Cardiology Division

University Hospitals of Leicester NHS

University of Leicester

NHS Trust

Glenfield Hospital

Cerebral Protection during Percutaneous Structural Cardiac Interventions

Jan Kovac
Glenfield Hospital
University of Leicester Hospitals
United Kingdom

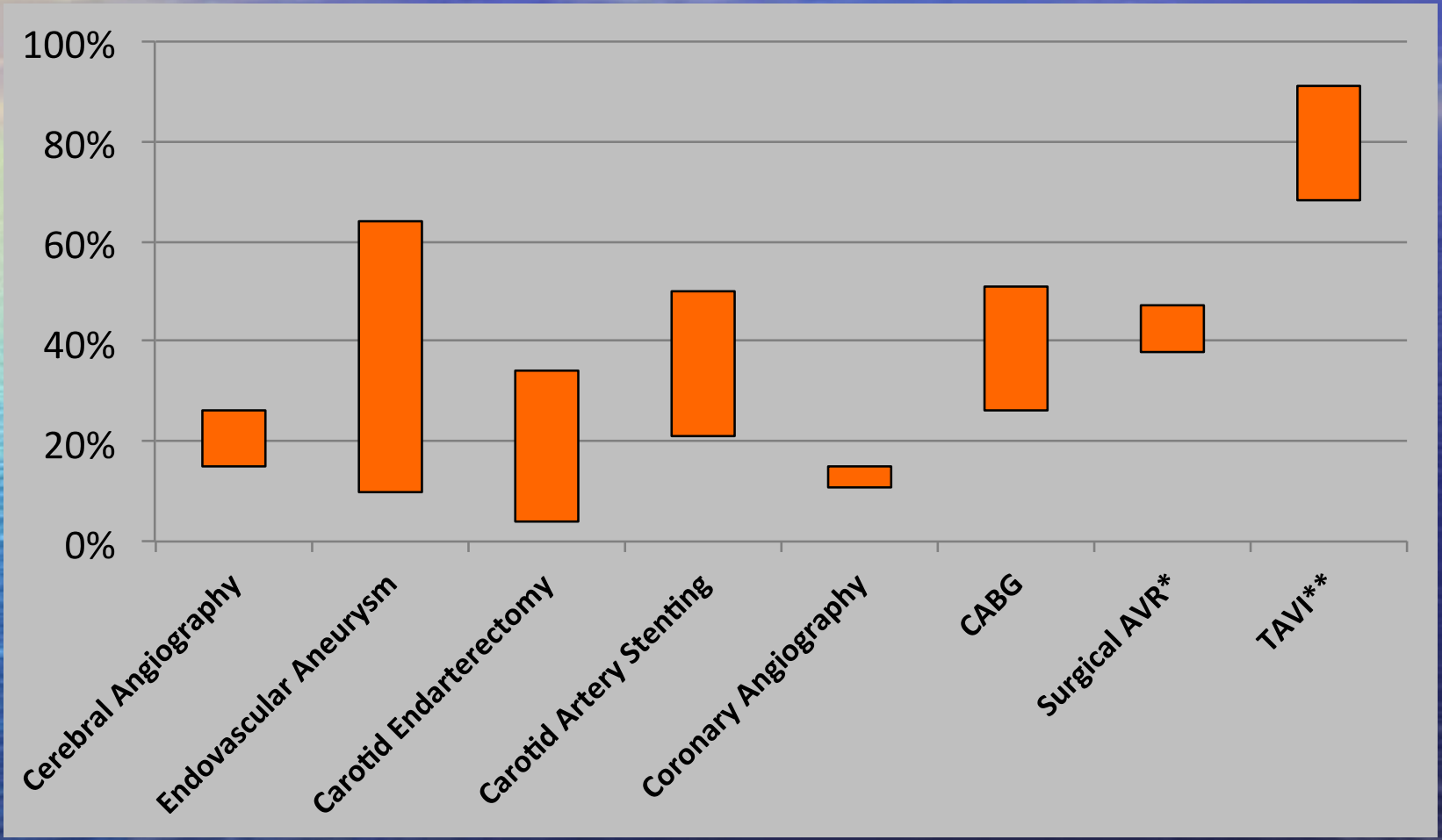
Heart and Brain Workshop, Prague 2018

ESC Council on Valvular Heart Disease

Valvular Heart Disease
ESC Working Group

EUROPEAN SOCIETY OF CARDIOLOGY®

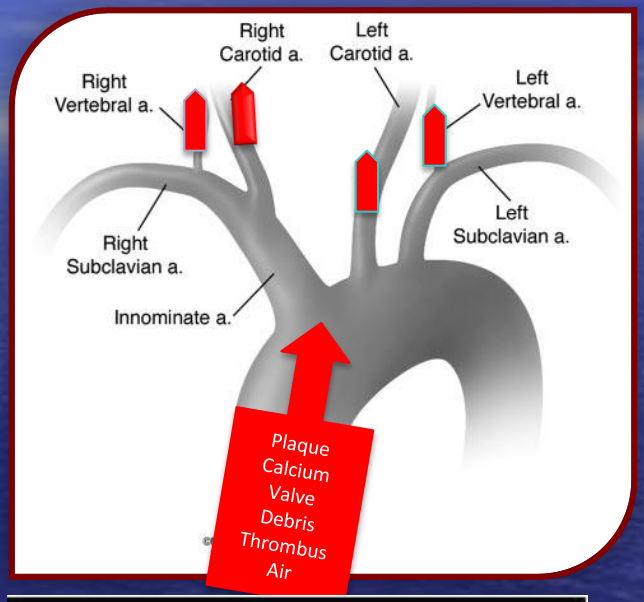
Incidence of New Brain Lesions

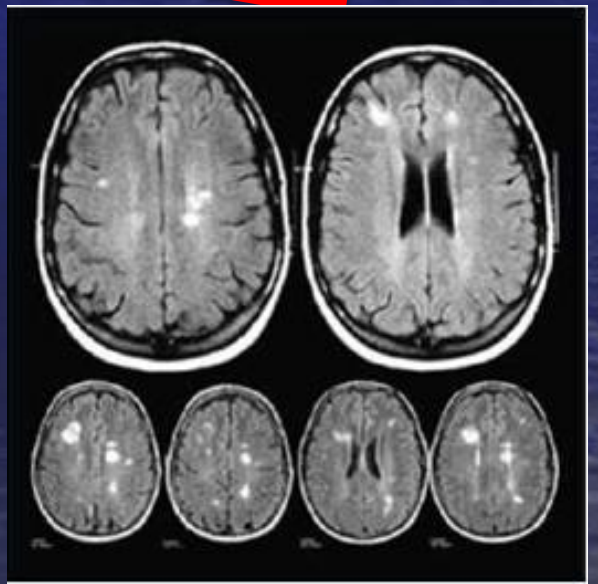


*Knipp 2005, Stolz 2004.
**Astarci 2011, Ghanem 2010, Kahlert 2010, Rodés-Cabau 2011.

Background

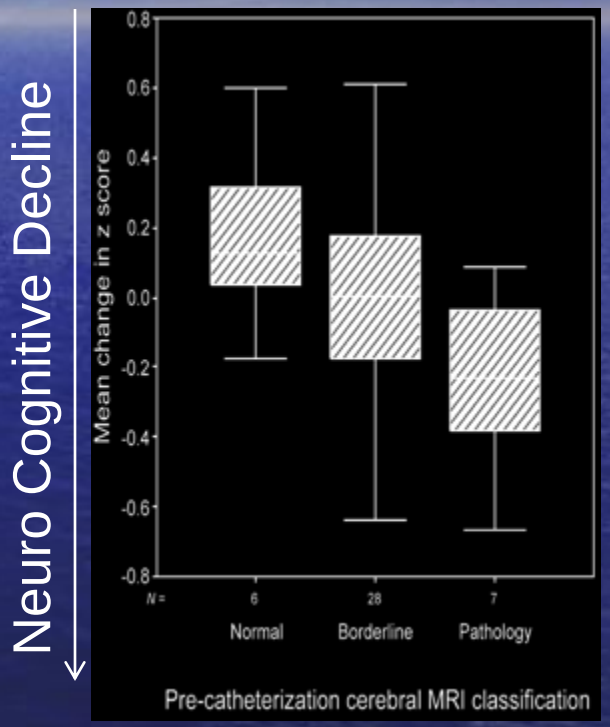
- Stroke is a rare but devastating complication of TAVI
- 50% of events occur periprocedurally
- Clinically 'silent' or non-detected strokes are frequent
- New embolic lesions in the brain can be detected in up to 100% of patients following a TAVI procedure
- Embolic events have been linked to neurocognitive decline





Neurocognitive Decline
and New Lesions

- Pre-existing and new lesions on DW-MRI after catheterization is related to cognitive decline
- Patients with new ischemic lesions post CABG (20%) had a larger neurocognitive decline than the patients with stable
- The link between new lesions on DW MRI in TAVI cohort yet to be established..



Lund et al, 2005 Restrepo et al Stroke 2002

TAVI is moving to Lower Risk Patient Groups

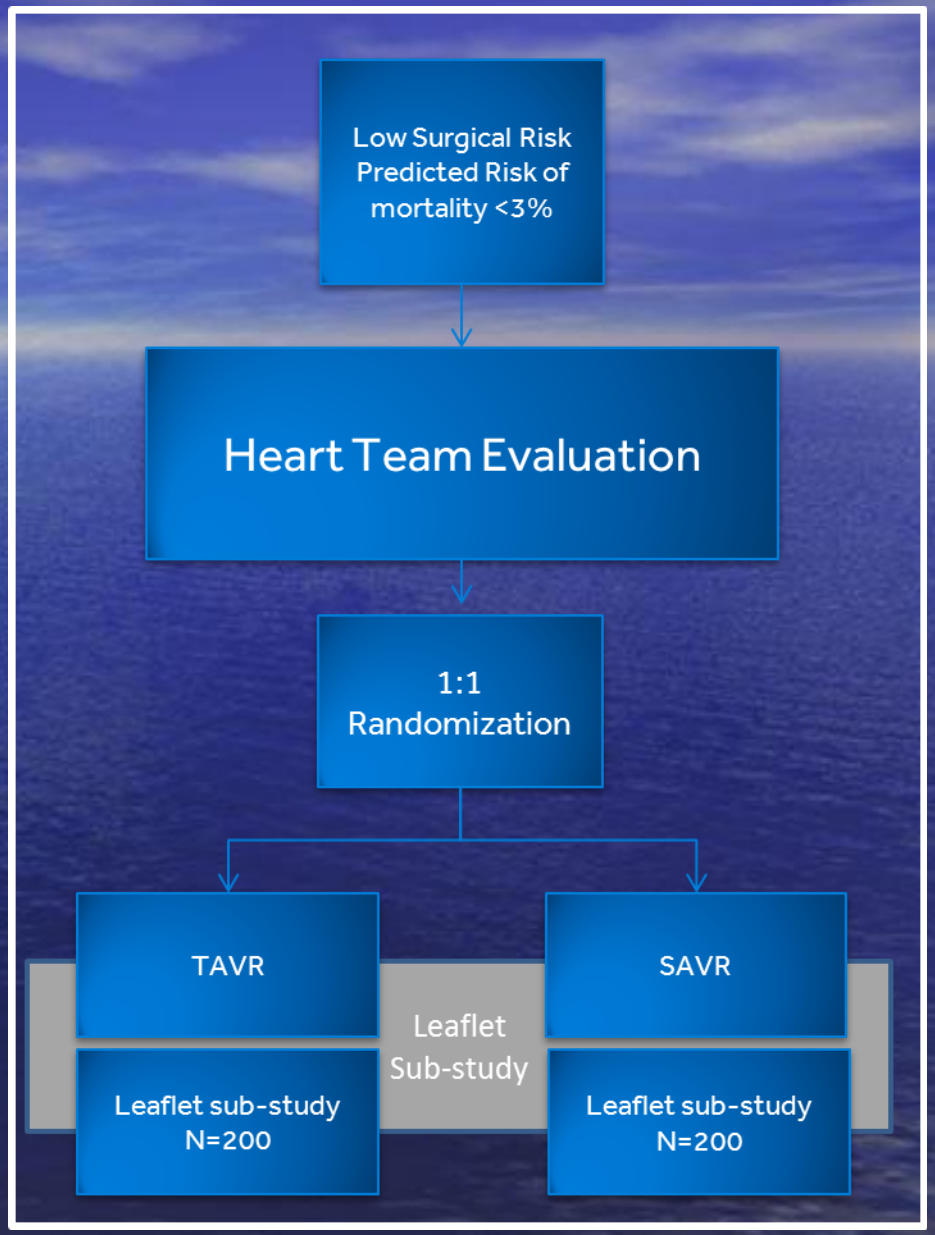
- Bicuspid Valves
- Lower Age
- Moderate AS
- Asymptomatic AS
- AS with Impaired LV

Speaker

Moving to Low Risk Patients

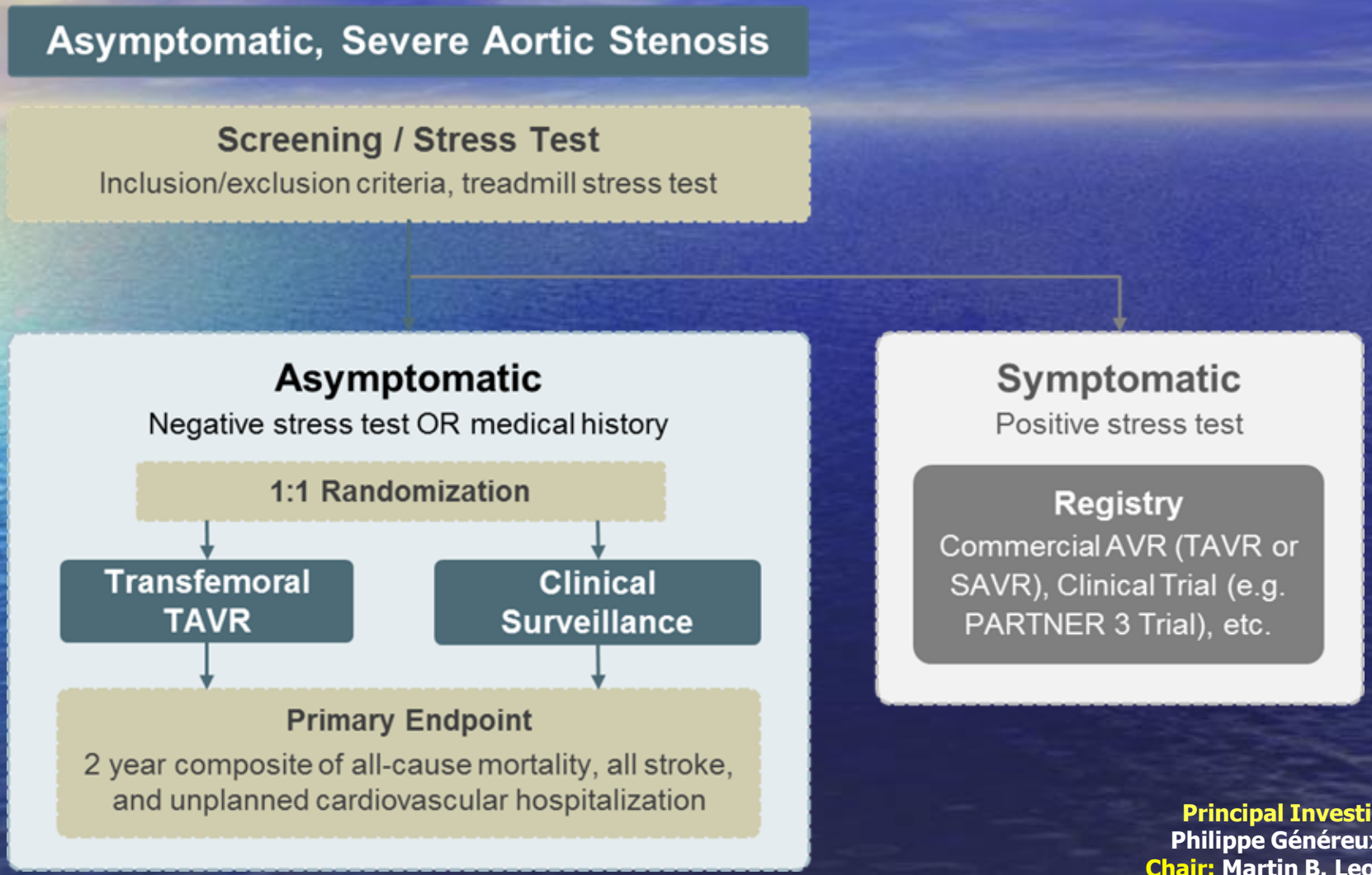
LOW RISK & LEAFLET SUB-STUDY

- **Patient Population: Low Risk Cohort**
  - Determined by Heart Team to be low surgical risk
- **Primary Endpoint:**
  - Safety: Death, all stroke, life-threatening bleeding, major vascular complications, or AKI at 30 days
  - Efficacy: Death or major stroke at 2 years
- **Sample Size: ~1200 Subjects**
- **Follow-up Evaluations:**
  - 30-days, 6-month , and 1 Through 5 years
- **Number of Sites: Up to 80 sites**



Study Flowchart

THE EARLY TAVR TRIAL

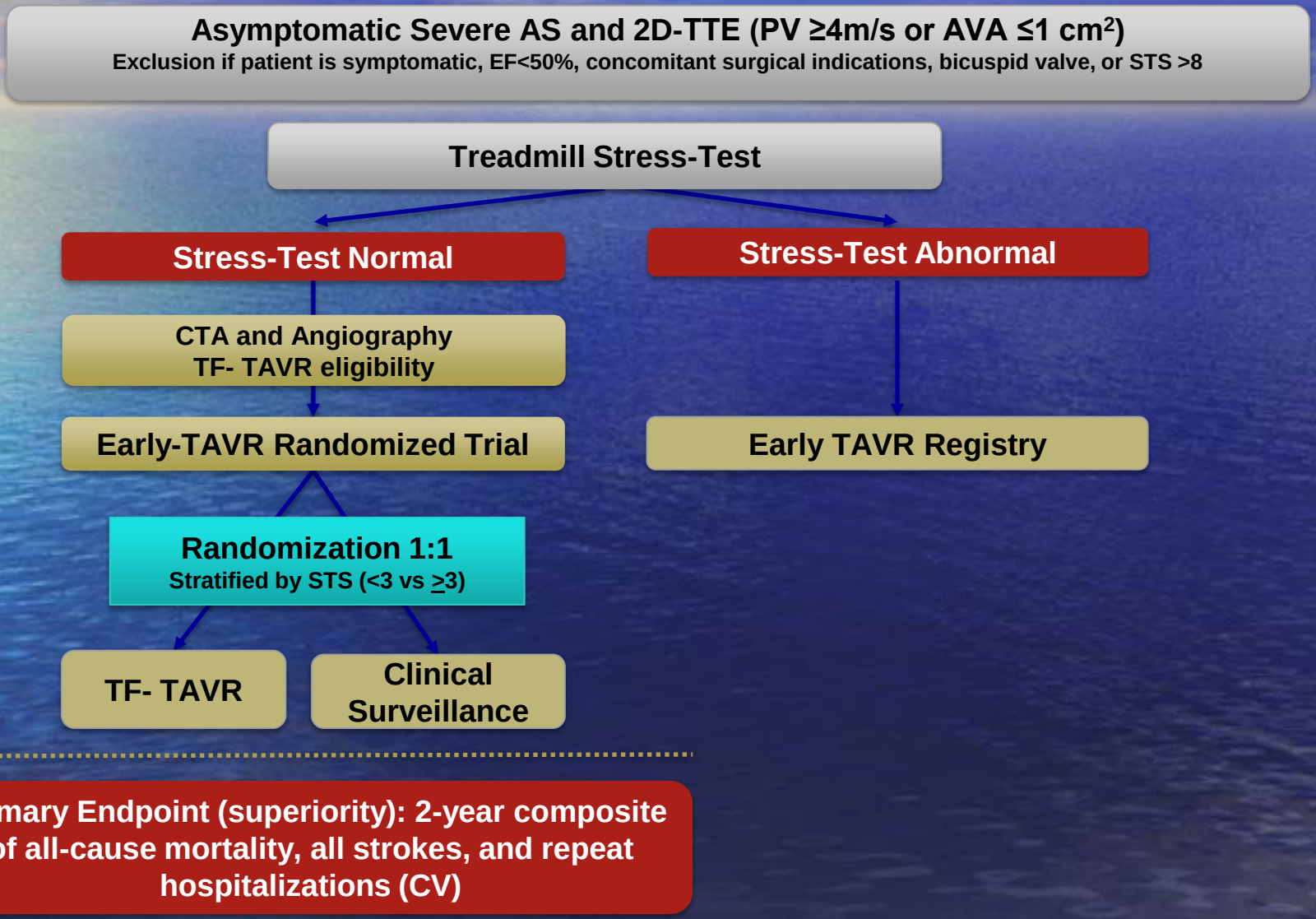


Principal Investigator:
Philippe Généreux, MD,
Chair: Martin B. Leon, MD

NCT03042104

EARLY TAVR Trial

Study Flow



TAVR UNLOAD Trial

Study Design

(600 patients, 1:1 Randomized)

TAVR UNLOAD Trial

International Multicenter Randomized

Heart Failure
LVEF < 50%
NYHA ≥ 2
Optimal HF therapy (OHFT)
Moderate AS

R

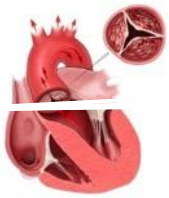
TAVR + OHFT

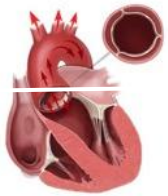
OHFT Alone

Follow-up:
1 month
6 months
1 year

Clinical endpoints
Symptoms
Echo
QoL

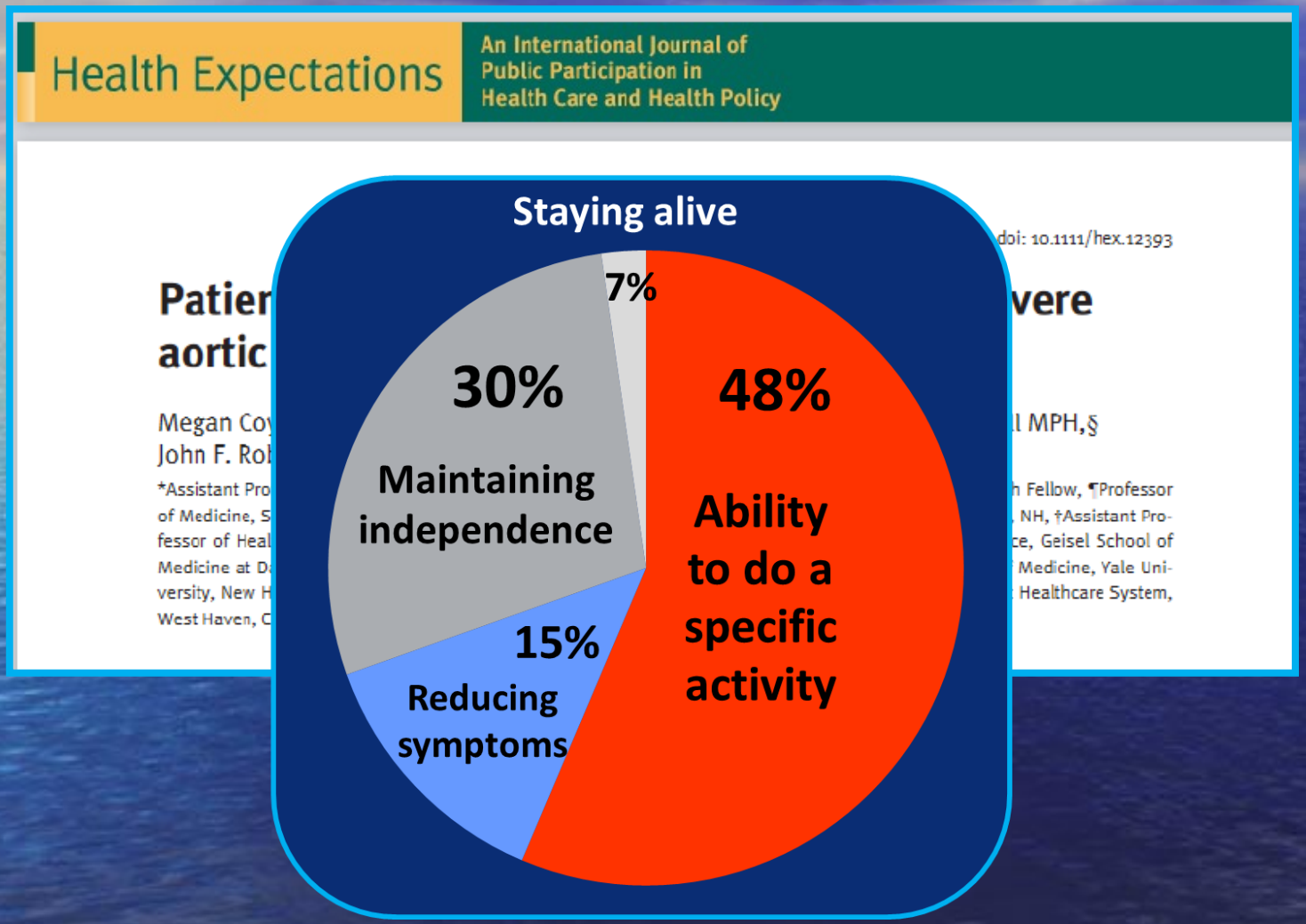
Primary Endpoint
Hierarchical occurrence of:
- **All-cause death**
- **Disabling stroke**
- **Hospitalizations for HF, aortic valve disease**
- **Change in KCCQ**





Reduced AFTERLOAD
Improved LV systolic and diastolic function

Patient Perceptions and Expectations



CLINICAL QUESTIONS

1. Is (embolic) stroke during TAVI/R a relevant clinical problem ?
2. Is there clinical/functional correlation of 'silent' microembolic events ?
3. Can we improve outcomes with embolic protection devices ?

Mechanisms of peri-procedural stroke

Embolic

- Wire and catheter manipulation
- BAV
- Device positioning in the root
- Valve deployment
- Post-dilatation

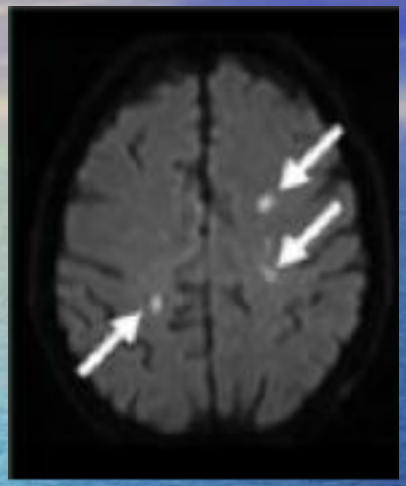
Haemorrhagic

- Bolus dose heparin
- Severe hypertension

Global Ischaemia

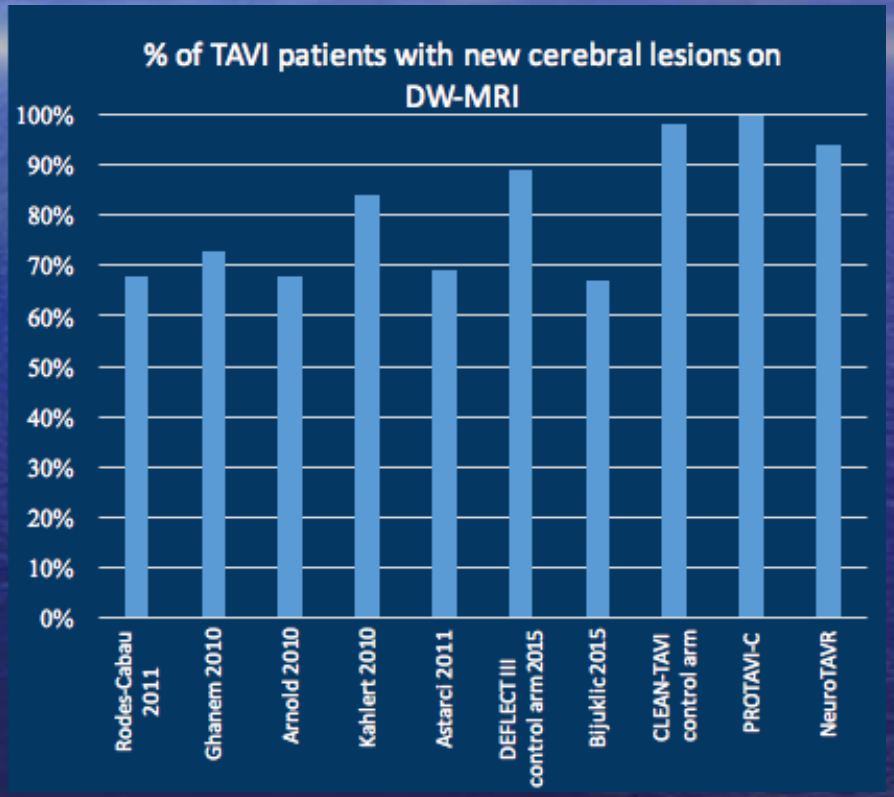
- Severe hypotension
- Rapid pacing

MRI imaging is "truly frightening" post TAVI…



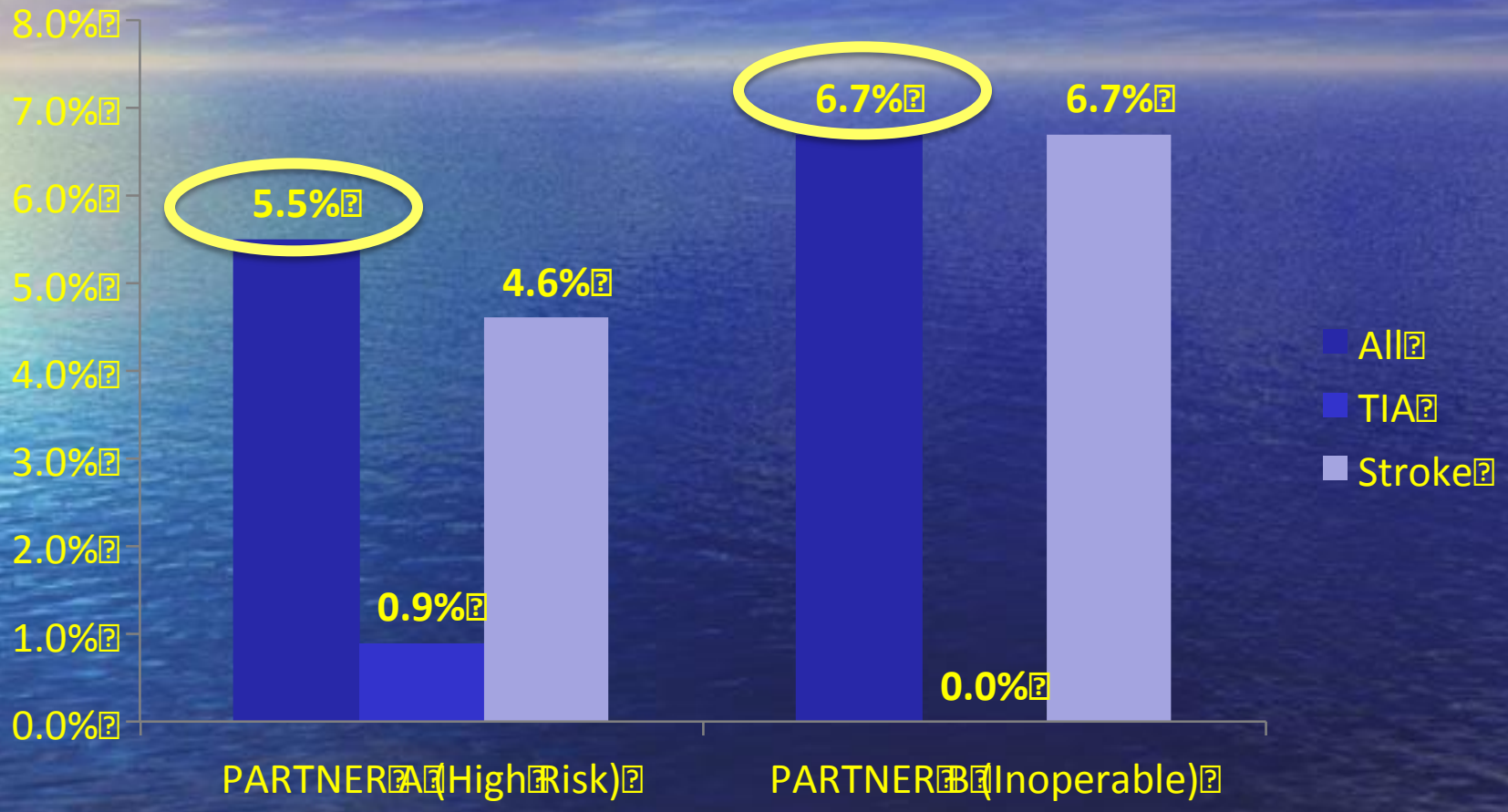
Ghanem, et. al, JACC 2010

- 68-100% of TAVI patients affected[1-10]
- Most patients have multiple infarcts
- "Silent" infarcts associated with[11-13]
  - 2-4-fold risk of future stroke
  - >3-fold risk of mortality
  - >2-fold risk of dementia
  - Cognitive decline
  - Dementia



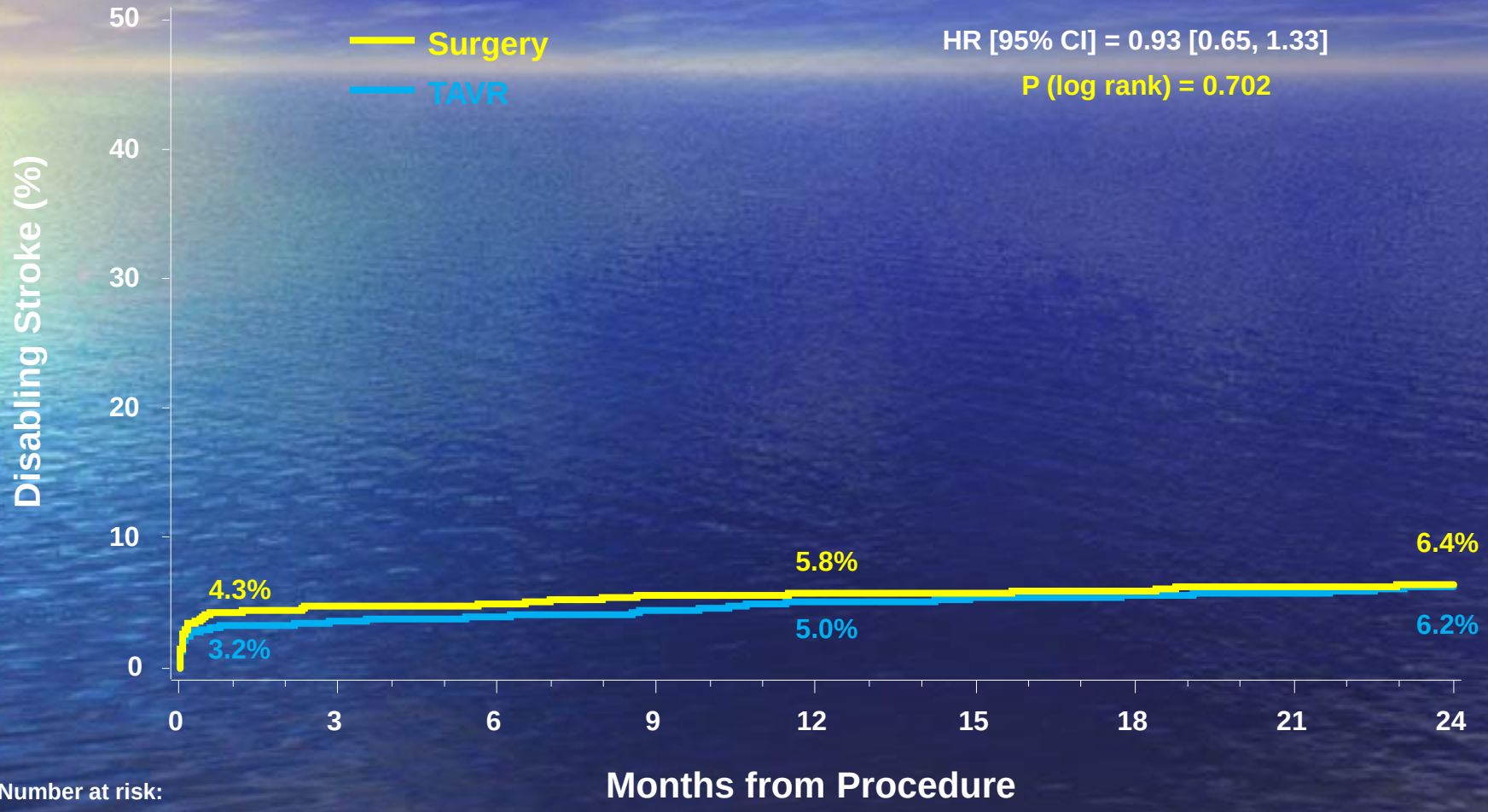
Insight from Pivotal studies

Acute Manifestations: PARTNER A and B (30-Day Events)



Smith et al. N Engl J Med 2011;364:2187-98. Leon et al. N Engl J Med 2010;363:1597-1607.

PARTNER 2A
Disabling Stroke (ITT)

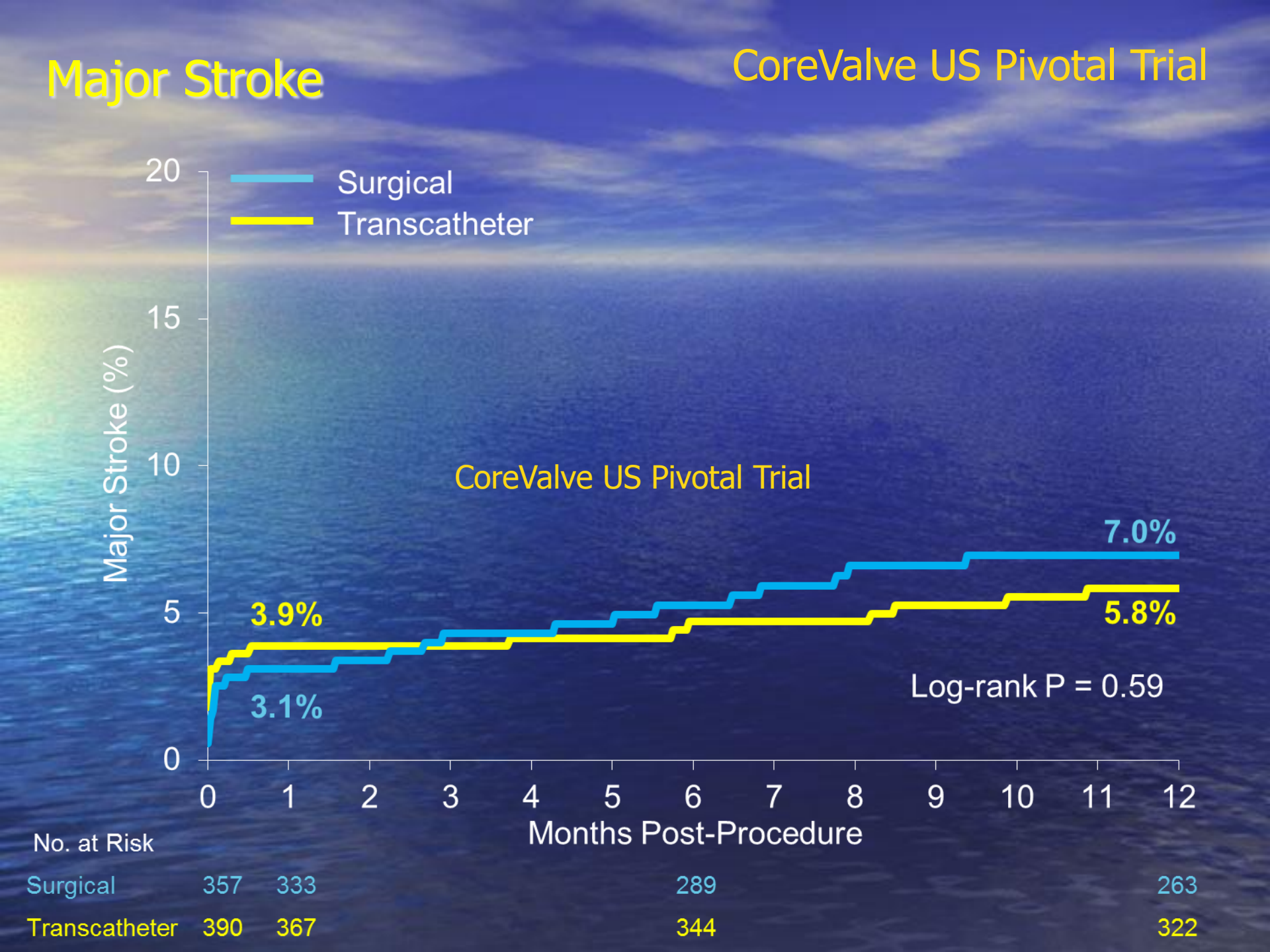


Number at risk:

TAVR	1011	918	901	870	842	825	811	801	774
Surgery	1021	838	812	783	770	747	735	717	695

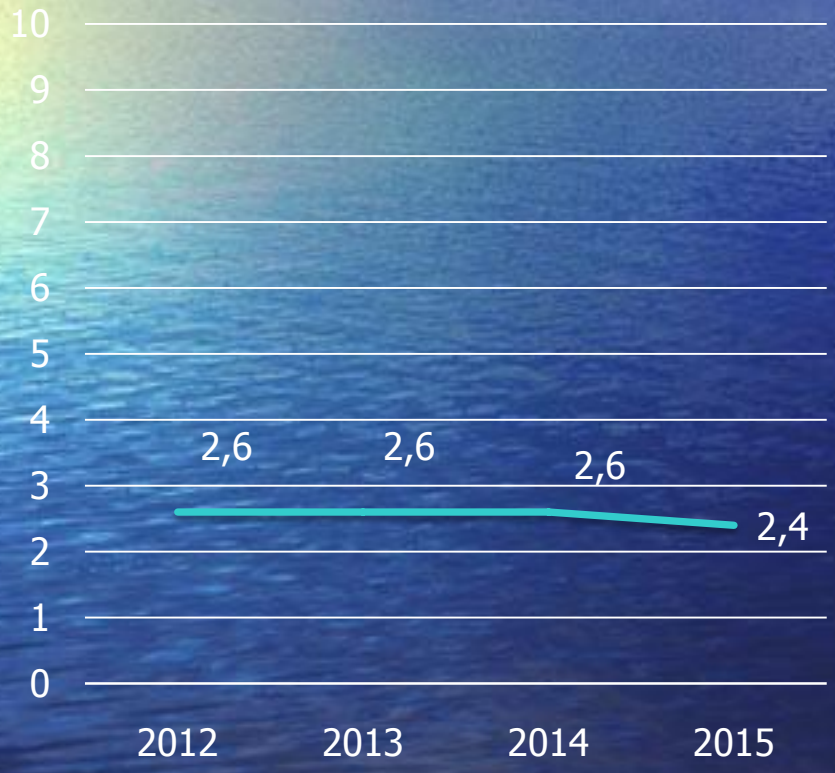
Major Stroke

CoreValve US Pivotal Trial

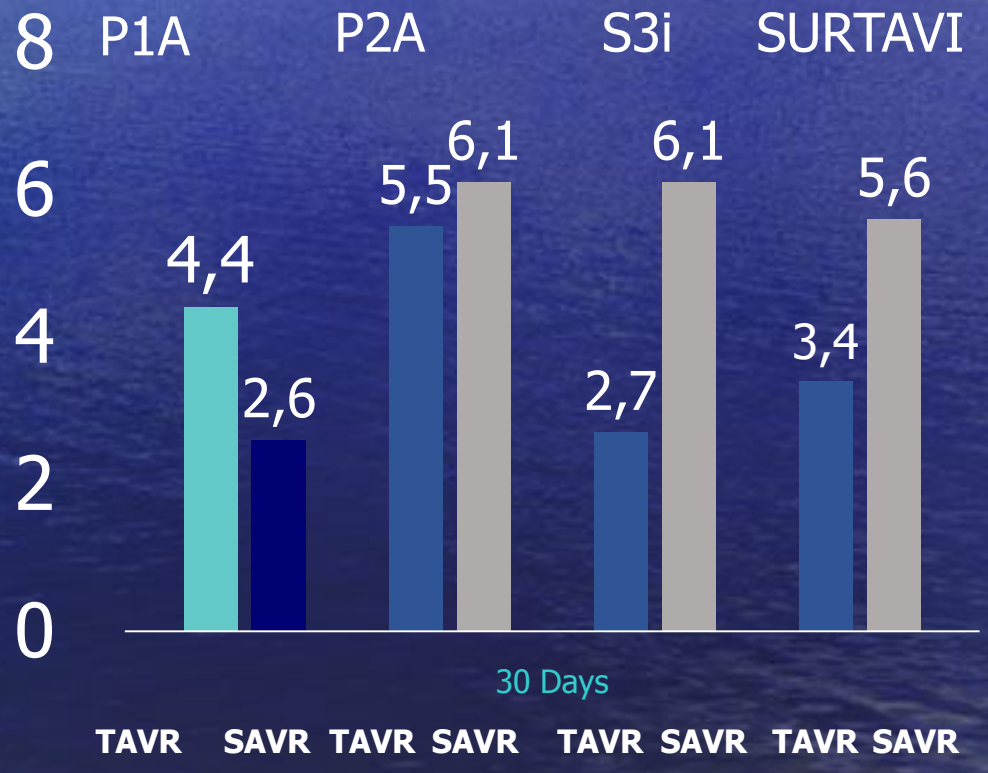


Major Stroke Rates:
Better with TAVR but Consistent over time

TVT 30 day Stroke rates



Stroke is lower with TAVR than SAVR



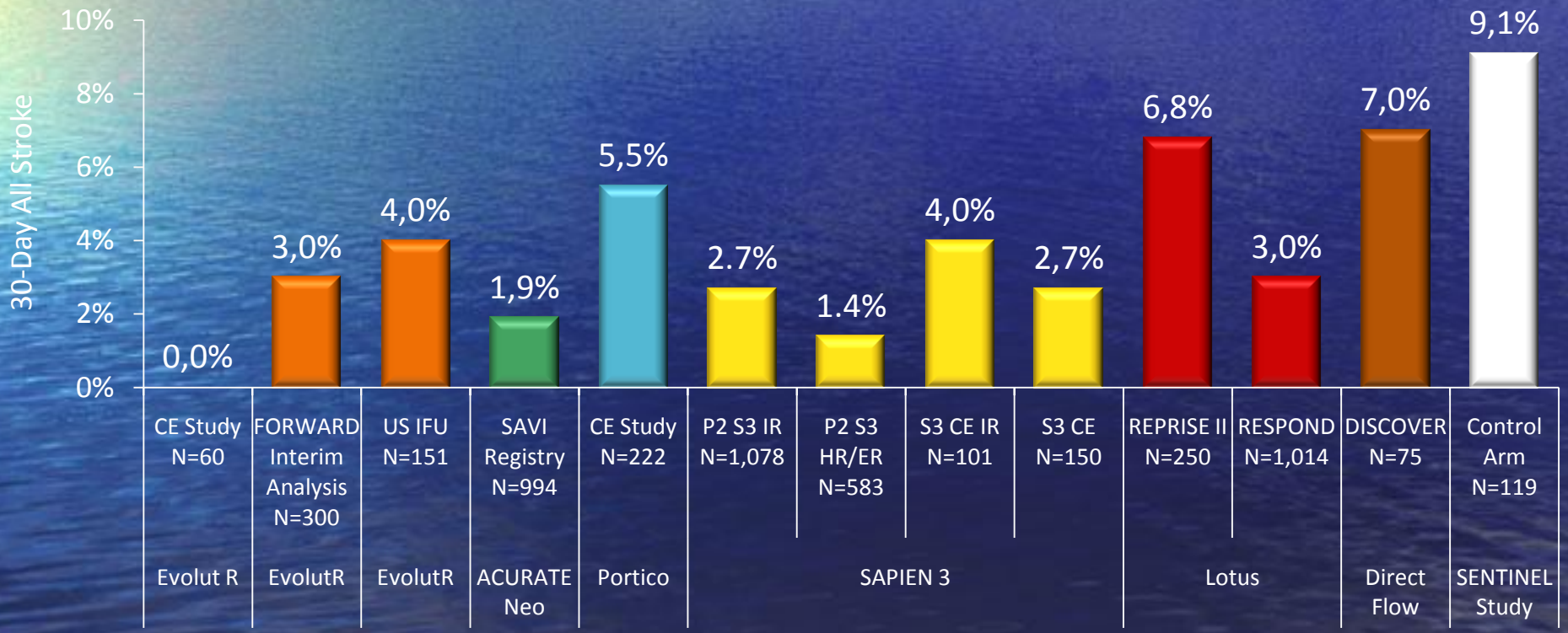
National registry-FRANCE 2

- N 3191 pts undergoing TAVI
- 3.98% reported CVE
  - 55% major strokes
  - 14.5% minor strokes
  - 30.5 % TIA
- Predictors: advanced age, multiple valves

Tchetche et al. J Am Coll Cardiol Intv 2014;7: epub

ALL Stroke Frequency with Contemporary TAVR Devices

Weighted average (n=4,795 pts) = ~3.5%

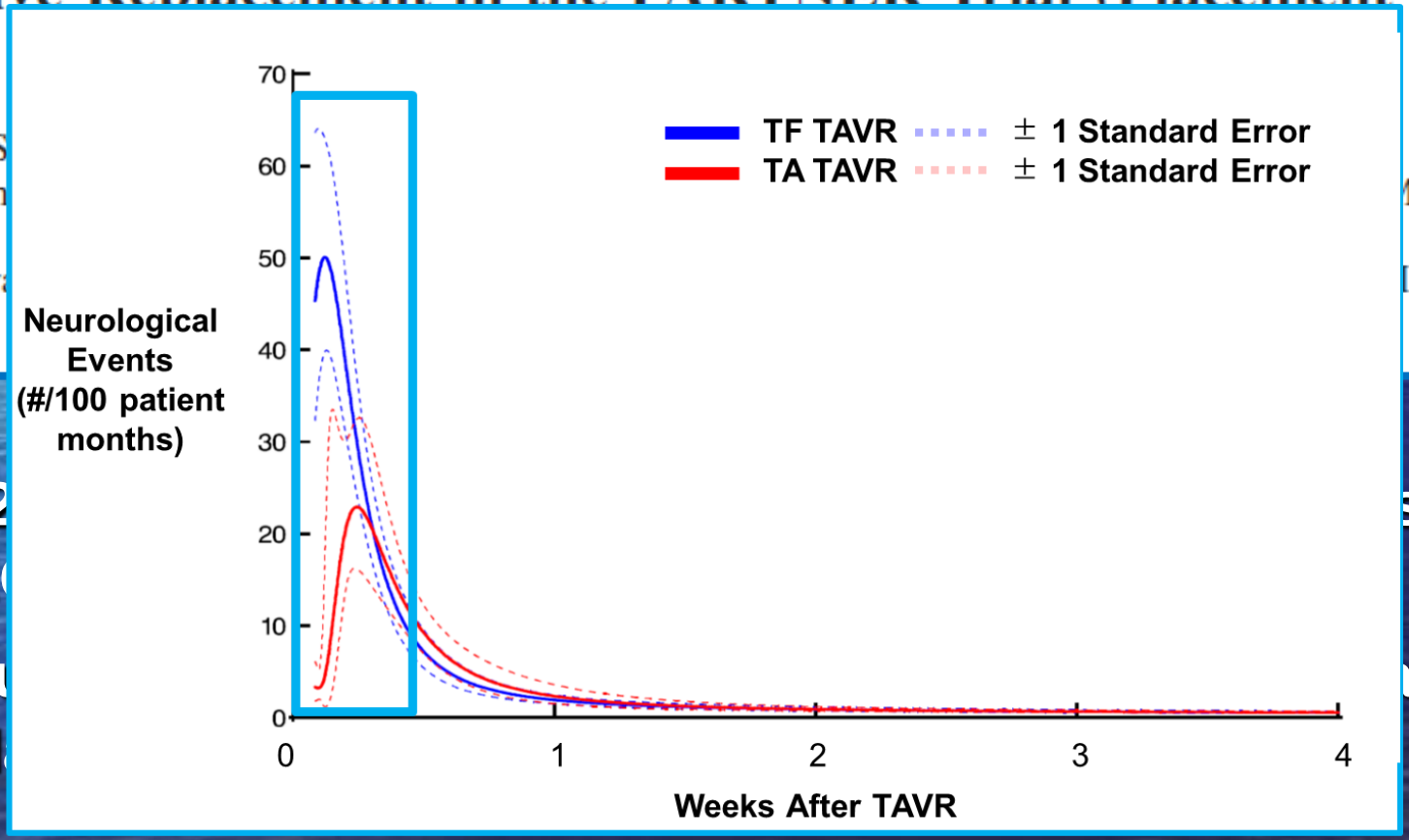


Timing of Strokes after TAVI

Insights Into Timing, Risk Factors, and Outcomes of Stroke and Transient Ischemic Attack After Transcatheter Aortic Valve Replacement in the PARTNER Trial (Placement of

S
Mich ID;

Jeev ID;



- 262 sk); CE
- Acu t 2 d

Kapadia S, et al. Circ Cardiovasc Interv 2016

FRANCE 2: Timing of Stroke

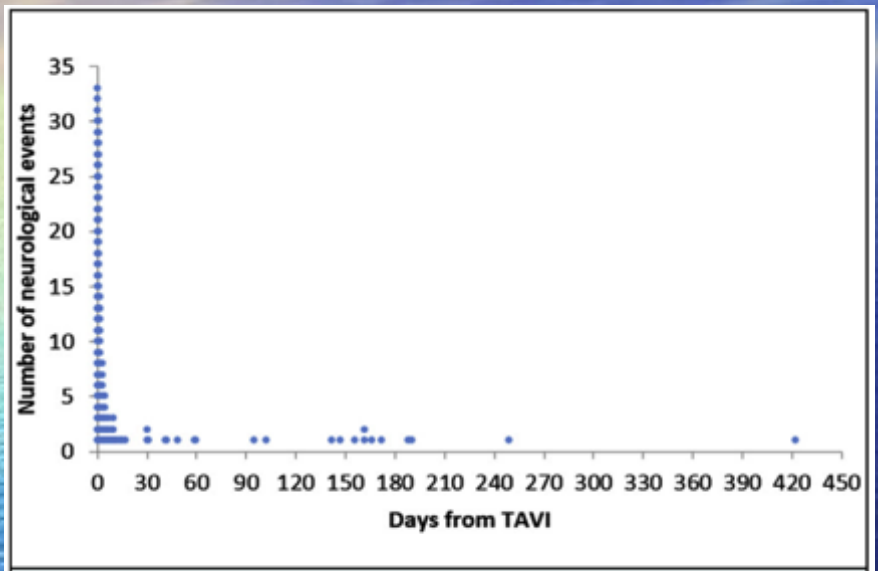


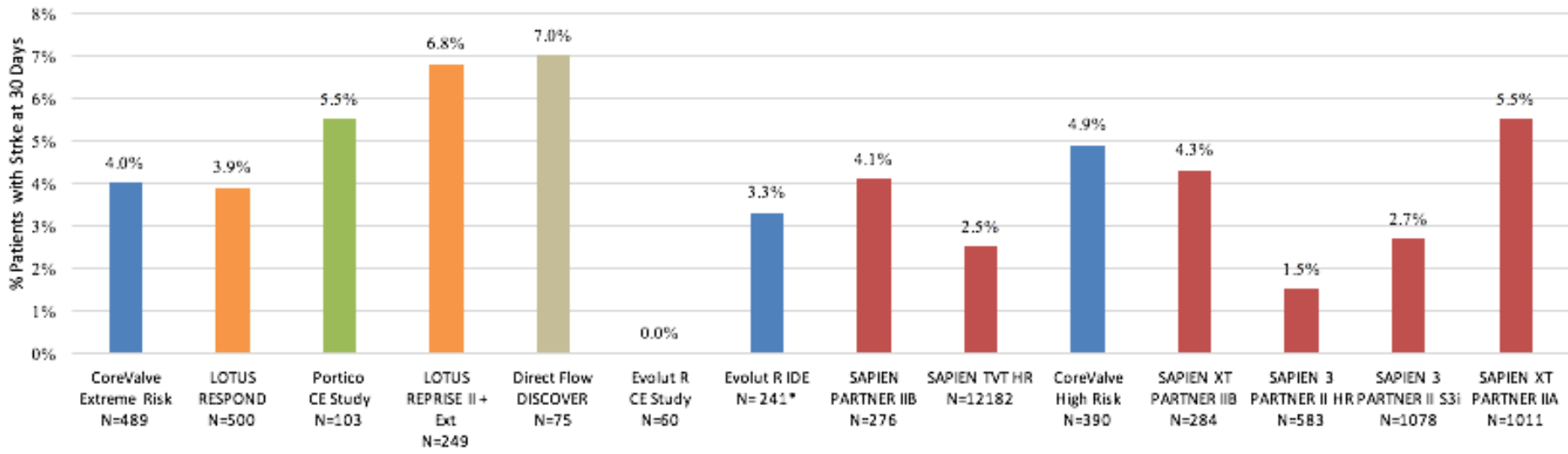
FIGURE 1 Timing of Cerebrovascular Events

50% periprocedural
Majority of major strokes on day 1

Time From Date of Valve Placement (in Calendar Days)	No.	Mean	SD	Median	Range
Overall	131	22.9	59.5	2	0–422
Major stroke	72	21.3	52.8	1	0–249
Minor stroke	19	28.2	96.3	2	0–422
Transient ischemic attack	40	23.1	48.8	2	0–188

Tchetche et al. J Am Coll Cardiol Intv 2014;7: epub

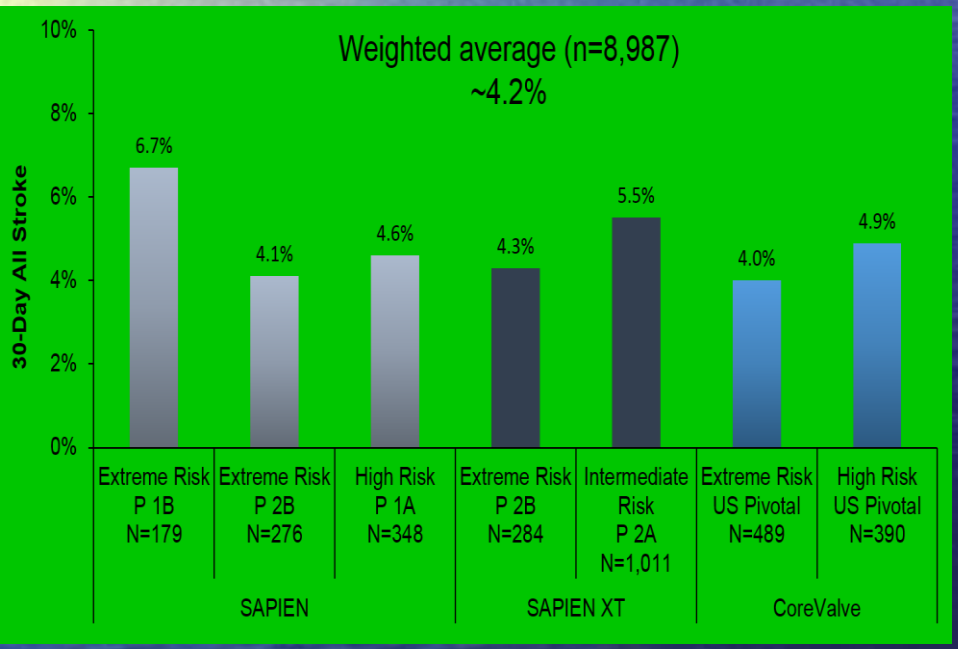
2nd generation devices and in intermediate risk patients-Stroke Remains Issue



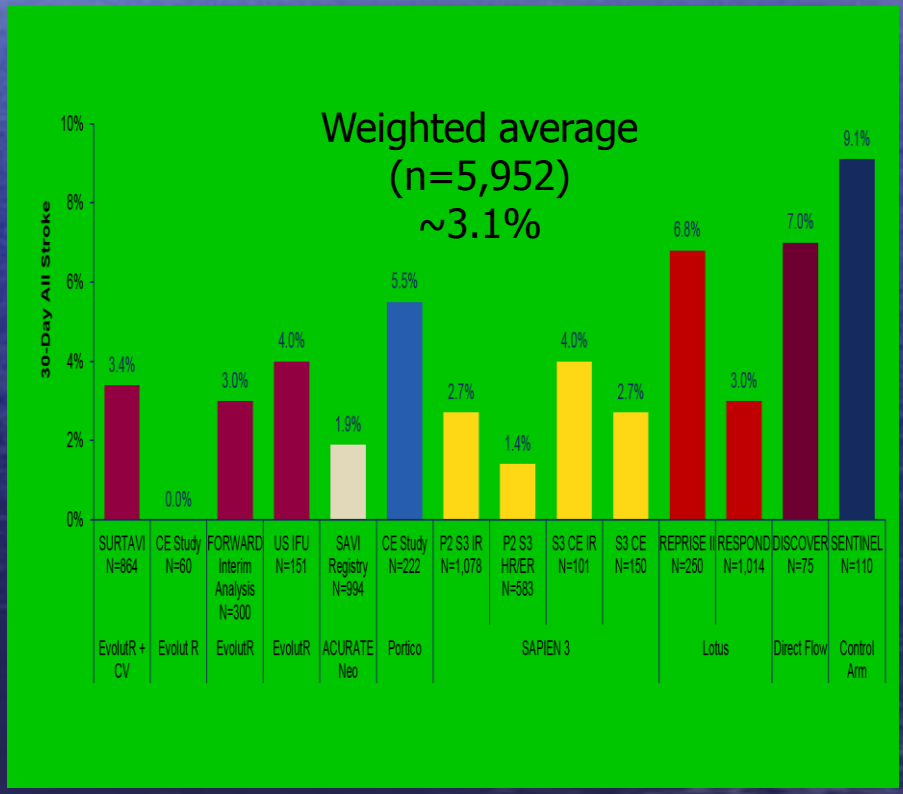
Meredith, et al., presented at PCR London Valves 2014; Adams, et al., *N Engl J Med* 2014; 370: 1790-8; Leon, et. al. presented at ACC 2013; Lefevre et al., *J Am Coll Cardiol* 2016; 1:; Popma, et al., *J Am Coll Cardiol* 2014; 63: 1972-81; Linke, et. al. presented at London Valves 2015; Van Mieghem, et al., presented at EuroPCR 2015; Kodali, et al., presented at ACC 2015; Holmes, et al., *JAMA* 2015; 313: 1019-28; Meredith, et al., presented at ACC 2015, ' Williams, et. al. presented at ACC 2016; Thourani, et al, presented at ACC 2016

Major Stroke Rates in Randomized TAVR Trials

1st Generation Devices



Current Generation Devices



[1]Leon, et al., *N Engl J Med* 2010;363:1597-1607; [2]Webb, et al., *J Am Coll Cardiol Intv* 2015;8:1797-806; [3]Smith, et al., *N Engl J Med* 2011;364:2187-98; [4]Leon, et al., *N Engl J Med* 2016;374:1609-20; [5]Popma, et al., *J Am Coll Cardiol* 2014;63:1972-81; [6]Adams, et al., *N Engl J Med* 2014;370:1790-8;;

[1]Manoharan, et al., *J Am Coll Cardiol Intv* 2015; 8: 1359-67; [2]Moellman, et al., presented at PCR London Valves 2015; [3]Linke, et al., presented at PCR London Valves 2015; [4]Kodali, et al., *Eur Heart J* 2016; doi:10.1093/eurheartj/ehw112; [5]Vahanian, et al., presented at EuroPCR 2015; [6]Webb, et. al. *J Am Coll Cardiol Intv* 2015; 8: 1797-806; [7]DeMarco, et al, presented at TCT 2015; [8]Meredith, et al., presented at PCR London Valves 2015; [10]Falk, et al., presented at EuroPCR 2016; [11]Kodali, presented at TCT 2016; Reardon, M Published in NEJM March 2017

Stroke Rates with Second Generation TAVR Valves

B Event rate for 30-day major stroke

Study name	Event rate	Lower limit	Upper limit	Total
DFM (DISCOVER)	0.040	0.013	0.117	3/75
Portico (CE mark)	0.029	0.009	0.086	3/103
Sadra Lotus (REPRISE II)	0.017	0.004	0.065	2/119
ACURATE TF (CE mark)	0.022	0.006	0.085	2/89
ACURATE TA (SAVI)	0.028	0.013	0.058	7/250
JenaValve (JUPITER)	0.011	0.003	0.043	2/180
JenaValve (CE mark)	0.030	0.008	0.113	2/66
Engager (CE trial)	0.008	0.001	0.055	1/125
DFM (FIM)	0.050	0.007	0.282	1/20
Portico (FIM)	0.023	0.001	0.277	0/21
Sadra Lotus (REPRISE I)	0.091	0.013	0.439	1/11
SAPIEN 3 (FIM)	0.019	0.001	0.236	0/26
CENTERA (FIM)	0.031	0.002	0.350	0/15
ACURATE TA (FIM)	0.033	0.011	0.098	3/90
JenaValve (FIM)	0.038	0.002	0.403	0/12
DFM (SALUS)	0.016	0.001	0.211	0/30
DFM registry (Naber)	0.019	0.005	0.073	2/105
DFM (DISCOVER registry)	0.007	0.001	0.045	1/153
SAPIEN 3 (Webb TF)	0.005	0.000	0.077	0/96
SAPIEN 3 (Webb TA)	0.009	0.001	0.129	0/54
Overall event rate	0.024	0.017	0.034	
Fixed effects	0.024	0.017	0.034	

Event rate and 95% CI: 0.00, 0.25, 0.50

Compare with: PARTNER IA=3.8%, PARTNER IB=5.0%, PARTNER IIB=3.1%, CoreValve High Risk=3.9%, CoreValve Extreme Risk=2.3%.
UK TAVI=4.1%*, FRANCE 2=2.3%, European Sentinel Registry=1.8%.

Meta-analysis of 2nd generation TAVI valves (I^2=36.471, tau^2=0.00)

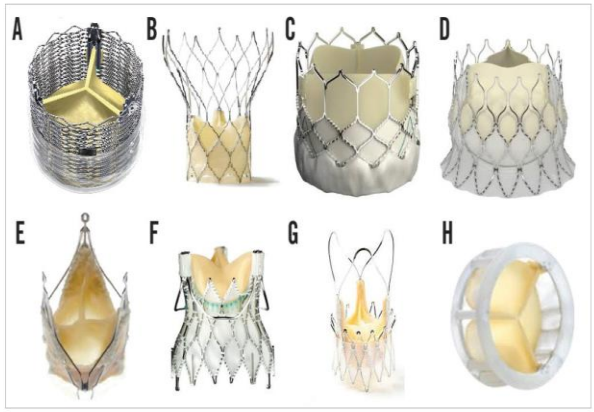


Figure 7. *Second-generation transcatheter aortic valves. A) Sadra™ Lotus Medical valve (Boston Scientific SciMed Inc, Maple Grove, MN, USA); B) Portico® valve (St. Jude Medical); C) Edwards SAPIEN 3 valve (Edwards Lifesciences); D) Edwards CENTERA valve (Edwards Lifesciences); E) JenaValve (JenaValve Technology); F) Engager™ valve (Medtronic Inc.); G) Symetis ACURATE™ valve (Symetis SA); H) Direct Flow Medical® valve (Direct Flow Medical).*

- Meta-analysis of ~20 non-randomized, mostly FIM, valve-company sponsored studies

2.4% major stroke at 30-days

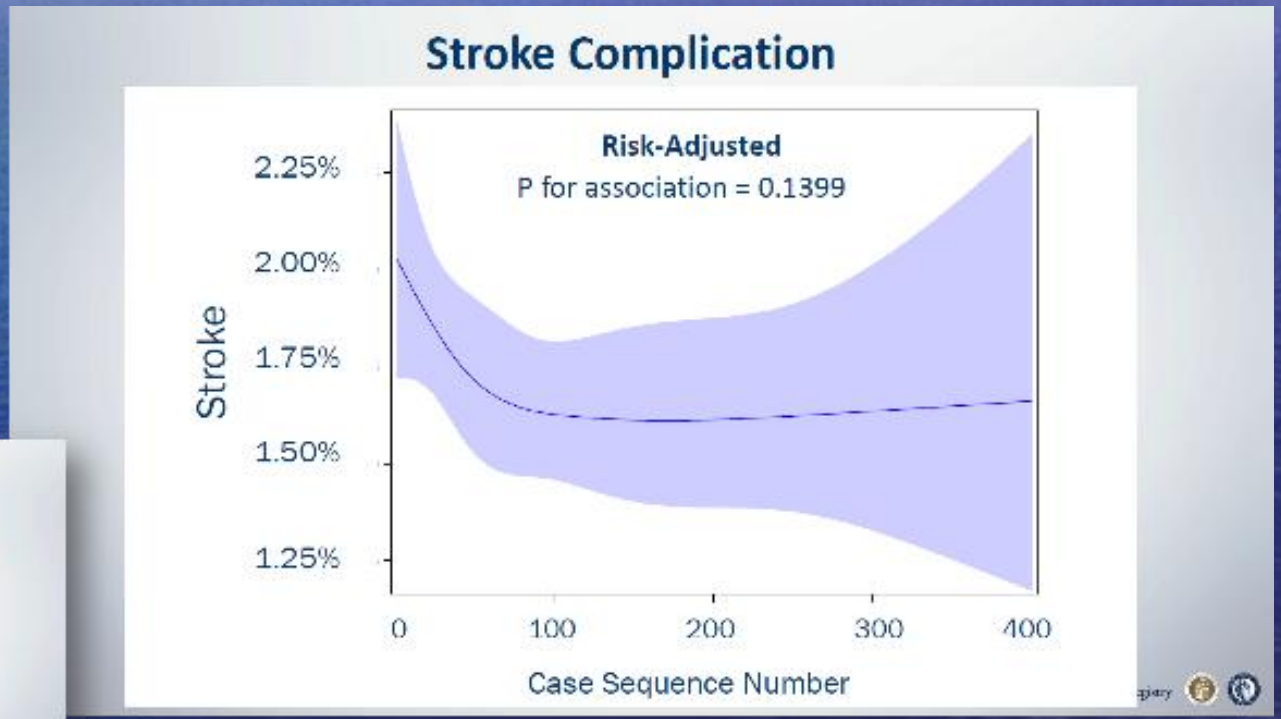
Athappan, et al. A systematic review on the safety of second-generation transcatheter aortic valves. *EuroIntervention* 2016;

Stroke risk seem to be independent of operator experience

>53000 TAVI patients from >350 US centres

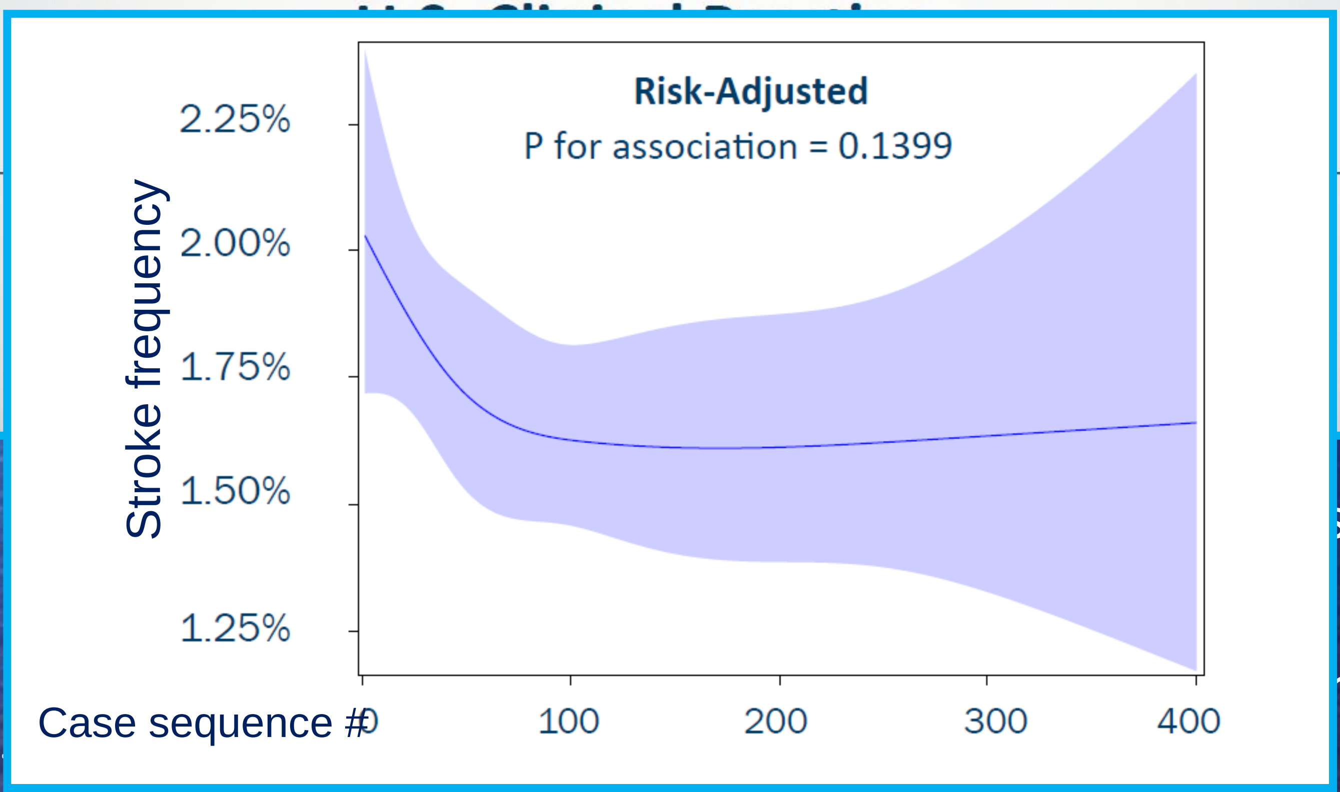
No decline in rates with increasing experience

'Self-reported' rates almost certainly an underestimate



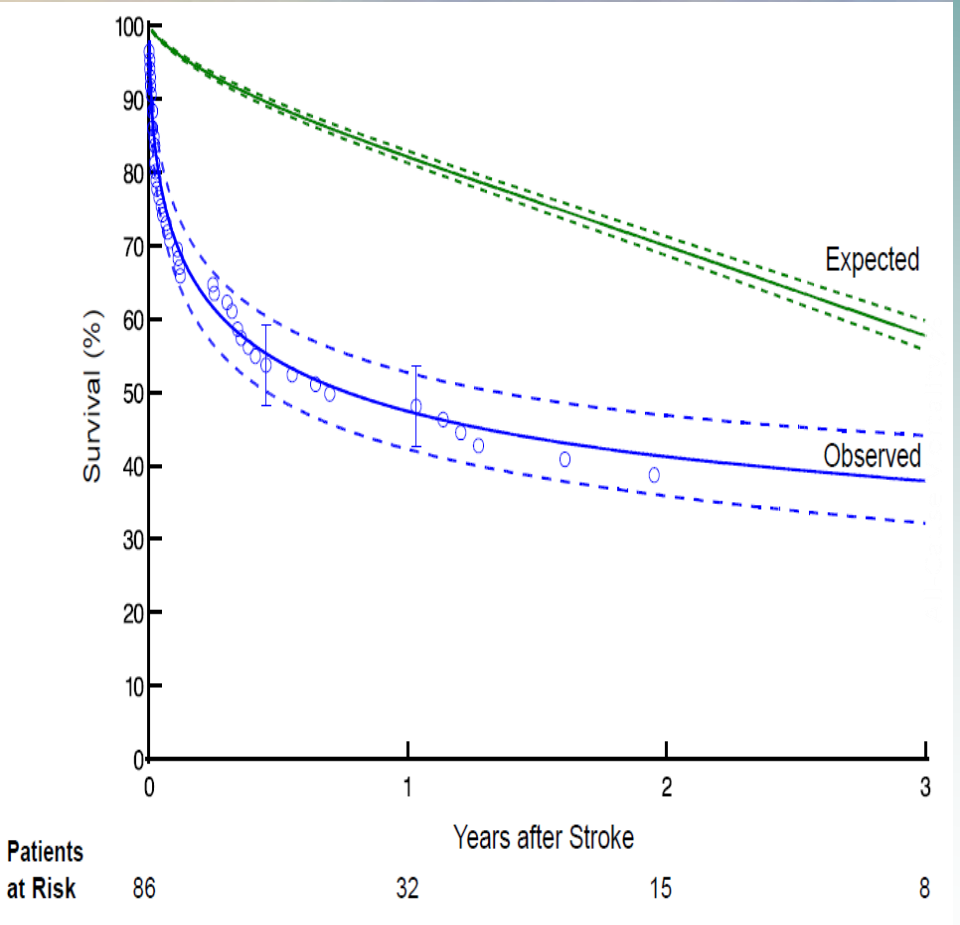
TVT Registry - TAVR in the U.S.

Relationship Between Procedure Volume and Outcome for Transcatheter Aortic Valve Replacement in



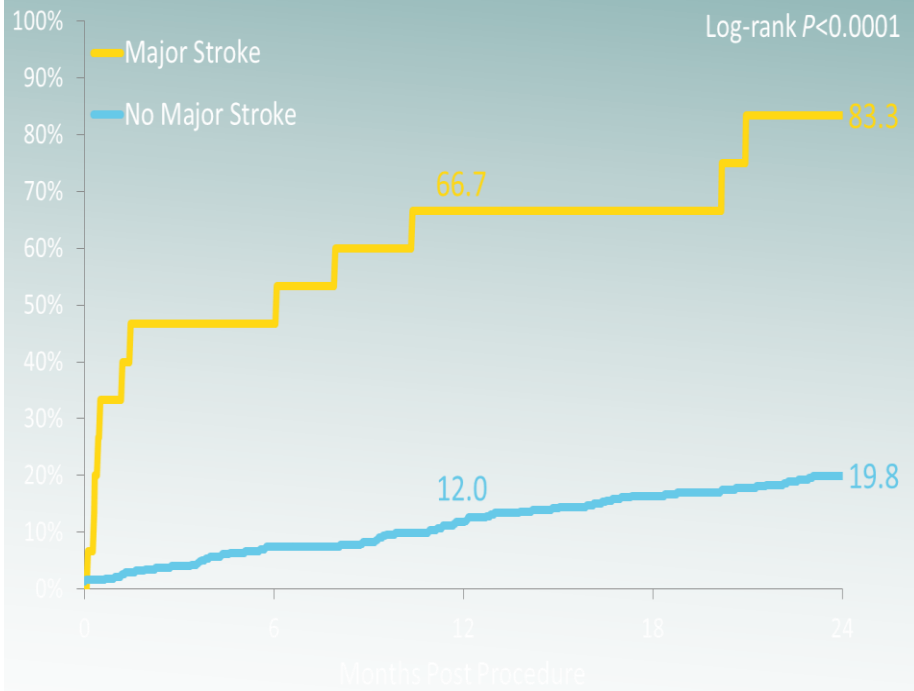
Major Stroke Increases Mortality 3-9 Fold

Partner Trials



Kapadia et al, Circ Int 2016

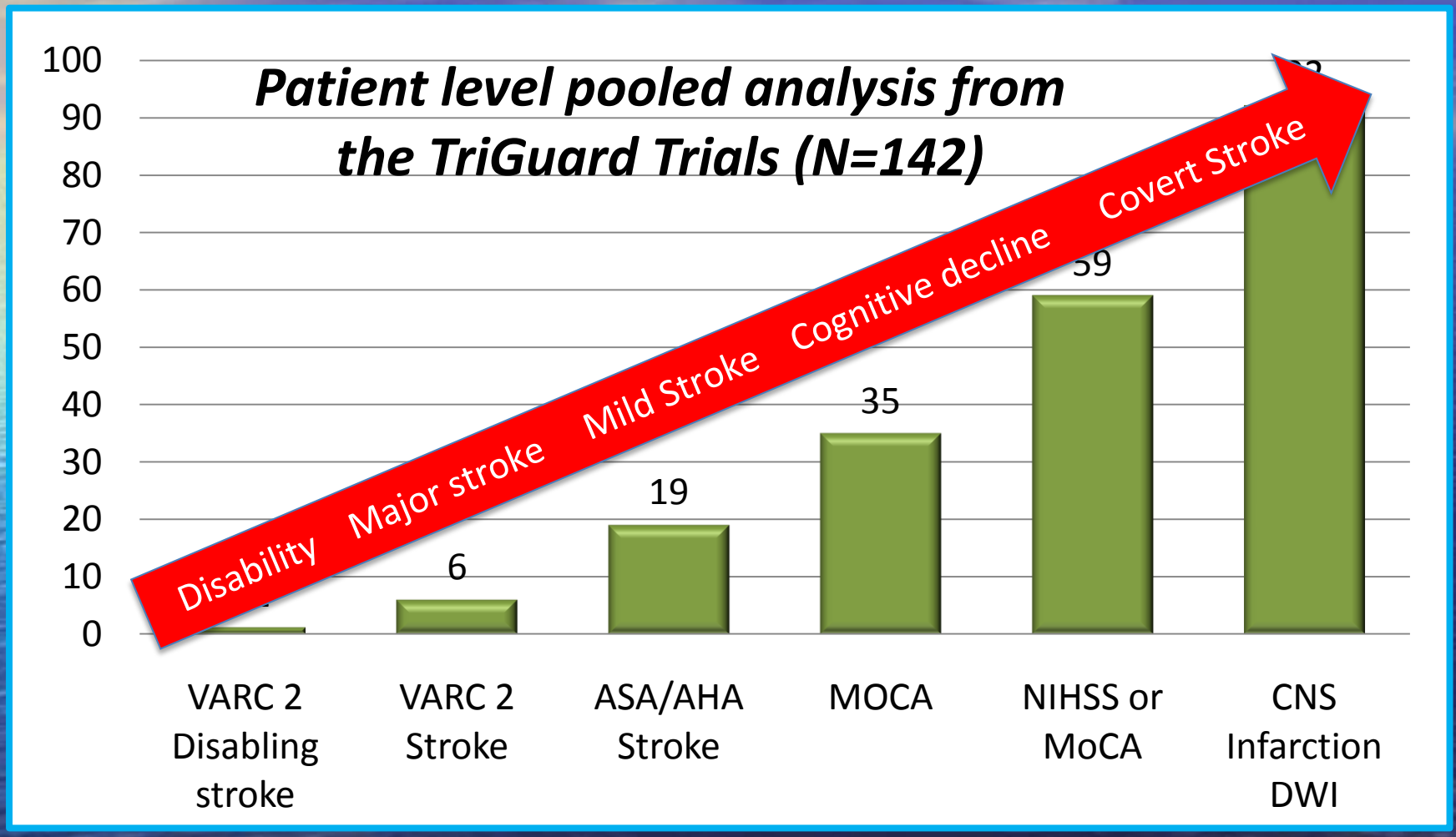
CoreValve High Risk Trial



No. at Risk

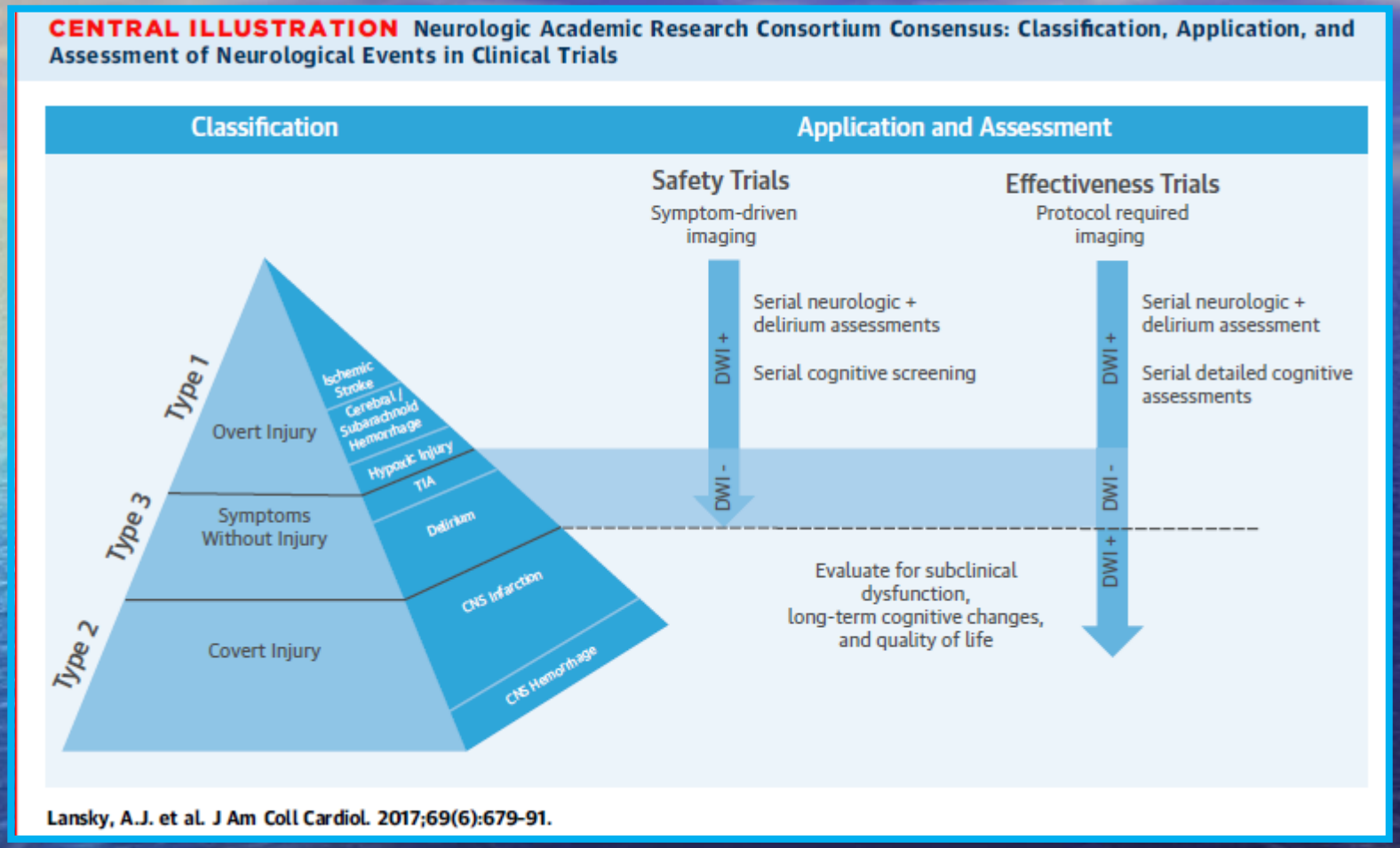
Major Stroke	15	10	5	2
No Major Stroke	37	368	329	217
	6			

The Dilemma: What is Cerebral Injury?



Lansky A, EuroPCR 2016

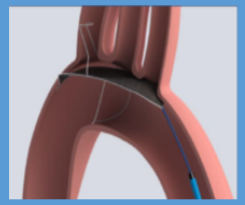
NeuroARC Consensus Report



Classification, Application, and Assessment of Neurological Events

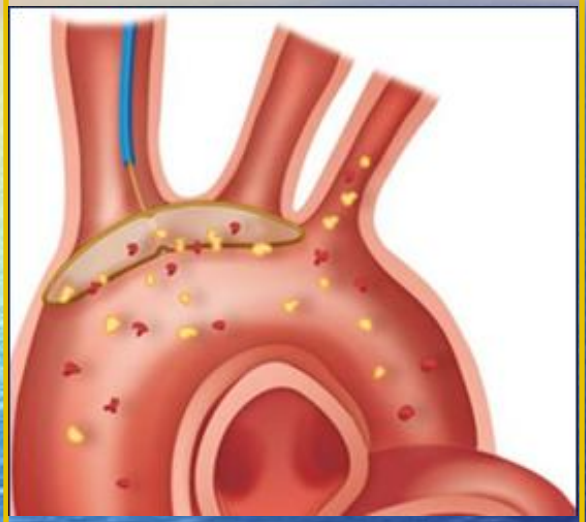
Lansky AJ et al. JACC 2017

Can we improve outcomes with embolic protection devices ?

Company and Product	Claret Medical Sentinel 	Keystone TriGuard 	Edwards Embrella 	ICS Emblok 	Transverse Point-Guard 
EU Status	CE Mark 97% market share	CE Mark 3% market share	CE Mark <3% market share	FIM first clinical case March 15, 2017	Pre-clinical/prototype
US Status	IDE study completed Positive FDA Panel Feb 23, 2017	IDE trial underway	No IDE yet	No IDE yet	No IDE yet
Access	6 Fr Right Radial	9Fr TF	Right Radial	12Fr TF sheath	TF
Debris	Captures and removes	Deflects downstream	Deflects downstream	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 ascending aorta Devices must pass over and back across	Sits in aortic arch. Devices must pass over and back across

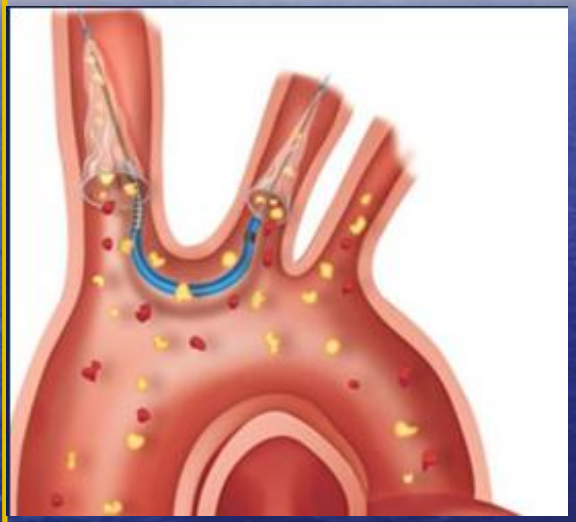
Current Devices

Embrella Embolic Deflector System (Edwards Lifesciences)



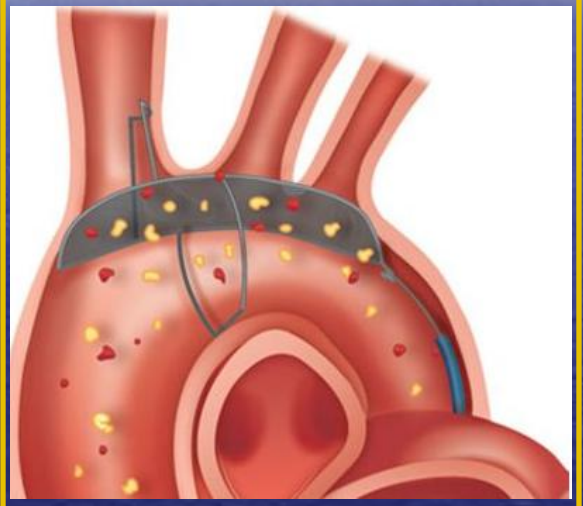
- ✓ Pore Size: 100 µm
- ✓ Delivery Sheath: 6F
- ✓ Access: Brachial
- ✓ Coverage: Brachiocephalic, left common carotid

Sentinel Cerebral Protection System (Claret Medical)



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

TriGuard Embolic Deflection Device (Keystone Heart)



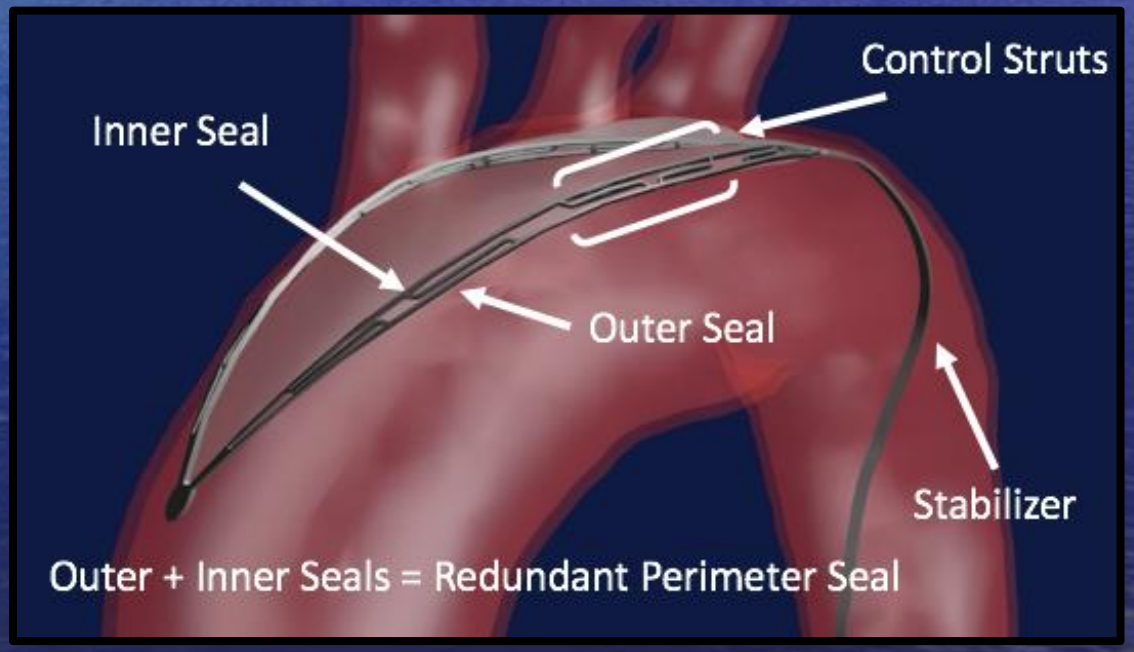
- ✓ Pore Size: 130 µm
- ✓ Delivery Sheath: 9F
- ✓ Access: Transfemoral
- ✓ Coverage: Brachiocephalic, left common carotid, left subclavian

Newer Devices…

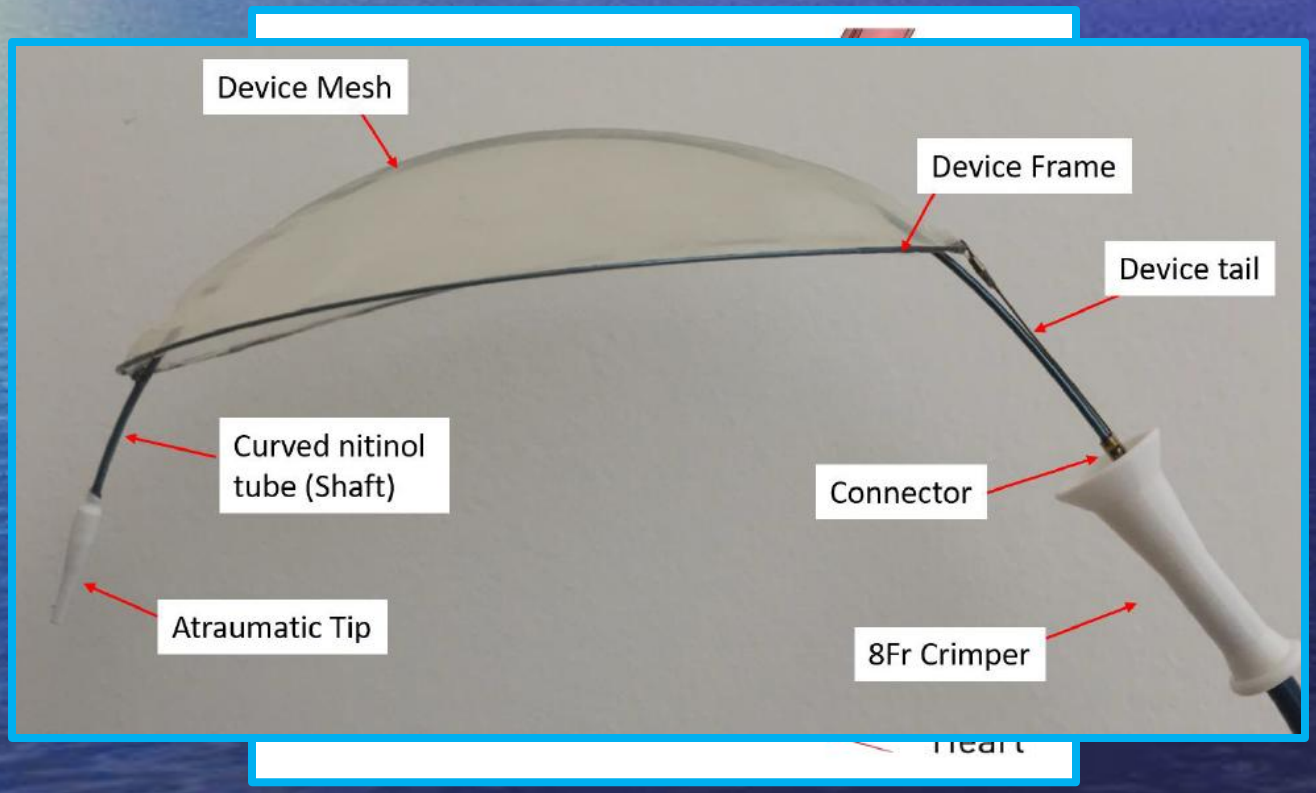
Transverse Medical POINTGUARD CEP Device

Maximum Filter Coverage

Balanced Filtration and Deflection

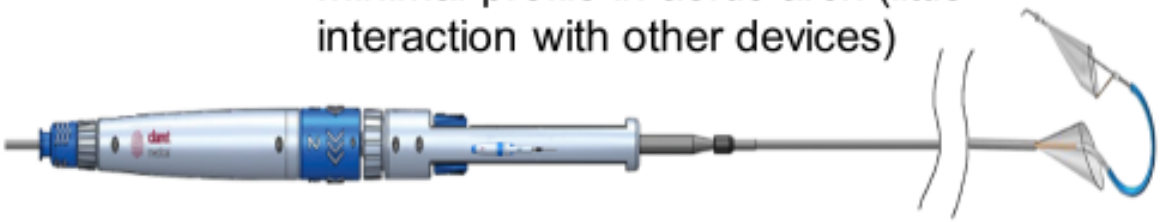


Keystone Heart NEW TriGUARD 3 CEP Device



CLARET

- Two independent filters capture & remove embolic material
- Polyurethane filter, pore size = 140 µm
- Standard R trans-radial sheath access (6F)
- One size accommodates most vessel sizes (brachiocephalic 9-15 mm and left common carotid [LCC] 6.5-10 mm)
- Deflectable compound-curve catheter facilitates cannulation of LCC
- Minimal profile in aortic arch (little interaction with other devices)



Claret data

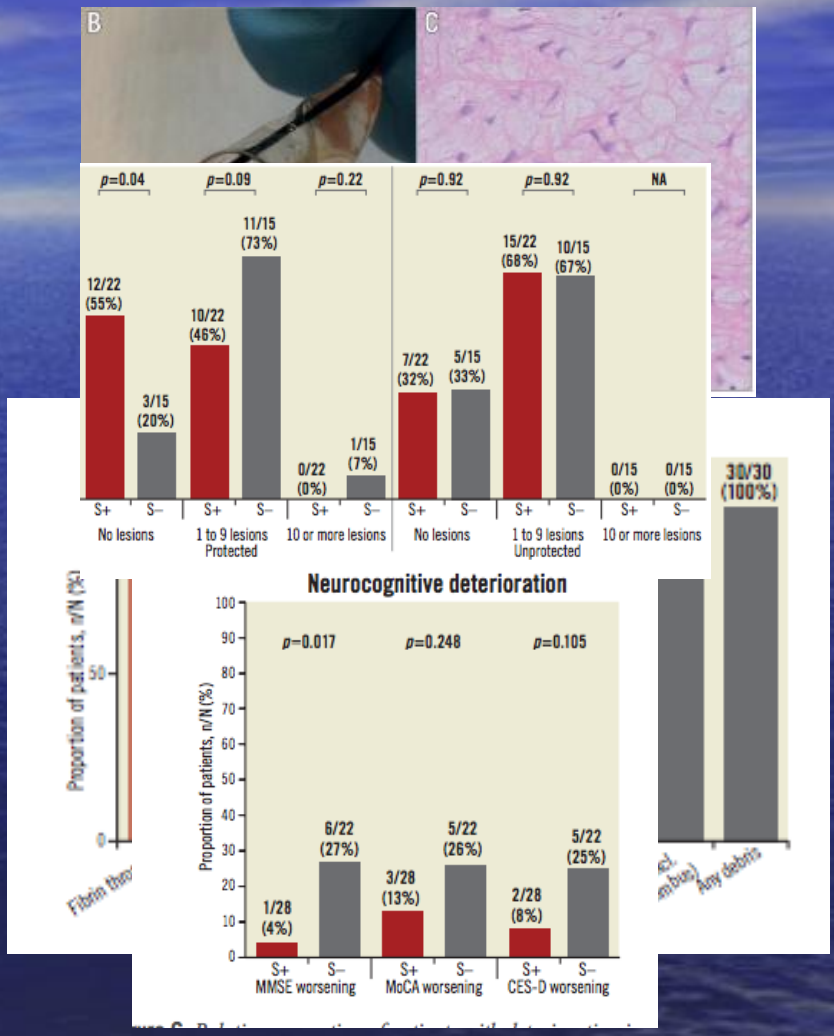
It does seem effective in capturing debris..

MISTRAL-C trial of 65 patients randomised to Claret vs no protection

Debris found in all deployed devices

But only a modest effect on number and size of MRI lesions (with ~65% MRI follow up...

Some suggestion that neurocognitive decline ameliorated



Van Mieghem et al Eurointervention 2016;12:499-507

CLEAN-TAVI

100 patient, single-centre RCT

Randomised to Claret vs no Claret

Reduction in new MRI lesion volume and number

no data on neurocognitive improvement

Neurological Outcome

intention-to-treat		cumulative	2 days (No, %)	7 days (No, %)	30 days (No, %)
Control	Any symptom	17 (34 %)	14 (28 %)	5 (10 %)	6 (12 %)
	- Ataxia	16 (32 %)	12 (24 %)	4 (8 %)	5 (10 %)
Filter	Any symptom	14 (28 %)	8 (16 %)	8 (16 %)	6 (12 %)
	- Ataxia	12 (24 %)	6 (12 %)	7 (14 %)	6 (12 %)

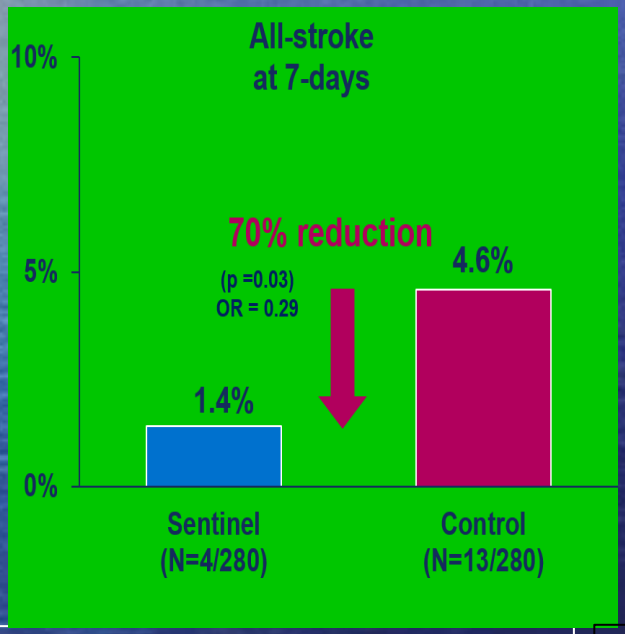
RR 1.379 (0.927 to 2.050), OR 2.042, p=0.175

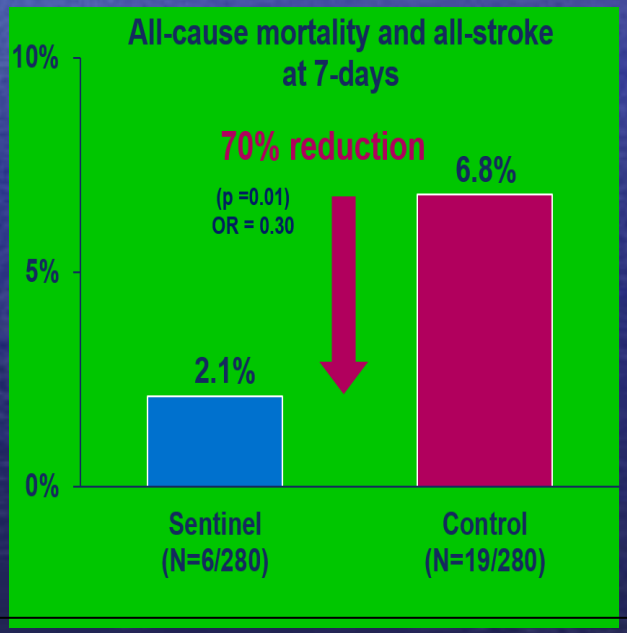
RR 1.439 (0.963 to 2.149), OR 2.316, p=0.118

Haussig et al JAMA 2016;316:592-601

Ulm Sentinel Study: Procedural Protection=Procedural Benefit

- 802 single center all-comer consecutive TAVR patients
- A propensity-matched analysis of 280 patients with Sentinel to 280 control patients





Predictor of Stroke at 7 days:

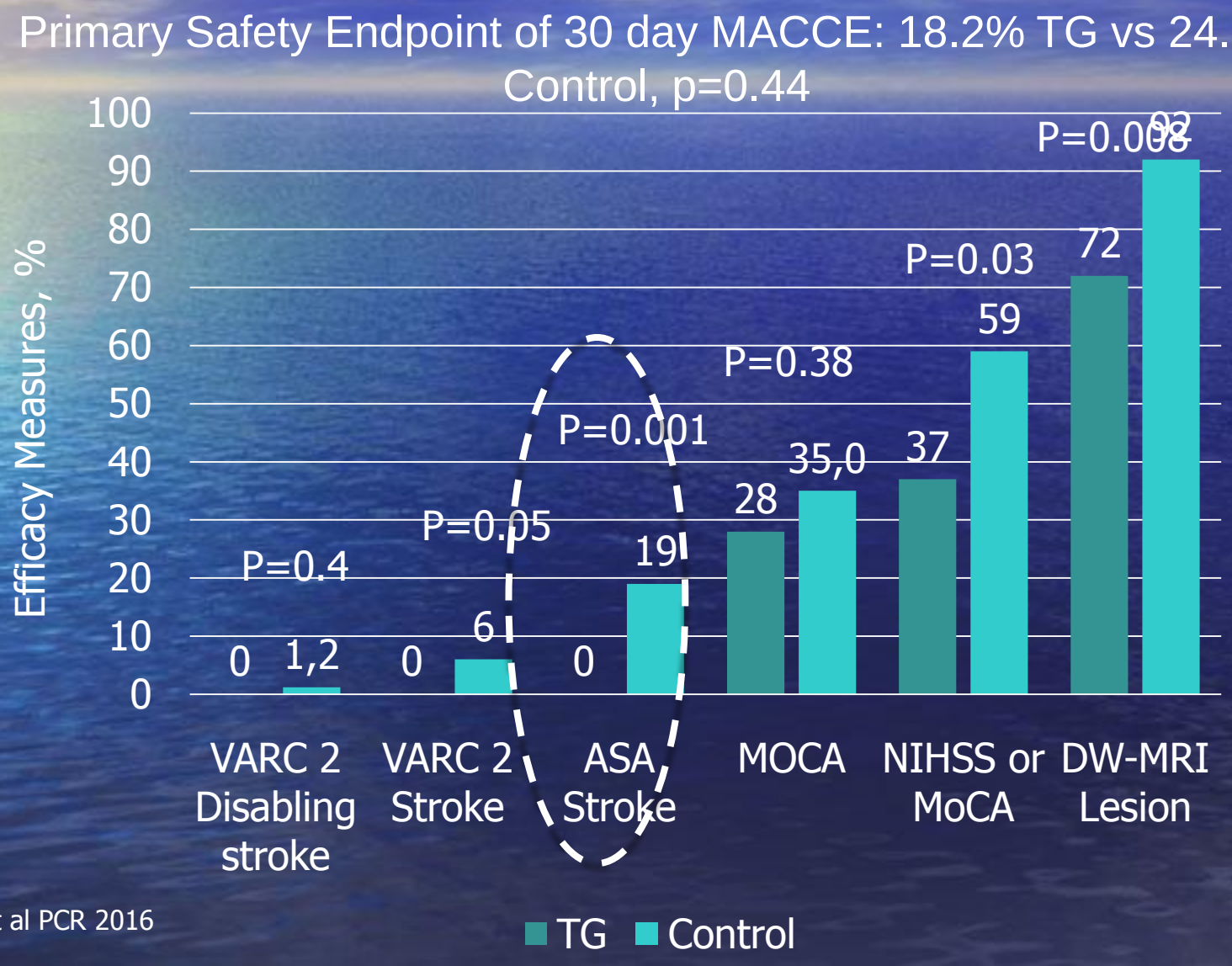
- No cerebral emboli protection (p=0.044)

Predictor of Stroke and Death at 7 deaths:

- No cerebral emboli protection (p=0.028)
- STS score (<8 vs. ≥8) (p=0.021)

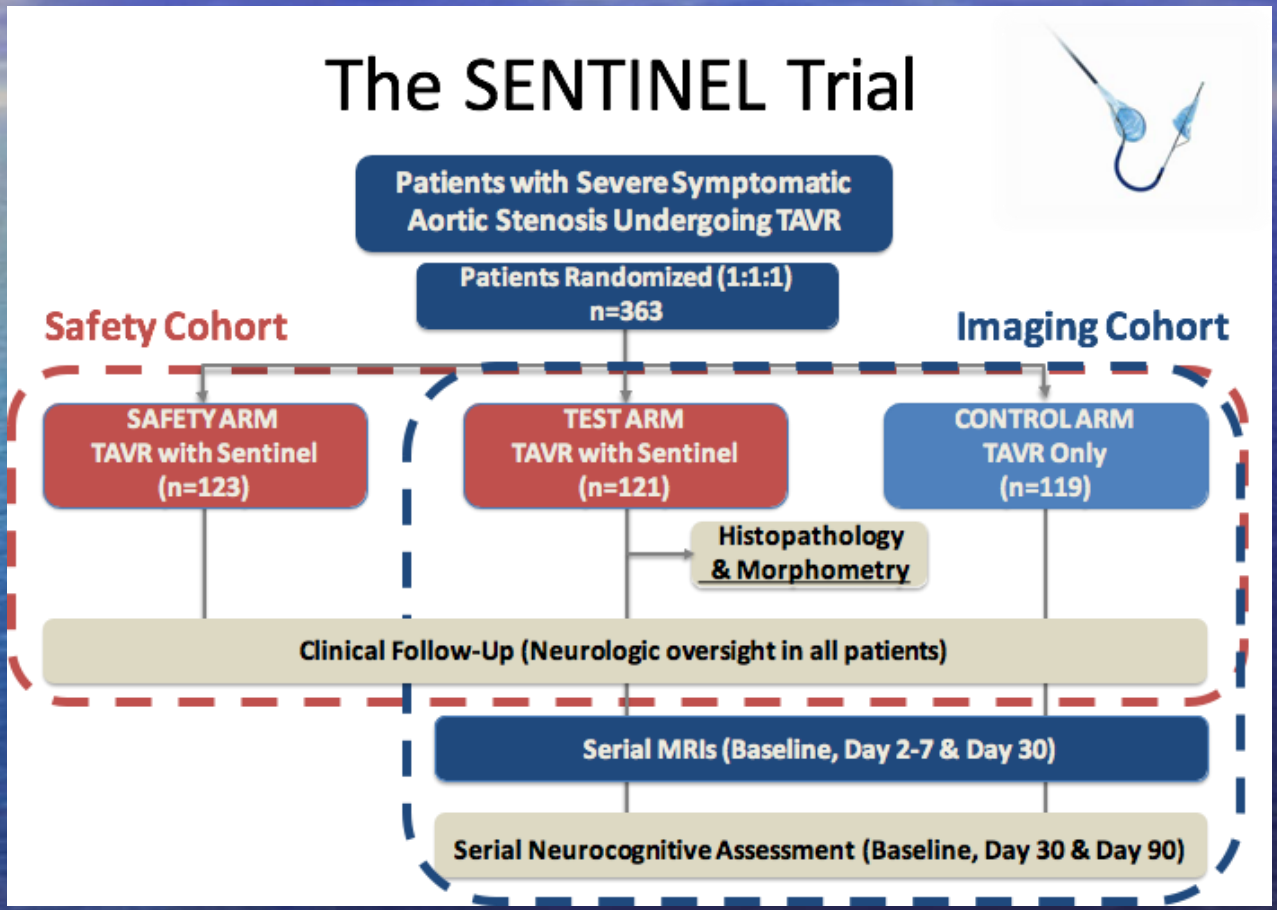
Wörhle J, Seeger J, et al. DGK Mannheim 2017; CSI-Ulm-TAVR Study clinicaltrials.gov NCT02162069

TriGuard HDH Pooled Analysis



Lansky et al PCR 2016

Claret Randomised data



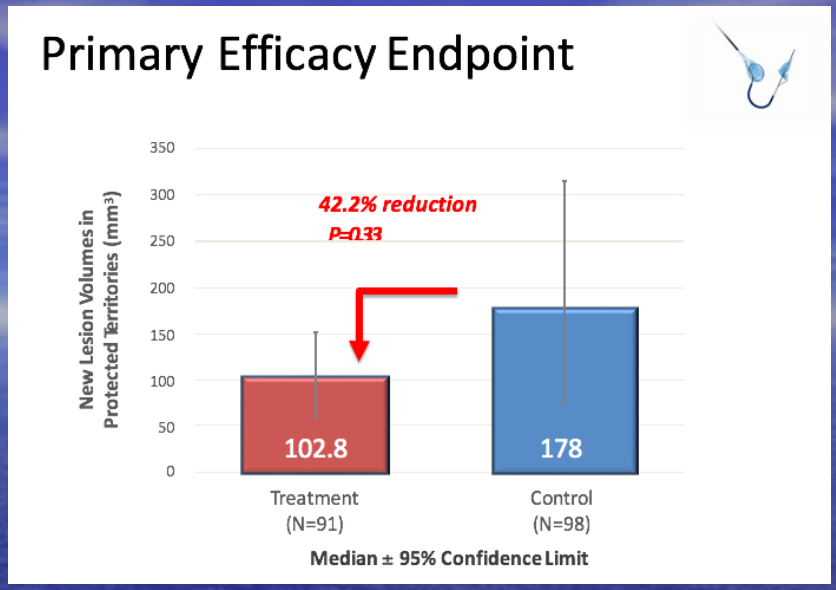
Kodali TCT 2016

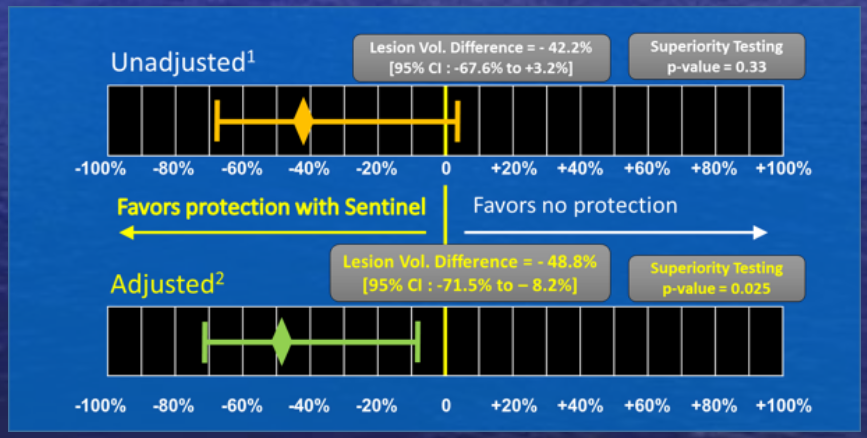
No difference in clinical stroke rates..

Despite a reduction in MRI lesion volume study failed to reach its primary end-point…

Favourable safety profile- ie no evidence of harm..

No difference in clinical stroke rates..

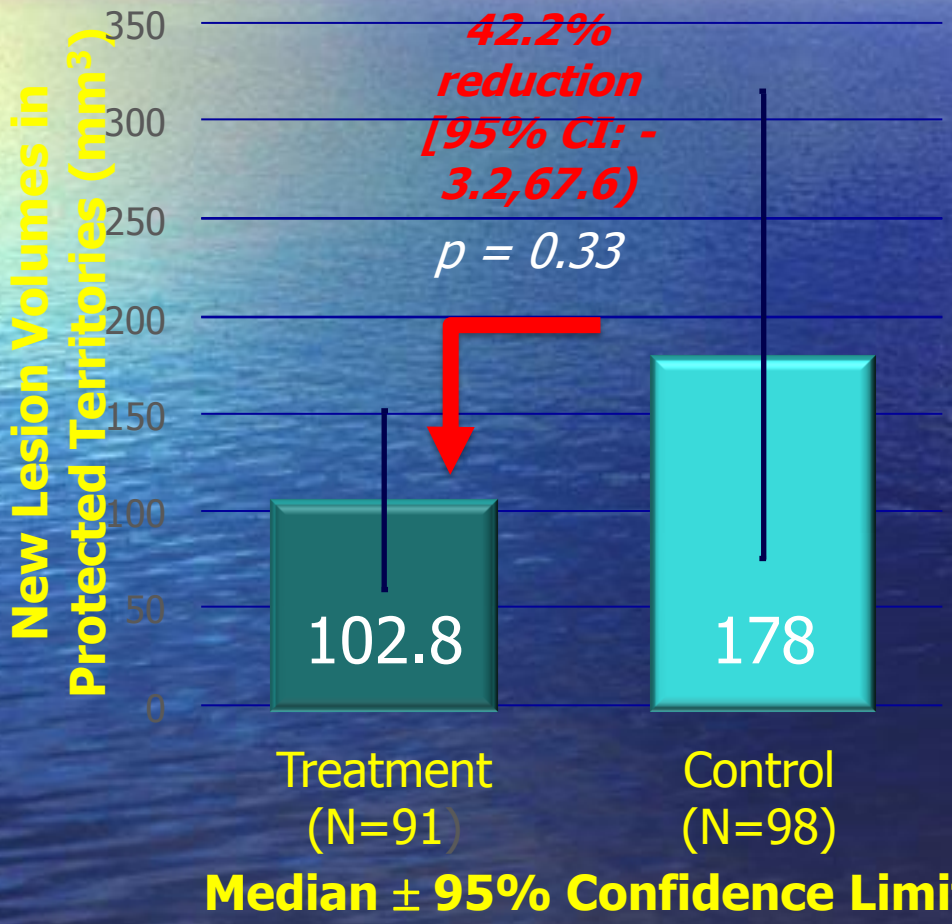




Kodali TCT 2016

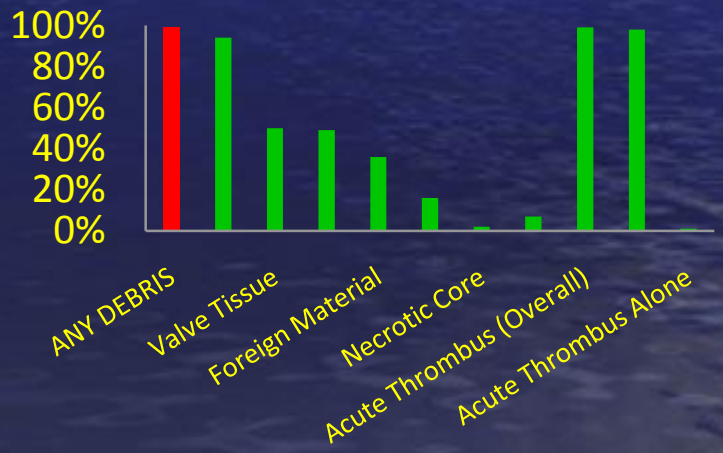
SENTINEL US IDE Trial (N=363)
Primary Efficacy Endpoint (Superiority)

Median TLV in protected territories assessed by DW-MRI at Day 2-7 post-procedure



HISTOPATHOLOGY

Debris Capture by Type

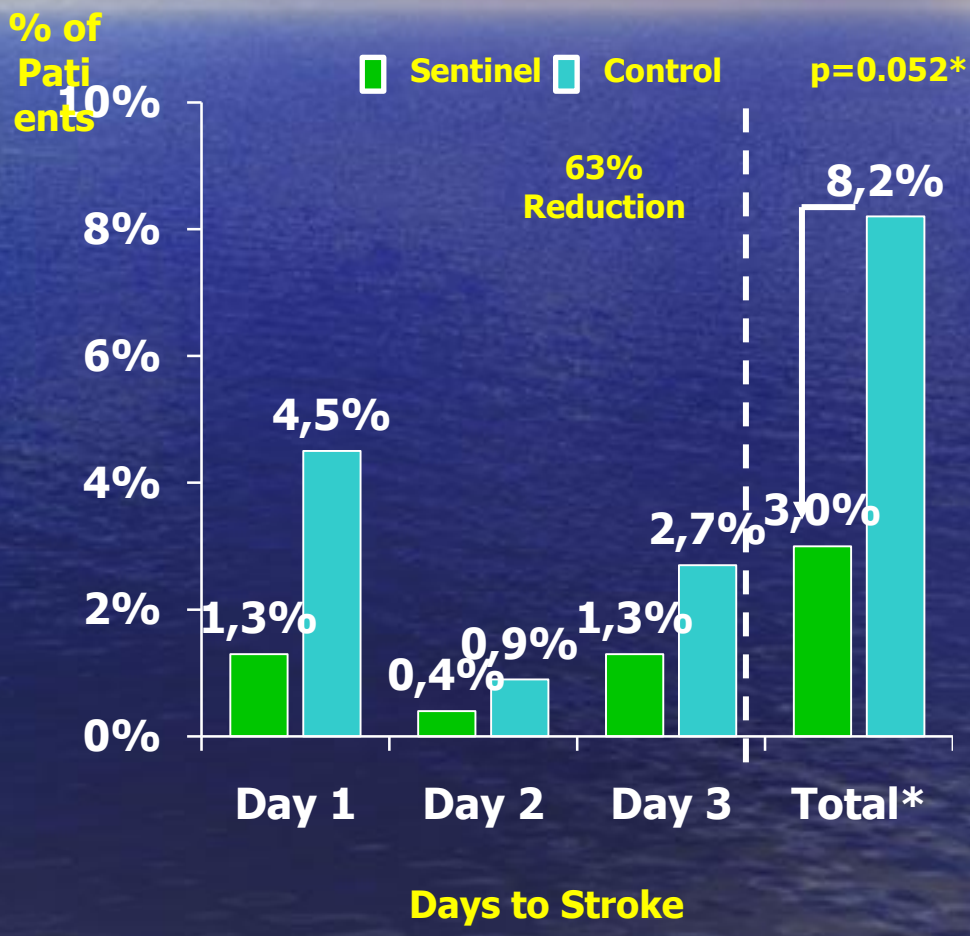


Lessons Learned : Timing of Ascertainment Sentinel Trial

30 Day Stroke Diagnosis (Analyzed ITT)

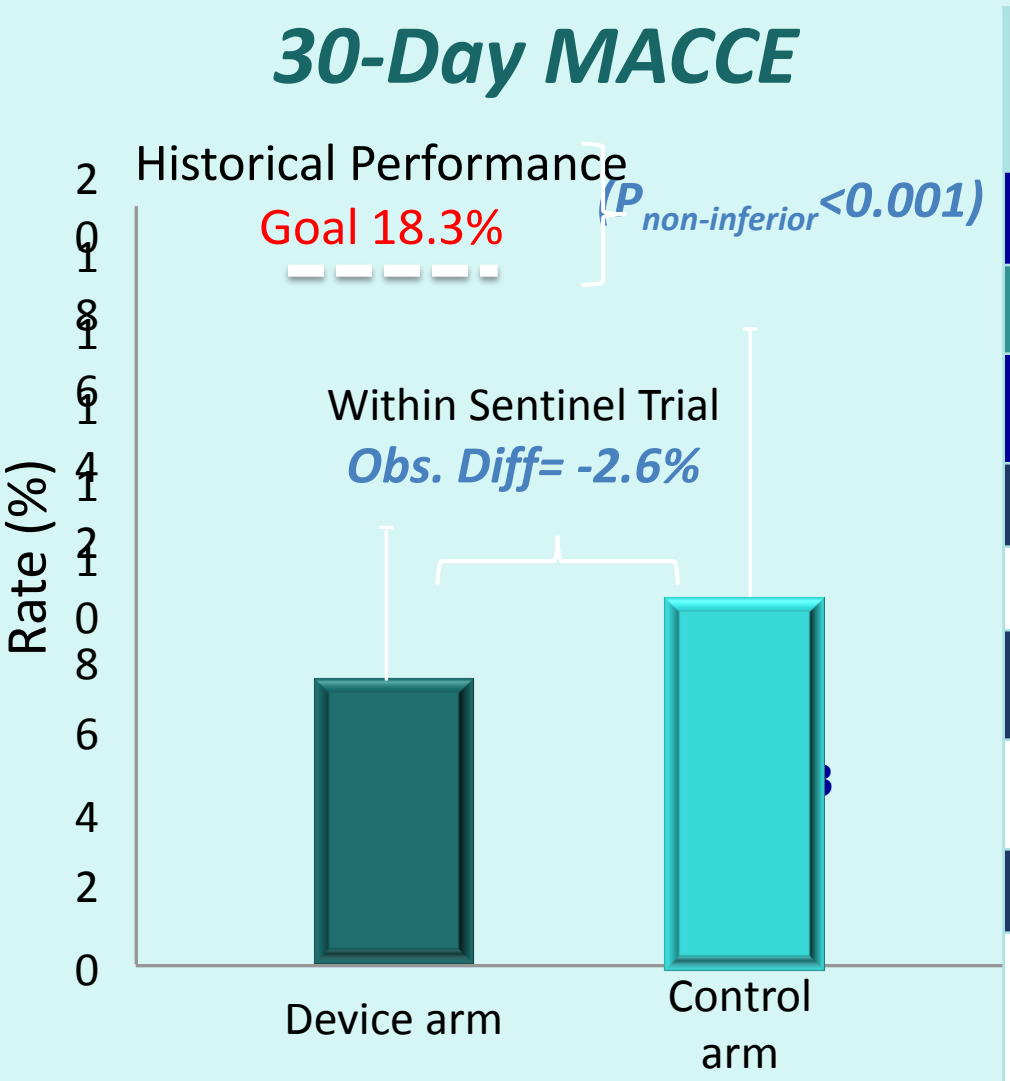
	Device Arm (n=234)	Control Arm (n=111)	p-value
30-day Clinical Outcomes			
Any MACCE†	7.3%	9.9%	0.40
Death (all-cause)	1.3%	1.8%	0.65
Stroke	5.6%	9.1%	0.25
Disabling	0.9%	0.9%	1.00
Non-disabling	4.8%	8.2%	0.22
AKI (Stage 3)	0.4%	0%	1.00
TIA	0.4%	0%	1.00
Sentinel Access Site Complications	0.4%	N/A	0.53

Stroke Diagnosis ≤72 hours (Analyzed ITT)



*Fisher Exact Test

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



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Sentinel Site Complications	0.4%	N/A	0.53

Where to use without definitive/compelling evidence?

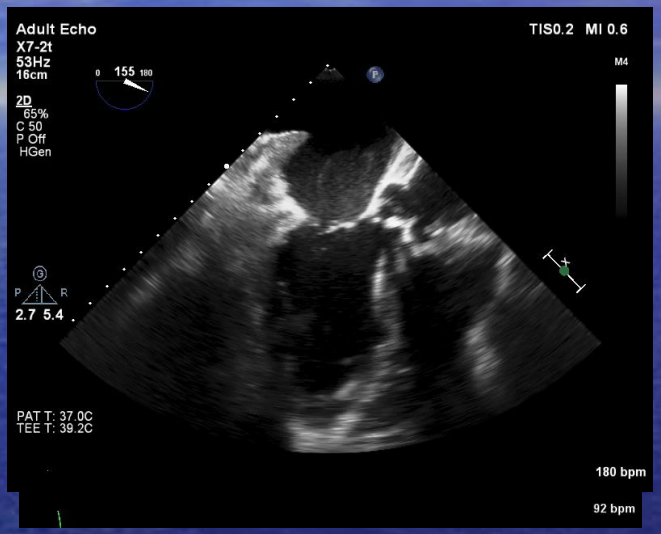
Selectively?

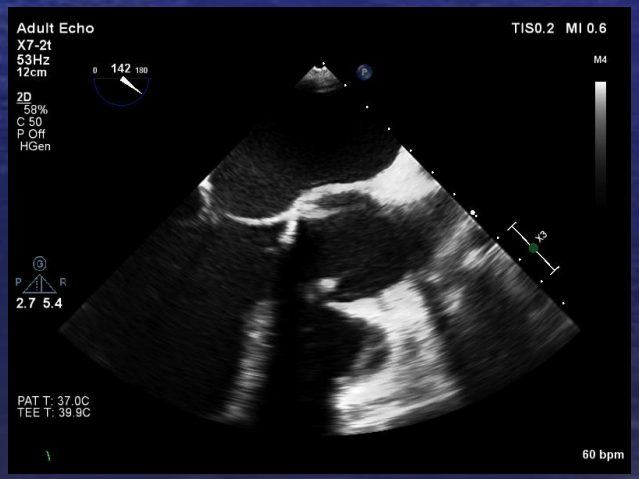
With mobile structures present on the AoV

Laminar LV thrombus in 'no option' patient

Large burden/mobile aortic atheroma..

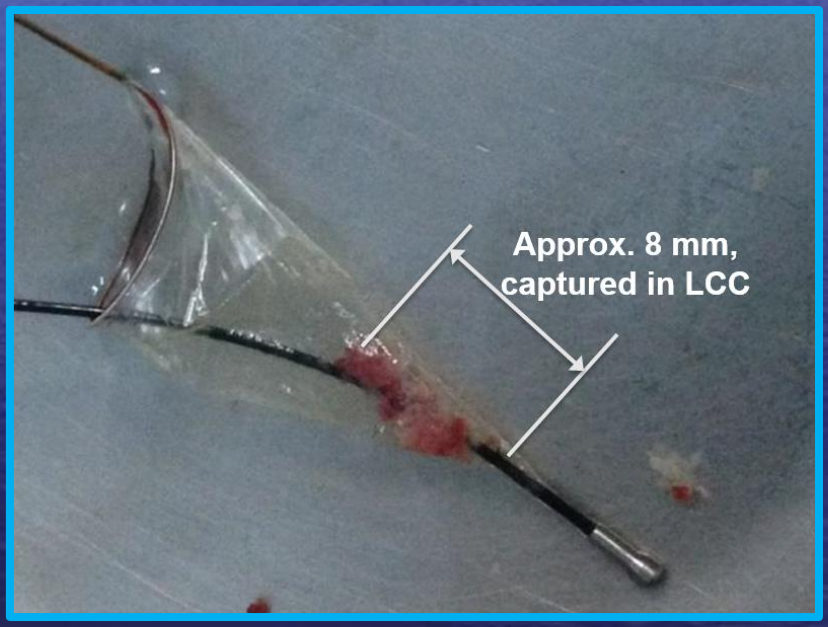
?LA appendage clot/SEC





Or better for Everyone?

Would you take a chance and drive without a seatbelt?!



You never know when you”ll need protection!?

Summary

- Stroke continues to be a clinically relevant problem in TAVI
- 'Silent' cerebral infarcts are frequent and are shown to have an impact on cognitive function
- While initial results with cerebral protection devices promising, so far failed to be validated in powered randomized trials
- As TAVI moves to lower risk groups…
- Freedom from new brain lesions should be a gold standard after TAVI?