510(k) Submission for TriGUARD 3™ Cerebral Embolic Protection Device

To minimize risk of cerebral damage by deflecting embolic debris away from the cerebral circulation during TAVR

Circulatory System Devices Panel

Keystone Heart

August 3, 2021

Introduction

Karen Jaffe, MS, MBA, RAC

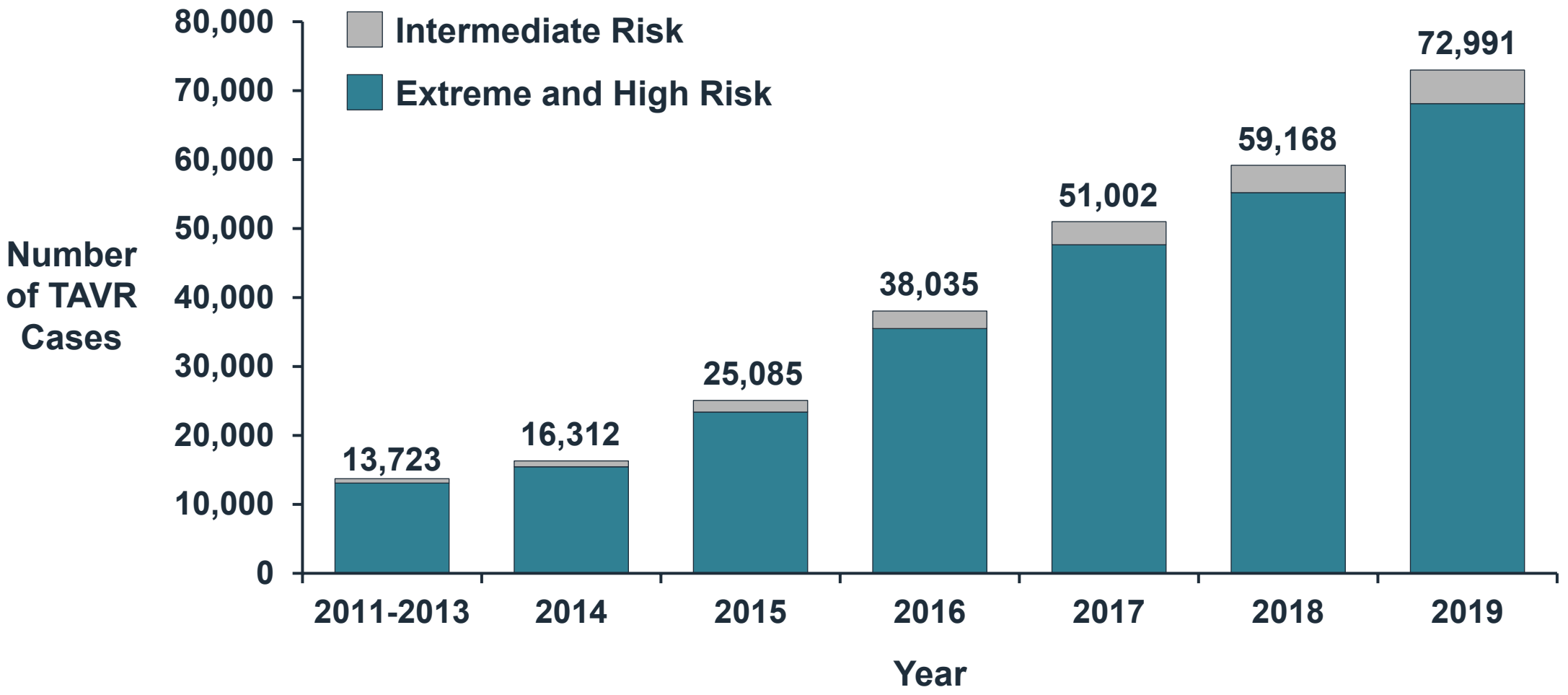
Regulatory Consultant

Keystone Heart

TriGUARD 3 Substantially Equivalent to Legally Marketed Predicate Device, Sentinel

- Clearance for TriGUARD 3 is based on 510(k) pathway
- TriGUARD 3 met primary safety endpoint
  - Minimal additional risks as accessory device to TAVR
- TriGUARD 3 deflects embolic debris from entering brain
- TriGUARD 3 is substantially equivalent to Sentinel device
  - Met all 510(k) Special Controls

TAVR has Become Standard of Care and Volume is Increasing



Carroll, 2020

Minimizing Adverse Events Related to TAVR Continues to be High Priority

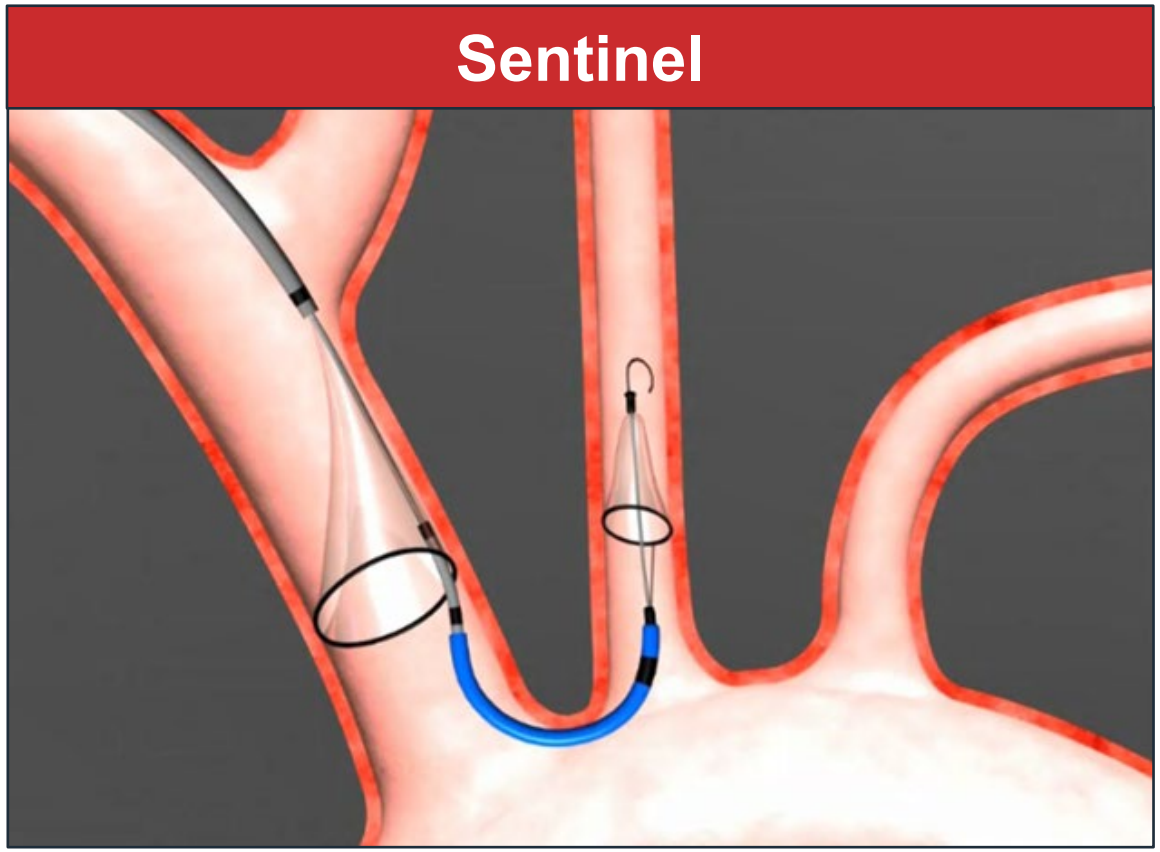
- Risk of TAVR is embolic material being dislodged during procedure traveling to cerebral circulation[1]
- 94% of patients will develop new brain lesions post TAVR[2]
- Stroke remains a significant risk for patients undergoing TAVR

1. Knipp 2008; Lund 2005; Restrepo 2002; Schwarz 2011; Vermeer 2003a; Vermeer 2003b
2. Claret Medical 2017

Cerebral Embolic Protection Systems are Accessory Devices for TAVR

- Minimize risk of brain damage by filtering blood entering cerebral circulation during TAVR
- Clinical need for cerebral embolic protection systems increases as number of TAVR procedures increase
- Majority of catheter-based innovations leverage transfemoral approach due to anatomical access and improved safety

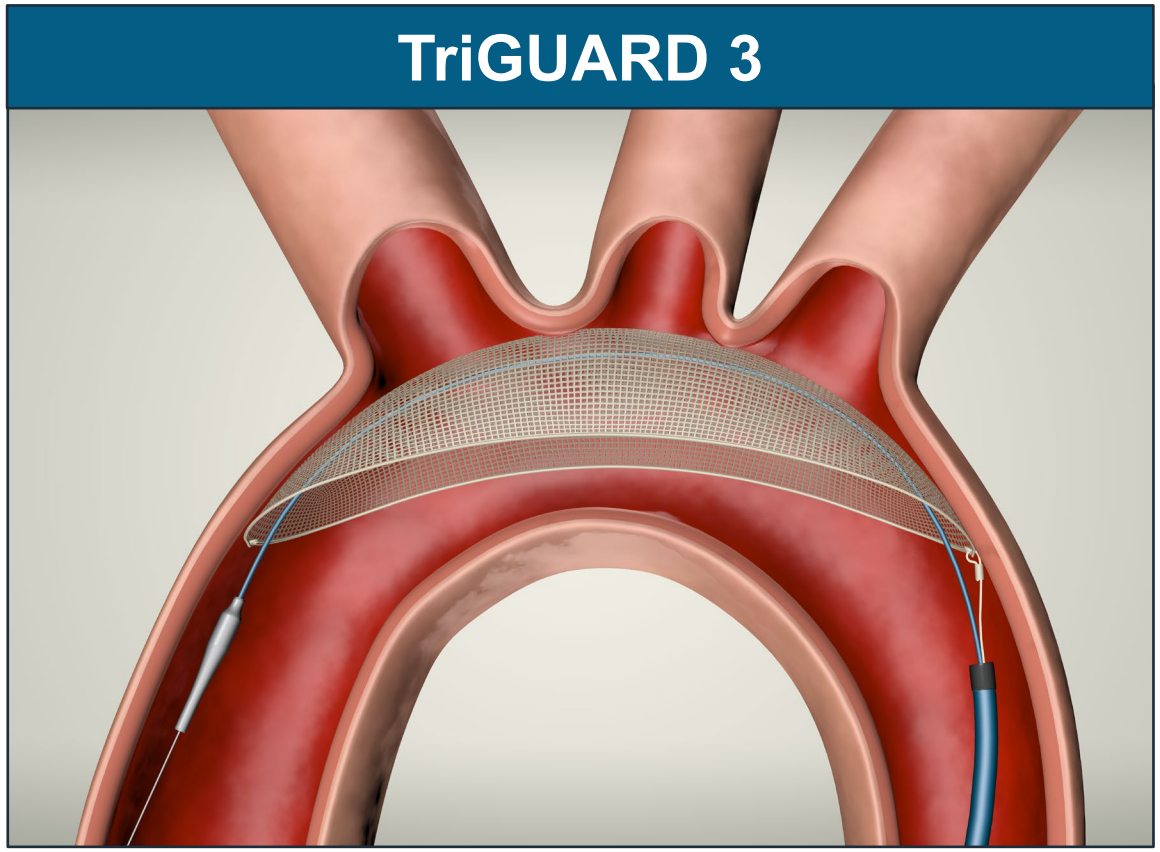
Sentinel is Only Cerebral Protection Device Available in US



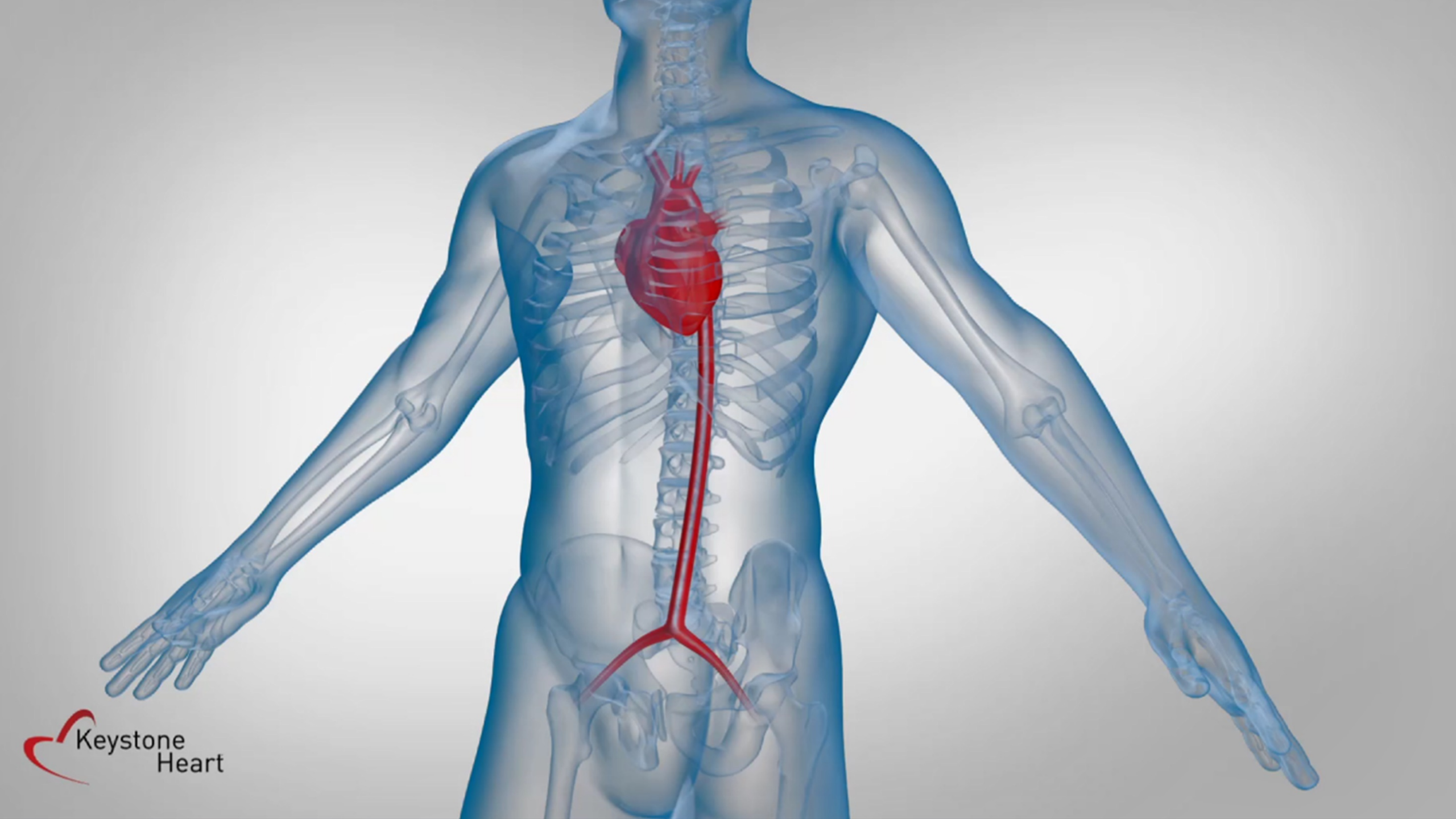
- Introduced via 3rd access site
- Captures and removes particles
- 2-vessel coverage
- 1 in 3 patients not eligible to receive Sentinel based on approved indication[1]
  - Brachiocephalic trunk (9 - 15 mm)
  - Left common carotid (6.5 - 10 mm)
- Requires manipulation of cerebral vessels during placement

1. Voss, 2020

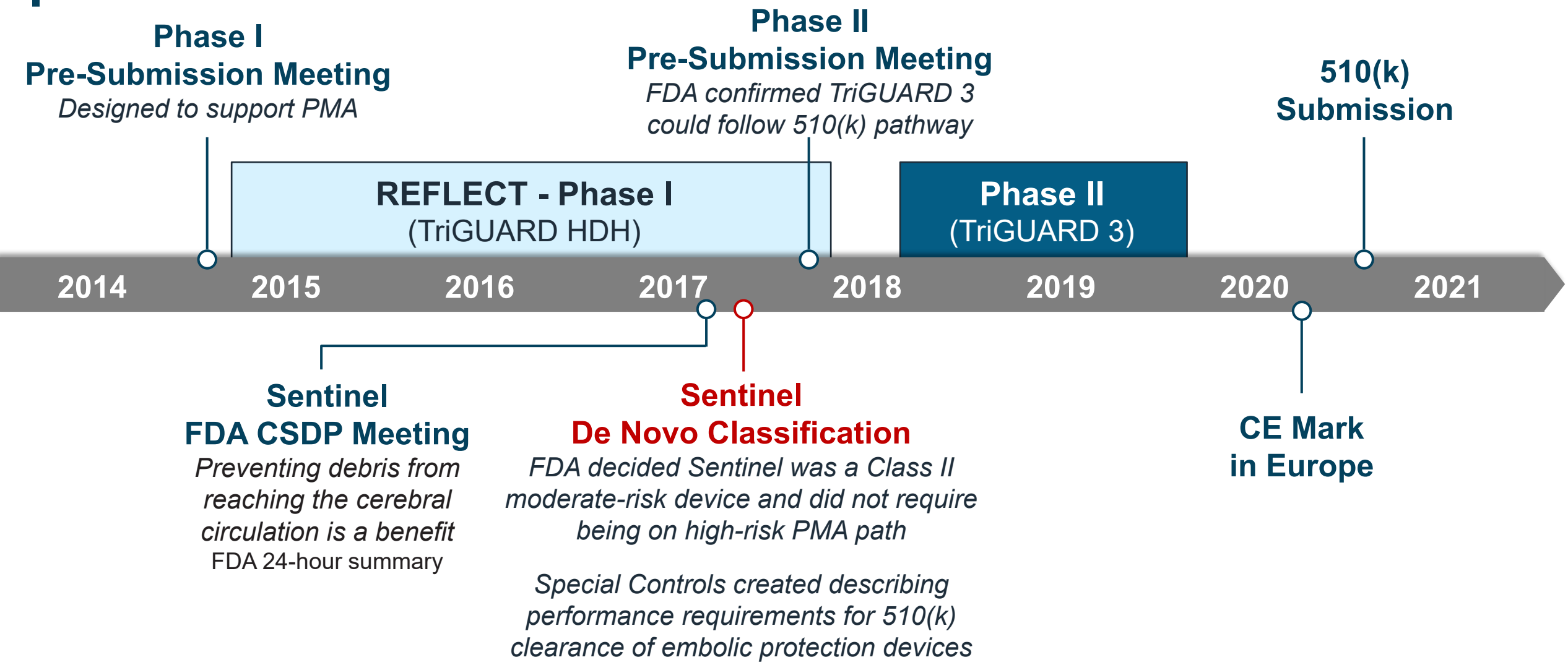
TriGUARD 3 is an Accessory Device for TAVR Procedures



- Protects all 3 cerebral branches of aortic arch
- Deflects embolic debris away from cerebral circulation
- No vessel size limitations
- Same femoral artery access point as pigtail catheter for TAVR procedure
  - No manipulation of cerebral vessels

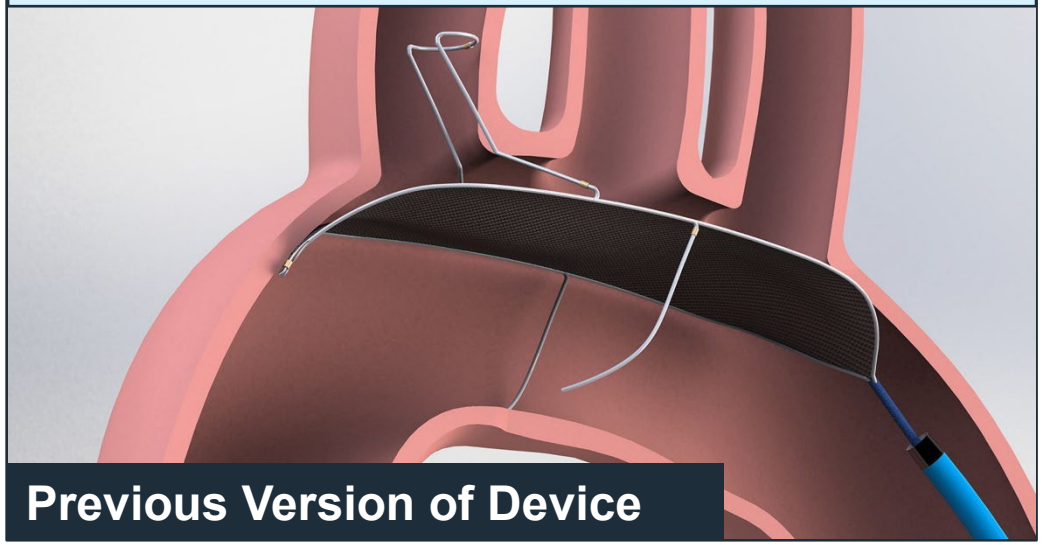

Keystone
Heart

Regulatory Requirements for TriGUARD 3 Evolved Throughout Development Program



Phase I Evaluated Completely Different TriGUARD Device; Primary Safety Endpoint Met

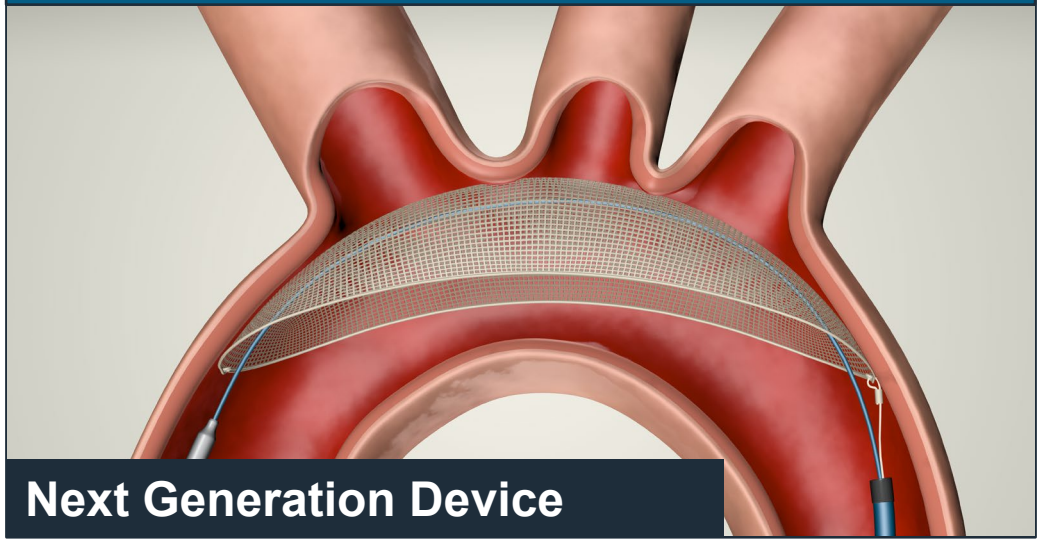
REFLECT - Phase I (TriGUARD HDH)



Previous Version of Device

- Primary safety endpoint met
- Benefit of 3-vessel coverage
- Suspended due to 1) conditional powering, 2) potential outcomes, and 3) availability of TriGUARD 3

REFLECT - Phase II (TriGUARD 3)



Next Generation Device

- TriGUARD 3 is next generation device with improved useability
- ***Only*** device under review today
- Substantially equivalent as predicate and meets 510(k) clearance standard

Agenda

510(k) Pathway	**Mark DuVal, JD, FRAPS** Legal/Regulatory Counsel DuVal and Associates
REFLECT - Phase II Design and Safety Results	**Jeff Moses, MD** Interventional Cardiologist Columbia Medical Center
REFLECT - Phase II Effectiveness Results	**Rahul Sharma, MD, MBBS, FRACP** Clinical Associate Professor Stanford Medical Center
Substantial Equivalence	**Karen Jaffe, MS, MBA, RAC** Regulatory Consultant Keystone Heart
Real-World Evidence	**Pieter Stella, MD, PhD** Associate Professor Utrecht Medical Center, The Netherlands
FDA Questions	**Karen Jaffe, MS, MBA, RAC**

Additional Experts

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Understanding the 510(k) Pathway

Mark DuVal, JD, FRAPS

Legal/Regulatory Counsel

President & CEO

DuVal and Associates

510(k) is Based on a Comparison, PMA is Not Based on a Comparison

PMA

- Class III, high-risk devices
- Most stringent device marketing application
- Safety and effectiveness proven in an absolute and independent sense

510(k)

- Class II, moderate-risk devices
- A standard dependent upon and compared to predicate
- “Substantially equivalent” to predicate

- FDA confirmed that 510(k) pathway is appropriate for TriGUARD 3 and that Sentinel is appropriate predicate

Sentinel De Novo Classification Created a New Predicate and Added Special Controls

- De Novo granted for Sentinel in 2017
  - Classification regulation (21 CFR 870.1251), product code (PUM), and Special Controls created
  - Allows future devices to use Sentinel as predicate
- Special Controls define performance standards for devices claiming Sentinel as predicate
- 510(k) program and Special Controls intended to streamline and simplify review of subsequent devices

Special Controls Create Additional Requirements for Devices on 510(k) Pathway

- Subject devices must meet
  1. Definitional requirements for substantial equivalence
  2. Special Controls (performance standards)
- Establish types of data required

Clinical Performance Special Controls for Cerebral Protection Devices

I. The ability to safely deliver, deploy, and remove the device
II. The ability of the device to filter embolic material while not impeding blood flow
III. Secure positioning and stability of the position throughout the transcatheter intracardiac procedure
IV. Evaluation of all adverse events including death, stroke, and vascular injury

Special Controls Can Be Met Based on a Variety of Data

- Sponsor's study, including post-hoc analyses
- Comparison to predicate's data
- Medical literature as an historical control
- "Valid scientific evidence" a statutory and regulatory standard including:
  - "…*well-documented case histories conducted by qualified experts, reports of significant human experience with a marketed device*…". 21 CFR 860.7(c)(2)
- Real world evidence is valid scientific evidence

Finding "Substantial" Equivalence Uses a Flexible Approach

*"**A new device does not need to be identical** to the predicate device for it to be found substantially equivalent to the predicate device. In FDA's experience, **it is rare for a new device to be identical to a predicate device**. Given the diversity of technologies evaluated under this review standard, **this guidance adopts a flexible approach to determining "substantial equivalence" to accommodate evolving technology** while maintaining predictability and consistency to promote confidence among device developers, practitioners, and patients."*

The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] (July 28, 2014), Page 6.

FDA has agreed technological differences between TriGUARD 3 and Sentinel do not raise new questions of safety or effectiveness

Question Today is Whether TriGUARD 3 is "Substantially Equivalent" to Sentinel

- Meeting Special Controls is part of determination
- Safety and effectiveness of cerebral protection devices considered established by predicate, Sentinel device
  - New devices not required to re-prove safety and effectiveness
- Statute governs substantial equivalence determination
  - Not required to meet clinical trial endpoints
  - Not required to demonstrate benefit over control
  - Not required to have head-to-head data

REFLECT - Phase II Design and Safety Results

Jeff Moses, MD

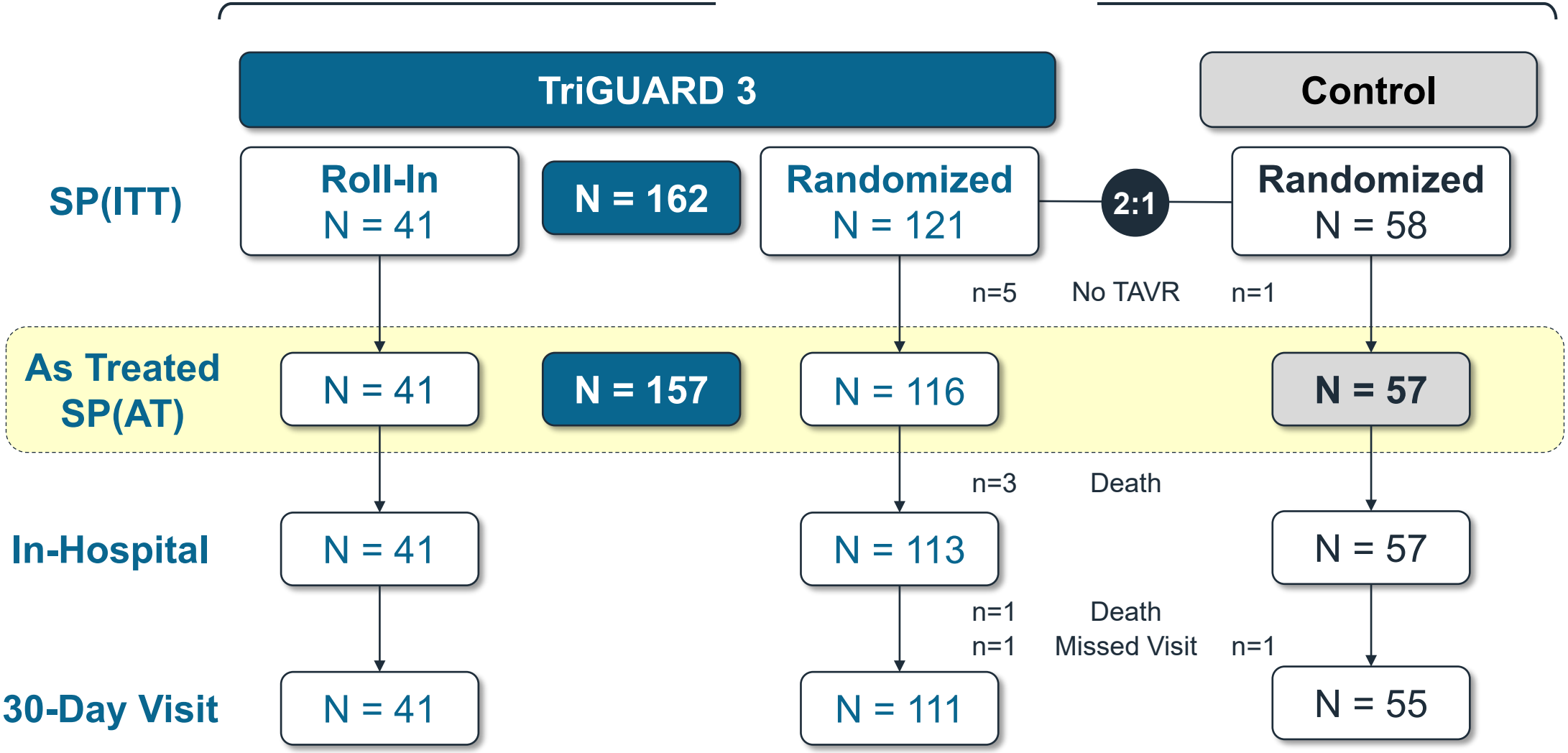
Interventional Cardiologist

Columbia Medical Center

Important Considerations for Cerebral Embolic Protection Device Trials

- Devices can only affect outcomes from delivery to removal
  - Safety events associated with device use occur **early**
- **30-day** safety endpoint recommended
  - Many events in large time window not related to device
  - Underscores importance of relatedness and temporal association
- Challenge to interpret differences in rates of infrequent events in studies with small sample sizes → lack of precision

REFLECT: Prospective, Single-Blind, Randomized, Multi-Center Trial



Primary Safety Endpoint Evaluated Composite of Clinical Events at 30 Days

REFLECT
▪ **All Death** ▪ **All Stroke** ▪ **Life-threatening/disabling bleeding** ▪ **Stage 2 AKI** ▪ **Stage 3 AKI** ▪ **Coronary artery obstruction** (intervention required) ▪ **Major vascular complication** ▪ **Valve related dysfunction** (repeat procedure required)

Performance Goal = 34.4%

34.4% Performance Goal Agreed Upon with FDA and Based on Historical Outcomes

- 25 studies in patients undergoing unprotected TAVR
  - 11,813 patients
  - Safety events reported via VARC-1 and VARC-2 definitions
  - 25% event rate
  - 37.5% relative margin
  - 9.4% absolute delta
- Performance Goal = 34.4% (25% event rate + 9.4% delta)

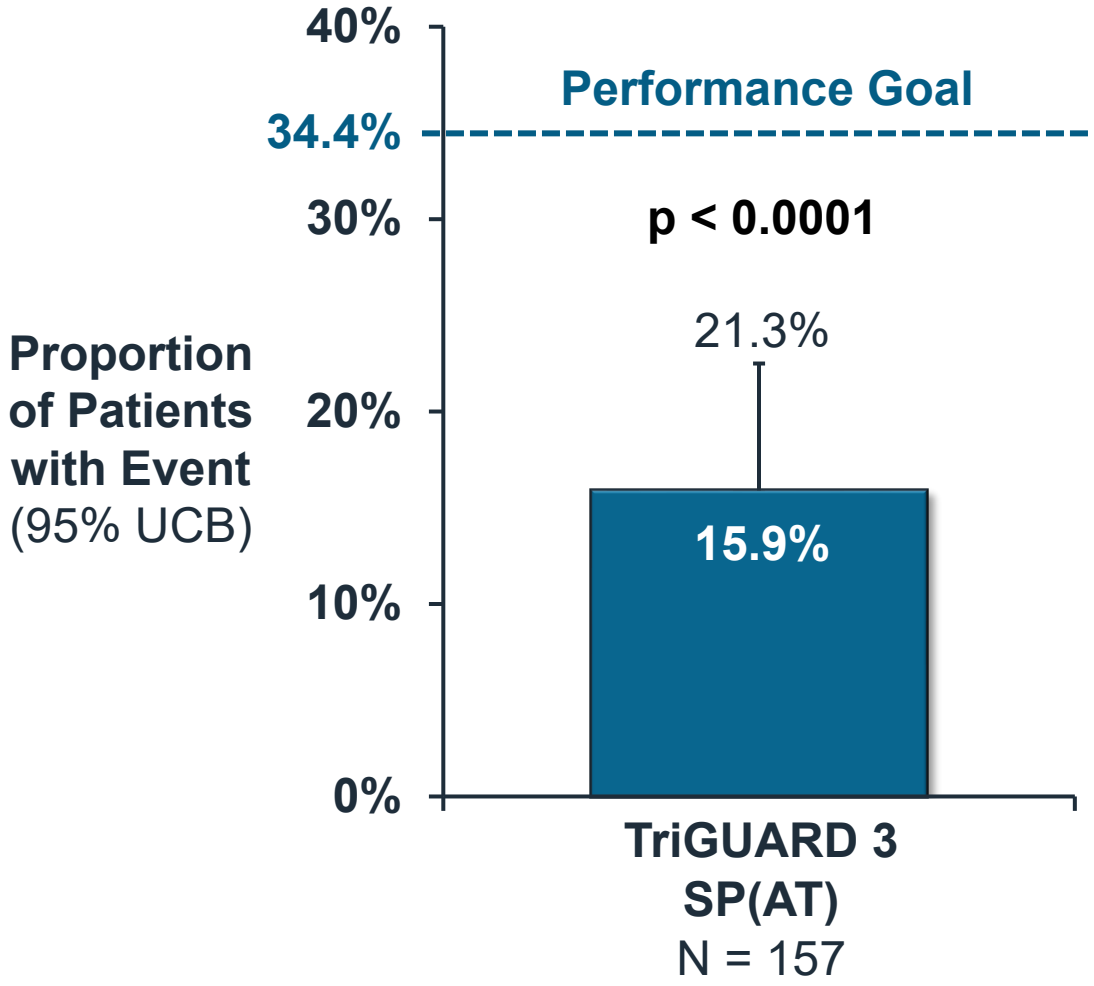
Secondary Safety Endpoints

- Primary safety endpoint components
- In-hospital procedural outcomes
- MACCE and MACCE components
- VARC-defined TAVR device success
- Assessment of neurologic events

REFLECT Enrolled Patients with Severe Symptomatic Aortic Stenosis

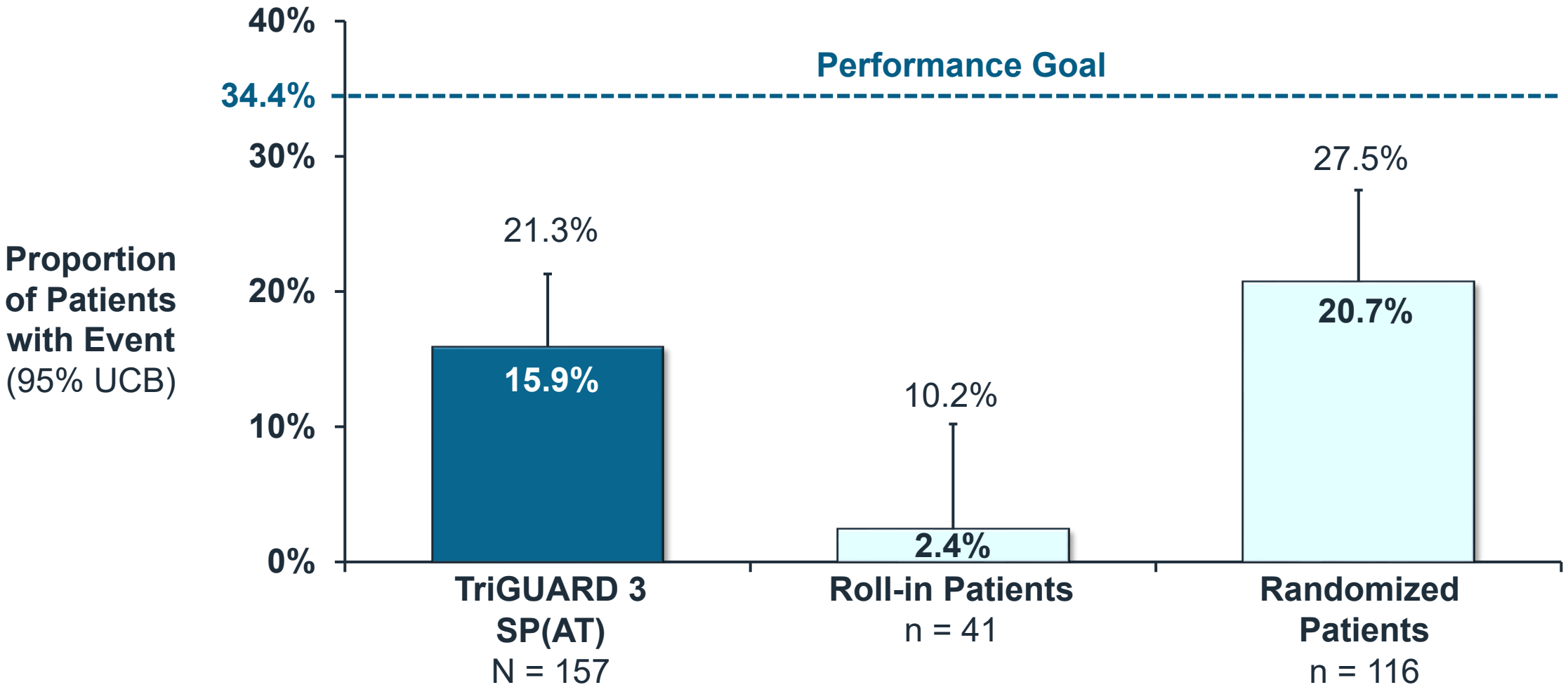
Preferred Term	TriGUARD 3 N = 157	Control N = 57
Age (years), Mean (SD)	**80.3** (7.7)	**78.1** (8.2)
Male	**55%**	**61%**
STS Score, Mean (SD)	**4.6** (2.8)	**4.5** (2.5)
Previous Stroke (CVA or TIA)	**17.2%**	**5.3%**
Diabetes	**39.1%**	**40.4%**
Insulin dependent	5.8%	10.5%
Diet-controlled	18.6%	7.0%
Prior atrial fibrillation	**28.0%**	**29.8%**
History of carotid artery disease	**19.9%**	**23.2%**
History of pulmonary vascular disease	**12.9%**	**19.3%**

TriGUARD 3 Met Primary Safety Endpoint; Significantly Lower Rate of Events at 30-Days



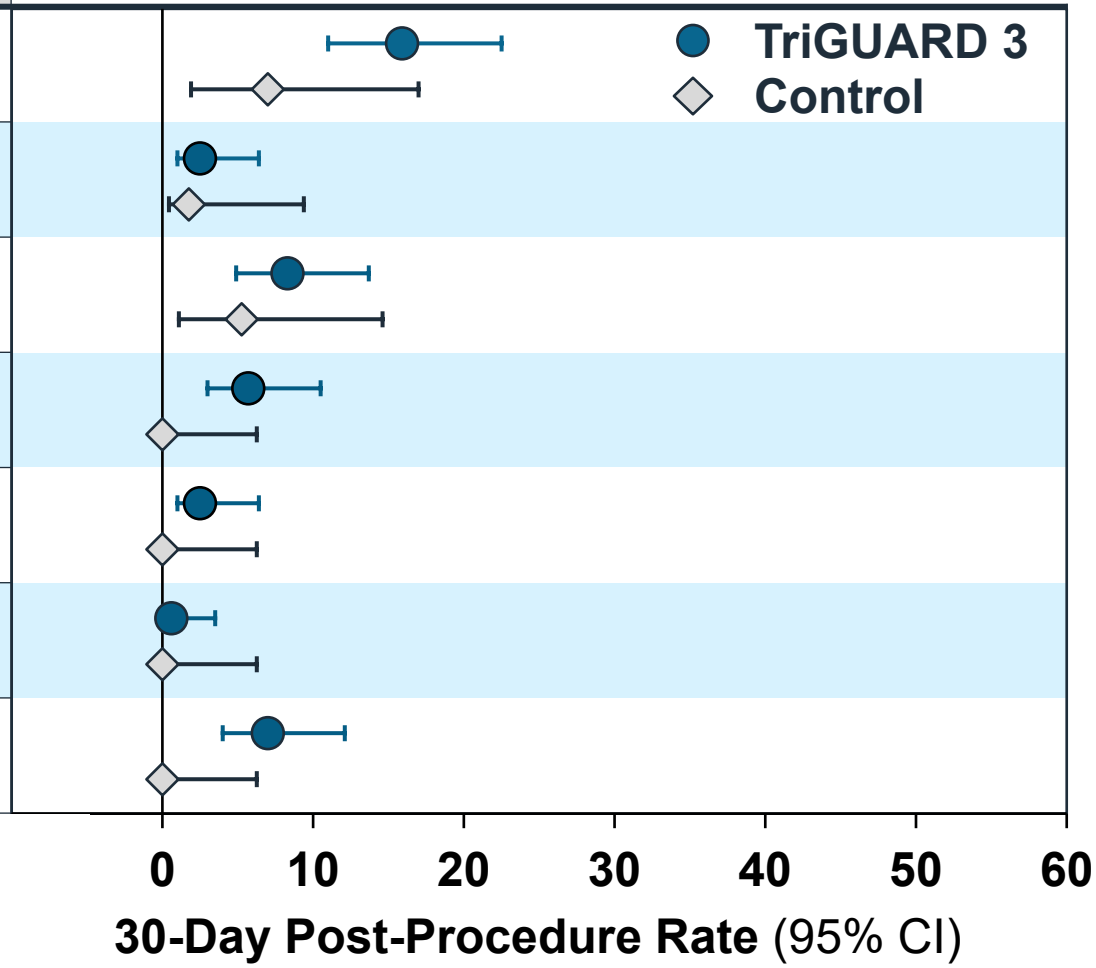
SP(AT)

SP(AT) Population Prespecified for Evaluation of Primary Safety Endpoint



Rate of Safety Events with TriGUARD 3 and Control Consistent with TAVR Procedure

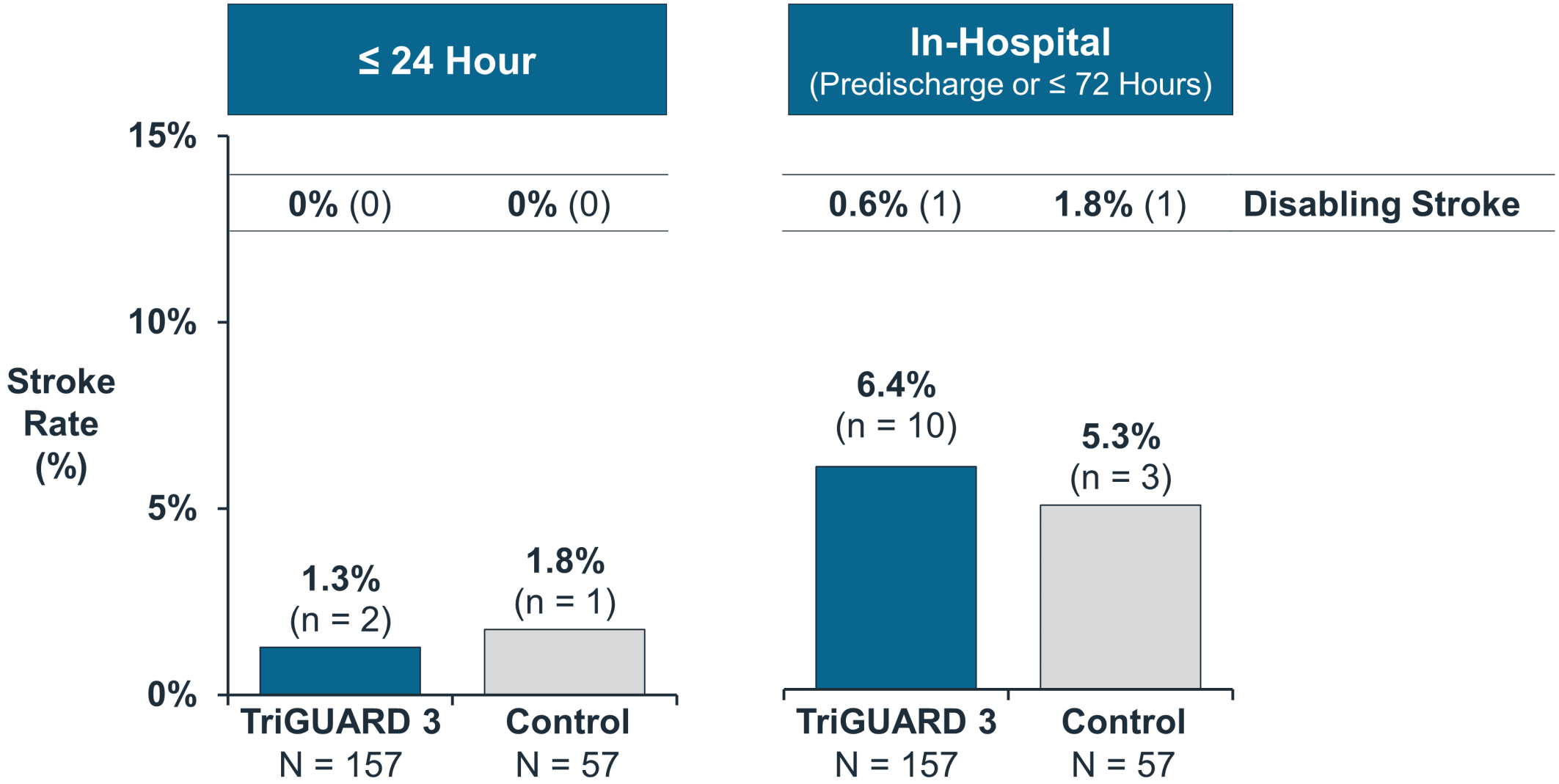
	TriGUARD 3 N = 157	Control N = 57
Combined Safety Endpoint	**15.9%** (25)	**7.0%** (4)
All-Cause Death	**2.5%** (4)	**1.8%** (1)
All Stroke	**8.3%** (13)	**5.3%** (3)
Life-Threatening Bleeding	**5.7%** (9)	**0**
Acute Kidney Injury (Stage 2/3)	**2.5%** (4)	**0**
Coronary Artery Obstruction	**0.9%** (1)	**0**
Major Vascular Complications	**7.0%** (11)	**0**



CEC Adjudicated All Deaths as Unrelated to TriGUARD 3

30-Day Outcome	Time from Procedure	Cause of Death
TriGUARD 3	< 24 hours	Aortic ring rupture
	10 days	Pneumonia and system organ failure
	6 days	Annular disruption, Type A dissection
	9 days	Stroke
Control	17 days	Sepsis secondary to pneumonia

In-Hospital Stroke Rate Clinically Relevant Evaluation of Accessory Device



All Primary Safety Events in REFLECT Adjudicated for Relatedness by CEC

Relatedness	Temporal Relationship to Device	Likelihood of Alternative Cause to Device
Related	Strong	Alternative cause unlikely
Probably related	Timely	Potential alternative cause
Possibly related	Timely	More likely alternative cause or significant uncertainty
Unlikely related	Little to none	More likely alternative cause
Not related	N/A	Other known cause

2 of 11 Major Vascular Complications Were Adjudicated as Related by CEC

30-Day Outcome, % (n)	TriGUARD 3 N = 157
Combined Safety Endpoint	**15.9%** (25)
All-Cause Death	**2.5%** (4)
Stroke (Disabling and Non-Disabling)	**8.3%** (13)
Life-Threatening or Disabling Bleeding	**5.7%** (9)
Acute Kidney Injury (Stage 2/3)	**2.5%** (4)
Coronary Artery Obstruction	**0.6%** (1)
Major Vascular Complication	**7.0%** (11)
Valve-Related Dysfunction	**0**

Note: All major vascular complications were included in the primary endpoint, even if the event occurred at the TAVR access site, contralateral to the TriGUARD device.

- **2 events related to vascular access site**
- **TAVR device successful implanted**

2 of 11 Major Vascular Complications Were Adjudicated as Related by CEC

- Case 1
  - Access site
  - Unsuccessful perclose
  - Converted to surgical repair
- Case 2
  - Retroperitoneal bleed
  - Hemodynamics stabilized with transfusion

1 Bleed Adjudicated as "Possibly" Related by CEC

30-Day Outcome, % (n)	TriGUARD 3 N = 157
Combined Safety Endpoint	**15.9%** (25)
All-Cause Death	**2.5%** (4)
Stroke (Disabling and Non-Disabling)	**8.3%** (13)
Life-Threatening or Disabling Bleeding	**5.7%** (9)
Acute Kidney Injury (Stage 2/3)	**2.5%** (4)
Coronary Artery Obstruction	**0.6%** (1)
Major Vascular Complication	**7.0%** (11)
Valve-Related Dysfunction	**0**

- **1 event CEC adjudicated as "possibly" related**

Similar Rate of Secondary Safety Events Between TriGUARD 3 and Control

30-Day Outcome	TriGUARD 3 N = 157	Control N = 57
Myocardial infarction	**0**	**1.8%** (1)
General safety event*	**9.6%** (15)	**7.0%** (4)
Transient ischemic attack (VARC-2)	**1.3%** (2)	**1.8%** (1)
Overt CNS injury (Type 1)	**8.3%** (13)	**5.3%** (2)
Covert CNS injury (Type 2)	**68.8%** (108)	**63.2%** (36)
Neurological dysfunction, no CNS injury (Type 3)	**1.9%** (3)	**5.3%** (3)
CNS infarction (NeuroARC defined)	**77.1%** (121)	**68.4%** (39)
CNS hemorrhage (NeuroARC defined)	**0**	**1.8%** (1)

* General safety event Include all-cause mortality, all stroke and AKI stage 3

Safety Summary

- TriGUARD 3 met pre-specified primary endpoint
- Rate of specific AEs numerically higher with TriGUARD 3
  - Direct comparison between groups challenging given limited sample sizes
  - Rates in line with expectations during TAVR procedure
- Few events related to TriGUARD 3

TriGUARD 3 is safe for intended use as accessory device to deflect embolic debris away from cerebral circulation

REFLECT Study Performance Data and Effectiveness Results

Rahul Sharma, MD, MBBS, FRACP

Director of Structural Interventions
Stanford Healthcare

Clinical Associate Professor of Medicine
Stanford University

TriGUARD 3 Safely Delivered, Deployed, and Retrieved in All Cases

	TriGUARD 3 N = 157
Successful device deployment	100%
Aortic arch successfully accessed	100%
Successful device retrieval	100%

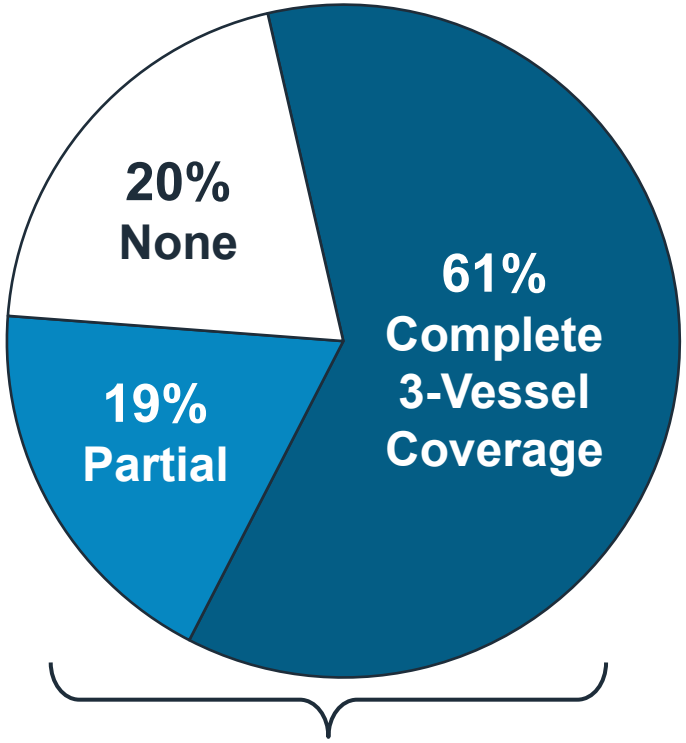
Comprehensive Assessment of Vessel Coverage with TriGUARD 3

- Goal in REFLECT was to assess deployment, coverage, and stability of TriGUARD at all 3 time points
  - Pre-, during- and post-TAVR procedure
- Main function of angiography during TAVR is to guide deployment of valve
  - Cases where TriGUARD not in field of view of camera
- Keystone Heart conservatively assessed complete coverage
  - Angiographic evidence required
  - Complete 3-vessel coverage for 2 of 3 timepoints

Majority of Patients had Complete 3-Vessel Coverage

Pre-TAVR
N = 129

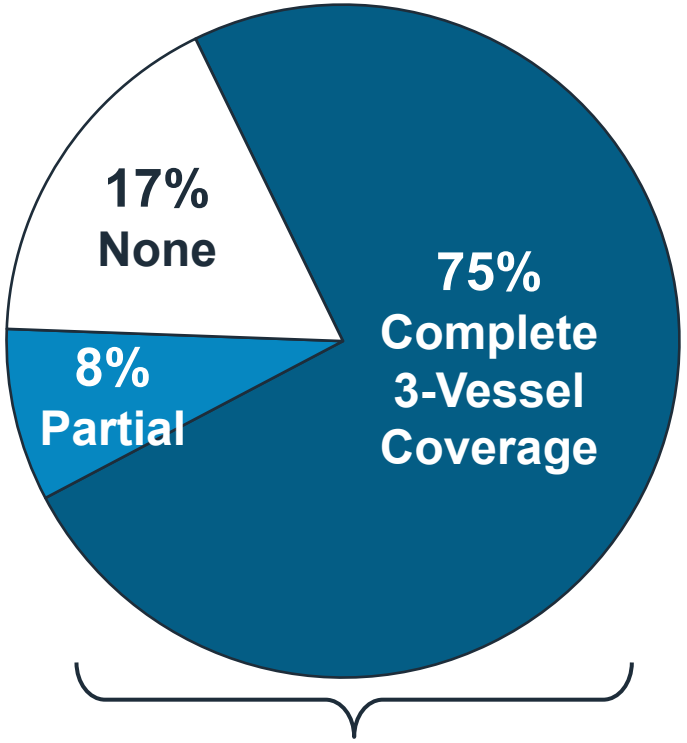
No imaging confirmation (n = 28)



Complete + Partial Coverage
80%

During-TAVR
N = 145

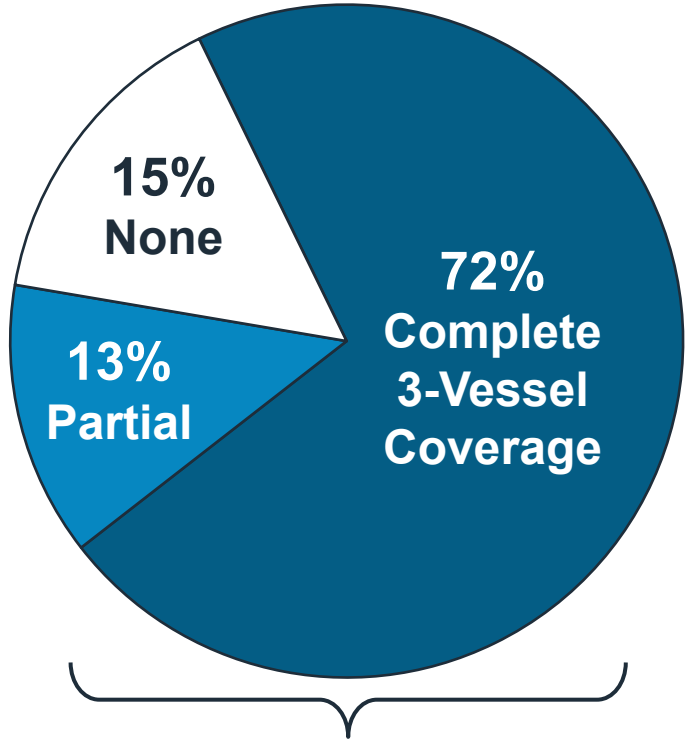
No imaging confirmation (n = 12)



Complete + Partial Coverage
83%

Post-TAVR
N = 152

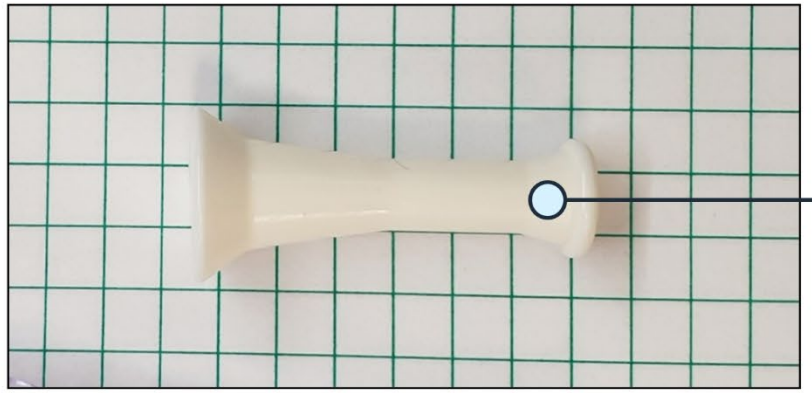
No imaging confirmation (n = 5)



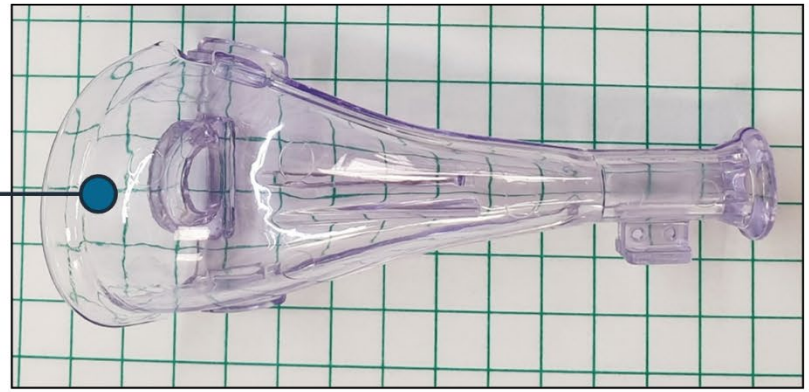
Complete + Partial Coverage
85%

Improved Crimper Facilitates Optimal Positioning

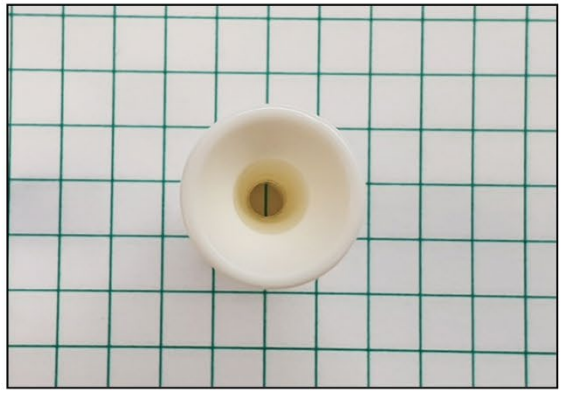
Crimper Used in REFLECT Study



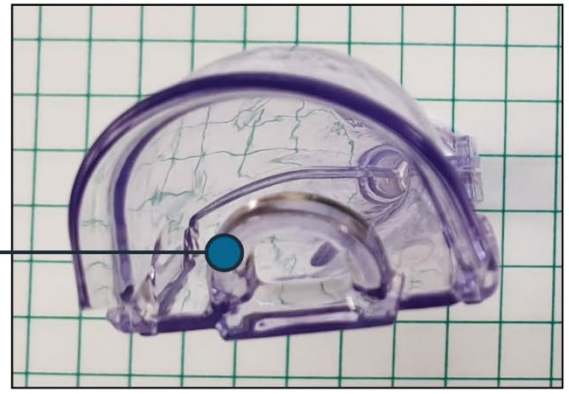
Improved Crimper Currently in Commercial Use



Translucent Crimper Material
Allows for confirmation of Hypotube positioning



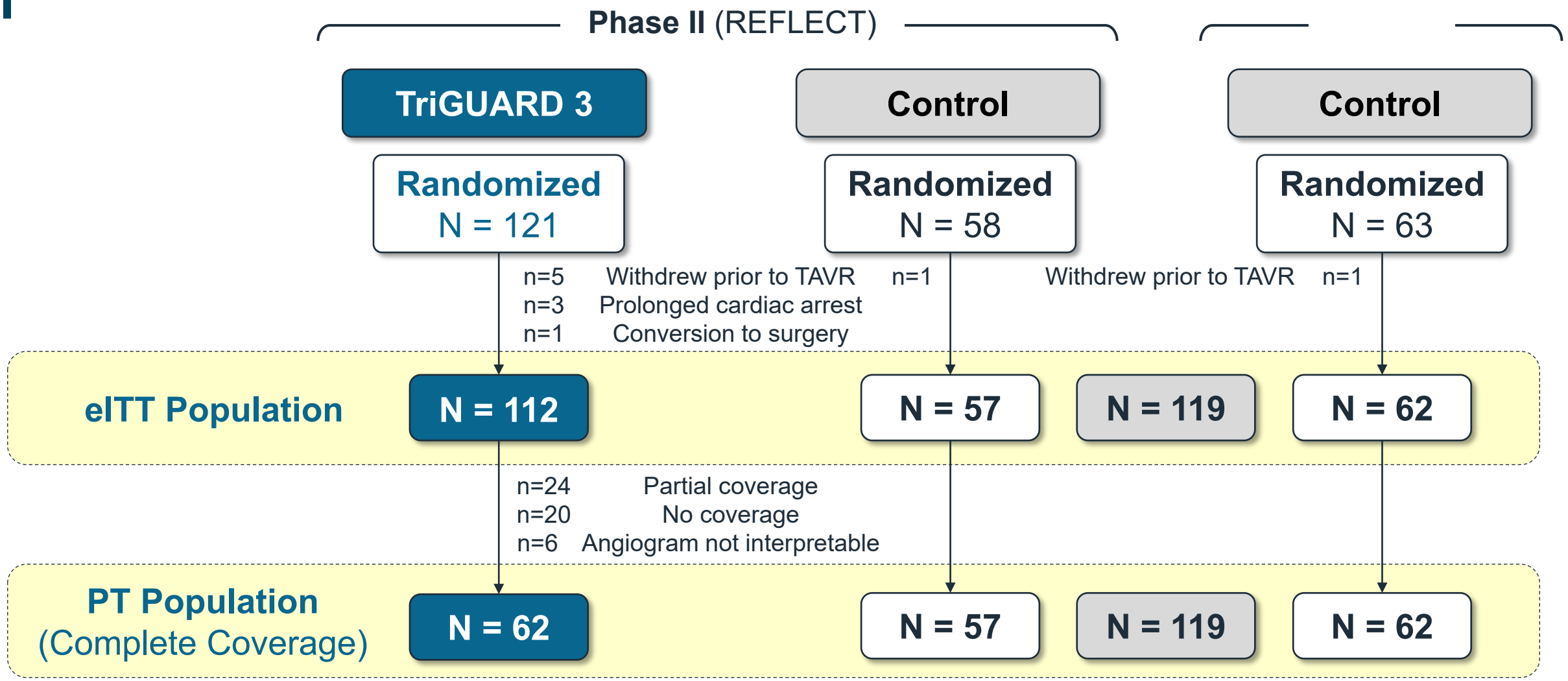
D-Ring Addition
Facilitates positioning of hypotube under TriGUARD filter



Enhanced Training Materials Improved TriGUARD 3 Delivery Technique

- Experience from REFLECT demonstrated that catheter was being torqued during advancement
  - Impacted optimal device positioning
- Training required for all new clinicians before TriGUARD device shipped to site
- Data from real-world experience demonstrate actions have addressed the prior concerns

Effectiveness Patient Disposition



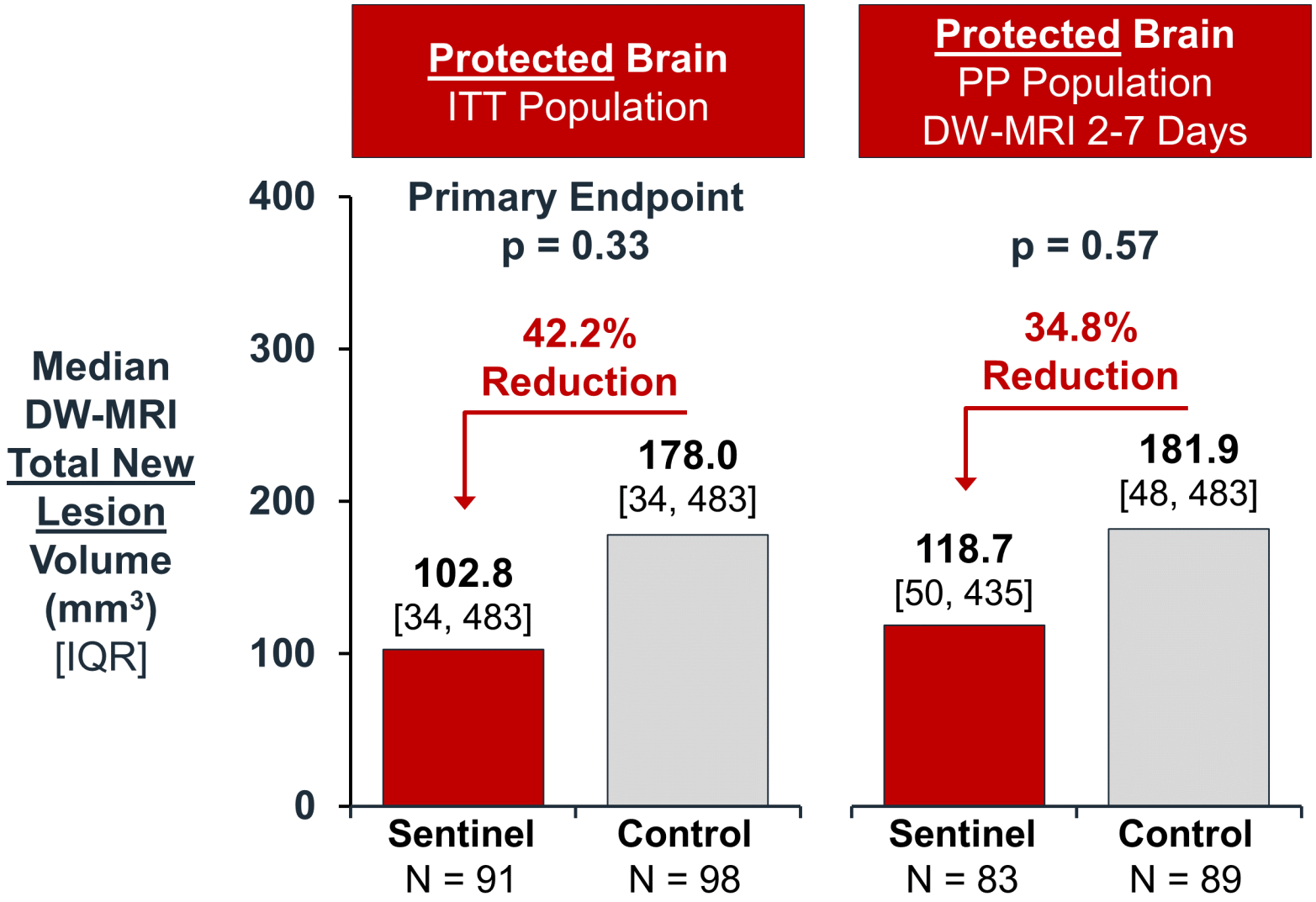
Primary Composite Effectiveness Endpoint

- Hierarchical evaluation of patient outcomes
  1. All-cause mortality or any stroke
  2. NIHSS worsening from baseline
  3. Freedom from any cerebral ischemic lesions
  4. Total volume of cerebral ischemic lesions

eITT Population: Primary Effectiveness Endpoint Not Met

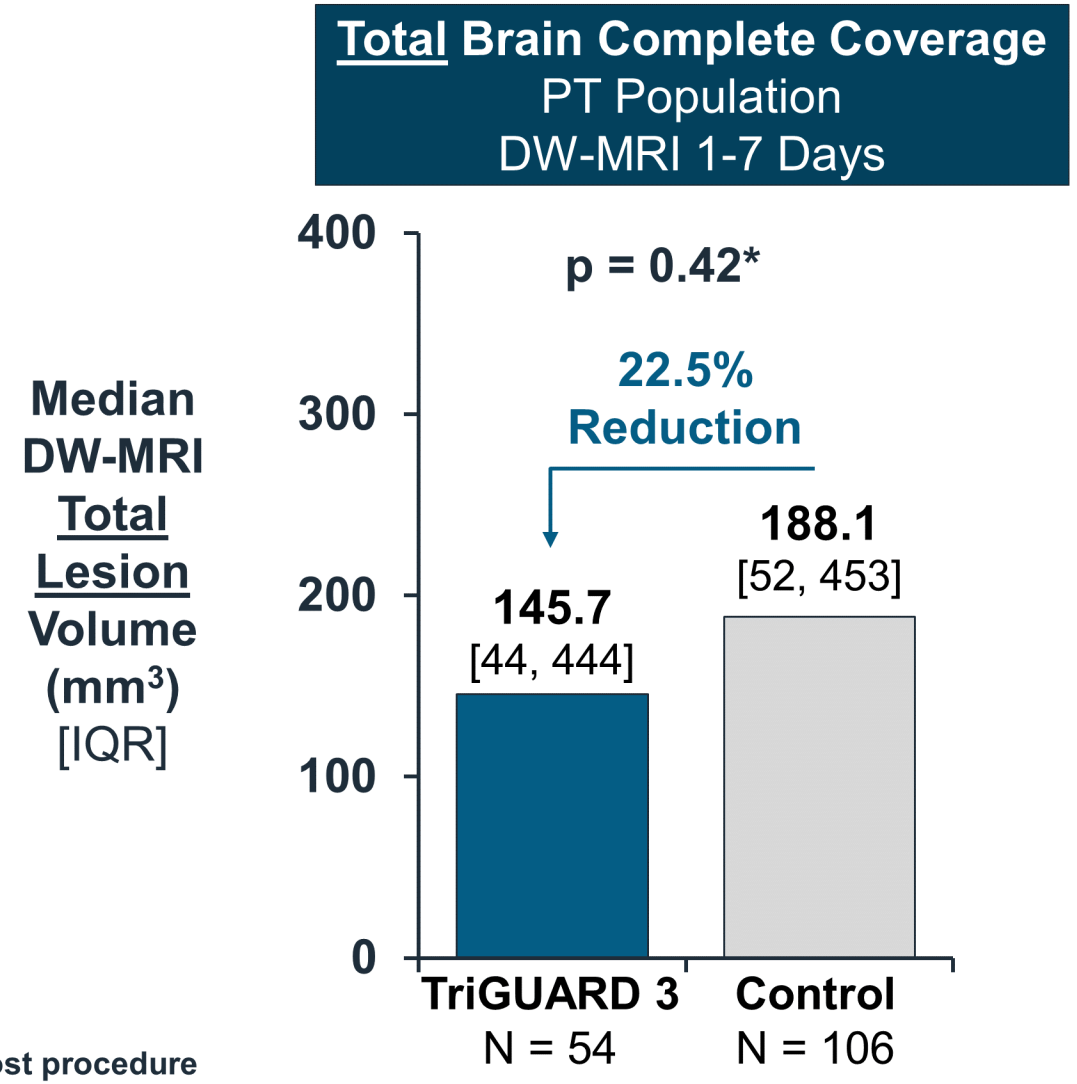
	TriGUARD 3 N = 112	Control N = 119	P-value
Primary effectiveness			**0.857**
Component event rates			
All-cause mortality or any stroke at 30 days	**9.8%**	**6.7%**	
NIHSS worsening predischarge	**14.1%**	**7.6%**	
Cerebral ischemic lesions	**85.0%**	**84.9%**	
Total lesion volume (mm^3), Median [IQR]	**215.39** [68, 620]	**188.09** [52, 453]	

Sentinel Failed to Show Significance on Primary Effectiveness Endpoint



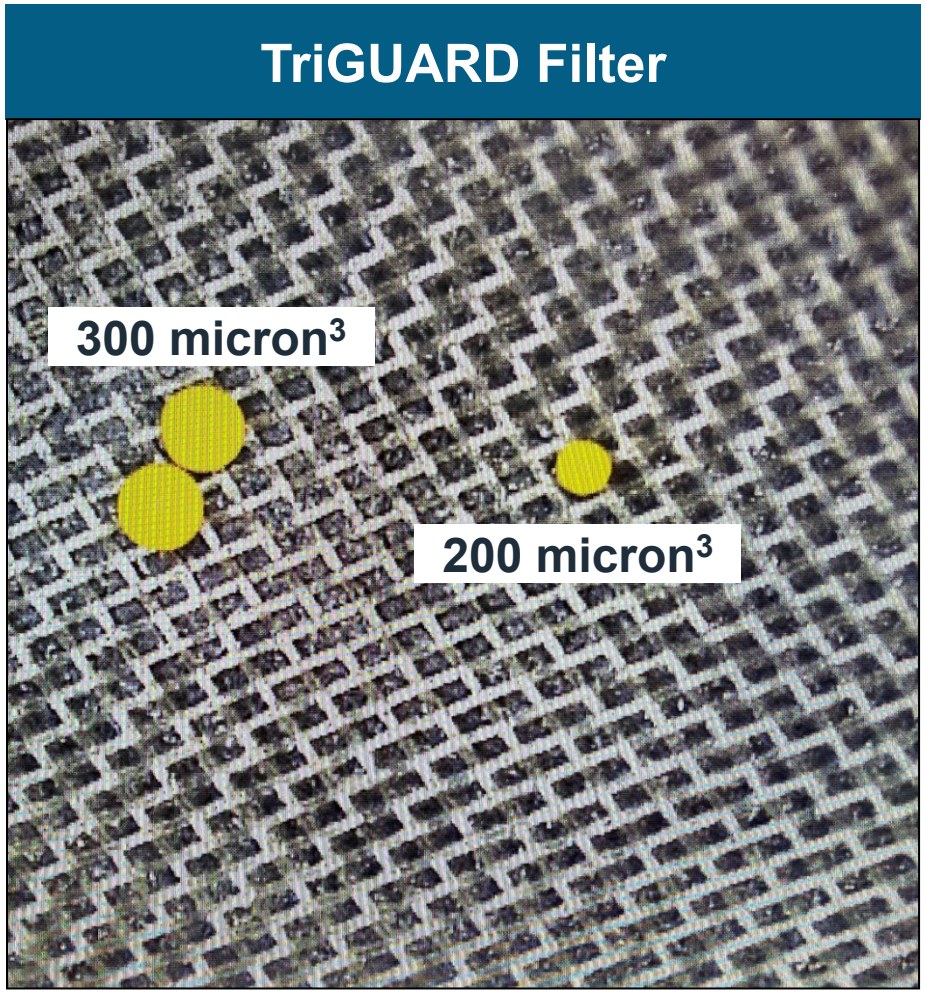
FDA Presentation at 2017 CSDP Meeting for Sentinel Device (Video Recording)

Imaging Results Show TriGUARD 3 Prevents Debris from Entering Brain During TAVR



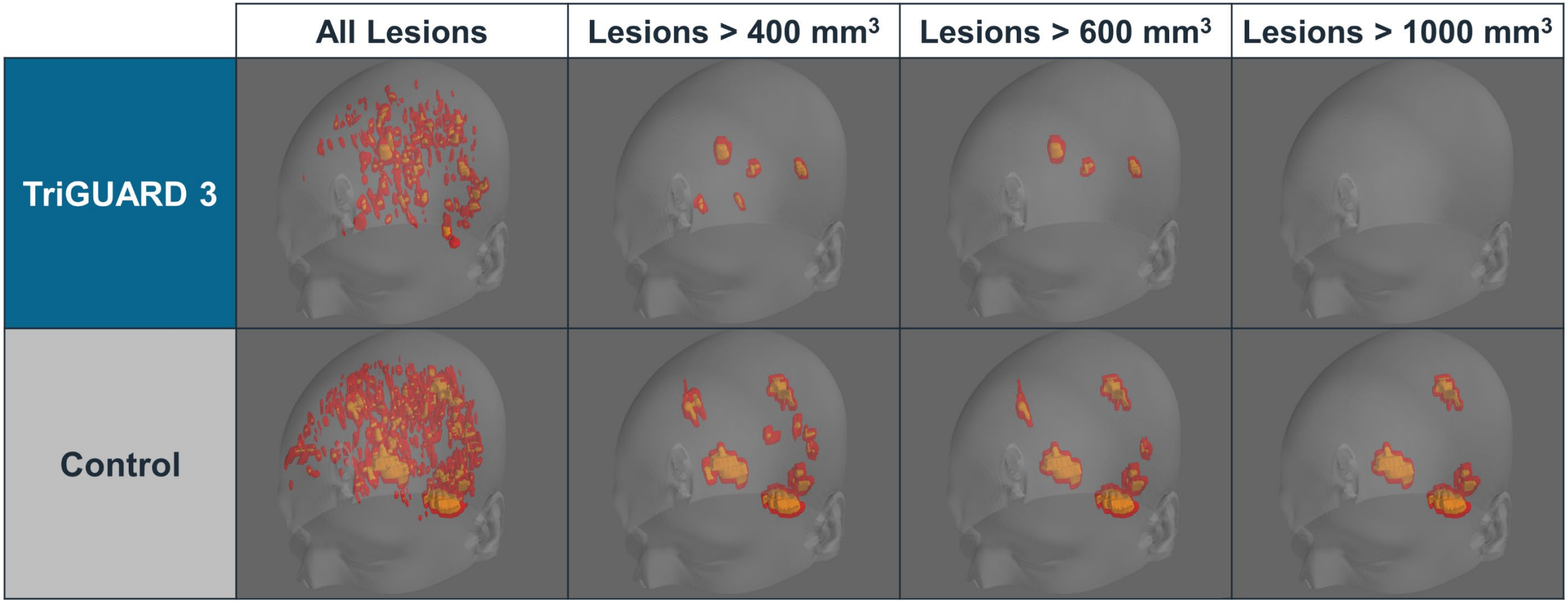
PT Population
Patients with DW-MRI 1 to 7 days post procedure
* Post hoc analysis

TriGUARD 3 Designed to Filter Blood Without Impeding Cerebral Flow Dynamics



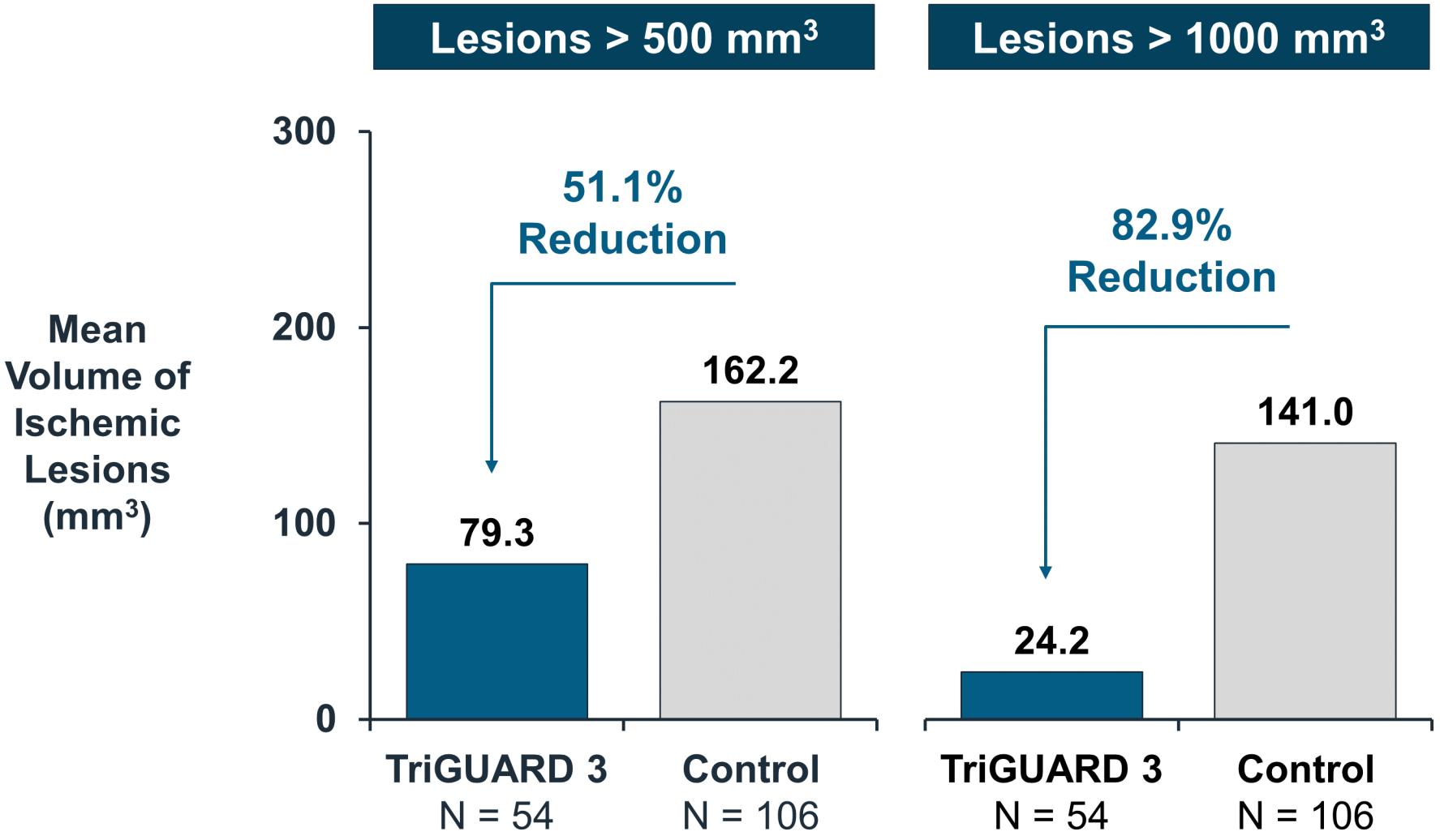
- Filter pore size: 145 x 115 microns
- TriGUARD does not prevent all debris from entering brain
  - Must facilitate normal blood flow dynamics

PT Population: MRI Analyses Demonstrate Reduction in Lesion Volume with TriGUARD 3



PT Population
Patients with DW-MRI 1 to 7 days post procedure

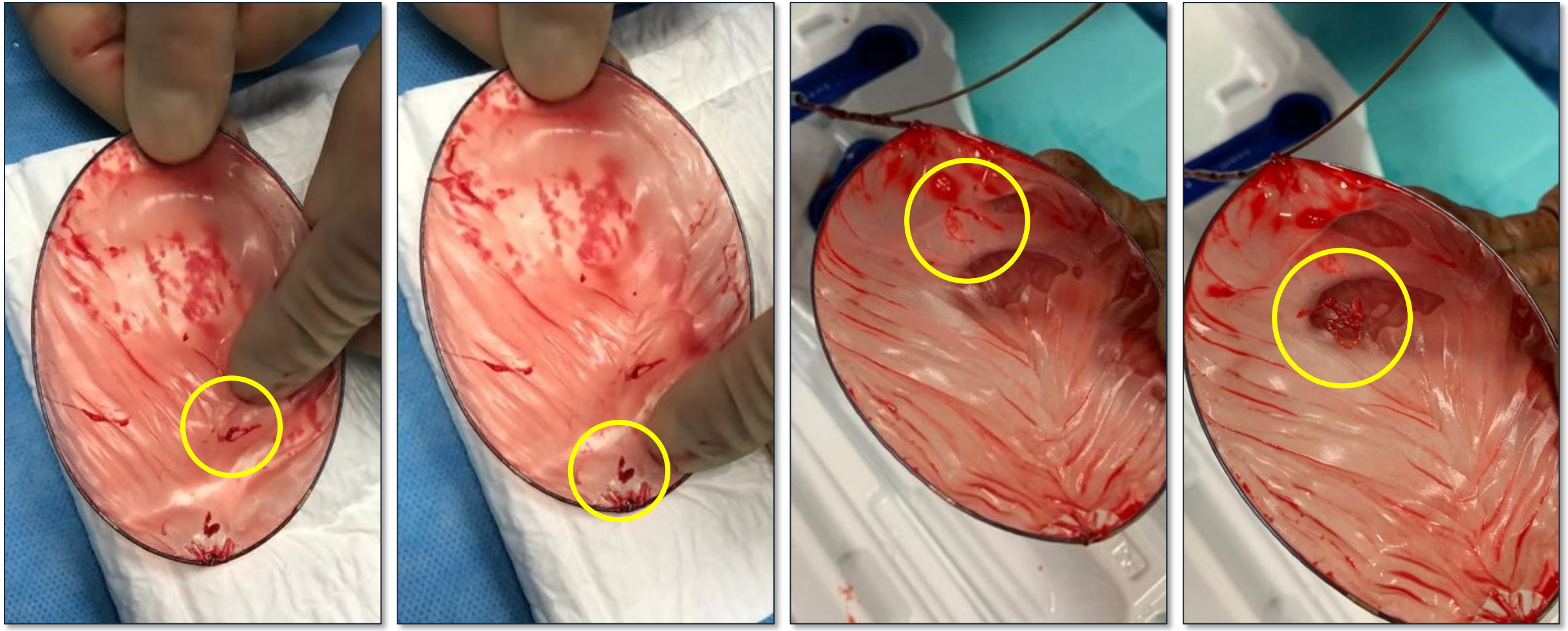
PT Population: TriGUARD 3 Provides Substantial Reduction in Large Lesions



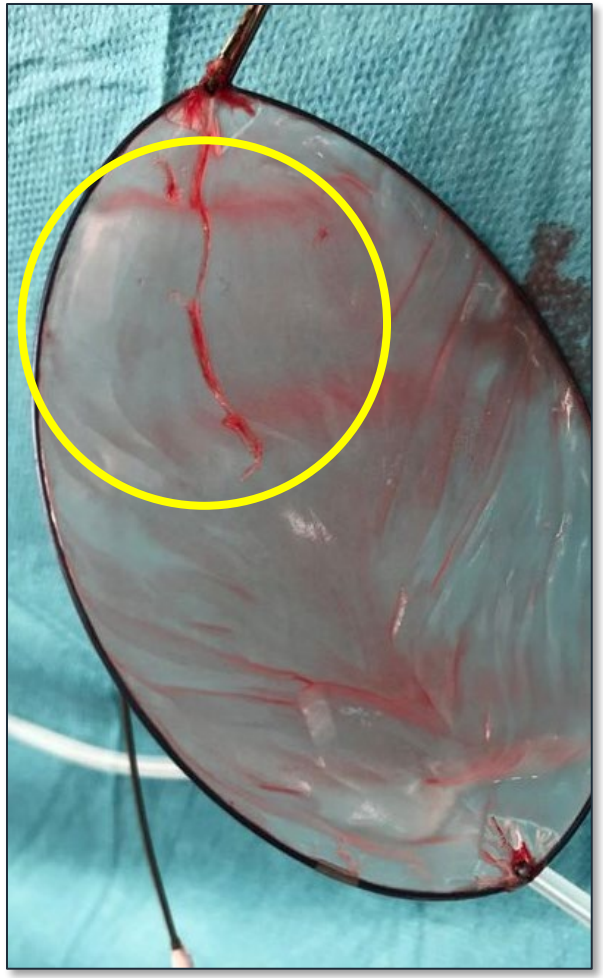
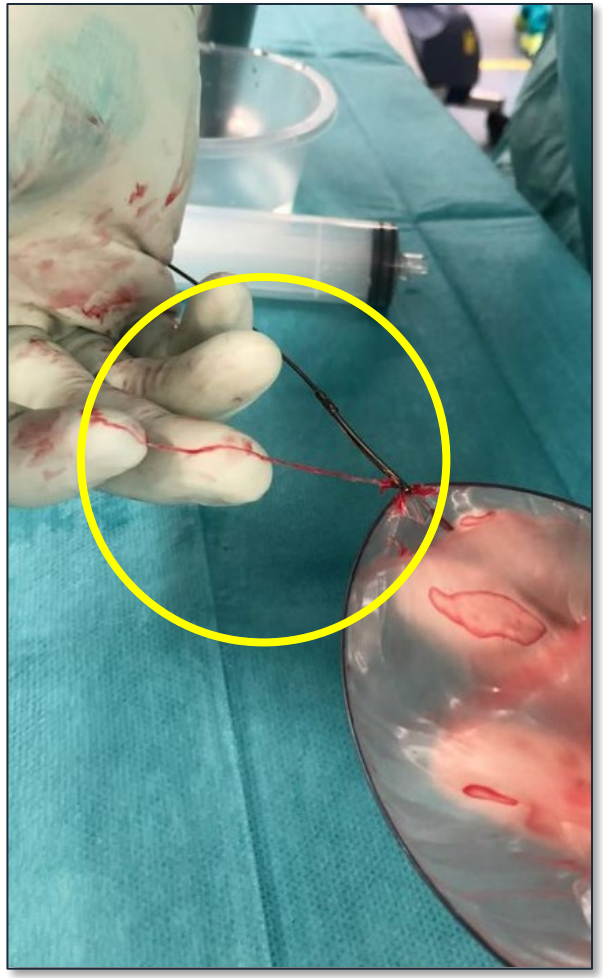
PT Population
Patients with DW-MRI 1 to 7 days post procedure

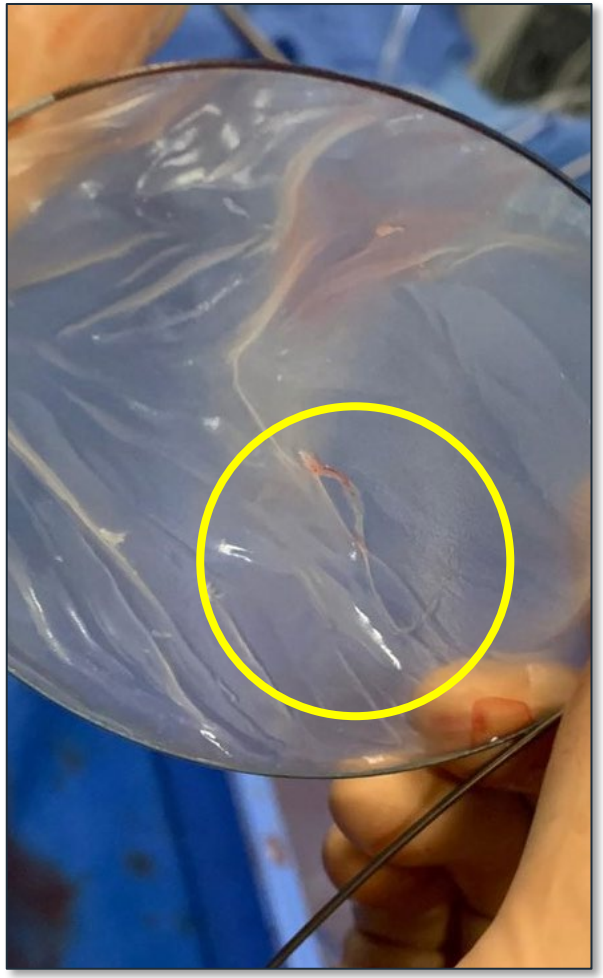
Representative Images of Debris Captured by TriGUARD 3 from Real-World Experience

TriGUARD 3 Captures Large Embolic Debris in Real-World Experience

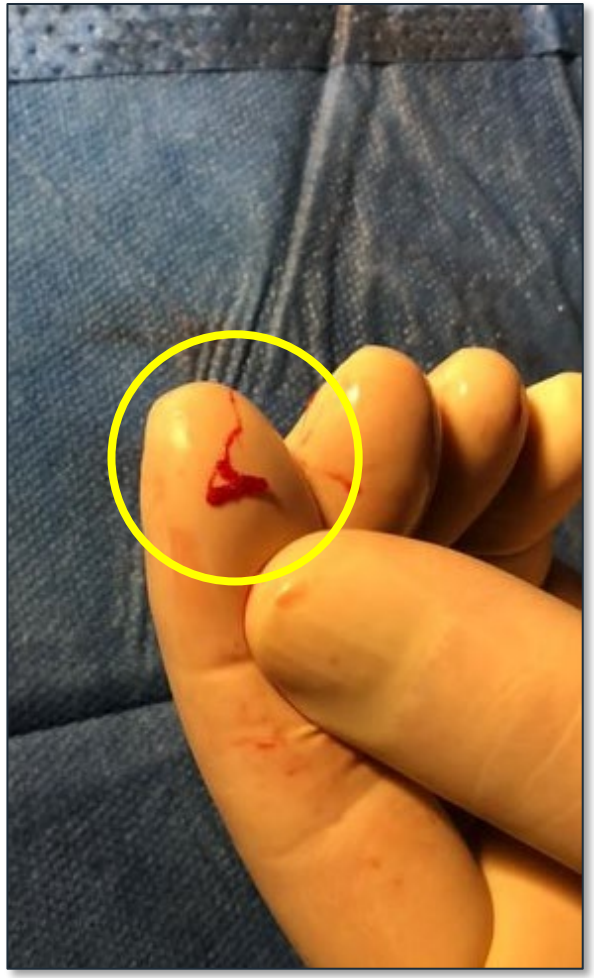


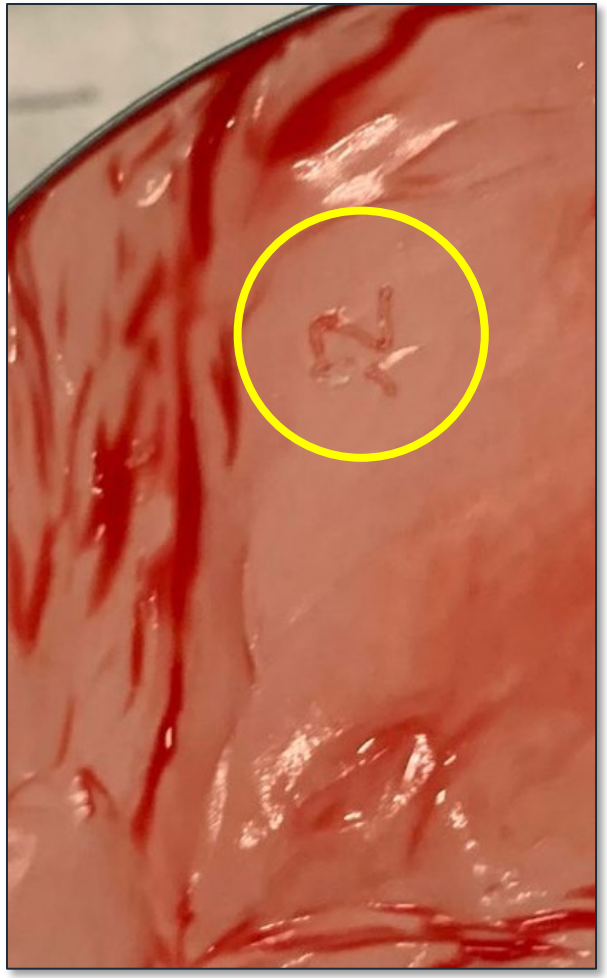
Debris and Foreign Material Captured by TriGUARD 3 in Real-World Experience

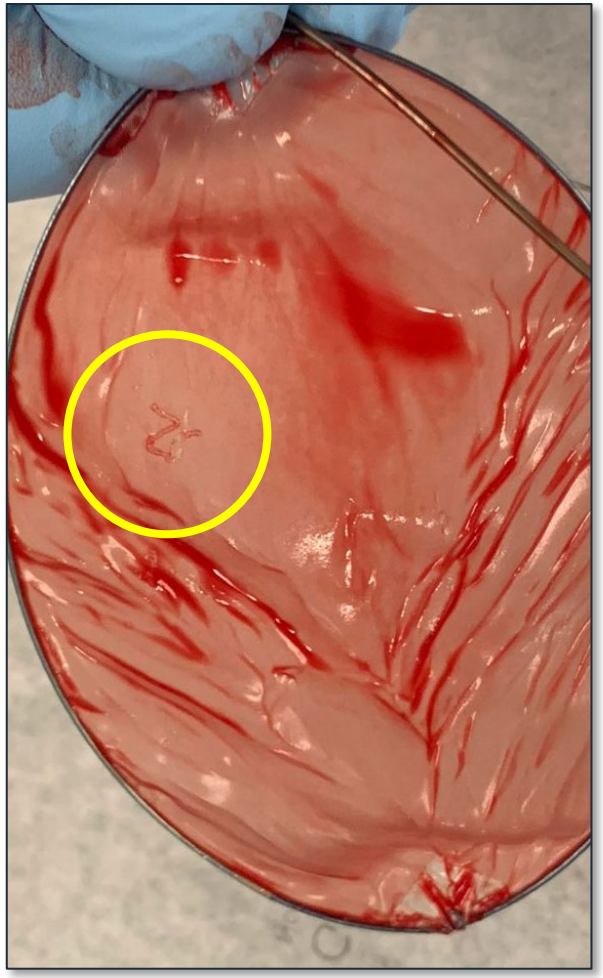





Debris of Different Origin Captured with TriGUARD 3 in Real-World Experience







Effectiveness Conclusion

- TriGUARD 3 successfully delivered, deployed, and retrieved in 100% of cases
- Complete 3-vessel coverage achieved in majority of cases
  - Higher coverage rates seen at key timepoints during TAVR
- Primary effectiveness endpoint not met
- Imaging data suggest TriGUARD 3 deflected embolic debris away from cerebral circulation as intended

Substantial Equivalence

Karen Jaffe, MS, MBA, RAC

Regulatory Consultant

Keystone Heart

Same Intended Use for TriGUARD 3 and Sentinel

	TriGUARD 3	Sentinel
Single-use percutaneous catheter system	**Yes** Single-use percutaneous system	**Yes** Single-use percutaneous system
Blood filter(s) at distal end	**Yes** Single filter spans all 3 arteries	**Yes** 2 filters covering 2 arteries
Indicated for use while performing TAVR procedure	**Yes**	**Yes**
Filter blood to prevent embolic material from entering brain during TAVR procedure	**Yes** Demonstrated through MRI and real-world experience	**Yes** Demonstrated through visual filter inspection

Clinical Performance Special Controls for Cerebral Protection Devices

I. The ability to safely deliver, deploy, and remove the device

II. The ability of the device to filter embolic material while not impeding blood flow

III. Secure positioning and stability of the position throughout the transcatheter intracardiac procedure

IV. Evaluation of all adverse events including death, stroke, and vascular injury

Both TriGUARD 3 and Sentinel Can Be Safely Delivered, Deployed, and Removed

	TriGUARD 3 As-Treated + Roll-In	Sentinel ITT
Delivery / retrieval successful	**100%** (157/157)	**94.4%** (218/231*)
Device-related vascular complication	**1.3%** (2/157)	**0.4%** (1/244**)

*Sentinel ITT Population minus cases where sentinel deployment not attempted
**Sentinel Study report rate of major vascular complications using ITT with imputation for missing data N = 244

Clinical Performance Special Controls for Cerebral Protection Devices

I. The ability to safely deliver, deploy, and remove the device

II. The ability of the device to filter embolic material while not impeding blood flow

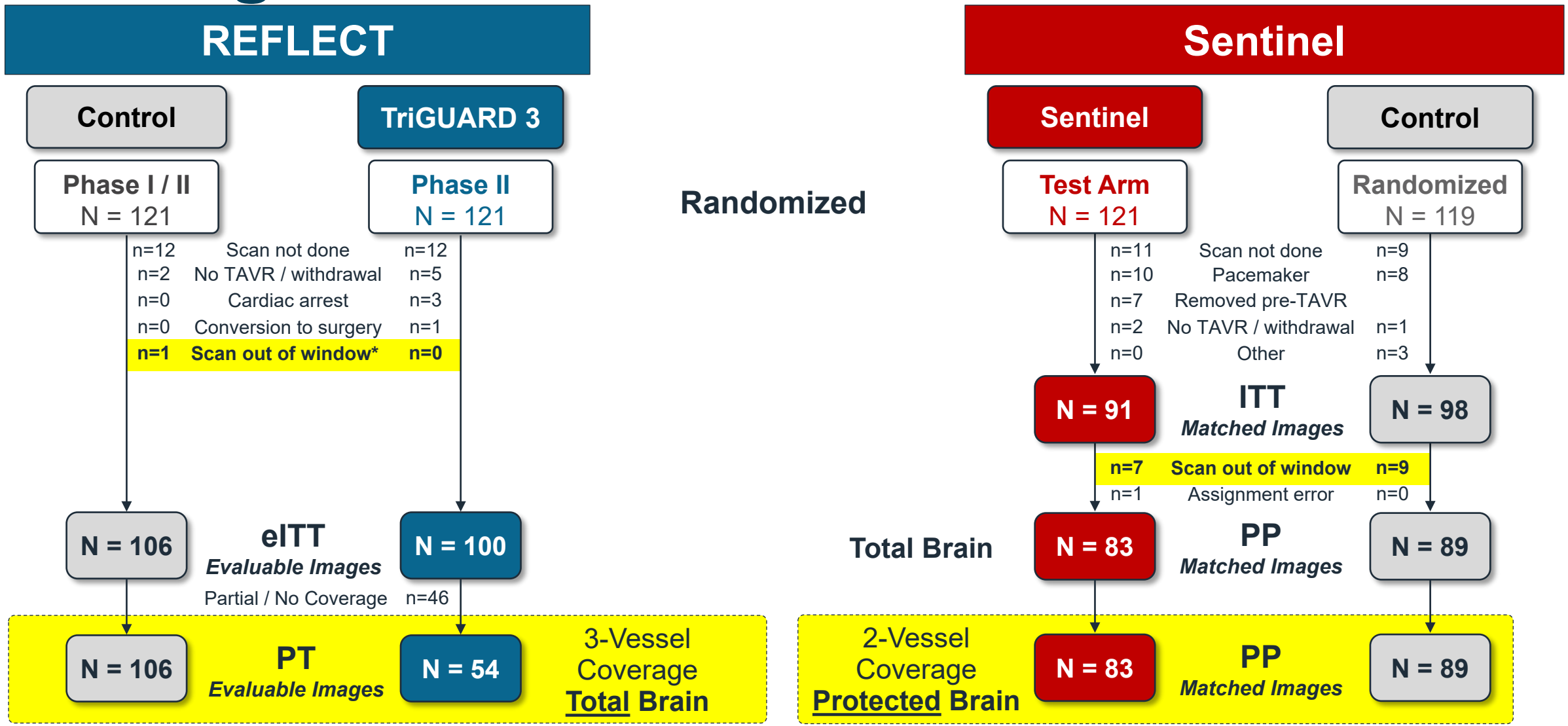
III. Secure positioning and stability of the position throughout the transcatheter intracardiac procedure

IV. Evaluation of all adverse events including death, stroke, and vascular injury

TriGUARD 3 Does Not Impede Blood Flow

- Confirmed by bench and animal testing
- Potential flow disturbances including reductions in flow rate and changes in pressure gradient
- < 2% reduction in cerebral blood flow and blood pressure with TriGUARD 3

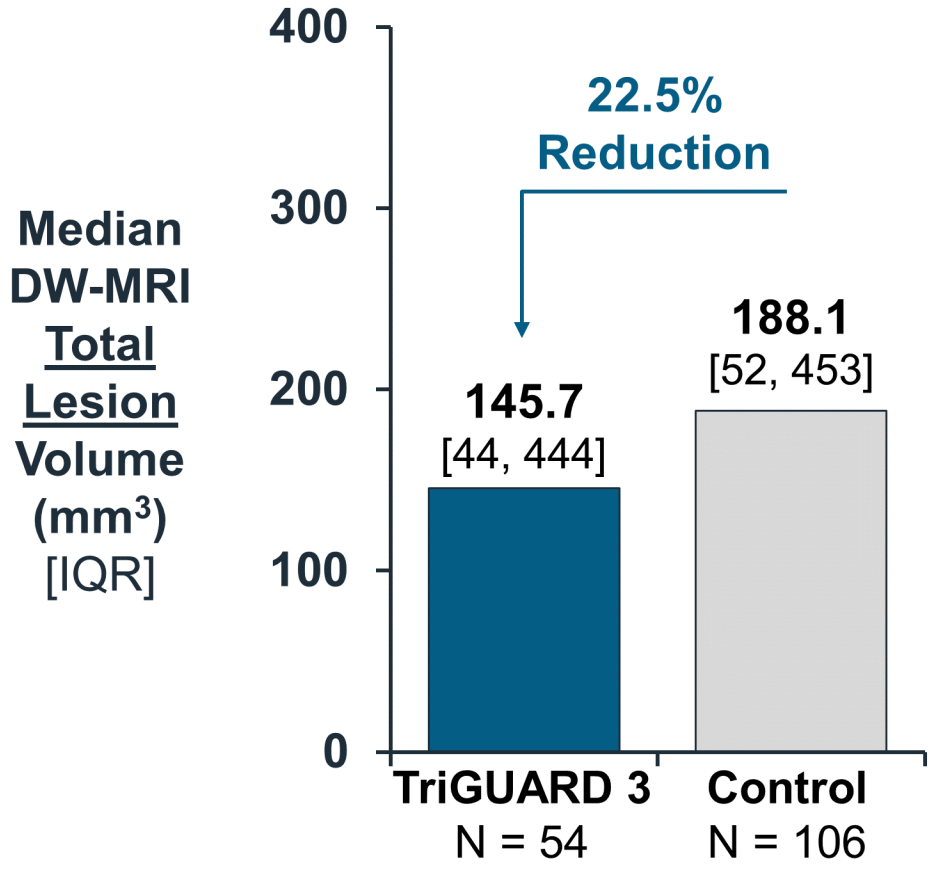
Effectiveness Comparisons Consider Vessel Coverage and Protected vs Total Brain



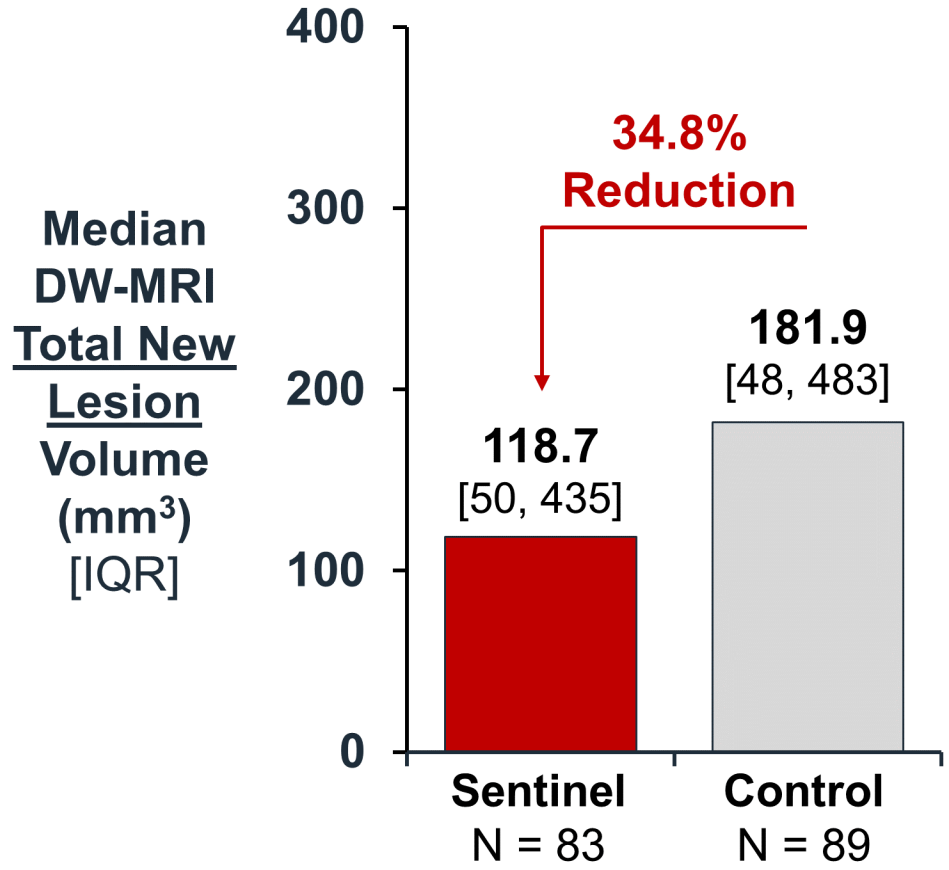
* Based on DW-MRI at 1-7 Days

PT Population: Both Devices Reduce Lesion Volume

Total Brain
Complete Coverage
PT Population
DW-MRI 1-7 Days

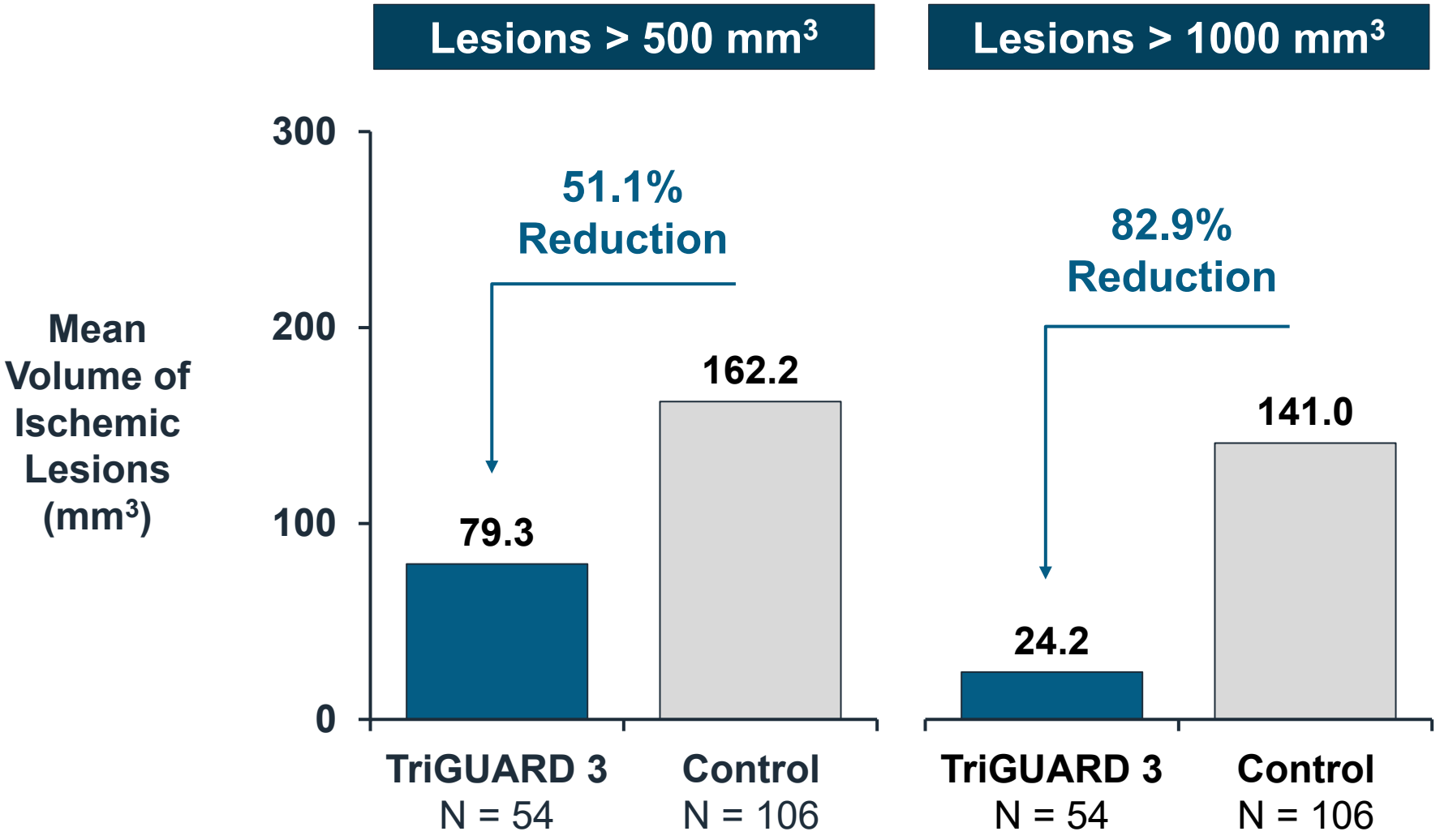


Protected Brain
PP Population
DW-MRI 2-7 Days



Sentinel Data from FDA Presentation at 2017 CSDP Meeting for Sentinel Device (Video Recording)

PT Population: TriGUARD 3 Reduces Volume of Larger Lesions



PT Population
Patients with DW-MRI 1 to 7 days post procedure

Clinical Performance Special Controls for Cerebral Protection Devices

- The ability to safely deliver, deploy, and remove the device
- The ability of the device to filter embolic material while not impeding blood flow

III. Secure positioning and stability of the position throughout the transcatheter intracardiac procedure

IV. Evaluation of all adverse events including death, stroke, and vascular injury

TriGUARD Successfully Deployed and Positioned Within Aortic Arch

	TriGUARD 3 N = 157	Sentinel N = 231*
Successful device deployment	**100%**	**94.4%** *Both filters deployed*
Complete 3-vessel coverage	**> 60%**	**0%** *2-vessel coverage design*
Partial vessel coverage during the TAVR procedure	**> 80%**	*Angiography not collected*

All available reports from commercial use indicate that crimper updates and training materials have further improved TriGUARD 3 positioning and 3-vessel coverage

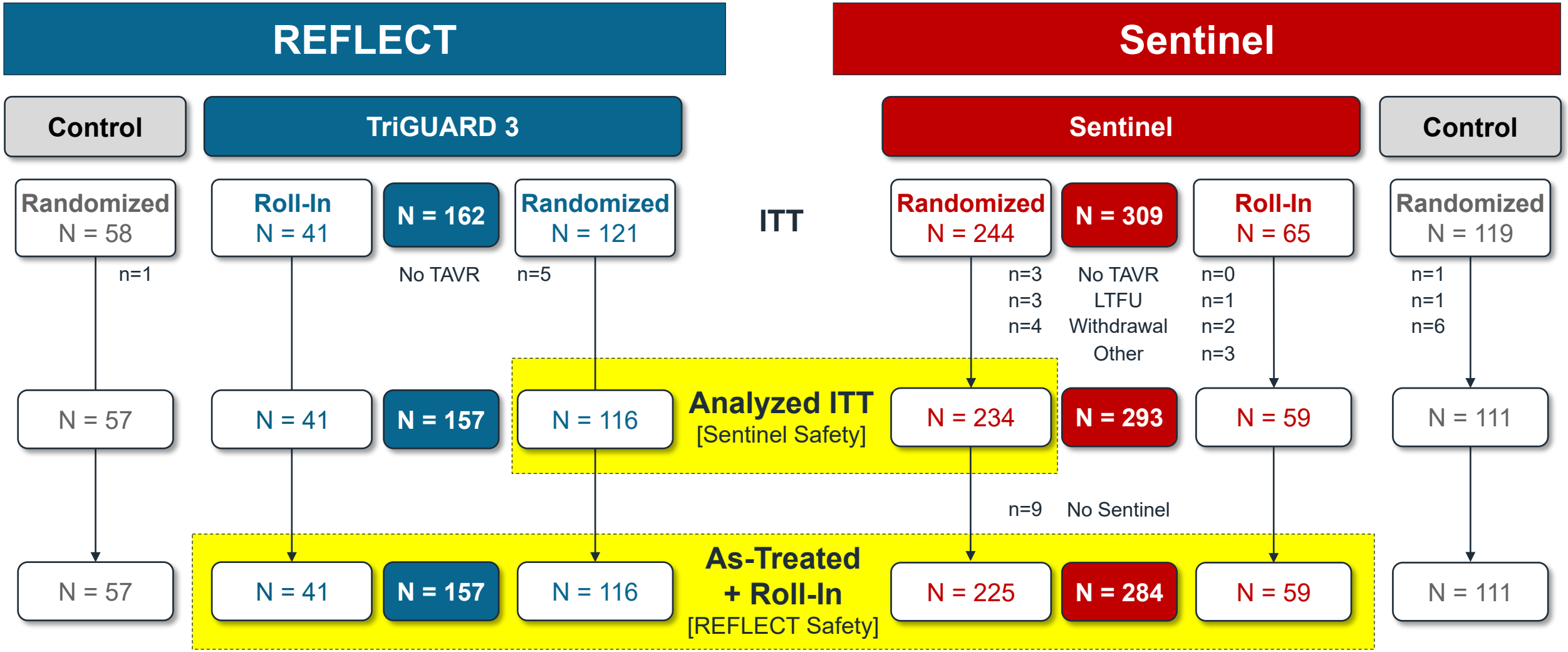
TriGUARD 3 - SP(AT)
*Sentinel - Safety + Imaging arms minus cases where Sentinel deployment not attempted

Clinical Performance Special Controls for Cerebral Protection Devices

- The ability to safely deliver, deploy, and remove the device
- The ability of the device to filter embolic material while not impeding blood flow
- Secure positioning and stability of the position throughout the transcatheter intracardiac procedure

IV. Evaluation of all adverse events including death, stroke, and vascular injury

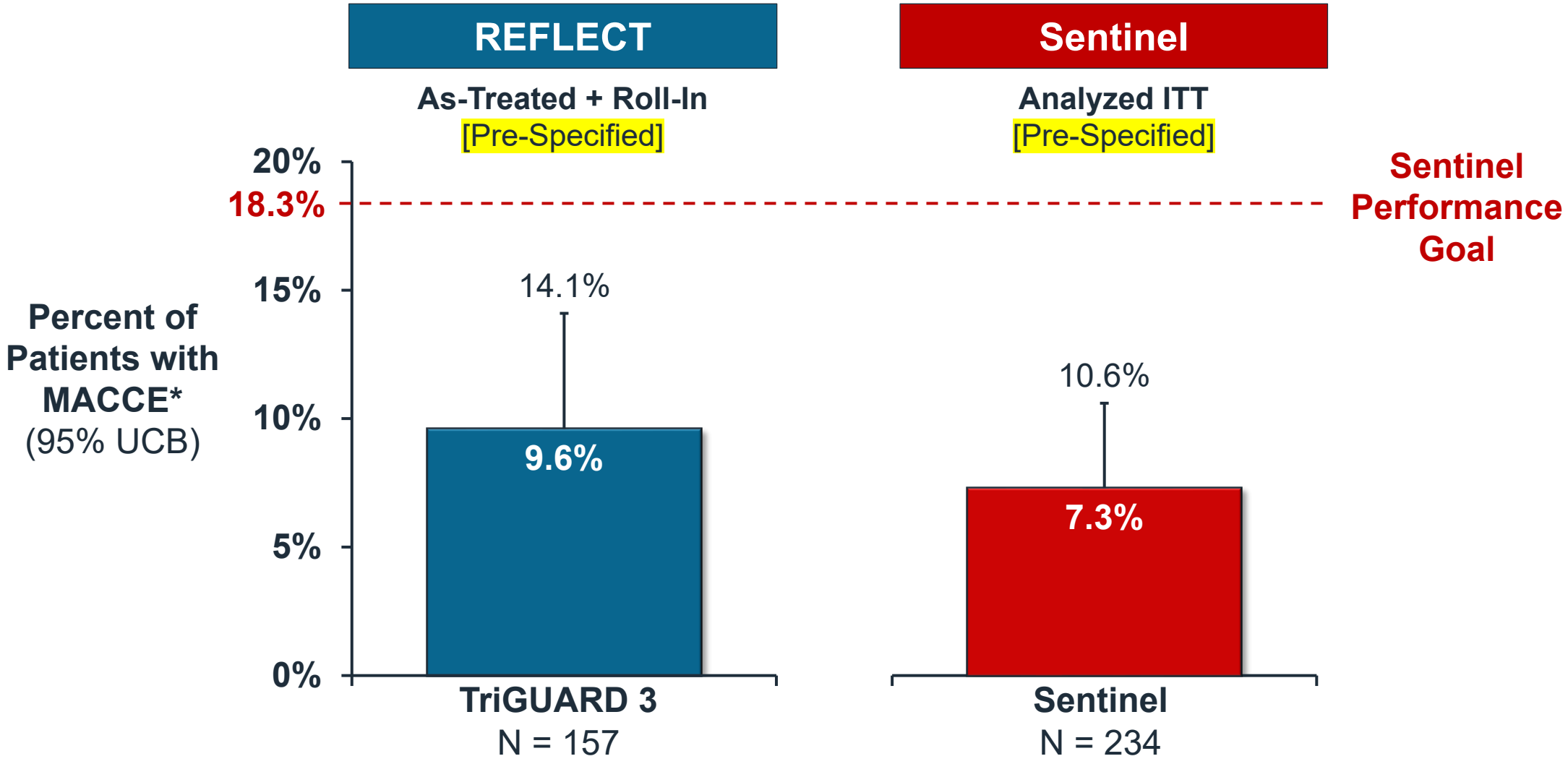
Substantial Equivalence Results Based on Similar Populations from REFLECT and Sentinel



Different Composite Primary Safety Endpoints in REFLECT and Sentinel

REFLECT	Sentinel
All Death	All Death
All Stroke	All Stroke
Life-threatening/disabling bleeding	Life-threatening/disabling bleeding
Stage 2 AKI	Stage 2 AKI
Stage 3 AKI	Stage 3 AKI
Coronary artery obstruction	Coronary artery obstruction
Major vascular complication	Major vascular complication
Valve related dysfunction	Valve related dysfunction
Performance Goal = 34.4%	**Performance Goal = 18.3%**

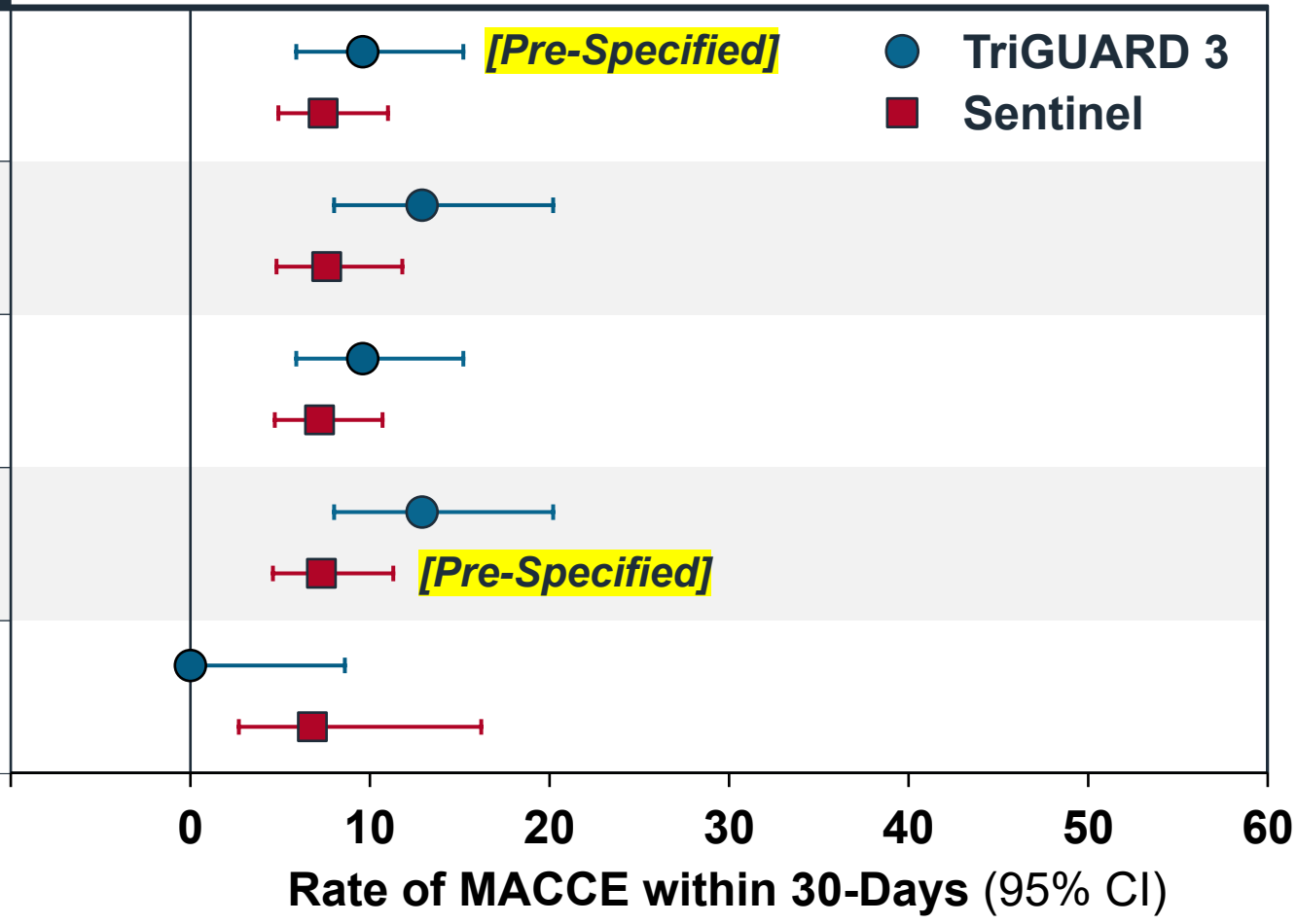
30-Day MACCE Rate Similar Between TriGUARD 3 and Sentinel Device



MACCE definition as per Sentinel Study

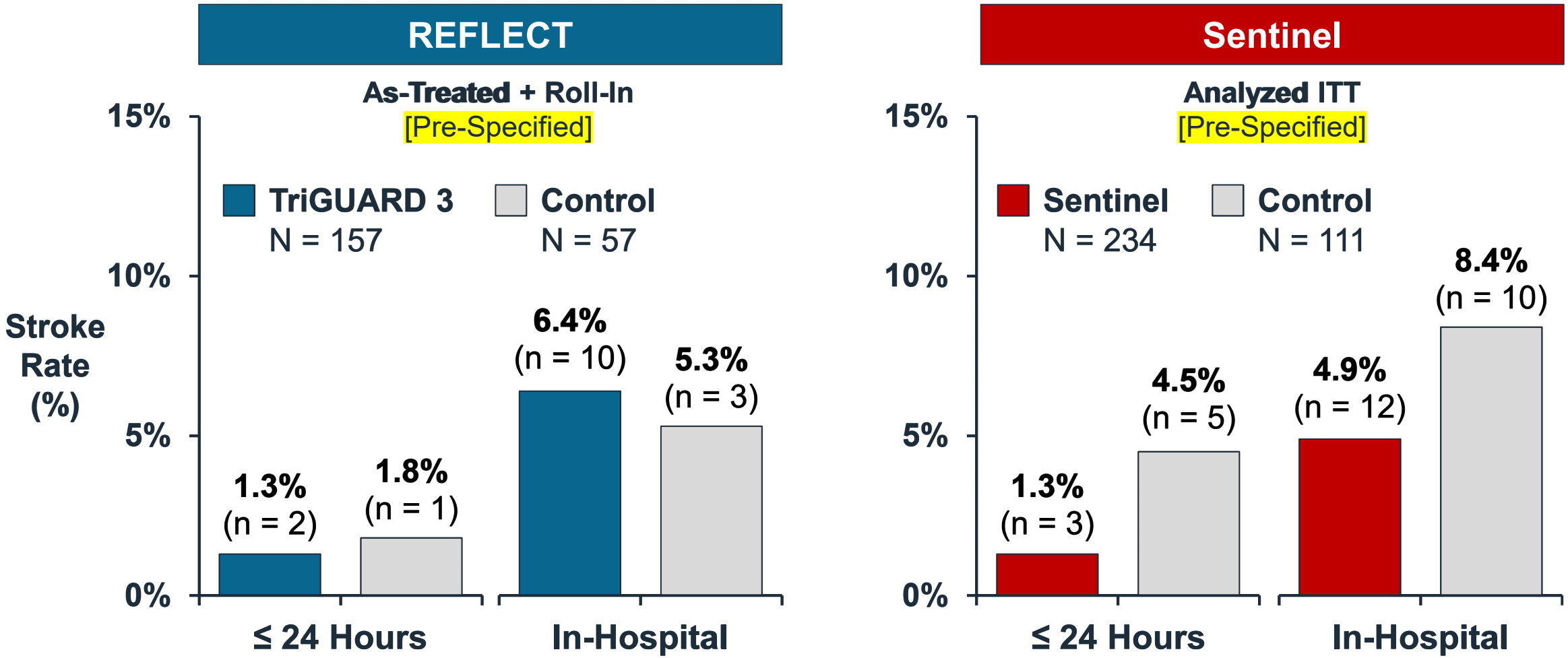
Regardless of Population, MACCE Rate Similar Between Groups

30-Day Outcomes	MACCE Events / N	MACCE %
As-Treated + Roll-In	15 / 157	9.6%
	21 / 284	7.4%
As-Treated	15 / 116	12.9%
	17 / 225	7.6%
Analyzed ITT + Roll-In	15 / 157	9.6%
	21 / 293	7.2%
Analyzed ITT	15 / 116	12.9%
	17 / 234	7.3%
Roll-In	0 / 41	0
	4 / 59	6.8%

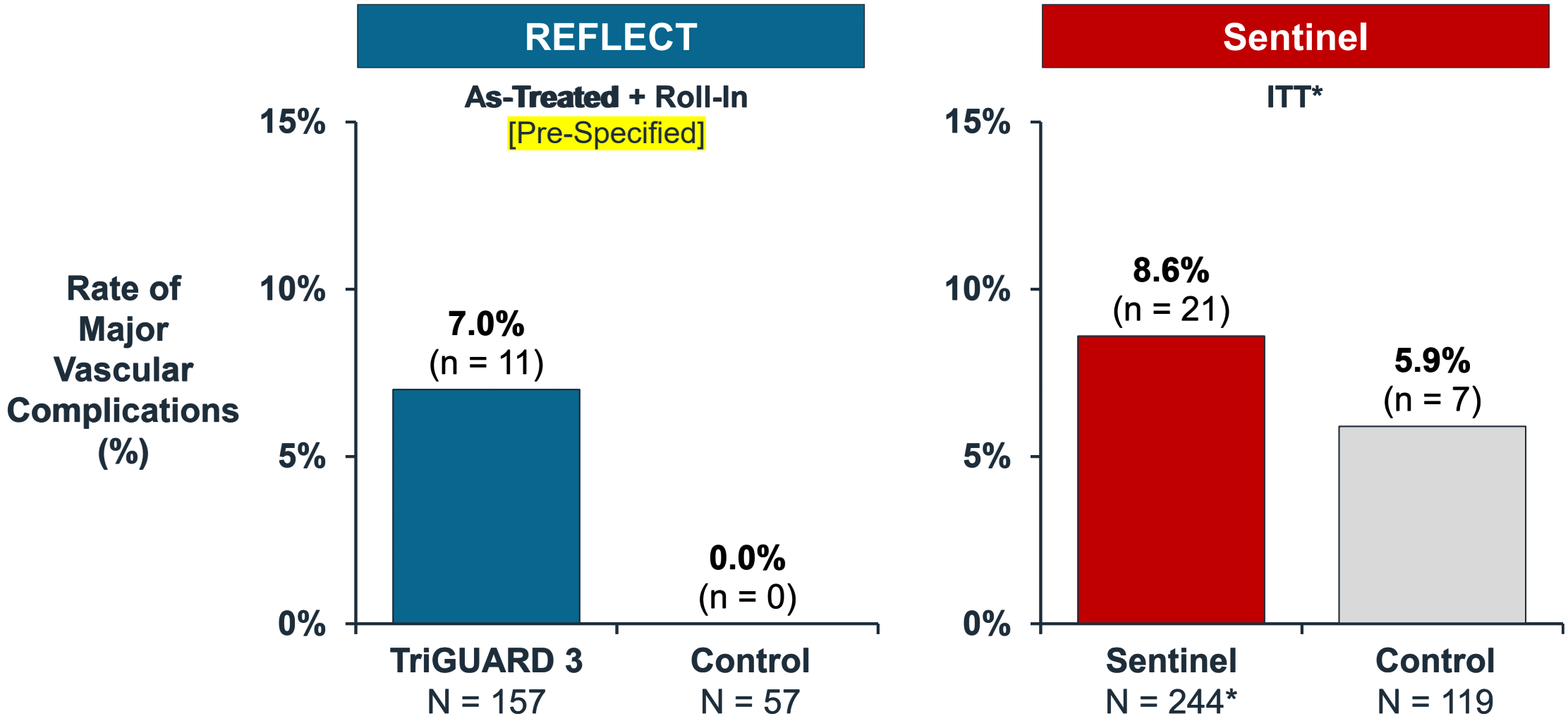


MACCE definition as per Sentinel Study

Rate of In-Hospital Stroke Similar Between Treatment Groups and Controls



Rate of All Major Vascular Complications Through 30-Days



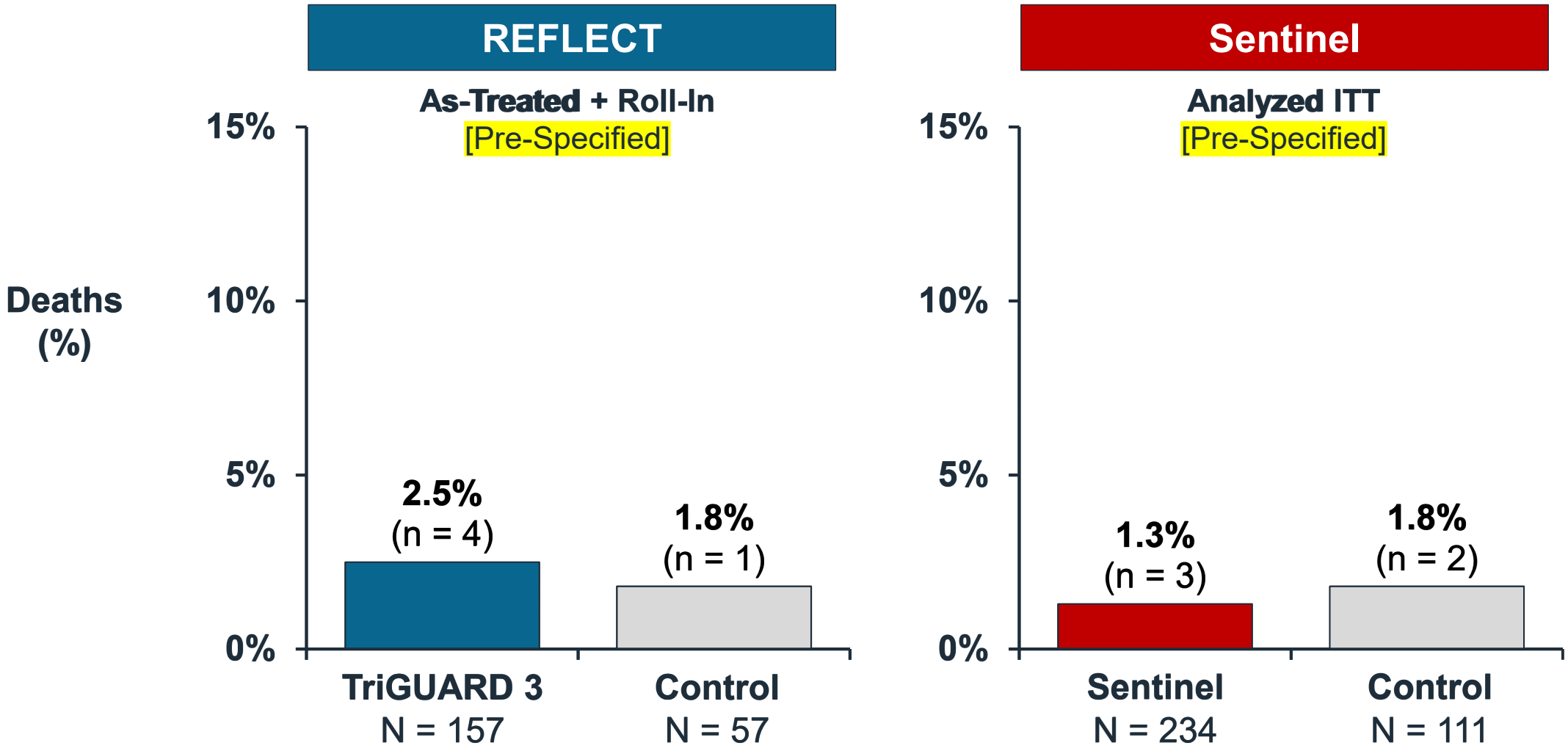
*Sentinel Study report rate of major vascular complications using ITT with imputation for missing data N = 244

TriGUARD Access Related and Sentinel Related Major Vascular Complications

	TriGUARD 3 As-Treated + Roll-In N = 157	Sentinel ITT N = 244*
Device-related vascular complication	**1.3%** (2)	**0.4%** (1)

*Sentinel Study report rate of major vascular complications using ITT with imputation for missing data N = 244

No Deaths in Either Study Adjudicated by CEC as Related to TriGUARD 3 or Sentinel



TriGUARD 3 is Substantially Equivalent to Sentinel, Meets all Special Controls

- The ability to safely deliver, deploy, and remove the device
- The ability of the device to filter embolic material while not impeding blood flow
- Secure positioning and stability of the position throughout the transcatheter intracardiac procedure
- Evaluation of all adverse events including death, stroke, and vascular injury

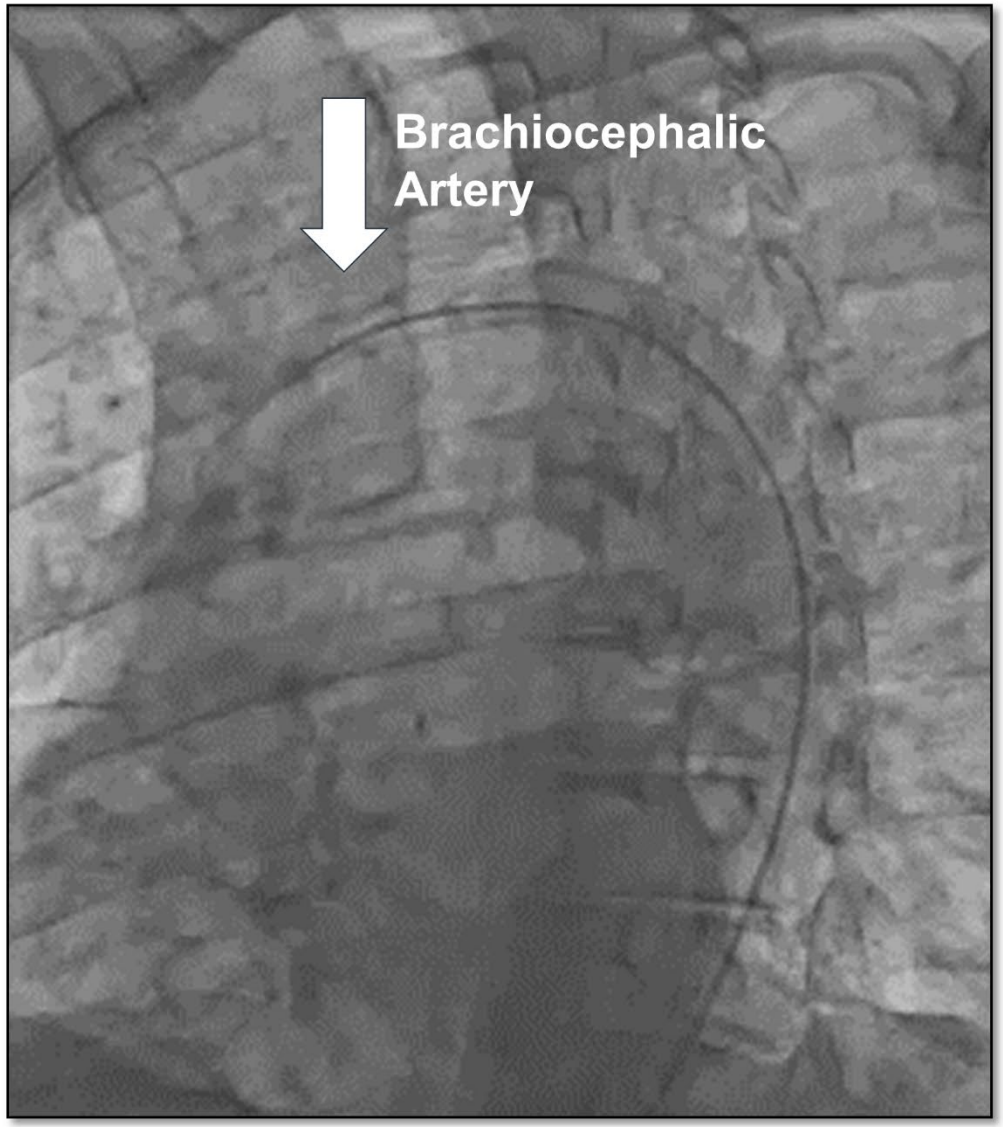
Real-World Evidence

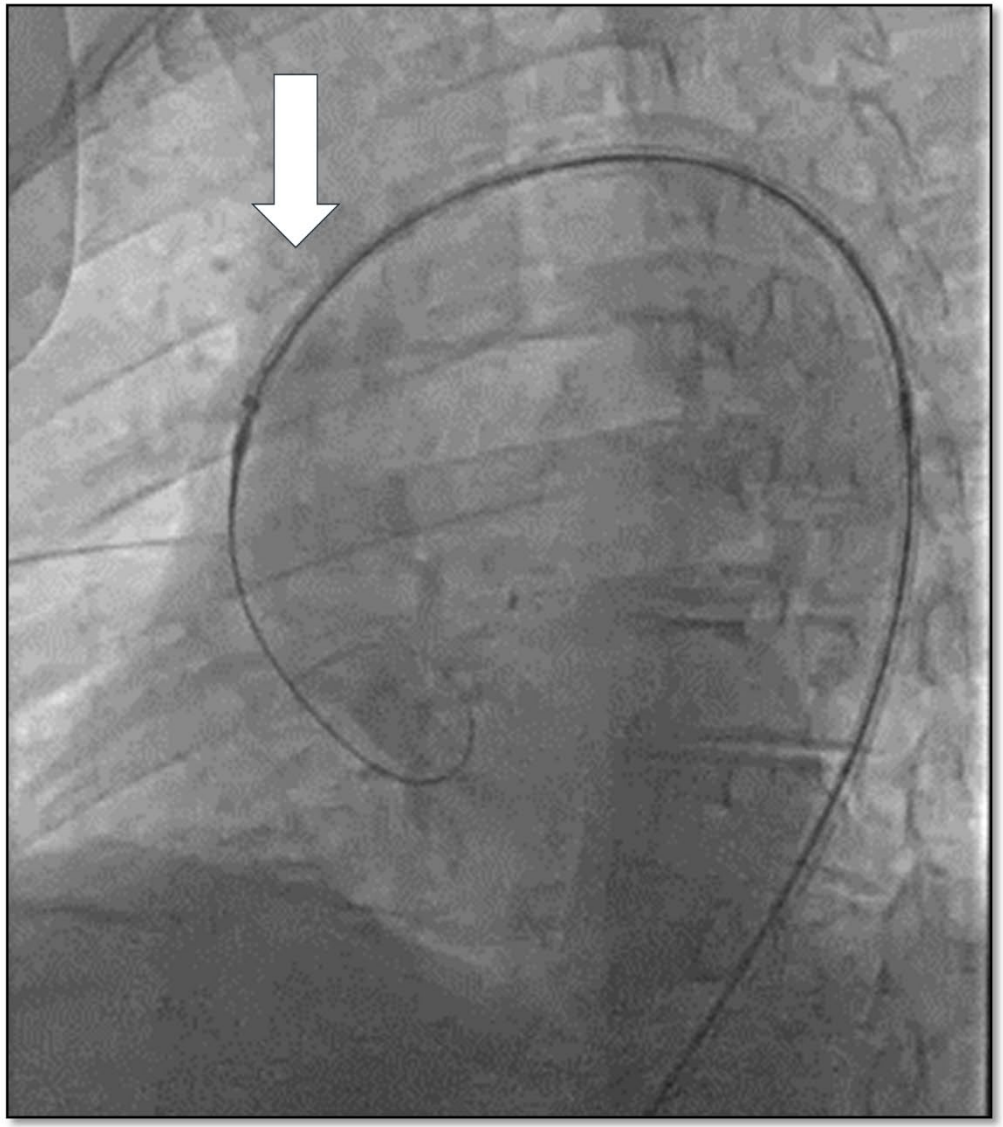
Pieter Stella, MD, PhD

Associate Professor,

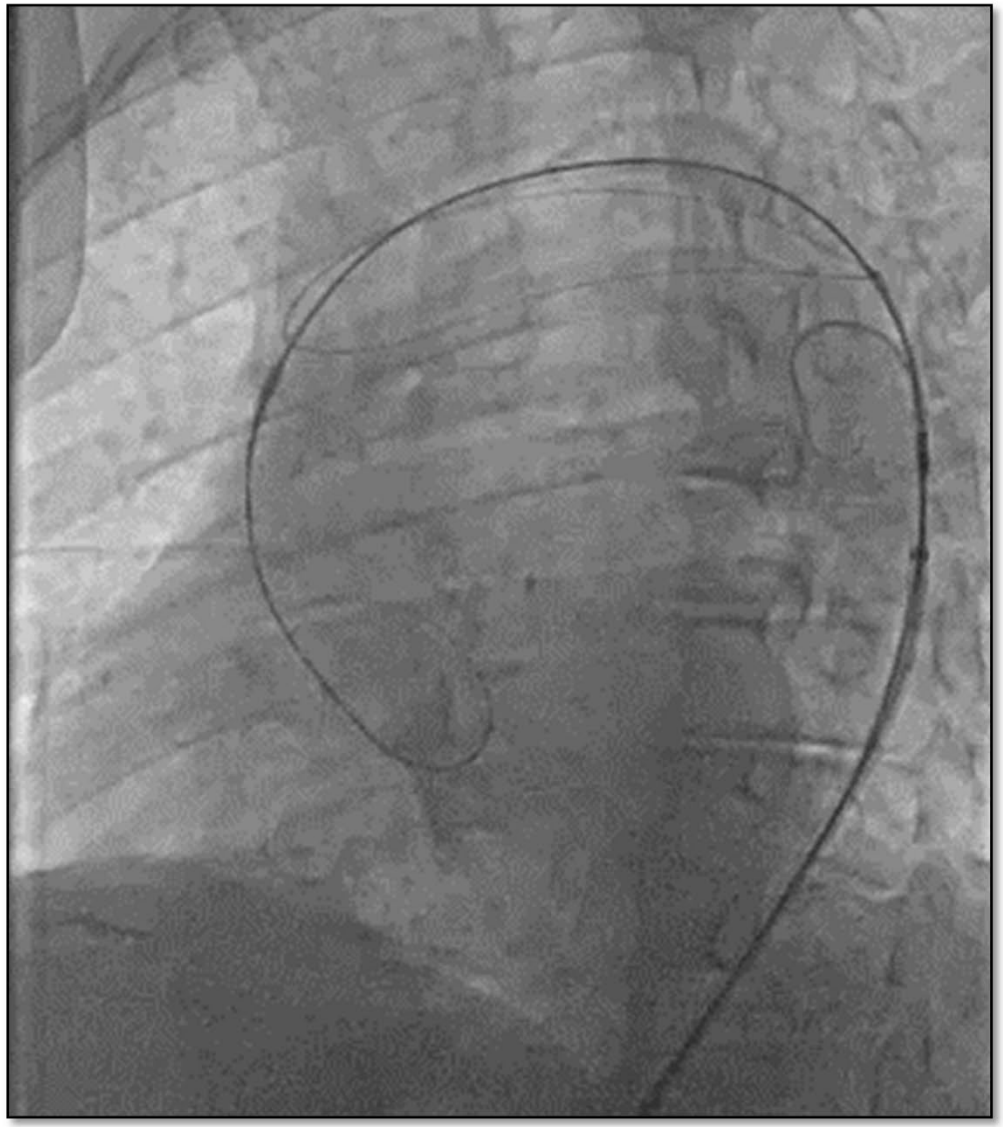
Utrecht Medical Center, The Netherlands

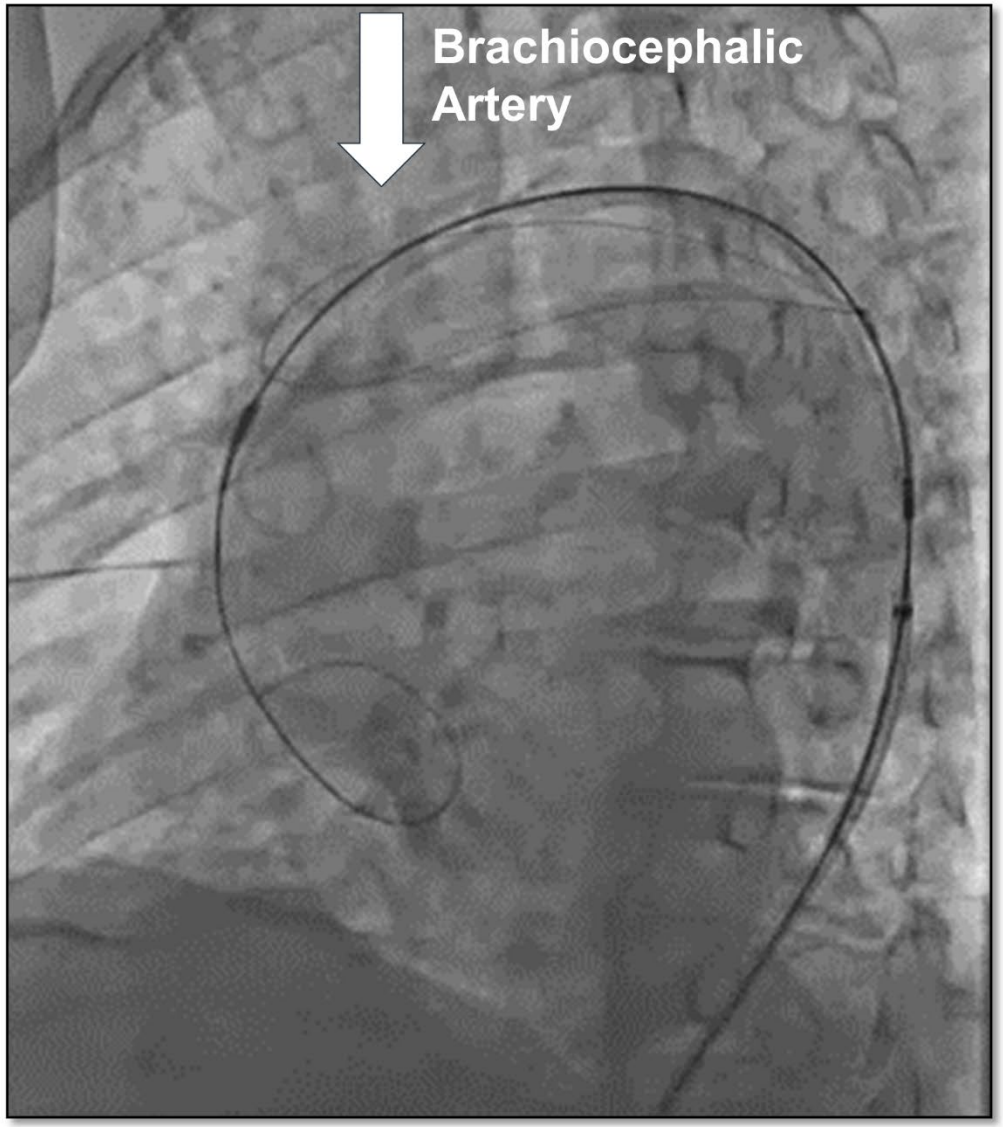
TriGUARD 3 - Initial Deployment



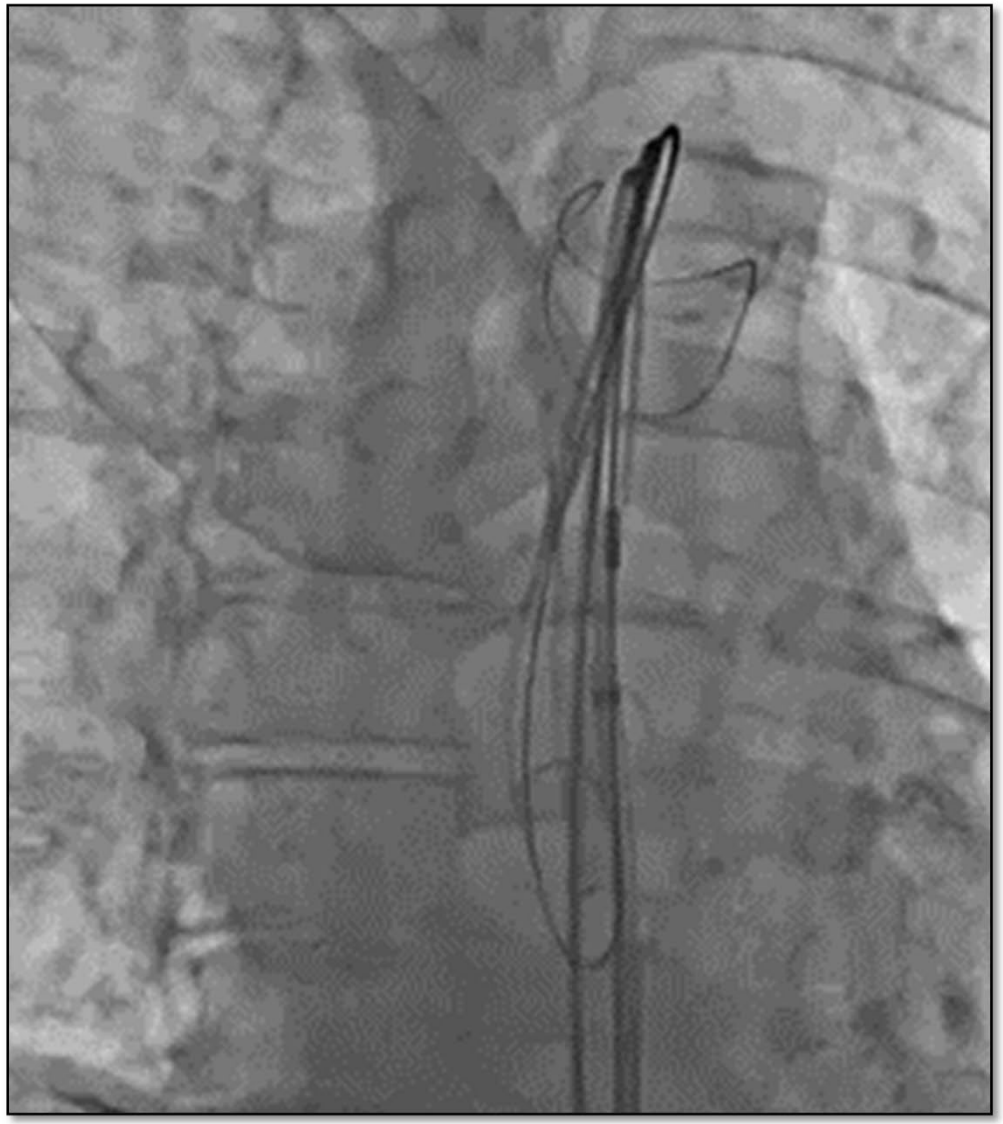


TAVR Pigtail Deployment

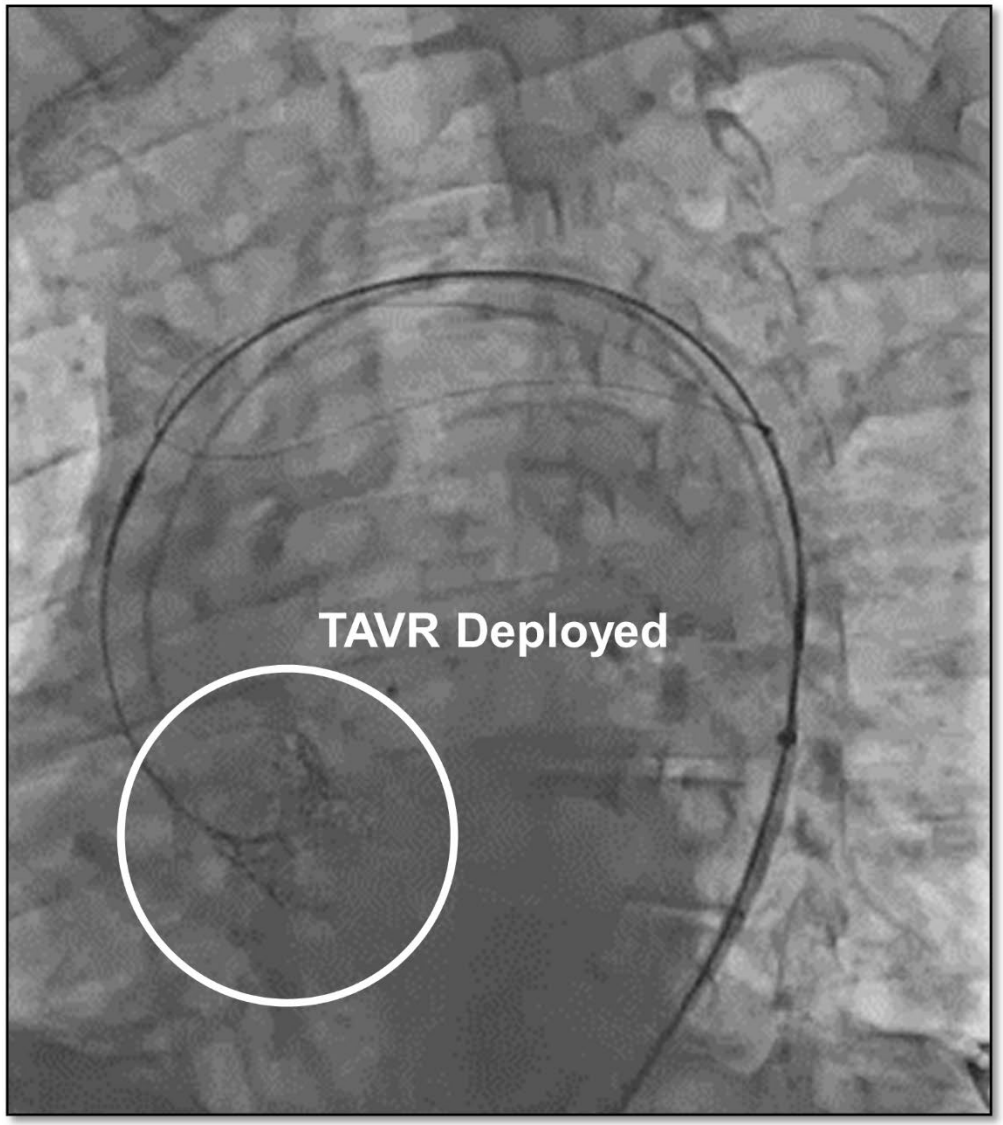




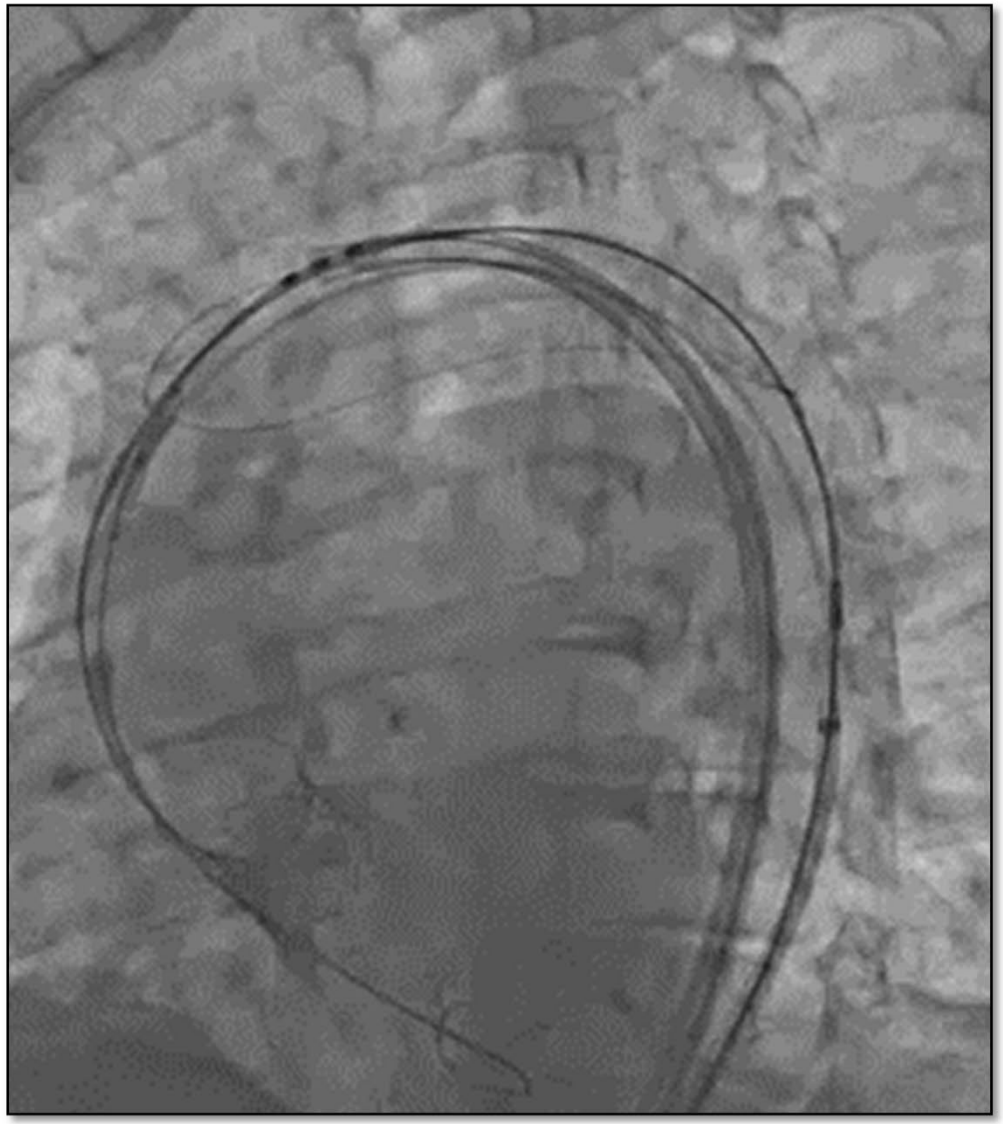
TAVR Crossing

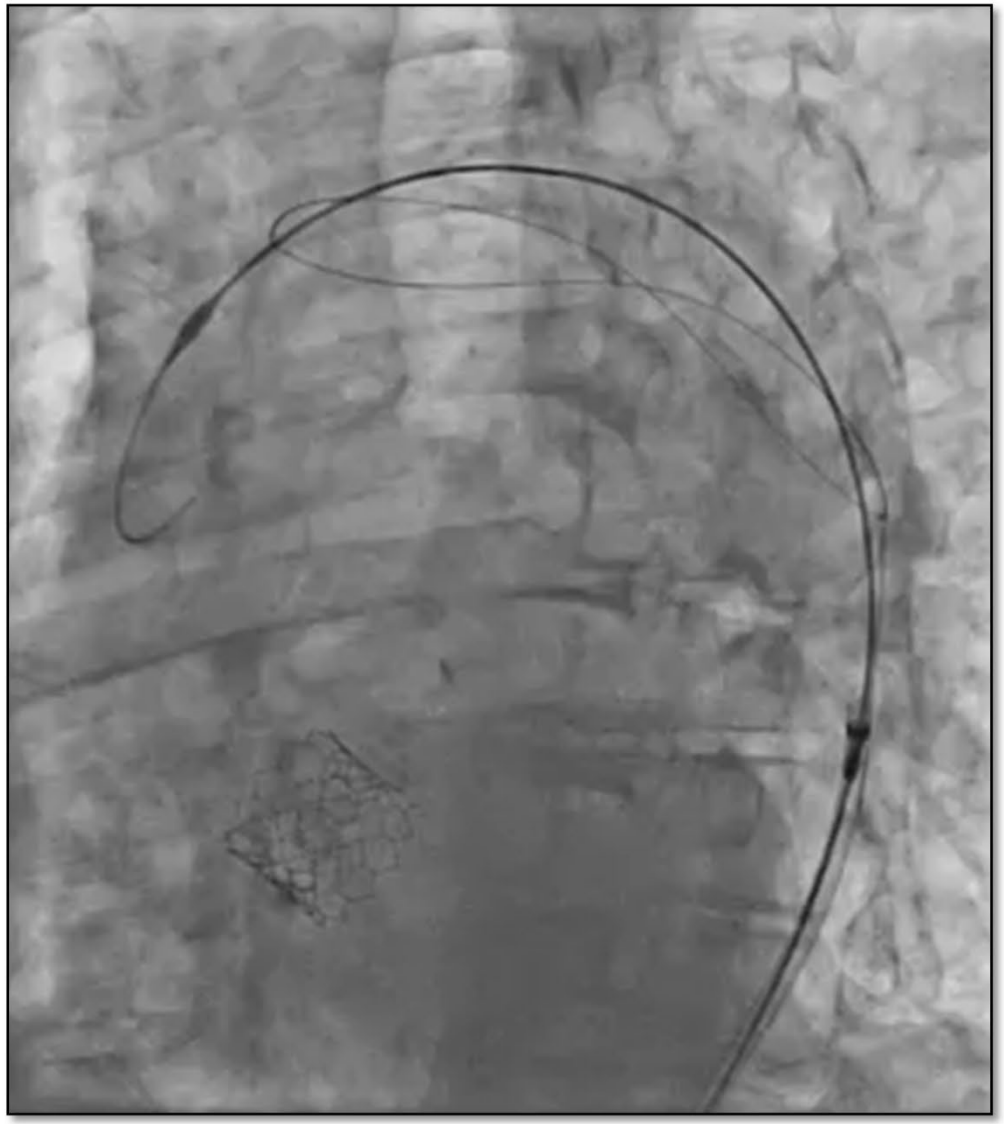


TAVR Deployment



TAVR Retrieval





75 Consecutive TriGUARD 3 Cases Since July of 2020

	UMC Utrecht		
	TriGUARD 3 First 50	TriGUARD 3 Next 25	TriGUARD 3 Total 75
Date range	Jul 2020 – Dec 2020	Dec 2020 – Jan 2021	Jul 2020 – Jan 2021
Number of patients	50	25	75
Presentation of data	Presented at CRT Provided to FDA	Presented at EuroPCR	Presented at EuroPCR

- > 400 TAVR cases with TriGUARD 3 completed in EU

First 50 subjects provided to FDA for review. Data on additional 25 subjects not reviewed by FDA.

Primary and Secondary Endpoints

Primary Endpoint

- Absence of neurological symptoms (Stroke or TIA) within 72 hours after TAVR
  - Assessed by treating physician

Secondary Endpoints

- Protection device related safety outcomes

Baseline Demographics and Characteristics Representative of TAVR Patients

	UMC Utrecht	
	TriGUARD 3 n = 50	TriGUARD 3 Total N = 75
Age (years), Mean (SD)	**80** (6)	**79** (11)
Male	**50%**	**53%**
Hypertension	**82%**	**71%**
NYHA Class III/IV	**26%**	**28%**
Prior stroke (CVA or TIA)	**20%**	**19%**
Diabetes	**22%**	**27%**
Prior atrial fibrillation	**40%**	**35%**
History of myocardial infarction	**10%**	**9%**
History of pulmonary obstructive disease	**10%**	**13%**

First 50 subjects provided to FDA for review. Data on additional 25 subjects not reviewed by FDA.

Complete 3-Vessel Coverage Achieved in 94.6% of Cases

Coverage	UMC Utrecht	
	TriGUARD 3 n = 50	TriGUARD 3 Total N = 75
Complete (3-vessel) confirmed	**100%** (50)	**94.6%** (71)
Removed during to TAVR due to Medical complication not related to TriGUARD 3	**0**	**5.4%** (4)

- Physician reports of angiographic imaging assessments at each important step of procedure

First 50 subjects provided to FDA for review. Data on additional 25 subjects not reviewed by FDA.

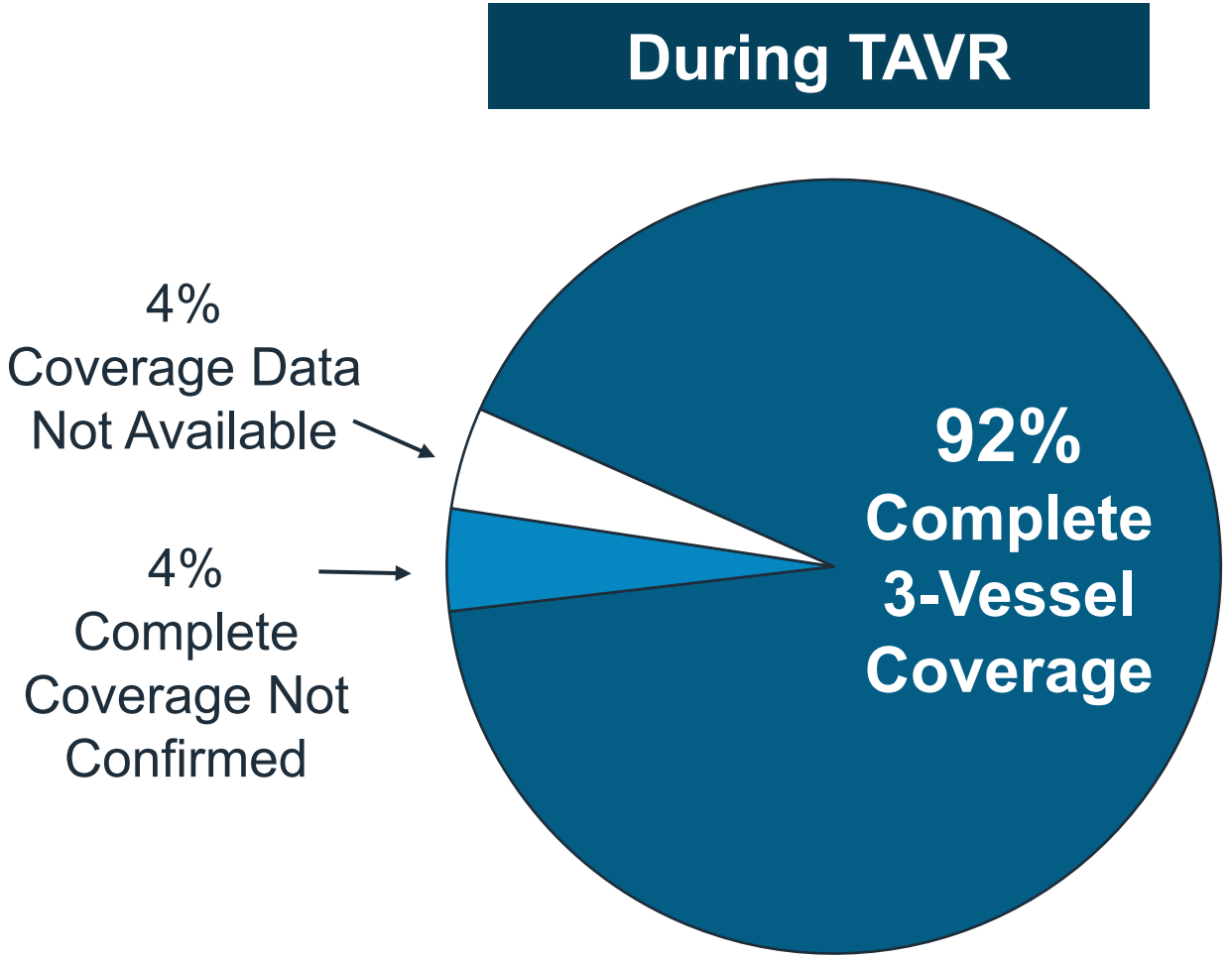
One Patient had Primary Safety Event

	UMC Utrecht		
	TriGUARD 3 n = 50	TriGUARD 3 Total N = 75	Outcomes
Stoke	0	0	
TIA	0	1.3% (1)	Resolved within 24 hours
Bleeding	0	0	
Dissection	0	2.7% (2)	Both resolved without sequalae

First 50 subjects provided to FDA for review. Data on additional 25 subjects not reviewed by FDA.

Other European Sites Confirmed 92% Coverage During TAVR Procedure

- 30 Sites
- 94 Procedures
- Mar 2020 – Dec 2021
- Physician reported coverage based on angiographic imaging



Data not previously reviewed by FDA

Conclusions from Real-World Experience

- TriGUARD 3 is easy and safe way to prevent cerebral embolic lesions during TAVR
- UMC Utrecht uses TriGUARD 3 as standard of care for patients undergoing TAVR procedures

Sponsor Perspective on FDA Questions

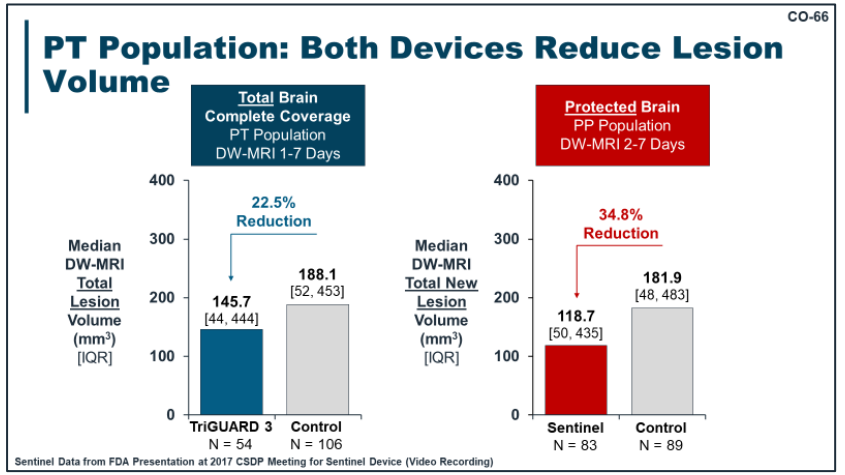
Karen Jaffe, MS, MBA, RAC

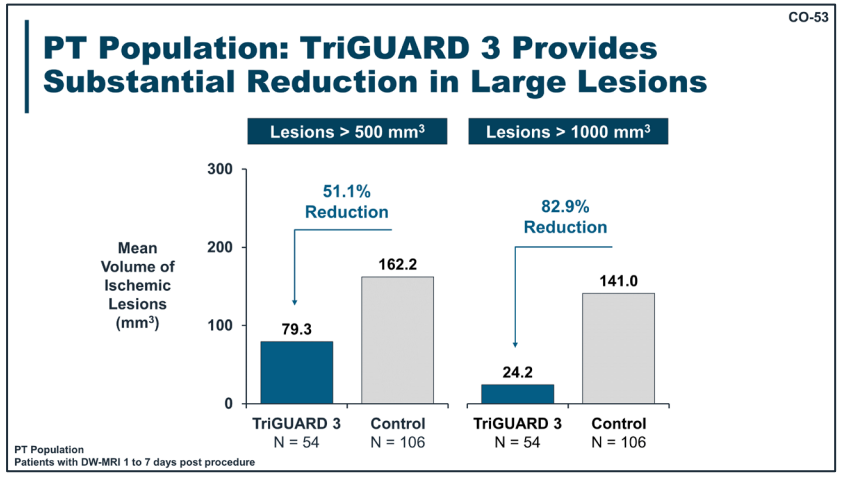
Regulatory Consultant

Keystone Heart

FDA Question: Clinical Significance of Effectiveness Endpoints

- Primary effectiveness endpoint not met
- 2017 CSDP supported favorable benefit risk profile of Sentinel and concluded
  - "*Preventing debris from reaching the cerebral circulation is a benefit.*"
- TriGUARD 3 and Sentinel provide consistent reduction in total lesion volume
- TriGUARD 3 reduces volume of large lesions
- Large lesions more likely to impact cognitive function[1]

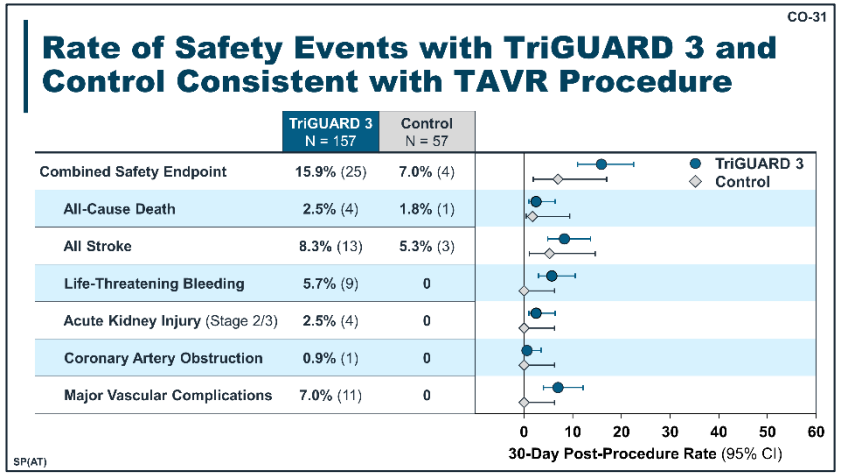


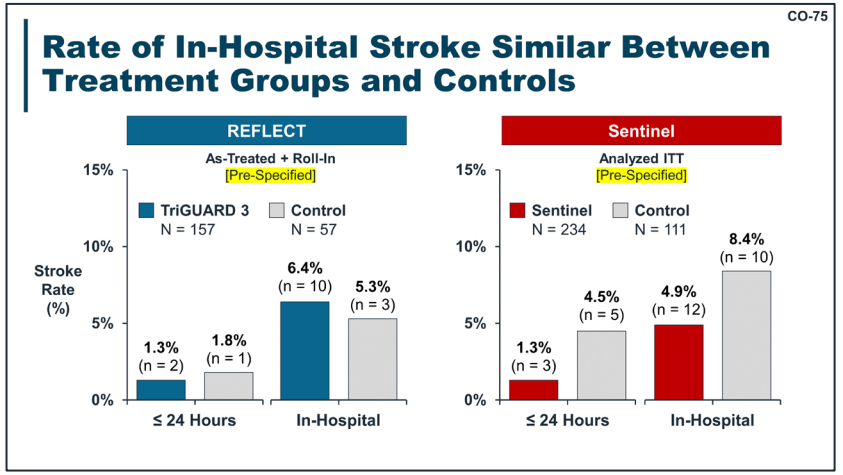


1. Choi, 2000; Nagaraja, 2020

FDA Question: Safety of TriGUARD 3 vs Control in REFLECT

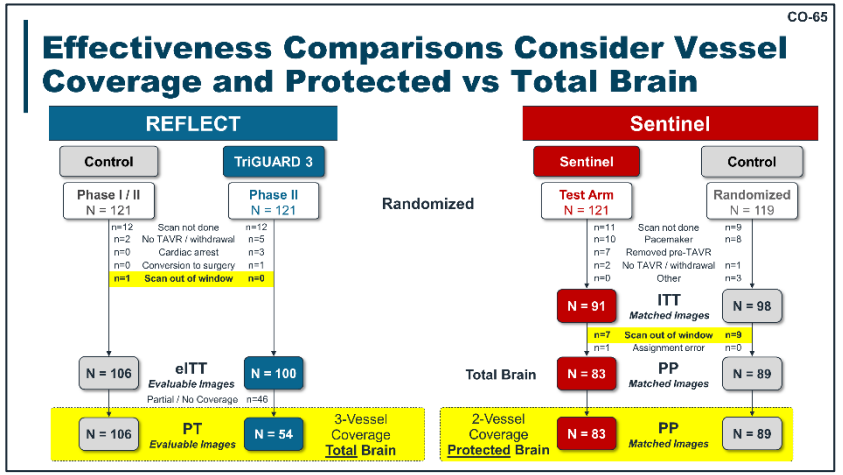
- REFLECT designed to evaluate TriGUARD safety vs pre-specified performance goal
  - Not powered for comparisons between groups on safety endpoints
- TriGUARD 3 does not increase risks associated with TAVR procedure
- Stroke rate ≤ 24 hours and in-hospital similar between TriGUARD 3 and Control
- In-hospital stroke rate between TriGUARD 3 and Sentinel support substantial equivalence

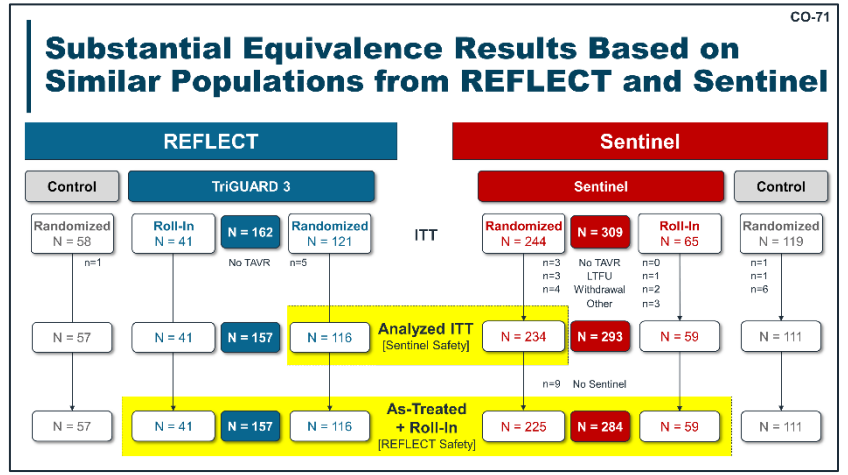




FDA Question: Appropriate Populations for Evaluation of Substantial Equivalence

- Cross-study comparisons should utilize similar populations and endpoints
- Effectiveness results use PT Population
- PT Population = Sentinel protected brain only
- Protocol defined assessment of poolability for control groups not met
  - Results provide increased precision
- Safety results based on similar outcomes across all populations in both studies

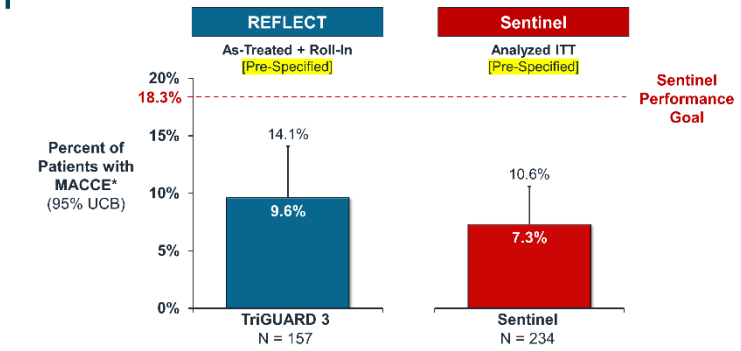




FDA Question: Importance of Device Relatedness

- Related adverse events should not be prioritized over all safety events
- All comparisons to Sentinel include all events
- TriGUARD 3 and Sentinel had similar MACCE rates
- Assessment of device relatedness are relevant to discussion of device safety
  - 2 of 25 primary safety events in REFLECT related or probably related to TriGUARD 3

30-Day MACCE Rate Similar Between TriGUARD 3 and Sentinel Device



MACCE definition as per Sentinel Study

2 of 11 Major Vascular Complications Were Adjudicated as Related by CEC

30-Day Outcome, % (n)	TriGUARD 3 N = 157
Combined Safety Endpoint	15.9% (25)
All-Cause Death	2.5% (4)
Stroke (Disabling and Non-Disabling)	8.3% (13)
Life-Threatening or Disabling Bleeding	5.7% (9)
Acute Kidney Injury (Stage 2/3)	2.5% (4)
Coronary Artery Obstruction	0.6% (1)
Major Vascular Complication	7.0% (11)
Valve-Related Dysfunction	0

Note: All major vascular complications were included in the primary endpoint, even if the event occurred at the TAVR access site, contralateral to the TriGUARD device.

- 2 events related to vascular access site
- TAVR device successful implanted

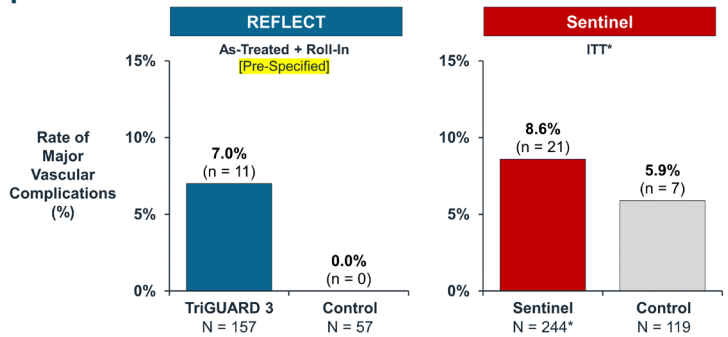
SP(AT)

FDA Question: Risk of 8-F Access Sheath

- TriGUARD utilizes contralateral access site
  - Does not require additional 3rd access
  - Benefit since each access site is potential opportunity for infection
- Major vascular complications
  - TriGUARD 3: 7.0% (1.3% related)
  - Sentinel: 8.6% (0.4% related)
- Major vascular complications with closure devices range between 6-10%

CO-76

Rate of All Major Vascular Complications Through 30-Days



*Sentinel Study report rate of major vascular complications using ITT with imputation for missing data N = 244

CO-77

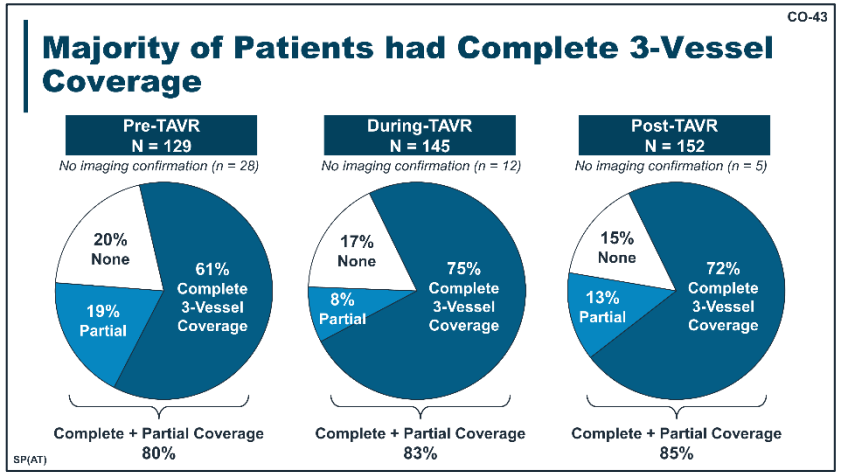
TriGUARD Access Related and Sentinel Related Major Vascular Complications

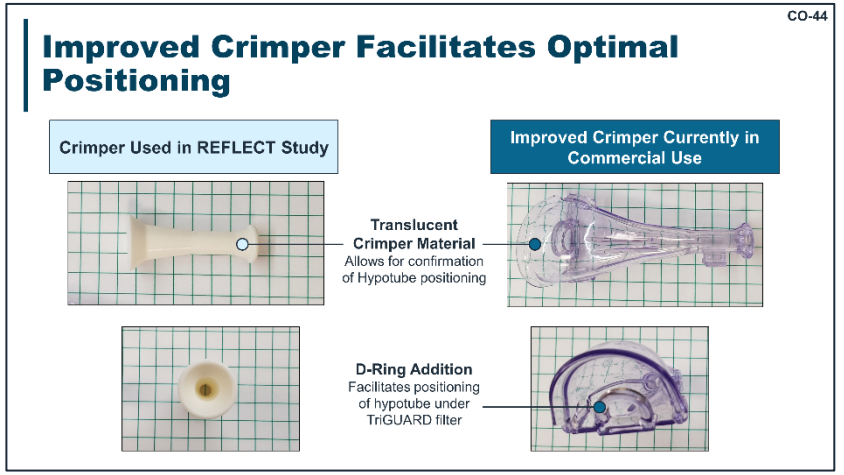
	TriGUARD 3 As-Treated + Roll-In N = 157	Sentinel ITT N = 244*
Device-related vascular complication	**1.3%** (2)	**0.4%** (1)

*Sentinel Study report rate of major vascular complications using ITT with imputation for missing data N = 244

FDA Question: Secure Positioning and Stability

- Conservative assessment of device positioning and coverage in REFLECT
- TriGUARD 3 maintained secure positioning and stability in 83 – 85% of cases
- Complete 3-vessel coverage in > 60% of cases
- > 72% of patients with 3-vessel coverage during and following TAVR deployment
- Updates to crimper and training materials have improved performance





FDA Question: Differences in Baseline Characteristics

- Numeric differences between study groups on certain baseline characteristics
  - Prior stroke or TIA
    17.2% TriGUARD 3 vs 5.3% in Control
  - Insulin-dependent diabetes
    5.8% TriGUARD 3 vs 10.5% Control
- Imbalances common in randomized trials with modest sample sizes
  - Not possible to accurately quantify impact on study results

CO-28

REFLECT Enrolled Patients with Severe Symptomatic Aortic Stenosis

Preferred Term	TriGUARD 3 N = 157	Control N = 57
Age (years), Mean (SD)	**80.3** (7.7)	**78.1** (8.2)
Male	**55%**	**61%**
STS Score, Mean (SD)	**4.6** (2.8)	**4.5** (2.5)
Previous Stroke (CVA or TIA)	**17.2%**	**5.3%**
Diabetes	**39.1%**	**40.4%**
Insulin dependent	5.8%	10.5%
Diet-controlled	18.6%	7.0%
Prior atrial fibrillation	**28.0%**	**29.8%**
History of carotid artery disease	**19.9%**	**23.2%**
History of pulmonary vascular disease	**12.9%**	**19.3%**

SP(AT)

TriGUARD 3 Substantially Equivalent to Legally Marketed Predicate Device, Sentinel

- Clearance for TriGUARD 3 is based on 510(k) pathway
- TriGUARD 3 met primary safety endpoint
  - Minimal additional risks as accessory device to TAVR
- TriGUARD 3 deflects embolic debris from entering brain
- TriGUARD 3 is substantially equivalent to Sentinel device
  - Met all 510(k) Special Controls

510(k) Submission for TriGUARD 3™ Cerebral Embolic Protection Device

To minimize risk of cerebral damage by deflecting embolic debris away from the cerebral circulation during TAVR

Circulatory System Devices Panel

Keystone Heart

August 3, 2021