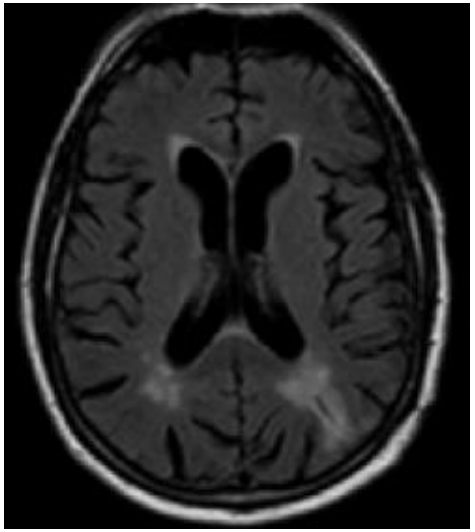
14:20 Stroke Michael, *Thomas Modine*

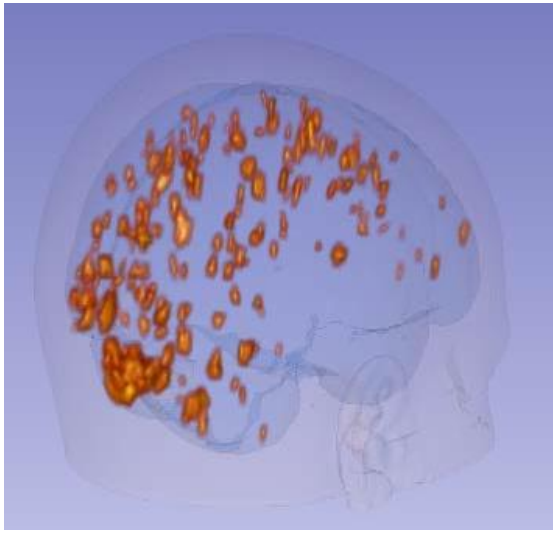
TAVI complication session: Stroke

Dr. Thomas Modine MD,PhD, MBA

Eurovalve 2016, Bruxelles

Centre Hospitalier Régional Universitaire de Lille





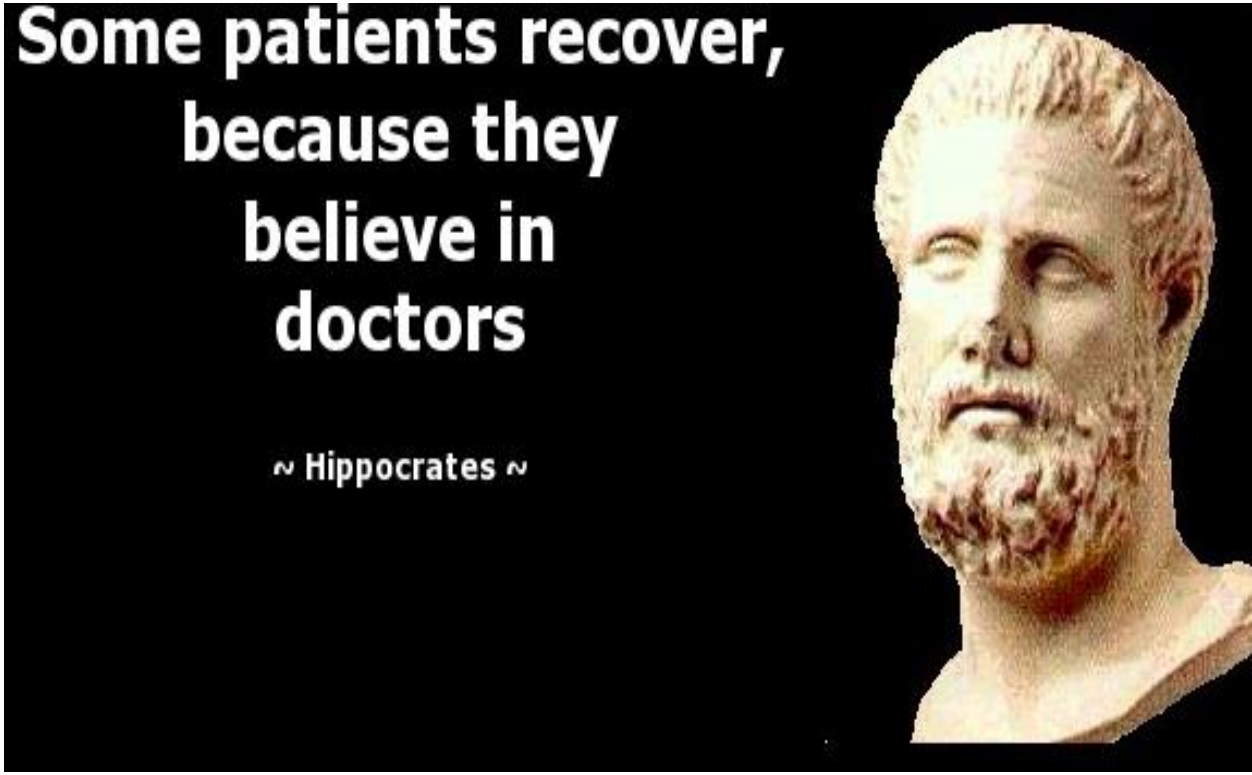
Disclosure

- Medtronic – Consultant, Proctor, advisory board and study investigator
- Boston scientific: Consultant, Proctor, steering committee
- Edwards: consultant
- GE: Consultant
- Directflow: consultant
- CardiaQ: study investigator
- Tendyne: study co-PI
- Twelve: study investigator
- Cephea: consultant
- Micrport: consultant and proctor

Hippocrates

Apoplexy = to strike down

“It is impossible to remove a strong attack of apoplexy, and not easy to remove a weak attack.”



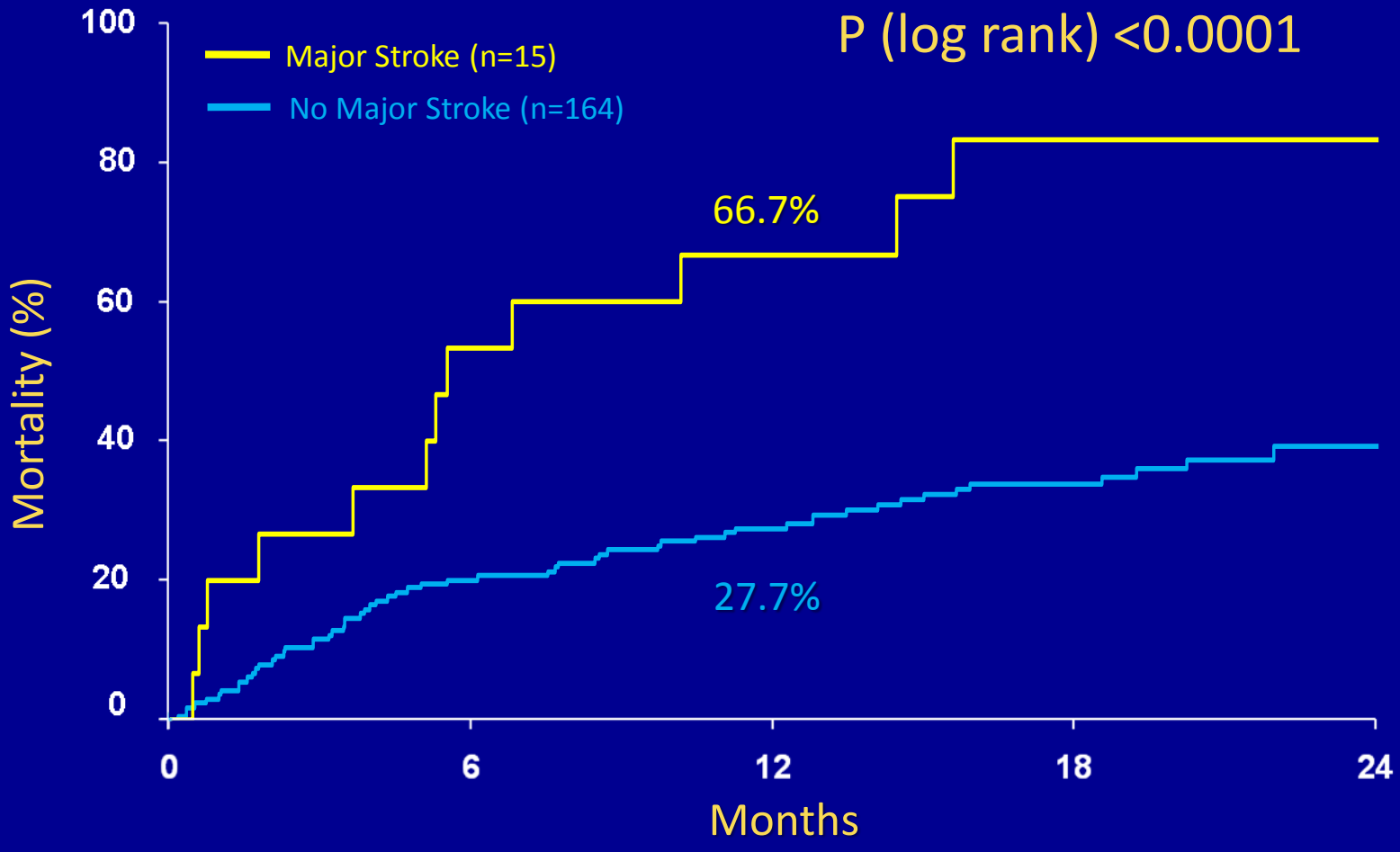
Thaler, TCT 2015

The brain is our most sensitive indicator of subtle organ injury.

Stroke is bad!

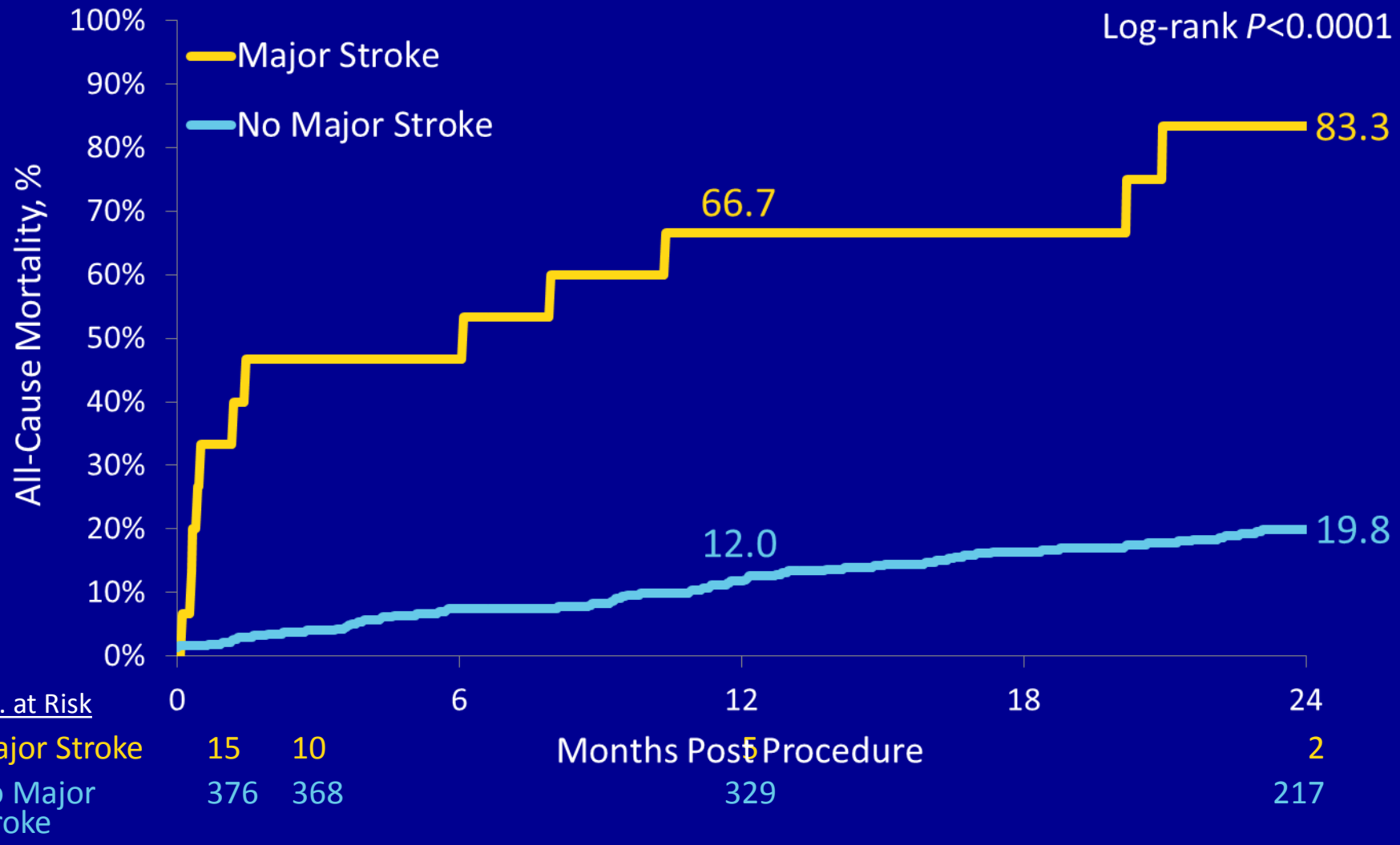
But how common is it?

Mortality and Major Stroke
PARTNER 1B TAVI patients



Leon, TCT 2010

Mortality after Stroke : TAVR Patients
CoreValve High Risk Trial



Adams, ACC 2014

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Transcatheter Aortic-Valve Implantation — At What Price?

Hartzell V. Schaff, M.D.

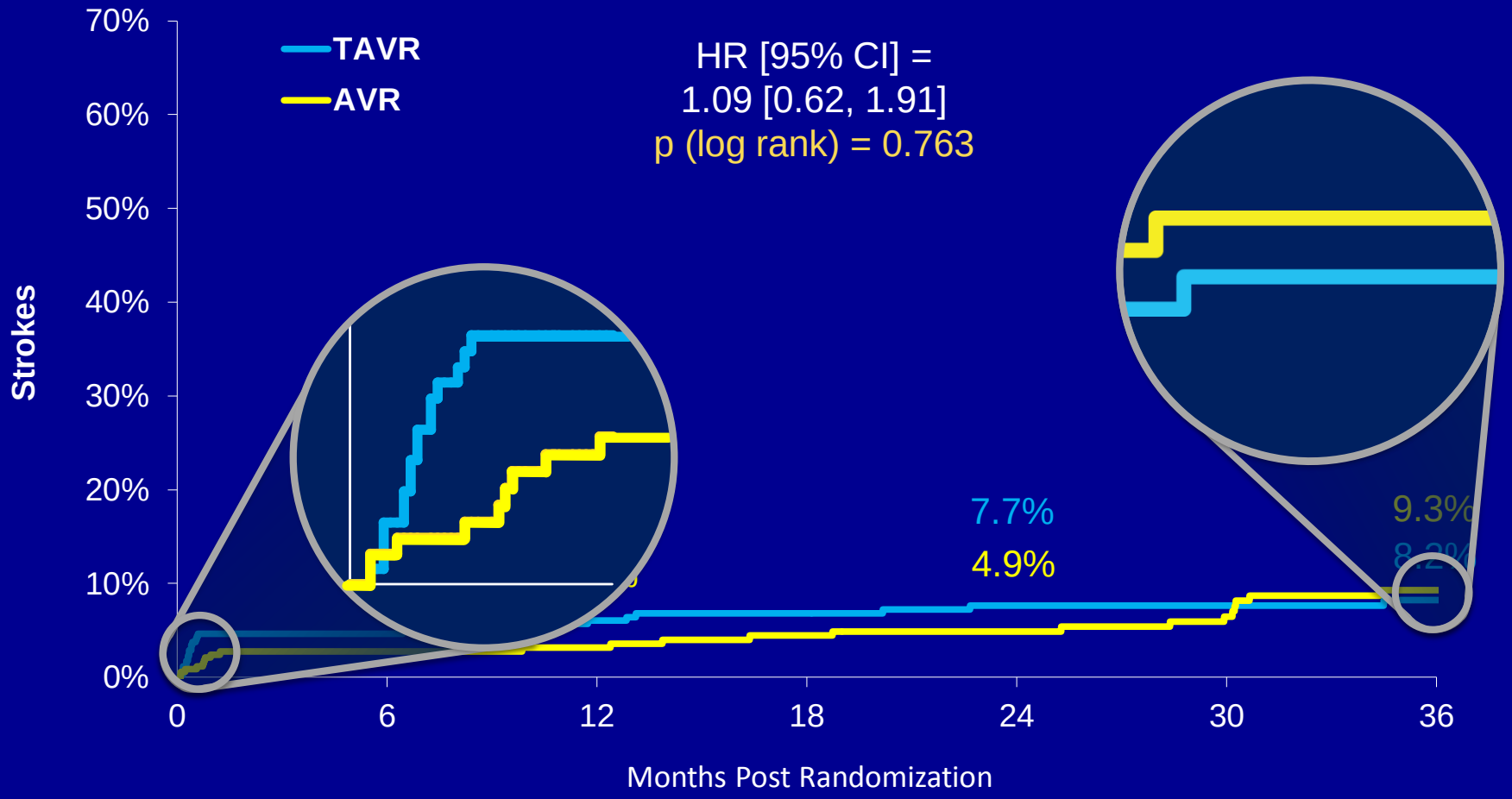
In 2000, Bonhoeffer et al. described transvenous placement of a pulmonary-valve prosthesis and speculated that similar technology might be used in other cardiac valves, including the aortic position.[1] Two years later, the first transcatheter insertion of an aortic-valve prosthesis was performed by Cribier et al.[2] Transcatheter aortic-valve

patients who are eligible for transfemoral insertion and may decrease vascular injury.

But the increased risk of stroke associated with transcatheter replacement, as compared with surgical replacement, is a special concern. Smith and colleagues report a 5.5% risk of stroke or transient ischemic attack within 30 days after

Schaff NEJM 2010

Strokes (ITT)- TAVR vs SAVR
PARTNER 1A

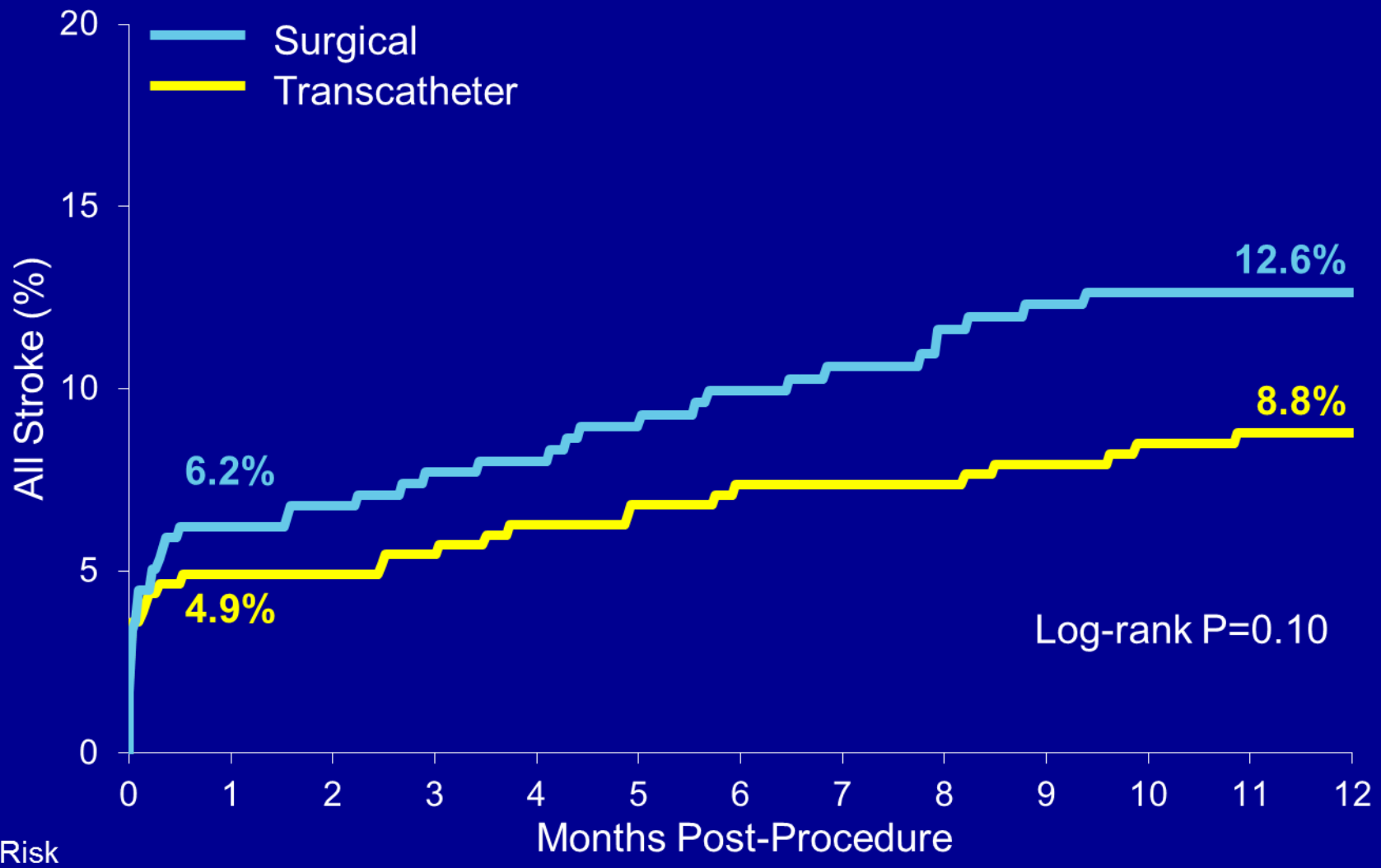


No. at Risk

TAVR	348	287	250	228	211	176	139
AVR	351	246	230	217	197	169	139

Leon, TCT 2013

Corevalve US Pivotal Trial- All Stroke



No. at Risk					
Surgical	357	322	274	249	
Transcatheter	390	363	334	314	

Adams, ACC 2014

Risk of stroke after transcatheter aortic valve implantation (TAVI): a meta-analysis of 10,037 published patients

53 studies, 10,037 patients

TF CoreValve (1.4±1.5%);
TF Edwards (2.1±3.0%)

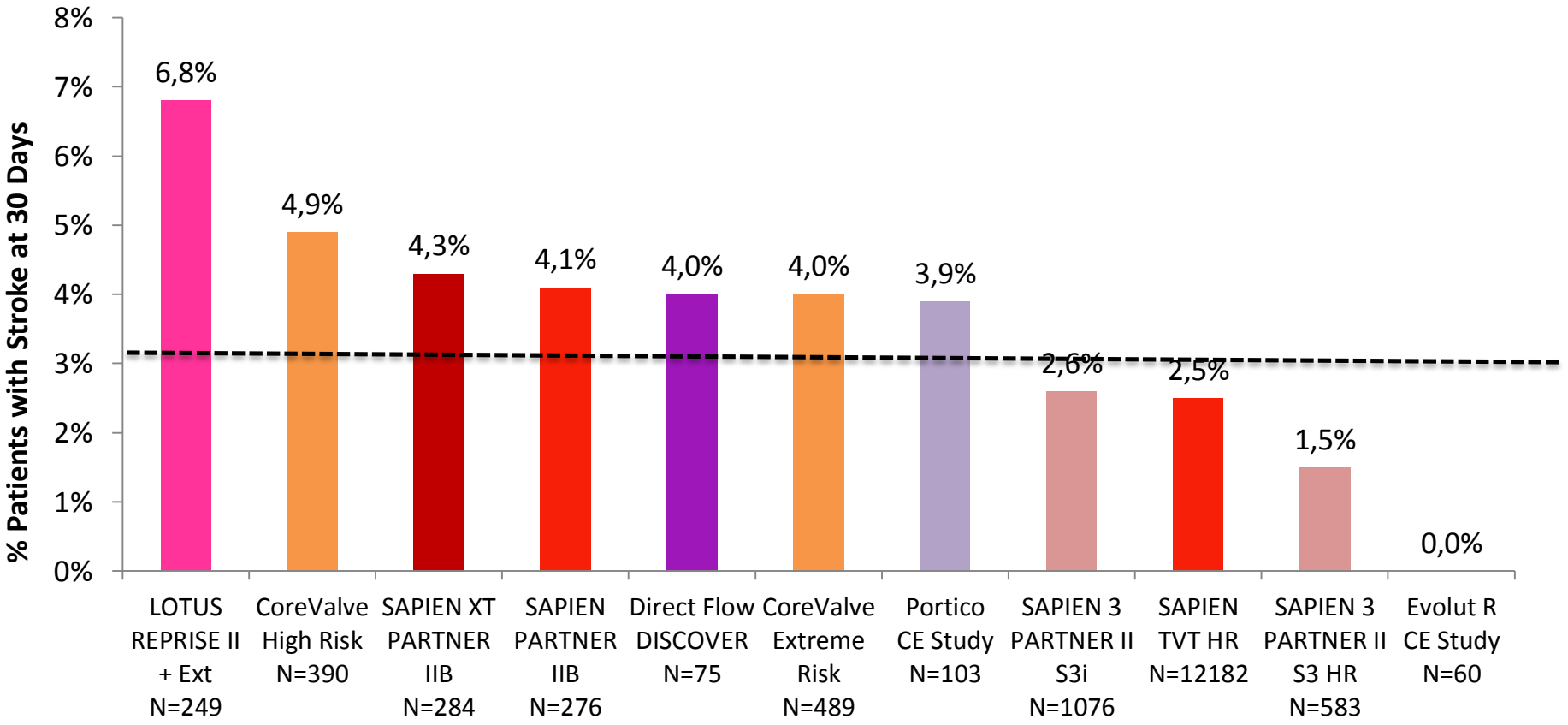
	Medtronic/CoreValve transarterial			Edwards SAPIEN transarterial		
	Number of publications with available data (n)	Overall number of patients with available data (n)	Weighted mean±SD	Number of publications with available data (n)	Overall number of patients with available data (n)	Weighted mean±SD
Patient age (years)	18	3236	81.1±1.3	23	1733	82.3±2.6
Female gender	16	2798	52.7±6.4%	22	1634	50.2±3.5%
Logistic EuroSCORE (%)	18	3236	22.09±3.66	20	1530	25.61±4.16
Procedural stroke (<24h)	9	1872	1.4±1.5%	11	571	2.1±3.0%
30-day stroke/TIA	18	3236	3.1±2.2%	24	1861	4.2±2.2%
30-day major stroke	14	1795	2.5±1.8%	20	1190	3.0±2.0%
30-day minor stroke/TIA	14	1795	0.7±1.4%	19	1091	1.7±1.8%
30-day overall mortality	18	3236	6.4±5.1%	22	1829	6.9±3.8%

Procedural stroke (<24 hr.) 1.5±1.4%
30-day stroke/TIA 3.3±1.8%
1-year stroke/TIA 5.2±3.4%

	Number of publications with available data (n)	Overall number of patients with available data (n)	Number of events (n)	Weighted mean±SD
Procedural stroke (<24h)	24	3041	47	1.5±1.4%
30-day stroke/TIA	53	10037	334	3.3±1.8%
30-day major stroke	42	5514	158	2.9±1.8%
30-day minor stroke/TIA	42	5514	53	1.0±1.3%
30-day overall mortality	52	10022	812	8.1±3.9%
30-day mortality in patients suffering stroke	29	4430	41	25.5±21.9%
30-day mortality in patients without stroke	29	4430	312	6.9±4.2%
6-month stroke	9	669	29	4.3±1.6%
12-month stroke	7	1507	78	5.2±3.4%

Eggebrecht et al. EuroIntervention 2012

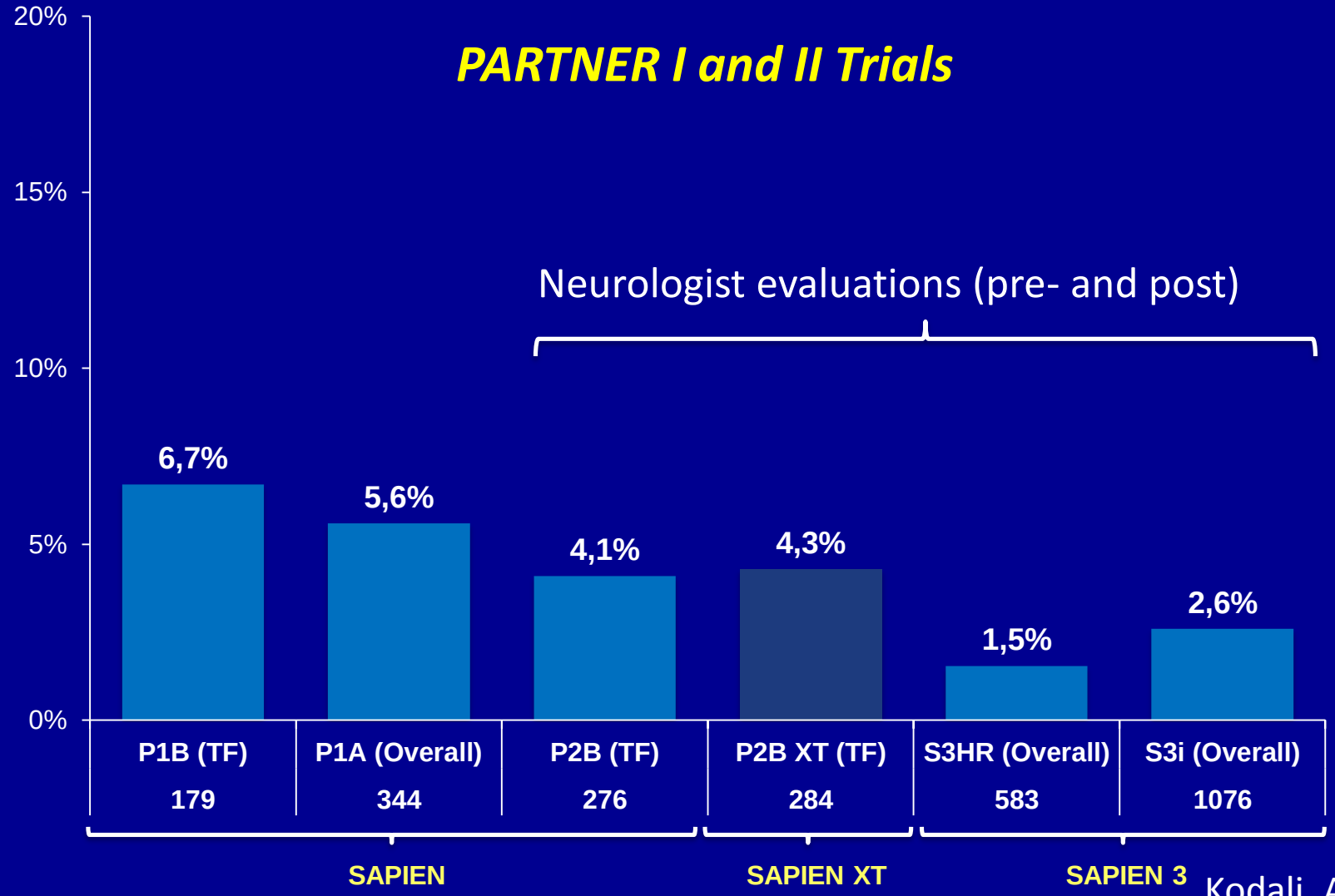
30-day stroke rate



[1]Meredith, et al., presented at PCR London Valves 2014; [2]Adams, et al., *N Engl J Med* 2014; 370: 1790-8; [3]Leon, et. al. presented at ACC 2013; [4]Schofer, et al., *J Am Coll Cardiol* 2014; 63: 763-8; [5]Popma, et al., *J Am Coll Cardiol* 2014; 63: 1972-81; [6]Manoharan, et al., et. al. presented at TCT 2014; [7]Kodali, et al., presented at ACC 2015; [8]Holmes, et al., JAMA 2015; 313: 1019-28 [9]Meredith, et al., presented at ACC 2015

All Strokes at 30 Days- device iterations (All clinically apparent strokes)

Edwards SAPIEN Valves



Kodali, ACC 2015

Neurologist evaluation results in the greater detection of (non major) stroke

Stroke After Aortic Valve Surgery

Results From a Prospective Cohort

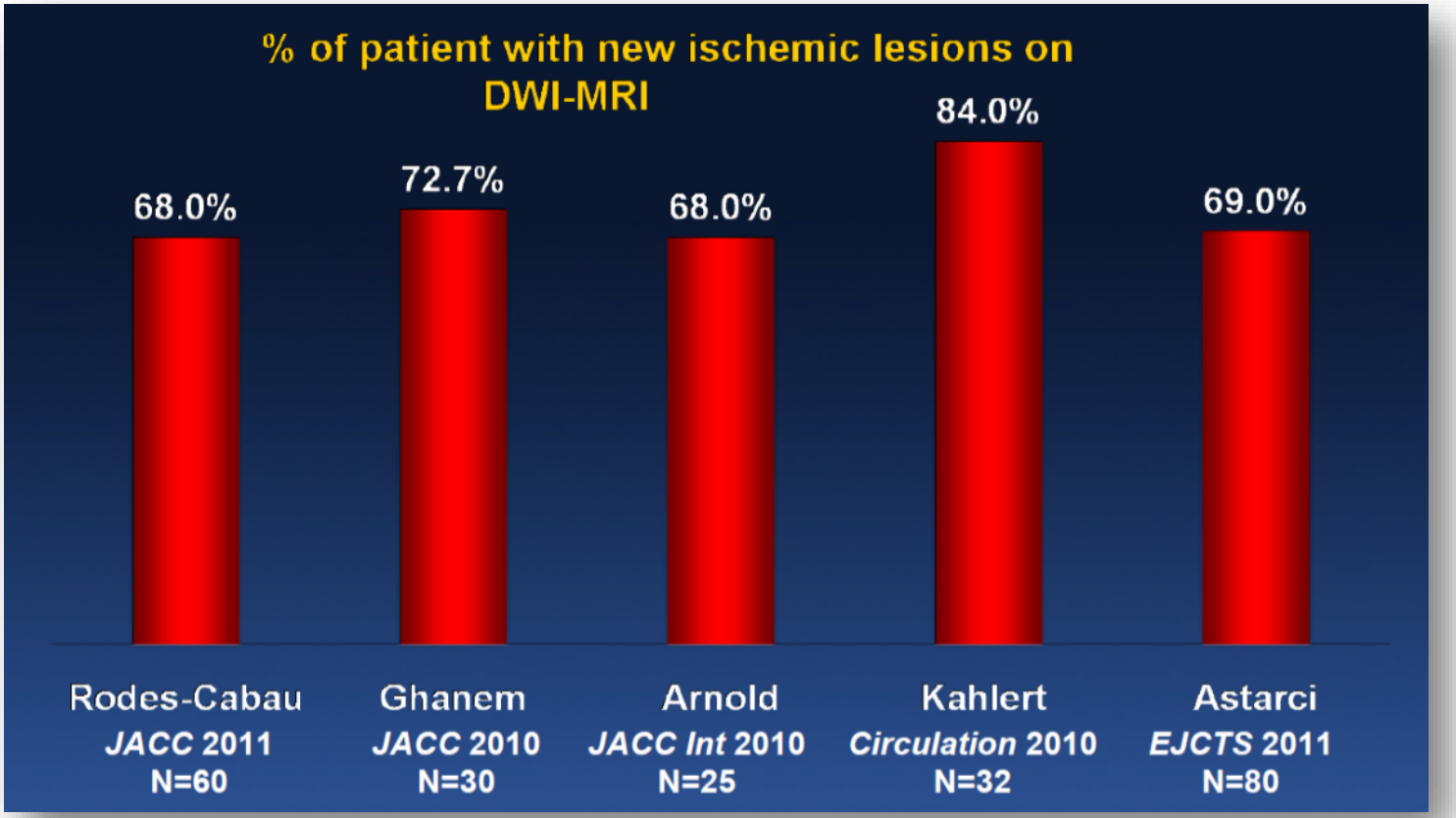
Steven R. Messé, MD; Michael A. Acker, MD; Scott E. Kasner, MD; Molly Fanning, BS; Tania Giovannetti, PhD; Sarah J. Ratcliffe, PhD; Michel Bilello, MD, PhD; Wilson Y. Szeto, MD; Joseph E. Bavaria, MD; W. Clark Hargrove, III, MD; Emile R. Mohler III, MD; Thomas F. Floyd, MD; for the Determining Neurologic Outcomes from Valve Operations (DeNOVO) Investigators

(*Circulation*. 2014;129:2253-2261.)

Historically:

Results:

DW-MRI imaging shows “silent infarcts” in TAVR

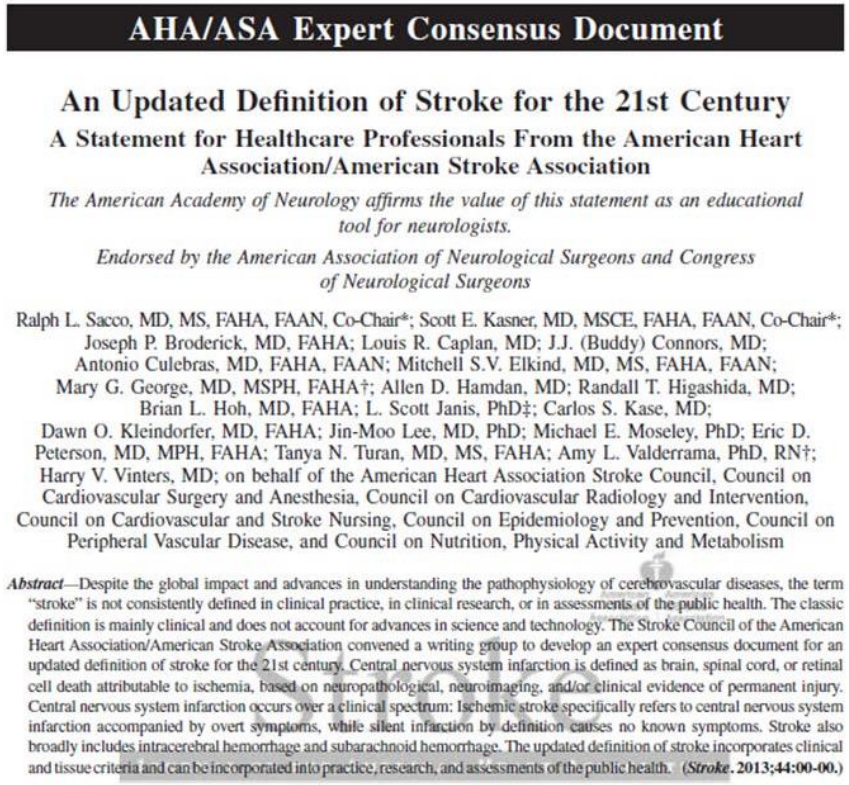


New lesions found in vast majority of diffusion-weighted MR images (DW-MRI) of the brain following TAVI

Daneault et al, JACC 2011;58: 2143-50

Stroke is bad!

Stroke redefined- “not so silent” infarction



AHA/ASA Expert Consensus Document

An Updated Definition of Stroke for the 21st Century

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

Ralph L. Sacco, MD, MS, FAHA, FAAN, Co-Chair*; Scott E. Kasner, MD, MSCE, FAHA, FAAN, Co-Chair*; Joseph P. Broderick, MD, FAHA; Louis R. Caplan, MD; J.J. (Buddy) Connors, MD; Antonio Culebras, MD, FAHA, FAAN; Mitchell S.V. Elkind, MD, MS, FAHA, FAAN; Mary G. George, MD, MSPH, FAHA†; Allen D. Hamdan, MD; Randall T. Higashida, MD; Brian L. Hoh, MD, FAHA; L. Scott Janis, PhD‡; Carlos S. Kase, MD; Dawn O. Kleindorfer, MD, FAHA; Jin-Moo Lee, MD, PhD; Michael E. Moseley, PhD; Eric D. Peterson, MD, MPH, FAHA; Tanya N. Turan, MD, MS, FAHA; Amy L. Valderrama, PhD, RN†; Harry V. Vinters, MD; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Council on Nutrition, Physical Activity and Metabolism

Abstract—Despite the global impact and advances in understanding the pathophysiology of cerebrovascular diseases, the term “stroke” is not consistently defined in clinical practice, in clinical research, or in assessments of the public health. The classic definition is mainly clinical and does not account for advances in science and technology. The Stroke Council of the American Heart Association/American Stroke Association convened a writing group to develop an expert consensus document for an updated definition of stroke for the 21st century. Central nervous system infarction is defined as brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury. Central nervous system infarction occurs over a clinical spectrum: Ischemic stroke specifically refers to central nervous system infarction accompanied by overt symptoms, while silent infarction by definition causes no known symptoms. Stroke also broadly includes intracerebral hemorrhage and subarachnoid hemorrhage. The updated definition of stroke incorporates clinical and tissue criteria and can be incorporated into practice, research, and assessments of the public health. (***Stroke***. 2013;44:00-00.)

- “Silent” infarcts associated with
  - Impaired mobility
  - Physical decline
  - Depression
  - Cognitive dysfunction
  - Dementia
  - Parkinson’s
  - Alzheimer’s

Sacco et al, Stroke. 2013;44:2064-2089

Stroke Timing post TAVI

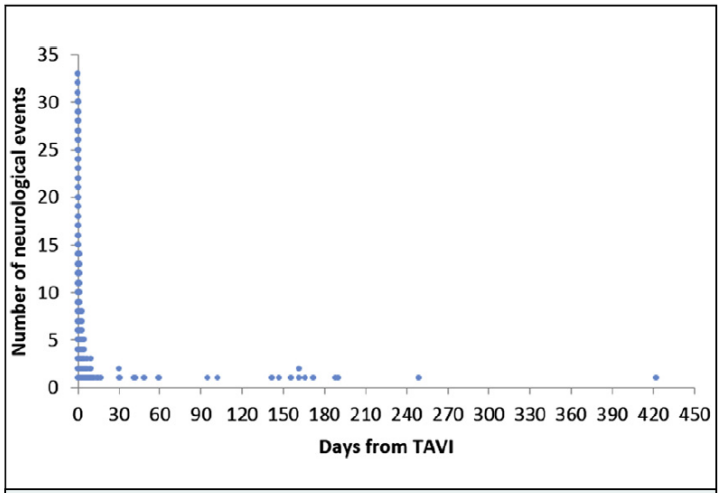


FIGURE 1 **Timing of Cerebrovascular Events**

Number of days elapsed from the index procedure before the occurrence of a cerebrovascular event.

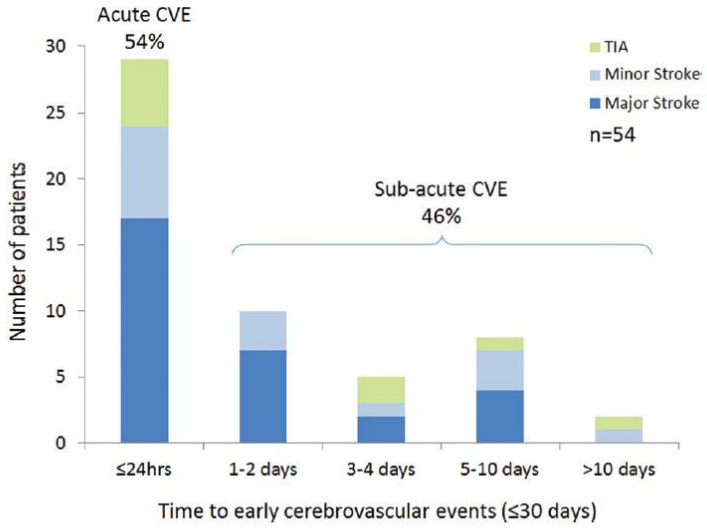


Figure 2. Timing of cerebrovascular events (CVEs) within 30 days after transcatheter aortic valve implantation. TIA indicates transient ischemic attack.

Timing of Cerebrovascular Events (CVE) in FRANCE-2 Registry (n=3,191)

- **CVE most frequently occur day 0-1**
- **>50% are major strokes**
- **Median time to major stroke is 1 day**

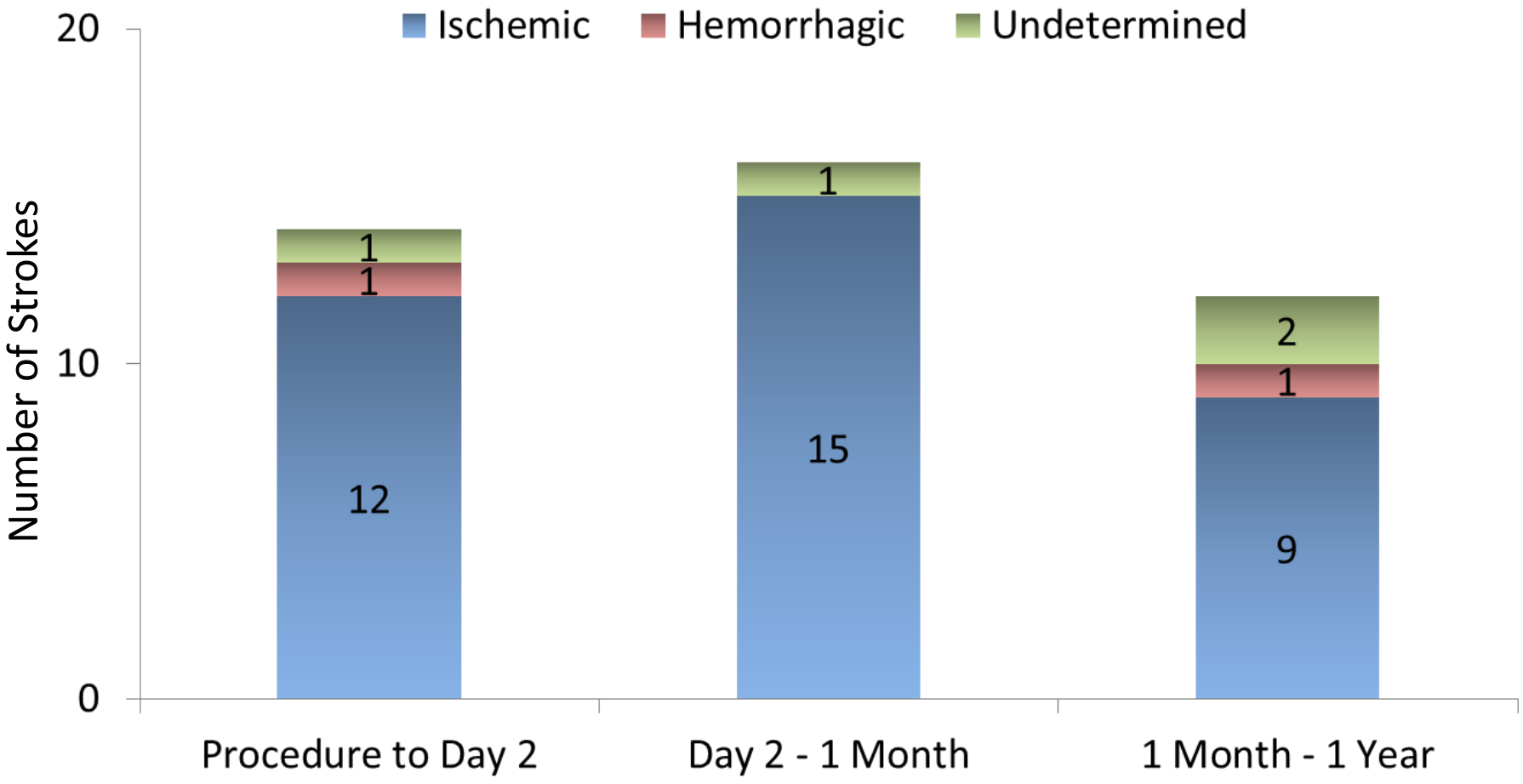
D. Tchetche et al. JACC CV Int. 2014;7:1138-1145

Multi-center cohort of 1,061 TAVI patients

- **CVE most frequently occur day 0-1**
- **>50% are major strokes**
- **>95% of strokes are ischemic**

Nombela-Franco et al., *Circulation* 2012;126:3041-53

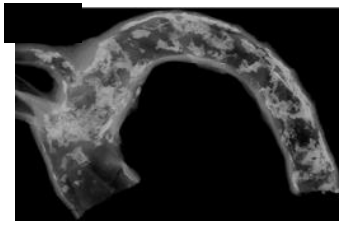
ADVANCE | Type and Timing of Stroke



996 patients implanted

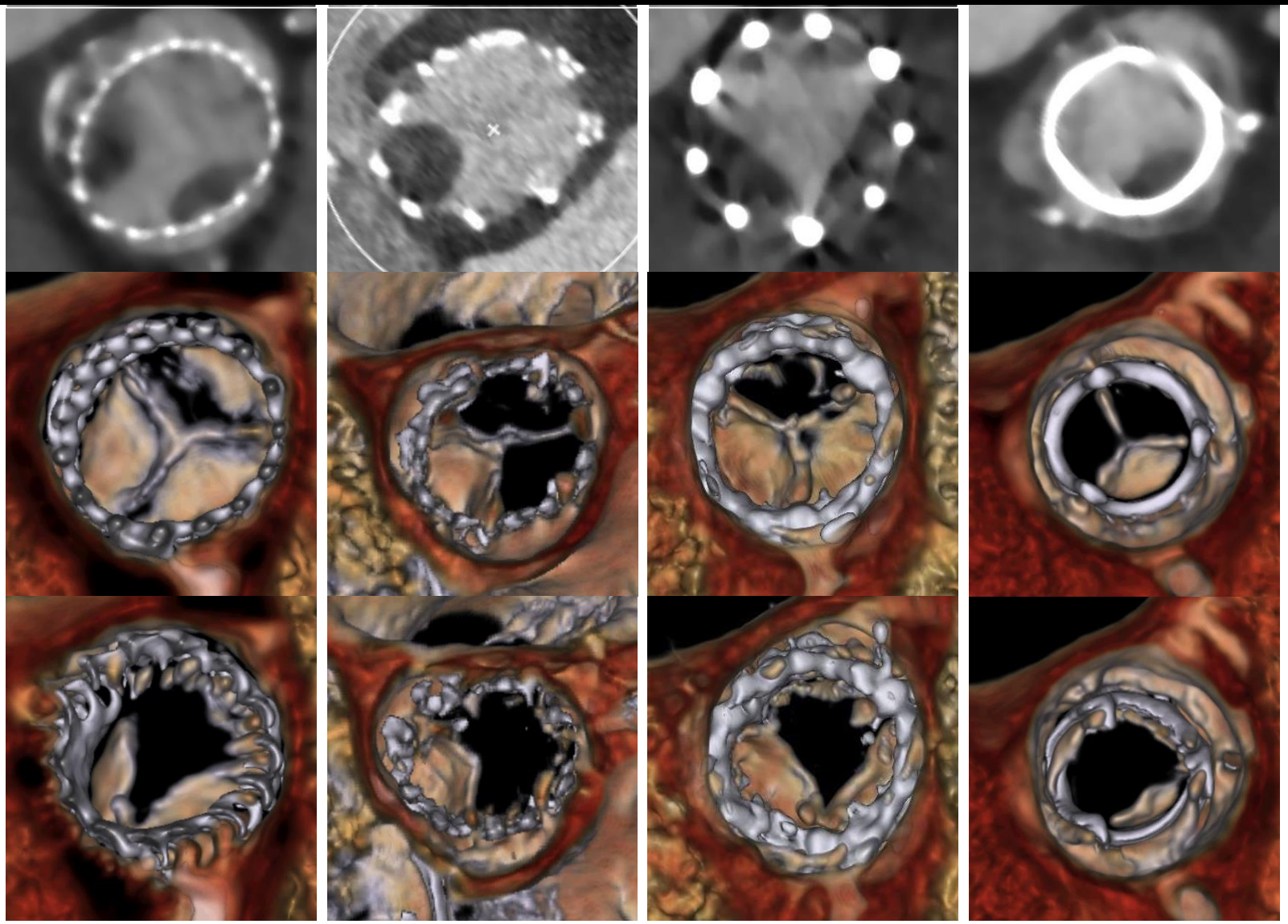
Substrates for thromboembolism in TAVI

- Presence and location of arch atheroma
- Micro-embolization of native valve calcification
- Catheter handling and device placement technique
- Secondary manoeuvers (post-dil/VinV)
- Procedural duration
- Pro-thrombotic/hypercoagulable state
- Arrhythmia (AF)
- Rapid RV pacing (cerebral hypoperfusion)
- Subclinical prosthetic leaflet thrombosis



Van Mieghem, TCT 2015

Reduced leaflet motion with possible subclinical leaflet thrombus



Makkar, Fontana, Jilaihawi et al, NEJM 2015

Subclinical leaflet thrombus

Unclear connection to stroke/TIA

	Normal Leaflet Motion	Reduced Leaflet Motion	P value
	Number of patients		
Registries			
Patients in study	115	17	
Death	0	0	>0.99
Myocardial infarction	0	0	>0.99
Stroke/TIA¶	1	3	0.007
Stroke	1	0	>0.99
TIA	0	3	0.002

Makkar, Fontana, Jilaihawi et al, NEJM 2015

Therapeutic actions

Predictors for Cerebrovascular Events with TAVI

	Incidence	Variable	Risk	95% CI	P-value
Acute <24h	29 (2.7%)	Balloon postdilatation	OR: 2.46	CI: 1.07 to 5.67	0.034
		Valve dislodgment/ embolization	OR: 4.36	CI: 1.21 to 15.69	0.024
Subacute 24h><30 Days	25 (2.4%)	New onset AF	OR: 2.76	1.11 to 6.83	0.028
Late >30 Days	35 (3.3%)	Chronic AF	HR: 2.84	1.46 to 5.53	
		PAD	HR: 2.02	1.02 to 3.97	
		Prior CVA	HR: 2.04	1.01 to 4.15	

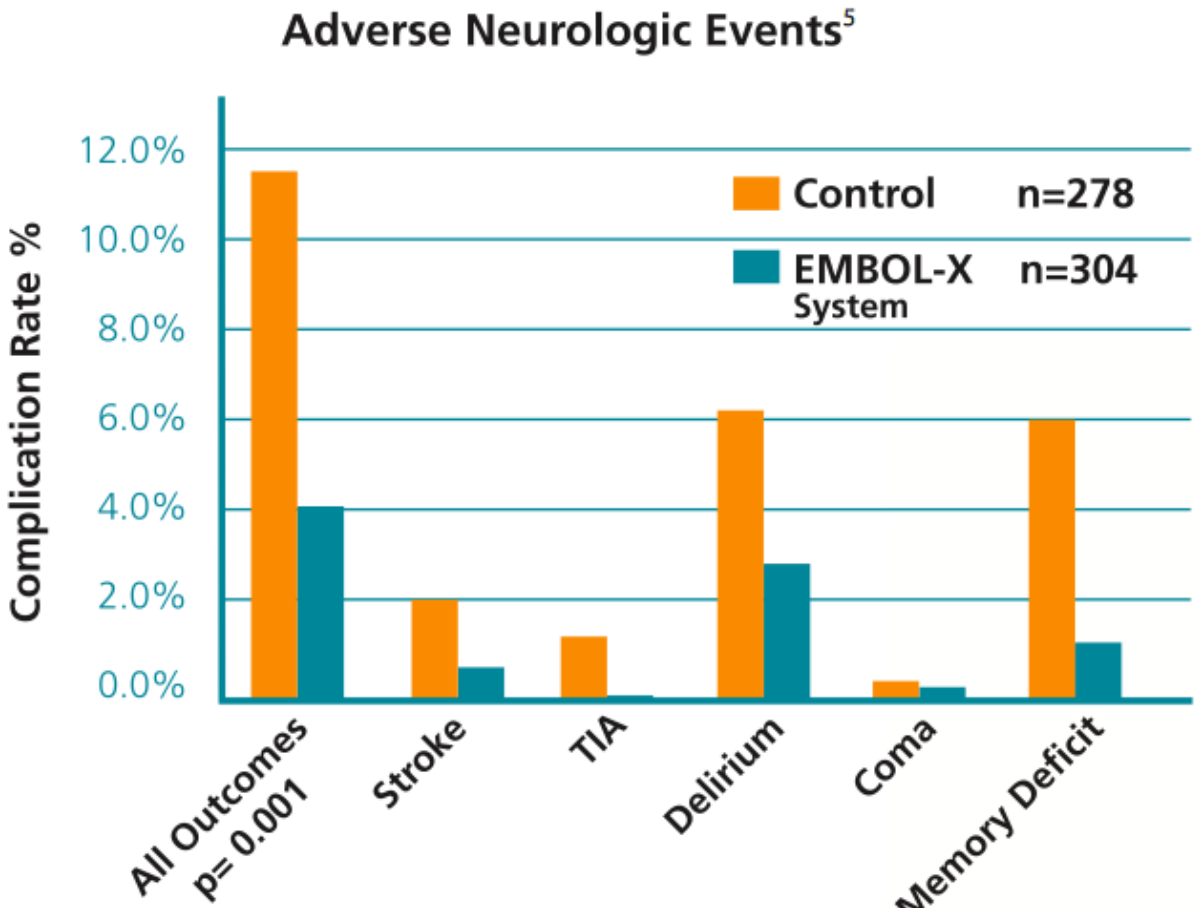
Nombela-Franco et al. Circulation 2012;126:3041-53

Predictors for Tissue Embolization (collected debris with Claret)

Independent Predictors of Tissue Embolization	OR	95% CI	p-value
Balloon-expandable THV	7.315	1.398-38.289	p=0.018
Cover index	1.141	1.014-1.283	p=0.028
Balloon post-dilation	2.67	0.675-10.073	p=0.17

Van Mieghem NM, et al. *J Am Coll Cardiol Intv* 2015;8:718-24

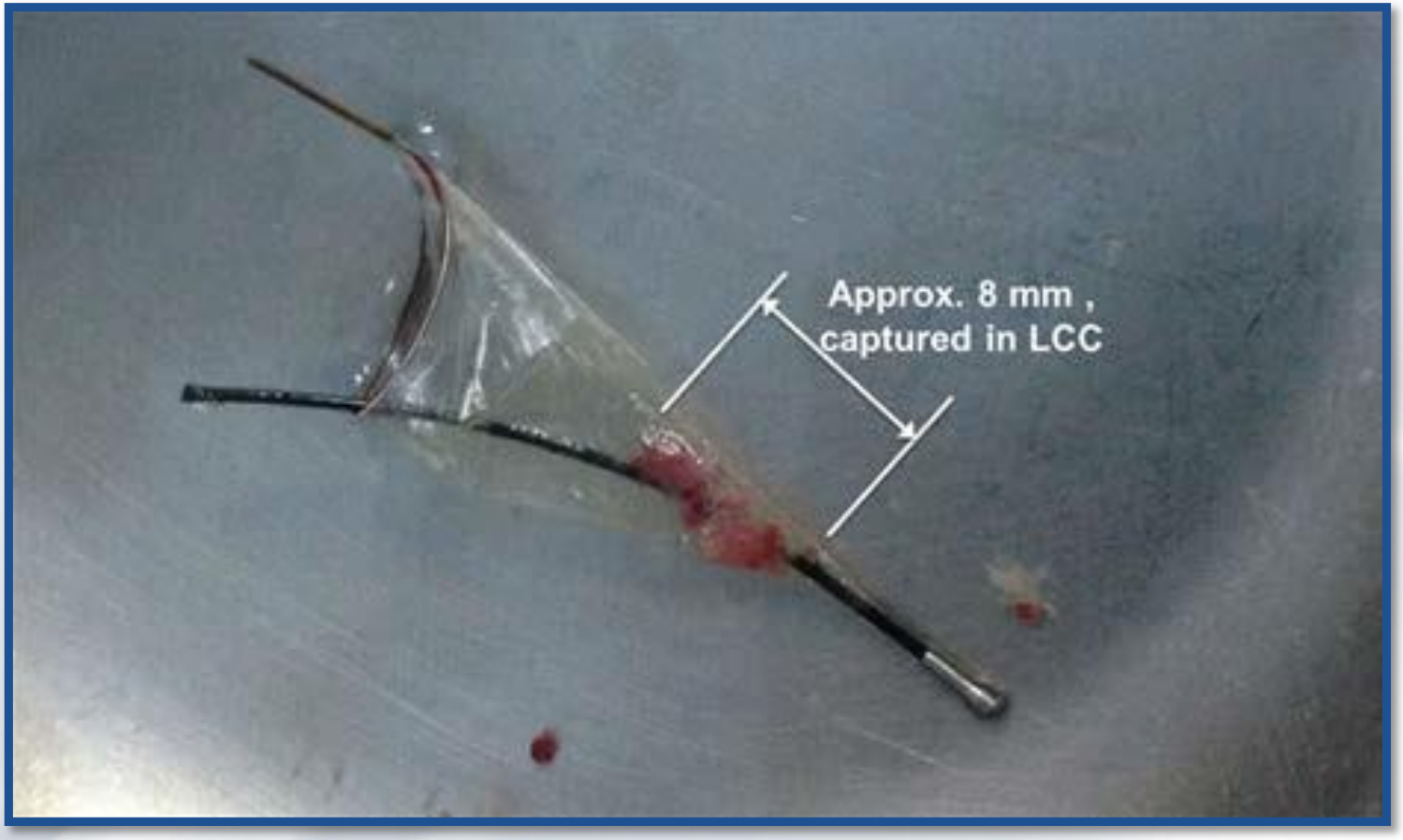
Device for cardiac surgery stroke prevention: Embol-X



Single center, Non-randomized
Neurologic assessment, physicians blinded to treatment group

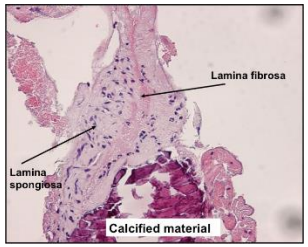
Schmitz et al, JCTVS 2003

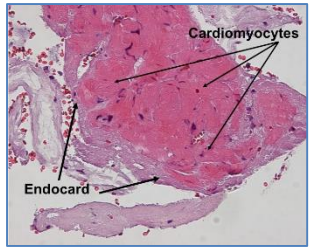
Embolic material collected during TAVR with the Claret device

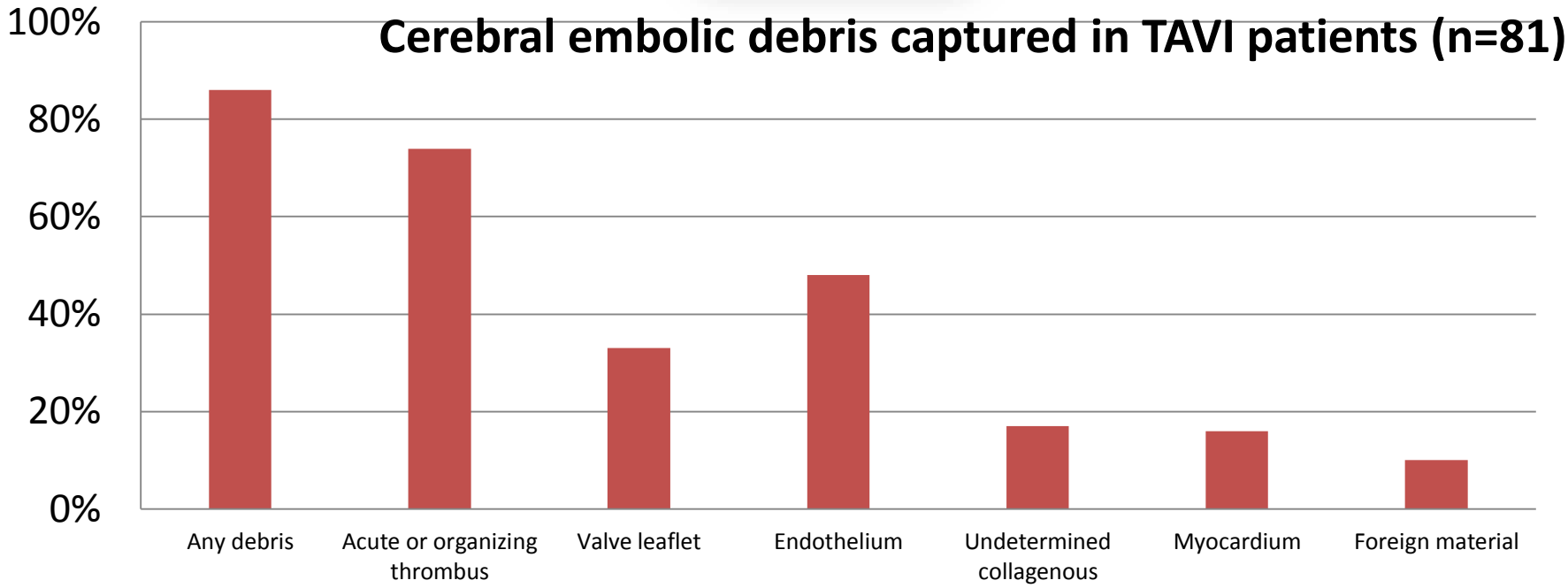


Captured during TCT 2013 Live Case: Courtesy of Dr. Alex Abizaid
Institute Dante Pazzanese de Cardiologia, São Paulo, Brazil

Embolic Etiology





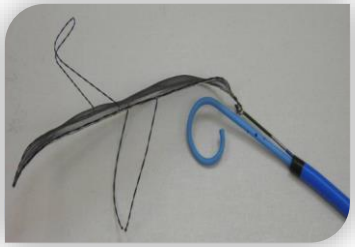


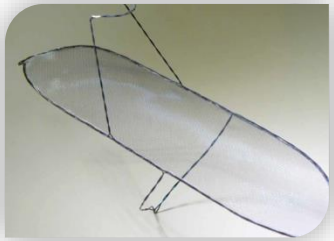
Note: percentages reflect percent of patients in the series in which each particular tissue type was captured. Some filters captured several types of debris, so percentages will not add to 100%

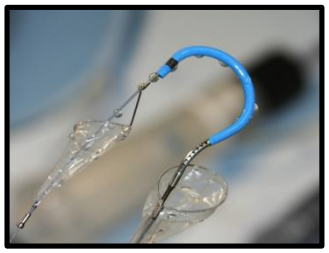
Van Mieghem NM, et al. *J Am Coll Cardiol Intv* 2015;8:718-24

Cerebral Embolic Protection

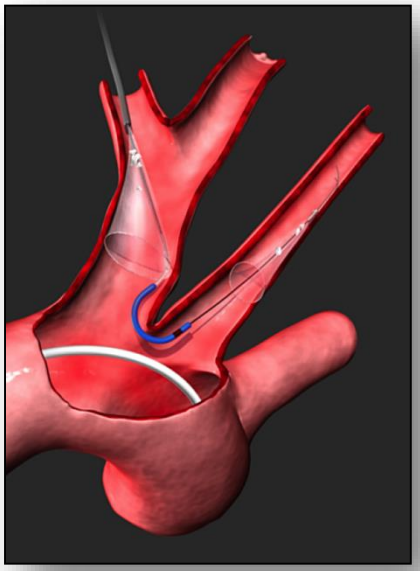
TriGuard Cerebral Deflector	Embrella Deflector	Claret Sentinel Filter
Deflector	Deflector	Filter
3 Vessels Covered	2 Vessel Coverage	2 Vessel Coverage
Femoral Access	Radial Access	Radial Access
Nitinol® Mesh	Polymer based Mesh	Polymer based Filter
130µm Pore Size	100 µm Pore Size	140 µm Pore Size
EU Feasibility	CE approved	CE approved
9F Sheath (Mullins)	6F Shuttle Sheath	6F Radial Sheath

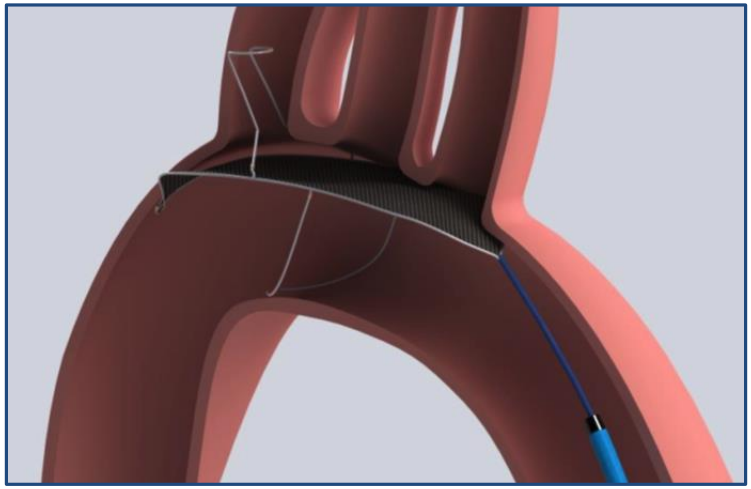






Randomized EPD Data





CLEAN TAVI, n=100

DEFLECT III, n=85

MISTRAL-C, n=65

SENTINEL (ongoing)

CLEAN-TAVI Study

Randomized study of CoreValve implantation with (n=50) and without (n=50) embolic protection (Total N = 100)

Neurological Outcome

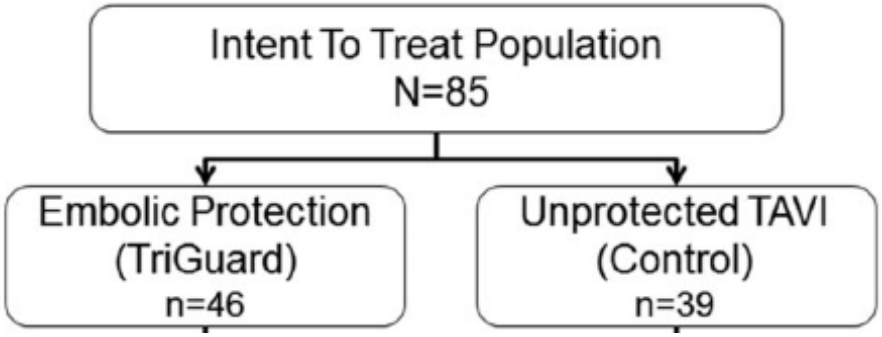
per protocol		cumulative	2 days (No, %)	7 days (No, %)	30 days (No, %)
Control	Any symptom	17 (34 %)	14 (28 %)	5 (10 %)	6 (12 %)
	- Ataxia	16 (32 %)	12 (24 %)	4 (8 %)	5 (10 %)
Filter	Any symptom	11 (24 %)	6 (13 %)	6 (13 %)	4 (12 %)
	- ataxia	9 (20 %)	4 (9 %)	5 (11 %)	4 (12 %)
	n=45				

RR 1.458 (1.006 to 2.114), OR 2.5, p=0.08

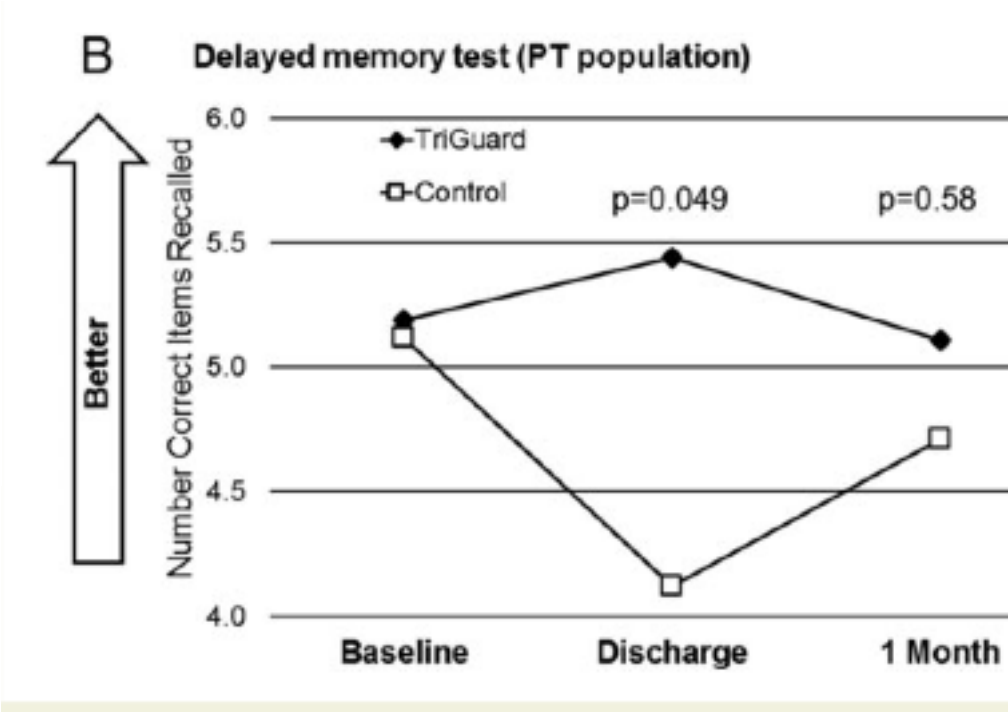
RR 1.559 (1.083 to 2.214), OR 3.2, p<0.05

The Claret device is investigational and not FDA approved

DEFLECT III



15 centers in Europe and Asia



There were 2 clinical strokes in each arm.

In the TriGuard arm, the single disabling stroke occurred in a patient who did not have full cerebral protection during the procedure; an additional non-disabling stroke occurred in a subject who appeared to have full coverage.

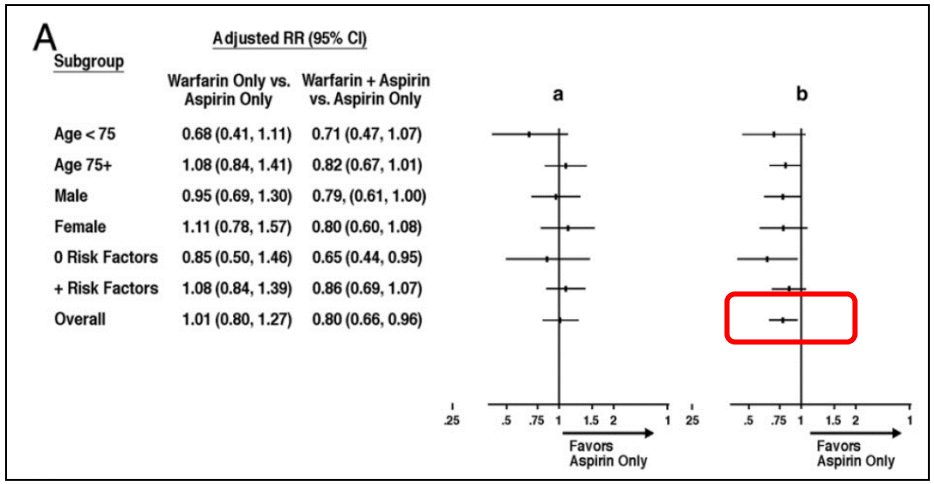
Lansky et al, Eur Heart J. 2015 Aug 14;36(31):2070-2078.

Association of warfarin therapy with clinical events after bioprosthetic AVR: STS database

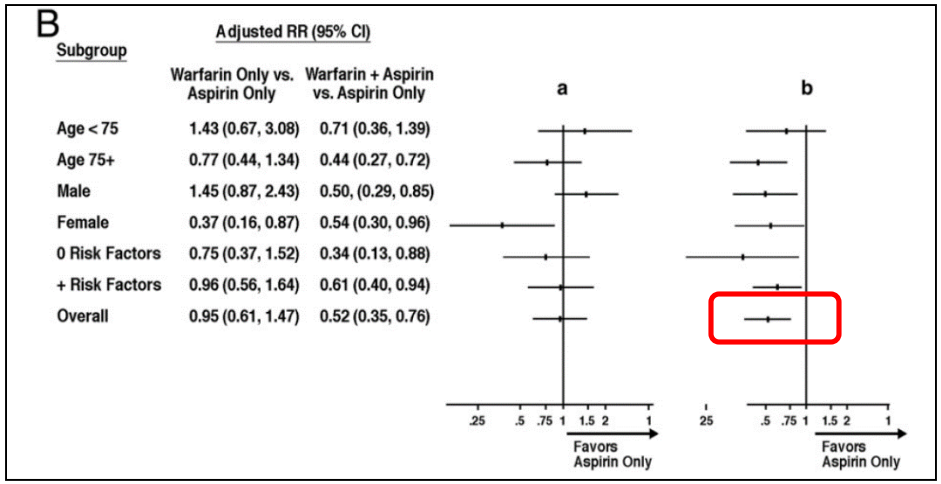
25,656 patients undergoing bioprosthetic AVR at 797 hospitals in the STS database

Warfarin plus aspirin associated with a reduced risk of death and embolic events, compared to aspirin alone

Death

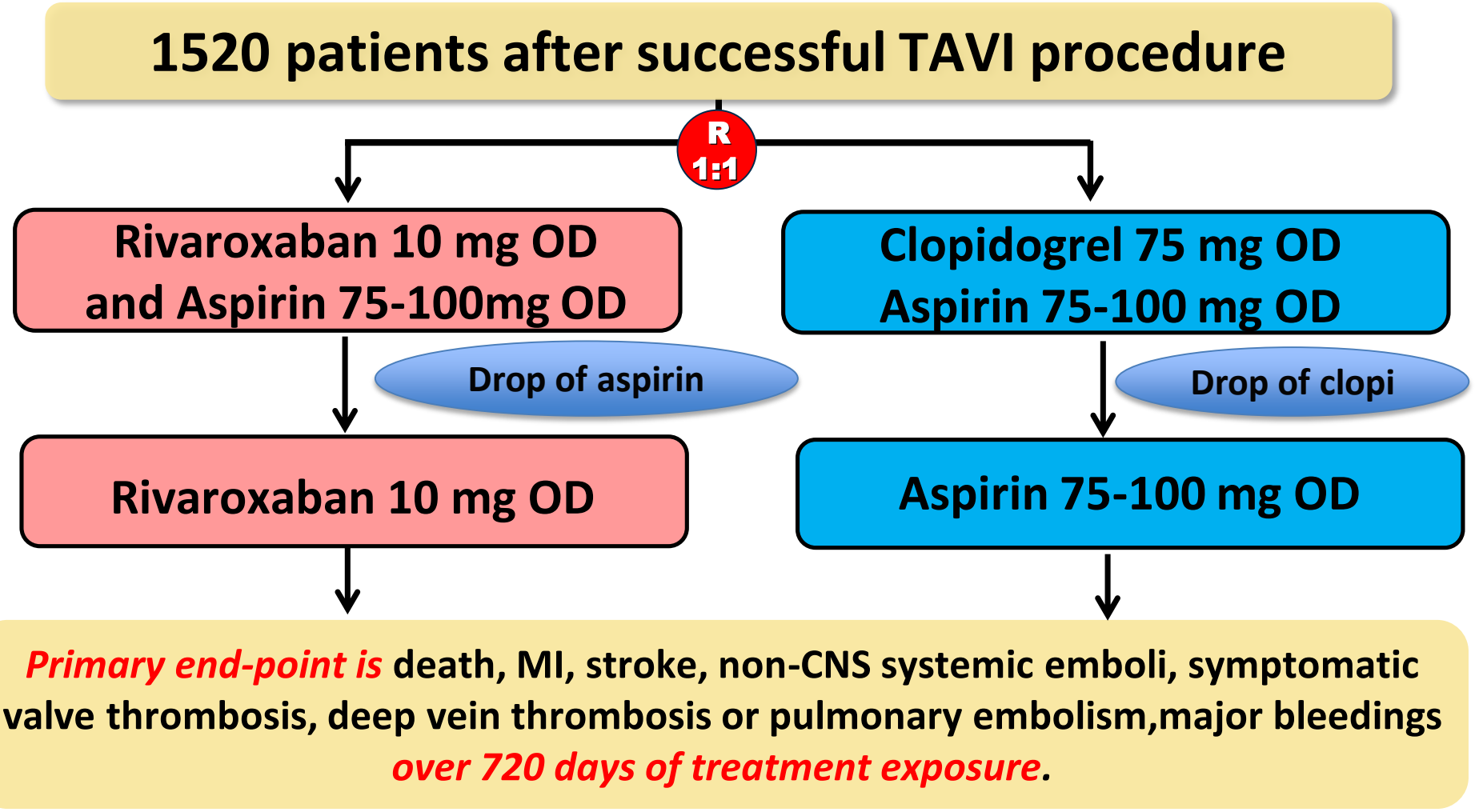


Thromboembolism



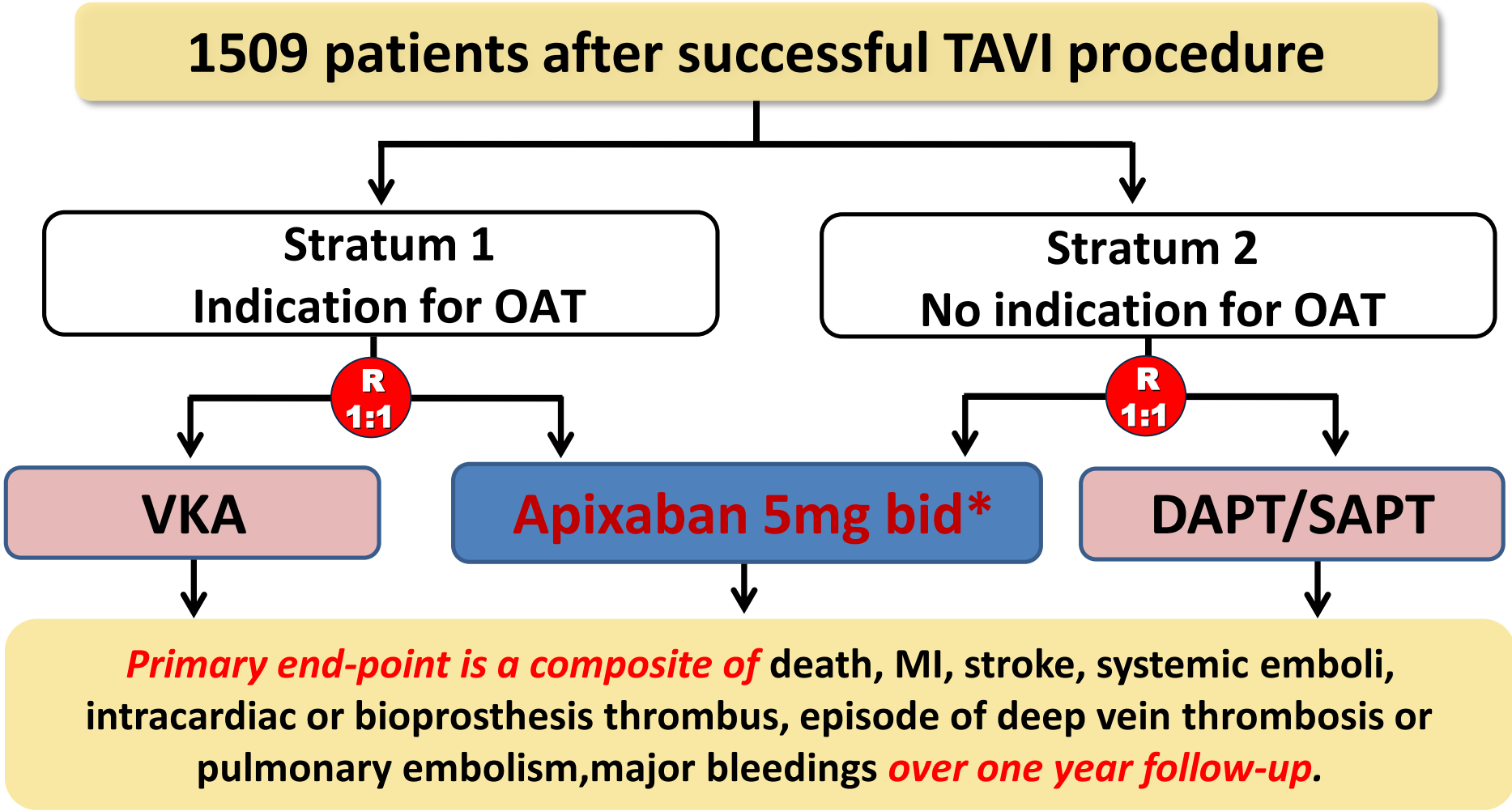
Brennan M. et al. JACC 2012

GALILEO (Global multicenter, open-label, randomized, event-driven, active-controlled study comparing a rivAroxaban-based antithrombotic strategy to an antipLatelet-based strategy after transcatheter aortIc vaLve rEplacement (TAVR) to Optimize clinical outcomes will compare rivaroxaban-based)



Primary end-point is **death, MI, stroke, non-CNS systemic emboli, symptomatic valve thrombosis, deep vein thrombosis or pulmonary embolism,major bleedings** ***over 720 days of treatment exposure*****.**

ATLANTIS (Anti-Thrombotic Strategy to Lower All cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis)



Primary end-point is a composite of **death, MI, stroke, systemic emboli, intracardiac or bioprosthesis thrombus, episode of deep vein thrombosis or pulmonary embolism,major bleedings** ***over one year follow-up*****.**

*2.5mg bid if creatinine clearance 15-29mL/min or if two of the following criteria: age≥80 years, weight≤60kg or creatinine≥1,5mg/dL (133µMol).

PCR london valves

Stroke diagnosis in the cath lab with dyna CT

00 min — Arrival at hospital

15 min — Neurological exam

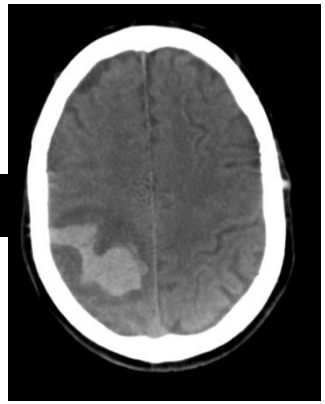
high NIH

30 min — Angio suite Imaging

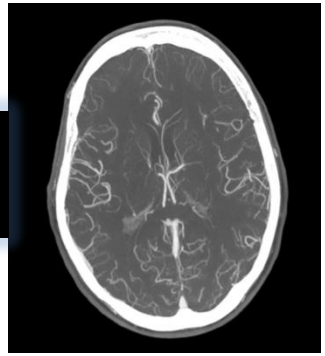
45 min — Angio suite, treatment

1h saved =
20% better chance for good outcome (mRS ≤ 2)

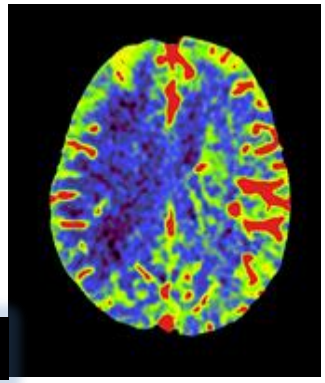
Hemorrhagic or ischemic?



Clot location?
Collaterals?



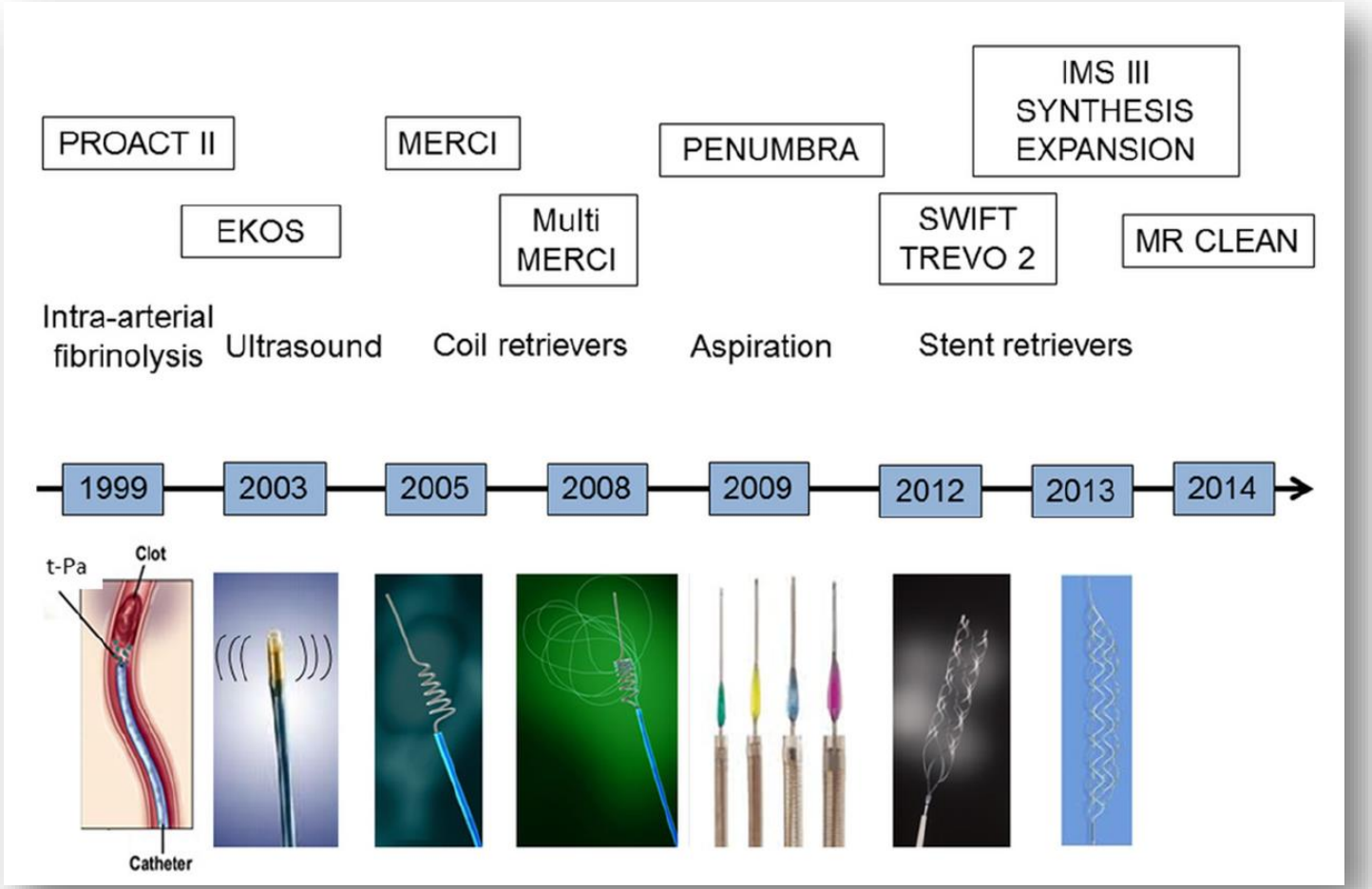
To treat or not to treat?



Law, TCT 2015

What about when a stroke has already occurred?

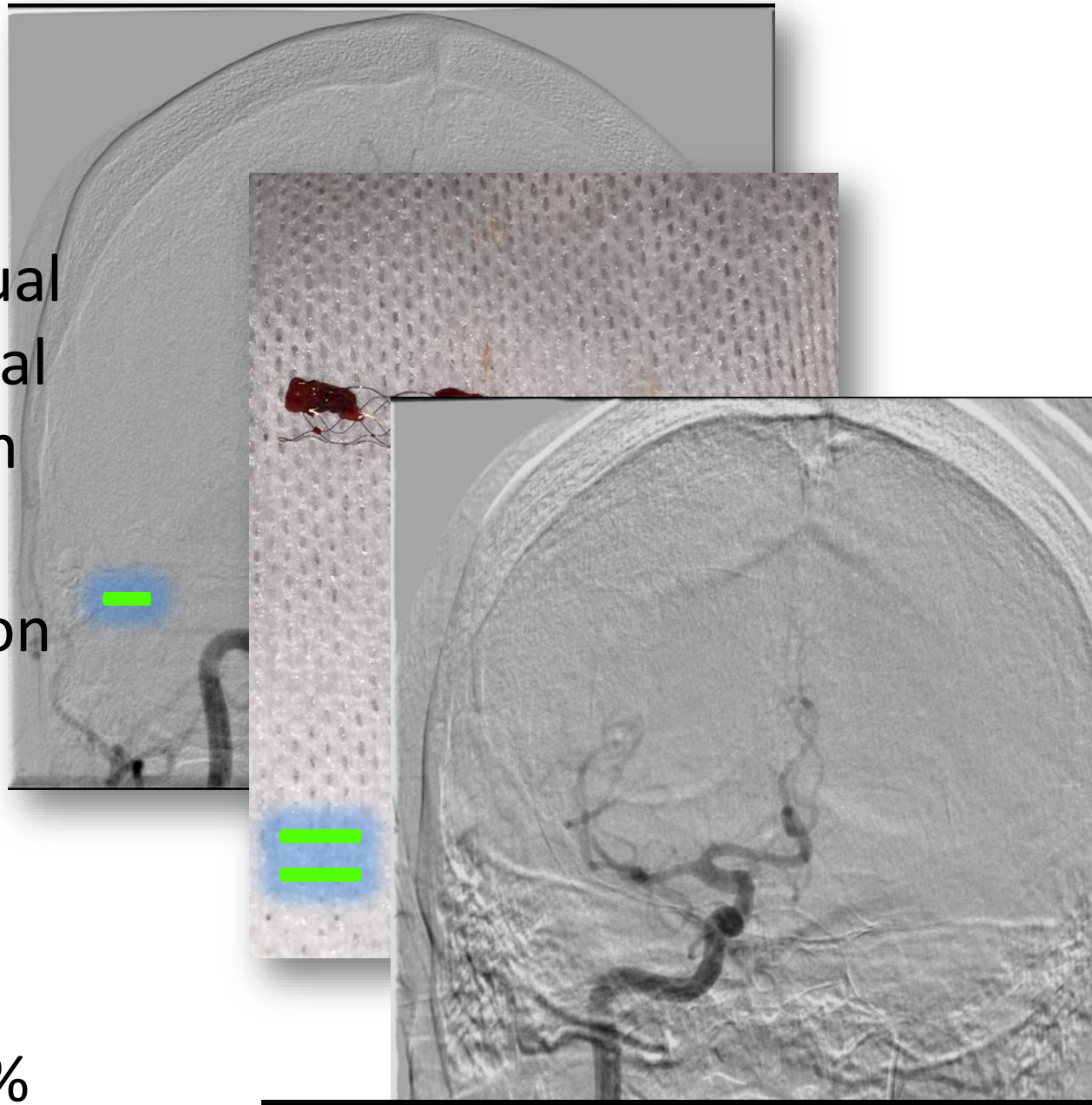
Endovascular treatment for acute ischemic stroke



(*Stroke* 2015 46:909-914)

MR CLEAN study

- Usual care vs. Usual care + intra-arterial therapy (<6h from onset)
- Anterior circulation large vessel occlusion
- ~90% received IV tPA
- TICI 2b or 3 in 59%



Berkhemer et al, *NEJM* 2015 372: 11-20

Post-TAVR Stroke: Conclusions I

- The incidence of presumed embolic phenomena on detailed neuroimaging (MRI) after TAVR is high (consistently $>$ 50%) but translates to low rates of clinical stroke
- The incidence of routinely detected stroke after surgical and transcatheter aortic valve replacement appears to be low and the reported rates are overall similar ($\cong$ 2-5%), mostly peri-procedural
- Major stroke rates are declining to $\cong$ 1-2% or less in contemporary TAVR practice even with neurology assessment

Post-TAVR Stroke: Conclusions II

- Peri-procedural stroke
  - In high and extreme risk groups, cost-benefit analysis will be important if use of neuro-protection is to be widespread ? Stratification of likelihood of stroke by anatomy
  - In intermediate and low risk groups, the impact of so-called “sub-clinical strokes” merits further study and may support use of neuro-protection
  - In all groups, the ability to treat post TAVR strokes with intra-arterial therapy is of enormous interest