

Stroke Basics after Cardiovascular Interventions: VARC 2 Definitions, Stroke Severity Assessment, Neuroimaging, & Neurocognitive Function

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Disclosure Statement of Financial Interest

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Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation / Financial Relationship

- Grant / Research Support
- Consulting Fees / Honoraria
- Shareholder / Equity

Company

- Abbott, Boston Scientific, Edwards Lifescience, Medtronic
- Meril Lifescience
- Claret, GDS, Medinol, Mitralign, Valve Medical

Strokes and TAVR

Background

Published on-line June 5, 2011
@ NEJM.org and print June 9, 2011

Editorial Response

EDITORIALS



Transcatheter Aortic-Valve Implantation — At What Price?

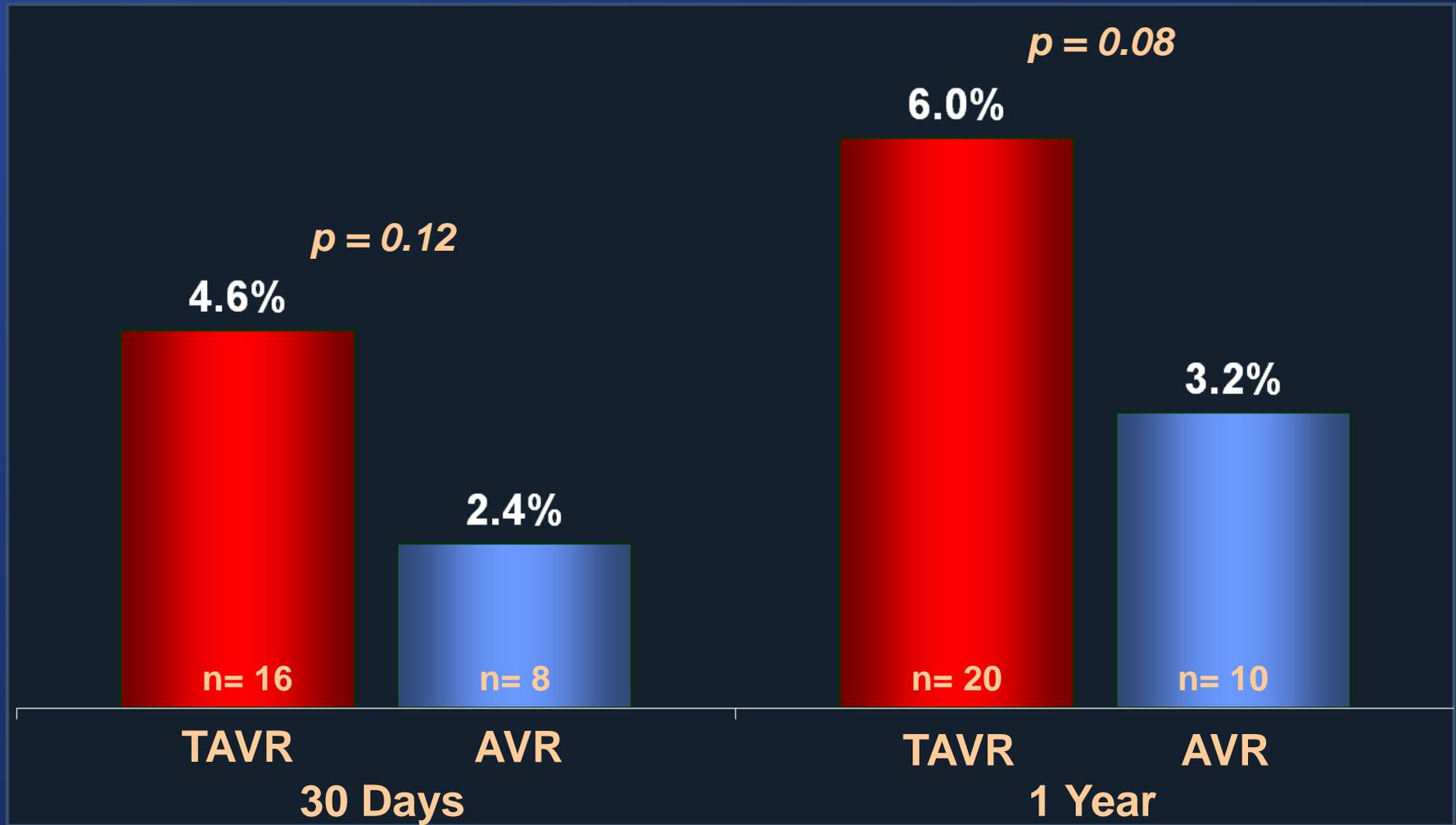
Hartzell V. Schaff, M.D.

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 in-

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

All Strokes (major and minor) at 30 Days & 1 Year



ITT Population

Strokes in PARTNER

High-risk cohort



Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: Occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial

D. Craig Miller, MD,^a Eugene H. Blackstone, MD,^b Michael J. Mack, MD,^c Lars G. Svensson, MD, PhD,^b Susheel K. Kodali, MD,^d Samir Kapadia, MD,^b Jeevanantham Rajeswaran, MSc,^b William N. Anderson, PhD,^e Jeffrey W. Moses, MD,^d E. Murat Tuzcu, MD,^b John G. Webb, MD,^f Martin B. Leon, MD,^d and Craig R. Smith, MD,^d on behalf of The PARTNER Trial Investigators and Patients, The PARTNER Stroke Substudy Writing Group and Executive Committee

Conclusions: After either treatment, there were 2 distinct hazard phases for neurologic events that were driven by different risk factors. Neurologic complications occurred more frequently after TAVR than AVR early, but thereafter the risk was influenced by patient- and disease-related factors. (J Thorac Cardiovasc Surg 2012;143:832-43)

D. Craig Miller et al; J Thorac Cardiovasc Surg 2012;143:832-43

All Strokes (high-risk cohort) RCT vs. NRCA



TAVR	RCT	NRCA	P-value
TA – 30 days	5.8% (104)	2.1% (988)	0.02
TA – 1 year	9.6% (104)	3.8% (988)	0.01
TF – 30 days	5.4% (423)	3.3% (1080)	0.06
TF – 1 year	7.3% (423)	4.8% (1080)	0.05

Important differences in stroke frequency for both TA and TF patients between the RCT and the NRCA cohorts = reduced strokes with increased operator experience!

Influence of Transcatheter Aortic Valve Replacement Strategy and Valve Design on Stroke After Transcatheter Aortic Valve Replacement



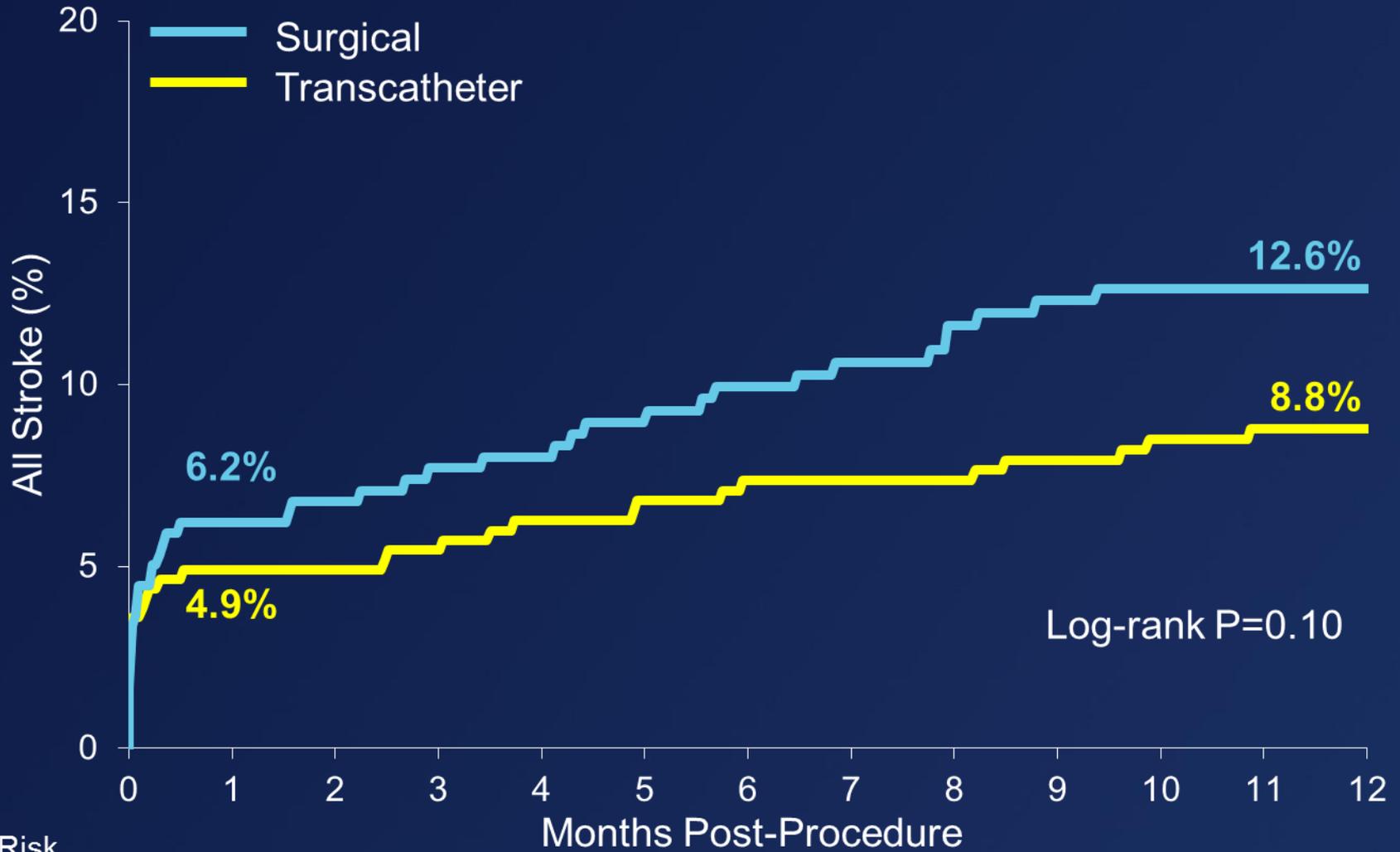
A Meta-Analysis and Systematic Review of Literature

Ganesh Athappan, MD,* R. Dilip Gajulapalli, MD,† Prasanna Sengodan, MD,* Anju Bhardwaj, MD,* Stephen G. Ellis, MD,† Lars Svensson, MD, PhD,† Emin Murat Tuzcu, MD,† Samir R. Kapadia, MD†
Cleveland, Ohio

- 25 multicenter registries and 33 single center studies
- No differences in 30-day stroke rates for...
 - TF vs. TA (multicenter 2.8% vs. 2.8% and single-center 3.8% vs. 3.4%)
 - CoreValve vs. SAPIEN (multicenter 2.4% vs. 3.0% and single-center 3.8% vs. 3.2%)
- ***Decline in stroke risk with increased operator experience and technological advancement (newer TAVR systems)***



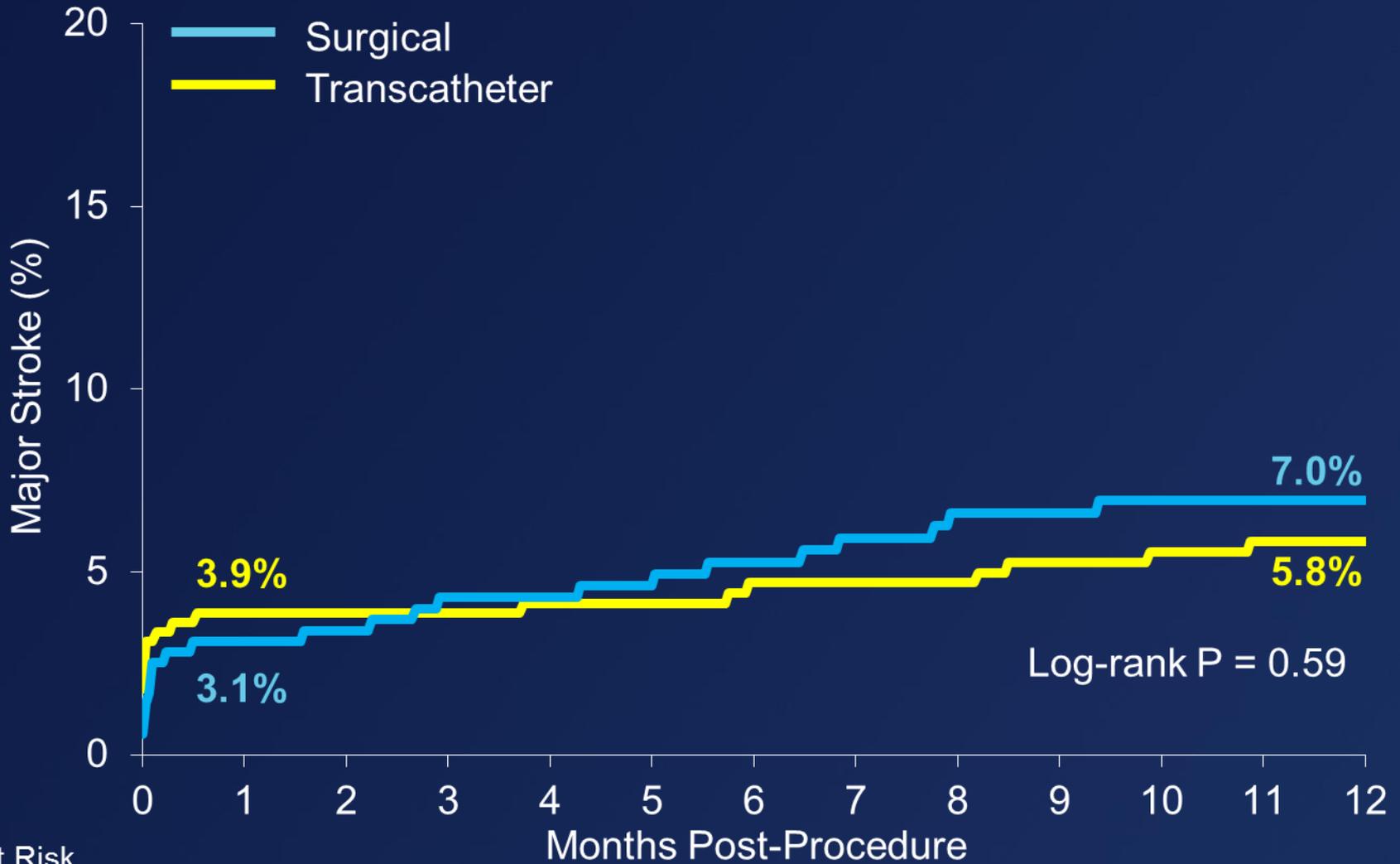
All Stroke



No. at Risk

Surgical	357	322	274	249
Transcatheter	390	363	334	314

Major Stroke



No. at Risk

Surgical	357	333	289	263
Transcatheter	390	367	344	322

Stroke after Aortic Valve Surgery: Results from a Prospective Cohort

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

- 196 patients with open surgical AVR at two sites, enrollment over 4 years (DeNOVO study)
- Pre and post-op neurological assessments and post-op MRI studies
- **Clinical strokes 17%, TIA 2%, in-hospital mortality 5%**
- **Mod-severe strokes (NIHSS ≥ 10) in 4% and strongly associated with increased in-hospital mortality (38% vs. 4%, $p = 0.005$)**
- In stroke-free pts (n=109), silent MRI infarcts in 59% (no Δ mortality or LOS)

Strokes and TAVR

VARC 2 Definitions

VARC 2 Definitions

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EXPEDITED REVIEW

Heart Valve Disease

Updated Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation

The Valve Academic Research Consortium-2 Consensus Document†

A. Pieter Kappetein,* Stuart J. Head, Philippe Généreux, Nicolo Piazza, Nicolas M. van Mieghem, Eugene H. Blackstone, Thomas G. Brott, David J. Cohen, Donald E. Cutlip, Gerrit-Anne van Es, Rebecca T. Hahn, Ajay J. Kirtane, Mitchell W. Krucoff, Susheel Kodali, Michael J. Mack, Roxana Mehran, Josep Rodés-Cabau, Pascal Vranckx, John G. Webb, Stephan Windecker, Patrick W. Serruys, Martin B. Leon

Rotterdam, the Netherlands

Kappetein AP et al. J Am Coll Cardiol 2012;60:1438-54

Table 4 Stroke and TIA

Diagnostic criteria

Acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke

Stroke: duration of a focal or global neurological deficit >24 h; OR <24 h if available neuroimaging documents a new haemorrhage or infarct; OR the neurological deficit results in death

TIA: duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct

No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumour, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the designated neurologist*

Confirmation of the diagnosis by at least one of the following:

Neurologist or neurosurgical specialist

Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone

Stroke classification

Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue

Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage

A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or haemorrhagic

Stroke definitions†

Disabling stroke: an mRS score of 2 or more at 90 days and an increase in at least one mRS category from an individual's pre-stroke baseline

Non-disabling stroke: an mRS score of <2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline

VARC 2 Definitions

1. Diagnostic Criteria

2. Stroke Classification

3. Stroke Definitions

*Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence of cerebral infarction-based upon neuroimaging studies (CT scan or Brain MRI).

†Modified Rankin Scale assessments should be made by qualified individuals according to a certification process (23-25).

mRS – modified Rankin Scale.

VARC 2 Stroke and TIA

1. *Diagnostic Criteria*

- ***Acute episode of a focal or global neurological deficit*** with clearly apparent neurological signs or symptoms consistent with stroke.
- ***Stroke:*** duration of focal or global neurological deficit > 24 h; OR < 24 h if neuroimaging documents hemorrhage or infarct; OR neurological deficit results in death.
- ***TIA:*** duration of a focal or global neurological deficit < 24 h AND neuroimaging doesn't show hem/infarct.
- ***No other readily identifiable non-stroke cause for the clinical presentation.***

VARC 2 Stroke and TIA

1. *Diagnostic Criteria*

- *Confirmation of the diagnosis by at least one of the following:*
 - Neurologist or neurosurgical specialist
 - Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone

VARC 2 Stroke and TIA

2. *Stroke Classification*

- ***Ischemic***: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue.
- ***Hemorrhagic***: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.
- ***A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic.***

VARC 2 Stroke and TIA

3. *Stroke Definitions**

- ***Disabling stroke:*** an mRS score of 2 or more at 90 days and an increase in at least one mRS category from an individual's pre-stroke baseline.
- ***Non-disabling stroke:*** an mRS score of < 2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline.

** Modified Rankin Scale assessments should be made by qualified individuals according to a certification process.*

VARC 2 Stroke and TIA

Miscellaneous

- ***Global encephalopathy*** should not be reported as a stroke unless there is unequivocal evidence of infarct/hemorrhage based upon neuroimaging studies.
- The FDA focuses on the ***clinically relevant consequences*** of vascular brain injury to determine the safety or effectiveness of a therapy.
- ***With regard to mRS, the FDA recommends:***
 - (1) determine the mRS in the context of other testing,
 - (2) have a defined set of questions,
 - (3) all scheduled visits should have neurological Sx surveillance (NIHSS, mRS, etc.)

VARC 2 Stroke and TIA

Miscellaneous

- ***A vascular/stroke neurologist*** should be included in trial planning, execution, and monitoring (CEC and DSMB)
- ***Low threshold for brain imaging to refine diagnostic accuracy*** (typically MRI for acute and chronic ischemia and hemorrhage and CT for acute and chronic hemorrhage and chronic ischemia)
- ***Strokes after TAVR are multifactorial:*** (1) document adjunct pharmacotherapy (esp. anti-thrombins and anti-platelet agents), (2) collect all relevant baseline characteristics (e.g. carotid disease), (3) report procedural events (e.g. post-Rx AF, hypotension, etc.)

VARC 2 Stroke and TIA

Miscellaneous

- ***Clinical endpoint for stroke is either all strokes or disabling strokes;*** often as a composite endpoint combined with death or incorporated into a MACCE definition.
- ***Must record in the CRF stroke therapy*** (e.g. thrombolysis or acute stroke intervention)

Strokes and TAVR

Stroke Scales

Diffusion-Weighted MRI Study

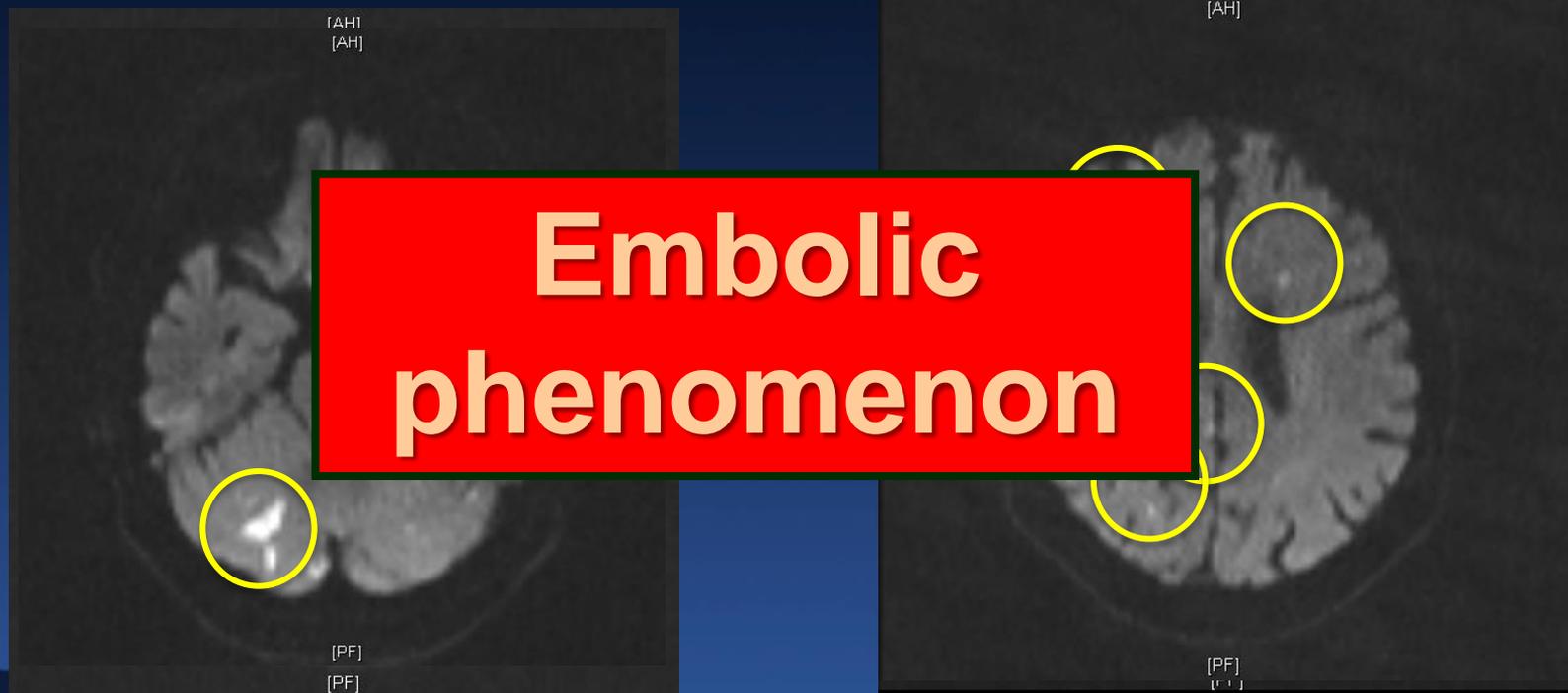
Philipp Kahlert, MD

West German Heart Center Essen

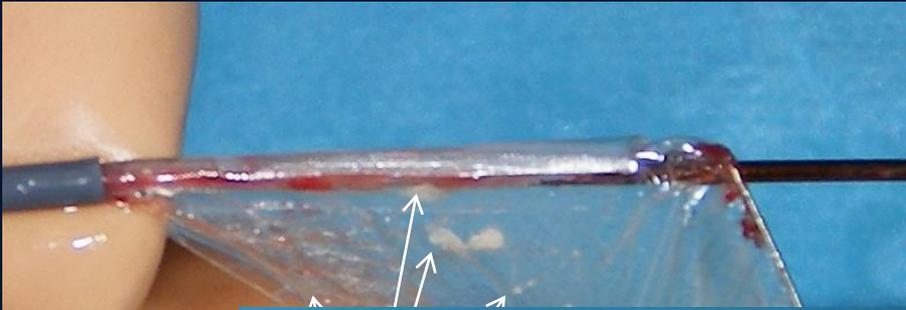
Pre-TAVI

Post-TAVI

Example of an 82-year-old patient two days after successful TAVI

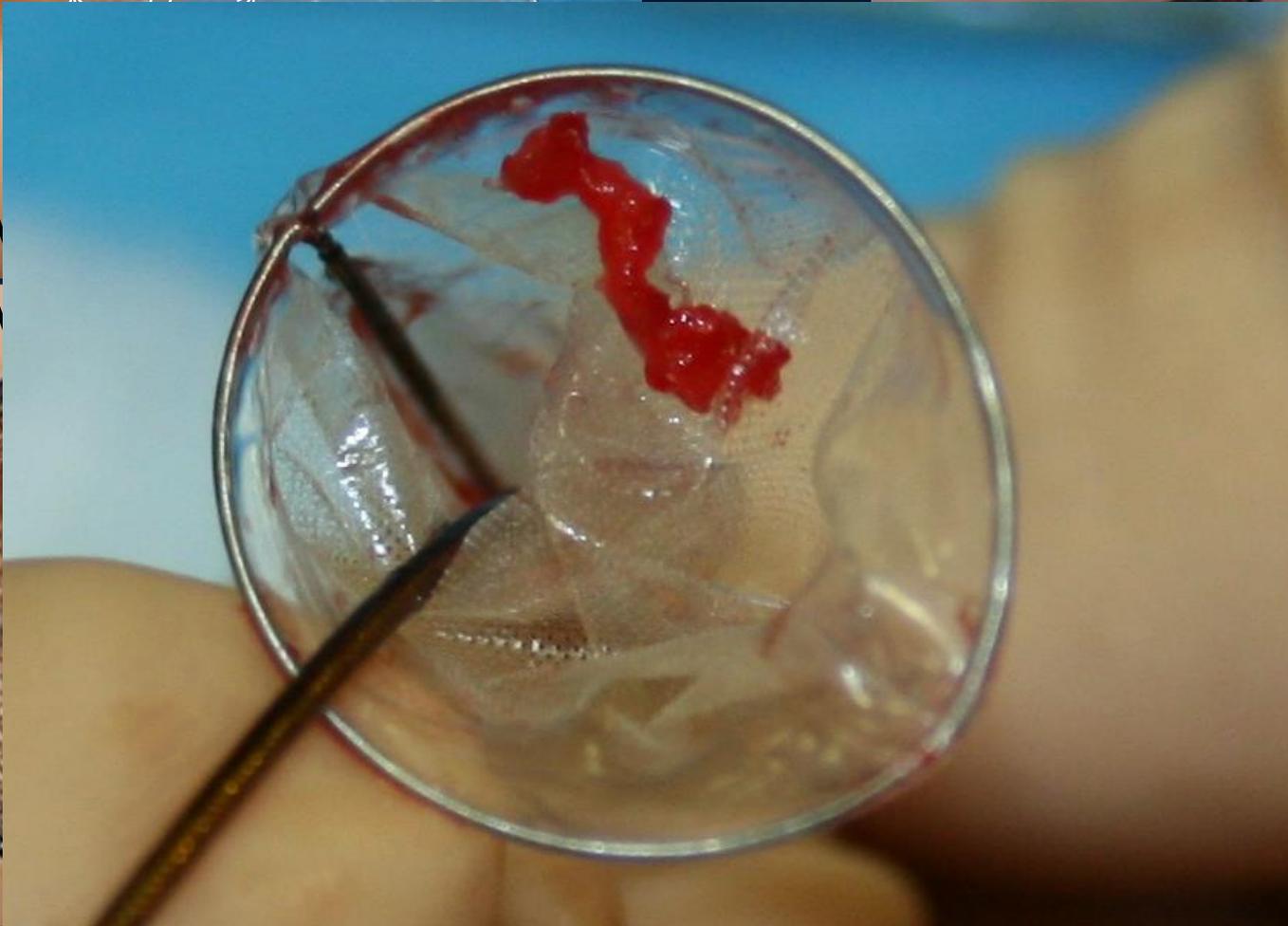


Embololic Material after TAVR



Embololic M

Embololic M



Modified Rankin Score

- 0 No symptoms at all
- 1 No significant disability despite symptoms; able to carry out all usual duties and activities
- 2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
- 3 Moderate disability; requiring some help, but able to walk without assistance
- 4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
- 5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention
- 6 Dead

Barthel Index

Barthel Index of Activities of Daily Living

Instructions: Choose the scoring point for the statement that most closely corresponds to the patient's current level of ability for each of the following 10 items. Record actual, not potential, functioning. Information can be obtained from the patient's self-report, from a separate party who is familiar with the patient's abilities (such as a relative), or from observation. Refer to the Guidelines section on the following page for detailed information on scoring and interpretation.

The Barthel Index

Bowels

- 0 = incontinent (or needs to be given enemas)
- 1 = occasional accident (once/week)
- 2 = continent

Patient's Score: _____

Bladder

- 0 = incontinent, or catheterized and unable to manage
- 1 = occasional accident (max. once per 24 hours)
- 2 = continent (for over 7 days)

Patient's Score: _____

Grooming

- 0 = needs help with personal care
- 1 = independent face/hair/teeth/shaving (implements provided)

Patient's Score: _____

Toilet use

- 0 = dependent
- 1 = needs some help, but can do something alone
- 2 = independent (on and off, dressing, wiping)

Patient's Score: _____

Feeding

- 0 = unable
- 1 = needs help cutting, spreading butter, etc.
- 2 = independent (food provided within reach)

Patient's Score: _____

Transfer

- 0 = unable – no sitting balance
- 1 = major help (one or two people, physical), can't
- 2 = minor help (verbal or physical)
- 3 = independent

Patient's Score: _____

Mobility

- 0 = immobile
- 1 = wheelchair independent, including corners, etc.
- 2 = walks with help of one person (verbal or physical)
- 3 = independent (but may use any aid, e.g., stick)

Patient's Score: _____

Dressing

- 0 = dependent
- 1 = needs help, but can do about half unaided
- 2 = independent (including buttons, zips, laces, etc.)

Patient's Score: _____

Stairs

- 0 = unable
- 1 = needs help (verbal, physical, carrying aid)
- 2 = independent up and down

Patient's Score: _____

Bathing

- 0 = dependent
- 1 = independent (or in shower)

Patient's Score: _____

Total Score: _____

(Collin et al., 1988)

National Institutes of Health Stroke Scale

TABLE 1

NATIONAL INSTITUTES OF HEALTH STROKE SCALE (NIHSS)

ITEM	SCORE
Level of consciousness	
Alert	0 points
Drowsy	1 point
Stupor	2 points
Coma	3 points
Response to 2 questions (orientation)	
Know age and current month	0 points
Answers 1 question correctly	1 point
Cannot answer either question correctly	2 points
Response to 2 commands	
Follows 2 commands correctly	0 points
Follows 1 command	1 point
Cannot follow either command	2 points
Best gaze (movement of eyes to left or right)	
Normal eye movements	0 points
Partial gaze paresis to one side	1 point
Forced gaze palsy to one side	2 points
Visual fields	
No visual loss	0 points
Partial homonymous hemianopia	1 point
Complete homonymous hemianopia	2 points
Bilateral visual loss	3 points
Facial motor function	
No facial weakness	0 points
Minor unilateral facial weakness	1 point
Partial unilateral facial weakness	2 points
Complete paralysis of 1 or both sides	3 points
Upper-extremity motor function (right and left scored independently 0 – 8 points)	
Normal movement	0 points
Drift of upper extremity	1 point
Some effort against gravity	2 points
No effort against gravity but moves	3 points
No movement	4 points
Lower-extremity motor function (right and left scored independently 0 – 8 points)	
Normal movement	0 points
Drift of lower extremity	1 point
Some effort against gravity	2 points
No effort against gravity but moves	3 points
No movement	4 points
Limb ataxia (cannot be tested in presence of paresis)	
No limb ataxia	0 points
Ataxia present in 1 limb	1 point
Ataxia present in 2 limbs	2 points
Sensory function	
No sensory loss	0 points
Mild-to-moderate sensory loss	1 point
Severe-to-total sensory loss	2 points
Language	
Normal language	0 points
Mild-to-moderate aphasia	1 point
Severe aphasia	2 points
Mute	3 points
Articulation	
Normal articulation	0 points
Mild-to-moderate dysarthria	1 point
Severe dysarthria	2 points
Extinction or inattention (neglect)	
No neglect or extinction	0 points
Visual or sensory inattention or extinction	1 point
Profound inattention to visual and sensation	2 points

National Institutes of Health Stroke Scale (NIHSS)

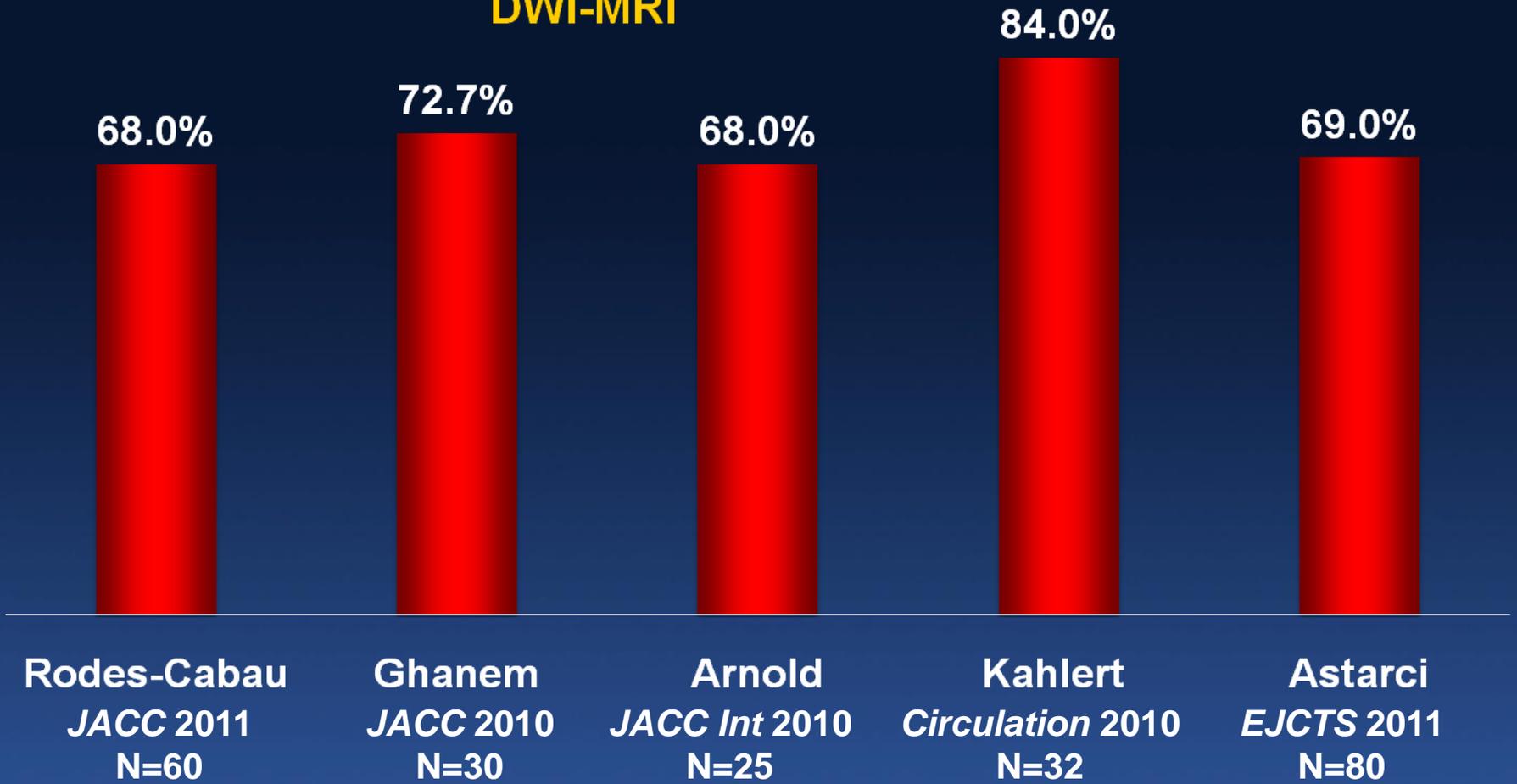
- 15-item neurologic exam to evaluate the effect of stroke on the levels of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss.
- Ratings for each item are scored with 3 to 5 grades with 0 as normal.
- Examiners should be certified (relatively easy).
- The stroke scale is valid for predicting lesion size and can serve as a measure of stroke severity.
- The NIHSS has been shown to be a predictor of both short and long term outcome of stroke patients.

Strokes and TAVR

Neurocognitive Function

Neuro-imaging with TAVR

**% of patient with new ischemic lesions on
DWI-MRI**





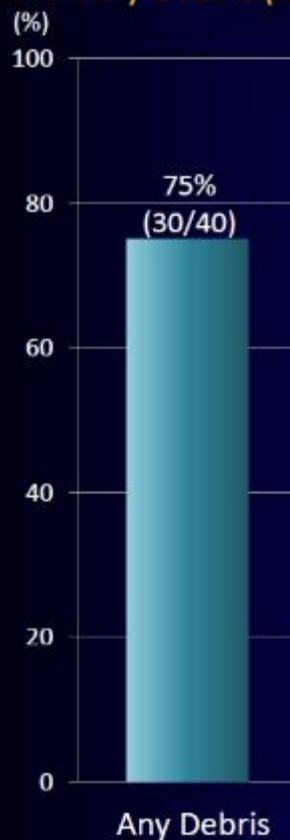
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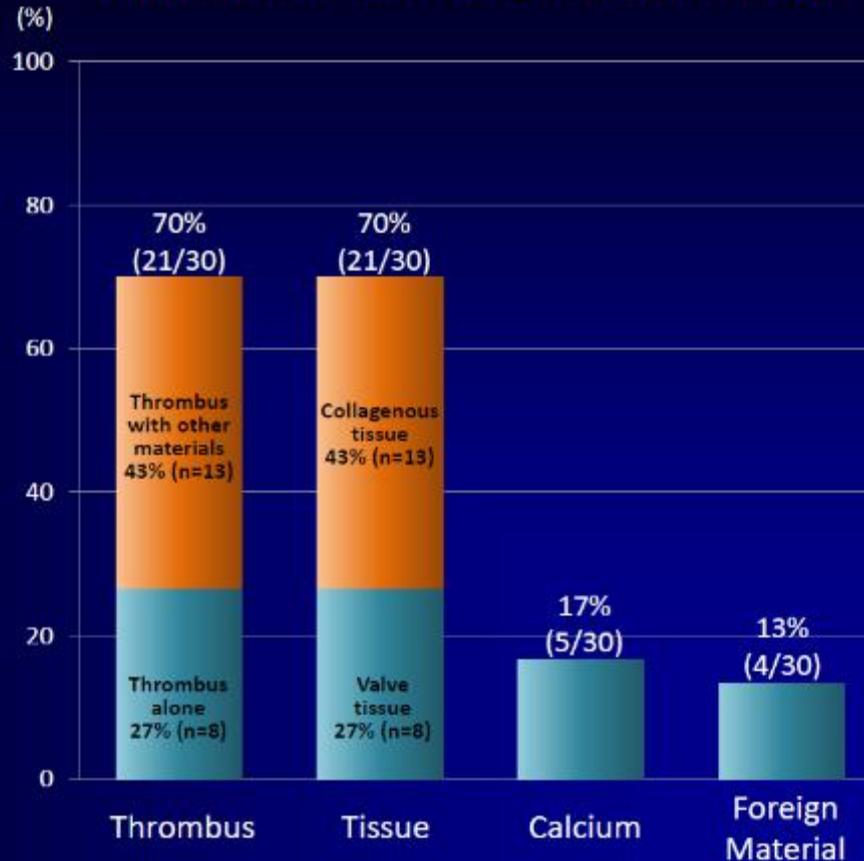
40%

stem

Prevalence of Cases with Any Debris (n=40)

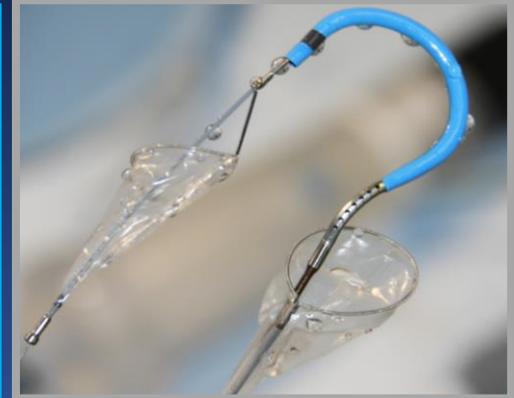
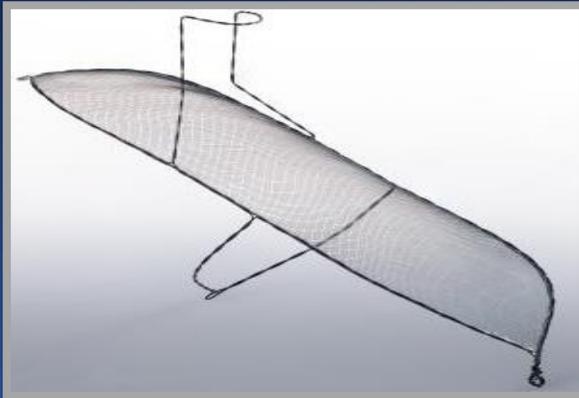


Distribution of Debris Captured (n=30)



Cerebral Embolic Protection Devices

TriGuard™ Cerebral	Embrella™	Claret Sentinel™
Deflector	Deflector	Dual Filter
Femoral Access	Radial Access	Radial Access
9F Sheath (7F Delivery)	6F Shuttle Sheath	6F Radial Sheath



Common Tests Used to Assess Brain Function post TAVR

- NIHSS (National Institutes of Health Stroke Scale); designed to assess the severity of clinically evident stroke
- mRS (modified Ranking Scale); designed for stroke patients to assess the degree of long term disability
- MMSA (Mini Mental State Assessment); tests 5 cognitive areas with 30 questions (5-10 min), relies heavily on verbal, writing and reading skills

The Dilemma: What is Cerebral Injury?



Circulation
Cardiovascular Interventions



Neurological Injury After Transcatheter Aortic Valve Implantation: Are the Trees Falling Silently or Is Our Hearing Impaired?
Jeffrey N. Browndyke and Joseph P. Mathew

Circ Cardiovasc Interv. 2013;6:599-601
doi: 10.1161/CIRCINTERVENTIONS.113.001017
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Print ISSN: 1941-7640. Online ISSN: 1941-7632



clinical

?%

injury

No

Diagnosis

VARC

Assessment

Heart-Team

+ NEURO / PSY

+ MRI

+LAB

Victim(s)

Patient / Relatives / Society

DWI Lesions and NeuroCognitive (NC) Function

First Author (ref#)	n	% of patients with NC decline	% of patients with new DWI lesions	Procedure/diagnosis	Comments
Restrepo (8)	13	77%	31%	CABG	Extensive NC testing Pts with new DWI lesions had larger NC decline
Choi (9)	25 10 w new mental 15 wo new mental	100%	70% 20%	Vascular Dementia	Extensive NC testing New lesions correlated with new mental change
Lund (10)	33 trans radial 9 trans femoral	16.7%	15% TR 0% TF	Left Heart Catheterization	Extensive NC testing Patients with new DWI lesions had larger NC decline
Zhoue (11)	68 CAS 100 CEA	2.9% 2%	46.3% 12%	Carotid stenting Carotid endarterectomy	With embolic protect protection NC examination not defined
Schwartz (12)	30 Cath 39 CABG 33 controls	Not reported	3.3% 17.9%	Coronary catheterization CABG	Extensive NC testing # of DWI lesions correlated with NC decline
Sweet (13)	42 PCI 43 CABG	6% 7%	Not done	Coronary stenting CABG	Extensive NC testing 1 year fu
Blum (14)	658	97%	26.4%	Elderly non-dementia patients	Extensive NC testing Brain infarcts are associated with memory loss
Tatemichi (15)	3697	27% dementia		Healthy elderly patients	Extensive NC testing, 3.6 years fu; silent infarcts > 2X risk of dementia and associated with worse NC decline
Omran (16)	101	3%	22%	Retrograde aortic valve cath	NIHHS level of stroke assessment
Zhou (17)	51 16 CAS, 35 CEA	41%	69%	Carotid stenting Carotid endarterectomy	Extensive NC testing; DWI lesions only significant predictor of NC decline
Knipp (18)	39	56% ac 23% 3 mo 31% 3 years	51%	CABG	Extensive NC testing 56% decline acutely and 31% decline at 3 years

Lack of Data Measuring NeuroCognitive Function post TAVR

First Author (ref#)	n	# of patients with neurological symptoms	% of patients with new DWI lesions	Total # (mean #) of DWI lesions	Procedure/valve	Comments
Kahlert (1)	22	0% acutely and at 3 months	86%	89	Balloon expandable	NIHSS*** acutely MMSA* and mRS** at 30 days,
Kahlert (1)	10	0% acutely and at 3 months	80%	26	Self-expanding	NIHSS, MMSA and mRS at 30 days
Astarci (2)	21	0% acutely	90%	(6)	Trans femoral	NIHSS
	14	0% acutely	93%	(6.6)	Trans apical	NIHSS
Ghanem (3)	22	10% acutely 3.6% at 3 months	72.7%	75	Self expanding	NIHSS
Stolz (4)	37	8.1% acutely	38%	20	Surgical	Neurological examination not defined
Knipp (5)	30	Mean decline acutely Mean recovery at 4 months	47%	41	Surgical 24 AVR, rest MVR or a combination,	Extensive neurocognitive testing
Arnold et al (6)	25	20% acutely (2.5% stroke)	68%	Not reported	Trans apical	NIHSS level of testing
Rodes-Cabau (7)	60	0% acutely (3.3% stroke)	66% TF 71% TA	Not reported	Trans femoral (29) Trans apical (31)	MMSA NIHSS

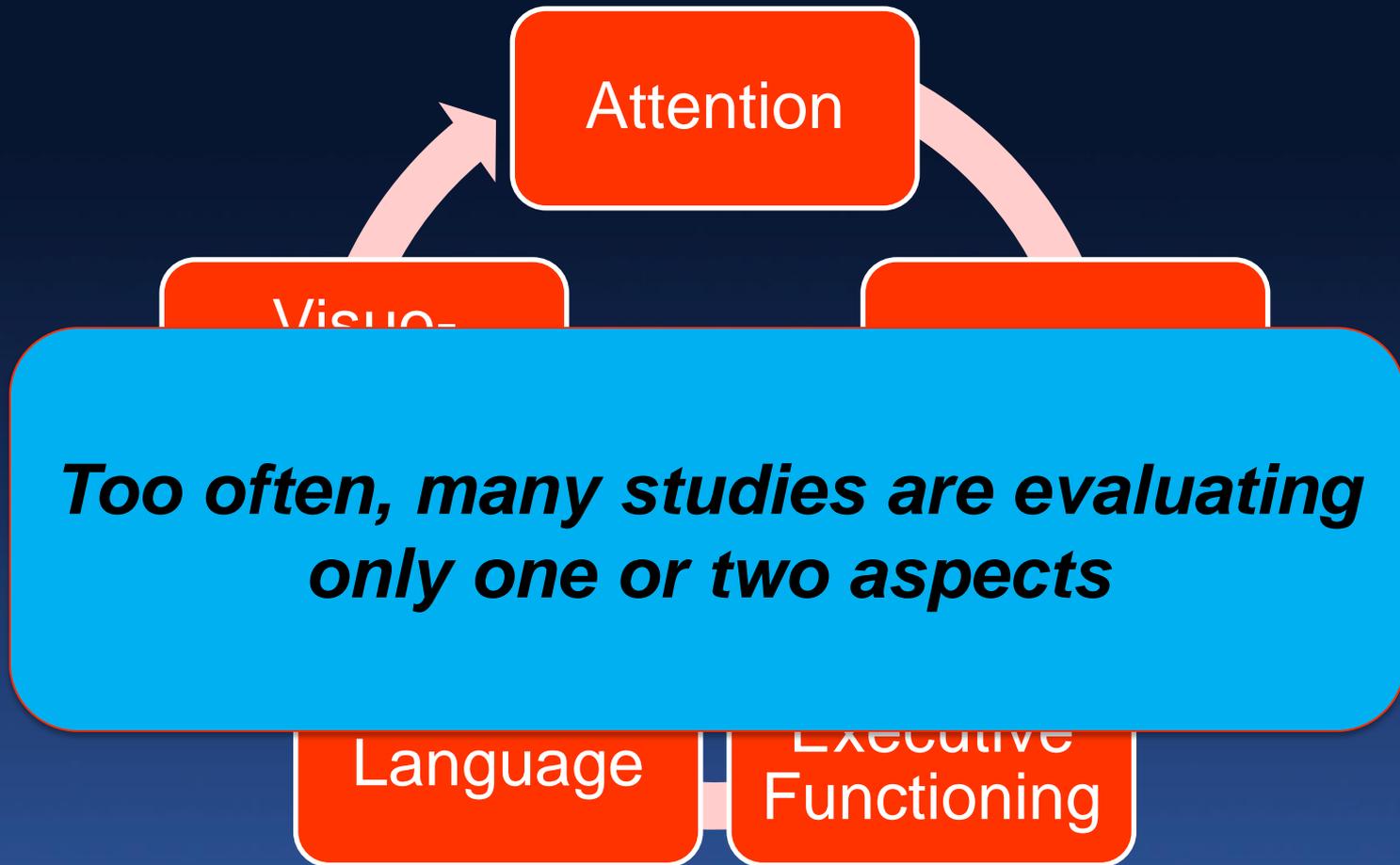
*MMSA (Mini Mental State Assessment); tests 5 cognitive areas with 30 questions (5-10 min), relies heavily on verbal, writing

**mRS (modified Ranking Scale); designed for stroke patients to assess the degree of long term disability

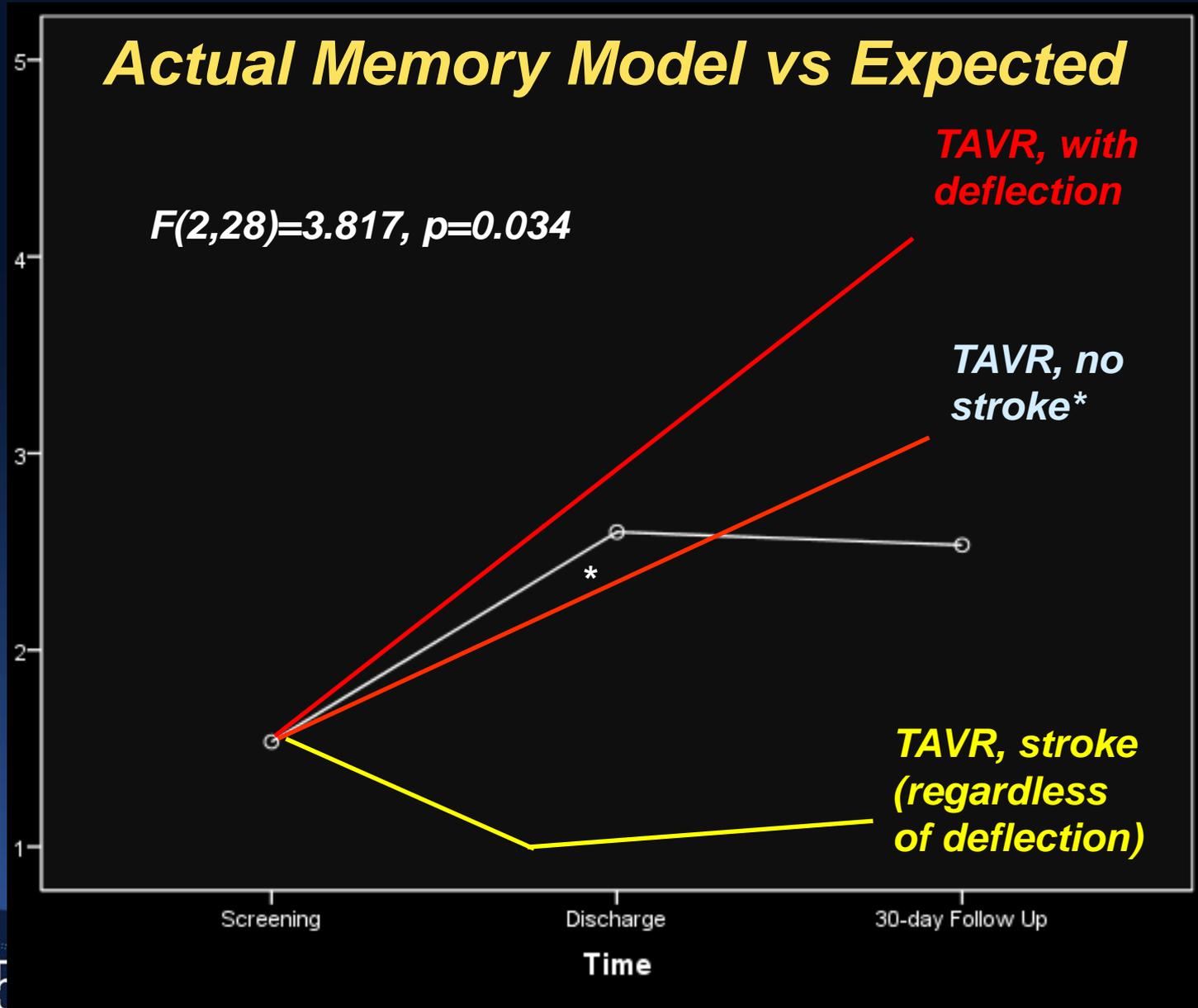
***NIHSS (National Institutes of Health Stroke Scale); designed to assess the severity of clinically evident stroke

Cognitive Function

Five Dimensions of Cognition

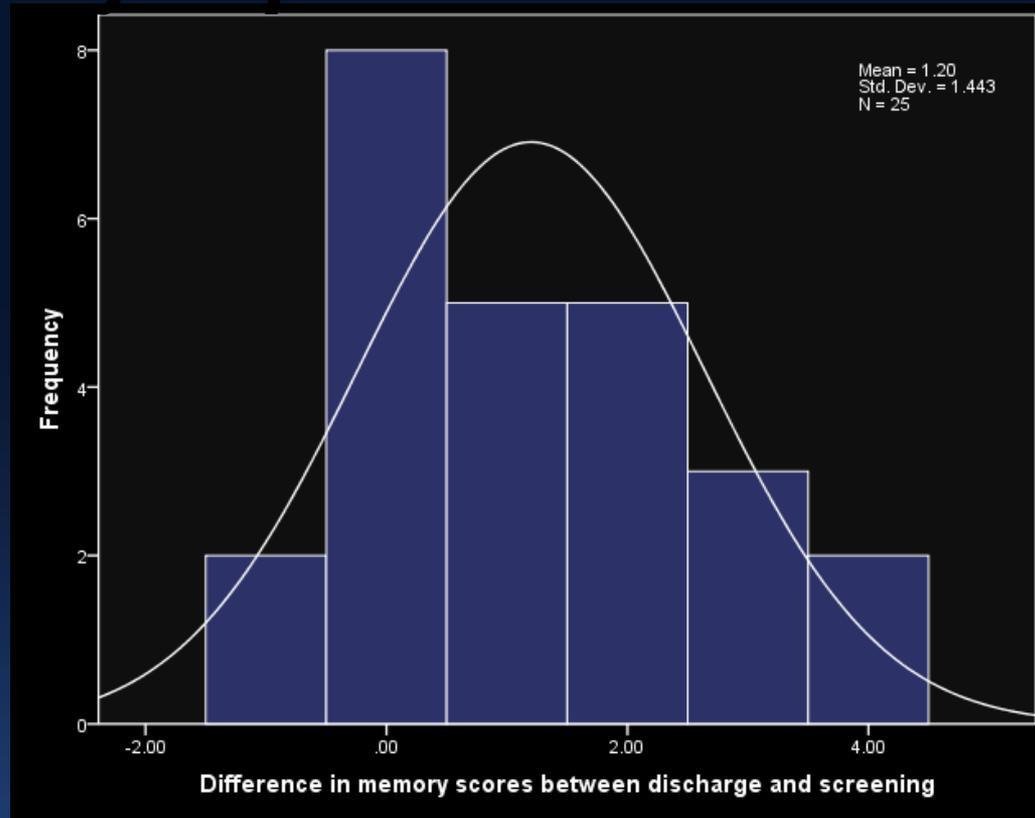
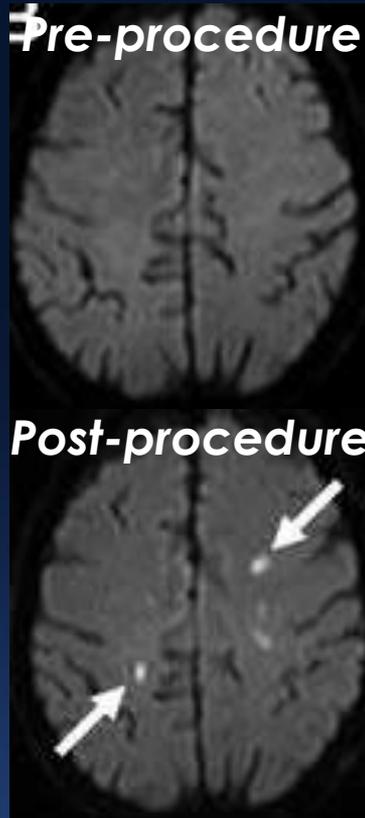


DEFLECT I Study



DEFLECT I Study

Max Lesion Volume correlates with less memory improvement after TAVR



	Memory Screen	Memory Discharge	Discharge-Screen
Total lesion no.	-0.286, p=0.236	-0.353, p=0.138	-0.102, p=0.678
Max lesion vol.	-0.105, p=0.669	-0.370, p=0.119	-0.348, p=0.145
Total lesion vol.	-0.275, p=0.255	-0.399, p=0.091	-0.174, p=0.476

Heart Disease and Neurocognition

- **CABG**
 - **Atrial Fibrillation**
 - **Cardiac Arrest**
 - **Heart Failure**
 - **TAVR**
- Embolic**
- Perfusion Deficit**
- Both?**

Continuum of Cognitive Complexity

*Attention, Working Memory
Executive Function
Reasoning
Processing Speed*

*Multiple Stroke,
Diffuse Vascular Disease,
Hemodynamic Compromise*

*Language
Memory
Praxis, Copying*

Focal Stroke

Sensory Discrimination

Sensory Perception

Strokes and TAVR

Final Thoughts

Strokes and TAVR

Final Thoughts

- **Strokes after TAVR will continue to be a clinical problem and a controversial issue, especially in a climate of careful systematic neurological scrutiny.**
- **The VARC 2 stroke definitions are robust, clinically relevant, and are useful for inter-study comparisons.**
- **The clinical impact of neuro-imaging perfusion deficits and the value of embolic protection devices requires further evaluation.**
- **Neurocognitive functional assessment is an area of confusion and excitement! In the future, changes in these more subtle cognitive findings may become a worthwhile clinical endpoint.**