2019 euroPCR

Latest developments in cerebral embolic protection
CEP clinical trials, what's next?

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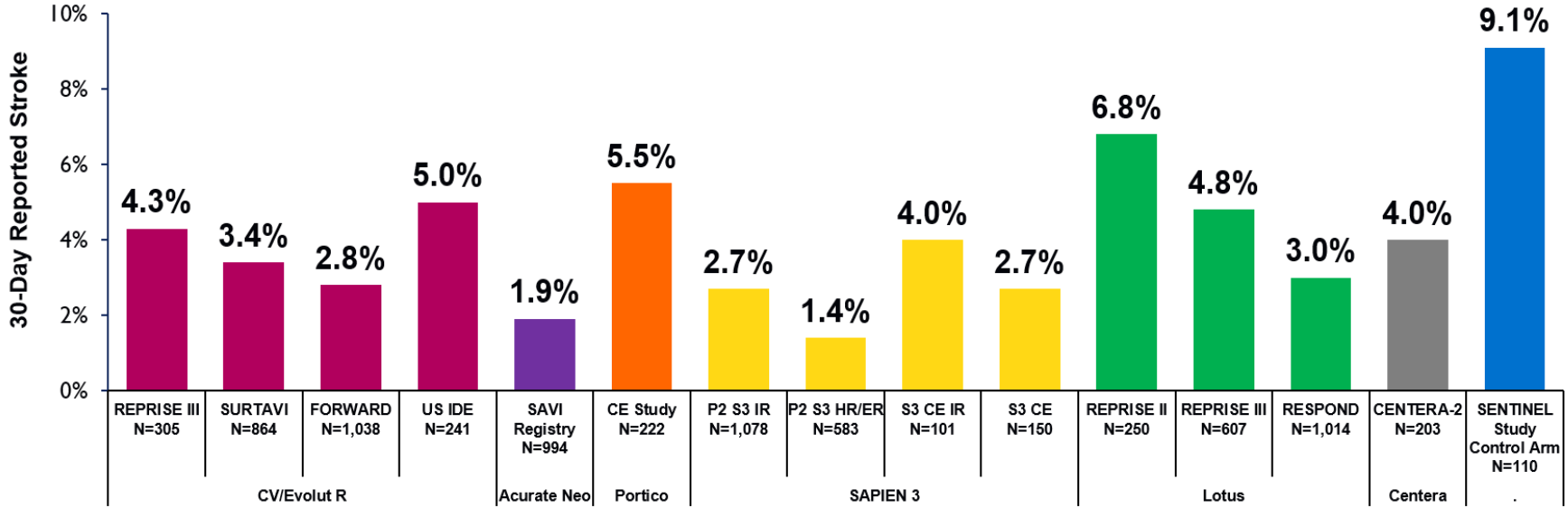
☑ I have the following potential conflicts of interest to declare:

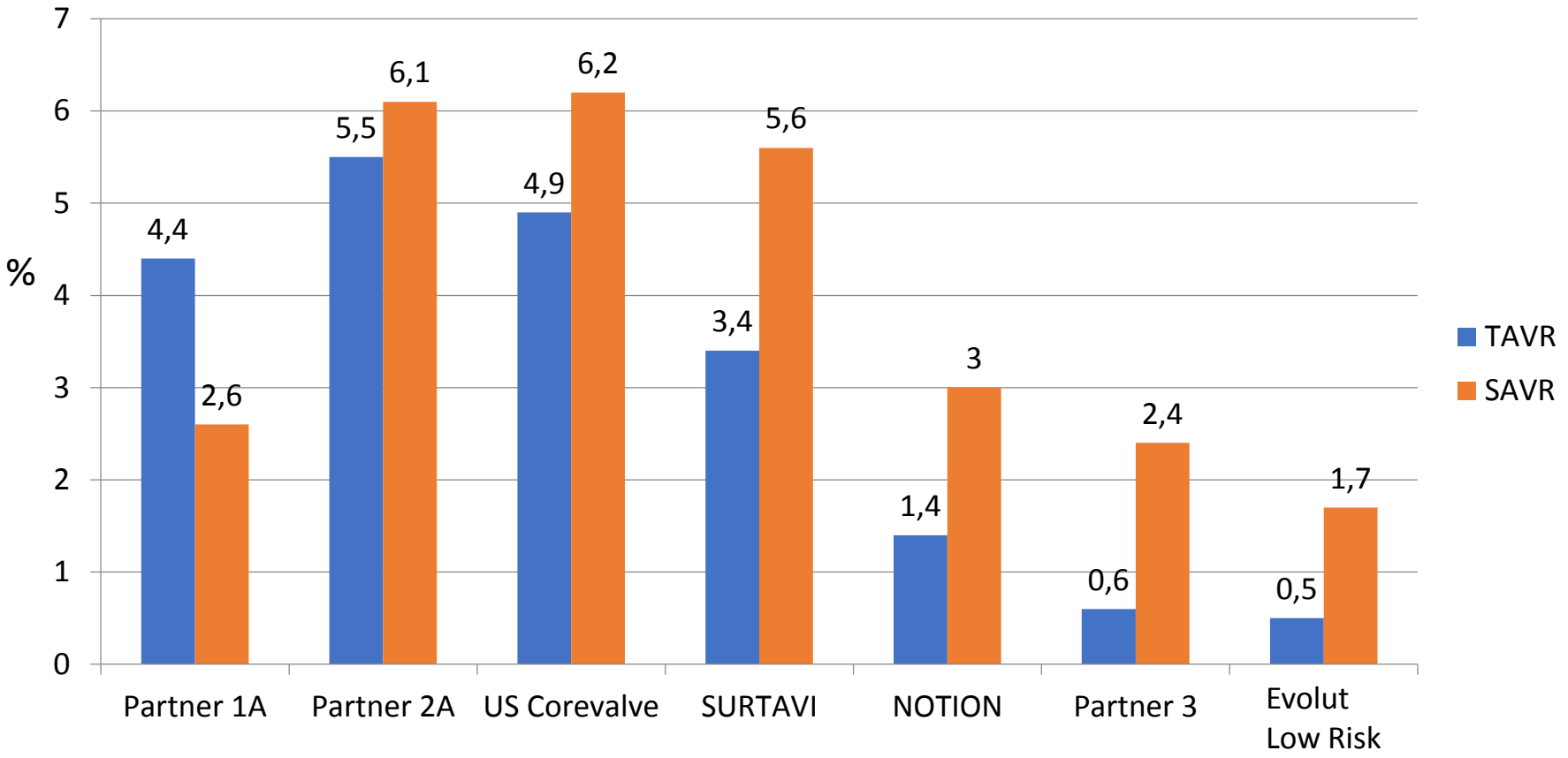
TAVR Stroke Rates Vary

- Stroke remains an issue (~4.4% average rate) in contemporary TAVR studies.
- TAVR device trials tend to emphasize only the major/disabling stroke rates.



[1] Feldman, et al., EuroPCR 2017; [2]Manoharan, et al., J Am Coll Cardiol Intv 2015; 8: 1359-67; [3]Moellman, et al., PCR London Valves 2015; [4]Grube, et al., EuroPCR 2017; [5]Kodali, et al., Eur Heart J 2016; [6]Vahanian, et al., EuroPCR 2015; [7]Webb, et. al. J Am Coll Cardiol Intv 2015; 8: 1797-806; [8]DeMarco, et al, TCT 2015; [9]Meredith, et al., PCR London Valves 2015; [10]Falk, et al. Eur Heart J 2017; [11]Kodali, TCT 2016; [12]Reardon, M NEJM 2017; [13]Reichenspurner H, et al., JACC 2017; [14]Popma et al, JACC:CVInt 2017;10(3):268-75

Stroke Rates - TAVR vs. SAVR



TAVR-Related Stroke - *Predictors*

Predictors of Early and Late Stroke

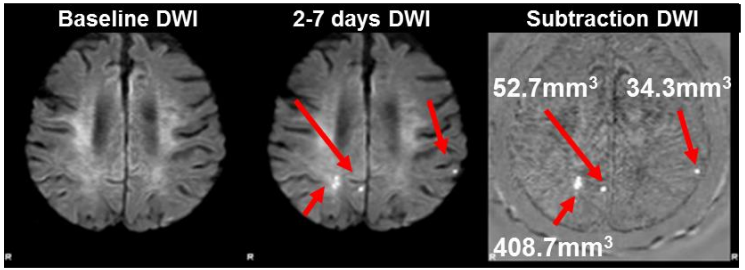
Procedure Stroke		Late Stroke (>10 days)
Patient Factors	Anatomical Factors	Predictors
Prior Stroke or TIA	Longer procedure times	Small BSA
New Onset A Fib	Rapid pacing	Severe Ao Calcium
CHA_2DS-VASc Score ≥5	Valve repositioning	Leaflet thickening
PVD	Post dilation	Chronic Atrial Fibrillation
Age	Small AVA	
	Aortic Atheroma	

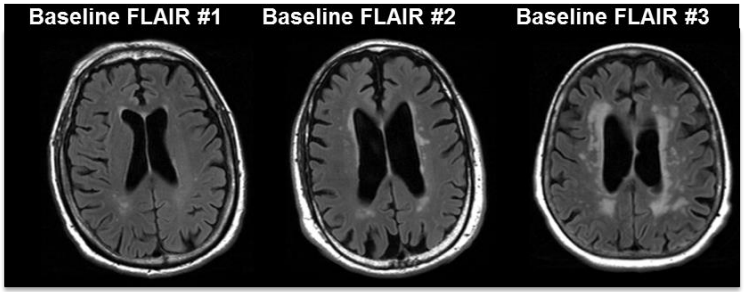
Kleiman NS et al. *JAHA* 2016; Tay et al 2011, Nuis et al, 2012; Amat Santos et al. 2012; Franco et al, 2012; Miller et al 2012; Cabau et al 2011; Fairbairn et al. 2012; Nombela-Franco et al. 2012; Controtto et al, 2016

Why Cerebral Protection in TAVR?

Cerebral ischemic injury is common during TAVR and can have immediate and long-term impacts

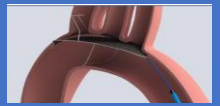
- Cerebral embolization and ischemic brain injury were detected by DW-MRI in 68-98% of cases.[1-3]
- Ischemic brain lesions increase risk of clinically overt stroke by 2-4 times.
  - Leads to cognitive dysfunction, depression, impaired mobility, dementia, and increased mortality[4-5].
- Increased lesion volume increases long-term risk of cognitive dysfunction and long-term dementia.[4-5]



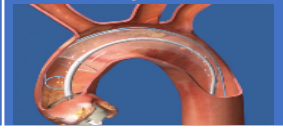


[1]Arnold S, *J Am Coll Cardiol Intv*. 2010 [3]Haussig S, *JAMA*. 2016 [3]Lansky AJ, *Eur Heart J.* 2015 [4]Sacco RL, *Stroke* 2013, [5]Vermeer SE, *Lancet Neurol* 2007

Cerebral Protection - *The Competitive Landscape*

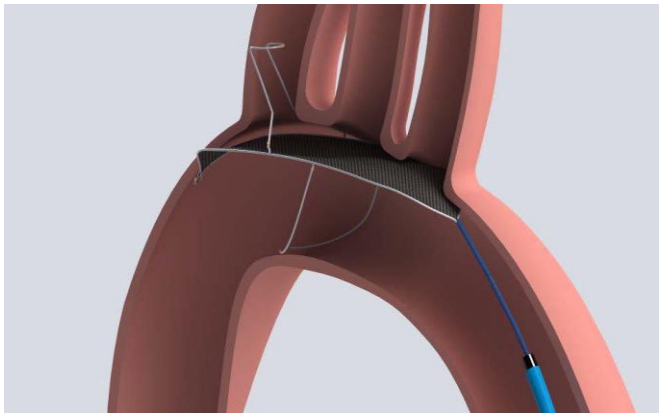
Company and Product	Claret Medical Sentinel 	Keystone TriGuard HDH 	Edwards Embrella 	Emboline Emboliner 	CardiOptis Embolisher 	Protembis ProtEmbo CPS 
EU Status	**CE Mark 97% market share**	**CE Mark 3% market share**	**CE Mark <3% market share**	**CE Mark Study underway**	**CE Mark expected**	**Pre-clinical/Feasibility FIM August 2017**
US Status	FDA Clearance June 2017	Reflect II Trial underway, Q2 2019	No IDE yet	No IDE yet	No IDE yet	No IDE yet
Access	6 Fr Right Radial	9Fr TF	Right Radial	6Fr TF	TF	6 Fr Left Radial
Debris	**Captures** and removes	**Deflects** downstream	**Deflects** downstream	Dual deflector/capture system	**Captures** and removes	**Deflects** downstream
Placement and Interaction with TAVR devices	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 aortic arch. Device must pass over and back across	Placed in in aortic arch; device must pass over and back across	Sits in aortic arch. Devices must pass over and back across
Website	www.claretmedical.com	www.keystoneheart.com/us/	tavrbyedwards.com; no other info no embrella	http://emboline.com/technology.html	https://www.f6s.com/cardioptimus	www.protembis.com

Cerebral Protection - *The Competitive Landscape*

Company And Product	Transverse Medical PointGuard	Filterlex Medical Filterlex	ICS Emblok	Capricon	TransAortic Capture System
					
EU Status	Pre-clinical/prototype	Pre-clinical/prototype	FIM first clinical case March 15, 2017	Pre-clinical/prototype	Pre-clinical/prototype
US Status	No IDE yet	No IDE yet	No IDE yet	No IDE yet	No IDE yet
Access	TF	TF	12Fr TF sheath	TF - no other data avail	TF – no other data avail
Debris	Deflects downstream	Dual deflector/capture system	**Captures** and removes	Deflector? Capture system?	Deflector?
Placement and interaction with TAVR devices	Sits in aortic arch. Devices must pass over and back across	Sits in aortic arch. Device must pass over and back across	Sits in ascending aorta Devices must pass over and back across	Appears to sit in the arch. Device must pass over and back across	Sits in aortic arch. Device must pass over and back across
Website	www.transversemedical.com	https://www.crunchbase.com/organization/filterlex-medical-ltd	www.emblok.com	No website	No website

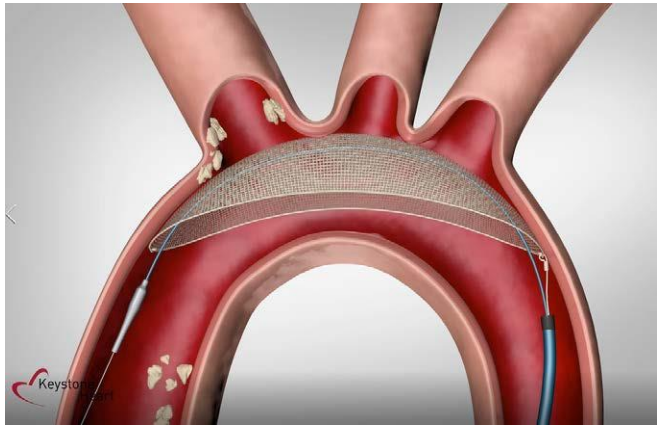
TriGuard HDH vs. TriGUARD *3*

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

Sentinel® Cerebral Protection System

Trial Design Overview

Patients with Severe Symptomatic Aortic Stenosis undergoing TAVR

Patients Randomized (1:1:1)
(N=363)

SAFETY ARM
TAVR with Sentinel
(N=123)

TEST ARM
TAVR with Sentinel
(N=121)

CONTROL ARM
TAVR Only
(N=119)

Histopathology & Morphometry

Clinical Follow-Up (Neurology Assessments in all patients)

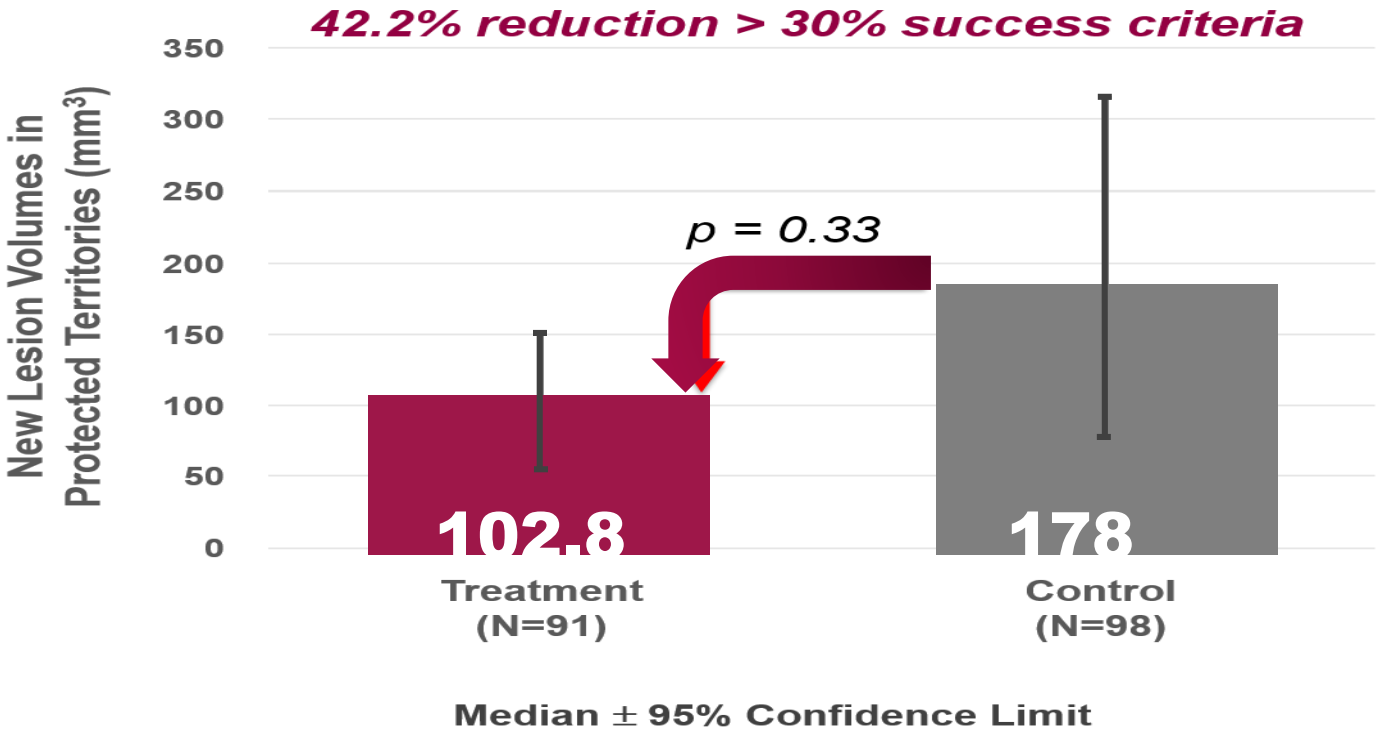
Serial MRIs (Baseline, Day 2-7 & Day 30)

Serial Neurocognitive Assessment
(Baseline, Day 30 & Day 90)

Kapadia et al. J Am Coll Cardiol 2017;69:367–377

Sentinel® Cerebral Protection System

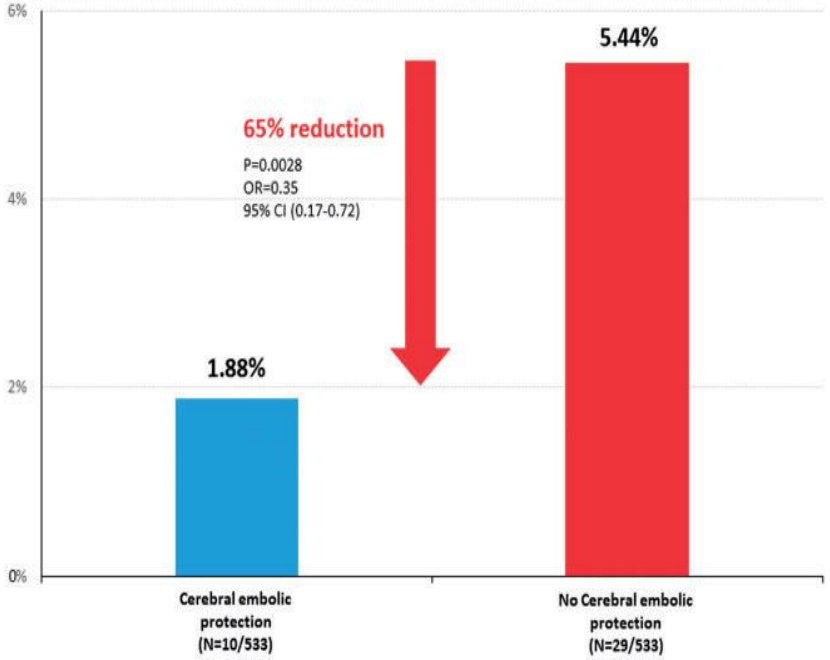
Primary Surrogate DW-MRI Endpoint



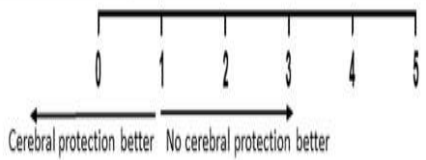
Kapadia et al. J Am Coll Cardiol 2017;69:367–377

CEP – Sentinel Patient-level Metaanalysis

CLEAN-TAVI (RCT), SENTINEL US IDE Trial RCT), SENTINEL-Ulm (Registry)
N=1306

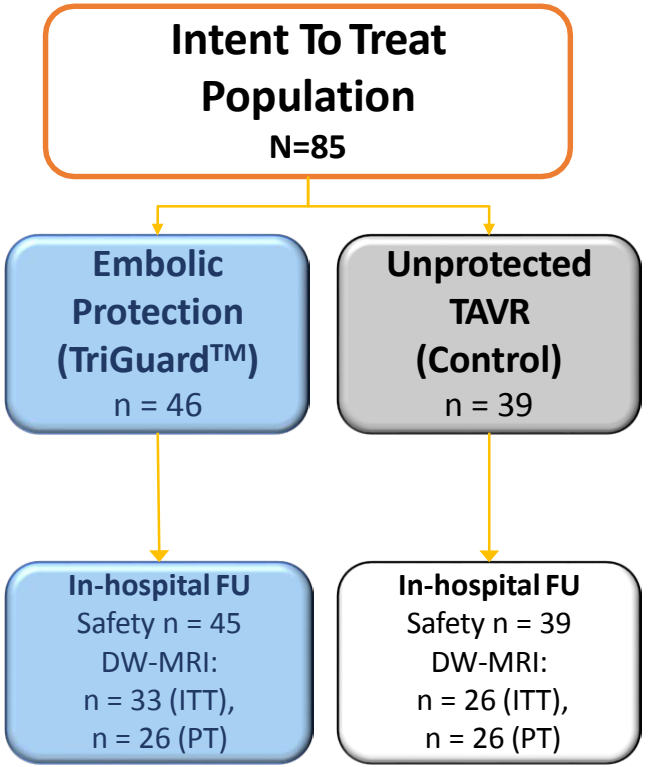


Subgroup	No. of patients	protection	no protection	Odds-ratio (95% CI)	p-value
Total population	1066	10/533 (1.88%)	29/533 (5.44%)	0.34 (0.17-0.68)	0.0013
Anesthesia					
general	200/1066 (18.8%)	3/120 (2.50%)	4/80 (5.00%)	0.49 (0.11-2.26)	0.36
non-general	860/1066 (80.8%)	7/412(1.70%)	25/448 (5.58%)	0.29 (0.13-0.68)	0.0045
Valve type					
balloon expandable	672/1066 (63.0%)	3/336 (0.89%)	12/336 (3.57%)	0.24 (0.07-0.82)	0.029
mechanically expandable	170/1066 (15.9%)	2/85 (2.35%)	6/85 (7.06%)	0.32 (0.06-1.64)	0.17
self expandable	224/1066 (21.0%)	5/112 (4.46%)	11/112 (9.82%)	0.43 (0.14-1.29)	0.13



Seeger e al. Eur Heart J. 2019;40:1334–1339

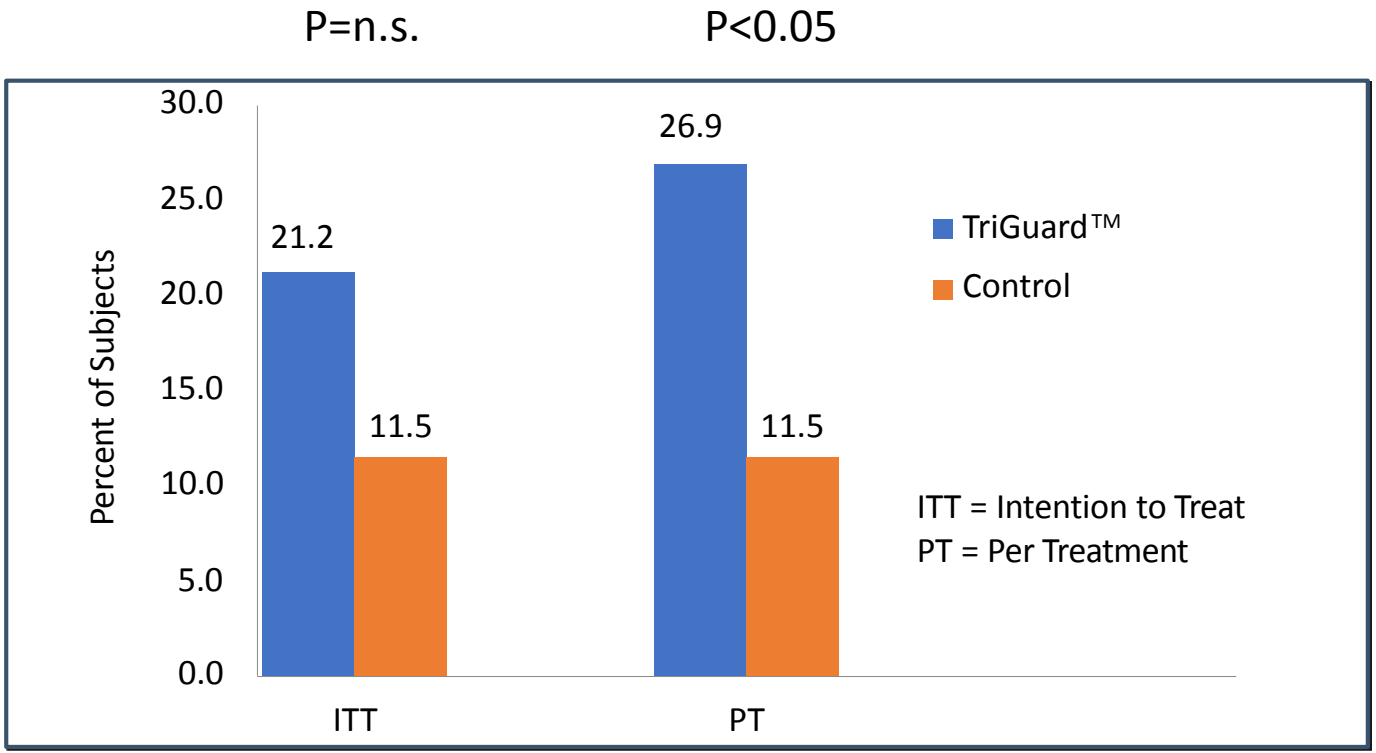
DEFLECT III Trial



- 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
- Stroke 2.2 vs 5.1%; P=0.46

Lansky et al. Eur Heart J. 2015;36:2070-2078

DEFLECT III Trial - Freedom From Ischemic Lesions

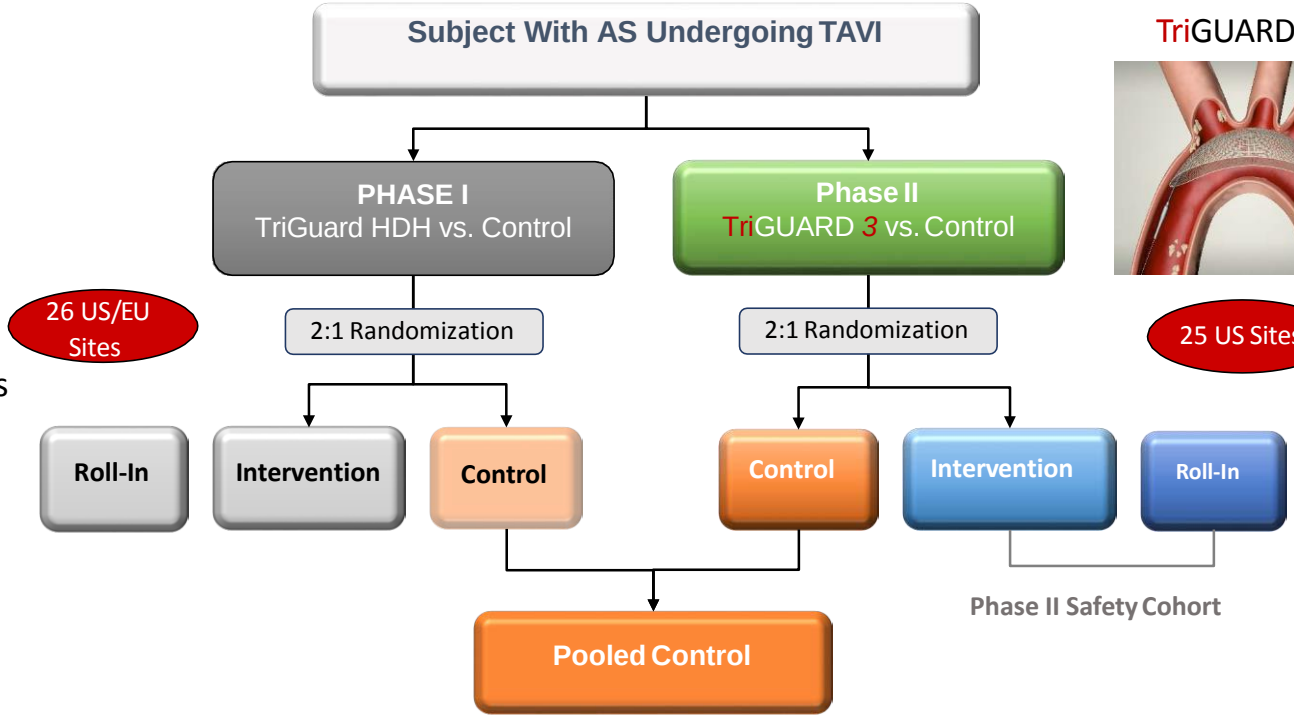


Lansky et al. Eur Heart J. 2015;36:2070-2078

REFLECT Trial Overview (Phase I & II)

REFLECT

- Prospective, single-blind, randomized (2:1 device: control), multi-center safety & efficacy trial in two phases of the Keystone Heart Cerebral Embolic Protection Devices
  - Ph 1- TriGuard HDH
  - Ph 2- TriGUARD *3*
- Study Chairman: Jeffrey Moses
- Study PI: Tamim Nazif
- Co-PIs: Alexandra Lansky
  Raj Makkar
  Andreas Baumbach
  Joachim Schofer



TriGUARD *3*

25 US Sites

CEP - Current Evidence

	Evidence from registries	Evidence from pooled analyses	Evidence from randomized trials
Safety and feasibility	✓	✓	✓
Mechanistic efficacy			
Capture of embolic debris	✓	✓	✓
Reduction of ischemic brain injury on cerebral MRI	✓	(✓)	(✓)
Clinical efficacy			
Reduction of peri-procedural stroke	✓	✓	X

Abdel-Wahab and Thiele. Eur Heart J. 2019;40:1340–1341

CHOICE-REFLECT - Trial Design

- IIT, EU, multicenter, open-label randomized trial
- Investigational device: TriGUARD 3 cerebral embolic protection device
- Patient population: Severe AS undergoing TAVR
- Treatment groups:
  - Interventional group: Use of TriGuard 3 CEP
  - Control group: no use of CEP

CHOICE-REFLECT - Trial Logistics

- Study Sponsor: Leipzig Heart Institute at University of Leipzig
- Study leadership:
  - Senior PI: Holger Thiele (Heart Center Leipzig, Germany)
  - Coordinating PI: Mohamed Abdel-Wahab (Heart Center Leipzig, Germany)
  - Co-PI: Nicolaus Dumonteil (France)
- Steering Committee:
  - PIs + Alexandra Lansky (USA), Tamim Nazif (USA), Didier Tchetche (France), Pauliina Margolis (USA), Darius Dudek (Poland), other national coordinators
- Data management: GIR, USA
- Supported by Keystone Heart, USA

CHOICE-REFLECT - Main Inclusion Criteria

1. Patients with an indication for transfemoral TAVI as judged by local heart team.

2. Informed consent.

CHOICE-REFLECT - Main Exclusion Criteria

1. History of a cerebral vascular accident or transient ischemic attack <6 months.
2. Carotid artery stenosis requiring intervention.
3. Patients in whom vascular anatomy precludes the use of a CEP device.
4. Contraindication for anti-platelet and/or anticoagulant therapy.
5. Participation in any other investigational trial or interventional trial of CEP.

CHOICE-REFLECT - Endpoints

- Primary endpoint: **Cardiovascular mortality or ischemic stroke within the first 72 hours after the procedure.**
- Secondary endpoints:

  1) Device success defined as successful placement and stability of the embolic protection device at its intended position.

  2) Cardiovascular mortality within 72 hours, in-hospital and at 30 days.

  3) Ischemic stroke in-hospital and at 30 days.

  4) Neurological dysfunction (TIA, delirium assessed by CAM-ICU score) within 72 hours, in-hospital and at 30 days.

  5) Contrast volume, fluoroscopy time, patient radiation exposure (expressed as kerma-area product (KAP)) or dose area product (DAP) and procedure duration.

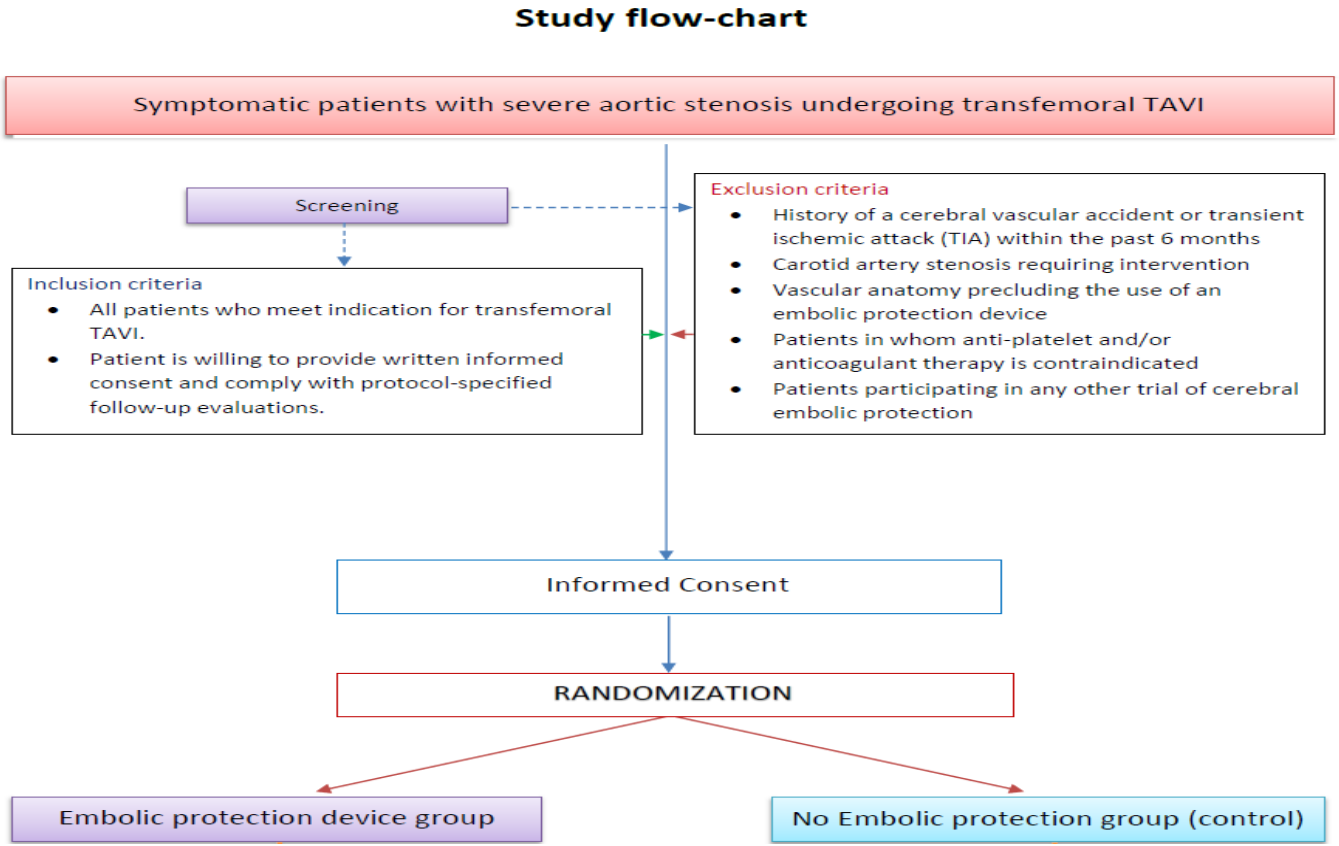
  6) Filter usage related vascular access site complications.

  7) TAVI access site vascular complications

CHOICE-REFLECT - Statistical Analysis

- Sample size:
  - ≈ 900 patients in each group – pending further assessment
- Statistical Analysis:
  - All randomized subjects to be analyzed on the intention-to-treat (ITT) basis and reported based on protection device/TAVI relationship
  - All randomized patients on the
    - Per Treatment (PT) (3 cerebral artery coverage) and
    - Modified ITT (mITT) (exclude patients with surgical conversion or prolonged resuscitation with no relationship to TG3 device) basis and
    - As-Treated (AT) (actual treatment received) population
  - Group comparison for the primary endpoint by Chi_2-test.
  - Kaplan-Meier analysis for time-to-event analyses.
  - Logistic regression to assess predictors of outcome.

CHOICE-REFLECT - Study Flow Chart



Thank you for your attention!

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