Cerebral Embolic Protection During TAVR

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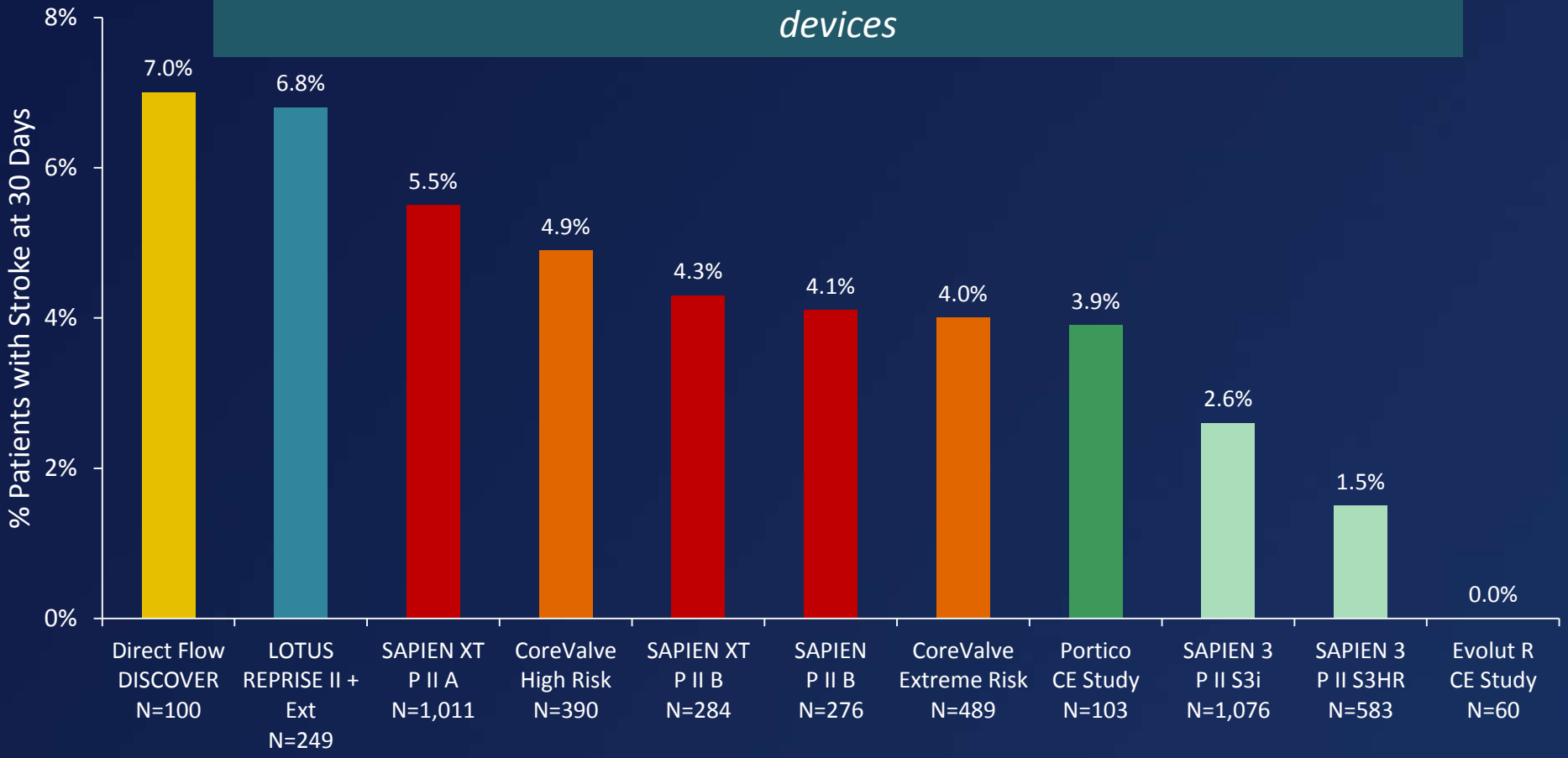
Neurologic Injury

The Clinical Need for Embolic Protection

The 30-day rate of clinically overt stroke in contemporary, rigorous studies hovers around 5%, even with lower-risk patients and next-generation TAVR devices

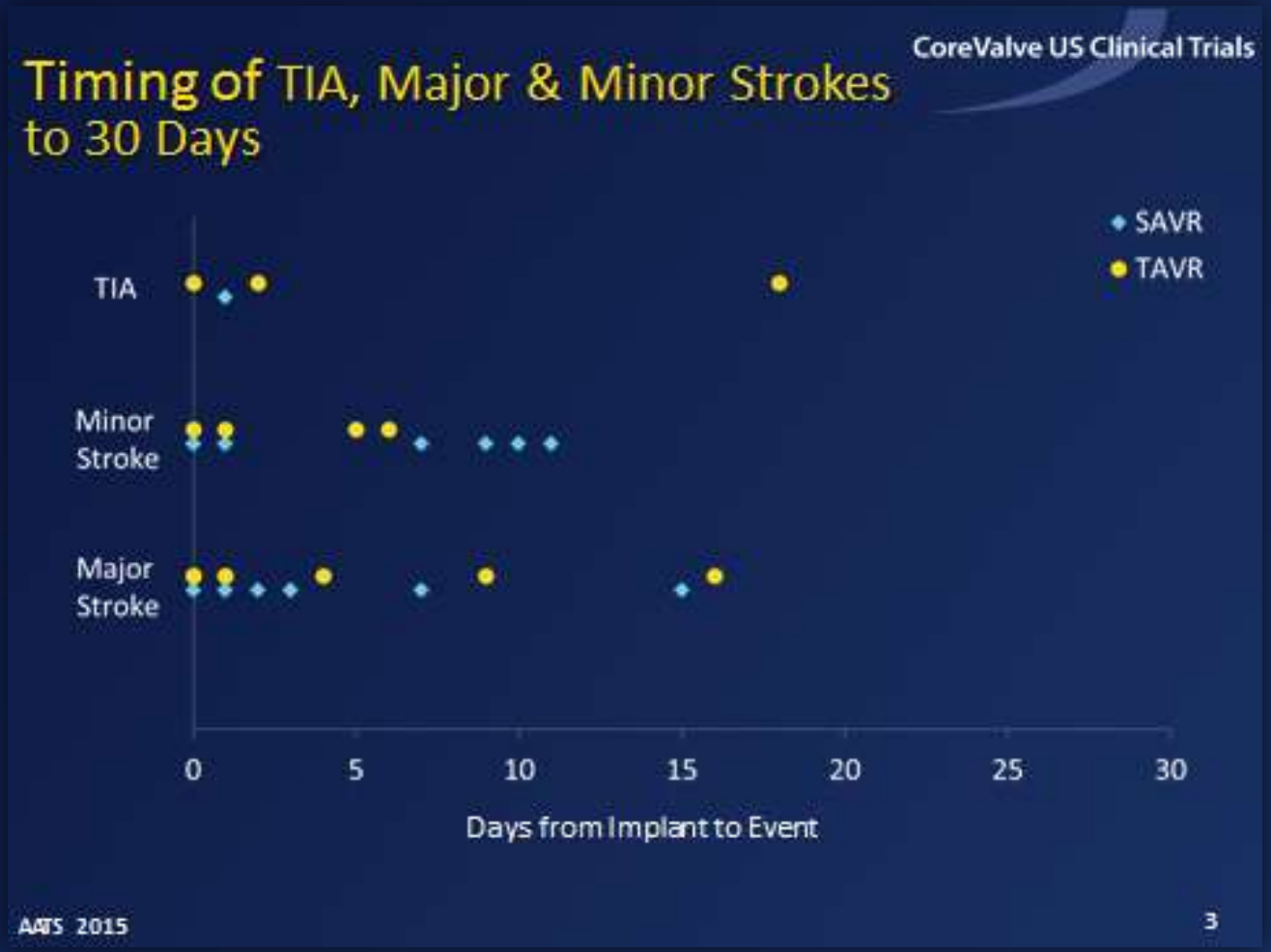


[1]Lefevre, et al., *J Am Coll Cardiol Intv* 2016; 9: 68-75; [2]Meredith, et al., presented at PCR London Valves 2014; [3]Leon, et al., *N Engl J Med* 2016 Apr 2 [E-pub ahead of print]; [4]Adams, et al., *N Engl J Med* 2014; 370: 1790-8; [5]Webb, et. al. *J Am Coll Cardiol Intv* 2015; 8: 1797-806; [6]Popma, et al., *J Am Coll Cardiol* 2014; 63: 1972-81; [7]Manoharan, et. al. presented at TVT 2014; [8]Kodali, et al., *Eur Heart J* 2016; doi:10.1093/eurheartj/ehw112; [9]Manoharan, et al., *J Am Coll Cardiol Intv* 2015; 8: 1359-67

Neurologic Injury

The Clinical Need for Embolic Protection

The CoreValve US Pivotal Trial recently confirmed that TAVR-related neurologic events can happen at any time within the first 30 days, however a significant subset of these events happen during the procedure itself



[1]Gleason, et al., presented at AATS 2015

Neurologic Injury

The Clinical Need for Embolic Protection

- Post-TAVR diffusion-weighted MRI studies show that neurological injury is nearly ubiquitous
- Many lesions are “silent” and do not manifest as overt stroke according to VARC-2

Stroke

Silent and Apparent Cerebral Ischemia After Percutaneous Transfemoral Aortic Valve Implantation

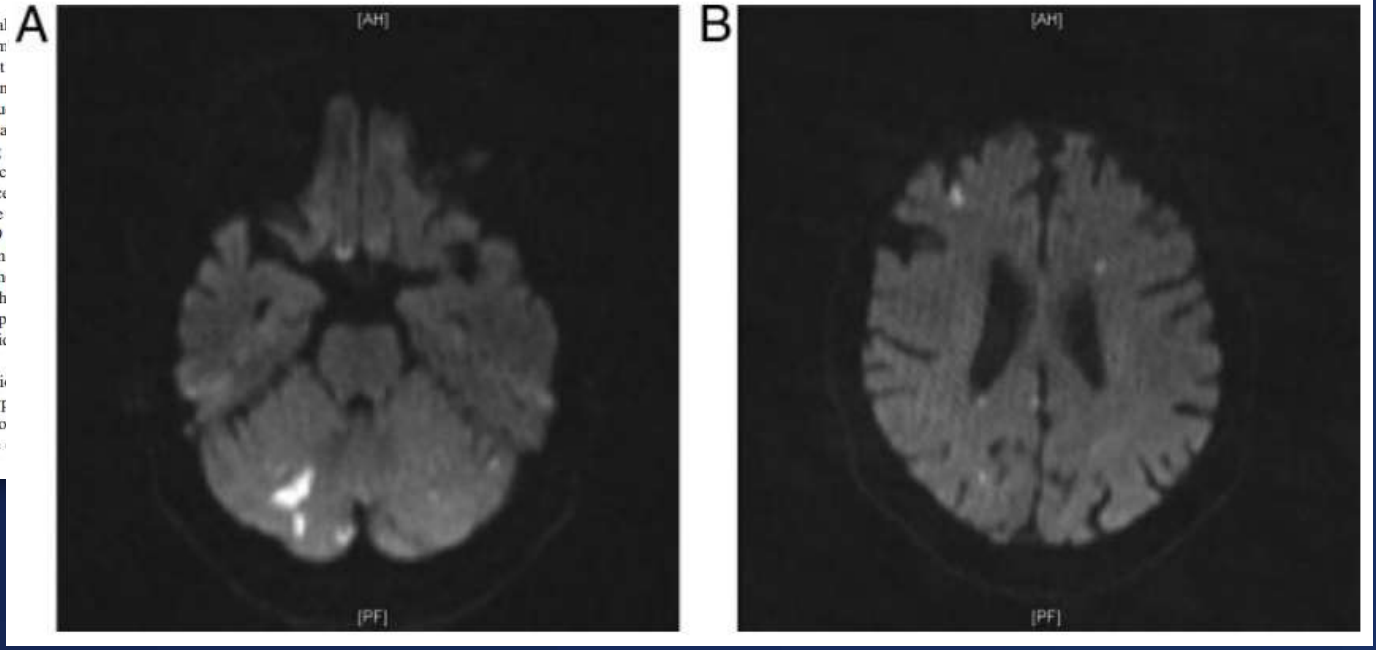
A Diffusion-Weighted Magnetic Resonance Imaging Study

Philipp Kahlert, MD*; Stephan C. Knipp, MD*; Marc Schlamann, MD; Matthias Thielmann, MD; Fadi Al-Rashid, MS; Marcel Weber, MD; Uwe Johansson, MD; Daniel Wendt, MD; Heinz G. Jakob, MD; Michael Forsting, MD; Stefan Sack, MD, FESC; Raimund Erbel, MD, FESC; Holger Eggebrecht, MD, FESC

***Background*—**The risk of stroke after transfemoral aortic val embolization of debris from aortic arch atheroma or from rate of clinically silent cerebral ischemia is unknown but

***Methods and Results*—**Thirty-two patients who underwen self-expandable (n=10) stent valve prosthesis were inclu control group of 21 patients undergoing open surgical a cerebral ischemia was assessed by neurological testing imaging at baseline, at 3.4 (2.5 to 4.4) days after the proc After the procedure, new foci of restricted diffusion on c found in 27 of 32 TAVI patients (84%) and were more $P=0.011$). These lesions were usually multiple (1 to 19 suggesting cerebral embolization. Volumes of these lesion [59 to 94] versus 224 [111 to 338] mm^3; $P<0.001$). Th function nor apparent neurological events during the in-h (5%) in the surgical patient group. On 3-month follow-up no new foci of restricted diffusion, and there was no resi foci detected in the periprocedural period.

***Conclusions*—**Clinically silent new foci of restricted diffusi almost all patients (84%) undergoing TAVI. Although ty neurological events or measurable deterioration of neuro needs to be directed to determine the clinical significance **2010;121:870-878.)**



[1]Kahlert, et al., *Circulation* 2010; 121: 870-8

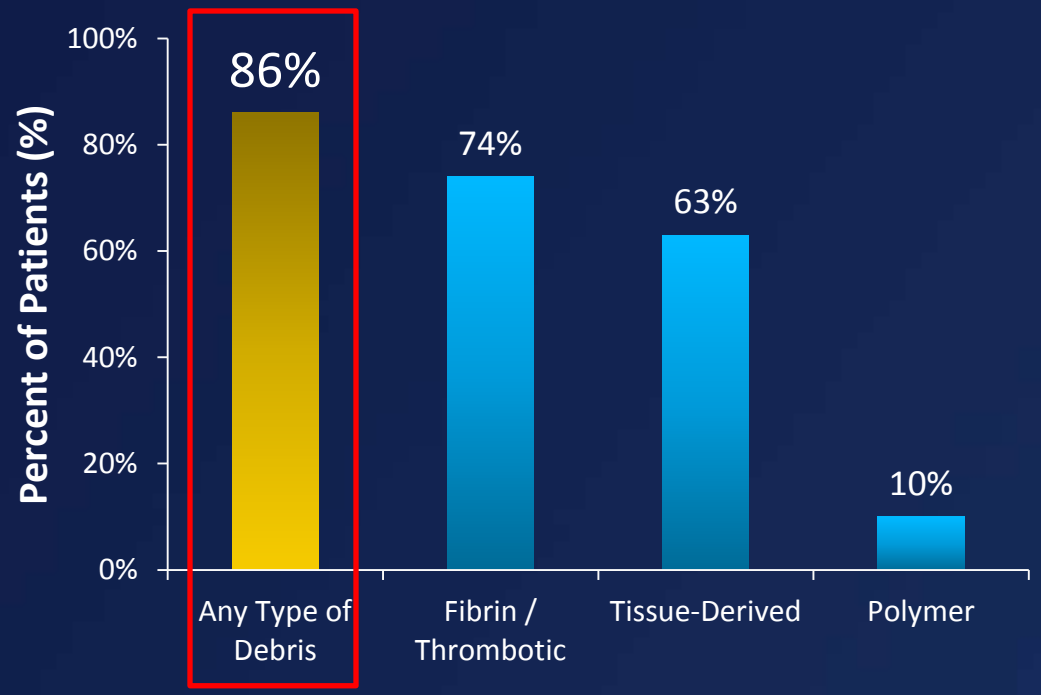
Neurologic Injury

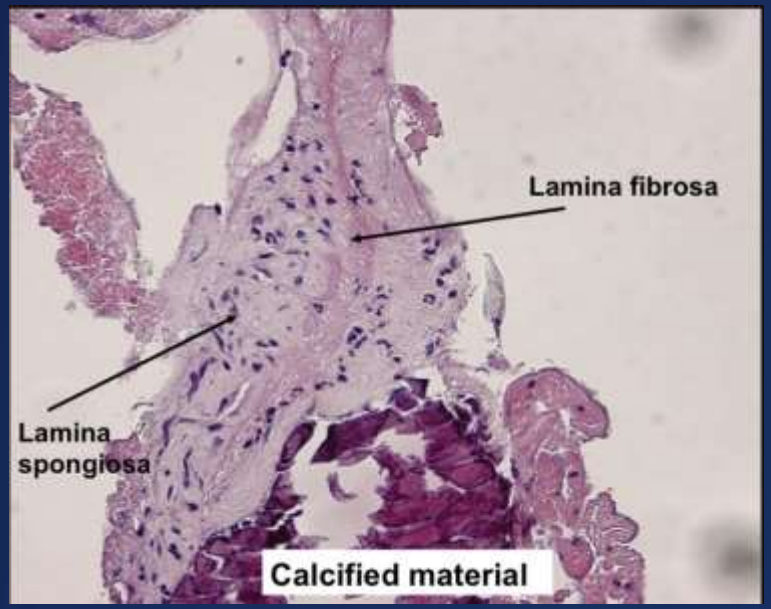
The Clinical Need for Embolic Protection

Van Mieghem, et al., have examined the contents of Claret Montage filters which were placed within the brachiocephalic and left common carotid arteries during TAVR

The key findings:

- *Macroscopic debris was released into the circulation in ~90% of TAVR procedures*
- *The debris was composed of thrombotic material, bits of valve leaflet, calcified particles, myocardial tissue, or plastic fragments from interventional tools*





Fragments of aortic valve leaflet

[1]Van Mieghem, et al., *J Am Coll Cardiol Intv* 2015; 8: 718-24

Neurologic Injury

The clinical need for neuro-protective strategies in TAVR is established:

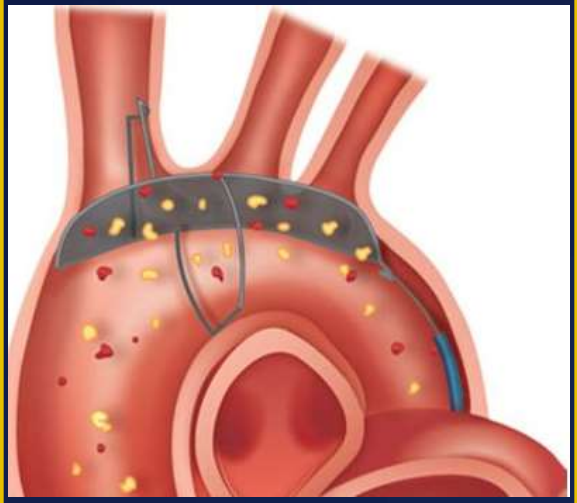
- Next-generation devices and vast clinical experience have not effectively reduced the rate of stroke associated with TAVR.
- Imaging studies show that even patients without clinically overt stroke sustain neurologic injury. How much of this injury is clinically relevant? Is there an acceptable level that is not harmful to patients?
- We know that silent infarcts have potential to cause neurocognitive deficits or predispose patients to neurodegenerative disease, so (much!) further study is (very!) necessary.
- One mechanism for neurologic injury is the release of embolic debris into the circulation during procedural manipulation of the aortic valve.

Embolic Protection Devices | The Evidence Base

Embolic Protection Devices

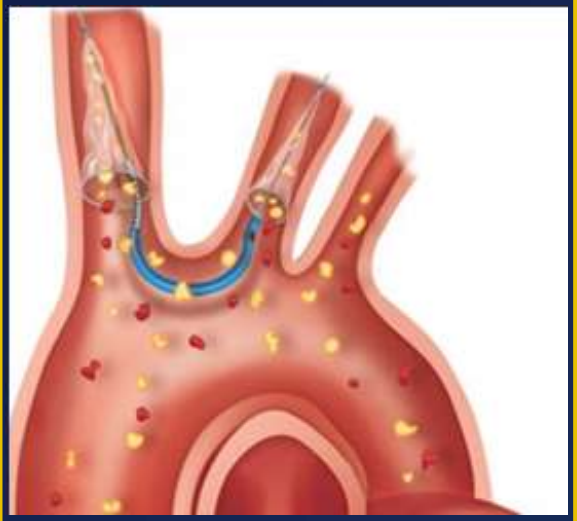
Main Attributes

TriGuard Embolic Deflection Device (Keystone Heart)[1]



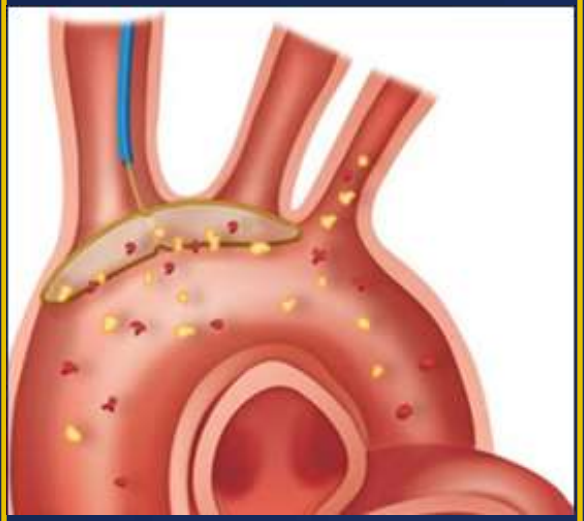
- ✓ Pore Size: 130 µm
- ✓ Delivery Sheath: 9F
- ✓ Access: Transfemoral
- ✓ Coverage: Brachiocephalic, left common carotid, left subclavian

Sentinel Cerebral Protection System (Claret Medical)[2]



- ✓ Pore Size: 140 µm
- ✓ Delivery Sheath: 6F
- ✓ Access: Brachial or radial
- ✓ Coverage: Brachiocephalic, left common carotid

Embrella Embolic Deflector System (Edwards Lifesciences)[3]



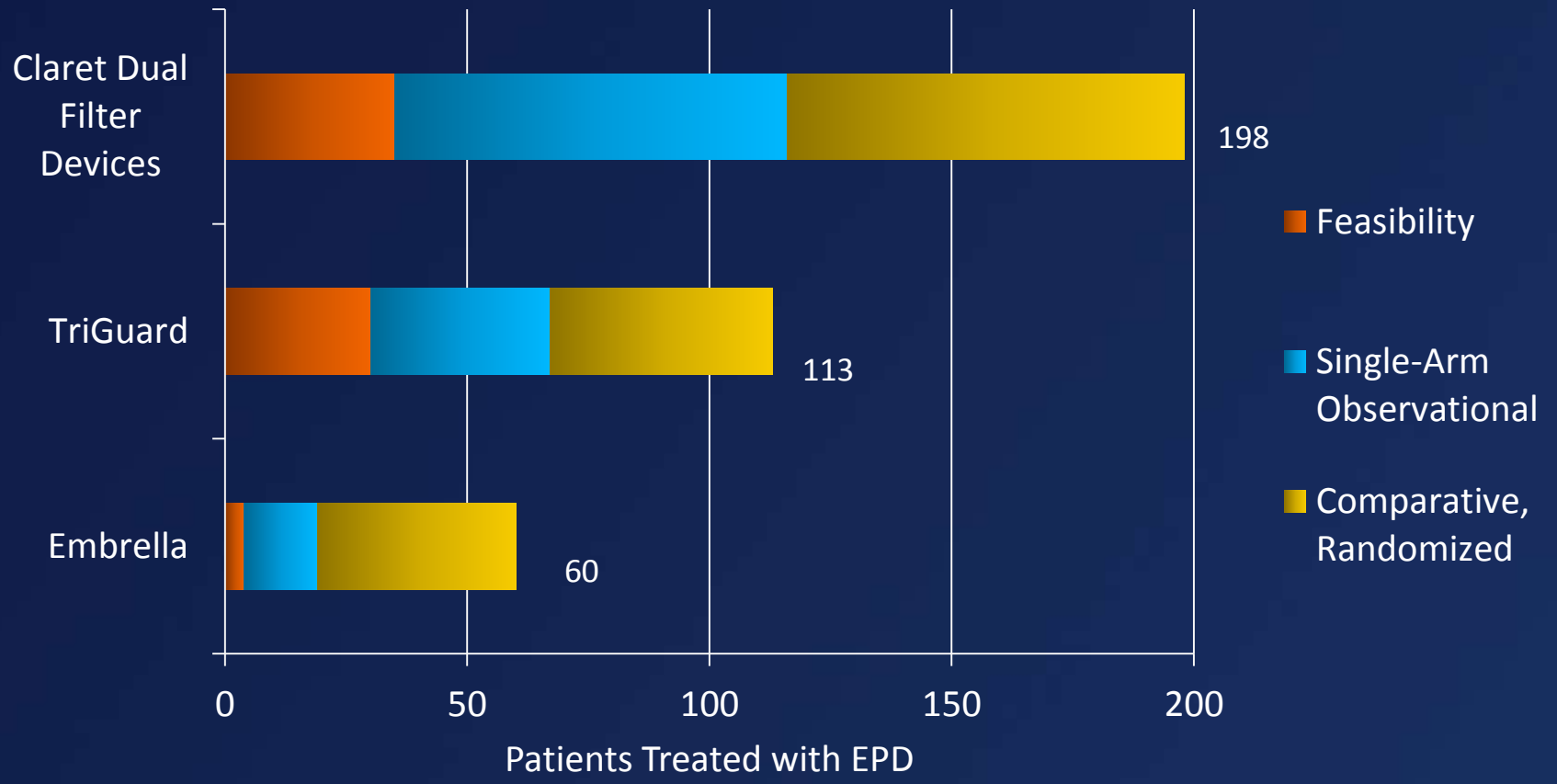
- ✓ Pore Size: 100 µm
- ✓ Delivery Sheath: 6F
- ✓ Access: Brachial
- ✓ Coverage: Brachiocephalic, left common carotid

[1]Lansky, et. al. , presented at TCT 2015; [2]Van Mieghem, et al., presented at TCT 2015; [3]Rodes-Cabau, et al., *J Am Coll Cardiol Intv* 2014;7:1146-55

Embolic Protection Devices

Evidence Base

Embolic protection devices have been under investigation in humans since 2010, however the clinical evidence generated with these devices remains limited



[1]Nietlispach, et. al. , *J Am Coll Cardiol Intv* 2010; 3: 1133-8; [2]Samim, et al., *J Thorac Cardiovasc Surg* 2015; 149:799-805; [3]Rodes-Cabau, et al., *J Am Coll Cardiol Intv* 2014;7:1146-55; [4]Naber, et al., *EuroIntervention* 2012; 8: 43-50; [5]Van Mieghem, et al., *J Am Coll Cardiol Intv* 2015; 8: 718-24; [6]Haussig, et al., *JAMA* 2016;316:592-601; [7]Van Mieghem, et al., *EuroIntervention* 2016;12:499-507; [8]Onsea, et al., *EuroIntervention* 2012;8:51-6; [9]Baumbach, et al., *EuroIntervention* 2015;11:75-84; [10]Lansky, et al., *Eur Heart J* 2015;36:2070-8

Embolic Protection Devices

Evidence Base

Four studies have looked at EPDs against untreated controls, all had slightly different designs

DEFLECT-III N=85	
Purpose:	Exploratory, benchmark event rates
Device:	Keystone TriGuard
Imaging:	1.5-T MRI at day 4, no baseline
Follow-up:	Baseline, day 4, day 30

PROTAVI-C N=52	
Purpose:	Exploratory safety and efficacy
Device:	Edwards Embrella
Imaging:	MRI
Follow-up:	Baseline, day 7, day 30

MISTRAL-C N=65	
Purpose:	Demonstrate reduction in brain lesions at day 5
Device:	Claret Sentinel
Imaging:	3-T MRI, transcranial doppler
Follow-up:	Baseline and day 5

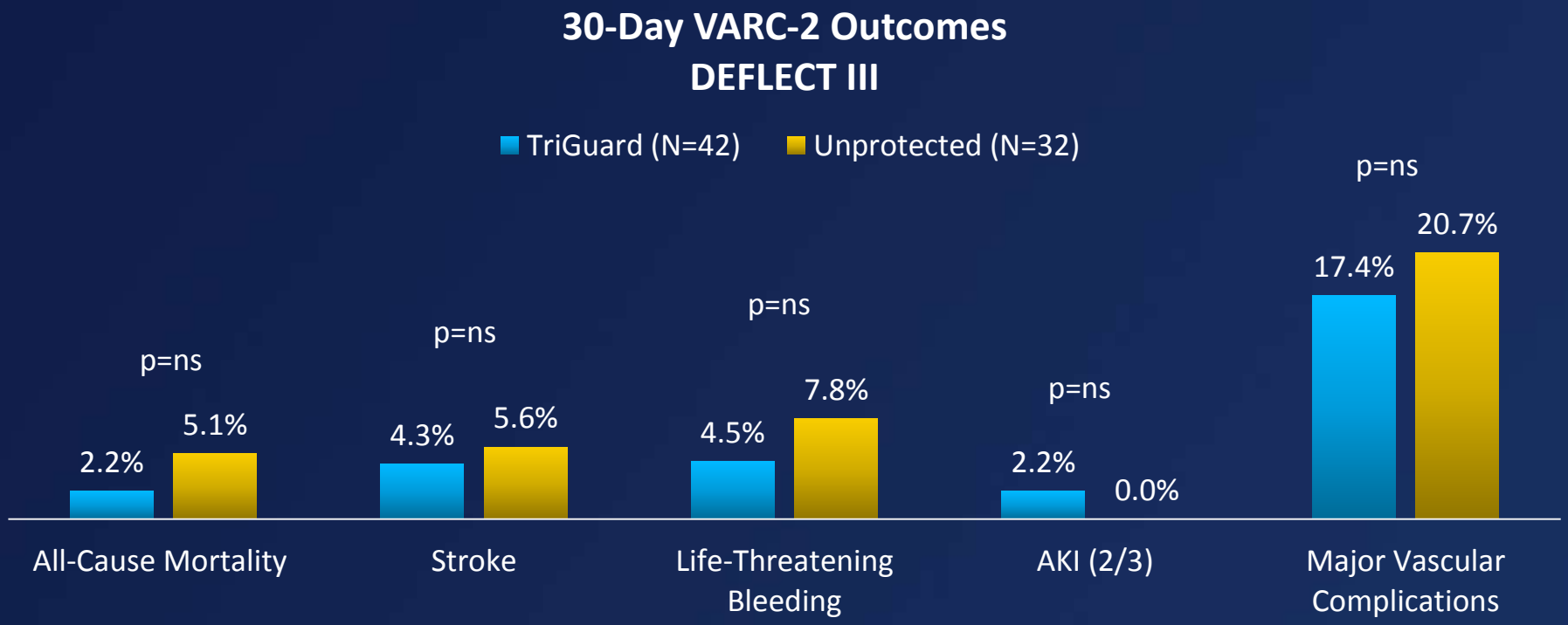
CLEAN-TAVI N=100	
Purpose:	Demonstrate reduction in brain lesions at day 2
Device:	Claret Montage
Imaging:	3-T MRI
Follow-up:	Baseline and day 2, 7, 30, 365

TriGuard

TriGuard (Keystone)

DEFLECT III | Safety

DEFLECT III (N=85) | Select Baseline Characteristics			
	TriGuard (N=46)	Control (N=39)	P value
Age	82.7 ± 6.5	82.5 ± 5.9	0.62
Male	40.9%	50.0%	0.41
STS	4.7%	7.4%	0.48



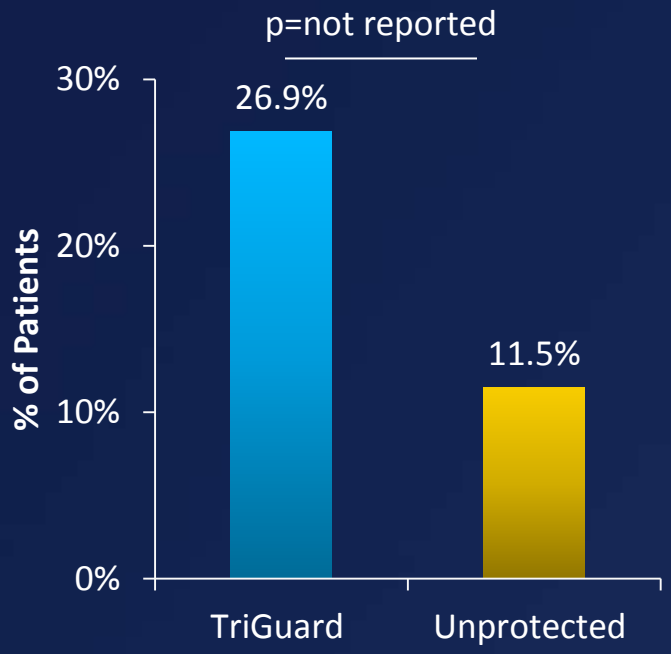
[1]Lansky, et al., *Eur Heart J* 2015;36:2070-8

TriGuard (Keystone)

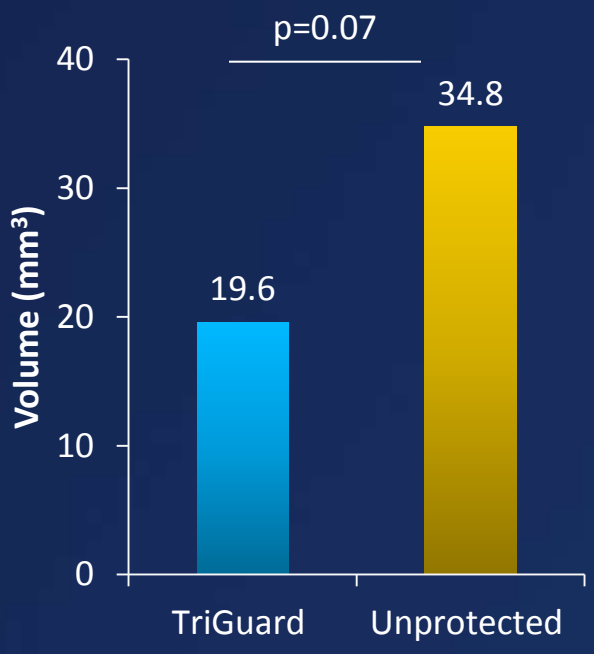
DEFLECT III | Day 4 Imaging

- *Complete freedom from neurologic injury was 57% higher in TriGuard patients*
- *Lesions that formed were 44% smaller in TriGuard patients*

Patients Free of Post-Procedural Ischemic Lesions



Median Single Lesion Volume



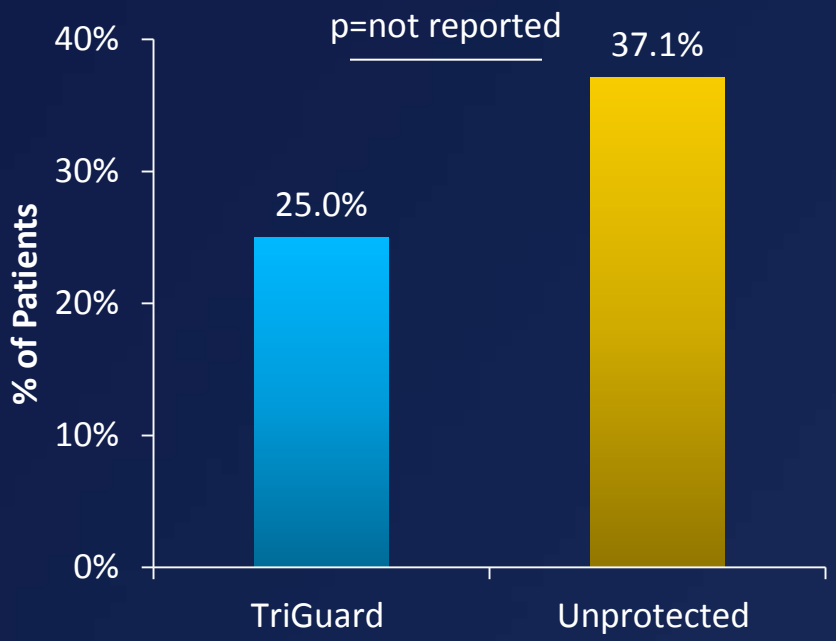
[1]Lansky, et al., *Eur Heart J* 2015;36:2070-8

TriGuard (Keystone)

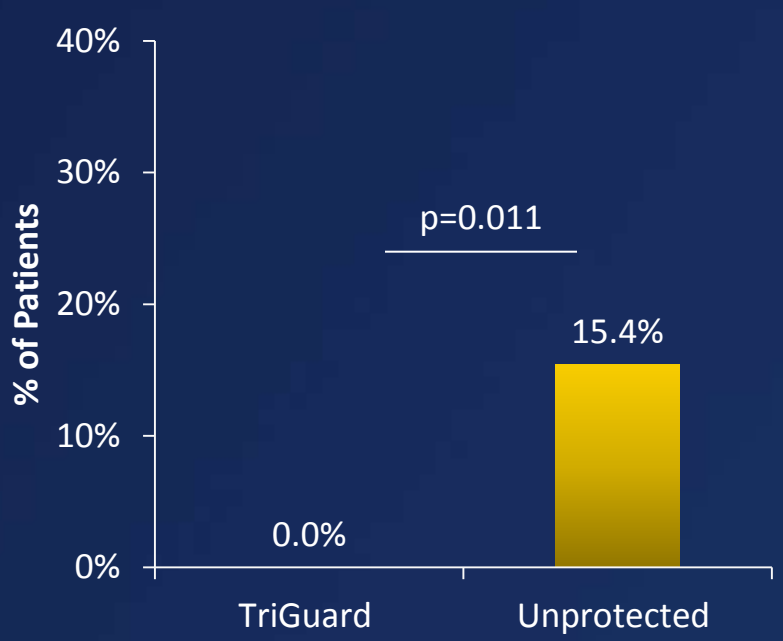
DEFLECT III | Neuro-function

Protected patients experienced less neurologic impairment at the time of hospital discharge

Patients with Worsening Montreal Cognitive Assessment
(relative to baseline)



Patients with Worsening NIHSS
(relative to baseline)



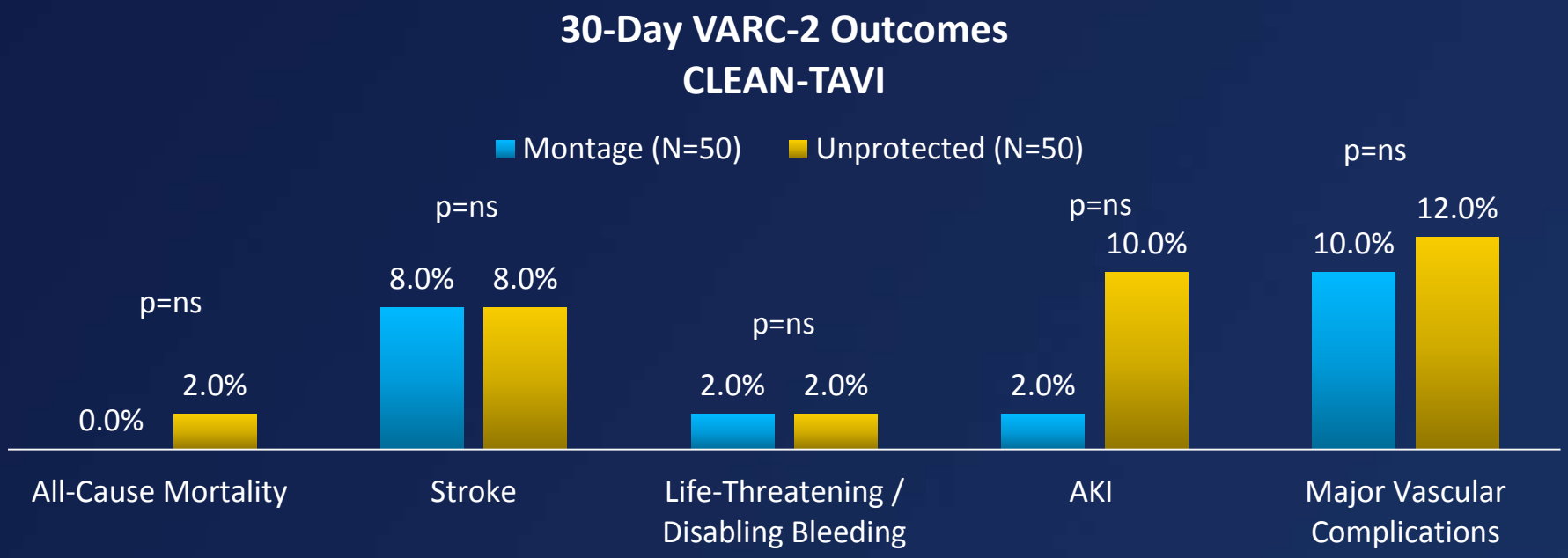
[1]Lansky, et al., *Eur Heart J* 2015;36:2070-8

Montage and Sentinel Dual Filters

Montage (Claret)

CLEAN-TAVI | Safety

CLEAN-TAVI (N=100) | Select Baseline Characteristics			
	Montage (N=50)	Control (N=50)	P value
Age	80 ± 5	79 ± 4	0.466
Male	40%	46%	0.545
STS	5.6 ± 3.3%	5.2 ± 2.7%	0.847

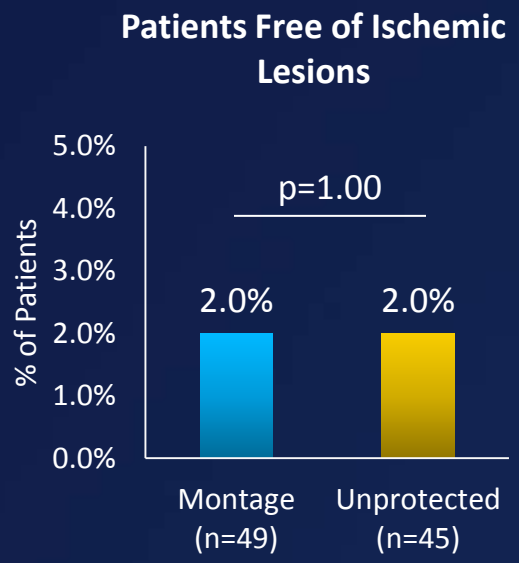


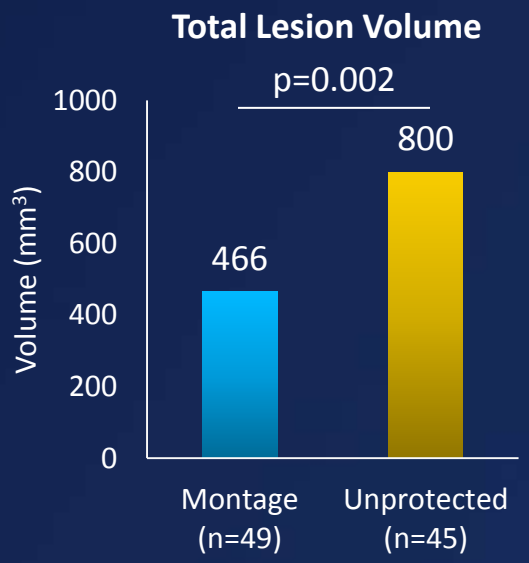
[1]Haussig, et al., *JAMA* 2016; 316:592-601

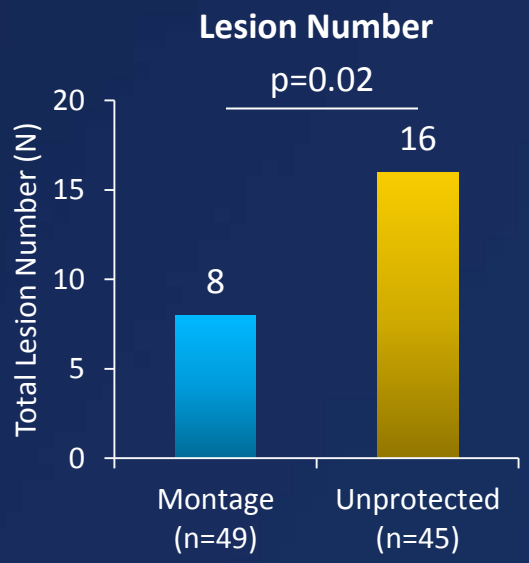
Montage (Claret)

CLEAN-TAVI | Day 2 Imaging

- *98% of patients (protected and unprotected) showed some form of neurologic injury on MRI*
  - *This high rate results from the sensitivity of the 3-T scanner*
- *Montage significantly reduced total lesion volume by 40% and total lesion number by 50%*





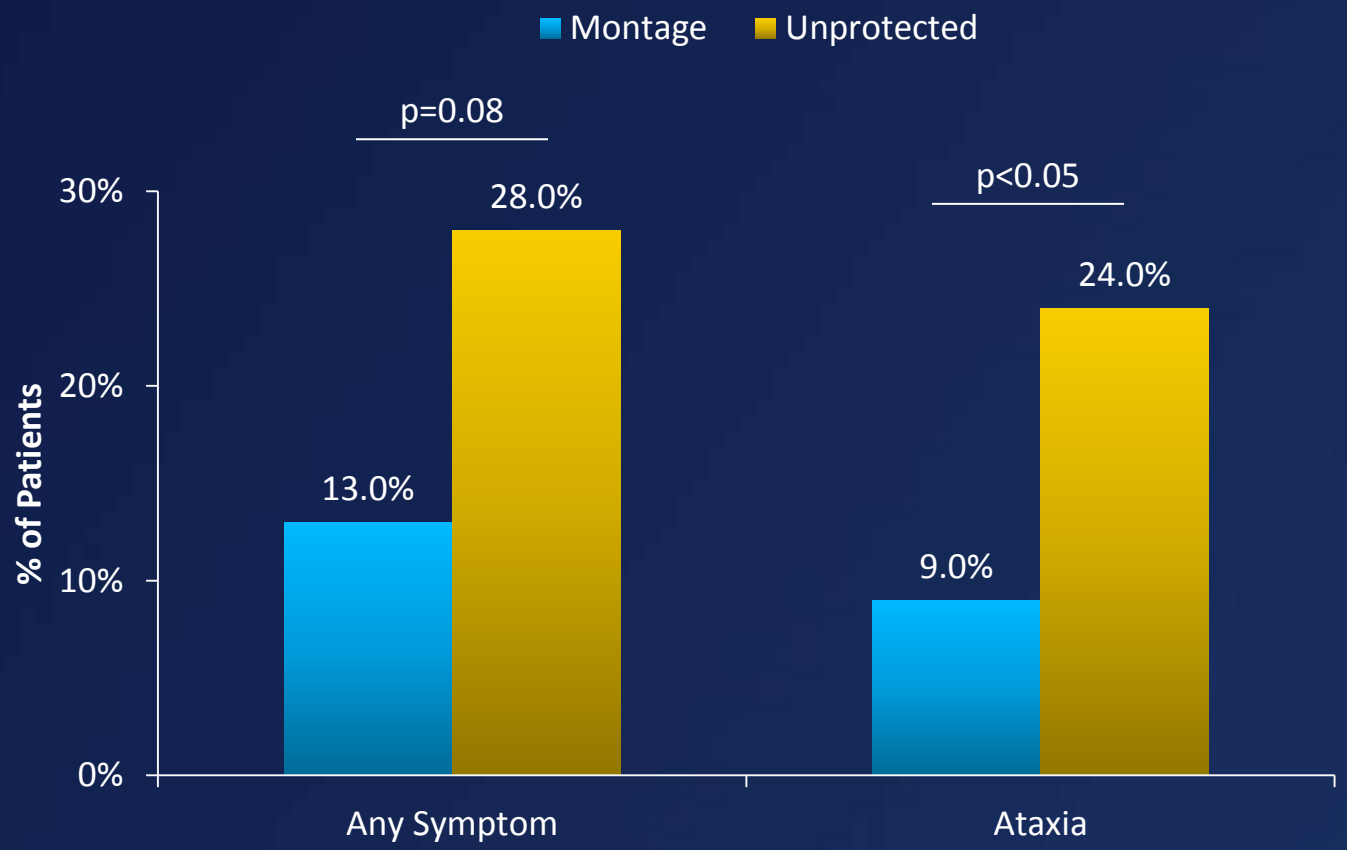


[1]Haussig, et al., *JAMA* 2016; 316:592-601

Montage (Claret)

CLEAN-TAVI | Neuro-function

Protected patients demonstrated better neurocognitive function at day 2

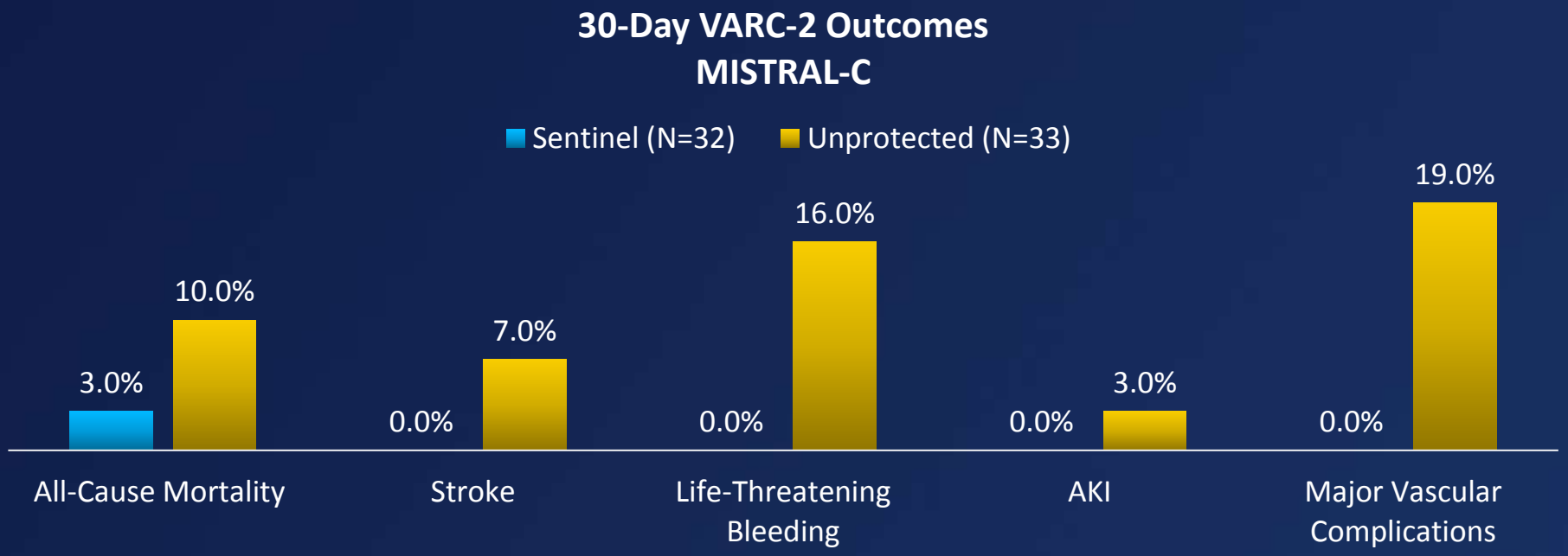


[1]Linke, et al., presented at TCT 2014

Sentinel (Claret)

MISTRAL-C | Safety

MISTRAL-C (N=65) | Select Baseline Characteristics			
	Sentinel (N=32)	Control (N=33)	P value
Age	81	82	0.60
Male	53%	51%	0.90
STS	Not reported		



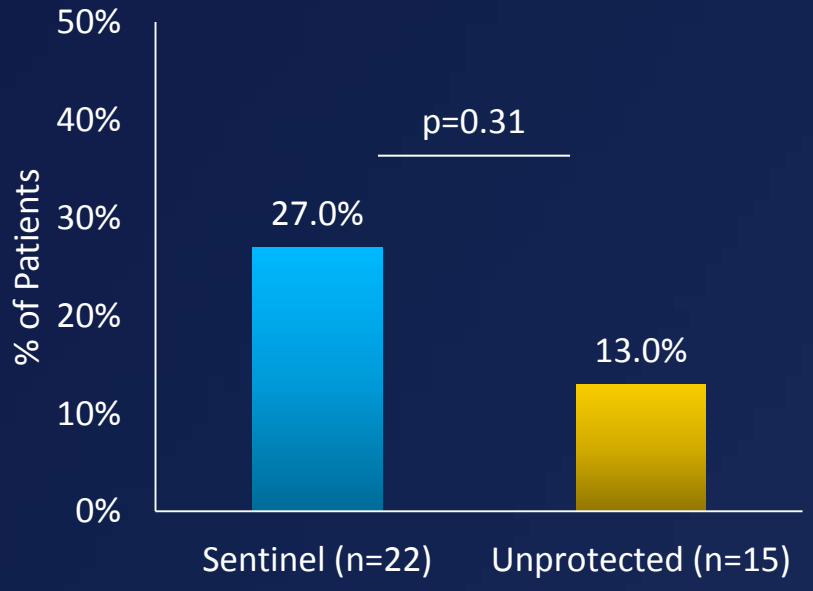
[1]Van Mieghem, et al., *EuroIntervention* 2016; 12:499-507

Sentinel (Claret)

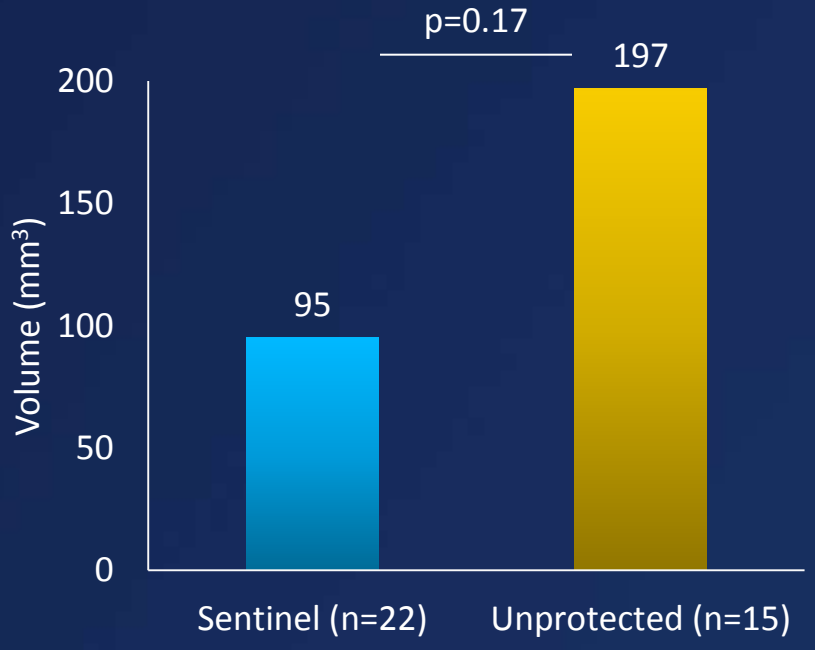
MISTRAL-C | Day 5 Imaging

- *57% of patients were lost to imaging follow-up due to implantation of MRI-incompatible pacemakers or other logistical reasons, therefore statistical power was lost*
- *Complete freedom from neurologic injury was 52% higher in Sentinel patients*
- *Sentinel significantly reduced total lesion volume by ~50%*

Patients Free of Ischemic Lesions



Total Lesion Volume

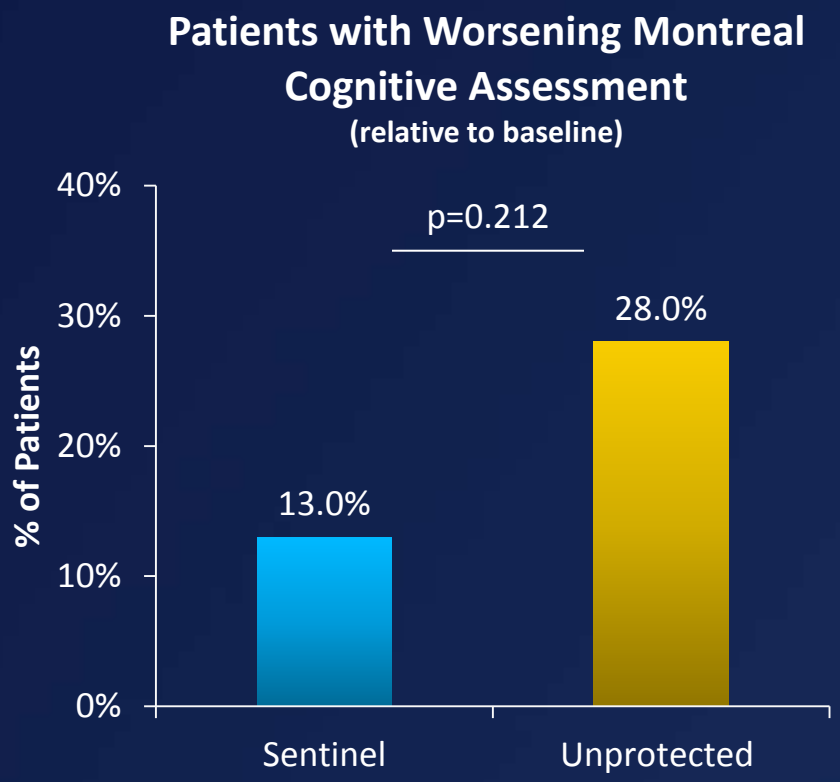


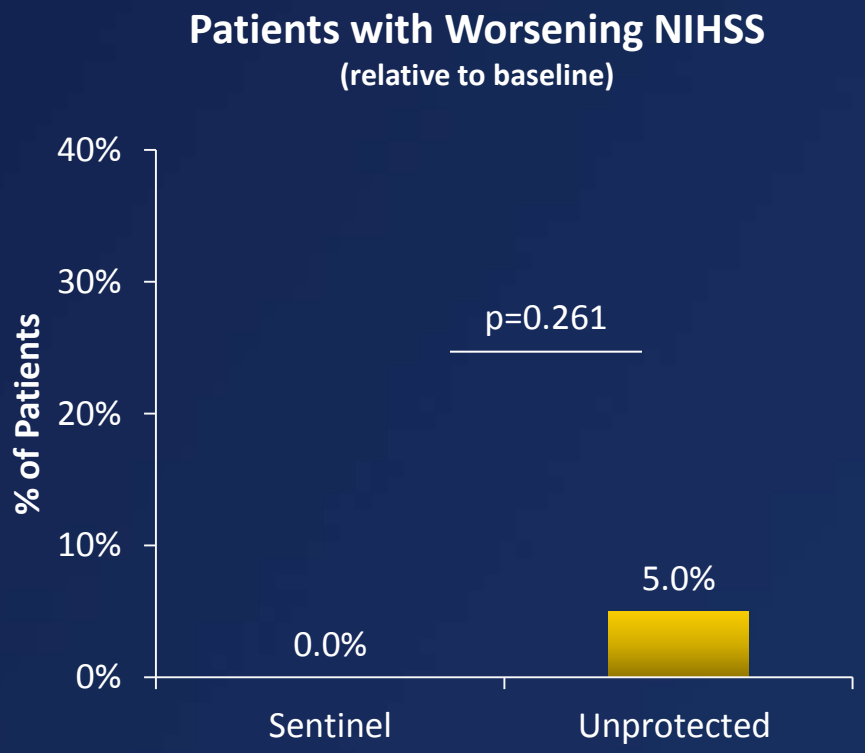
[1]Van Mieghem, et al., *EuroIntervention* 2016; 12:499-507

Sentinel (Claret)

MISTRAL-C | Neuro-function

Protected patients experienced less neurologic impairment at day 5



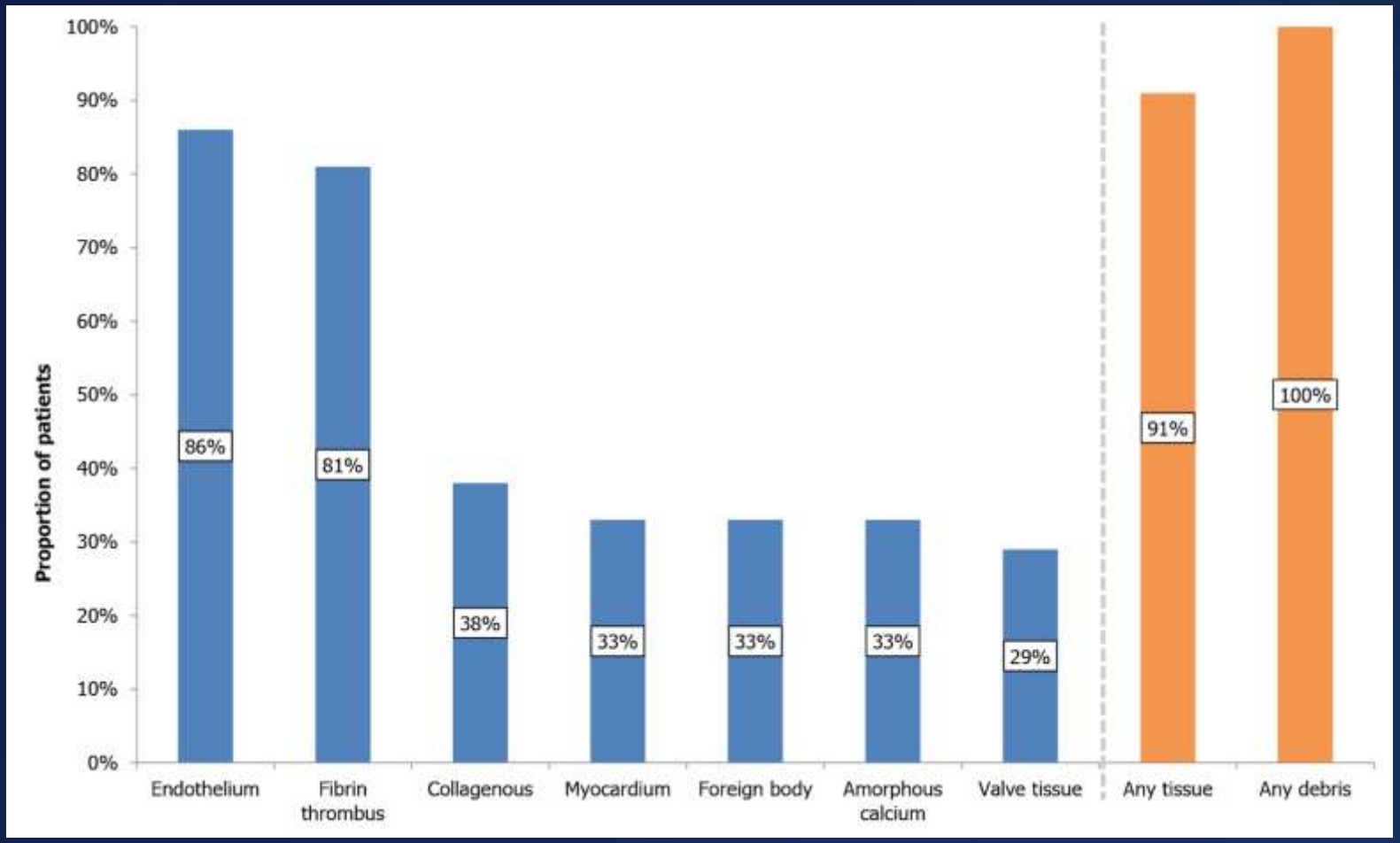


[1]Van Mieghem, et al., presented at TCT 2015

Sentinel (Claret)

MISTRAL-C | Histopathology

*Histological examination of the Sentinel filters showed that debris was captured in **100%** of the patients*



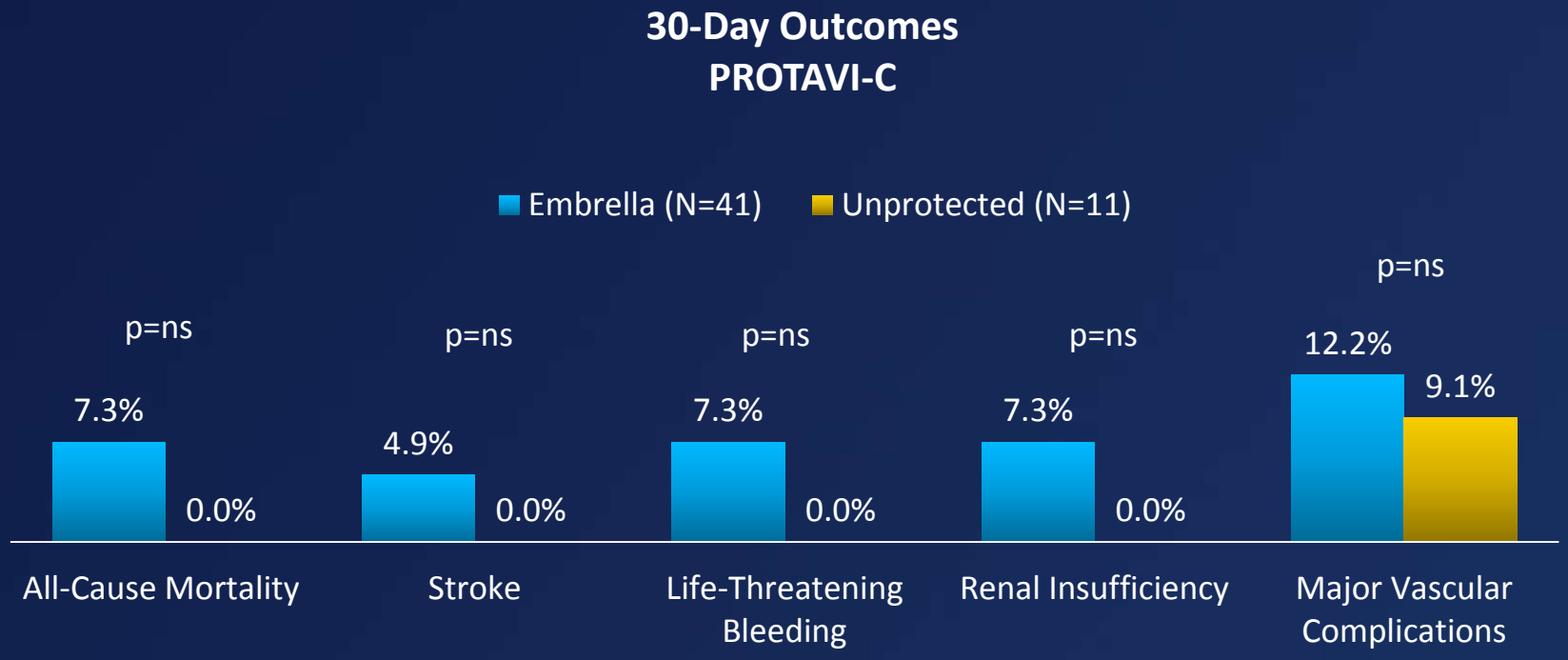
[1]Van Mieghem, et al., presented at TCT 2015

Embrella

Embrella (Edwards)

PROTAVI-C | Safety

PROTAVI-C (N=52) | Select Baseline Characteristics			
	Embrella (N=41)	Control (N=11)	P value
Age	83	84	0.72
Male	46.3%	72.7%	0.18
STS	5.4%	6.6%	0.93



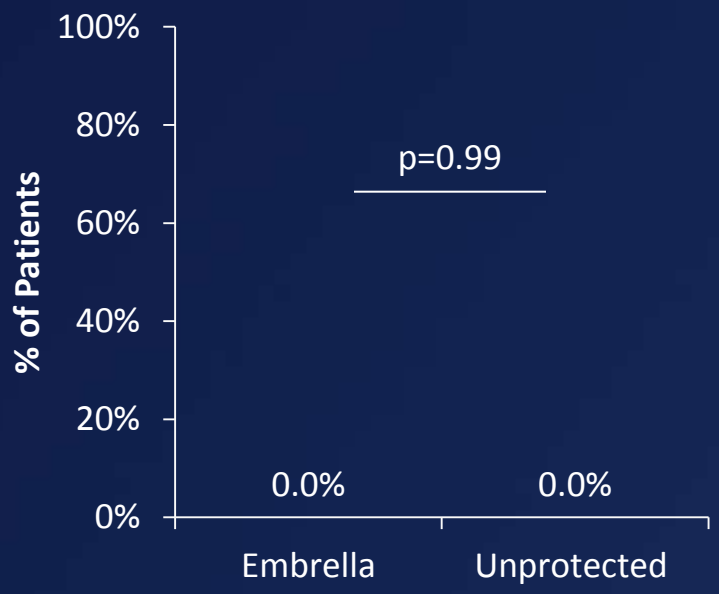
[1] Rodes-Cabau, et al., *J Am Coll Cardiol Intv* 2014;7:1146-55

Embrella (Edwards)

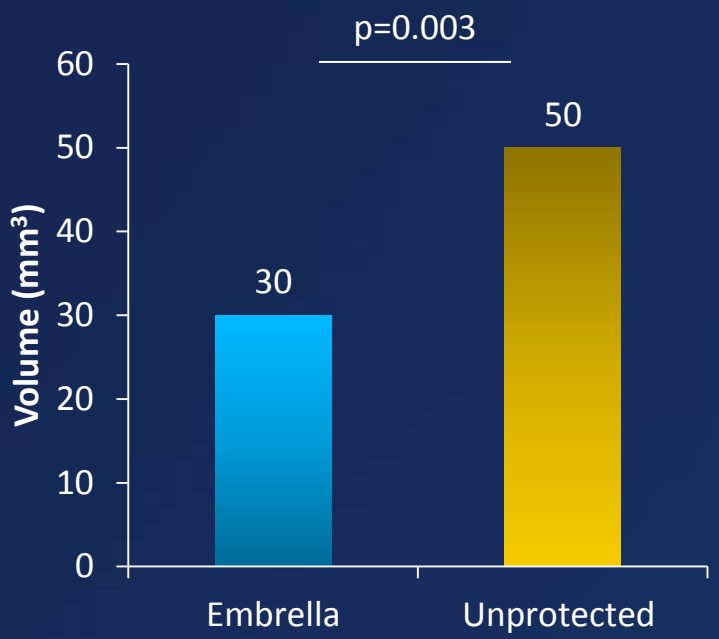
PROTAVI-C | Day 7 Imaging

- *All patients (protected and unprotected) showed some form of neurologic injury on MRI*
- *Embrella significantly reduced the size of the lesions that formed by 40%*

Patients Free of Post-Procedural Ischemic Lesions



Average Single Lesion Volume

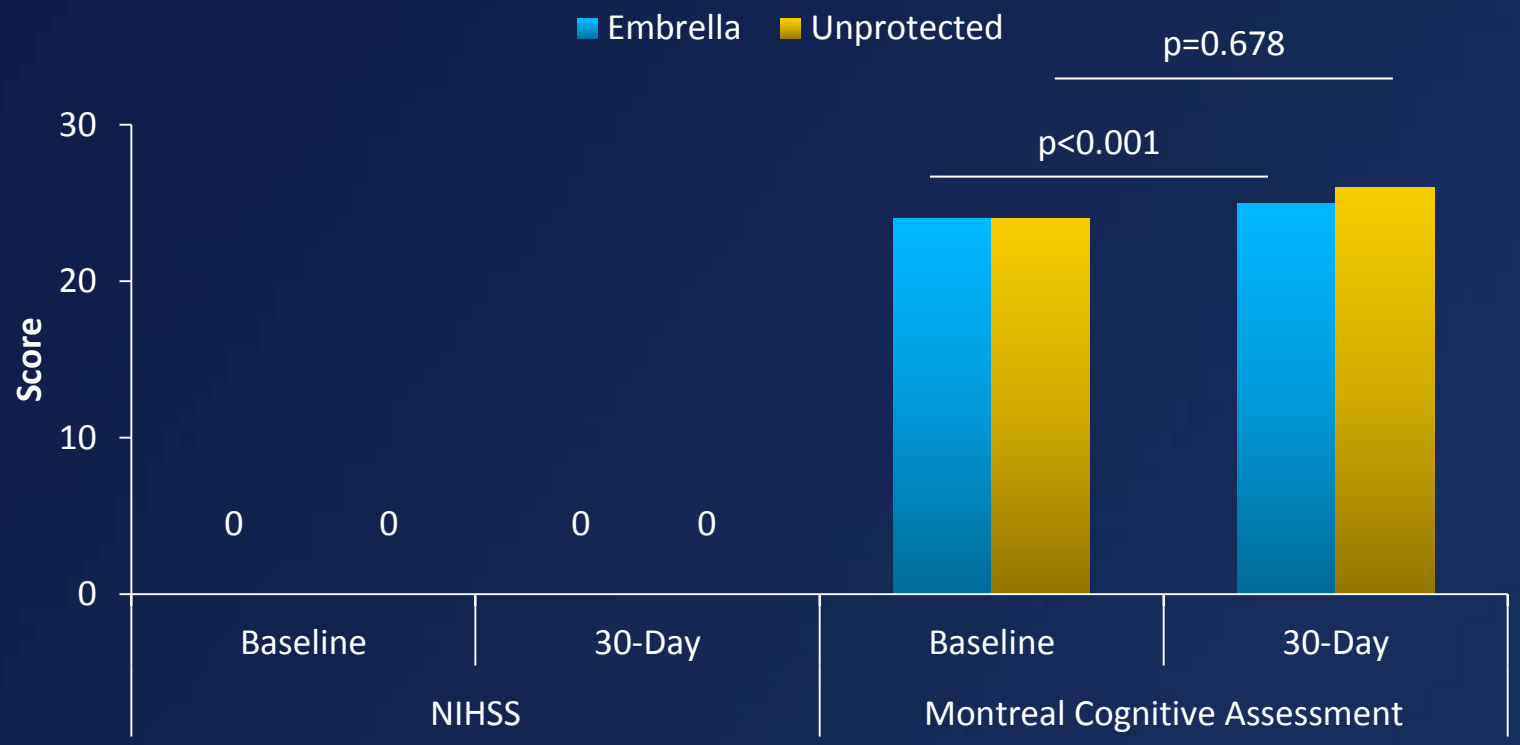


[1] Rodes-Cabau, et al., *J Am Coll Cardiol Intv* 2014;7:1146-55

Embrella (Edwards)

PROTAVI-C | Neuro-function

- *Protected patients showed a statistically significant improvement in cognitive status at 30 days as assessed by MoCA.*
- *The NIHSS failed to show a difference in protected and unprotected patients*



[1] Rodes-Cabau, et al., *J Am Coll Cardiol Intv* 2014;7:1146-55

In Summary…

Embolic Protection Devices

The Findings

DEFLECT-III N=85	
Purpose:	Exploratory, benchmark event rates
Achieved?	• Better outcomes with EPD • Stage set for US IDE Trial (REFLECT)

PROTAVI-C N=52	
Purpose:	Exploratory safety and efficacy
Achieved?	• Better MRI outcomes with EPD, worse with transcranial doppler

MISTRAL-C N=65	
Purpose:	Demonstrate reduction in brain lesions at day 5
Achieved?	• Better outcomes with EPD, lost statistical power with patients lost to follow-up

CLEAN-TAVI N=100	
Purpose:	Demonstrate reduction in brain lesions at day 2
Achieved?	• Statistically better outcomes with EPD • Stage set for US IDE Trial (SENTINEL)

Ongoing and Future Studies

Study	Device	Design	# Subjects	Primary Endpoint	Results Expected
SENTINEL (NCT02214277)	Claret Sentinel	Randomized	363	Reduced New Lesion Volume at day 4-7	TCT 2016 
REFLECT (NCT02536196)	Keystone TriGuard	Randomized	285	Reduced New Lesion Volume at day 2-5	After Sept 2017

Final Thoughts

- The studies reported so far have fulfilled their intended purpose:
  - They validate the notion that reduced embolic debris in the cerebral circulation results in fewer signals on MRI, and this translates clinically into better neurocognitive function.
  - They provide information on sample size and assessment tools needed to a show statistically significant benefit of embolic protection in larger studies.
- Further study is needed to define the level of embolic protection necessary to provide clinical benefit. Is 100% protection a requirement for success? Or is there a level of neurologic injury that can be tolerated?
- How do we define this threshold and how will we measure success?

Thank you for your kind attention!