Building the Evidence for CEP in TAVR: A Critical Review of the Clinical Trial Data

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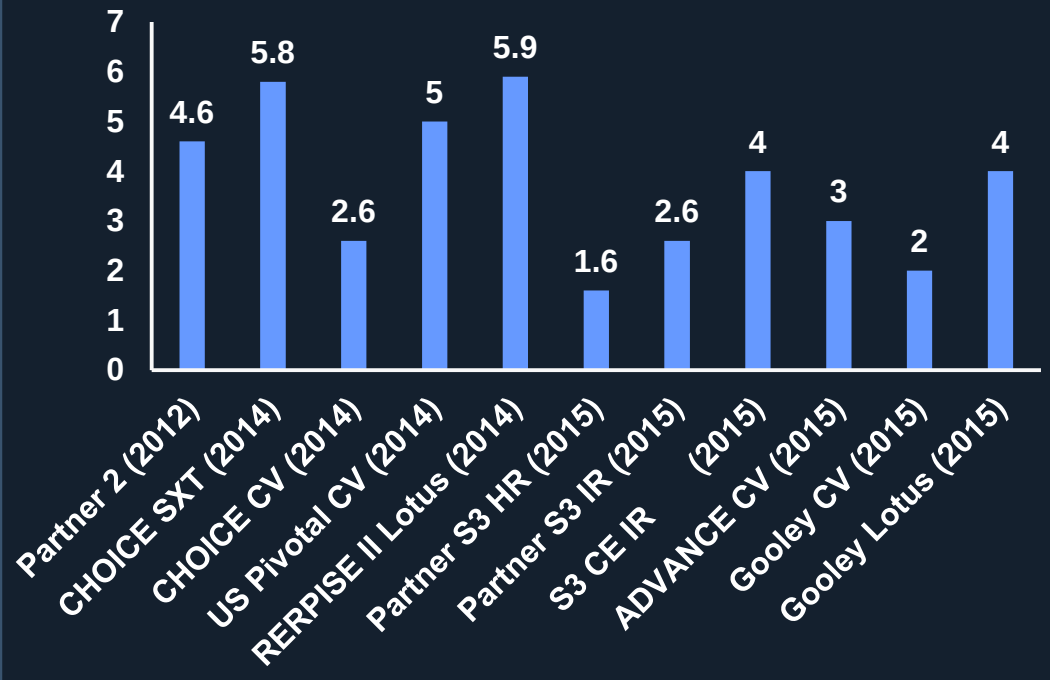
Disclosure Statement of Financial Interest

I, Jeffrey W. Moses, the following to disclose:

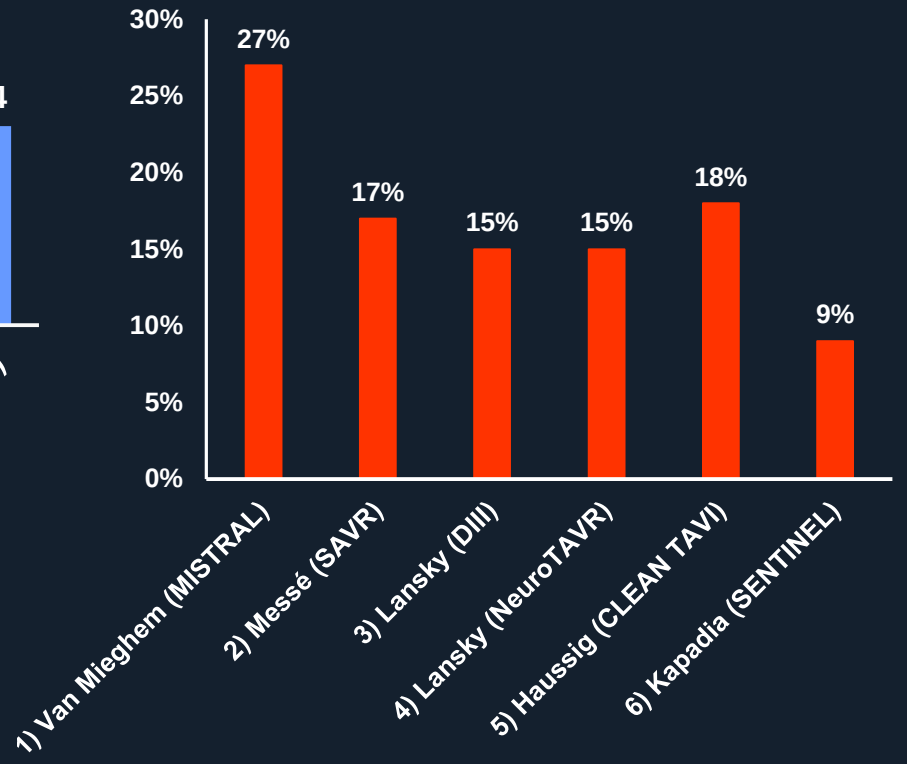
Equity: Claret , KSH

Stroke Underreported in TAVR Studies

In reported clinical trials stroke rates with TAVR range from 1.6%-5.9%



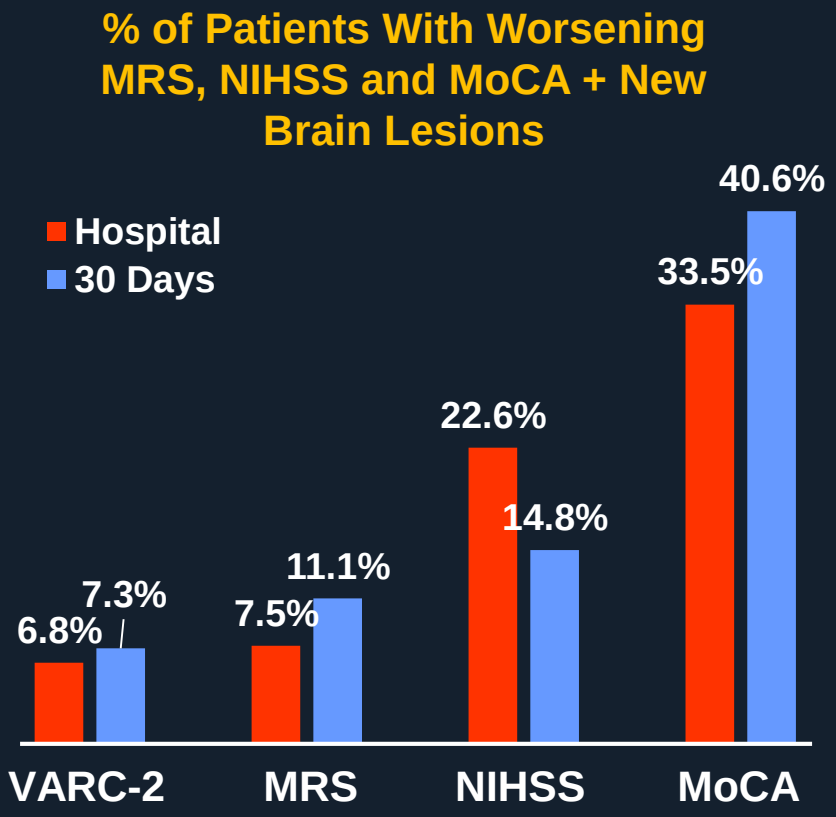
- Neurologist identified deficits and worsening neurocognition with new Brain MRI lesions and/or higher lesion volume
- Stroke range is 9-27% by AHA/ASA guidelines



1 Van Mieghem NM, *EuroIntervention*. 2016;12:499.
2 Messe S, *Circulation*. 2014;129:2253.
3 Lansky AJ, *Eur Heart J*. 2015;36:2070.
4 Lansky AJ, *AJC* 2016;118:1519.
5 Haussig S, *JAMA*. 2016;316:592.
6 Kapadia SR, *JACC*. 2017;69:367.

US NeuroTAVR Trial: Outcome

Neurologic And Cognitive Impairment After Unprotected TAVR In USA (5 High Volume TAVR Centers)



- Contemporary US Registry of 44 patients undergoing unprotected TAVR
- Stroke defined by AHA/ASA stroke definitions are common:
  - Discharge: 22.6%
  - 30-Days: 14.8%
- MoCA scores (surrogate of Cognition) get worse in 40% of patients after TAVR

Lansky et al *AJC* (2016),
http://dx.doi.org/10.1016/j.amjcard.2016.08.013

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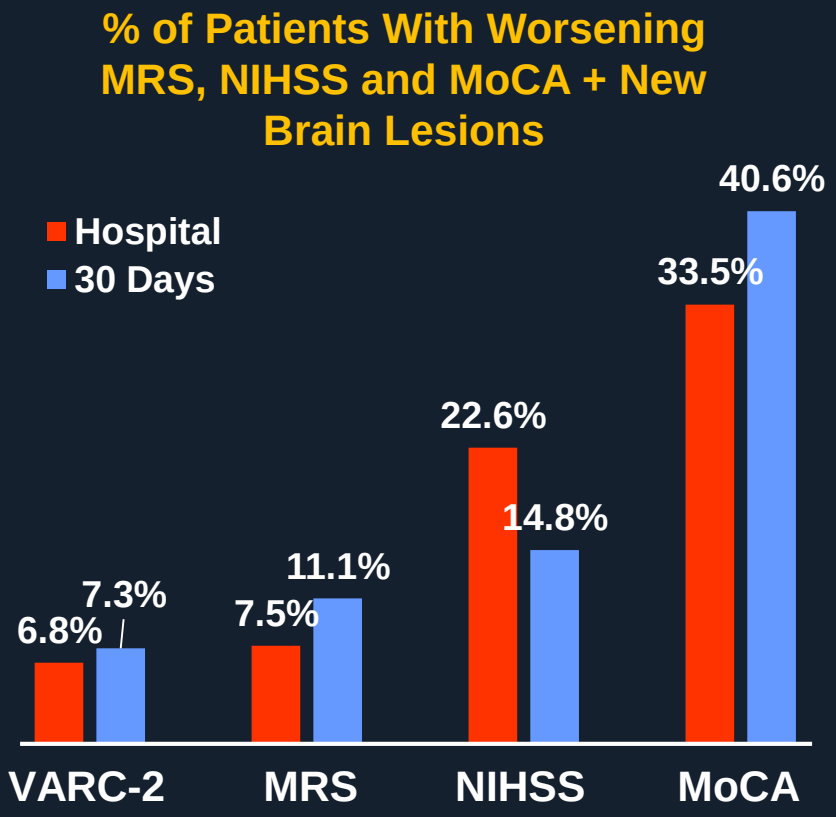

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Consequences of Stroke

Mortality:

TAVR patients suffering disabling stroke : 1-year mortality of 67% vs. 12% and 2-year mortality of 83% vs. 20%.[1]

PHYSICAL FUNCTIONING:

40% : moderate to severe permanent disability

55%-75% of “fully recovered” withresidual dysfunction in at least one limb.[2-3]

EFFECT OF STROKE AND WHITE MATTER LESIONS IN WORKING POPULATION

44% return to work,

33% significant financial strains,

79% report social isolation[4].

even without a stroke note impaired social cognition, leading predictor of occupational disability, and ability to maintain relationships with family and friends[5]

[1] Adams DH, *N Engl J Med.* 2014;370:1790. [2] Connolly SJ, *N Engl J Med*. 2009;361:1139. [3] Daniel K, Stroke. 2009;40:e431. [4] Lai SM, *Stroke*. 2002;33:1840, [5] Cotter *J Neurology* 2017;87:1727

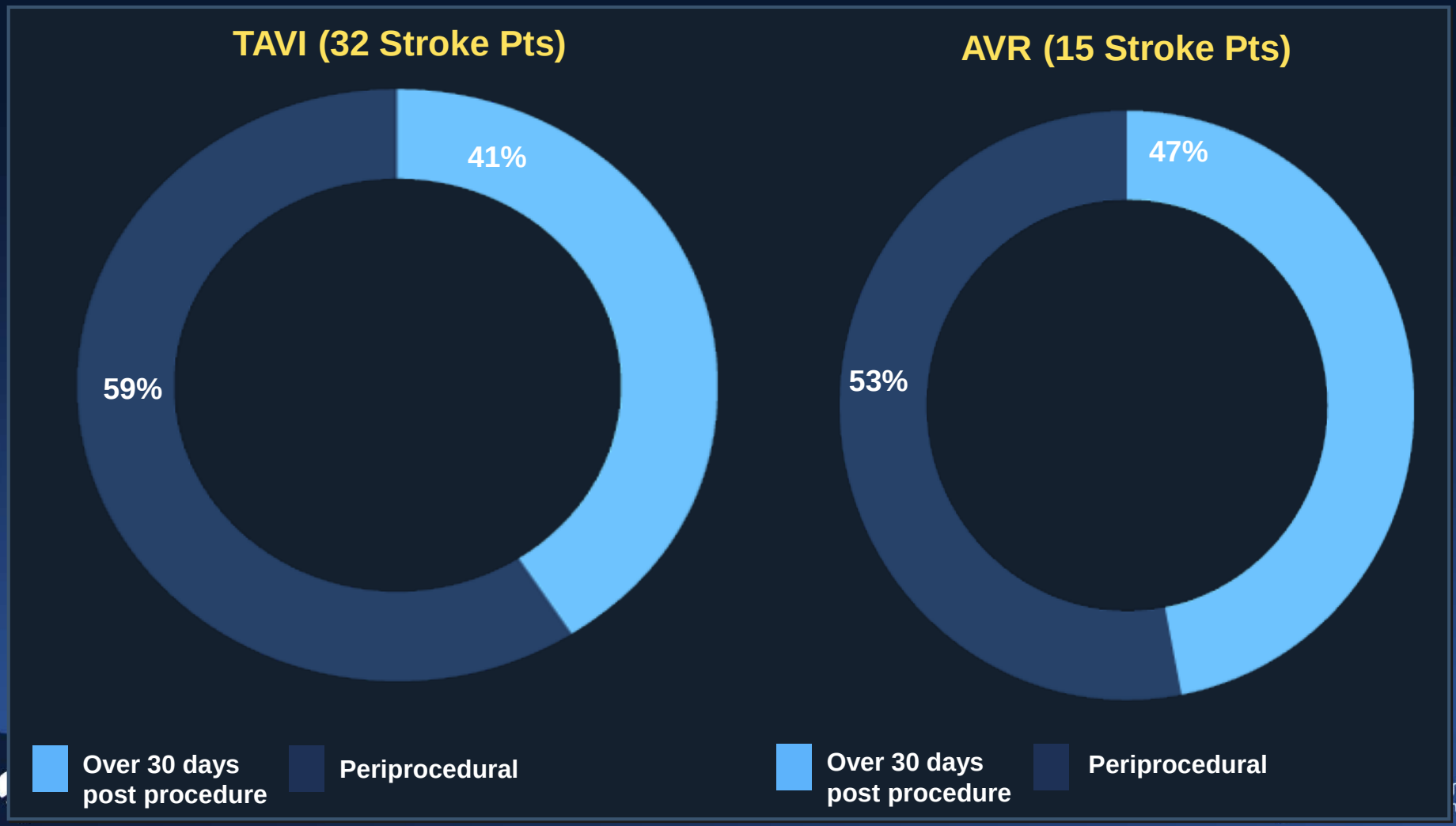
“Silent” Cerebral Emboli &TAVR

- Every step of TAVR puts a patient at risk of stroke (crossing the aortic valve, valvuloplasty, valve placement, etc.)[1]
- Cerebral embolization demonstrated by DWI MRI is common with TAVR occurring in 68-98% of cases.[2-4]
- Cerebral emboli detected on DWI MRI increase the risk of clinically overt stroke by 2-4 times and lead to cognitive dysfunction, depression, impaired mobility, dementia, and increased mortality.[5-6]
- The greater the volume of DWI lesions seen on MRI the greater the long-term risk of cognitive dysfunction and long-term dementia.[5-6]

[1]Kahlert, *Circulation*. 2012;216:1245-1255
[2]Arnold S, *J Am Coll Cardiol Intv.* 2010;3:1126
[3]Haussig S, *JAMA* 2016;316:592
[4]Lansky AJ, *Eur Heart J.* 2015;36:2070. | [5]Sacco RL, *Stroke*. 2013;44:00
[6]Vermeer SE, *Lancet* Neurol 2007;6:611

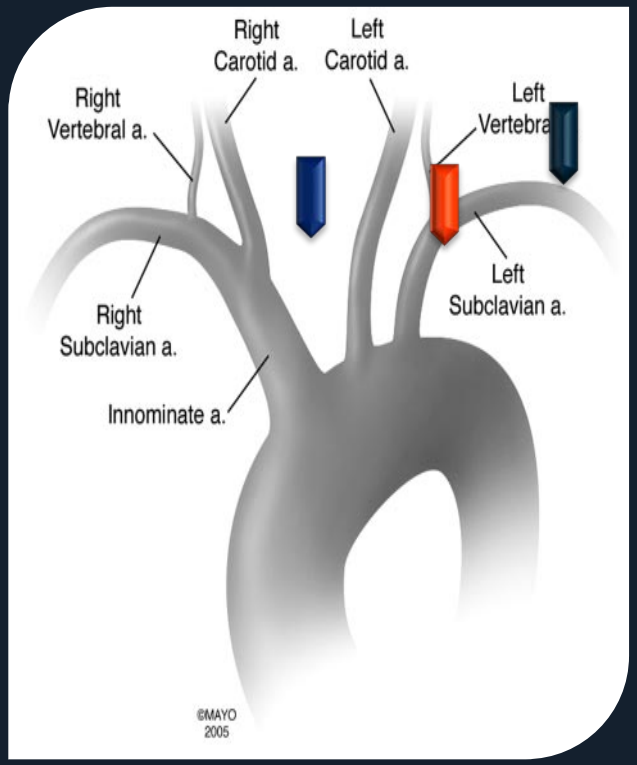
Most Of The Stroke Events Take Place Peri-Procedural

PARTNER (Cohort A)



Equal Distribution Of Cerebral Embolization To All Cerebral Vessels Validates The Need For Complete 3 Vessel Protection

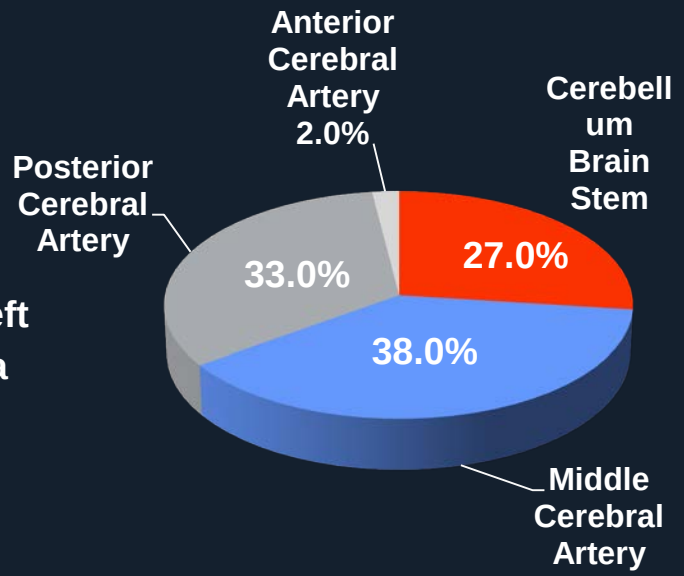
Potential Paths of Cerebral Embolism



- Vertigo, falling to left
- Diplopia, dysarthria
- Hemiparesis or quadriparesis
- Hemisensory loss
- Hemianopia or cortical blindness

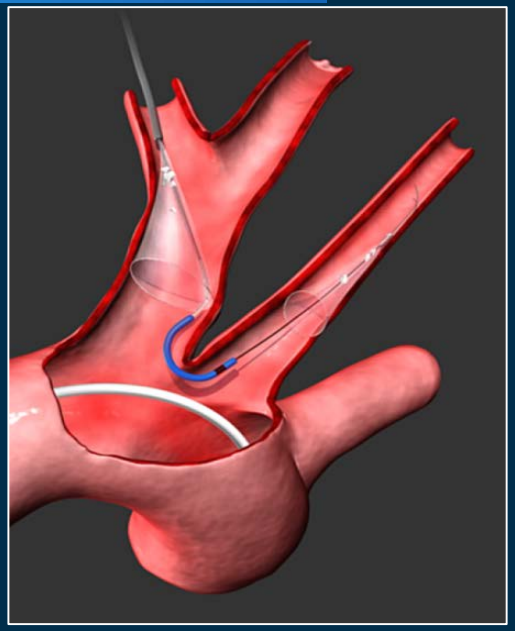
Layton KF et al. Bovine Aortic Arch Variant in Humans. AJNR 2006.

Distribution of Embolic Cerebral Damage by DWI



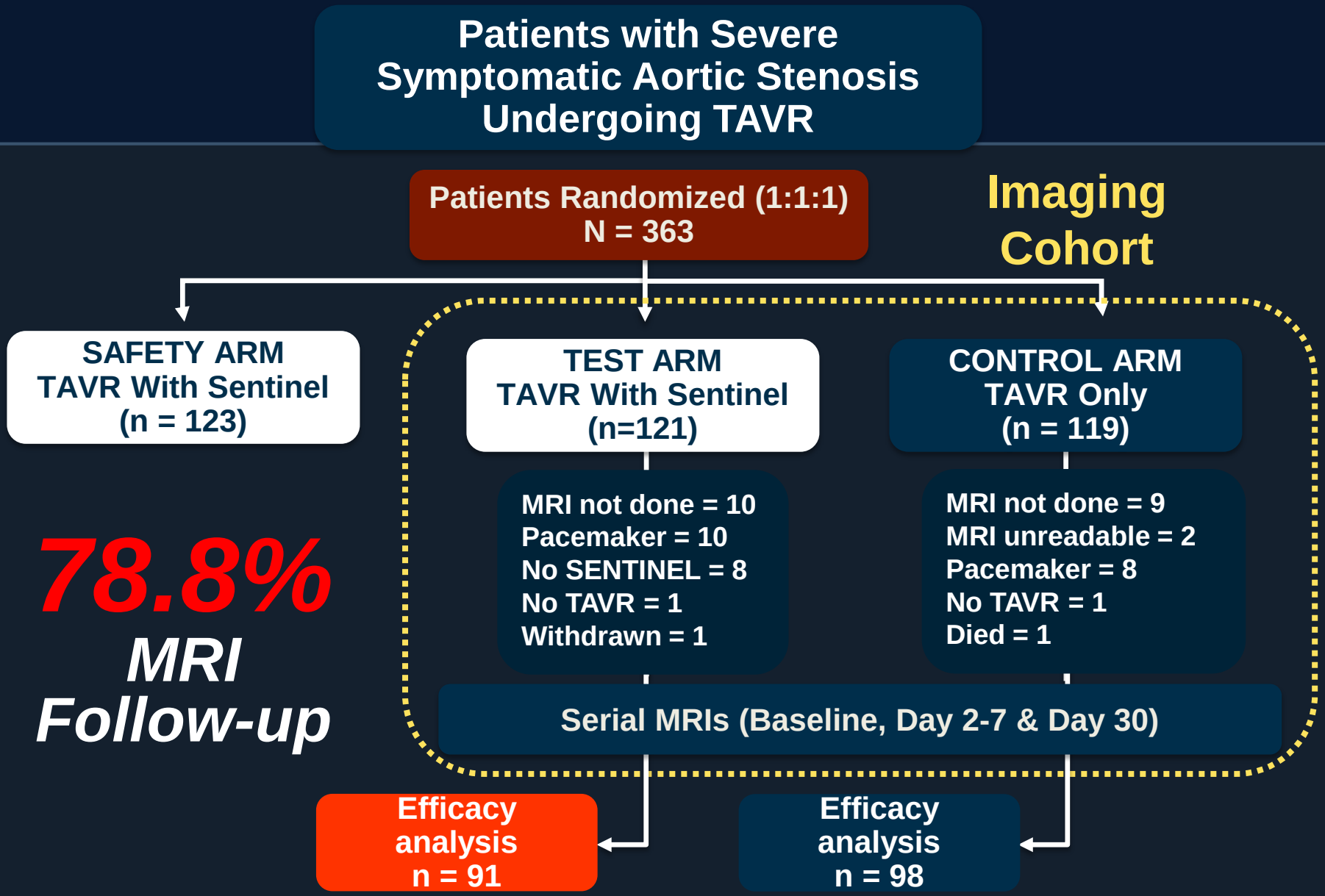
Arnold et al. Embolic Cerebral Insults After TAVI Detected by MRI. *JACC* 2010.

Sentinel Cerebral Protection Systems



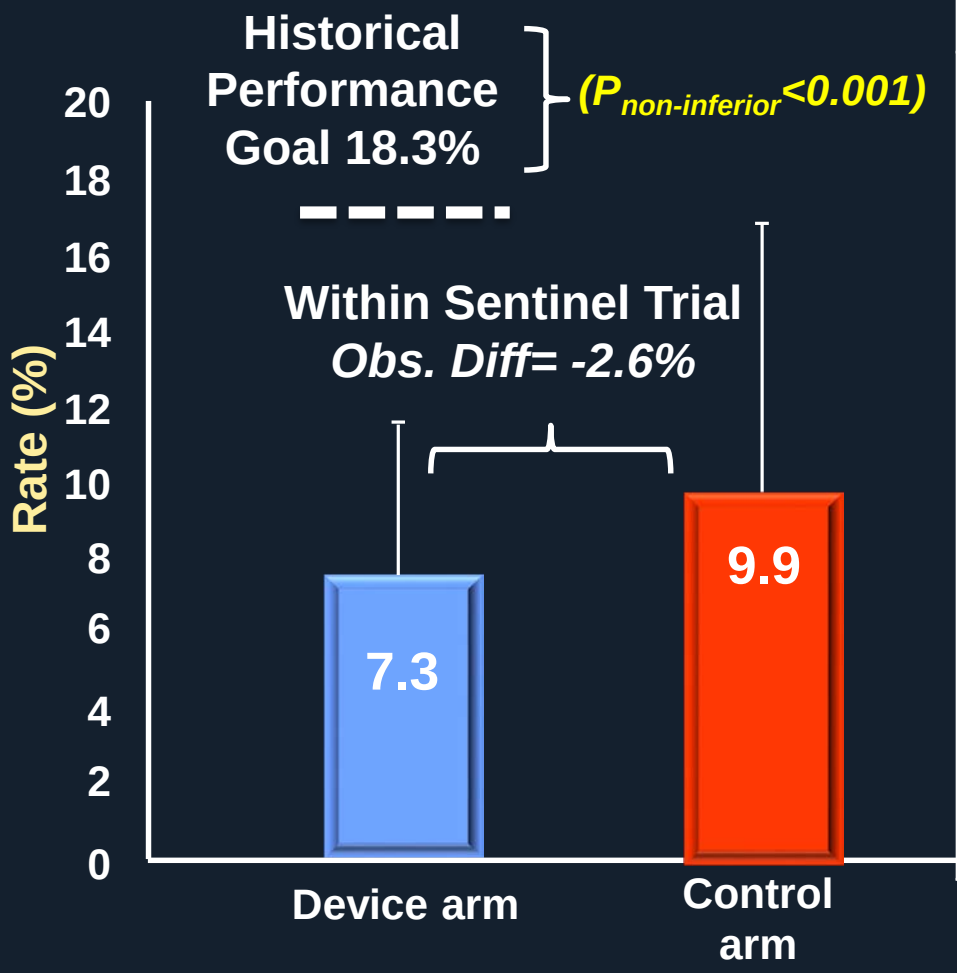
- Dual independent filters designed for embolic debris capture and removal
  in two of the three cerebral branches
  - Innominate artery and left common carotid artery
- Right transradial 6F sheath access

Study Flow


Patients with Severe Symptomatic Aortic Stenosis Undergoing TAVR
Patients Randomized (1:1:1)
N = 363
Imaging Cohort
SAFETY ARM
TAVR With Sentinel
(n = 123)
TEST ARM
TAVR With Sentinel
(n=121)
CONTROL ARM
TAVR Only
(n = 119)
MRI not done = 10
Pacemaker = 10
No SENTINEL = 8
No TAVR = 1
Withdrawn = 1
MRI not done = 9
MRI unreadable = 2
Pacemaker = 8
No TAVR = 1
Died = 1
78.8%
MRI Follow-up
Serial MRIs (Baseline, Day 2-7 & Day 30)
Efficacy analysis
n = 91
Efficacy analysis
n = 98

Primary Safety Endpoint (NI):
All Cause Death, Stroke, AKI Stage 3

30-Day MACCE

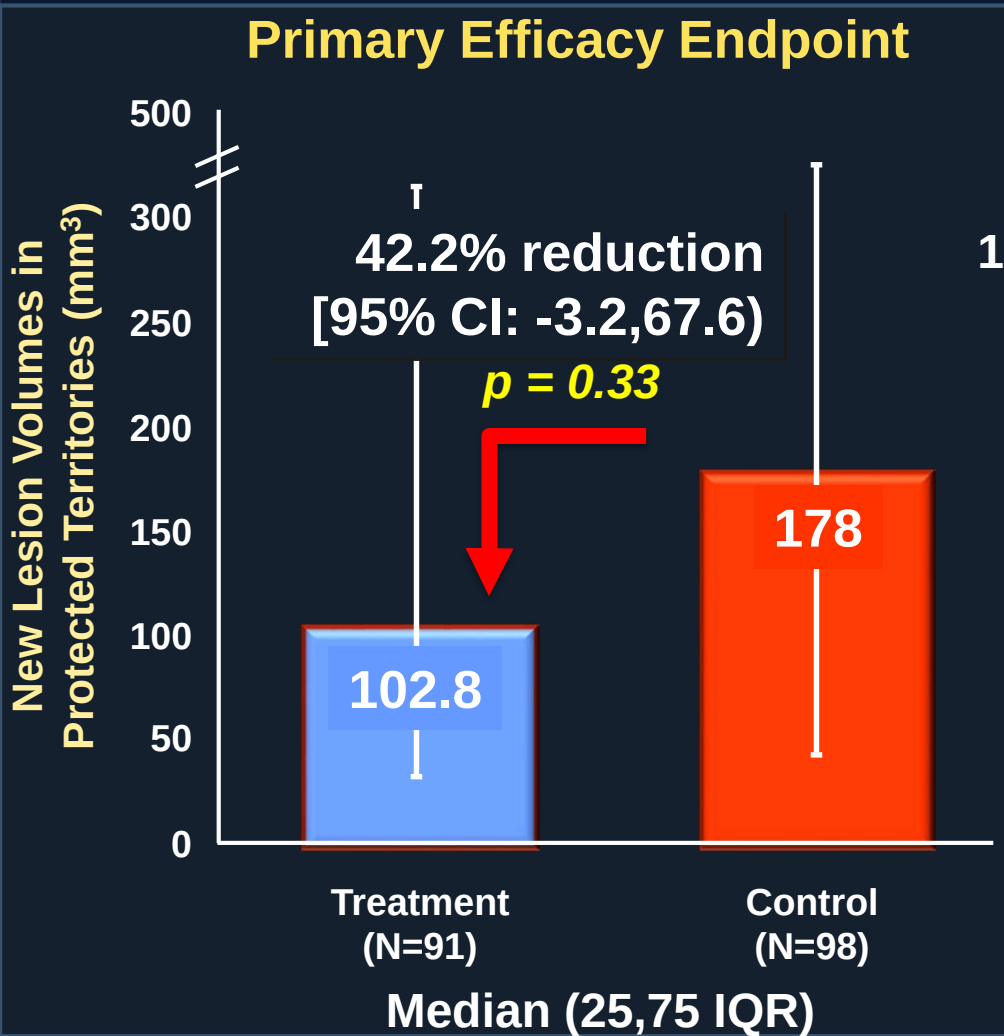


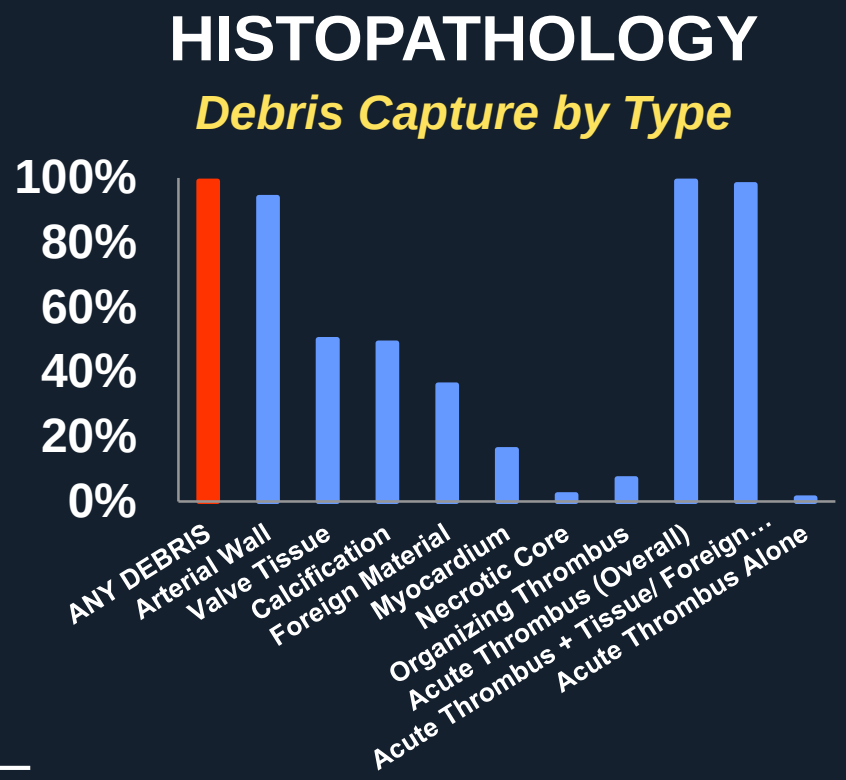
	Device Arm (n=234)	Control Arm (n=111)	*P* value
30-Day Clinical Outcomes			
Any MACCE†	7.3%	9.9%	0.40
Death (all-cause)	1.3%	1.8%	0.65
Stroke	5.6%	9.1%	0.25
Disabling	0.9%	0.9%	1.00
Non-disabling	4.8%	8.2%	0.22
AKI (Stage 3)	0.4%	0%	1.00
TIA	0.4%	0%	1.00
Sentinel Site Complications	0.4%	N/A	0.53

Primary Efficacy Endpoint (Superiority)

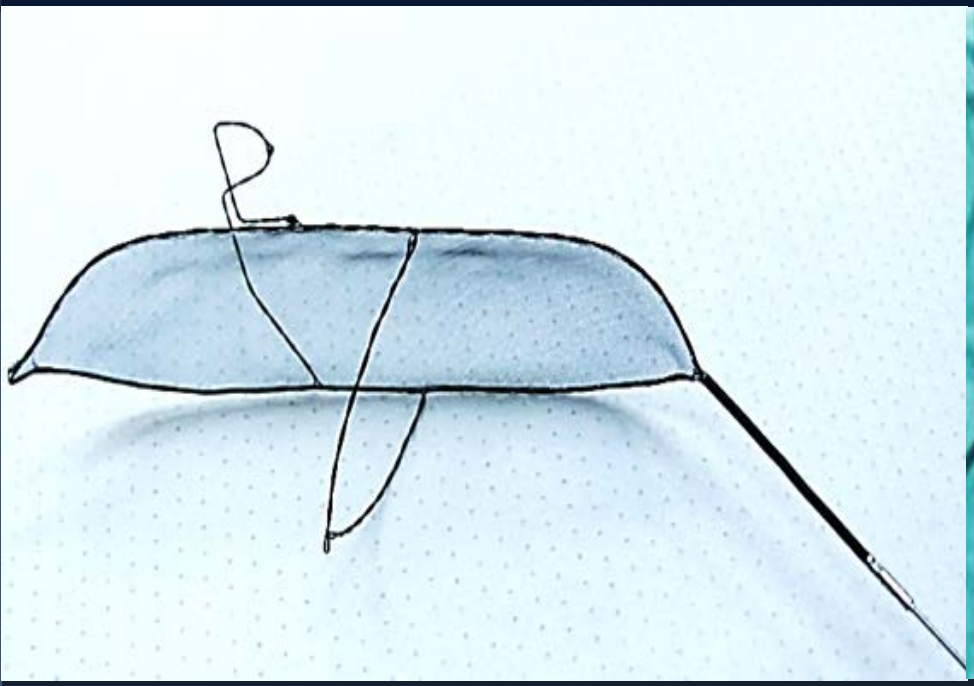
Median TLV In Protected Territories Assessed By DW-MRI At Day 2-7 Post-Procedure

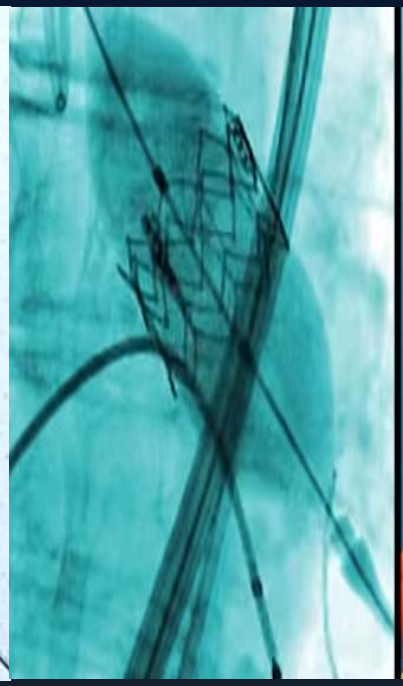
No Difference Between ALL Territories

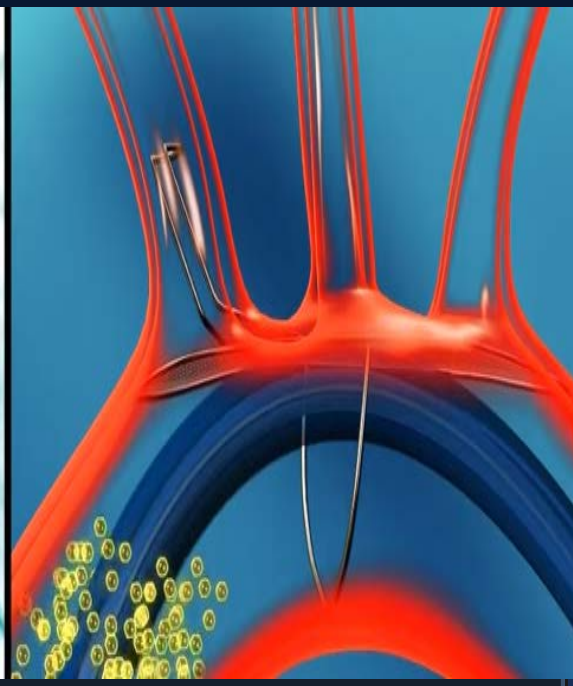




TriGuard™: Cerebral Embolic Protection





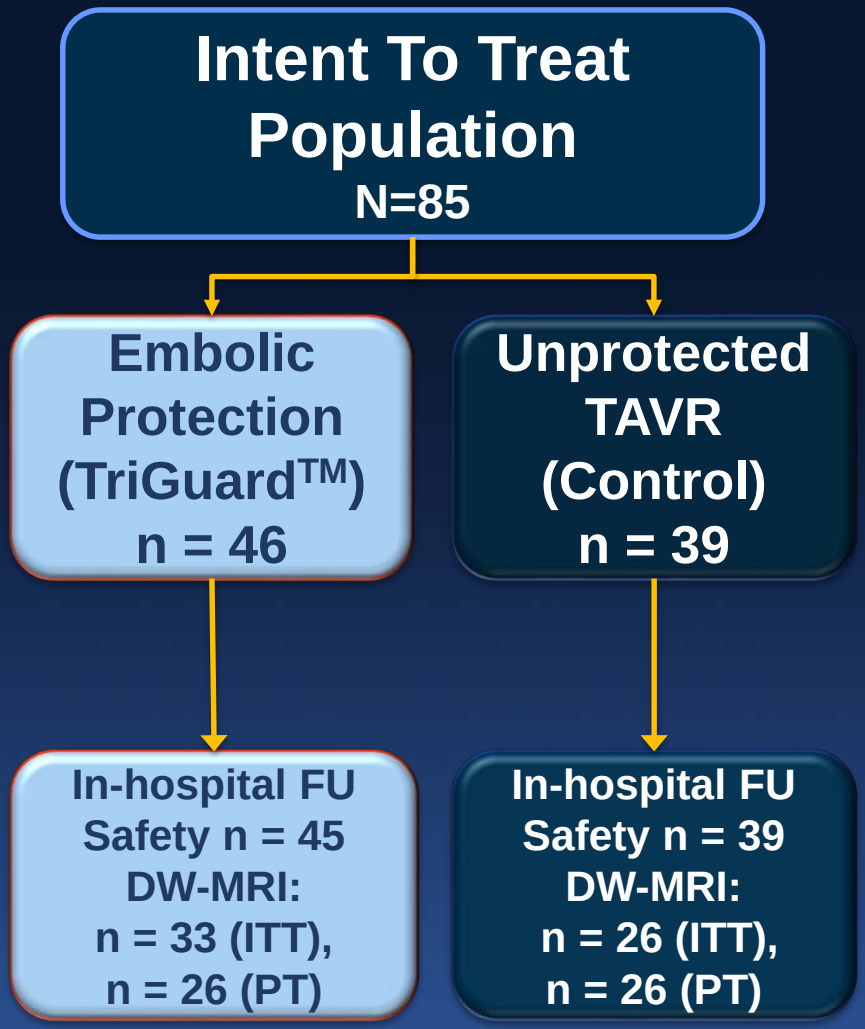


- Highly flexible nitinol frame and mesh
- Low profile
- Reduced mesh pore size (130µ X 250µ) improves efficacy without compromising hemodynamics
- Easily maneuverable
- 4 marker bands on frame for visibility

- **Designed to cover ALL major cerebral vessels** entire cerebro-vascular system: innominate, left carotid, and subclavian
- Over the arch delivery vs down the carotids designed to minimize brain emboli

TriGuard is an Investigational device for investigational use only in the USA

DEFLECT III Trial

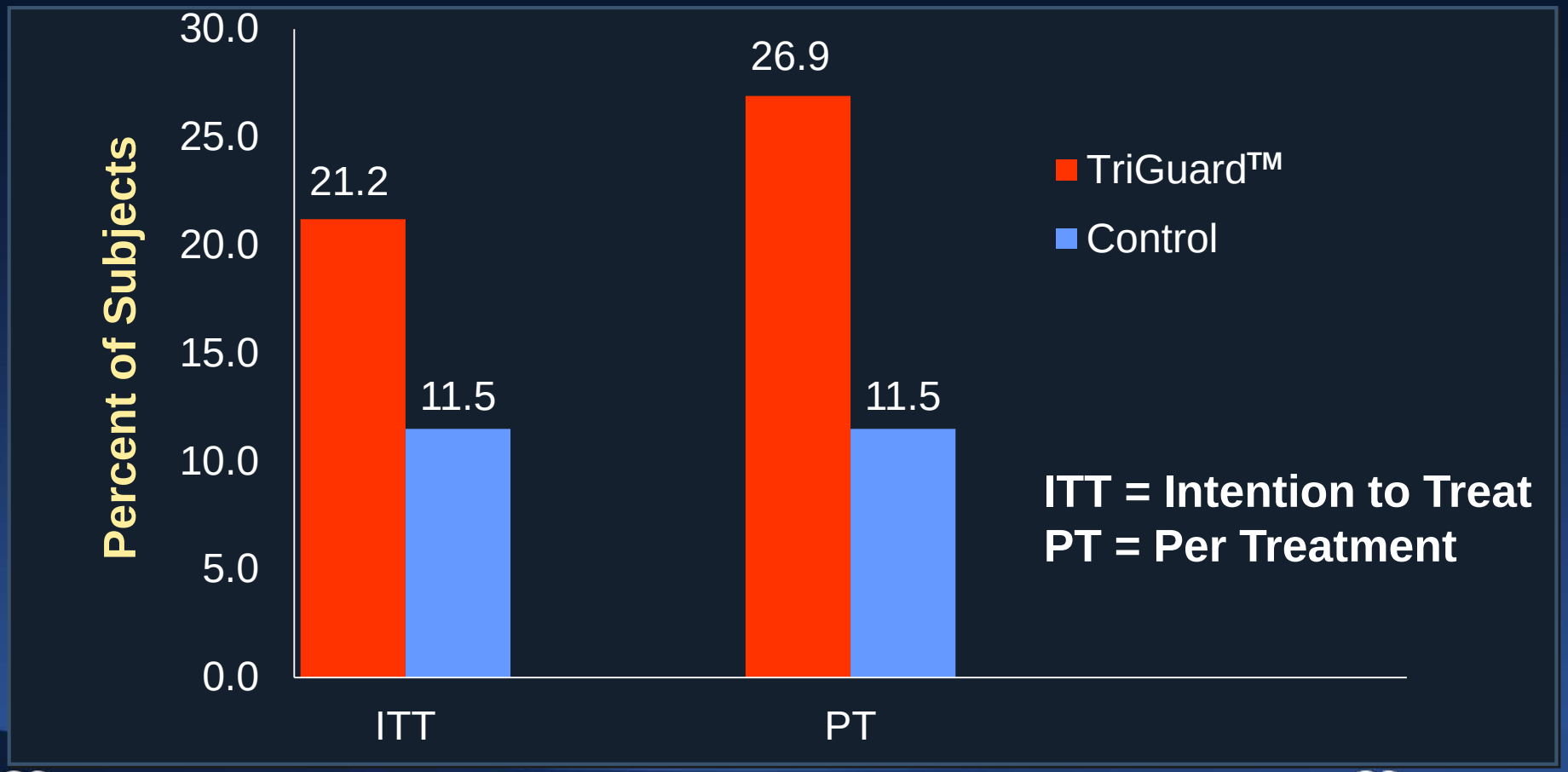


- **Deployment Success: 93.5%**
- **Successful positioning: 87% (complete 3-vessel coverage until final valve deployment of first valve, verified by QCA)**
- **Safety at 30 days (death, stroke, life threatening bleed, AKI, major vascular Complications) 26% TG vs 31% control**

Lansky AJ, *Eur Heart J*. 2015; 36:2070.

DW-MRI Results – Patients with No Ischemic Brain Lesions

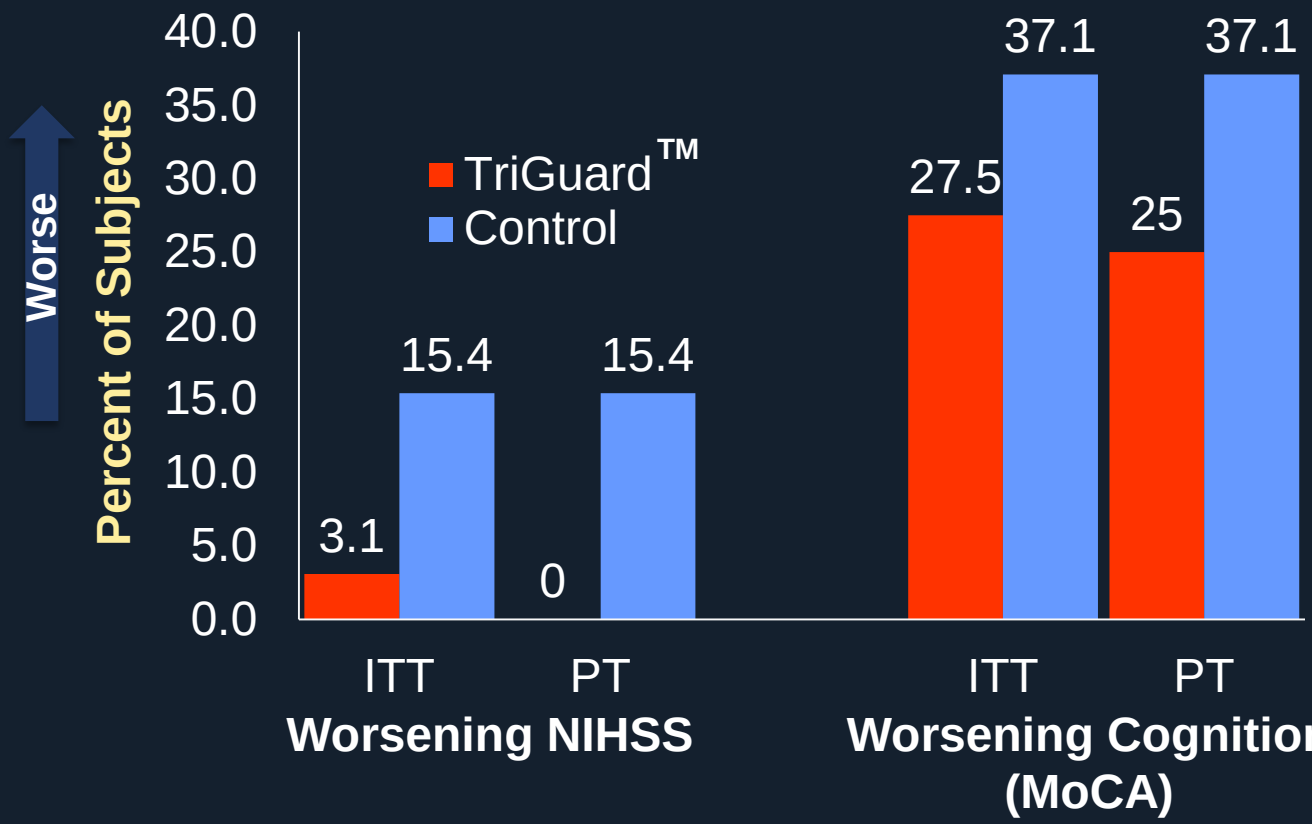
Protection Increases Freedom From Ischemic Lesions



Clinical Efficacy Outcomes – Stroke and Cognition

Protection Reduces Worsening Of Neurologic And Cognitive Outcomes

Patients With Worsening NIHSS And MoCA with MRI Brain Injury From Baseline To Discharge



Pooled Analysis of Keystone Heart Clinical Trials

OBJECTIVES:

To evaluate the safety and efficacy of the TriGuard™ device as an adjunct to TAVI compared to no protection in an expanded patient level pooled analysis of 3 prospective clinical trials

METHODS:

A total of 142 patients (TriGuard™ N=59 vs Controls N=83).

This per-treatment analysis includes all TG patients with adjudicated complete cerebral coverage.

Trials included: DEFLECT I, DEFLECT III and NeuroTAVR

ENDPOINTS:

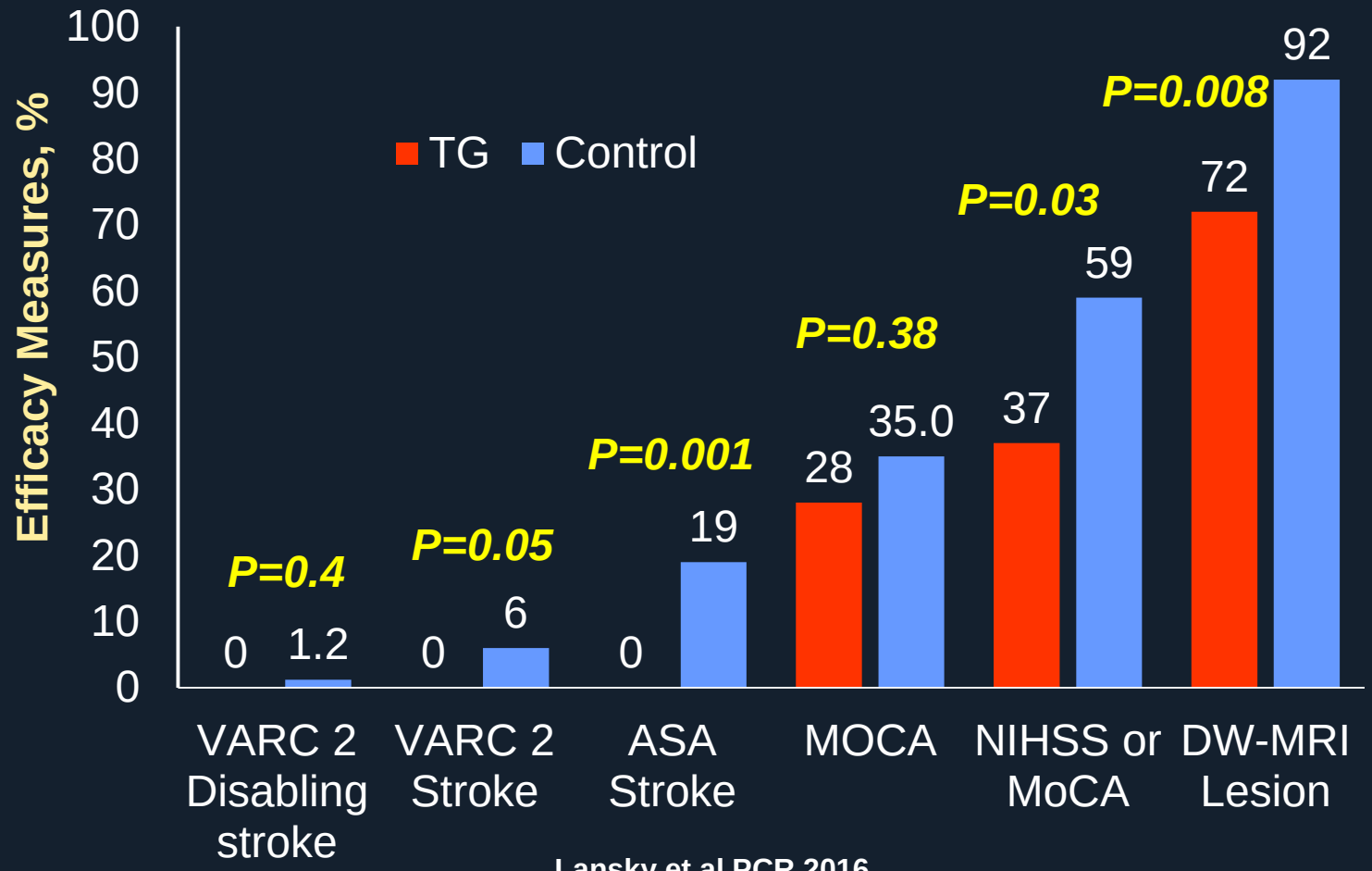
- MACCE: all death, stroke, bleeding, AKI, Vasc Complications
- Stroke: VARC2 defined * and AHA/ASA defined:**
- CNS infarction: Number an Volume New MRI lesions
- Worsening NIHSS and cognitive function (MoCA)

*AP Kappetein et al. *EHJ* (2012) 33, 2403–2418;
**Sacco et al. *Stroke*. 2013;44:2064-2089

TriGuard™ Pooled Analysis: Covering All Three Cerebral Branches Can Improve Clinical Outcome Significantly

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)

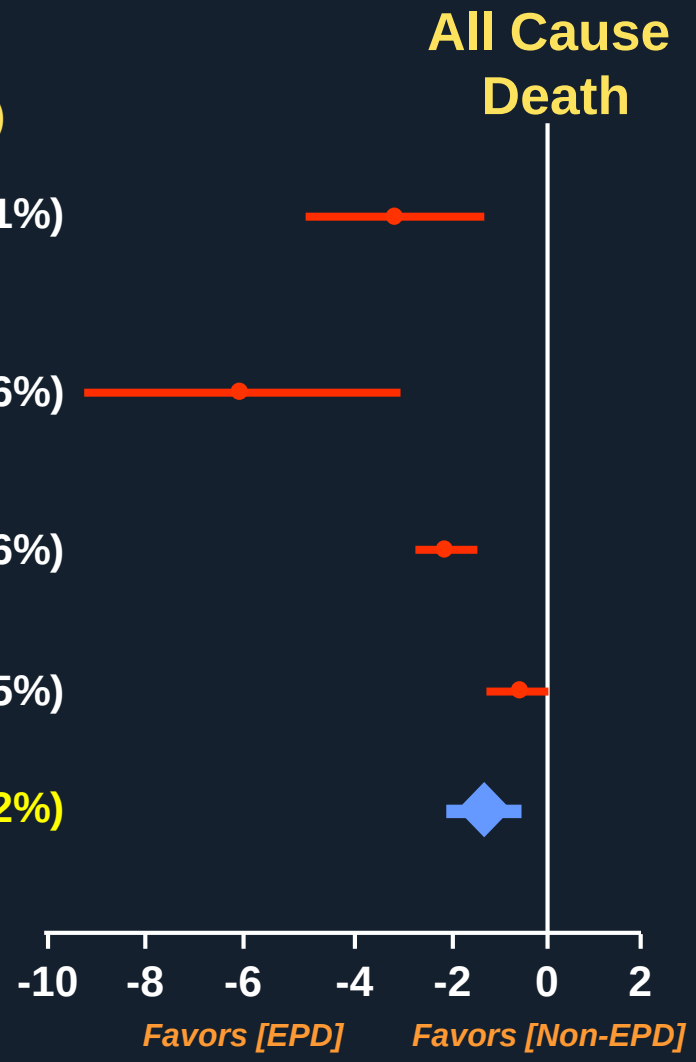


Lansky et al PCR 2016

TriGuard is an Investigational device for investigational use only in the USA

New CRF Meta-analysis
4 RCTs 595 Pts

Trial	Total	Device	Ctrl	Risk. Diff. (95 CI)
DEFLECT III	85	2.17%	5.13%	-2.95% (-4.60%, -1.31%)
MISTRAL-C	65	3.12%	9.09%	-5.97% (-8.97%, -2.96%)
CLEAN TAVI	100	0.00%	2.00%	-2.00% (-2.54%, -1.46%)
SENTINEL	345	1.28%	1.80%	-0.52% (-0.89%, -0.15%)
Overall	595	1.60%	3.83%	-1.23% (-1.83%, -0.62%)

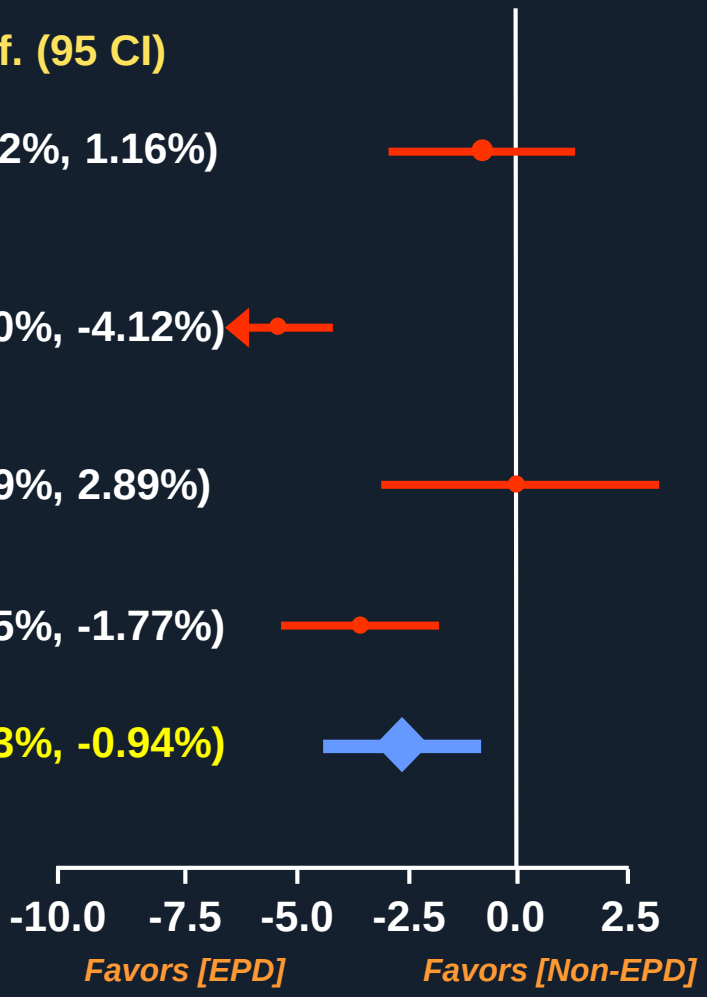


Golomb et al, manuscript in preparation

New CRF Meta-analysis
4 RCTs 591 Pts

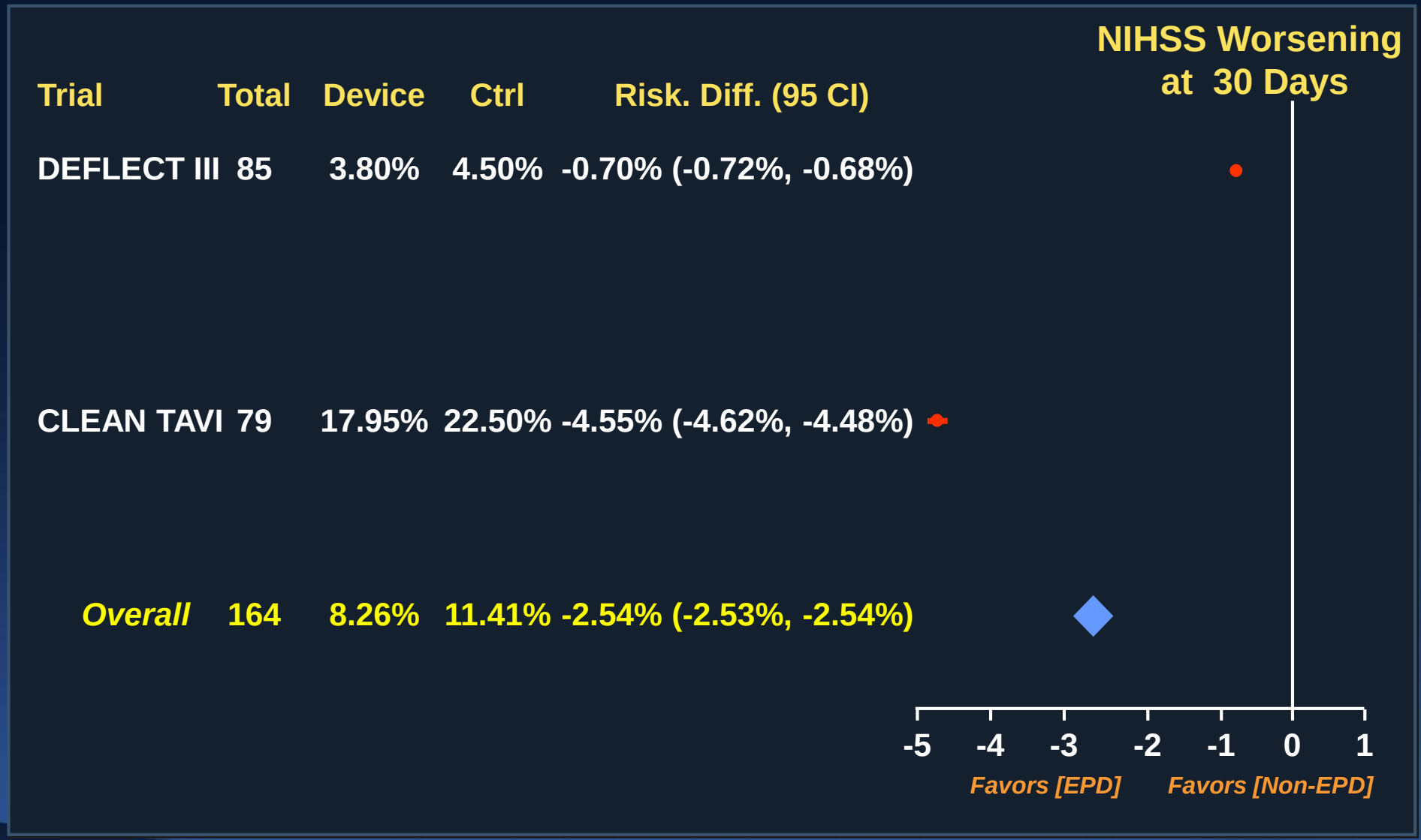
Stroke at 30 days

Trial	Total	Device	Ctrl	Risk. Diff. (95 CI)
DEFLECT III	85	4.35%	5.13%	-0.78% (-2.72%, 1.16%)
MISTRAL-C	65	0.00%	6.06%	-6.06% (-8.00%, -4.12%)
CLEAN TAVI	100	8.00%	8.00%	0.00% (-2.89%, 2.89%)
SENTINEL	341	5.63%	9.09%	-3.46% (-5.15%, -1.77%)
Overall	591	5.09%	7.26%	-2.54% (-4.13%, -0.94%)



Golomb et al, manuscript in preparation

New CRF Meta-analysis
2RCTs164 Pts



Golomb et al, manuscript in preparation

New CRF Meta-analysis
4 RCTs 214 Pts

Trial	Total	Device	Ctrl	Risk. Diff. (95 CI)
DEFLECT III	59	78.79%	88.46%	-9.67% (-16.60%, -2.75%)
EMBOL-X	30	57.14%	68.75%	-11.61% (-28.20%, 4.99%)
MISTRAL-C	37	72.73%	86.67%	-13.94% (-24.08%, -3.80%)
CLEAN-TAVI	94	97.96%	97.78%	0.18% (-0.66%, 1.03%)
Overall	214	1.60%	3.83%	-1.23% (-1.83%, -0.62%)

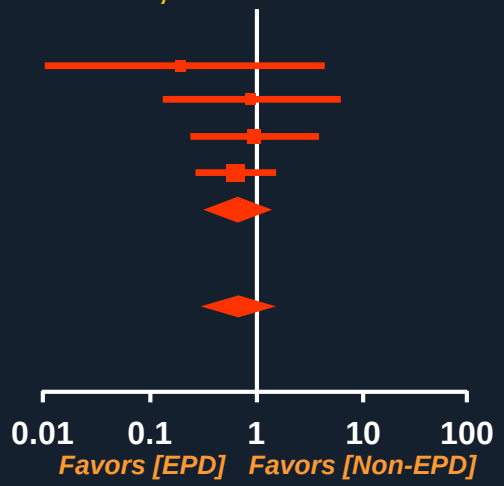
Golomb et al, manuscript in preparation

Meta-analyses of Embolic Protection Device (EPD)

16 Studies, 1,170 Patients (865/305 with / without EPD)

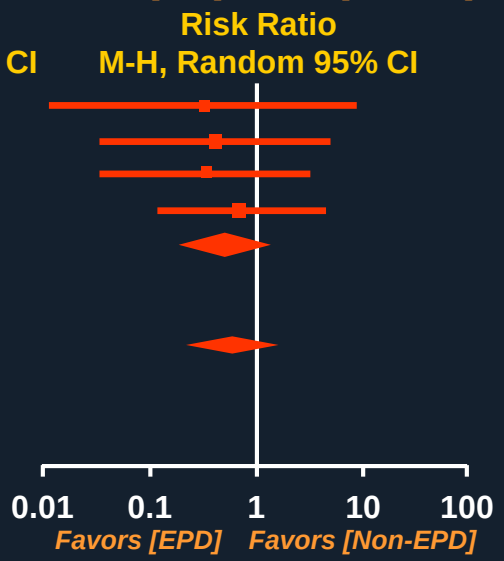
30-day Stroke

Study or Subgroup Randomized Studies	Risk Ratio M-H, Random 95% CI
Wendt et al 2015	Not estimable
Van Mieghem et al 2016	0.21 [0.01, 4.13]
Lansky et al 2015	0.85 [0.13, 5.74]
Haussig et al 2016	1.00 [0.26, 3.78]
Kapadia et al 2016	0.62 [0.28, 1.37]
Subtotal (95% CI)	0.68 [0.36, 1.27]
Heterogeneity: Tau²=0.00; Chi²=1.04, df=3 (P=0.79); I²=0%	
Test for overall effect: Z=1.21 (P=0.23)	
Total (95% CI)	0.70 [0.38, 1.29]
Heterogeneity: Tau²=0.00; Chi²=1.27, df=4 (P=0.87); I²=0%	
Test for overall effect: Z=1.14 (P=0.26)	
Test for subgroup differences: Chi²=0.23, df=1 (P=0.63); I²=0%	



30-day Mortality

Study or Subgroup Randomized Studies	Risk Ratio M-H, Random 95% CI
Haussig et al 2016	0.33 [0.01, 7.99]
Lansky et al 2015	0.42 [0.04, 4.50]
Van Mieghem et al 2016	0.34 [0.04, 3.13]
Kapadia et al 2016	0.71 [0.12, 4.20]
Subtotal (95% CI)	0.48 [0.16, 1.46]
Heterogeneity: Tau²=0.00; Chi²=0.34, df=3 (P=0.95); I²=0%	
Test for overall effect: Z=1.29 (P=0.20)	
Total (95% CI)	0.58 [0.20, 1.64]
Heterogeneity: Tau²=0.00; Chi²=1.15, df=4 (P=0.89); I²=0%	
Test for overall effect: Z=1.03 (P=0.30)	
Test for subgroup differences: Chi²=0.82, df=1 (P=0.37); I²=0%	



American Heart Association

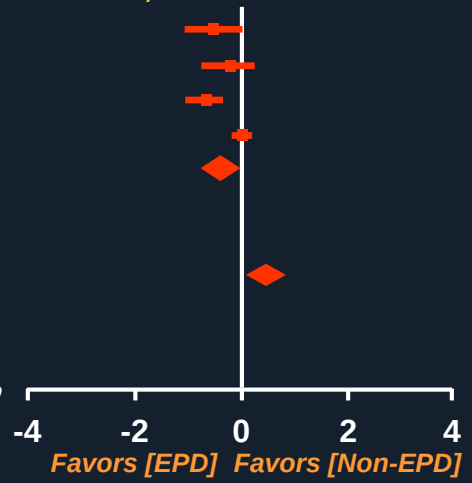
Rodrigo Bagur et al. *Stroke* 2017;48:1306-1315

Meta-analyses of Embolic Protection Device (EPD)

16 Studies, 1,170 Patients (865/305 with / without EPD)

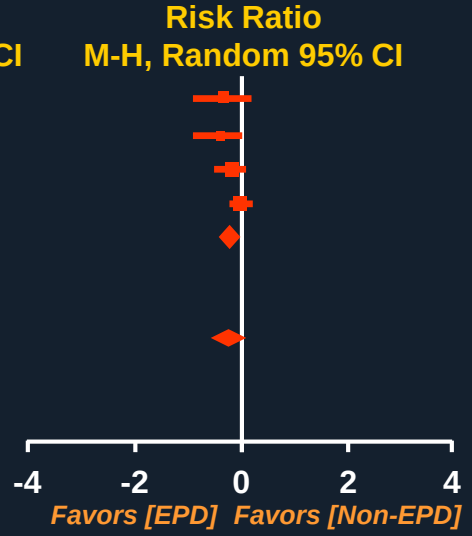
Number of Lesions per Patient

Study or Subgroup Randomized Studies	Risk Ratio M-H, Random 95% CI
Wendt et al 2015	-0.71 [-1.45, 0.03]
Van Mieghem et al 2016	-0.39 [-1.05, 0.28]
Haussig et al 2016	-0.99 [-1.42, -0.56]
Kapadia et al 2016	-0.11 [-0.40, 0.17]
Subtotal (95% CI)	-0.53 [-1.02, -0.04]
Heterogeneity: Tau²=0.18; Chi²=11.94, df=3 (P=0.008); I²=75%	
Test for overall effect: Z=2.13 (P=0.03)	
Total (95% CI)	-0.19 [-0.71, 0.34]
Heterogeneity: Tau²=0.33; Chi²=27.64, df=5 (P<0.0001); I²=82%	
Test for overall effect: Z=0.70 (P=0.49)	
Test for subgroup differences: Chi²=11.46, df=1 (P=0.0007); I²=91.3%	



Total Volume of Lesions per Patient

Study or Subgroup Randomized Studies	Risk Ratio M-H, Random 95% CI
Wendt et al 2015	-0.47 [-1.20, 0.25]
Van Mieghem et al 2016	-0.60 [-1.27, 0.07]
Haussig et al 2016	-0.30 [-0.70, 0.11]
Kapadia et al 2016	-0.08 [-0.36, 0.21]
Subtotal (95% CI)	-0.22 [-0.43, -0.01]
Heterogeneity: Tau²=0.00; Chi²=2.84, df=3 (P=0.42); I²=0%	
Test for overall effect: Z=2.04 (P=0.04)	
Total (95% CI)	-0.23 [-0.42, -0.03]
Heterogeneity: Tau²=0.00; Chi²=2.90, df=5 (P=0.72); I²=0%	
Test for overall effect: Z=2.29 (P=0.02)	
Test for subgroup differences: Chi²=0.03, df=1 (P=0.87); I²=0%	



American Heart Association

Rodrigo Bagur et al. *Stroke* 2017;48:1306-1315

- **While the weight of evidence strongly favors EPD in TAVR we are still lacking a single definitive trial trial of efficacy**
- **We believe the REFLECT Trial provides the field with this best opportunity**

REFLECT US IDE Trial Design

Chair Jeffrey Moses, CO PIs A Lansky, R Makkar (US) and J Schofer, A Baumbach (EU)

DSMB: Dr J Petersen, Dr A Geirsson, Ms H Parise (stats)
CEC: Dr S Messe, Dr J Brennan, Dr J Brener

Subject With AS Undergoing TAVI N=285

Roll-In N≤90

2:1 Randomization

TriGuard™ Embolic Protection n=190

Unprotected TAVI n=95

SAFETY

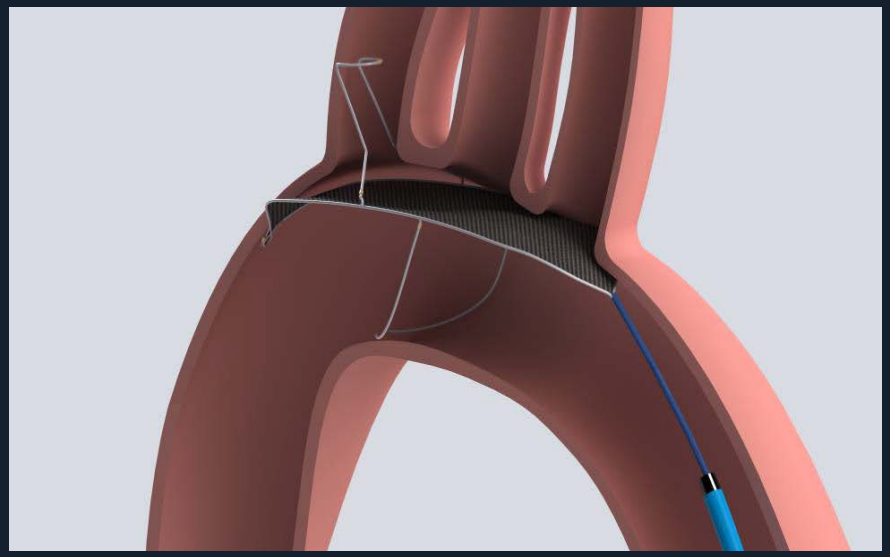
- Combined safety endpoint (VARC-2) at 30 days
- TriGuard™ vs. Performance Goal

EFFICACY

- Hierarchical composite efficacy endpoint (Finkelstein-Schoenfeld):
  - Death or stroke (30 d)
  - NIHSS (in-hospital) or MoCA worsening (30 days)
  - Total lesion volume by DW-MRI (post-procedure)
- TriGuard™ vs. Control

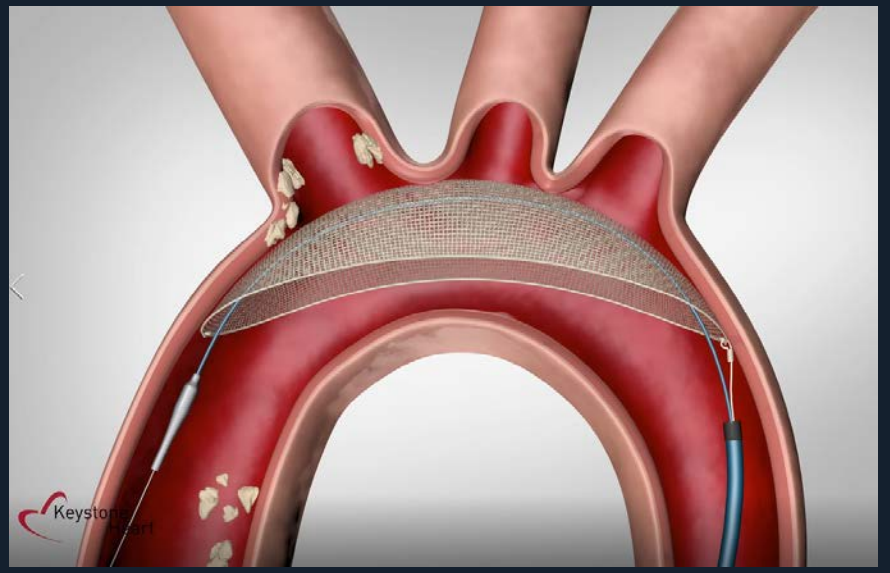
TriGuard HDH vs. TriGUARD *3*

TriGuard HDH



- Nitinol frame with upper and lower stabilizers
- Nitinol mesh (pore size 130 x 250 µm)
- Filter area = 20.9 cm^2
- 9 Fr RX delivery

TriGUARD *3*



- Self-positioning, nitinol frame without stabilizers
- PEEK mesh (pore size 115 x 145 µm)
- Filter area = 68.3 cm^2
- 8 Fr OTW delivery

Identical principle of operation and intended use

REFLECT US IDE Trial Design

Chair Jeffrey Moses, CO PIs A Lansky, R Makkar (US) and J Schofer, A Baumbach (EU)

DSMB: Dr J Petersen, Dr A Geirsson, Ms H Parise (stats)

Enrollment in REFLECT has been halted after enrolling a total of 258 subjects (54 roll-ins and 204 randomized subjects including 63 controls) due to the development and production of a new generation device designed for increased efficacy, ease of use, and improved safety- the TriGUARD™ 3.

The Trial design has changed to include a second phase with another intervention arm- patients undergoing TAVR with TriGUARD 3 protection.

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90

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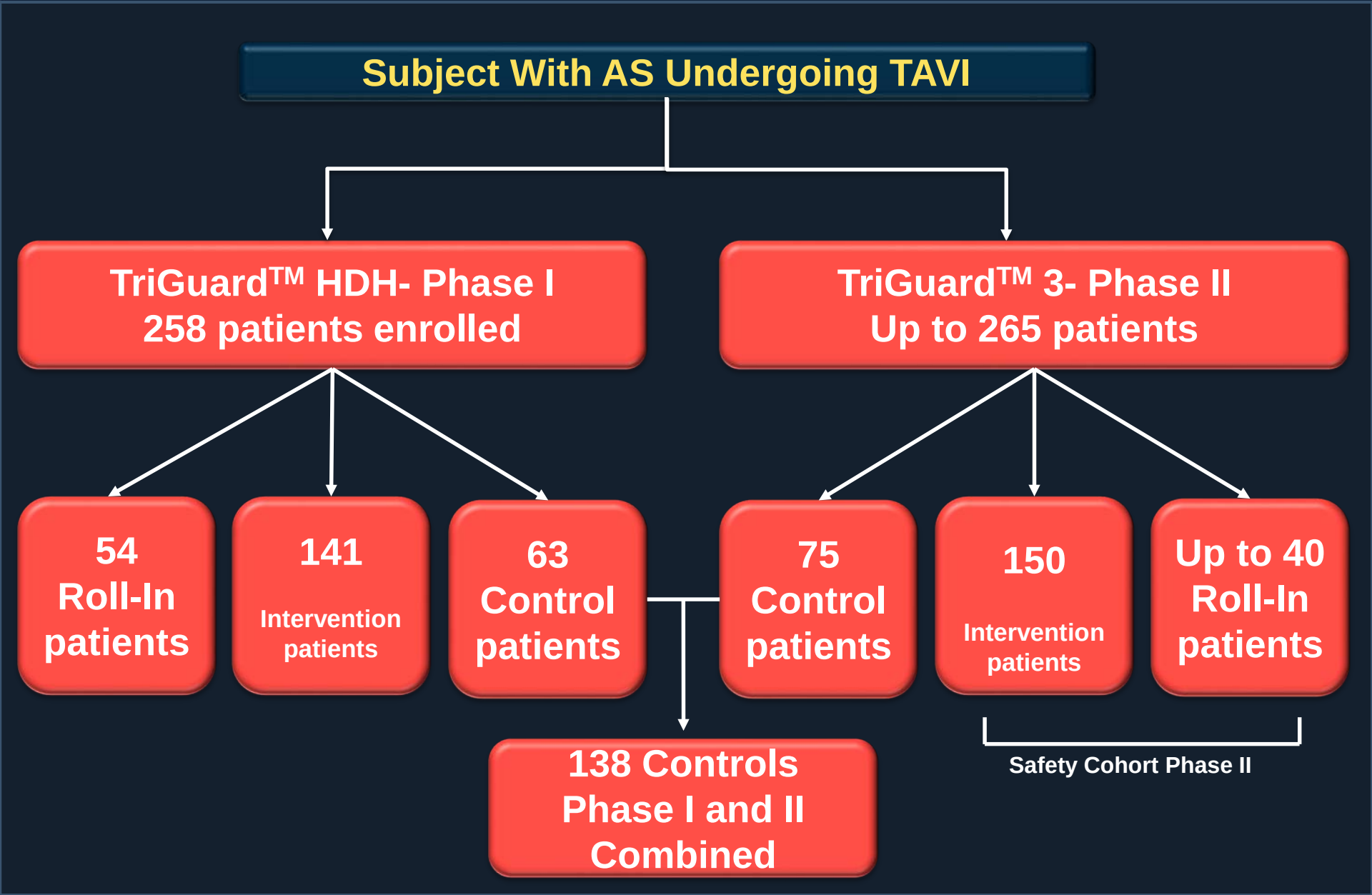
- TriGuard™ vs. Performance Goal

- Death or stroke (30 d)
- NIHSS (in-hospital) or MoCA worsening (30 days)
- Total lesion volume by DW-MRI (post-procedure)

- TriGuard™ vs. Control

REFLECT US IDE Trial Design

Chair Jeffrey Moses, CO PIs A Lansky, R Makkar (US) and J Schofer, A Baumbach (EU)



REFLECT US IDE Trial Design – Phase II

Chair Jeffrey Moses, CO PIs A Lansky, R Makkar (US) and J Schofer, A Baumbach (EU)

SAFETY

- Combined safety endpoint (VARC-2) at 30 days
- TriGuard™ 3 vs. Performance Goal

EFFICACY

- Hierarchical composite efficacy endpoint (Finkelstein-Schoenfeld):
  - CV death or stroke (30 d)
  - NIHSS worsening (30 days)
  - Freedom from any cerebral ischemic lesions detected by DW-MRI (2-5 days post-procedure)
  - Total volume of cerebral ischemic lesions detected by DW-MRI (2-5 days post-procedure)
- TriGuard™ 3 vs. Control

Conclusions

- Overt and covert stroke are significant complications of TAVR which may be of greater consequence as we move in to lower risk, younger populations
- The weight of evidence indicates that CEP reduces these events
- By covering all 3 cerebral vessels TriGuard cerebral embolic protection may further reduce risk
- TriGuard cerebral protection is safe and does not add procedural risk
- Aim is to resume phase 2 Q1 2018 and hopefully provide definitive evidence of clinical efficacy of EPD in TAVR