TAVR Durability
: Leaflet Thrombosis and HALT
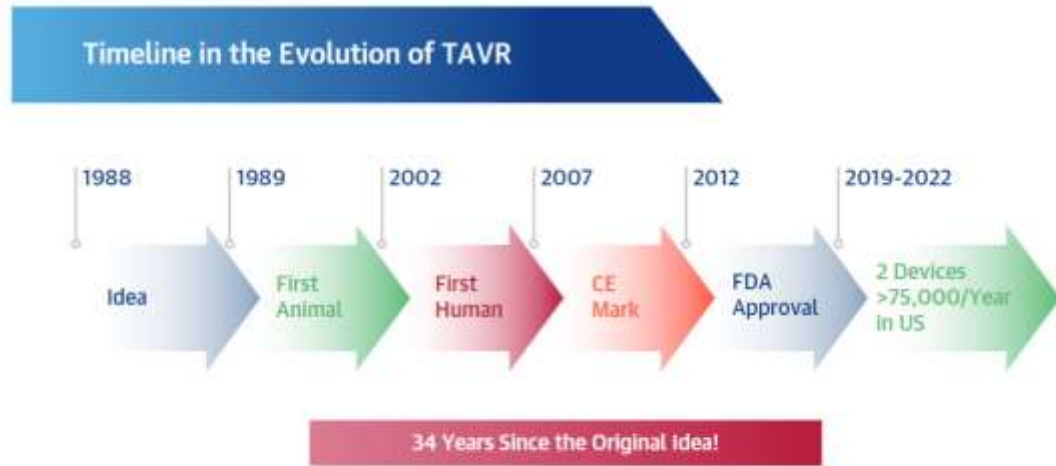
Jeehoon Kang

Cardiovascular Center,

Seoul National University Hospital, Korea

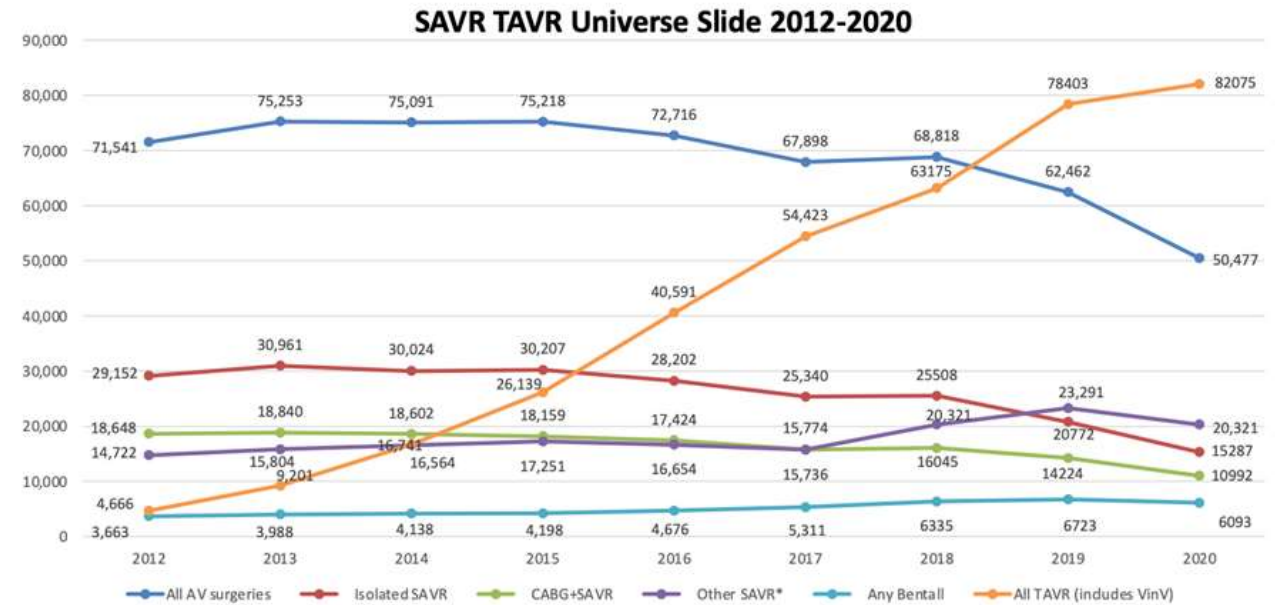# Current trend of TAVI

- During a >30 years evolution, rapid(?) increase of TAVI
- To lower risk/younger age patients.

Carroll et al. STS-ACC TVT Registry of Transcatheter Aortic Valve Replacement, JACC 2020

Expanding indications of TAVI

Expanding Indications of TAVI
- New generation devices
- Less complications

NOTION All Comer PARTNER 3 CoreValve Low Risk	PARTNER 2A PARTNER S3i SURTAVI	PARTNER 1A	PARTNER 1B
Low STS <4%	**Intermediate** STS 4-10%	**High** STS 10-15%	**Extreme** STS >15% / **Futile**

Operable — Inoperable

Expansion in the metrics of *'what matters?'*

PROCEDURAL SUCCESS METRICS

Higher risk + **Lower Risk**

LIFETIME MANAGEMENT METRICS

Mortality & Stroke
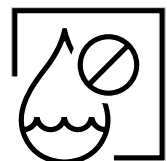
Quality of Life

Conduction Disturbance (PPI)

AGE

| 80+ | 65+, CAD |

ANATOMY

| Tri-leaflet | More Bicuspid |

ACTIVITY

| Low | High(er) |
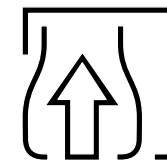
Hemodynamics & PPM
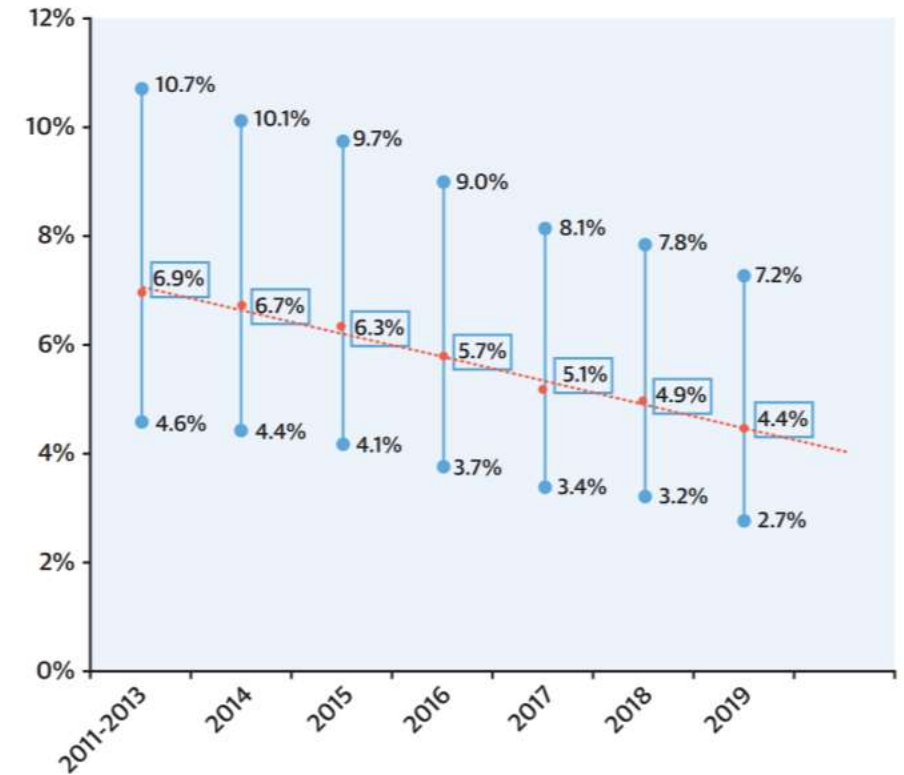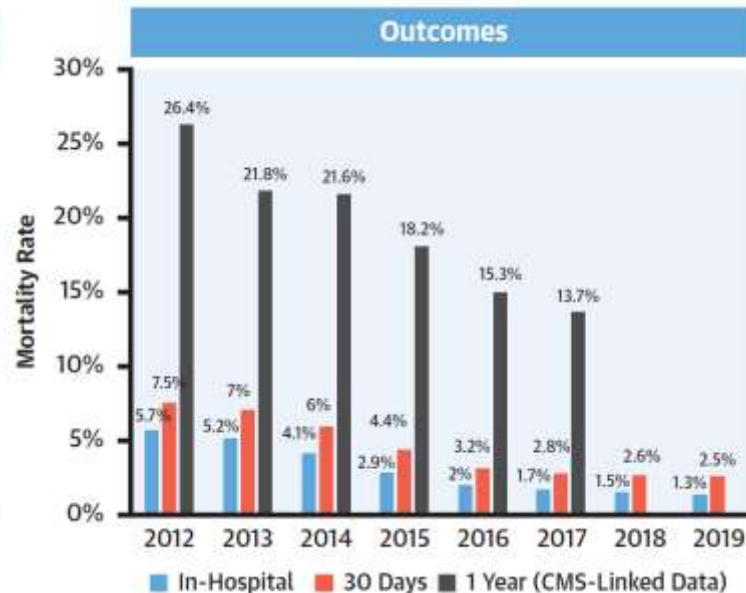
Durability < Life Expectancy

Coronary Access (PCI) & TAV-in-TAV

Changing Risk Profile in the STS TVR Registry

- The median age was reduced from **84 years** (IQR: 78, 88 years) in 2013 or earlier to **80 years** (IQR: 73, 85 years) in 2019.

- AND, is expected that the median age will continue to decline more lower risk patients are treated with TAVI.

- *"Young", low risk patients*

Long-term valve durability

- **Long-term valve durability includes..**
  - Hemodynamic Valve Deterioration
  - Bioprosthetic Valve Dysfunction
  - *Thrombosis* & Endocarditis

Hemodynamic valve deterioration is defined as a rising gradient after the aortic valve replacement suggesting valve degeneration[1]
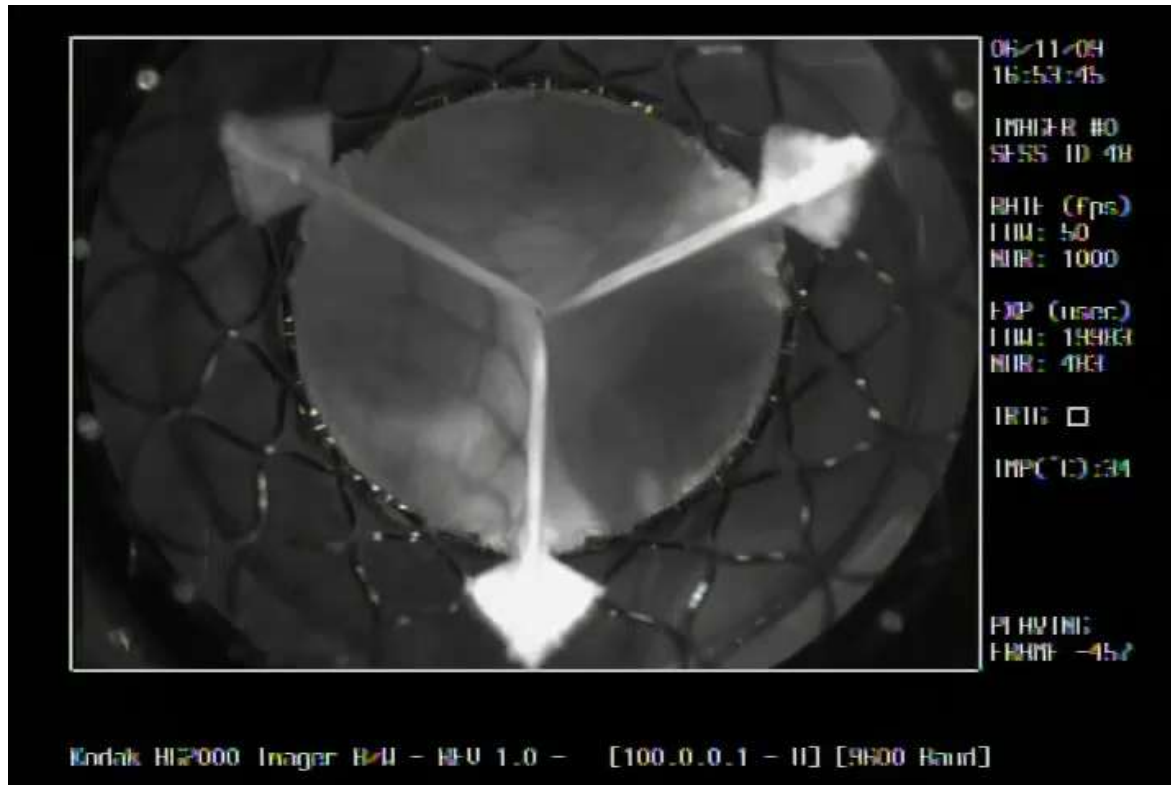
Impact of HVD on Outcomes

No HVD	119	111	101	79	40
HVD	18	7	6	4	4

Salaun E, et al. JACC. 2018;72:241-251.
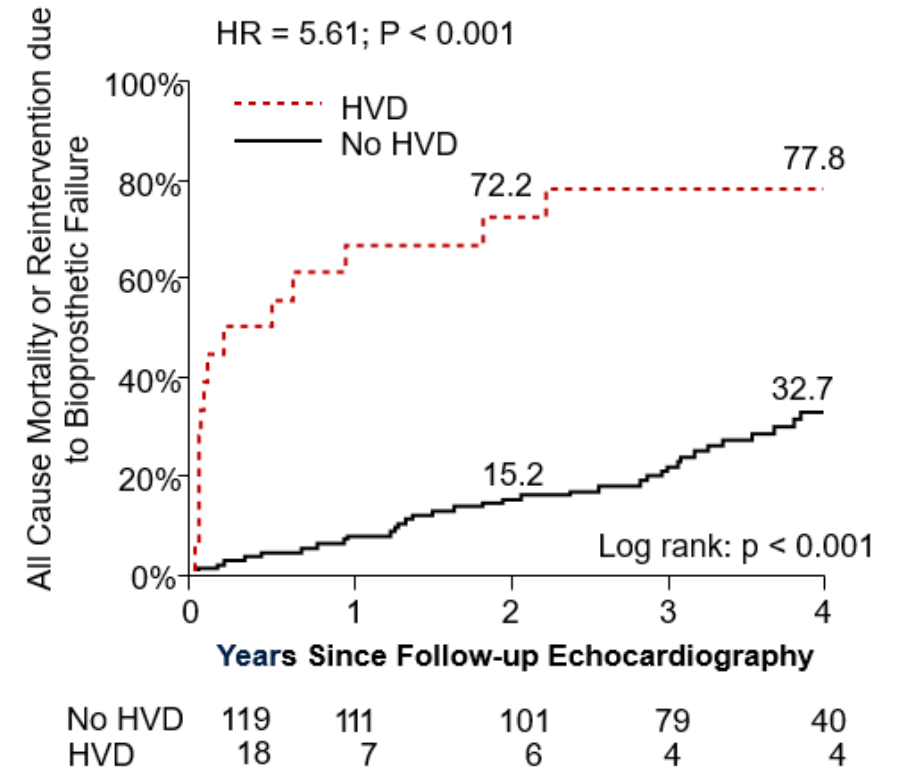
Thrombosis

✓ **What is a Clinical Thrombosis?**
 ✓ "Any thrombus attached to or near an implanted valve that occludes part of the **blood flow path**, interferes with **valve function**, or is sufficiently large to **warrant treatment**" (**VARC-2 definitions**)

✓ *Presentation*
 ✓ Suddenly elevated gradients and symptoms such as shortness of breath
 ✓ Prevalence of clinical leaflet thrombosis reported in bioprosthetic valves has been low (<1% - 3%)
 ✓ Minimizing risk of thrombosis will be increasingly important as TAVI reaches younger, healthier patients with longer life expectancies

	Study	Patients	Clinical leaflet thrombosis
TAVI	Latib et al. 2015	n =4266	0.61%
	Jose et al. 2017	n=642	2.8%
	Franzone et al. 2018	n=1396	0.71%
	Hansson et al. 2018	n=246	2.0%
	Mack, presented at ACC 2020	n=496	2.6%
SAVR	Brown et al. 2012	N=4,568	0.18%
	Egbe et al. 2015	N=3,843	0.57%
	Mack, presented at ACC 2020	n=454	0.7%

Thrombosis

- **Thrombosis in previous trials**
  - ✓ Long-term results from the CHOICE trial: Comparison of THV in **High Risk Patients** with Severe AS

5-Year Outcomes After TAVR With Balloon-Expandable Versus Self-Expanding Valves

Results From the CHOICE Randomized Clinical Trial

TABLE 1 Clinical Outcome at 5 Years

	Balloon-Expandable Valve (n = 121)	Self-Expanding Valve (n = 120)	p Value
Death			
From any cause	63 (53.4)	54 (47.6)	0.38
From cardiovascular causes	37 (31.6)	25 (21.5)	0.12
Stroke	21 (17.5)	19 (16.5)	0.73
Repeat hospitalization for heart failure	30 (28.9)	26 (22.5)	0.75
Myocardial infarction	2 (1.6)	7 (6.1)	0.08
Bleeding			
Life threatening	21 (17.3)	18 (16.2)	0.77
Major	28 (26.3)	20 (22.0)	0.26
Minor	17 (14.3)	12 (10.4)	0.37
Vascular complications			
Major	14 (11.6)	14 (12.1)	0.89
Minor	5 (4.2)	3 (2.6)	0.51
New pacemaker*	28 (25.4)	40 (40.4)	0.01

TABLE 2 Echocardiographic Follow-Up at 5 Years

	Balloon-Expandable Valve (n = 36)	Self-Expanding Valve (n = 41)	p Value
Effective orifice area, cm^2	1.6 ± 0.5	1.9 ± 0.5	0.02
Number of patients	39	45	
Mean gradient, mm Hg	12.2 ± 8.7	6.9 ± 2.7	0.001
Number of patients	47	52	
Transvalvular aortic regurgitation			0.62
None/trace	46 (97.9)	49 (94.2)	
Mild	1 (2.1)	3 (5.8)	
Moderate	0 (0.0)	0 (0.0)	
Severe	0 (0.0)	0 (0.0)	
Number of patients	47	52	
Paravalvular aortic regurgitation			0.69
None/trace	28 (59.6)	28 (53.8)	
Mild	19 (40.4)	24 (46.2)	
Moderate	0 (0.0)	0 (0.0)	
Severe	0 (0.0)	0 (0.0)	
Number of patients	47	52	
Total aortic regurgitation			0.42
None/trace	27 (57.4)	25 (48.1)	
Mild	20 (42.6)	27 (51.9)	
Moderate	0 (0.0)	0 (0.0)	
Severe	0 (0.0)	0 (0.0)	
Left ventricular ejection fraction, %	54.4 ± 10.2	57.2 ± 8.4	0.15
Left ventricular end-systolic dimension, mm	34.4 ± 12.0	29.1 ± 6.7	0.02
Left ventricular end-diastolic dimension, mm	45.5 ± 7.7	41.7 ± 6.8	0.02
Systolic pulmonary artery pressure, mm Hg	30.9 ± 12.0	29.0 ± 12.7	0.49
Moderate/severe mitral regurgitation	15/47 (31.9)	9/48 (18.7)	0.13
Moderate/severe tricuspid regurgitation	10/45 (22.2)	13/47 (27.6)	0.54

TABLE 3 BVD and Its Components Through 5 Years

	Balloon-Expandable Valve (n = 121)	Self-Expanding Valve (n = 120)	p Value
Bioprosthetic valve dysfunction	28 (22.5)	26 (20.9)	0.91
Components			
SVD	6 (6.6)	0 (0.0)	0.018
Moderate SVD	4 (5.6)	0 (0.0)	0.047
Severe SVD	2 (0.9)	0 (0.0)	0.20
NSVD	17 (17.8)	23 (26.7)	0.20
Moderate/severe PPM	14 (15.9)	13 (16.0)	1.0
Moderate/severe PVL	3 (2.5)	10 (8.5)	0.08
Valve thrombosis	6 (7.3)	1 (0.8)	0.06
Endocarditis	2 (1.6)	4 (3.4)	0.39

- Forward flow hemodynamics were significantly better with the SE valve. Structural valve deterioration was uncommon but occurred more frequently with the BE valve

Abdel-Wahab et al., J Am Coll Cardiol Intv 2020;13:1071–82

Thrombosis

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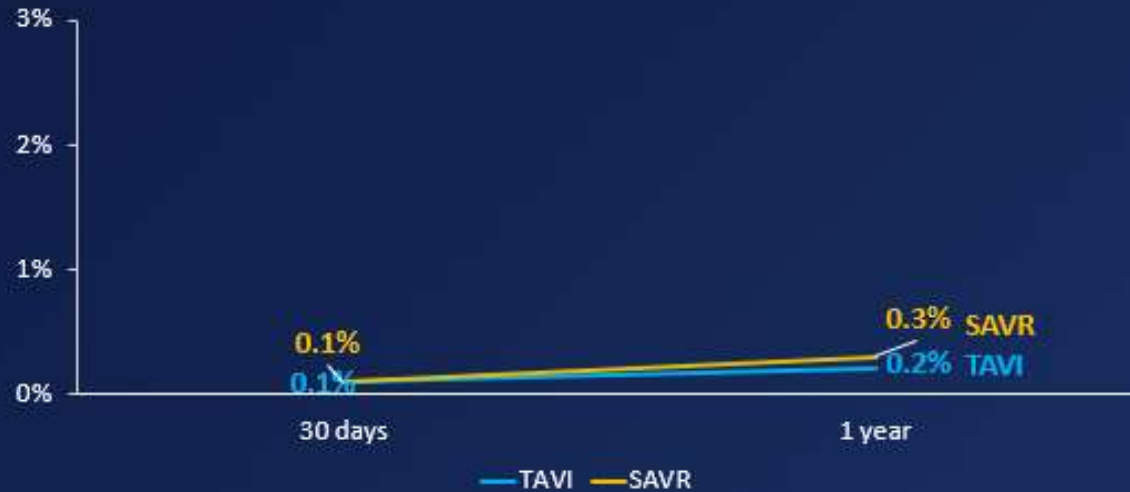
Abdel-Wahab et al., J Am Coll Cardiol Intv 2020;13:1071–82

Thrombosis

- **Thrombosis in previous trials**
  - Obstructive thrombosis or other valve dysfunction secondary to thrombosis appears infrequent in TAVR and SAVR, but may be underreported
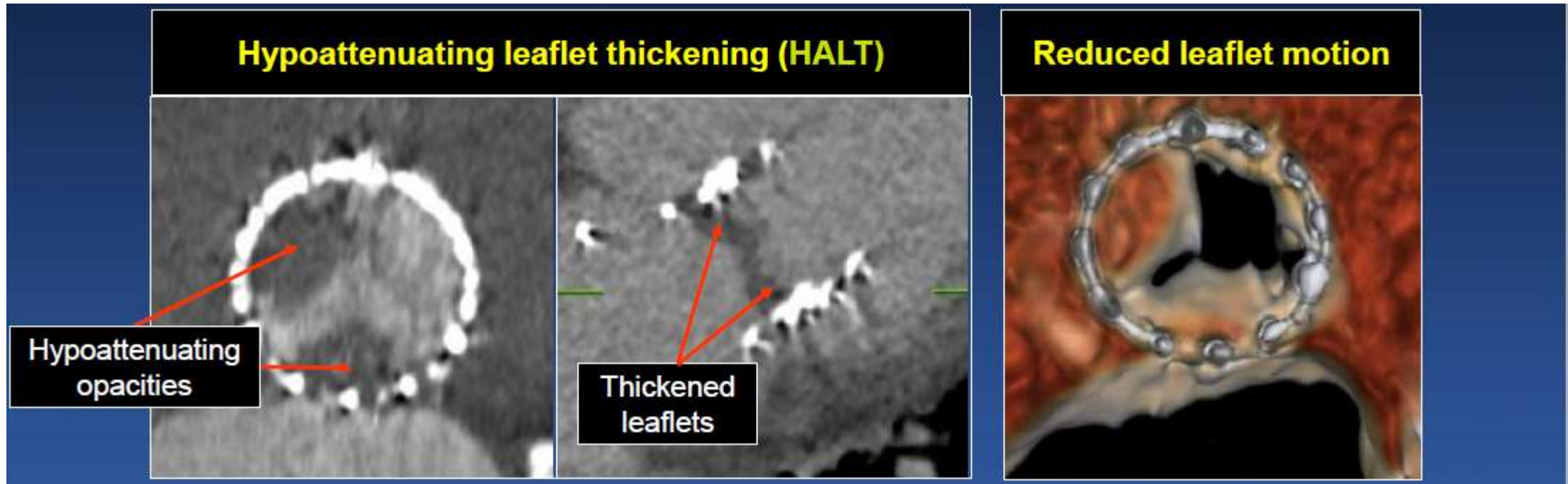
Thrombosis: Early detection or subclinical

- **Early detection for thrombosis ?**
  - *Subclinical Leaflet Thrombosis characterized by **hypoattenuated leaflet thickening (HALT) and reduced leaflet motion** has been frequently observed in transcatheter and surgical aortic bioprosthetic valves.*

Makkar R. et al. NEJM 2015

Thrombosis: subclinical

- **Prevalence of Subclinical Thrombosis in the Literature**

Study	Subclinical thrombosis rates		Definition of subclinical thrombosis	Median timing of CT assessment post-TAVI	Valve type
Yanagisawa et al. 2019	**9.3%**	N=485	HALT extending >3 mm on the leaflet on 2D CT + evidence of RELM	3 days (0-30 range)	Sapien 3, Sapien XT, CoreValve
Jiminez et al. 2019	**35% HALT** **15.3% HAM**	N=85	HALT assessed in diastole in 2 reconstructed planes HAM defined as HALT with >50% RELM	114 days (IQR 65–205)	Sapien 3, Sapien XT, CoreValve, Evolut R
Tang et al. 2019	**9.1%**	N=287	HALT with or without RELM of 1 or more leaflets identifiable in at least 2 reconstructed planes and time intervals	At discharge or at 30 days	Sapien XT, Sapien 3, CoreValve, Evolut R, Evolut Pro
Chakravarty et al. 2017	**13%**	N=752	>50% RELM of at least 1 leaflet on 4D CT (all patients with RELM also had HALT)	58 days (IQR 32–236 days)	Sapien XT, Corevalve, Lotus, Protico, Centera
Ruile et al. 2018	**15.9%**	n=754	HALT with or without RELM in 1-2 leaflets on CT	5 days (IQR 3-6)	Sapien 3, Sapien XT, CoreValve, Evolut R, Lotus, Portico, Symetis, Jena Valve
Pache et al. 2016	**10.3%**	N=156	HALT with or without RELM of 1 or more leaflets on CT	5 days (IQR 5-6)	Sapien 3
Vollema et al. 2017	**12.5%**	N=128	HALT and/or RELM of one or more transcatheter valve leaflets	35 days (IQR 19-210)	Sapien, Sapien XT
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Yanagisawa et al. Circ Cardiovasc Interv. 2019; Tang et al. Am J Cardiol 2019; Jiminez et al. J Clin Med 2019; Chakravarty *et al,* Lancet 2017;
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Thrombosis: subclinical

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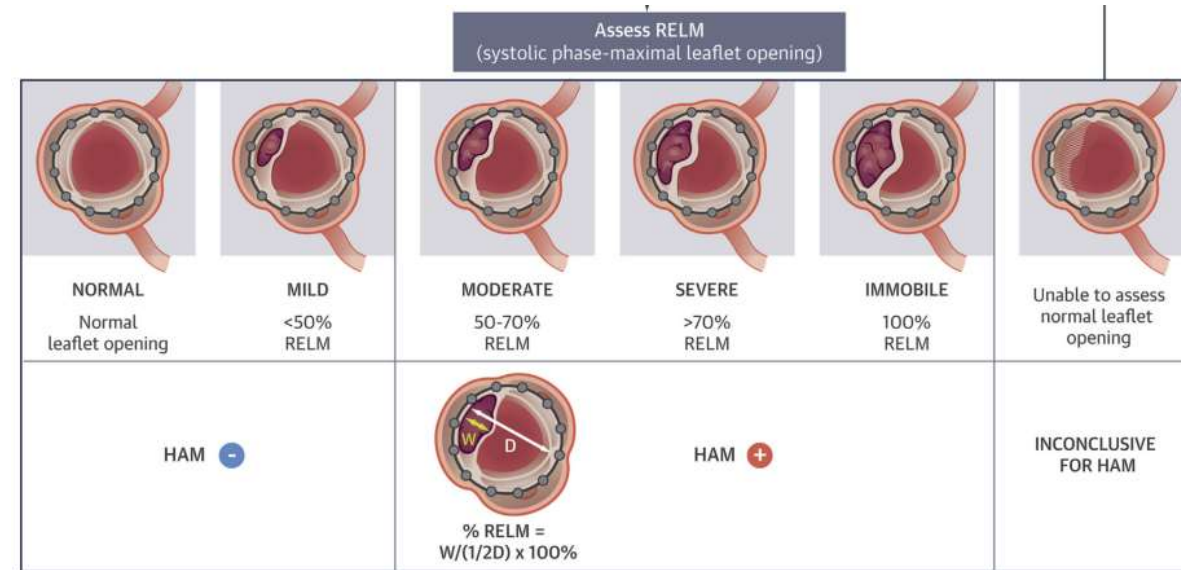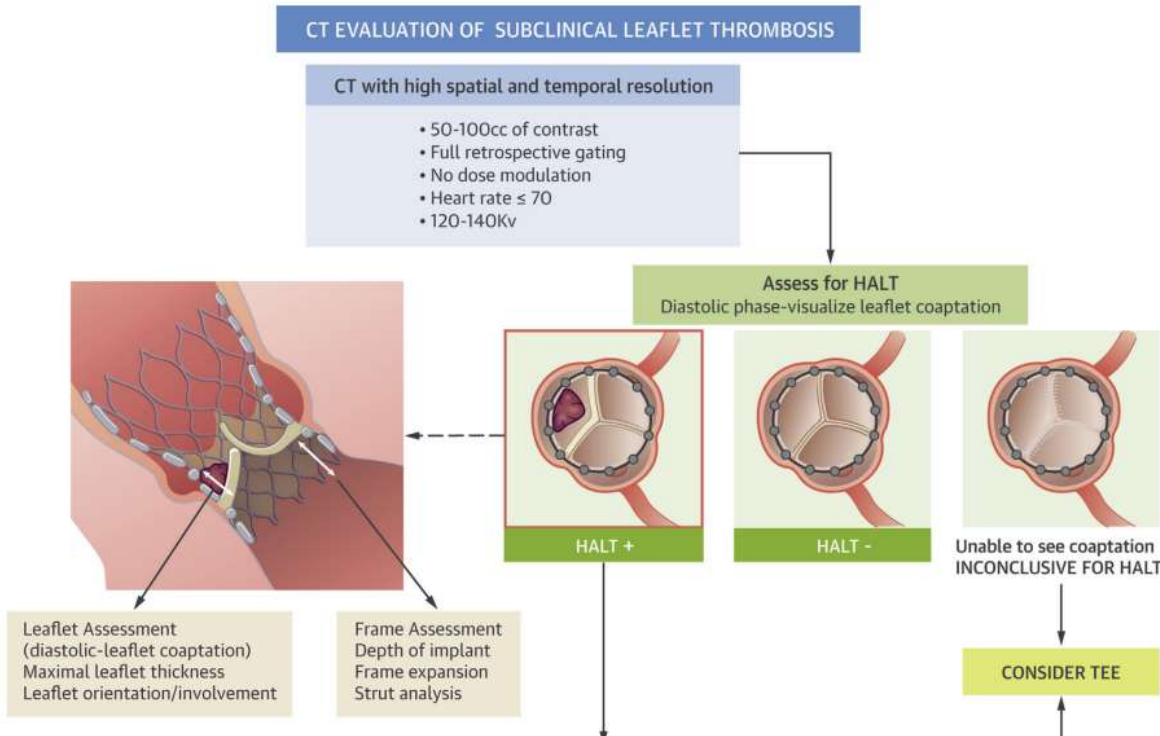| Study	Subclinical thrombosis rates		Definition of subclinical thrombosis	Median timing of CT assessment post-TAVI	Valve type
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Definitions of subclinical thrombosis (HALT vs RELM vs HAM, etc.) and the timing of CT vary across studies, and are important to consider when evaluating the literature.

Yanagisawa et al. Circ Cardiovasc Interv. 2019; Tang et al. Am J Cardiol 2019; Jiminez et al. J Clin Med 2019; Chakravarty *et al,* Lancet 2017; Ruile et al. JACC Cardiovasc Interv 2018; Pache et al. Eur Heart J 2016; Vollema et al. Eur Heart J 2017; Yanagisawa et al. JACC Img 2017;

Subclinical Thrombosis

- **Classification of Subclinical Thrombosis**
    - *Hypoattenuated leaflet thickening (HALT)*
    - *Reduced leaflet motion (RELM)*
    - *Hypoattenuation affecting motion (HAM): when leaflet thickening and reduced motion are present*
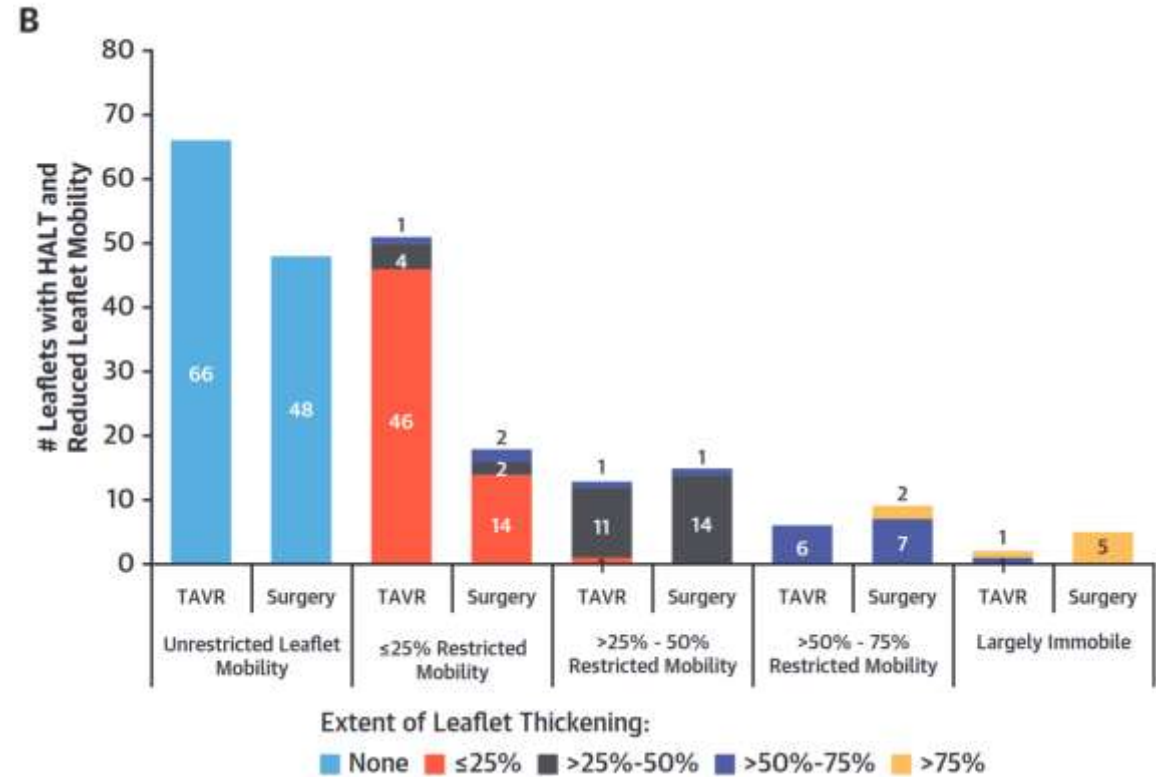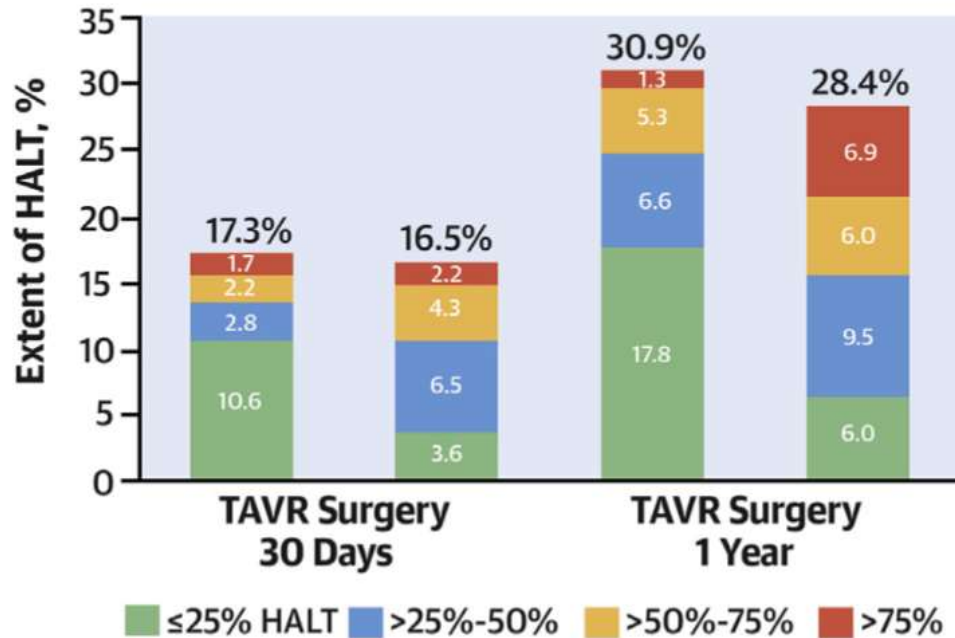

Jilaihawi, et al. J Am Coll Cardiol Img 2017;10:461–70.

Subclinical Thrombosis : TAVI vs. SAVR

- **Leaflet Thrombosis in Low-Risk Patients: Evolut Low Risk CT Substudy**

Bioprosthetic Aortic Valve Leaflet Thickening in the Evolut Low Risk Sub-Study

Philipp Blanke, MD,[a] Jonathon A. Leipsic, MD,[a] Jeffrey J. Popma, MD,[b] Steven J. Yakubov, MD,[c]
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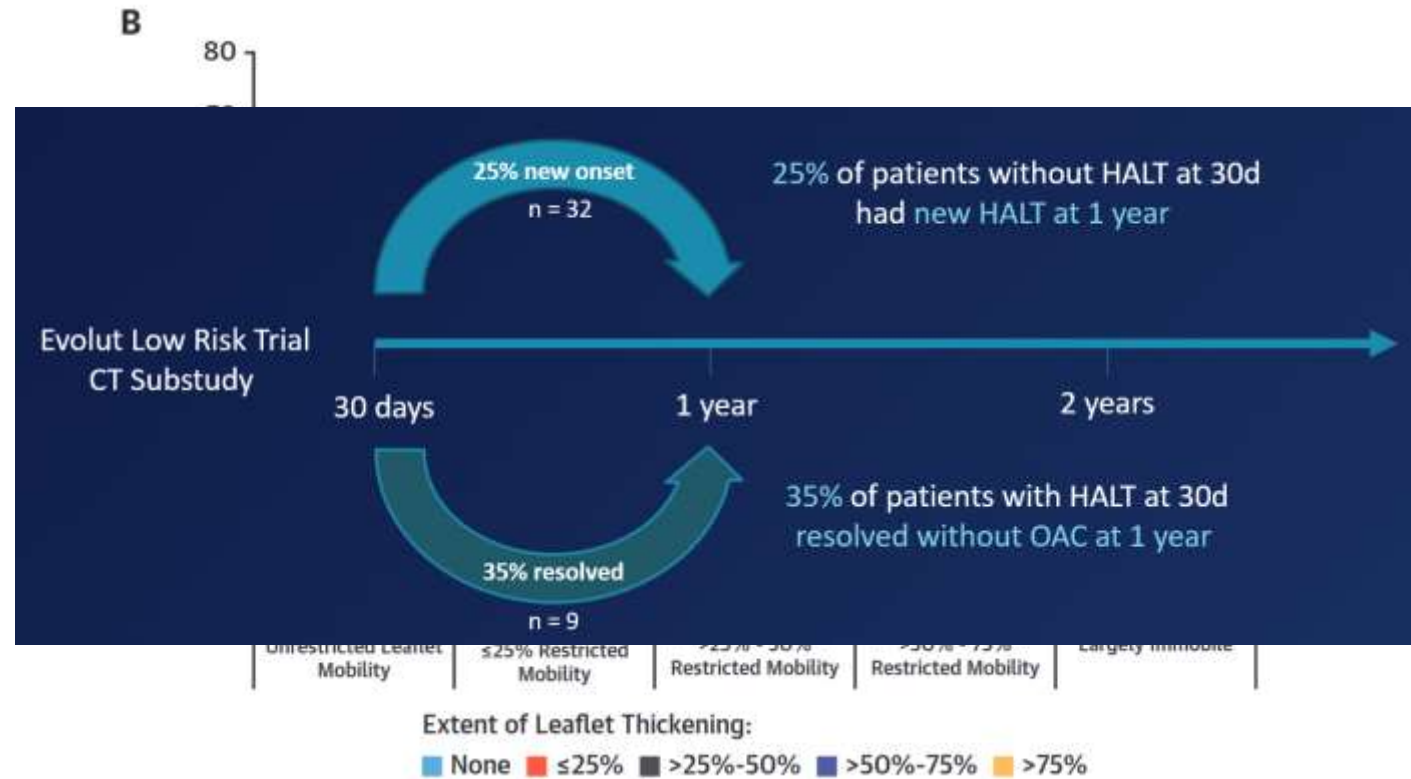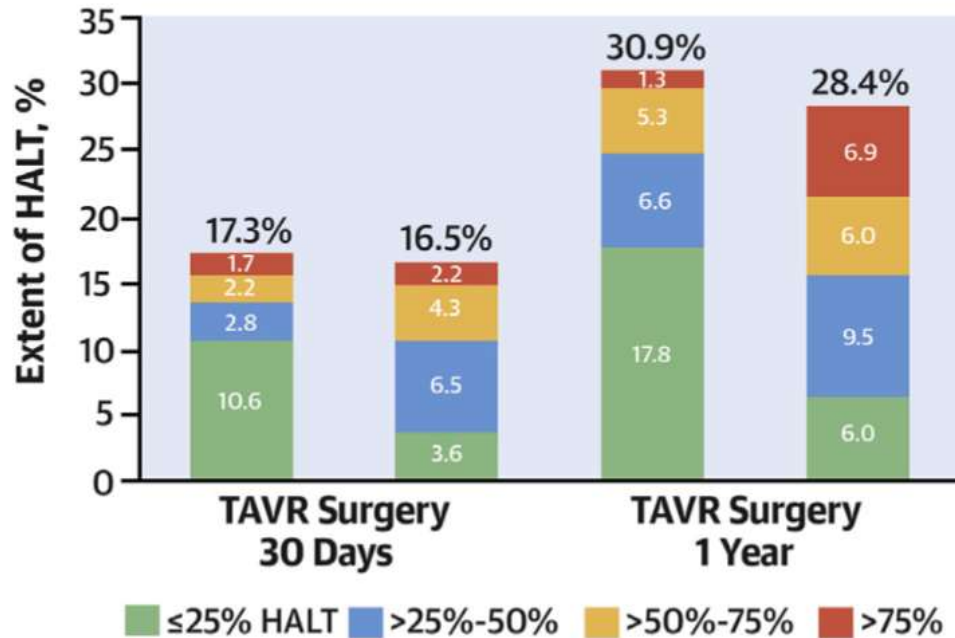
Blanke, P. et al. J Am Coll Cardiol. 2020;75(19):2430–4.

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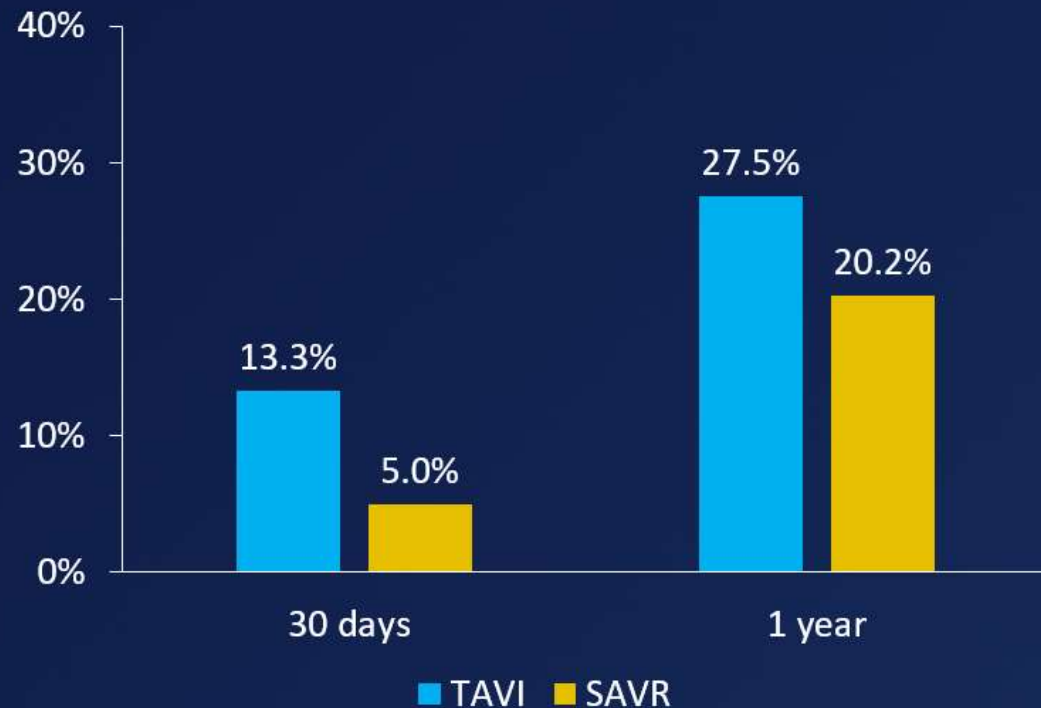
Subclinical Thrombosis : TAVI vs. SAVR

- **Leaflet Thrombosis in Low-Risk Patients: PARTNER3 CT Substudy**

Results from the PARTNER 3 substudy on leaflet thrombosis yielded a significantly higher rate of HALT in the TAVR cohort compared to SAVR at 30 days, however rates at 1 year were not significantly different between both groups.

Full results from the PARTNER 3 CT Substudy have not yet been published in full.

Any HALT

	30 days	1 year
TAVI	13.3%	27.5%
SAVR	5.0%	20.2%

Patients with 3 Leaflets affected by HALT

	30 days	1 year
TAVI	9.1%	11.9%
SAVR	0%	0%

Makkar. Presented at TCT 2019

Predicting Subclinical Thrombosis

- **Predictors of HALT and clinical thrombosis?**

  - **Causes of leaflet thickening and clinical thrombosis are likely multifactorial**

  - **A single-center study of 642 patients[1] found the following predictors of clinical thrombosis:**

    - Use of antiplatelet therapy alone
    - Balloon-expandable valves
    - Valve-in-valve procedures
    - Obesity

  - **Predictors of HALT from other studies include:**

    - Low deployment
    - Low-flow, low-gradient aortic stenosis
    - Severe PPM
    - Valve size

What were the important predictors of clinical valve thrombosis?

- Balloon-expandable valves

- Valve-in-valve TAVR

- Use of antiplatelet therapy alone

Jose et al., JACC Cardiovasc Interv. 2017;10(7):686-697

Subclinical Thrombosis: Clinical impact

- **What is the clinical impact of HALT?**

In the Evolut Low Risk trial, HALT was not associated with poorer hemodynamic outcomes out to 1 year, regardless of the extent of leaflet thickening.

In the PARTNER 3 substudy, there was no significant difference in hemodynamics according to presence or severity of HALT.

Reardon. Presented at ACC 2020.   Makkar. Presented at TCT 2019

Subclinical Thrombosis: Clinical impact

- **What is the clinical impact of HALT?**

Neither of the low risk trial CT substudies were powered to assess the association between HALT and cerebroembolic events.

Early Relationship between HALT and Clinical Outcomes* (Evolut Low Risk Trial)

	TAVR		SAVR	
	HALT N = 35	No HALT N = 162	HALT N = 23	No HALT N = 155
Death or stroke or TIA	0 (0.0)	2 (1.3)	0 (0.0)	1 (0.7)
All-cause mortality	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any stroke	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.7)
TIA	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)

*between 7-30 Days

PARTNER 3 TRIAL — 30-day HALT and Clinical Events

All Patients with Evaluable CTs – TAVR & SAVR

Clinical Events (n)	Day 7-30		Day 31-365	
	HALT at 30 Days (N=35)	No HALT at 30 Days (N=311)	HALT at 30 Days (N=35)	No HALT at 30 Days (N=311)
Death	0	0	0	4
Heart Failure	0	1	1	6
Angina	0	0	0	9
Myocardial Infarction	0	0	0	3
Clinical Valve Thrombosis*	0	0	3	1
Stroke	1	0	0	1
TIA	0	1	1	2
Retinal Artery Embolism	0	0	1	1

Reardon. Presented at ACC 2020.   Makkar. Presented at TCT 2019

Subclinical Thrombosis: Clinical impact

- **What is the clinical effect of HALT?**

ORIGINAL RESEARCH ARTICLE

Deformation of Transcatheter Aortic Valve Prostheses: Implications for Hypoattenuating Leaflet Thickening and Clinical Outcomes

Table 4. One-Year Clinical Outcomes

Variable	All patients (n=565)	HALT (n=108)	No HALT (n=457)
All-cause death	40 (7%)	16 (15%)	24 (5%)
Cardiac death	18 (3%)	9 (8%)	9 (2%)
HF hospitalization	35 (6%)	10 (9%)	25 (6%)
Composite (all cause death + HF hospitalization)	66 (12%)	21 (19%)	45 (10%)
Myocardial infarction	9 (2%)	6 (6%)	3 (1%)
Stroke/TIA	21 (4%)	8 (7%)	13 (3%)
Bleeding event	56 (10%)	11 (10%)	45 (10%)

- Nonuniform expansion of TAVR prostheses resulting in frame deformation, asymmetric leaflet, and smaller neo-sinus volume is related to HALT.
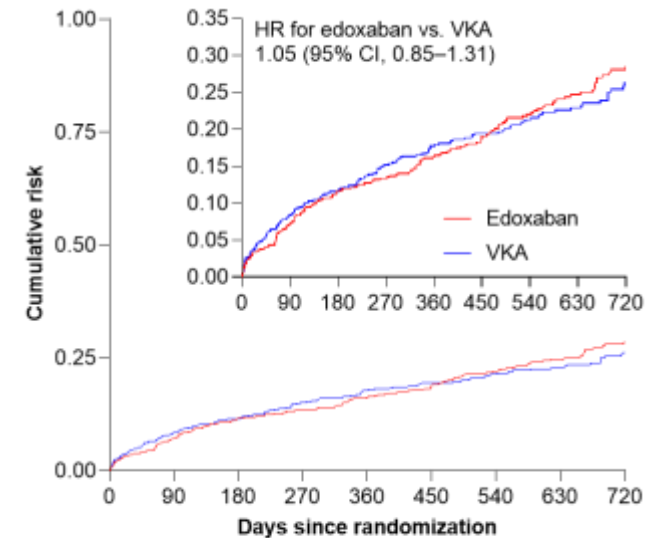- HALT is independently associated with long-term mortality

Fukui M. et al. Circulation 2022
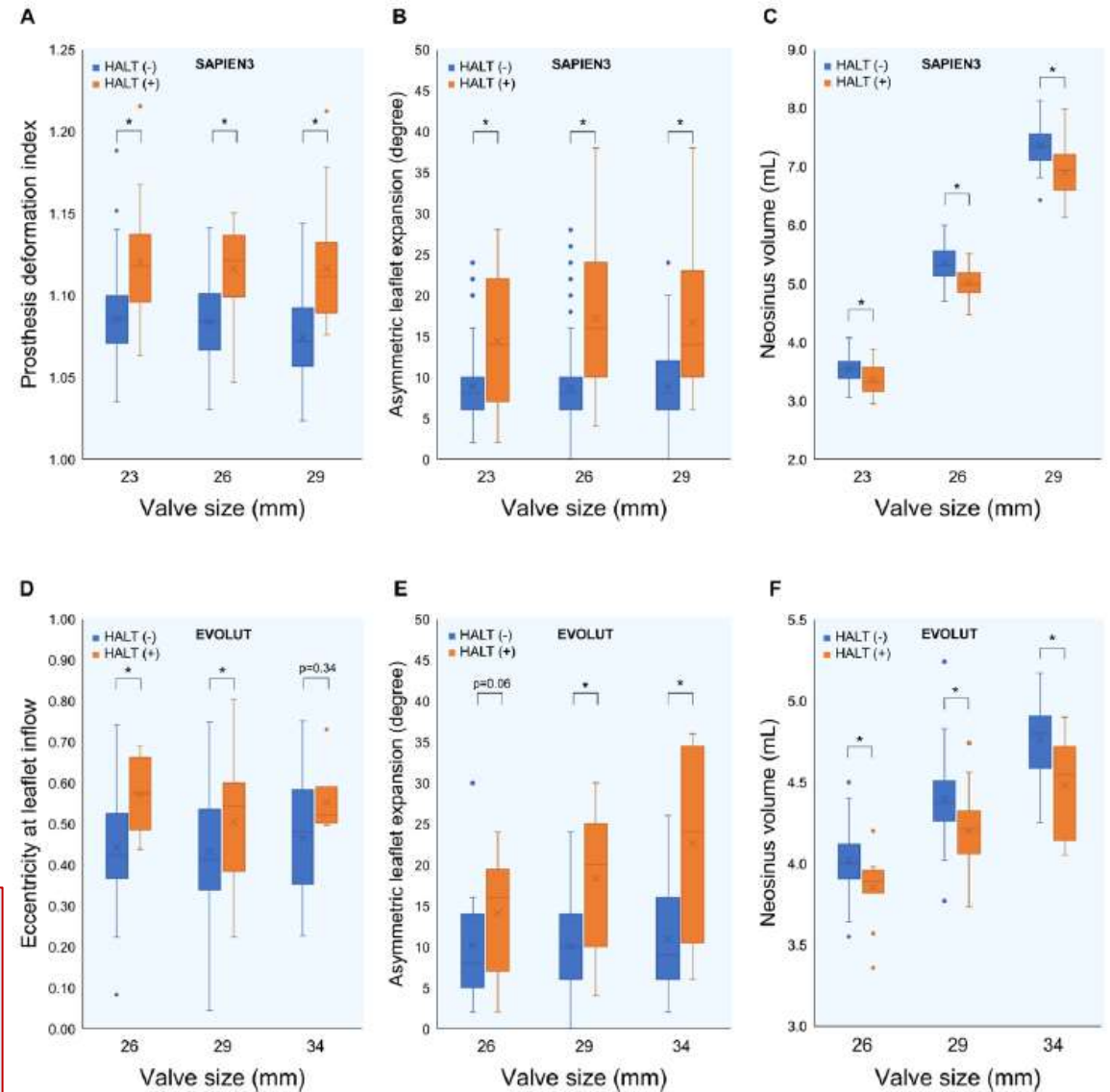
Thrombosis and antithrombotics
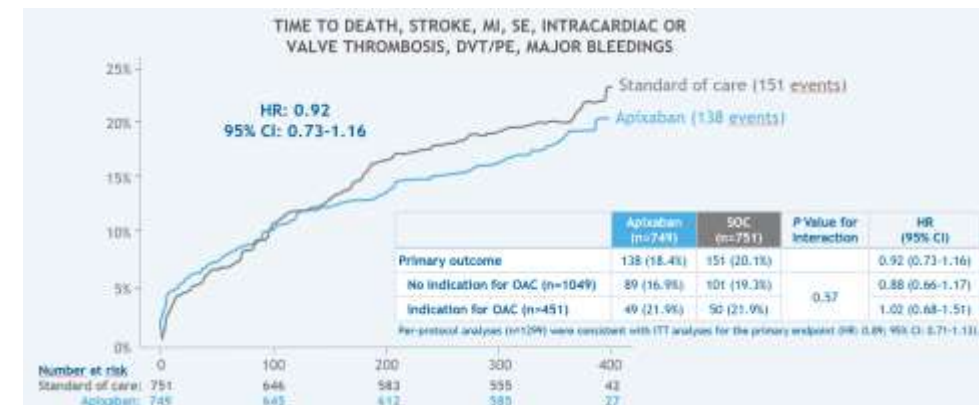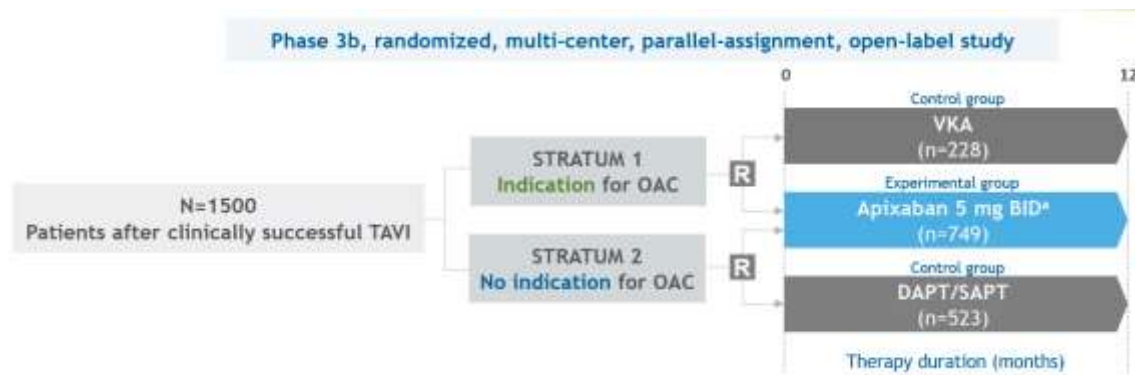
The ENVISAGE TAVI AF study

Primary endpoint: NACE (ie, all-cause death, MI, ischaemic stroke, systemic thromboembolic event, **valve thrombosis**, and ISTH-defined major bleeding)

The ATLANTIS study

Primary endpoint: Net clinical benefit = composite of death, MI, stroke/TIA or SE, intracardiac or **bioprosthesis thrombus**, DVT/PE, life-threatening or disabling bleeding or major bleeding over 1 year of follow-up

Collet JP et al. Euro Heart J 2022, Van Mieghem NM et al. N Engl J Med 2021

Conclusion

✓ Rates of clinical thrombosis appear low in TAVI and SAVR, especially in the low surgical risk population.

✓ Subclinical leaflet thickening may have a large impact on the long term valve durability. Reported prevalence of HALT and RELM ranges from about 9 – 35% after TAVI.

✓ Various risk factors of HALT have been proposed: including balloon-expandable valves, small valve size and asymmetric valve expansion, etc.

✓ Formation/Resolution of HALT is a dynamic process, while the role of medical therapy need to be further determined.