Stroke – When and How?

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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:	
Consulting Fees/Honoraria:	**Edwards Lifesciences (consultant & proctor)**
Major Stock Shareholder/Equity Interest:	
Royalty Income:	
Ownership/Founder:	
Salary:	
Intellectual Property Rights:	
Other Financial Benefit:	

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Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients

Table 2. Clinical Outcomes at 30 Days and 1 Year in the Intention-to-Treat Population.*

Outcome	30 Days			1 Year		
	Transcatheter Replacement (N=348)	Surgical Replacement (N=351)	P Value	Transcatheter Replacement (N=348)	Surgical Replacement (N=351)	P Value
	no. of patients (%)			*no. of patients (%)*		
Death						
From any cause	12 (3.4)	22 (6.5)	0.07	84 (24.2)	89 (26.8)	0.44
From cardiac causes	11 (3.2)	10 (3.0)	0.90	47 (14.3)	40 (13.0)	0.63
Repeat hospitalization	15 (4.4)	12 (3.7)	0.64	58 (18.2)	45 (15.5)	0.38
Death or repeat hospitalization	25 (7.2)	33 (9.7)	0.24	120 (34.6)	119 (35.9)	0.73
Stroke or transient ischemic attack						
Either	19 (5.5)	8 (2.4)	0.04	27 (8.3)	13 (4.3)	0.04
Transient ischemic attack	3 (0.9)	1 (0.3)	0.33	7 (2.3)	4 (1.5)	0.47
Stroke						
Minor	3 (0.9)	1 (0.3)	0.34	3 (0.9)	2 (0.7)	0.84
Major	13 (3.8)	7 (2.1)	0.20	17 (5.1)	8 (2.4)	0.07

Editorial Response to PARTNER A

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

TAVI – Contemporary Results

	TVT Registry	Euro-Sentinel Registry	GARY Transvascular	GARY Transapical	FRANCE 2
N	7,710	4,571	2,695	1,181	3,195
Time Period	2011 – 13	2011 – 12	2011	2011	2010 – 11
Age	84	81.4	81.1	80.3	82.7
STS PROM	7%	N / A	N / A	N / A	14.4%
Logistic EuroScore	N / A	20.2%			21.9%
30 day Mortality	7.6%	7.4%	5.1%	7.7%	9.7%
30 day Stroke	2.8%	1.8%	1.7%	2.2%	4.1%
1 year Mortality	26.2%	N / A	N / A	N / A	24.0%

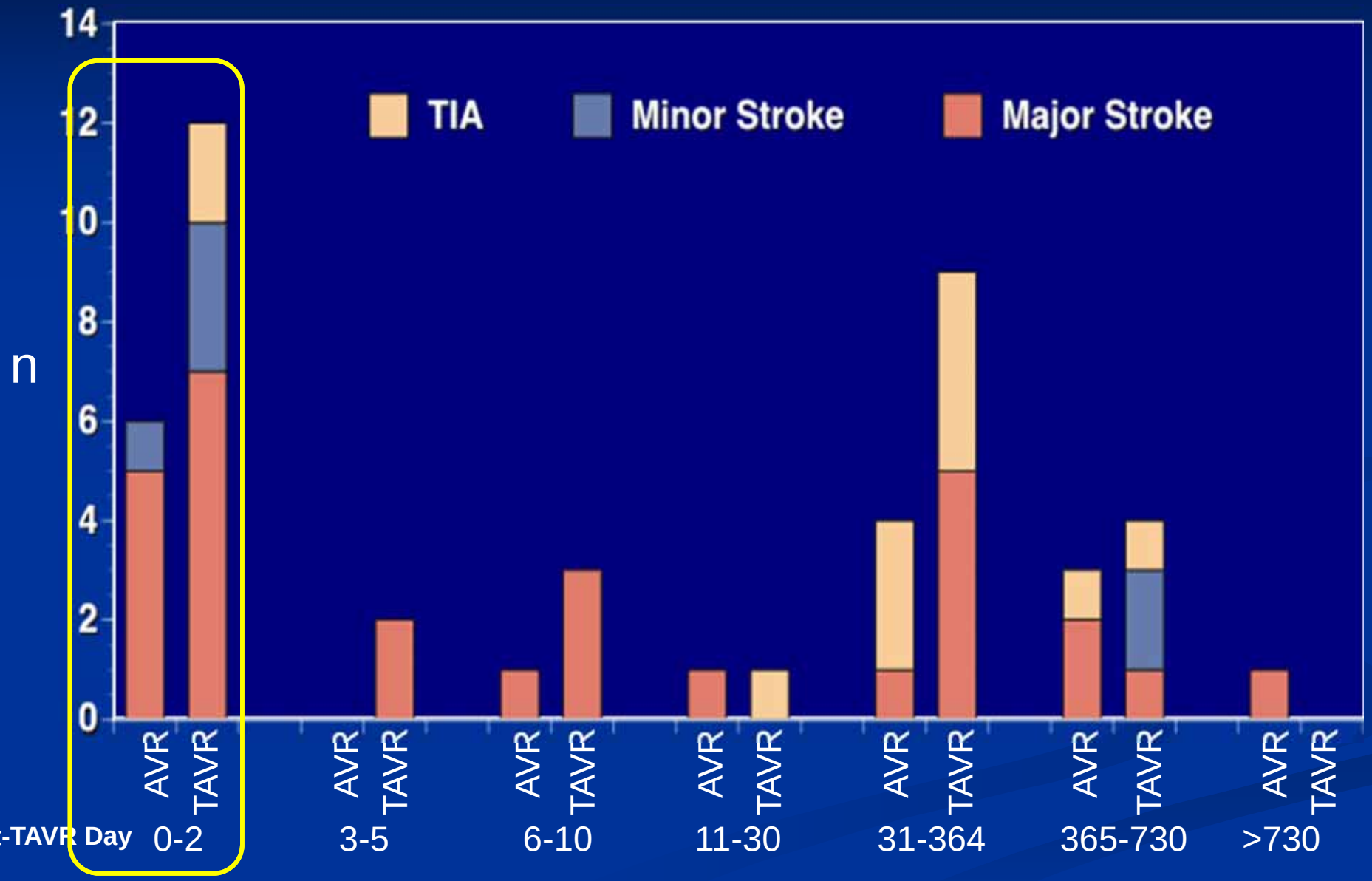
Risk of stroke after transcatheter aortic valve implantation (TAVI): a meta-analysis of 10,037 published patients

Holger Eggebrecht[1], MD, FESC; Axel Schmermund[1], MD, FESC; Thomas Voigtländer[1], MD, FESC; Philipp Kahlert[2], MD; Raimund Erbel[2], MD, FESC, FACC, FAHA; Rajendra H. Mehta[3], MD, MS

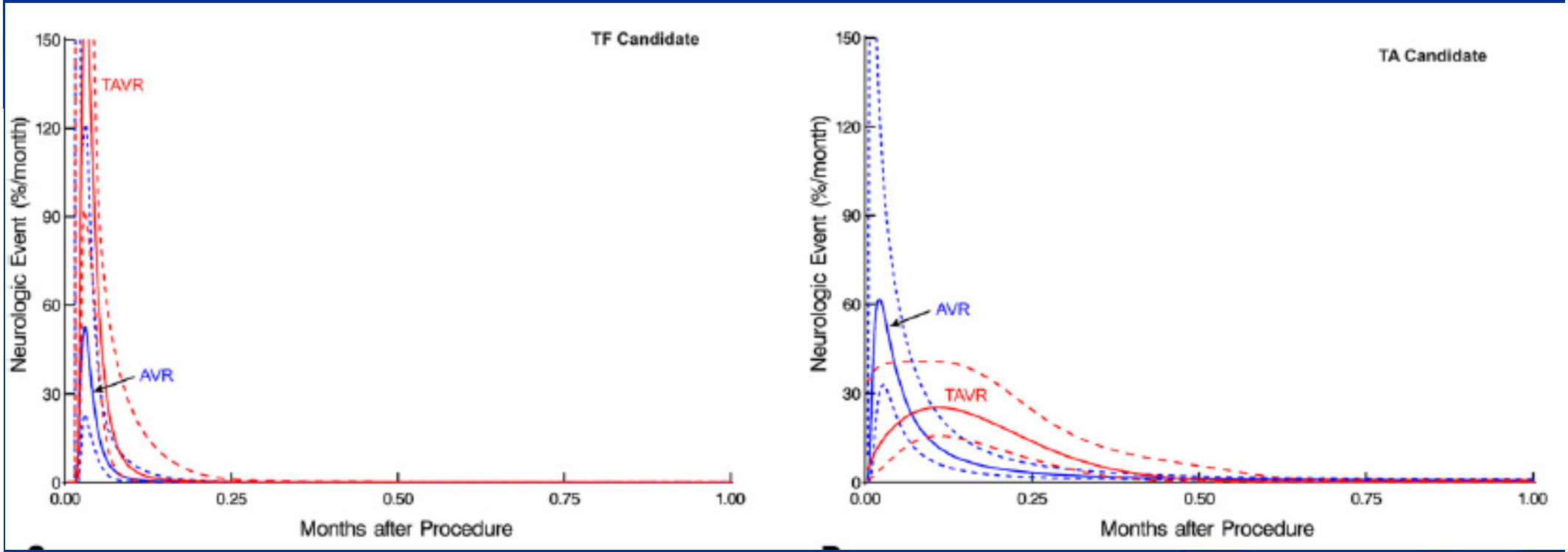
	Number of publications with available data (n)	Overall number of patients with available data (n)	Number of events (n)	Weighted mean±SD
Procedural stroke (<24h)	24	3041	47	1.5±1.4%
30-day stroke/TIA	53	10037	334	3.3±1.8%
30-day major stroke	42	5514	158	2.9±1.8%
30-day minor stroke/TIA	42	5514	53	1.0±1.3%
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, H., EuroIntervention. 2012;8:129-38

Timing of Stroke – PARTNER A

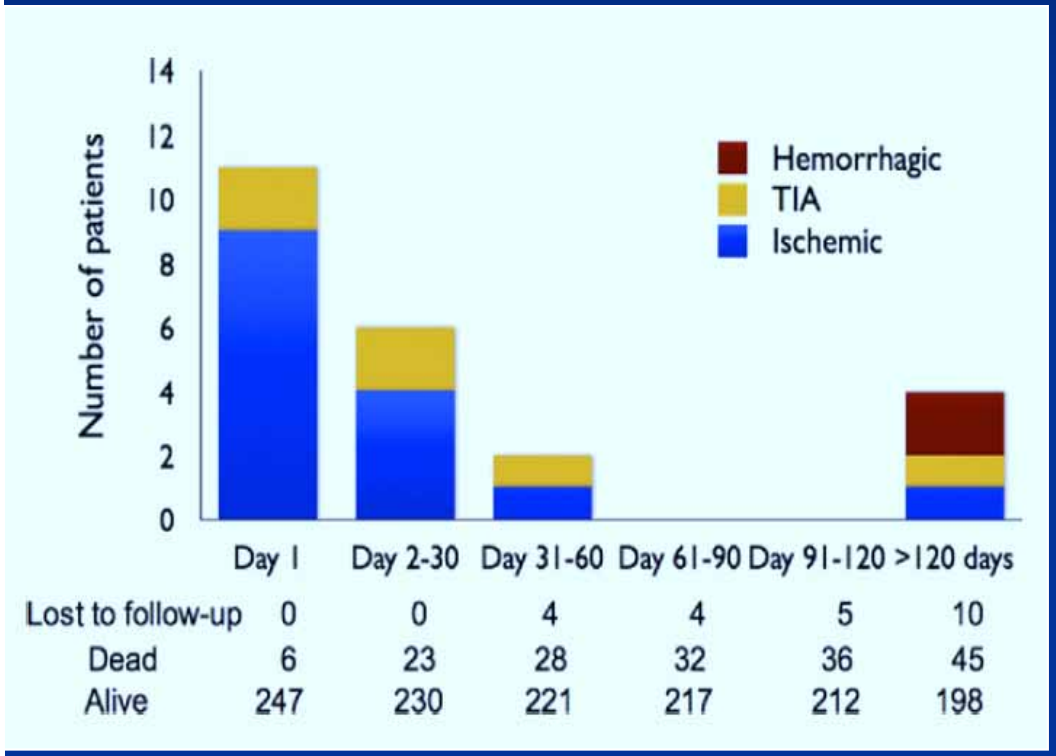


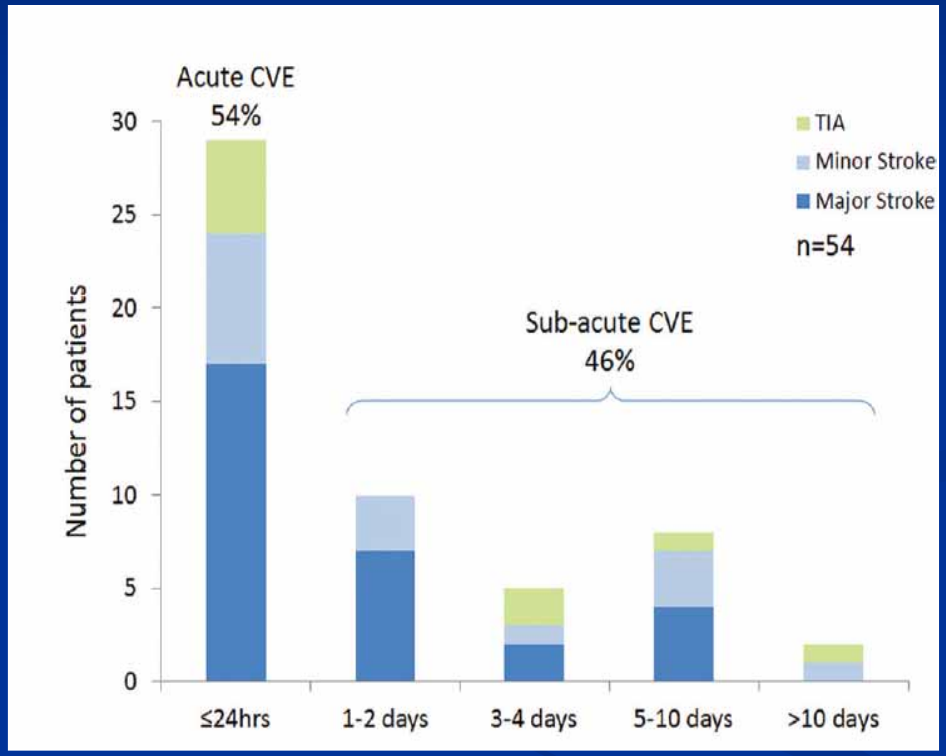
Timing of Stroke – PARTNER A



Miller, D. C., J Thorac Cardiovasc Surg. 2012;143:832-843 e13

Timing of Neurological Event





Tay et al, J Am Coll Cardiol Intv 2011;4:1290 –7

Nombela-Franco et al. Circulation. 2012;126(25):3041-53

Predictors of Stroke, Neuro events or MRI findings

Author	N	Event rate	Approach	Clinical predictors	Anatomical predictors
Tay et al 2011	253	9%	TA/TF	H/O stroke/TIA	Carotid stenosis*
Nuis et al 2012	214	9%	TF	New onset AF	Baseline AR >3+
Amat Santos et al 2012	138	6.5%	TA/TF	New onset AF	None
Franco et al 2012	211	4.7%	TA/TF	None	Post-dilation
Miller et al 2012	344	9%	TA/TF	History of stroke Non TF-TAVR candidate	Smaller AVA
Cabau et al 2011	60	68% (MRI)	TA/TF	Male, History of CAD	Higher AVG
Fairbairn et al 2012	31	77% (MRI)	TF	Age	Aortic atheroma
Nombela-Franco et al 2012	1061	5.1%	TA/TF	Balloon postdilatation, valve dislodgement, New onset AF, PVD, Prior CVA	

Predictors of Stroke by Timing

	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, L., Circulation. 2012;126:3041-53

Potential Mechanism for Stroke post-TAVR Acute Stroke (<24hrs)

- Thrombo-embolism from valve area or aorta
  - Passage of bulky valve devices
  - Post-dilatation
- Hypotension asociated with rapid ventricular pacing or hemodynamic instability during procedure

Potential Mechanism for Stroke post-TAVR Sub-acute Late Stroke

- Thromboembolism from valve site
- Atrial fibrillation – acute or chronic
- Atherosclerotic burden

Circulation
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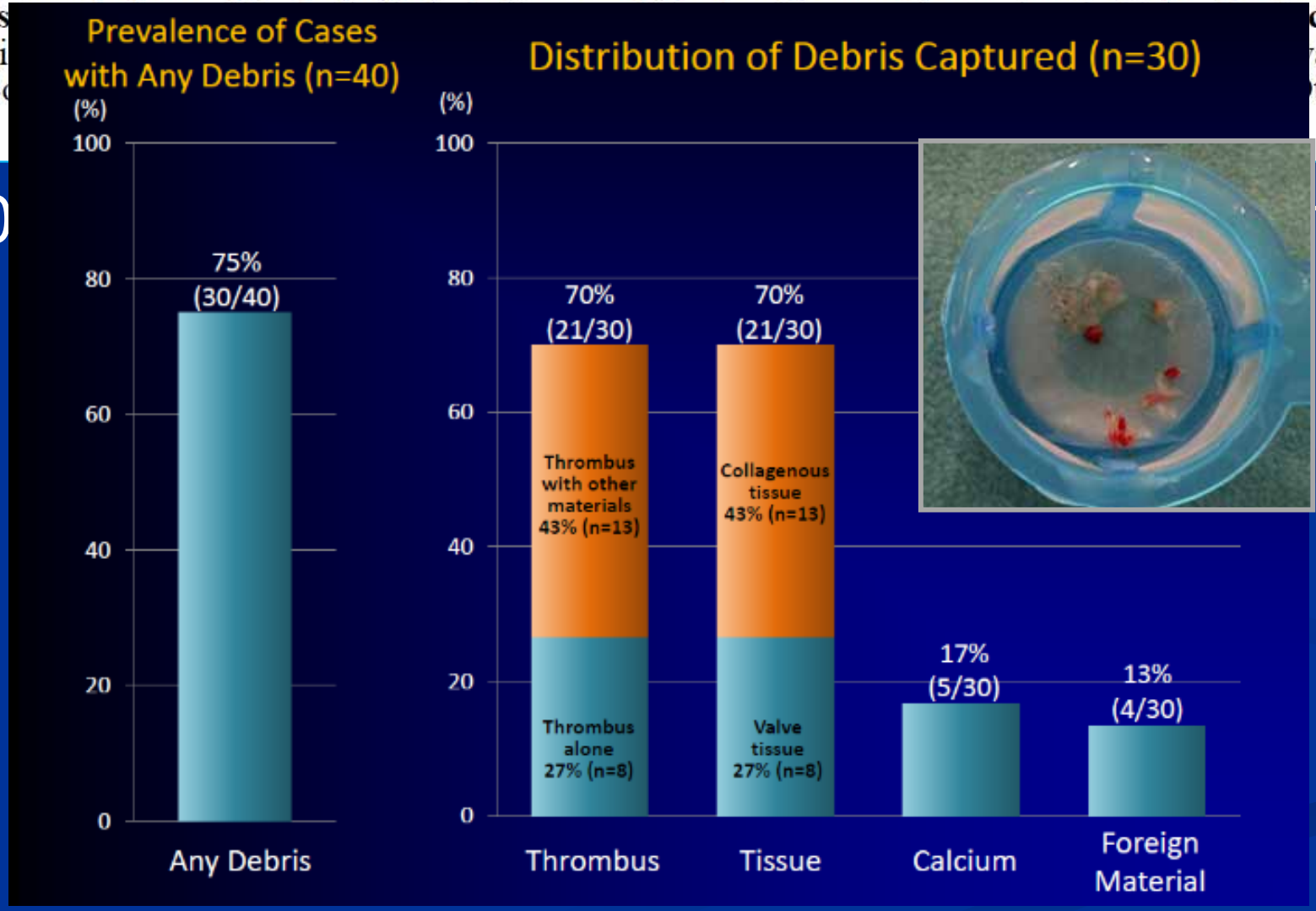
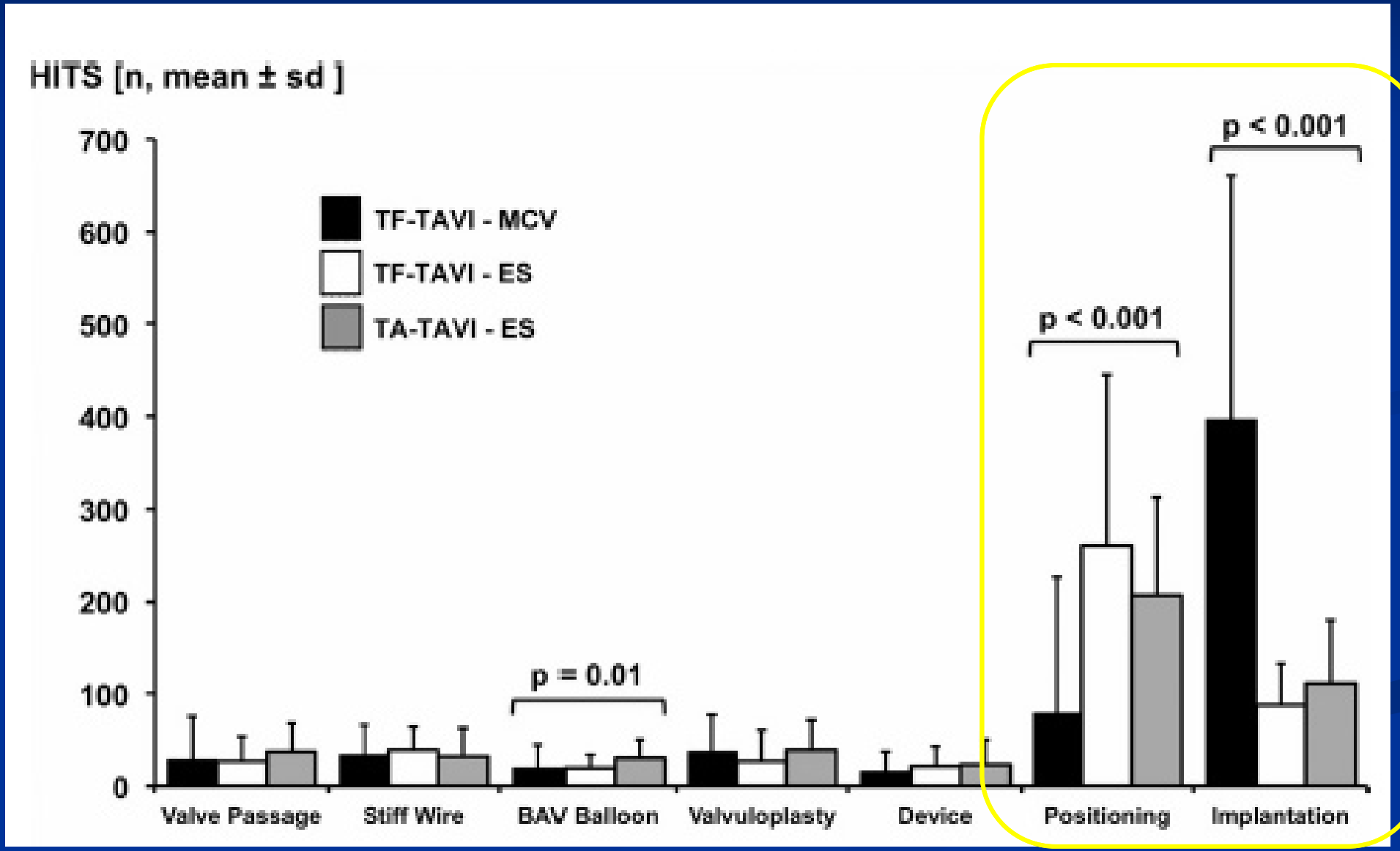


Van Mieghem, N. M., Circulation. 2013;127:2194-201

Timing of Emboli during TAVR



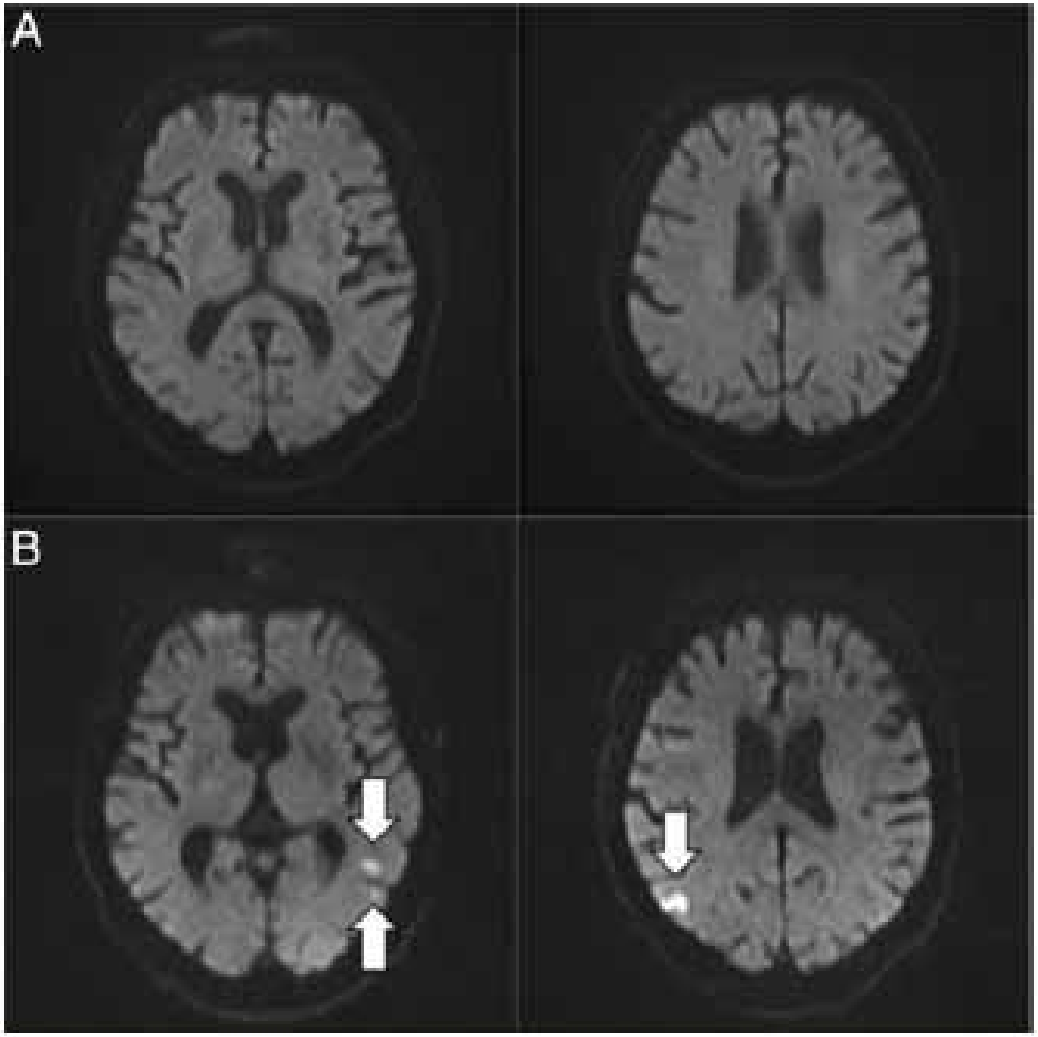
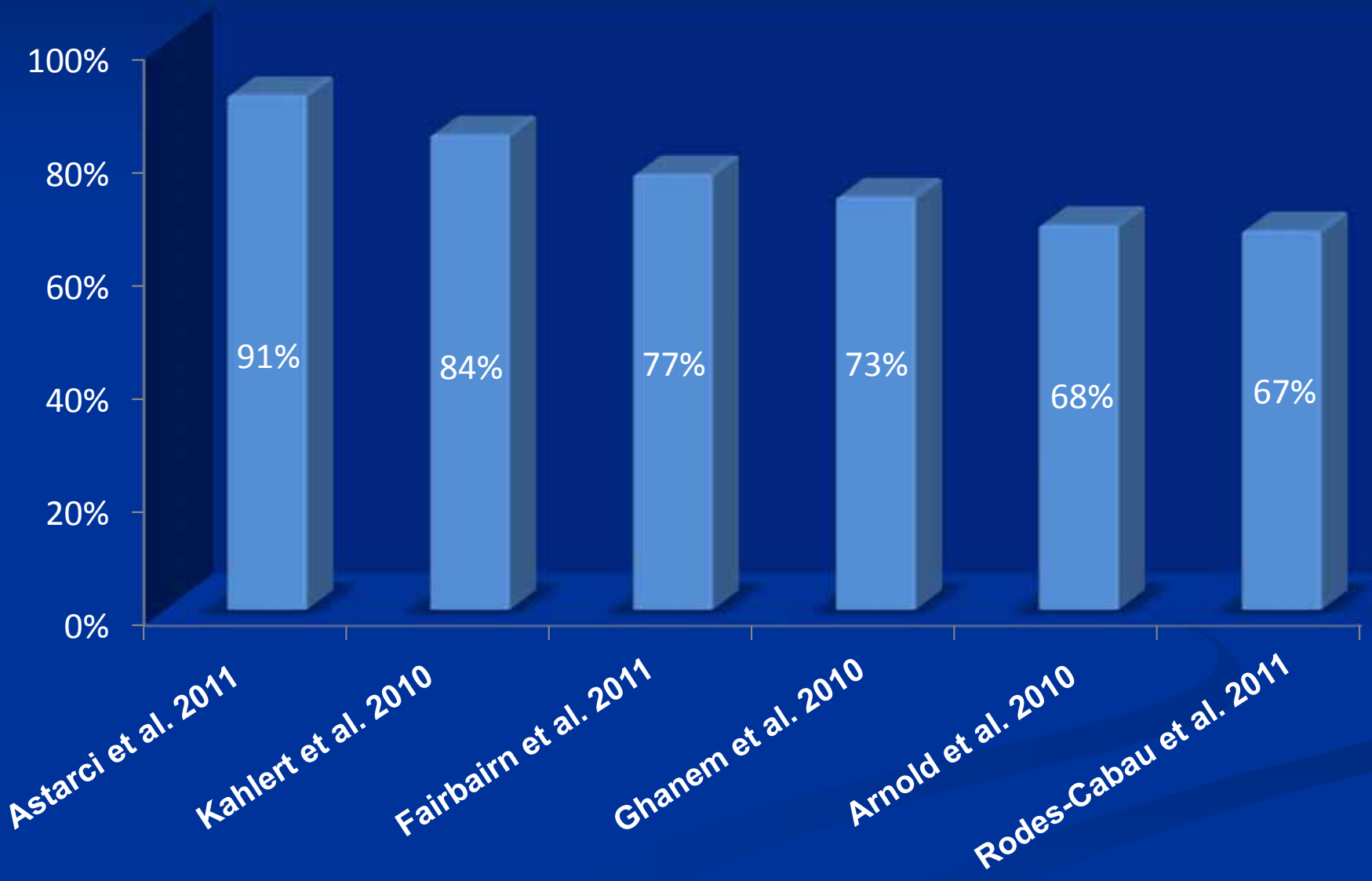
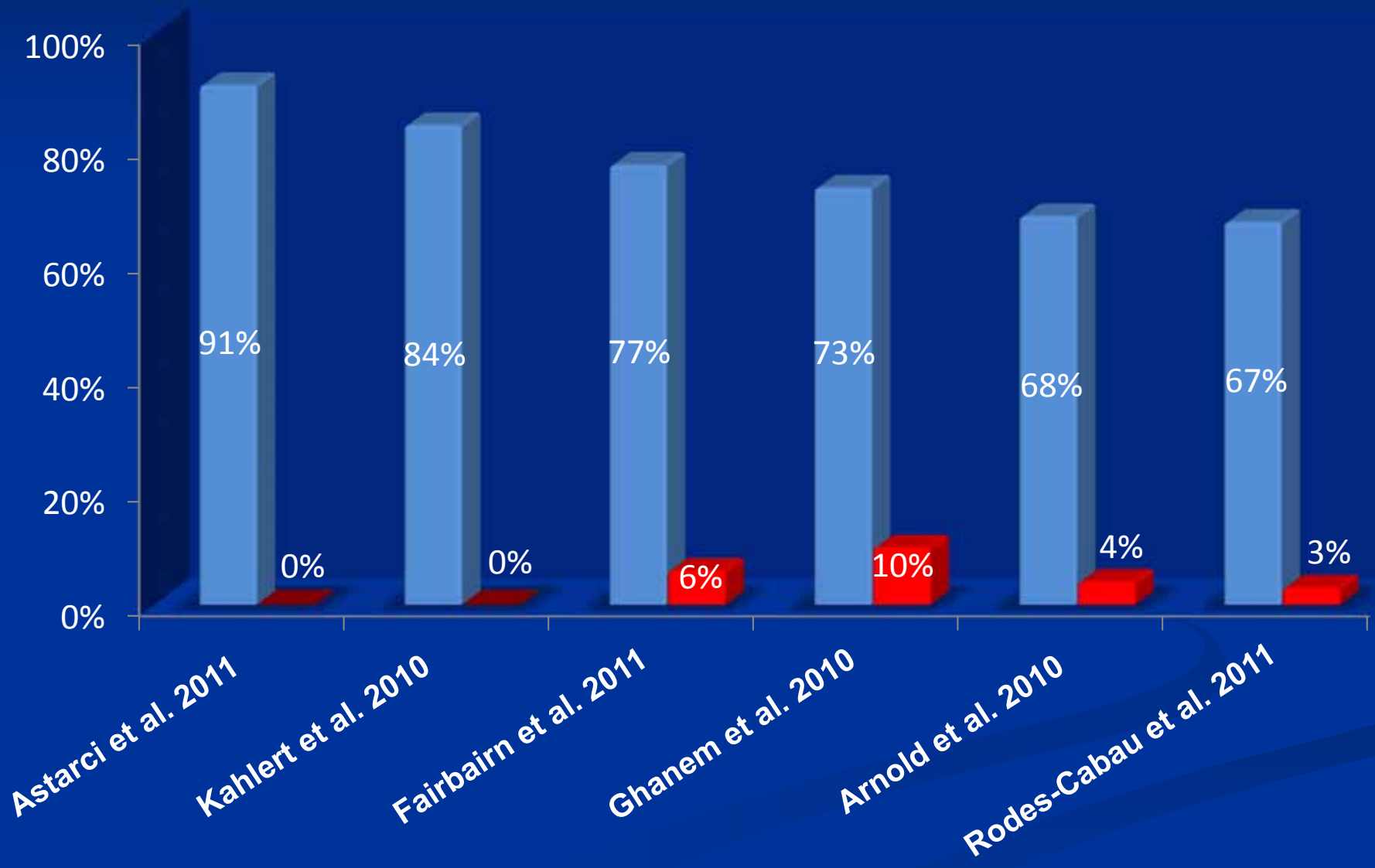


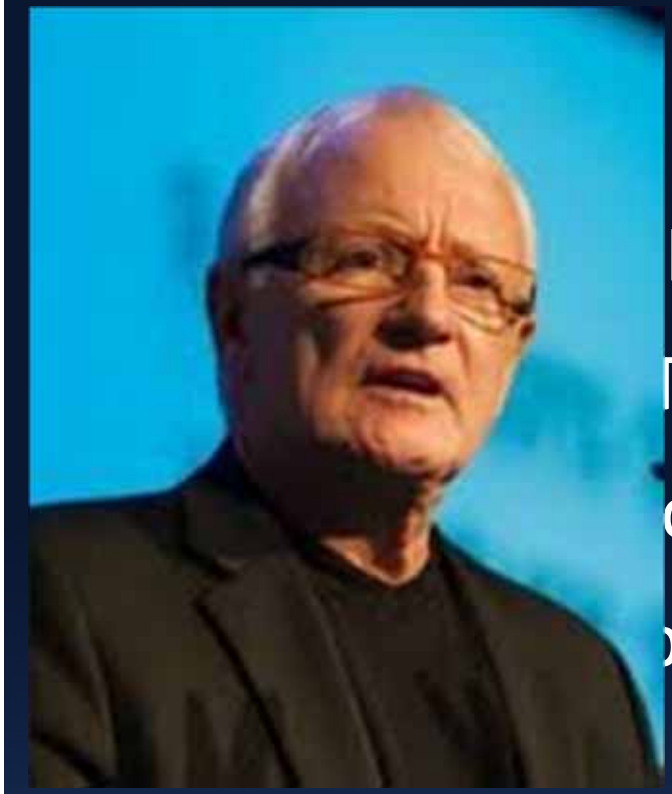
Figure 9 Magnetic resonance imaging to detect cerebral lesions as a surrogate for procedural embolization after TAVI. Pre- (*A*) and post-interventional (*B*) diffusion-weighted magnetic resonance imaging of a patient undergoing transfemoral transcatheter aortic valve implantation with new foci of restricted diffusion in the right and left posterior hemisphere (arrows). DW-MRI, diffusion-weighted magnetic resonance imaging.

New Cerebral Lesions on MRI post-TAVR



Does it matter?...





My Conclusion

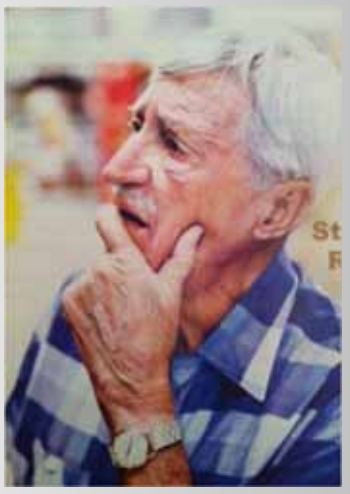
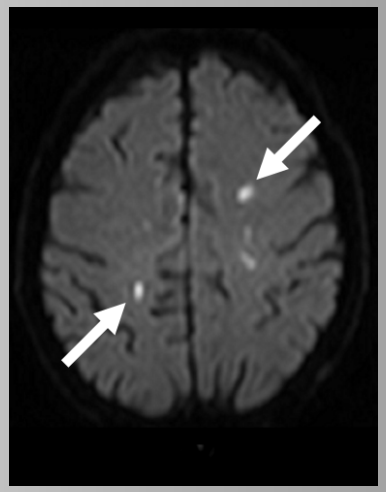
- Improving
- Techniques are improving
- ction is Improving
- pharma therapy is improving

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

Cerebral Protection <u>will</u> (and should) become Standard of Care

Spectrum of Cerebral Injury




obvious - apparent - quiet - subtle - silent - subclinical

2-4% 3-10% 15-20% 68-84% ?%

Diagnosis	***Stroke/ TIA***		***MCI / VD****		***Cerebral injury***
VARC	***Yes***	***Yes***	***No***	***No***	***No***
Assessment	***Heart-Team***	***+ NEURO / PSY***		***+ MRI***	***+LAB***
Victim(s)	***Patient / Relatives / Society***				

****mild cognitive impairment / vascular dementia***

Adapted from Leon TVT 2014

“Silent MRI Lesions” Causes Neuro-cognitive dysfunction in non-TAVR settings

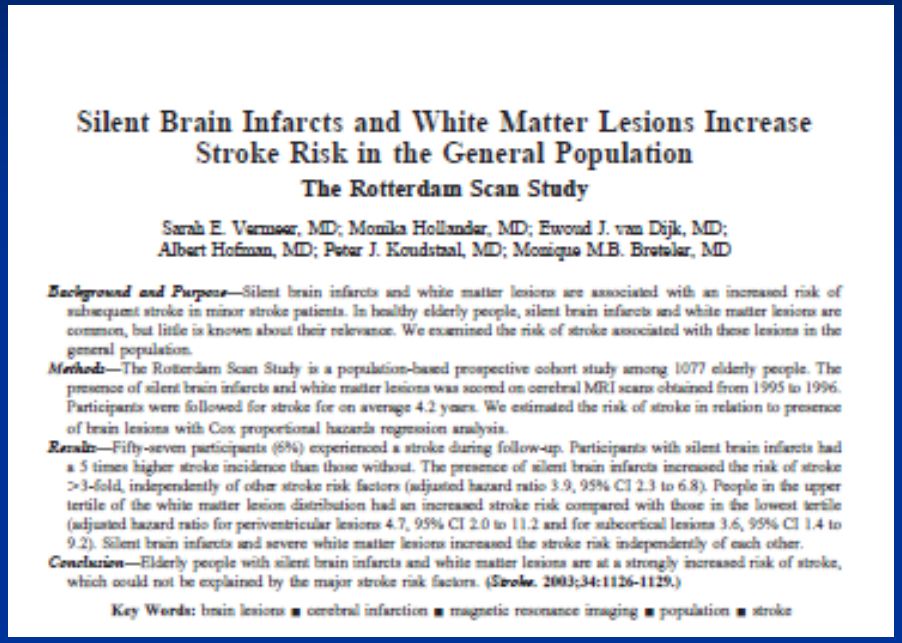
First Author (ref#)	n	% of patients with NC decline	% of patients with new DWI lesions	Procedure / diagnosis	Comments
Restrepo (8)	13	77%	31%	CABG	Extensive NC testing Pts with new DWI lesions had larger NC decline
Choi (9)	25 10 w new mental 15 wo new mental	100%	 70% 20%	Vascular Dementia	Extensive 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 infracts 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 and reac
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**

MRI White Matter Lesions



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

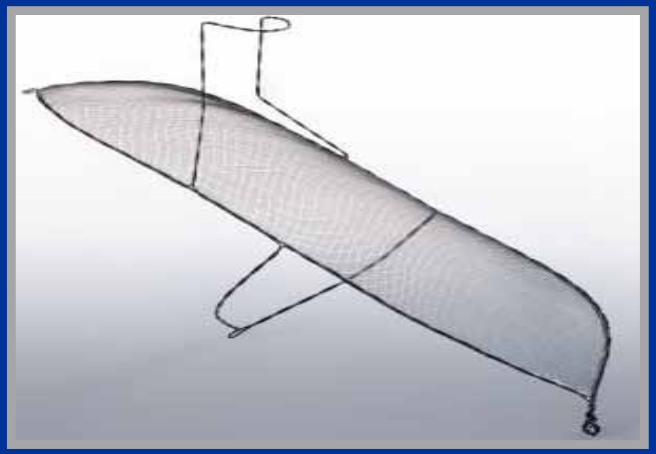
- Population based cohort study of 1077 elderly people followed for 4+ years
- 14.3% with silent brain infarcts developed a stroke during follow up period
- Presence of silent brain infarcts increased risk of stroke by >3 fold

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

Cerebral Embolic Protection Devices

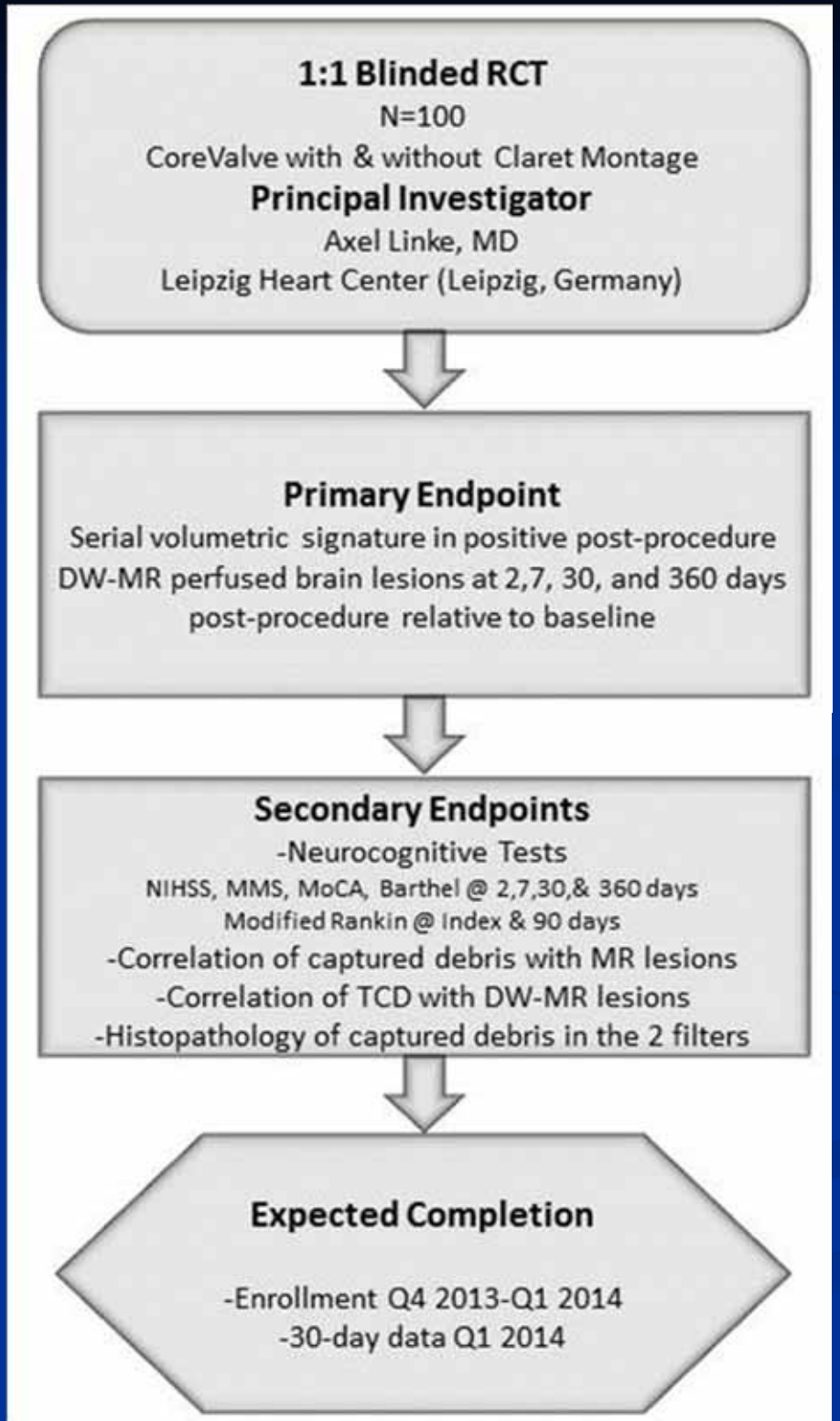
TriGuard™ Cerebral	Embrella™	Claret Sentinel™
Deflector	Deflector	Dual Filter
Femoral Access	Radial Access	Radial Access
9F Sheath (7F Delivery)	6F Shuttle Sheath	6F Radial Sheath



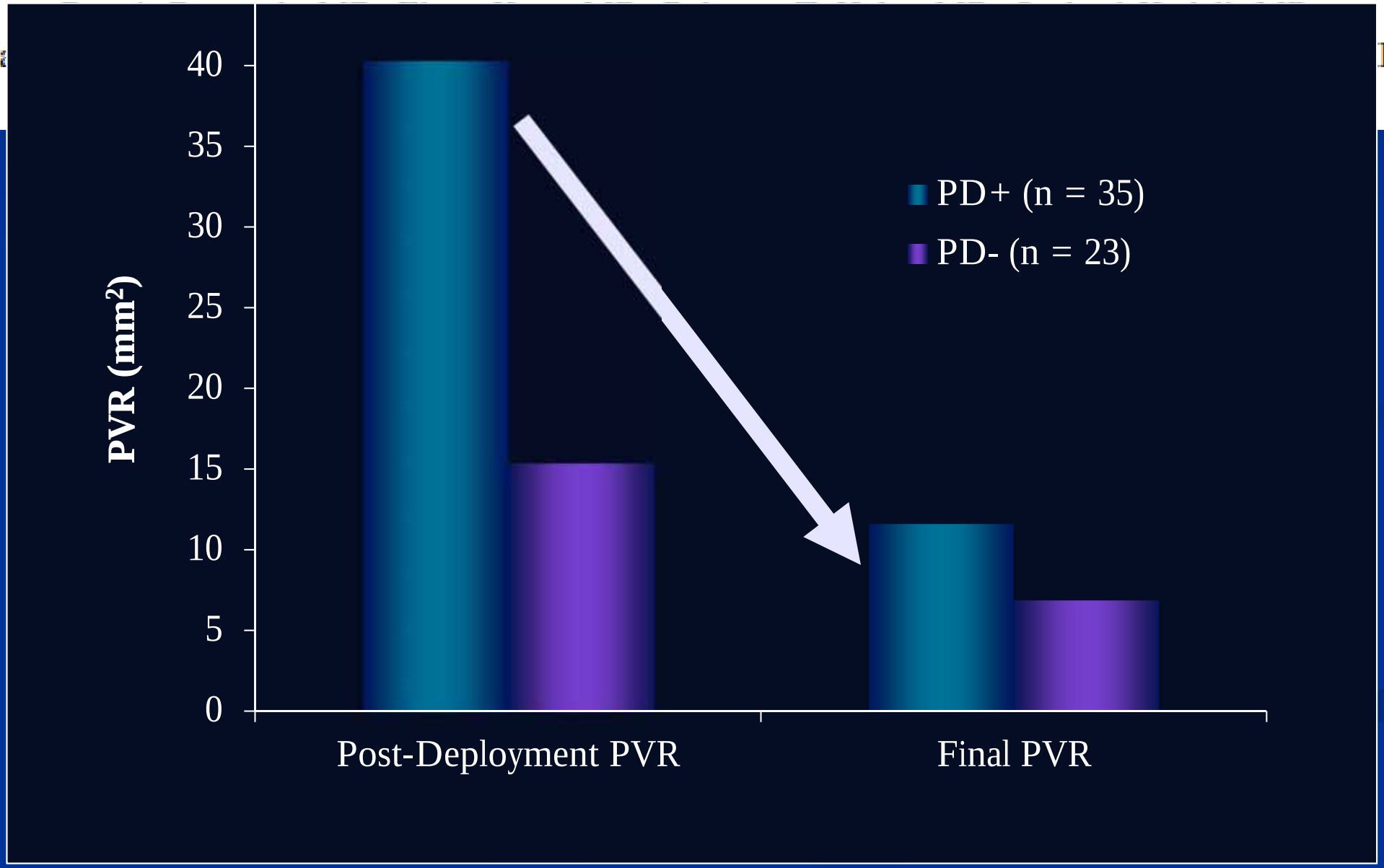
Embrella
All Patients Had New MRI Lesions
But potential for reduced lesion volume

Study	n	Valve Type	New Ischemic Defects	Median Number of Lesions Per Patient	Lesion Volume (Per Lesion, mm^3)
Kahlert et al. Circulation 2010	53	SAPIEN (n=22) CoreValve (n=10) SAVR (n=21)	SAPIEN: 86% CoreValve: 80% SAVR: 48%	SAPIEN: 4 (2.1-6.0) CoreValve: 2.6 (0.3-4.9) SAVR: 1.6 (0.6-2.69)	81 (60-103) 61 (37-86) 224 (111-338)
Ghanem et al. JACC 2010	22	CoreValve	73%	2.5 (1.0-5.5)	NA
Rodés-Cabau et al. JACC 2011	60	SAPIEN/ SAPIEN XT	TF: 66% TA: 71%	TF: 3 (1-7) TA: 4 (2-9)	NA
Fairbairn et al. Heart 2011	31	CoreValve	77%	2 (1-5)	205 ± 350
Arnold et al. JACC Intv 2010	25	SAPIEN	68%	NA	NA
PROTAVI-C Pilot	33	SAPIEN XT with Embrella	100%	8 (1-70)	42.3 (27.5, 85)

Rodes-Cabau PCR 2013


1:1 Blinded RCT
N=100
CoreValve with & without Claret Montage
Principal Investigator
Axel Linke, MD
Leipzig Heart Center (Leipzig, Germany)
Primary Endpoint
Serial volumetric signature in positive post-procedure DW-MR perfused brain lesions at 2,7, 30, and 360 days post-procedure relative to baseline
Secondary Endpoints
-Neurocognitive Tests
NIHSS, MMS, MoCA, Barthel @ 2,7,30,& 360 days
Modified Rankin @ Index & 90 days
-Correlation of captured debris with MR lesions
-Correlation of TCD with DW-MR lesions
-Histopathology of captured debris in the 2 filters
Expected Completion
-Enrollment Q4 2013-Q1 2014
-30-day data Q1 2014

Efficacy and Safety of Postdilatation to Reduce Paravalvular Regurgitation During Balloon-Expandable Transcatheter Aortic Valve Replacement



Daneault, B., et al. *Circ Cardiovasc Interv.* 2013;6:85-91

30-day Clinical Outcomes
Post-dilatation vs No Post-dilatation

Table 3. Clinical Outcomes

	Postdilatation (n=106)	No Postdilatation (n=153)	OR (95% CI)	*P* Value
30-day mortality	2 (1.9%)	11 (7.2%)	0.25 (0.05–1.14)	0.06
30-day cardiac mortality	1 (0.9%)	6 (3.9%)	0.23 (0.03–1.97)	0.25
In-hospital cerebrovascular events				
All stroke or TIA	5 (4.7%)	2 (1.3%)	3.74 (0.71–19.64)	0.13
All stroke	4 (3.8%)	1 (0.7%)	5.96 (0.66–54.10)	0.16
Aortic dissection	1 (0.9%)	1 (0.7%)	1.45 (0.09–23.4)	1.00
Aortic wall hematoma	1 (0.9%)	3 (2.0%)	0.48 (0.05–4.64)	0.65
PPM implantation during index hospitalization	6 (5.7%)	13 (8.5%)	0.65 (0.24–1.76)	0.39

Daneault, B., et al. *Circ Cardiovasc Interv.* 2013;6:85-91

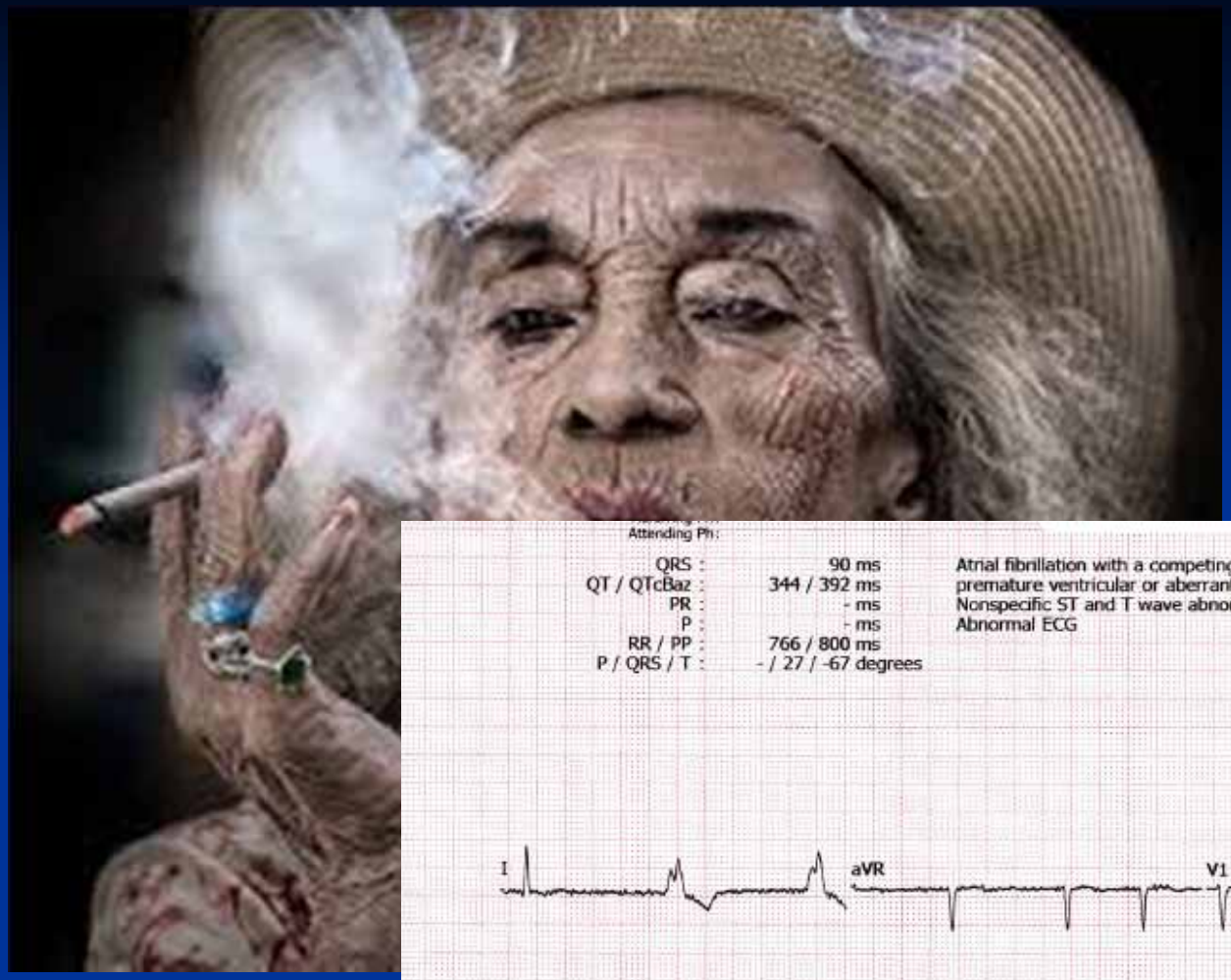
Feasibility of Transcatheter Aortic Valve Implantation Without Balloon Pre-Dilation

A Pilot Study

Eberhard Grube, MD,* Christoph Naber, MD,† Alexandre Abizaid, MD,‡
Eduardo Sousa, MD,‡ Oscar Mendiz, MD,§ Pedro Lemos, MD,‖ Roberto Kalil Filho, MD,‖
Jose M

Bonn a *l*

	No Predilatation Group	Control Group (CoreValve S&E)
	n=60	n=126
All-cause Mortality	6.7% (4)	14.3% (18)
Myocardial infarction	0	5.6% (7)
Stroke/TIA	5.0% (3)	11.9% (15)
Need for pacemaker implantation	11.7% (7)	27.8% (35)
Vascular Access Complication	10.0% (6)	9.5% (12)
Post-dilatation	16.7%	0



Attending Ph:

QRS :	90 ms
QT / QTcBaz :	344 / 392 ms
PR :	- ms
P :	- ms
RR / PP :	766 / 800 ms
P / QRS / T :	- / 27 / -67 degrees

Atrial fibrillation with a competing junctional pacemaker with premature ventricular or aberrantly conducted complexes
Nonspecific ST and T wave abnormality , probably digitalis effect
Abnormal ECG

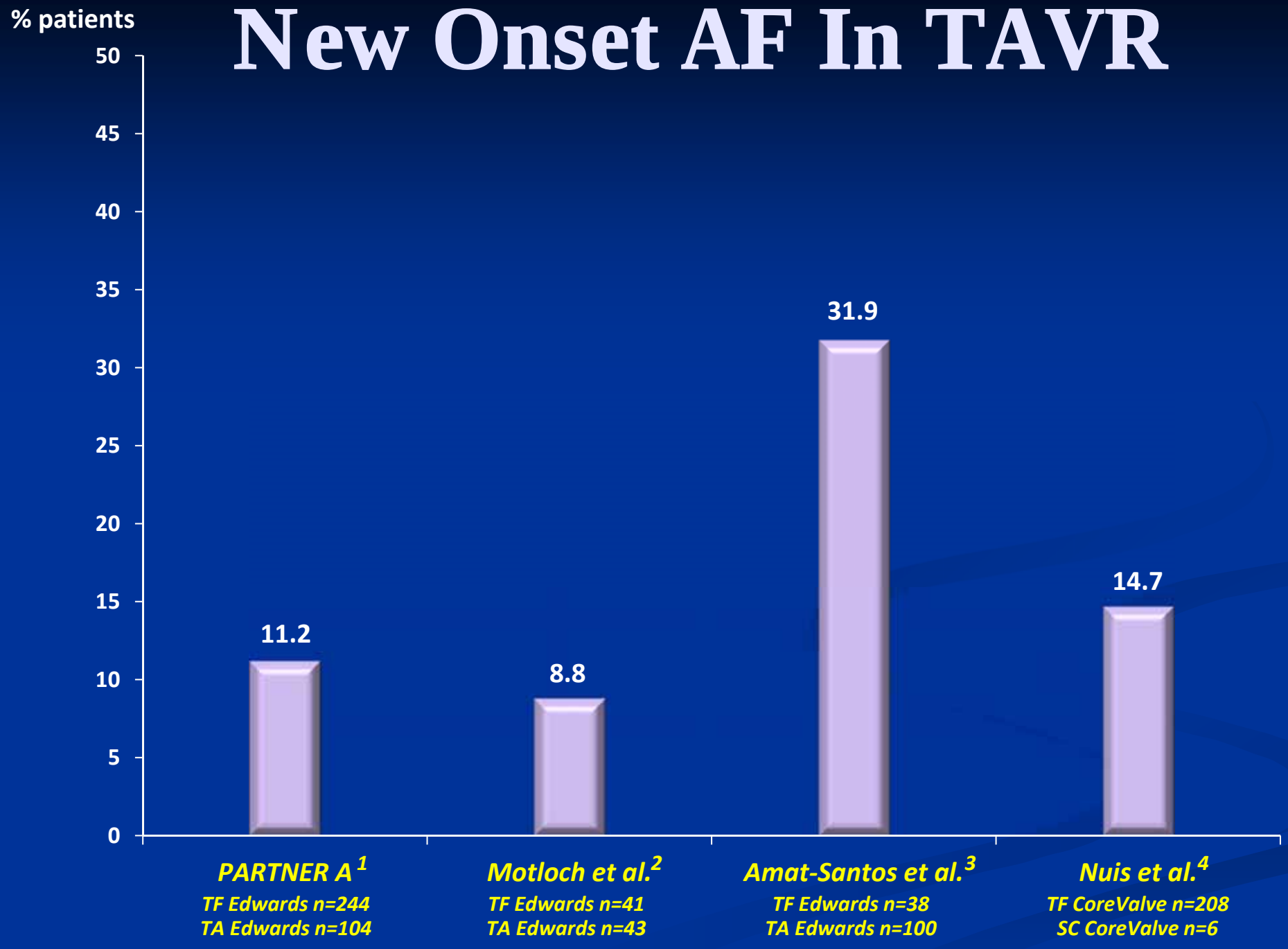
Clinically Significant / Not Clinically Significant
If CS, please comment
(eg: AE/SAE Term, brief descriptions of event & treatment):

Signature & Date:

I aVR V1 V4
II aVL V2 V5
III aVF V6
II

GE MAC1600 1.0.4 12SL™ v239 25 mm/s 10 mm/mV 0.16-40 Hz 50 Hz Unconfirmed 4x2.5x3_25_R1 1/1

New Onset AF In TAVR



1-Smith et al, NEJM 2011
2-Motloch et al, Ann Thorac Surg 2011
3-Amat-Santos et al, JACC 2012
4-Nuis et al, Am J Cardiol 2012

TAVI EXPERIENCE – PUBLISHED REGISTRIES
Patient characteristics

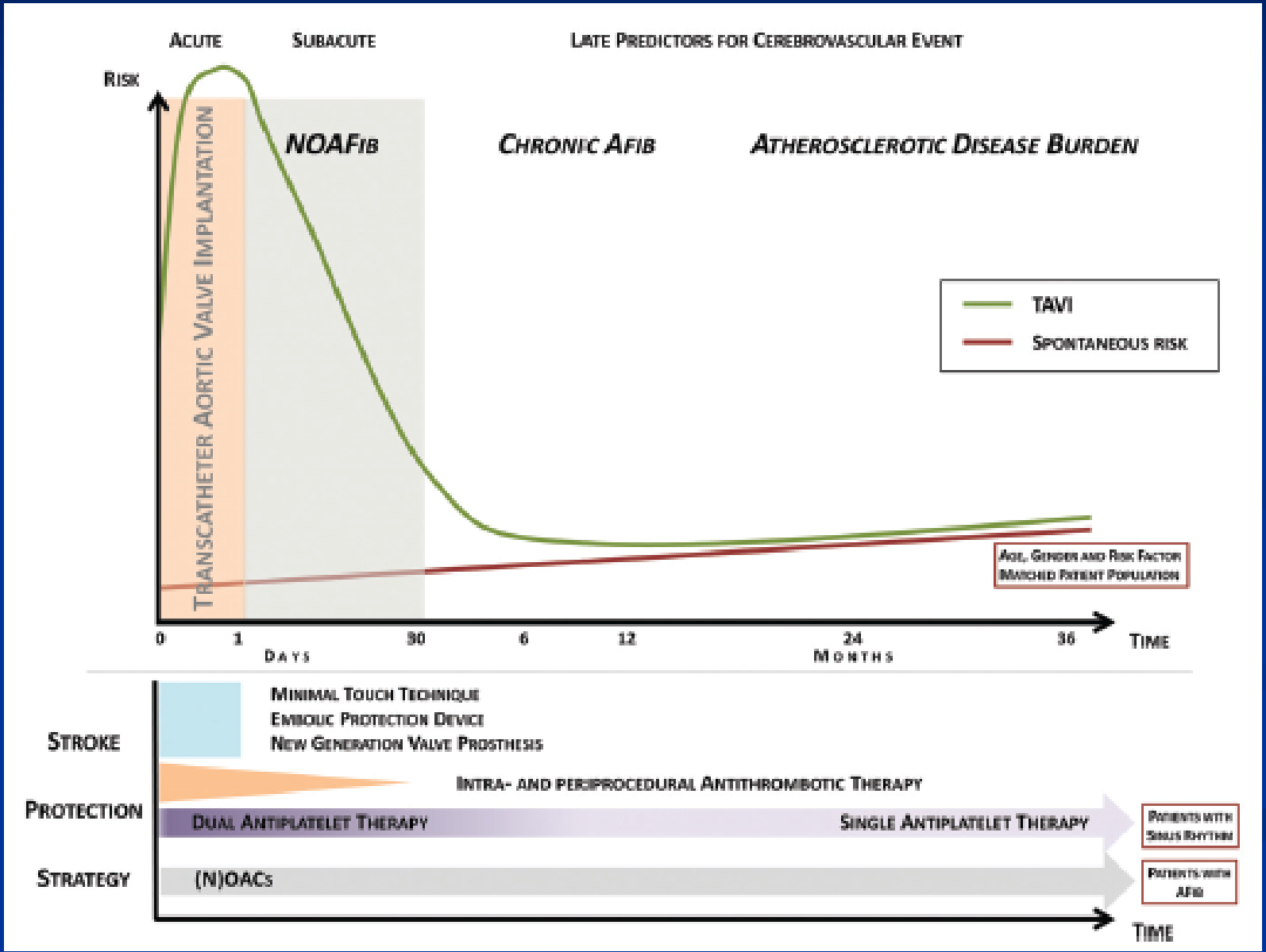
Variables	Mean (min-max)
Age (years)	82 (50-98)
Male sex (%)	44 (24-57)
Diabetes (%)	28 (23-35)
Hypertension	60 (36-85)
Chronic renal failure (%)	35 (20-62)
COPD (%)	26 (21-30)
Prior stroke (%)	9 (7-11)
Peripheral vascular disease (%)	19 (7-35)
TA	30 (11-50)
TF	11 (4-19)
Porcelain aorta (%)	12 (7-18)
Frailty (%)	21 (17-25)

Mean CHADS2 score ~ 3

Conclusion

- Stroke remains a devastating complication post-TAVR
- 40-50% stroke post-TAVR occurs within 24 hours
  - Thromboembolism
  - Related to intervention at aortic valve
  - Improvement in device and technique
  - Cerebral protection devices
- Subacute / late stroke can occur secondary to
  - Atrial fibrillation
  - Atheroembolic burden

Conclusion



Stortecky, S. Circulation. 2012;126:2921-4