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Has Stroke Frequency Declined after TAVI?16:06 – 16:14

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Disclosure Statement of Financial Interest

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

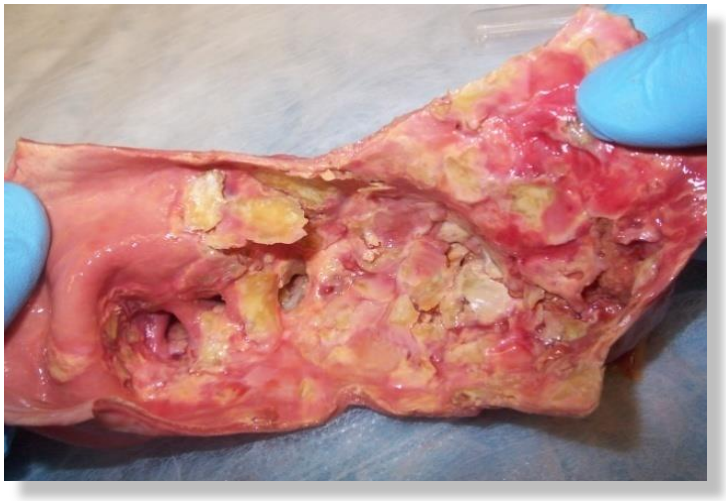
Affiliation/Financial Relationship	Company
• Grant/Research Support	• Claret Inc; Medtronic, Boston Scientific, Abbott Vascular
• Consulting Fees/Honoraria	

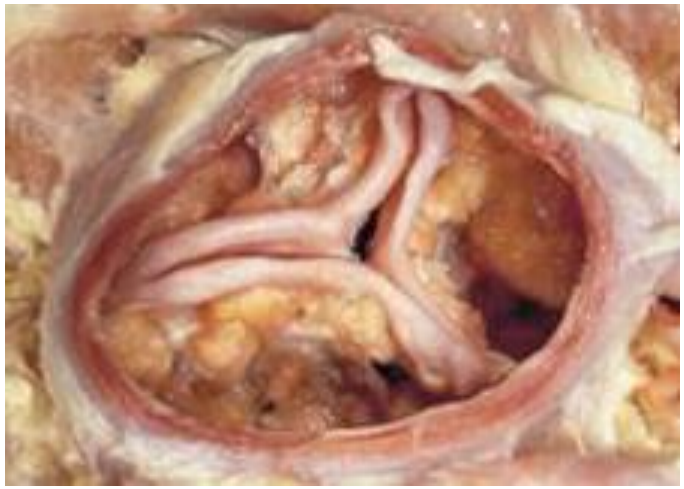
OUTLINE

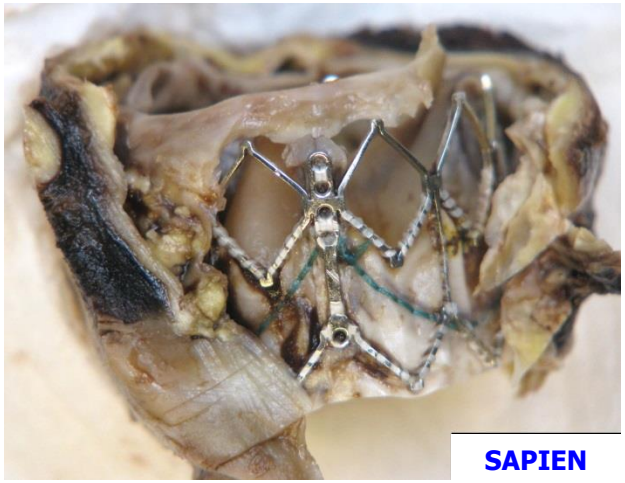
- ✓ **Introduction**
- ✓ **Initial Findings**
- ✓ **Updated Analysis**
- ✓ **MISTRAL-C**

Cerebral Embolization during TAVI
=
INEVITABLE

Cerebral embolization in TAVI







SAPIEN

Procedural Stroke

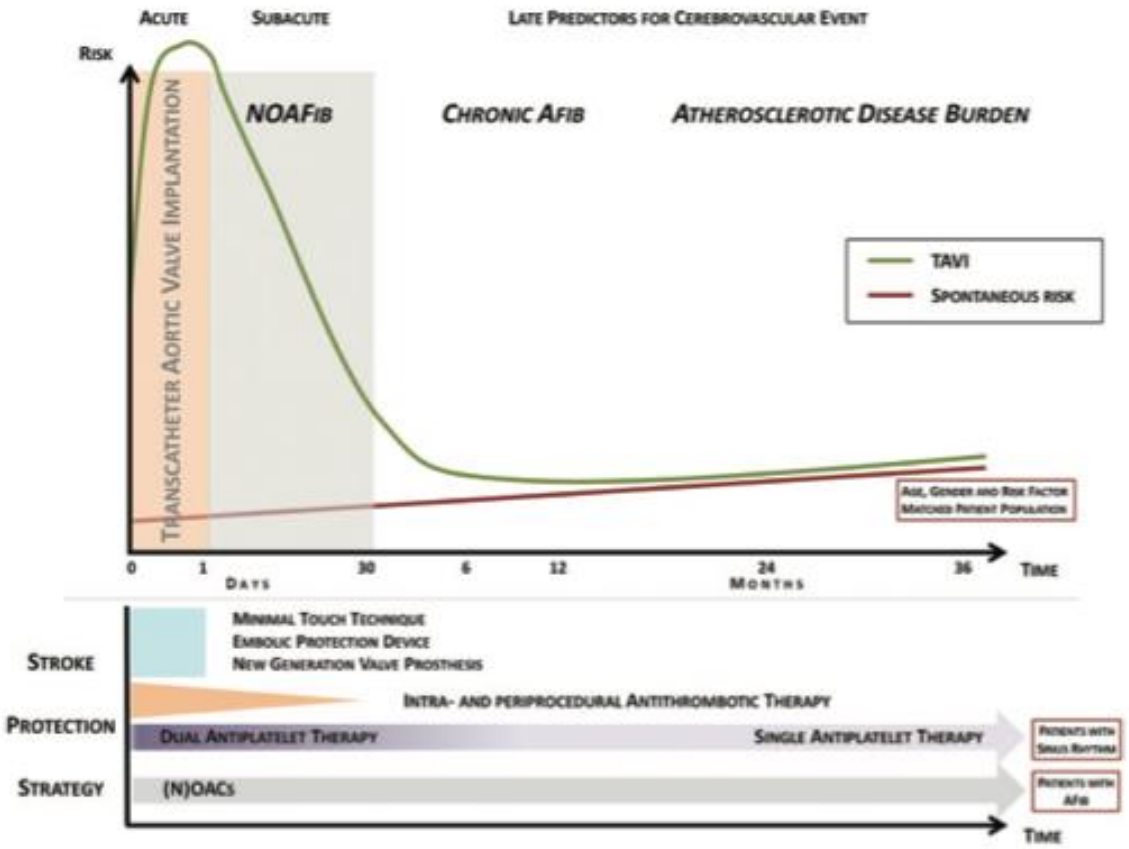


Figure. Risk of cerebrovascular events according to time after transcatheter aortic valve implantation (green line indicates patients undergoing transcatheter aortic valve implantation [TAVI]; red line displays the risk of an age-, sex-, and risk factor–matched population). AFib indicates atrial fibrillation; NOAFib, new onset atrial fibrillation; and (N)OAC, (novel) oral anticoagulants.

Stortecky S, Windecker S. Circulation 2012;126:2921-24

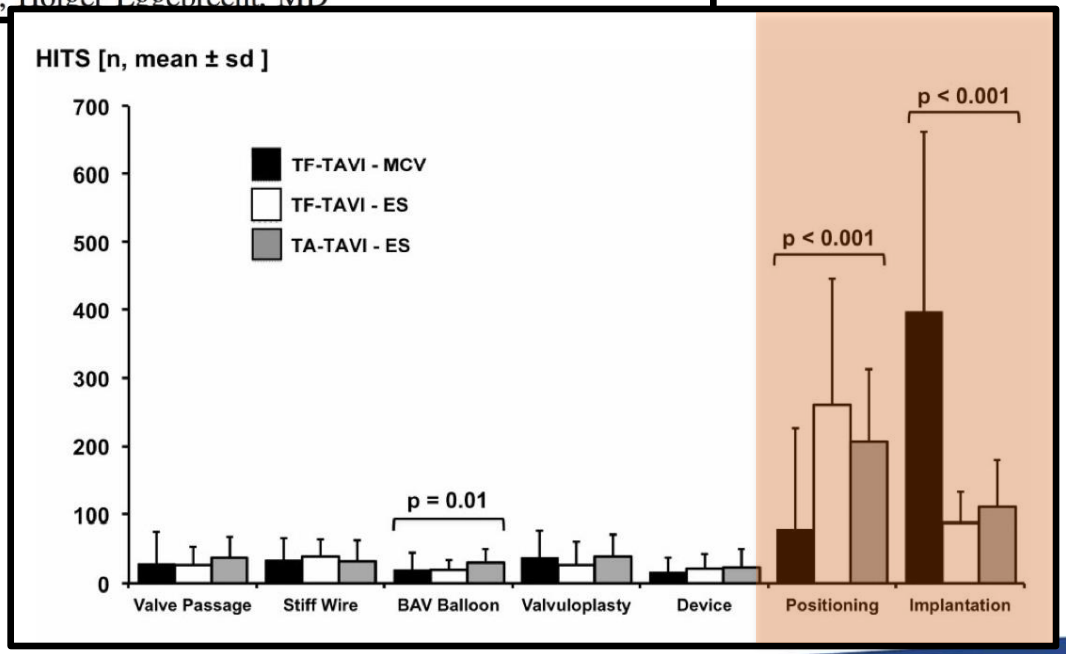
TAVI & Timing of Cerebral Embolization (TCD)

Stroke

Cerebral Embolization During Transcatheter Aortic Valve Implantation

A Transcranial Doppler Study

Philipp Kahlert, MD; Fadi Al-Rashid, MD; Philipp Döttger, MS; Kathrine Mori, MS; Björn Plicht, MD; Daniel Wendt, MD; Lars Bergmann, MD, DESA; Eva Kottenberg, MD; Marc Schlamann, MD; Petra Mummel, MD; Dagny Holle, MD; Matthias Thielmann, MD; Heinz G. Jakob, MD; Thomas Konorza, MD; Gerd Heusch, MD; Raimund Erbel, MD; Holger Eggebrecht, MD

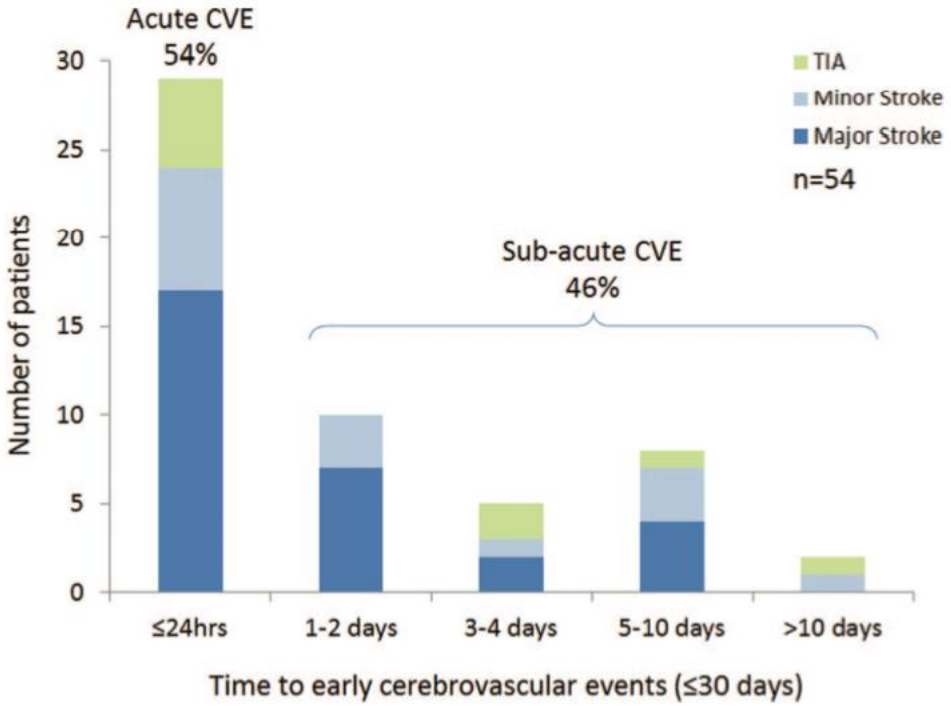


Circulation 2012;126:1245-55

Timing, Predictive Factors, and Prognostic Value of Cerebrovascular Events in a Large Cohort of Patients Undergoing Transcatheter Aortic Valve Implantation

Luis Nombela-Franco, MD; John G. Webb, MD; Peter P. de Jaegere, MD, PhD; Stefan Toggweiler, MD; Rutger-Jan Nuis, MSc; Antonio E. Dager, MD; Ignacio J. Amat-Santos, MD; Anson Cheung, MD; Jian Ye, MD; Ronald K. Binder, MD; Robert M. van der Boon, MSc; Nicolas Van Mieghem, MD; Luis M. Benitez, MD; Sergio Pérez, MD; Javier Lopez, MD, PhD; José A. San Roman, MD, PhD; Daniel Doyle, MD; Robert DeLarochellière, MD; Marina Urena, MD; Jonathon Leipsic, MD; Eric Dumont, MD; Josep Rodés-Cabau, MD

Multi-centre study Cohort
1061 Patients



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

Predictors for Cerebral Embolization 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

Identification of Cerebral Embolisms

Interventional Cardiology

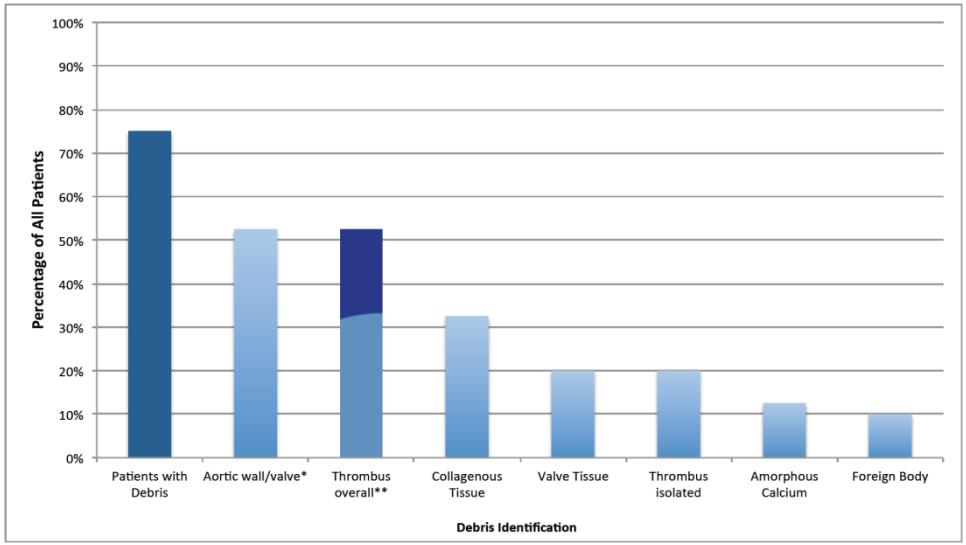
Histopathology of Embolic Debris Captured During Transcatheter Aortic Valve Replacement

Nicolas M. Van Mieghem, MD; Marguerite E.I. Schipper, MD; Elena Ladich, MD; Elham Faqiri, MSc; Robert van der Boon, MSc; Abas Randjgari, MD; Carl Schultz, MD, PhD; Adriaan Moelker, MD, PhD; Robert-Jan van Geuns, MD, PhD; Fumiyuki Otsuka, MD; Patrick W. Serruys, MD, PhD; Renu Virmani, MD; Peter P. de Jaegere, MD, PhD

Background—Recent transcatheter aortic valve replacement studies have raised concerns about adverse cerebrovascular events. The etiopathology of the embolized material is currently unknown.

Methods and Results—A total of 40 patients underwent transcatheter aortic valve replacement with the use of a dual filter–based embolic protection device (Montage Dual Filter System, Claret Medical, Inc). Macroscopic material liberated during the transcatheter aortic valve replacement procedure was captured in the device filter baskets in 30 (75%) patients and sent for histopathologic analysis. The captured material varied in size from 0.15 to 4.0 mm. Amorphous calcified material (size, 0.55–1.8 mm) was identified in 5 patients (17%). In 8 patients (27%), the captured material (size, 0.25–4.0 mm) contained valve tissue composed of loose connective tissue (collagen and elastic fibers) with focal areas of myxoid stroma, with or without coverage by endothelial cells and intermixed with fibrin. In another 13 (43%) patients, collagenous tissue, which may represent elements of vessel wall and valvelike structures, was identified. In 9 patients (30%), thrombotic material was intermixed with neutrophils (size, 0.15–2.0 mm). Overall, thrombotic material was found in 52% of patients, and tissue fragments compatible with aortic valve leaflet or aortic wall origin were found in 52% (21/40) of patients.

Conclusions—Embolic debris traveling to the brain was captured in 75% of transcatheter aortic valve replacement procedures where a filter-based embolic protection device was used. The debris consisted of fibrin, or amorphous calcium and connective tissue derived most likely from either the native aortic valve leaflets or aortic wall. **(*Circulation*. 2013;127:2194-2201.)**



Van Mieghem N et al. Circulation 2013;176:2194-2201

FREQUENCY

	N	Device	30-Day Major Stroke	30-Day All CVE
SOURCE	463 (TF)	SAPIEN	4	
SOURCE XT	2706	SAPIEN XT		2.2
SAPIEN 3	150	Sapien3	0	2.7
PORTICO	102	PORTICO	2.9	3.9
REPRISE 2	120	Lotus	1.7	5.9
GARY	9282	Sapien XT & MCS	1.3	
STS ACC/TVT Registry	7710	Sapien	2	
18F S&E	126	MCS		9.6
Italian Registry	772	MCS	1.7	
Australia/NZ Corevalve Registry	441	MCS	3.5	
Canada TAVR	345 (2012)	Sapien & XT	2.3	
EU TAVI Exp	Meta-Analysis	Corevalve	2.8	
FRANCE 2	3933	Sapien & XT & MCS	4.6	

National Registries - Assets & Pitfalls

✓**Projection of Real Life**

✓**Large Cohorts**

✓**Notion Safety/Efficacy**

✓**Selected Centers**

✓**Self-reporting**

✓**Non-Uniformity**

Meta-analyses

Genereux et al.
JACC 2012

- VARC reports
- 3323 patients included
- 30-day mortality 7.8%
- Stroke:
  - Major 3.8 %
  - Minor 0.9 %
  - TIA 1.5 %

Eggebrecht et al.
EuroIntervention 2012

- TAVI reports in geneal
- 10037 patients included
- 30-day mortality: 8.1%
- Stroke:
  - Procedural stroke (<24h): 1.5%
  - Major stroke at 30 days: 2.9%
  - Stroke/TIA at 30 days: 3.3%

PRAGMATIC Plus - Experience

Propensity score matched analysis –
Impact of experience & technological refinements

793 consecutive TF TAVI patients
November 2005 – August 2011

Per center 3 equal tertiles
based on enrolment date

T1: up to 2009	T2: 2009 – 8/10	T3: 8/10 – 8/11
264	264	265

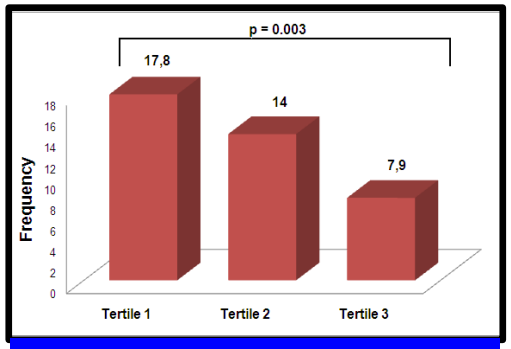
Propensity Score Matching

T1: up to 2009	T2: 2009 – 8/10	T3: 8/10 – 8/11
214	214	214

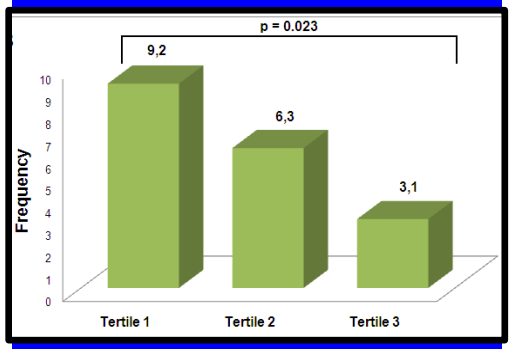
- **Rotterdam EMC**
- **Toulouse Pasteur**
- **Toulouse Rangeuil**
- **San Raffaele Milan**
- **986 Patients overall**

Van Mieghem N. et al. AHJ 2013,165:183-92

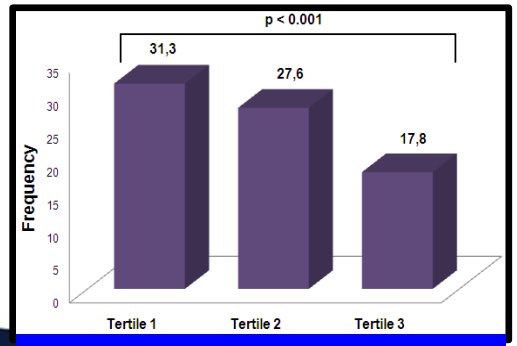
Clinical Endpoints



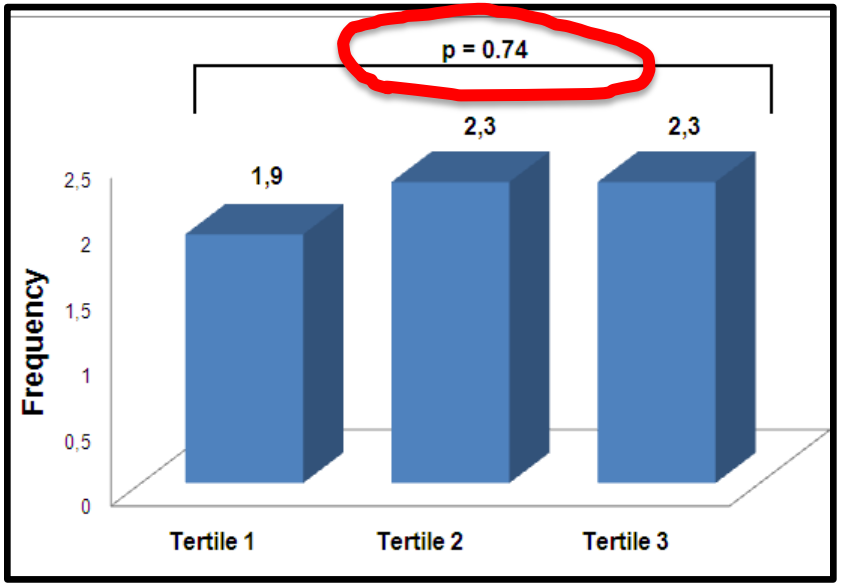
Life-threatening bleeding



Major Vascular Complications



Combined Safety Endpoint



Major Stroke

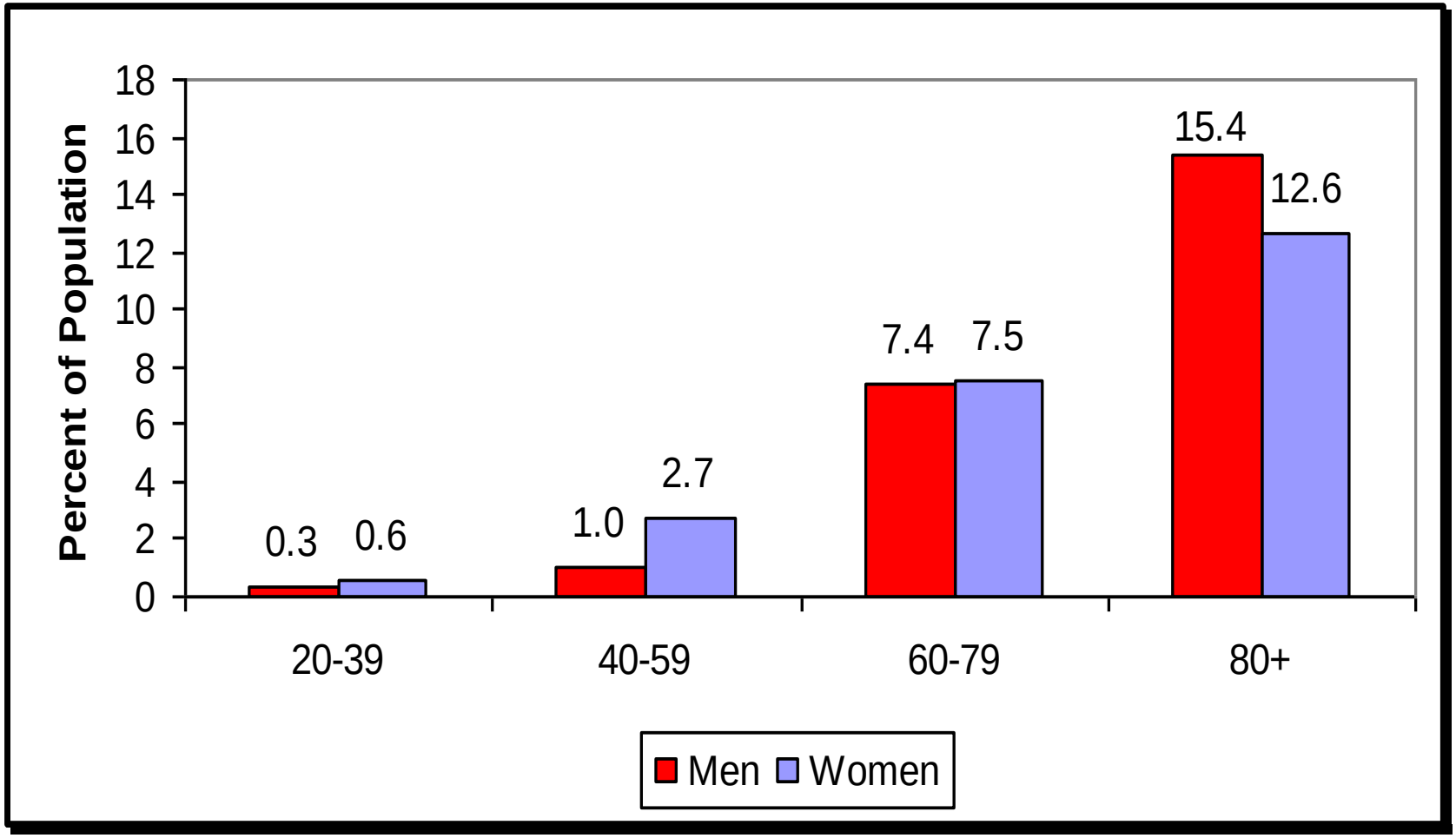
Van Mieghem N. et al. AHJ 2013,165:183-92

TAVI & Neurological Events

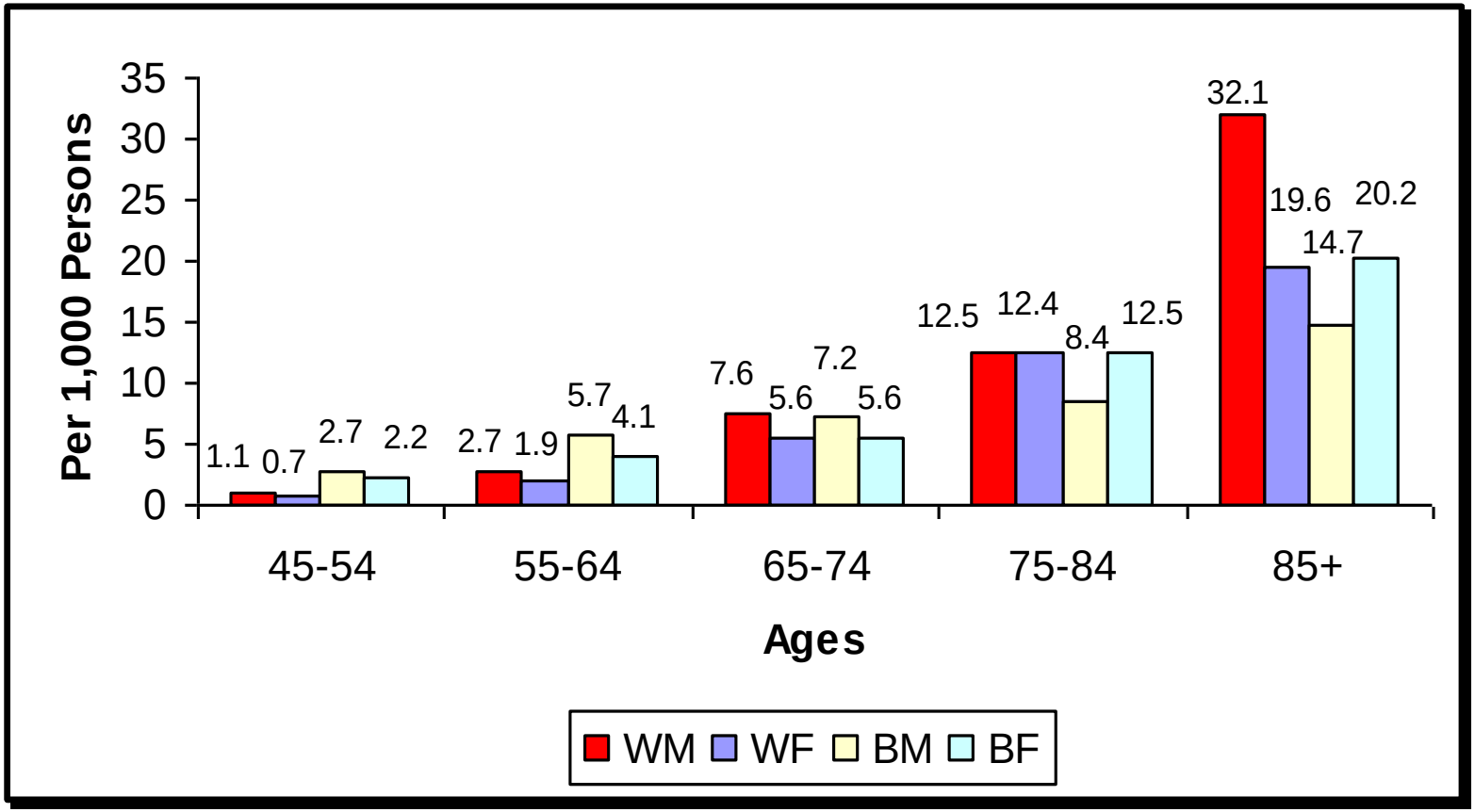
	Baseline AF	30-day major stroke	30-day CVE (Stroke + TIA)	1-year major stroke	1-year CVE (Stroke + TIA)	Independent CEC
ADVANCE	33.2	1.2%	3.3	2.2	6.1	+
TVT Registry		1.7 (In hospital)		3.6		
Corevalve Extreme Risk	46.8	2.3	4.6	4.3	5.4	+
PARTNER Cohort B	32.9	5.0	6.7	7.8	10.6	+
Corevalve High-Risk TAVI	41	3.9	5.7	5.8	10.4	+
Corevalve High-Risk SAVR	47.5	3.1	6.5***	7.0	14.2	+
PARTNER Cohort A TAVI	40.8	3.8	5.5	5.1	8.3	+
PARTNER Cohort A SAVR	42.7	2.1	2.4	2.4	4.3	+
CHOICE Edwards	33.3	2.5	5.8 (no TIA)			
CHOICE Corevalve	24.8	2.5	2.5 (no TIA)			

Is there a Stroke Problem with TAVI?

PREVALENCE STROKE (NHANES: 2003-2006)



Source: NCHS and NHLBI.


Per 1,000 Persons
35
30
25
20
15
10
5
0
1.1
0.7
2.7
2.2
2.7
1.9
5.7
4.1
7.6
5.6
7.2
5.6
12.5
12.4
8.4
12.5
32.1
19.6
14.7
20.2
45-54
55-64
65-74
75-84
85+
Ages
WM
WF
BM
BF

DeNOVO Study

Cardiovascular Surgery

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

Background—The incidence and impact of clinical stroke and silent radiographic cerebral infarction complicating open surgical aortic valve replacement (AVR) are poorly characterized.

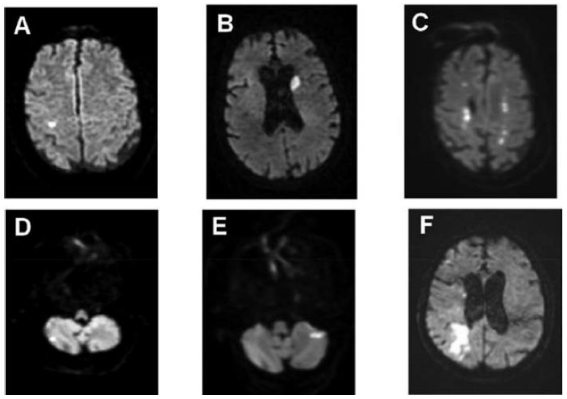
Methods and Results—We performed a prospective cohort study of subjects ≥65 years of age who were undergoing AVR for calcific aortic stenosis. Subjects were evaluated by neurologists preoperatively and postoperatively and underwent postoperative magnetic resonance imaging. Over a 4-year period, 196 subjects were enrolled at 2 sites (mean age, 75.8±6.2 years; 36% women; 6% nonwhite). Clinical strokes were detected in 17%, transient ischemic attack in 2%, and in-hospital mortality was 5%. The frequency of stroke in the Society for Thoracic Surgery database in this cohort was 7%. Most strokes were mild; the median National Institutes of Health Stroke Scale was 3 (interquartile range, 1–9). Clinical stroke was associated with increased length of stay (median, 12 versus 10 days; P=0.02). Moderate or severe stroke (National Institutes of Health Stroke Scale ≥10) occurred in 8 (4%) and was strongly associated with in-hospital mortality (38% versus 4%; P=0.005). Of the 109 stroke-free subjects with postoperative magnetic resonance imaging, silent infarct was identified in 59 (54%). Silent infarct was not associated with in-hospital mortality or increased length of stay.

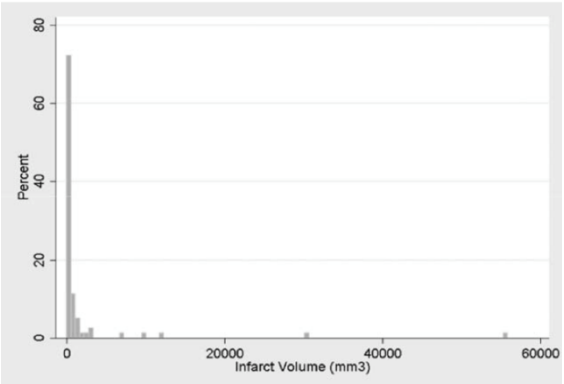
Conclusions—Clinical stroke after AVR was more common than reported previously, more than double for this same cohort in the Society for Thoracic Surgery database, and silent cerebral infarctions were detected in more than half of the patients undergoing AVR. Clinical stroke complicating AVR is associated with increased length of stay and mortality. (***Circulation***. 2014;129:2253-2261.)

- ✓ **Prospective Study in 2 centers in Pennsylvania**
- ✓ **196 Patients with SAVR**
- ✓ **Mean age 75 years, 36% Female**
- ✓ **Pre- and serial postop assessment by neurologist**
- ✓ **Brain MRI post SAVR median Day 6**

Messe et al. Circulation 2014;129:2253-61

DeNOVO Study



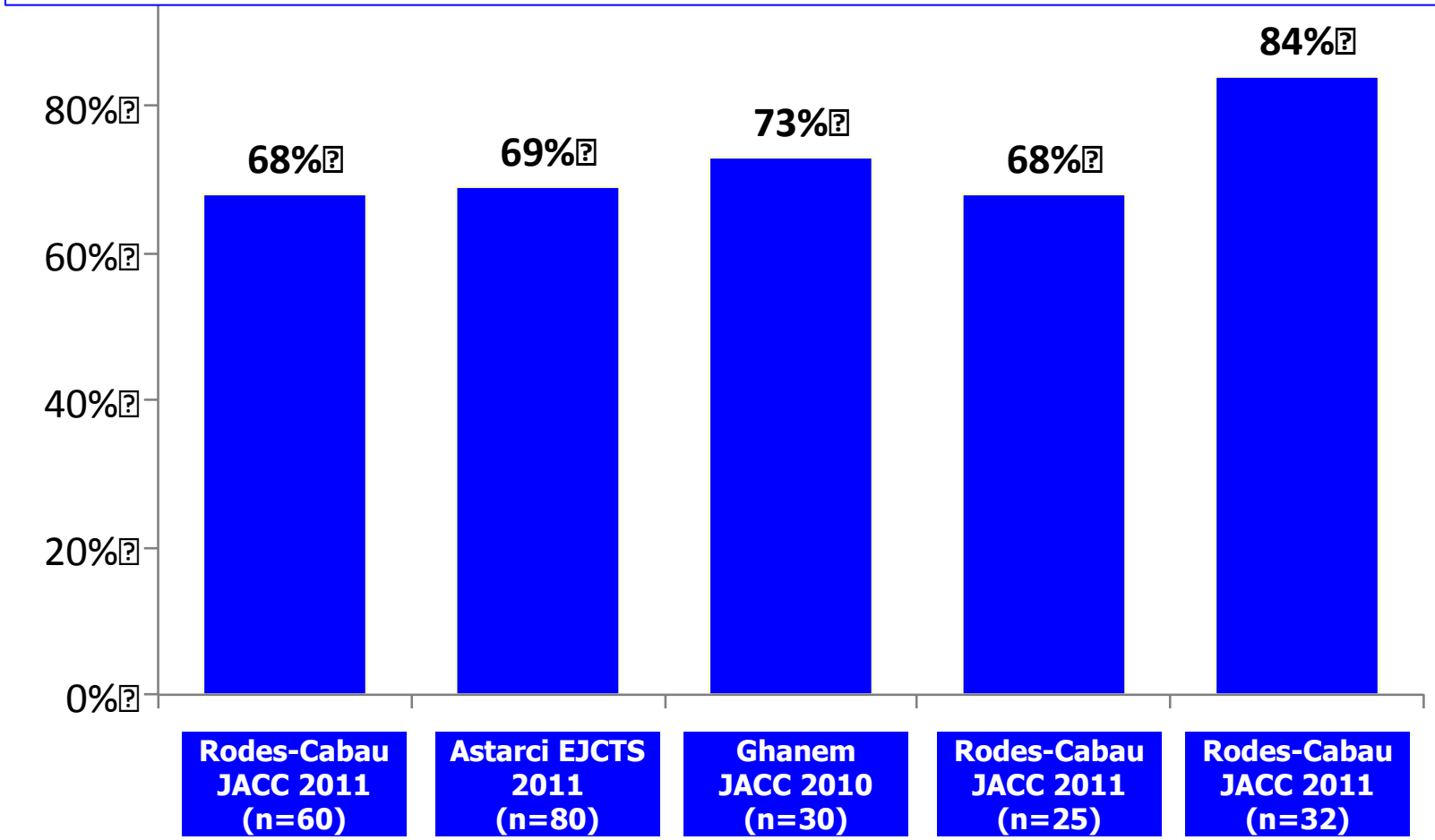


- ✓ **Clinical Strokes in 17% (median NIHSS 3 = mild)**
  - ✓ **58% on Day 1**
  - ✓ **Moderate to severe stroke (NIHSS > 10) in 4%**
- ✓ **109 patients with no clinical stroke underwent brain MRI**
  - ✓ **Silent infarct in 54%!**

Messe et al. Circulation 2014;129:2253-61

Subclinical Brain Lesions & TAVI

Diffusion Weighted MRI



Impact of Microinfarcts/subclinical Brain Lesions

The Problem With Asymptomatic Cerebral Embolic Complications in Vascular Procedures

What If They Are Not Asymptomatic?

- **Controversy remains!**
- **Given its high incidence after TAVI, is this acceptable moving towards lower risk/younger patient cohorts**

more subclinical events are
decline, and dementia relat
ing events lead to an estima
States alone. Given the mag
ture senescence in a vulnera
1614–6) © 2012 by the Am

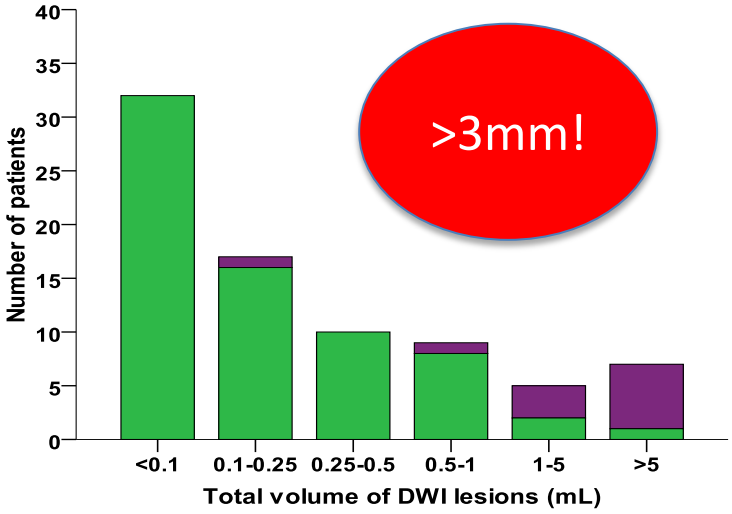
Methods—Four hundred twenty-five subjects enrolled in the Religious Orders Study underwent annual clinical evaluations, including 19 neuropsychological tests and assessment for dementia, and brain autopsy (39% men; mean age at death, 87; Mini-Mental State Examination score, 21). Neuropathologic examination documented the presence, number, and location of chronic microinfarcts on 6-μm hematoxylin–eosin-stained sections from cortical and subcortical regions. Multiple regression analyses adjusted for age at death, sex, education, macroscopic infarcts, Alzheimer disease pathology, and Lewy bodies.

Results—Microinfarcts were present in 129 of 425 (30%) persons (54 cortical, 80 subcortical, 49 multiple); 58 of 129 (45%) of persons with microinfarcts did not exhibit macroscopic infarcts. Persons with microinfarcts had increased odds of dementia (OR, 1.77; 95% CI, 1.07–2.92), especially those persons with multiple cortical microinfarcts. Microinfarcts were also associated with lower average global cognition (estimate, −0.287; SE, 0.113; P=0.012), particularly for persons with multiple cortical microinfarcts. Microinfarcts were specifically associated with lower episodic memory (estimate, −0.279; SE, 0.138; P=0.044), semantic memory (estimate, −0.391; SE, 0.130; P=0.003), and perceptual speed (estimate, −0.400; SE, 0.117; P<0.001). In addition, single, multiple, and cortical microinfarcts were associated with worse semantic memory and perceptual speed (all P<0.028). Neither macroscopic infarcts nor AD pathology modified these associations (all P>0.154).

Conclusions—Microinfarcts are common, and persons with multiple cortical microinfarcts have higher odds of dementia. Microinfarcts are also associated with lower cognition, specifically perceptual speed and semantic and episodic memory. **(*Stroke*. 2011;42:722-727.)**

Lesion Volume Matters

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



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

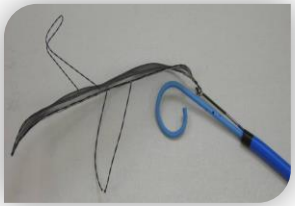
How to reduce Cerebral Embolization

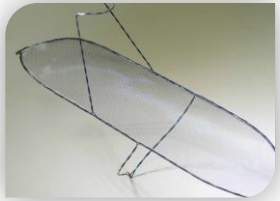
1. Smaller Profile device platforms

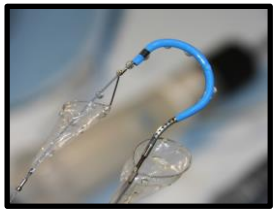
2. Technical Adjustments (no BAV, less post-Dil)

3. Scientifically sound anti-thrombotic therapy during en after TAVI

4. Embolic Protection Device







In Conclusion

1. Is there a Stroke issue with TAVI? ☑
2. More Stroke after TAVI than SAVR? ✗
3. Is Stroke Rate after TAVI Declining? ?
4. Can Stroke Rate after TAVI decline ? ☑
5. Should we do all it takes to prevent stroke after TAVI? ☑