The Keystone Heart Technology and Clinical Program

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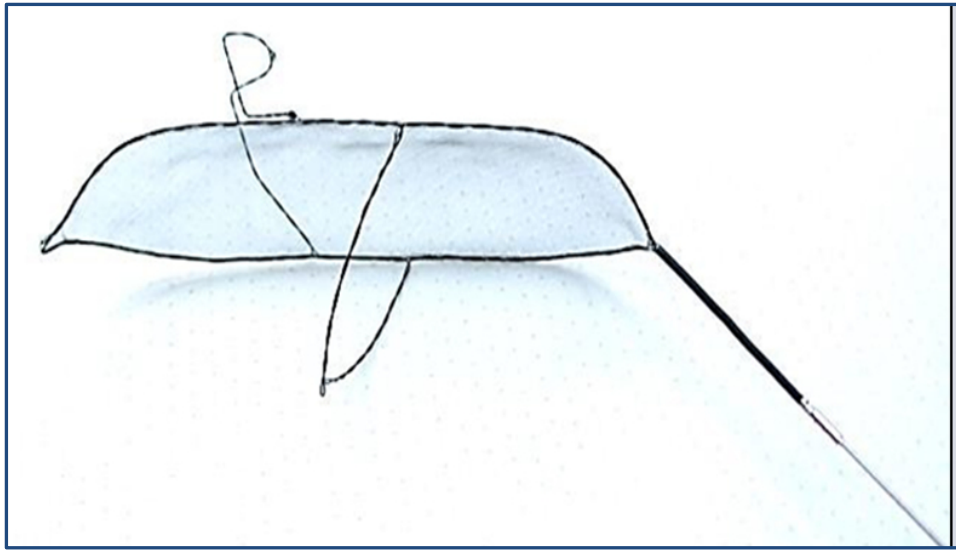
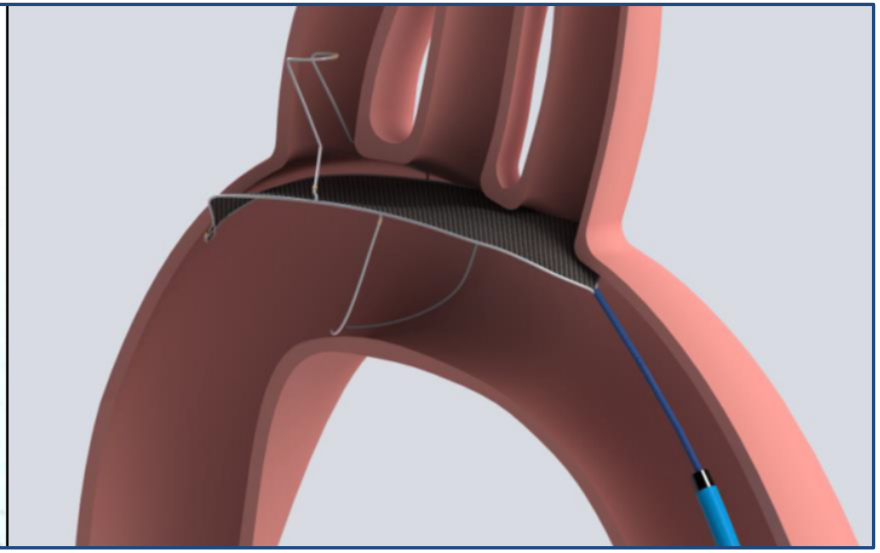
The TriGuard™ HDH Device

- 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
N=107 in clinical trials
N= 29 commercial EU cases

Study	Description	N (TriGuard)	Status
First in Human	Single center (NL)	15	Complete
DEFLECT I	Prospective multicenter (EU)	37	Complete – CE Mark received in 2013
DEFLECT II	Single center (NL)	12	Complete
DEFLECT III	RCT (EU/IL)	43	30-day follow up ongoing
REFLECT	Pivotal IDE Trial (US + EU)	TBD	IDE Approved – first subject in 2015

Keystone Heart Overall Clinical Program Completed

- **DEFLECT I (N=37)**
  - Gen 1.0 TriGuard device
  - Observational, compared to historical controls
  - Reduction in lesion volume and total ischemic burden
  - CE Mark in 2013
  - PI: M Mullen, MD

- **DEFLECT II (N=15)**
  - FIM to assess the next generation TriGuard 1.5 device (EU)
    - Steerable
    - Pore size 120 micron with radiopaque markers for good visibility
  - PI: P Stella

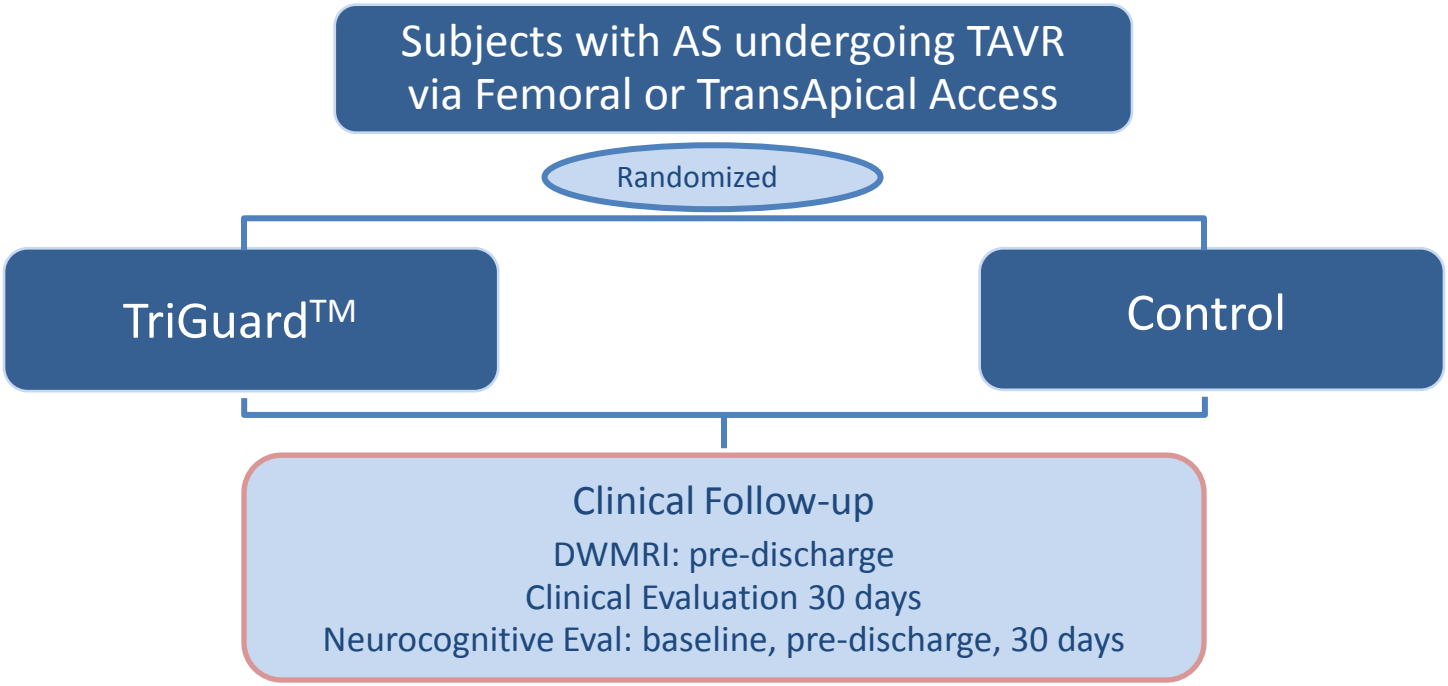
Overall Clinical Program Enrolling

- **TransAortic (N=20)**
  - Observational, compared to single center data without protection (Canada)
  - PI J Rhodes-Cabau
- **NeuroTAVR (N=60)**
  - Observational multicenter study of contemporary TAVR (US)
  - PI: A Lansky
- **DEFLECT III (N=86)**
  - Multicenter, randomized 1:1 (EU) protection vs none in unrestricted TAVR population
  - PI: A Lansky and A Baumbach

REFLECT US IDE Trial

A prospective multicenter randomized trial of TriGuard™ neuro protection vs no protection in patients undergoing TAVR in EU and US

Chair: J Moses PI: A Baumbach/ A Lansky



Co-Primary Safety Endpoint (NI)
VARC Device safety at 30 days

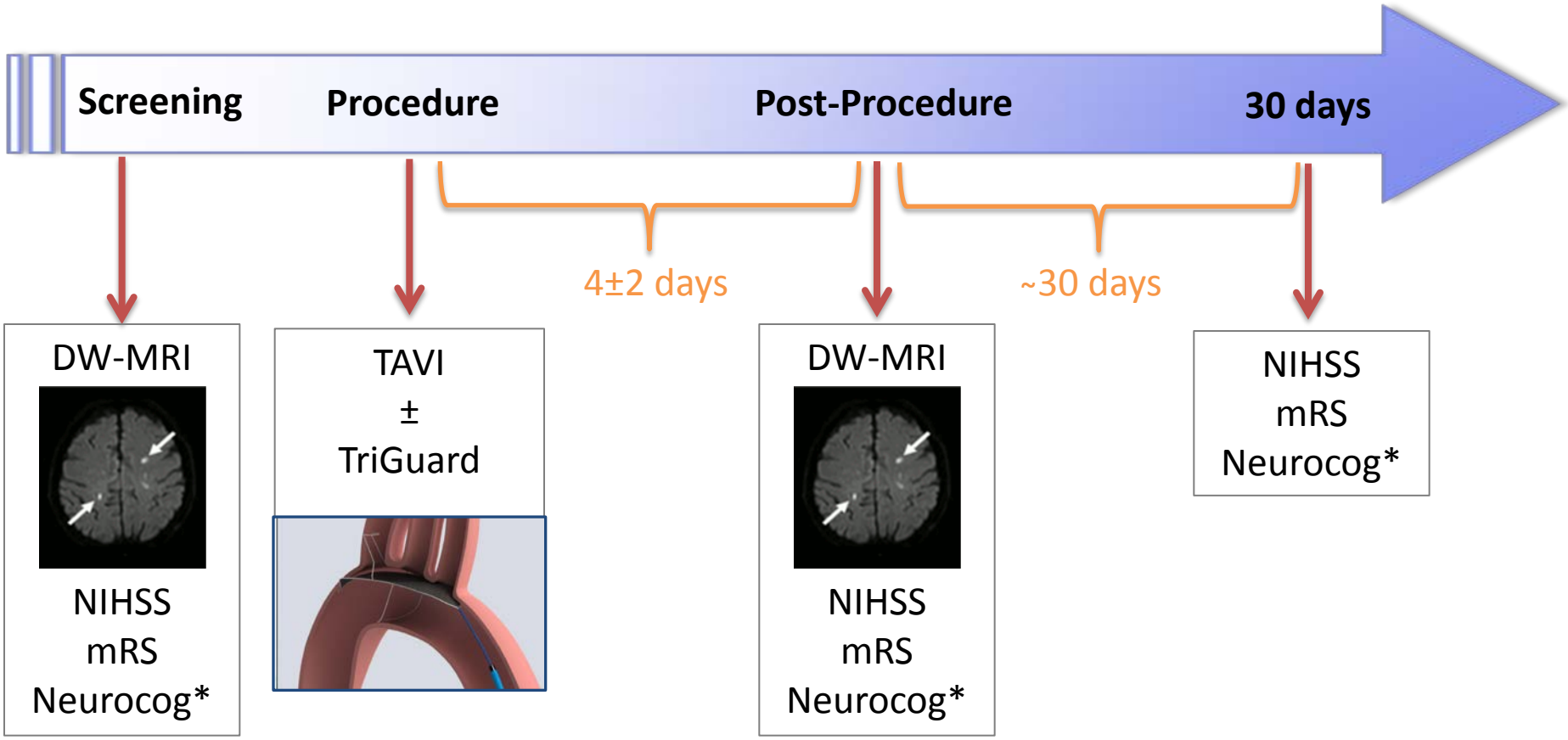
Primary Efficacy Endpoint (superiority)
New DWMRI Lesions

MACCE: Composite of all cause death, Stroke, life threatening bleed, AKI 2-3, major vascular complications

Key Secondary Endpoints: NeuroCognitive change

WHAT HAVE WE LEARNT SO FAR?

DEFLECT I Procedures & Assessments



*__Neurocognitive test battery:__ Montreal Cognitive Assessment (MoCA)

DEFLECT I TriGuard™ Performance Success: 80%

Characteristic	Before TAVR	After TAVR	After TAVR Removal
TriGuard™ access to Aortic Arch	37 (100%)		
TriGuard™ positioned in arch	37 (100%)	34 (97%)	29 (81%)
TriGuard™ Covers all 3 vessels	33 (98%)	28 (80%)	23 (64%)
TriGuard™ stabilized anchored in innominate	31 (84%)	27 (79%)	22 (61%)
TriGuard™ retrieved intact			37 (100%)

A Baumbach, EuroIntervention 2015 in press

Hierarchial TAVR Safety Endpoint

VARC Defined	Overall Composite Safety	
Characteristic	In-hospital	Cumulative 30 Days
Composite Procedure-related Safety	16.2% (6)	18.9% (7)
All cause mortality	0%	2.7% (1)*
Major stroke disability	5.4% (2)	5.4% (2)*
Life threatening bleeding	8.1% (3)	8.1% (3)
Acute Kidney Injury-Stage 3	2.7% (1)	2.7% (1)
Peri-procedural MI	2.7% (1)	2.7% (1)*
Major vascular complication	8.1% (3)	8.1% (3)
Repeat procedure for valve dysfunction	2.7% (1)	2.7% (1)*

* Not EDD related; 1 non-cardiac death (pneumonia)

2 disabling strokes (not TriGuard™ related) occurred 1 day after TAVR.

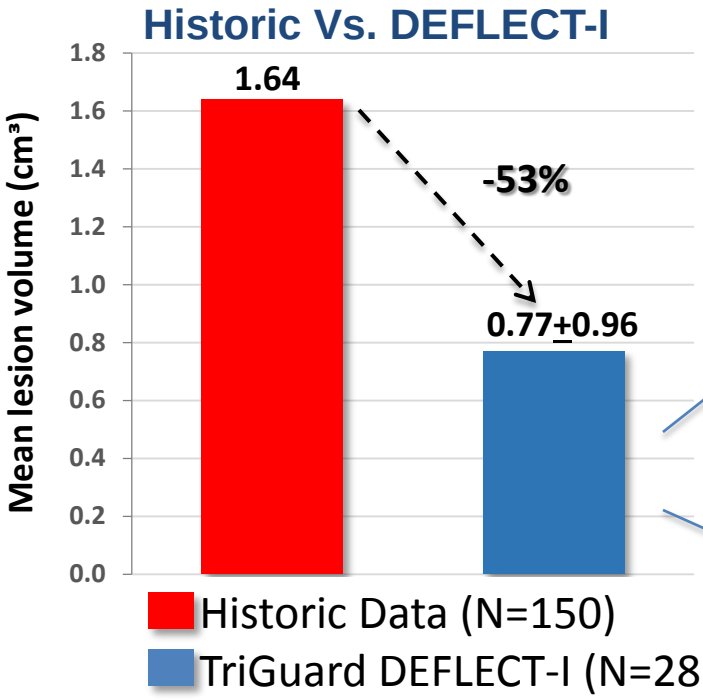
(1) in association with urgent surgical conversion of failed TAVR and

(2) Following prolonged cardiac resuscitation.

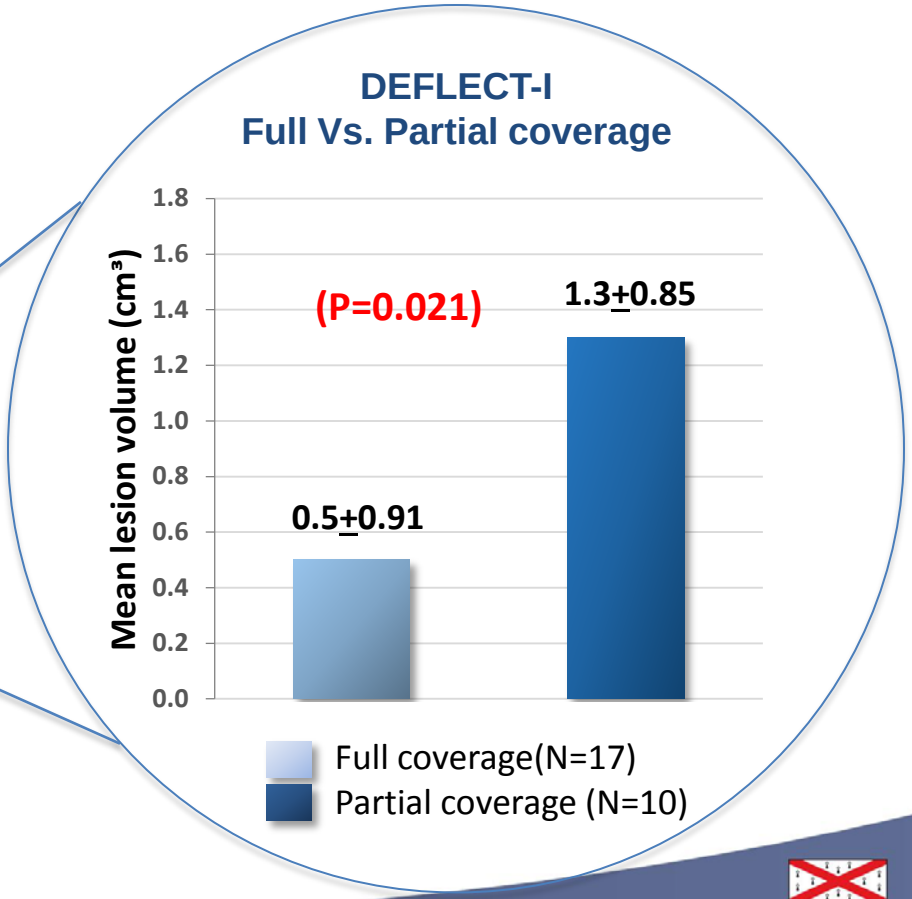
DEFLECT I: DW-MRI Results

Number of DW MRI Lesions were lower (70% vs 76%)

Total Lesion Volume (cm^3)



Historical Data: Astarci 2010, Ghanem 2010, Kahlert 2010, Fairbarn 2011, Knipp 2012



A Baumbach, EuroIntervention 2015 in press

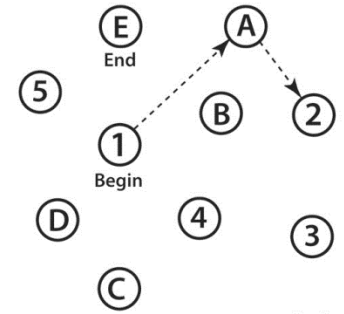
Measuring cognition: MoCA

- 30-item ***screening*** instrument. Score<26 suggest impairment.
- Comprises total score and individual domain scores.
- Does the degree of cognitive change relate to DWI measures?

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

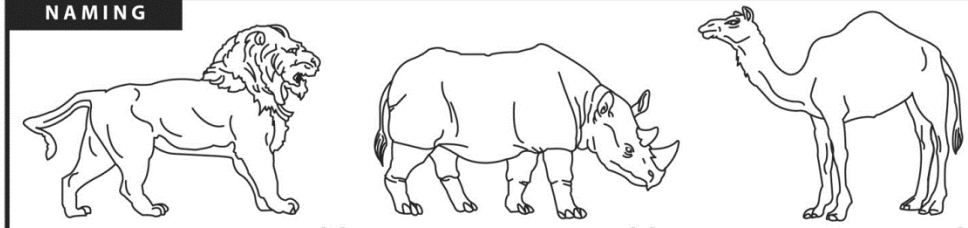
NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — Copy cube — Draw CLOCK (Ten past eleven) (3 points) — POINTS



[ ] [ ] [ ] Contour [ ] Numbers [ ] Hands __/5

NAMING



[ ] [ ] [ ] __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4. Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

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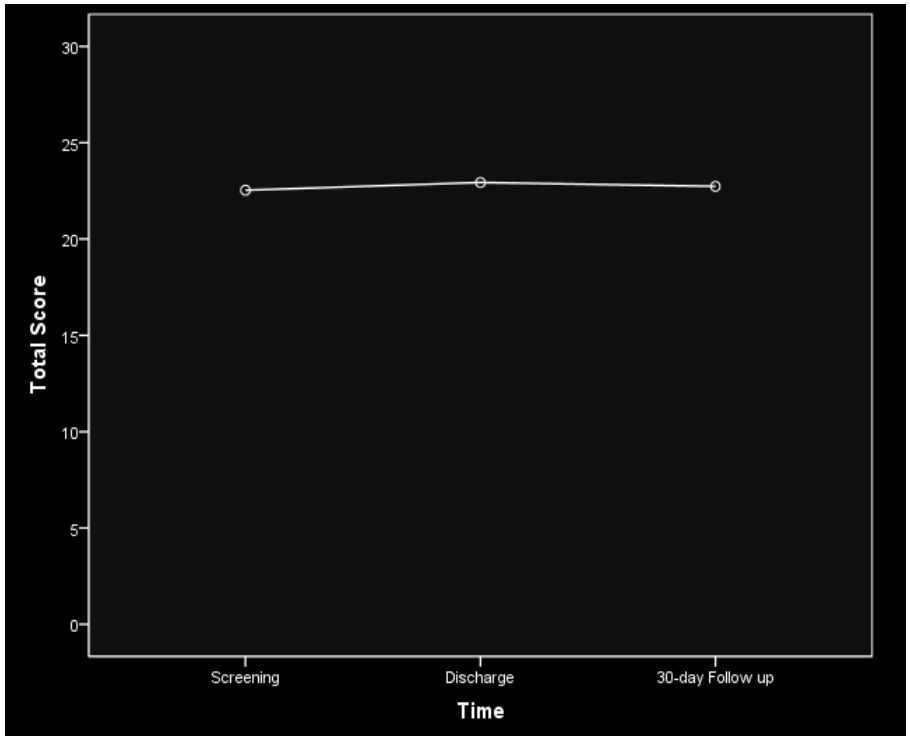
Add 1 point if ≤ 12 yr edu

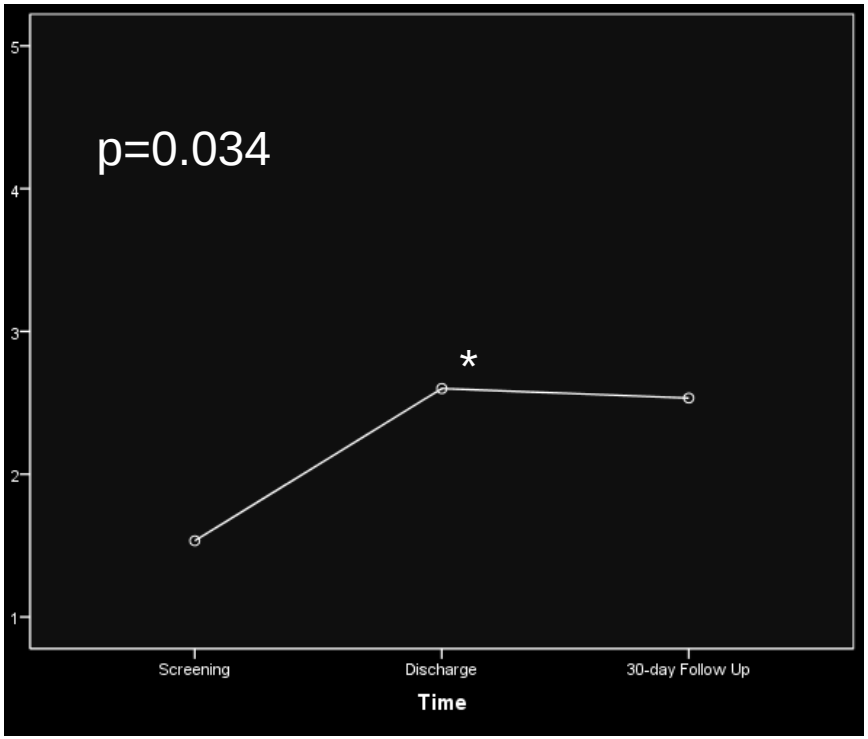
Administered by: _____

Neuro Cognitive Assessment
Are we making a difference?

MoCA Total Score



Memory Score



Neuro TAVR

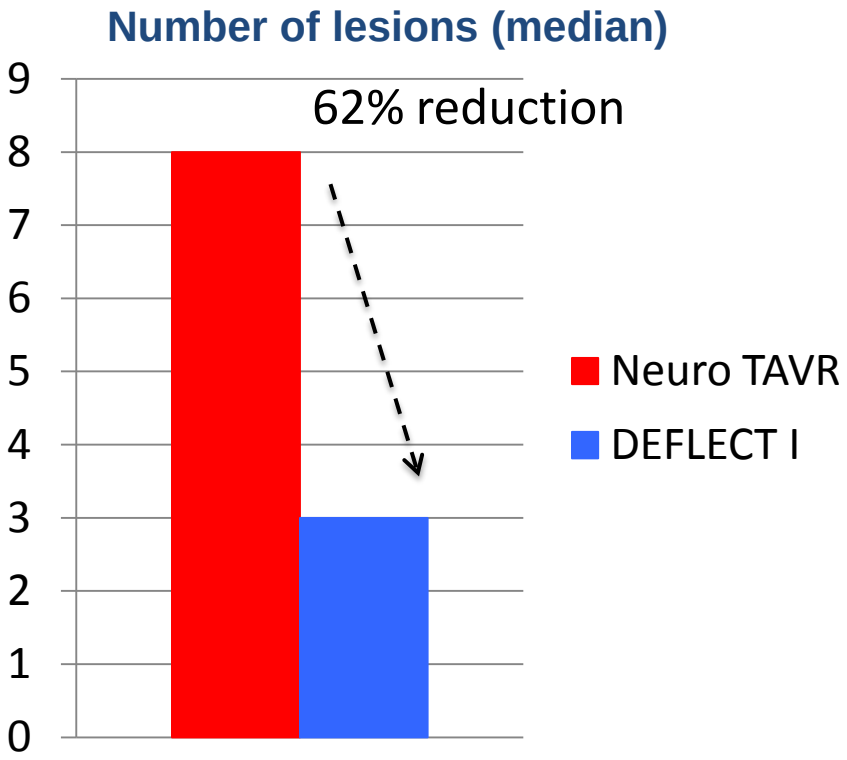
- Multicenter, prospective US registry to assess the incidence of new ischemic lesion by DWI MRI after TAVR and impact on neurocognitive function
- 5 US Centers (Yale, Columbia, WHC, Baylor, Baptist Florida)
- PI: Dr Alexandra Lansky
- N= up to 60 patients (33 enrolled)
- Same protocol inclusion/exclusion as DEFLECT I
- Enrolling

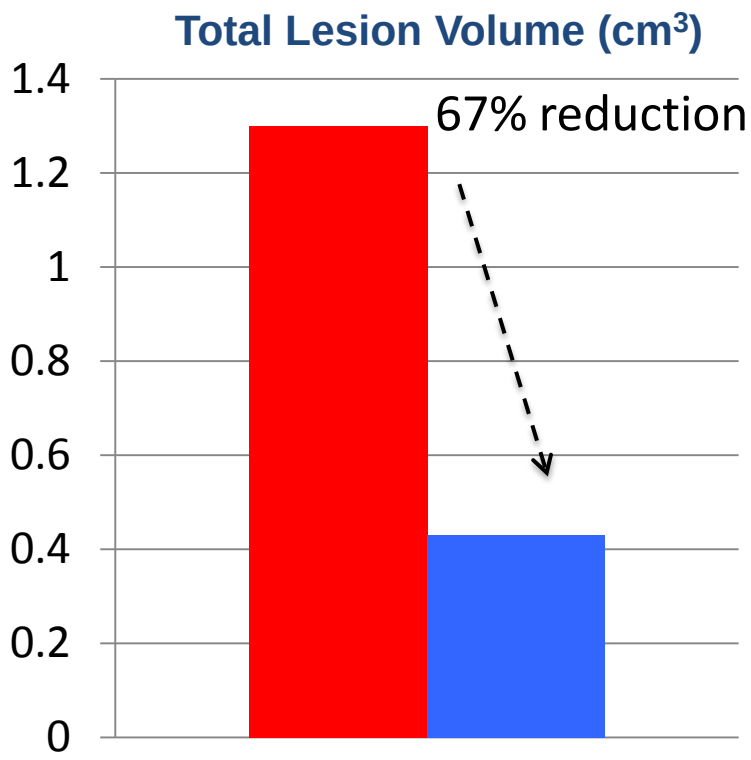
Baseline Demographics

Characteristic	DEFLECT N=37	NeuroTAVR (N=17)
Age	83.1±6.3	83.1±17.5
Female	24 (65%)	4 (23.5%)
DM	5 (14%)	8 (47.1%)
COPD	5 (13.5%)	3 (17.7%)
Atrial Fibrillation	14 (38%)	7 (41%)
Prior CABG/PCI	7 (19%)/ 4 (11%)	9 (56%)/ 11 (65%)
NYHA Class I, II, III, IV	6 (17%)/7 (20%)/21(58%)/2(6%)	0 (0%)/6 (38%)/8(50%)/2(12.5%)
Prior CVA	2 (5%)	2 (11%)
Renal insufficiency	6 (16%)	6 (35.3%)

DW-MRI Results

Neuro TAVR vs DEFLECT I



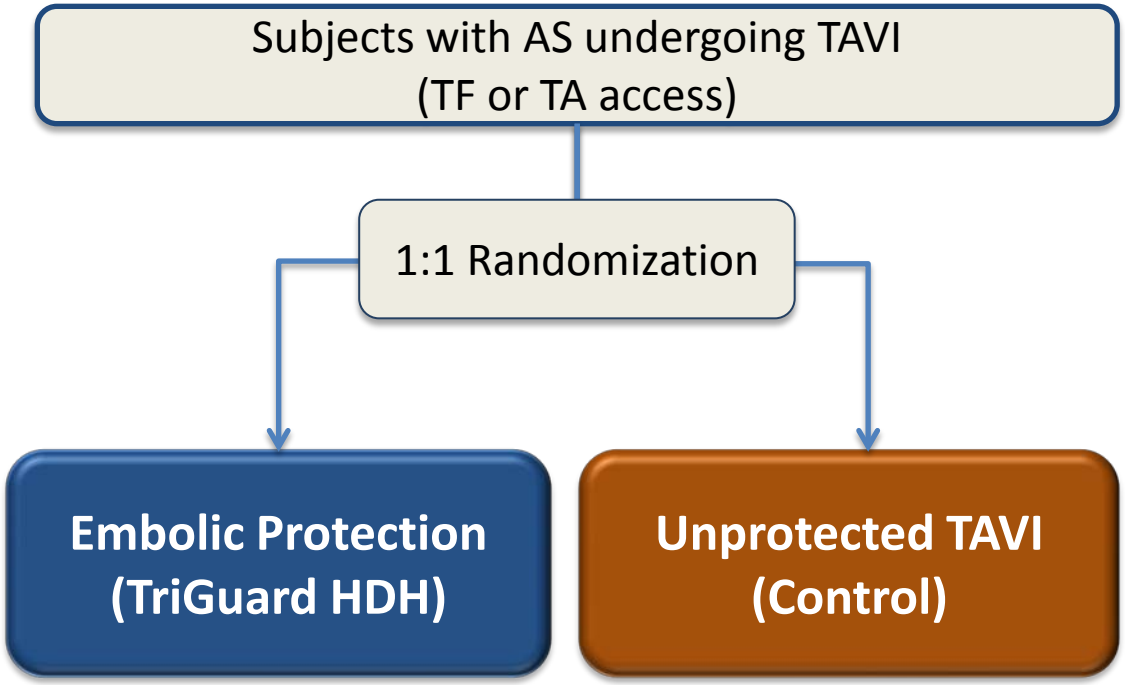


DEFLECT III Study Overview

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

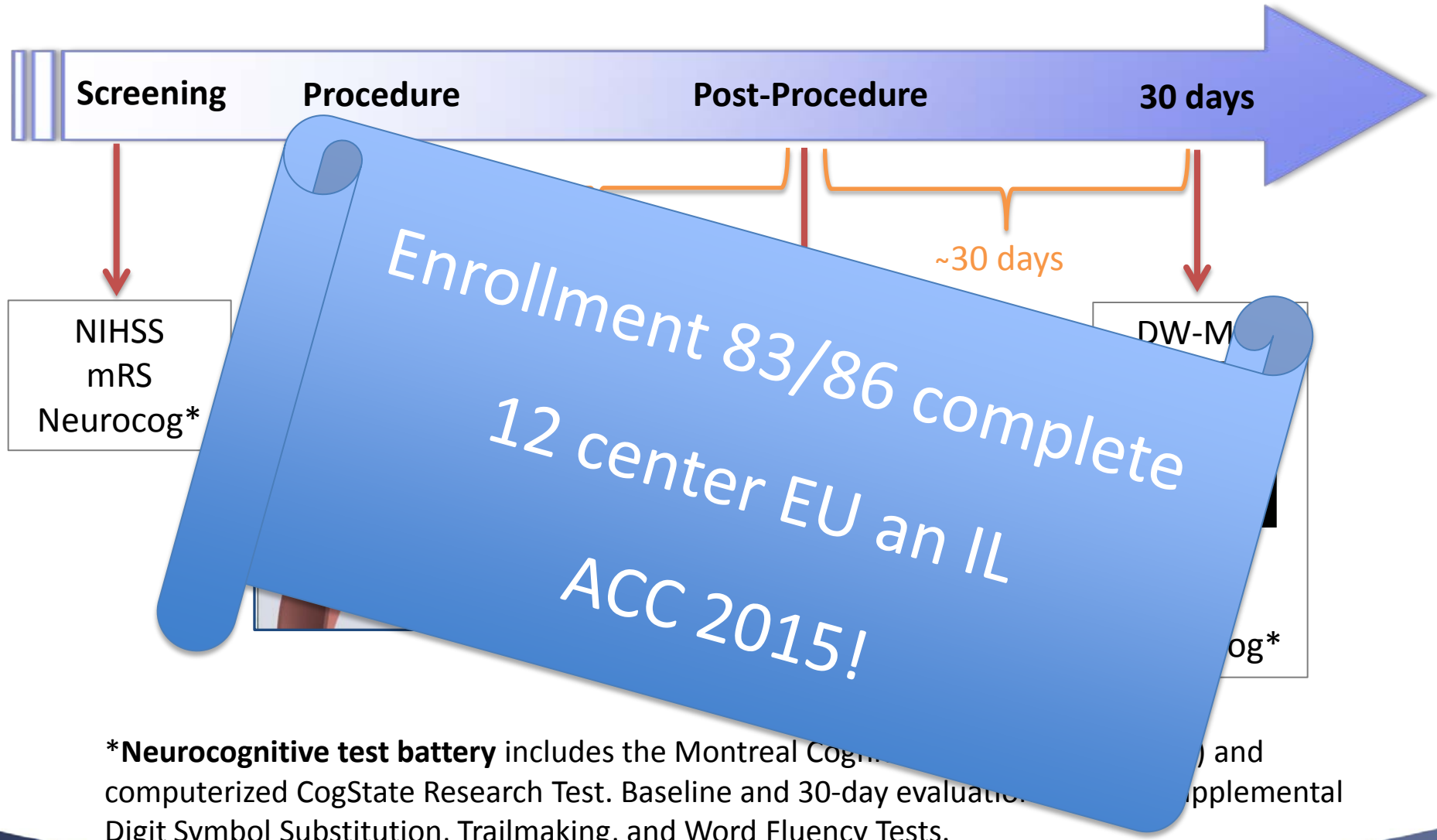
Objective: To evaluate the safety, efficacy and performance of TriGuard HDH embolic protection compared with unprotected TAVI.

Sample Size: No formal hypothesis testing. 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 Cogn) and computerized CogState Research Test. Baseline and 30-day evaluatio pplemental Digit Symbol Substitution, Trailmaking, and Word Fluency Tests.

Lessons learned from DEFLECT so far…

- TG device is safe and reduces ischemic burden compared to historic controls
- On average Memory measured by MoCA improved at discharge
- DEFLECT III at ACC and PCR 2015
- REFLECT US IDE initiated Q1-2/2015