

Strokes After TAVR

**Multi-factorial Origin, Incidence (past and present),
and Management Considerations (present and
future)**

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Conflict

- **Co-PI for Santinel Trial (Claret)**

EDITORIALS



Transcatheter Aortic-Valve Implantation — At What Price?

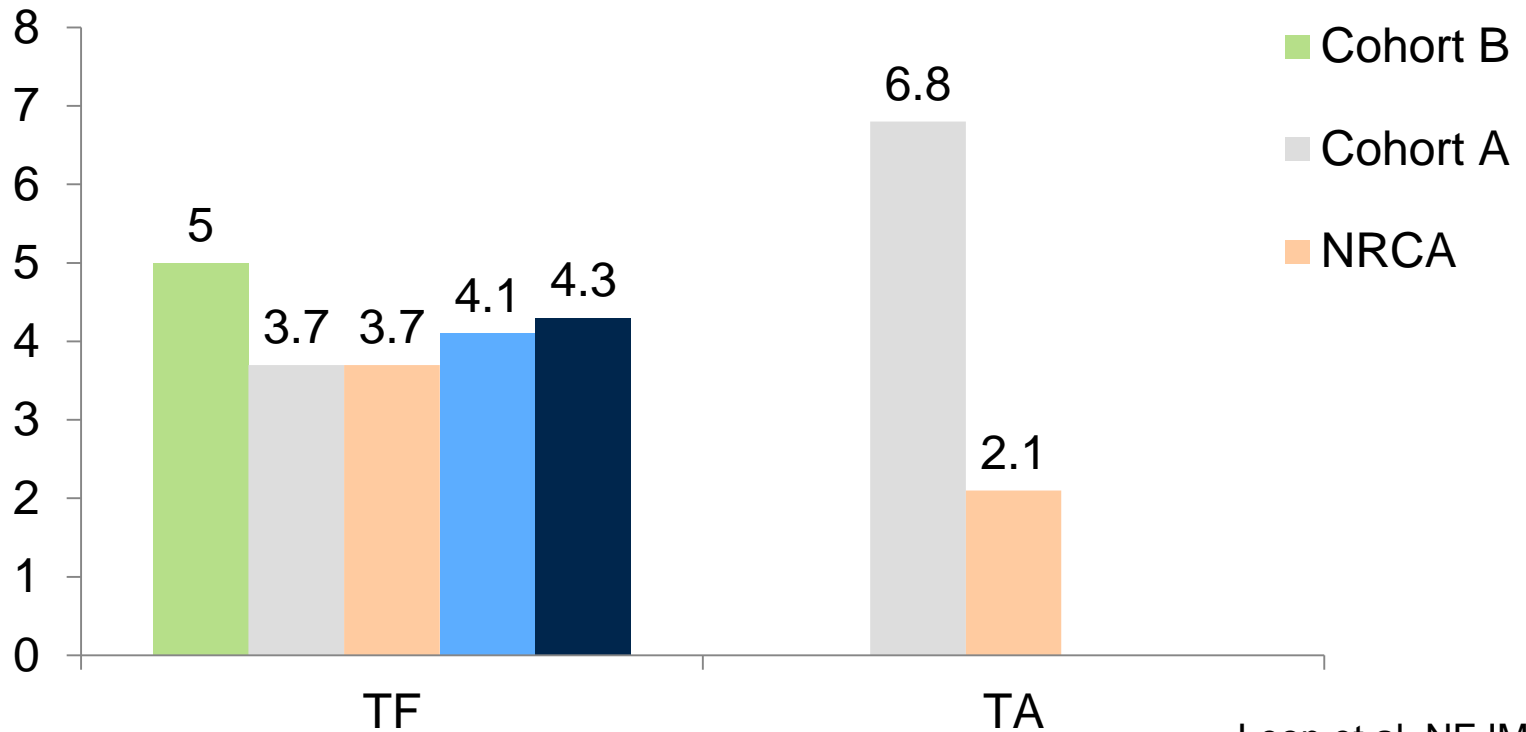
Hartzell V. Schaff, M.D.

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



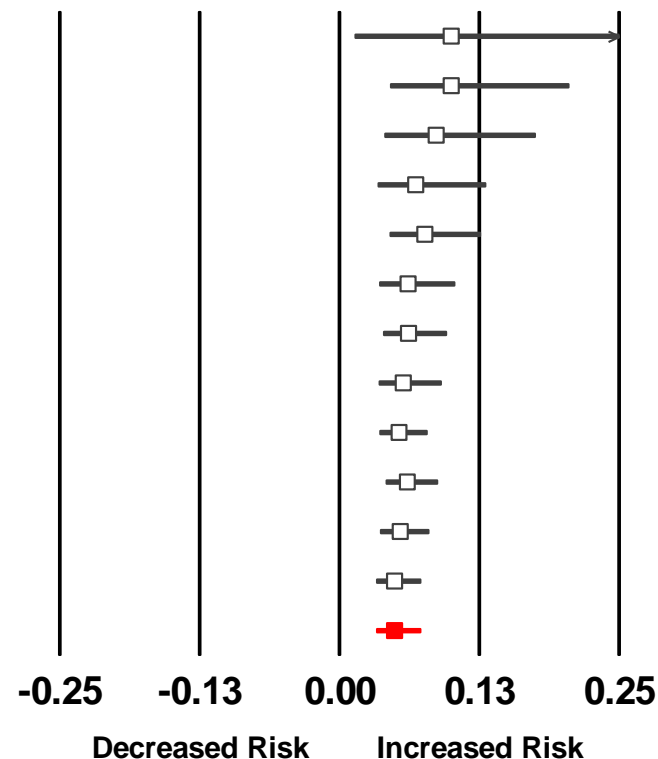
Leon et al, NEJM
Smith et al, NEJM
Kodali et al, ACC 2013
Leon et al, ACC 2013
Dewey et al, STS 2012

Stroke : Feasibility Trials

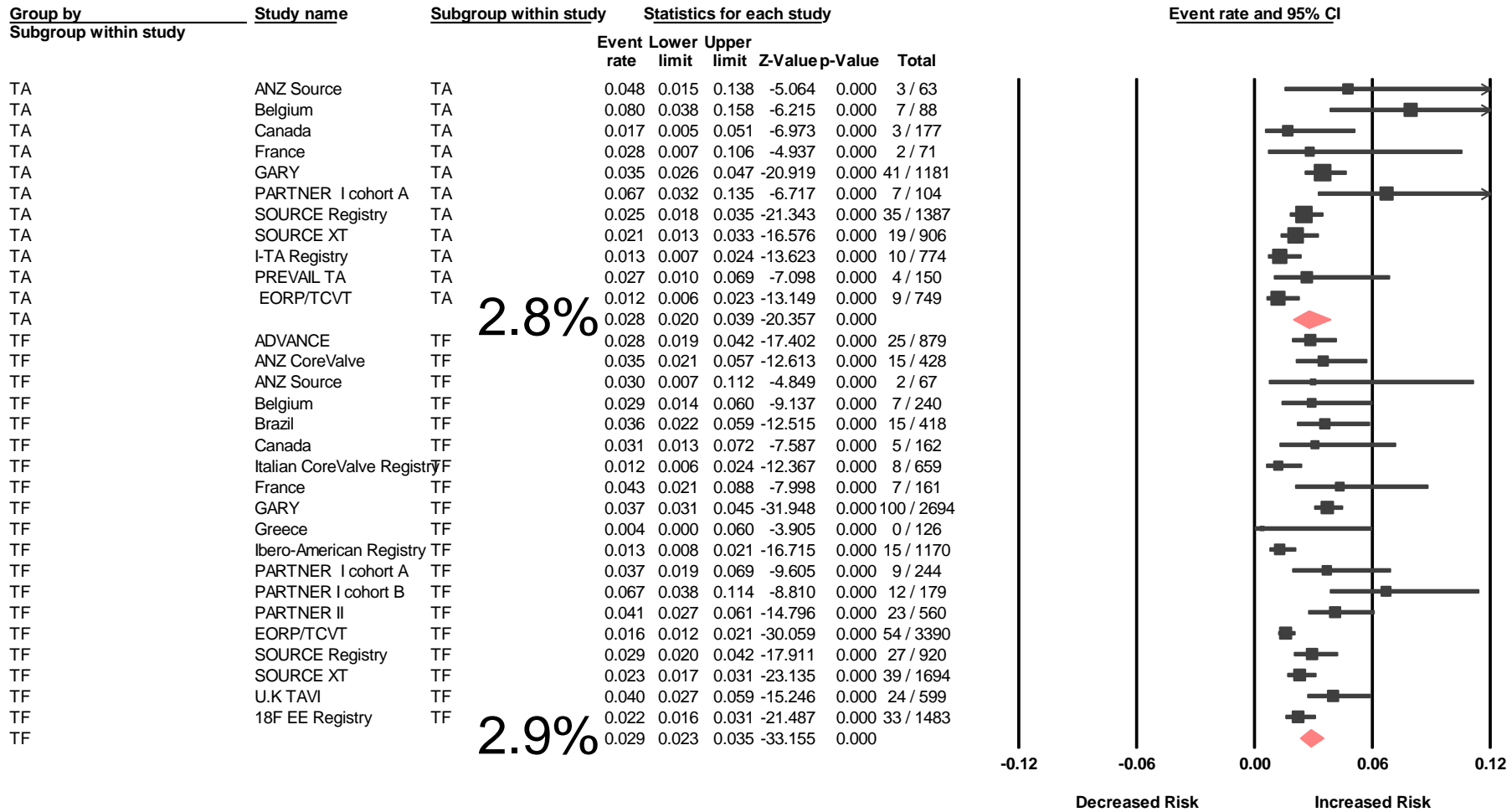
<u>Study name</u>	<u>Cumulative statistics</u>					<u>Total</u>
	<u>Point</u>	<u>Lower limit</u>	<u>Upper limit</u>	<u>Z-Value</u>	<u>p-Value</u>	
24 F	0.100	0.014	0.467	-2.084	0.037	1 / 10
21 F	0.100	0.046	0.205	-5.106	0.000	6 / 60
Walther***	0.087	0.041	0.175	-5.721	0.000	6 / 90
Walther **	0.068	0.034	0.131	-7.108	0.000	8 / 149
REVIVAL	0.076	0.045	0.126	-8.765	0.000	13 / 204
REVIVE 2	0.061	0.036	0.103	-9.466	0.000	16 / 310
REVIVAL 2	0.062	0.039	0.096	-11.244	0.000	18 / 350
Walther*	0.057	0.035	0.091	-10.909	0.000	18 / 400
Vancouver Exp	0.053	0.036	0.078	-13.662	0.000	25 / 568
18 F	0.061	0.042	0.088	-13.517	0.000	37 / 694
PARTNER EU	0.054	0.037	0.080	-13.533	0.000	40 / 824
Traverce	0.049	0.033	0.073	-13.969	0.000	44 / 992

4.9%

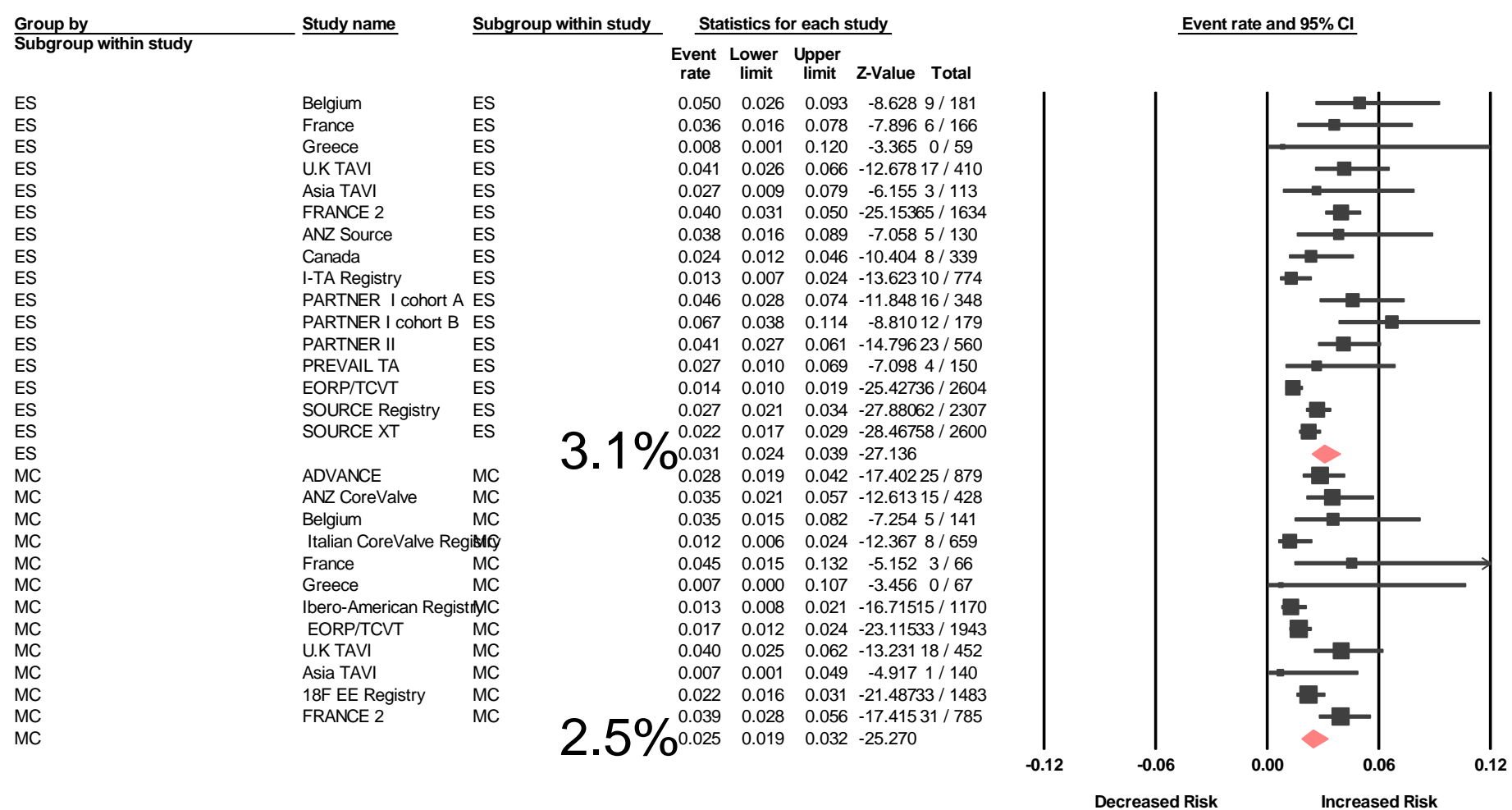
Cumulative event rate (95% CI)



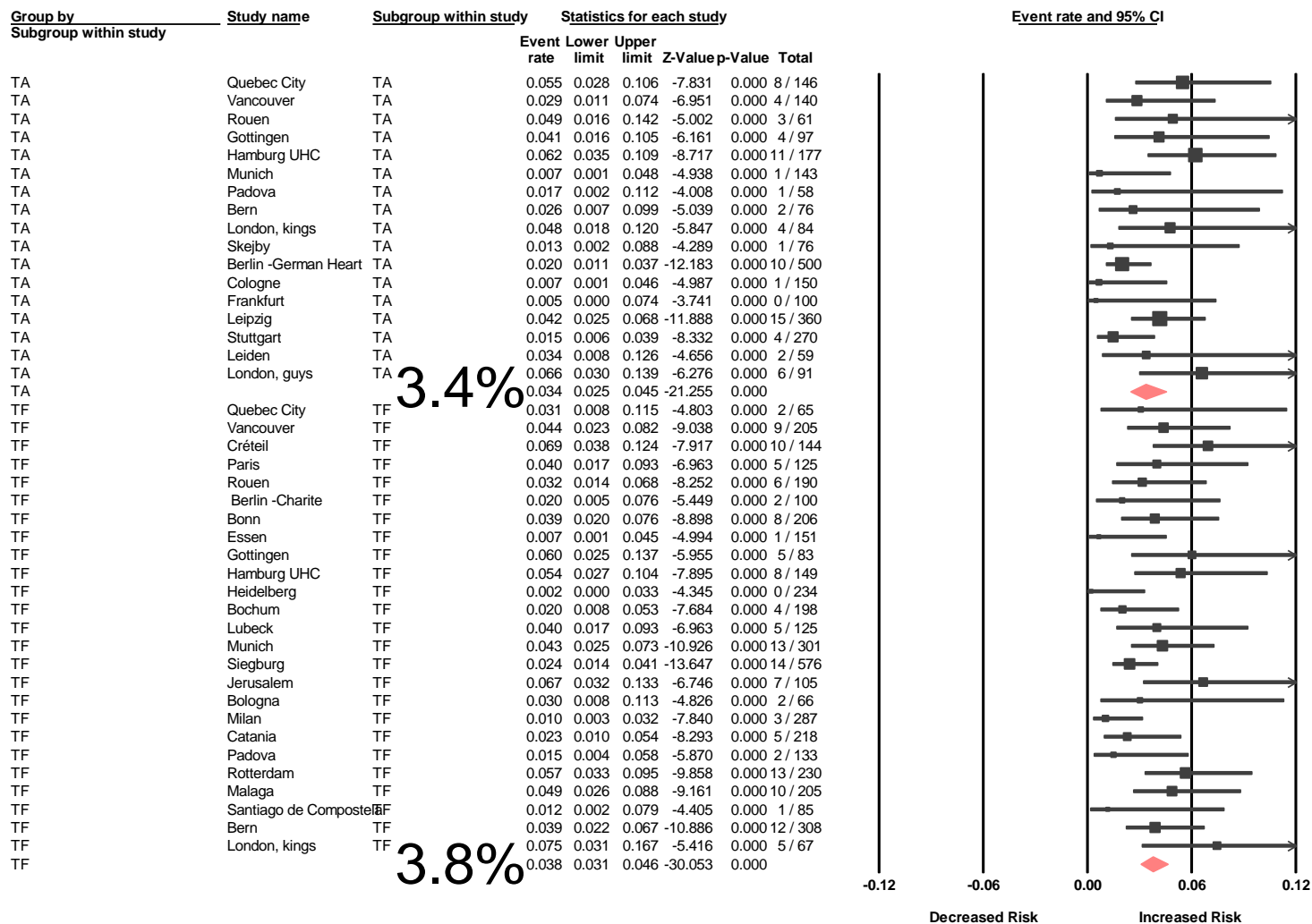
In hospital or 30 day stroke TA versus TF (Major Registries)



In Hospital or 30 Day Stroke ES versus MC – Major Registries



Single Center (TF versus TA)

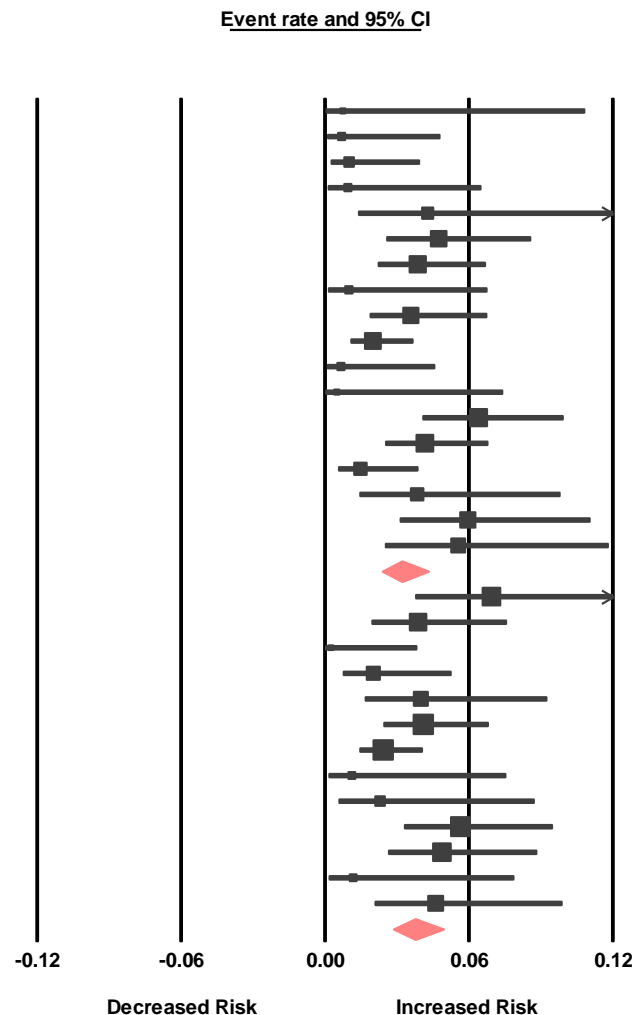


30 day or in hospital stroke MC versus ES – single center

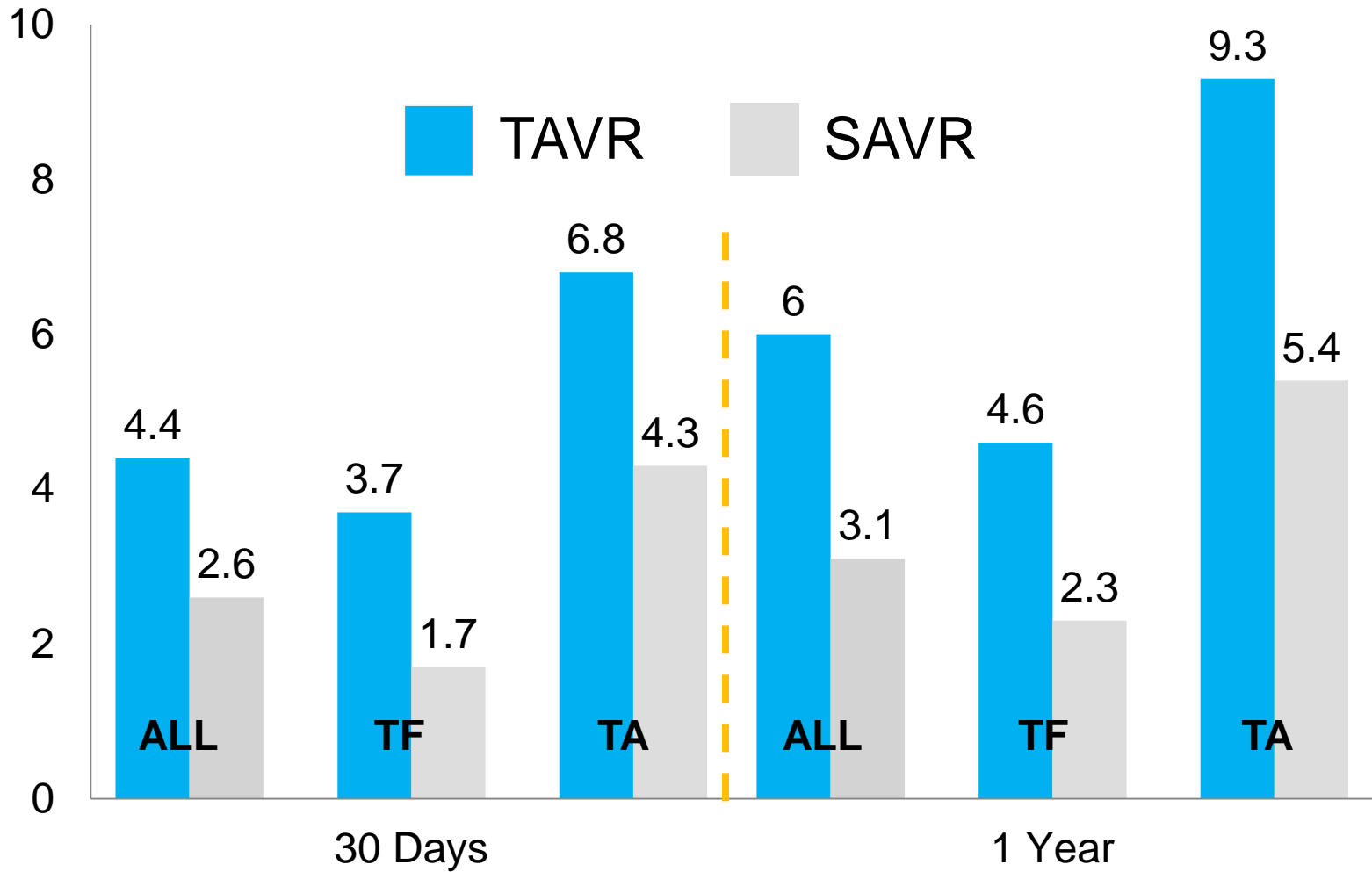
Group by Subgroup within study	Study name	Subgroup within study	Statistics for each study					
			Event rate	Lower limit	Upper limit	Z-Value	p-Value	Total
ES	Heidelberg	ES	0.007	0.000	0.108	-3.445	0.001	0 / 66
ES	Munich	ES	0.007	0.001	0.048	-4.938	0.000	1 / 143
ES	Milan	ES	0.010	0.003	0.039	-6.451	0.000	2 / 198
ES	Padova	ES	0.010	0.001	0.065	-4.612	0.000	1 / 104
ES	Bern	ES	0.043	0.014	0.125	-5.263	0.000	3 / 70
ES	Quebec City	ES	0.047	0.026	0.086	-9.262	0.000	10 / 211
ES	Vancouver	ES	0.039	0.022	0.067	-10.910	0.000	12 / 310
ES	Skejby	ES	0.010	0.001	0.068	-4.572	0.000	1 / 100
ES	Rouen	ES	0.036	0.019	0.067	-9.696	0.000	9 / 251
ES	Berlin -German Heart	ES	0.020	0.011	0.037	-12.183	0.000	10 / 500
ES	Cologne	ES	0.007	0.001	0.046	-4.987	0.000	1 / 150
ES	Frankfurt	ES	0.005	0.000	0.074	-3.741	0.000	0 / 100
ES	Hamburg UHC	ES	0.064	0.041	0.099	-11.007	0.000	18 / 281
ES	Leipzig	ES	0.042	0.025	0.068	-11.888	0.000	15 / 360
ES	Stuttgart	ES	0.015	0.006	0.039	-8.332	0.000	4 / 270
ES	Leiden	ES	0.038	0.015	0.098	-6.313	0.000	4 / 104
ES	London - Kings	ES	0.060	0.031	0.111	-8.025	0.000	9 / 151
ES	London -Guys	ES	0.056	0.025	0.118	-6.744	0.000	6 / 108
ES			0.032	0.024	0.043	-21.790	0.000	
MC	Créteil	MC	0.069	0.038	0.124	-7.917	0.000	10 / 144
MC	Bonn	MC	0.039	0.020	0.076	-8.898	0.000	8 / 206
MC	Heidelberg	MC	0.002	0.000	0.038	-4.237	0.000	0 / 201
MC	Bochum	MC	0.020	0.008	0.053	-7.684	0.000	4 / 198
MC	Lubeck	MC	0.040	0.017	0.093	-6.963	0.000	5 / 125
MC	Munich	MC	0.041	0.024	0.068	-11.545	0.000	14 / 341
MC	Siegburg	MC	0.024	0.014	0.041	-13.647	0.000	14 / 576
MC	Milan	MC	0.011	0.002	0.075	-4.452	0.000	1 / 89
MC	Padova	MC	0.023	0.006	0.087	-5.241	0.000	2 / 87
MC	Rotterdam	MC	0.057	0.033	0.095	-9.858	0.000	13 / 230
MC	Malaga	MC	0.049	0.026	0.088	-9.161	0.000	10 / 205
MC	Santiago de Compostela	MC	0.012	0.002	0.079	-4.405	0.000	1 / 85
MC	Bern	MC	0.046	0.021	0.099	-7.245	0.000	6 / 130
MC			0.038	0.028	0.049	-22.231	0.000	

3.2%

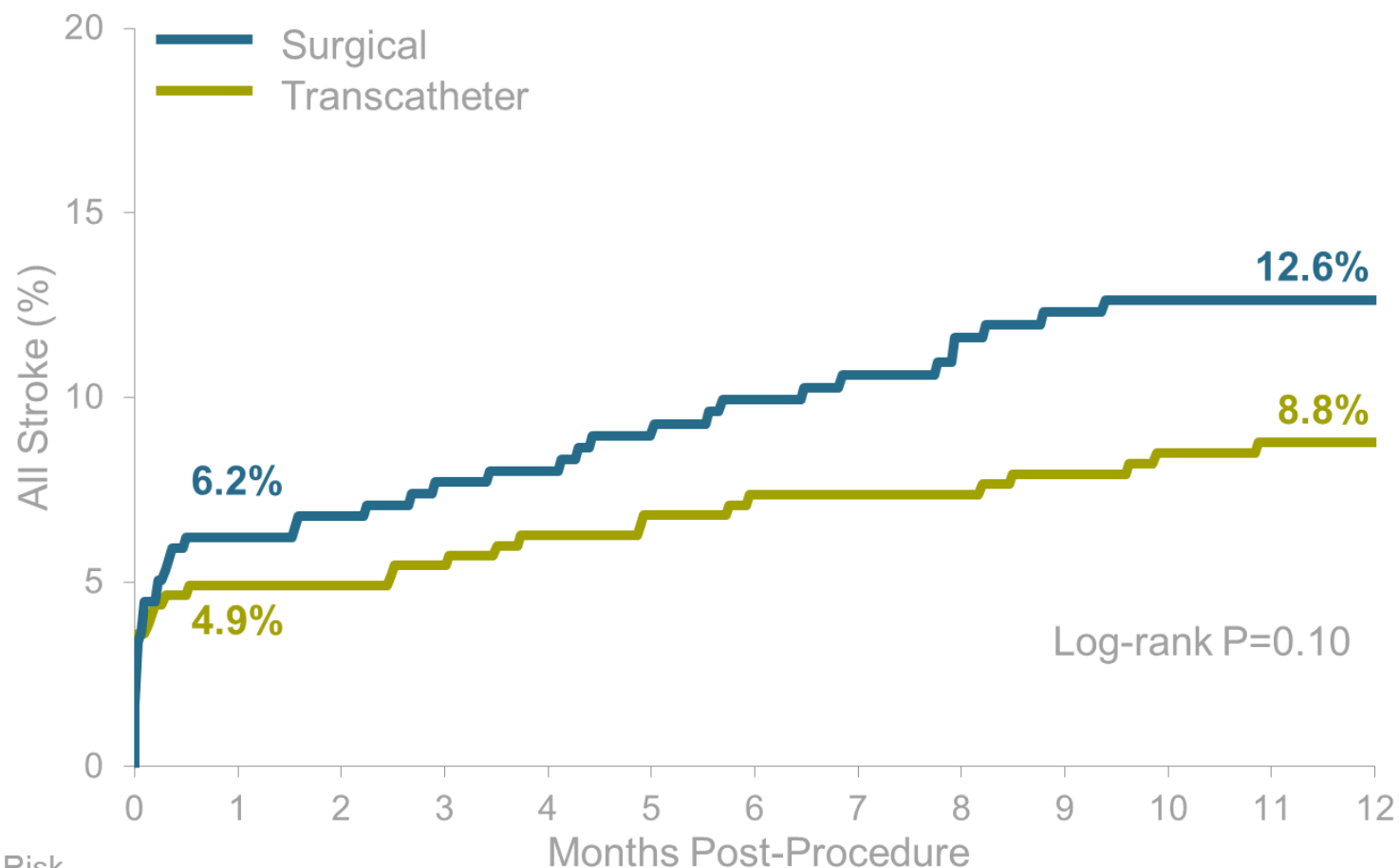
3.8%



All Stroke : PARTNER A (ITT)



CoreValve Trial : All Stroke



No. at Risk

Surgical	357	322	274	249	
Transcatheter	390	363	334	314	27

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

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

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%)

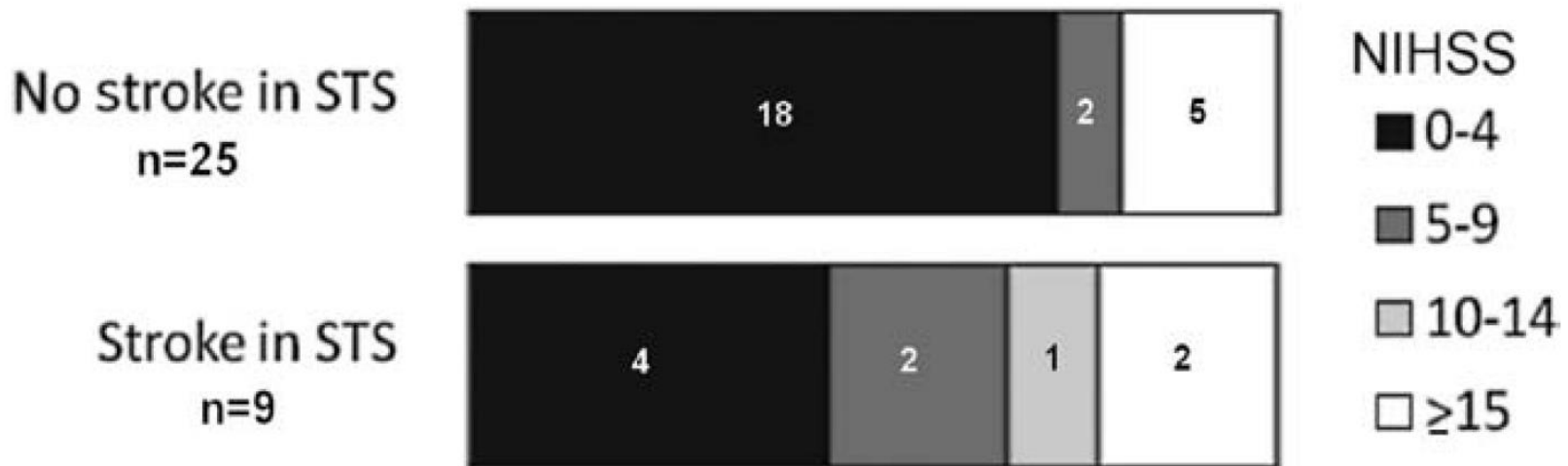
>POD 7 = 3 (9%)

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 **$\leq 9.7\%$** of subjects.

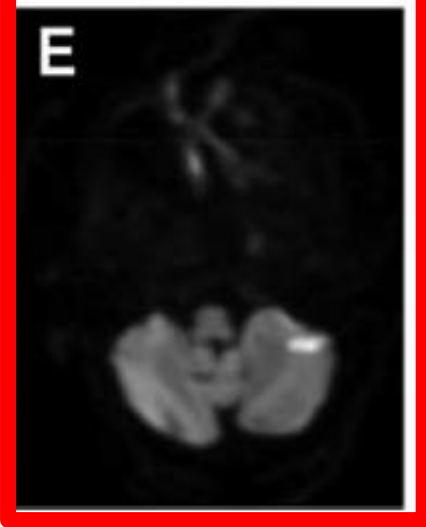
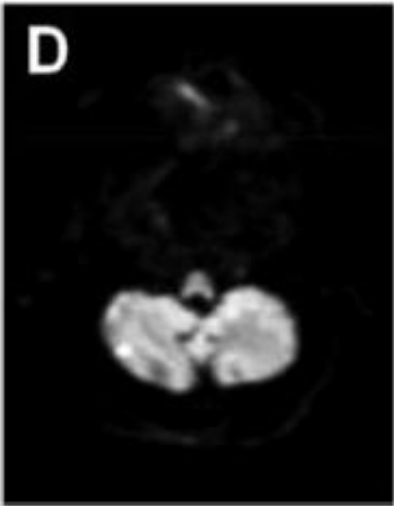
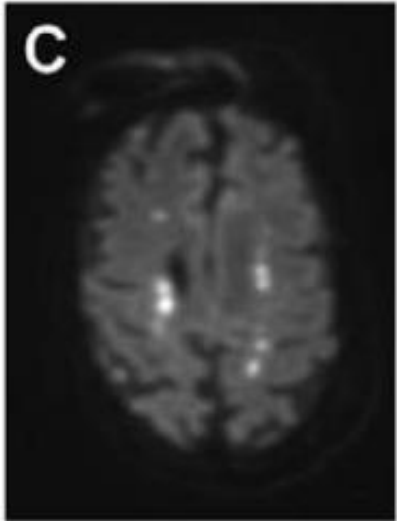
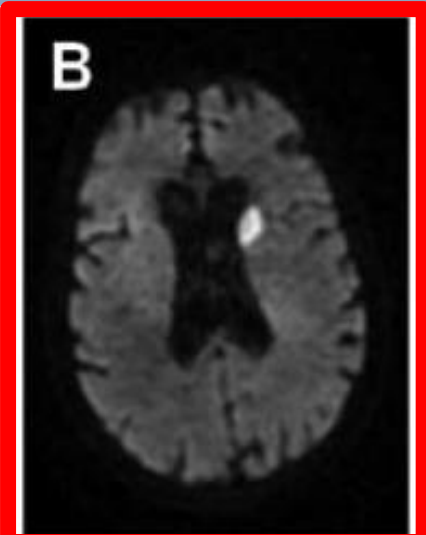
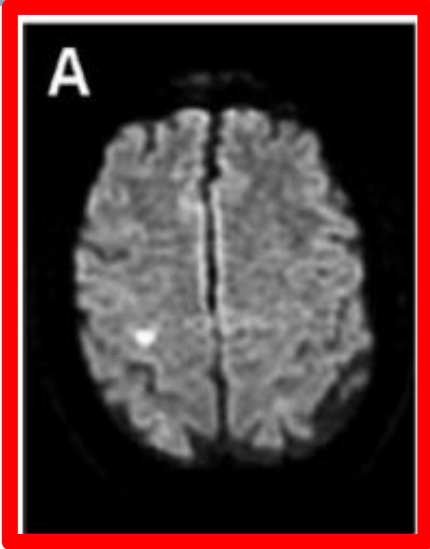
Stroke Detection and Reporting

25 “strokes” were not included in STS database

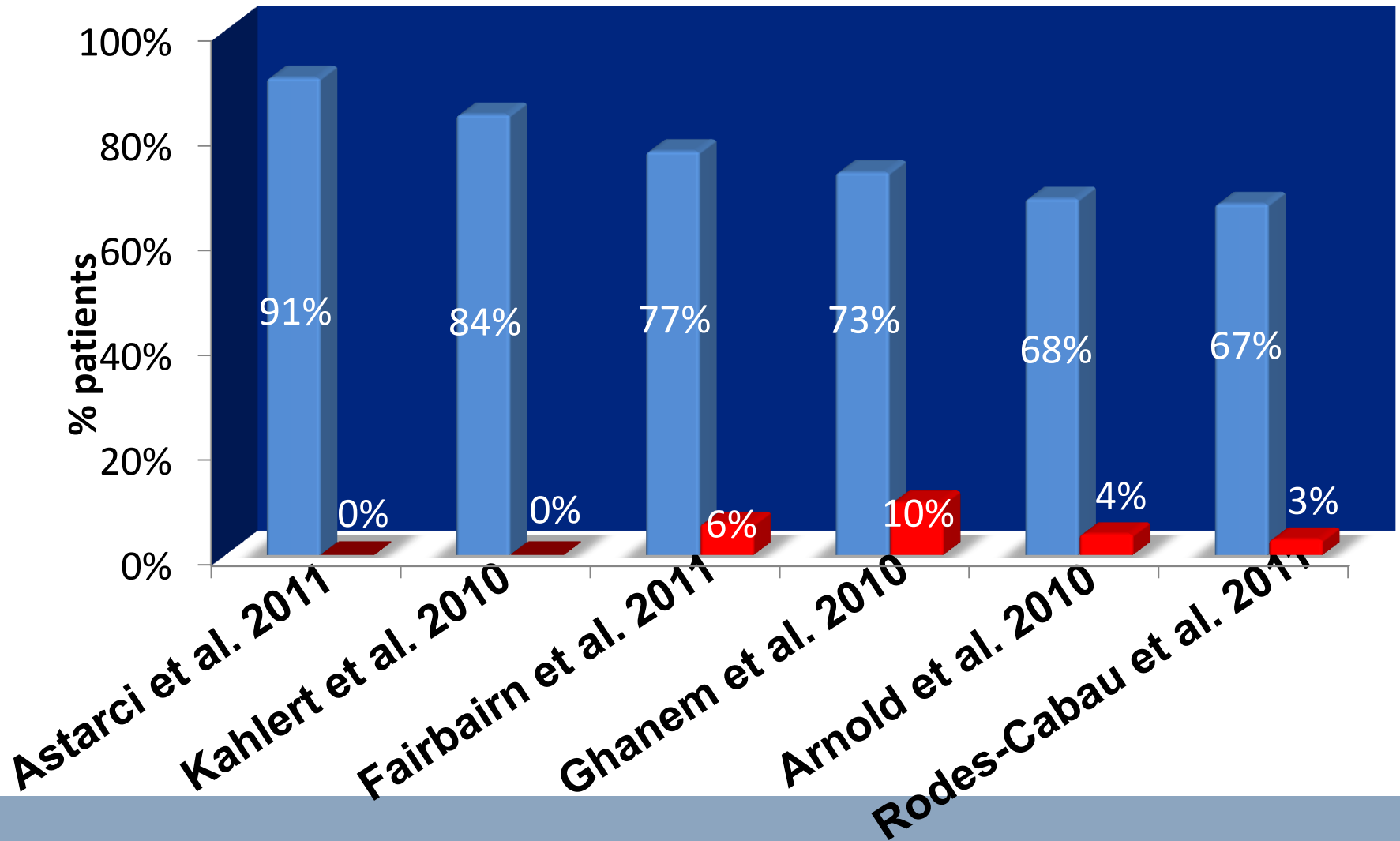


STS database reported 13 patients (6.6%) with stroke but 4 did not have stroke by DeNOVO (alcohol withdrawal, no deficit by day 7)

MRI (61% with lesions, 2.3/pt)



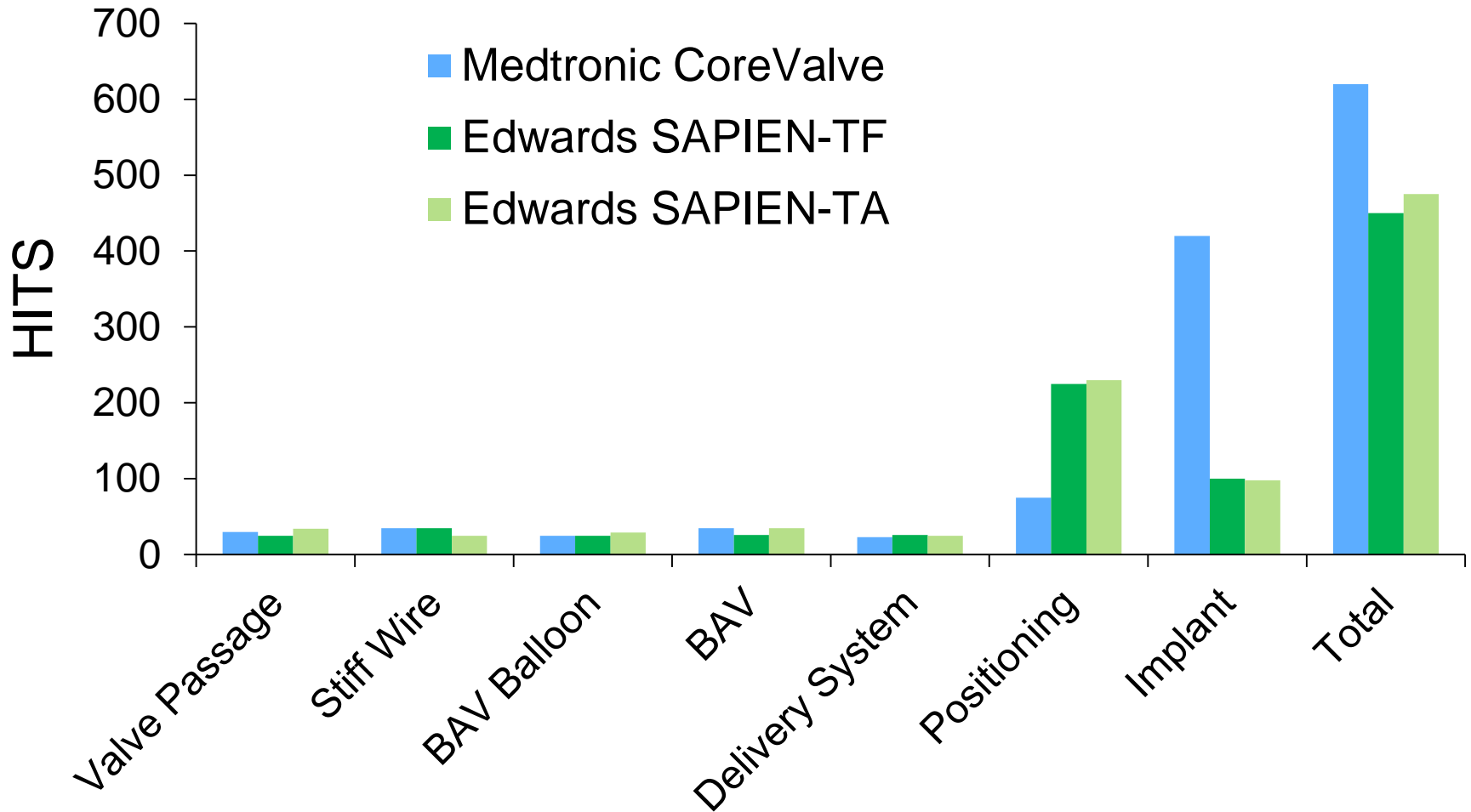
Subclinical Embolization and Stroke



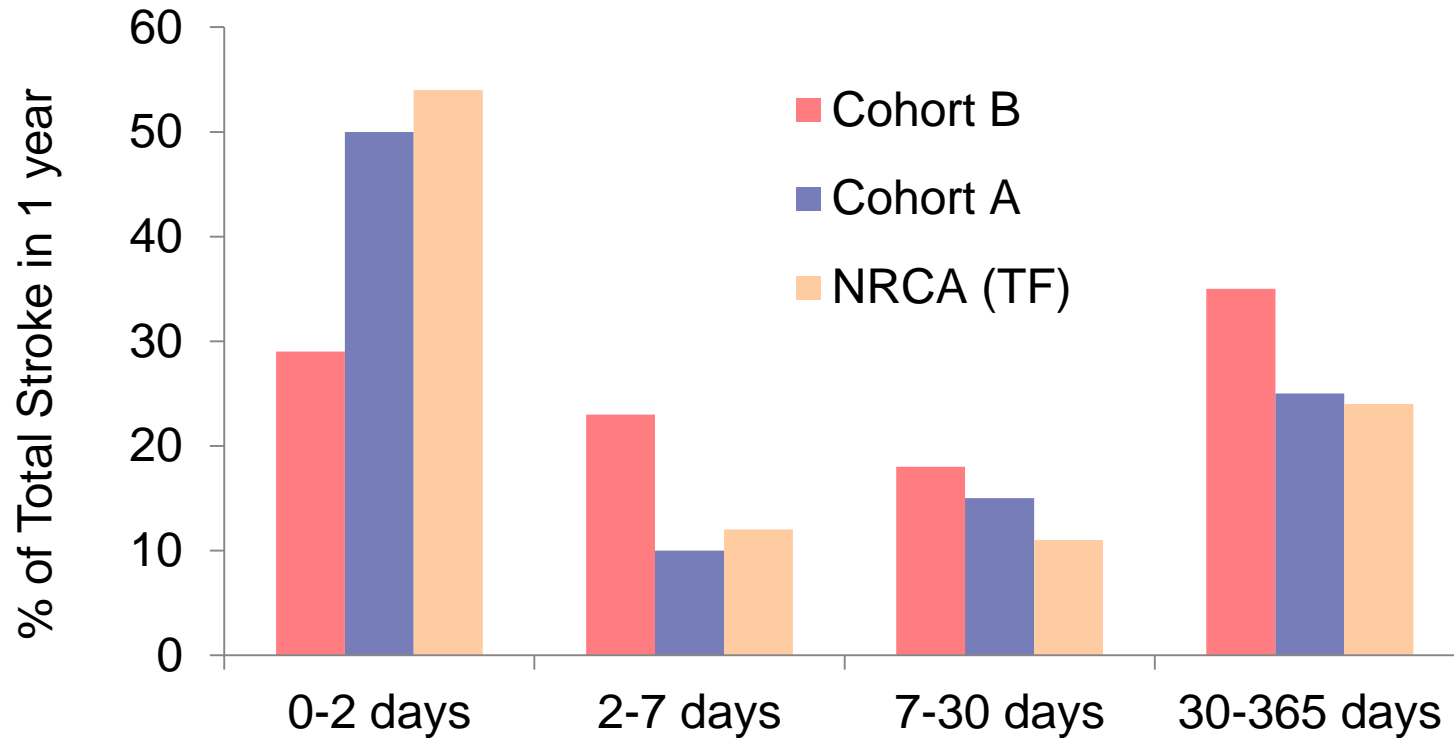
MRI Lesions According to Access

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

Timing of Emboli: TCD



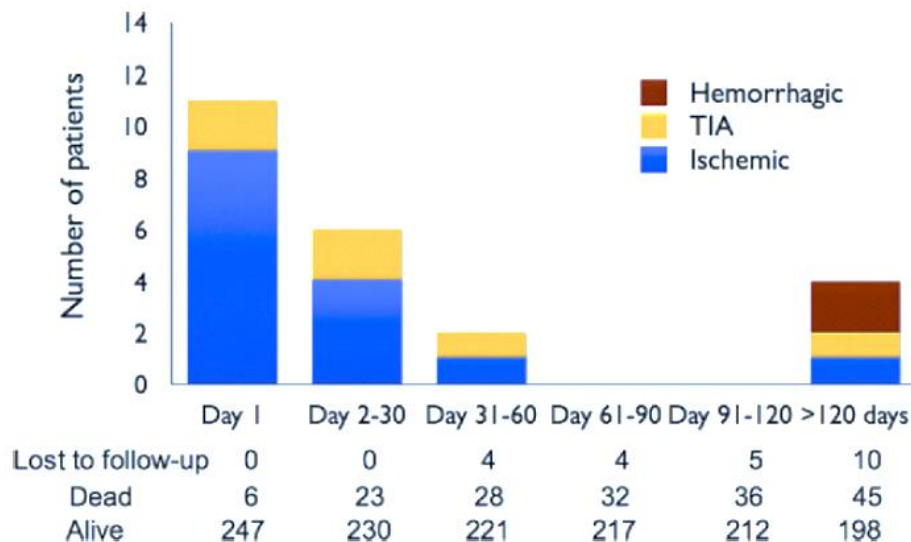
Stroke Timing within 1 year



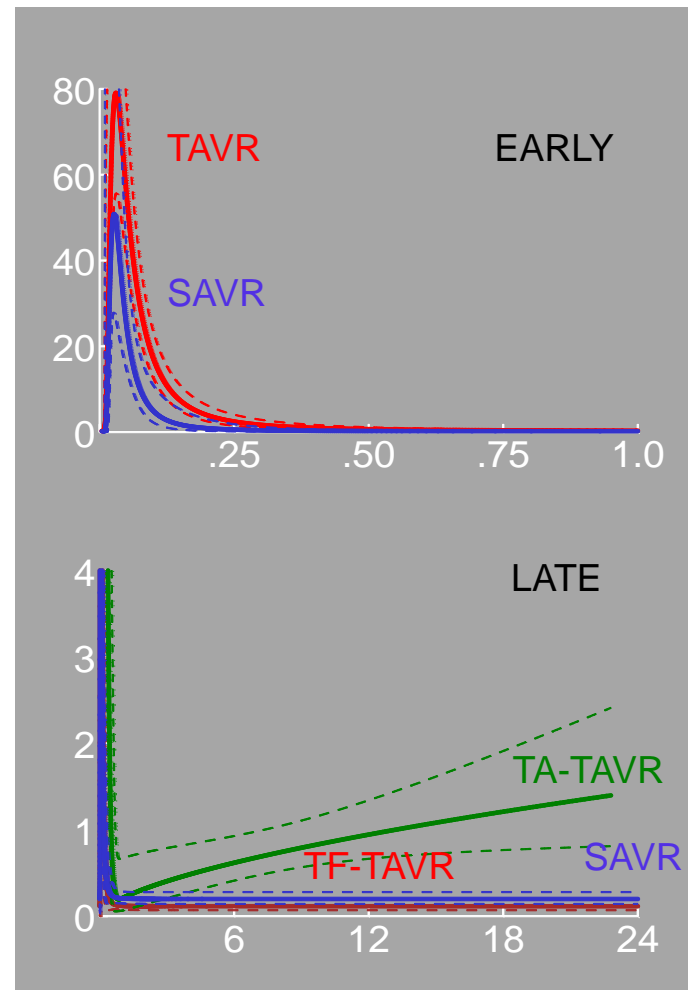
Leon et al, NEJM
Smith et al, NEJM
Kodali et al, ACC 2013

Timing of Neurological Event

Emboli Prevention versus Pharmacotherapy

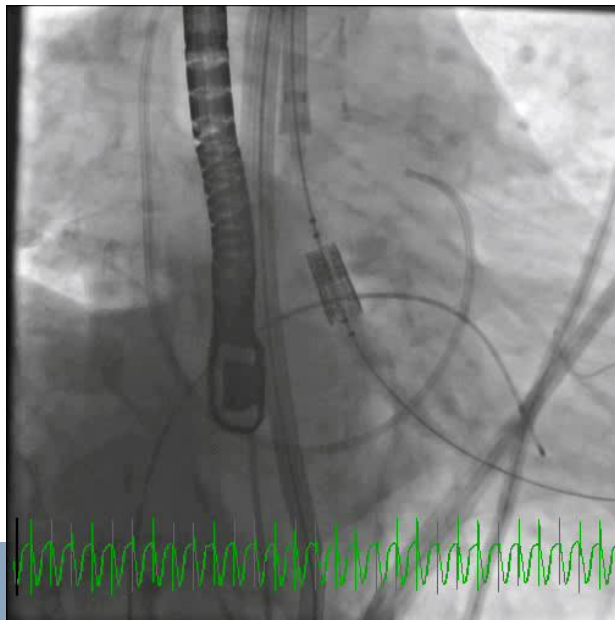
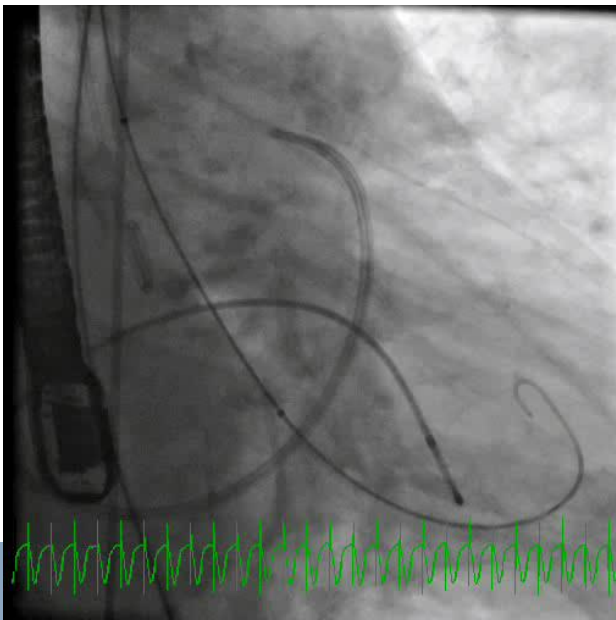
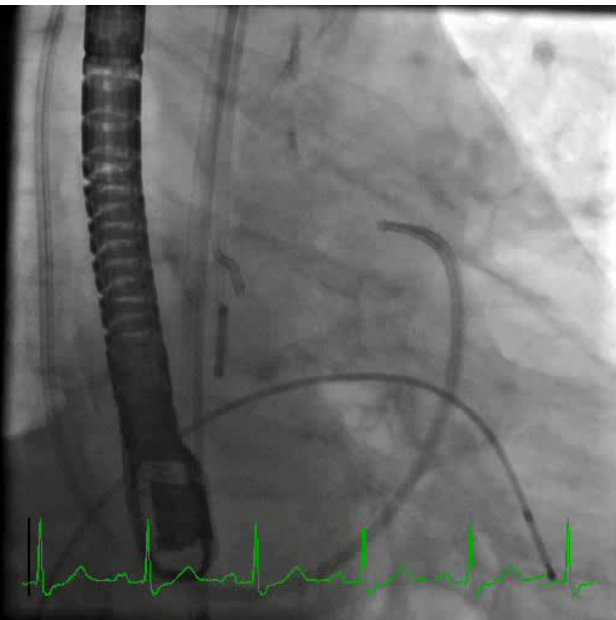
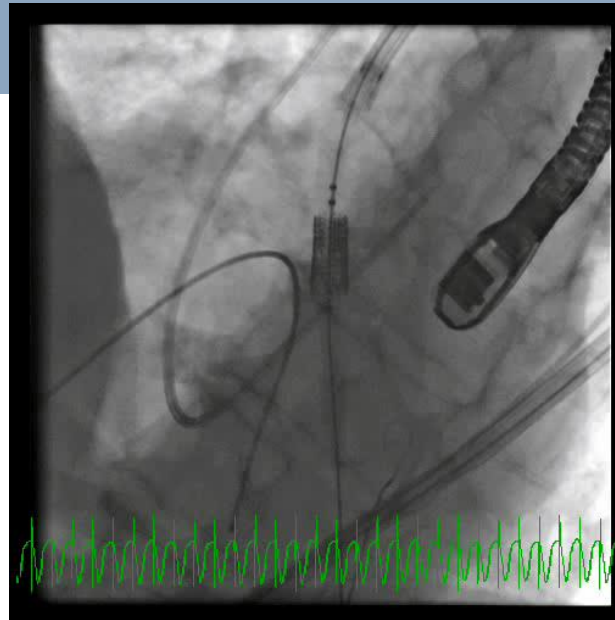
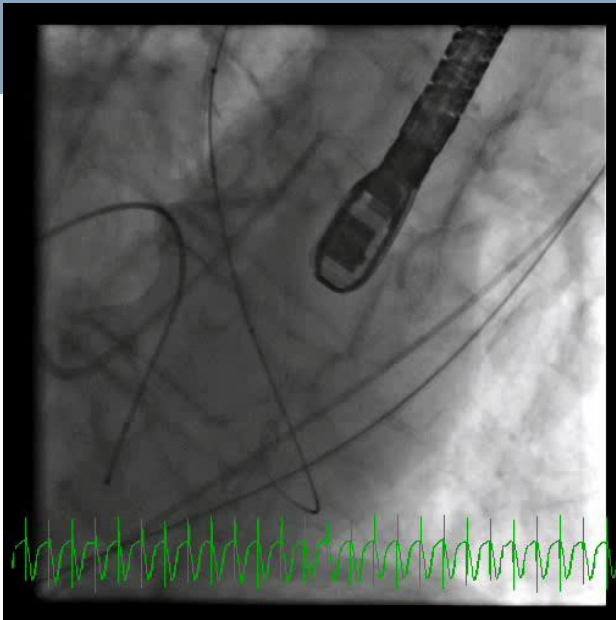


Tay et al, J Am Coll Cardiol Intv 2011;4:1290 –7



Miller et al, 2012;143:832-43

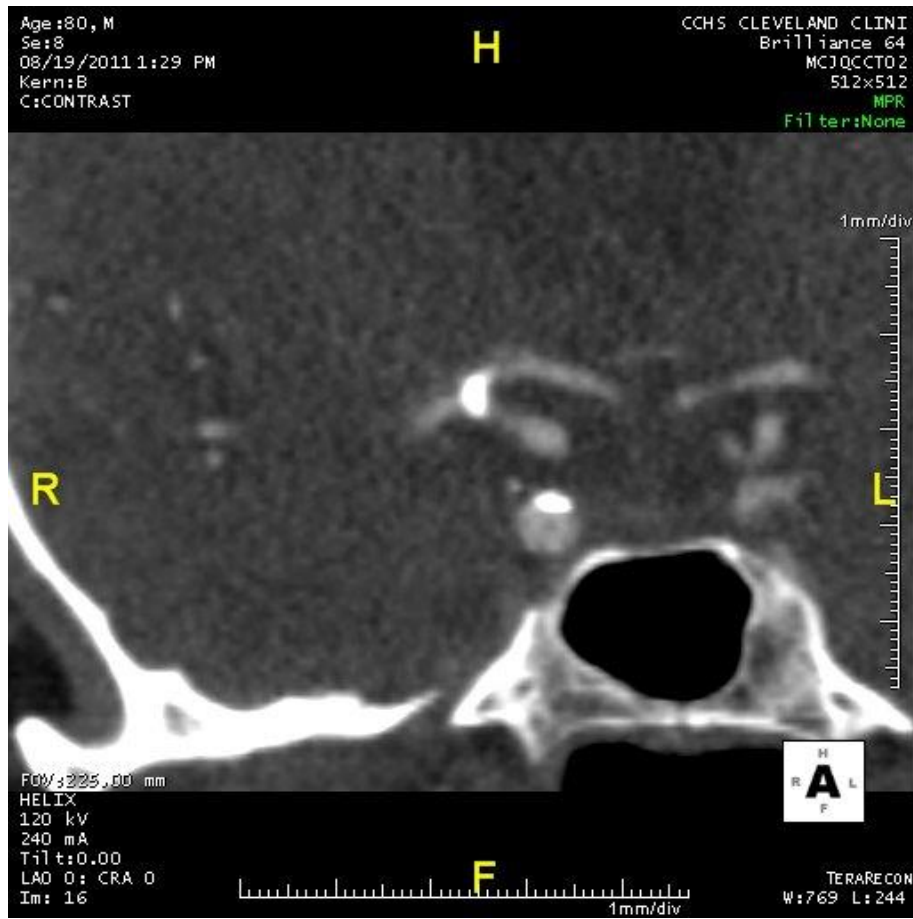
Uncomplicated TAVR – 91 year old



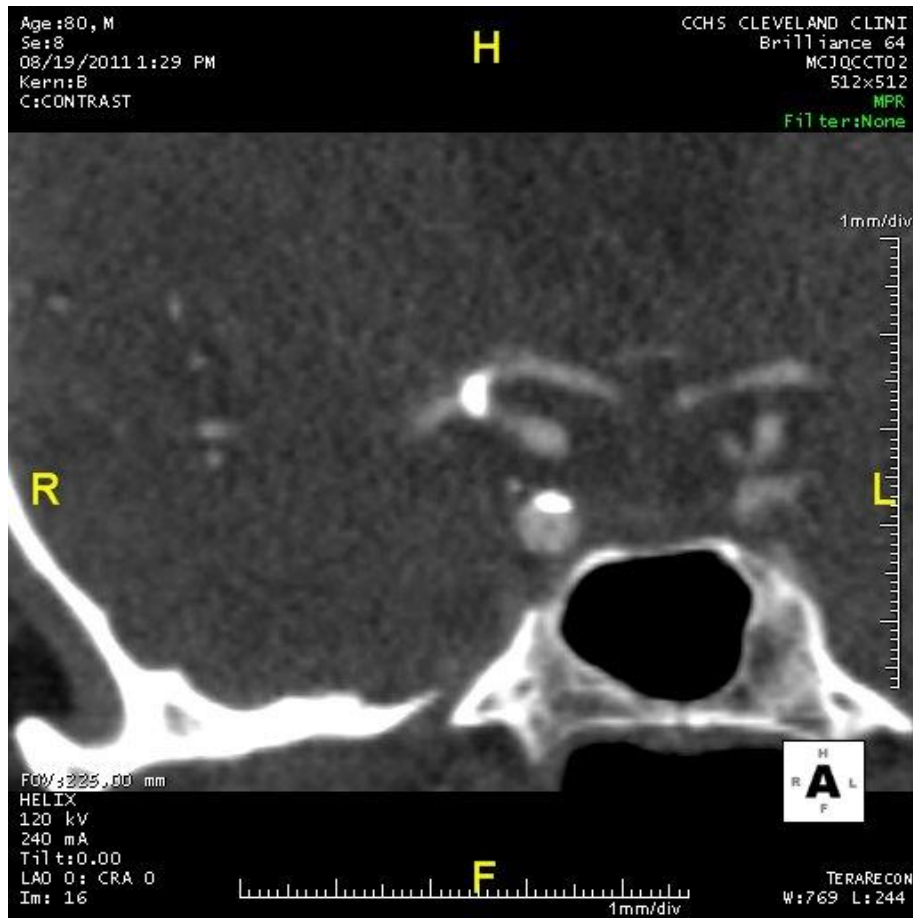
Post Procedural Course

- **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

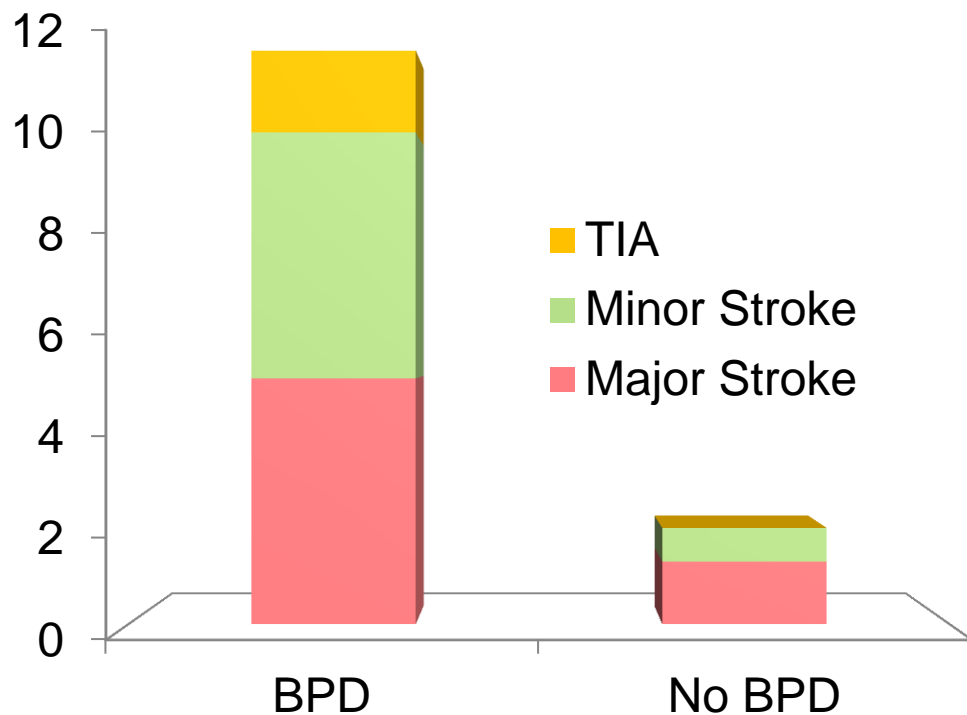
TAVR and Stroke : Registry Data

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

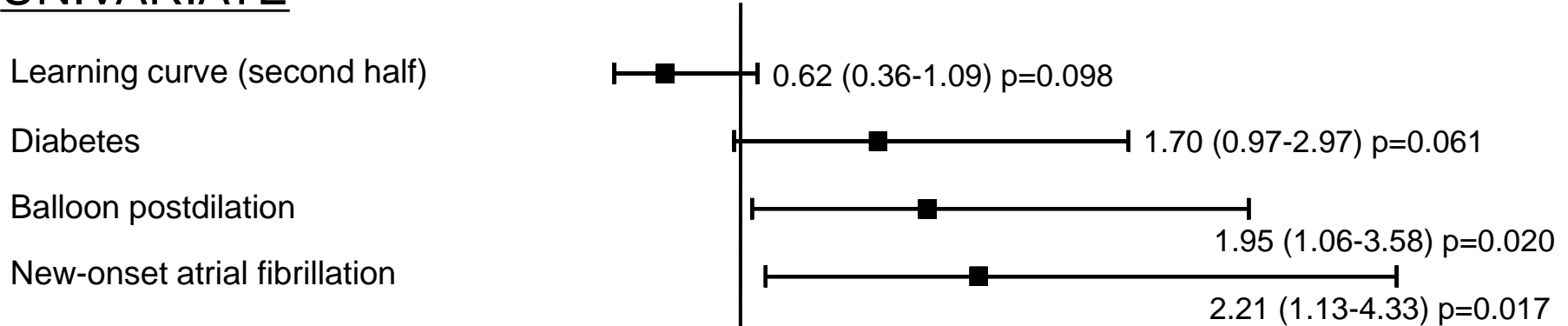
To what degree was post-dilation just a marker of a more calcified valve intrinsically more likely to release embolic material at the time of valve positioning or expansion? We do not know.

Canadian Experience

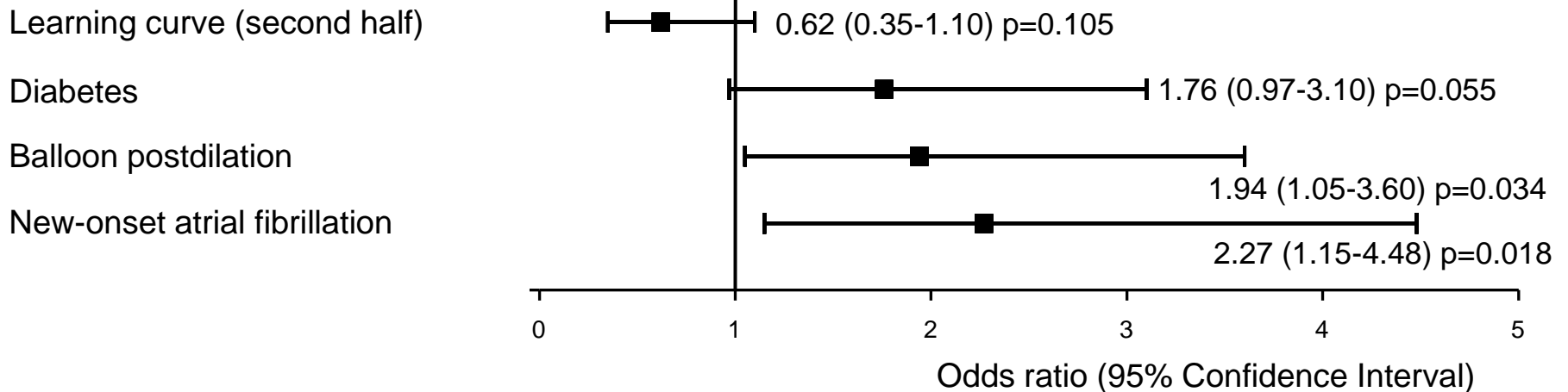
- **1061 Patients**
- **5 centers**
 - **679 (65%) Balloon expandable**
 - **361 (34%) Self expandable**
- **Analysis of events depending on timing of stroke**

Predictors of Early (30-Day) CVEs

UNIVARIATE



MULTIVARIATE



Predictors of Late CVEs (>30-day)

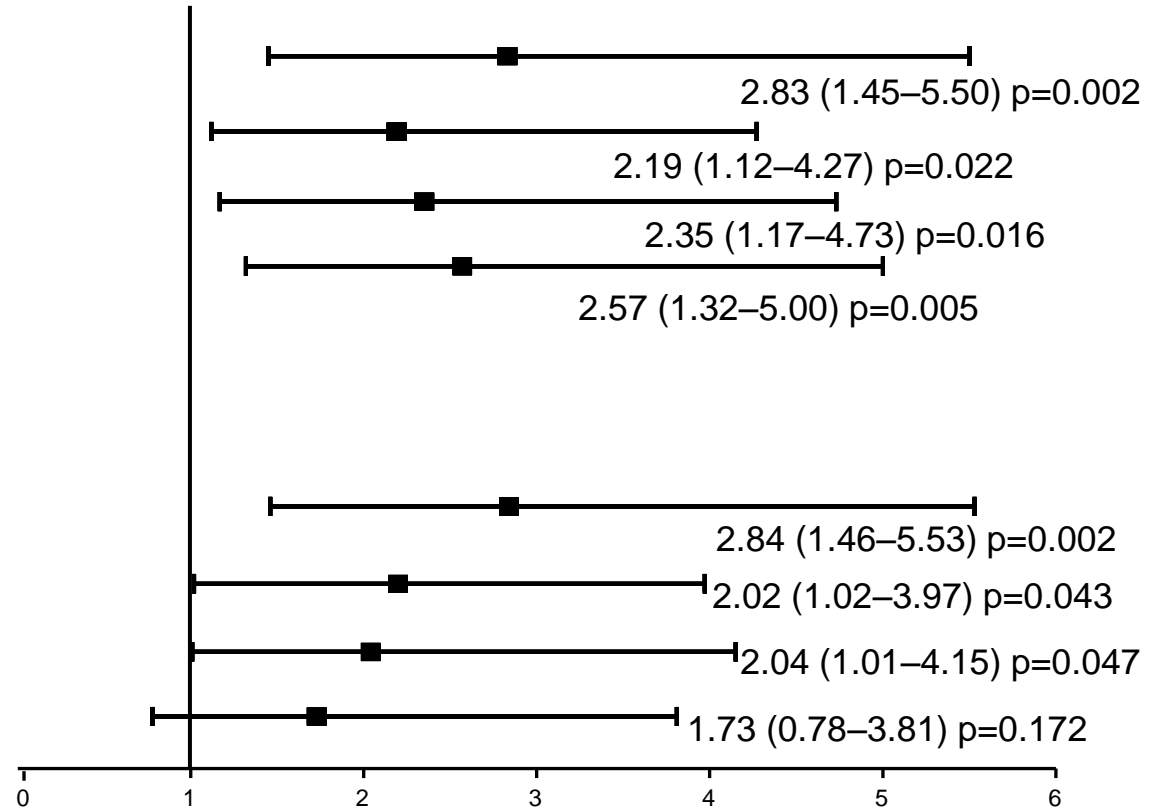
UNIVARIATE

Chronic atrial fibrillation

Peripheral vascular disease

Cerebrovascular disease

Anticoagulation treatment at hospital discharge



MULTIVARIATE

Chronic atrial fibrillation

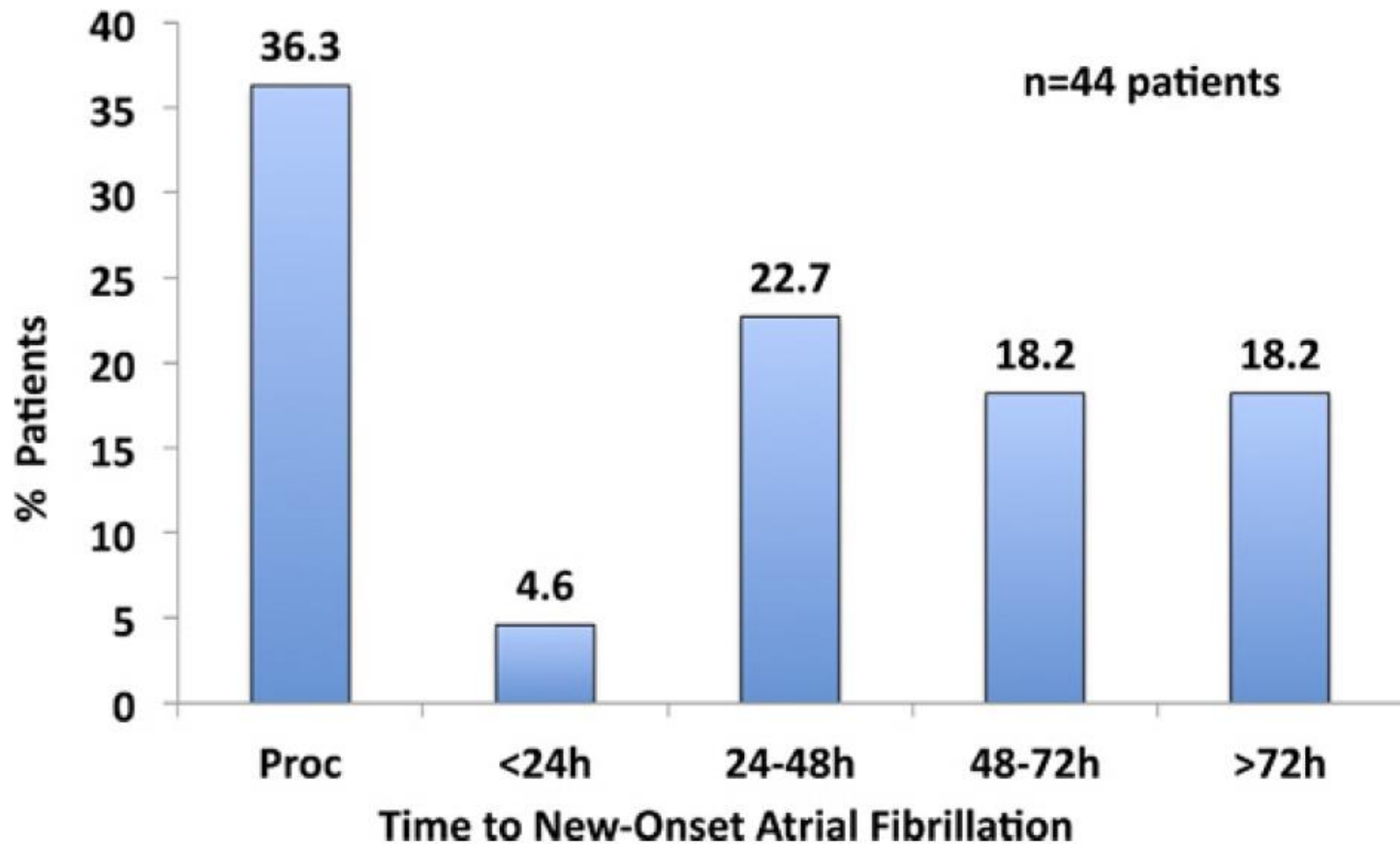
Peripheral vascular disease

Cerebrovascular disease

Anticoagulation treatment at hospital discharge

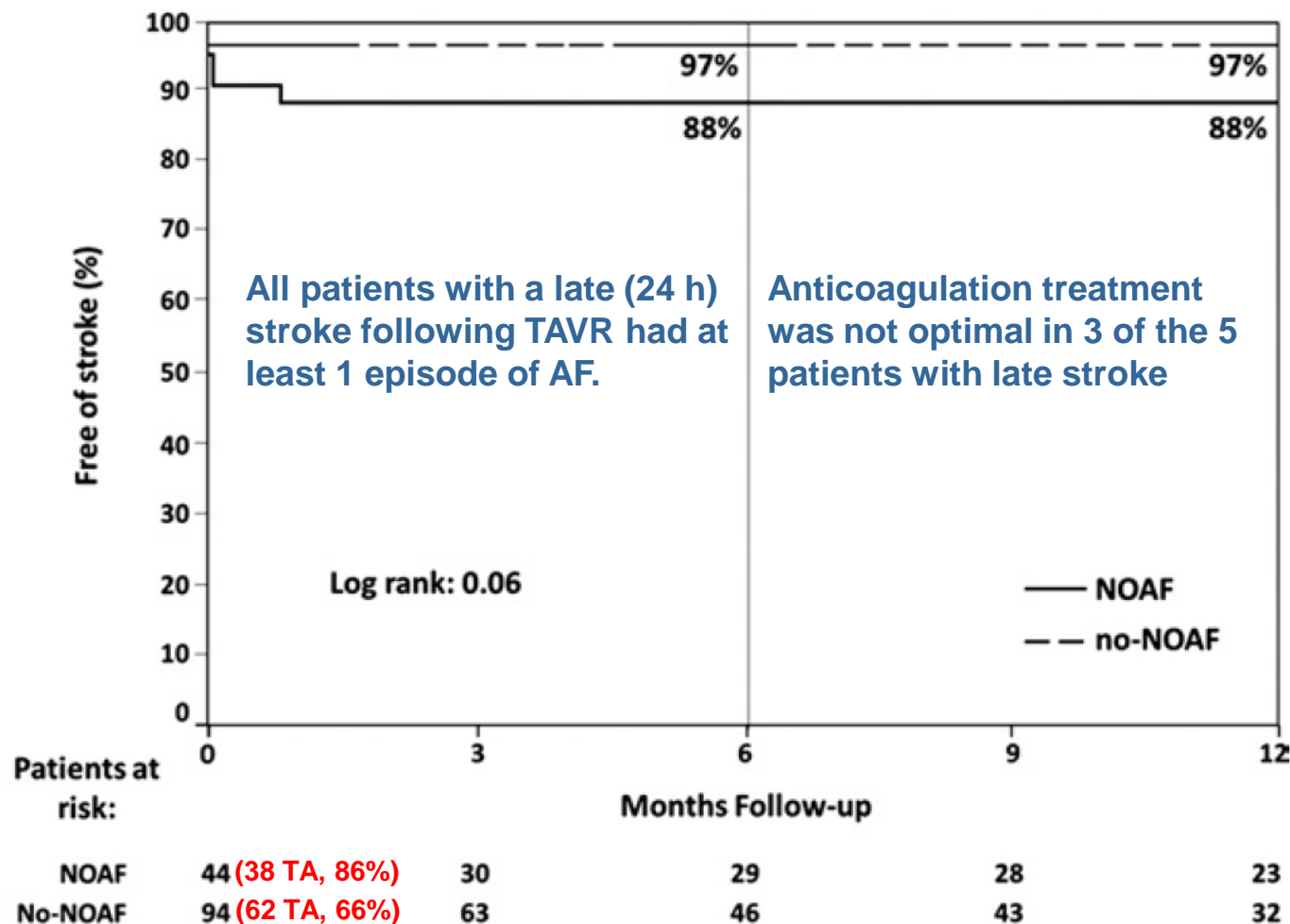
Hazard ratio (95% Confidence Interval)

Timing of NOAF after TAVR



Predictors of NOAF were LA size > 27 mm/m² and TA approach

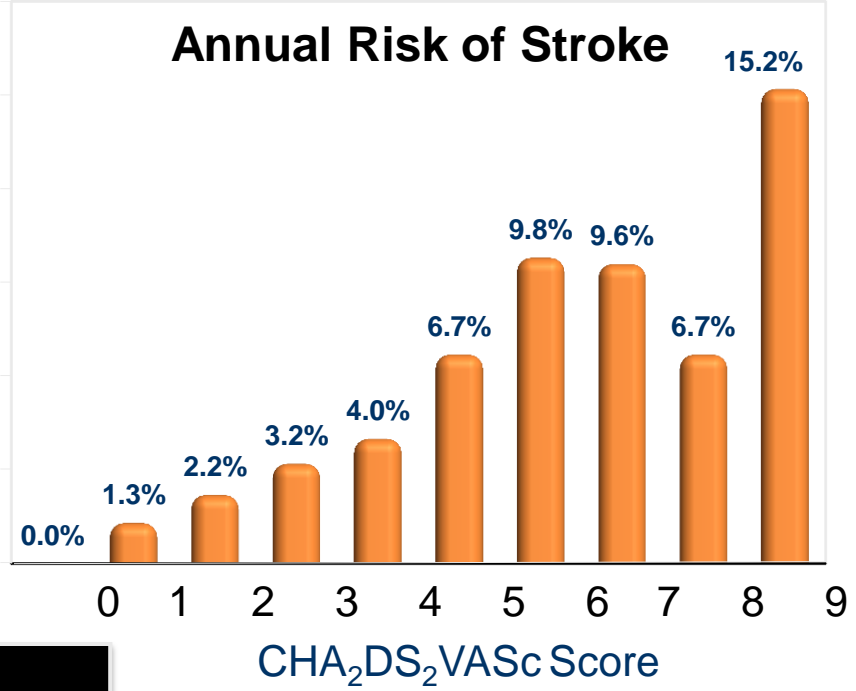
New Onset AF after TAVR and Stroke



CHA₂DS₂VASc : 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%

Risk of Stroke



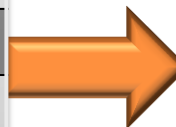
CHA ₂ DS ₂ -VASc Score	Treatment
0	No treatment
1	Aspirin or warfarin or dabigatran
≥2	Warfarin or dabigatran

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	??



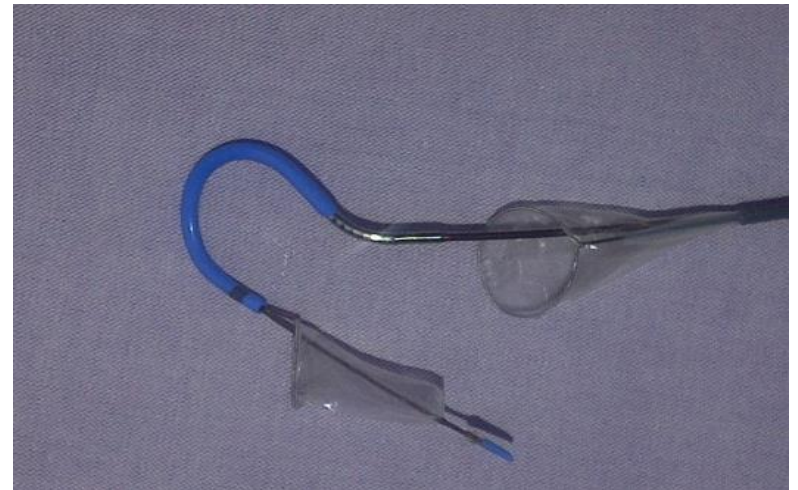
Bleeding Risk

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

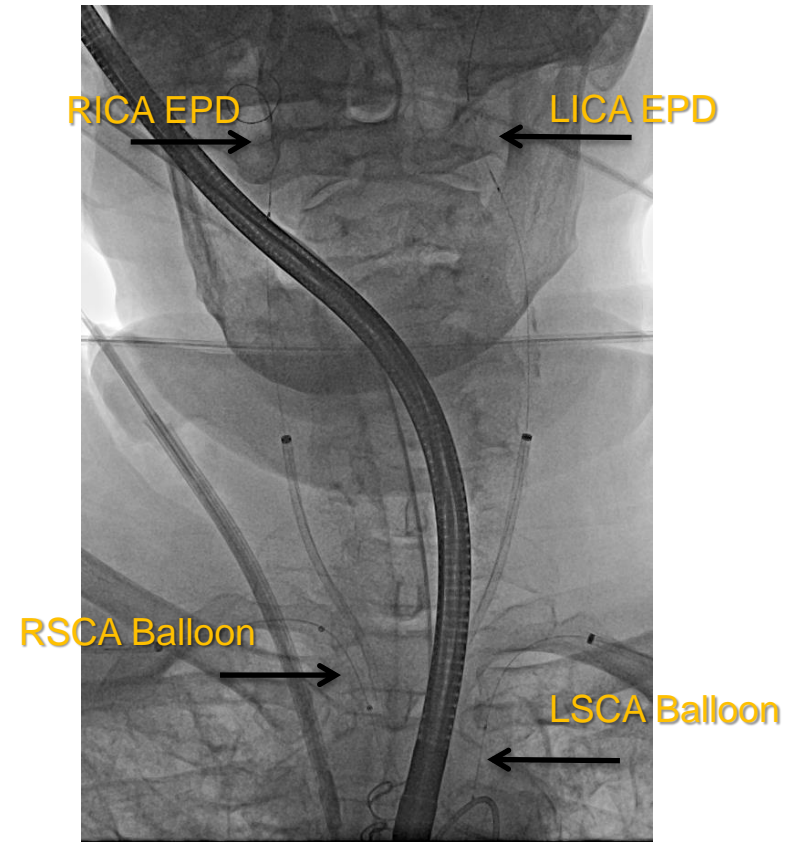
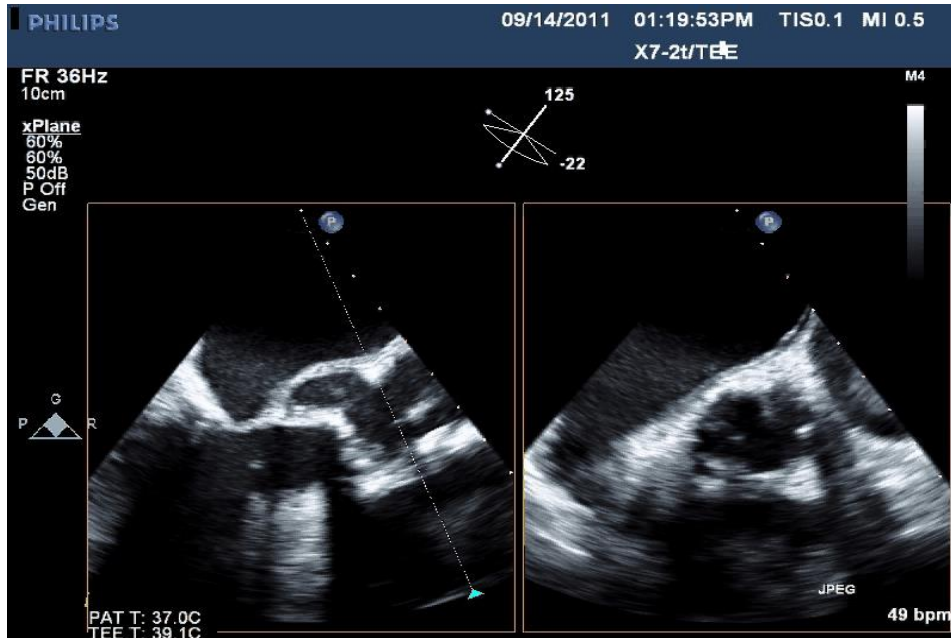
Hypertension, stroke and age are also variables in the CHADS scores

Stroke Prevention Measures

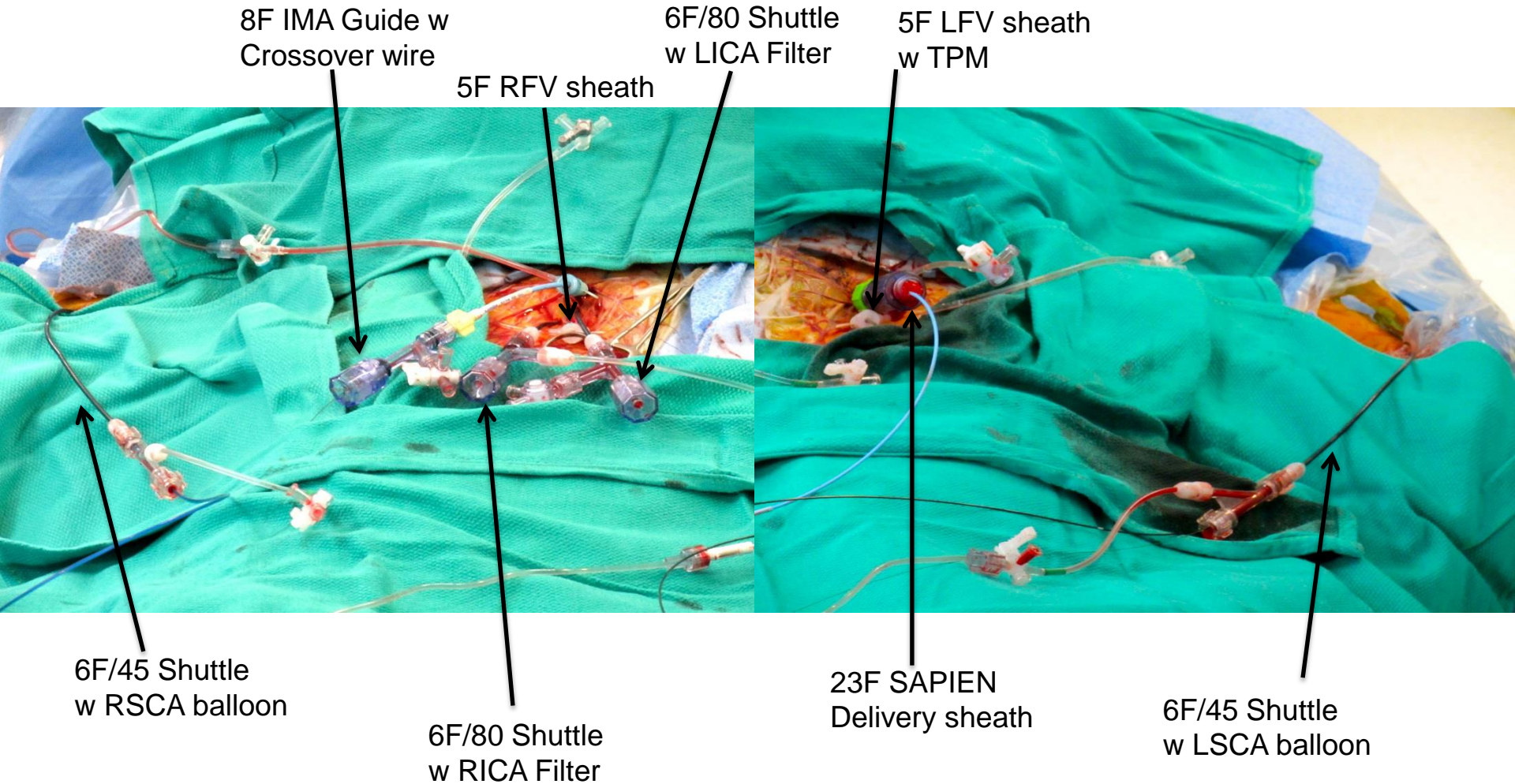
- **Emboli prevention devices**
 - **Claret device - Sentinel Trial**
 - **Embrella Device - ProTAVI**
- **Carotid pressure at the time of advancing the sheath**
- **Careful manipulations**
- **Minimize postdilations**
- **? Pretreat carotid disease**



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)