Strokes in TAVR
Is it a Deal Breaker?

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The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

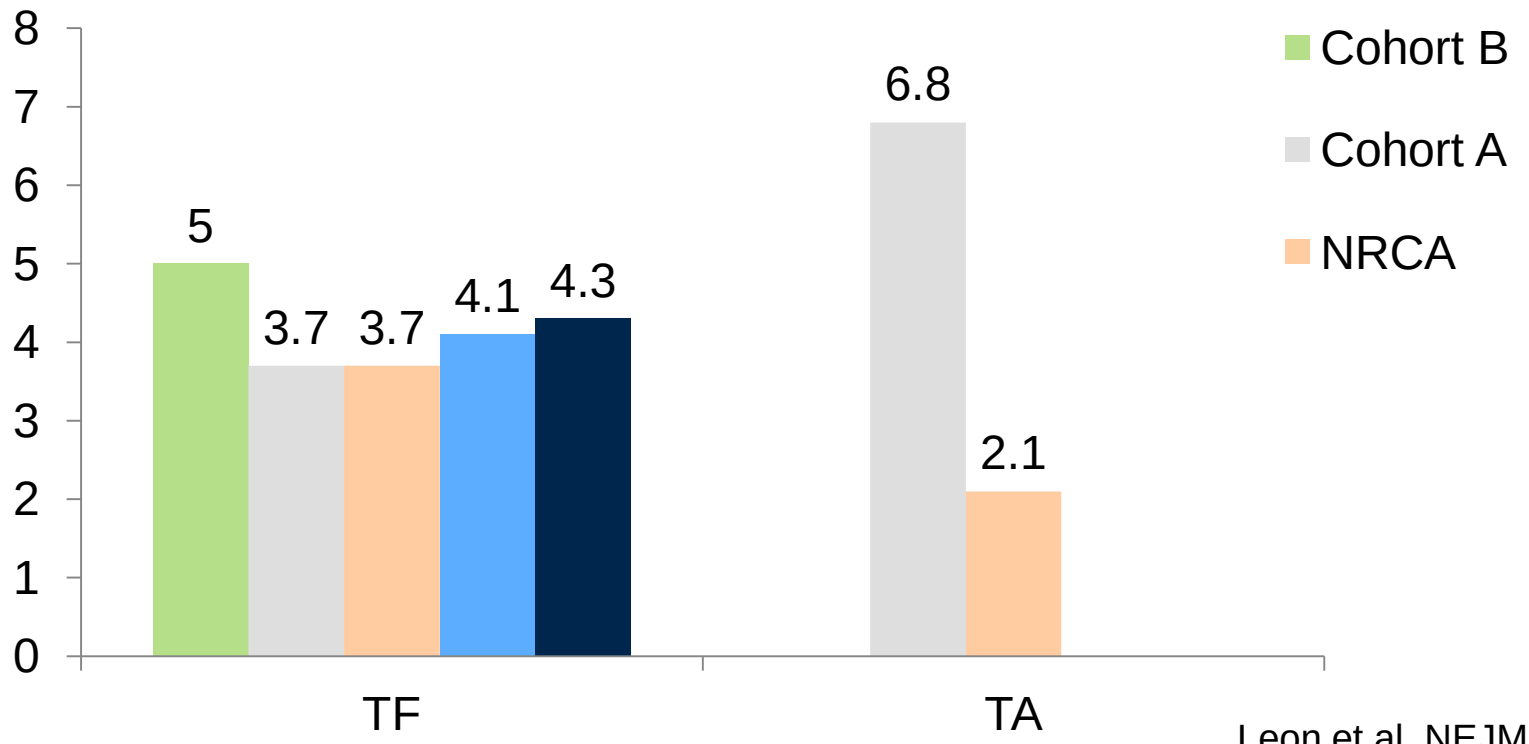
Transcatheter Aortic-Valve Implantation — At What Price?

Hartzell V. Schaff, M.D.

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

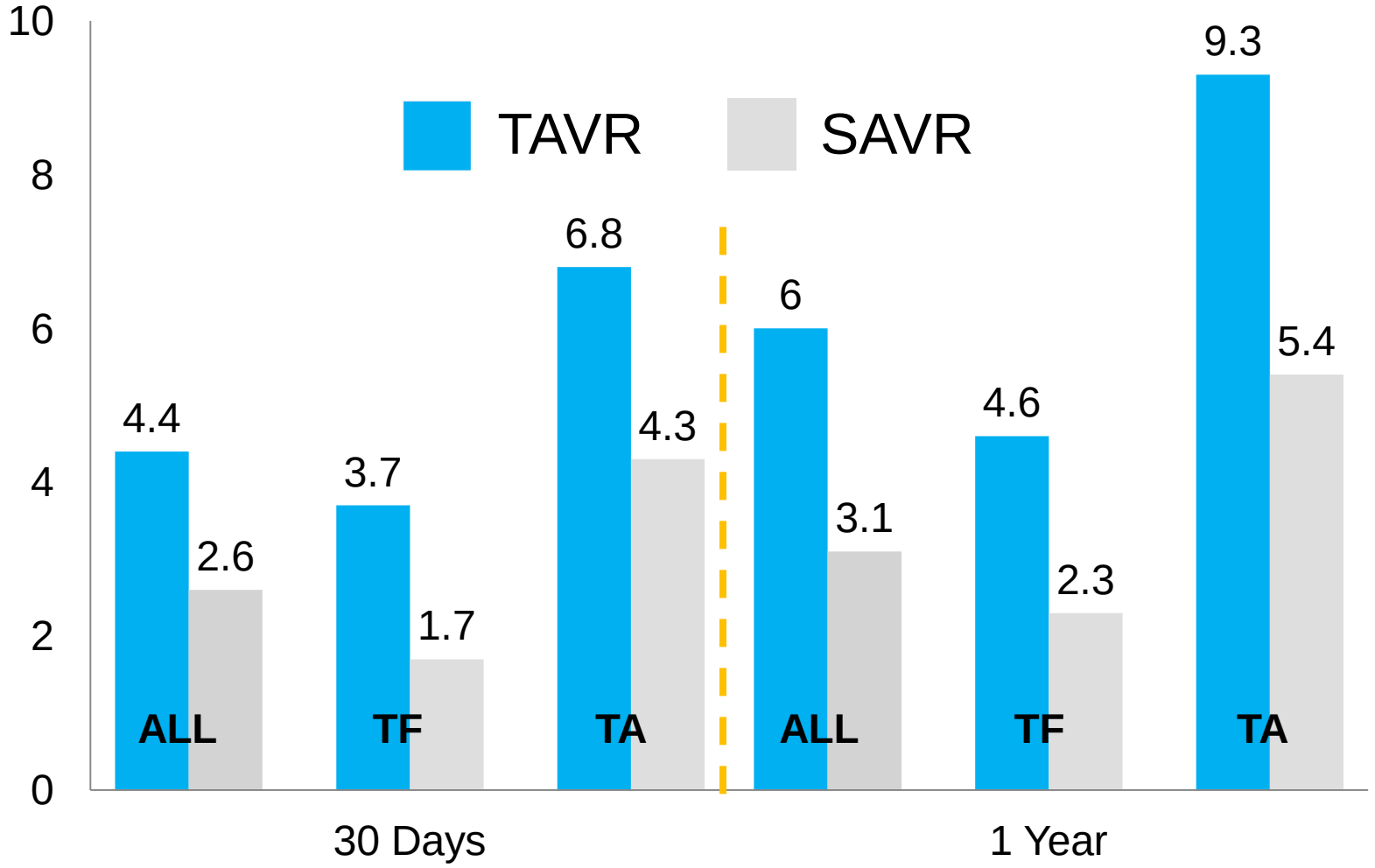
But the increased risk of stroke associated with transcatheter replacement, as compared with surgical replacement, is a special concern. Smith and colleagues report a 5.5% risk of stroke or transient ischemic attack within 30 days after

30 Days - All Stroke from PARTNER Trials



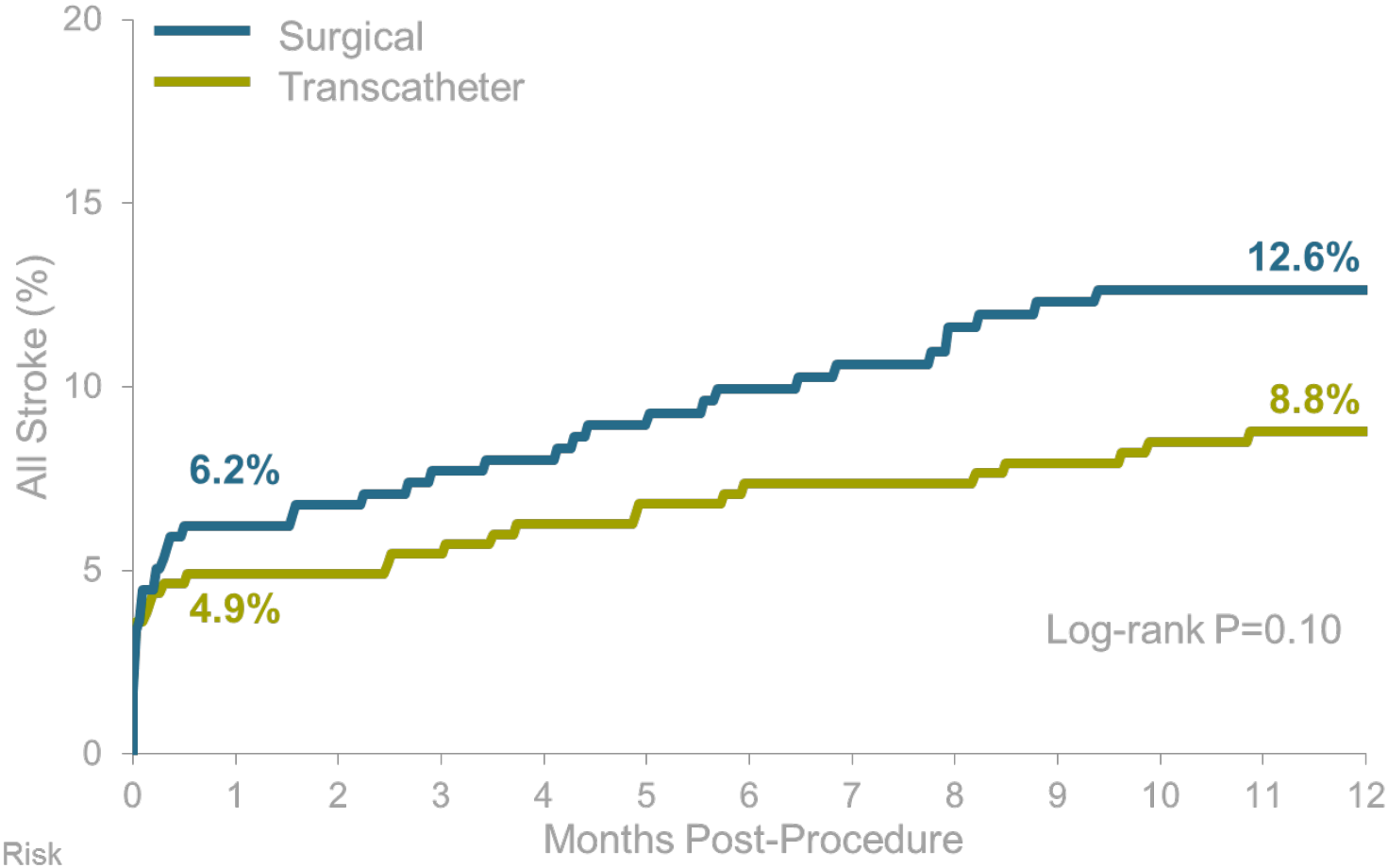
Leon et al, NEJM
Smith et al, NEJM
Kodali et al, ACC 2013
Leon et al, ACC 2013
Dewey et al, STS 2012

All Stroke : PARTNER A (ITT)



Smith et al, NEJM, June 2011

CoreValve Trial : All Stroke



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

Adams, NEJM, 2014

What is the risk of stroke with surgery?

- **2.6% PARTNER -SAVR**
- **6.2% CoreValve - SAVR**

High Risk Surgical AVR and Stroke

Outcome	Patients (n=159)
Death (In-Hospital)	26 (16.4%)
Permanent Neurological Event	7 (4.4%)
Transient Neurological Event	4 (2.5%)

- Isolated AVR
- 2002-2007
- STS >10 at 4 academic institutions

Thourani et al, Ann Thorac Surg 2011;91:49 –56

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

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.)**

AVR and Stroke

2008-2012 – 196 patients (U Penn)

Strokes = 34 patients (17%; 95% CI, 12-23%)
TIA = 4 patients (2%; 95% CI, 0 -4%)

NIHSS <5 = 22
NIHSS 5-9 = 4
NIHSS 10-15 = 3
NIHSS >15 = 5

POD 1 = 17 (58%)
POD 2-3 = 7 (21%)
POD 4-7 = 7 (21%)
>POD 7 = 3 (9%)

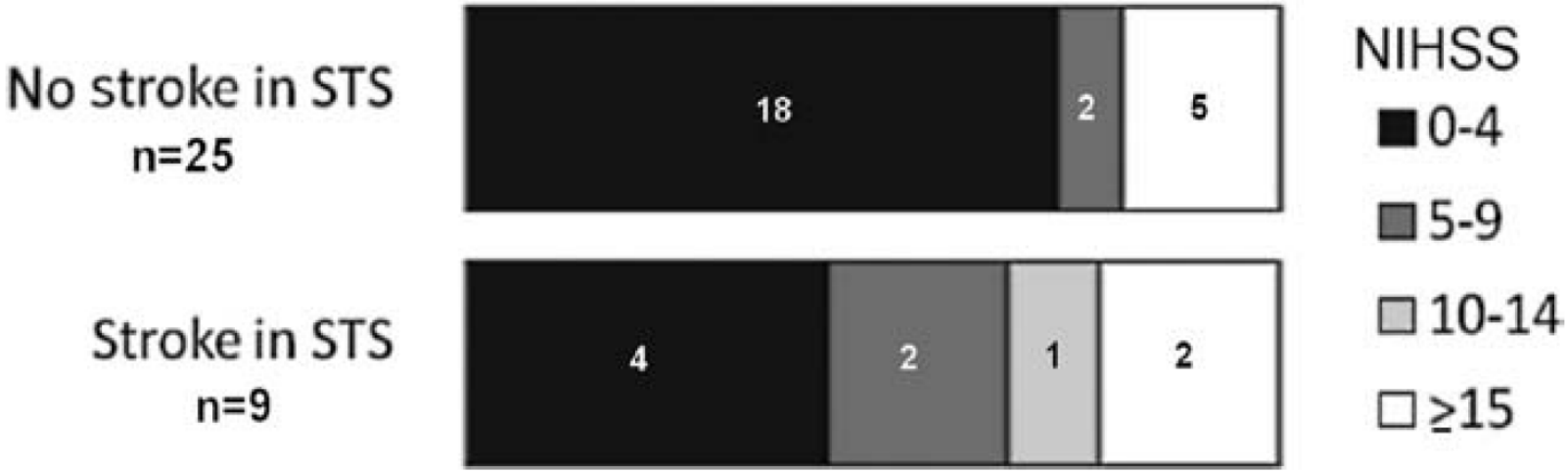
Masse, circulation, 2014

AVR and Stroke

- A meta-analysis of 48 observational studies including 13,216 subjects ≥80 years old who underwent isolated AVR reported that stroke occurred in 2.4%.
- A separate meta-analysis of 40 studies evaluating outcome from combined aortic valve and coronary artery bypass grafting (CABG) found a higher stroke rate of 3.7%.
- The STS national database reported a stroke rate of 1.5% from >67,000 isolated AVR procedures and 2.7% from >66,000 subjects who underwent AVR plus CABG.
- The highest risks of neurologic complications have been reported in subjects undergoing multivalve procedures, with stroke occurring in ≤9.7% of subjects.

Stroke Detection and Reporting

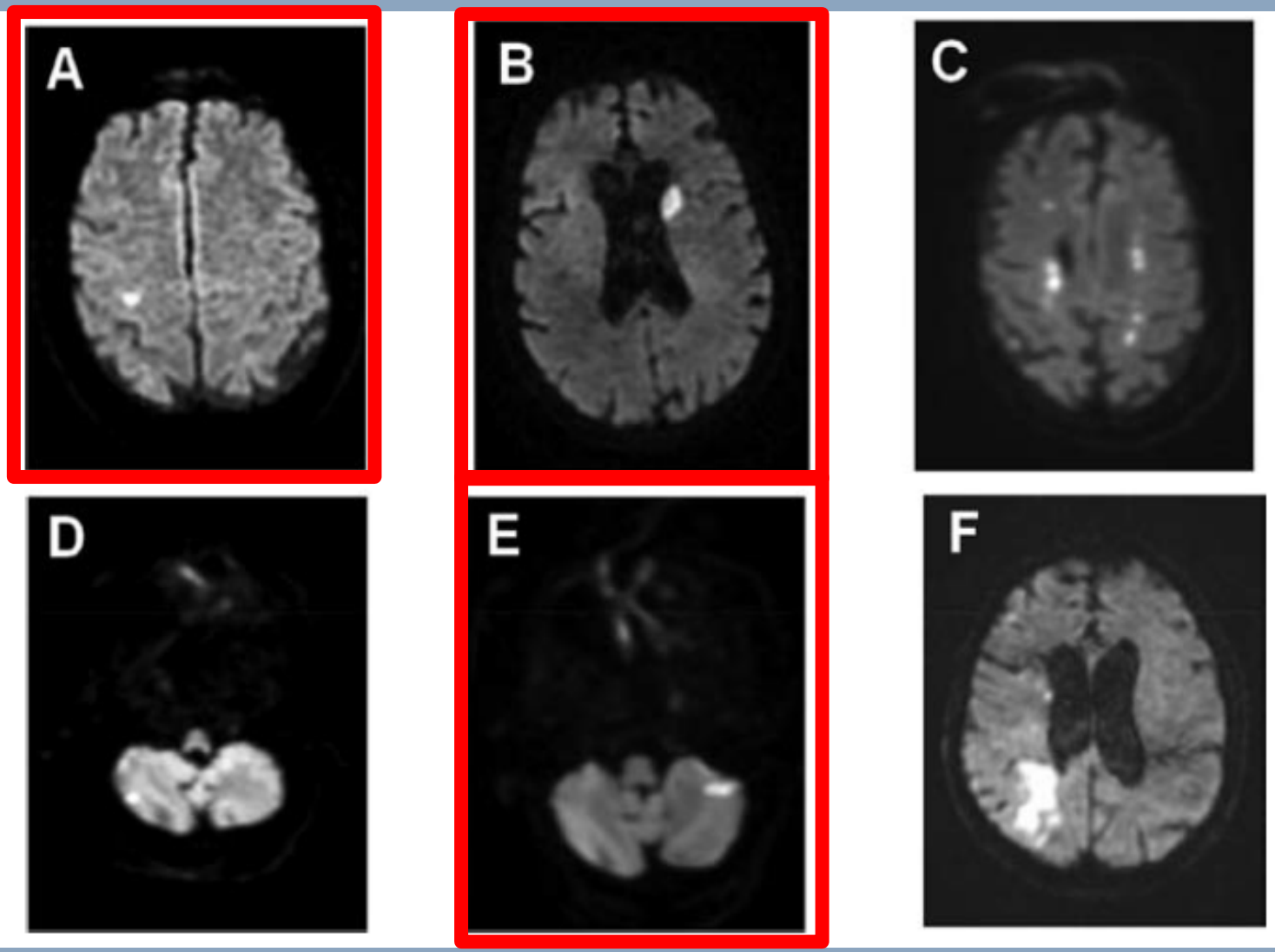
25 “strokes” were not included in STS database



STS database reported 13 patients (6.6%) with stroke but 4 did not have stroke by DeNOVO (alcohol withdrawal, no deficit by day 7)

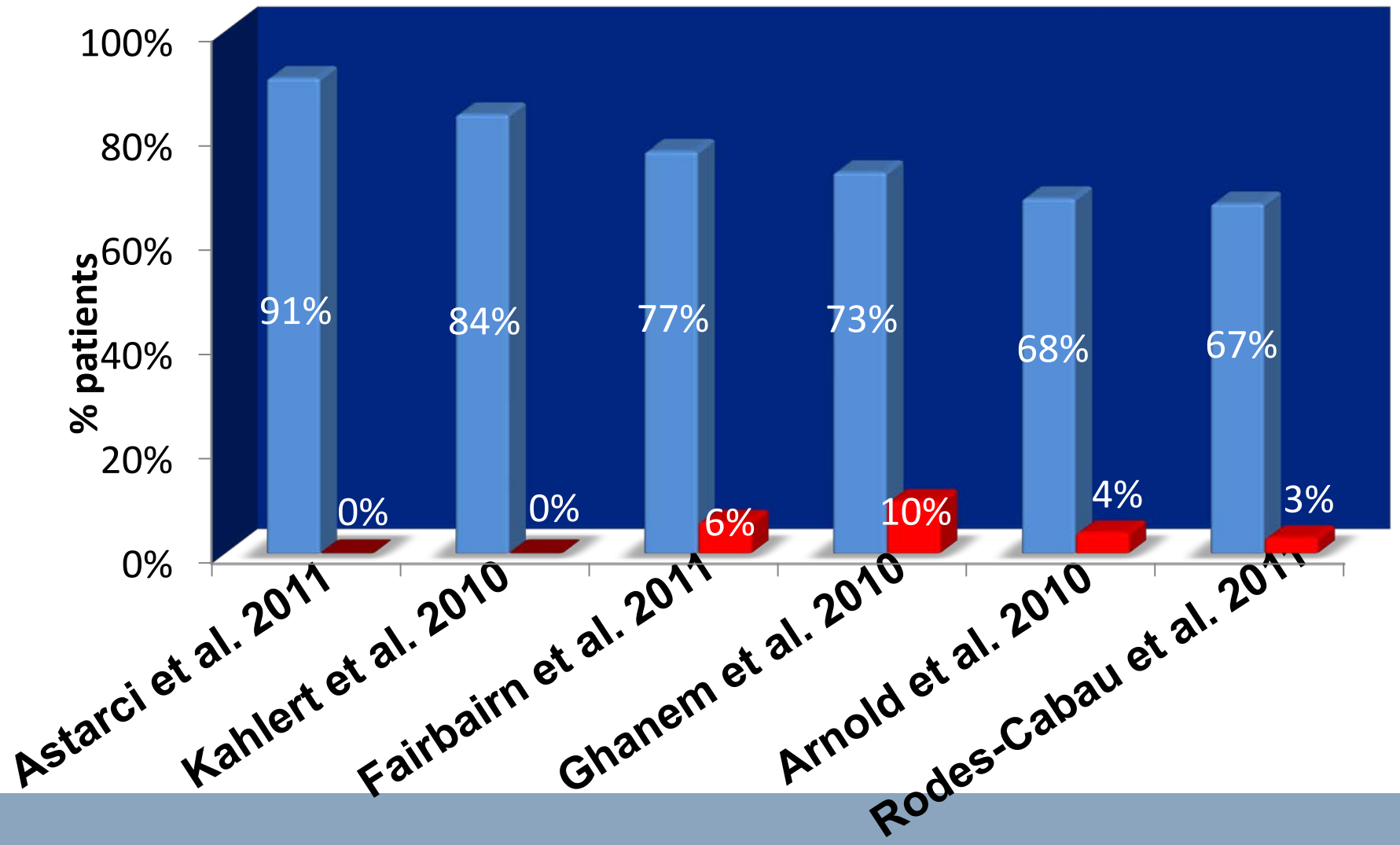
Masse, circulation, 2014

MRI (61% with lesions, 2.3/pt)



Masse, circulation, 2014

Subclinical Embolization and Stroke

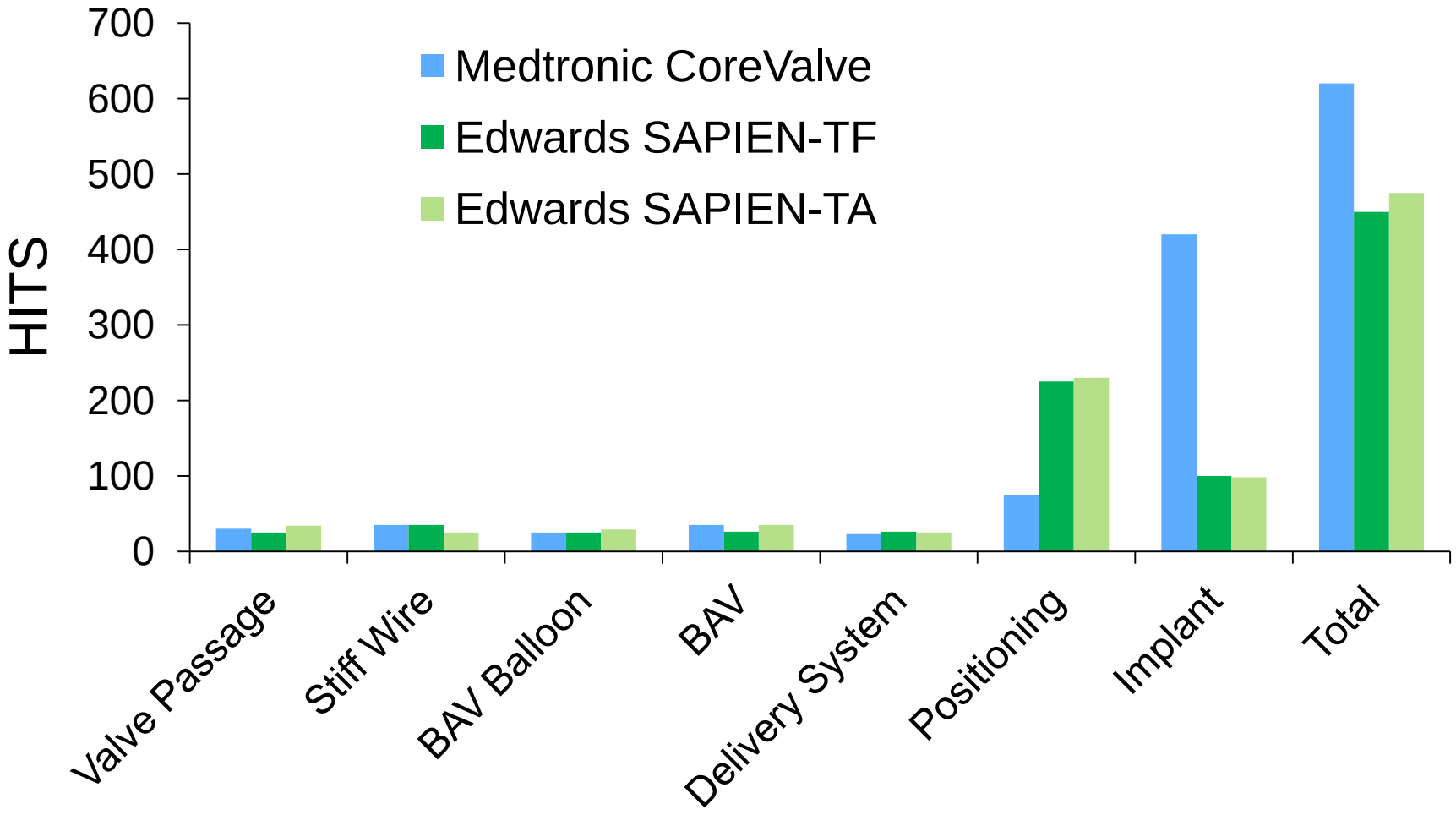


MRI Lesions According to Access

Variables	All Patients (n = 60)	Transfemoral (n = 29)	Transapical (n = 31)	p Value
Patients with new lesions	41 (68)	19 (66)	22 (71)	0.78
Total number of lesions	251	83	168	
Lesions per patient	3 (2–8)	3 (1–7)	4 (2–9)	0.38
Patients with single lesion	10 (24)	5 (26)	5 (23)	1.00
Patients with multiple lesions	31 (76)	14 (74)	17 (77)	
Lesion location, patients				
Right hemisphere	7 (17)	4 (21)	3 (14)	0.68
Left hemisphere	4 (10)	1 (5)	3 (14)	
Bilateral lesions	30 (73)	14 (74)	16 (73)	
Anterior circulation territory	9 (22)	5 (26)	4 (18)	0.58
Posterior circulation territory	5 (12)	3 (16)	2 (9)	
Anterior and posterior circulation territories	27 (66)	11 (58)	16 (73)	
Lesion size, cm				
<1	229 (91)	76 (92)	153 (91)	1.00
1–5	22 (9)	7 (8)	15 (9)	1.00
>5	0	0	0	—
Time of post-procedural DW-MRI, days	4 (2–6)	4 (2–6)	5 (3–6)	0.37

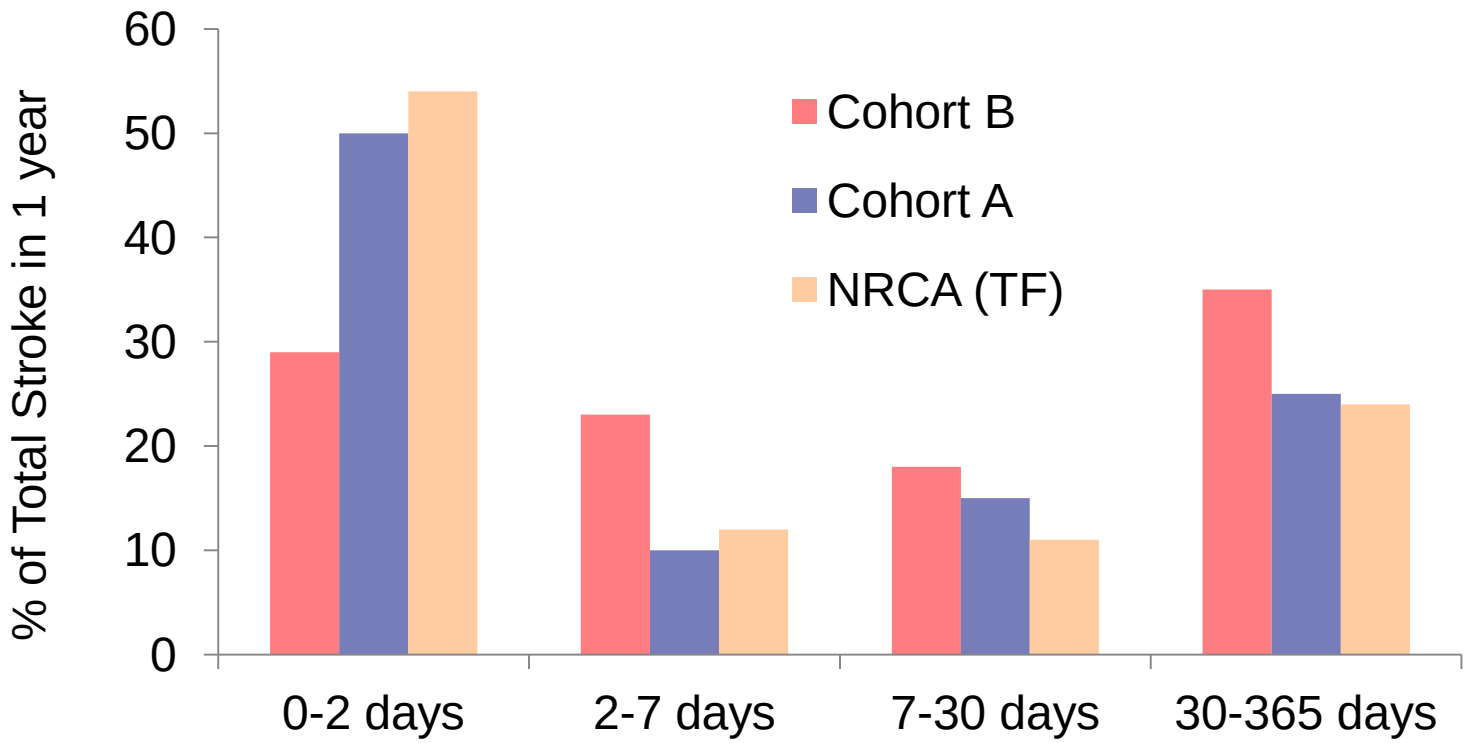
Rodés-Cabau et al, J Am Coll Cardiol 2011;57:18–28

Timing of Emboli: TCD



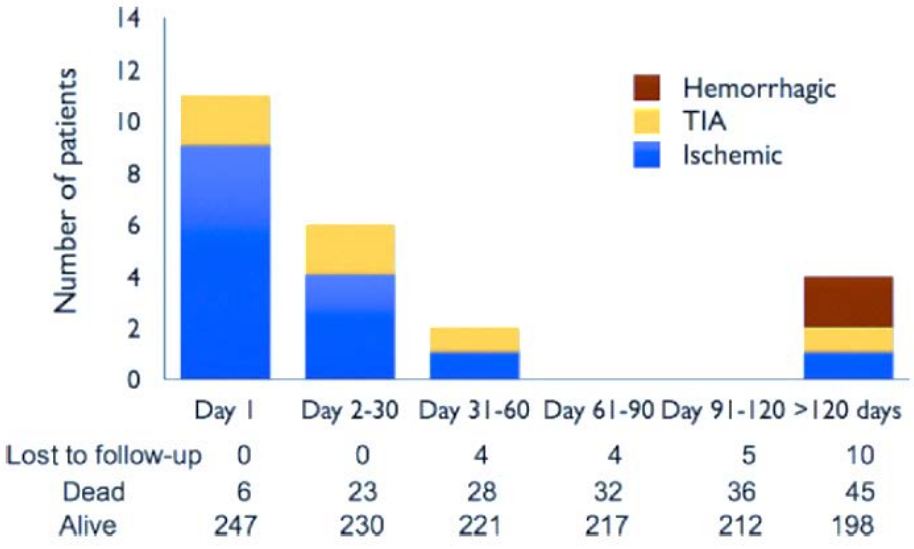
Adapted from Kahlert, AHA 2010

Stroke Timing within 1 year

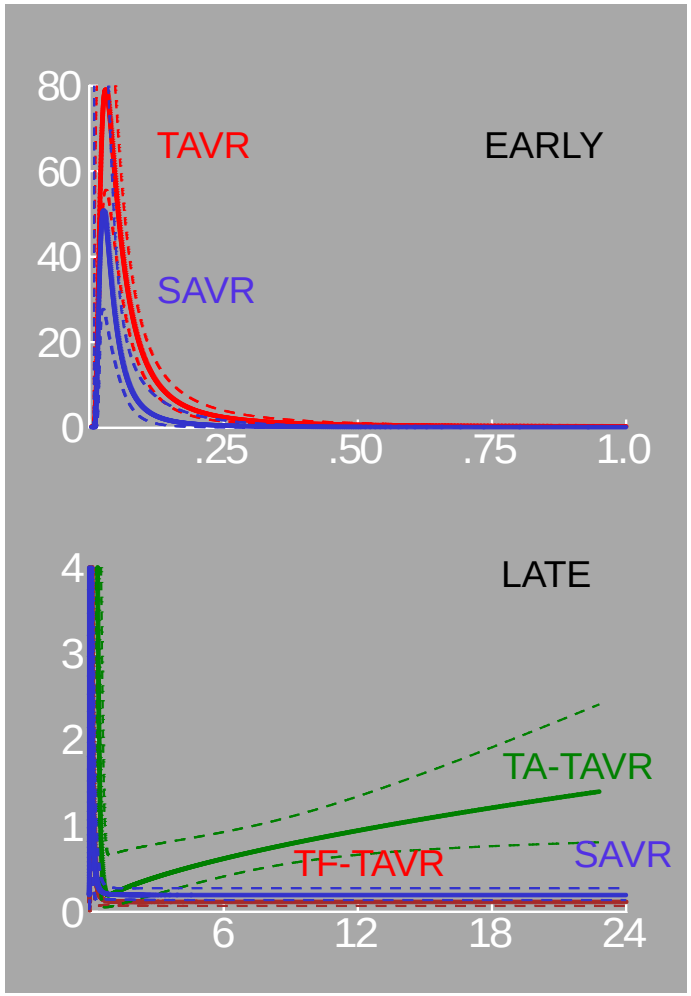


Leon et al, NEJM
Smith et al, NEJM
Kodali et al, ACC 2013

Timing of Neurological Event
Emboli Prevention versus Pharmacotherapy

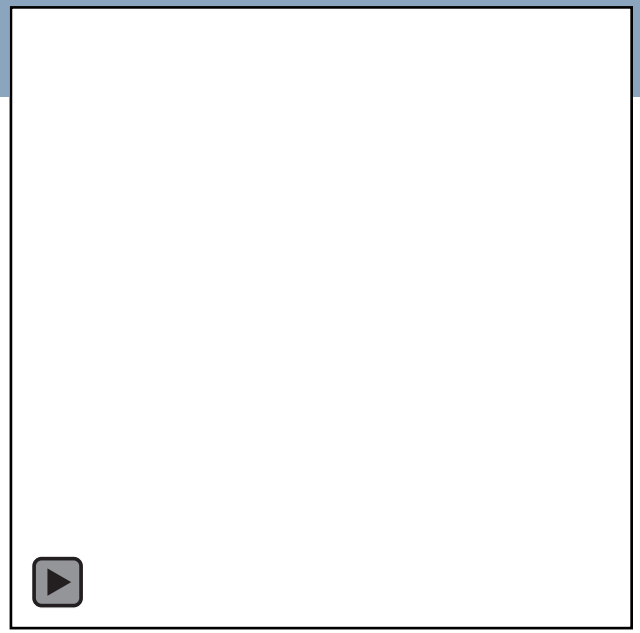
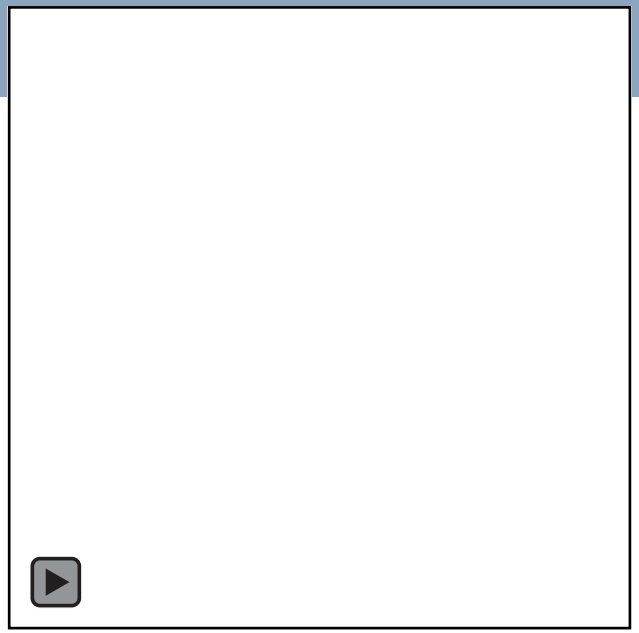
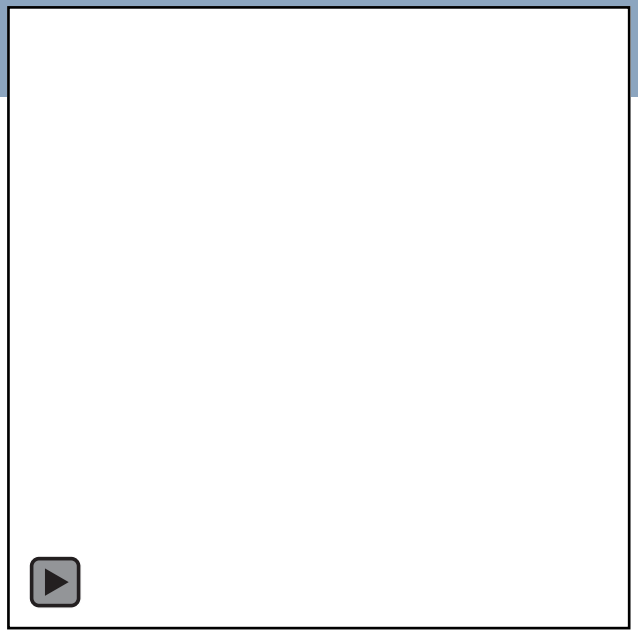
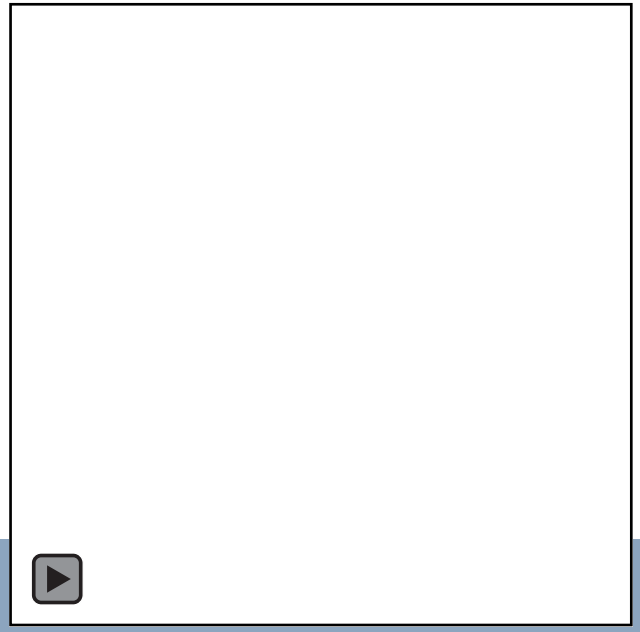
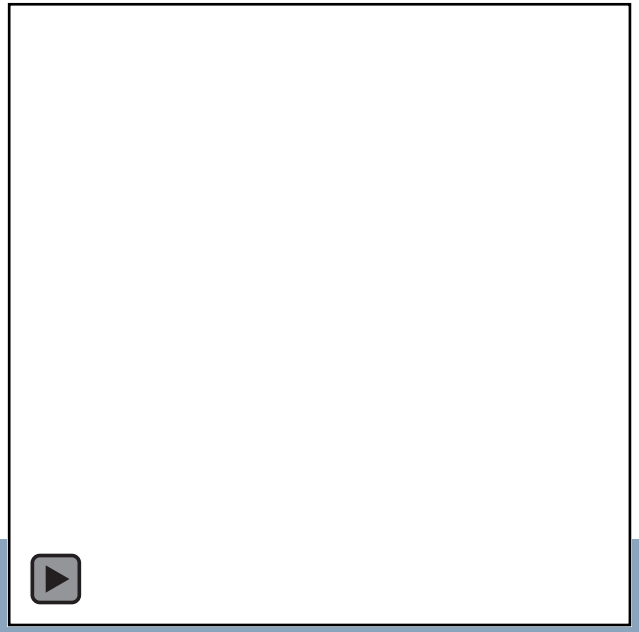
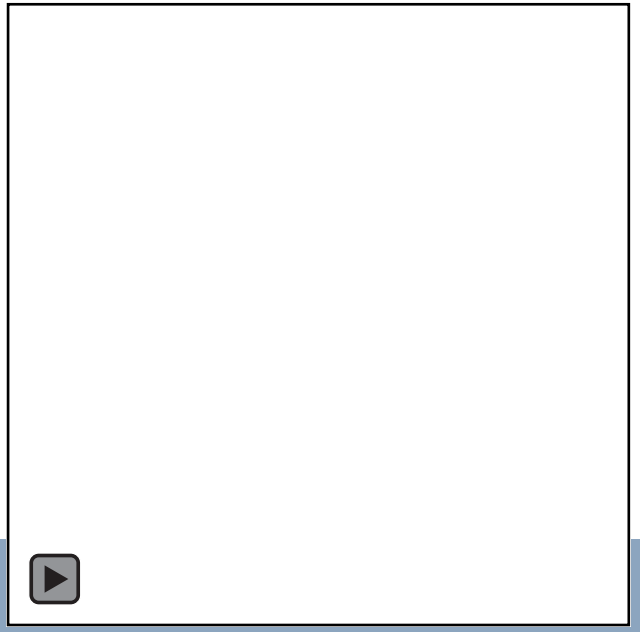


Tay et al, J Am Coll Cardiol Intv 2011;4:1290 –7



Miller et al, 2012;143:832-43

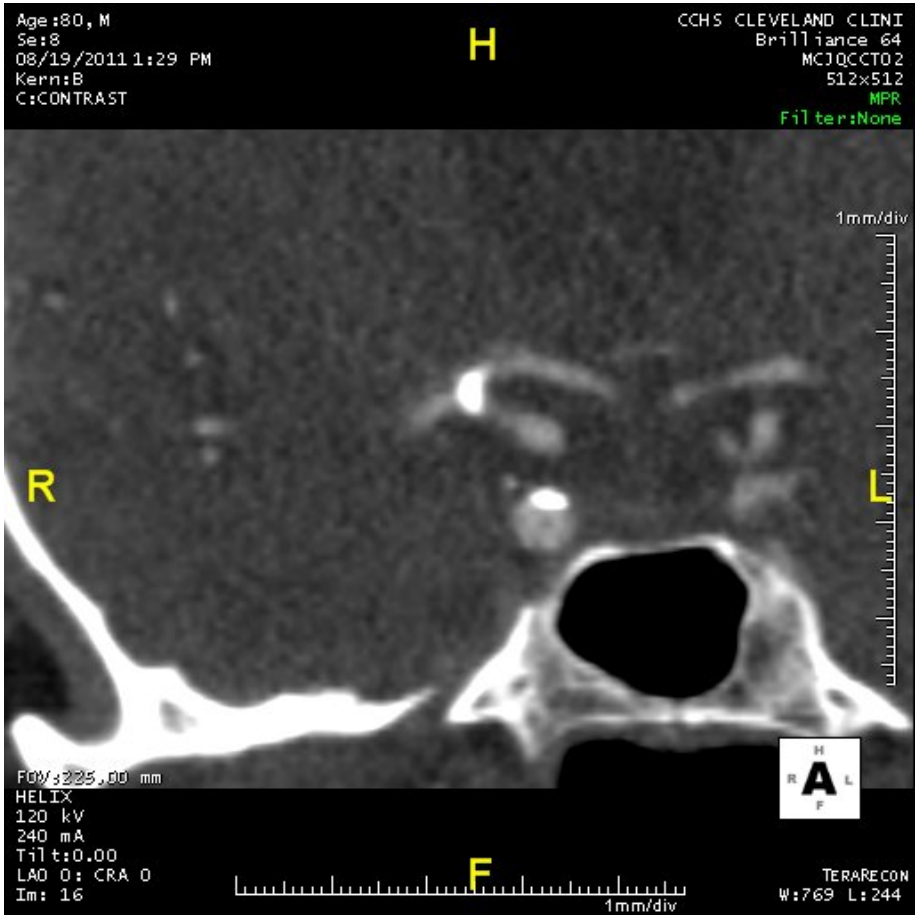
Uncomplicated TAVR – 91 year old

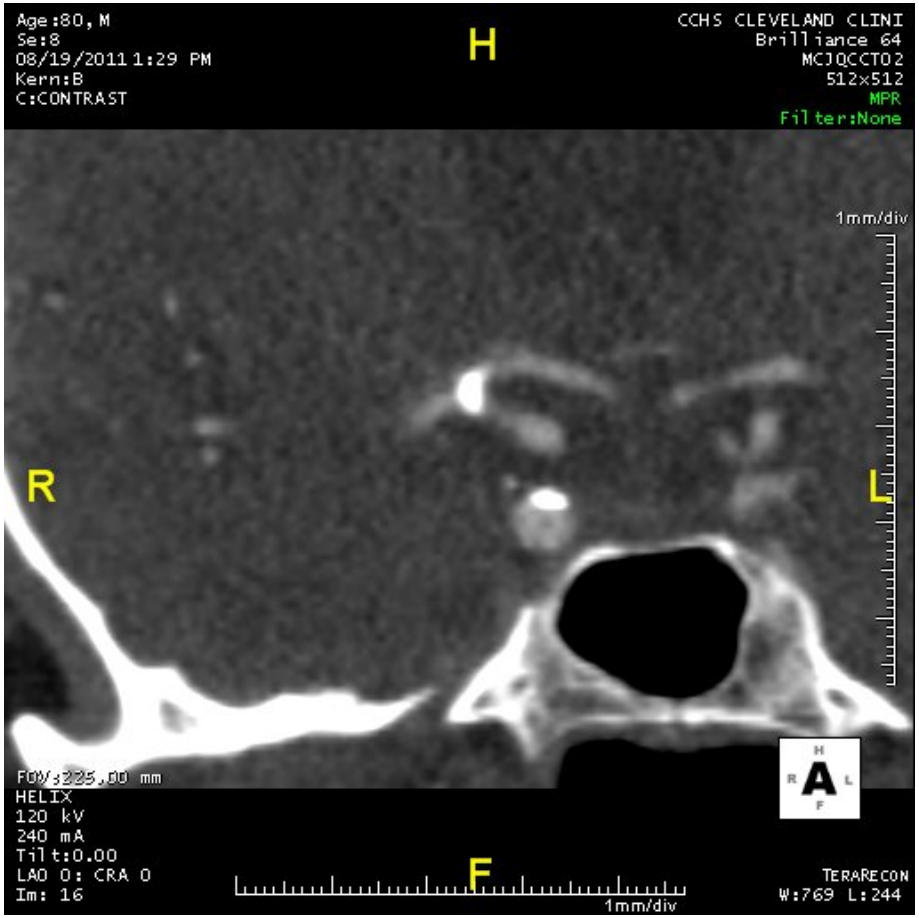
Post Procedural Course

- Patient extubated in the catheterization laboratory
- Neurologically intact and doing fine
- Ready to go home on post procedure day 2
- Developed hemiparesis and difficulty in speech after captopril, BP in 80s, treated with fluid and getting him back in bed
- Complete resolution with BP in 140s

CTA and Cerebral Angiogram



CTA and Cerebral Angiogram



Timing of Stroke

- When did the embolus happen?
  - Procedural – most likely
  - Importance – Emboli prevention will work or not

- Can there be a lag between embolus and complete occlusion of the cerebral arteries?
  - If so, is there role for different pharmaco-therapy?

Risk factors for Neurologic Events

Multiphase, multivariable non-proportional hazard analysis

- *Early high peaking hazard phase*
- *Later constant hazard phase*

Risk Factor	Coefficient ± SD	P	R (%)
Early hazard phase			
TAVR	2.21±0.68	.001	59
Cerebrovascular disease	0.76±0.45	.09	44
(Smaller) indexed native aortic valve area in TAVR group	-11.8±5.1	.02	57
Constant hazard phase			
TAVR	0.40±0.43	0.4	22
(Higher) NYHA	0.95±0.40	.02	75
Stroke or TIA within 6-12 months	1.93±0.64	.002	60
Non-TF TAVR candidate	2.3±0.45	<.0001	96
History of PCI (less risk)	-1.60±0.63	.01	77
COPD (less risk)	-1.06±0.47	.03	79

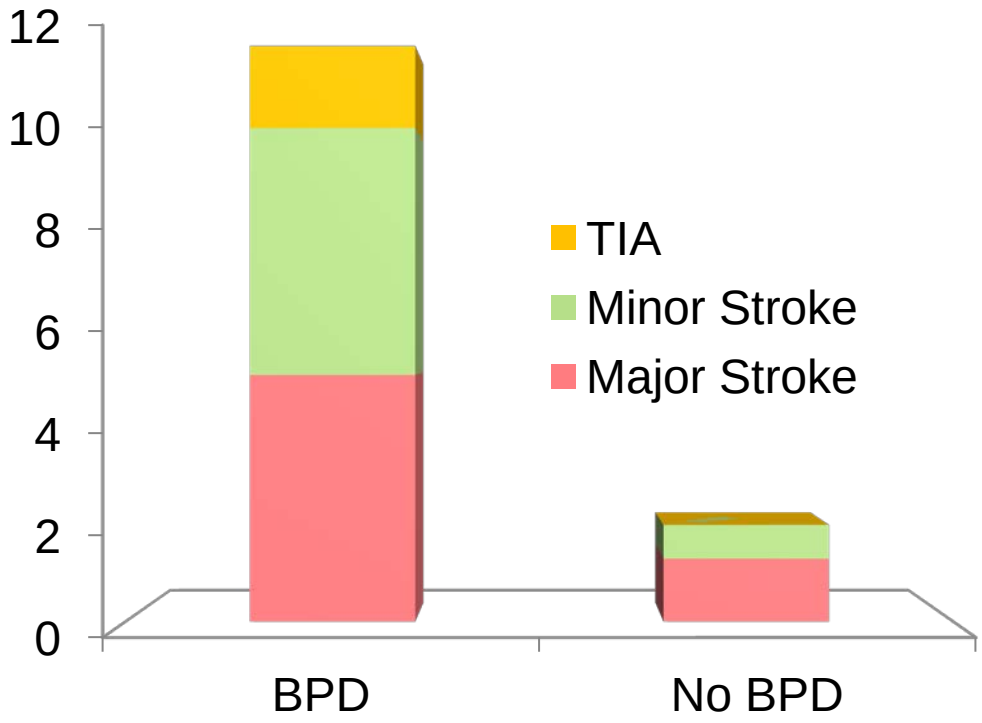
TAVR and Stroke : Registry Data

Registry	n	30 day	1 year	Prior stroke
FRANCE 2	3195	-	4.1	10
Canadian	339	2.3		22.7
PARTNER-EU	130	2.3	6.9	-
Australia NZ	118	1.7		-
UK-TAVI	870	4.1		-
Belgian	328	4.4		15
FRANCE	244	3.6		10.2
SOURCE	1038	2.6		-
European Registry	646	1.9		7.4
German	697	2.8		8.2
Italian	663	1.2	2.6	7.2

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	

Impact of Post-Dilatation



EDITORIAL COMMENT

Post-Dilating Transcatheter Heart Valves*

John G. Webb, MD, Ronald K. Binder, MD

Vancouver, British Columbia, Canada

To what degree was post-dilation just a marker of a more calcified valve intrinsically more likely to release embolic material at the time of valve positioning or expansion? We do not know.

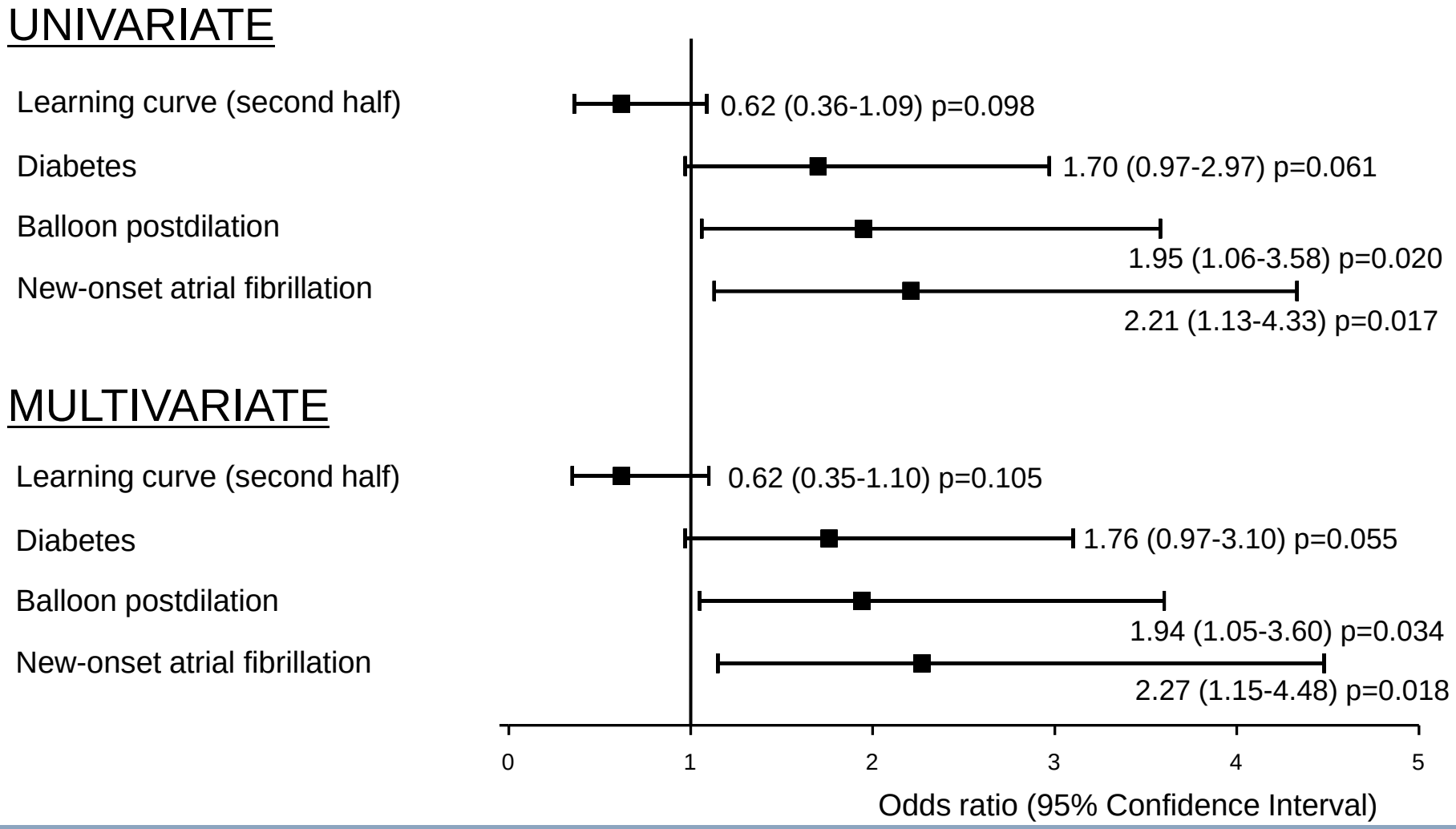
Nombela-Franco et al, J Am Coll Cardiol Intv 2012;5:499 –512

Canadian Experience

- **1061 Patients**
- **5 centers**
  - **679 (65%) Balloon expandable**
  - **361 (34%) Self expandable**
- **Analysis of events depending on timing of stroke**

Nombela-Franco et al. Circulation. 2012 Dec 18;126(25):3041-53

Predictors of Early (30-Day) CVEs



Nombela-Franco et al. Circulation. 2012 Dec 18;126(25):3041-53

Predictors of Late CVEs (>30-day)

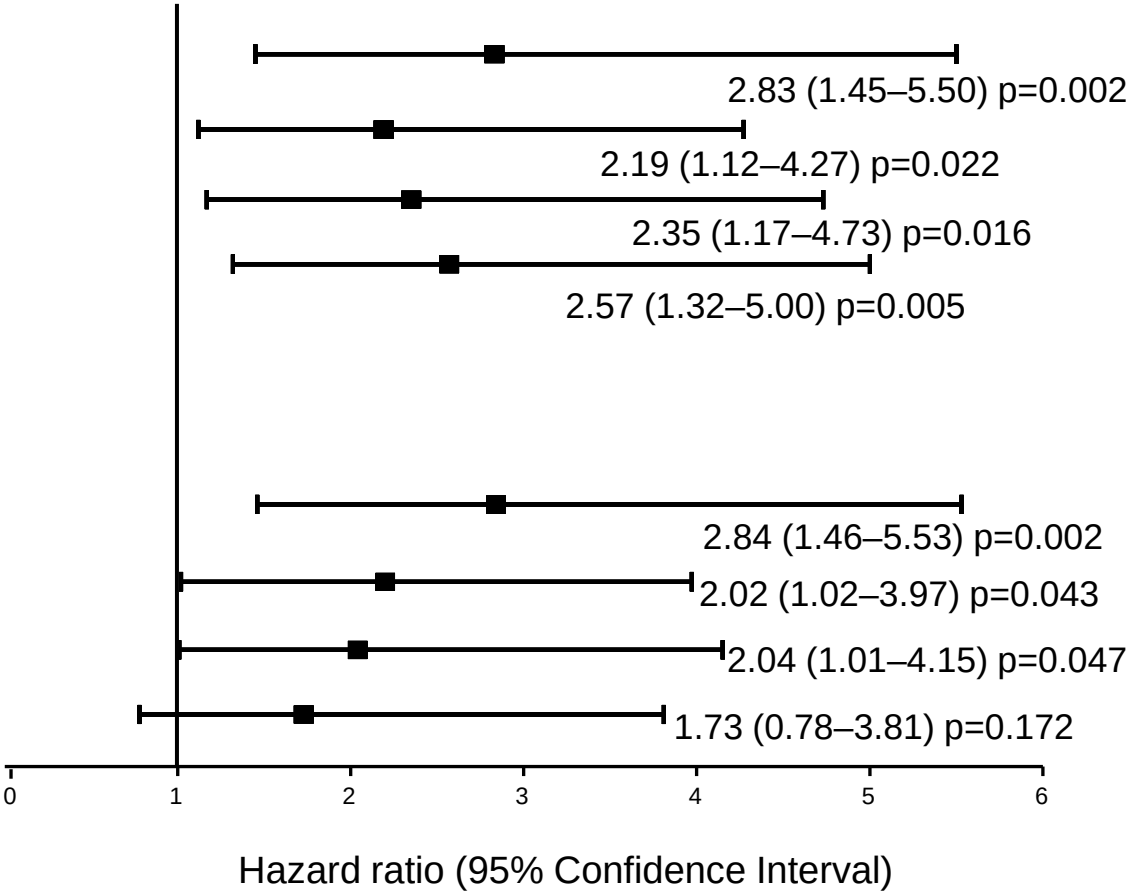
UNIVARIATE

Chronic atrial fibrillation

Peripheral vascular disease

Cerebrovascular disease

Anticoagulation treatment at hospital discharge



MULTIVARIATE

Chronic atrial fibrillation

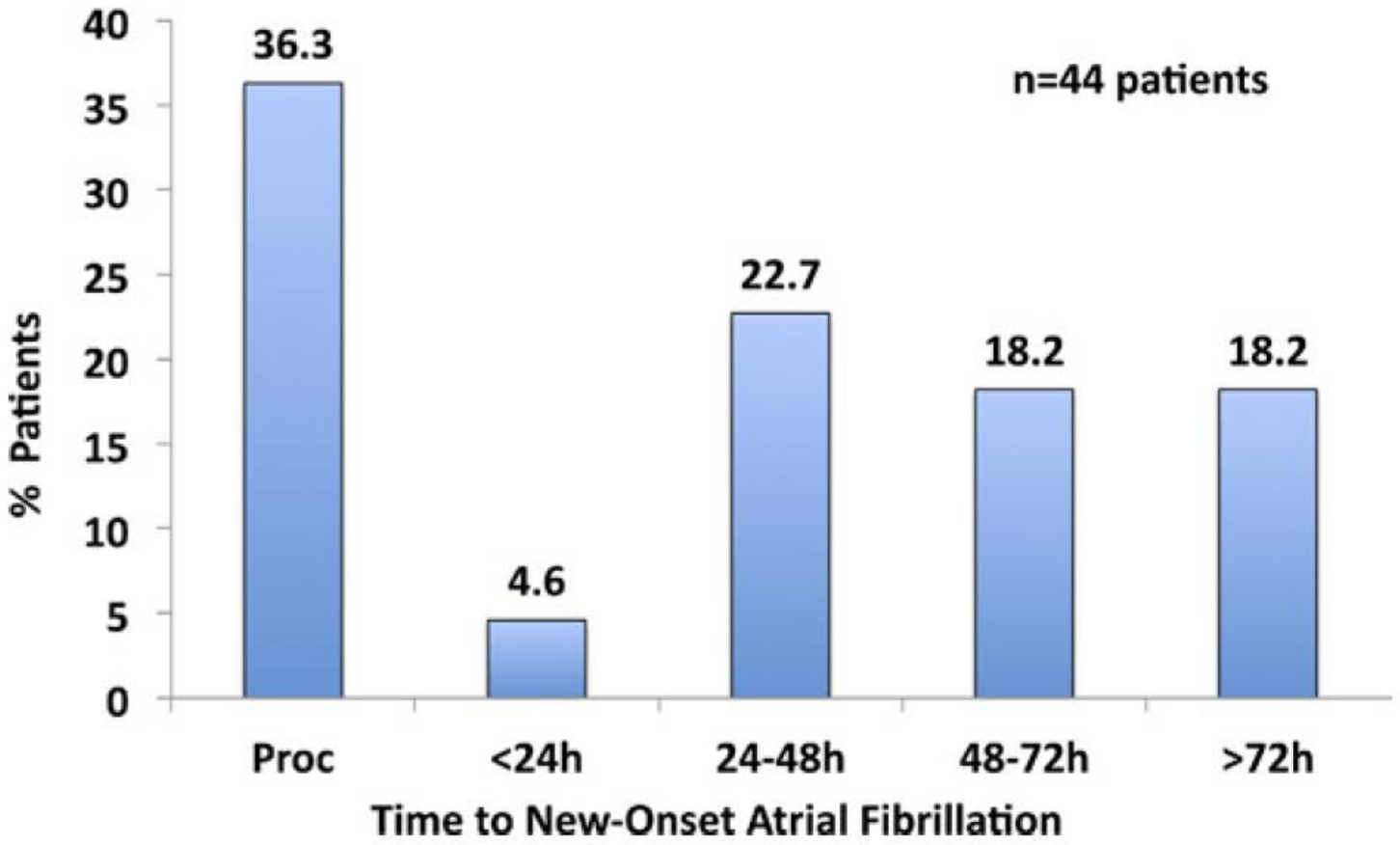
Peripheral vascular disease

Cerebrovascular disease

Anticoagulation treatment at hospital discharge

Nombela-Franco et al. Circulation. 2012 Dec 18;126(25):3041-53

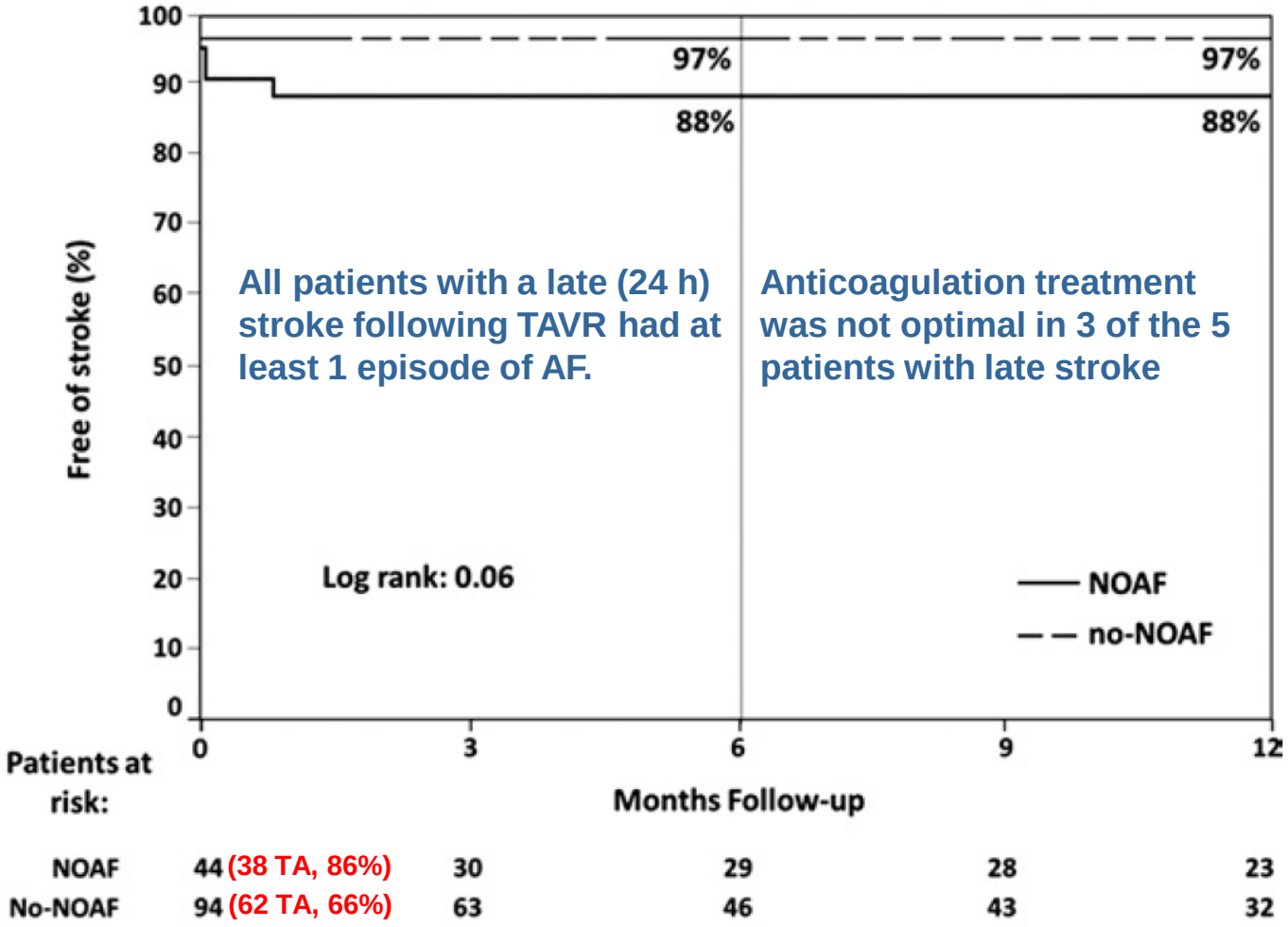
Timing of NOAF after TAVR



Predictors of NOAF were LA size > 27 mm/m^2 and TA approach

Amat-Santos et al, JACC 2012;59:178–88

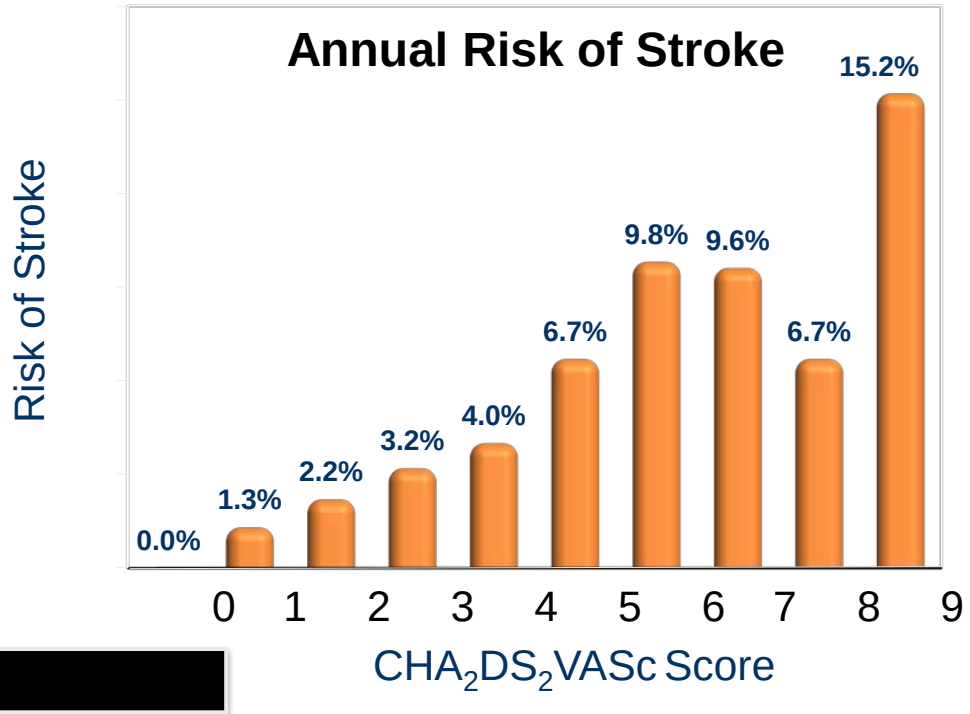
New Onset AF after TAVR and Stroke



Amat-Santos et al, JACC 2012;59:178–88

CHA_2DS_2VASc : For Typical TAVR patient

	Condition/Risk Factor	Points	TAVR pt
C	Congestive heart failure	1	100 %
H	Hypertension	1	85-90%
A	Age ≥75 years	2	80-90%
D	Diabetes mellitus	1	30-40%
S_2	Previous stroke or TIA	2	10-15%
V	Vascular disease	1	30-50%
A	Age 65-74 years	1	95-100%
Sc	Sex (female gender)	1	50-60%



CHA_2DS_2-VASc Score	Treatment
0	No treatment
1	Aspirin or warfarin or dabigatran
≥2	Warfarin or dabigatran

1. Lip GY et al, *Chest.* 2010;137(2):263-72
2. Camm AJ et al, *Eur Heart J.* 2010;31:2369–2429

HAS-BLED: Risk of Bleeding TAVR patients

HAS-BLED Score

	Condition	Points	TAVR
H	Hypertension	1	85-90%
A	Abnormal liver and renal function	1 or 2	10%
S	Stroke	1	10-20%
B	Bleeding	1	30%
L	Labile INR	1	?
E	Elderly (age >65)	1	>95%
D	Drugs or alcohol	1 or 2	??

Bleeding Risk

Score	Bleeds Per 100 Patient Years
0	1.13
1	1.02
2	1.88
3	3.74
4	8.7

Hypertension, stroke and age are also variables in the CHADS scores

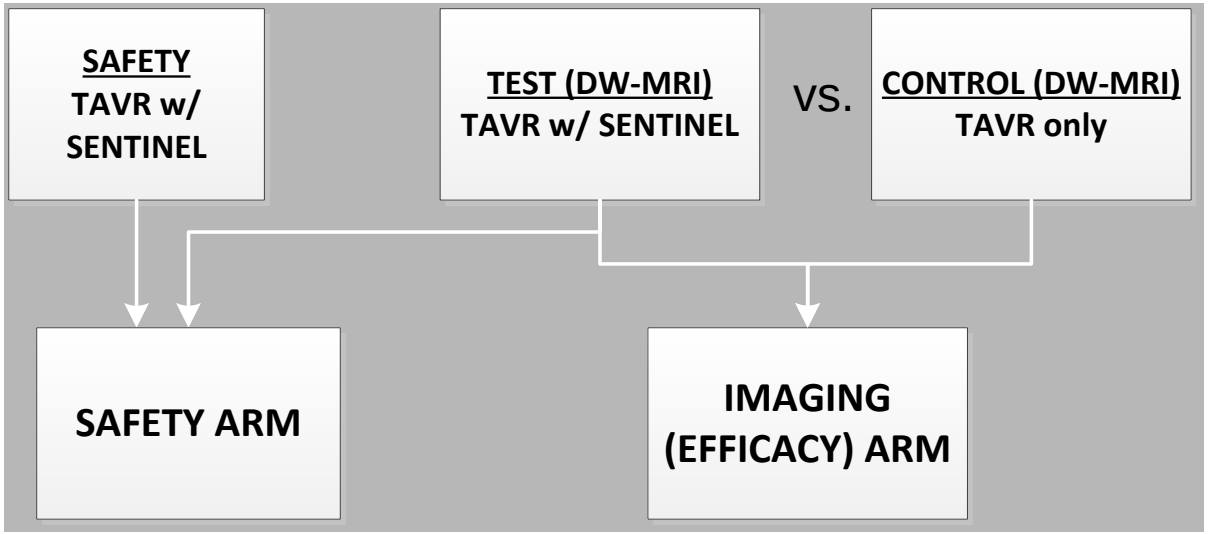
Camm et al, European Heart Journal doi:10.1093/eurheartj/ehq278
Pisters R, et al Chest 2010; 138:1093-100

Stroke Prevention Measures

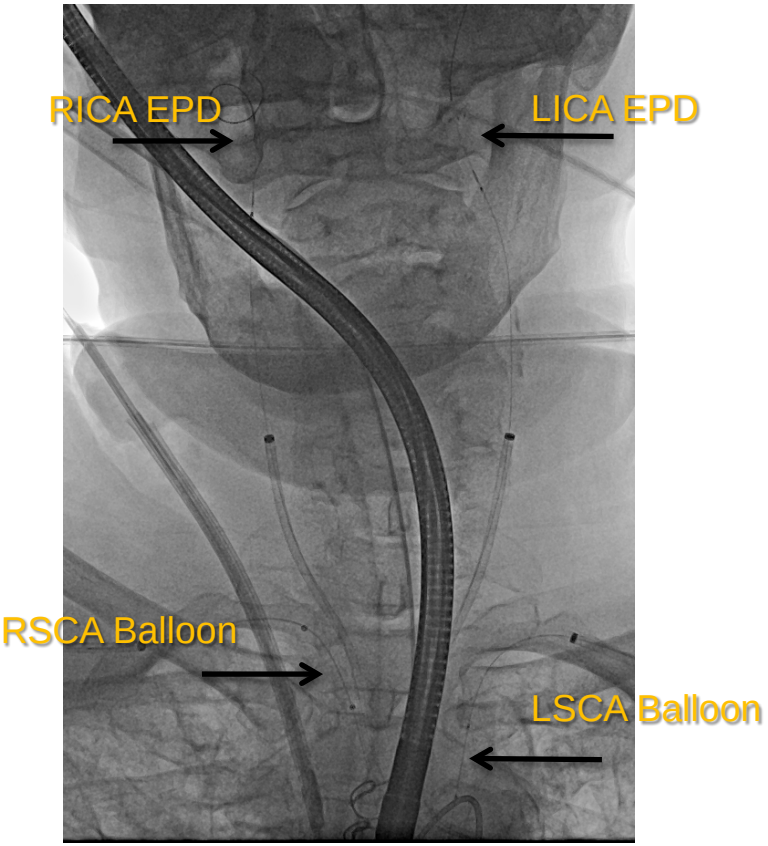
- Emboli prevention devices
  - Claret device - Sentinel Trial
  - Embrella Device - ProTAVI
- Carotid pressure at the time of advancing the sheath
- Careful manipulations
- Minimize postdilations
- ? Pretreat carotid disease

IDE Study Design - Overview

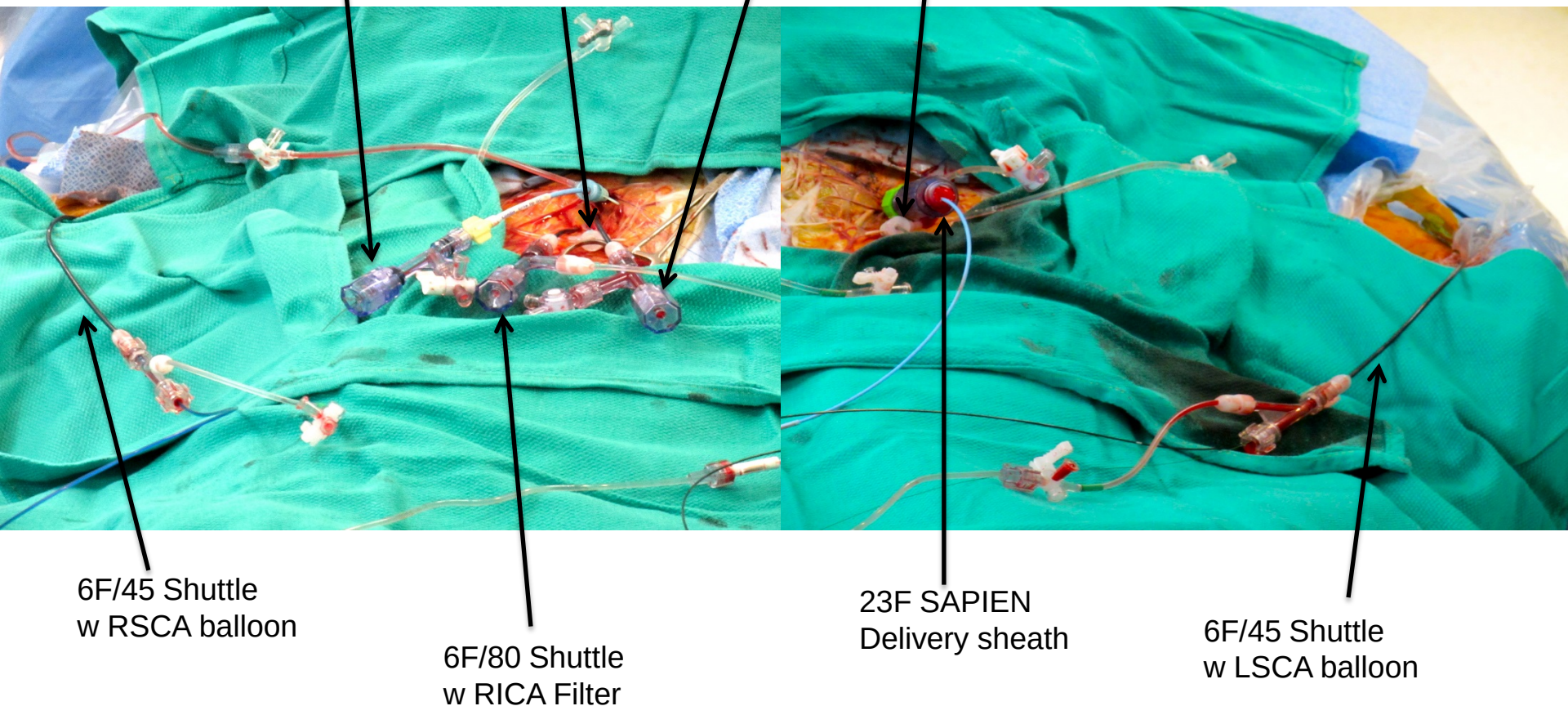
- Prospective, multicenter, blinded, randomized controlled trial
- 284 subjects randomized into a three-arm study
- Enrollment at up to 15 centers in the United States



What Will it Replace?



What will it replace?



Implication

- Stroke prevention will help to move to lower risk patients
- It may be an advantage rather than disadvantage for TAVR compared to SAVR (similar to PCI compared to CABG)
- Stroke is not a deal breaker but deal maker!