The DEFLECT III Trial: A Prospective Randomized Evaluation of the TriGuard™ HDH Embolic DEFLECTion Device during Transcatheter Aortic Valve Implantation

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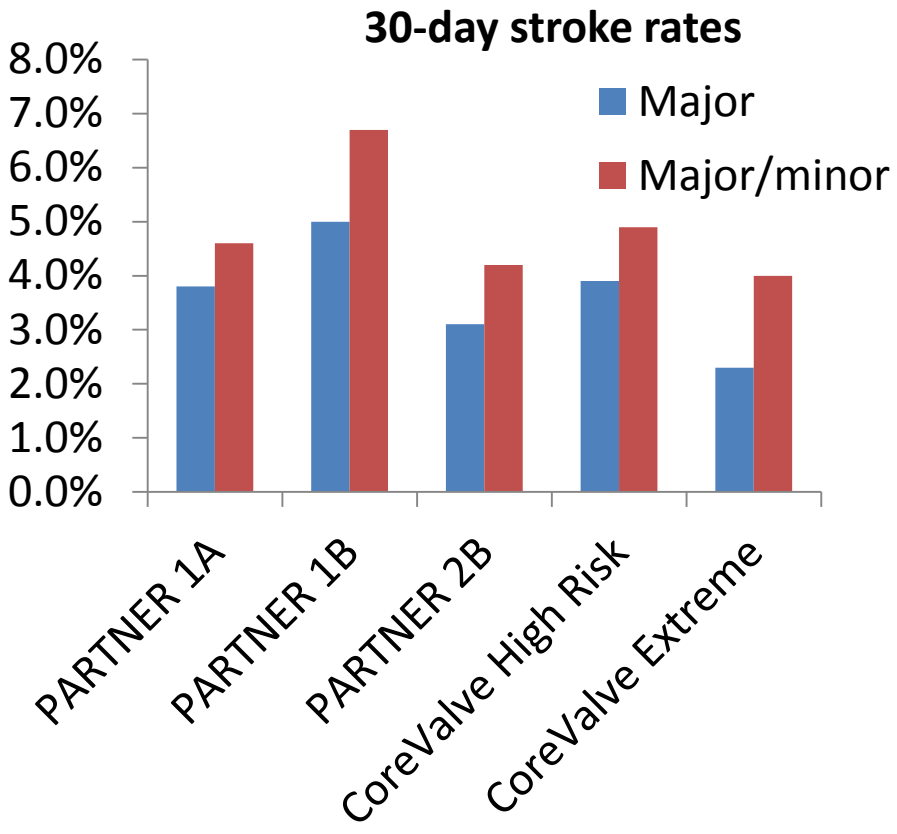
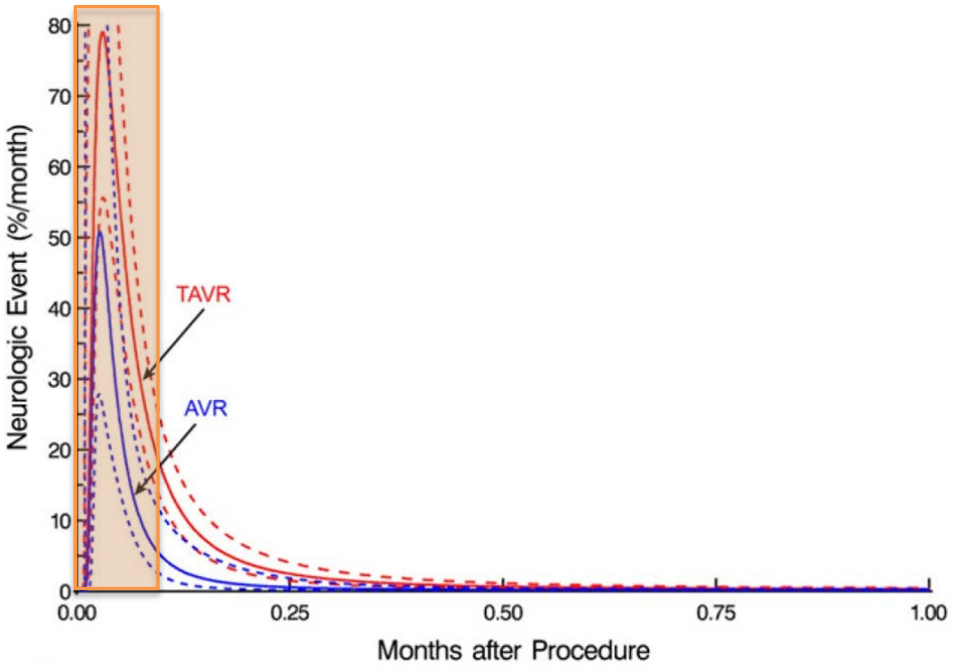
Clinical Stroke after TAVI

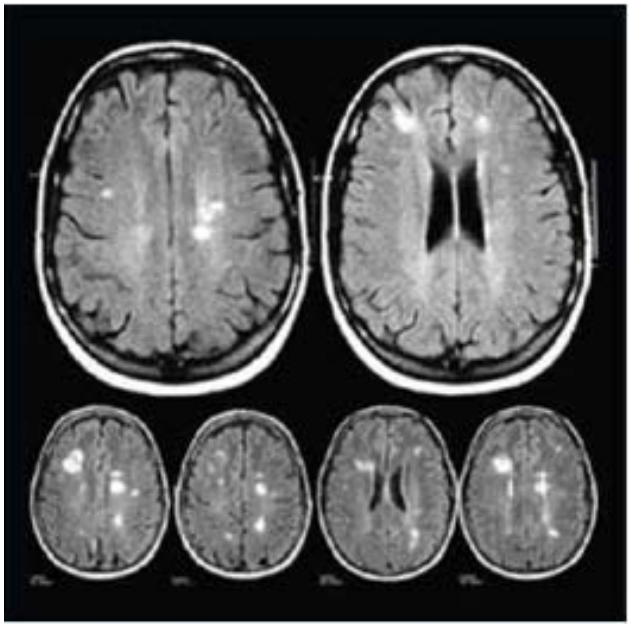


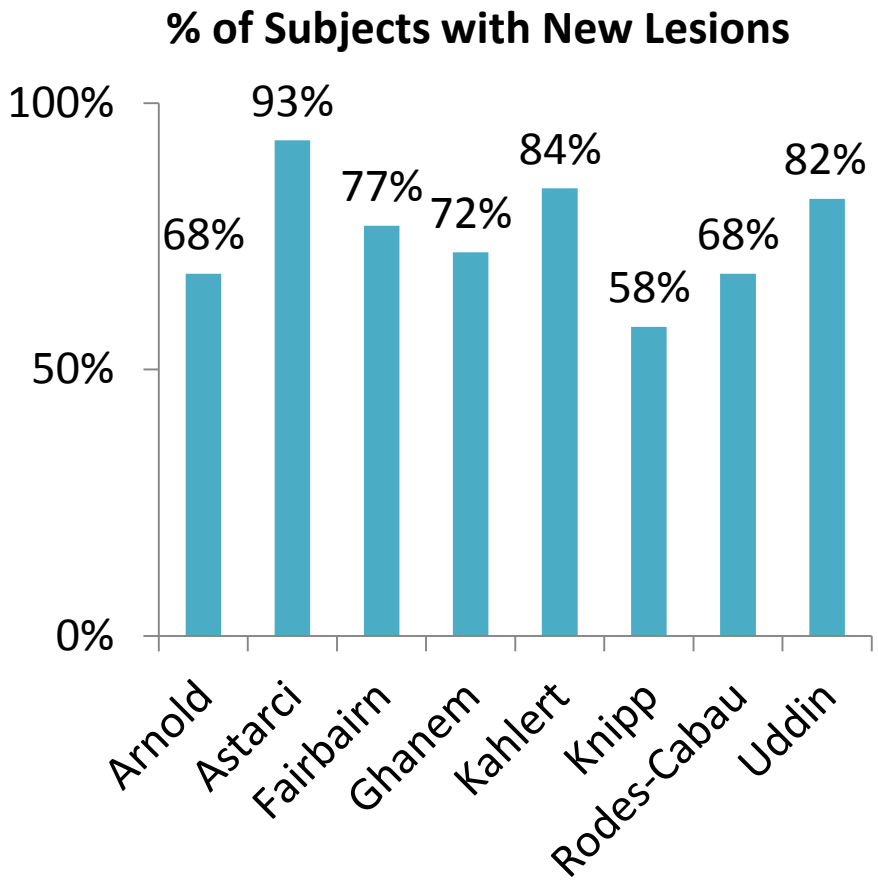
- 4-7% at 30 days in RCTs
- Generally under-reported (17% after SAVR when evaluated by neurologist)
- Confer 3- to 9-fold increased risk of mortality
- 50% are peri-procedural



Leon et al. *NEJM*. 2010;363:1597, Smith et al. *NEJM*. 2011;364:2187, Adams et al. NEJM 2014;370:1790, Leon MB ACC 2013, Popma et al. *JACC* 2014;63:1872, Eggebrecht et al. *EuroIntervention*. 2012;8:129, Messe et al. *Circulation* 2014;129:2253, Tchetche et al. *JACC Cardiovasc Interv* 2014;7:1138, Miller et al. *J Thorac Cardiovasc Surg* 2012;143:832

Silent Embolic Events on DW-MRI after TAVI



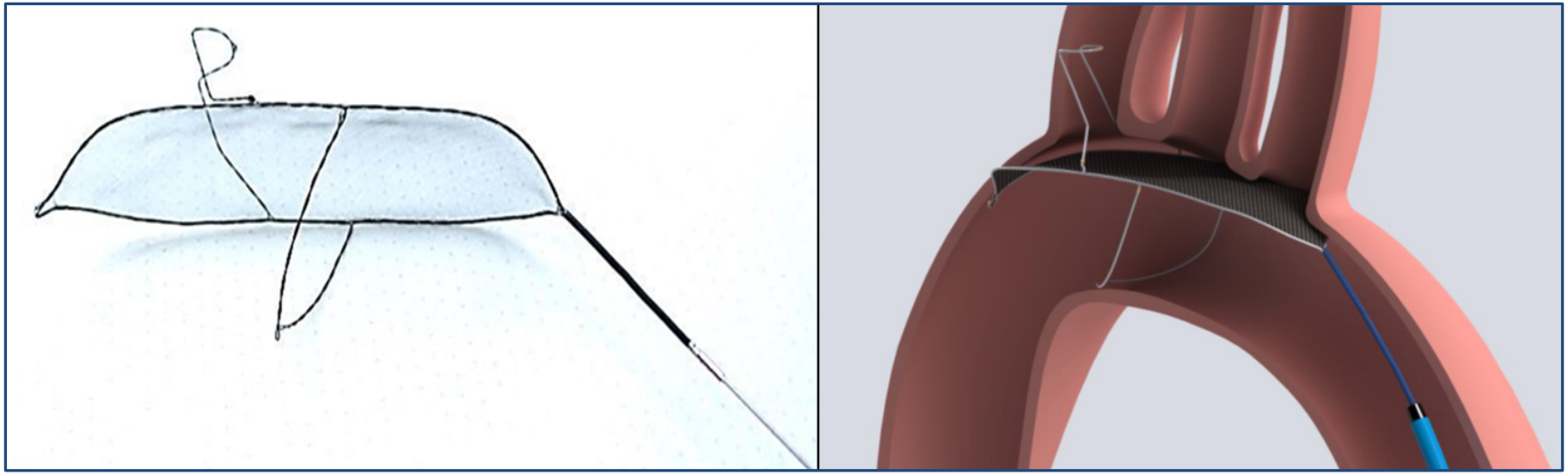


- Affect 58-93% of subjects
- Multiple infarcts (≤36, $\bar{x}$ = 4.6)
- Associated with:
  - Neurocognitive decline
  - >2 fold risk of dementia
  - **>3 fold risk of stroke**

Restrepo et al. *Stroke* 2002;33:2909, Lund et al. *Eur Heart J.* 2005;26:1269, Schwarz et al. *Am Heart J* 2011;162:756, Knipp et al. *Ann Thorac Surg* 2008;85:872, Vermeer et al. *NEJM* 2003; 348:1215, Vermeer et al. *Stroke* 2003; 34:1126, Arnold et al. *JACC Cardiovasc Interv*. 2010;3:1126, Astarci et al. *J Heart Valve Dis*. 2013;22:79, Fairbairn et al. *Heart* 2012;98:18, Ghanem et al. *EuroIntervention*. 2013;8:1296, Kahlert et al. *Circ.* 2010;121:870, Knipp et al. *Interact Cardiovasc Thorac Surg.* 2013;16:116

The TriGuard™ HDH Device

- Nitinol single-wire frame and mesh filter with pore size of 130µm designed to deflect cerebral emboli while allowing maximal blood flow
- Device is positioned across all 3 cerebral vessels and maintained by a stabilizer in the innominate
- Delivered via 9 Fr sheath from femoral artery



TriGuard Clinical Program

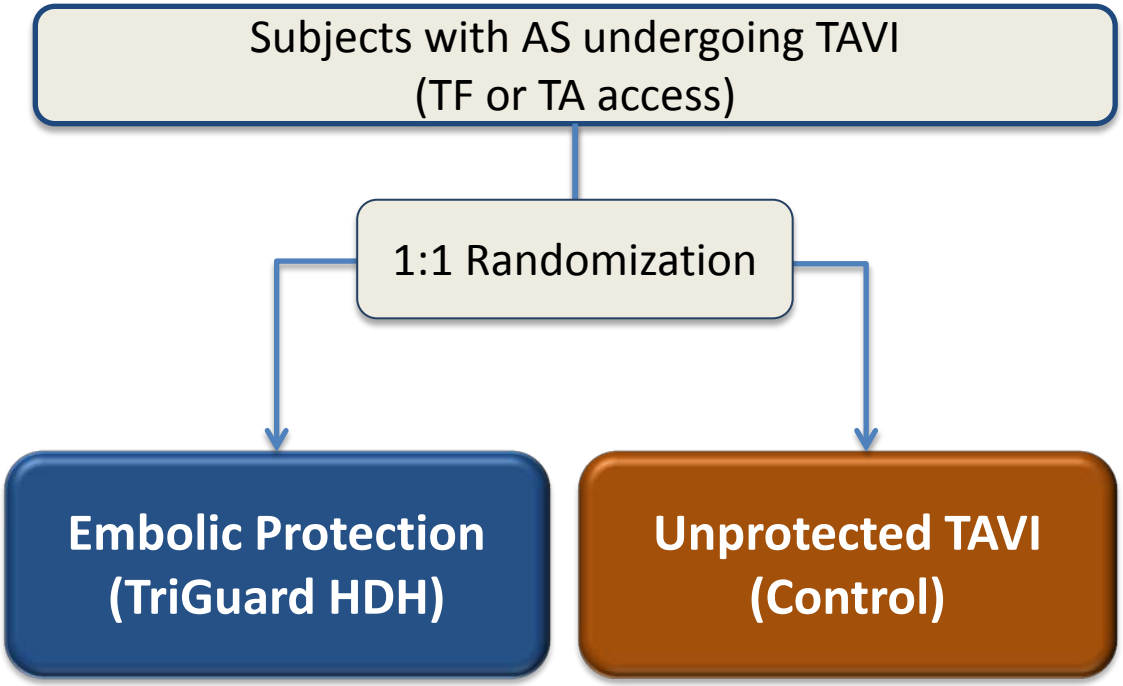
Study	Description	N (TriGuard)	Status
First in Human	Single center (NL)	15	Complete
DEFLECT I	Prospective multicenter (EU)	37	Complete – CE Mark received in 2014
DEFLECT II	Single center (NL)	12	Complete
DEFLECT III	RCT (EU/IL)	45	30-day follow up ongoing
REFLECT	Pivotal IDE Trial (US + EU)	TBD	IDE Approved – first subject in 2015

DEFLECT III Study Overview

Design: Prospective single-blind randomized controlled trial at 12 sites (EU/IL)

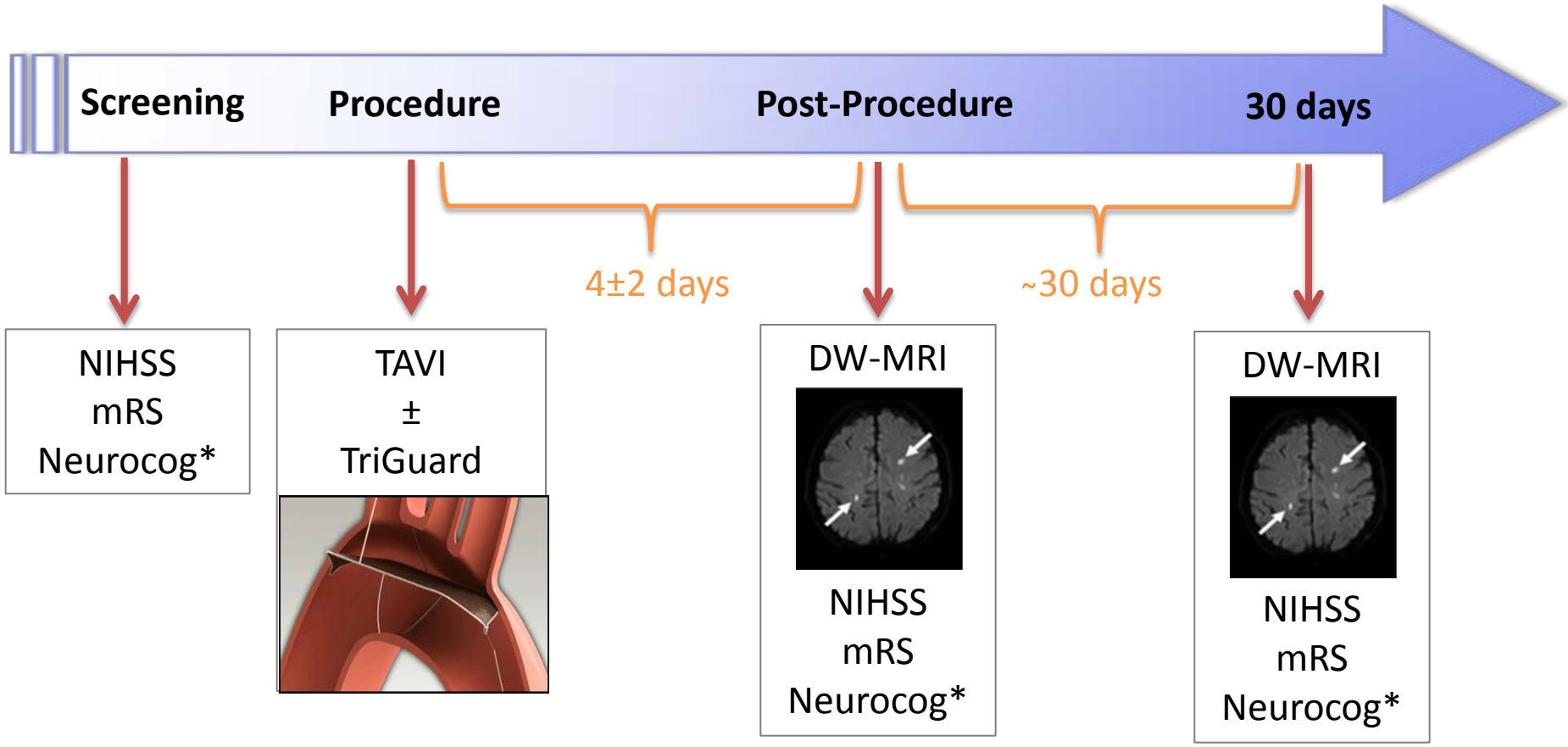
Objective: To evaluate the safety, efficacy and performance of TriGuard HDH embolic protection compared with unprotected TAVI.

Sample Size: No formal hypothesis testing. Up to 86 subjects (43 per group) selected to provide safety and efficacy benchmarks for the design of a pivotal RCT.



Primary Endpoint: **In-hospital MACCE** defined as the composite of death, stroke, life-threatening or disabling bleeding, AKI (2/3), and major vascular complications

DEFLECT III Procedures & Assessments



*__Neurocognitive test battery__ includes the Montreal Cognitive Assessment (MoCA) and computerized CogState Research Test. Baseline and 30-day evaluations include supplemental Digit Symbol Substitution, Trailmaking, and Word Fluency Tests.

DEFLECT III Eligibility Criteria

- **Key Inclusion Criteria**
  - Planned to undergo TAVI via the transfemoral or transapical approach
- **Exclusion Criteria**
  - Other TAVI approaches (axillary, subclavian, direct aortic)
  - Stroke or TIA within prior 6 months
  - Anatomic irregularities of the aortic arch or innominate artery that could prevent positioning and stability of the device (ostium diameter <11 mm, transverse aortic diameter >40 mm)
  - Contraindication to cerebral MRI (e.g., pacemaker)
  - Any other cardiac intervention within prior 2 weeks

DEFLECT III Key Secondary Endpoints

- **Safety**
  - **TAVI device success** (VARC-2) in-hospital
  - **TAVI early safety** (VARC-2) at 30 days
  - **Components**: death (CV/non-CV), MI, neurological events, bleeding complications, AKI, vascular complications
- **Efficacy**
  - **DW-MRI:** Frequency, number, and per-patient average single, maximal single, and total volume of DW-MRI lesions at 4+2 days (range 2-6 days)
  - **Neurocognitive:** Postoperative cognitive function, change in cognitive function from baseline to postprocedure and 30 days
- **Performance**
  - **Technical success:** successful device deployment, positioning (3-vessel coverage verified by angiography), and retrieval without interference with TAVI

DEFLECT III Statistical Analysis Plan

- Exploratory analysis - no formal hypothesis testing was planned.
- **Endpoints analysis:**
  - **Primary endpoint (safety):** In-hospital procedural safety (Hierarchical composite) evaluated in the **Intention to Treat (ITT)** analysis population
  - **Efficacy endpoints**:
    - **Non-parametric analysis** (DW-MRI volumetric data is non-normally distributed)
      - **ITT population**
      - **Per treatment (PT) population**: excludes subjects with incomplete TriGuard cerebral vessel coverage (core lab adjudicated)

DEFLECT III Trial Organization

Coordinating Principal Investigators	Alexandra Lansky, MD — *Yale University School of Medicine,USA* Andreas Baumbach, MD — *Bristol Heart Institute, UK*
MRI Core Lab	Szilard Voros (Director) *Global Institute for Research, Richmond, VA, USA*
Angiographic Core Lab Biostatistic	Alexandra Lansky (Director) — Helen Parise (Statistics) *Yale University School of Medicine, New Haven, CT, USA*
Neurocognitive Assessment	Adam Brickman (Director) *Columbia University, New York, USA*
Clinical Events Committee	Michael Cleman, MD (Chair) — Joseph Brennan, MD John Forrest, MD — Abeel Mangi, MD *Yale University School of Medicine, New Haven, CT, USA*
Monitoring, Site Mgmt. Data Mgmt	Genae International, Inc. Harvard Clinical Research Institute

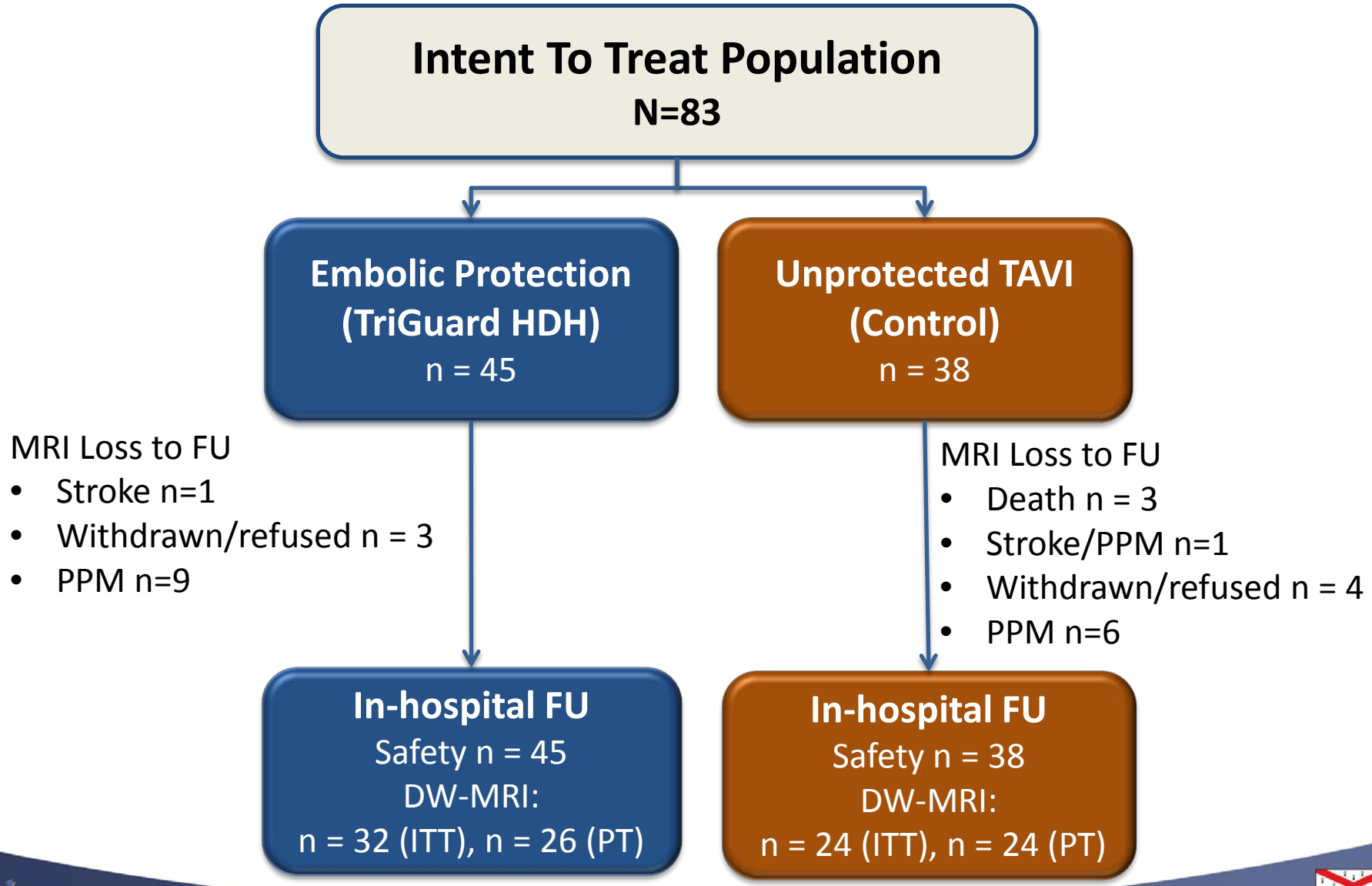
DEFLECT III Trial – Enrollment Highlights

Feb 26, 2014	Feb 24, 2015	March 24, 2015
Enrollment Start	RCT Enrollment Complete	30 day FU Complete

5 Countries / 12 Centers

Joachim Schofer (17) *Hamburg, Germany*	Andreas Baumbach (8) *Bristol, United Kingdom*	Med Spitzer (2) *Dresden, Germany*
Didier Tchetche (13) *Toulouse, France*	Pieter Stella (9) *Utrecht, Netherlands*	Martine Gilard (2) *Brest, France*
Christophe Bode (10) *Frieburg, Germany*	Daniel Blackman (6) *Leeds, United Kingdom*	Michael Haude (1) *Neuss, Germany*
Thomas Cuisset (10) *Marseille, France*	Gil Bolotin (4) *Haifa, Israel*	David Hildick-Smith (1) *Brighton, United Kingdom*

DEFLECT III Patient Disposition



Baseline Clinical Characteristics

ITT population	TriGuard HDH N=45	Controls N=38	P value
Age (y) ± SD	82.7 ± 6.5	82.5 ± 5.9	0.62
Male	40.9%	50.0%	0.41
STS Score	4.7	7.4	0.48
EuroSCORE II	10.1	7.4	0.66
NYHA Class			
I or II (%)	83.3%	78.9%	0.65
III or IV (%)	45.0%	37.8%	0.85
Atrial Fibrillation	25.0%	44.7%	0.06
CKD	25.0%	26.3%	0.89
COPD	31.8%	32.4%	0.95
O_2 Dependent	6.8%	0.0%	0.10
Previous stroke/TIA	14.0%	18.4%	0.58
Frailty	11.9%	18.4%	0.42
Porcelain Aorta	4.5%	0.0%	0.18

Procedure Details

ITT population	TriGuard HDH N=45	Controls N=38	P value
General Anesthesia	76.7%	76.3%	0.96
Valvuloplasty Pre-TAVI	61.1%	70.4%	0.45
TAVI Implants	n=44	n=37	
CoreValve	31.8%	26.3%	0.59
Edwards Sapien/3/XT	63.6%	65.8%	0.84
Other*	2.3%*	5.3%**	0.47
Total Fluoro time (min)	28.2	18.6	<0.001
Total Contrast time (min)	165.8	138.6	0.16
Adjunct Pharmacology			
ASA + clopidogrel	69%	67.6%	0.89
ASA only	16.7%	16.2%	0.96
Clopidogrel only	11.9%	8.1%	0.58
Warfarin	11.9%	18.9%	0.39

*Direct Flow; **Lotus Valve

Device Performance

ITT population	TriGuard HDH % (n/N) N=46 devices*	95% CI
Technical success (composite):	87 (40/46)	[68.6, 92.2]
Successful deployment	93.5 (43/46)	[82.1, 98.6]
Successful positioning (complete 3-vessel coverage until final valve deployment of first valve, verified by QCA)	87.0 (40/46)	[73.7, 95.1]
Successful retrieval	97.8 (45/46)	[88.5, 99.9]
Device interference (with TAVI system)	0 (0/46)	[0.0, 7.7]
Device Failure	0% (0/46)	[0.1, 11.5]

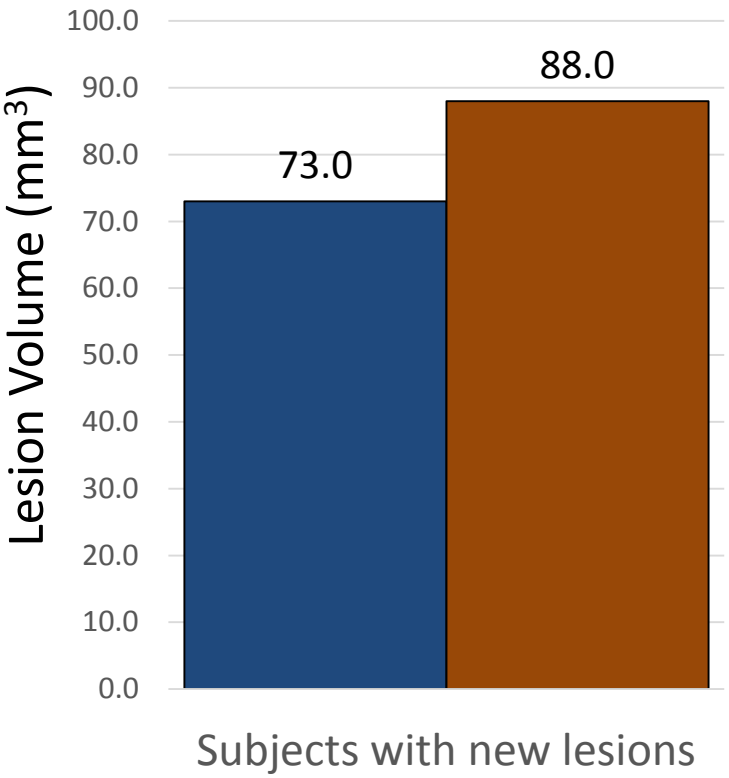
*One subjects had 2 TriGuard HDH devices used

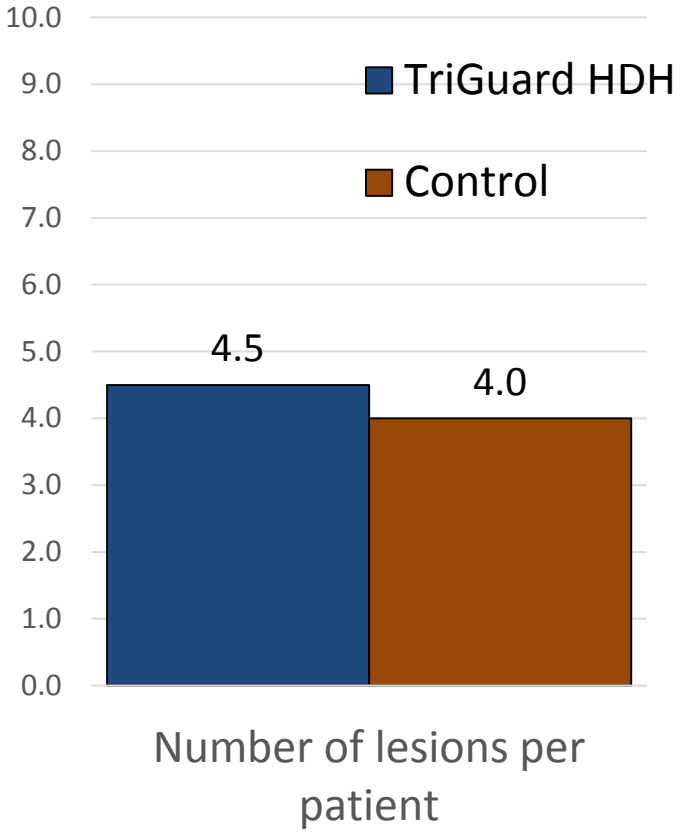
In-hospital Safety Outcomes (ITT)

ITT population	TriGuard HDH % (n/N)	Controls % (n/N)	Relative Risk [95% CI]
Hierarchical Composite	22.2 (10/45)	31.6 (12/38)	0.70 [0.34, 1.45]
In-hospital MACCE			
Death	2.2 (1/45)	5.3 (2/38)	0.42 [0.04, 4.48]
All stroke	2.2 (1/45)	5.3 (2/38)	0.42 [0.04, 4.48]
Life-threatening bleed	2.2 (1/45)	5.3 (2/38)	0.42 [0.04, 4.48]
AKI (Stage 2/3)	2.2 (1/45)	0 (0/38)	2.54 [0.11, 60.7]
Major vascular comp.	15.6 (7/45)	15.8 (6/38)	0.99 [0.36, 2.68]
Non-hierarchical components			
Death	2.2 (1/45)	5.3 (2/38)	0.42 [0.04, 4.48]
All stroke	4.4 (2/45)	5.3 (2/38)	0.84 [0.12, 5.71]
Life-threatening bleed	2.2 (1/45)	7.9 (3/38)	0.28 [0.03, 2.60]
AKI (Stage 2/3)	2.2 (1/45)	0 [0, 38]	2.54 [0.11, 60.7]
Major vascular comp.	17.8 (8/45)	21.1 (8/38)	0.84 [0.35, 2.04]
TAVI Device Success (VARC-2 Composite)	97.8 (44/45)	94.7 (36/38)	1.03 [0.95, 1.13]

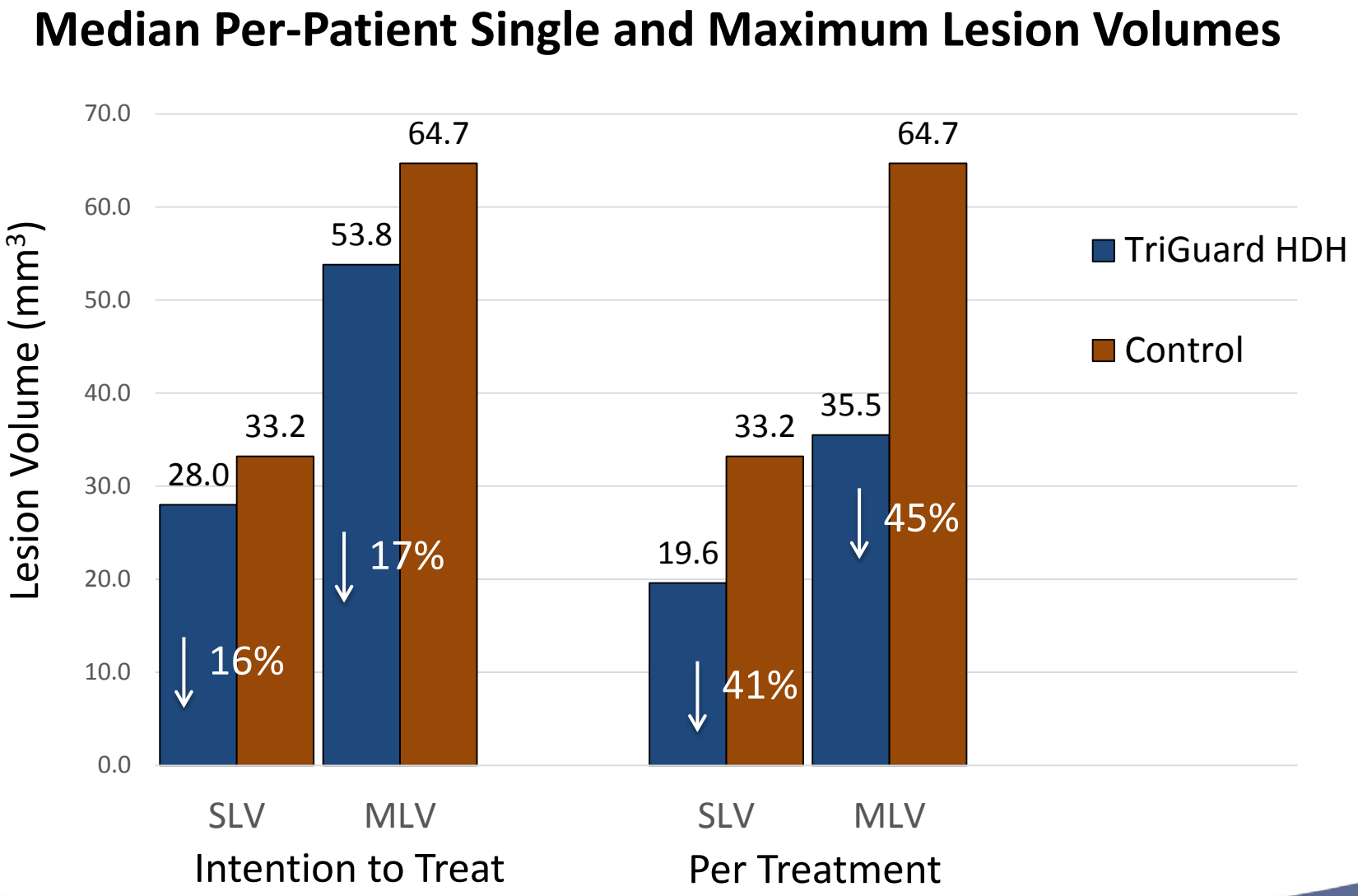
DW-MRI Results – Frequency and Number

Frequency and Number of New Lesions by Treatment Group (PT population)

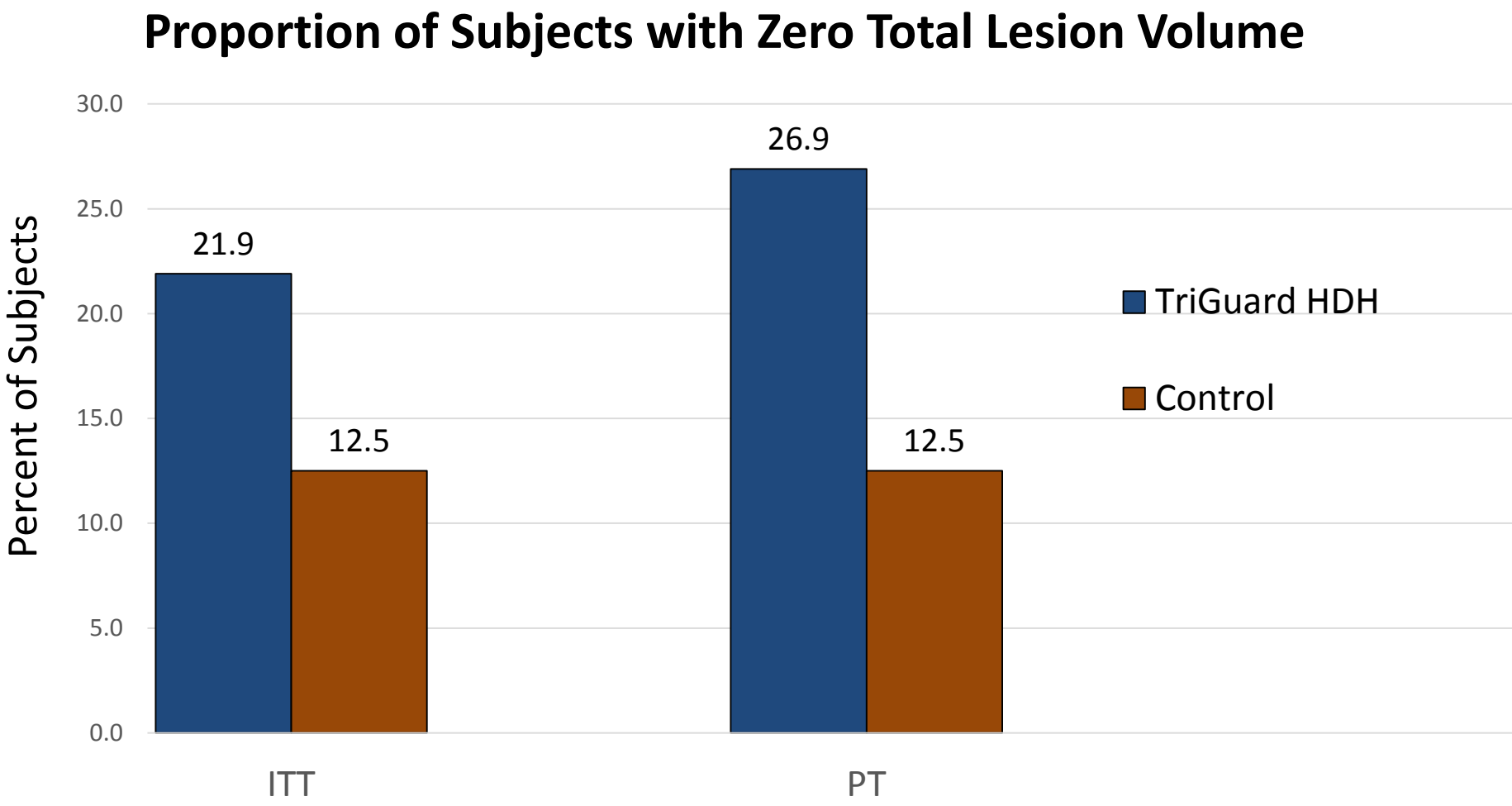




DW-MRI Results – Single and Max Lesion Volume

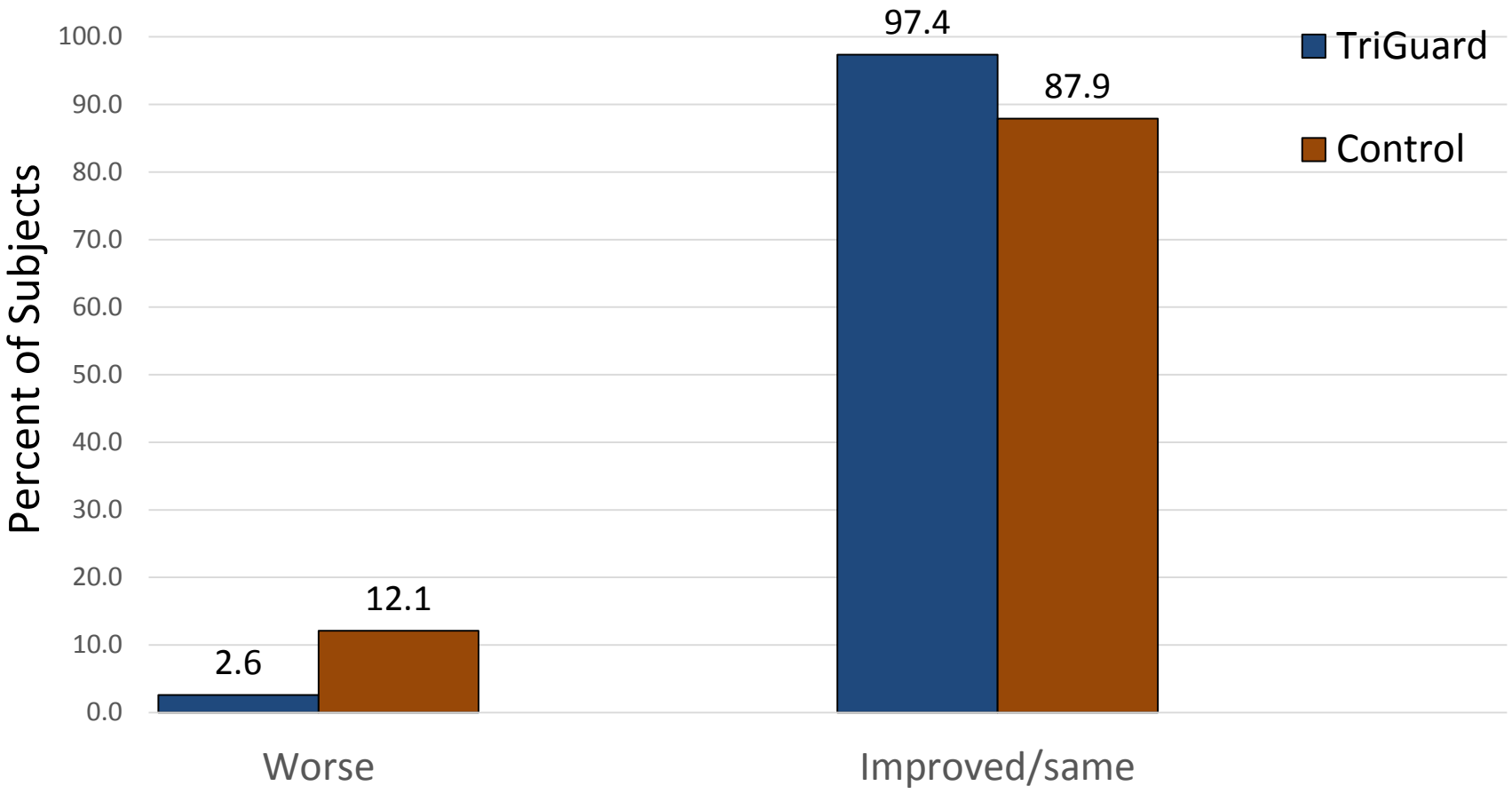


DW-MRI Results – Zero Total Lesion Volume



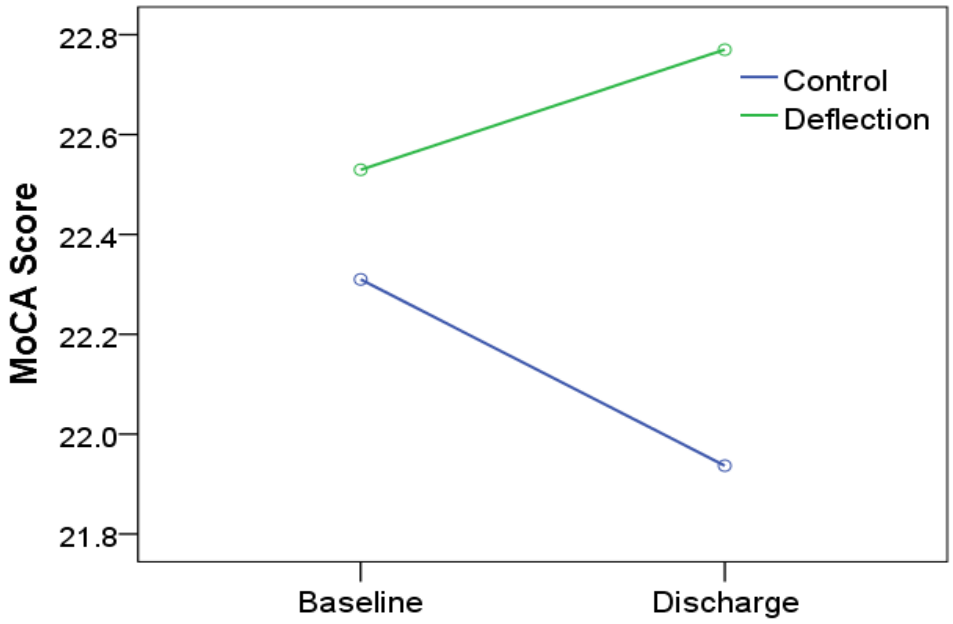
Efficacy Outcomes – Discharge NIHSS

Proportion of Subjects with and without a net NIHSS decrement from baseline to discharge (ITT population)



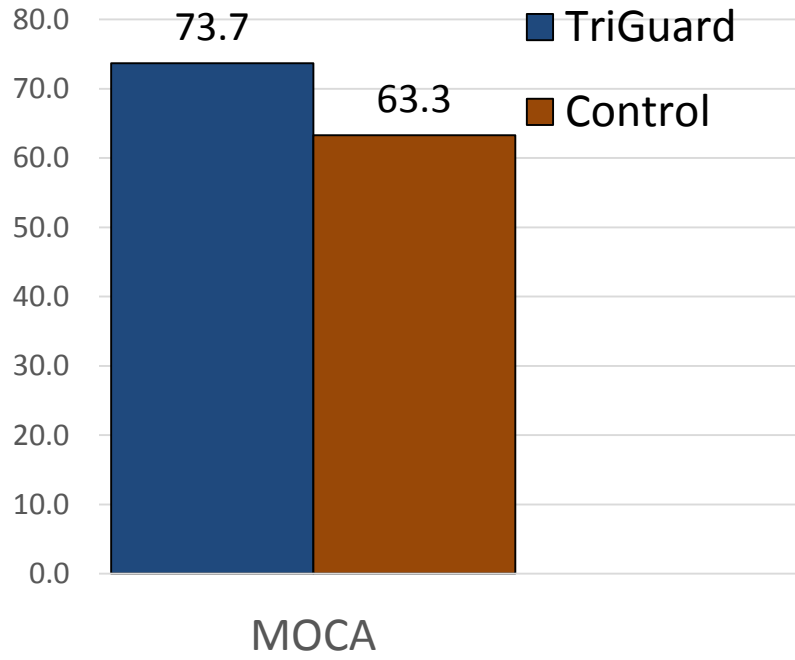
MoCA Score – Trends (ITT)

On average, MoCA scores improved in the TriGuard arm and decreased in the control arm



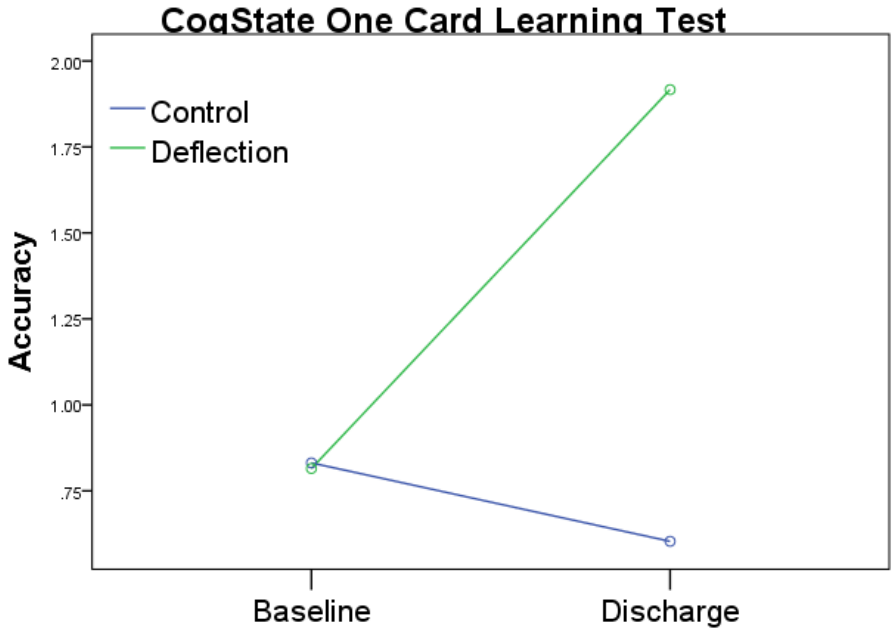
Covariates appearing in the model are evaluated at the following values: Age = 82.672

MOCA at Discharge
% Same/improved



CogState-Test Results (PT)

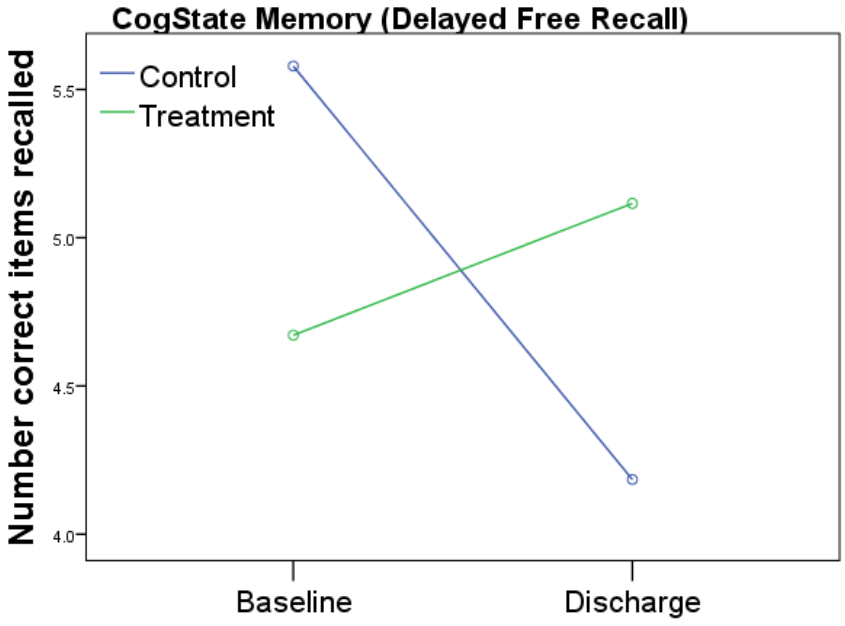
Visual learning and short term memory test



Covariates appearing in the model are evaluated at the following values: Age = 81.732

Treatment X Time interaction, p=0.043

Delayed memory test



Covariates appearing in the model are evaluated at the following values: Age = 81.450

Treatment X Time interaction, p=0.028

Conclusions

- DEFLECT III is the first multicenter randomized clinical trial of neuro-protection (non-powered) designed to explore safety and novel neurocognitive and DW-MRI surrogate efficacy endpoints
- Loss to DW-MRI was high (35%) and loss to NC evaluation was 17% from baseline to post procedure
- Use of the TriGuard HDH device was safe and provided complete cerebral coverage in 87% of cases.
- Neurocognitive function, based on novel measures used, appear to improve from baseline to discharge
- The prevalence of DW-MRI lesions was numerically lower in patients treated with the TriGuard device, and subjects in whom the device was properly positioned may be protected from the largest lesions.
- DEFLECT III will benchmark event rates for a future randomized trial that will be able to truly examine the potential benefits of the TriGuard device