Incidence, Predictors, and Clinical Impact of Valvular and Perivalvular Thrombosis after TAVR : ADAPT-TAVR Cardiac CT Substudy

Yeonwoo Choi, MD

Asan Medical Center, South Korea

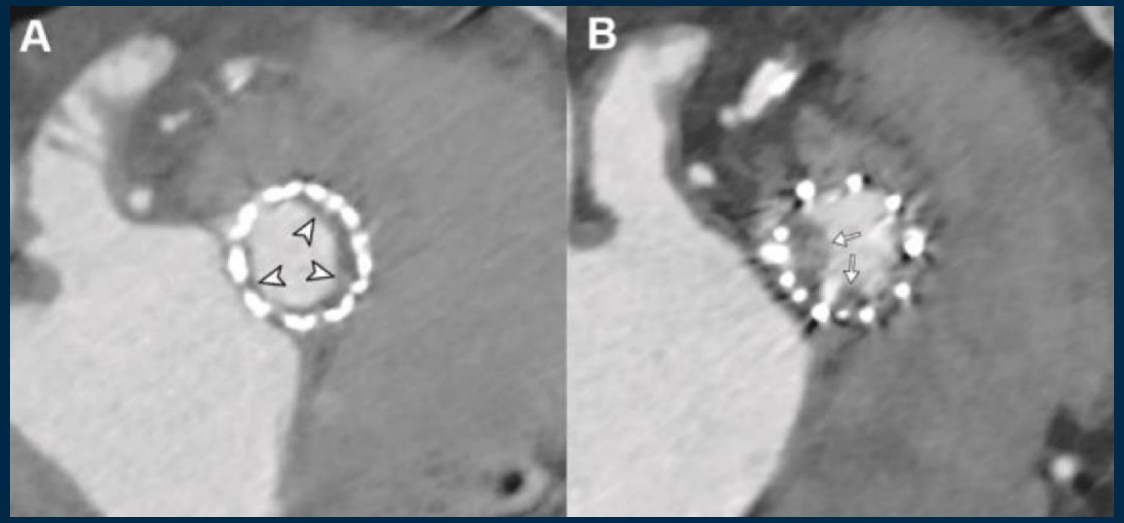
Disclosure

- I, Yeonwoo Choi, have NO conflict of interest related to this presentation

Introduction

- **Transcatheter aortic-valve replacement (TAVR) for the treatment of symptomatic severe aortic stenosis (AS) has become the standard of care for a broad range of clinical indications**

- Subclinical leaflet thrombosis or hypoattenuated leaflet thickening (HALT) and reduced leaflet motion (RLM) observed on 4-dimensional computed tomography (CT) was not uncommon (7% - 38%)



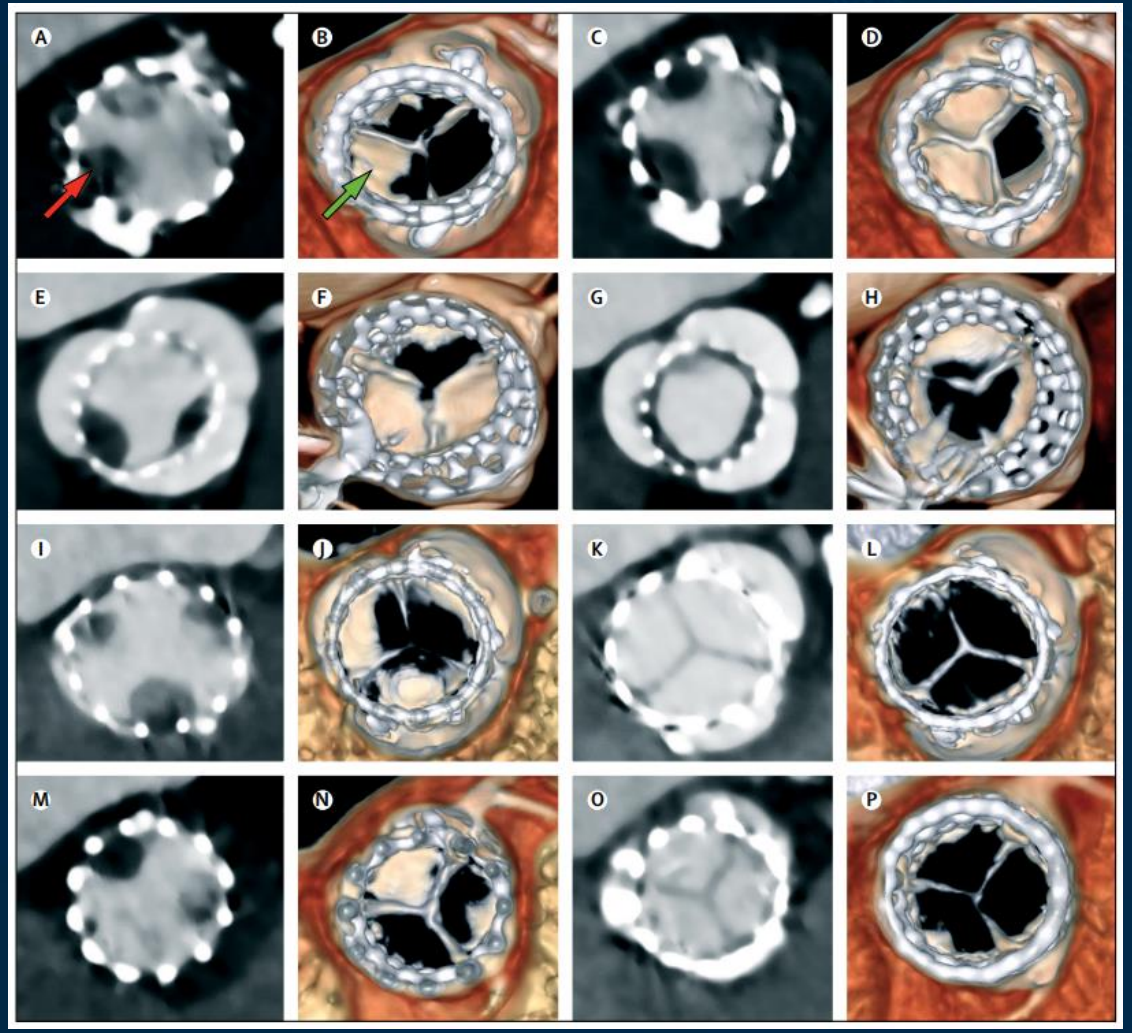
Otto CM et al. Circulation 2021 Feb 2;143(5):e35-e71.
Hyun Jung Koo et al. Am J Cardiol 2020 Feb 15;125(4):597-606.

Introduction

- Leaflet thrombosis following aortic valve replacement is associated with a significantly increased risk of adverse cerebrovascular events, such as stroke or transient ischemic attack

- In addition, perivalvular (supravalvular, subvalvular, and sinus of Valsalva) thrombosis has been reported

- The overall incidence and clinical implications of these imaging-detected phenomena are still uncertain



Hashrul N Rashid et al. EuroIntervention 2018 Feb 2;13(15):e1748-e1755.
Lim SJ et al. Korean Circ J 2020;50:572-82.
Tarun Chakravarty et al. Lancet 2017;389:2383-92.

Introduction

- Incidence of valvular or perivalvular thrombosis after TAVR
- The predictors of these thrombosis
- Clinical impact and its relationship with neurological outcomes

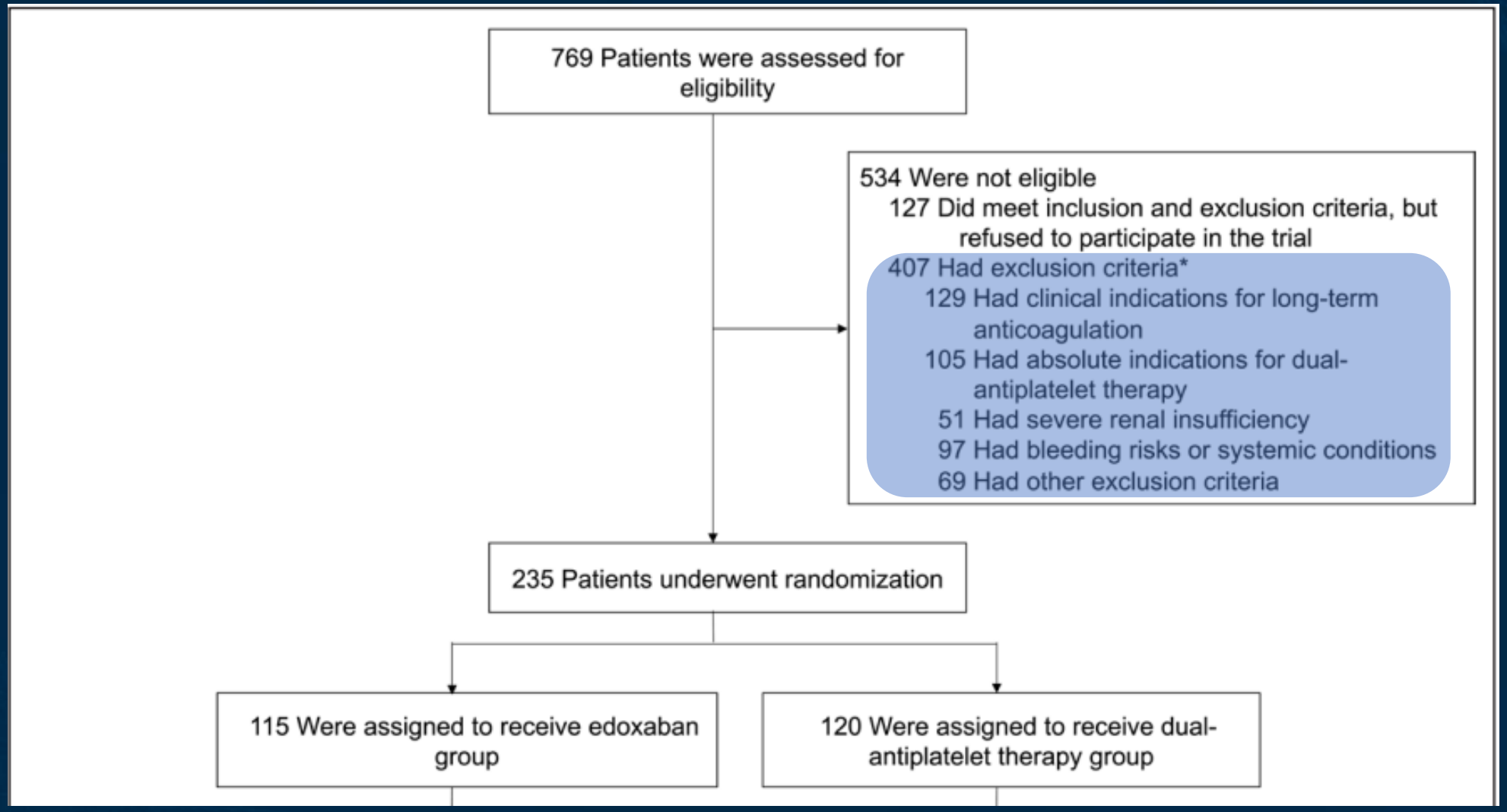
Methods

ADAPT-TAVR trial

- Anticoagulation Versus Dual Antiplatelet Therapy for Prevention of Leaflet Thrombosis and Cerebral Embolization After Transcatheter Aortic Valve Replacement

- Patients
  - Duration : March 2018 ~ April 2021
  - 769 patients undergoing TAVR were assessed for eligibility
    - ➢ Patients 18 years of age or older without an indication for long-term anticoagulation
    - ➢ Exclusion criteria : indication for anticoagulation, for DAPT, and severe renal insufficiency

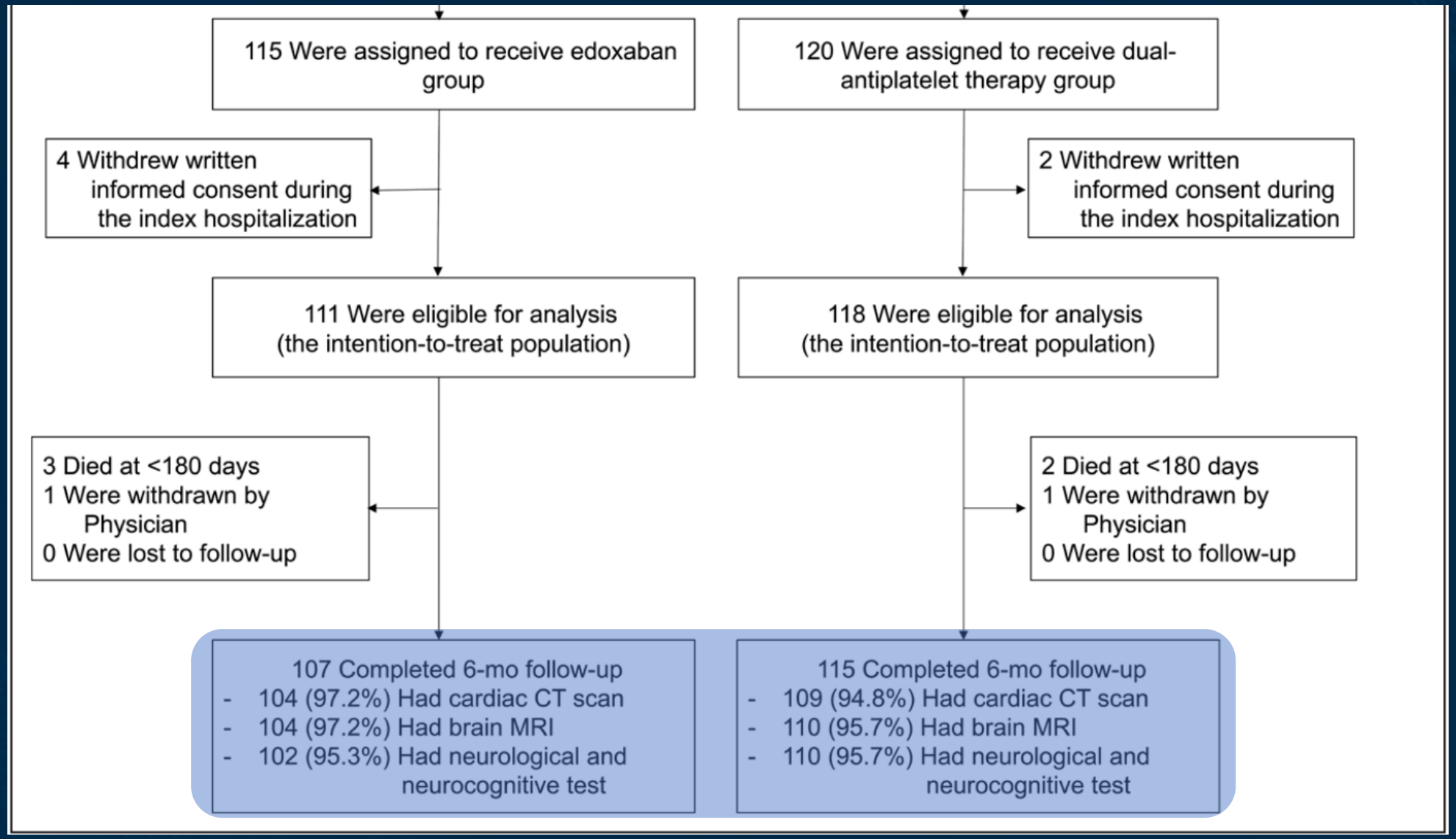
Methods


769 Patients were assessed for eligibility
534 Were not eligible
127 Did meet inclusion and exclusion criteria, but refused to participate in the trial
407 Had exclusion criteria*
129 Had clinical indications for long-term anticoagulation
105 Had absolute indications for dual-antiplatelet therapy
51 Had severe renal insufficiency
97 Had bleeding risks or systemic conditions
69 Had other exclusion criteria
235 Patients underwent randomization
115 Were assigned to receive edoxaban group
120 Were assigned to receive dual-antiplatelet therapy group

Methods

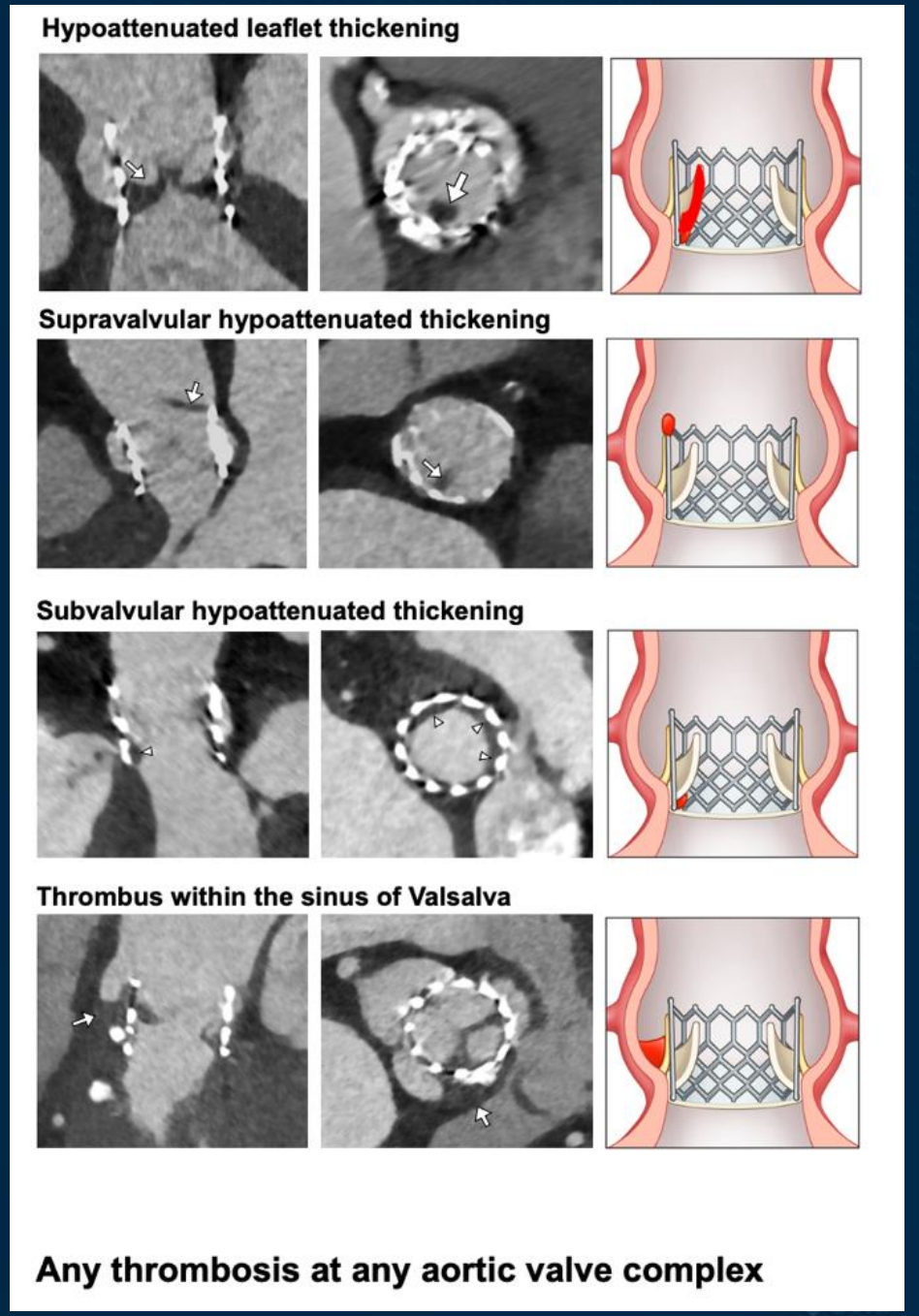
- Patients
  - A total of 235 underwent randomization after successful TAVR in 5 centers in 3 contries (South Korea, Hong Kong, and Taiwan)
  - In the final intention to treat population, 111 patients for edoxaban / 118 patients for DAPT
  - 211 patients, available cardiac CT data, were included

Methods


115 Were assigned to receive edoxaban group
120 Were assigned to receive dual-antiplatelet therapy group
4 Withdrew written informed consent during the index hospitalization
2 Withdrew written informed consent during the index hospitalization
111 Were eligible for analysis (the intention-to-treat population)
118 Were eligible for analysis (the intention-to-treat population)
3 Died at <180 days
1 Were withdrawn by Physician
0 Were lost to follow-up
2 Died at <180 days
1 Were withdrawn by Physician
0 Were lost to follow-up
107 Completed 6-mo follow-up
- 104 (97.2%) Had cardiac CT scan
- 104 (97.2%) Had brain MRI
- 102 (95.3%) Had neurological and neurocognitive test
115 Completed 6-mo follow-up
- 109 (94.8%) Had cardiac CT scan
- 110 (95.7%) Had brain MRI
- 110 (95.7%) Had neurological and neurocognitive test

Methods

- Imaging studies
  - Contrast-enhanced, electrocardiogram-gated cardiac CT scans with full cardiac-cycle coverage (four-dimensional CT) at 6 months
  - Incidence of valvular or perivalvular thrombosis



Methods

- Imaging studies
  - Magnetic resonance imaging (MRI)
  - ➢ To detect possible subclinical cerebral thromboembolism
  - ➢ Routinely scheduled at baseline (1-7 days after TAVR and before discharge) and at 6-month follow-up
  - ➢ Diffusion-weighted imaging (DWI), fluid-attenuated inversion recovery (FLAIR) T2*-gradient (GRE) images

Methods

- Neurological and neurocognitive functional assessments
  - At baseline and at 6-month follow-up
  - ➢ the National Institutes of Health Stroke Scale (NIHSS)
  - ➢ modified Rankin Scale (mRS)
  - ➢ Montreal Cognitive Assessment

  - Worsening of neurological or neurocognitive end points

    ≥ 1 point increase in NIHSS, mRS

    ≥ 1 point decrease in Montreal Cognitive Assessment score

Methods

- Endpoint
  - Primary endpoint : the incidence of any subclinical thrombosis at aortic valve complex (valvular and perivalvular)
  - Secondary endpoint : the presence and number of new cerebral lesion and total new lesion volume on brain MRI, and serial changes of neurological and neurocognitive assessments
  - Other secondary end point : efficacy/safety clinical outcomes at 6 months

- Statistical analysis
  - Categorical variables : Chi square test or Fisher's exact test
  - Continuous variables : Student's t-test or Wilcoxon rank-sum test
  - Predictors of subclinical aortic valve complex (valvular and perivalvular)
    - Univariate and multivariable analysis using logistic regression models
  - *P* value < 0.05 was considered as statistically significant
  - All statistical analysis was conducted by SAS software version 9.4 and R programming

Results

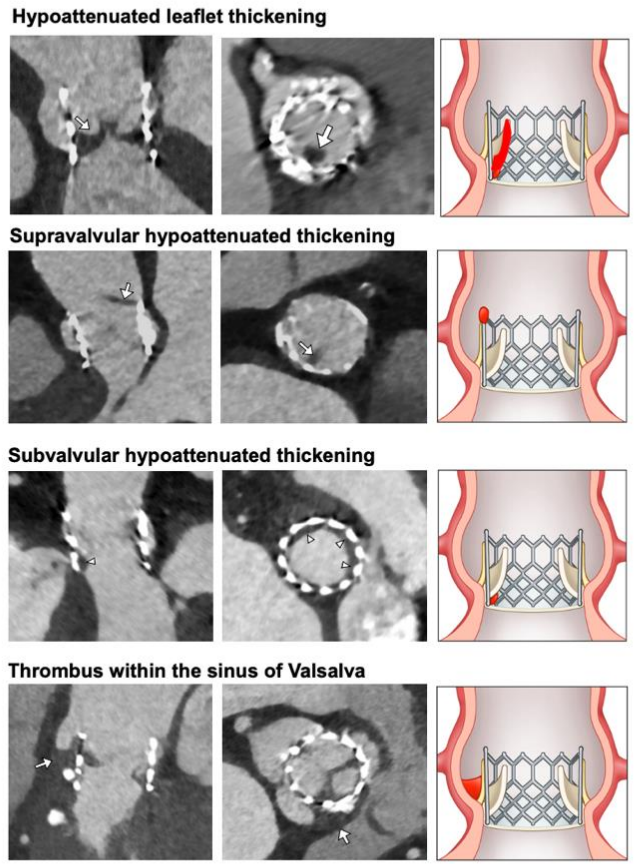
- Study population
  - with 6-month CT evaluations, analysis included 211 patients

✓Thrombosis at aortic valve complex : 91 patients (43.1%)

- 30 (14.2%) : leaflet thrombosis
- 78 (38.0%) : perivalvular thrombosis

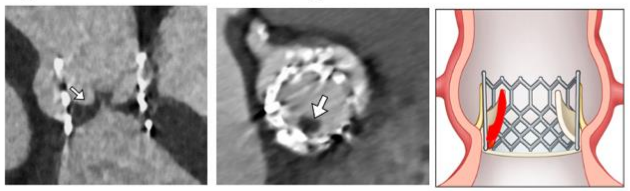
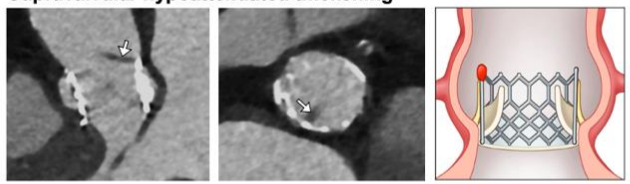
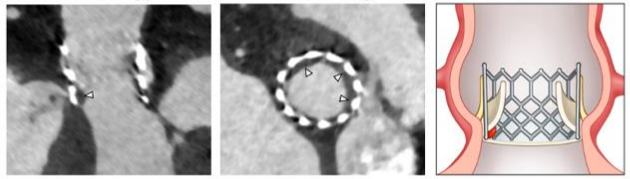
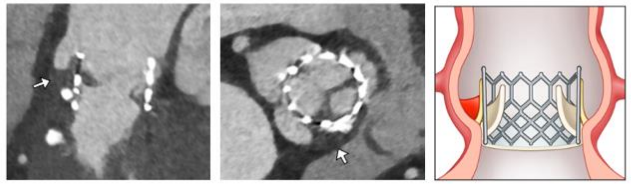
; 1 had supravalvular, 57 had subvalvular
37 had thrombosis within sinus of Valsalva

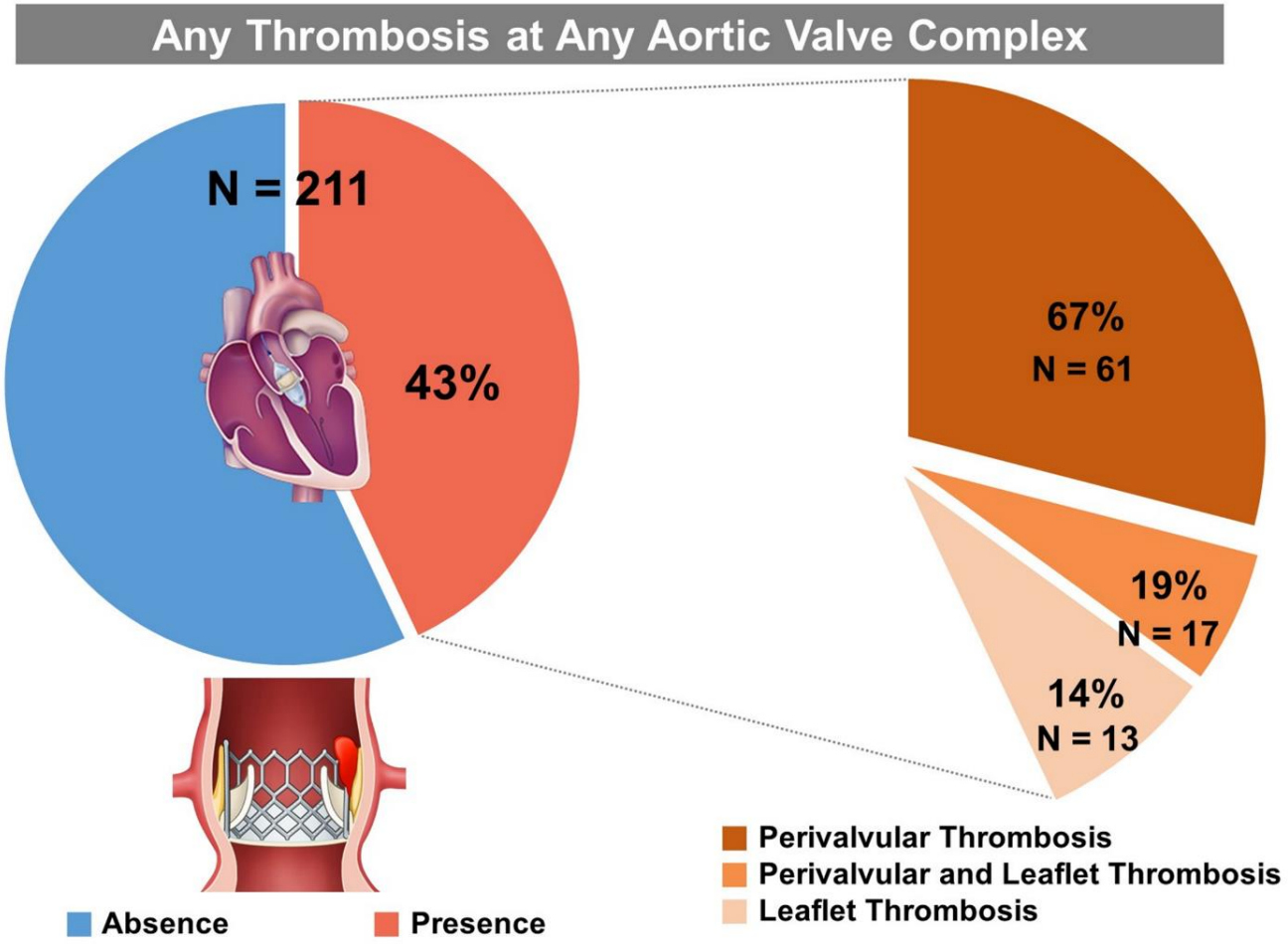
Cardiac CT Assessment for Thrombosis at Aortic Valve Complex



Results

Cardiac CT Assessment for Thrombosis at Aortic Valve Complex

	n / N (%)
Hypoattenuated leaflet thickening 	30 / 211 (14.2%)
Supravalvular hypoattenuated thickening 	1 / 211 (0.5%)
Subvalvular hypoattenuated thickening 	57 / 211 (27.0%)
Thrombus within the sinus of Valsalva 	37 / 211 (17.5%)
Any thrombosis at any aortic valve complex	91 / 211 (43.1%)



Results

Characteristics	Thrombosis at Any Aortic Valve Complex (Valvular and Perivalvular)* Yes (N=91)	No (N=120)	*P* value
Age, yrs	79.7 ± 5.9	80.4± 4.8	0.33
Male sex	31 (34.1)	57 (47.5)	0.07
Body weight ≤60kg	52 (57.1)	52 (43.3)	0.07
Body-mass index (kg/m^2)†	25.0 ± 3.9	25.1 ± 4.2	0.89
Body-surface area (m^2)	1.56 ± 0.17	1.63 ± 0.16	0.001
STS PROM score‡			
Mean	3.26 ± 2.19	3.20 ± 2.46	0.86
Category			0.44
Low (<4)	66 (72.5)	94 (78.3)	
Intermediate (4 to 8)	23 (25.3)	22 (18.3)	
High (>8)	2 (2.2)	4 (3.3)	
EuroSCORE II value§	2.52 ± 4.17	2.15 ± 1.35	0.42
NYHA class III or IV	24 (26.4)	31 (25.8)	>0.99
Diabetes mellitus	27 (29.7)	37 (30.8)	0.98
Hypertension	64 (70.3)	92 (76.7)	0.38
Hyperlipidemia	71 (78.0)	86 (71.7%)	0.37
Current smoker	4 (4.4)	7 (5.8)	0.88
Congestive heart failure	10 (11.0)	14 (11.7)	>0.99
Coronary artery disease¶	22 (24.2)	36 (30.0)	0.42

Characteristics	Thrombosis at Any Aortic Valve Complex (Valvular and Perivalvular)* Yes (N=91)	No (N=120)	*P* value
Prior MI	1 (1.1)	0 (0.0)	0.89
Prior PCI	14 (15.4)	16 (13.3)	0.82
Prior CABG	2 (2.2)	2 (1.7)	>0.99
Prior cerebrovascular disease	10 (11.0)	7 (5.8)	0.27
Carotid disease	3 (3.3)	7 (5.8)	0.60
Peripheral arterial disease	7 (7.7)	11 (9.2)	0.90
Chronic lung disease	21 (23.1)	31 (25.8)	0.77
Serum Creatinine (mg/dl)	0.95 ± 0.30	0.92 ± 0.24	0.46
Creatinine clearance by Cockcroft-Gault formula	58.0 ± 18.5	62.1 ± 20.8	0.14
Creatinine clearance ≤50 ml/min	38 (41.8)	39 (32.5)	0.22
Randomized group			0.13
Edoxaban	38 (41.8)	64 (53.3)	
DAPT	53 (58.2)	56 (46.7)	
Actual use of antithrombotic drugs			0.27
Edoxaban	37 (40.7)	62 (51.7)	
DAPT	51(56.0)	54 (45.0)	

Values are mean ± SD, n (%), or n/N (%).

Results

Characteristics	Thrombosis at Any Aortic Valve Complex (Valvular and Perivalvular)* Yes (N=91)	Yes (N=120)	*P* value
Procedural characteristics			
Pre-TAVR balloon valvuloplasty	37 (40.7)	42 (35.0)	0.49
Valve type			>0.99
Balloon-expandable	81 (89.0)	107 (89.2)	
Self-expandable	10 (11.0)	13 (10.8)	
Specific valve type			0.39
Sapien 3	81 (89.0)	107 (89.2)	
Evolut R	4 (4.4)	6 (5.0)	
CoreValve	1 (1.1)	0 (0.0)	
Evolut PRO	5 (5.5)	3 (2.5)	
Acurate Neo	0 (0.0)	4 (3.3)	
Valve size			0.35
20 mm	6 (6.6)	4 (3.4)	
23 mm	36 (39.6)	36 (30.0)	
25 mm	0 (0.0)	1 (0.8)	
26 mm	36 (39.6)	60 (50.0)	
29 mm	12 (13.2)	18 (15.0)	
31 mm	1 (1.1)	0 (0.0)	
34 mm	0 (0.0)	1 (0.8)	
Valve-in-valve procedure	0 (0.0)	4 (3.3)	0.21

Characteristics	Thrombosis at Any Aortic Valve Complex (Valvular and Perivalvular)* Yes (N=91)	Yes (N=120)	*P* value
Procedural characteristics			
Transfemoral approach	91 (100.0)	118 (98.3)	0.60
Type of anesthesia			0.42
General	19 (20.9)	32 (26.7)	
Monitored care	72 (79.1)	88 (73.3)	
Post-TAVR permanent pacemaker	8 (8.8)	16 (13.3)	0.42
Post-TAVR echocardiographic data			
Aortic valve area (cm^2)	1.53 ± 0.35	1.58 ± 0.37	0.42
Mean aortic valve gradient (mm Hg)	14.7 ± 5.1	13.4 ± 5.5	0.09
Left ventricular ejection fraction (%)	65.4 ± 8.9	64.0 ± 9.6	0.26
Paravalvular aortic regurgitation			>0.99
None or mild	88 (96.7)	117 (97.5)	
Moderate or severe	3 (3.3)	3 (2.5)	
Patient-Prosthesis Mismatch†			0.80
Moderate	16 (18.6)	23 (22.1)	
Severe	2 (2.3)	3 (2.9)	

Values are mean ± SD, n (%), or n/N (%).

Results

Characteristics	Univariate			Multivariable		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Thrombosis at Any Aortic Valve Complex						
Age	0.97	0.92–1.03	0.31	0.95	0.90–1.01	0.10
Male sex	0.57	0.33–1.00	0.05	1.18	0.55–2.54	0.66
Body-surface area per 0.01 increase	0.97	0.96–0.99	<0.01	0.98	0.96–1.00	0.05
STS PROM score per 1 increase	1.01	0.90–1.14	0.85	0.94	0.82–1.07	0.32
Creatinine clearance ≤50 ml/min	1.49	0.85–2.62	0.17	1.41	0.73–2.70	0.30
DAPT use	1.59	0.92–2.76	0.10	1.24	0.81-2.60	0.21
Procedural characteristics						
Self-expandable	1.22	0.50–3.02	0.66	1.24	0.46–3.37	0.67
Post-TAVR echocardiographic data						
Trans aortic valve peak velocity (m/sec) per 1.0 m/sec increase	1.86	1.03–3.34	0.04	1.28	0.64–2.58	0.48
Patient-prosthesis mismatch†	0.89	0.45–1.75	0.74			
CT parameter						
Valve level maximum diameter (mm) per 1.0 mm increase	0.80	0.70–0.91	<0.01	0.85	0.72–1.00	0.05

Results

Characteristics	Univariate			Multivariable		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Leaflet Thrombosis						
Age	1.03	0.95–1.11	0.43	1.01	0.93–1.10	0.83
Male sex	0.92	0.42–2.03	0.84	1.00	0.43–2.33	0.99
Body-surface area per 0.01 increase	0.99	0.97–1.01	0.43			
STS PROM score per 1 increase	1.00	0.84–1.18	0.96	0.94	0.76–1.16	0.55
Creatinine clearance ≤50 ml/min	3.10	1.40–6.86	<0.01	3.02	1.28–7.09	0.01
DAPT use	2.07	0.92–4.66	0.08	1.96	0.85–4.52	0.12
Procedural characteristics						
Self-expandable	2.06	0.69–6.13	0.19	1.73	0.56–5.37	0.34
Post-TAVR echocardiographic data						
Trans aortic valve peak velocity (m/sec) per 1.0 m/sec increase	0.79	0.36–1.78	0.57			
Patient-prosthesis mismatch†	0.73	0.26–2.03	0.54			
CT parameter						
Valve level maximum diameter (mm) per 1.0 mm increase	1.04	0.88–1.23	0.64			

Results

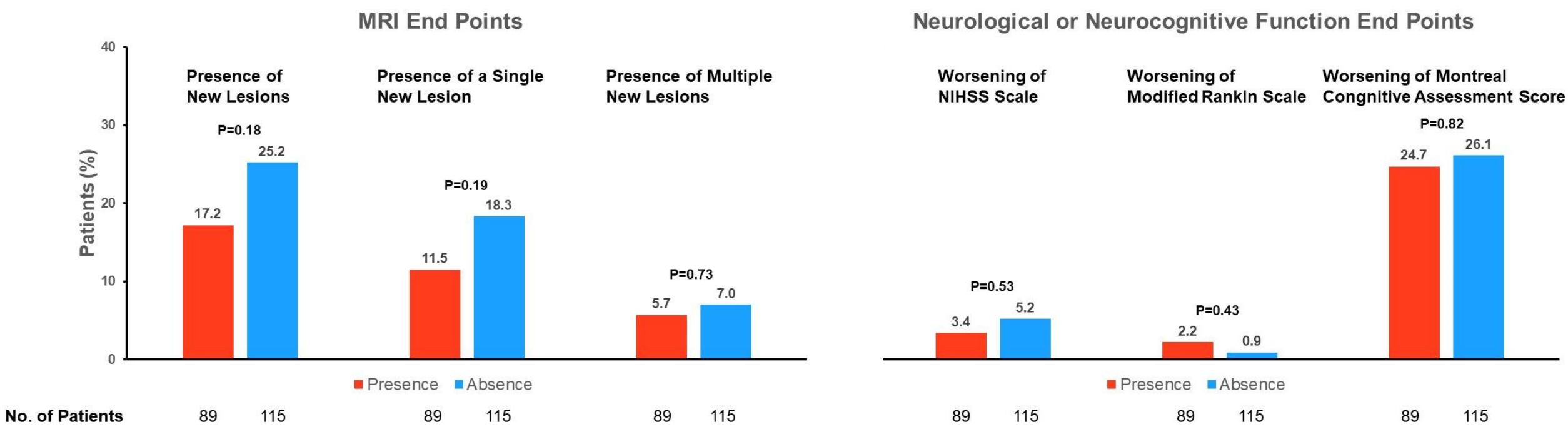
Characteristics	Univariate			Multivariable		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Perivalvular Thrombosis						
Age	0.97	0.92–1.02	0.26	0.95	0.90–1.01	0.11
Male sex	0.52	0.29–0.94	0.03	1.33	0.60–2.96	0.49
Body-surface area per 0.01 increase	0.97	0.95–0.99	<0.01	0.98	0.95–1.00	0.04
STS PROM score per 1 increase	1.02	0.91–1.15	0.69	0.95	0.83–1.09	0.47
Creatinine clearance ≤50 ml/min	1.14	0.64–2.04	0.65			
DAPT use	1.25	0.71–2.19	0.44	1.12	0.61–2.04	0.72
Procedural characteristics						
Self-expandable	1.32	0.53–3.28	0.56	1.57	0.57–4.32	0.39
Post-TAVR echocardiographic data						
Trans aortic valve peak velocity (m/sec) per 1.0 m/sec increase	2.21	1.20–4.09	0.01	1.43	0.69–2.96	0.33
Patient-prosthesis mismatch†	0.85	0.43–1.72	0.66			
CT parameter						
Valve level maximum diameter (mm) per 1.0 mm increase	0.75	0.66–0.86	<0.01	0.80	0.67–0.95	0.01

Results

Outcomes	Thrombosis at Any Aortic Valve Complex (Valvular and Perivalvular)*		OR	95% CI	*P* value
	Yes (N=91)	No (N=120)			
Brain MRI end points†					
Presence of new lesions — no./total.no (%)	15/89 (17.2)	29/115 (25.2)	0.62	0.31-1.24	0.18
Presence of a single new lesion — no./total.no (%)	10/89 (11.5)	21/115 (18.3)	0.58	0.26-1.31	0.19
Presence of multiple new lesion — no./total.no (%)	5/89 (5.7)	8/115 (7.0)	0.82	0.26-2.59	0.73
Number of total new lesions, median (IQR)	1 (1-3)	1 (1-2)	NA	NA	0.60
Total new lesion volume (mm^3), median (IQR)	40.2 (10.7-95.9)	31.6 (16.5-74.2)	NA	NA	0.62
Neurological and neurocognitive function‡					
NIHSS assessment — no./total.no (%)					
Worsening, any	3/89 (3.4)	6/115 (5.2)	0.63	0.15-2.61	0.53
Worsening with new cerebral lesions	1/89 (1.1)	2/115 (1.7)	0.64	0.06-7.20	0.72
Modified Rankin Scale — no./total.no (%)					
Worsening, any	2/89 (2.2)	1/115 (0.9)	2.62	0.23-29.4	0.43
Worsening with new cerebral lesions	1/89 (1.1)	0/115 (0.0)	NA	NA	>0.99
Montreal Cognitive Assessment — no./total.no (%)					
Worsening, any	22/89 (24.7)	30/115 (26.1)	0.93	0.49-1.76	0.82
Worsening with new cerebral lesions	4/89 (4.5)	6/115 (5.2)	0.85	0.23-3.13	0.81

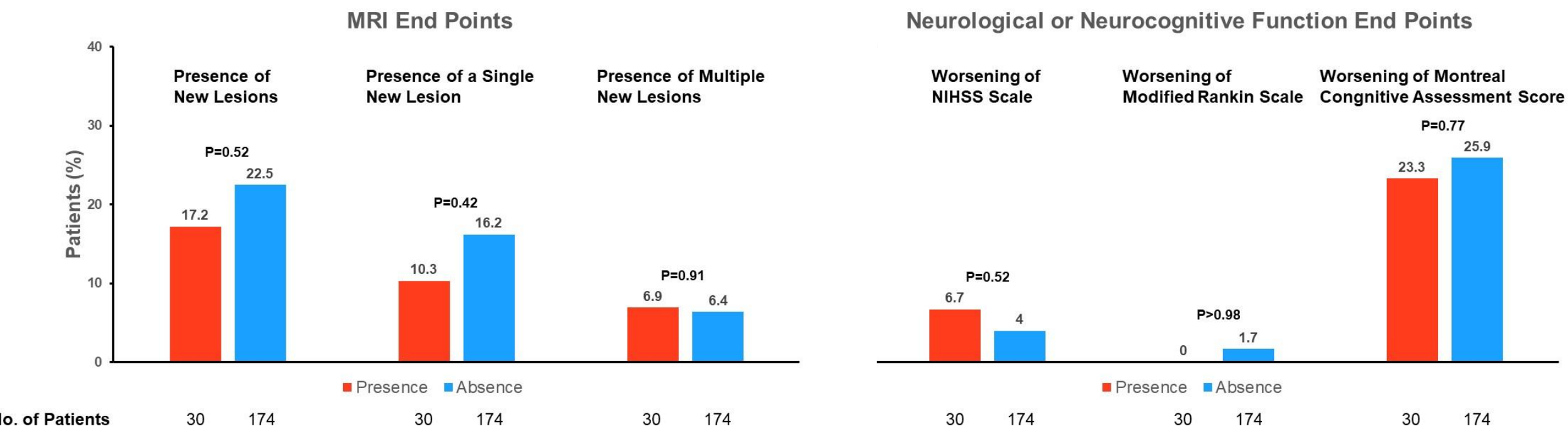
Results

- Brain MRI and Neurological Endpoint of Thrombosis at Any Aortic Valve Complex



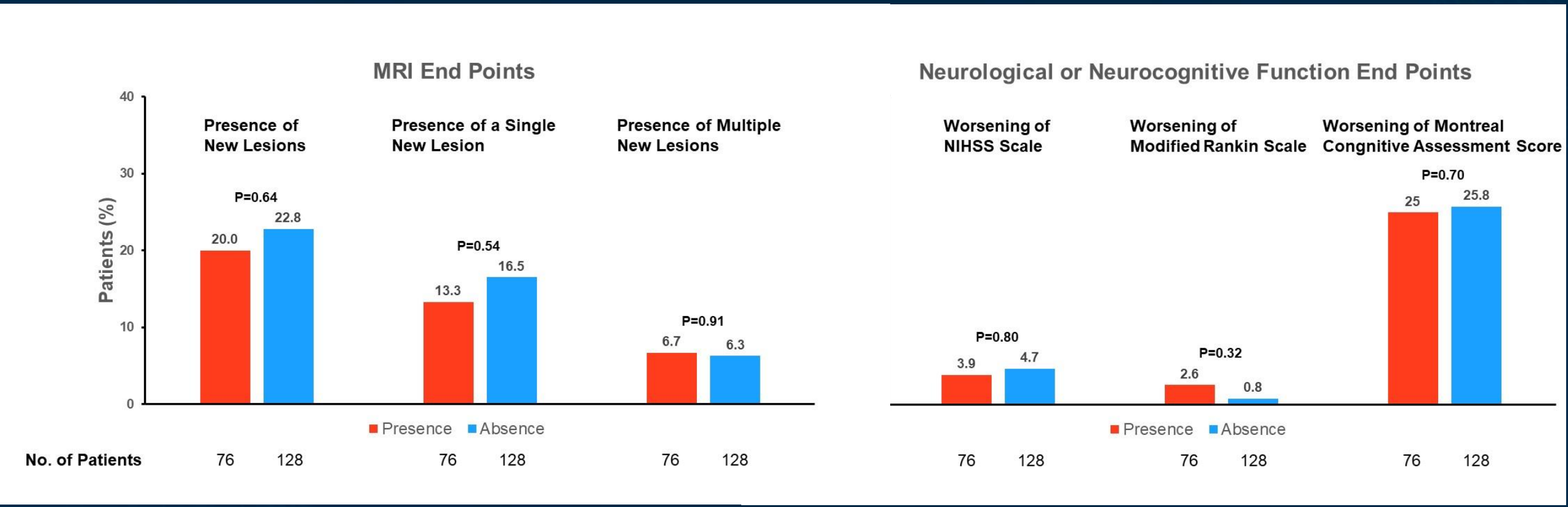
Results

- Brain MRI and Neurological Endpoint of Leaflet Thrombosis



Results

- Brain MRI and Neurological Endpoint of Perivalvular Thrombosis



Results

- Clinical Outcomes

	Thrombosis at Any Aortic Valve Complex (Valvular and Perivalvular)				
Risk factor	**Yes (N=91)**	**No (N=120)**	**OR**	**95% CI**	***P* value**
Clinical end points at 6 months					
Death	0/91 (0.0)	0/120 (0.0)	NA	NA	NA
Myocardial infarction	1/91 (1.1)	3/120(2.5)	0.43	0.02-3.45	0.47
Stroke	0/91 (0.0)	3/120 (2.5)	NA	NA	>0.99
Systemic thromboembolic event	0/91 (0.0)	1/120 (0.8)	NA	NA	>0.99
Bleeding event	11/91 (12.1)	12/120 (10.0)	1.24	0.51-2.96	0.63
Rehospitalization according to VARC-3 criteria	8/91 (8.8)	16/120 (13.3)	0.63	0.24-1.50)	0.31

Discussion

- Overall percentages of patients with thrombosis
  - Aortic valve complex 43.1 %
  - Valvular 14.2% Perivalvular 37.0%

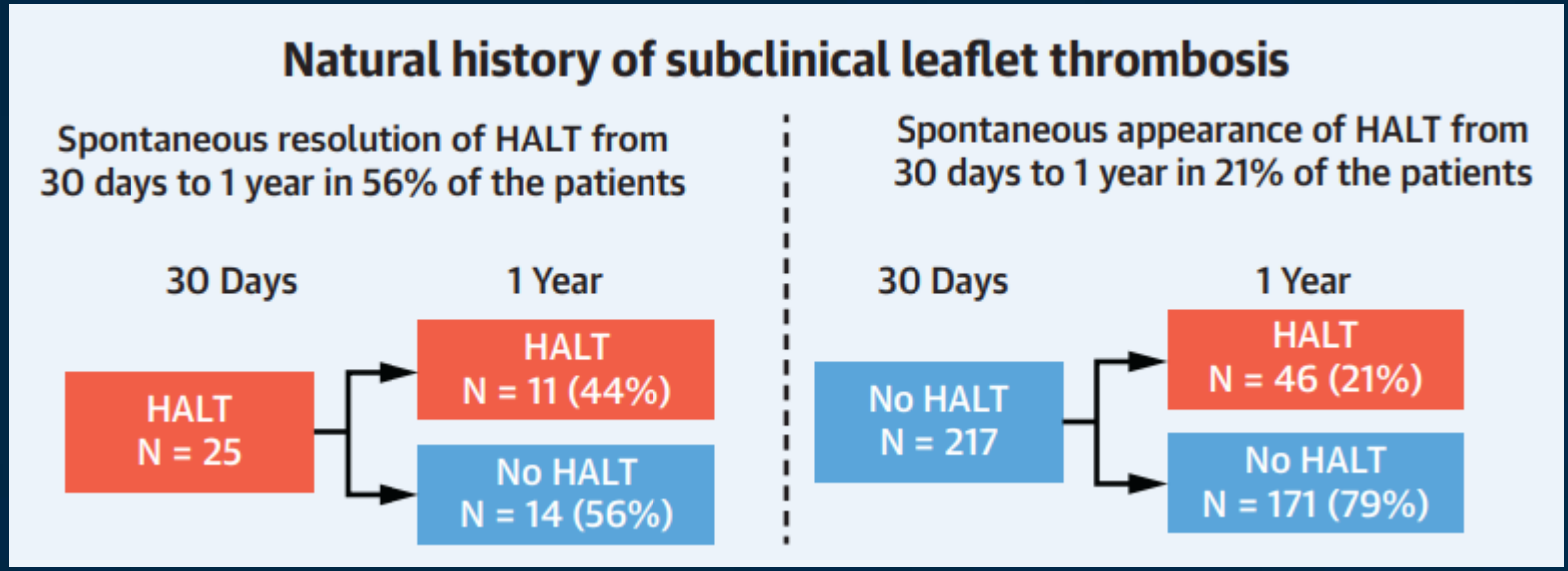
- Predictors of aortic valve thrombosis
  - Smaller body-surface area
  - Reduced renal function
  - Small post-TAVR aortic valve area

Discussion

- Overall percentages of patients with thrombosis
  - Reduced leaflet motion was noted on CT in 22 of 55 patients (40%) in the clinical trial and in 17 of 132 patients (13%) in the two registries.
  - 106 (12%) of 890 patients had subclinical leaflet thrombosis

R.R. Makkar et al. N Engl J Med 2015;373:2015-24.

Chakravarty T et al. Lancet 2017;389:2383-2392.

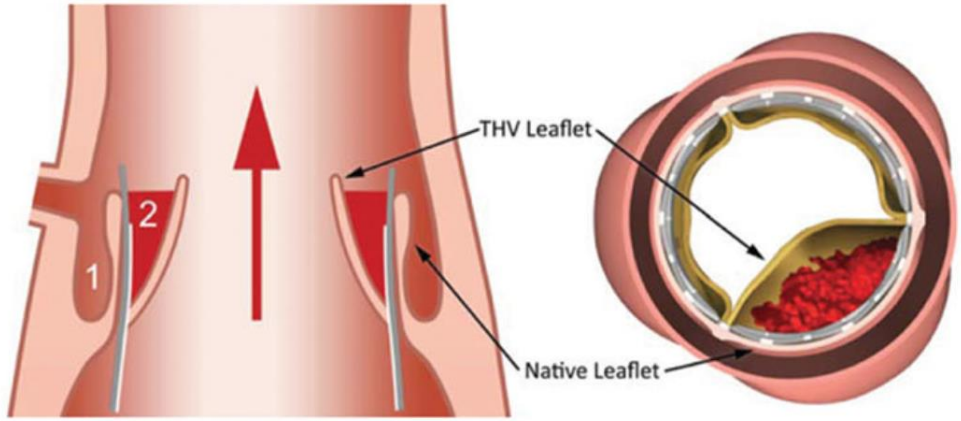


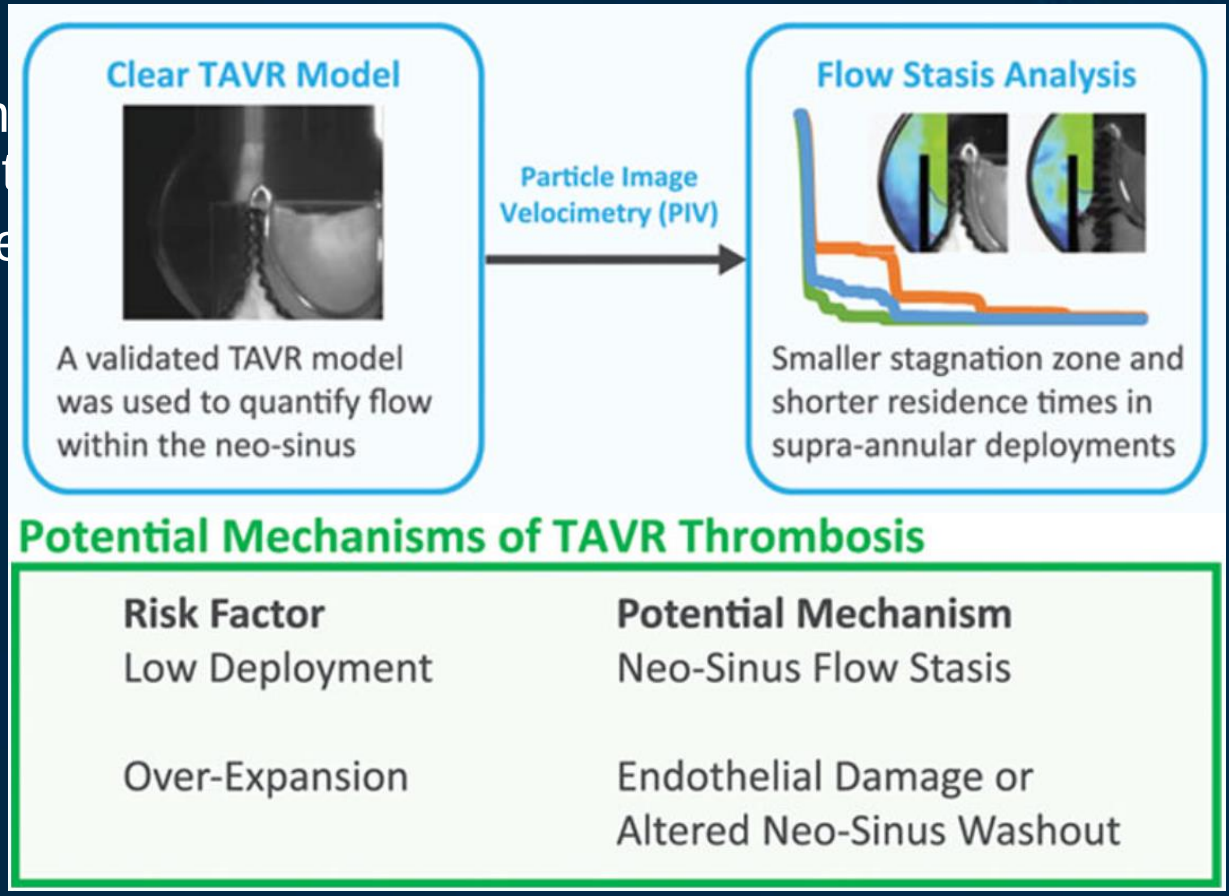
Raj R. Makkar et al. J Am Coll Cardiol. 2020 Jun 23;75(24):3003-3015.

Discussion

- Overall percentages of patients with thrombosis

Transcatheter aortic valves divide the aortic sinus into two spaces: a diminished native sinus (1) and a **neo-sinus** (2). The neo-sinus is a region between the native and transcatheter aortic valve leaflets where thrombus has been observed.

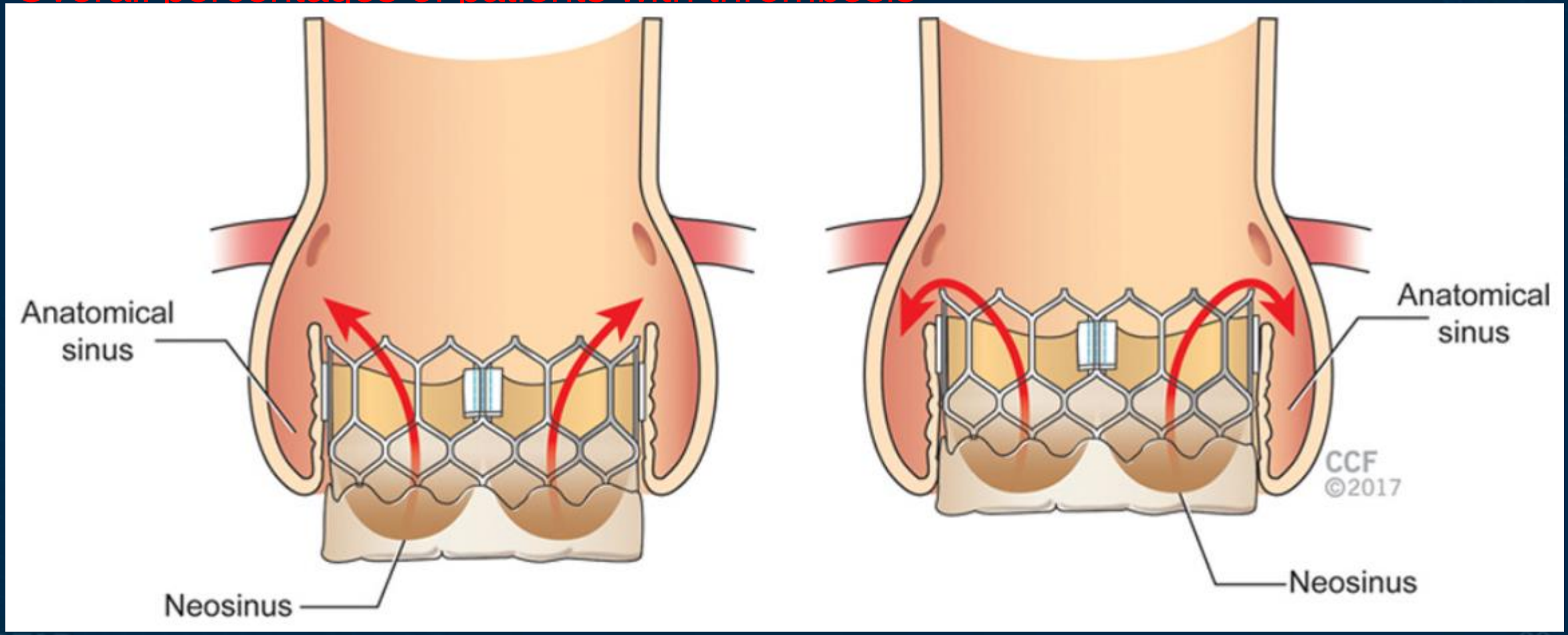




Midha PA et al. Circulation 2017;136:1598-1609.

Discussion

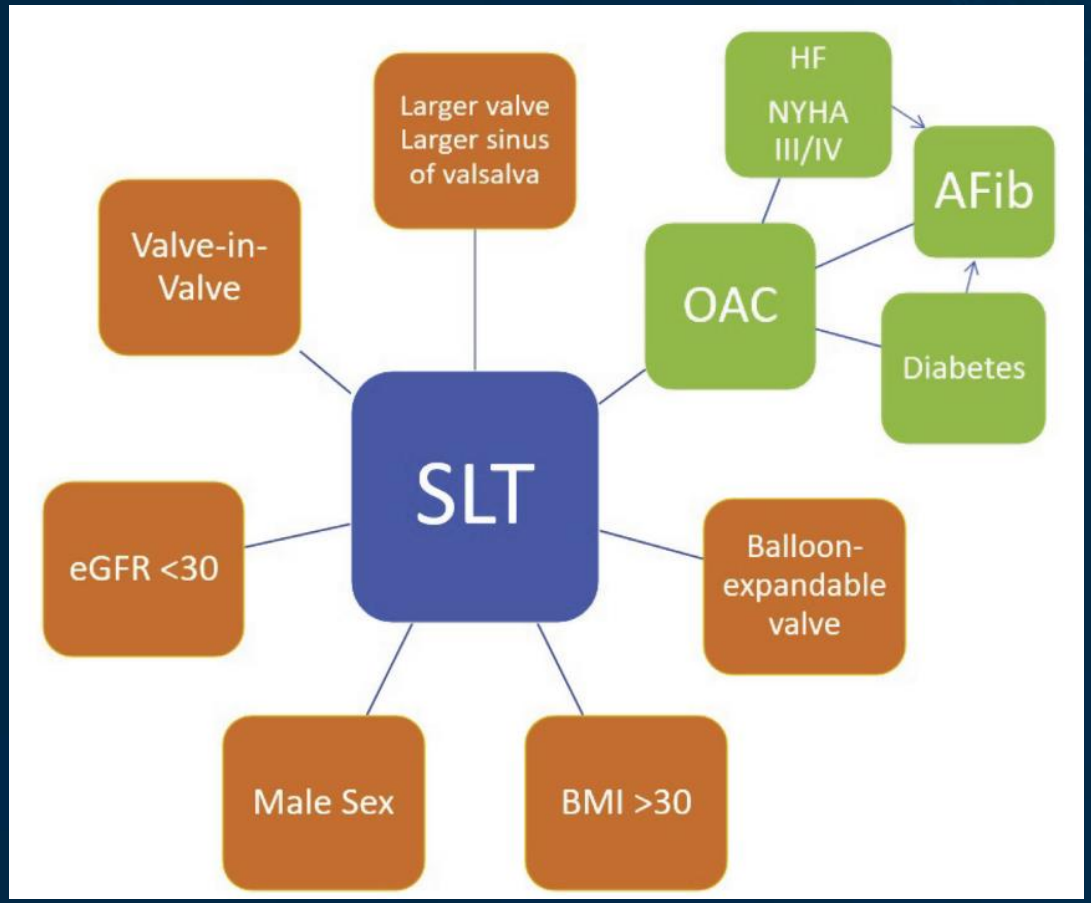
- Overall percentages of patients with thrombosis



Samir Kapadia et al. Circulation. 2017 Oct 24;137(17):1610-1612.

Discussion

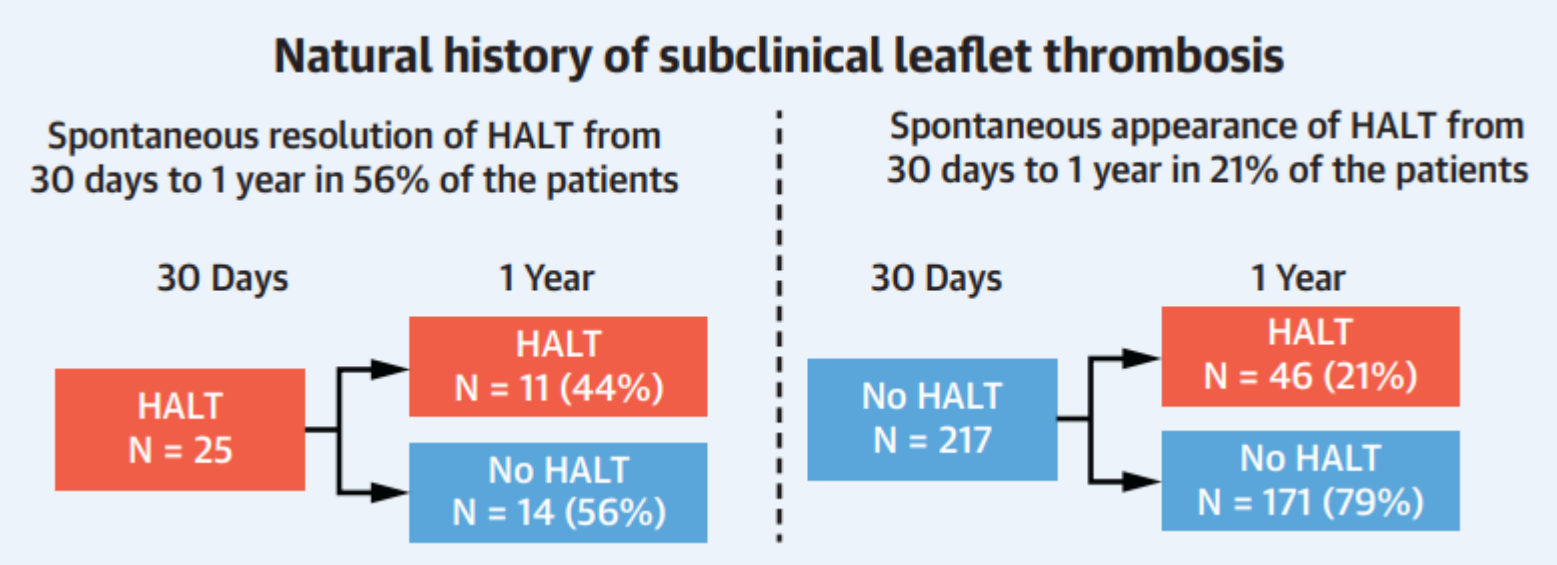
- Predictors of aortic valve thrombosis
  - Smaller body-surface area
  - Reduced renal function
  - Small post-TAVR aortic valve area



Matthias Bogyi et al. JACC Cardiovasc interv. 2021 Dec 27;14(24):2643-2656.

Discussion

- Presence of aortic valve complex thrombosis



- No difference in aortic valve mean gradients between patients with or without HALT at 30 days or 1 year
- Increased aortic valve gradients in patients with increasing severity of HALT; and in patients with persistent HALT at 30 days and 1 year
- Increased rates of clinical valve thrombosis and composite endpoint of stroke/transient ischemic attack/thromboembolic complications in patients with HALT

Raj R. Makkar et al. J Am Coll Cardiol. 2020 Jun 23;75(24):3003-3015.

Discussion

- Presence of aortic valve complex thrombosis

➢ was not associated with new cerebral thromboembolism on brain MRI
with new neurological or neurocognitive dysfunction
with clinical outcomes

Discussion

- Limitation
  - Small sample size to allow for a sufficient correlation of imaging with events
  - Relatively short follow-up period (6 months)
  - CT imaging was performed at specific times after TAVR
  - Not necessarily representative of an unselected population
  - Did not study the long-term effect on valve durability

Conclusion

- Observed incidences of thrombosis at any aortic valve complex, valular and perivalvular area were very common.
- However, advanced imaging-detected aortic valve complex thrombosis was not associated with new cerebral thromboembolism on brain MRI, new neurological or neurocognitive dysfunction, clinical outcomes.
- The long-term impact of such aortic valve complex thrombosis on structural valve degeneration and durability of transcatheter bioprosthetic valves needs to be assessed in larger studies with long-term follow-up.