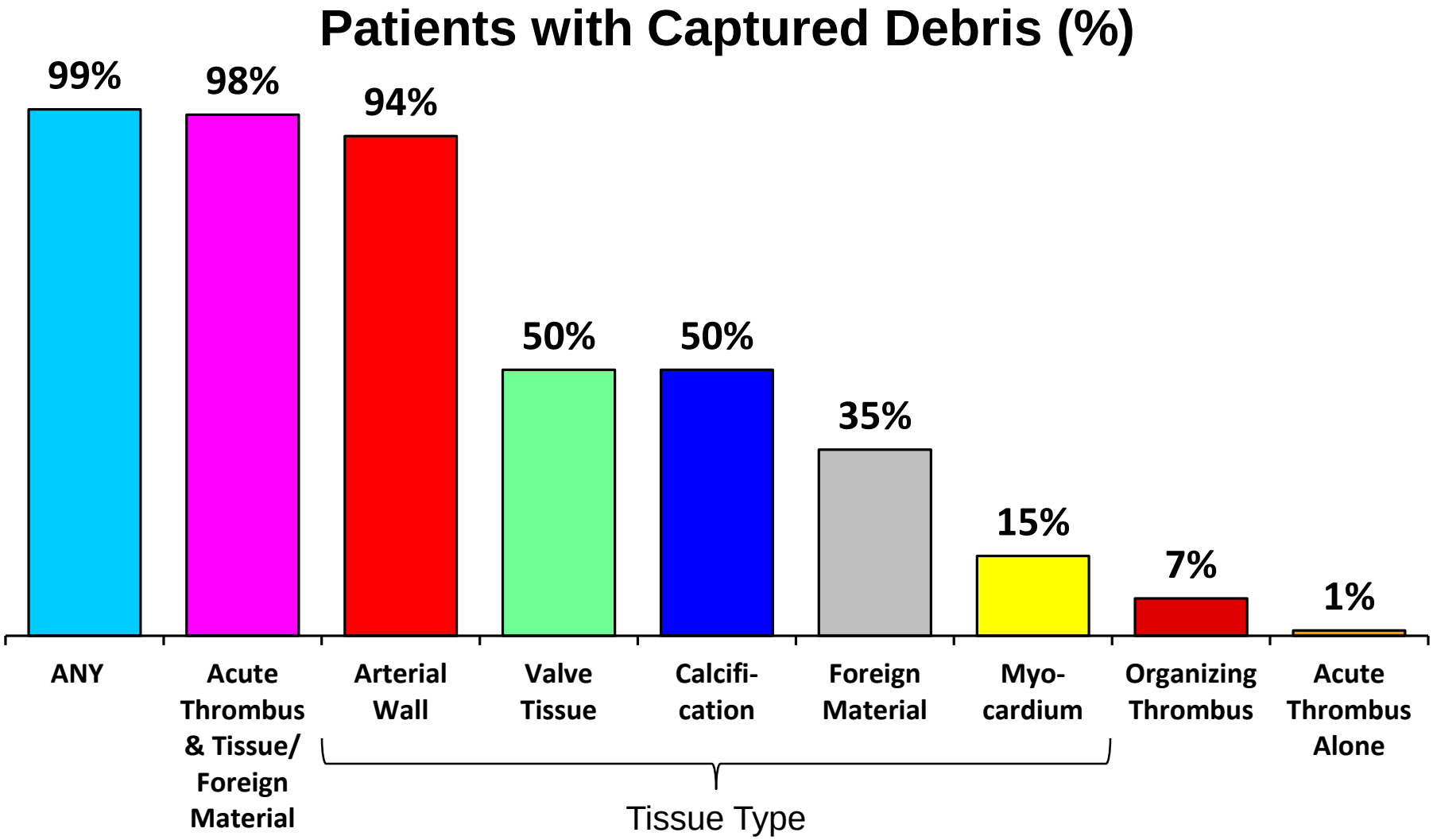

Myocardium + thrombus



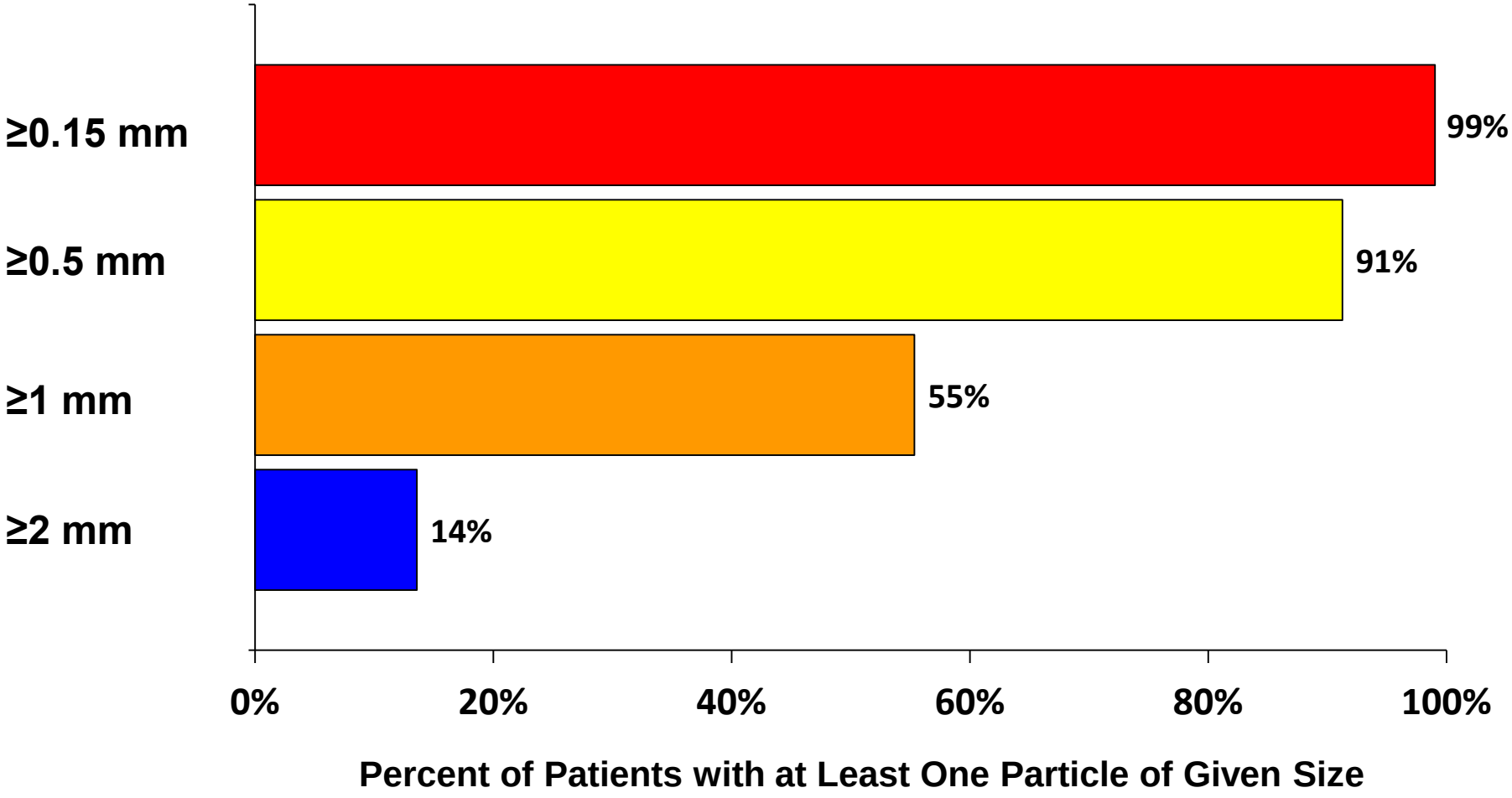
# Type of Morphometric Analysis Performed

- Automated analysis for particle size (HALO software)
- Five largest tissue samples measured manually in largest and smallest dimensions
- Morphology of tissue characterized

# SENTINEL Histopathology: Total Embolic Material by Type



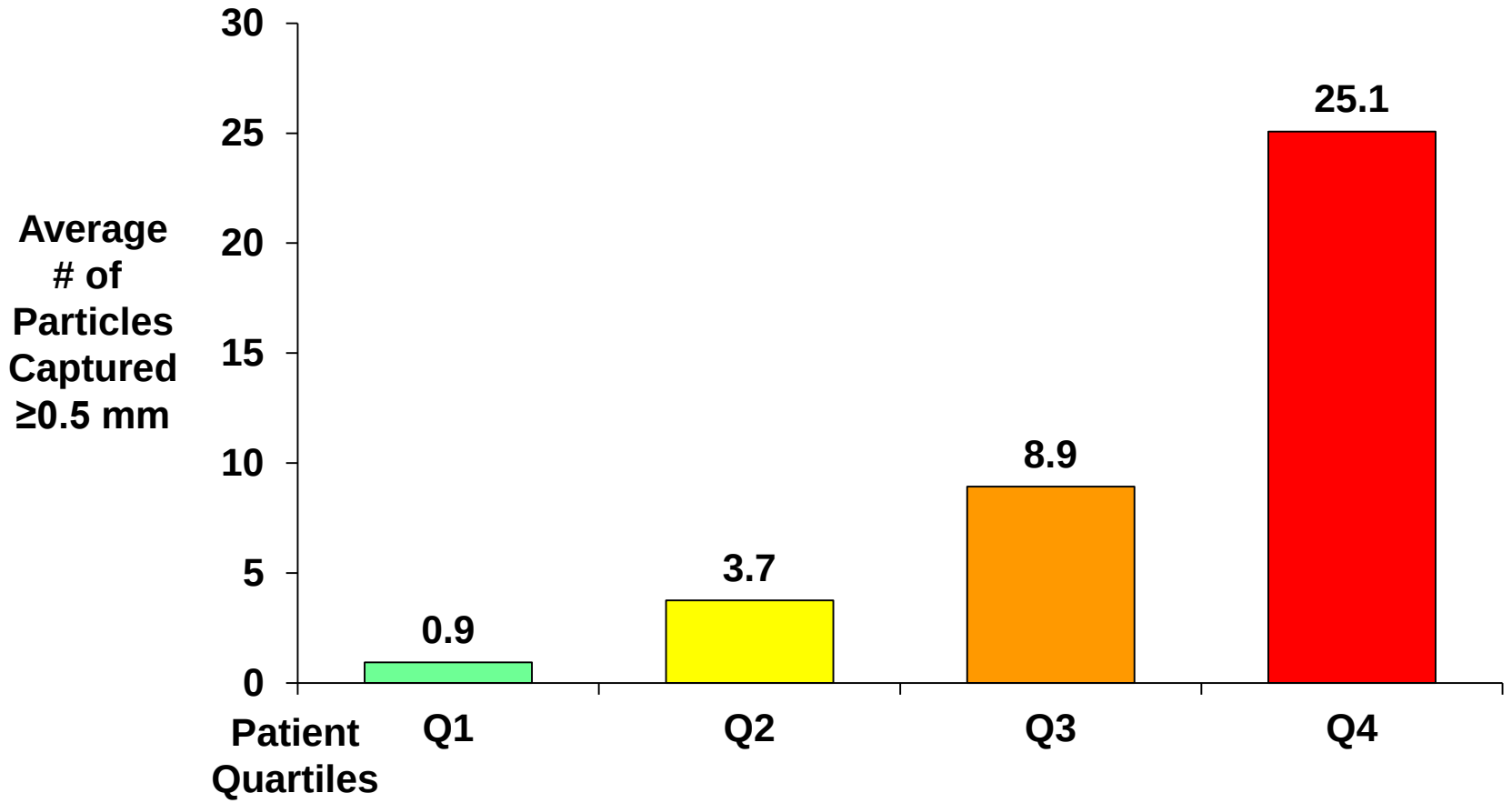
# Morphometric Analysis: Embolic Material by Particle Size




Automated measurement

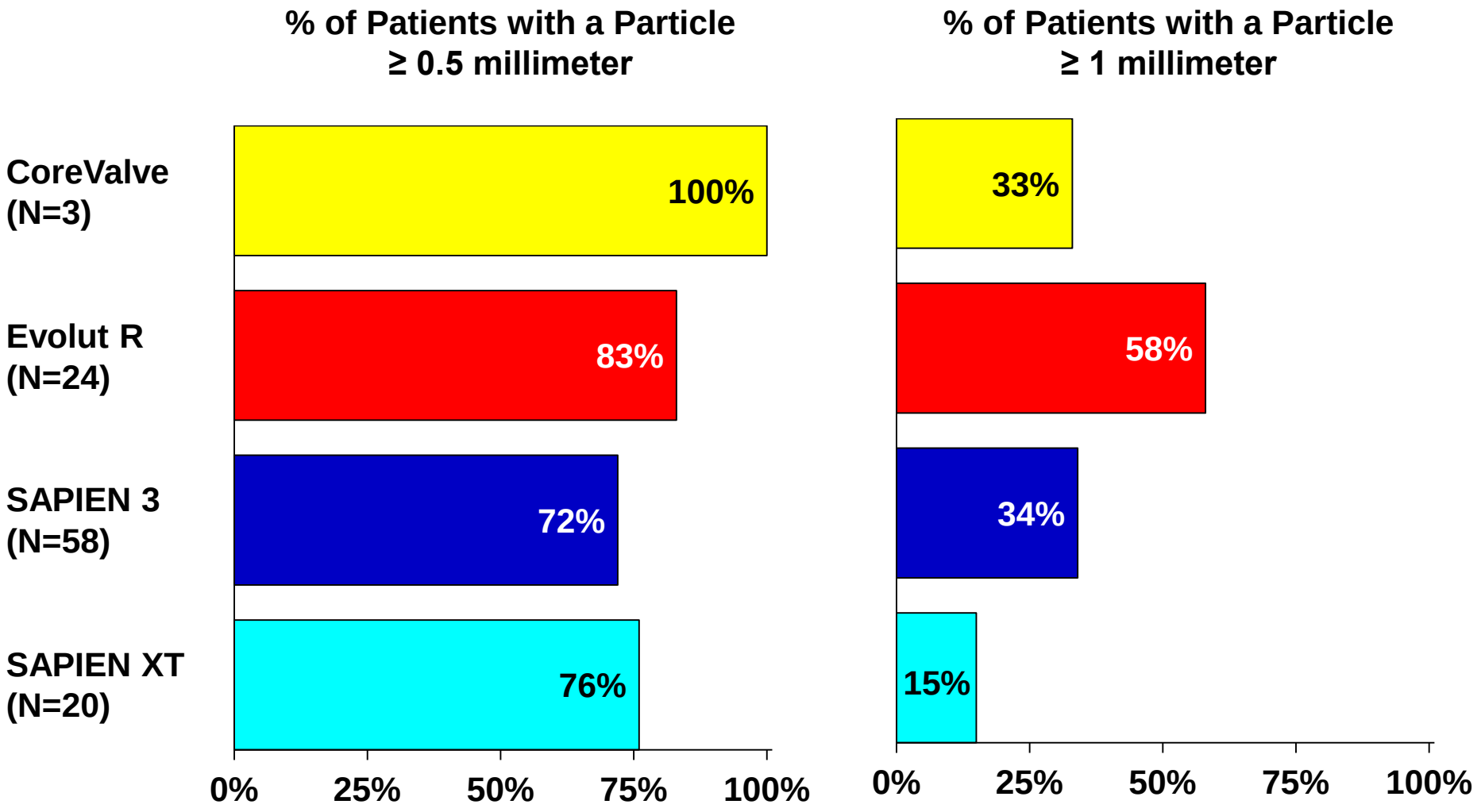
# Patient Quartile Analysis: Average Number of Particles ≥0.5 mm

## 1 in 4 Patients had 25 Particles ≥0.5 mm in Size




Automated measurement

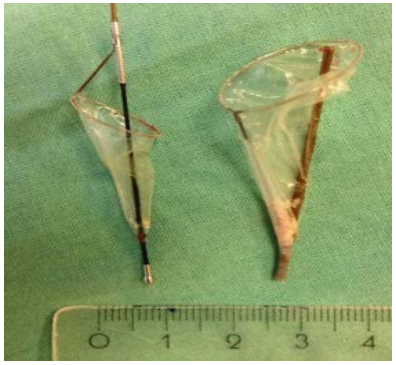
# Morphometric Analysis: Embolic Material by Valve Type ≥ 0.5 and ≥ 1 Millimeter



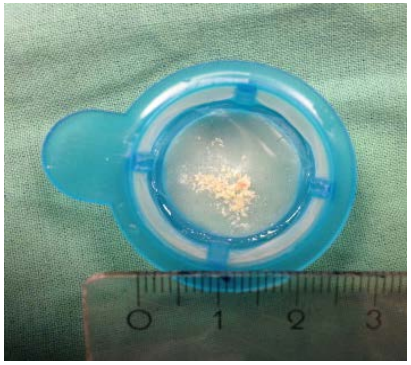

Manual measurement

# Process Methodology

**Sentinel filters**
**(with collected debris)**

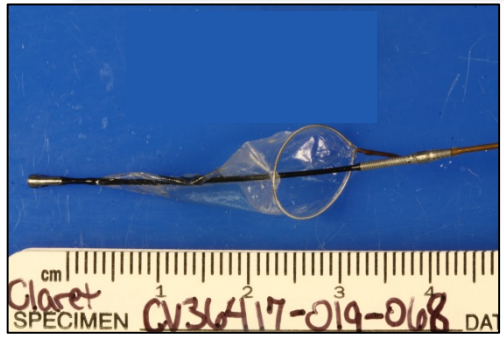


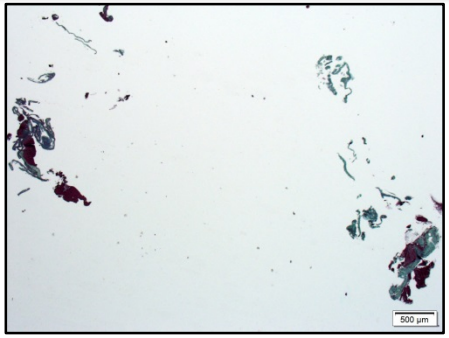
**CVPath filter**
**(40 micron pore size)**

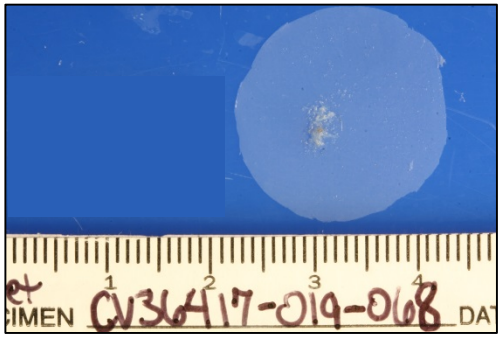


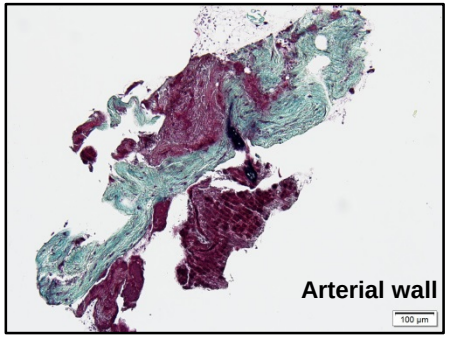
- Filtered through 40-micron mesh
- Processed, embedded in paraffin
- Sectioned at 4-6 microns
- Sections are stained, total of 5 sections per filter
- Assessed by light microscopy

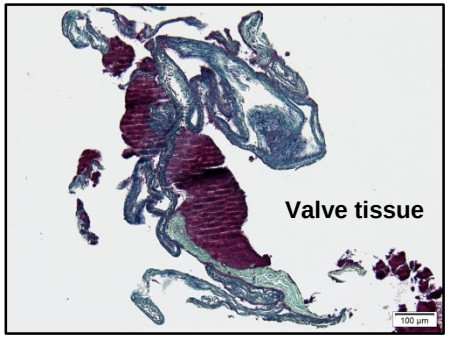
# Arterial Wall & Valve Tissue



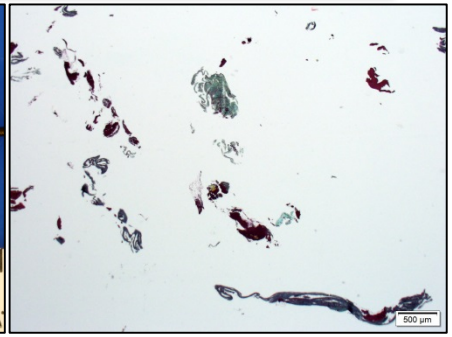



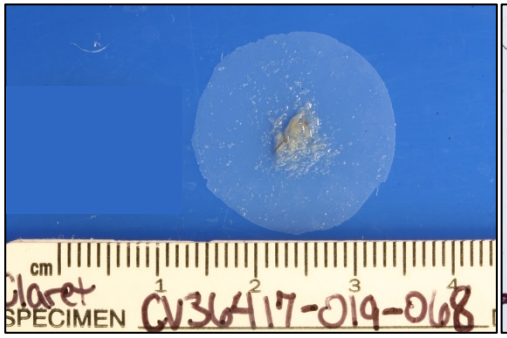



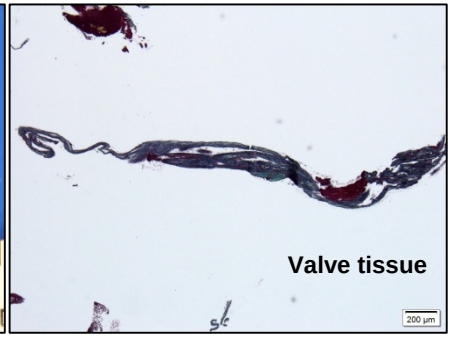



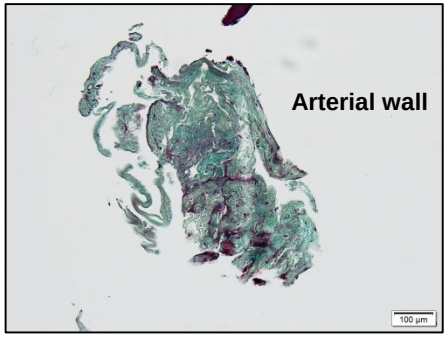

**Distal Filter**

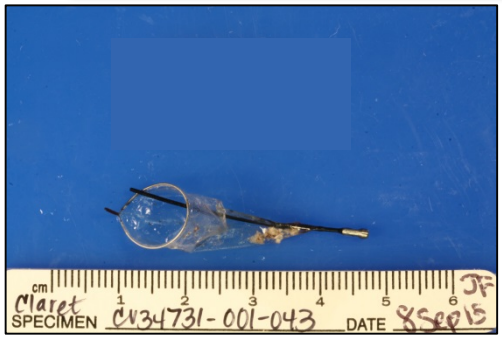



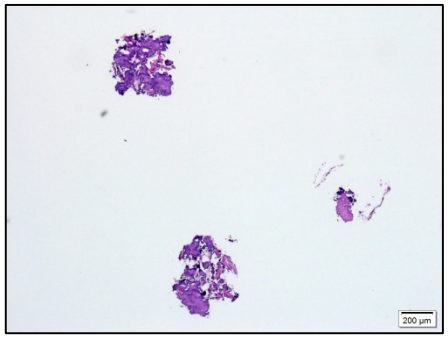



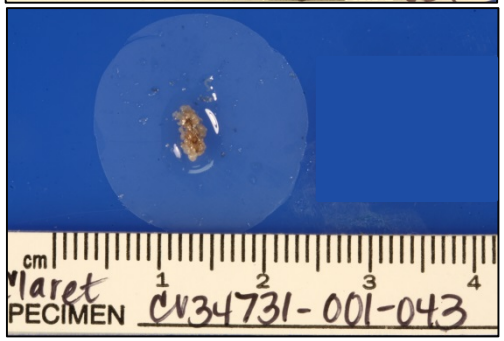

**Proximal Filter**

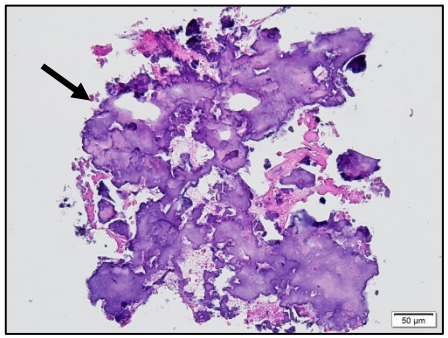


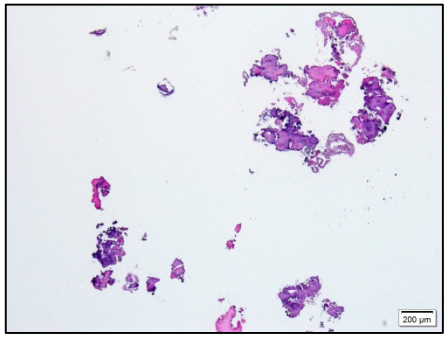
# Calcium Nodules



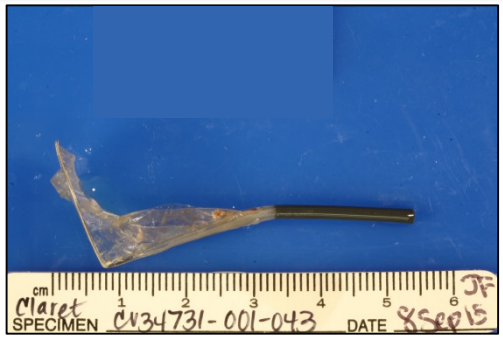



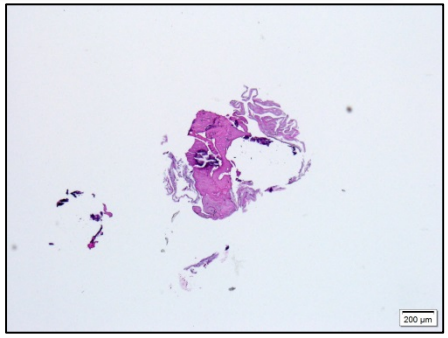


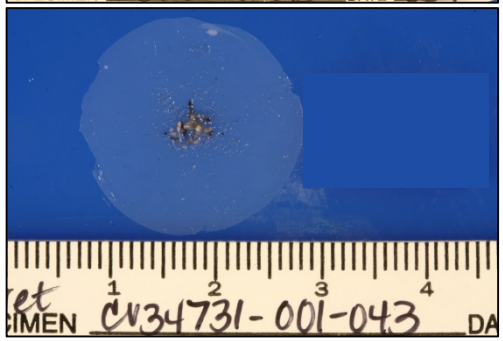



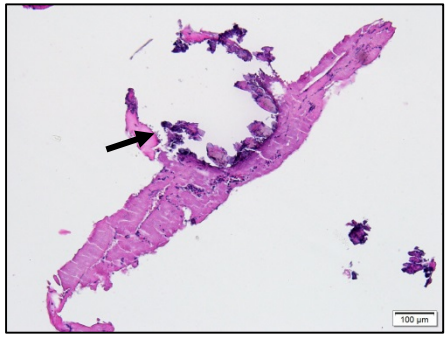


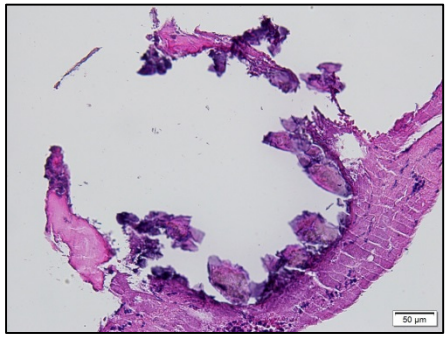
**Distal Filter**



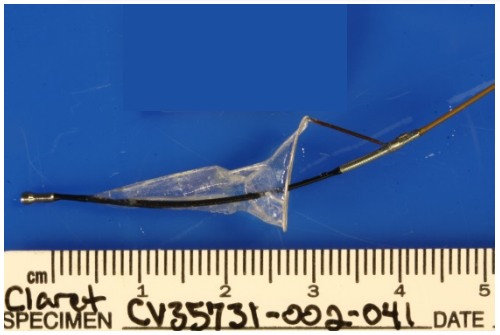


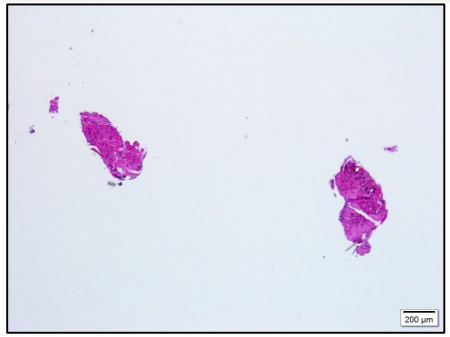



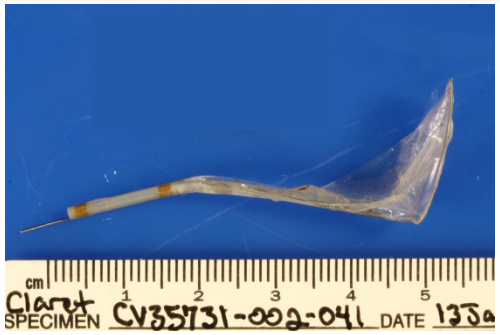


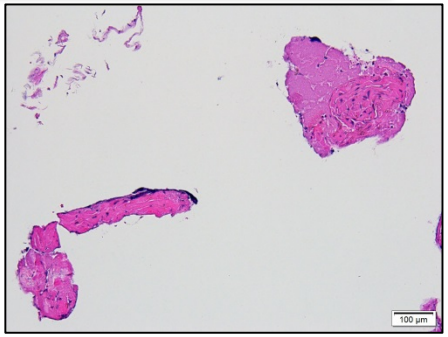
**Proximal Filter**

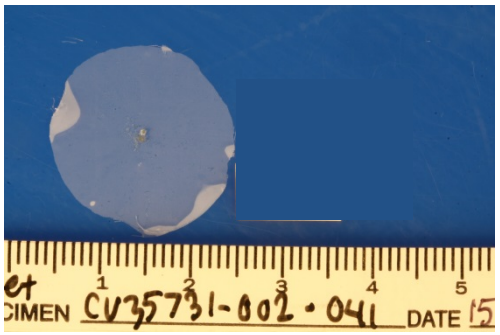
# Myocardium

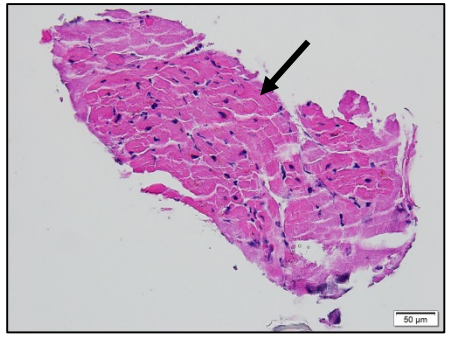


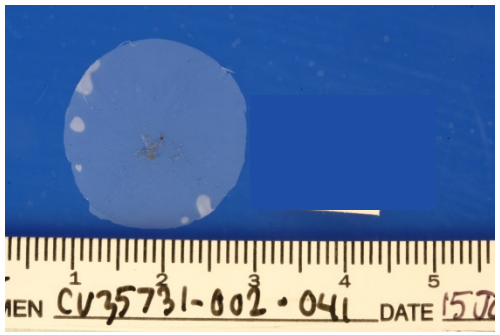



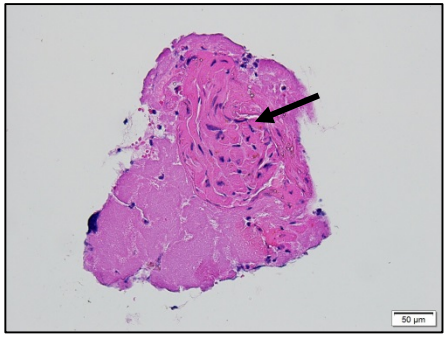


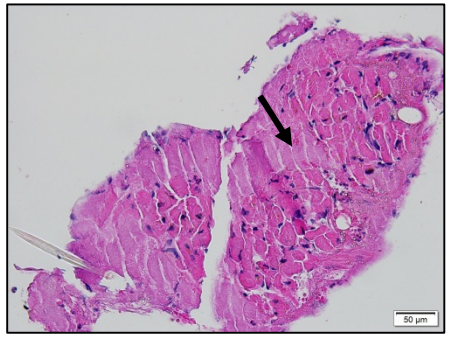


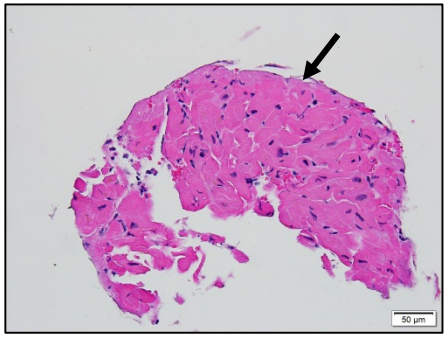


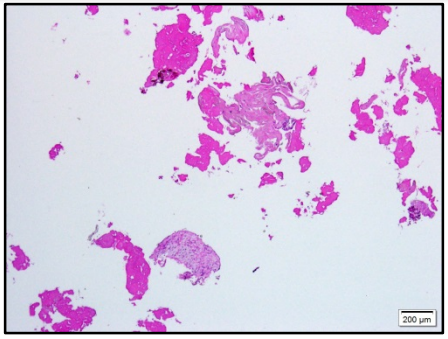
**Distal Filter**

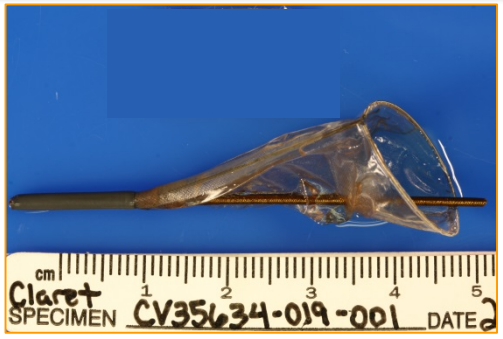


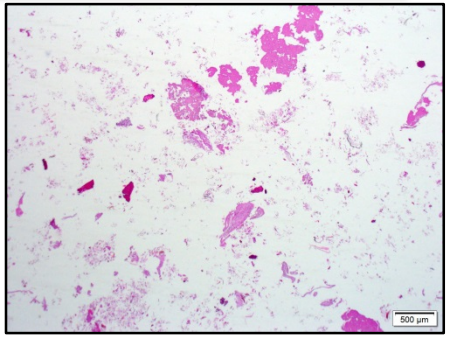
**Proximal Filter**

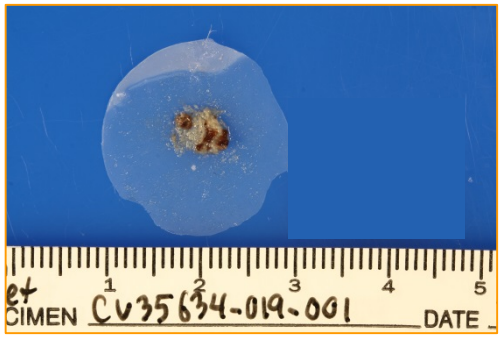


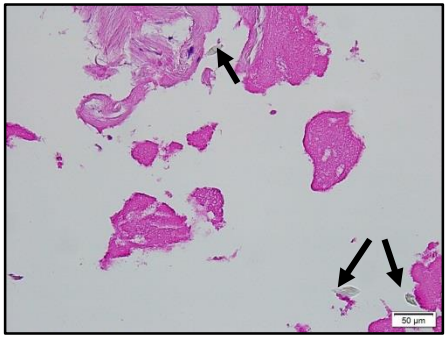
# Foreign Material

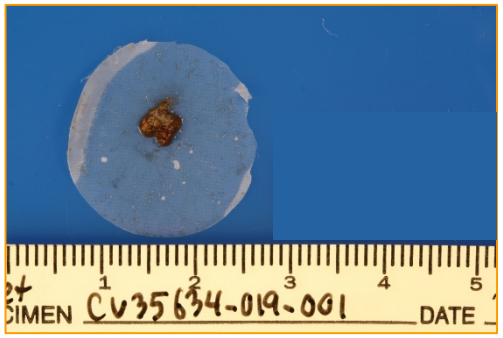



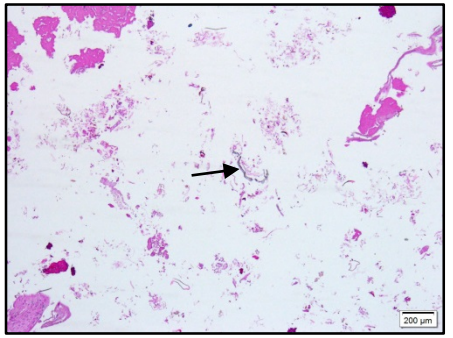


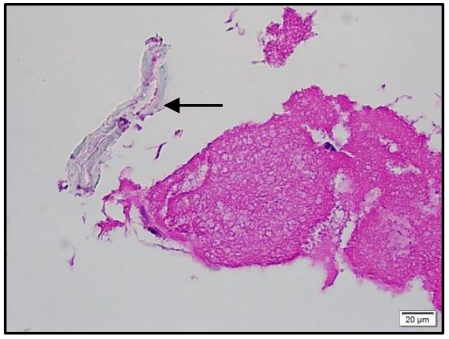


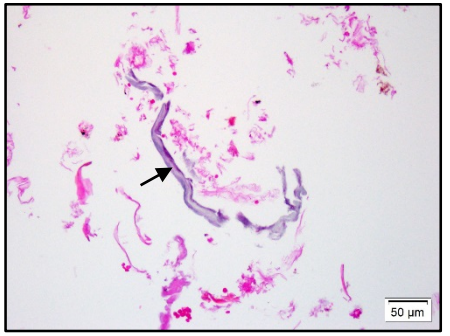


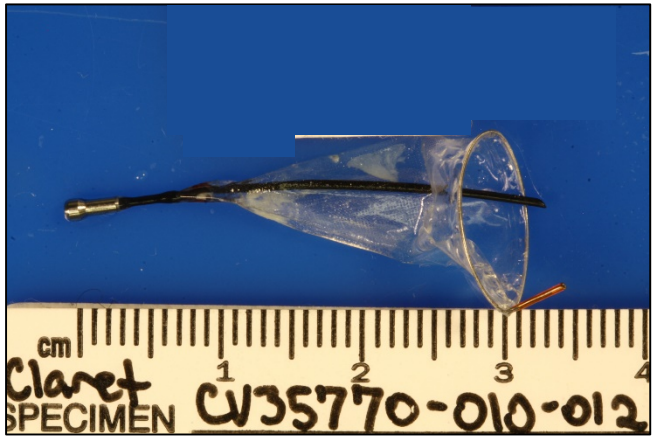
**Distal Filter**



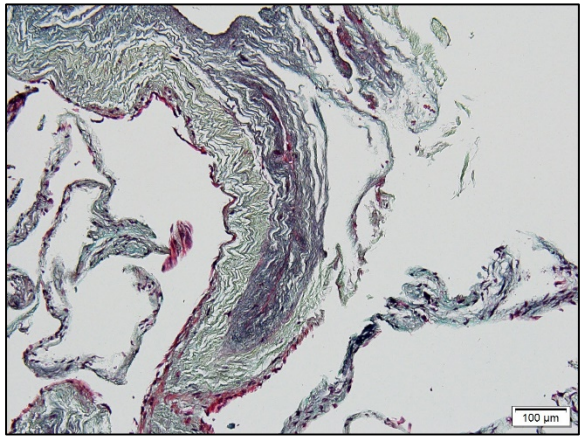
**Proximal Filter**

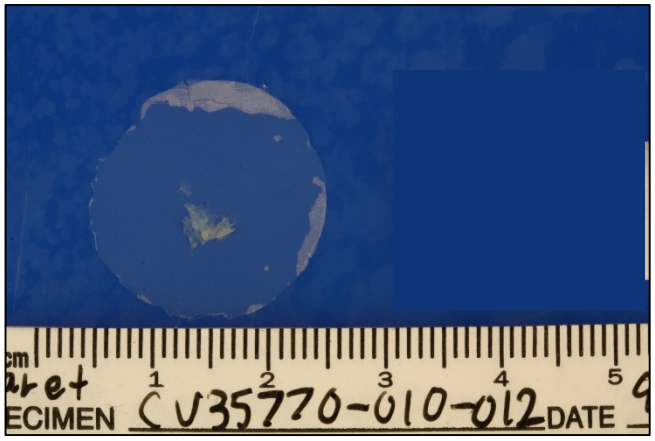


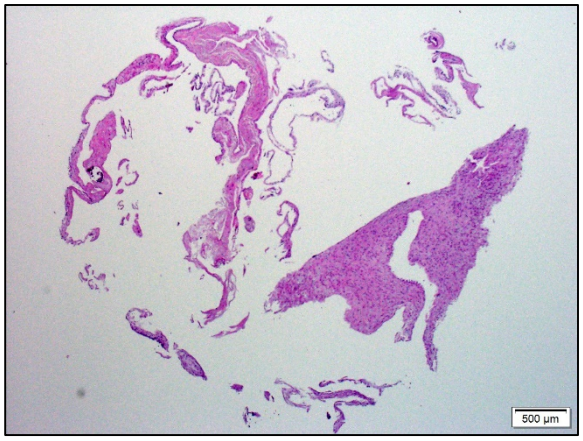
# Largest Piece – Valve and Arterial Wall (5.4 mm)

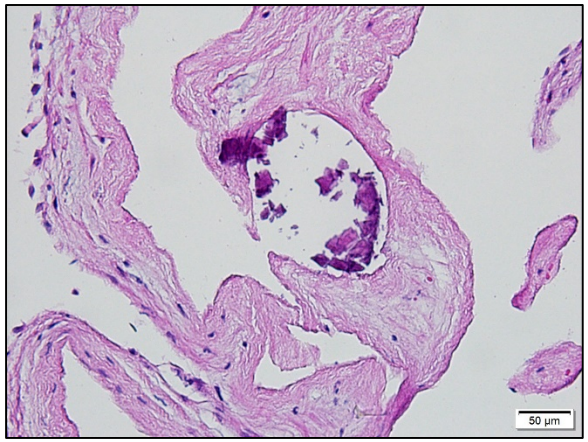







**Distal Filter**

# Sentinel vs. TAVR Catheter Profile Comparison

- TAVR devices are larger, stiffer than Sentinel
- TAVR device features such as exposed metal frames or flared tubes or tips are prone to interacting with vessel wall

**Profile in arch**

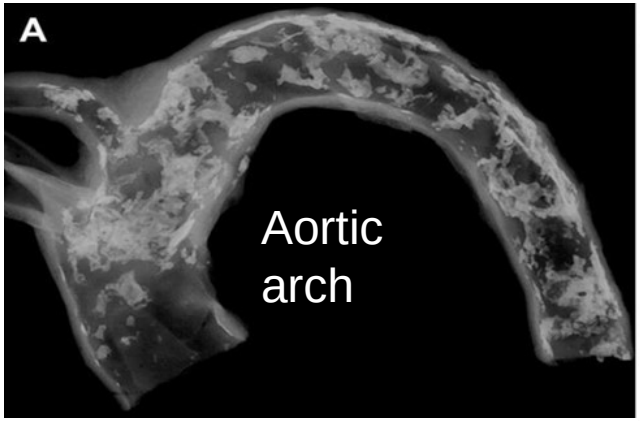
**16-20 F**

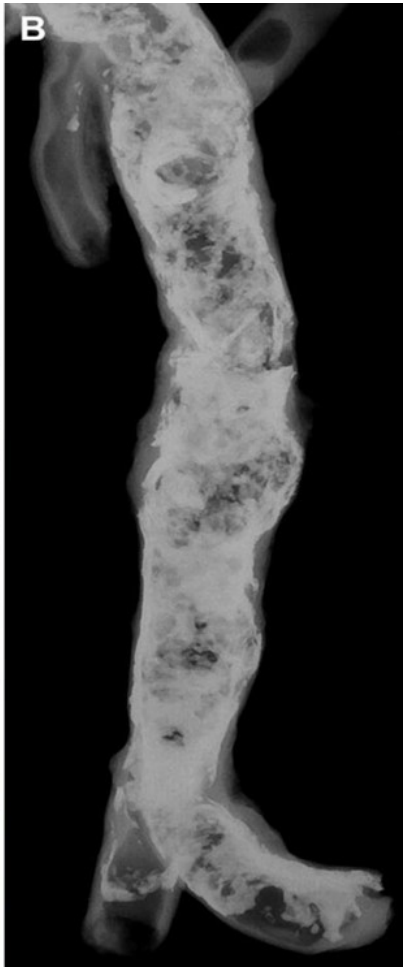
**6 F**

**Sentinel**

# Debris From TAVR

- TAVR traverses:
  - Iliac artery
  - Abdominal aorta
  - Thoracic aorta
  - Aortic arch
  - Ascending aorta




Thoracic and abdominal aorta with iliac bifurcation

Roberts WC, et al. Am J Cardiol 2013;111(3):448-52

# Histopathology Summary

- Tissue or foreign material combined with acute thrombus was found in 98%
- Debris captured from all valve types
- Acute thrombus alone observed in only 1% of patients
- Valve tissue and calcium nodules captured in 50% of patients
- Foreign material captured in 35% of patients
- 1 in 4 Patients had 25 Particles ≥0.5 mm in size

# SENTINEL Trial Effectiveness

**Martin B. Leon, MD**

Professor of Medicine

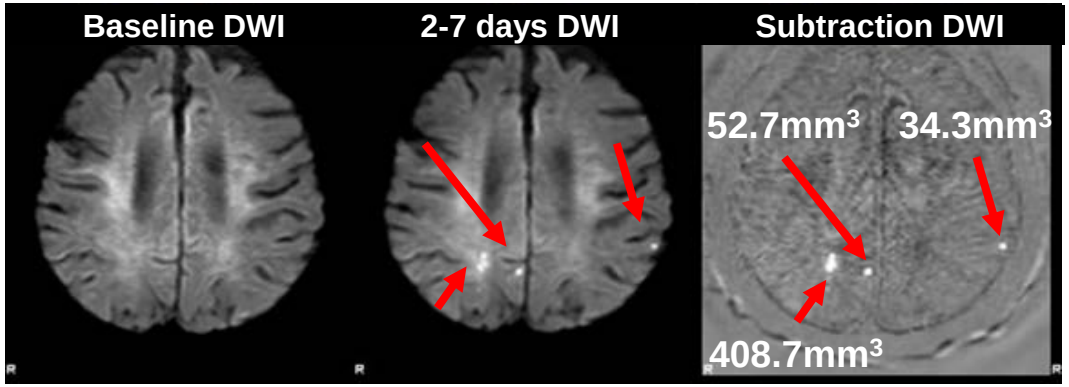
Columbia University Medical Center

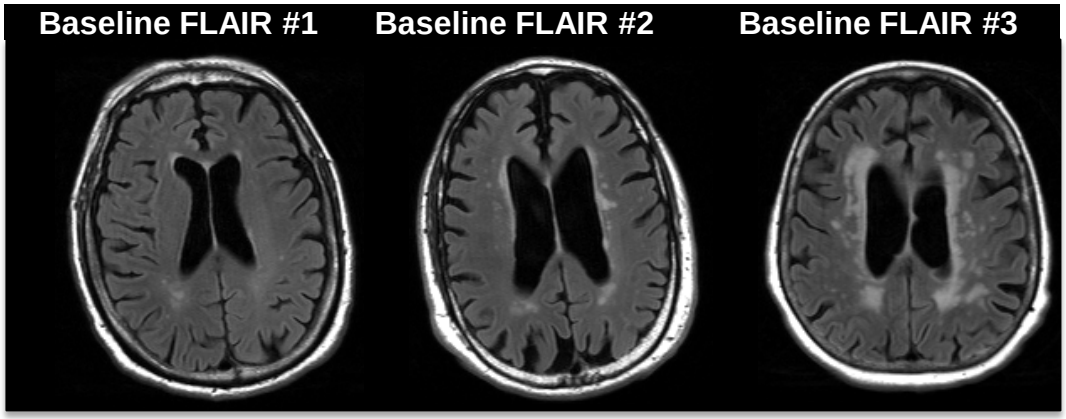
# MRI Methodology and Acquisition Protocol

- Serial 3T scan acquisition at baseline, 2-7 days and 30 days on the same scanner
- All sites imaging core lab certified according to MRI technologist manual and approved by MRI physicist
- Sequences acquired:
  - Diffusion weighted (acute changes)
  - T2/FLAIR (chronic changes)
  - B0 Field Map
  - High-resolution 3D T1-weighted anatomical image
- Scans transferred, queried, accepted in real time

# MRI Analysis of New DWI Lesion Volume and Number

- Blinded core lab analysis of all scans
- Serial co-registration and subtraction
- Artifact/distortion correction
- Per-lesion quantification and longitudinal tracking

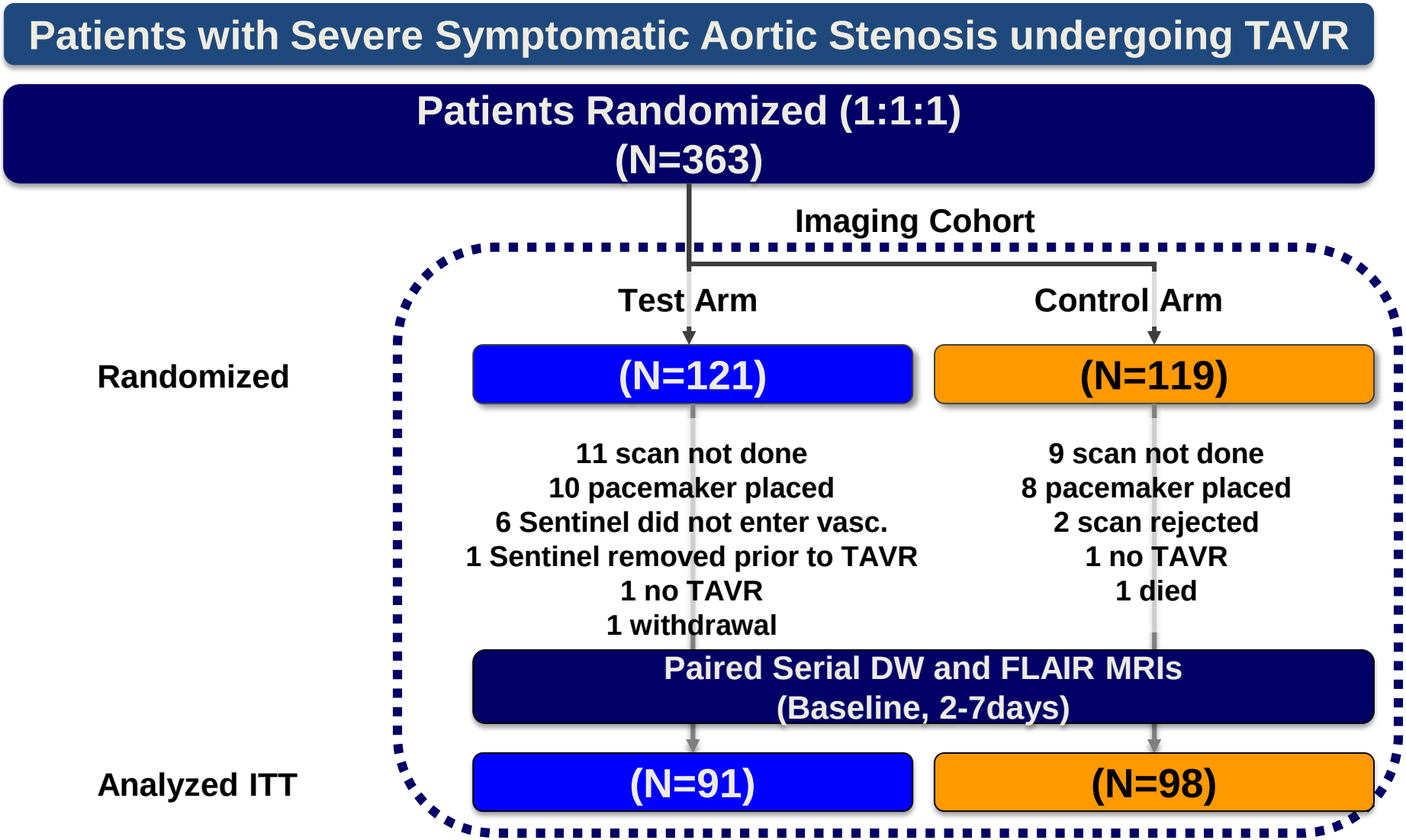



DWI – diffusion weighted image

FLAIR – attenuated inversion recovery

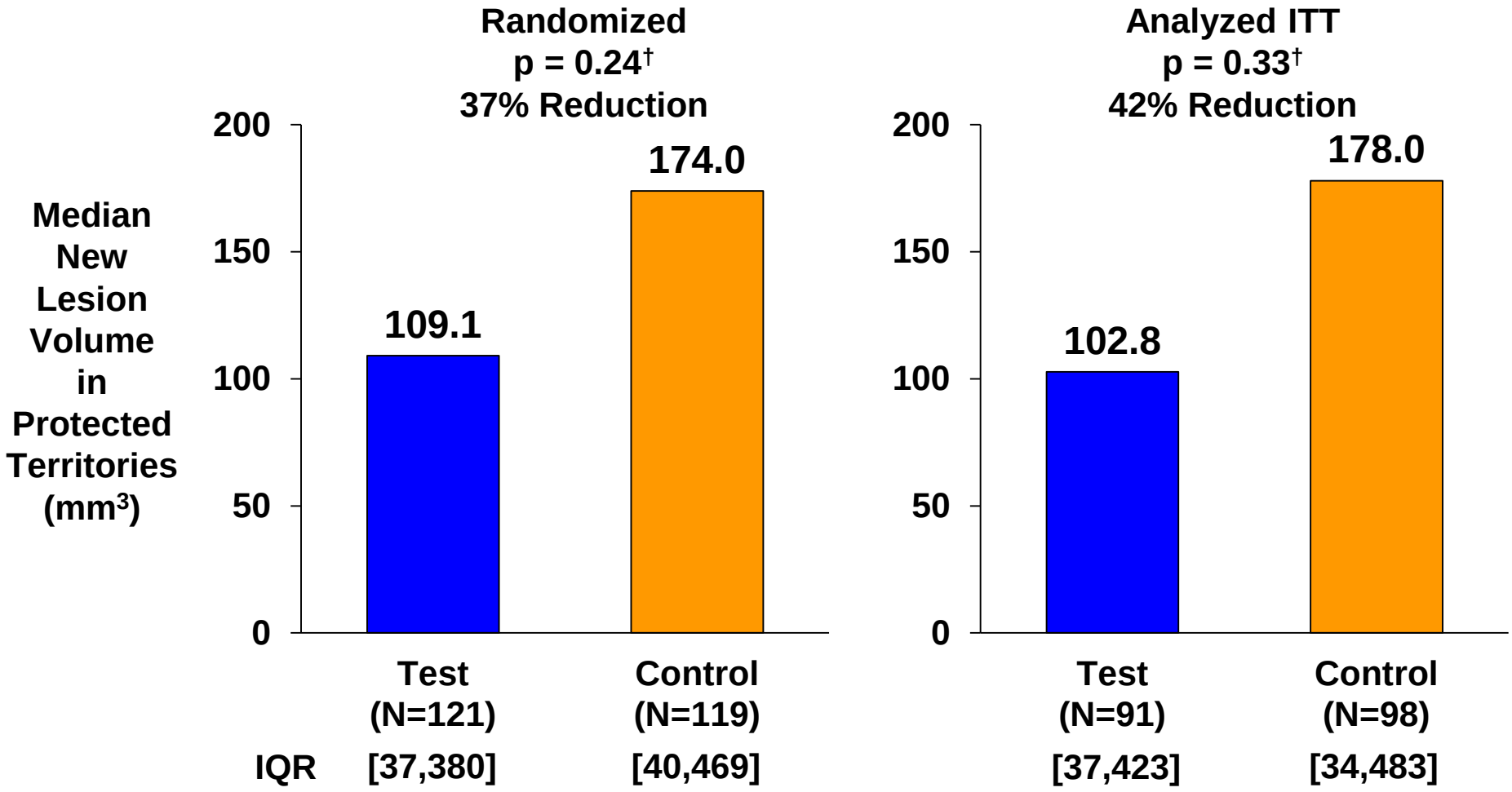
# SENTINEL Imaging Study



# Primary Effectiveness Endpoint and Success Criteria

- Primary Effectiveness Endpoint
  - Median total new lesion volume in protected territories at Day 2-7 based on DW-MRI
- Study Success Criterion - Reduction in Median Total New Lesion Volume (Test vs. Control) in protected territories
  - Criterion #1: statistical superiority
  - Criterion #2: observed treatment effect ≥30%

# Primary Effectiveness Endpoint: New Lesion Volume in Protected Territories




Imputation method based on the predictive mean matching method.
Factors used in imputation algorithm based on blinded aggregate data: 850 Hounsfield Unit calcification score; BMI; Valve type; Procedural stroke; Pre/post dilatation; Mean aortic valve gradient

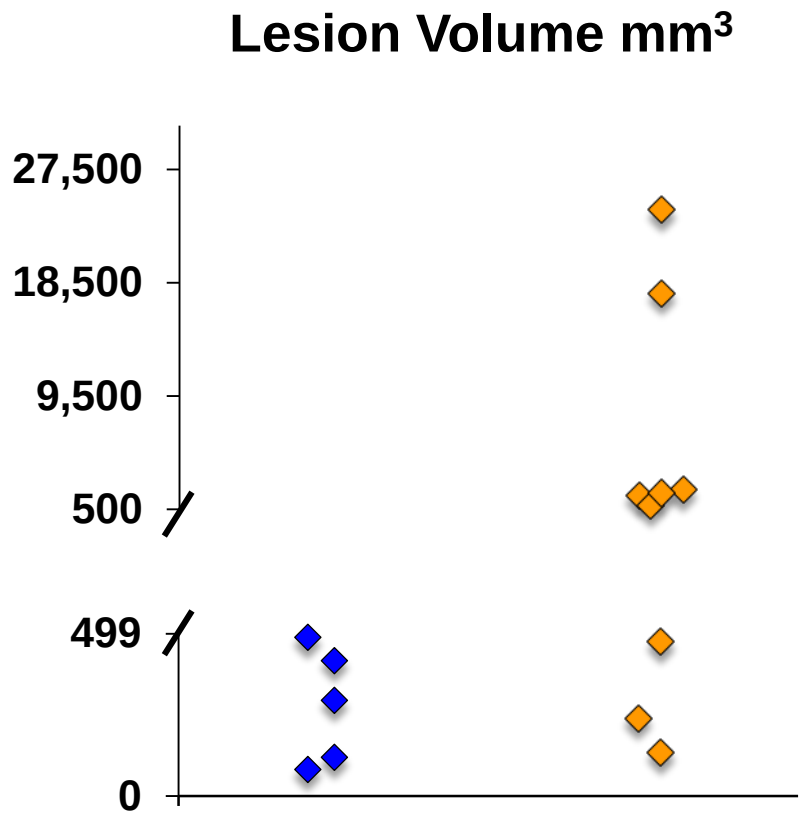
† Wilcoxon Test

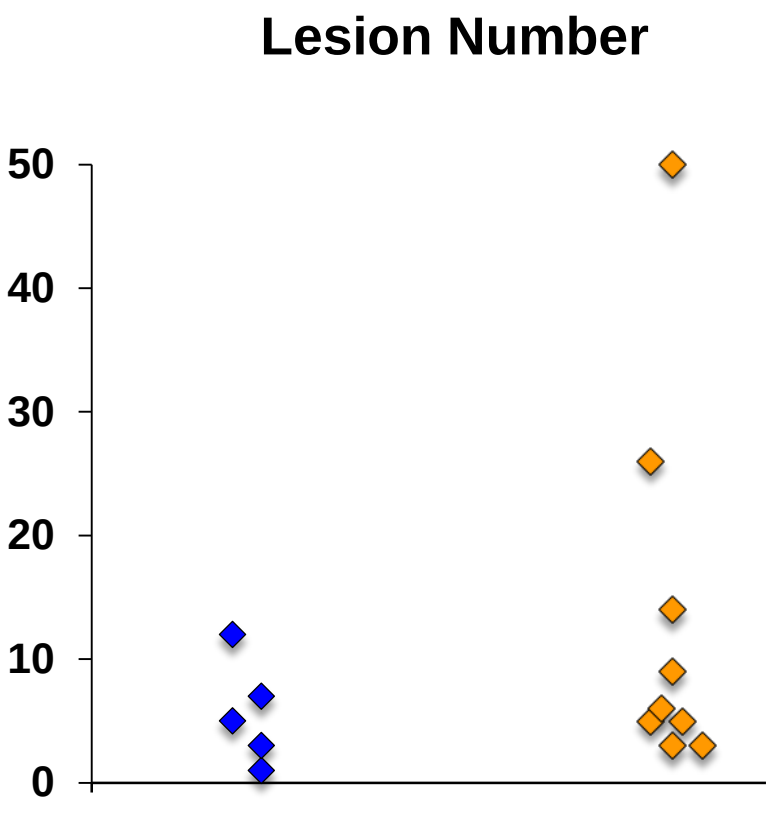
# Median New Lesion Volume by Territory (Analyzed ITT)

| Territory | Median New Lesion Volume, $mm^3$ [IQR] | | P-value† |
|---|---|---|---|
| | Test | Control | |
| **Protected** | **102.8** [37,423] | **178.0** [34,483] | 0.33 |
| **Partially Protected** | **69.2** [0,269] | **59.0** [0,229] | 0.73 |
| **Unprotected** | **0** [0,53] | **0** [0,0] | 0.20 |
| **All** | **294.0** [69,786] | **309.8** [100,886] | 0.81 |

† Wilcoxon Test

# Total Lesion Number and Volume for Patients with Stroke in All Territories

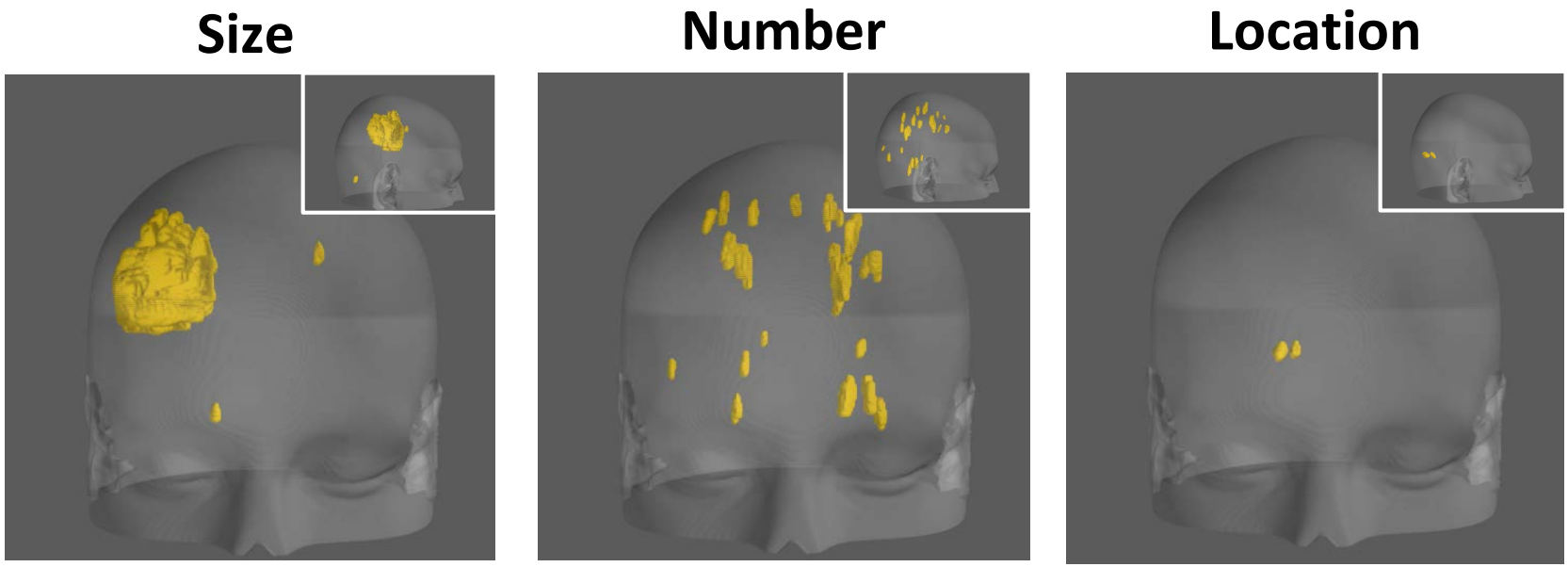



| | Test (Sentinel) N=5 | Control (No protection) N=9 | Test (Sentinel) N=5 | Control (No Protection) N=9 |
|---|---|---|---|---|
| [min, max] | [81, 487] | [134, 24300] | [1, 12] | [3, 50] |

# Renderings of 2-7 day DW-MRI Scans in Control Patients

- In stroke patients, lesion size, number, and location are ALL important




3D renderings of 2-7d DW-MRI scans from 3 control stroke patients

# Post Hoc Analysis of RCTs
# Meta-Analysis of Effectiveness

# Comparison of CLEAN-TAVI vs. SENTINEL Outcomes

- Test arm results consistent in both studies

| Protected Territories | Mean New Lesion Volume, $mm^3$ (Coefficient of Variation) | | Mean % Reduction |
|---|---|---|---|
| | Test | Control | |
| CLEAN-TAVI[1] | 474 (172%) | 1030 (235%) | 54% |
| SENTINEL | 413 (190%) | 696 (363%) | 41% |

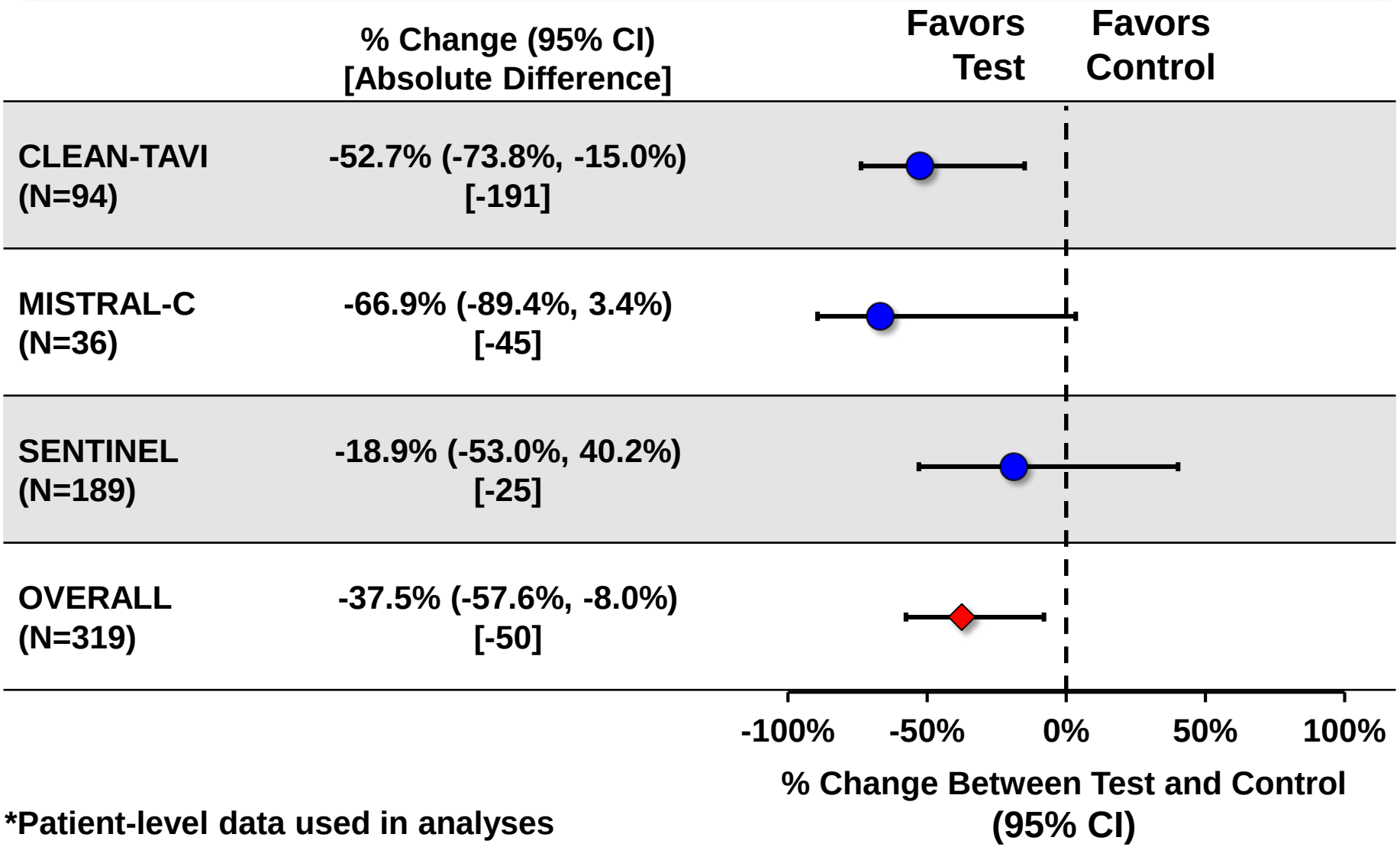
- SENTINEL underpowered due to:
  - Observed lower new lesion volumes in the control arm
  - Higher variability in control vs design assumptions

[1] Raw mean calculated and used in the SENTINEL protocol

# Trials Available for Meta-Analysis of Effectiveness

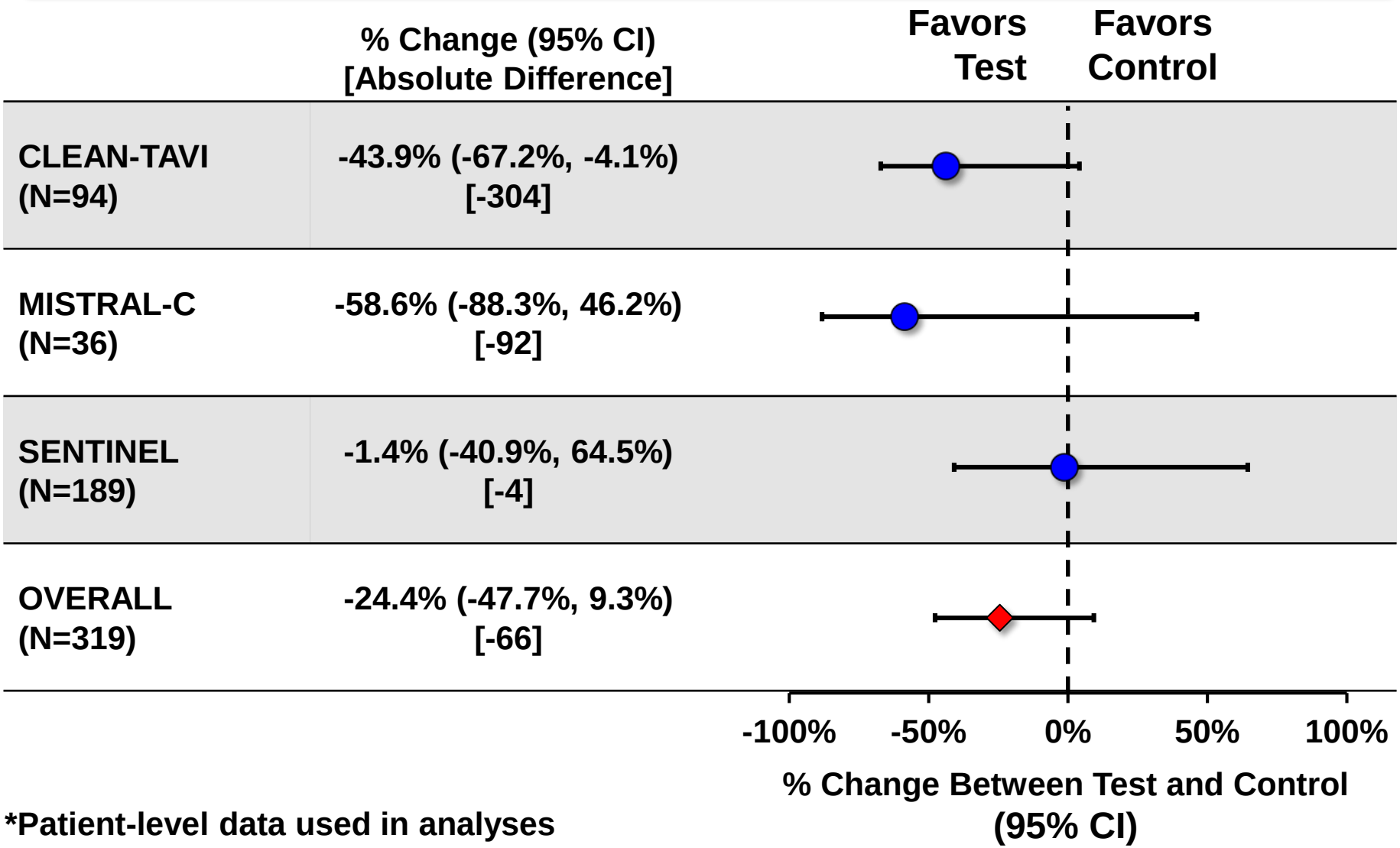
| | CLEAN-TAVI | MISTRAL-C | SENTINEL |
|---|---|---|---|
| Single Blind | Yes | Yes | Yes |
| Randomized 1:1 | Yes | Yes | Yes |
| Independent core lab analysis of DW-MRI | Yes | Yes | Yes |
| Study Sites | 1 Site<br>EU | 4 Sites<br>EU | 19 Sites<br>US & Europe |
| Valve Type(s) | CoreValve | CoreValve<br>SAPIEN 3<br>SAPIEN XT | CoreValve<br>SAPIEN 3<br>SAPIEN XT<br>Evolut R |
| Number of Patients with DW-MRI data | 94 | 37 | 189 |

# Meta-Analysis of Effectiveness* Change in Mean New Lesion Volumes (Protected Territories)




*Patient-level data used in analyses

# Meta-Analysis of Effectiveness* Change in Mean New Lesion Volumes (All Territories)




*Patient-level data used in analyses

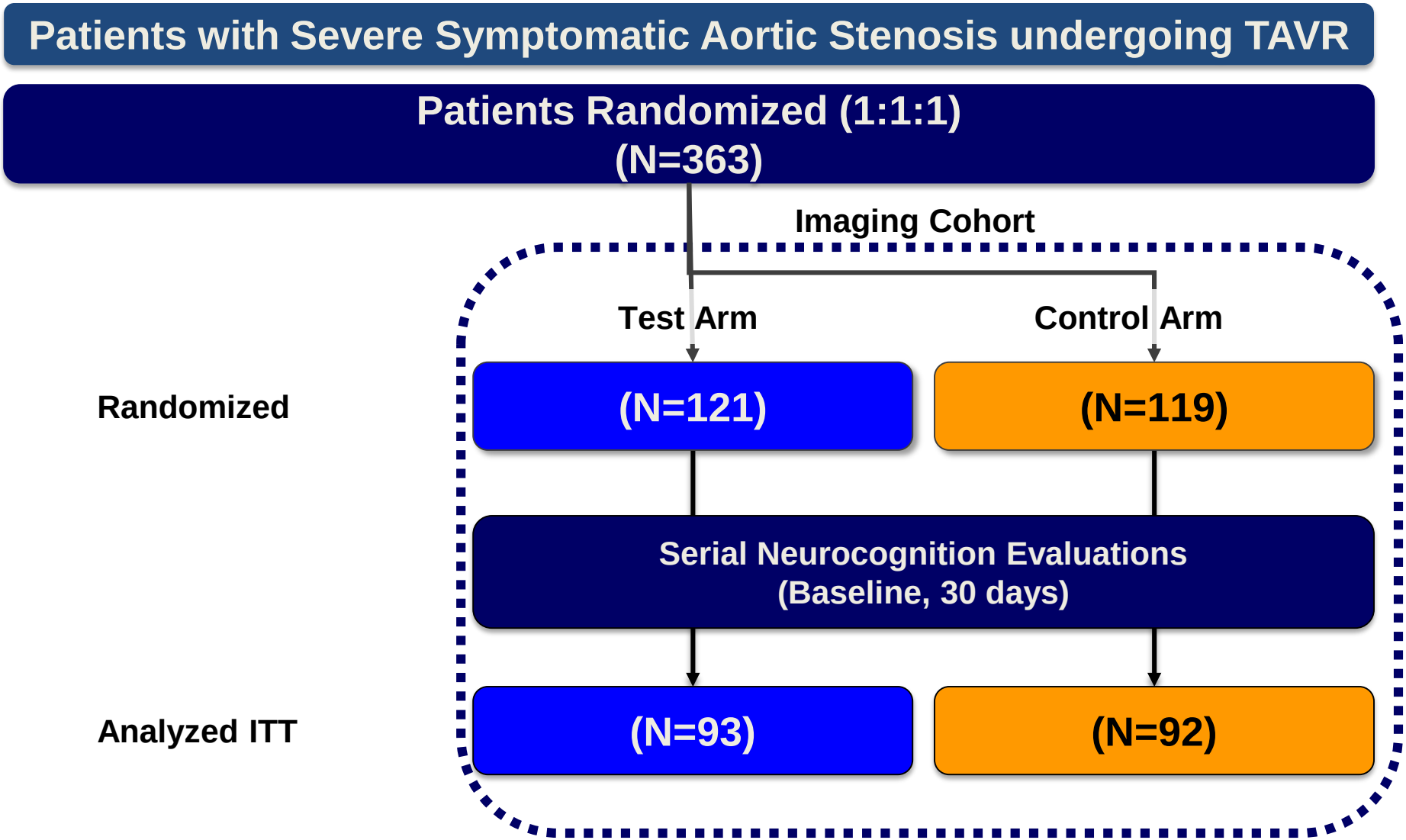
# Neurocognitive Sub-Study

# Methodology

| Domain | Neurocognitive Test |
|---|---|
| Attention | Digit Span<br>Trail Making Part A |
| Verbal Memory | Hopkins Verbal Learning Test |
| Visual Memory | Brief Visual Memory Test |
| Executive Function | Letter Number Sequencing<br>Trail Making Part B<br>Rey Complex Figure Test (Copy) |
| Processing Speed | Digit Symbol<br>Controlled Oral Word Association |

Corrected for the Covariates of Mental Status and Depression

# SENTINEL Trial Design Overview Neurocognition Sub-study



# Primary Outcome: Z-score Change at 30 Days (ITT)

| | Sentinel | | |
|---|---|---|---|
| | Test (N=93) | Control (N=92) | P-value* |
| Composite Z-Score | -0.09 ± 0.44 | -0.03 ± 0.37 | 0.42 |
| **Components of Z-Score** | | | |
| Attention | 0.14 ± 0.51 | 0.03 ± 0.55 | 0.18 |
| Executive Function | 0.25 ± 0.86 | 0.14 ± 0.86 | 0.47 |
| Processing Speed | 0.12 ± 0.39 | 0.14 ± 0.43 | 0.55 |
| Verbal Memory | -0.32 ± 0.8 | -0.28 ± 0.85 | 0.46 |
| Visual Memory | -0.36 ± 0.79 | -0.46 ± 0.91 | 0.43 |

*Data presented as Mean ± SD, model adjusted for education and baseline Geriatric Depression Score and baseline Mini Mental State Score.

# SENTINEL Trial Effectiveness Summary

- Primary Effectiveness – Median New Lesion Volume (Protected Territories)
  - Observed treatment effect ≥ 30% – Achieved
  - Test vs. Control – not achieved
- Meta analysis (3 RCTs) provides additional evidence of effectiveness

# SENTINEL Results in the Context of Neuroprotection History

**William A. Gray, MD**

System Chief of the Division of Cardiovascular Disease

Main Line Health

# Accessory Devices: Catheter-based Filters Used in Carotid Artery Stenting Are Similar to Sentinel

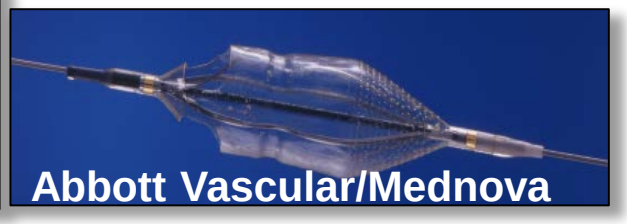
**Common Features**

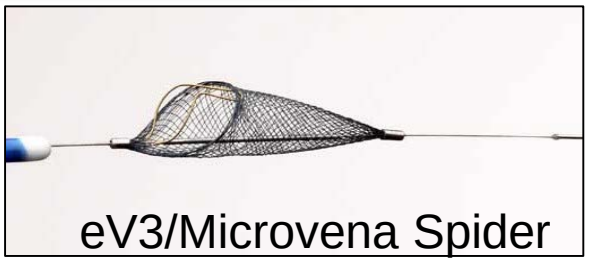
**Pores ~100-140m**

**Atraumatic wire frames for centering and sealing**

**Deployed over a 0.014” wire from a collapsed state**




# SENTINEL: First RCT in Filter Embolic Protection

- Evaluation metrics are not established
  - Low incidence of clinical endpoints (e.g., stroke) limits their utility
  - DW-MRI surrogate is therefore valuable, but still being refined (timing, effect of pre-existing abnormalities, etc.)
  - DW-MRI lesions – relevancy of volume vs number vs location not established
- Expected treatment effect of DW-MRI surrogate not established or clinically validated

# Filters Used in Sentinel and Carotid Artery Stenting Are Safe

- Vascular trauma from filter embolic protection in CAS is rare
- Similarly there was no filter-related vascular trauma reported in SENTINEL
  - Finding is consistent with parallels in filter construction
- Dwell times are short

# Both CAS and TAVR EPD Capture Significant Amounts of Liberated Debris

# 57% Debris Collected in CAS EPD: ARCHeR Study

- Types of embolic material collected by filters
  - Foam cells
  - Smooth muscle cells
  - Cholesterol
  - Collagen/elastin
  - Platelet/fibrin

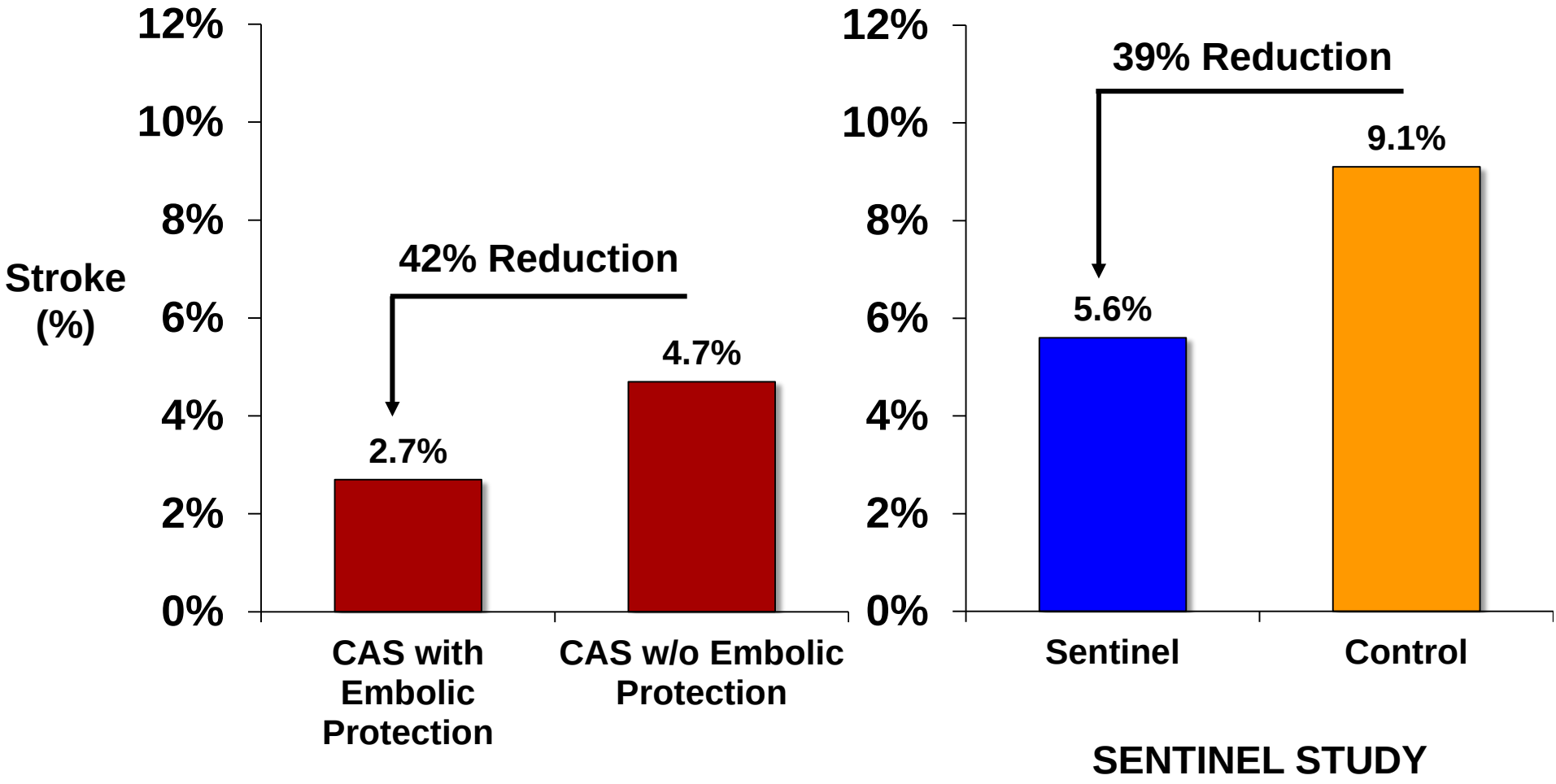
***57% of samples contained embolic material***

# Analysis of Particles Collected Per Filter in ARCHeR and in SENTINEL

| Filter Type | | French Size | Debris Captured % | ≥20 Particles Per Patient % |
|---|---|---|---|---|
| RX Accunet |  | 6 Fr | 57%[1] | 24%[1] |
| Sentinel |  | 6 Fr | 99% | 53% |

[1]Gray W A et. al. J Vasc Surg 2006,;44:258-69

# EPD with Both CAS and TAVR Demonstrate Similar Stroke Reduction




Adapted from Garg, et al. (2009). Neuroprotection and Stroke, Endovascular Thoracic: 16: 412-427

# The Impact of Device Approval

- Carotid artery stent coupled with EPD approval in US in 2004
- Approval led to significant increase in use of protected carotid artery stenting
  - 5,000 to 75,000
  - 50% decrease in overall complication rates after device approval
- Improvements likely secondary to
  - Widespread EPD availability
  - Refinements in patient selection and technique

# Summary: 5 Perspectives

- SENTINEL is the first pivotal multicenter US IDE study to isolate EPD neuroprotective procedural and outcomes
- SENTINEL safety profile is consistent with prior carotid artery (CAS) EPD studies
- Similar to carotid EPD, SENTINEL filter collection resulted in a high percentage of debris capture
- Incorporation of Sentinel into TAVR resulted in stroke reduction similar to that seen after adoption of carotid stenting embolic protection
- Further outcome improvements possible once TAVR EPD is broadly available

# Concluding Remarks

**Azin Parhizgar, PhD**

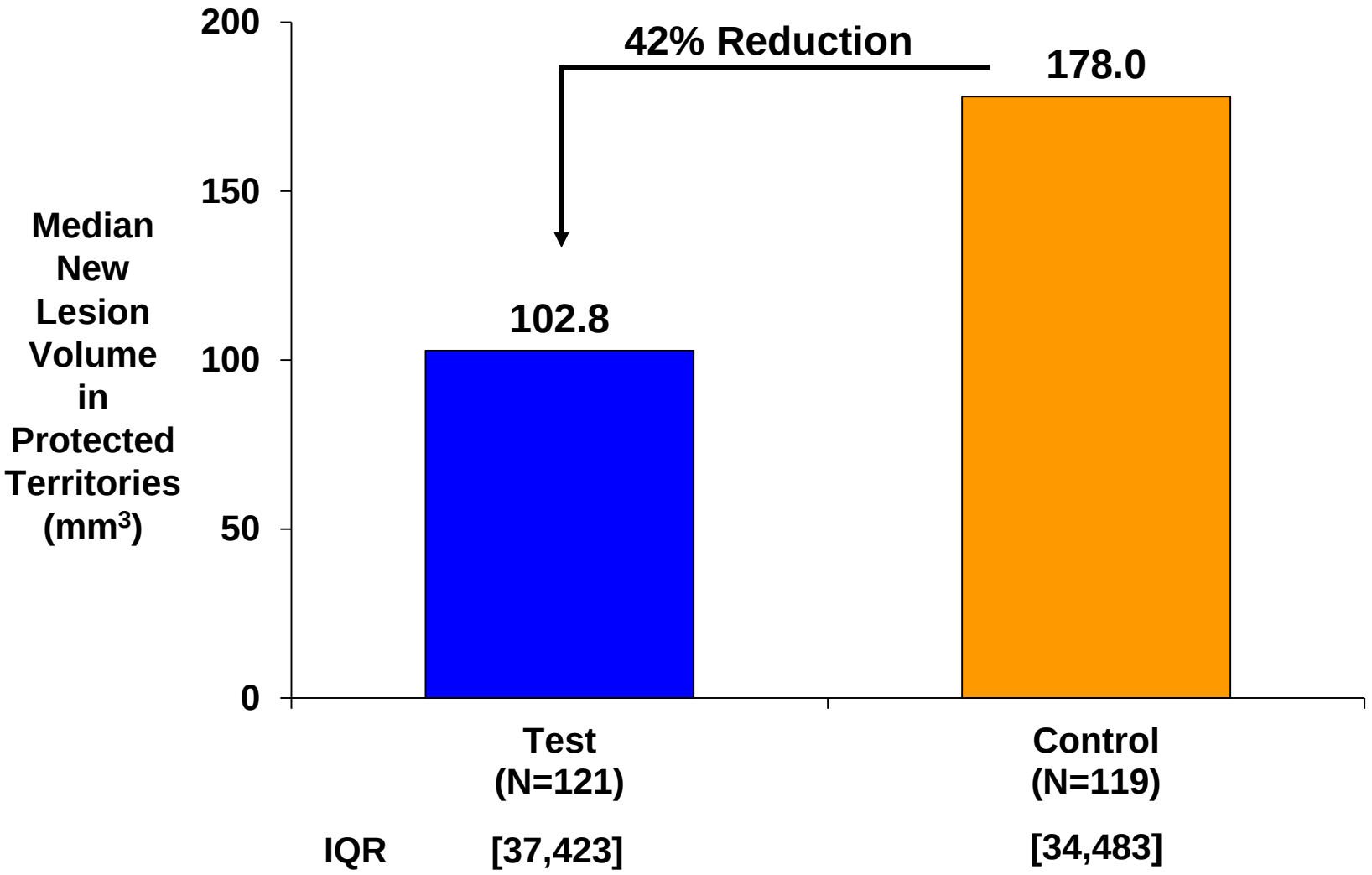
President and Chief Executive Officer

Claret Medical, Inc.

# Company Perspective

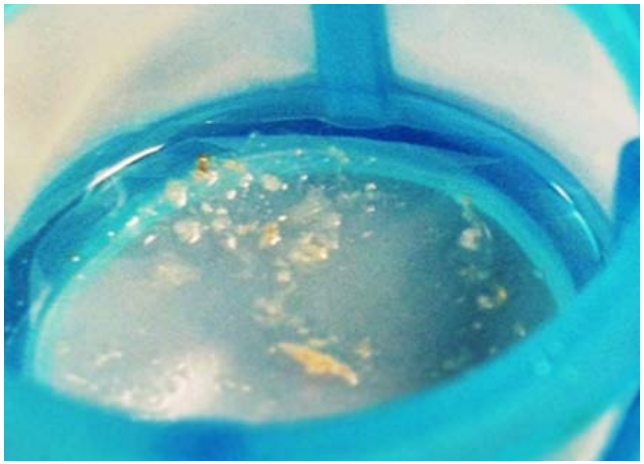
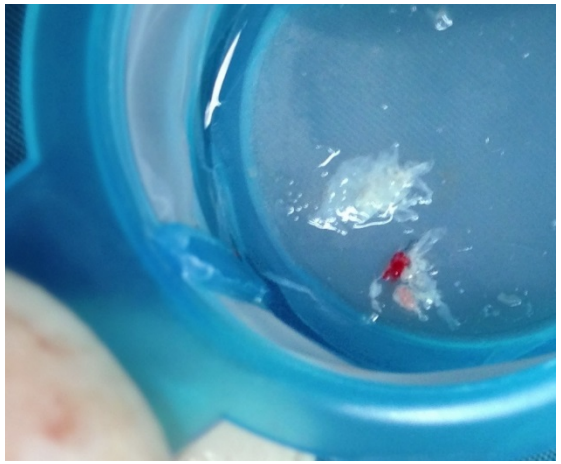
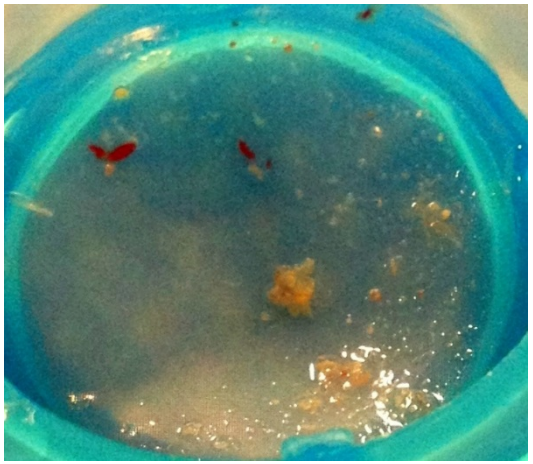
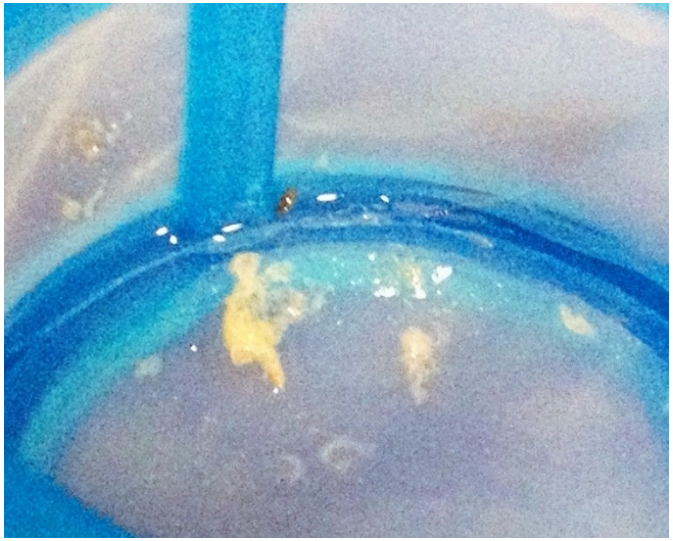
- Claret focused on developing best cerebral protection device to protect from acute embolic ischemic injury or stroke
- 4-year commercial history outside US
- SENTINEL: first US/EU, multicenter, randomized, controlled EPD trial
- Provides safety in a rapidly evolving TAVR field

# Effectiveness Endpoint Success Criteria: ITT New Lesion Volume in Protected Territories



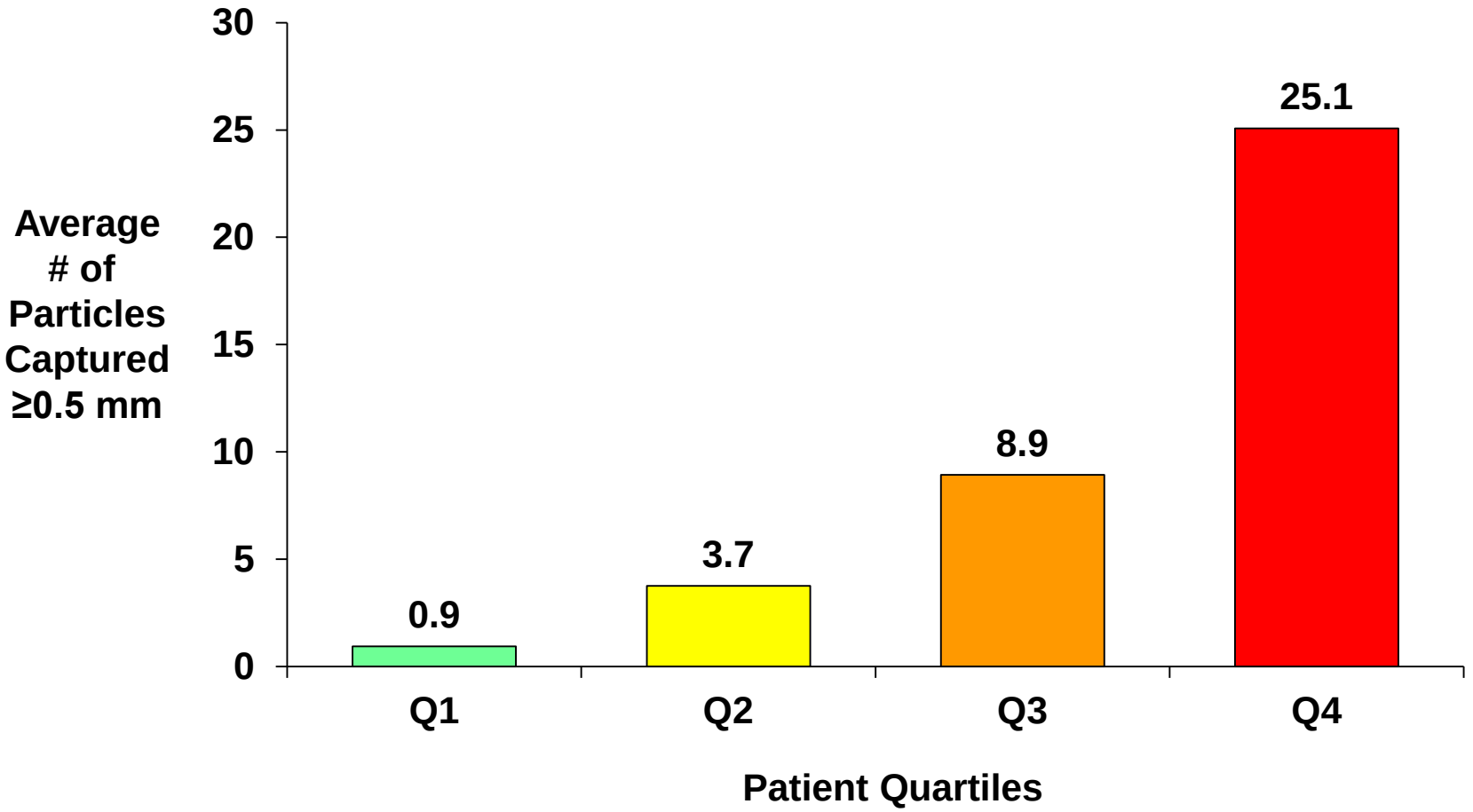

Analyzed ITT

# Sentinel Debris Type

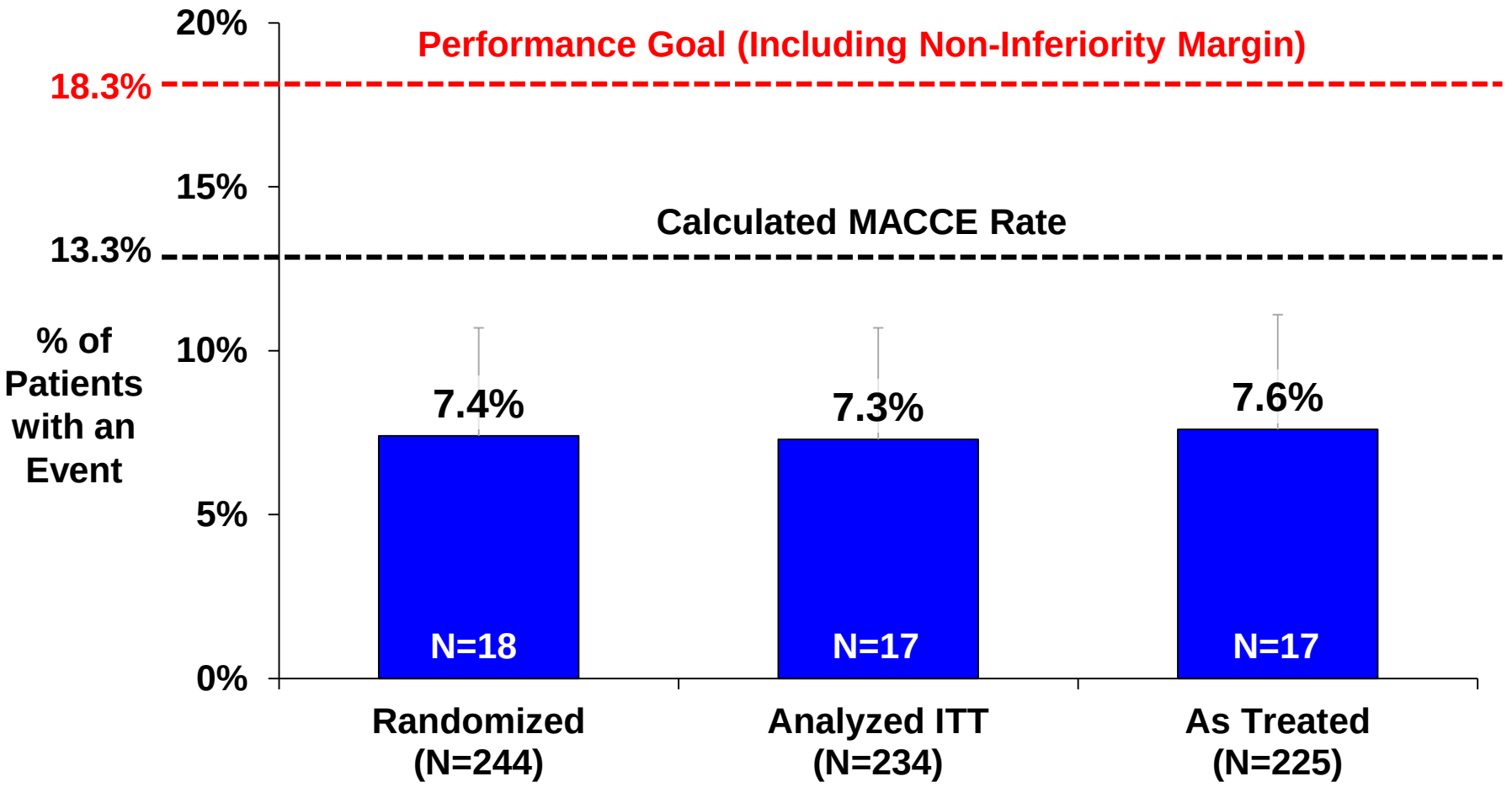






# Patient Quartile Analysis: Average Number of Particles ≥0.5 mm

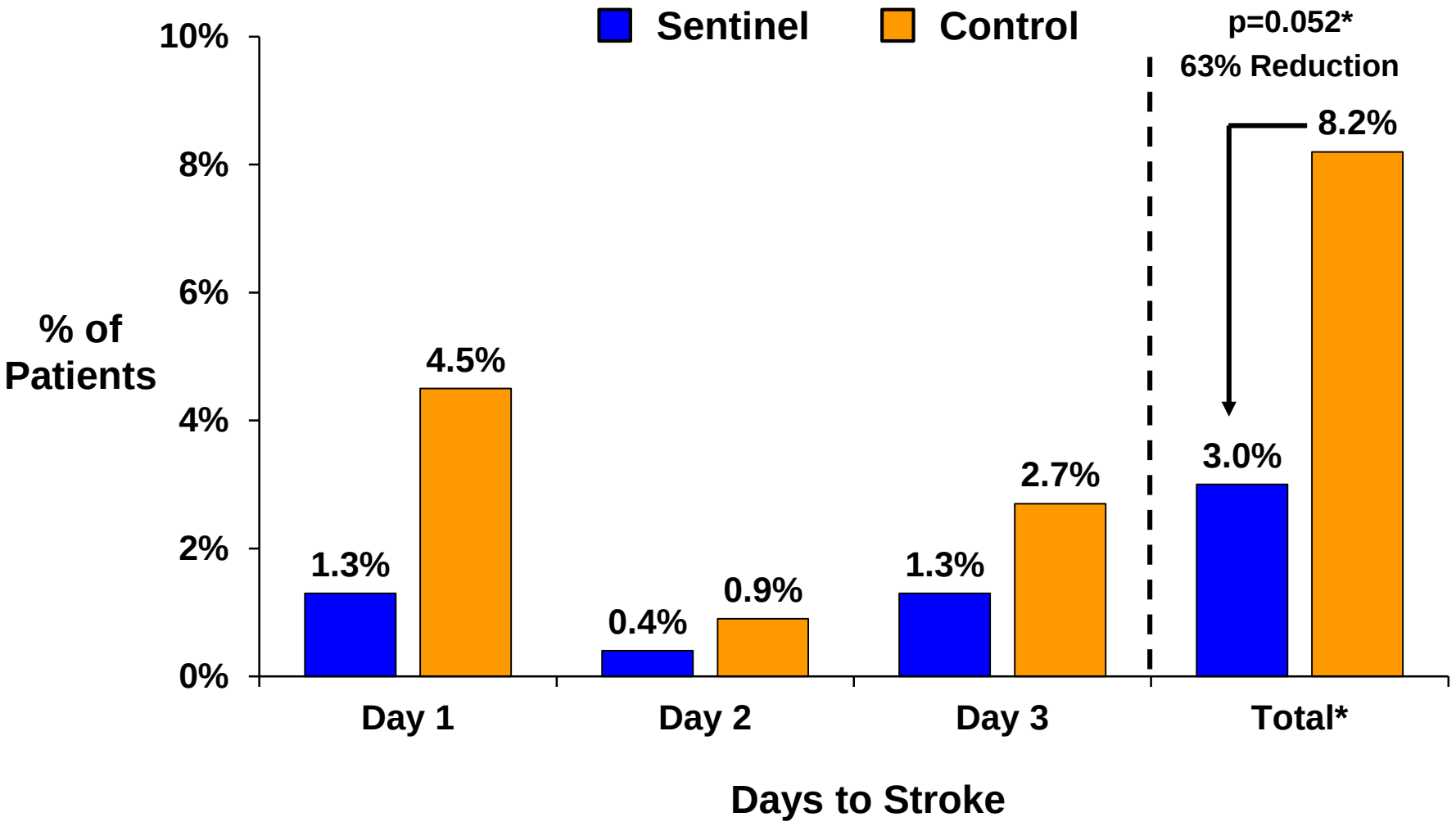
## 1 in 4 Patients had 25 Particles ≥0.5 mm in Size



# Primary Safety Endpoint Met (30-Day MACCE)



# Stroke Diagnosis ≤72 hours (ITT)




*Fisher Exact Test

# Summary

- Sentinel
  - is safe, with minimal complications, injury or disruption of the TAVR workflow
  - performs as intended
  - reduced the peri-procedural stroke rate compared to control (3% vs 8.2%)
  - yields an observed treatment of effect of 42%
  - captures a wide spectrum of emboli destined for the brain in 99% of the patients

# Post-approval Training Program

- Committed to comprehensive training
- Sentinel safety and technical success demonstrated that IDE training was effective
- Elements of training program to mimic IDE study:
  - Comprehensive didactic training
  - Hands on learning with anatomical model
  - Proctor up to 5 cases at each site

# Post-Market Surveillance Recommendations

- Close collaboration with FDA in formulating an effective PMS program to ensure a safe commercial roll out
- Program to include:
  - Post-market registry
    - Collect additional data in a real-world setting
    - A registry or TVT module

# Sentinel® Cerebral Protection System During TAVR

February 23, 2017

Claret Medical, Inc.

Circulatory System Devices Panel