

# **Changing Frequency, Comparison With SAVR, Diagnosis and Treatment in the “Modern” Era, and Use of Cerebral Protection**

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# Disclosure

- **Co PI for Sentinel trial**
- **No financial conflicts**

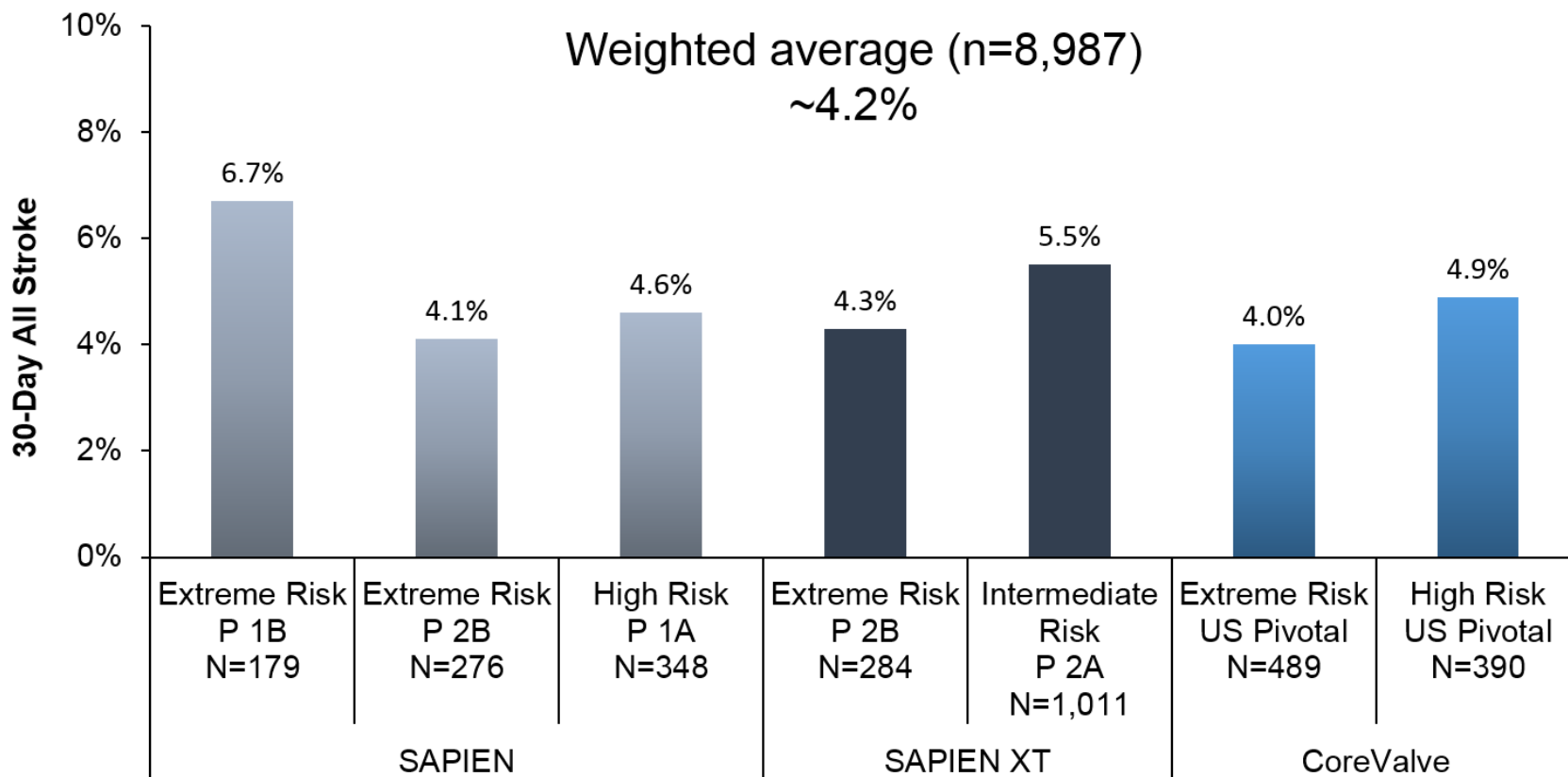
# Topics

- **Changing Frequency**
- **Comparison With SAVR**
- **Diagnosis and Treatment in the “Modern” Era**
- **Use of Cerebral Protection**

# Topics

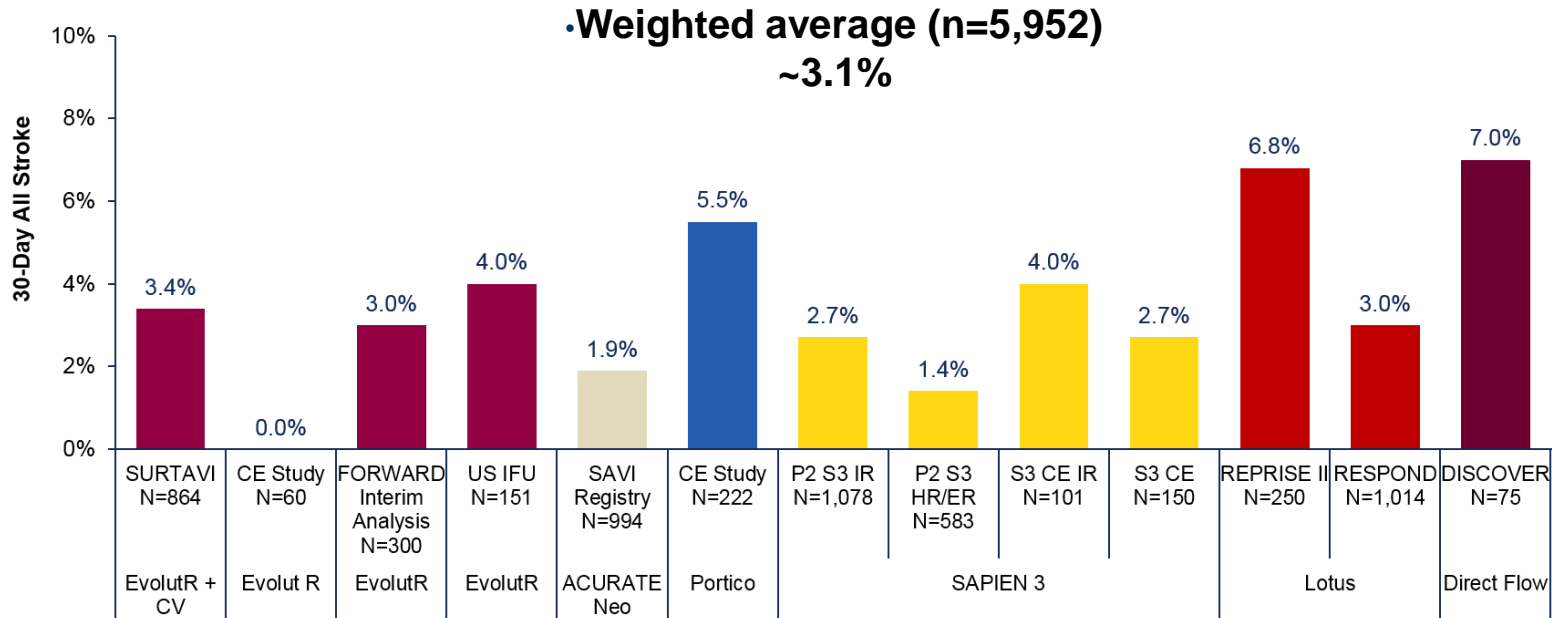
- **Changing Frequency**
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# Stroke Rates in Randomized Trials



<sup>1</sup>Leon, et al., *N Engl J Med* 2010;363:1597-1607; <sup>2</sup>Webb, et al., *J Am Coll Cardiol Intv* 2015;8:1797-806; <sup>3</sup>Smith, et al., *N Engl J Med* 2011;364:2187-98;  
<sup>4</sup>Leon, et al., *N Engl J Med* 2016;374:1609-20; <sup>5</sup>Popma, et al., *J Am Coll Cardiol* 2014;63:1972-81; <sup>6</sup>Adams, et al., *N Engl J Med* 2014;370:1790-8;;

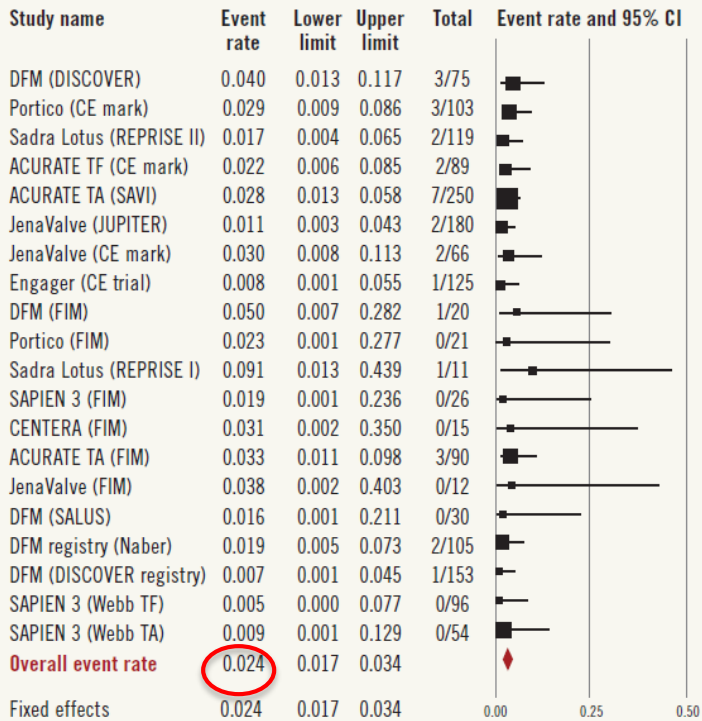
# Stroke Rates with Contemporary Devices



<sup>1</sup>Manoharan, et al., *J Am Coll Cardiol Interv* 2015; 8: 1359-67; <sup>2</sup>Moellman, et al., presented at PCR London Valves 2015; <sup>3</sup>Linke, et al., presented at PCR London Valves 2015; <sup>4</sup>Kodali, et al., *Eur Heart J* 2016; doi:10.1093/eurheartj/ehw112; <sup>5</sup>Vahanian, et al., presented at EuroPCR 2015; <sup>6</sup>Webb, et al. *J Am Coll Cardiol Interv* 2015; 8: 1797-806; <sup>7</sup>DeMarco, et al, presented at TCT 2015; <sup>8</sup>Meredith, et al., presented at PCR London Valves 2015; <sup>10</sup>Falk, et al., presented at EuroPCR 2016; <sup>11</sup>Kodali, presented at TCT 2016; Reardon, M Published in NEJM March 2017

# Stroke Risk With Second Generation TAVR valves

## B Event rate for 30-day major stroke



Compare with: PARTNER IA=3.8%, PARTNER IB=5.0%, PARTNER IIB=3.1%, CoreValve High Risk=3.9%, CoreValve Extreme Risk=2.3%. UK TAVI=4.1%\*, FRANCE 2=2.3%, European Sentinel Registry=1.8%. Meta-analysis of 2nd generation TAVI valves ( $I^2=36.471$ ,  $\tau^2=0.00$ )

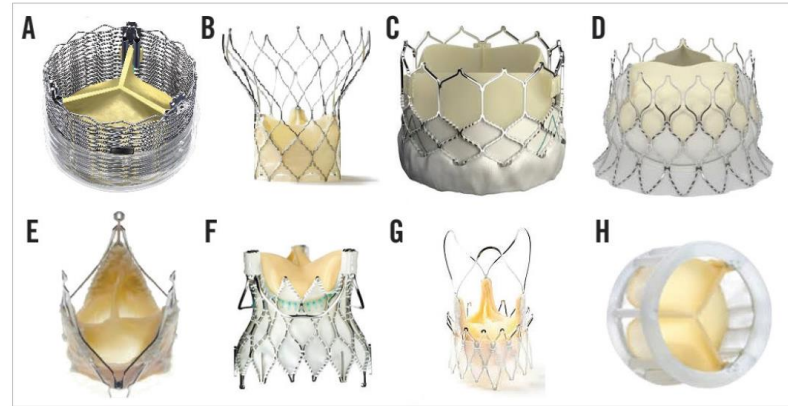
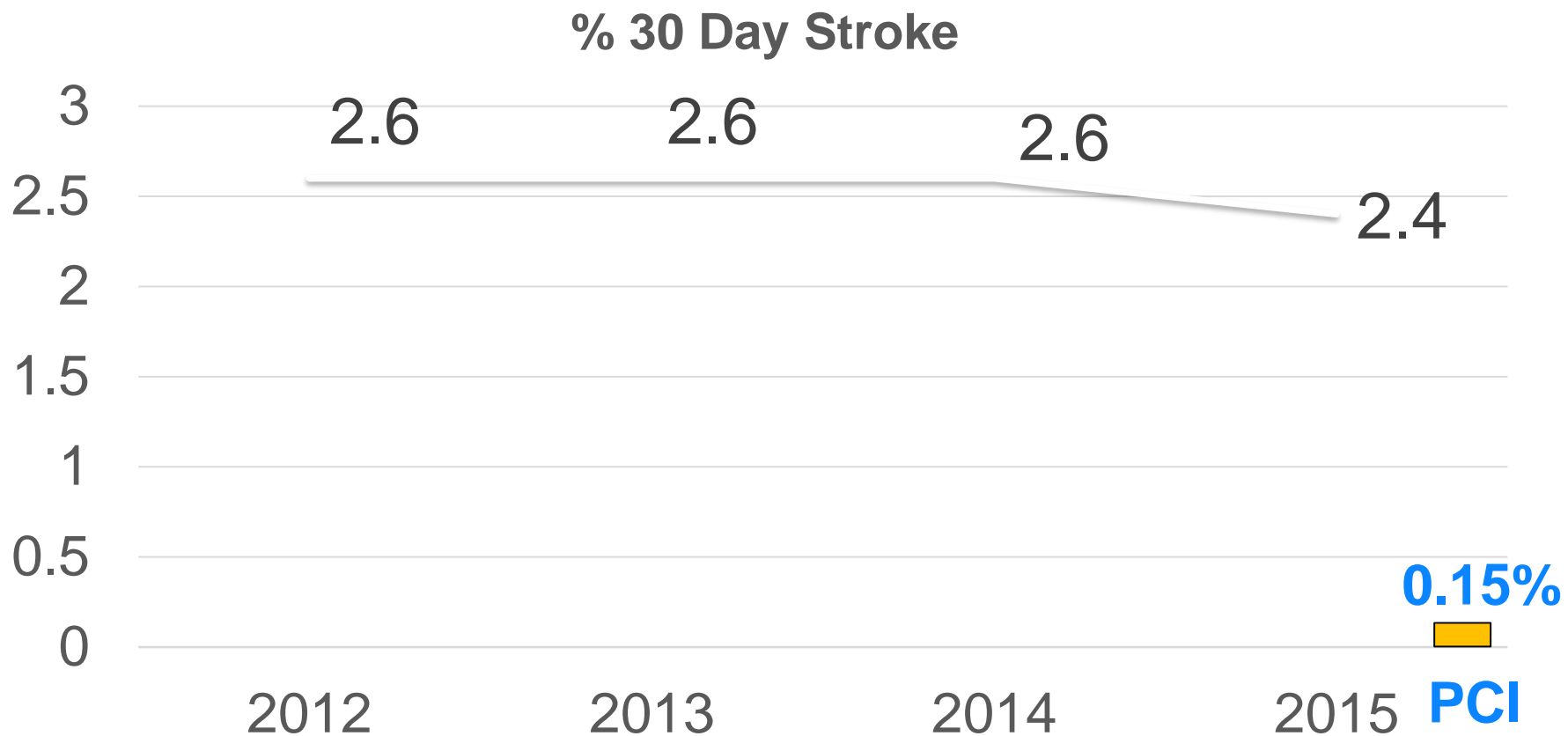


Figure 7. Second-generation transcatheter aortic valves. A) Sadra™ Lotus Medical valve (Boston Scientific SciMed Inc, Maple Grove, MN, USA); B) Portico® valve (St. Jude Medical); C) Edwards SAPIEN 3 valve (Edwards Lifesciences); D) Edwards CENTERA valve (Edwards Lifesciences); E) JenaValve (JenaValve Technology); F) Engager™ valve (Medtronic Inc.); G) Symetis ACURATE™ valve (Symetis SA); H) Direct Flow Medical® valve (Direct Flow Medical).

- **Meta-analysis of ~20 non-randomized, mostly FIM, valve-company sponsored studies**
- **2.4% major stroke at 30-days**

Athappan, et al. A systematic review on the safety of second-generation transcatheter aortic valves. *EuroIntervention* 2016; 11:1034-1043

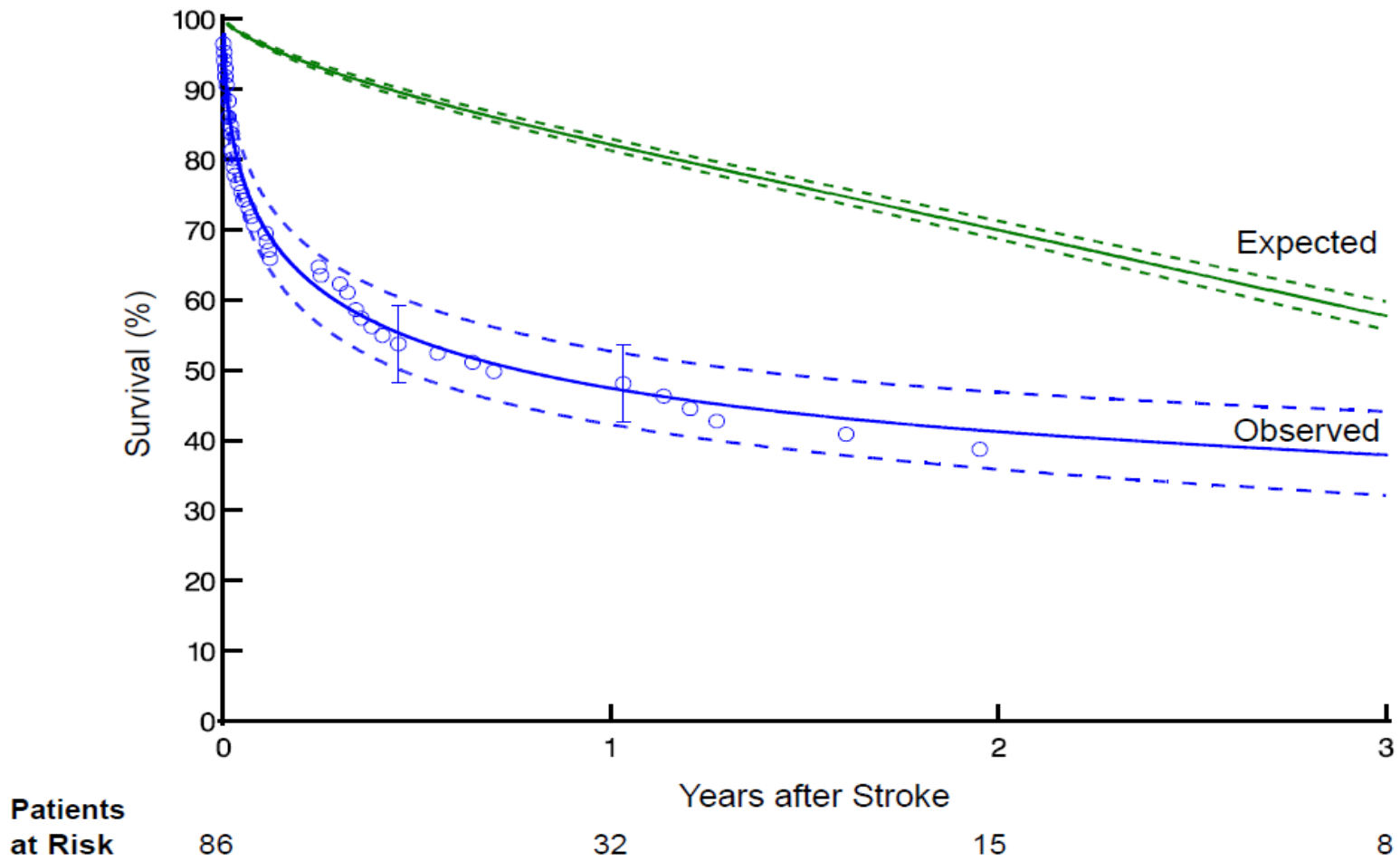
# TVT Stroke Rate





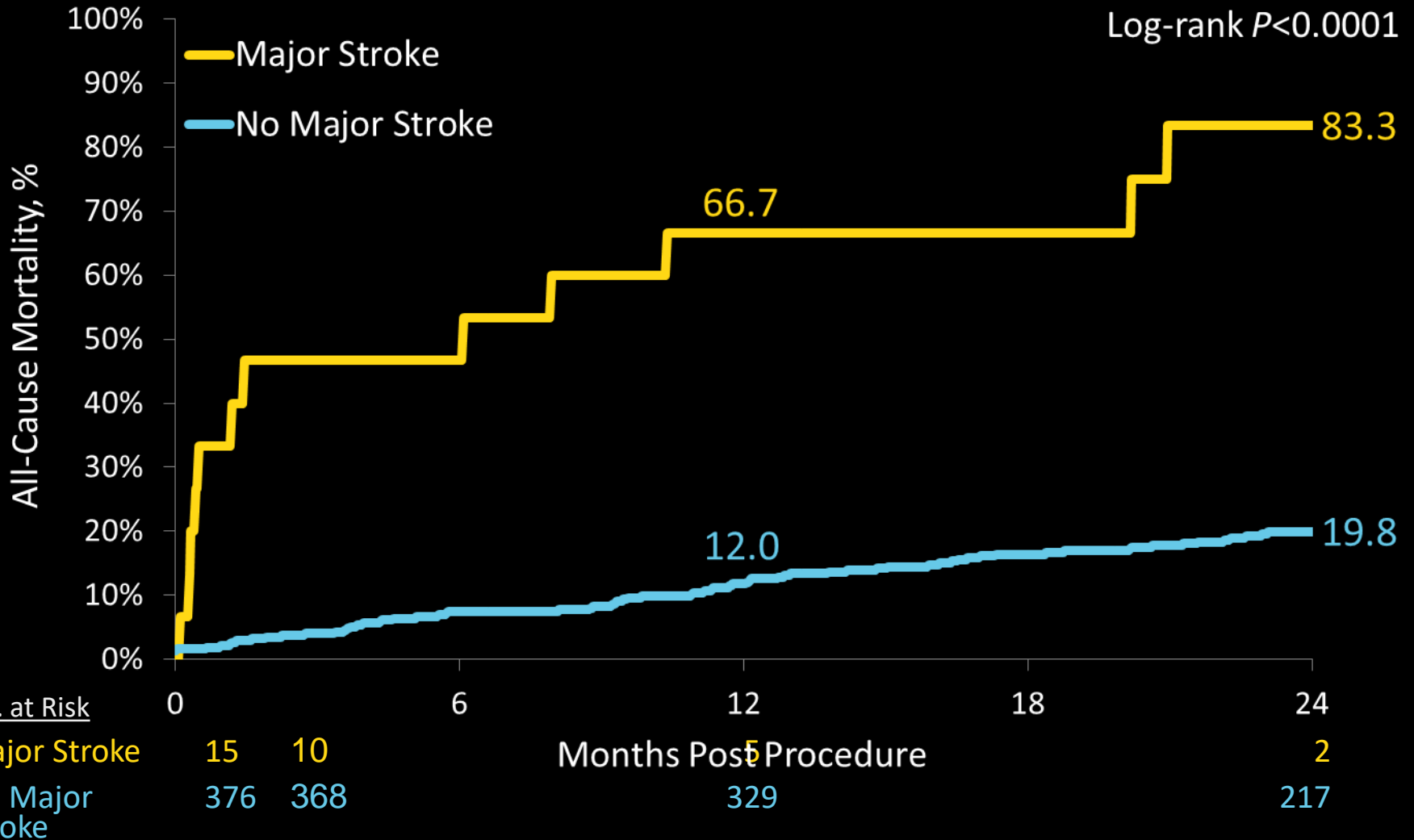
# Mortality After Stroke

## TF TAVR – PARTNER Trial



# Mortality after Stroke

## CoreValve High Risk Trial



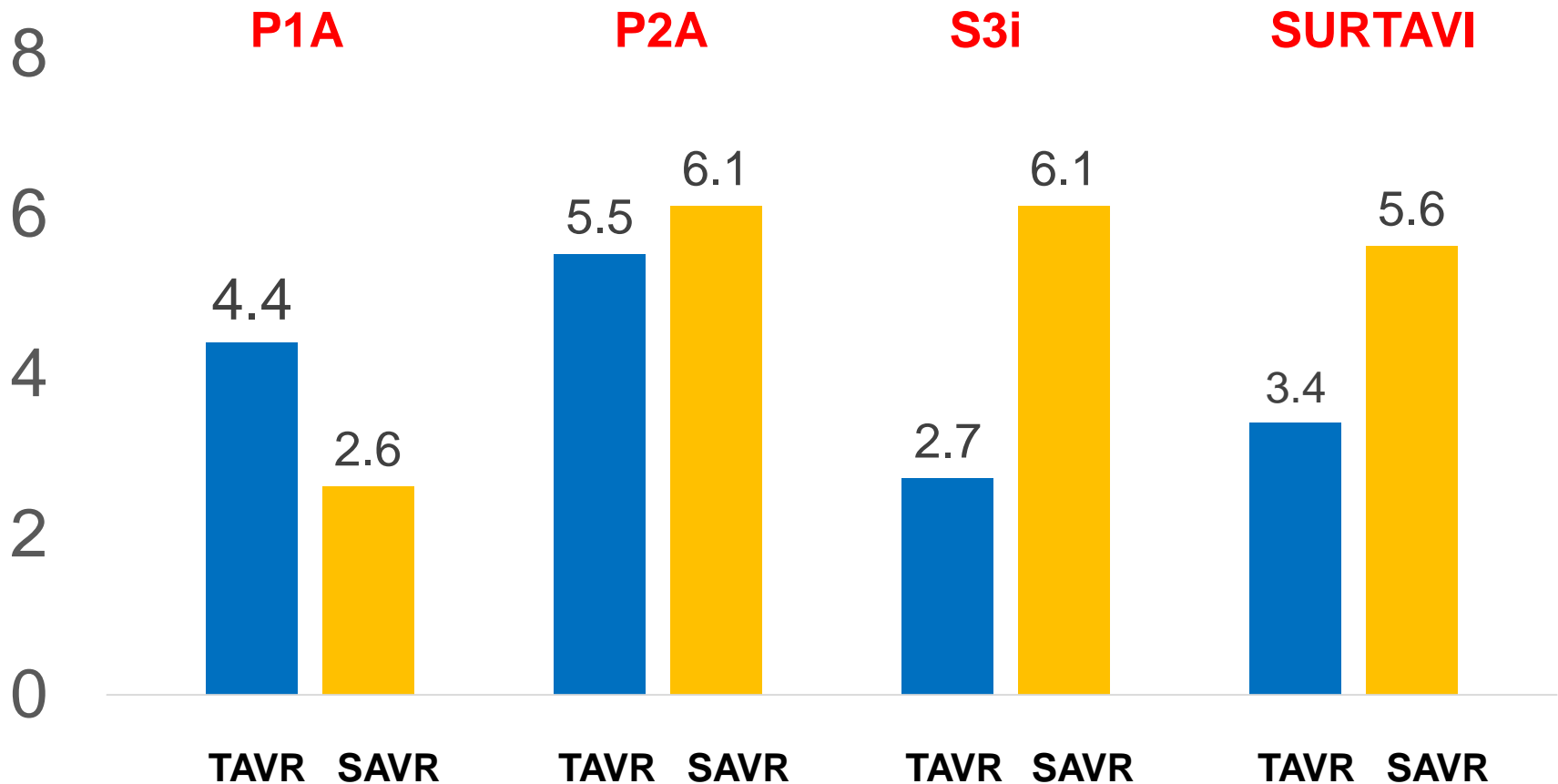
# Stroke Risk Summary

**Stroke risk is decreased compared to early feasibility trials (but not much) and is still a significant clinical problem**

# Topics

- **Changing Frequency**
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# Stroke : TAVR versus SAVR



# Superiority Analysis

## Components of Primary Endpoint (VI)

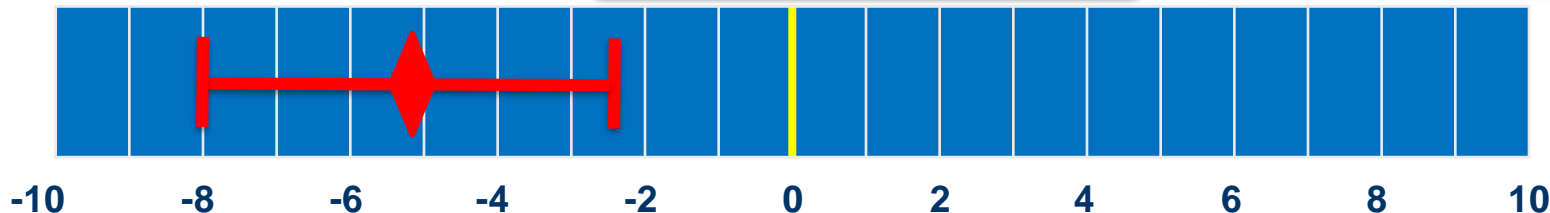


Favors TAVR Favors Surgery

### Mortality

Weighted Difference -5.2%  
Upper 2-sided 95% CI -2.4%

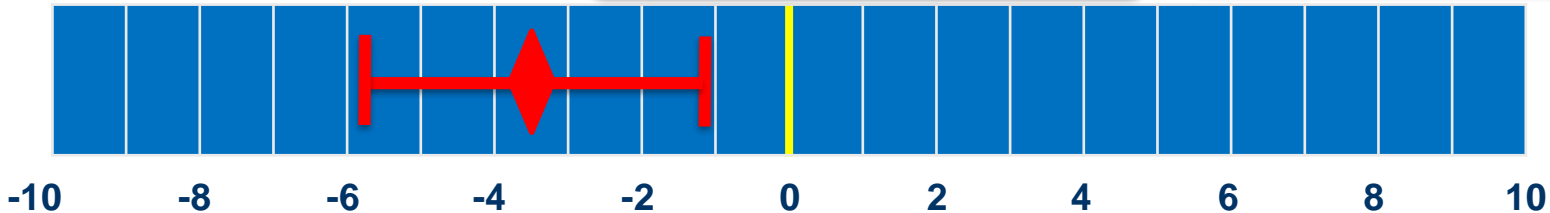
Superiority Testing  
p-value < 0.001



### Stroke

Weighted Difference -3.5%  
Upper 2-sided 95% CI -1.1%

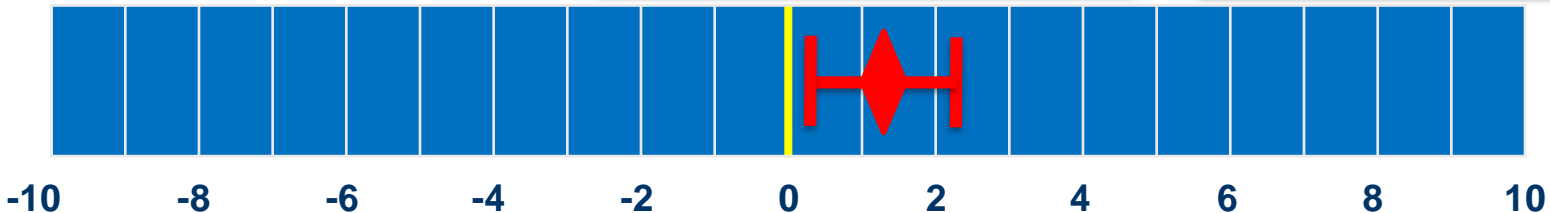
Superiority Testing  
p-value = 0.004



### AR ≥ Moderate

Weighted Difference +1.2%  
Lower 2-sided 95% CI +0.2%

Superiority Testing  
p-value = 0.0149



# Stroke with TAVR and SAVR

- **Equal or less with TAVR compared to SAVR**

# Topics

- **Changing Frequency**
- **Comparison With SAVR**
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- **Use of Cerebral Protection**



# Cardiovascular Surgery

## Stroke After Aortic Valve Surgery Results From a Prospective Cohort

Steven R. Messé, MD; Michael A. Acker, MD; Scott E. Kasner, MD; Molly Fanning, BS;  
Tania Giovannetti, PhD; Sarah J. Ratcliffe, PhD; Michel Bilello, MD, PhD;  
Wilson Y. Szeto, MD; Joseph E. Bavaria, MD; W. Clark Hargrove, III, MD;  
Emile R. Mohler III, MD; Thomas F. Floyd, MD;  
for the Determining Neurologic Outcomes from Valve Operations (DeNOVO) Investigators

**Conclusions**—Clinical stroke after AVR was more common than reported previously, more than double for this same cohort in the Society for Thoracic Surgery database, and silent cerebral infarctions were detected in more than half of the patients undergoing AVR. Clinical stroke complicating AVR is associated with increased length of stay and mortality. (*Circulation*. 2014;129:2253-2261.)

# Stroke Detection and Reporting

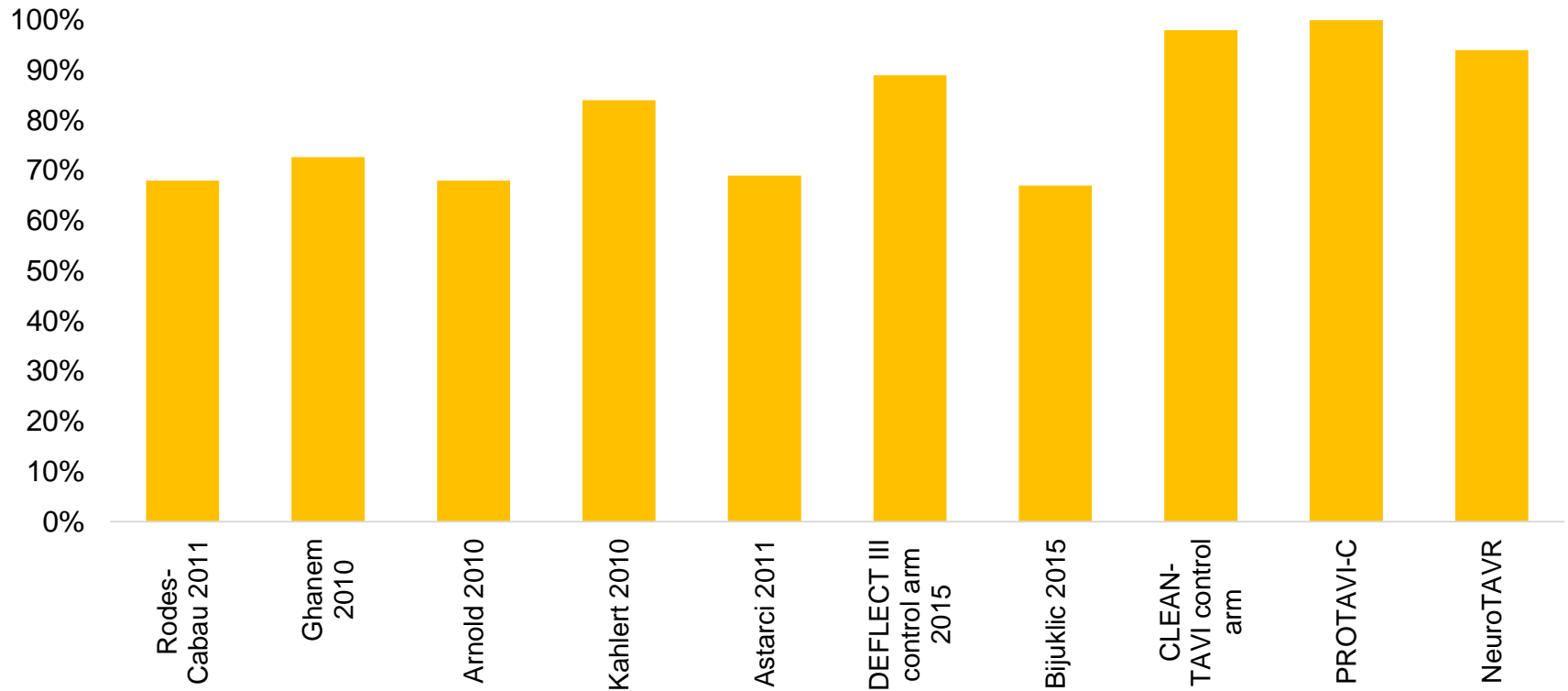
- **Strokes = 34 patients (17%; 95% CI, 12-23%)**
- **TIA = 4 patients (2%; 95% CI, 0 -4%)**
- **25 “strokes” were not included in STS database**



- **STS database reported 13 patients (6.6%) with stroke but 4 did not have stroke by DeNOVO (alcohol withdrawal, no deficit by day 7)**

# MRI Lesions After TAVR

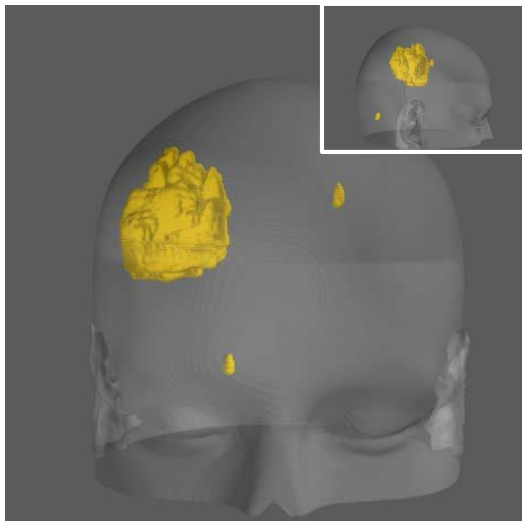
% of TAVI patients with new cerebral lesions on DW-MRI



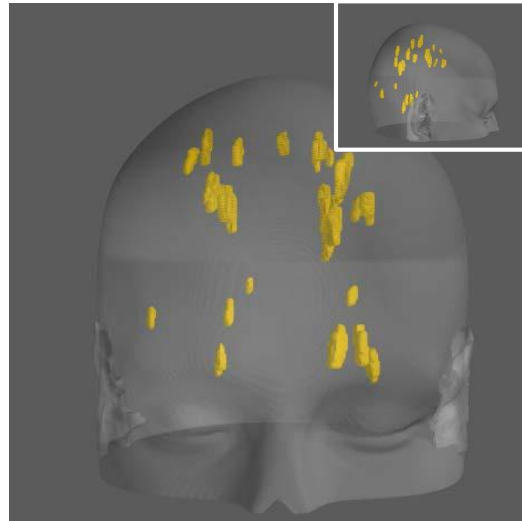
- 1. Rodes-Cabau, et al., JACC 2011; 57(1):18-28
- 2. Ghanem, et al., JACC 2010; 55(14):1427-32
- 3. Arnold, et al., JACC:CVI 2010; 3(11):1126-32
- 4. Kahlert, et al., Circulation. 2010;121:870-878
- 5. Astarci, et al., EJCTS 2011; 40:475-9
- 6. Lansky, et al., EHJ 2015; May 19
- 7. Bijuklic, et al., JACC: CVI 2015
- 8. Linke, et al., TCT 2014
- 9. Vahanian, TCT 2014
- 10. Lansky, et al. London Valves 2015
- 11. Sacco et al., Stroke 2013
- 12. Vermeer et al., Stroke 2003
- 13. Vermeer et al., New Engl J Med 2009

# Overt Stroke – Size, Number, LOCATION

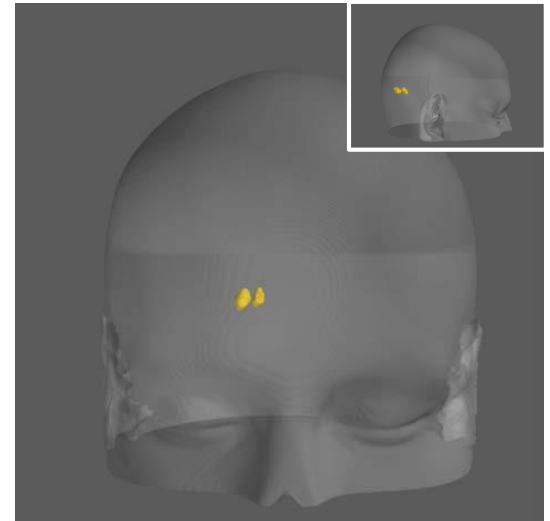
**Size**



**Number**

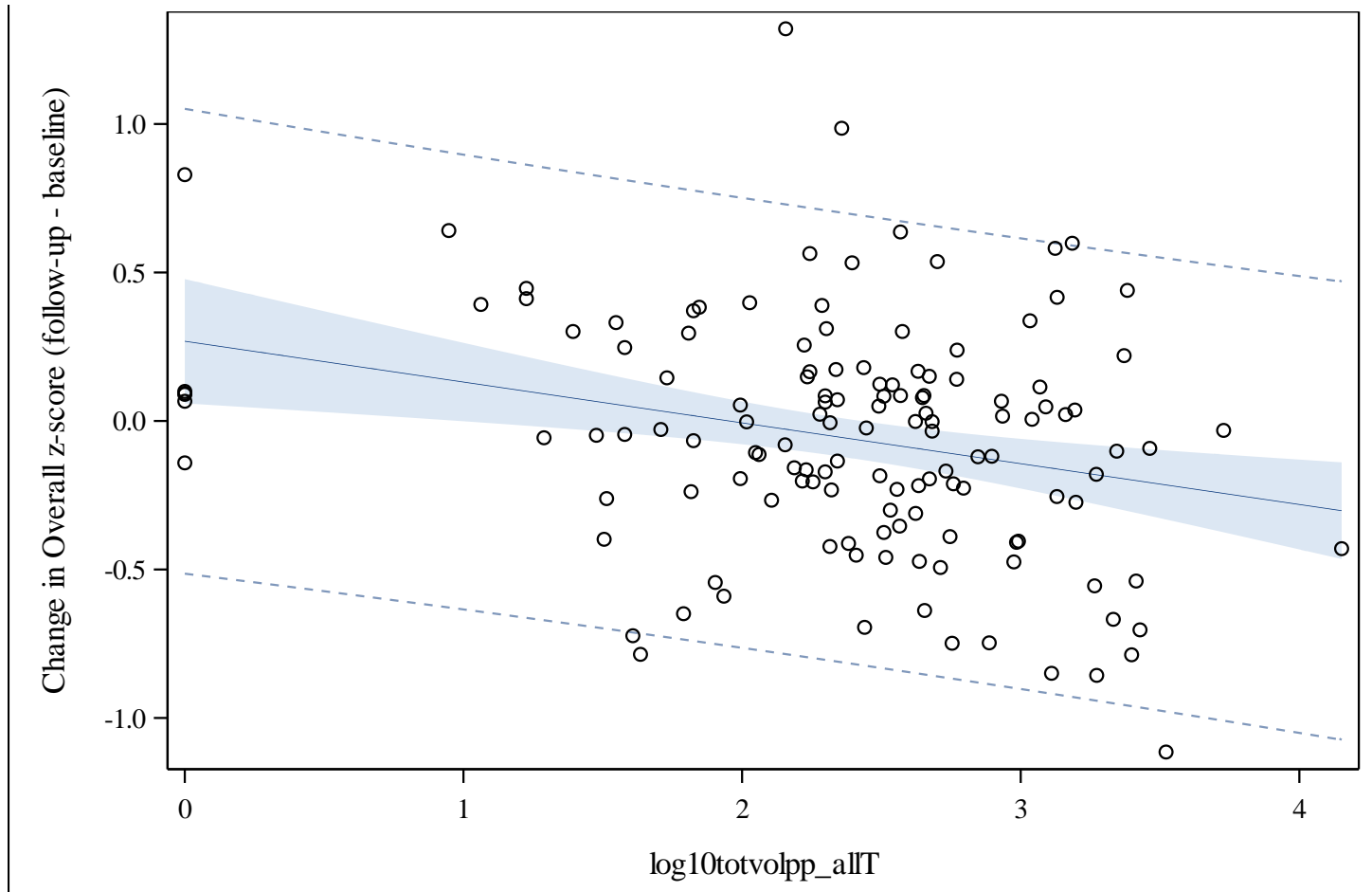


**Location**



# Neurocognitive Changes and Lesions

Lesion Volume, All Territories,  $P=0.0015$




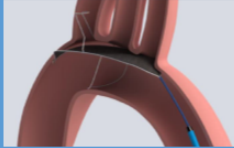



# Summary of Diagnosis

- **Stroke diagnosis requires careful neurologist evaluation for being accurate**
- **Brain infarction (“covert stroke”) is more common**
- **Neurocognitive changes may correlate with “covert strokes”**

# Topics

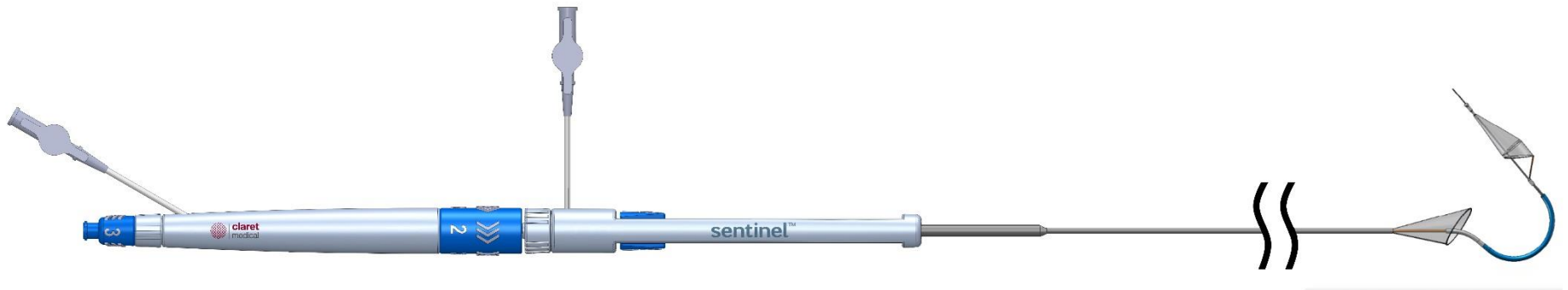
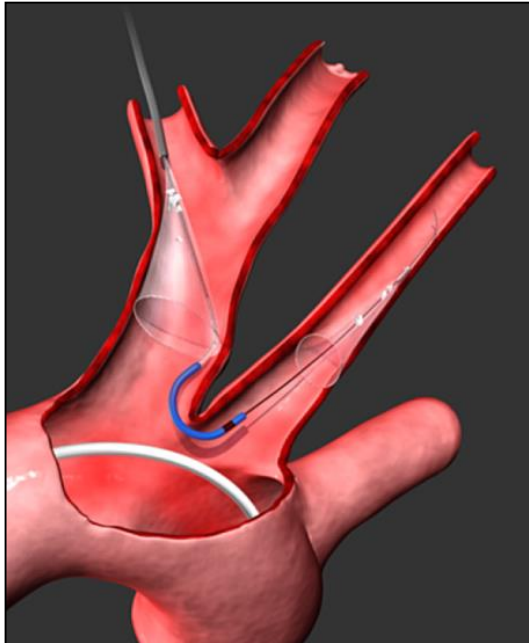
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# Cerebral Protection

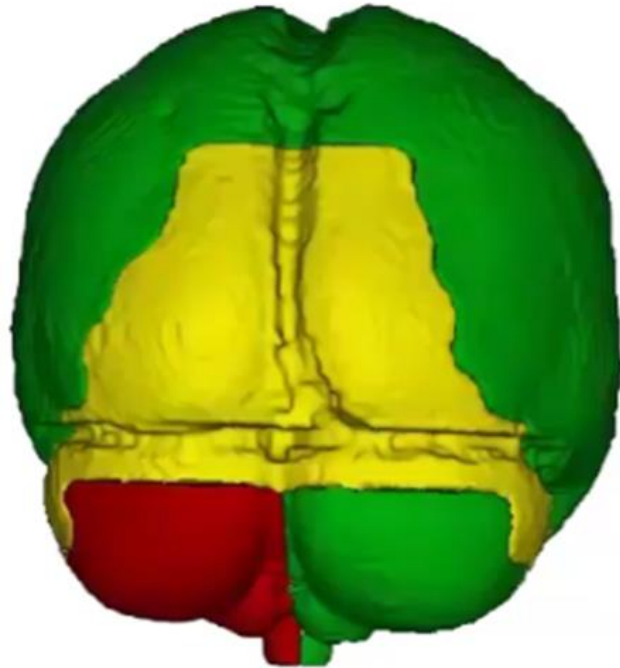
Company and Product	Claret Medical Sentinel 	Keystone TriGuard 	Edwards Embrella 	ICS Emblok 	Transverse Point-Guard 
<b>EU Status</b>	CE Mark 97% market share	CE Mark 3% market share	CE Mark <3% market share	FIM first clinical case March 15, 2017	Pre-clinical/prototype
<b>US Status</b>	IDE study completed Positive FDA Panel Feb 23, 2017	IDE trial underway	No IDE yet	No IDE yet	No IDE yet
<b>Access</b>	6 Fr Right Radial	9Fr TF	Right Radial	12Fr TF sheath	TF
<b>Debris</b>	Captures and removes	Deflects downstream	Deflects downstream	Captures and removes	Deflects downstream
<b>Placement and Interaction with TAVR devices</b>	Not in aortic arch	Sits in aortic arch. Devices must pass over and back across	Sits in aortic arch. Devices must pass over and back across	Sits in ascending aorta Devices must pass over and back across	Sits in aortic arch. Devices must pass over and back across





# Claret Medical™ Sentinel™ Cerebral Protection System



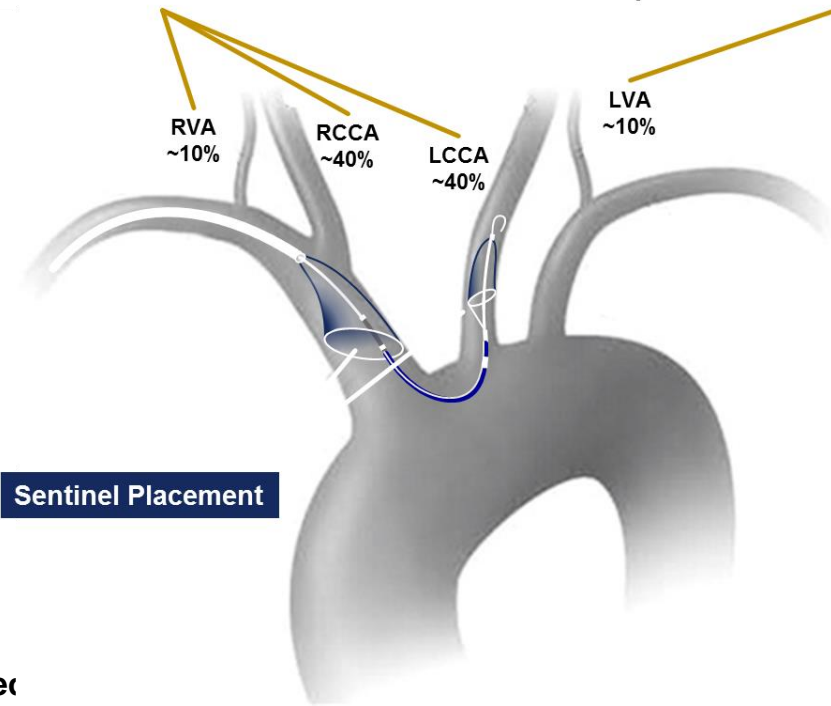
# Sentinel Filters Protection



-  **·Fully Protected**  
·74% brain volume
-  **·Partially Protected**  
·24% brain volume
-  **·Unprotected**  
·2% brain volume

Protected blood flow to the brain

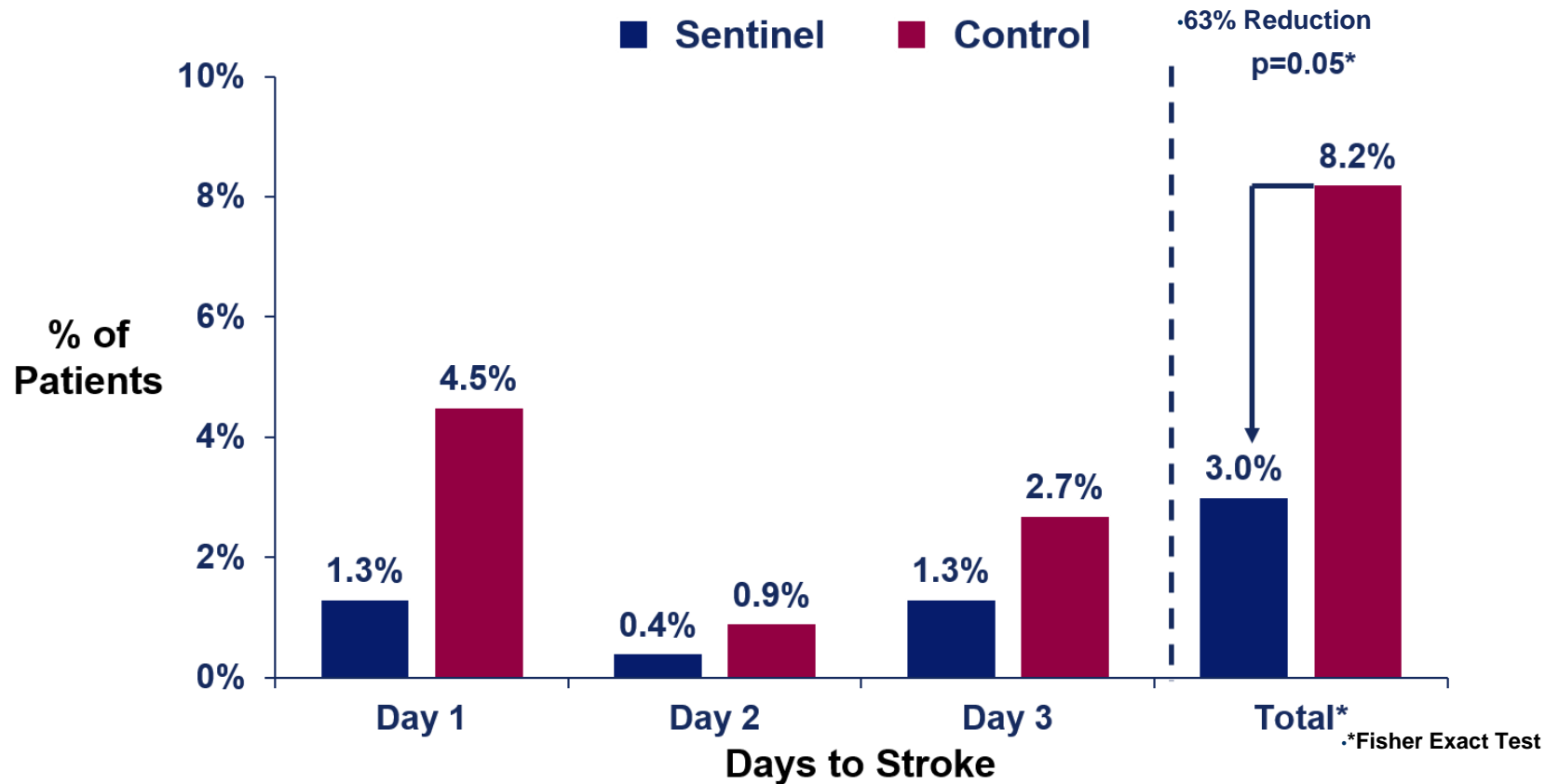
Unprotected blood flow to the brain



Sentinel Placement

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

# SENTINEL Study: Procedural Stroke



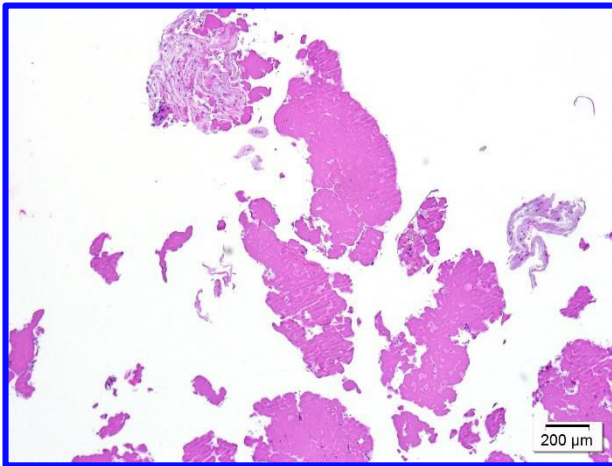
·95% of SENTINEL patients were evaluated by neurologists

·Clinical Events Committee included 2 stroke neurologists

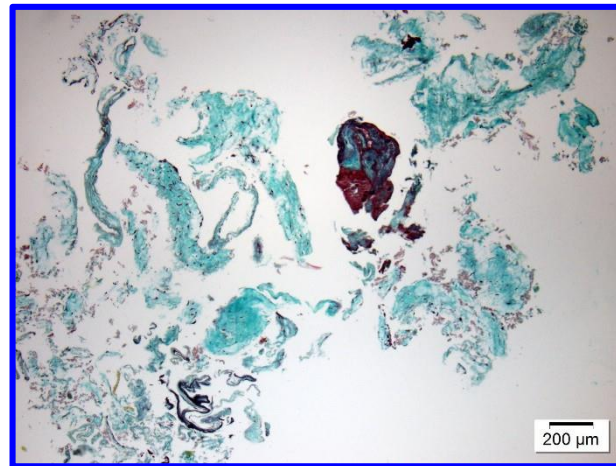
·SENTINEL trial. Data presented at Sentinel FDA Advisory Panel, February 23, 2017

# Type of Tissue Identified

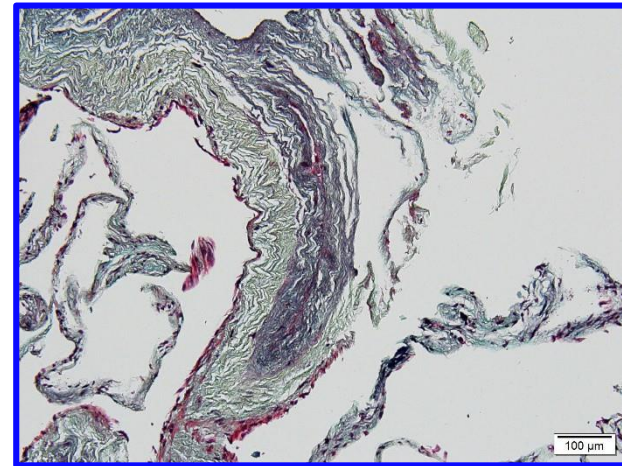
**Acute + organizing thrombus**



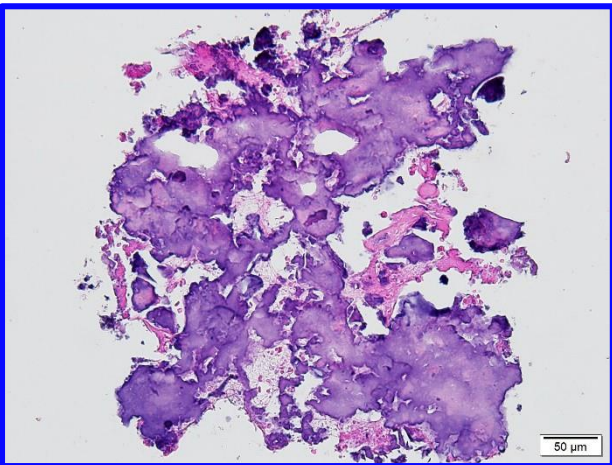
**Arterial wall + thrombus**



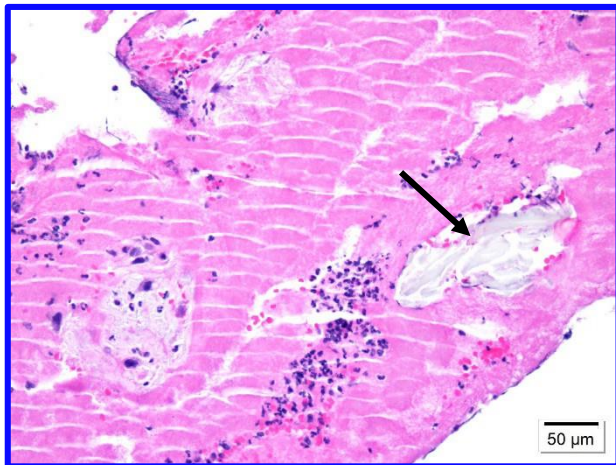
**Valve tissue**



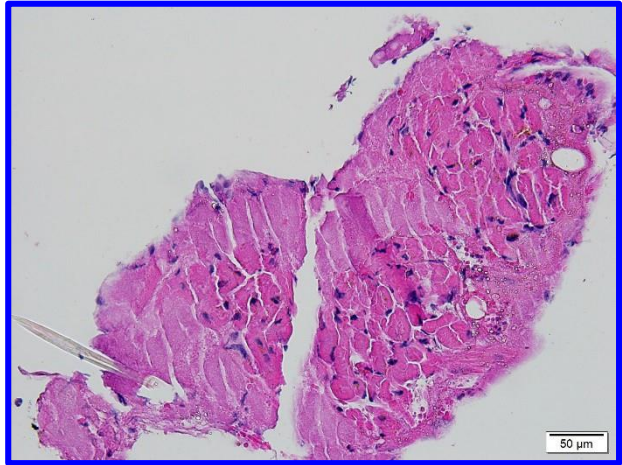
**Calcium nodules**



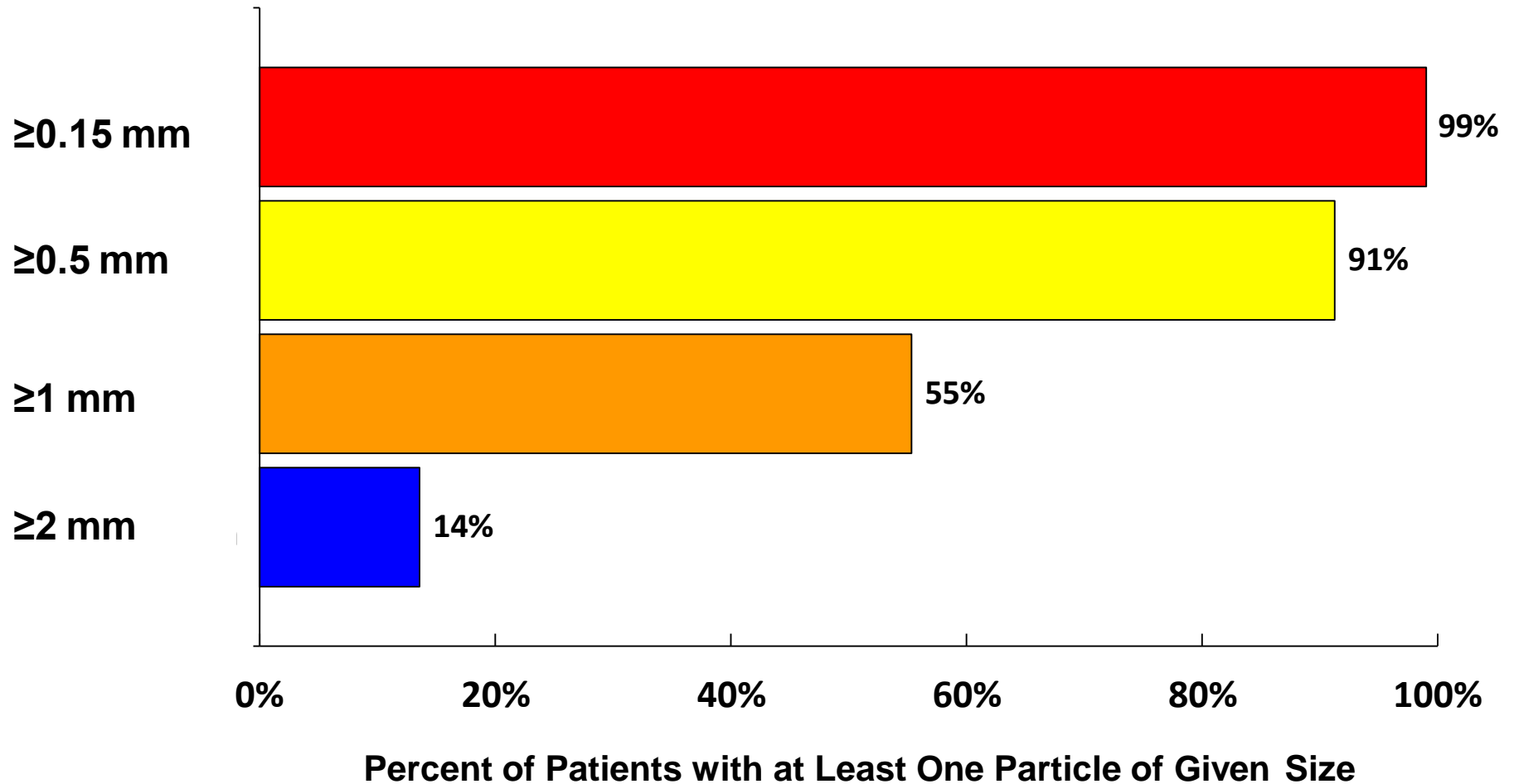
**Foreign material + thrombus**



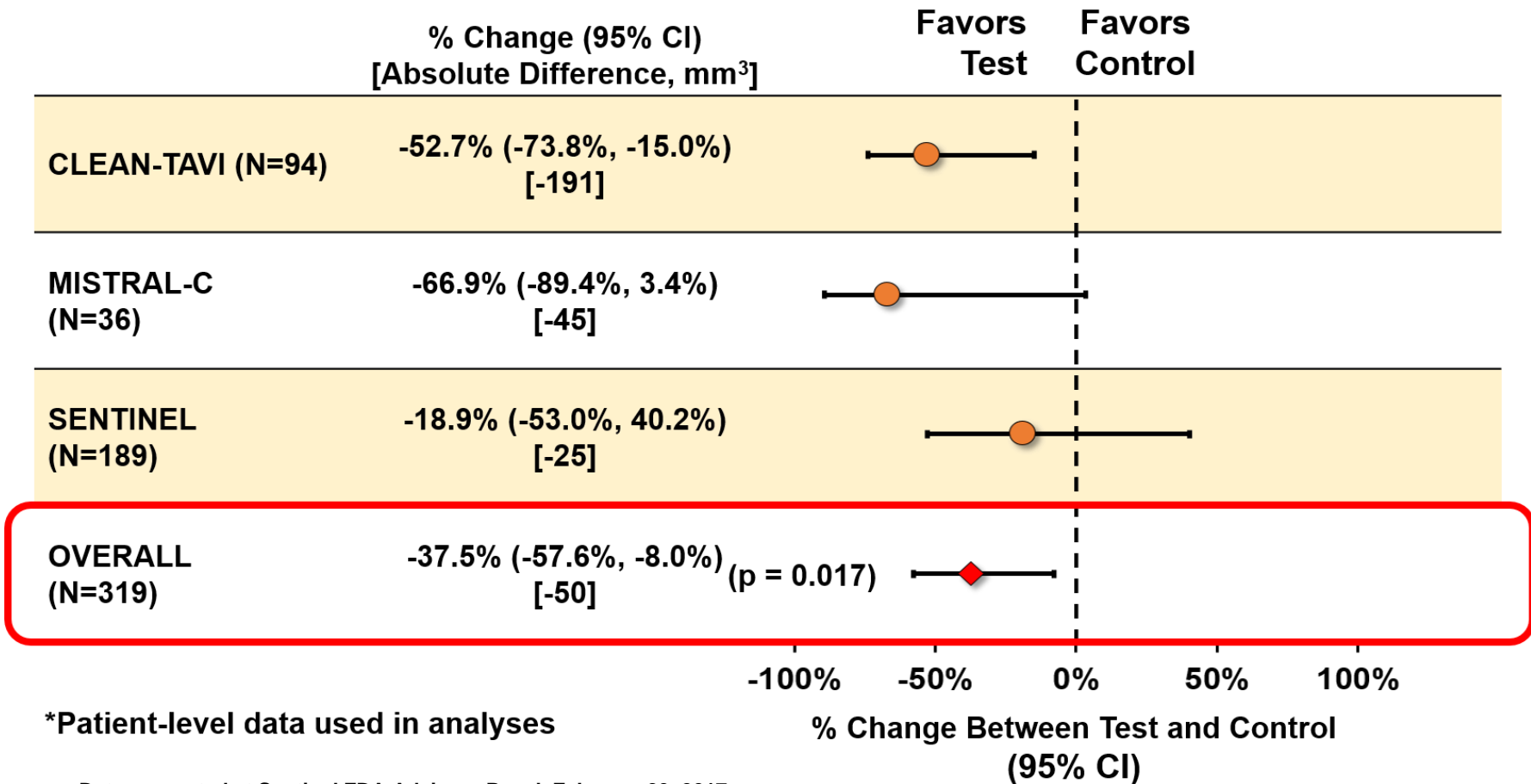
**Myocardium + thrombus**



# Morphometric Analysis: Embolitic Material by Particle Size

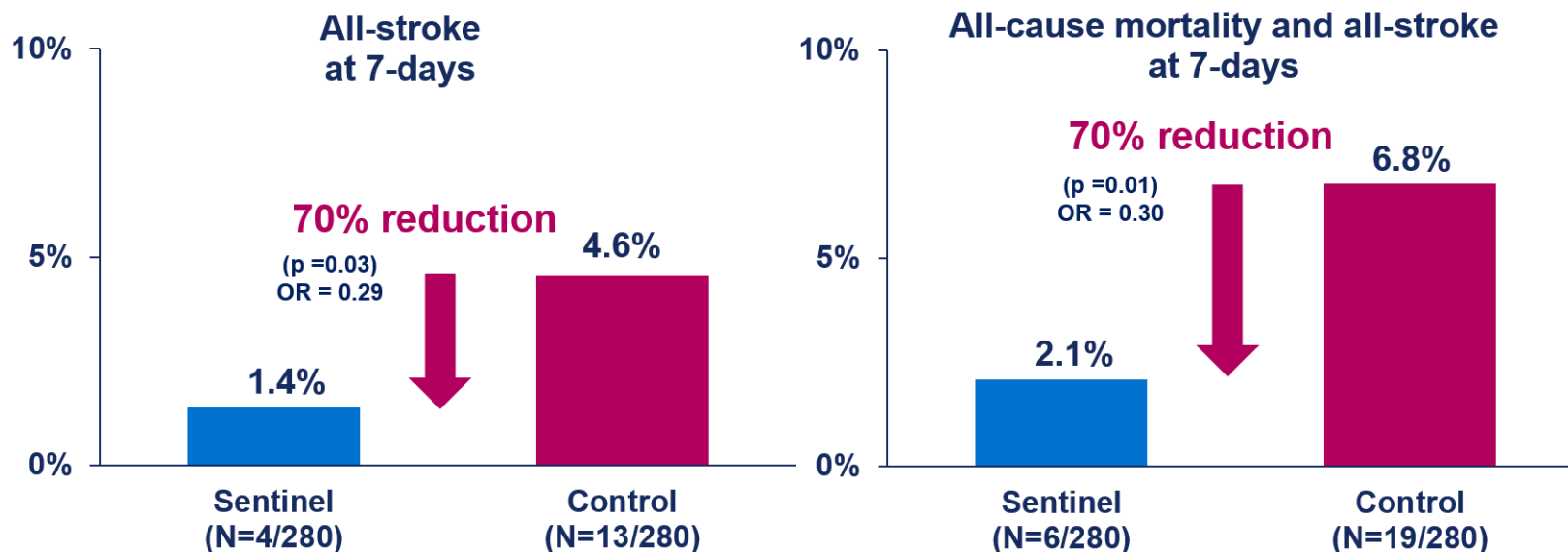


# Patient Level Meta-analysis: CLARET Lesion Volume in Protected Territories



# Ulm Sentinel study

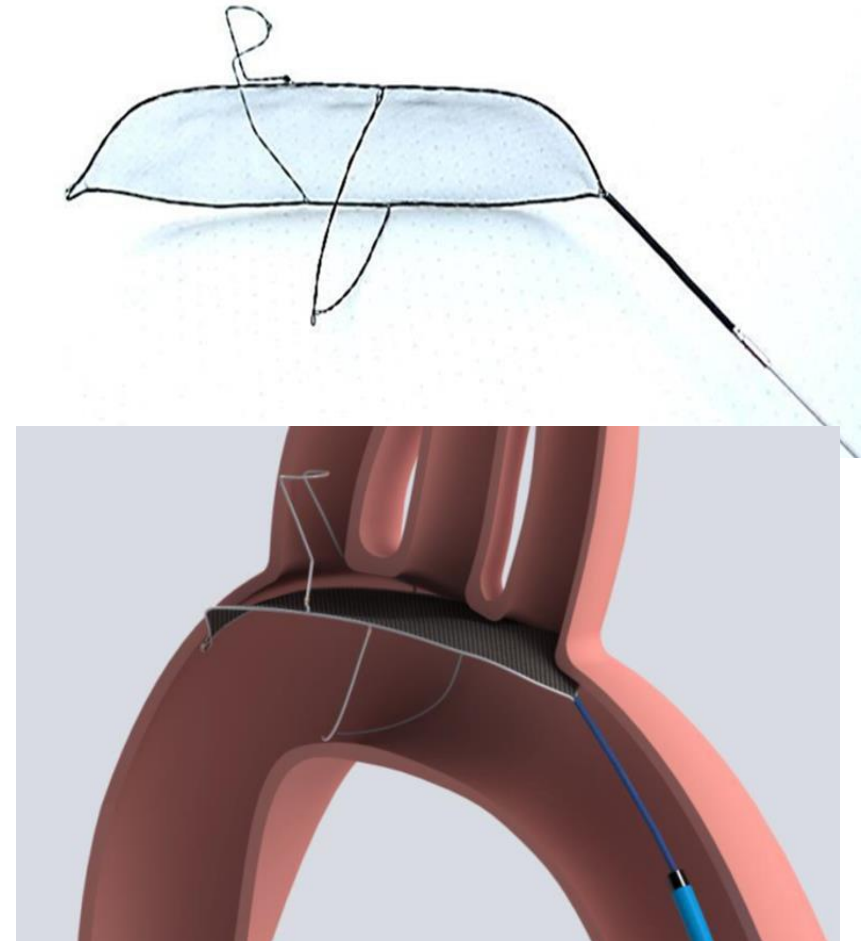
- 802 all-comer consecutive TAVR patients at University of Ulm were prospectively enrolled
- A propensity-score analysis was done matching the 280 patients protected with Sentinel to 280 control patients



- In multivariable analysis, TAVR without cerebral emboli protection ( $p=0.044$ ) was the only independent predictor for stroke at 7-days
- TAVR without cerebral emboli protection ( $p=0.028$ ) and STS score ( $<8$  vs.  $\geq 8$ ) ( $p=0.021$ ) were the only independent predictors for mortality and stroke at 7-days

# TriGuard Device: REFLECT trial

- **Single-wire nitinol frame and mesh filter with pore size of 130 $\mu$ m designed to deflect cerebral emboli during TAVI while allowing maximal blood flow**
- **Positioned across all 3 cerebral vessels and maintained by a stabilizer in the innominate**
- **Delivered via 9 Fr sheath from the**
  - **femoral artery**

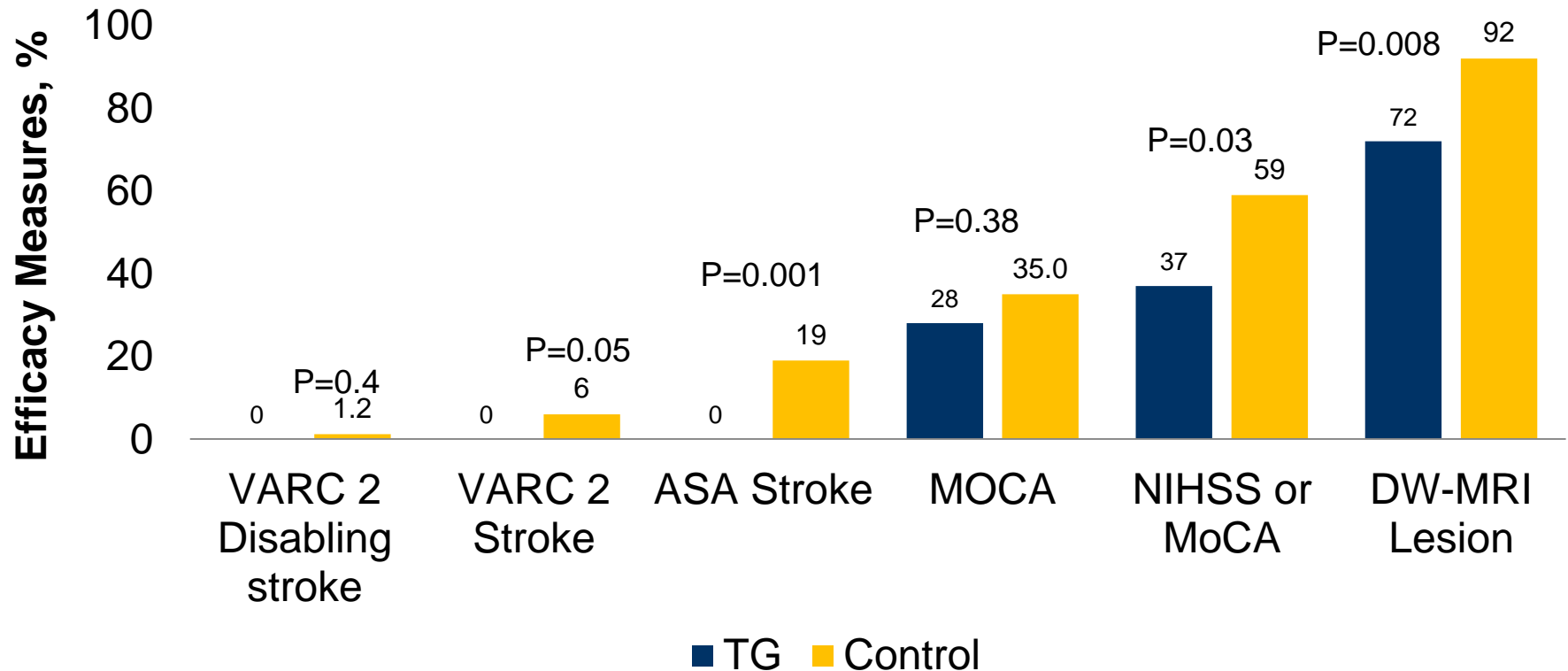




# TriGuard™ Pooled Analysis: In Hospital Results

Primary Safety Endpoint Of 30 Day MACCE: 18.2% TG vs 24.1% Control, p=0.44

Patient level pooled analysis from the TriGuard™ Trials (N=142)



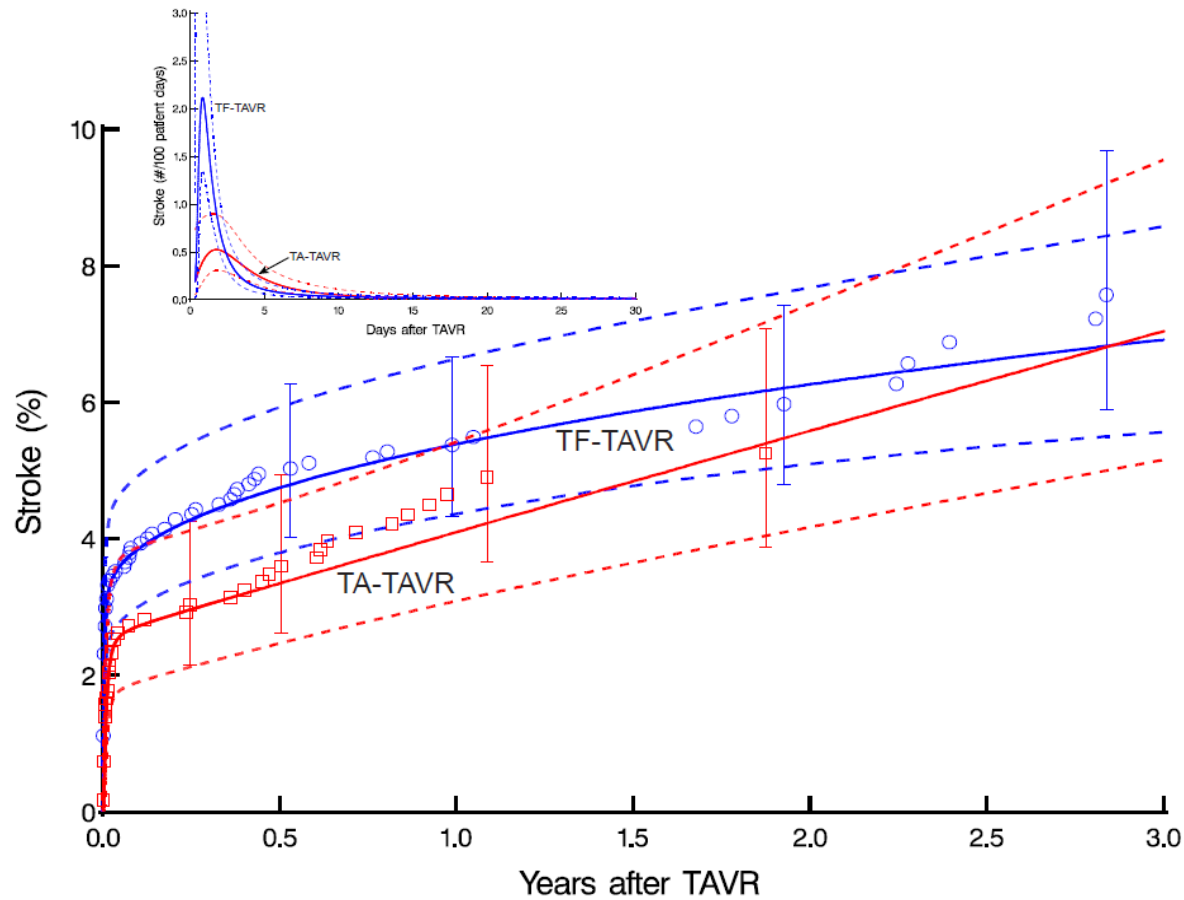
# Predictors of Stroke, Neuro events or MRI findings

Author	N	Event rate	Approach	Clinical predictors	Anatomical predictors
Tay et al 2011	253	9%	TA/TF	H/O stroke/TIA	Carotid stenosis*
Nuis et al 2012	214	9%	TF	New onset AF	Baseline AR >3+
Amat Santos et al 2012	138	6.5%	TA/TF	New onset AF	None
Franco et al 2012	211	4.7%	TA/TF	None	Post-dilation
Miller et al 2012	344	9%	TA/TF	History of stroke Non TF-TAVR candidate	Smaller AVA
Cabau et al 2011	60	68% (MRI)	TA/TF	Male, History of CAD	Higher AVG
Fairbairn et al 2012	31	77% (MRI)	TF	Age	Aortic atheroma
Nombela-Franco et al 2012	1061	5.1%	TA/TF	Balloon postdilatation, valve dislodgement, New onset AF, PVD, Prior CVA	

# Summary

- **There is benefit of emboli prevention**
  - **Clinical benefit**
  - **“Covert” stroke benefit**
- **We can’t reliably identify patients at risk and 99% patients have embolic material in filter**
- **Device is safe**
- **Emboli prevention devices should be considered in all patients undergoing TAVR**

# Is There Continued Risk of Stroke



## Patients at Risk

TF-TAVR	1521	1231	929	648	468	295	201
TA-TAVR	1100	830	554	316	191	75	45

# Predictors of Late CVEs (>30-day)

## UNIVARIATE

Chronic atrial fibrillation

Peripheral vascular disease

Cerebrovascular disease

Anticoagulation treatment at hospital discharge

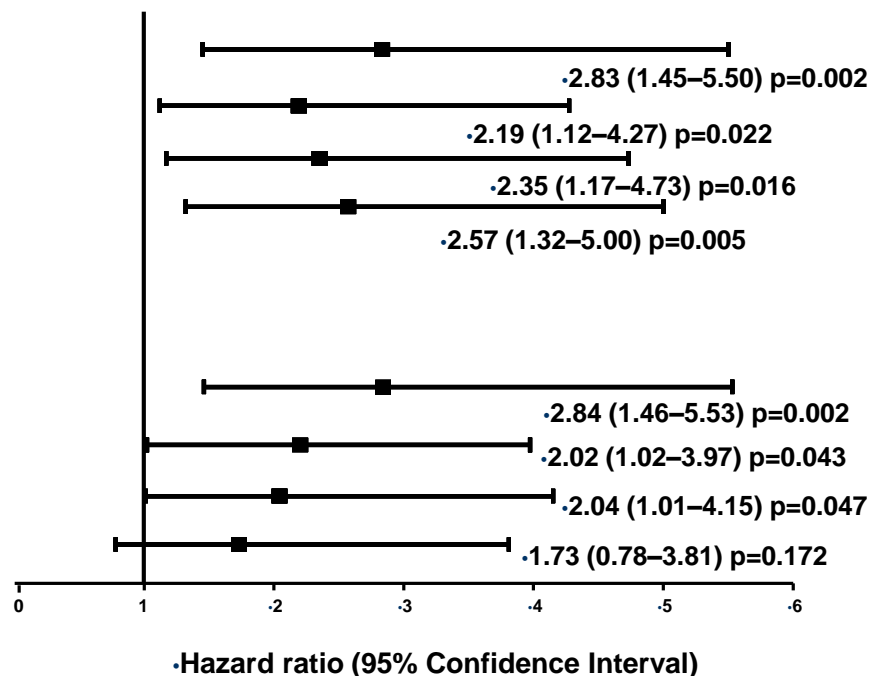
## MULTIVARIATE

Chronic atrial fibrillation

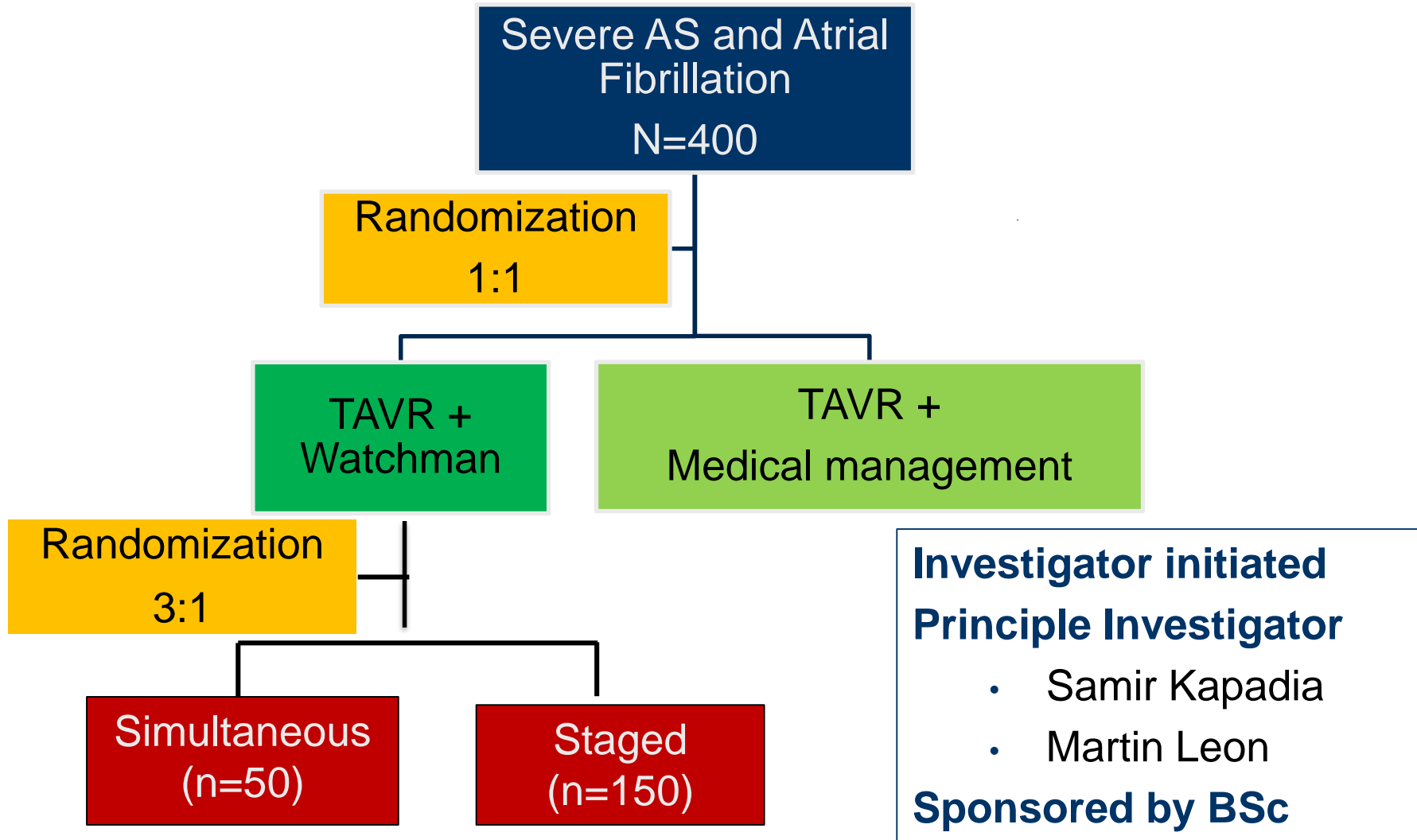
Peripheral vascular disease

Cerebrovascular disease

Anticoagulation treatment at hospital discharge



# Watch-TAVR



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