Pathological Findings of Self-Expanding Transcatheter Aortic Valves and Hypo-Attenuated Leaflet Thickening (HALT)

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Disclosure Statement of Financial Interest

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I, Yu Sato, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

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Faculty disclosure information can be found on the app

Background

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- Thrombus morphology evolves over time from a loose mesh of fibrin and platelets (acute stage) to a compact structure of acellular and cellular components (organizing thrombus) with eventual infiltration by smooth muscle cells and collagen (organized thrombus) that is resistant to treatment[1,2]
- The gold standard for diagnosis of subclinical leaflet thrombosis after surgical or TAVR is 4-dimensional computed tomography (4DCT) scan. The characteristic finding on 4DCT is a hypo-attenuating opacity at the base of valve leaflets, or hypo-attenuating leaflet thickening (HALT)

1. Czaplicki C et al., Cardiovasc Diagn Ther. 2017;7:S186-S196. 2. Sellers SL, et al. JACC Cardiovasc Interv. 2019;12:135-145.

Background

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- HALT identified on functional cardiac CT can affect valve function and clinical outcomes, and thus identifying HALT may be important for improving the long-term durability of TAVs[1]
- Higher resolution imaging such as microCT may yield further insights into the pathophysiology of HALT and is likely to be able to distinguish different stages of HALT
- Here for the first time, we compared microCT changes of HALT with histologic changes of valve thrombosis and characterization over time

1. Hein M, et al. JACC Cardiovasc Interv 2022;15:1113-1122.

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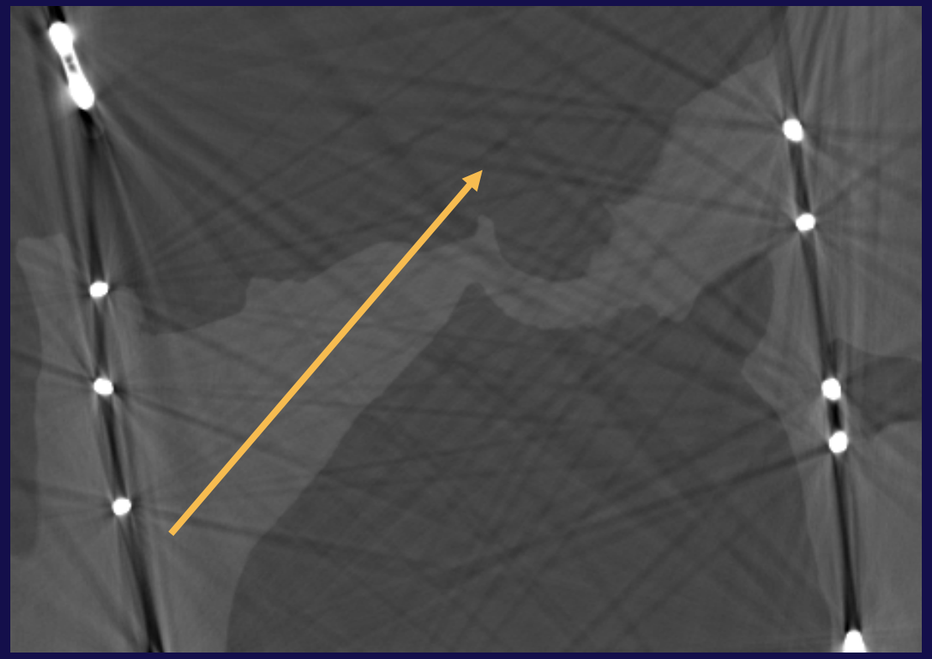
Aim

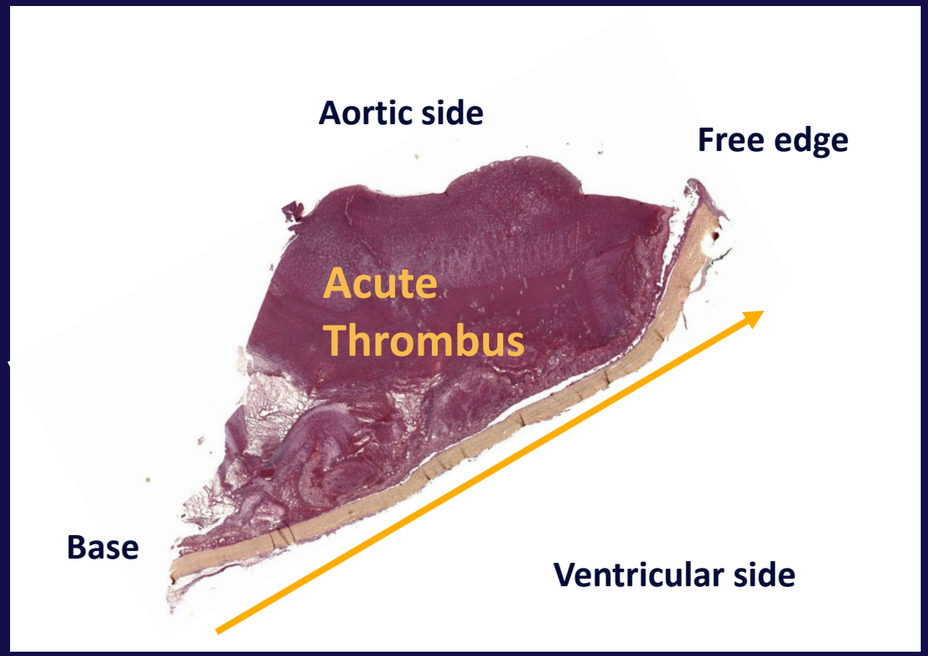
1. To evaluate the extent of pathologic changes of valve thrombosis, neointimal thickening, inflammation, and calcification over time in TAVs explanted at surgery or autopsy
2. To compare microCT findings of HALT with histologic findings of acute, organizing, and organized thrombosis (resolution of microCT is in microns vs clinical CT in 0.5 mm)

MicroCT



Correlation

Histology



Study design

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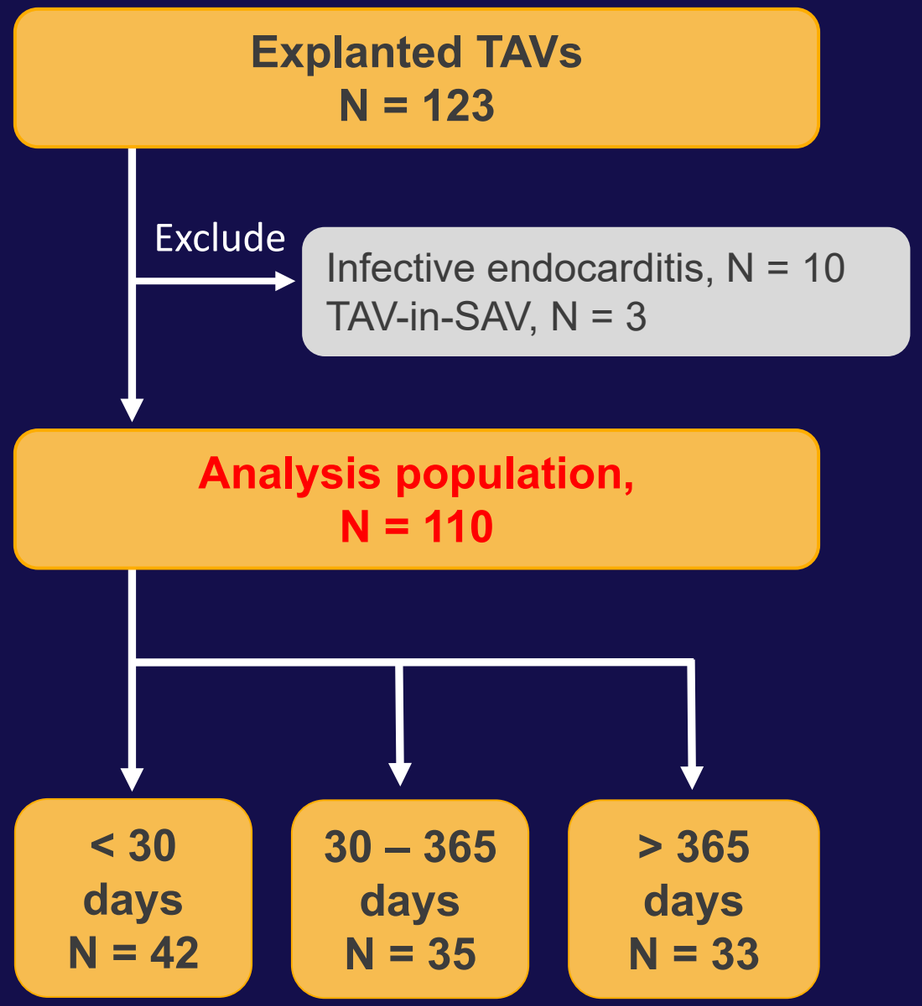
- ✓ 123 explanted self-expanding TAVs were assessed from a population of >7500 participants from 11 clinical trials across surgical risk groups[1]
  - Explanted valves represent <2% of all patients
- ✓ Clinical thrombosis rates were 0%–1.3% in these trials
- ✓ Valves were explanted due to surgery (N = 34) or autopsy (N = 89)



[1]CoreValve US Pivotal Trials (ER and HR); CoreValve Continued Access Studies (ER and HR); CoreValve Expanded Use Study; SURTAVI Trial; SURTAVI Continued Access Study; Evolut Low Risk Trial; Low Risk Continued Access Study; Evolut US Trial; Low Risk Bicuspid Study

Methods: Histological leaflet semi-quantitative scoring[1]

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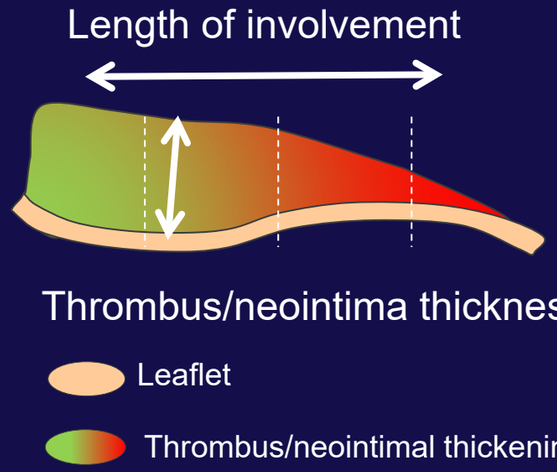
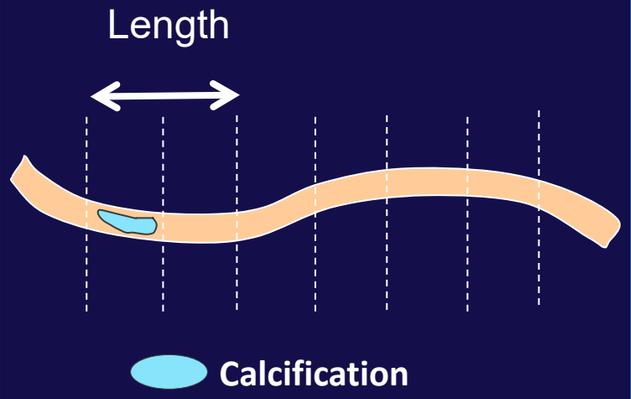
Thrombus & Neointima



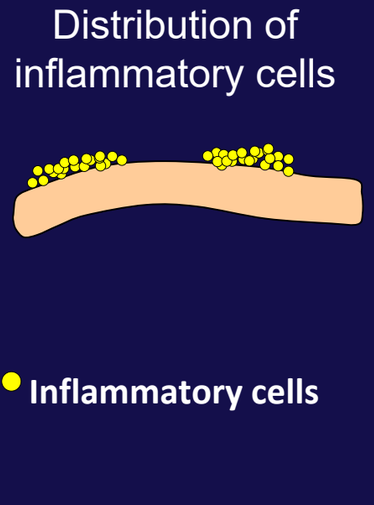
	Thrombus/ Neointima score	Length <1/4	1/4 to <1/2	1/2 to <3/4	≥3/4
Thickness	Absent	0	0	0	0
	<1x leaflet thickness	0	1	2	3
	>1x but <2x leaflet thickness	1	2	3	4
	>2x but <4x leaflet thickness	2	3	4	5
	>4x thickness	3	4	5	5

Calcification



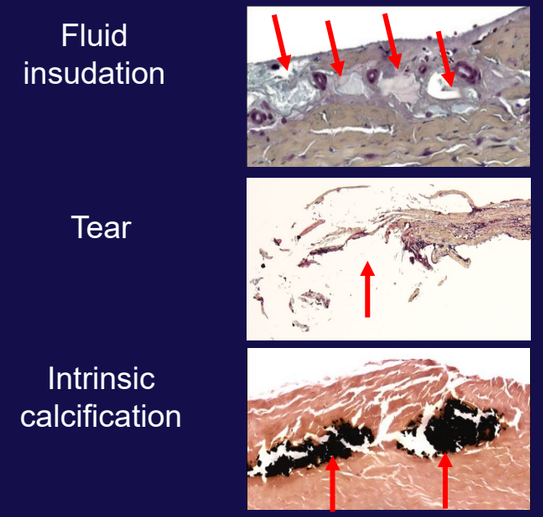
Score	Length
0	Absent
1	Microcalcification
2	<1/4 the length of the leaflet
3	1/4 to <1/2 the length of the leaflet
4	>1/2 the length of the leaflet

Inflammation



Inflammation Score	Focal	Multifocal	Diffuse
Absent	0	0	0
Single layer/superficial	0	1	2
Multilayered/superficial	1	2	3
Multilayered with superficial infiltration	2	3	4
Multilayered with deep infiltration	3	4	4

Structural change



Score	Description of structural change
0	Prosthetic leaflet collagen layers intact
1	Minimal fraying or splitting of surface collagen bundles with neointimal in-growth; with/without fluid insudation; minimal separation of collagen bundles
2	Mild separation of superficial collagen bundles with or without fluid insudation
3	Moderate separation, fracture, or fraying of collagen bundles with or without fluid insudation, and/or mild intrinsic calcification confined in the leaflet area
4	Vertical tears, fissures, or perforations in the leaflet collagen bundles with or without fluid insudation, and/or moderate or severe intrinsic calcification extending beyond the thickness of the leaflet

[1] *Yahagi K, et al. Catheter Cardiovasc Interv. 2017 ;90:1048-1057.*

MicroCT HALT and histological leaflet thickening grading

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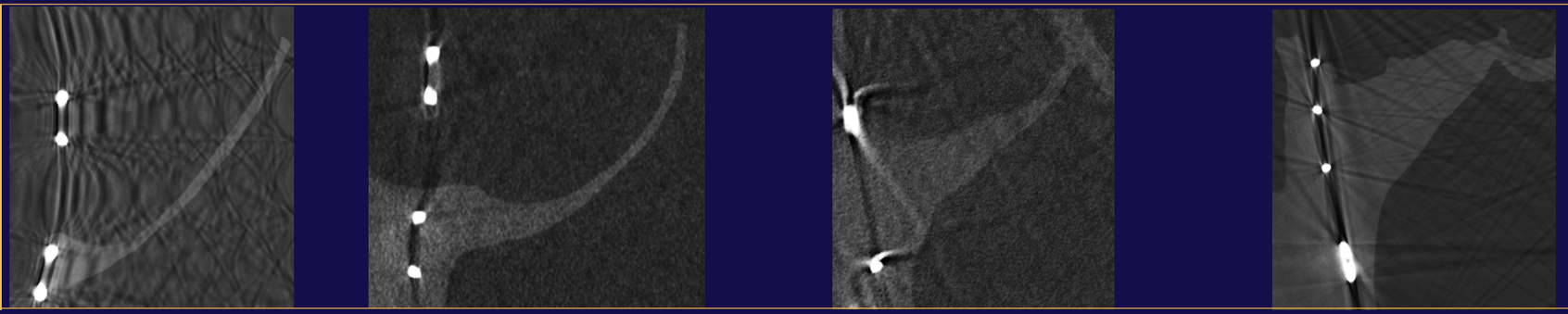
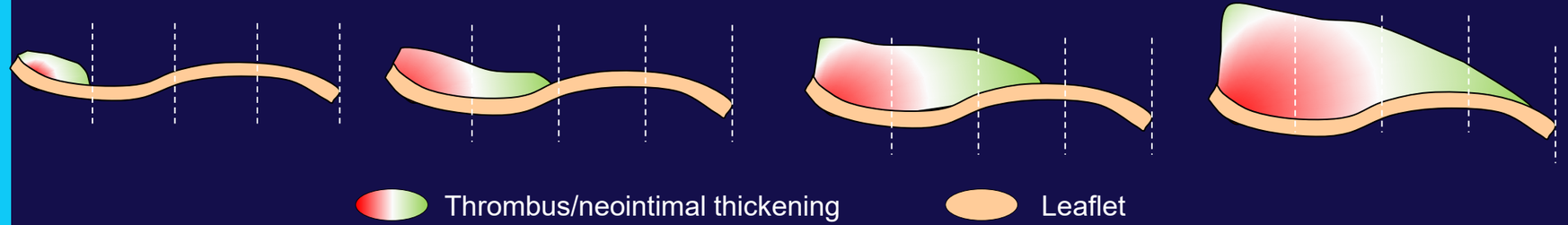
- ✓ Of 110 TAVs, microCT image acquisition was performed in 40 cases
  - ✓ 4 cases excluded (3 severe intrinsic calcification; 1 poor image quality)
  - ✓ 36 cases available for microCT analysis
- ✓ HALT on microCT was defined as increased leaflet thickness (>normal) and graded based on length of leaflet involvement (visual assessment)
- ✓ The composition of leaflet thickening was determined histologically and compared to HALT

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
	<25% of leaflet	25%–<50% of leaflet	50%–<75% of leaflet	>75% of leaflet
MicroCT				
Histology				

Thrombus/neointimal thickening

Leaflet

MicroCT HALT scoring

Based on the length of involvement of visible leaflet thickening[1]

1. Blanke P, et al. JACC. 2020;75:2430-2442.

Histological Scoring

Based on thrombus/neointima thickness (>normal pericardial leaflet thickness) and length of leaflet involvement

Case characteristics

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	Overall	<30 Days	30-365 Days	>365 Days	p Value
No. of cases	110	42 (38)	35 (32)	33 (30)	
Age, years	80.1 ± 9.5	82.4 ± 9.2	79.7 ± 9.4	77.4 ± 9.7	0.080
Female	41 (37)	21 (50)	9 (26)	11 (33)	0.077
Duration of implant, days	66 (12.8-622.5)	7.5 (1.8-15.3)	73 (48-133)	976 (793.5-1349.5)	<0.001
Valve type					0.120
CoreValve	90 (82)	37 (88)	28 (80)	25 (76)	
Evolut R	18 (16)	3 (7)	7 (20)	8 (24)	
Evolut PRO	2 (2)	2 (5)	0	0	
STS PROM, %	8.6 ± 5.9	10.8 ± 7.3	7.6 ± 4.2	6.7 ± 4.7	0.006
Hypertension	98 (89)	36 (86)	33 (94)	29 (88)	0.469
Diabetes mellitus	39 (36)	15 (36)	12 (34)	12 (36)	0.983
Baseline CrCl, ml/min	61.9 ± 35.7	57.3 ± 40.5	56.1 ± 27.2	73.5 ± 35.3	0.078
Reason of explant					0.444
Autopsy	82 (75)	34 (81)	24 (69)	24 (73)	
Aortic valve reintervention	28 (25)	8 (19)	11 (31)	9 (27)	
Baseline antiplatelet therapy	91/108 (84)	32/40 (80)	31 (89)	28 (85)	0.362
Baseline anticoagulants (VKA or DOAC)	24/108 (22)	11/40 (28)	8 (23)	5 (15)	0.297

CrCl = creatinine clearance; DOAC = direct oral anticoagulants; STS PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; VKA = vitamin K antagonist
Data are presented as n (%), median (Q1-Q3) or mean ± SD.

Histological semi-quantitative scores by implant duration

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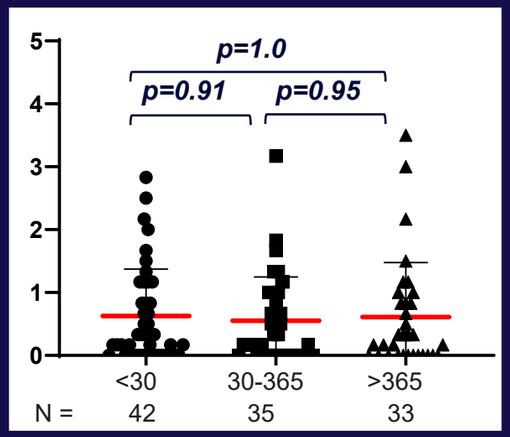
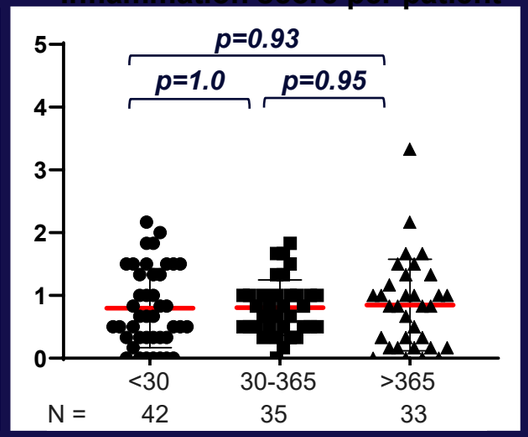
- ✓ No change in thrombus and inflammation scores was observed over time
- ✓ Neointimal thickness, structural change, and calcification scores increased with greater implant duration

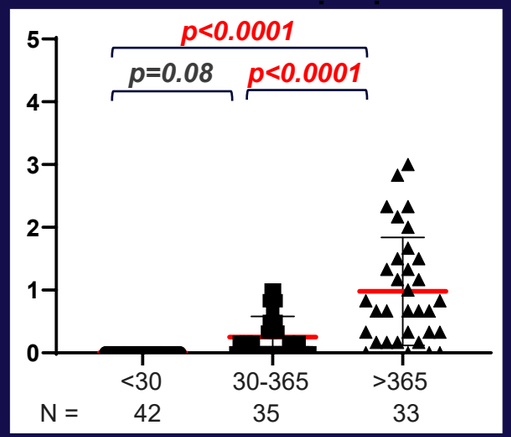
Thrombus score



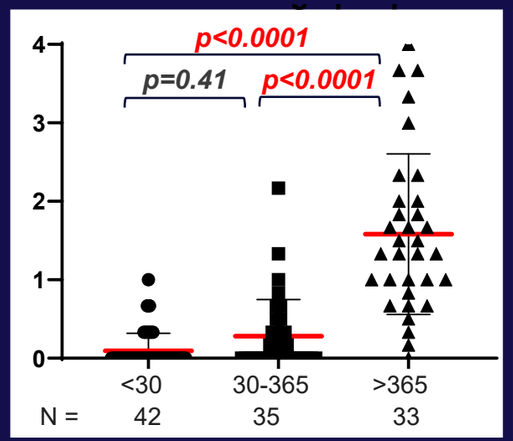
Inflammation score



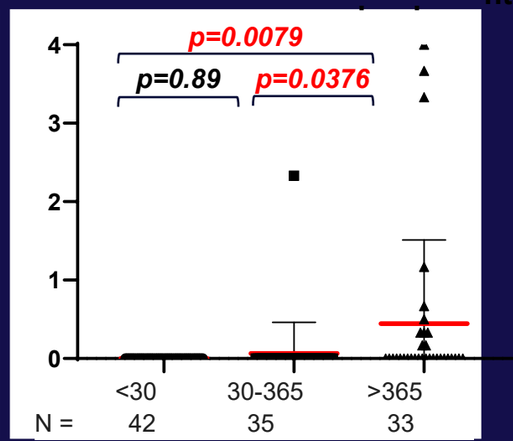
Neointima score



Structural change score



Calcification score



No change with time

Increased with time

Statistical comparisons were made using a nonparametric Steel-Dwass all pairs test.

Evaluation of leaflet thickening

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- ✓ Histological leaflet thickening was evaluated in 320 leaflets from 110 cases including cases with severe intrinsic calcification
- ✓ Of 320 leaflets, microCT was analyzed in 106 leaflets from 36 cases excluding severe intrinsic calcification

Case characteristics	Histology group	MicroCT group	p Value
No. of cases	110	36	
No. of leaflets evaluated	320	106	
Age, years	80.1 ± 9.5	78.6 ± 8.8	0.43
Female	41 (37)	13 (36)	0.90
Duration of implant, days	66 (12.8-622.5)	125 (14.5-1182)	0.25
Reason of explant			<0.001
Autopsy	82 (75)	16 (44)	
AV reintervention	28 (25)	20 (56)	
STS PROM, %	8.6 ± 5.9	5.7 ± 3.7	0.008
Valve type			0.016
CoreValve	90 (82)	21 (58)	
Evolut R	18 (16)	13 (36)	
Evolut PRO	2 (2)	2 (6)	
Baseline antiplatelet therapy	91/108 (84)	28/34 (82)	0.47
Baseline anticoagulants	24/108 (22)	9/34 (27)	0.43

Data are presented as n (%), mean ±. SD, or median (Q1-Q3).

Distribution of leaflet thickening grades in explanted valves

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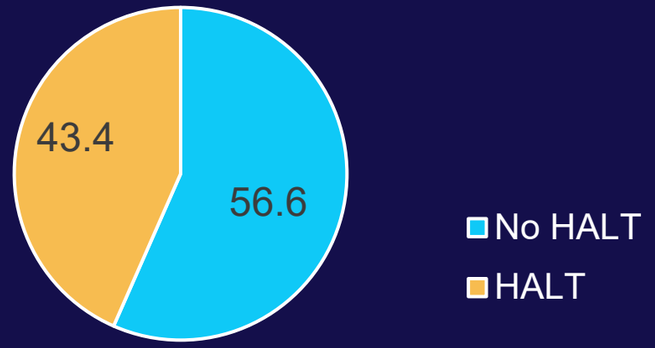
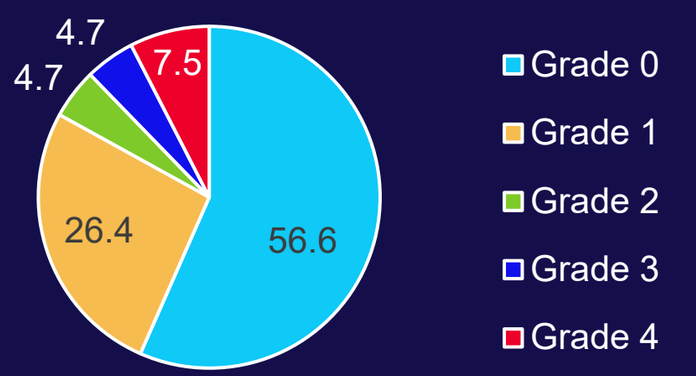
- ✓ Approximately 45% of leaflets showed at least some degree of leaflet thickening
- ✓ Prevalence of leaflet thickening was comparable with microCT and histology

MicroCT Analysis (N = 106 leaflets)

Prevalence of MicroCT HALT

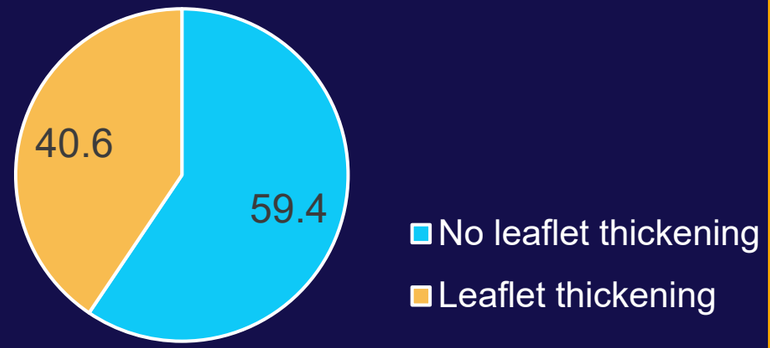


Distribution of leaflet thickening grade in microCT

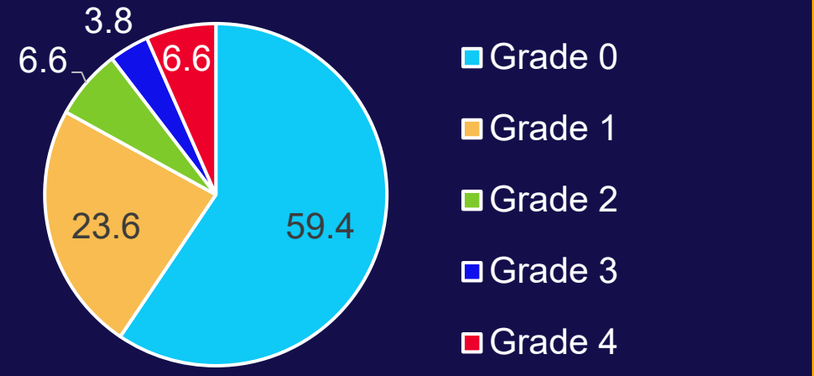


Histological Analysis (N = 106 leaflets)

Prevalence of leaflet thickening in histology



Distribution of leaflet thickening grade in histology



Histologic HALT occurred from acute, organizing, and organized thrombus

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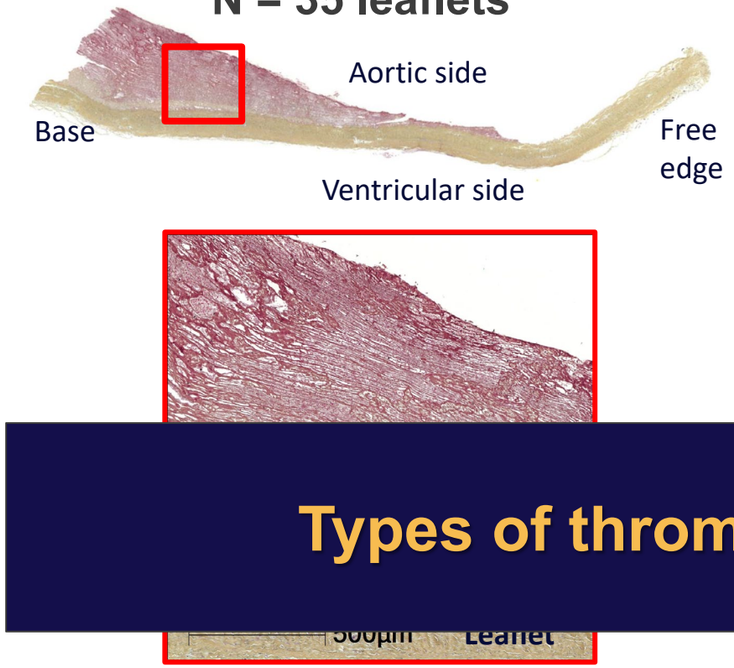
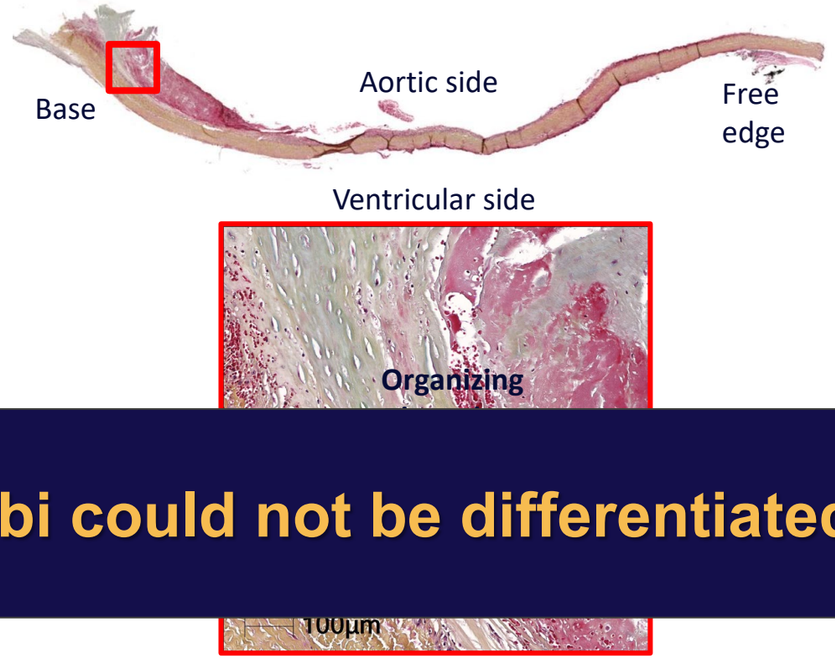
149 of 320 leaflets (46.6%) had any degree of leaflet thickening

Histology

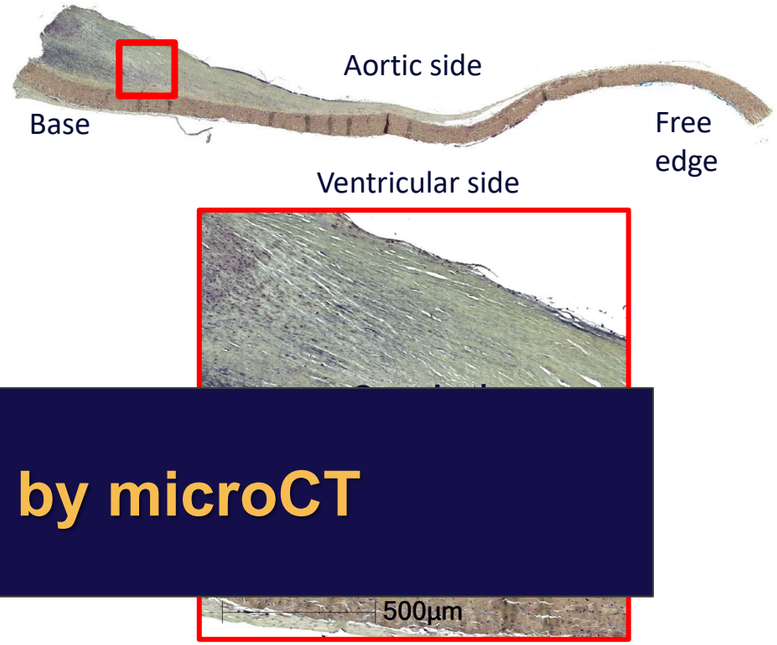
Acute Thrombus
N = 35 leaflets



Organizing Thrombus
N = 93 leaflets

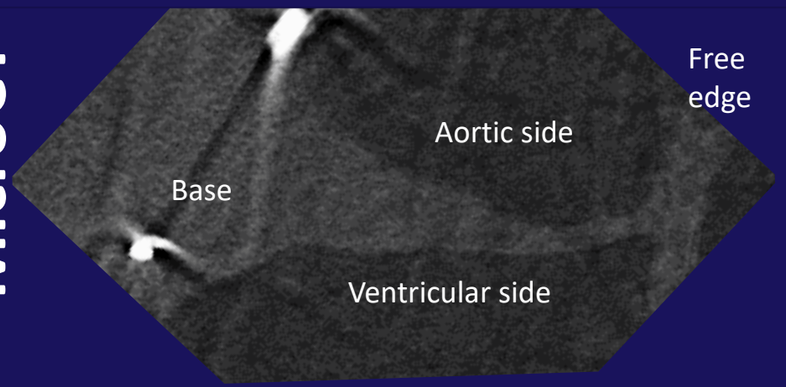


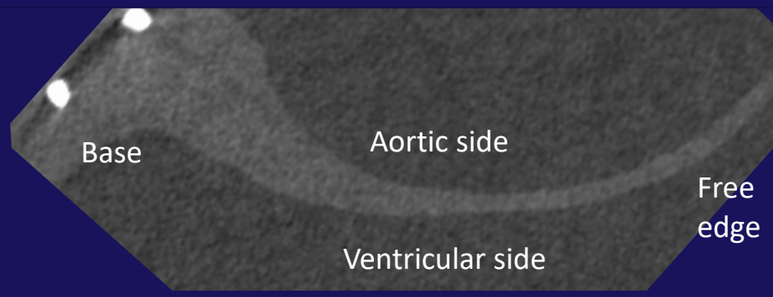
Organized Thrombus
N = 21 leaflets

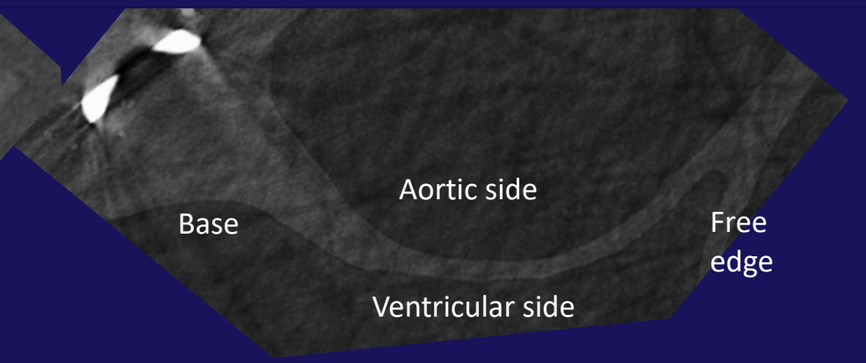


Types of thrombi could not be differentiated by microCT

MicroCT







Histological characteristics of leaflet thickening

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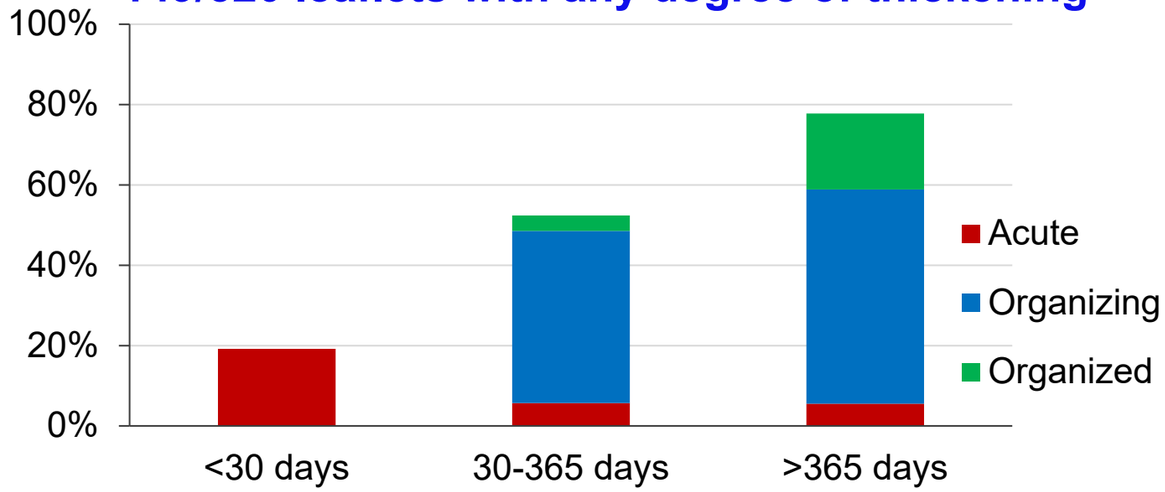
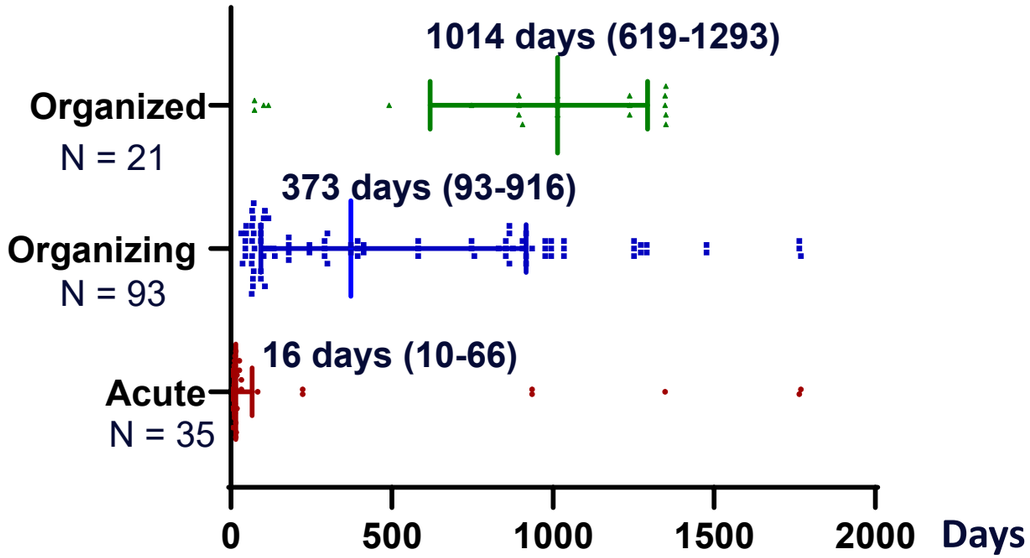
- ✓ Leaflet thickening was observed more frequently in implants of longer duration
- ✓ All thrombi were acute at <30 days, while most organizing thrombi occurred after 30 days
- ✓ Thrombi were most organized after 1 year

Types of thrombus by duration of implant: 149/320 leaflets with any degree of thickening



No. of leaflets	125	105	90	Total
Acute	24	6	5	35
Organizing	0	45	48	93
Organized	0	4	17	21
None	101	50	20	171

Median (Q1-Q3) duration of implant for each type of thrombus



Limitations

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- This was a pathological analysis of a small subset (<2%) of self-expanding valves implanted from 11 clinical trials
- Valves explanted at autopsy could be obtained from patients with cardiovascular or noncardiovascular death and may not be representative of a population with valve failure
- Pathological findings are not linked to clinical outcomes and cases cannot be compared to living patients

Summary

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- ✓ This is the first study to compare microCT and histology findings of leaflet thickening (45% of explanted valves)
  - ✓ Clinical thrombosis rates are extremely low in clinical trials of self-expanding TAVs (0%–1.3% across 11 clinical trials)
- ✓ There was no relationship between duration of implant and thrombus and inflammation scores, while neointimal thickening, structural change, and calcification scores increased with time, and were most pronounced after 1 year
- ✓ Histologic examination confirmed 3 types of thrombi: acute, organizing, and organized (which could not be differentiated by microCT). Implants greater than 30 days showed findings consistent with organization while the majority of those greater than 1 year were either organizing or organized
  - ✓ These findings may explain why oral anticoagulation therapy is not always effective and suggests that identification of HALT, and response to treatment, may be most effective within the first year after implantation, especially in younger patients.