

Autopsy Studies of TAVR – What Have We Learnt ?

Renu Virmani MD

CVPath Institute,
Gaithersburg, MD, USA



Speaker name: Renu Virmani, MD.

Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Consultant: 480 Biomedical, Abbott Vascular, Medtronic, and W.L. Gore.

Employment in industry: No

Honorarium: 480 Biomedical, Abbott Vascular, Boston Scientific, CeloNova, Claret Medical, Cordis J&J, Lutonix, Medtronic, Merck, ReCor, Terumo Corporation, and W.L. Gore.

Institutional grant/research support: 480 Biomedical, Abbott Vascular, Atrium, BioSensors International, Biotronik, Boston Scientific, Cordis J&J, GSK, Kona, Medtronic, MicroPort Medical, OrbusNeich Medical, ReCor, SINO Medical Technology, Terumo Corporation, and W.L. Gore.

Cage ball prosthesis
In ascending aorta



Hufnagel



Starr-Edwards
Ball-and-Cage
valve



1976: Carpentier-
Edward Porcine
Xenograft

1976: Ionescu-Shiley
Pericardial Xenograft

Hancock Porcine
Bioprosthesis valve

Bonhoeffer
implanted
Percutaneous
Pulmonary valve

2000



1951

1954

1961

1962

1970

1989

2002

Extracorporeal
Circulation

First AV
replacement
surgery

Mid-1960
Development
Of low profile
Caged-disk valve

Anderson
implanted
Percutaneous
valve in
descending
aorta of a dog

Cribier
Percutaneous
Aortic
Valve



**History of Artificial Heart
Valve Development**

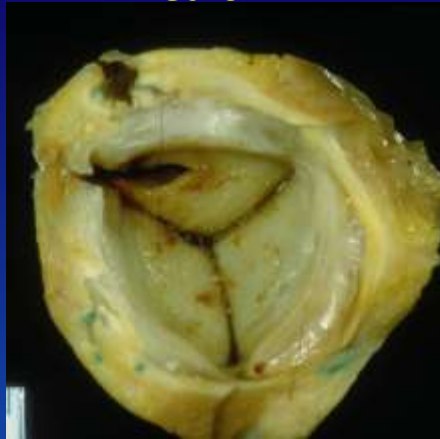
Surgically Implanted Bioprosthetic Valve: Summary

Disadvantages: Limited durability beyond 10 years in younger patients: Cusp degeneration (tears) leading to regurgitation or Ca^{++} leading to stenosis
Pannus formation common to mechanical and bioprosthetic valves in latter can extend into the leaflet and lead to regurgitation and rarely stenosis
Endocarditis, although rare seen mostly in drug abusers

Normal



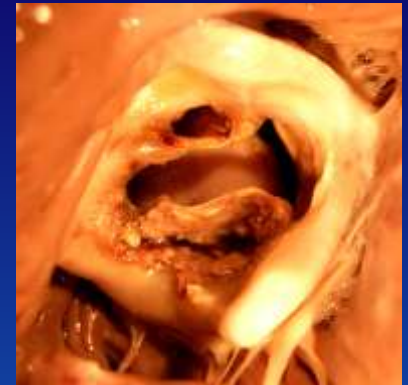
Tears



Calcification



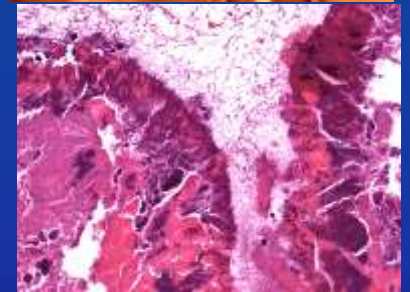
Infective endocarditis



Pannus

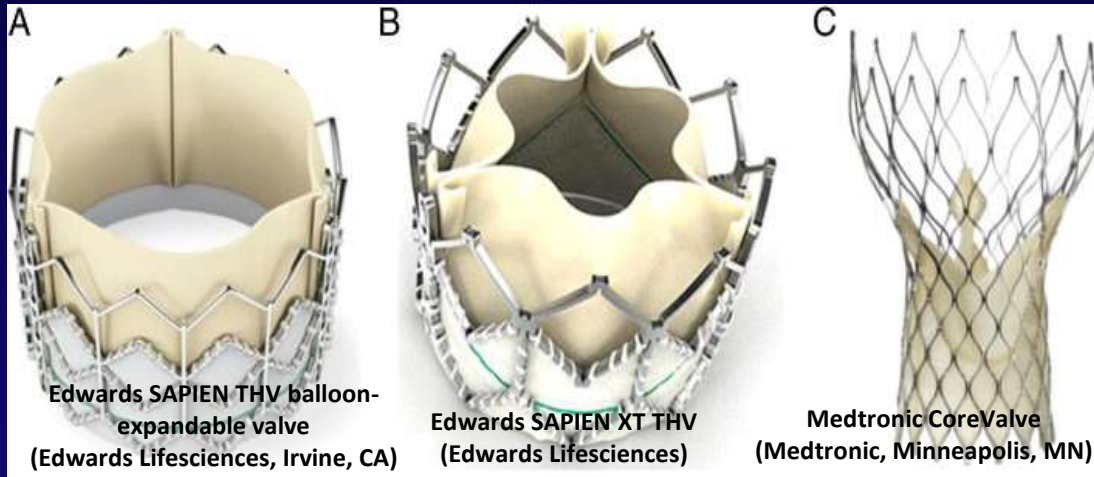


Thrombus



Current Widely Available Transcatheter Valves

New Generation Valve



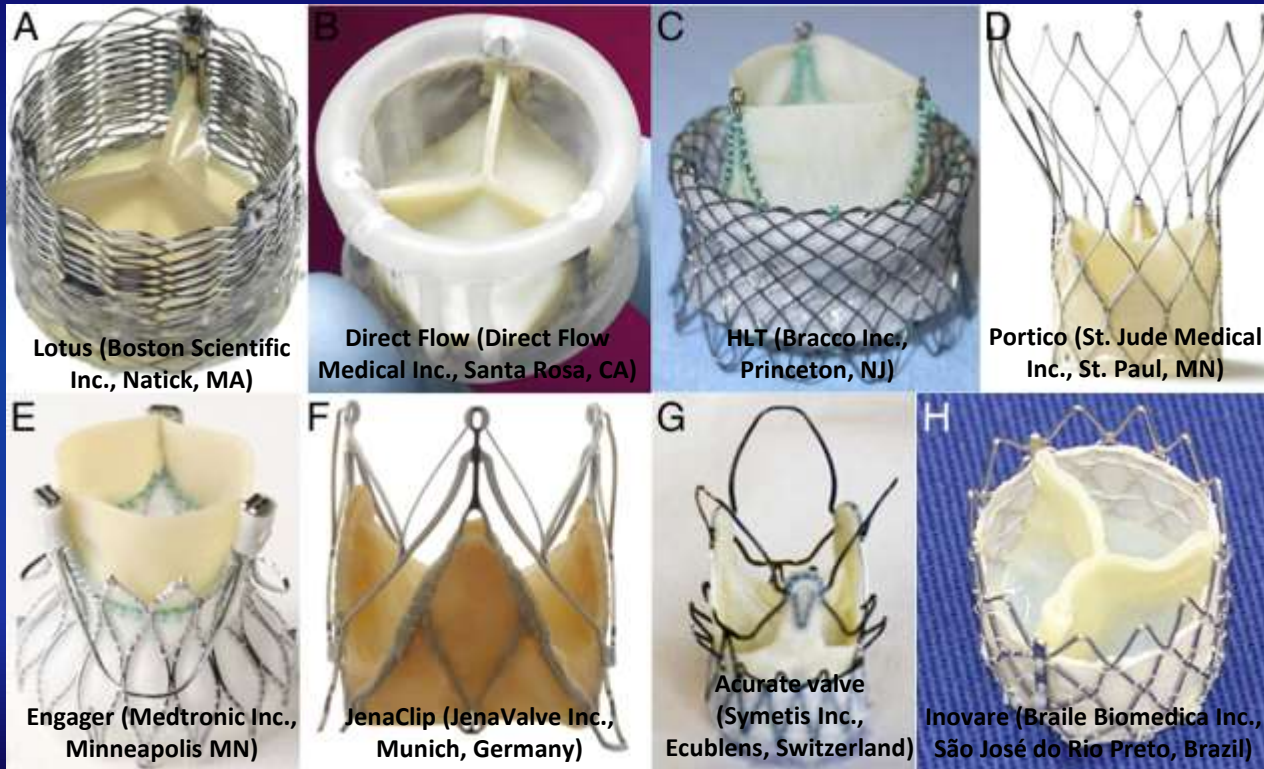
A. Stainless steel frame, bovine pericardial leaflets, and a fabric sealing cuff.

B. Cobalt chromium alloy frame, compatible with lower profile delivery catheters.

C. Self-expandable frame, porcine pericardial leaflets, and a pericardial seal.



Valves Undergoing Early Evaluation



CVPath Institute Experience of TAVR seen at Autopsy or Surgical Removal

Edwards Valve: Mean Age 82.4±7.1, Male 20 (48%)

Medtronic Valve: Mean Age 82.9±9.9, Male 30 (48%)

Type of trial	Valve type	Number of cases
Edwards Lifesciences		45
FIM (including REVIVE I)	Cribier-Edwards Valve	9
PARTNER IA and IB	Edward SAPIEN THV	15
PARTNER IIA and IIB	Edwards SAPIEN/SAPIEN XT THV	18
PARTNER IIS3	Edwards SAPIEN 3 THV	3
Medtronic		64
Expanded Clinical Evaluation	2 nd and 3 rd Generation CoreValve	7
US PIVOTAL High Risk	CoreValve (Medtronic)	22
US PIVOTAL Extreme High Risk	CoreValve (Medtronic)	1
Access Continued Clinical Trial	CoreValve (Medtronic)	27
SURTAVI Clinical Trial	CoreValve (Medtronic)	3
Expanded Clinical Trial	CoreValve (Medtronic)	4
TOTAL (Edwards and Medtronic)		109

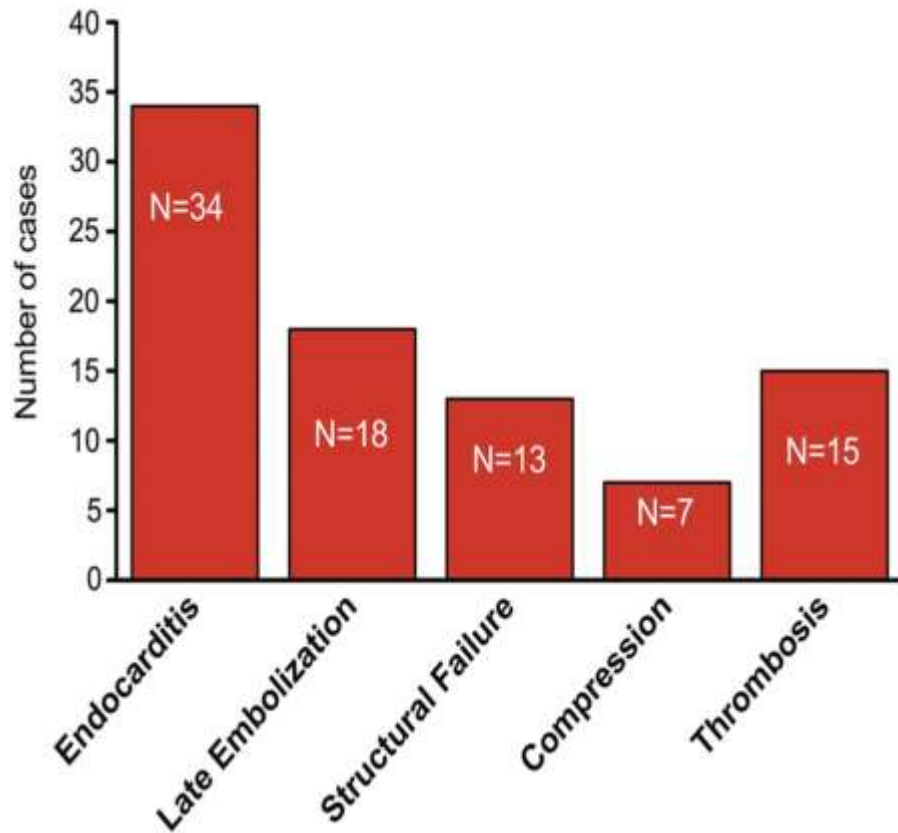
Transcatheter Heart Valve (THV)

Failure: Literature Review

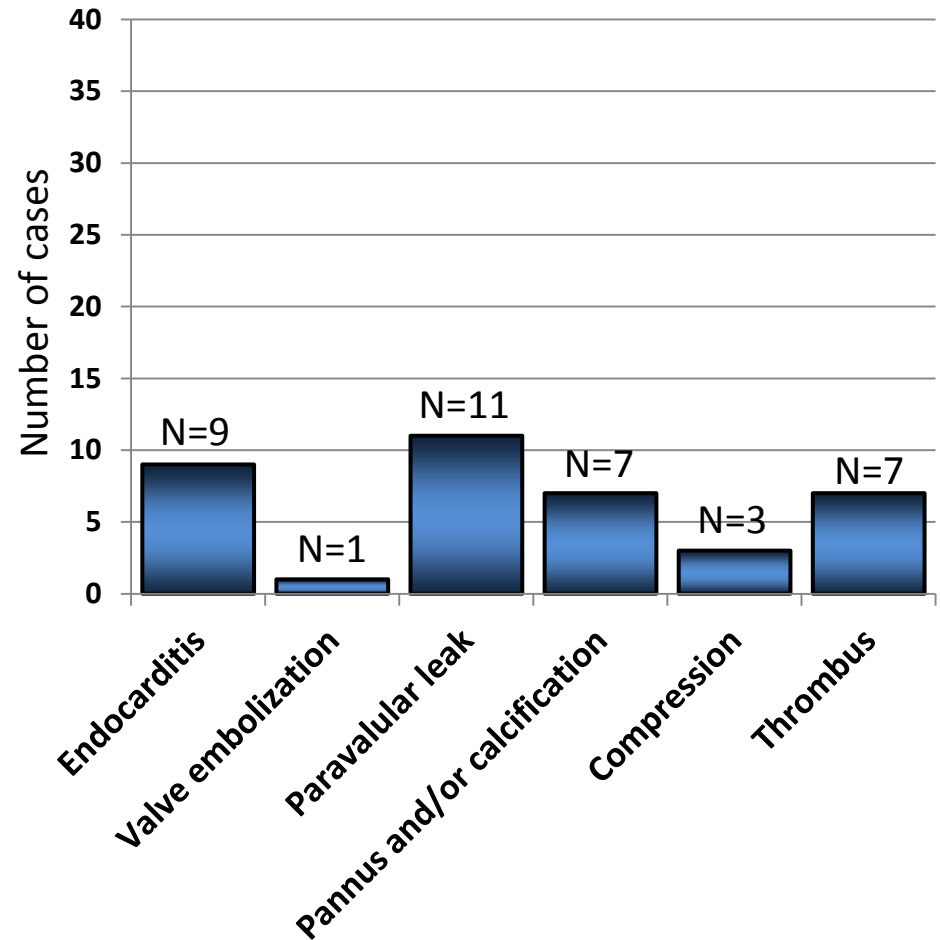
- Between January 2002 and October 2013, 56 separate publications on pathology of THV, involving 69 individuals cases were reviewed:
 - Prosthetic valve endocarditis reported in 29 cases (42%), the median age was 82 (77, 85) years and most (n=19, 66%) had predisposing risk factors to IE; 25 (86%) cases of definite and 4 (14%) cases of possible prosthetic valve IE, The median time to IE diagnosis was 6 (3, 12) months, Edwards SAPIEN (n=17, 59%) and Medtronic CoreValve (n=12, 41%) prostheses
 - Structural valve failure 8 (12%): 5 had severe stenosis and 3 had regurgitation from: leaflet calcification (n=3), cusp rupture (1), THV underexpansion (n=1), tissue ingrowth (n=1), mode of failure unclear in 2.
 - Transcatheter heart valve thrombosis 12 (9%): 11 Edward SAPIEN and 1 Core Valve, mean time to diagnosis was 8 ± 7 months (range: 1 to 24 mo)
 - Late THV Embolization: 13 cases late THV embolization, Edwards SAPIEN valve; age 77 ± 6 years; occurred 35 ± 41 days (range: 4 hours to 123 days) after the index procedure

Transcatheter Heart Valve Failure

Systematic Review of Literature



CVPath Institute



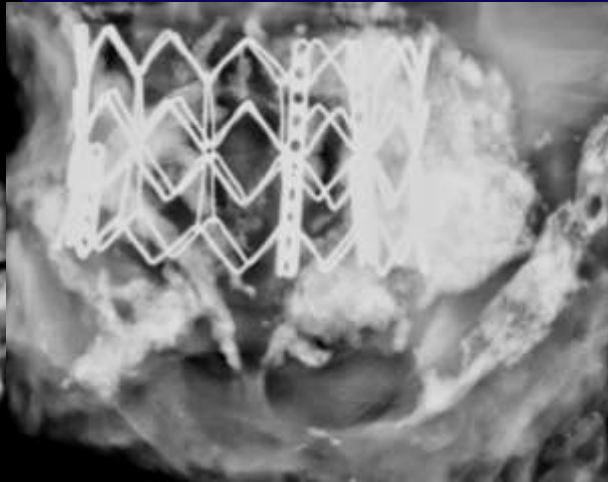
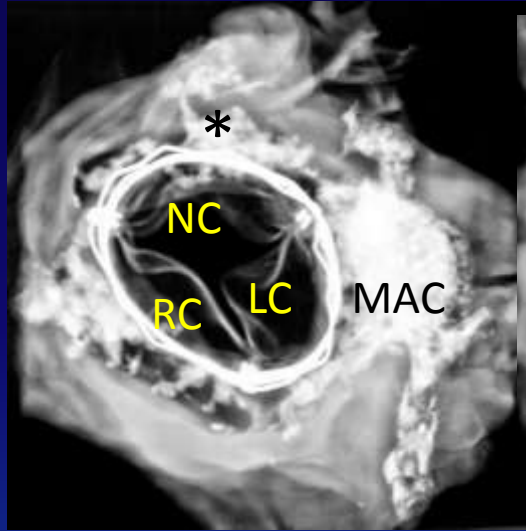
Cause of Death or Explantation: Edwards SAPIEN valve (45 cases)

Cause of Death	
Autopsy	39 cases
Valve-related death	12
Infective endocarditis	5
Paravalular leak	2
Valve thrombus (severe stenosis or stroke)	2
Valve compression	2
Severe stenosis due to pannus with commissural fusion and leaflet calcification	1
Procedure-related death	7
LV perforation	3
Aortic root rupture	1
Retroperitoneal hemorrhage / bleeding	2
Evulsed native valve to left coronary artery ostia	1
Non-TAVR related cardiac death	4
Coronary artery disease (CAD)	3
Chronic heart failure with CAD	1
Non-cardiac death	7
Stroke	1
Respiratory failure	2
Pneumonia	2
Pulmonary embolism	1
Aortic dissection, late	1
Unknown	9

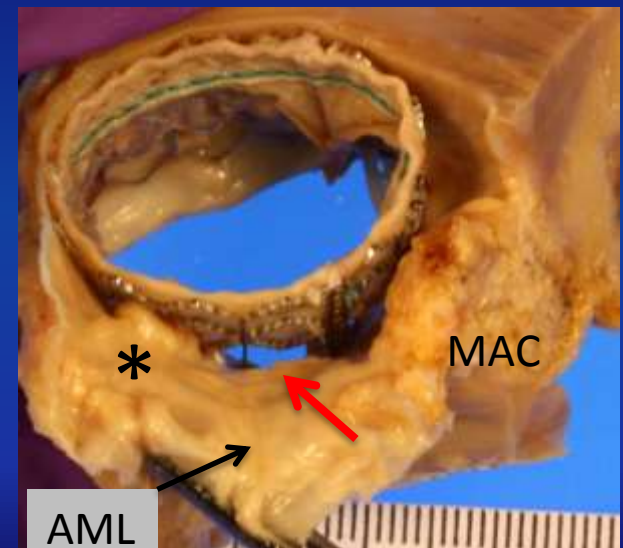
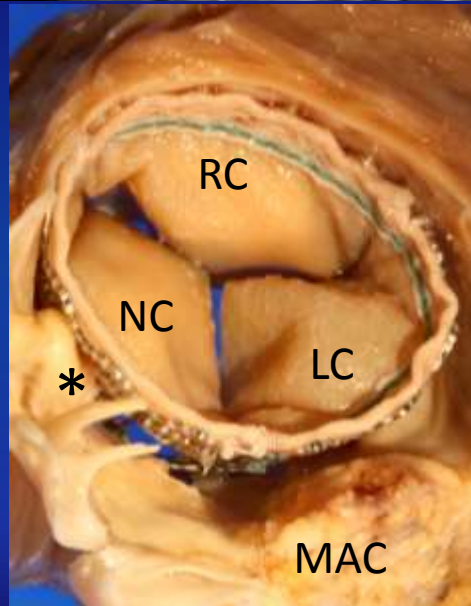
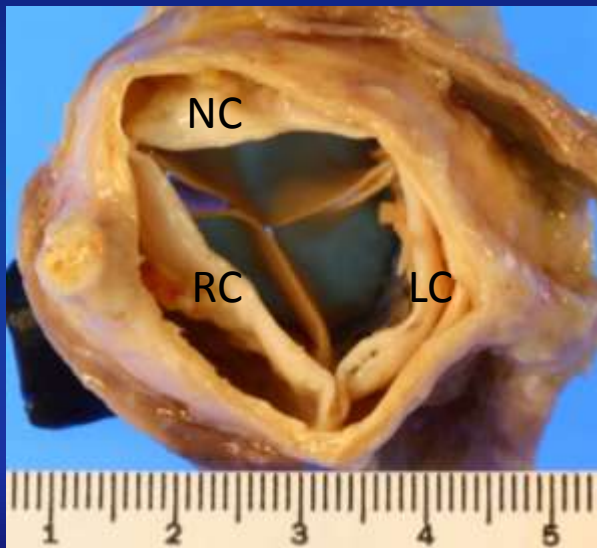
- **First in man study (including REVIVE trial): 9 cases**
- **PARTNER IA and IB: 15 cases**
- **PARTNER IIA and IIB: 18 cases**
- **PARTNER IIS3: 3 cases**

Reason for Explantation	
Explantation	6 cases
Infective endocarditis	1
LV perforation	1
Paravalular leak	2
Valve embolization	1
Valve stenosis from calcification	1

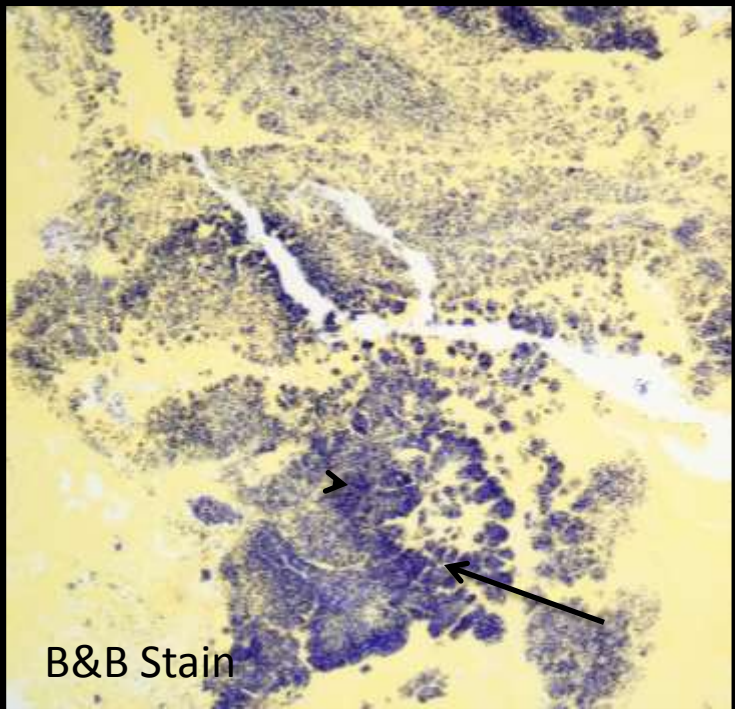
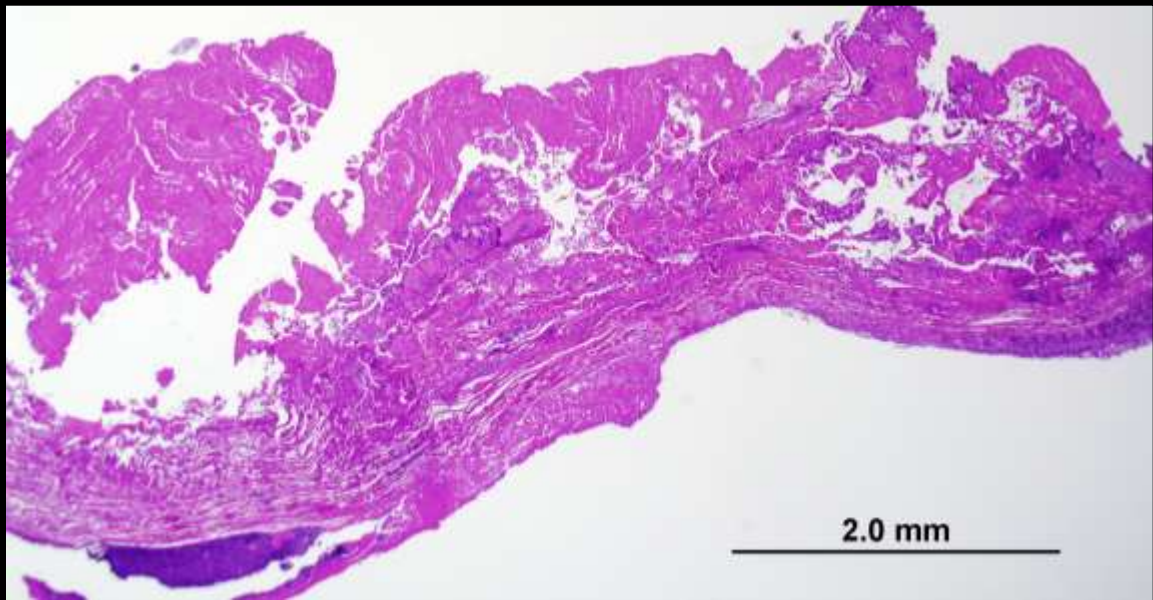
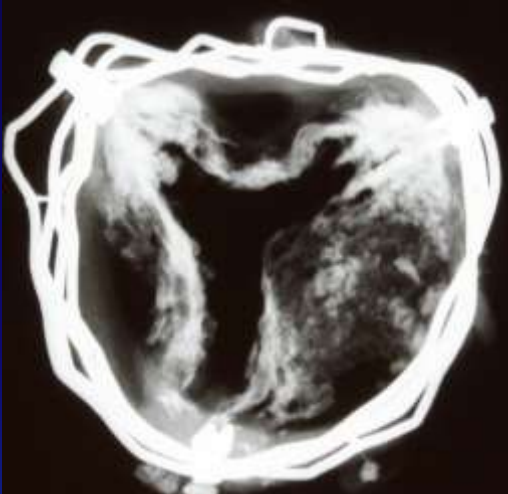
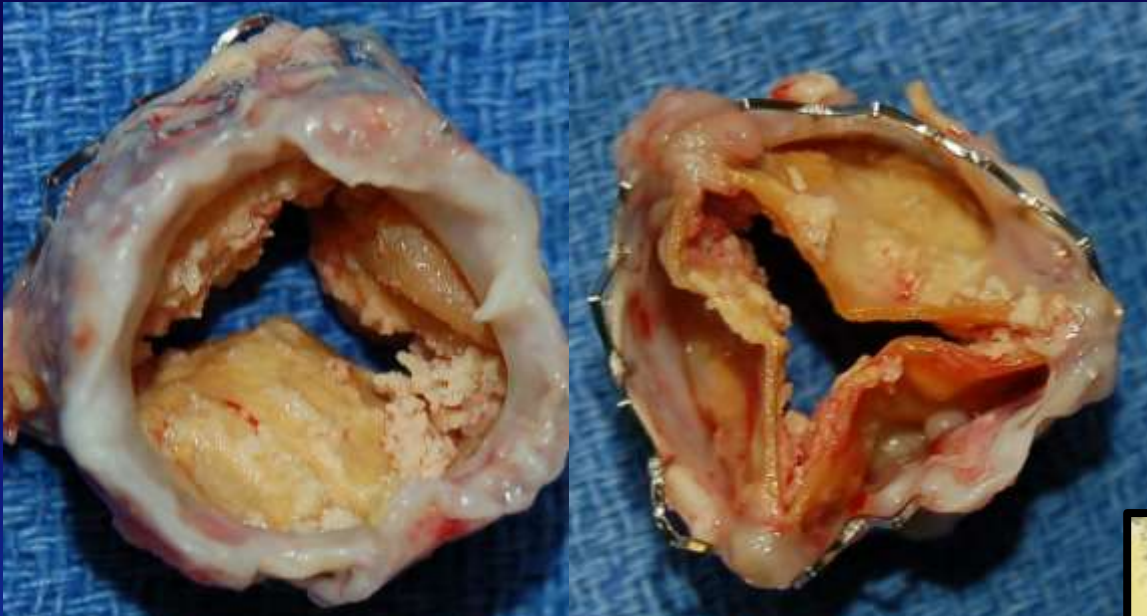
89 M status post percutaneous valve replacement (44 days) with subsequent paravalvular leak, severe and at death had pneumonia



Paravalvular gap between NCC and LCC. Linear calcification of NCC that extends into anterior mitral leaflet (*) and the mitral annular calcification extends into the medial commissure

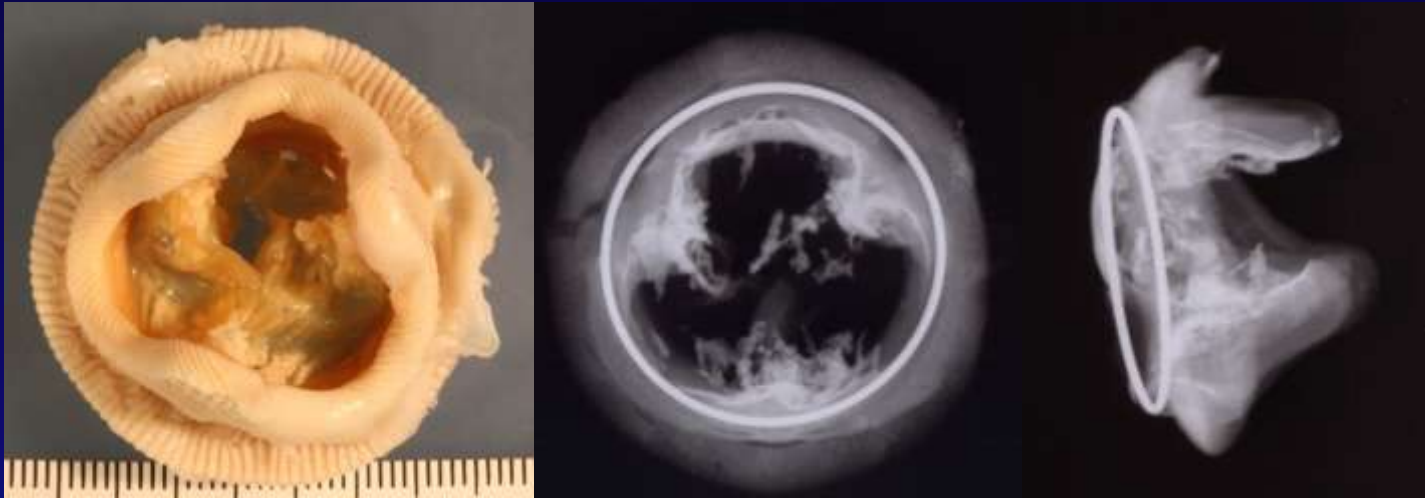


Edward Sapien valve explanted surgically 20 months after implantation. Patient had 3 episodes of bacteremia with *Strep bovis* 6 months and had positive culture 7 days prior to surgery attributed to extensive diverticulosis. He had developed severe AS.



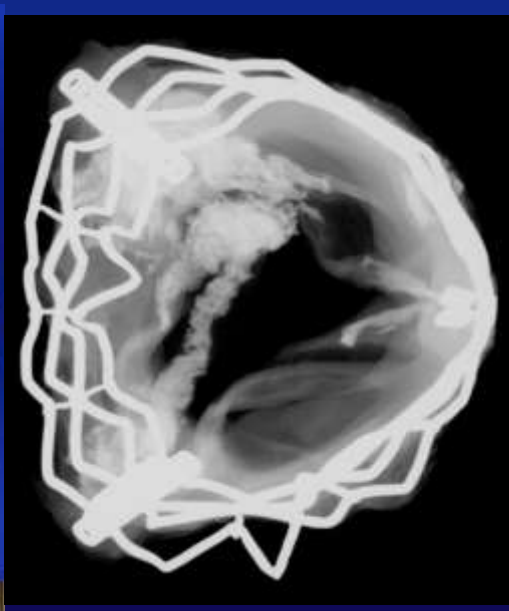
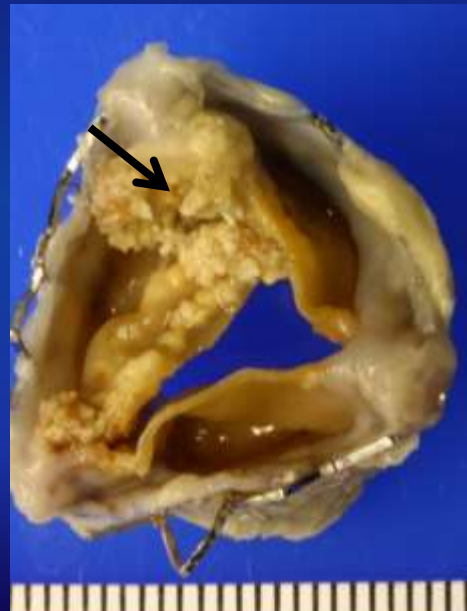
Porcine Surgical Valve:

42 year old male with congenital bicuspid aortic valve. Implantation duration- 5 years.



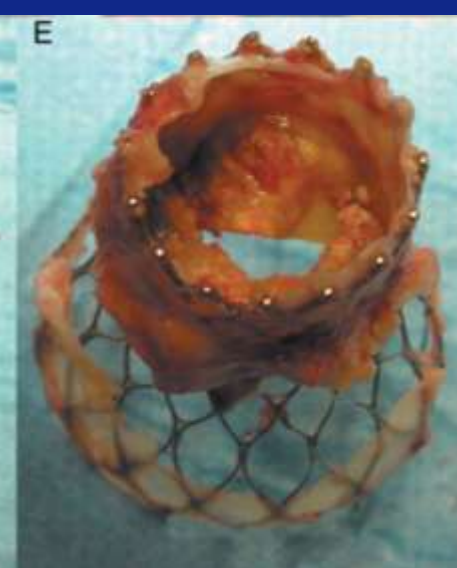
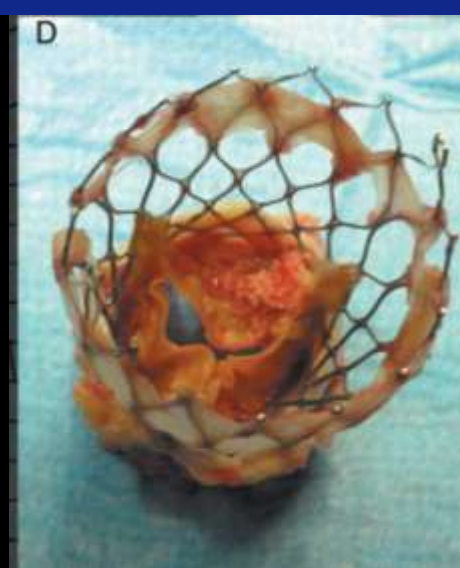
Edwards Sapien Transcatheter Valve:

77- year-old female with severe aortic stenosis.
Implant duration- 5 years.



CoreValve Transcatheter Valve:

74-year old male had TAVR
5-years earlier developed AS (gradient 53mmHg)



Edwards Sapien/ CoreValve Transcatheter Valve

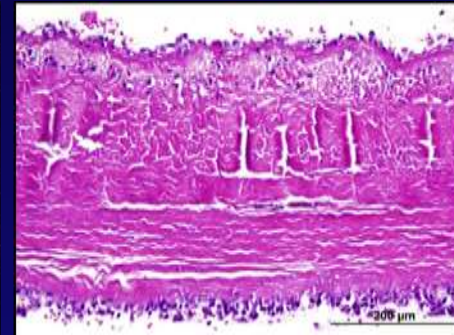
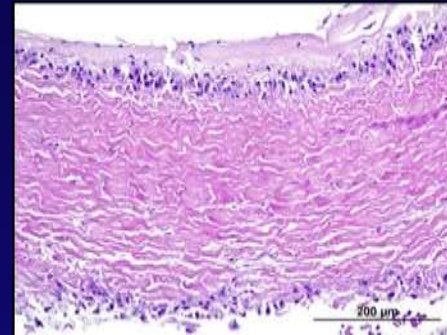
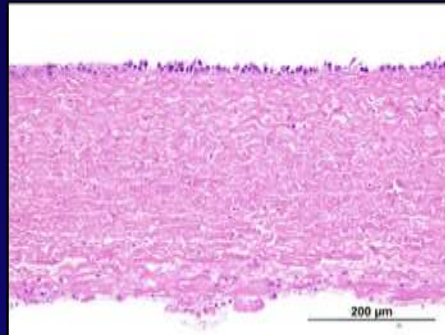
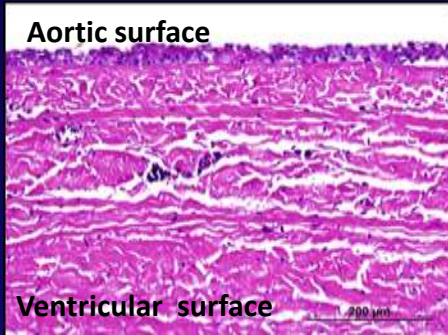
≤30 days

31 days – 1 year

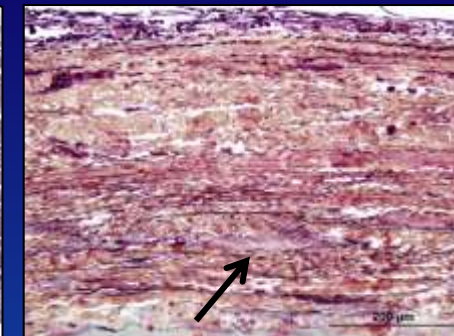
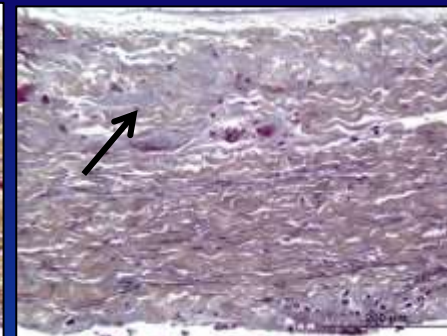
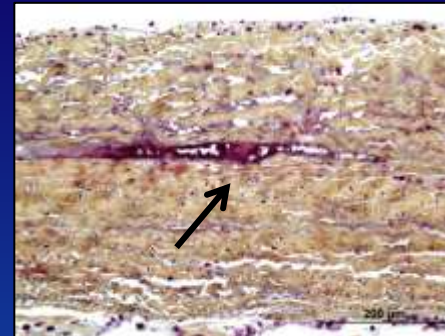
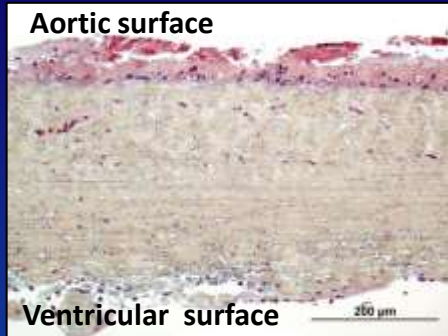
1 year – 3 years

≥3 years

Inflammation



Degeneration



Thrombus

≤30 days

31 days – 90 days



31 days – 90 days

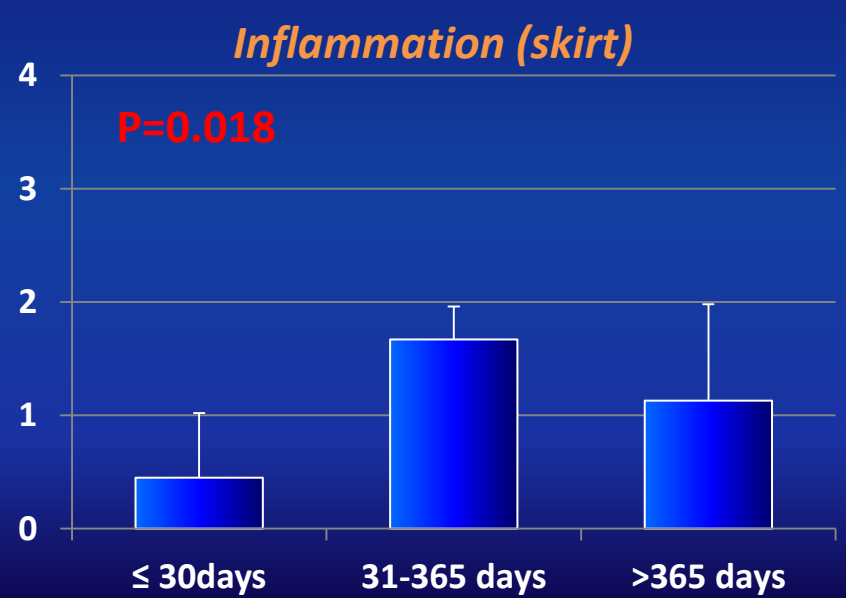
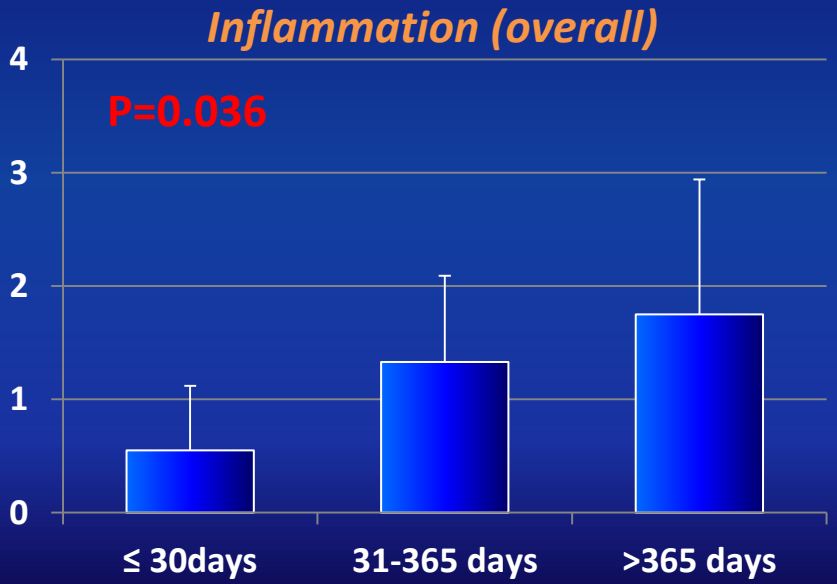
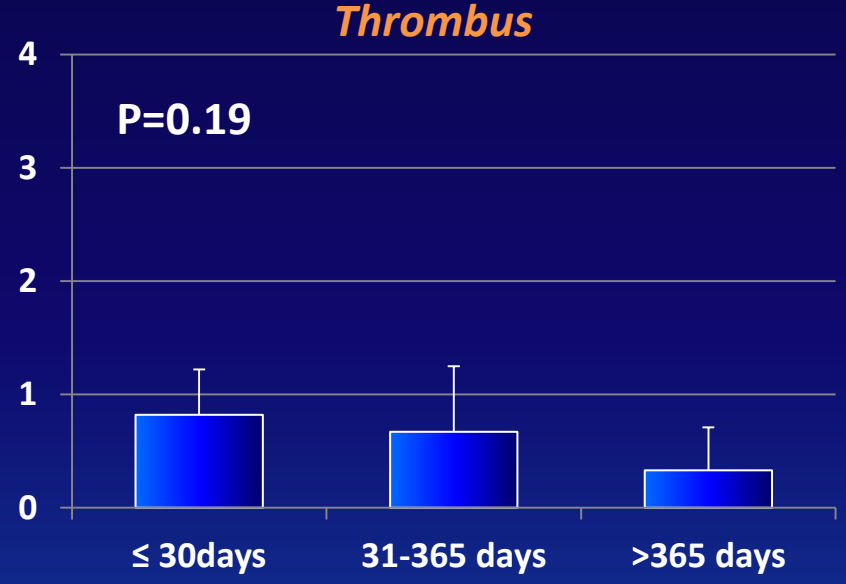
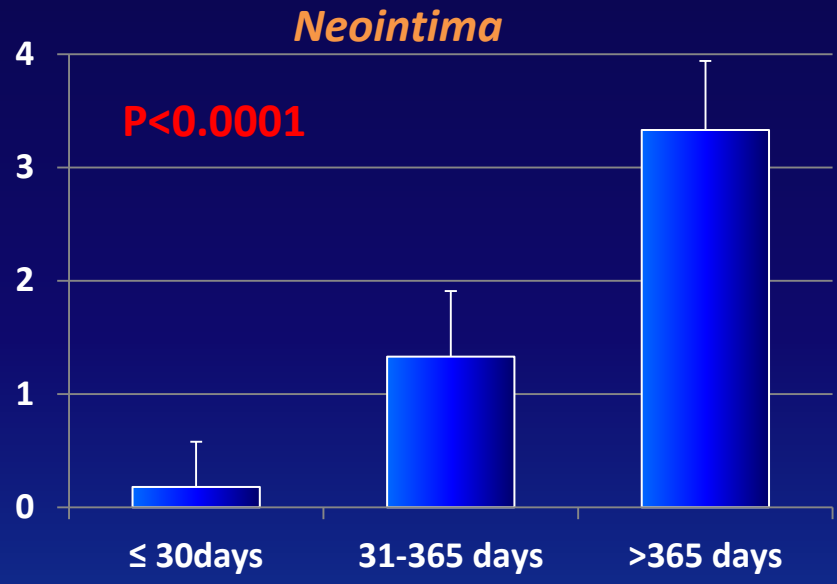


Valve thrombus



Histopathologic Analysis (Valve Frame): SAPIEN single valve without infective endocarditis in 21 cases

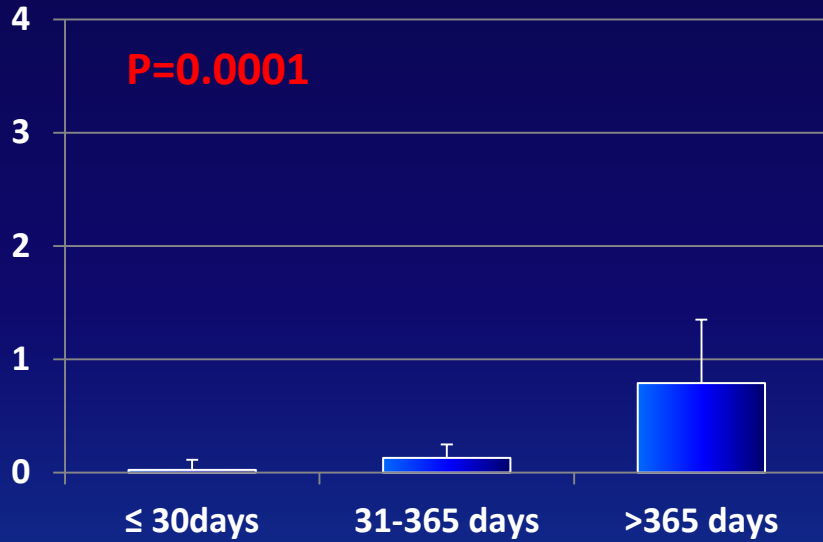
≤30 days (n=14), 31-365 days (n=3), >365 days (n=4)



Histopathologic Analysis (Leaflets): SAPIEN single valve without infective endocarditis in 21 cases

≤30 days (n=14), 31-365 days (n=3), >365 days (n=4)

Neointima



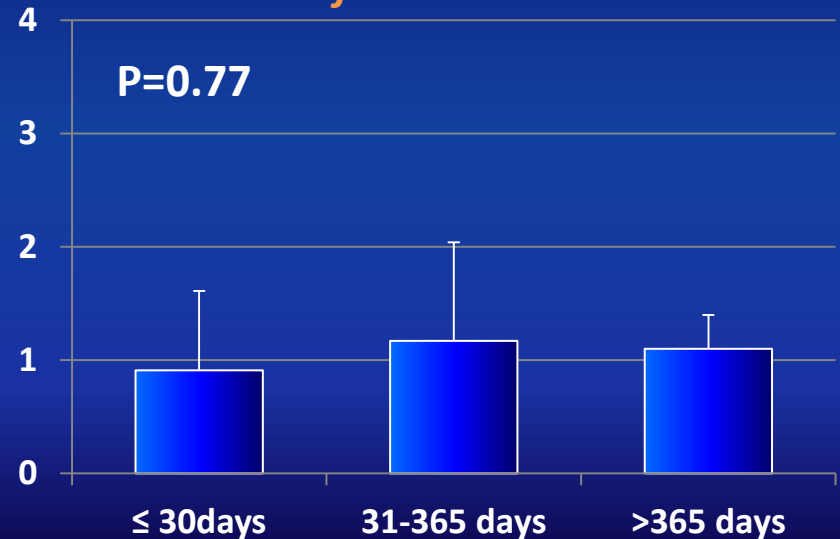
Structural changes



Thrombus



Inflammation



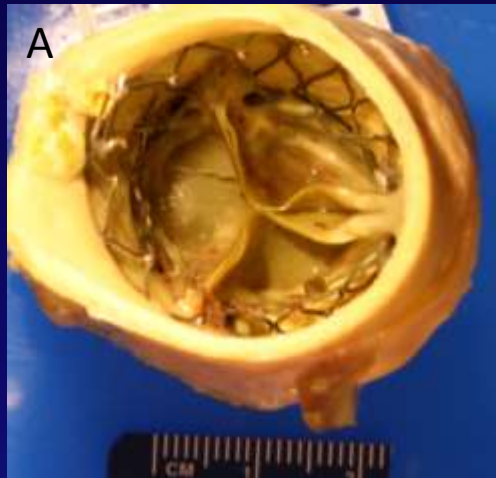
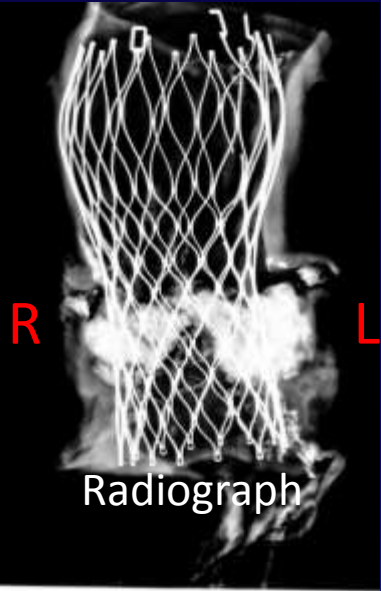
Cause of Death or Explantation CoreValve (64 cases)

- Expanded clinical evaluation: 7 cases
- US PIVOTAL: 23 cases
- ACCESS Continued Trial: 27 cases
- SURTAVI Clinical Trial: 3 cases
- Expanded Clinical Trial: 4 cases

Cause of Death	
Autopsy	62 cases
Valve-related death	16
Infective endocarditis	2
Paravalular leak	7
Valve thrombus (severe stenosis or stroke)	5
Valve compression	1
Severe stenosis due to pannus	1
Procedure-related death	13
LV perforation	2
Aortic root rupture	4
Retroperitoneal hemorrhage / bleeding	1
Anesthesia related death	1
Renal failure or AMI from embolus	3
Heart Block and/or bradycardia	2
Non-TAVR related cardiac death	7
Coronary artery disease (CAD)	4
Chronic heart failure with CAD	3
Non-cardiac death	20
Stroke/ subdural hematoma	4/1
Respiratory failure	6
Pneumonia	1
Pulmonary embolism	1
Multiorgan failure/sepsis	4
Suicide/Accident/Cancer	3
Unknown	6

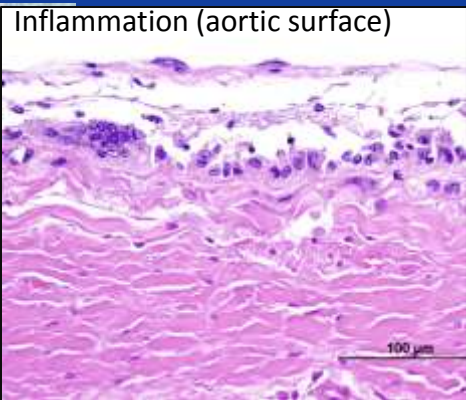
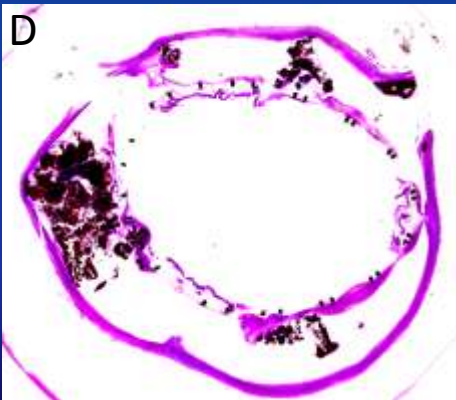
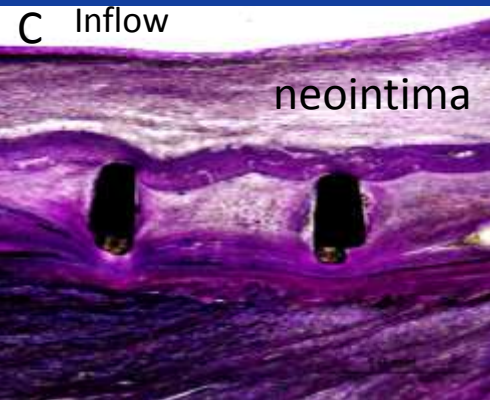
Reason for Explantation	
Explantation	2 cases
Infective endocarditis	1
LV perforation	0
Paravalular leak	0
Valve embolization	0
Valve calcification	1

CoreValve 2 years post implantation (89F with metastatic adenoCA)



A,B) Inflow : frame incorporated by thin neointimal coverage
Radiograph: Moderate: Native leaflets calcified;
frame excludes native leaflets;
C, D) Thin neointima covers frame

Valve Leaflets

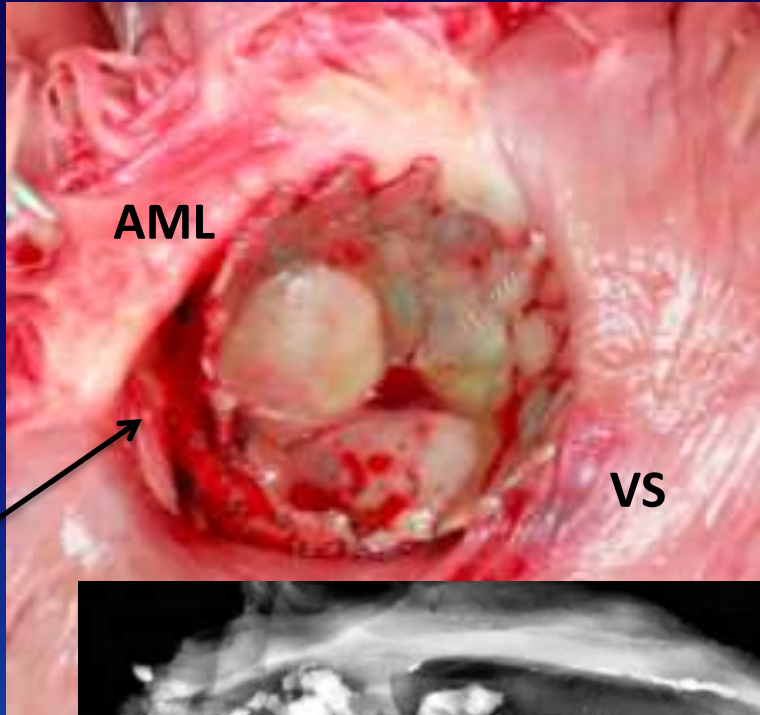


200 μm

100 μm

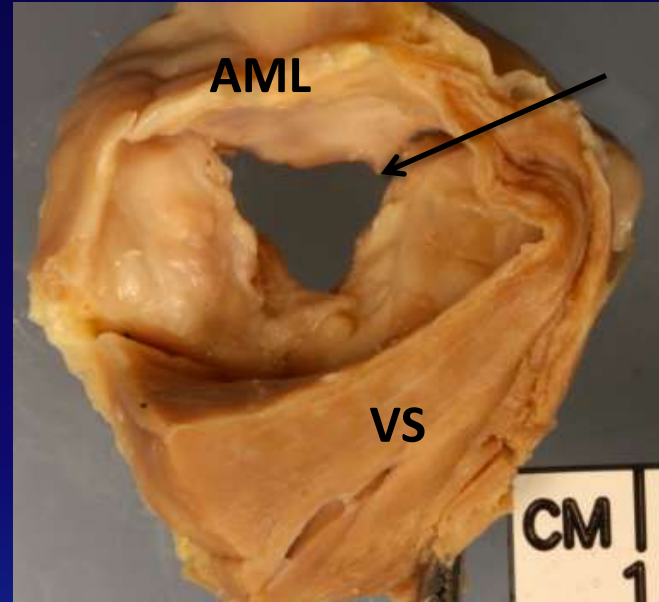
84-year old M with AS had CoreValve
Implanted 22 days prior to death developed
aortic regurgitation post TAVI.

Left ventricular out flow

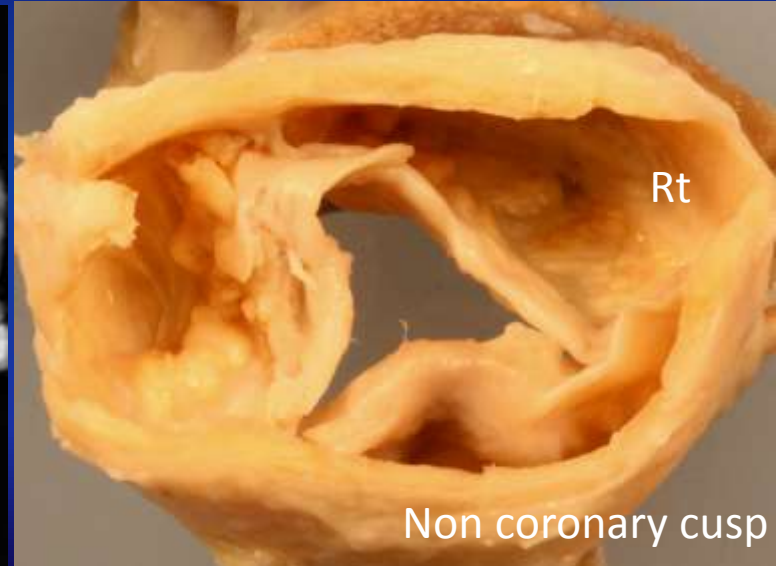
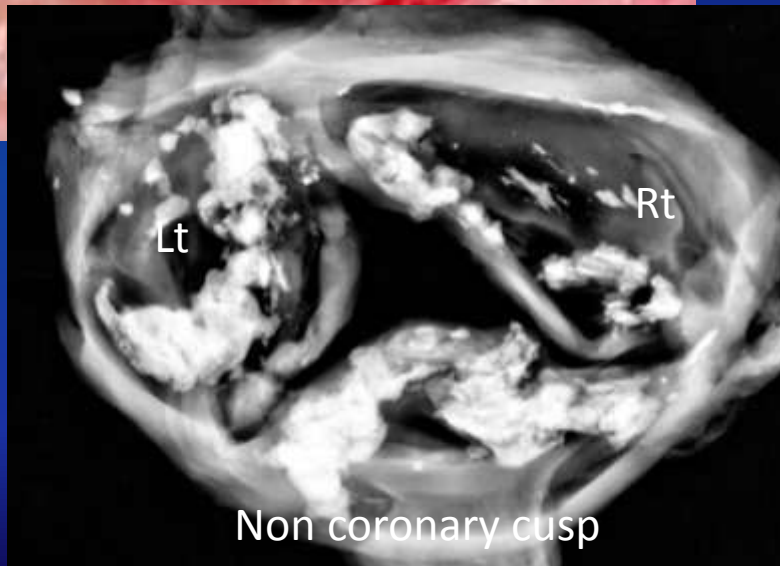


Inferior view

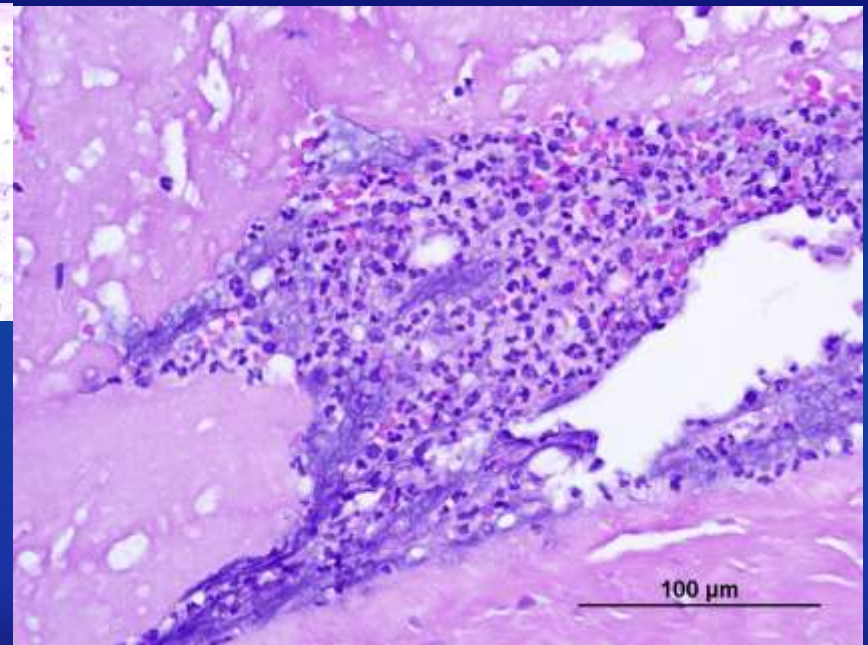
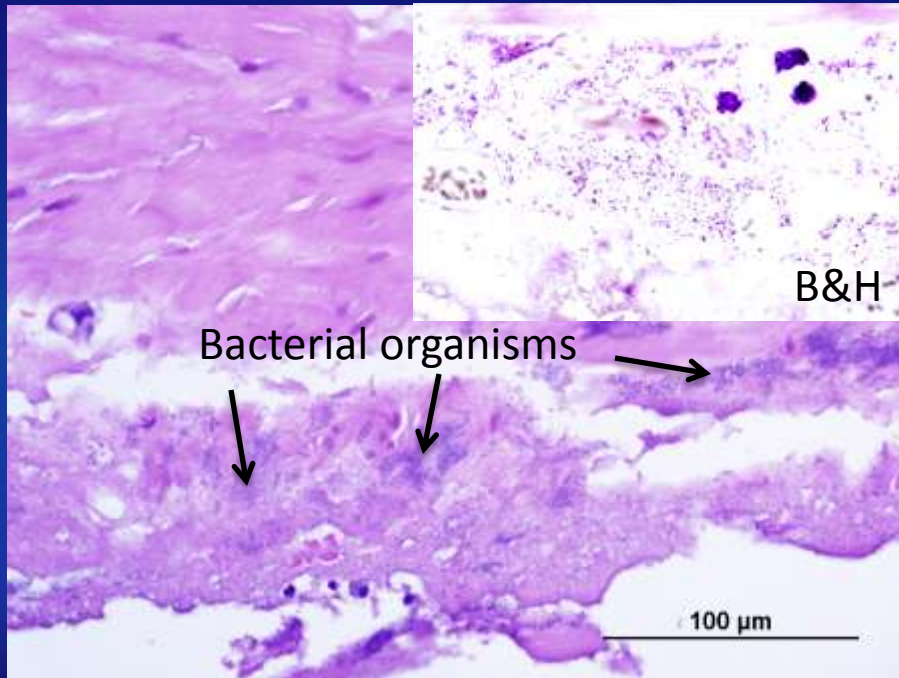
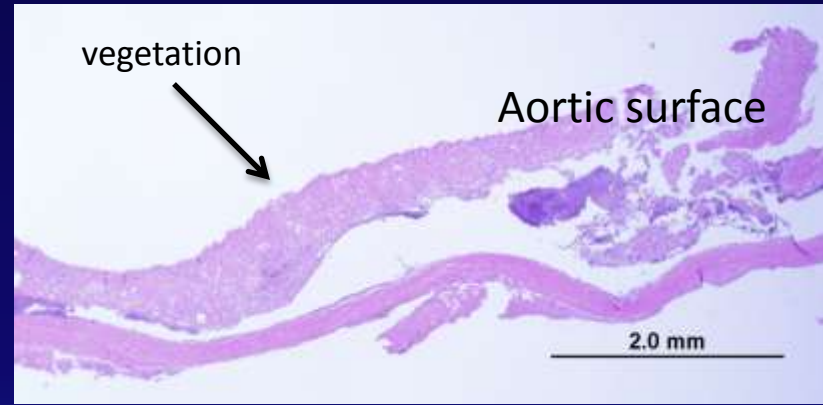
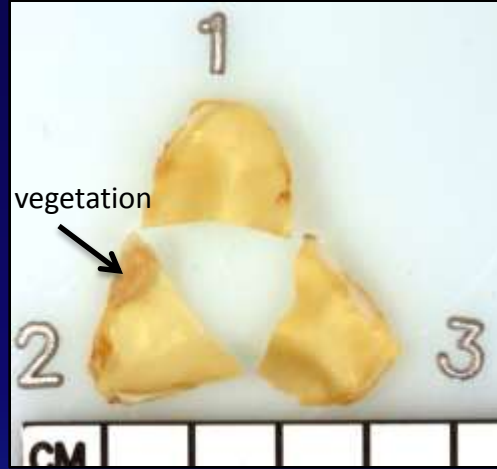
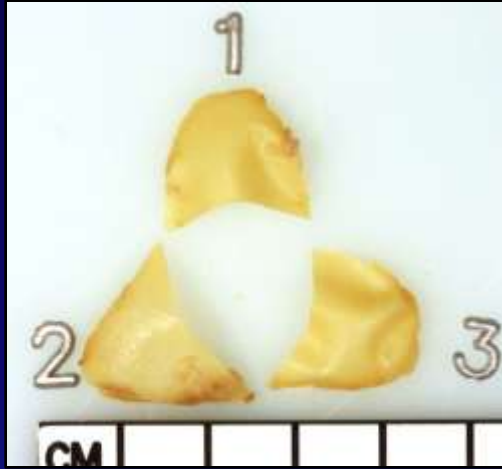
Non-coronary cusp



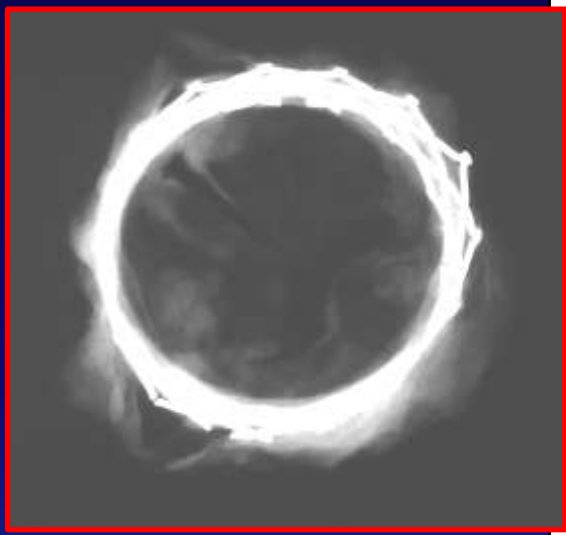
Superior View



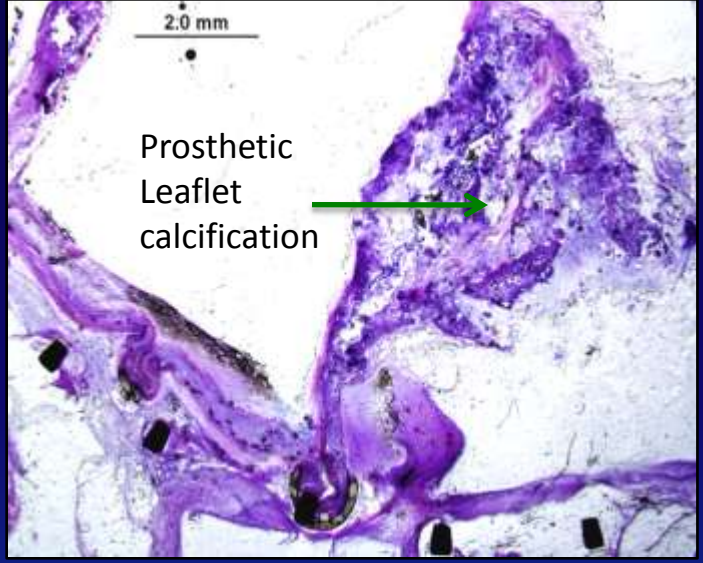
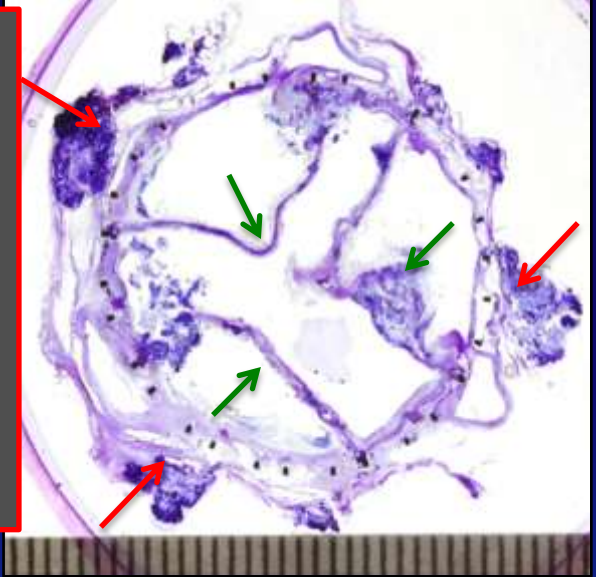
83-year-old man diagnosed with infective endocarditis 8 months following implantation of CoreValve (Blood cultures positive for *Staphylococcus aureus*).



74-year-old man had CoreValve Implantation 5 years ago, developed AS (gradient 53mm Hg). Structural valvular failure due to calcification, surgically replaced.

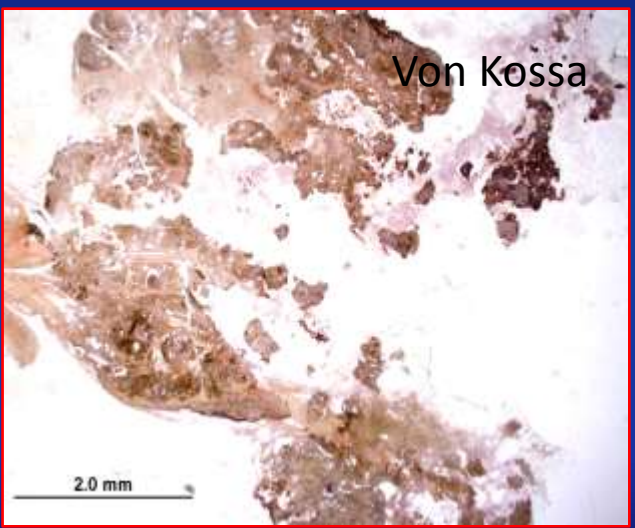
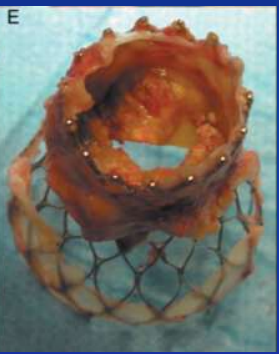


Superior view



Aortic view

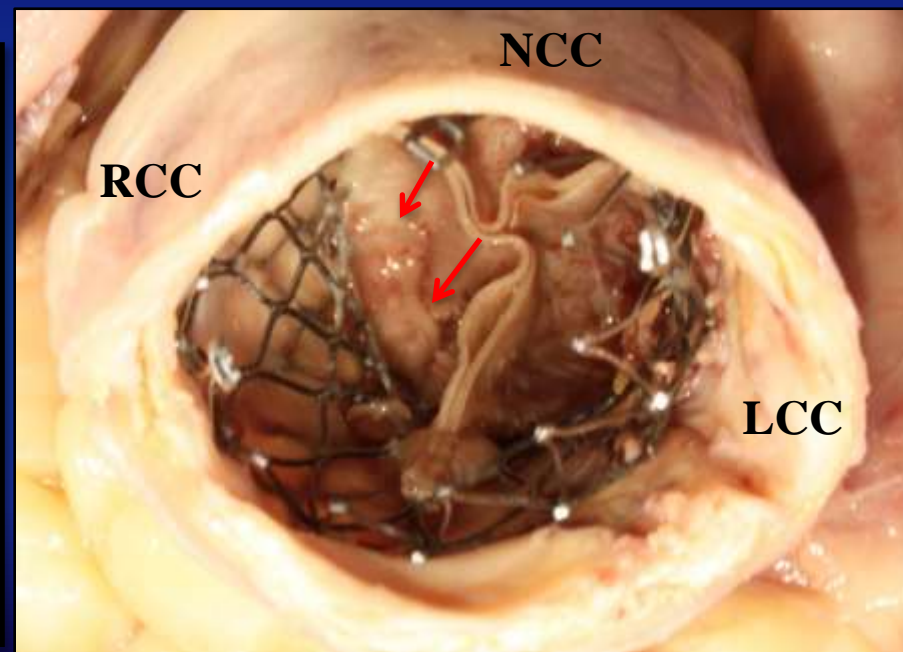
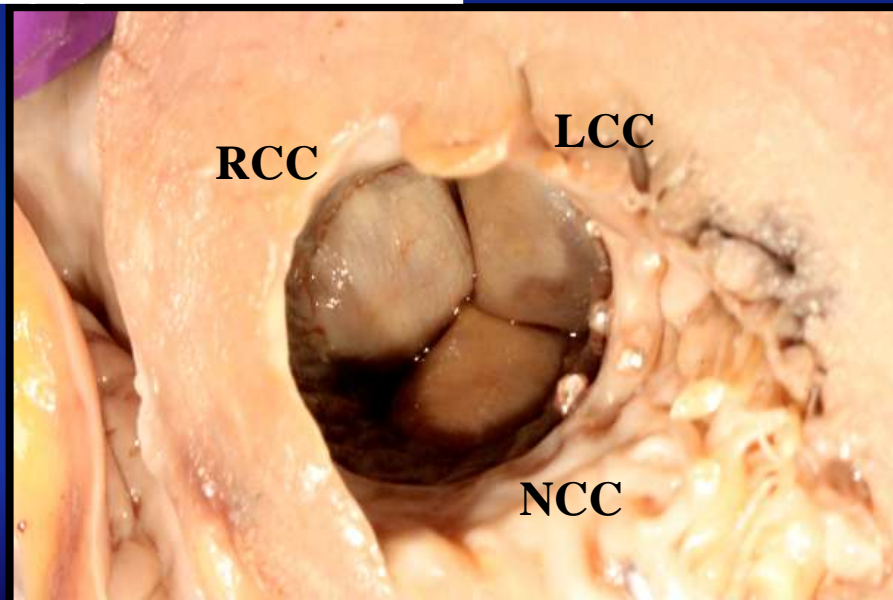
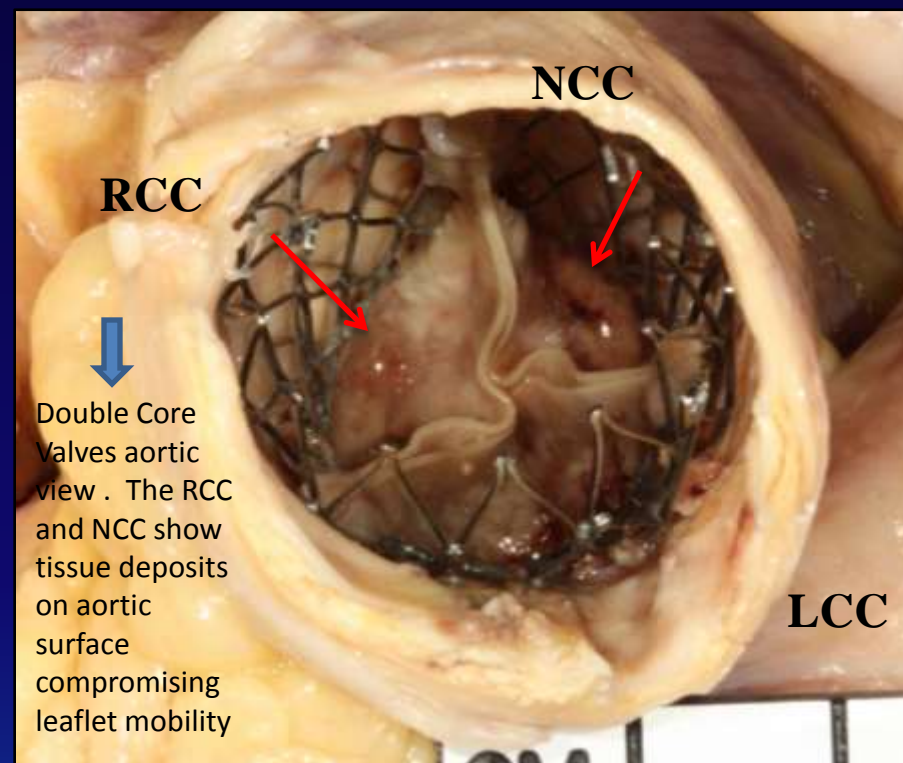
Ventricular view



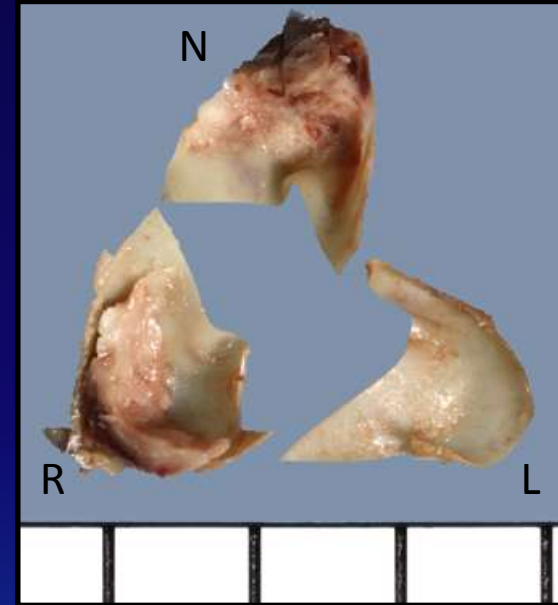
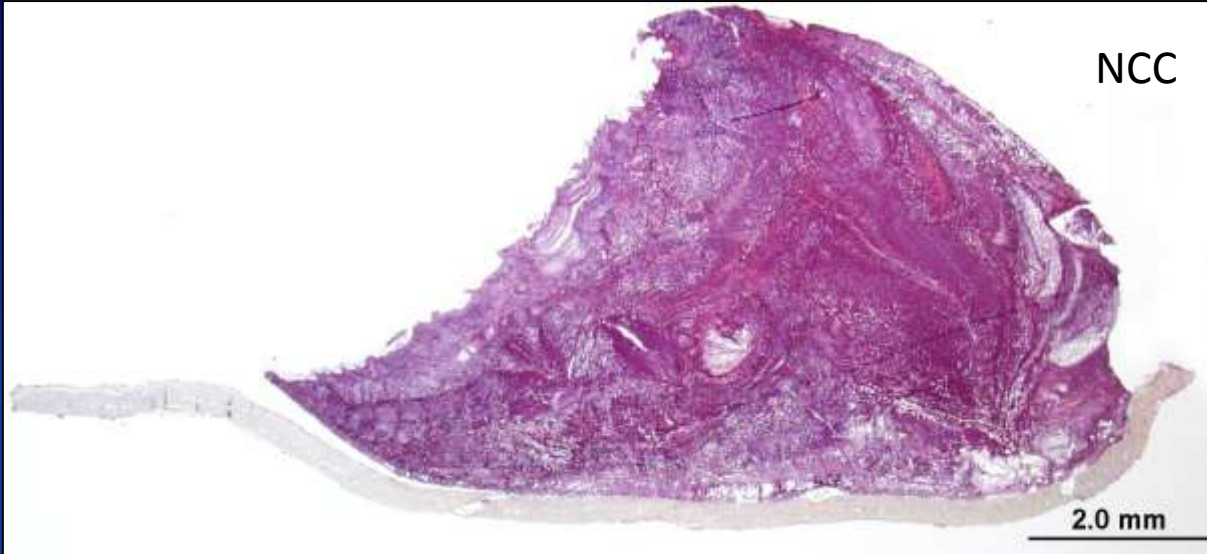
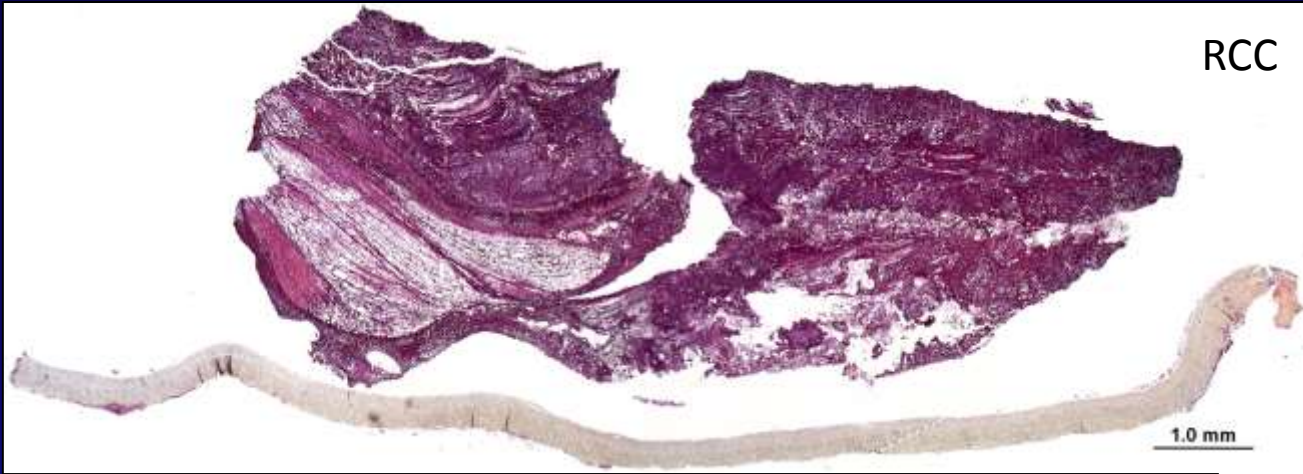
Case reports of TAVR thrombus (upto Feb. 2015)

	Author	Age	Sex	Type of THV	Follow up after TAVR			Anti-platelet therapy after TAVR	Treatment
					Duration	Symptom	Examination		
Clinical cases									
1	Trepels T, et al.	84	F	SAPIEN (23 mm)	8 M	Dyspnea	Mean PG; 11 to 53 mmHg	Discontinuing DAPT after 6 W	THV retrieval and SAVR
2	Kefer J, et al.	78	M	SAPIEN (26 mm)	4 M	NSTEMI; CHF	Mean PG; 15 to 72 mmHg	DAPT. Clopidogrel stopped after 1 M	Anticoagulation (heparin followed by coumadin)
3	Pergolini A, et al.	87	M	SAPIEN XT (29 mm)	8 M	Dyspnea NYHA I to III	Mean PG; 8 to 50 mmHg	DAPT, Clopidogrel stopped after 3 M Clopidogrel was reinstated instead of aspirin due to nasal bleeding after 4 M	Anticoagulation (heparin followed by coumadin)
4	Greason K, et al.	74	F	SAPIEN (23 mm)	2 W	Dyspnea NYHA I to III	Mean PG increased to 43 mmHg	Aspirin	THV retrieval and SAVR
5	Cota L, et al.	80	M	SAPIEN XT (23 mm)	10 M	Dyspnea NYHA I to III	Mean PG increased to 54 mmHg TEE:	DAPT	Anticoagulation (OAT)
6	Cota L, et al.	81	M	SAPIEN XT (23 mm) in Carpentier Edwards (25mm).	4 M	Dyspnea NYHA I to III	Mean PG increased to 51 mmHg TEE:	N/A	Anticoagulation (OAT)
7	Cota L, et al.	74	F	SAPIEN XT (26 mm)	2 M	Dyspnea NYHA I to II	Mean PG increased to 34 mmHg TEE	DAPT	Anticoagulation (OAT)
8	Latib A, et al.	83	M	SAPIEN XT (26 mm)	6 M	Dyspnea NYHA I to II	Mean PG increased to 68 mmHg TEE	DAPT	Anticoagulation (OAT)
9	Latib A, et al.	81	M	SAPIEN XT	15 M	Dyspnea NYHA I to III	Mean PG increased to 45 mmHg	DAPT, Clopidogrel stopped after 3 M	Anticoagulation (OAT)
10	Latib A, et al.	83	M	SAPIEN XT (26 mm)	24 M	Dyspnea NYHA I to III	Mean PG increased to 37 mmHg	N/A	Anticoagulation (OAT)
11	Al-Rashid F, et al.	72	M	SAPIEN	6 M	Dyspnea NYHA II to III	TEE: Thickened restricted THV leaflets without thrombus	Discontinuing DAPT after 4 M	DAPT
12	Tay E, et al.	66	M	SAPIEN(23 mm)	3 D	Cardiac arrest	TEE: Thrombus on the THV at post implantation	DAPT	Heparin continued post TAVI
13	Tay E, et al.	77	F	SAPIEN (26 mm) within MVR	1 M	Dyspnea	TEE: Thrombus on edge of THV	DAPT	Anticoagulation
14	Lancellotti P, et al.	86	M	CoreValve (26 mm)	12 M	Dyspnea NYHA I to III	Mean PG increased to 41 mmHg	DAPT, clopidogrel stopped at 3 M	THV retrieval and SAVR
15	Pache et al.	86	M	SAPIEN XT (29 mm)	7 D	NA	CTA: Restricted leaflet mobility with thrombus (incidental)	DAPT	Anticoagulation (Coumadin)
Autopsy cases									
1	CVPath Institute	68	F	CoreValve (26mm) in CoreValve (26mm)	1 st ; 6 M 2 nd ; 17 D	Dyspnea NYHA II to III	1 st ; Mean PG; 16 to 50 mmHg	Aspirin	6 months; TAVR, death
2	CVPath Institute	88	F	SAPIEN (23mm)	48 D	Dyspnea NYHA I	Mean PG; 9 mmHg (same as immediate post implant)	DAPT	Death
3	CVPath Institute	90	M	CoreValve (29mm)	15 D	Unknown	Unknown	Unknown	Death
4	CVPath Institute	77	F	SAPIEN XT (23mm)	16 M	Chest pain	Mean PG; 29 to 97 mmHg	Aspirin	Death

70-years WF, h/o hypertension, dyslipidemia, PVD, moderate chronic lung disease on home oxygen, anemia and NYHA functional class III; a 26 mm Core Valve was implanted on 6/6/2011, and a new LBBB and 1st degree AV block were noted at discharge on 6/11/2011; at one month there was mild paravalvular AR and NYHA functional class II; at 6-month there was transvalvular and paravalvular AS, NYHA functional class III, on echo pannus/aortic stenosis; a valve-in-valve procedure was performed on 1/6 /2012 without complications and died on 1/23 /2012 (17-days post valve-in-valve) of AS

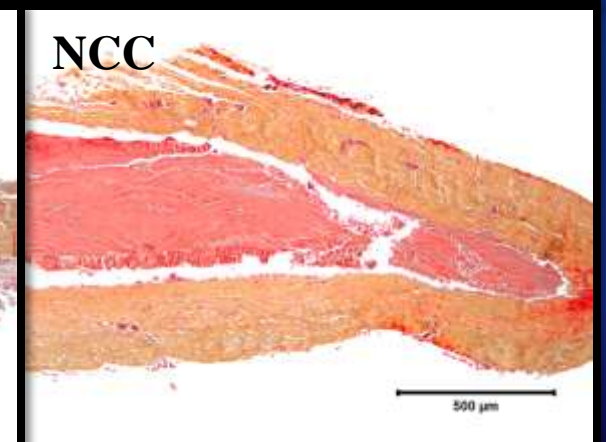
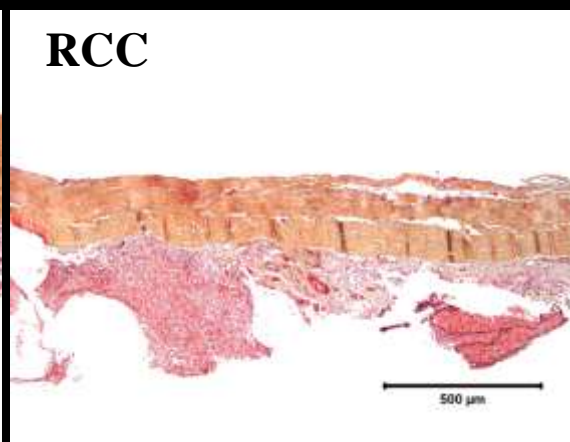
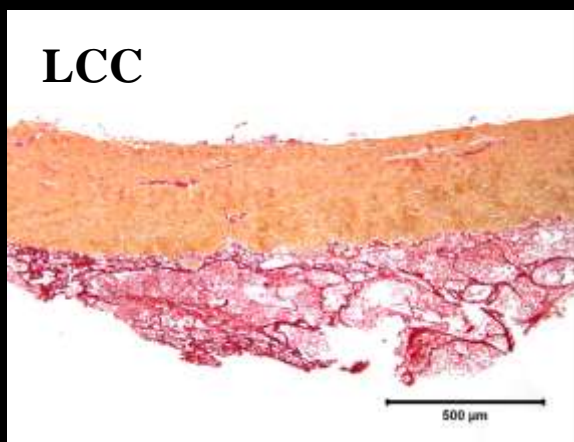
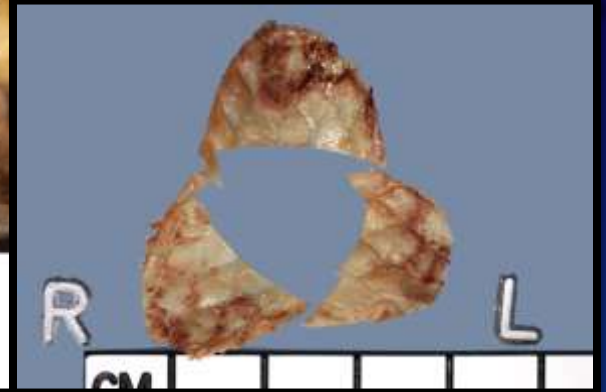
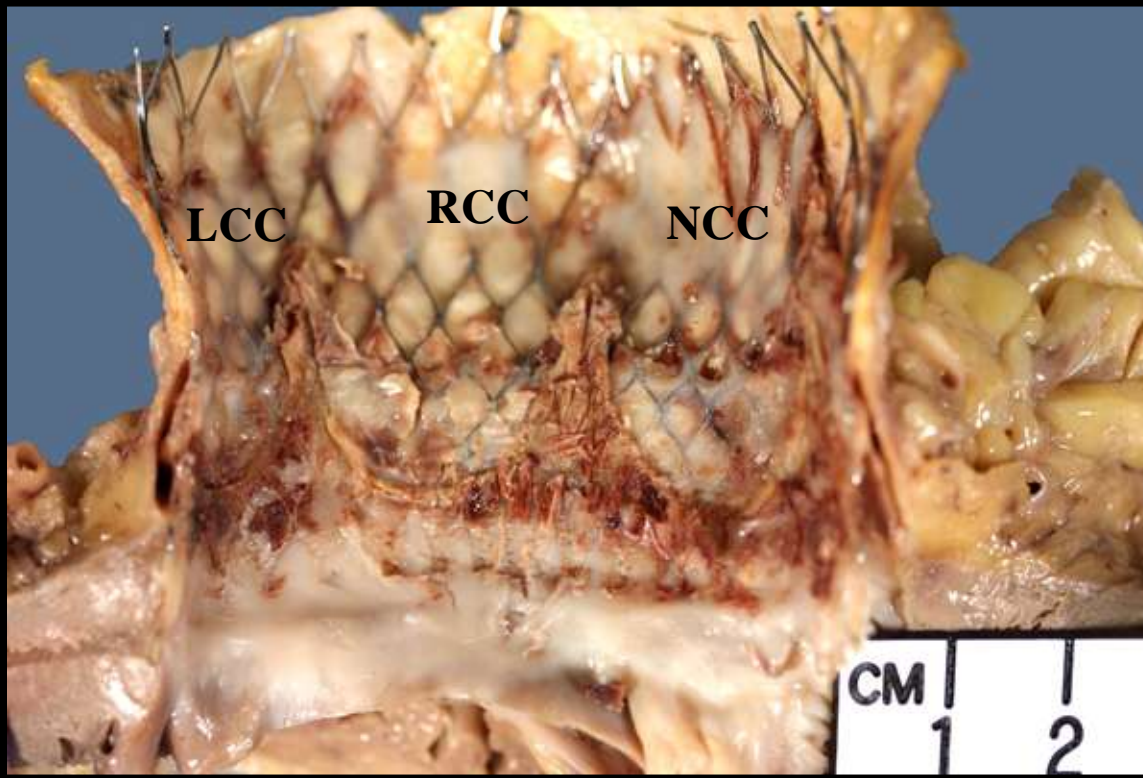


Inner CoreValve

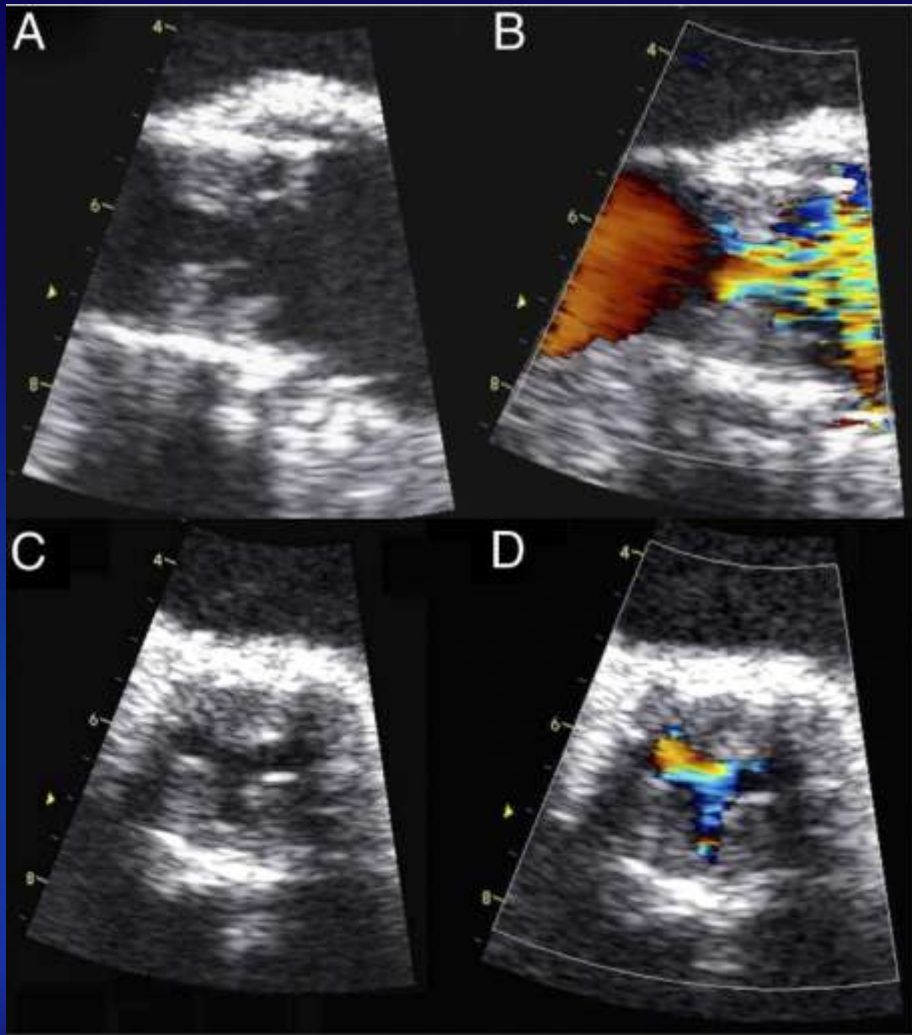


Ventricular surface

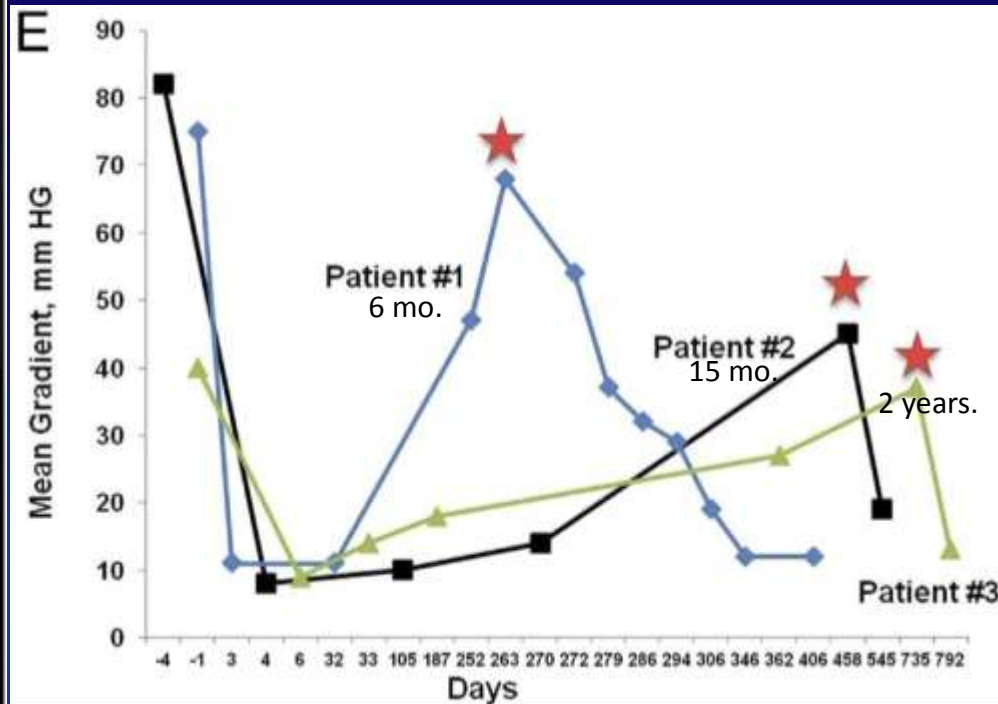
Outer Core Valve



Reversible Edward Sapien XT Dysfunction Due to Prosthesis Thrombosis



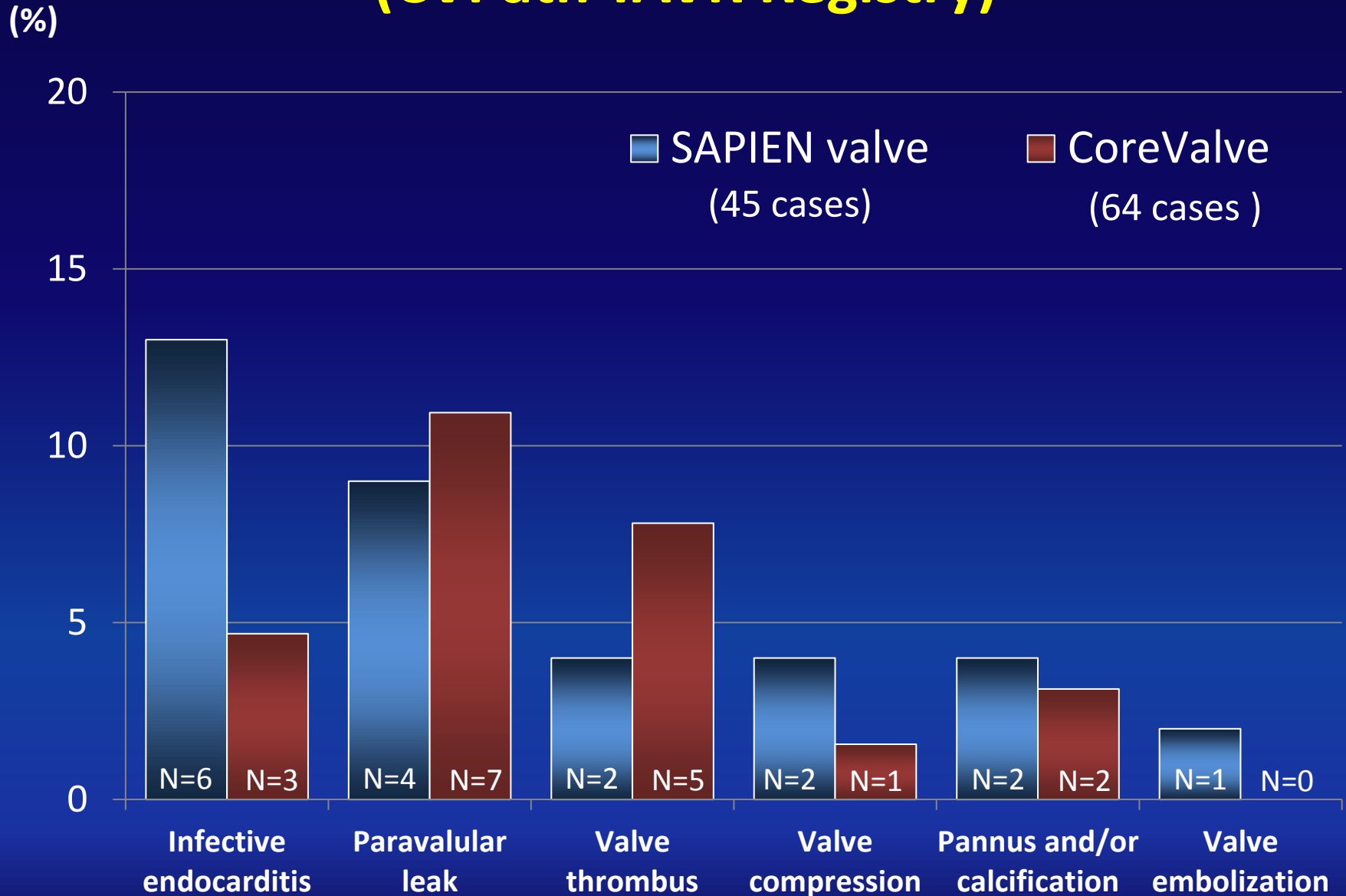
All patients received Vit K antagonists plus aspirin following increase in gradient with symptom improvement and gradient normalization.



Patient 1. 83-yrs-old M H/O stroke, CABG, high risk Euro Score 30%, DAPT, MPG 11 mm Hg, 6 mo, MPG 47mm Hg, increased to 68mm Hg thickened leaflets.
 Patient 2. 81-yrs-old M, Euro score 11%, post procedure MPG 8mm Hg. Discharged on DAPT, which was stopped at 3-months. At 15-moMPG 45mm Hg.
 Patient 3. 83-yrs old M, Euro Score 20%, discharge post-procedure MPG 9mm Hg, Remained well 1, 6, and 12-mo. At 2 years SOB, MPG 37mm Hg worsening paravalvular leak. Latib A, et al. JACC2013;61:787-89

Restricted Leaflet Motion with reduced opening

Transcatheter Heart Valve Failure (CVPaTh TAVR Registry)



Autopsy Studies of TAVR

➤ The main causes of TAVR failure are:

- ✓ Valve related death
- ✓ Procedure related death
- ✓ Non TAVR related cardiac deaths and non-cardiac death

➤ Main causes of valve failure are:

- ✓ Infective endocarditis
- ✓ Pannus
- ✓ Thrombosis
- ✓ Calcification –rarest (but we have very few late cases)

Acknowledgments

Funding

CVPath Institute Inc.

CVPath Institute

Kazuyuki Yahagi, MD

Hiroyoshi Mori, MD

Oscar D. Sanchez, MD

Tobias R. Koppara, MD

Elena Ladich, MD

Robert Kutz, MS

Ed Acampado, DVM

Youhui Liang, MD

Abebe Atiso, HT

Jinky Beyer

Giselle Magsalin

Hedwig Avallone, HT

Lila Adams, HT

Hengying Ouyang, MD

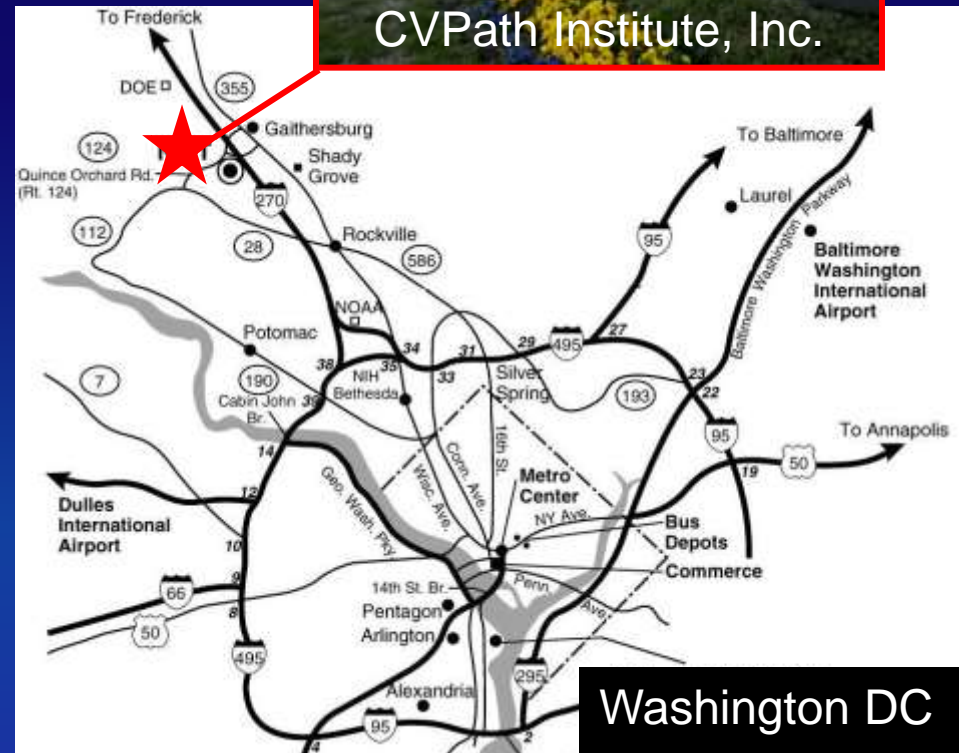
Frank D Kolodgie, PhD

Harry Davis, MD

Micael Joner, MD



CVPath Institute, Inc.



TAVI-Related Complications

Valve Procedure Related Death

- Conversion to open surgery, or open sternotomy secondary to procedure –related complication or unplanned use of CPB
- Coronary obstruction
- Ventricular septal perforation, aortic perforation
- Mitral valve dysfunction
- Cardiac tamonade

Complication from prosthetic valve

- Endocarditis
- Valve thrombosis
- Valve calcification
- Valve malpositioning – valve migration, embolization, ectopic valve deployment
- Paravalvular leak, moderate to severe
- Valve-in-valve