Why Cerebral Protection after TAVR Will Become the Standard of Care

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Stanford University, Palo Alto, California, USA

Eberhard Grube, MD

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

Physician Name	Company/Relationship
Eberhard Grube, MD	Medtronic, CoreValve: C, SB, AB, OF Direct Flow: C, SB, AB Mitralign: AB, SB, E Boston Scientific: C, SB, AB Biosensors: E, SB, C, AB Cordis: AB Abbott Vascular: AB InSeal Medical: AB, E, Valtech: E, SB, Claret: SB Keystone: AB

Key

G – Grant and or Research Support E – Equity Interests S – Salary, AB – Advisory Board
C – Consulting fees, Honoraria R – Royalty Income I – Intellectual Property Rights
SB – Speaker's Bureau O – Ownership OF – Other Financial Benefits'

Let Me Lay out my Position in Advance.

1. I am a TRUE believer in TAVR and its role in treating AS in defined patient groups
2. However, TAVR undoubtedly causes embolic showers to the Brain, which cause lesions: some ‘silent’, some more clinically obvious
3. Many TAVR studies under-report Stroke & few employ independent neurologists
4. Percentages do not always tell the whole story and Stroke is truly devastating
5. If cerebral protection can reduce or eliminate lesions in the brain, then it should become routine practice

Stroke Remains a Real Risk

Clinical Outcome at 30 Days (I)

CHOICE

	Balloon-expandable (n=121)	Self-expandable (n=117)	p-value
Death			
From any cause	5/121 (4.1%)	6/117 (5.1%)	0.77
From CV causes	5/121 (4.1%)	5/117 (4.3%)	0.99
Stroke	7/121 (5.8%)	3/117 (2.6%)	0.33
Major	3/121 (2.5%)	3/117 (2.6%)	0.99
Minor	4/121 (3.3%)	0/117 (0.0%)	0.12
Myocardial infarction	1/121 (0.8%)	0/117 (0.0%)	0.99
Bleeding			
Life threatening	10/121 (8.3%)	14/117 (12.0%)	0.35
Major	23/121 (19.0%)	17/117 (14.5%)	0.36
Minor	11/121 (9.1%)	9/117 (7.7%)	0.70
Major or minor	34/121 (28.1%)	26/117 (22.2%)	0.30
Vascular complications			
All	17/121 (14.0%)	15/117 (12.8%)	0.78
Major	12/121 (9.9%)	13/117 (11.1%)	0.76
Minor	5/121 (4.1%)	2/117 (1.7%)	0.28

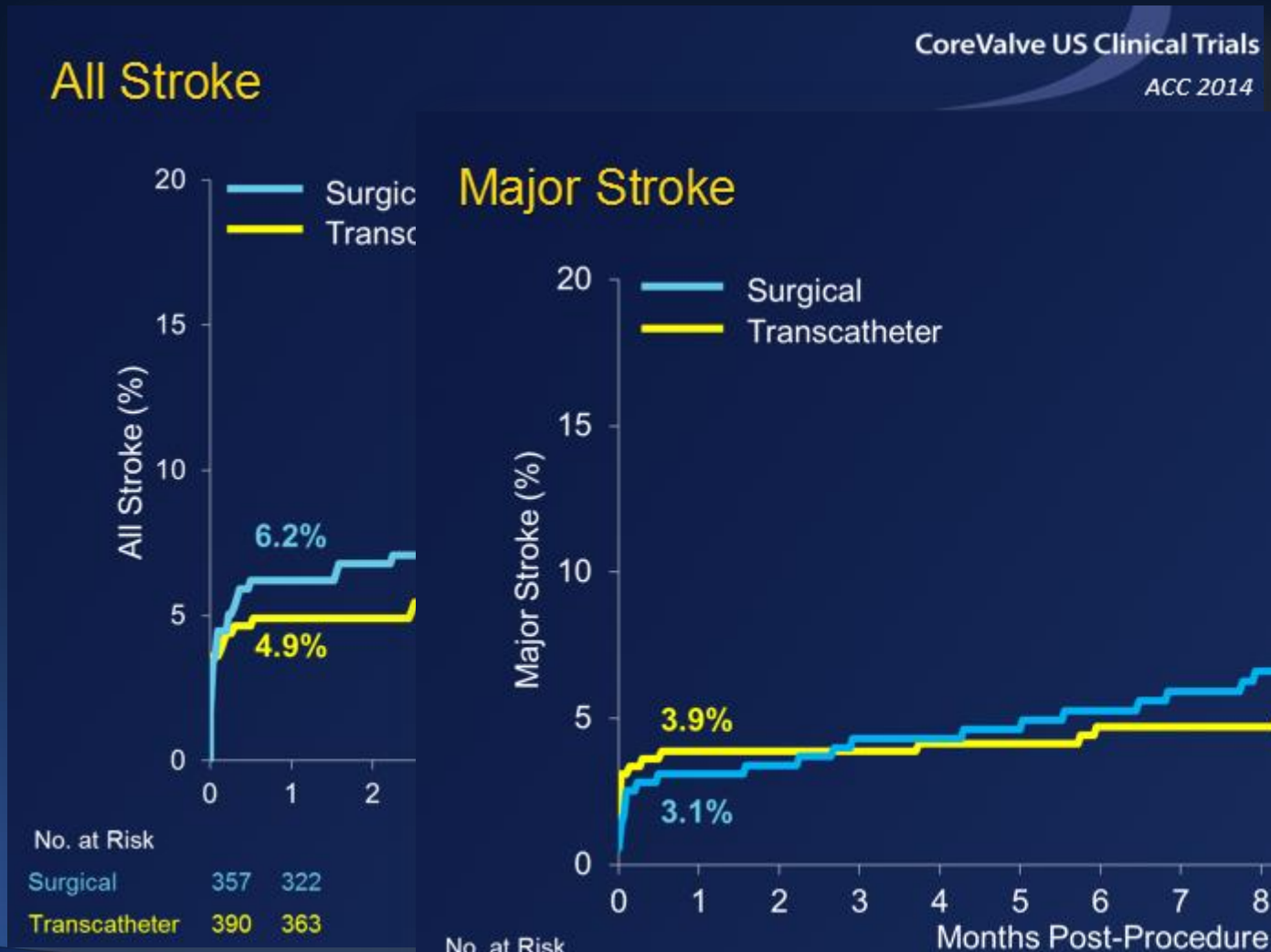
ACC.14

24

SEGEBERGER KLINIKEN

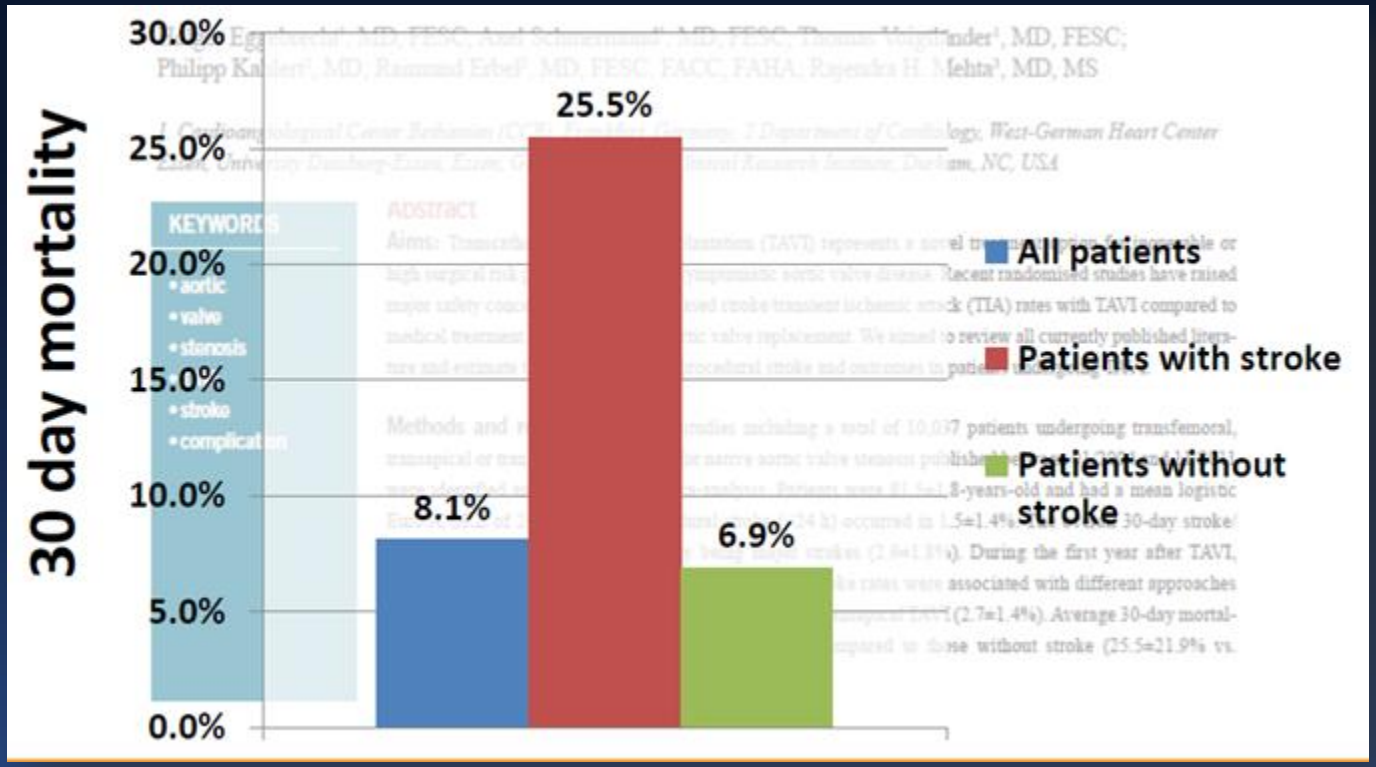
JAMA. 2014;311(15):1503-1514. doi:10.1001/jama.2014.3316
Published online March 30, 2014

CoreValve High Risk Pivotal RCT from ACC 2014



Stroke Has a Significant Impact on Mortality

Meta-analysis of 10,037 published patients



H. Eggebrecht et al, EuroIntervention 2012, 8: 129-138

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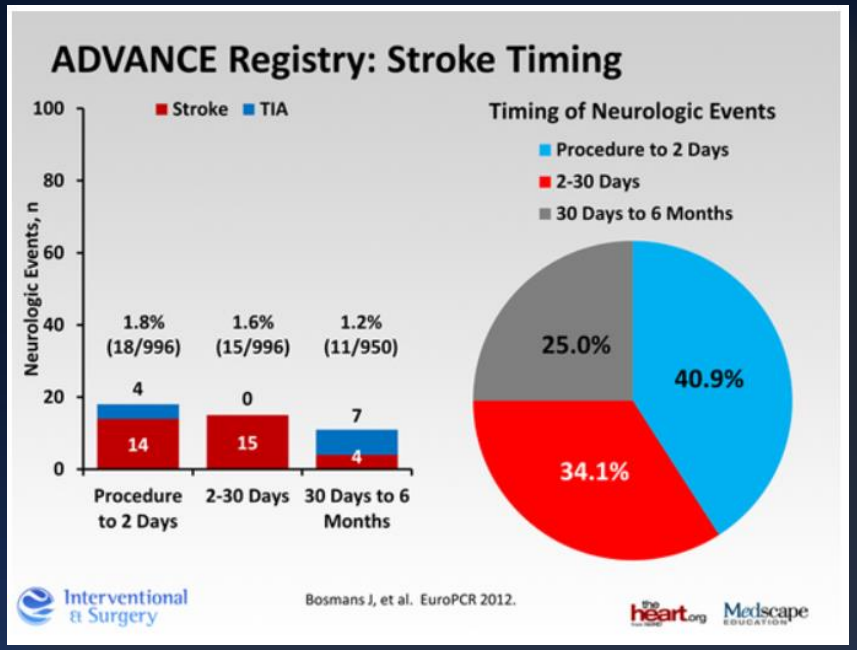
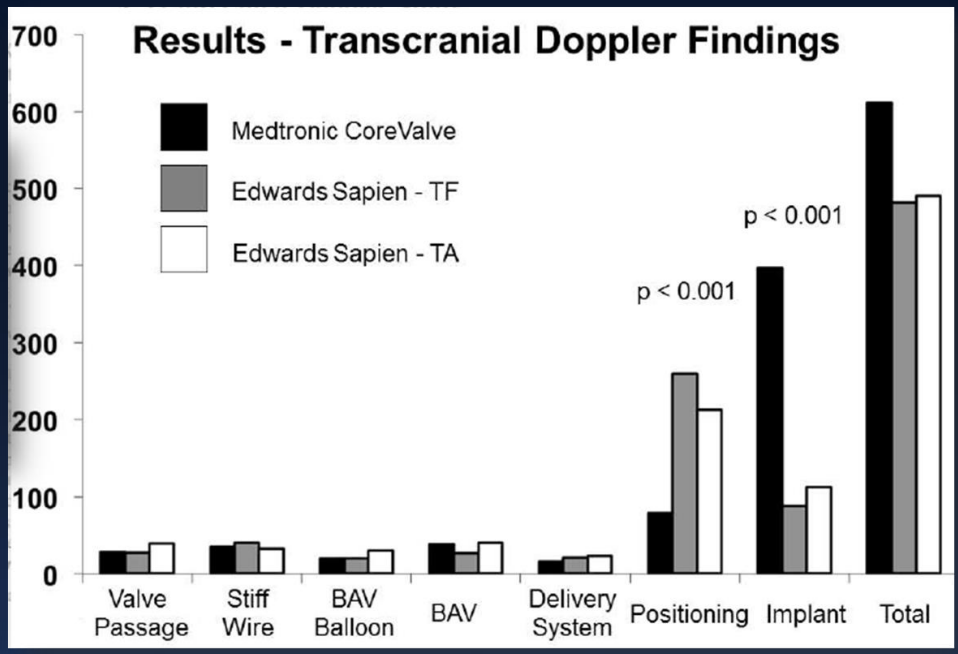
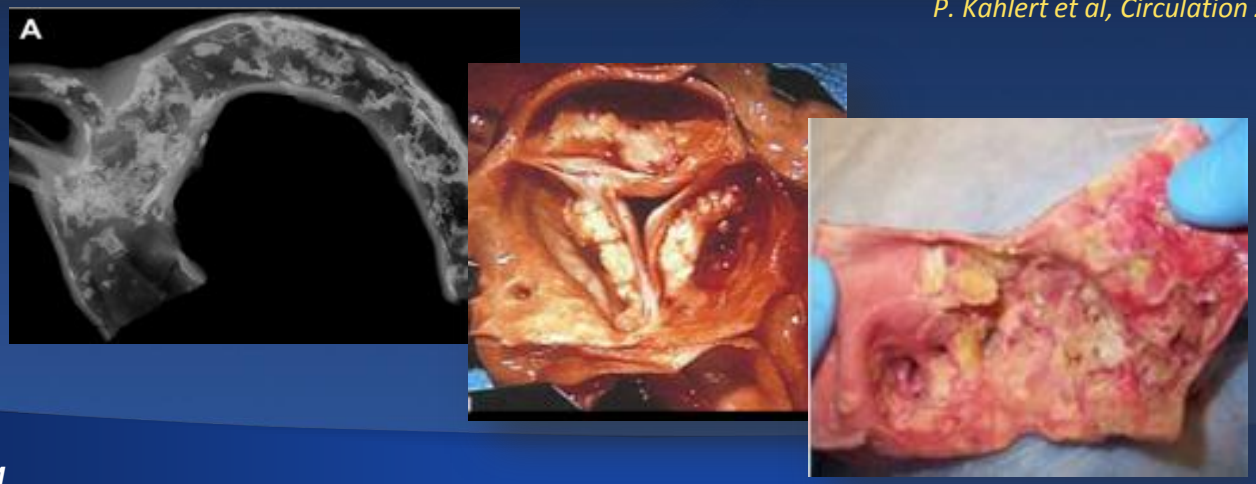
Many Strokes Occur Periprocedurally



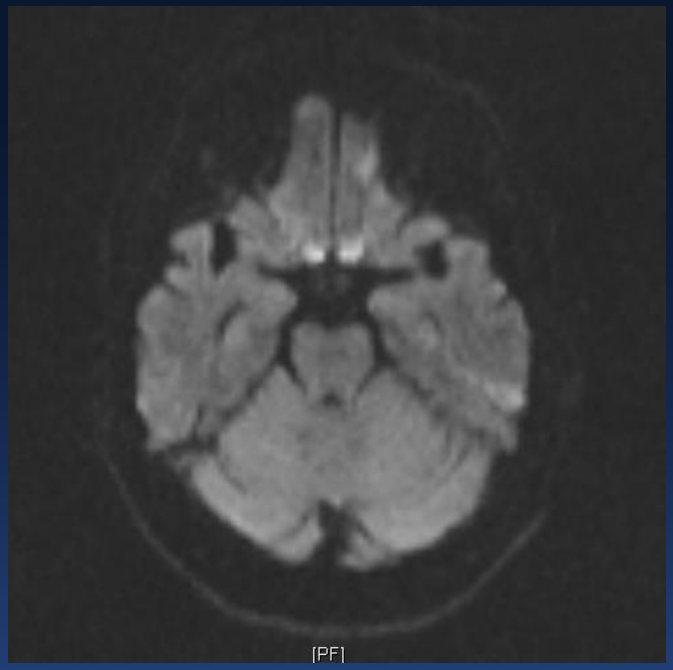


P. Kahlert et al, Circulation 2012;126:1245-1255

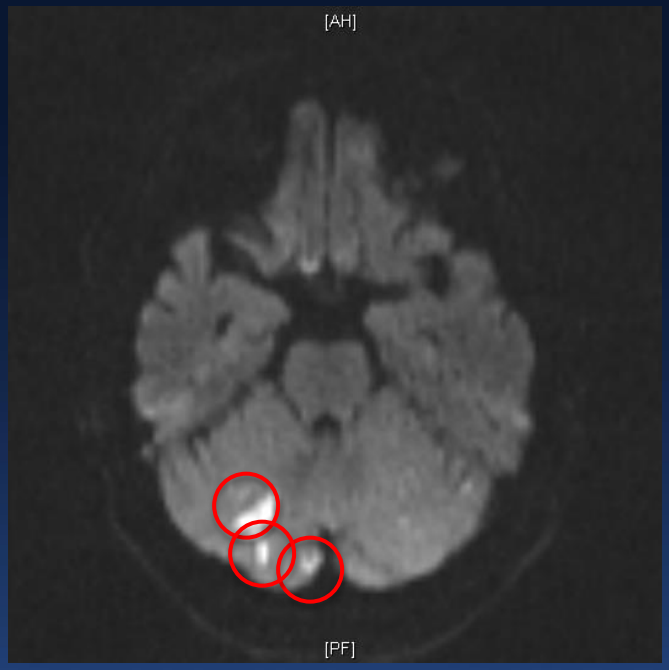


Diffusion Weighted MRI Study

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



Before TAVR



Two days after TAVR

Treating Physician:
Philipp Kahlert, MD
West German Heart Center Essen
University Duisburg-Essen

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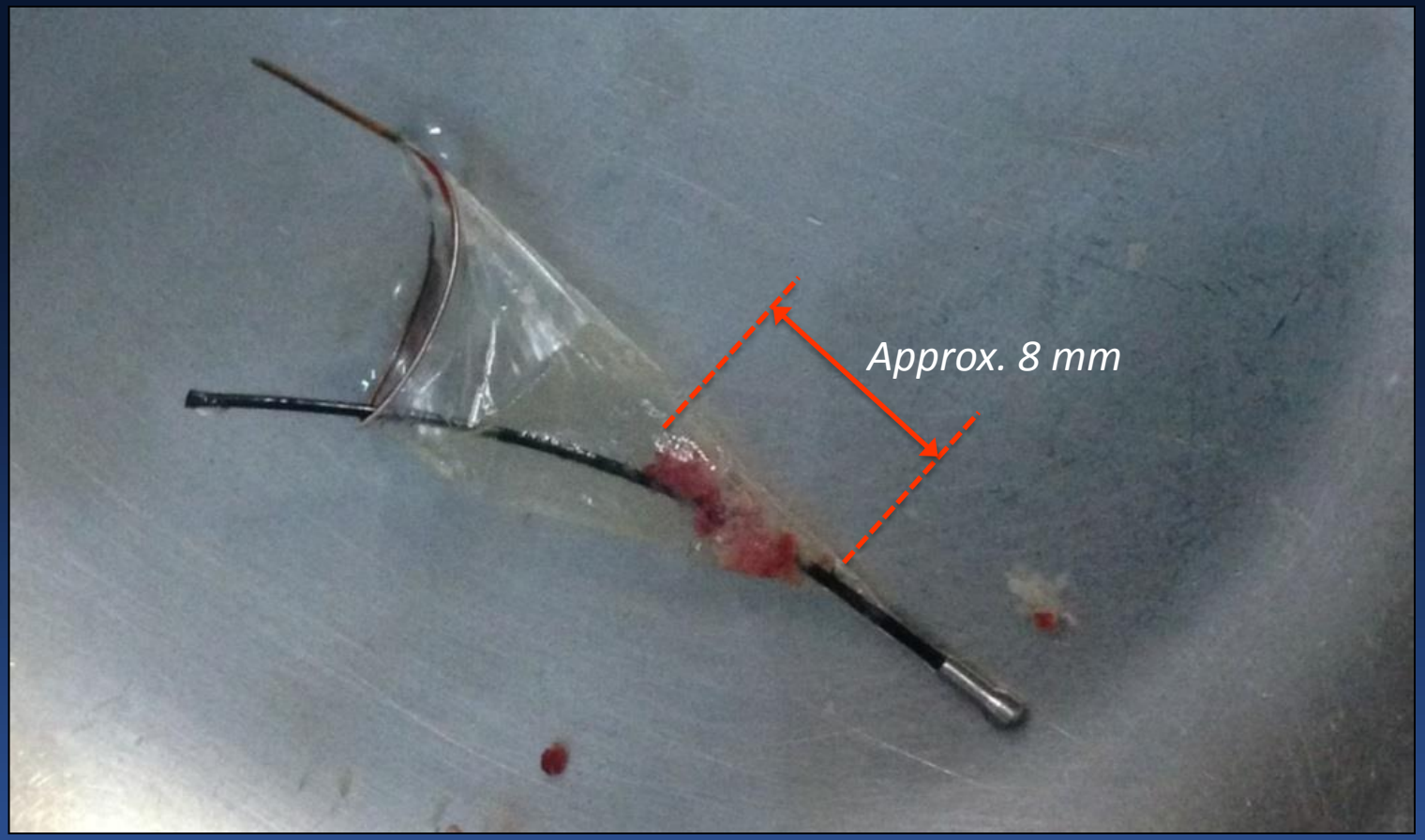
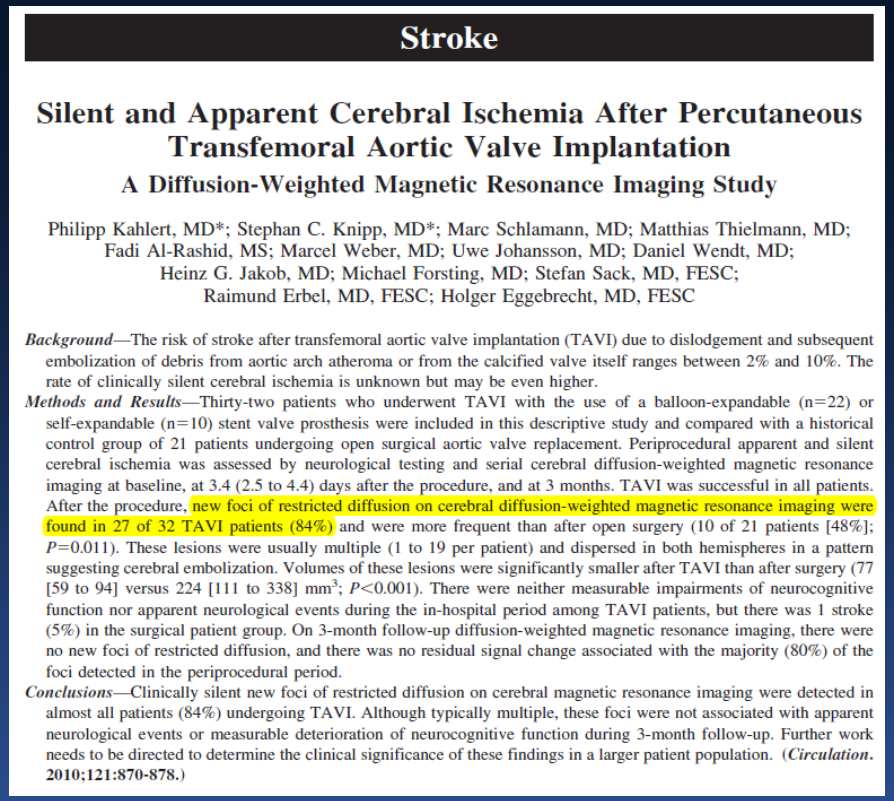
TCT 2013 Live TAVR Case: Dr. Alex Abizaid, Brazil

...”this would have definitely stroked the patient…”



Clinical Need—Stroke, Silent and Apparent

A closer look at the patients reveals a looming risk: >70% of TAVR patients have ischemic brain lesions when examined by DW-MRI



Stroke

Silent and Apparent Cerebral Ischemia After Percutaneous Transfemoral Aortic Valve Implantation

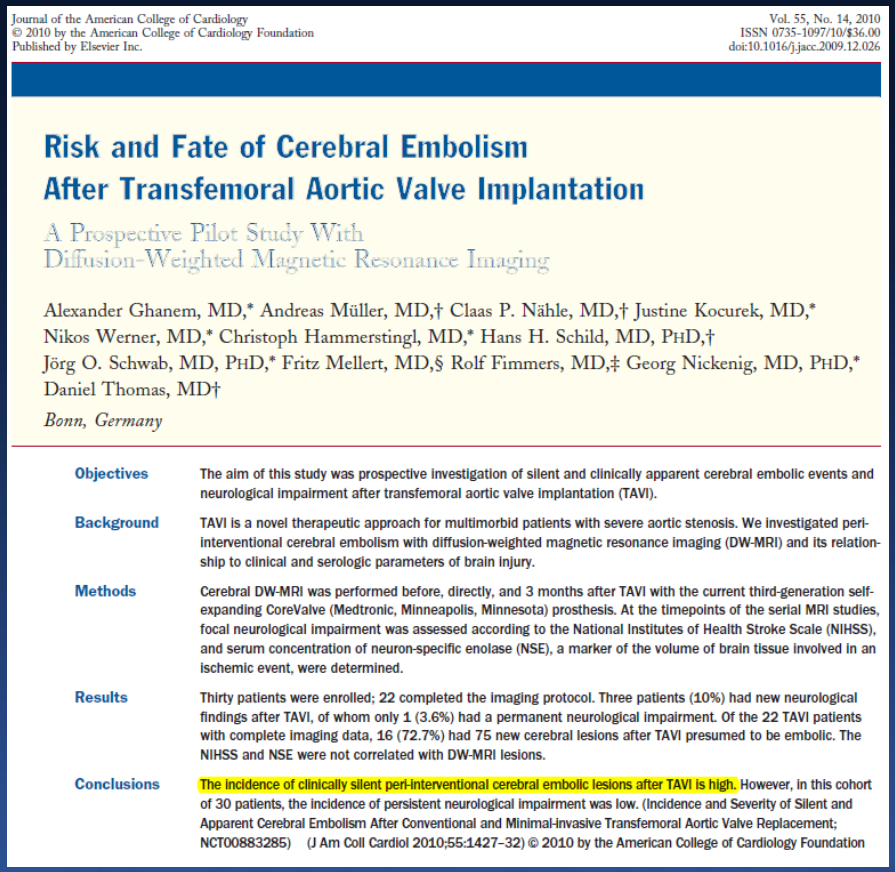
A Diffusion-Weighted Magnetic Resonance Imaging Study

Philipp Kahlert, MD*; Stephan C. Knipp, MD*; Marc Schlamann, MD; Matthias Thielmann, MD; Fadi Al-Rashid, MS; Marcel Weber, MD; Uwe Johansson, MD; Daniel Wendt, MD; Heinz G. Jakob, MD; Michael Forsting, MD; Stefan Sack, MD, FESC; Raimund Erbel, MD, FESC; Holger Eggebrecht, MD, FESC

Background—The risk of stroke after transfemoral aortic valve implantation (TAVI) due to dislodgement and subsequent embolization of debris from aortic arch atheroma or from the calcified valve itself ranges between 2% and 10%. The rate of clinically silent cerebral ischemia is unknown but may be even higher.

Methods and Results—Thirty-two patients who underwent TAVI with the use of a balloon-expandable (n=22) or self-expandable (n=10) stent valve prosthesis were included in this descriptive study and compared with a historical control group of 21 patients undergoing open surgical aortic valve replacement. Periprocedural apparent and silent cerebral ischemia was assessed by neurological testing and serial cerebral diffusion-weighted magnetic resonance imaging at baseline, at 3.4 (2.5 to 4.4) days after the procedure, and at 3 months. TAVI was successful in all patients. After the procedure, new foci of restricted diffusion on cerebral diffusion-weighted magnetic resonance imaging were found in 27 of 32 TAVI patients (84%) and were more frequent than after open surgery (10 of 21 patients [48%]; $P=0.011$). These lesions were usually multiple (1 to 19 per patient) and dispersed in both hemispheres in a pattern suggesting cerebral embolization. Volumes of these lesions were significantly smaller after TAVI than after surgery (77 [59 to 94] versus 224 [111 to 338] mm^3; $P<0.001$). There were neither measurable impairments of neurocognitive function nor apparent neurological events during the in-hospital period among TAVI patients, but there was 1 stroke (5%) in the surgical patient group. On 3-month follow-up diffusion-weighted magnetic resonance imaging, there were no new foci of restricted diffusion, and there was no residual signal change associated with the majority (80%) of the foci detected in the periprocedural period.

Conclusions—Clinically silent new foci of restricted diffusion on cerebral magnetic resonance imaging were detected in almost all patients (84%) undergoing TAVI. Although typically multiple, these foci were not associated with apparent neurological events or measurable deterioration of neurocognitive function during 3-month follow-up. Further work needs to be directed to determine the clinical significance of these findings in a larger patient population. (***Circulation.*** **2010;121:870-878.**)



Journal of the American College of Cardiology
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 55, No. 14, 2010
ISSN 0735-1097/10/$36.00
doi:10.1016/j.jacc.2009.12.026

Risk and Fate of Cerebral Embolism After Transfemoral Aortic Valve Implantation

A Prospective Pilot Study With Diffusion-Weighted Magnetic Resonance Imaging

Alexander Ghanem, MD,* Andreas Müller, MD,† Claas P. Nähle, MD,† Justine Kocurek, MD,* Nikos Werner, MD,* Christoph Hammerstingl, MD,* Hans H. Schild, MD, PHD,† Jörg O. Schwab, MD, PHD,* Fritz Mellert, MD,§ Rolf Fimmers, MD,‡ Georg Nickenig, MD, PHD,* Daniel Thomas, MD†

Bonn, Germany

Objectives The aim of this study was prospective investigation of silent and clinically apparent cerebral embolic events and neurological impairment after transfemoral aortic valve implantation (TAVI).

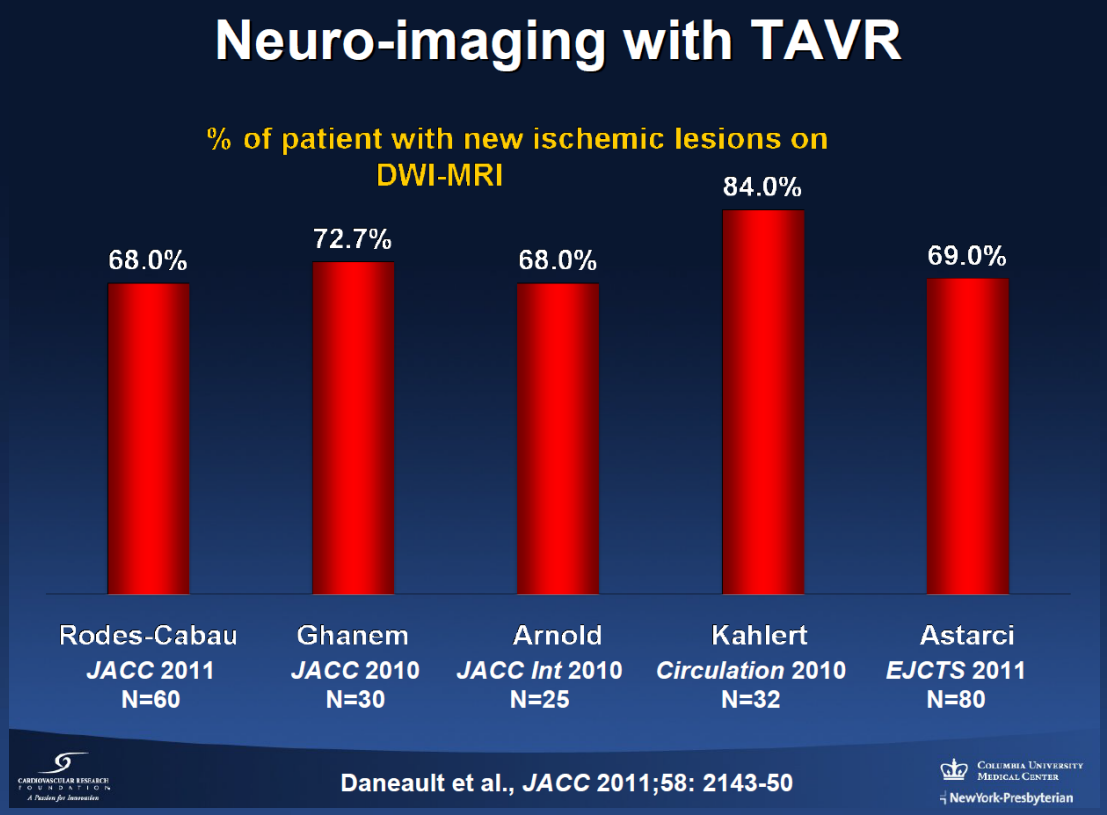
Background TAVI is a novel therapeutic approach for multimorbid patients with severe aortic stenosis. We investigated peri-interventional cerebral embolism with diffusion-weighted magnetic resonance imaging (DW-MRI) and its relationship to clinical and serologic parameters of brain injury.

Methods Cerebral DW-MRI was performed before, directly, and 3 months after TAVI with the current third-generation self-expanding CoreValve (Medtronic, Minneapolis, Minnesota) prosthesis. At the timepoints of the serial MRI studies, focal neurological impairment was assessed according to the National Institutes of Health Stroke Scale (NIHSS), and serum concentration of neuron-specific enolase (NSE), a marker of the volume of brain tissue involved in an ischemic event, were determined.

Results Thirty patients were enrolled; 22 completed the imaging protocol. Three patients (10%) had new neurological findings after TAVI, of whom only 1 (3.6%) had a permanent neurological impairment. Of the 22 TAVI patients with complete imaging data, 16 (72.7%) had 75 new cerebral lesions after TAVI presumed to be embolic. The NIHSS and NSE were not correlated with DW-MRI lesions.

Conclusions The incidence of clinically silent peri-interventional cerebral embolic lesions after TAVI is high. However, in this cohort of 30 patients, the incidence of persistent neurological impairment was low. (Incidence and Severity of Silent and Apparent Cerebral Embolism After Conventional and Minimal-invasive Transfemoral Aortic Valve Replacement; NCT00883285) (J Am Coll Cardiol 2010;55:1427–32) © 2010 by the American College of Cardiology Foundation

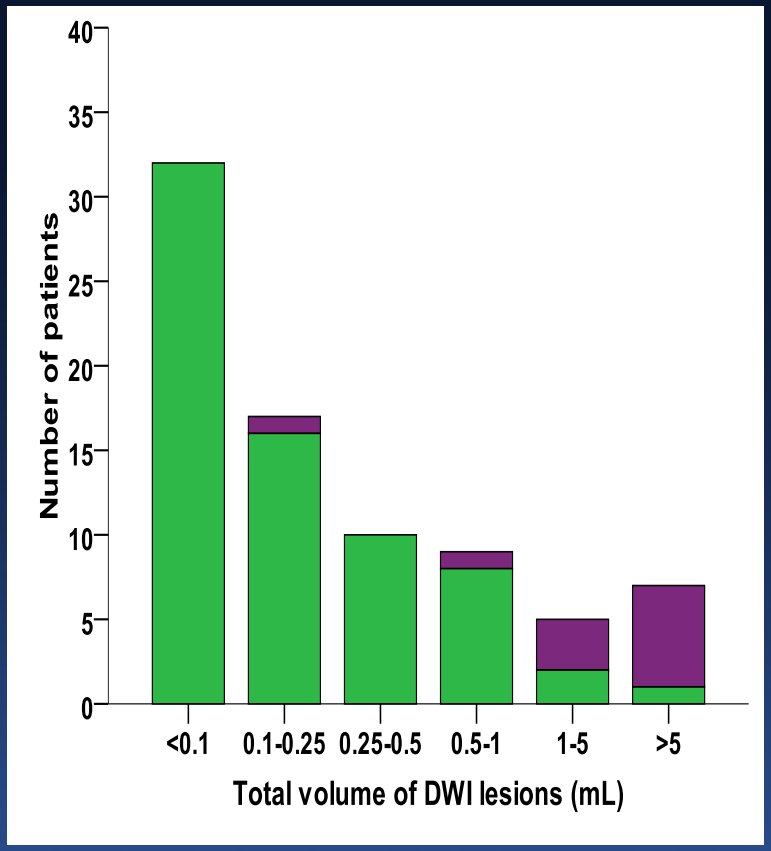
DW-MRI Imaging of "Silent Lesions" Following TAVR



Can these really all be benign?

Lesion Volume Matters

Larger total DWI lesion volumes are associated with significantly higher risk of clinically evident stroke (p<0.001)



Clinical Presentation

- *Hemispheric ischaemic stroke*
- *No focal deficit*

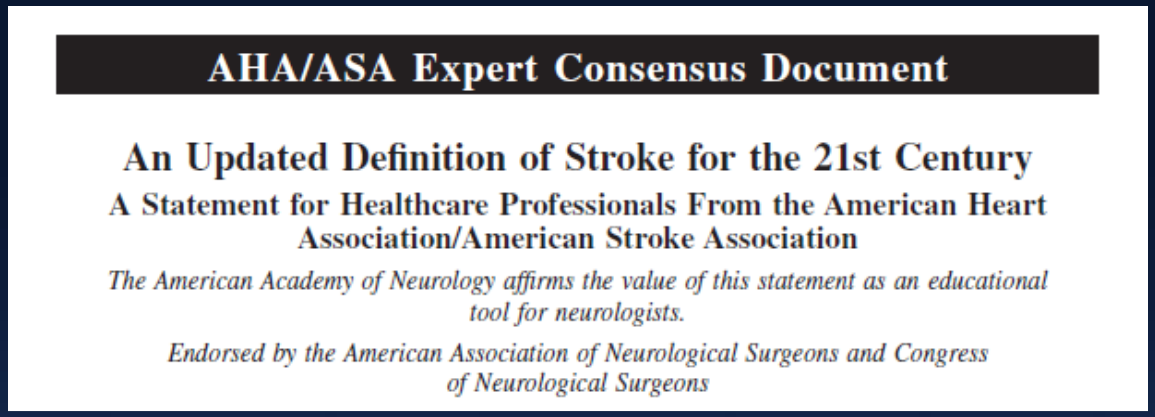
Claret Can Capture & Remove Embolic Material Before it reaches the Brain

Bonati et al., Lancet Neurol 2010; 9: 353–62

TAVR Expanding to Healthier Patients

SURTAVI		PARTNER IIa
≥4 and ≤10	**STS Inclusion**	≥4 and ≤10
>22	**Syntax Exclusion**	>32
AVA ≤ 1.0cm^2 Indexed AVA < 0.6 cm^2/m^2	**Valve Area Inclusion**	AVA ≤ 0.8cm^2 Indexed AVA < 0.5cm^2/m^2
Discharge, 30 days, 3 months, 6 months, 12 months, 18 months, 24 months, annually for 5 years	**Follow-up Visits**	Discharge, 30 days, 6 months, 1 year, annually for 5 years
All-cause death + disabling stroke @ 2 yrs (~2600 pts)	**Primary endpoint (sample size)**	All-cause death + disabling stroke @ 2 yrs (2000 pts)
Global - US, EU, Canada (up to 115 centers)	**Geography**	United States (up to 60 centers)

New Expanded AHA/ASA Consensus Definition of Stroke, May 2013



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

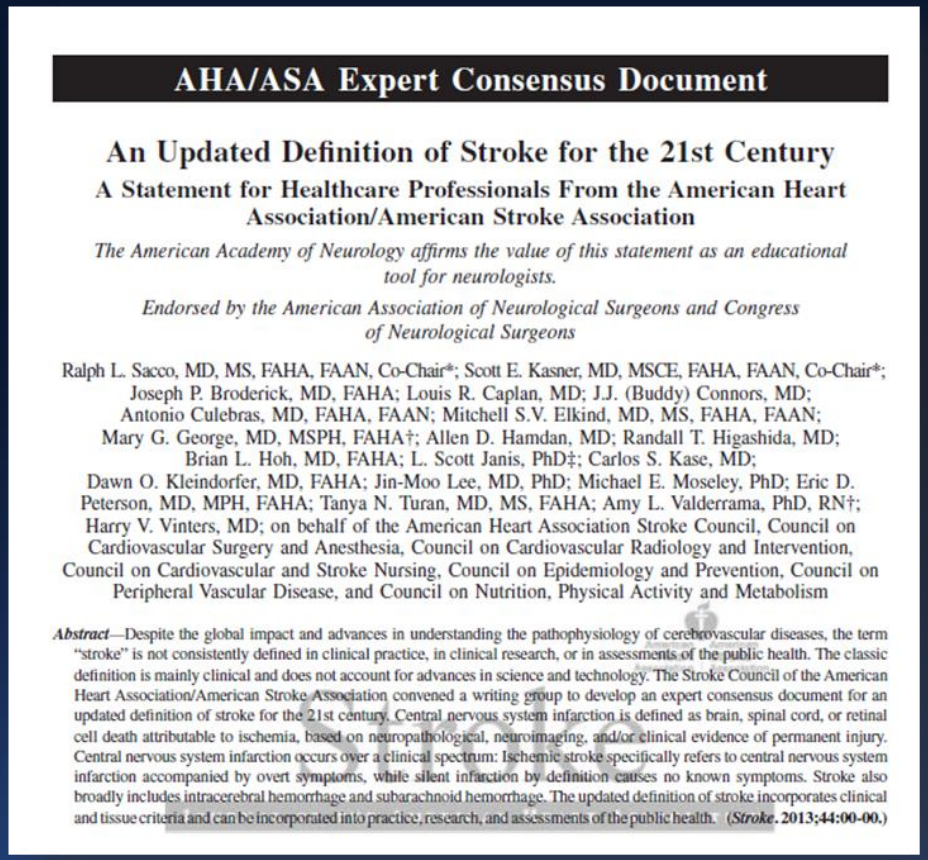
The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

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

- "Silent brain infarcts increase the risk of clinical infarction by 2 to 4 times in population-based studies"
- "…silent infarcts are associated with risk of Alzheimer disease as well as of vascular dementia."

Several studies have shown that patients with silent brain infarcts had a 5 times higher stroke incidence than those without.

Stroke Redefined



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

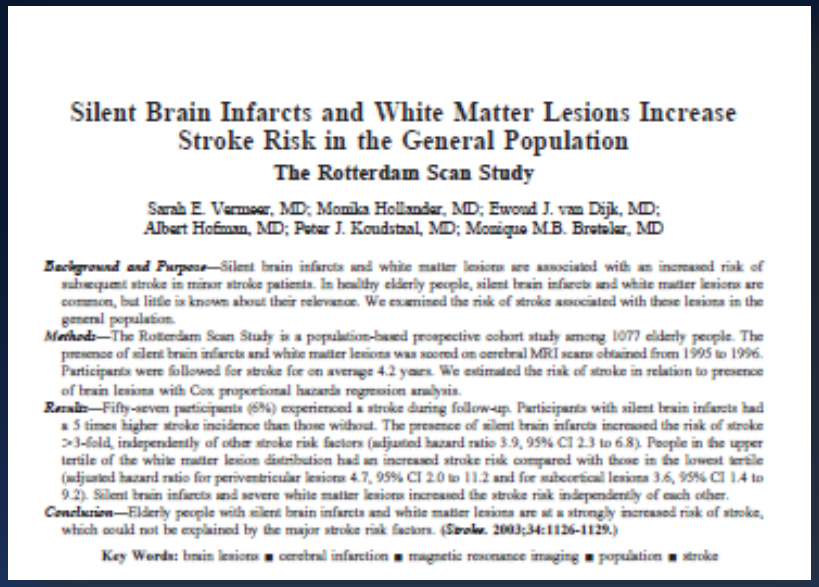
Abstract—Despite the global impact and advances in understanding the pathophysiology of cerebrovascular diseases, the term "stroke" is not consistently defined in clinical practice, in clinical research, or in assessments of the public health. The classic definition is mainly clinical and does not account 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 are well recognized to be associated with several adverse neurological and cognitive consequences:

- Impaired mobility
- Physical decline
- Depression
- Cognitive dysfunction
- Dementia
- Parkinson's disease
- Alzheimer disease

An Updated Definition of Stroke for the 21st Century : A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association, Stroke. published online May 7, 2013

„Not So Silent“ Lesions and Disabling Stroke



Silent Brain Infarcts and White Matter Lesions Increase Stroke Risk in the General Population

The Rotterdam Scan Study

Sarah E. Vermeer, MD; Monika Hollander, MD; Ewoud J. van Dijk, MD; Albert Hofman, MD; Peter J. Koudstaal, MD; Monique M.B. Breteler, MD

Background and Purpose—Silent brain infarcts and white matter lesions are associated with an increased risk of subsequent stroke in minor stroke patients. In healthy elderly people, silent brain infarcts and white matter lesions are common, but little is known about their relevance. We examined the risk of stroke associated with these lesions in the general population.

Methods—The Rotterdam Scan Study is a population-based prospective cohort study among 1077 elderly people. The presence of silent brain infarcts and white matter lesions was scored on cerebral MRI scans obtained from 1995 to 1996. Participants were followed for stroke for on average 4.2 years. We estimated the risk of stroke in relation to presence of brain lesions with Cox proportional hazards regression analysis.

Results—Fifty-seven participants (6%) experienced a stroke during follow-up. Participants with silent brain infarcts had a 5 times higher stroke incidence than those without. The presence of silent brain infarcts increased the risk of stroke >3-fold, independently of other stroke risk factors (adjusted hazard ratio 3.9, 95% CI 2.3 to 6.8). People in the upper tertile of the white matter lesion distribution had an increased stroke risk compared with those in the lowest tertile (adjusted hazard ratio for periventricular lesions 4.7, 95% CI 2.0 to 11.2 and for subcortical lesions 3.6, 95% CI 1.4 to 9.2). Silent brain infarcts and severe white matter lesions increased the stroke risk independently of each other.

Conclusion—Elderly people with silent brain infarcts and white matter lesions are at a strongly increased risk of stroke, which could not be explained by the major stroke risk factors. (***Stroke.*** **2003;34:1126-1129.**)

Key Words: brain lesions ■ cerebral infarction ■ magnetic resonance imaging ■ population ■ stroke

- *Population based cohort study of 1077 elderly people followed for 4+ years*
- *14.3% with silent brain infarcts developed a stroke during follow up period*
- *Presence of silent brain infarcts increased risk of stroke by >3 fold*

Conclusion – “Elderly people with silent brain infarcts and white matter lesions are at a strongly increased risk of stroke, which could not be explained by the major stroke risk factors”

Silent Brain Infarcts and White Matter Lesions Increase Stroke Risk in the General Population: The Rotterdam Scan Study
Sarah E. Vermeer, MD et al;Stroke. 2003;34:1126-1129

Second Generation 'Repositionable' TAVR Devices Still Require Finesse

Safety: Death & Stroke at 30 Days

REPRISE II (N=120)

Event	*Patients (N=119)**
All-cause mortality (primary safety endpoint)	4.2% (5)
Cardiovascular mortality	4.2% (5)
All stroke†	5.9% (7)
Disabling stroke	1.7% (2)
Non-disabling stroke	4.2% (5)

† All patients were assessed by a neurologist before and after TAVR

* One patient withdrew consent

All patients were assessed by a neurologist before and after TAVR

Dr. Ian Meredith, TCT 2013

Under Reporting Remains an Issue & is Even Seen in Surgical AVR

Stroke After Aortic Valve Surgery

196 patients aged 65 years or older were evaluated by neurologists for clinical stroke and silent infarct before and after aortic valve replacement.

In-Hospital Mortality	Clinical Stroke (n = 34)	No Clinical Stroke (n = 162)	*P* Value
All NIHSS Scores	9%	4%	NS
NIHSS Score > 10	38%	4%	.005

Clinical stroke was identified in 17% of patients. The same cohort had a stroke rate of 6.6% reported in the Society for Thoracic Surgery database.

Conclusion: Clinical stroke after AVR occurs more often than previously thought and can be associated with higher risk of in-hospital mortality.

Messé SR, et al. *Circulation.* 2014;Epub ahead of print.

tctmd The Source for Interventional Cardiovascular News and Education

Messé SR, Acker MA, Kasner SE, et al. Stroke after aortic valve surgery: results from a prospective cohort. Circulation. 2014;Epub ahead of print

Future Reporting Must be Consistent

Valve Academic Research Consortium (VARC) 2: Updated Definitions[a]

Updated Stroke Definitions

Non Disabling	Modified Rankin score < 2 at 30 and 90 days* OR an increase in the modified Rankin score of ≤ 1
Disabling	Modified Rankin score ≥ 2 at 30 and 90 days AND an increase in the modified Rankin score of ≥ 1

Supercedes original VARC[b] stratification of TIA, minor and major strokes. Ischemic or hemorrhagic stroke classified per proposed FDA consensus panel definitions.

*Modified Rankin score assessments should be made by qualified individuals according to a certification process. If there is discordance between 30- and 90-day scores, a final determination will be adjudicated by the neurology members of the clinical events committee.

Interventional & Surgery

a. Serruys P, et al. TVT 2012. b. Leon MB, et al. *J Am Coll Cardiol.* 2011;57:253-269.

theheart.org Medscape EDUCATION

Studies must encourage Independent Neurologist pre & post assessment to ensure correct reporting

Neuro Cognition Testing Post-TAVR is Complex and Needs Specific Battery of Assays

- Heart Disease & Neurocognition
  - CABG
  - Atrial Fibrillation
  - Cardiac Arrest
  - Heart Failure
  - TAVR

Embolism

Perfusion Failure

Both?

Cerebral Protection Reduces Periprocedural Strokes During Carotid Angioplasty & Stenting

Pooled Analysis for Total Stroke Rate Within 30 Days After Protected and Unprotected Carotid Stenting in 134 Studies*

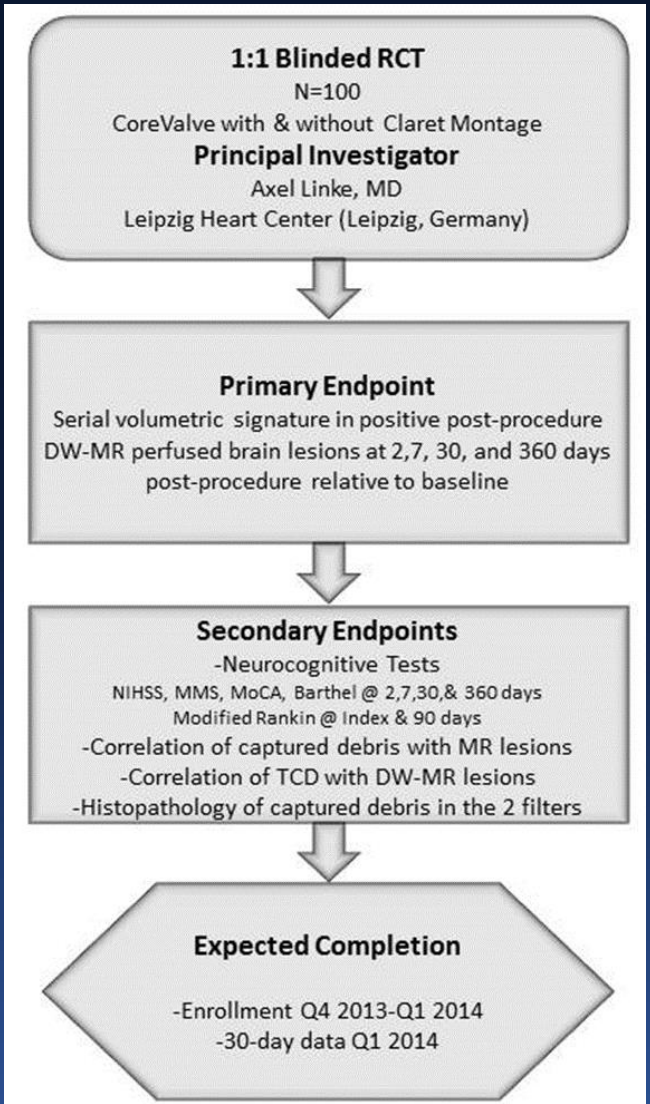
	With Protection (n=82)		Without Protection (n=76)			
	Procedures	Total Strokes	Procedures	Total Strokes	RR	CI
All patients	12,263	324 (2.6%)	11198	474 (4.2%)	0.62†	0.54 to 0.72
Symptomatic	2427	91 (3.8%)	3149	176 (5.6%)	0.67†	0.52 to 0.86
Asymptomatic	2460	41 (1.7%)	2032	56 (2.8%)	0.61†	0.41 to 0.9

RR: relative risk, CI: confidence interval.
* 24 studies included data on both protected and unprotected CAS. Of all studies, only 67 studies reported outcomes on symptomatic patients (34 with protected and 39 with unprotected stenting), while 56 reported outcomes on asymptomatic patients (28 with protected and 30 with unprotected stenting).
† $P<0.05$.

Why should this be different in TAVR?

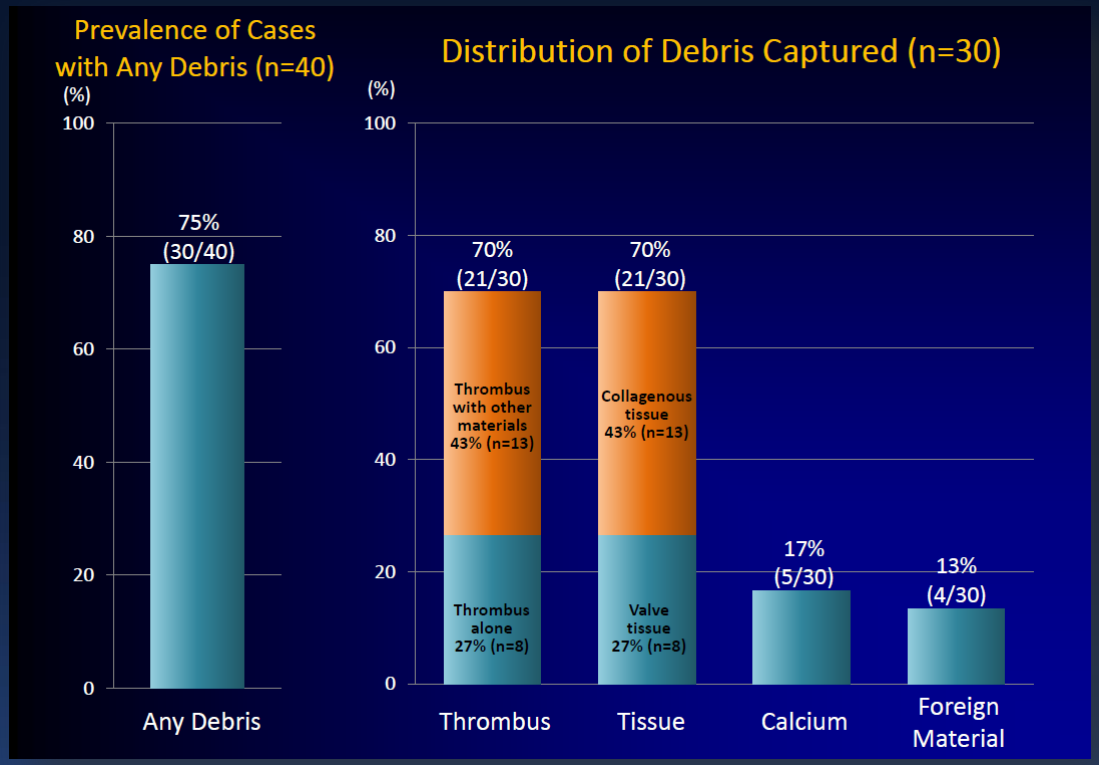
Garg et al: J Endovasc Ther. 2009;16:412-427

The Answers Are Coming Soon



CLEAN TAVI Study to be Presented at TCT 2014

Devices Are Shown to be Effective in Extracting Debris



So why would you NOT use them routinely?

Van Mieghem et al, Circulation 2013;127:2194-2201
Debris analysis by Dr. Renu Virmani, CVPath Institute of Histopathology

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Accepted Wisdoms are Sometimes Flawed…

In-Stent Restenosis is NOT Benign

euro PCR

Barts and The London
Queen Mary's School of Medicine and Dentistry

In-Stent Restenosis is not simply a benign clinical entity: It presents as ACS in 40% of cases

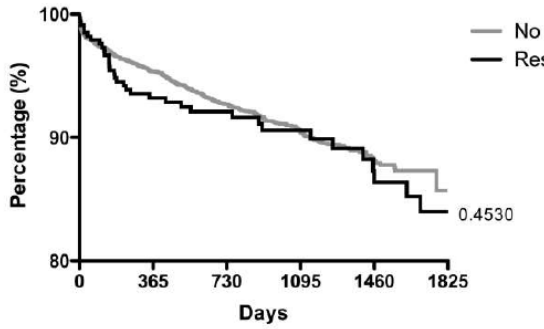
Rathod KS, Jones DA, Rathod VS, Akhtar M, Guttmann O, Pain T, Behar J, Jain A, Mathur A, Knight C and Wragg A

Department of Cardiology, Barts and the London NHS Trust, London, United Kingdom

euro PCR

Restenosis in All Patients

Comparison of Mortality between Restenosis and No Restenosis in ACS



Neither are 'silent' lesions in the brain

Abu-Own et al: doi:10.1136/heartjnl-2011-300198.36

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My Conclusion

- Devices are Improving
- Procedural Techniques are improving
- Patient Selection is Improving
- Adjunctive pharma therapy is improving

BUT: Embolic Stroke still remains an issue in TAVR and is truly devastating!!!

Cerebral Protection will (and should) become Standard of Care