TAVR: The Latest Information & Team Strategy

Samir Kapadia, MD

Professor of Medicine

Section head, Interventional Cardiology

Director, Cardiac Catheterization Laboratory

Cleveland Clinic

TAVR – Where Did We Start?

Questions in 2003-4

1. Is there an unmet need for patients with AS?

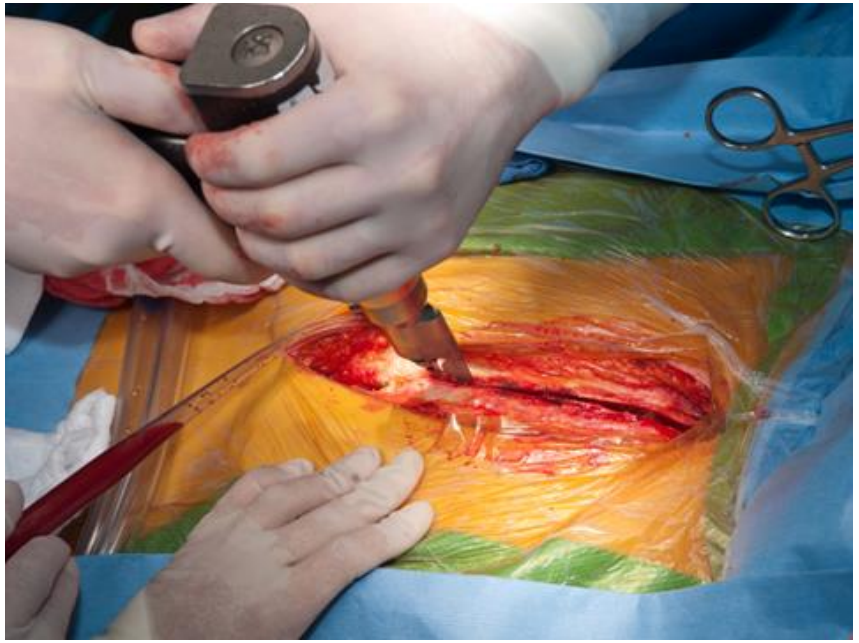
- **May be for inoperable patients**

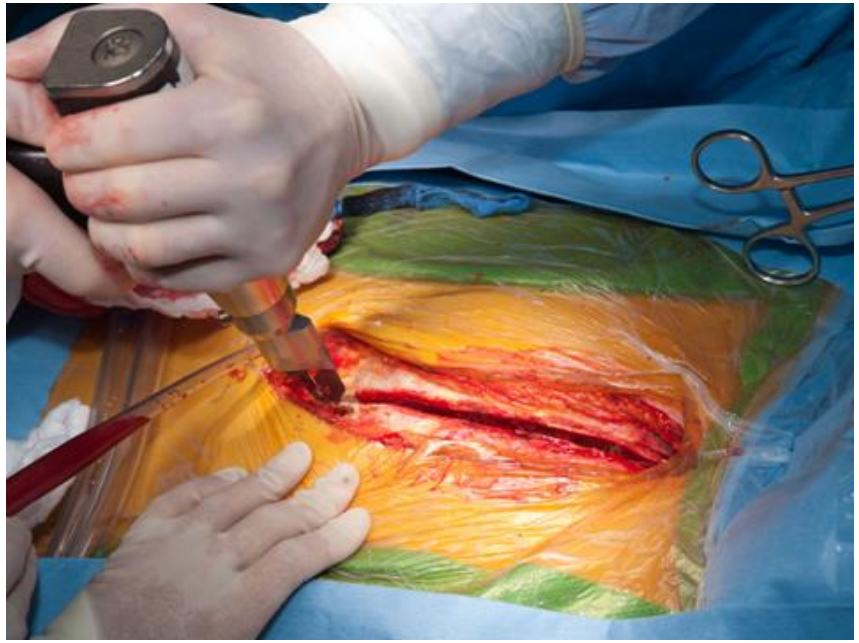
2. How can one improve on outstanding results of SAVR?

Aortic Stenosis – “typical” patient
2003

- 75 year old patient
- No prior cardiac history
- Presents with shortness of breath with exertion
- No CP
- No lightheadedness
- O/E BP 120/80, HR 90
- No JVD
- S1 normal A2 not heard, late peaking systolic murmur
- No edema
- Lungs clear

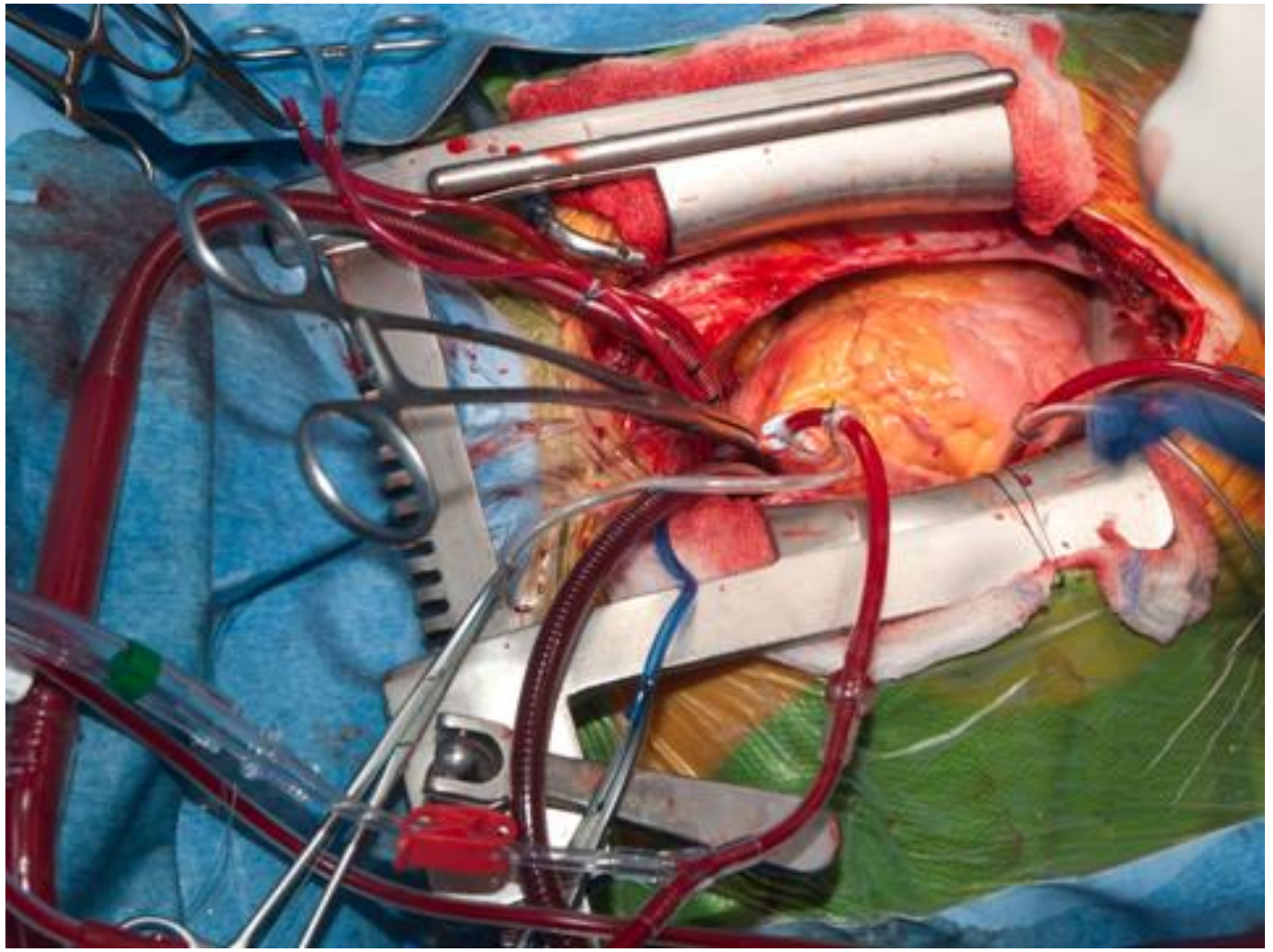
Sternotomy



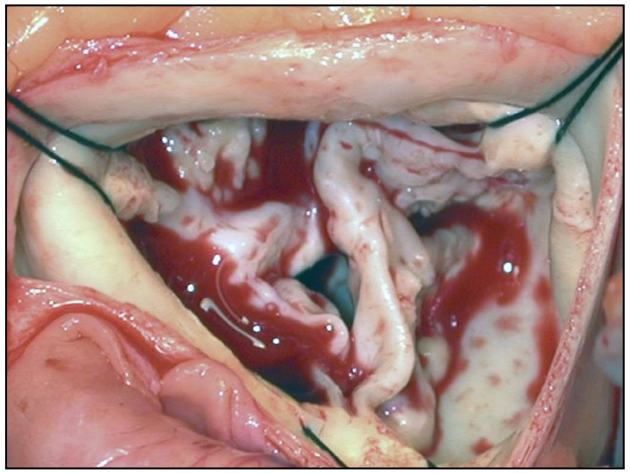
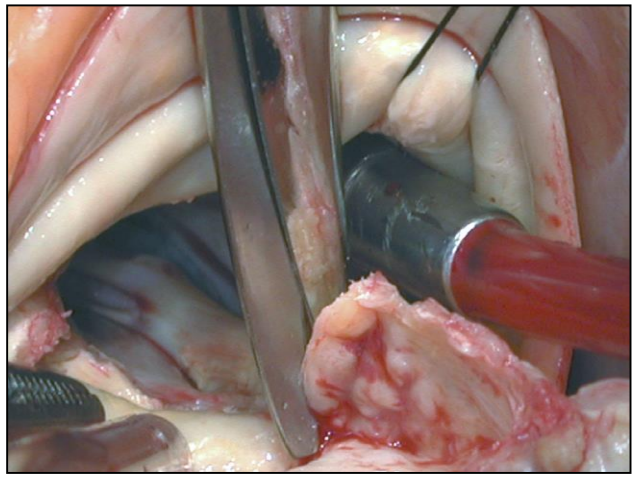
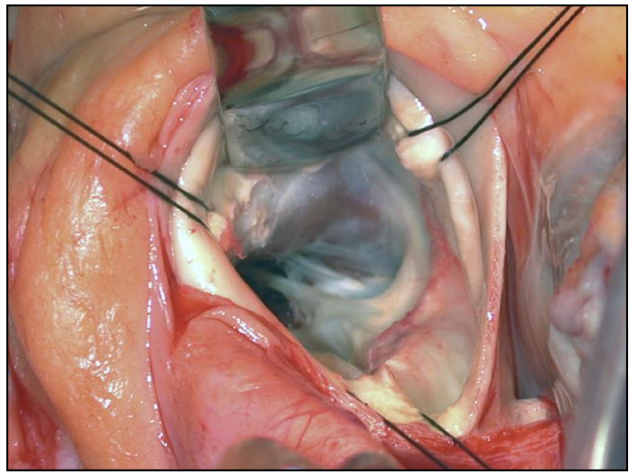
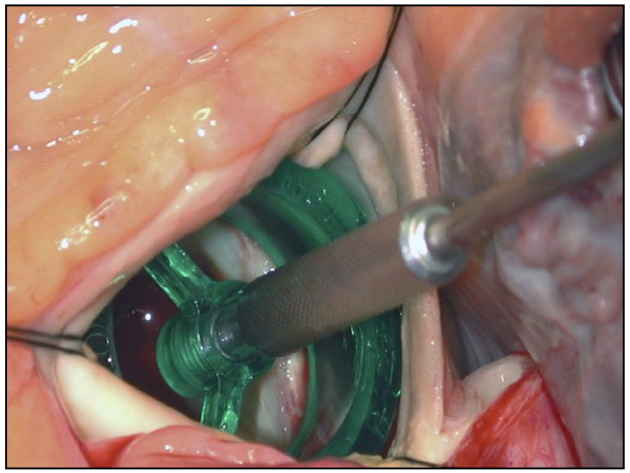
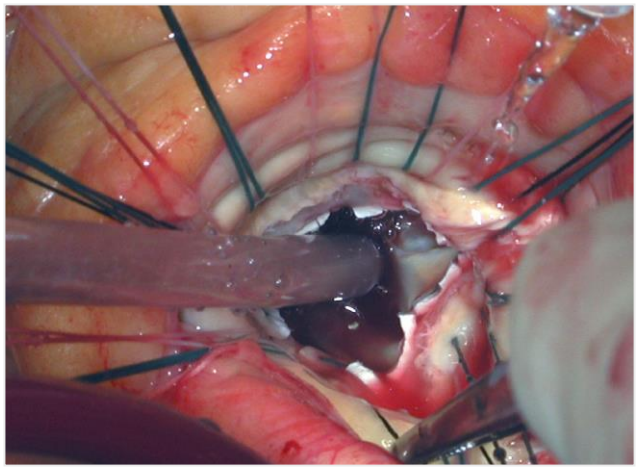
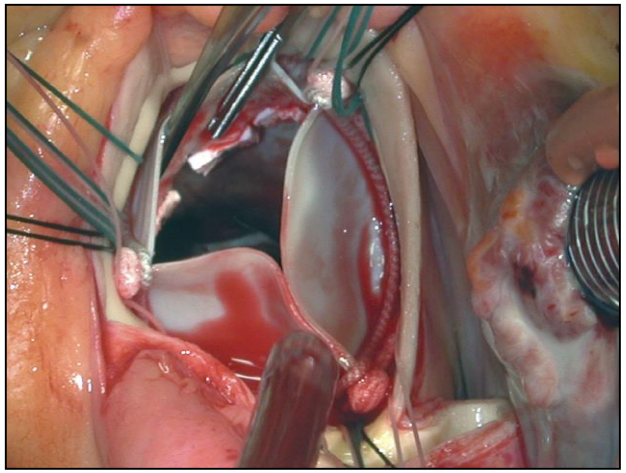


Courtesy Dr. Mick

Aorta Cross-clamped

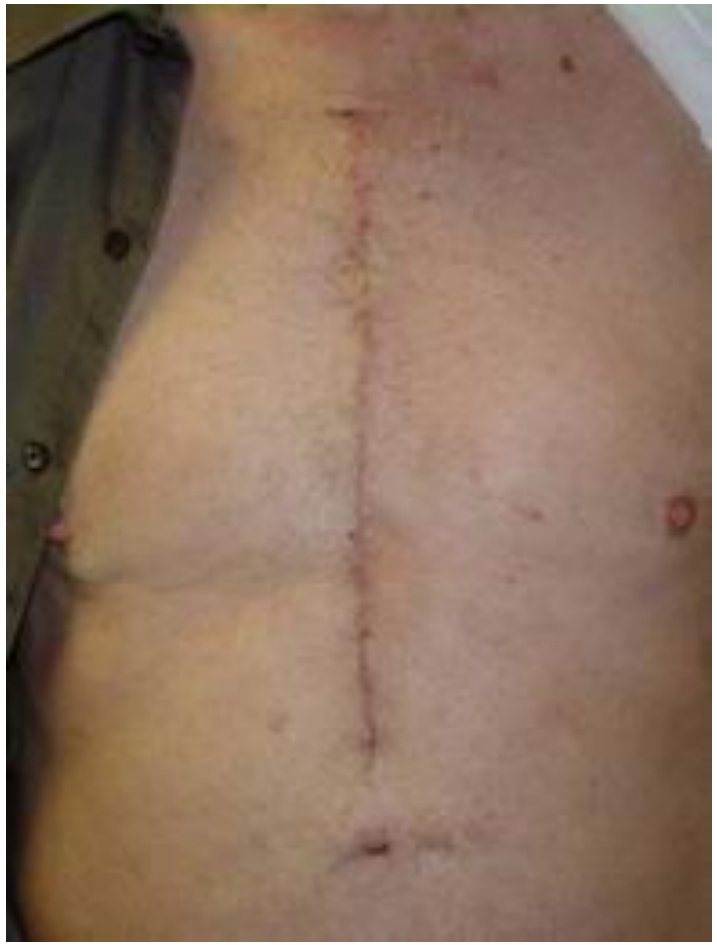


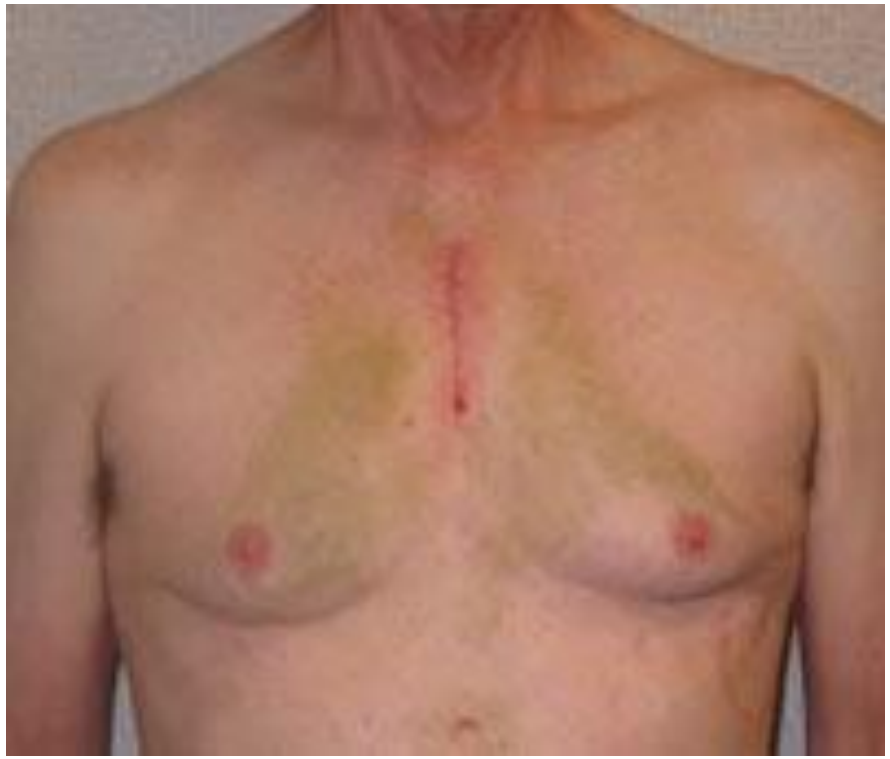
Surgical Aortic Valve Replacement

Courtesy of Dr. Gosta Pettersson

Surgical AVR

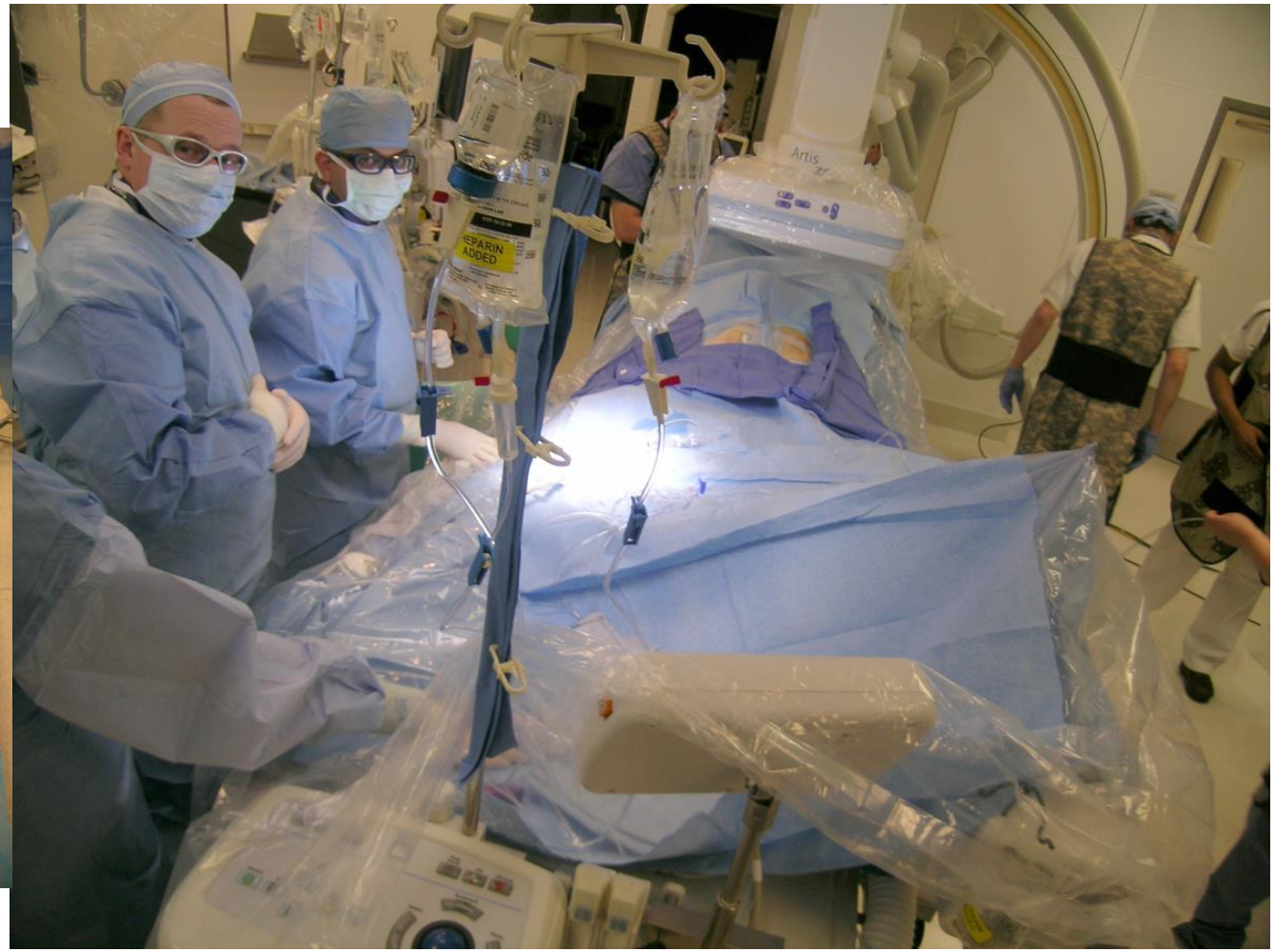




Clinical Presentation - 2006

- 88 yr old, male Ht:171.5cm Wt: 70.1kg BMI: 23
- NYHC III
- HTN, CAD, A fib
- Mild CAD
- Former Smoker- Quit 1973
- Hb:12.3 Ht: 37.1
- FEVI: 1.5 L
- Cr 1.8
- EF 45%
- AVA 0.7, peak gradient 64, mean gradient 40 mm

- STS score 8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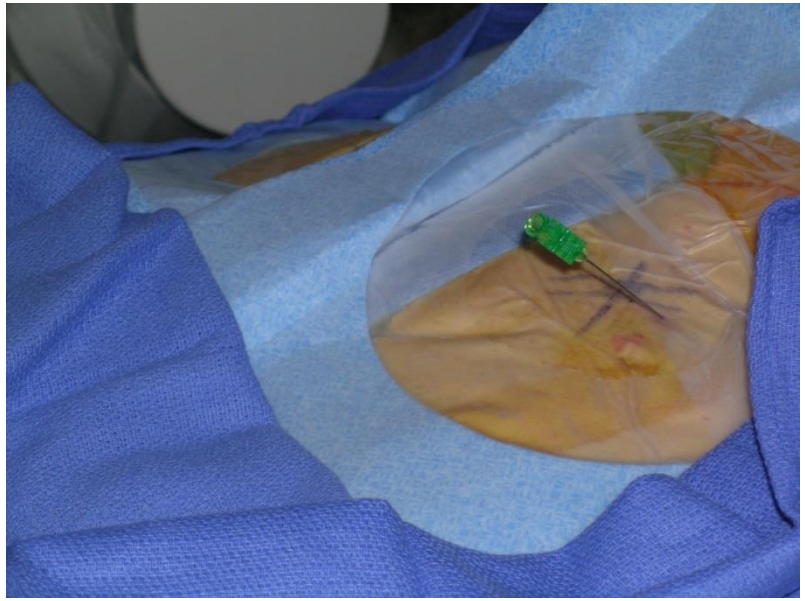
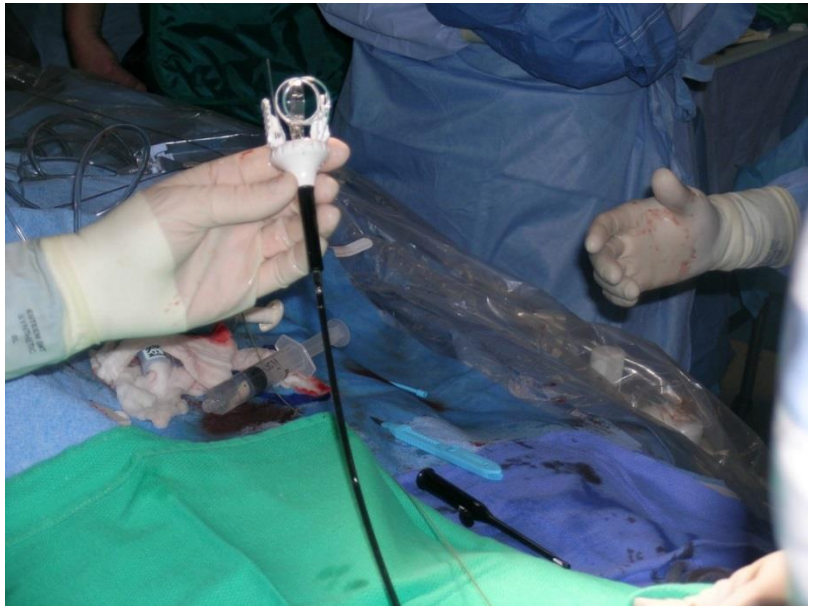
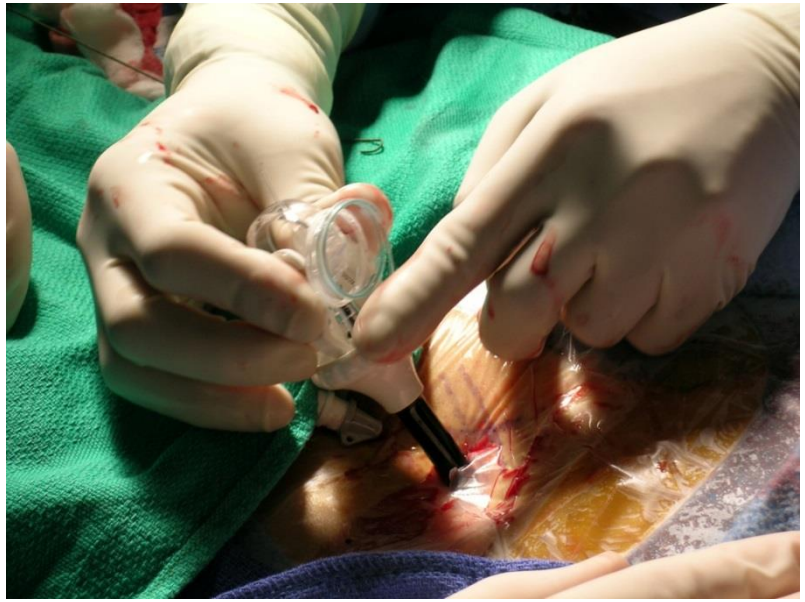
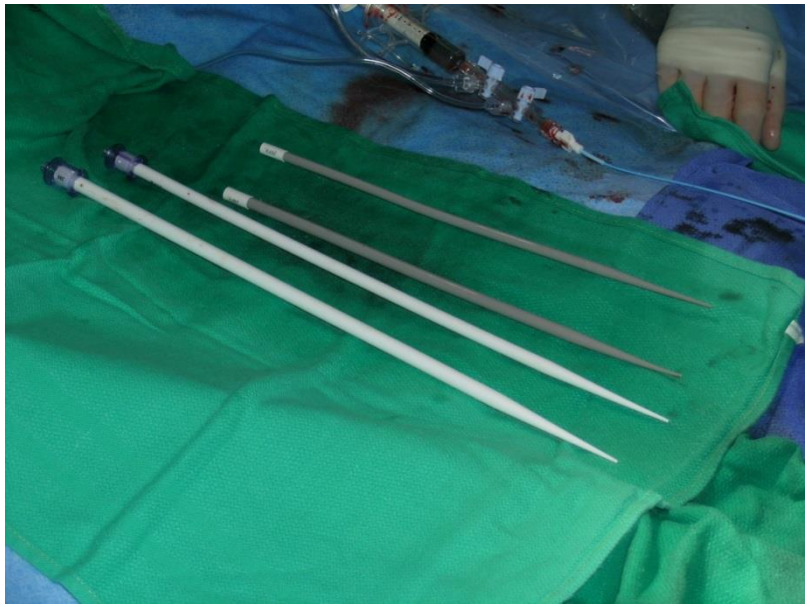
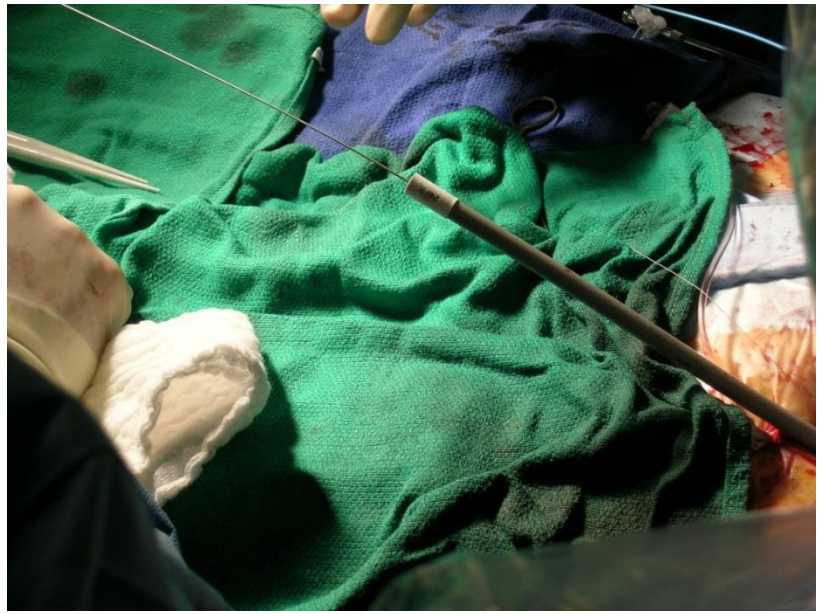
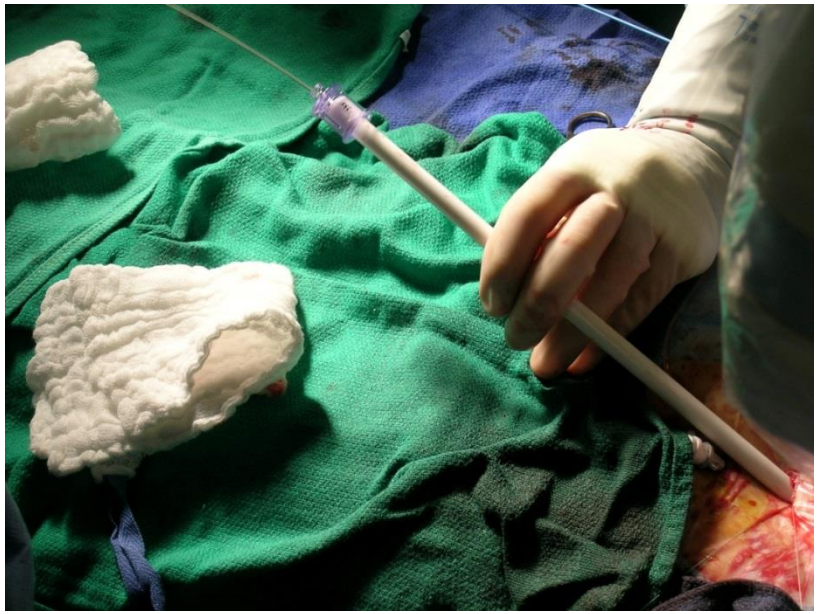
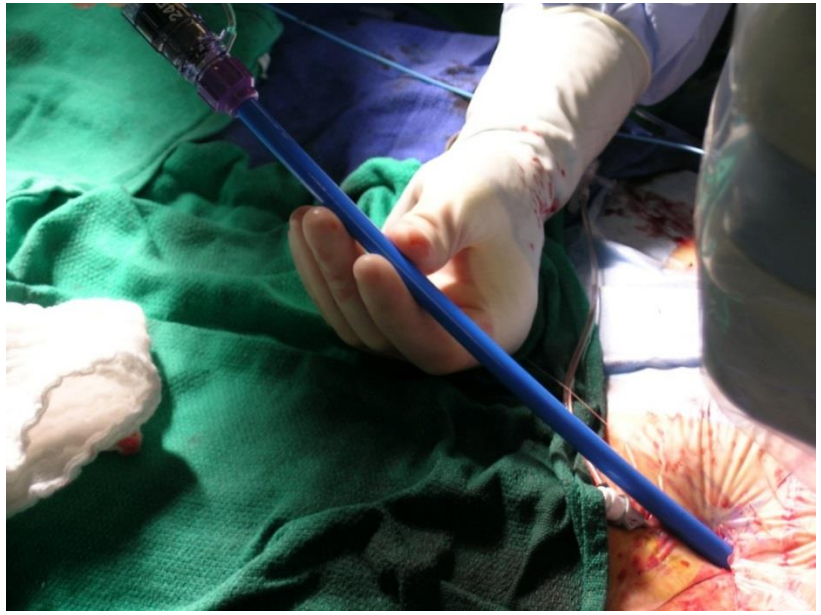
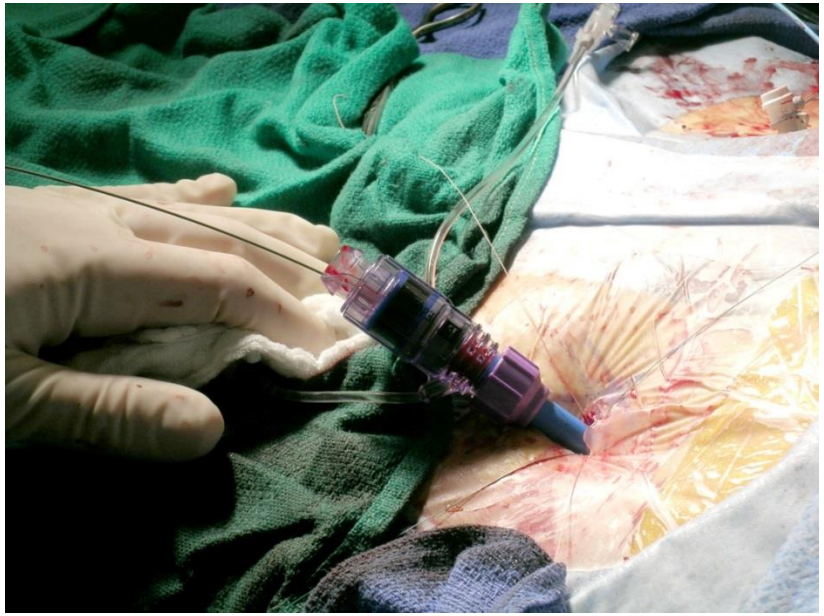


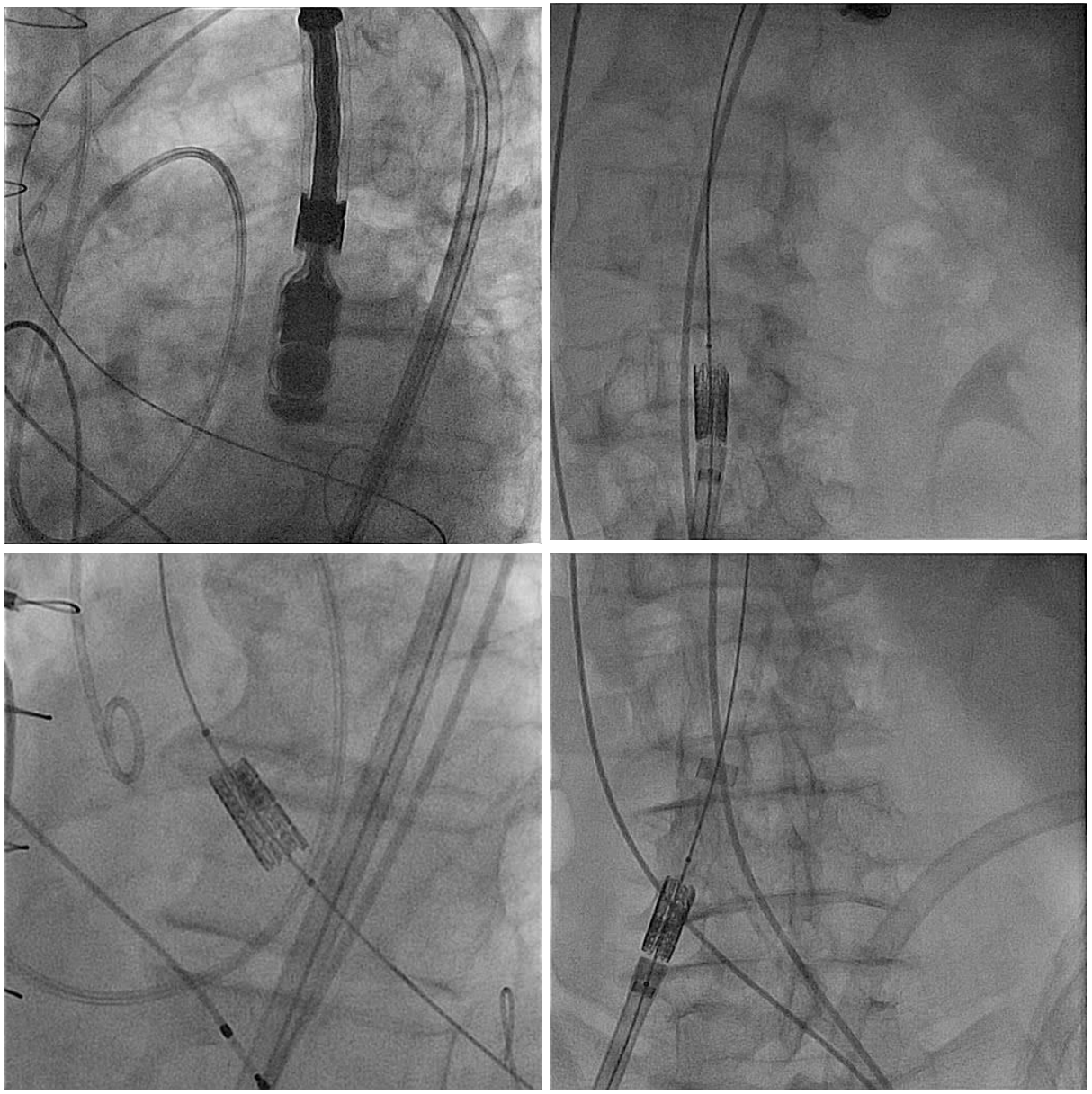




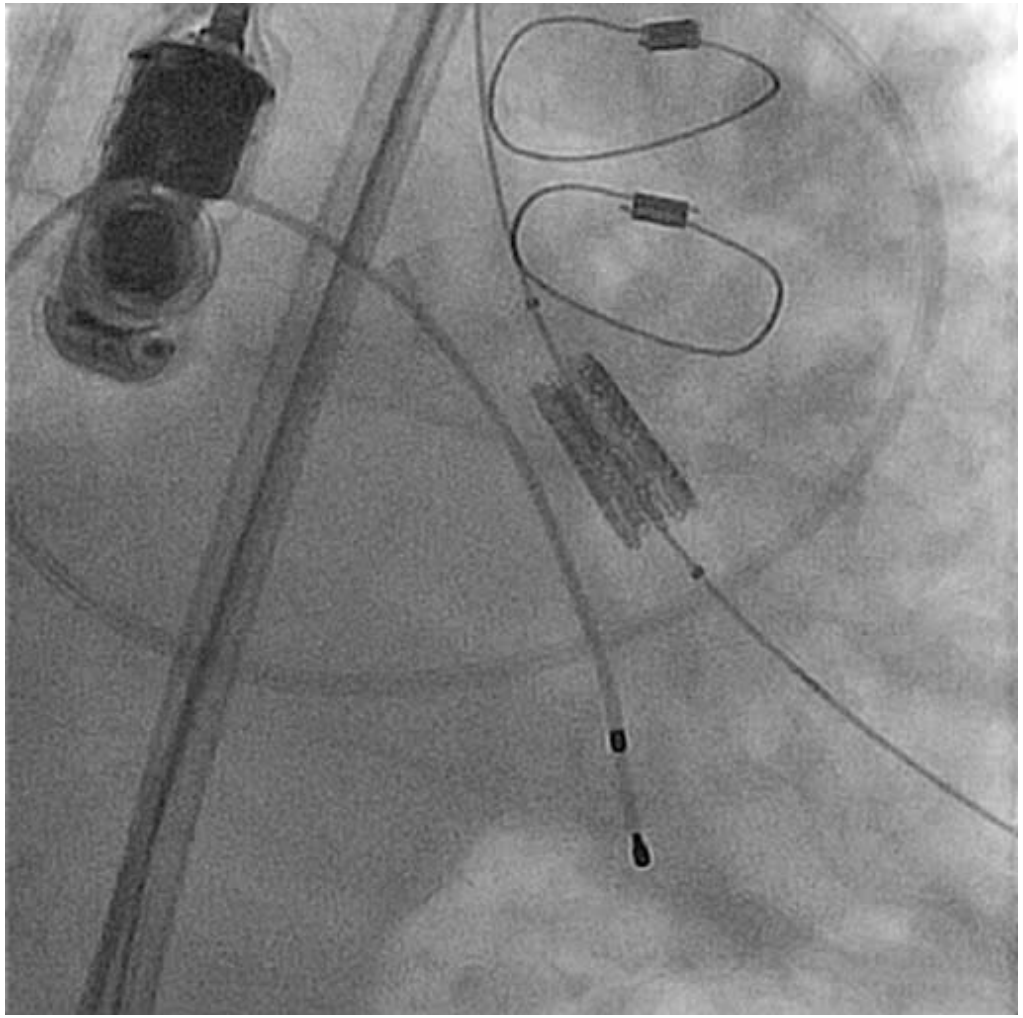


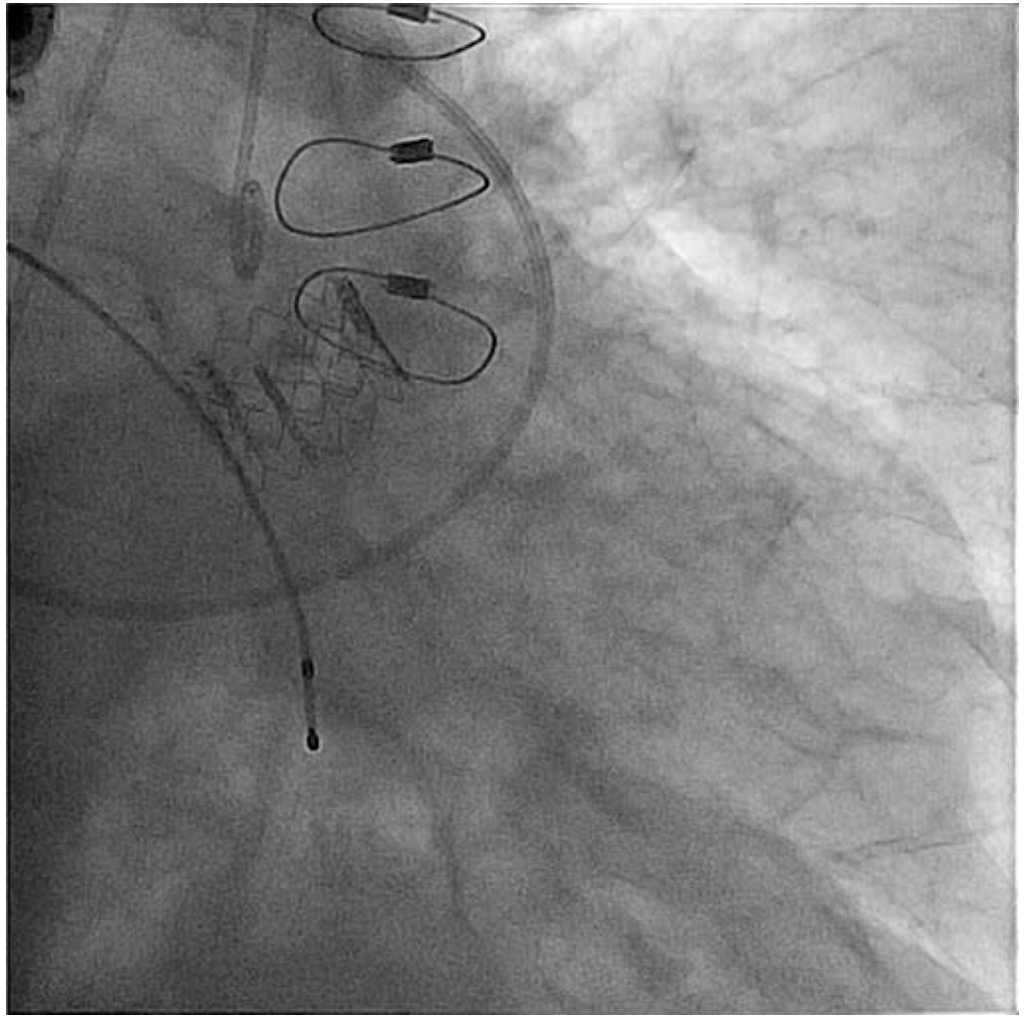





Retrograde Approach



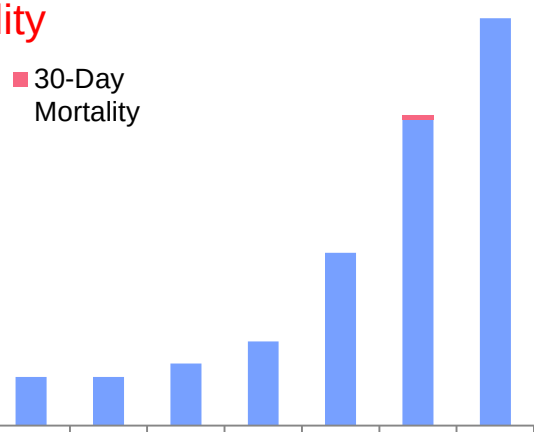
Final Result





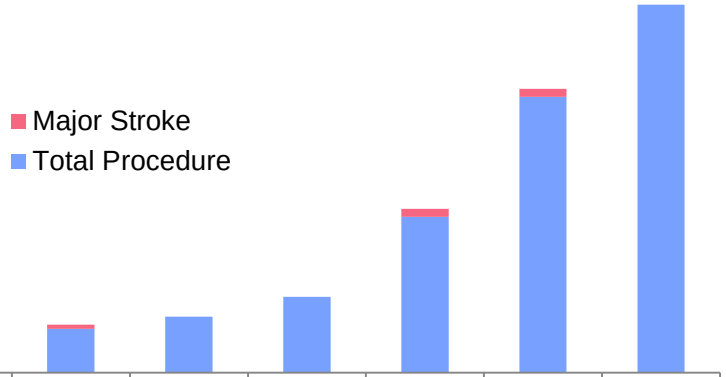
Outcome of Patients TF-TAVR at Cleveland Clinic 2006-12 (Initial 262 TF TAVR patients)

30 day mortality



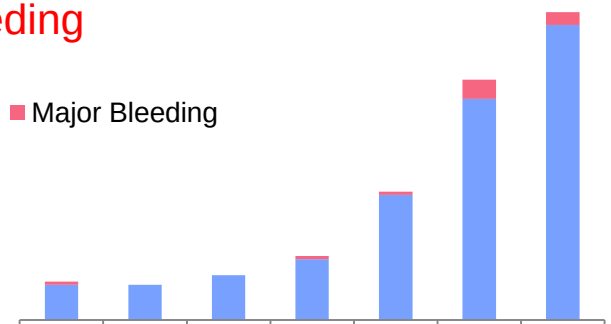
	2006	2007	2008	2009	2010	2011	2012
30-Day Mortality	0	0	0	0	0	1	0
Total Procedure	11	11	14	19	39	69	92

Stroke



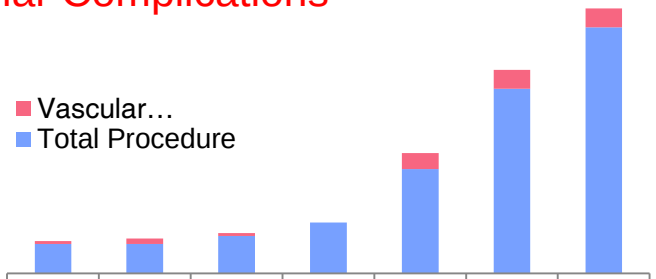
	2006	2007	2008	2009	2010	2011	2012
Major Stroke	0	1	0	0	2	2	0
Total Procedure	11	11	14	19	39	69	92

Major bleeding



	2006	2007	2008	2009	2010	2011	2012
Major Bleeding	1	0	0	1	1	6	4
Total Procedure	11	11	14	19	39	69	92

Vascular Complications



	2006	2007	2008	2009	2010	2011	2012
Vascular Complications	1	2	1	0	6	7	7
Total Procedure	11	11	14	19	39	69	92

History: 88M

6’2’’, 162lb (73 kg)

Relevant PMH:

-**Prostate CA**

-**PAD**

-**AF**

-**s/p PPM**

-**Asbestosis nml PFT**

-**Iliac aneurysm**

Echo (6/11/15)

EF: 63%

AVA, Gradients:
0.77 cm2, 52/29 mmHg
DI: 0.22, SVI 32 ml/m2
Trivial AI, 2+ MR/TR
RV: dilated, nml fxn
RVSP 56

Annular Area

CTA
Annulus 594 mm2 (AG)

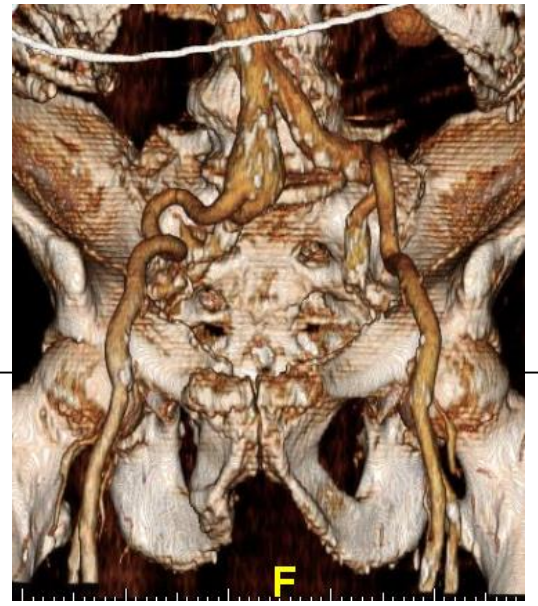
Access: TF (commercial)

Valve size: #29 S3

Coronary dist: RCA 23, LMT 23

Angles: RAO 0/Cau 25

LAO 25/Cran 15



Allergies: **NKDA**

Labs
BUN/Cr: 16/1.1
Hgb/Hct: 11/31
Plt: 112
INR: 1.1

LHC/PCI

LMT:, Mild

LAD:, long 40% narrowing

LCX: 60% proximal narrowing

RCA: 40% proximal narrowing

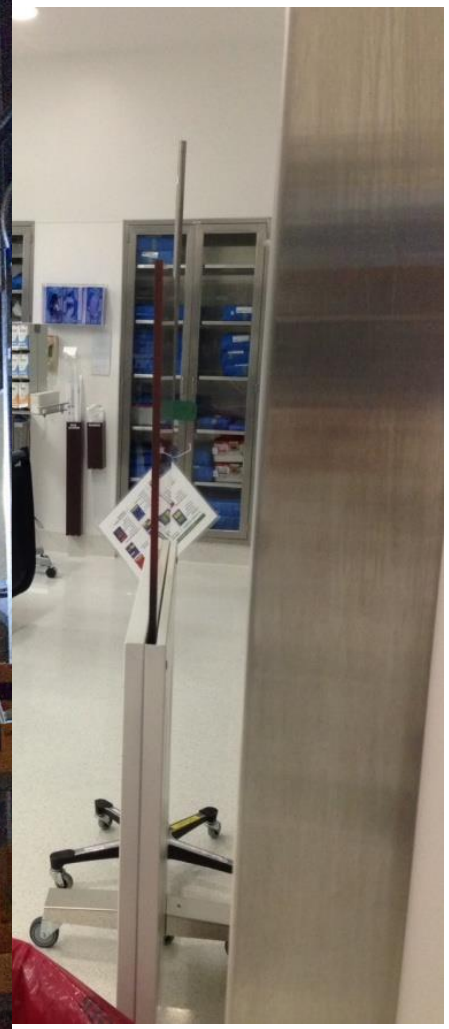
Procedural issues
- **Right CIA aneurysm w/ thrombus**
- Tortuous left CIA and abd ao

Planning : Heart Team

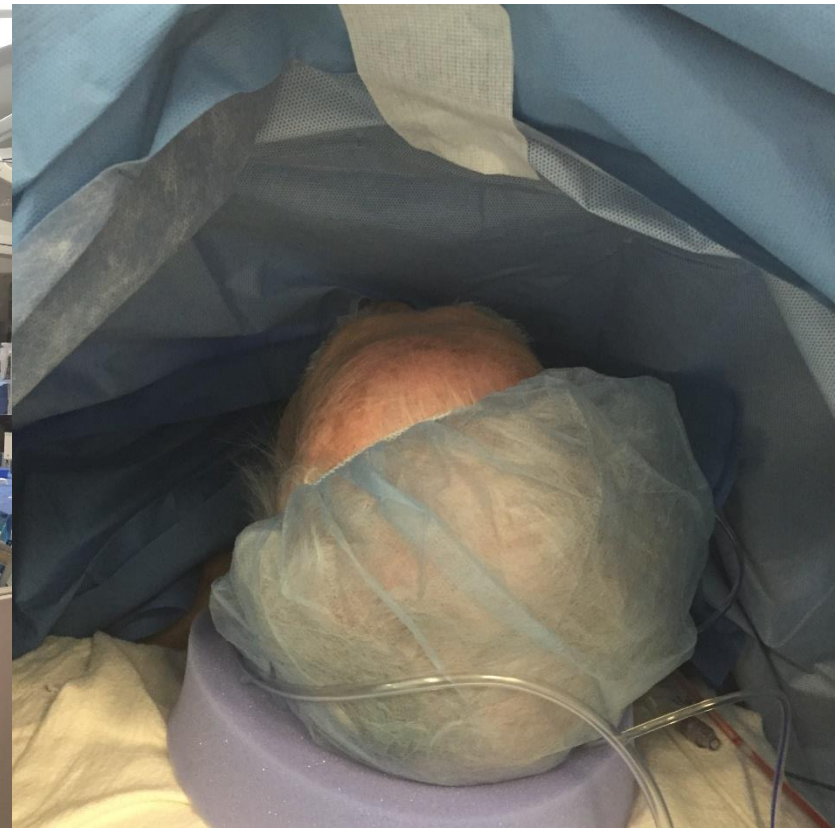
Cardiologist – Surgeon Collaboration

- Co-leadership
- Continuous and open communication
- Early conflict resolution
- Consensus building
- Shared resources
- Shared credits
- Great facility

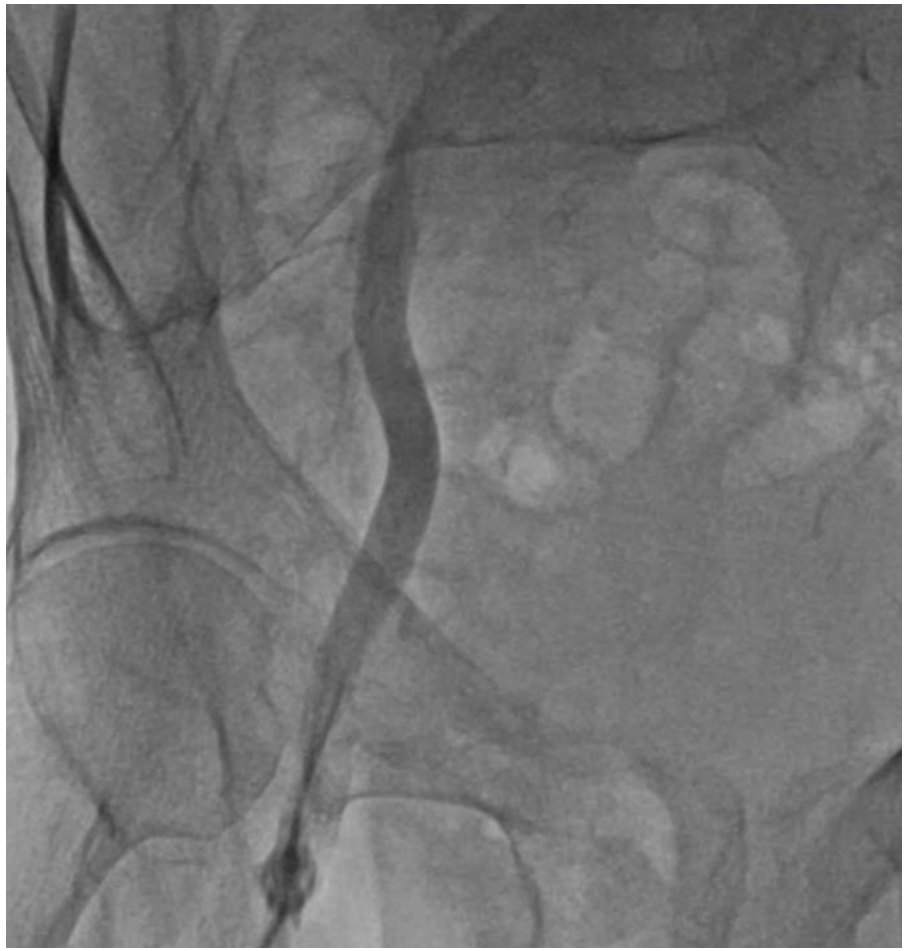
Hybrid Room

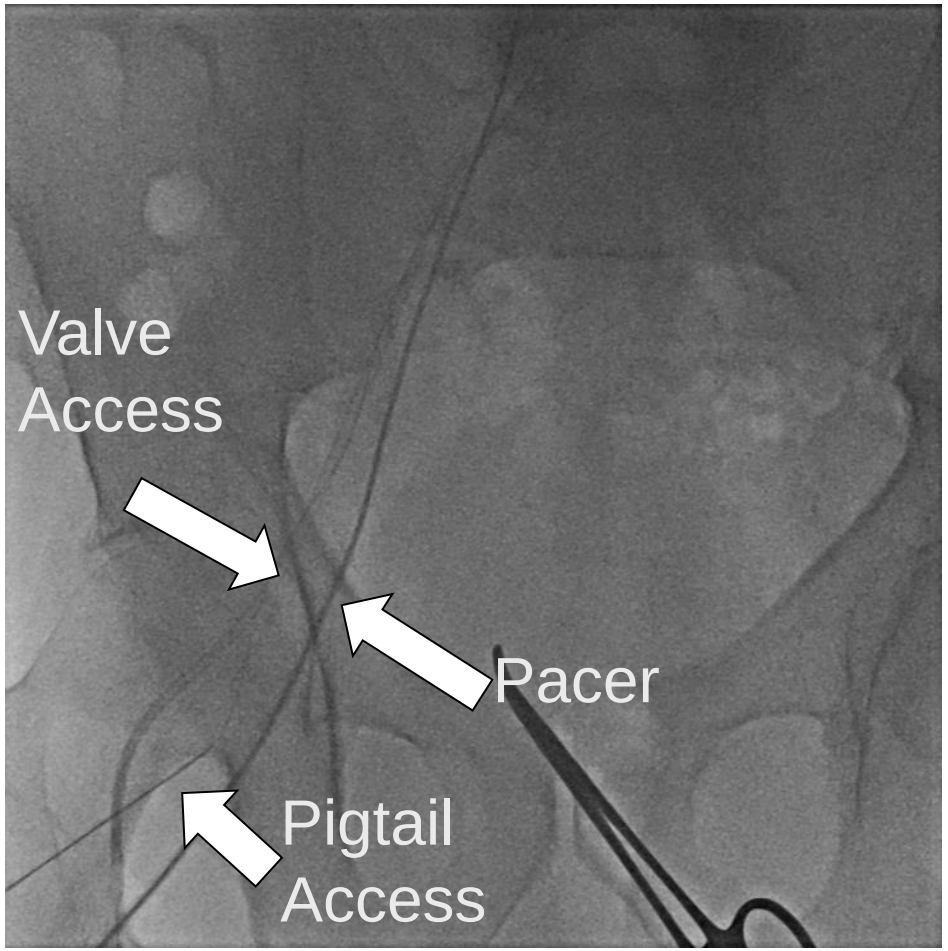


Minimalist Approach
Conscious sedation, No SG, TTE

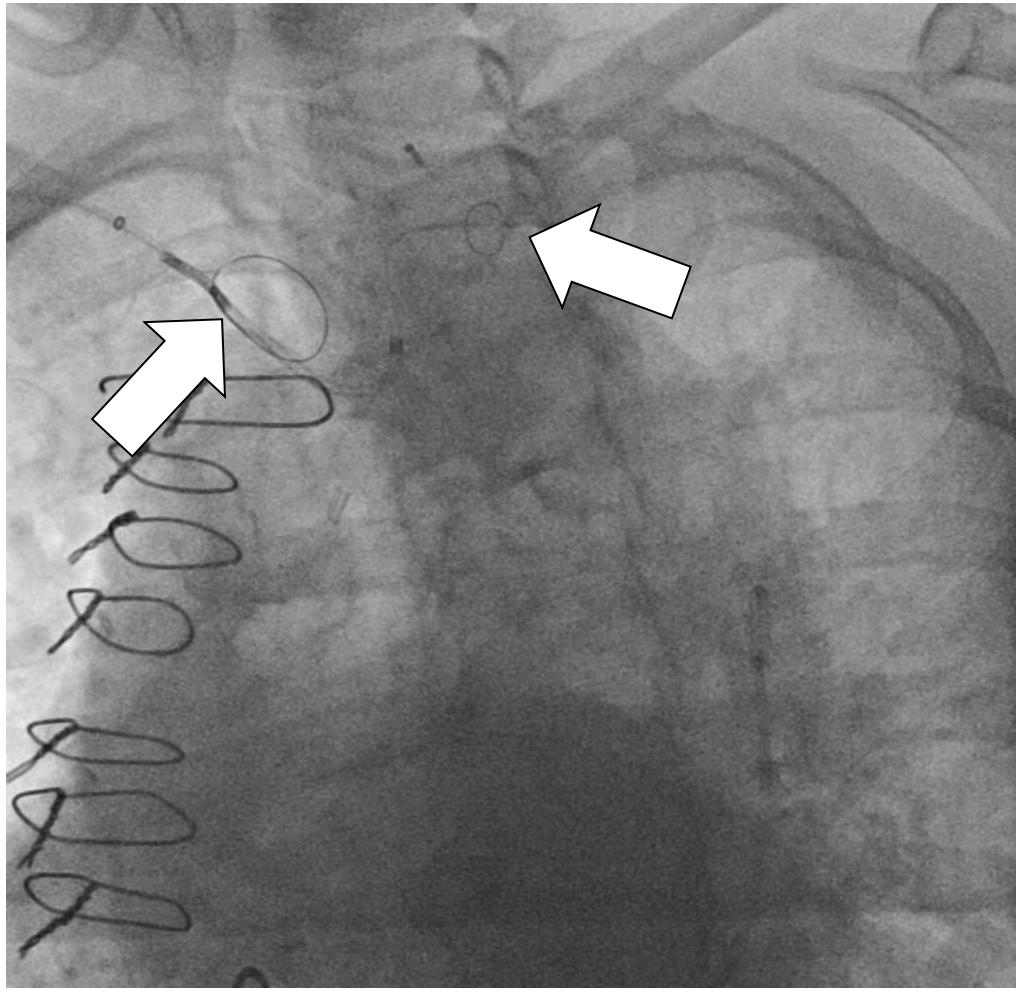


One Perclose and Same Side Sheath

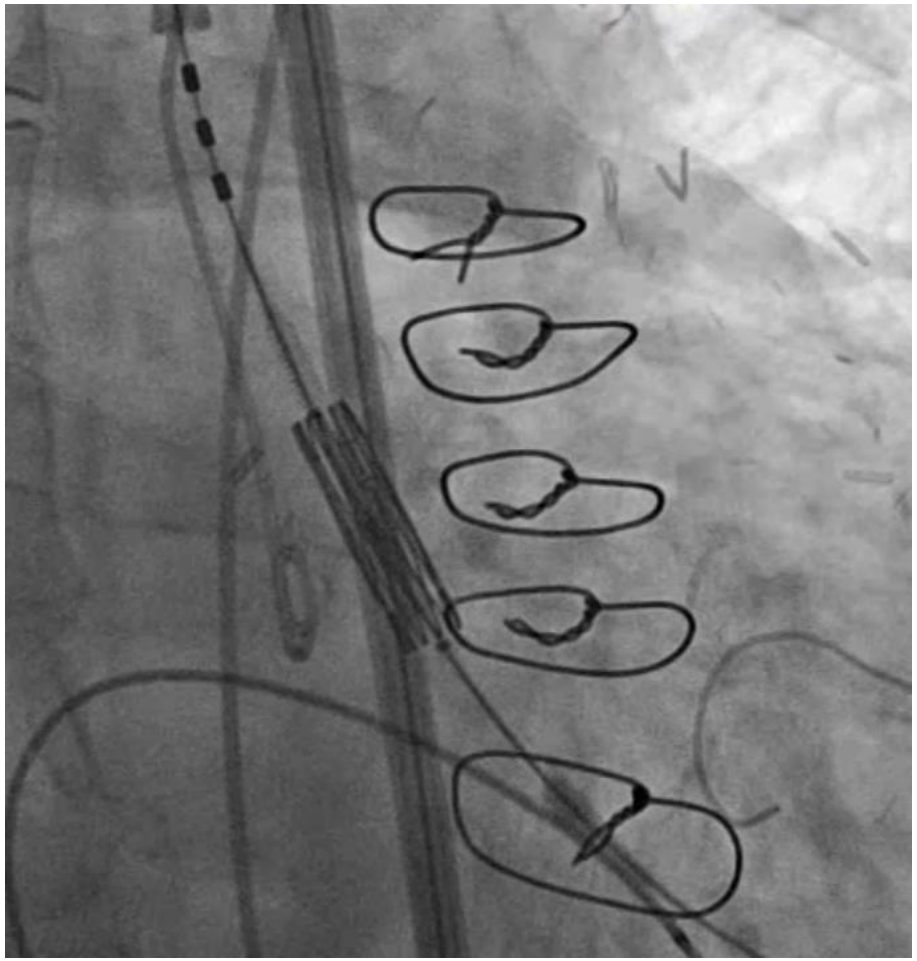


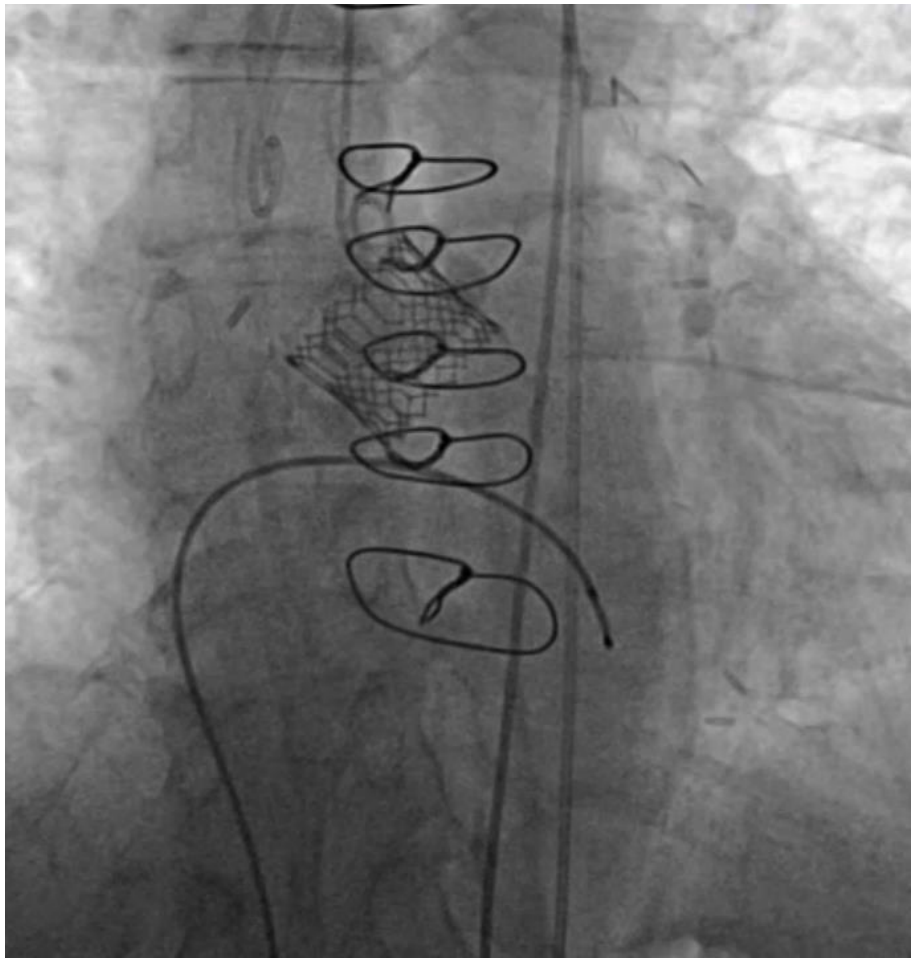


Sentinel

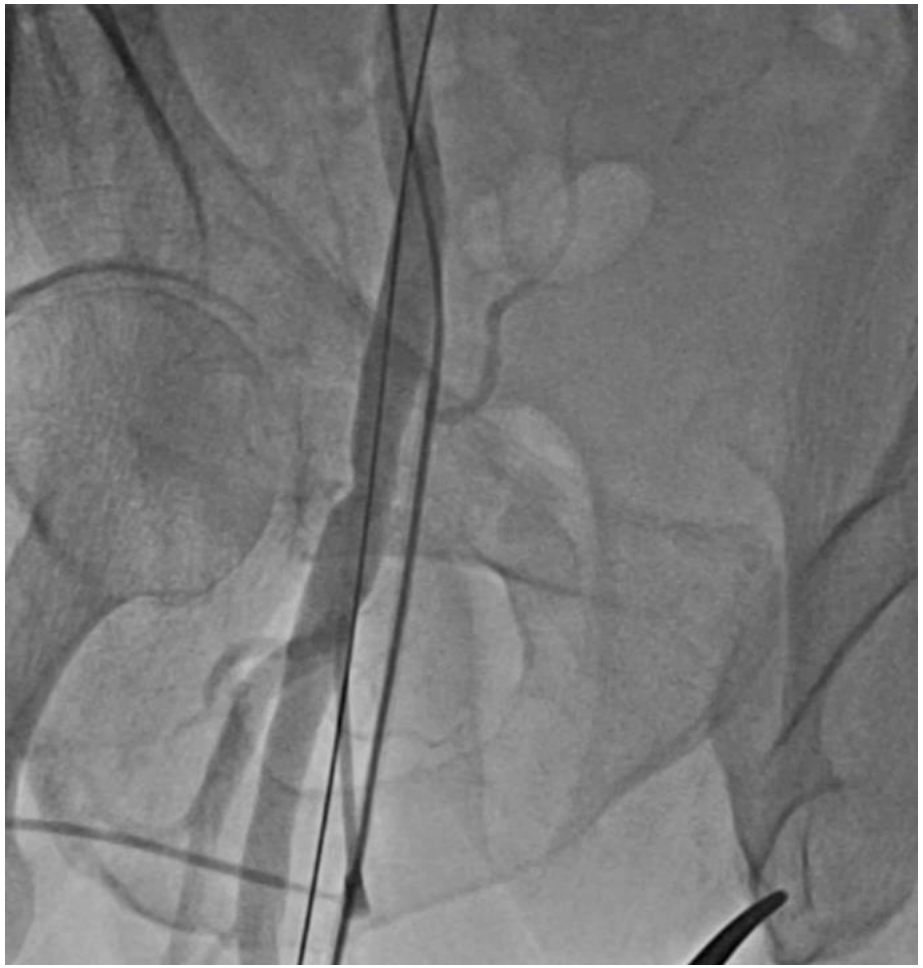


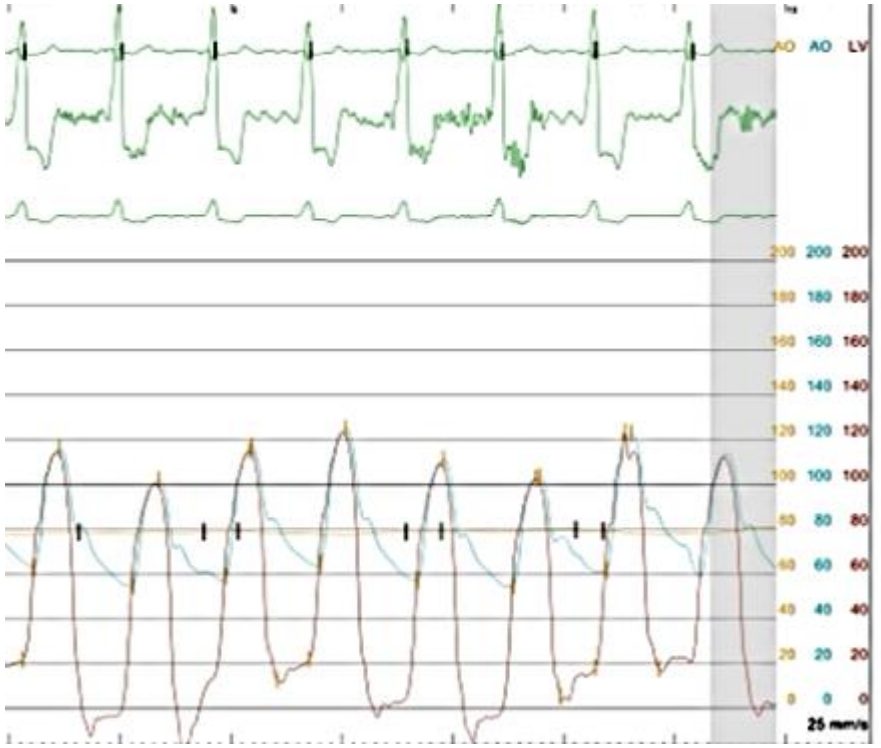
Valve Deployment





Final Picture





Procedural Log

08:47 "5 F Temporary Pacing wire inserted and advanced to RV. Position verified under fluoroscopy and connected to external device. Thresholds are checked. Settings remain at: Rate= 30 BPM, MA= 20."
08:57 Advancing Sentinel Filter system
09:09 26 mm Sapien 3 Valve implanted paced @ 180 bpm
09:13 Filter system removed
09:15 Right femoral angiogram performed.

8:47 to 9:15 = 28 minutes

Access, temp wire, Sentinel, Valve deployment

Closure of groin

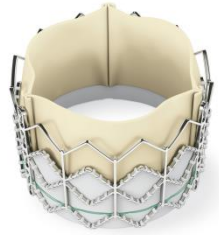
Fluorotime 11 miutes

Radiation 159 mGy

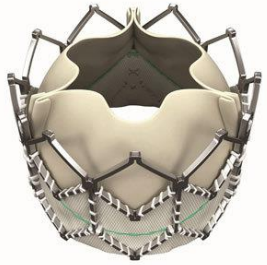
Commercially available and investigational devices for TAVI

Balloon Expandable

SAPIEN (Edwards)
*no longer available

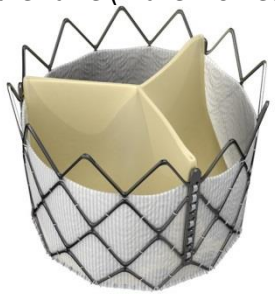


SAPIEN XT (Edwards)

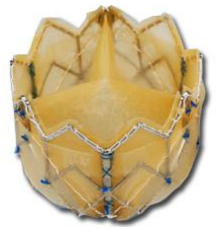


S3 (Edwards)

Inovare valve (Braile Biomedica)

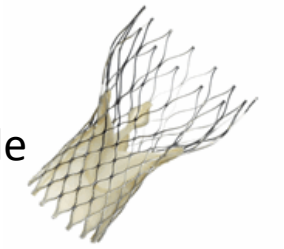


Colibri Heart Valve



Self Expandable

CoreValve (Medtronic)



Evolut R (Medtronic)

Portico (St. Jude Medical)

Centera (Edwards)

Venus (Medtech)

Other Designs

Lotus (Boston Scientific)

Direct Flow Valve (DFM)

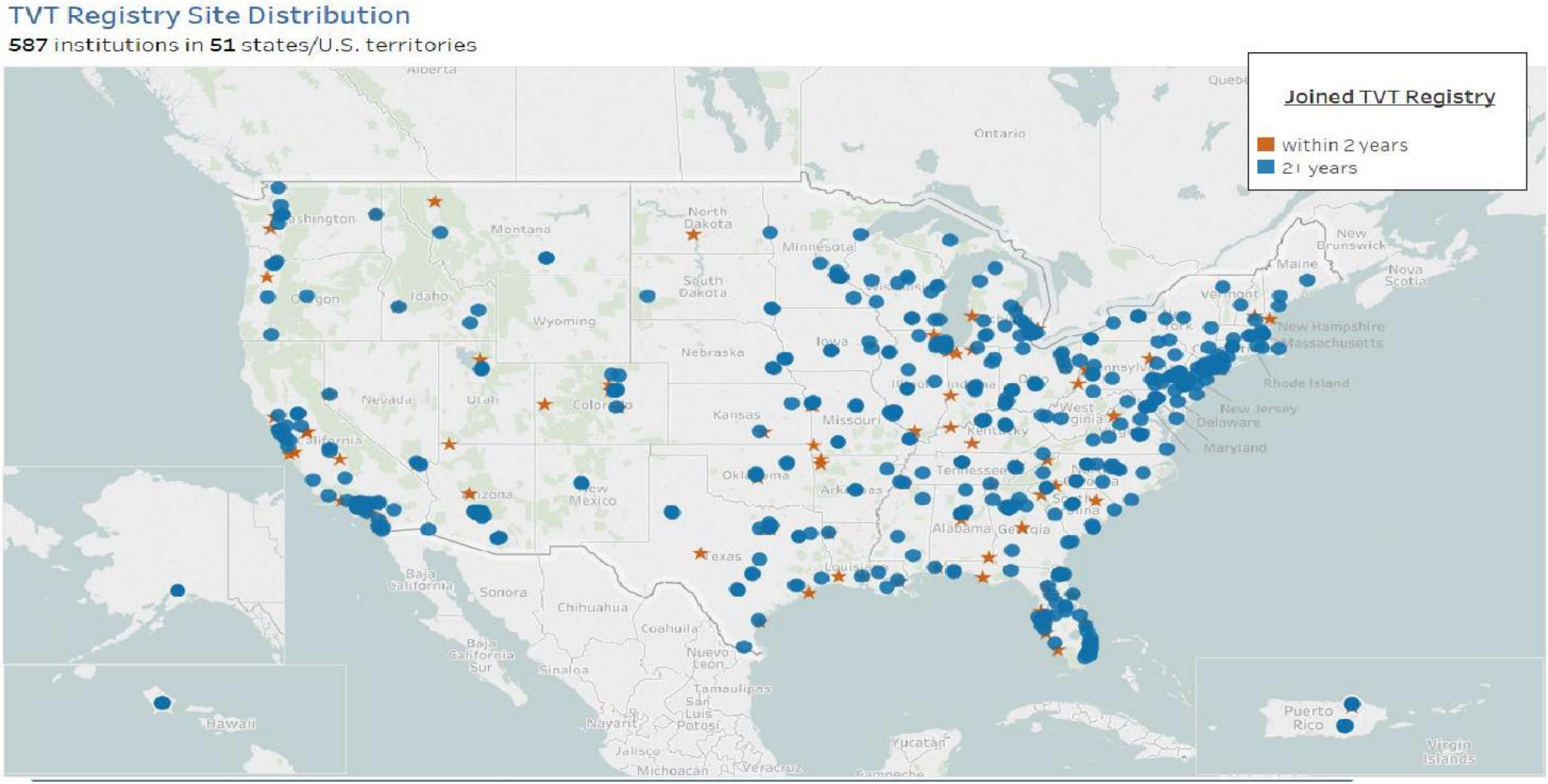
Acurate (Symetis Inc)

Engager (Medtronic)

JenaValve

HLT (Heart Leaflet Technologies)

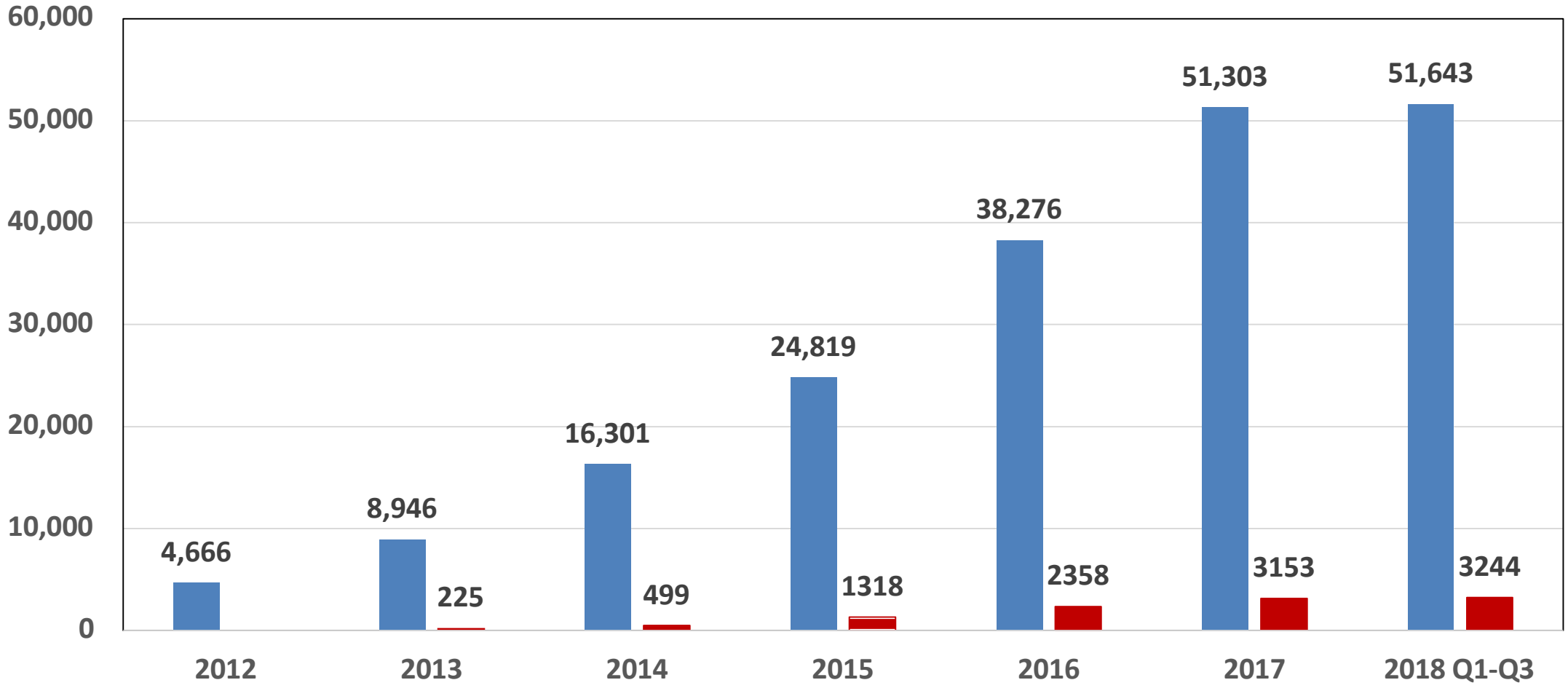
STS/ACC TVT Registry Participating Sites



STS National Database™
Using data to drive quality

NCDR®
NATIONAL CARDIOVASCULAR DATA REGISTRY

TVT Registry
TAVR and TAVR ViV Procedures



STS National Database™
Using data to drive quality

TVT Registry Datamart Data as of 1/22/2019

NCDR®
NATIONAL CARDIOVASCULAR DATA REGISTRY

Which Patients?

RCT

PARTNER1B	PARTNER1B CoreValve	S3i SURTAVI	NOTION P3 & CoreValve
Standard Vs TAVR	SAVR Vs TAVR	SAVR Vs TAVR	SAVR Vs TAVR

RCT - TAVR versus SAVR

Risk Category/Device	Trial/Registry (Ref. #)	30-Day Mortality		30-Day Stroke		1-Year Mortality	
		TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
Inoperable							
Balloon-expandable	PARTNER 1B (1)	5.0	N/A	6.7	N/A	30.7	N/A
Self-expanding	CoreValve Extreme Risk (2)	8.4	N/A	4.0	N/A	24.3	N/A
High							
Balloon-expandable	PARTNER 1A (3)	3.4	6.5	3.8	2.1	24.2	26.8
Self-expanding	CoreValve High Risk (4)	3.3	4.5	4.9	6.2	14.2	19.1
Intermediate							
Balloon-expandable	PARTNER 2A (5)	3.9	4.1	5.5	6.1	12.3	12.9
Balloon-expandable (propensity matched)	PARTNER S3i (9)	1.1	4.0	2.7	6.1	7.4	13.0
Self-expanding	CoreValve Intermediate Risk (6)	2.2	1.7	3.4	5.6	6.7	6.8
Low risk							
Self-expanding	NOTION trial (7)	2.1	3.7	1.4	3.0	4.9	7.5
All comers	STS/ACC TVT Registry*	3.0		1.8		15.3	

Mack, JACC 2018, 72, 18, 2018, 2106-8

Complications For TAVR versus SAVR

	P1A TAVR N=348	P1A SAVR N=351	CoreValve High Risk TAVR N=390	CoreValve High Risk SAVR N=357	PIIA XT N=994	PIIA SAVR N=1021	S3i S3 N=1077	Notion TAVR N=145	Notion SAVR N=135
All Stroke	5.5	2.4	4.9	6.2	5.5	6.1	2.7	2.8	3.0
Disabling Stroke	3.8	2.1	3.9	3.1	3.2	4.3	1.0	1.4	3.0
TIA	0.9	0.3	0.8	0.3	0.9	0.4	NA	1.4	0
Major Vascular	11.0	3.2	5.9	1.7	7.9	5.0	5.6	5.6	1.5
Bleeding	9.3	19.5	13.6	35.0	10.4	43.4	5.4	11.3	20.9
AKI	2.9	3.0	6.0	15.1	1.3	3.1	0.5	0.7	6.7
New Afib	8.6	16.0	11.7	30.5	9.1	26.4	5.0	16.9	57.8

Stroke After TAVR and SAVR

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ORIGINAL INVESTIGATIONS

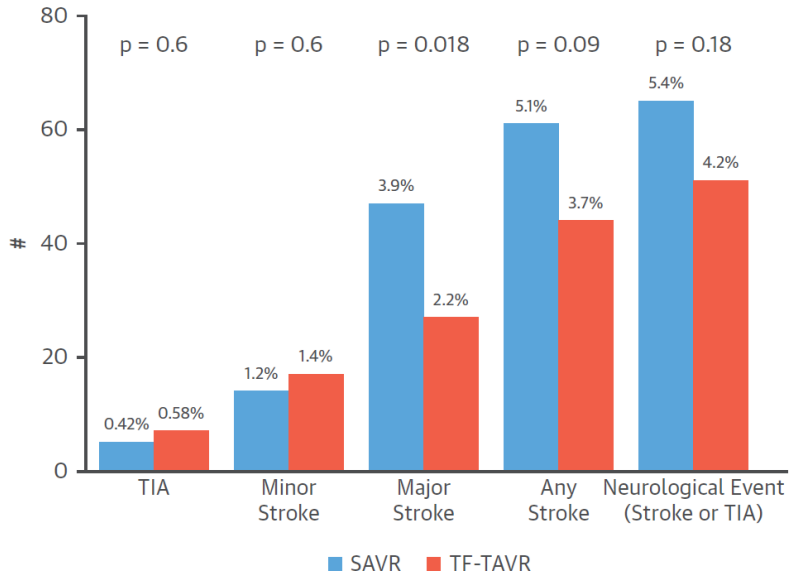
Stroke After Surgical Versus Transfemoral Transcatheter Aortic Valve Replacement in the PARTNER Trial

Samir R. Kapadia, MD,[a] Chetan P. Huded, MD, MSc,[a] Susheel K. Kodali, MD,[b] Lars G. Svensson, MD, PhD,[c] E. Murat Tuzcu, MD,[a] Suzanne J. Baron, MD,[d] David J. Cohen, MD,[d] D. Craig Miller, MD,[e] Vinod H. Thourani, MD,[f] Howard C. Herrmann, MD,[g] Michael J. Mack, MD,[h] Molly Szerlip, MD,[i] Raj R. Makkar, MD,[j] John G. Webb, MD,[k] Craig R. Smith, MD,[l] Jeevanantham Rajeswaran, PhD,[m] Eugene H. Blackstone, MD,[c,m] Martin B. Leon, MD,[n] for the PARTNER Trial Investigators

ABSTRACT

BACKGROUND Transfemoral-transcatheter aortic valve replacement (TF-TAVR) is increasingly used to treat aortic stenosis, but risk of post-procedure stroke is uncertain.

OBJECTIVES The purpose of this study was to assess stroke risk and its association with quality of life after surgical aortic valve replacement (SAVR) versus TF-TAVR.



CONCLUSION

Despite similar early-peaking (<1 day post-procedure) neurological risk profiles, SAVR is associated with a higher risk of early major stroke than TF-TAVR.

What to Expect from Low Risk Trials

Surgery Data Comparison
High to Intermediate Risk

Characteristic	Surgery P1A (n = 351)	Surgery P2A (n = 944)
Anesthesia Time (min)	330	333
Procedure Time (min)	230	237
Aortic Cross-clamp Time (min)	74	75
Total CPB Time (min)	105	104
Median ICU Stay (days)	5.0	4.0
Median Total Length of Stay (days)	12	9.0

Surgical Data Comparison

Events (%)	30 Days	
	Surgery P1A (n = 351)	Surgery P2A (n = 1021)
Death (all-cause) and Stroke (disabling)	8.2	8.0
Death		
All-cause	6.5	4.1
Cardiovascular	3.0	3.2
Neurological Events		
All Stroke	2.4	6.1
Disabling Stroke	2.1	4.3
TIA	0.3	0.4

TAVR Data Comparison

Events (%)	30 Days		
	P1A Sapien N=348	PIIA XT N=994	S3i S3 N=1077
Death (all-cause) and Stroke (disabling)	6.9	6.1	2.0
Death			
All-cause	3.4	3.9	1.1
Cardiovascular	3.2	3.3	0.9
Neurological Events			
All Stroke	5.5	5.5	2.7
Disabling Stroke	3.8	3.2	1.0
TIA	0.9	0.9	NA

*Event rates are KM estimates, p-values are point in time

TAVR Comparison

Complication	P1A (n = 348)	P2A (n = 994)	S3i (n = 1076)
Procedural deaths (0-3 days)	3 (0.9%)*	12 (1.2%)	2 (0.2%)
≥ 2 transcatheter valves	7 (2.0%)	26 (2.6%)	2 (0.2%)
Valve embolization	7 (2.0%)	10 (1.0%)	0 (0%)
Coronary Occlusion	0.0	0.4	0.4
Annular Rupture	NA	0.3	0.2
Fluoro time	31	20	19
Procedure Time	133	103	90**
ICU stay	3	2	2
LOS	8	6	4

** Preliminary * During procedure

TAVR Outcomes Overtime

Events (%)	30 Days		
	P1A (n = 348)	P2A (n = 1011)	s3i (n = 1077)
Rehospitalization	4.4	6.5	4.6
MI	0	1.2	0.3
Major Vascular Complications	7.9	7.9	5.6
Life-Threatening / Disabling Bleeding	9.3	10.4	5.4
AKI (Stage III)	2.9	1.3	0.5
New Atrial Fibrillation	8.6	9.1	5.0
New Permanent Pacemaker	3.8	8.5	10.2

LRT – Prospective Study of Low Risk Patients

	Observed		
	TAVR	SAVR	p Value
Age, yrs	73.6 ± 6.1	70.0 ± 8.3	<0.001
Male	123/200 (61.5)	438/719 (60.9)	0.88
Body mass index, kg/m^2	31.1 ± 6.6	30.9 ± 12.9	0.73
NYHA functional class III or IV	35/200 (17.5)	145/714 (20.3)	0.38
STS-PROM score, %*	1.8 ± 0.5	1.6 ± 0.6	<0.001
Diabetes mellitus	61/200 (30.5)	186/719 (25.9)	0.19
Renal insufficiency†	12/200 (6.0)	52/717 (7.3)	0.54
Hypertension	171/200 (85.5)	574/719 (79.8)	0.07
Peripheral vascular disease	4/200 (2.0)	46/719 (6.4)	0.02
Cerebrovascular disease	16/200 (8.0)	61/719 (8.5)	0.83
Prior CVA/TIA	19/200 (9.5)	51/719 (7.1)	0.26
Chronic lung disease	16/200 (8.0)	125/719 (17.4)	0.001
LVEF	63.5 ± 7.5	58.7 ± 8.7	<0.001
Prior PCI	42/200 (21.0)	67/719 (9.3)	<0.001
Prior CABG	2/200 (1.0)	22/719 (3.1)	0.11
Pre-existing PPM	7/200 (3.5)	30/713 (4.2)	0.65
Prior myocardial infarction	12/200 (6.0)	51/717 (7.1)	0.58
Arrhythmia	34/200 (17.0)	83/719 (11.5)	0.04

	TAVR	SAVR	p Value
Length of stay post-procedure, days	2.0 ± 1.1	6.4 ± 3.9	<0.001
VARC 2 life-threatening or major bleeding*	5/200 (2.5)	74/719 (10.3)	<0.001
VARC 2 major vascular complications	5/200 (2.5)	–	–
Acute kidney injury†	0/200 (0.0)	–	–
All-cause death	0/200 (0.0)	5/719 (0.7)	0.591
Stroke	0/200 (0.0)	4/719 (0.6)	0.582
MI	0/200 (0.0)	–	–
Endocarditis	0/200 (0.0)	–	–
New-onset atrial fibrillation	6/200 (3.0)	293/719 (40.8)	<0.001
New PPM implantation	10/200 (5.0)	32/719 (4.5)	0.742
Coronary artery obstruction	1/200 (0.5)	–	–

Waksman et al, J Am Coll Cardiol 2018;72:2095–105

The PARTNER 3 Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients

M.J. Mack, M.B. Leon, V.H. Thourani, R. Makkar, S.K. Kodali, M. Russo, S.R. Kapadia, S.C. Malaisrie, D.J. Cohen, P. Pibarot, J. Leipsic, R.T. Hahn, P. Blanke, M.R. Williams, J.M. McCabe, D.L. Brown, V. Babaliaros, S. Goldman, W.Y. Szeto, P. Genereux, A. Pershad, S.J. Pocock, M.C. Alu, J.G. Webb, and C.R. Smith, for the PARTNER 3 Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 21, 2010 VOL. 363 NO. 17

Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery

Martin B. Leon, M.D., Craig R. Smith, M.D., Michael Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., David L. Brown, M.D., Peter C. Block, M.D., Robert A. Guyton, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Pamela S. Douglas, M.D., John L. Petersen, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., and Stuart Pocock, Ph.D., for the PARTNER Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 28, 2016 VOL. 374 NO. 17

Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients

Martin B. Leon, M.D., Craig R. Smith, M.D., Michael J. Mack, M.D., Raj R. Makkar, M.D., Lars G. Svensson, M.D., Ph.D., Susheel K. Kodali, M.D., Vinod H. Thourani, M.D., E. Murat Tuzcu, M.D., D. Craig Miller, M.D., Howard C. Herrmann, M.D., Darshan Doshi, M.D., David J. Cohen, M.D., Augusto D. Pichard, M.D., Samir Kapadia, M.D., Todd Dewey, M.D., Vasilis Babaliaros, M.D., Wilson Y. Szeto, M.D., Mathew R. Williams, M.D., Dean Kereiakes, M.D., Alan Zajarias, M.D., Kevin L. Greason, M.D., Brian K. Whisenant, M.D., Robert W. Hodson, M.D., Jeffrey W. Moses, M.D., Alfredo Trento, M.D., David L. Brown, M.D., William F. Fearon, M.D., Philippe Pibarot, D.V.M., Ph.D., Rebecca T. Hahn, M.D., Wael A. Jaber, M.D., William N. Anderson, Ph.D., Maria C. Alu, M.M., and John G. Webb, M.D., for the PARTNER 2 Investigators*

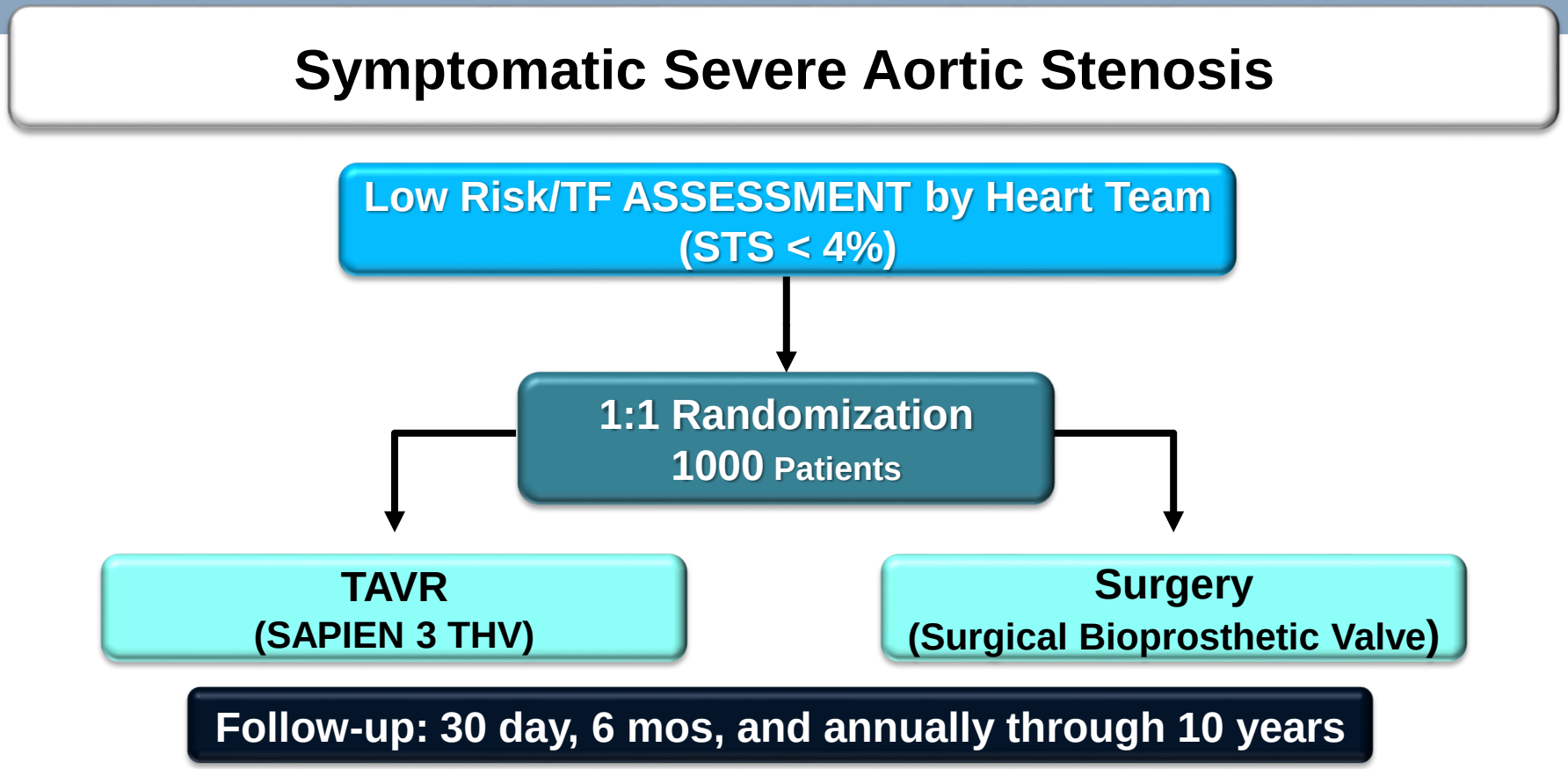
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 9, 2011 VOL. 364 NO. 23

Transcatheter and Surgical Aortic-Valve Replacement in High-Risk Patients

Craig R. Smith, M.D., Martin B. Leon, M.D., Michael J. Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., Mathew Williams, M.D., Todd Dewey, M.D., Samir Kapadia, M.D., Vasilis Babaliaros, M.D., Vinod H. Thourani, M.D., Paul Corso, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., and Stuart J. Pocock, Ph.D., for the PARTNER Trial Investigators*

PARTNER 3 Study Design



PRIMARY ENDPOINT:
Composite of all-cause mortality, stroke, or CV re-hospitalization at 1 year post-procedure

Key Inclusion Criteria

Severe Calcific Aortic Stenosis

- AVA ≤ 1.0 cm^2 or AVA index ≤ 0.6 cm^2/m^2
- Jet velocity ≥ 4.0 m/s or mean gradient ≥ 40 mmHg, AND
  - NYHA Functional Class ≥ 2, OR
  - Abnormal exercise test with severe SOB, abnormal BP response, or arrhythmia, OR
  - Asymptomatic with LVEF < 50%

Low Surgical Risk

- Determined by multi-disciplinary heart team
- STS < 4%
- Adjudicated by case review board

Key Exclusion Criteria

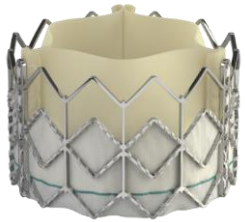
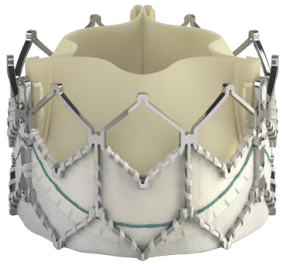
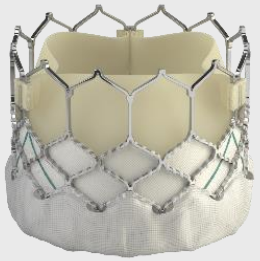
Anatomic

- Aortic annulus diameter < 16 mm or > 28 mm (3D imaging)
- Bicuspid valve (CT imaging)
- Severe AR (> 3+) or MR (> 3+) Severe LV dysfunction (LVEF < 30%)
- Severe calcification of aortic valvar complex (esp. LVOT)
- Vascular anatomy not suitable for safe femoral access
- Complex CAD: ULM, Syntax score > 32, or not amenable for PCI
- Low coronary takeoff (high risk for obstruction)

Clinical

- Acute MI within 1 month
- Stroke or TIA within 90 days
- Renal insufficiency (eGFR < 30 ml/min) and/or renal replacement Rx
- Hemodynamic or respiratory instability
- Frailty (objective assessment; > 2/4+ metrics)

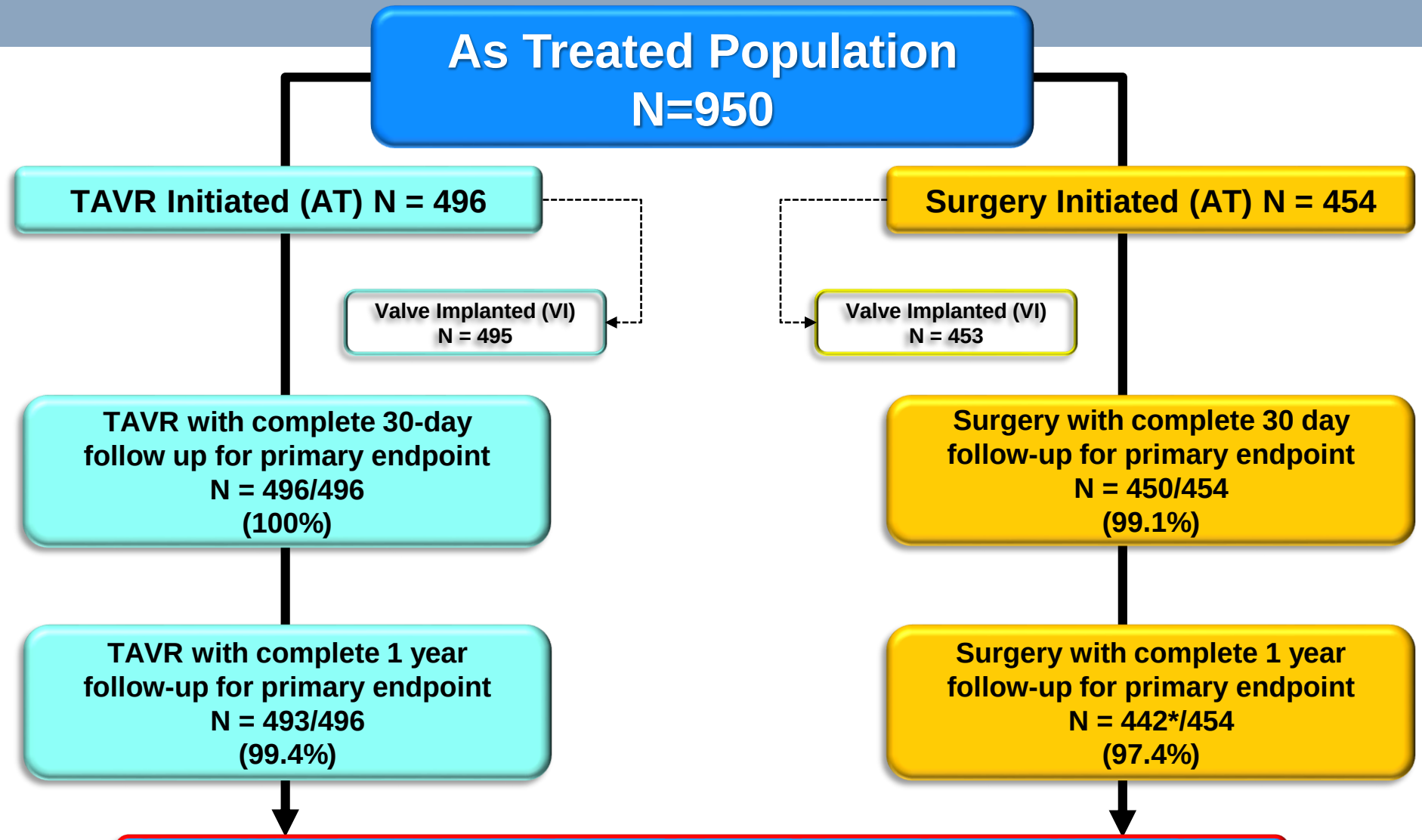
SAPIEN Valve Evolution

	SAPIEN	SAPIEN XT	SAPIEN 3
Valve Technology			
Sheath Compatibility			
Available Valve Sizes			
	PARTNER 1	**PARTNER 2**	**PARTNER 3**
	2011	2014	2015

Primary Endpoint

- **Non-hierarchical composite of all-cause mortality, all strokes, or CV re-hospitalization at 1 year**
  - Primary analysis was non-inferiority, followed by superiority
  - Analysis cohort was the ‘as-treated’ (AT) population, defined as all randomized patients in whom the procedure was initiated.
  - Multiple sensitivity analyses performed

Patient Disposition



b/c they had already experienced an endpoint event prior to withdrawing from the study.

Baseline Patient Characteristics

% or mean ± SD

Demographics & Vascular Disease	TAVR (N=496)	Surgery (N=454)	Other Co-Morbidities	TAVR (N=496)	Surgery (N=454)
Age (years)	73.3 ± 5.8	73.6 ± 6.1	Diabetes	31.3%	30.2%
Male	67.5%	71.1%	COPD (any)	5.1%	6.2%
BMI – kg/m^2	30.7 ± 5.5	30.3 ± 5.1	Pulmonary Hypertension	4.6%	5.3%
STS Score	1.9 ± 0.7	1.9 ± 0.6	Creatinine > 2mg/dL	0.2%	0.2%
NYHA Class III or IV*	31.3%	23.8%	Frailty (overall; > 2/4+)	0	0
Coronary Disease	27.7%	28.0%	Atrial Fibrillation (h/o)	15.7%	18.8%
Prior CABG	3.0%	1.8%	Permanent Pacemaker	2.4%	2.9%
Prior CVA	3.4%	5.1%	Left Bundle Branch Block	3.0%	3.3%
Peripheral Vascular Disease	6.9%	7.3%	Right Bundle Branch Block	10.3%	13.7%

*p = 0.01

Baseline Echo and CT Characteristics

% or mean ± SD

Characteristic	TAVR (N=496)	Surgery (N=454)
Aortic Valve Area (cm^2)	0.8 ± 0.2	0.8 ± 0.2
Mean Gradient (mmHg)	49.4 ± 12.8	48.3 ± 11.8
LVEF (%)	65.7 ± 9.0	66.2 ± 8.6
LV Mass Index (g/m^2)	104.5 ± 25.7	101.5 ± 25.4
≥ Moderate MR	1.3%	3.2%
≥ Moderate AR	3.9%	2.5%
≥ Moderate TR	1.7%	2.3%
CT – Annulus Perimeter (mm)	78.1 ± 6.9	78.6 ± 7.2
CT – Annulus Area (mm^2)	473.5 ± 83.3	479.6 ± 87.6

Procedural & Hospital Findings

% or mean ± SD

Variable	TAVR (N=496)	Surgery (N=454)	P-value
Conscious Sedation	65.1%	NA	NA
Procedure Time (min)	58.6 ± 36.5	208.3 ± 62.2	<0.001
Fluoroscopy Time (min)	13.9 ± 7.1	NA	NA
Aortic Cross-Clamp Time (min)	NA	74.3 ± 27.8	NA
Total CPB Time (min)	NA	97.7 ± 33.8	NA
Median ICU Stay (days)	2.0	3.0	<0.001
Median Total LOS (days)	3.0	7.0	<0.001
Discharge to Home/Self-care	96.0%	73.1%	<0.001
Concomitant Procedures	7.9%	26.4%	<0.001

Procedural Complications

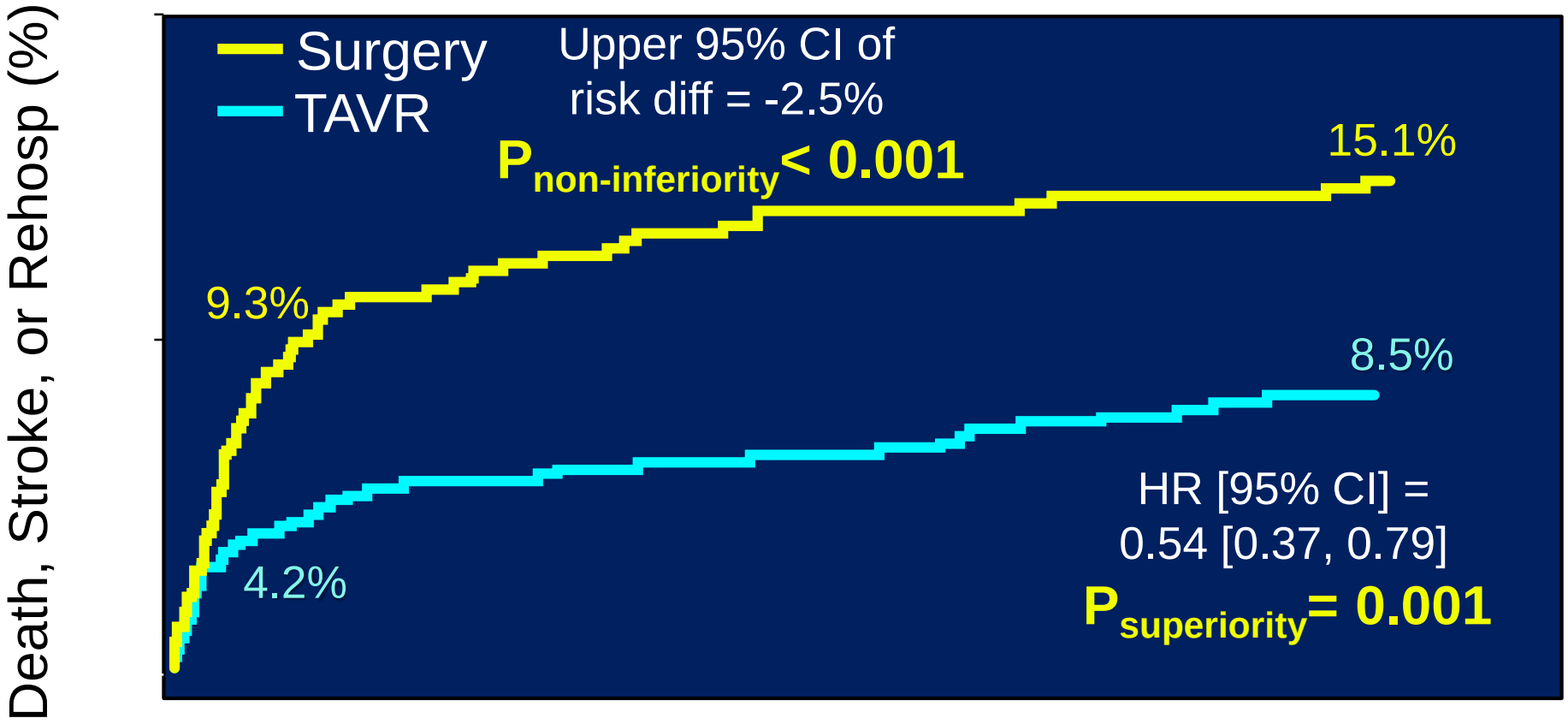
In-Hospital

% or mean ± SD

Complication	TAVR (N=496)	Surgery (N=454)	P-value
In-hospital Death	0.4% (2)	0.9% (4)	0.43
≥ 2 Transcatheter Valves Implanted*	0.2% (1)	NA	NA
Valve Embolization	0	NA	NA
Aortic Dissection	0	NA	NA
Annular Rupture	0.2% (1)	NA	NA
Ventricular Perforation	0.2% (1)	0.4% (2)	0.61
Coronary Obstruction	0.2% (1)	0.4% (2)	0.61
Access Site Infections	0.4% (2)	1.3% (6)	0.16

*Valve-in-valve

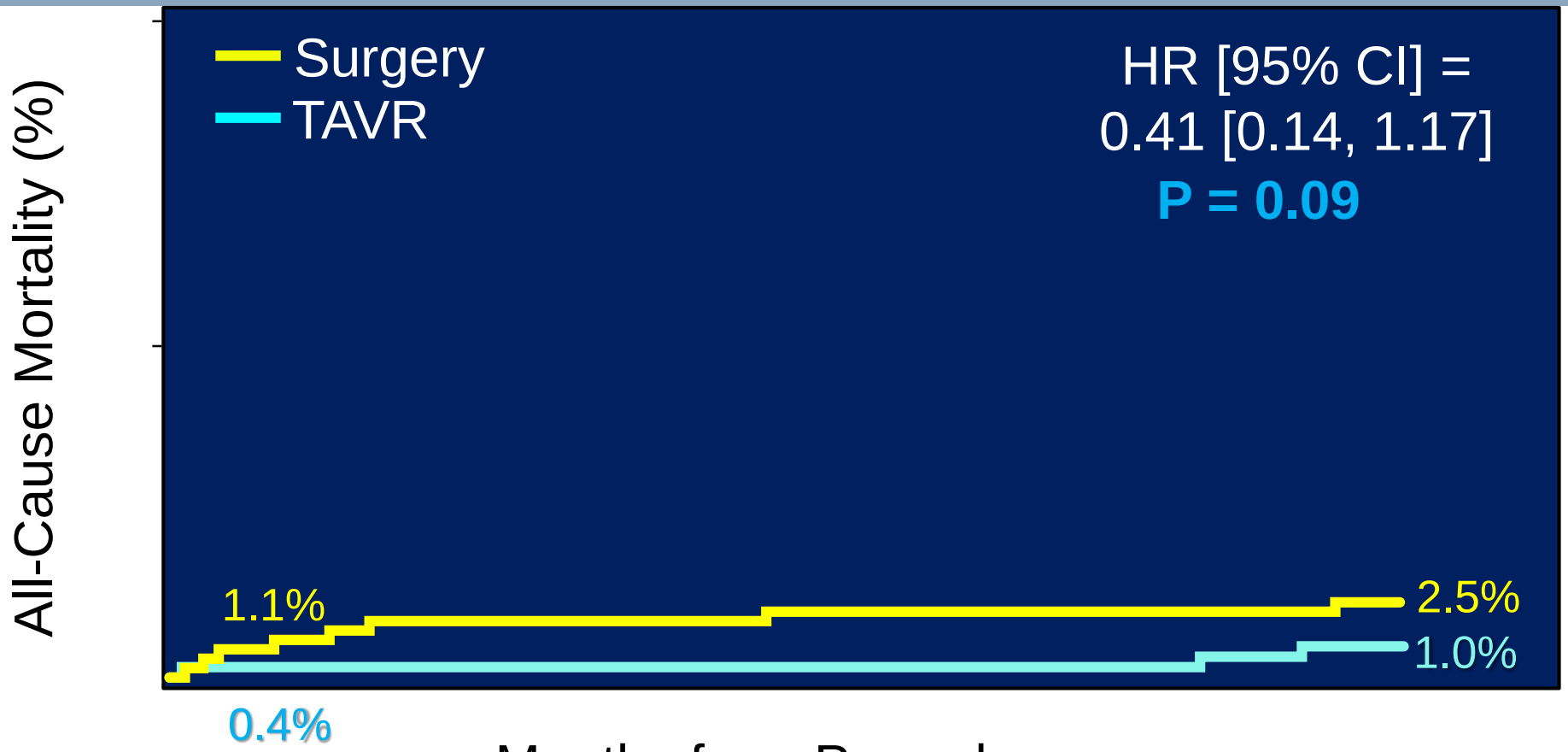
Primary Endpoint



Number at risk:

Surgery	**454**	**408**	**390**	**381**	**377**	**374**
TAVR	**496**	**475**	**467**	**462**	**456**	**451**

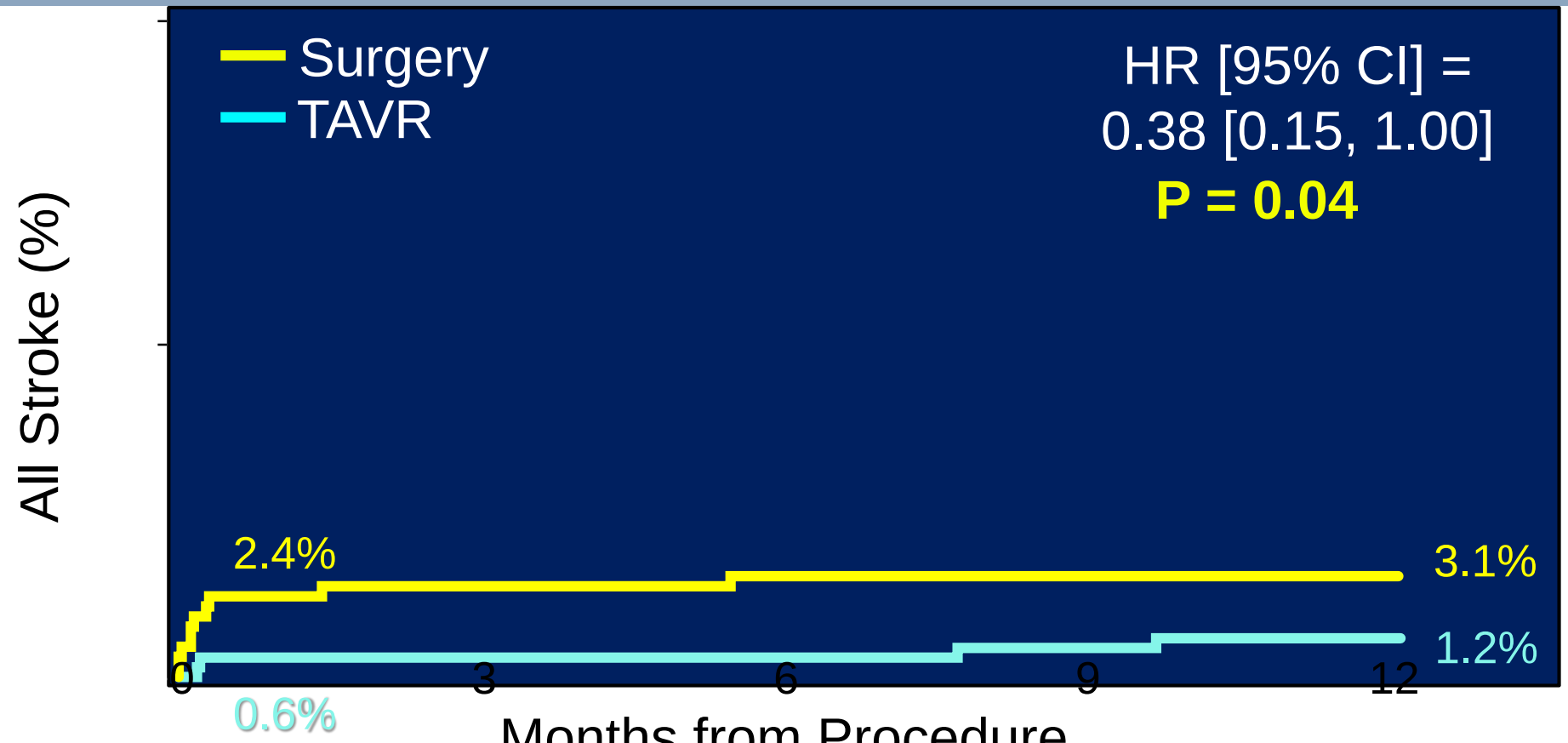
All-Cause Mortality



Number at risk:

Surgery	**454**	**445**	**438**	**433**	**431**	**427**
TAVR	**496**	**494**	**494**	**493**	**492**	**488**

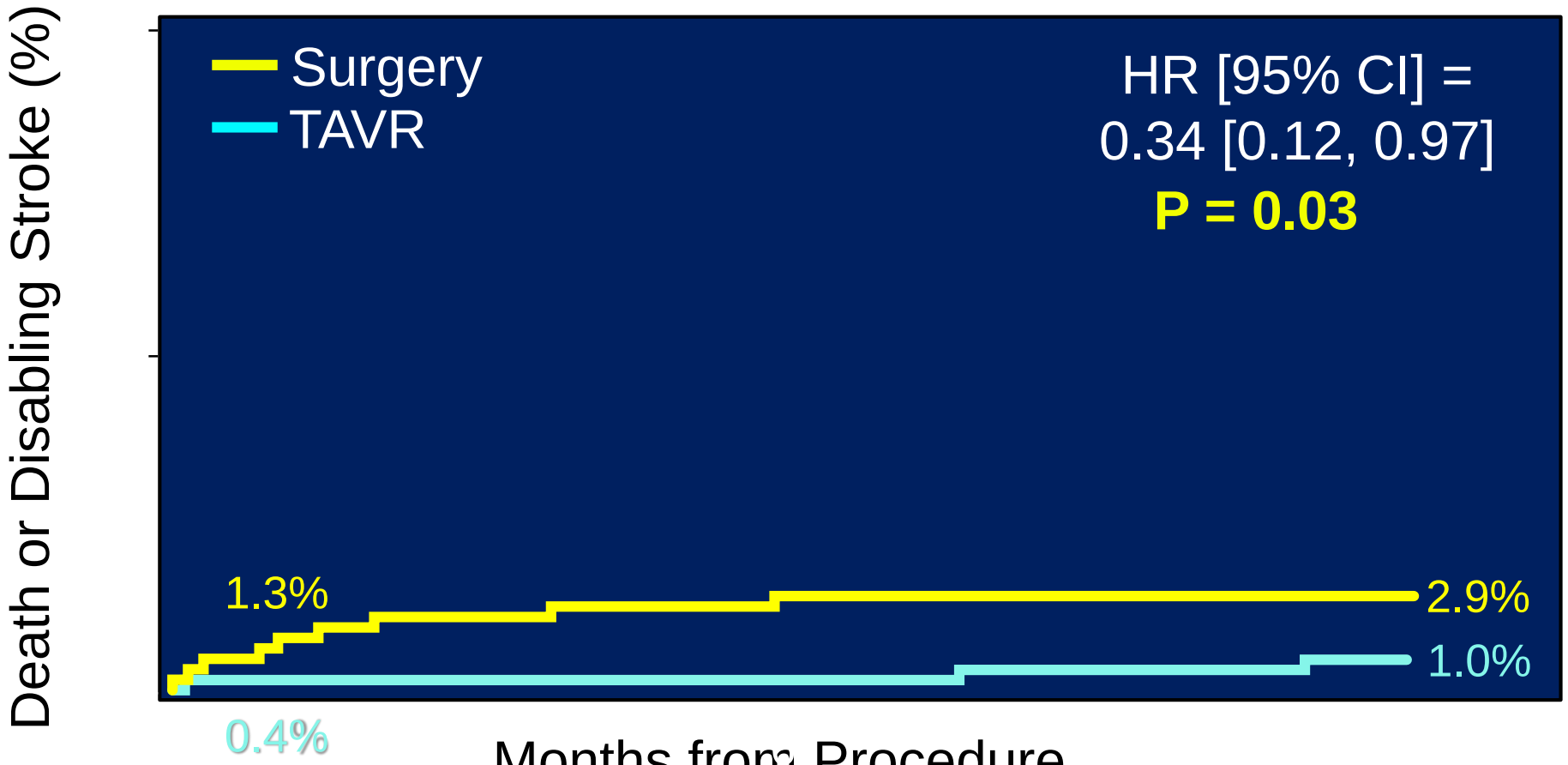
All Stroke



Number at risk:

Surgery	**454**	**435**	**427**	**423**	**421**	**417**
TAVR	**496**	**491**	**491**	**489**	**487**	**484**

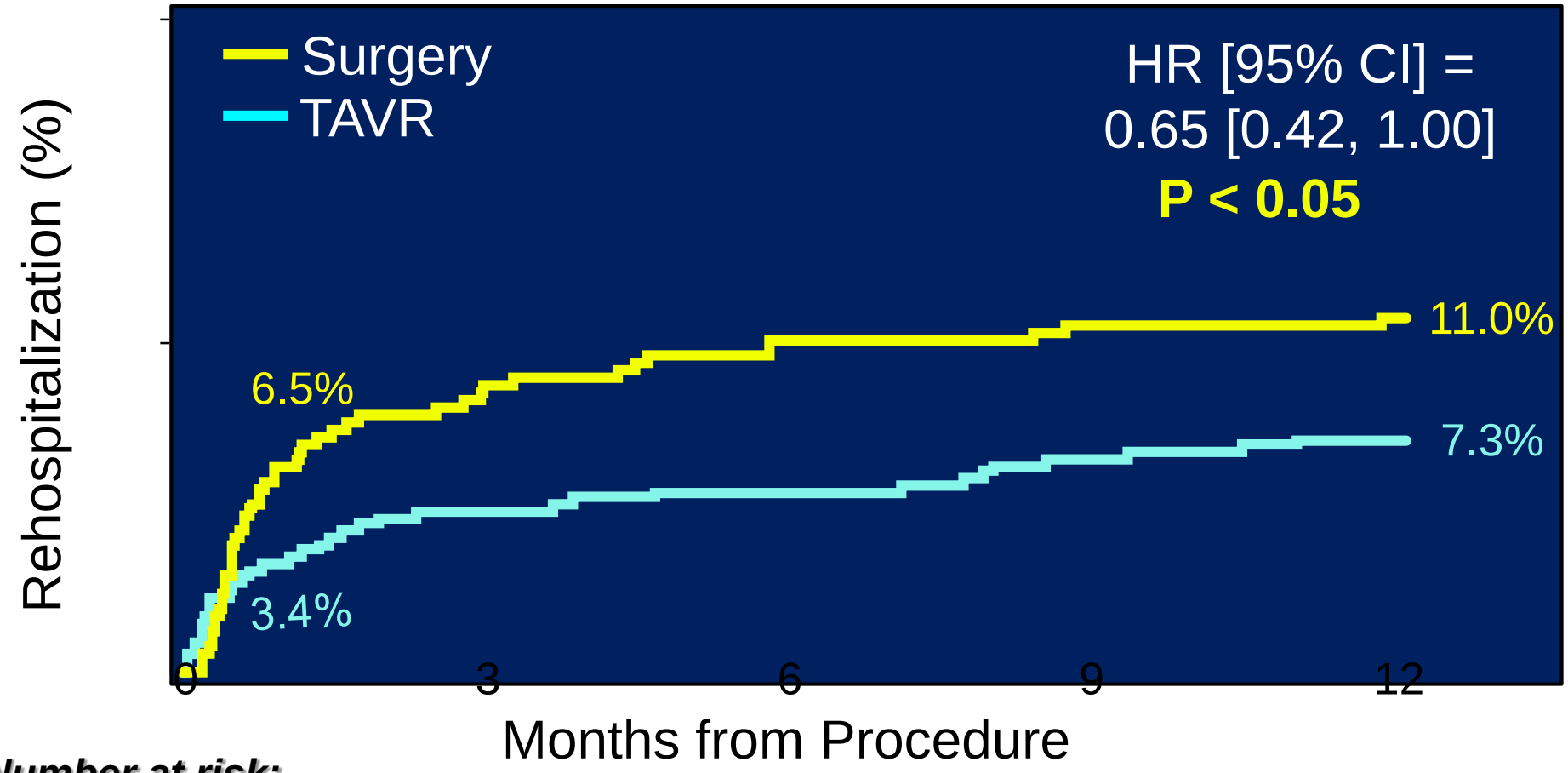
Death or Disabling Stroke



Number at risk:

Surgery	**454**	**444**	**436**	**432**	**430**	**426**
TAVR	**496**	**494**	**494**	**493**	**491**	**488**

Rehospitalization



Number at risk:

Surgery	**454**	**416**	**399**	**389**	**385**	**382**
TAVR	**496**	**477**	**469**	**465**	**459**	**453**

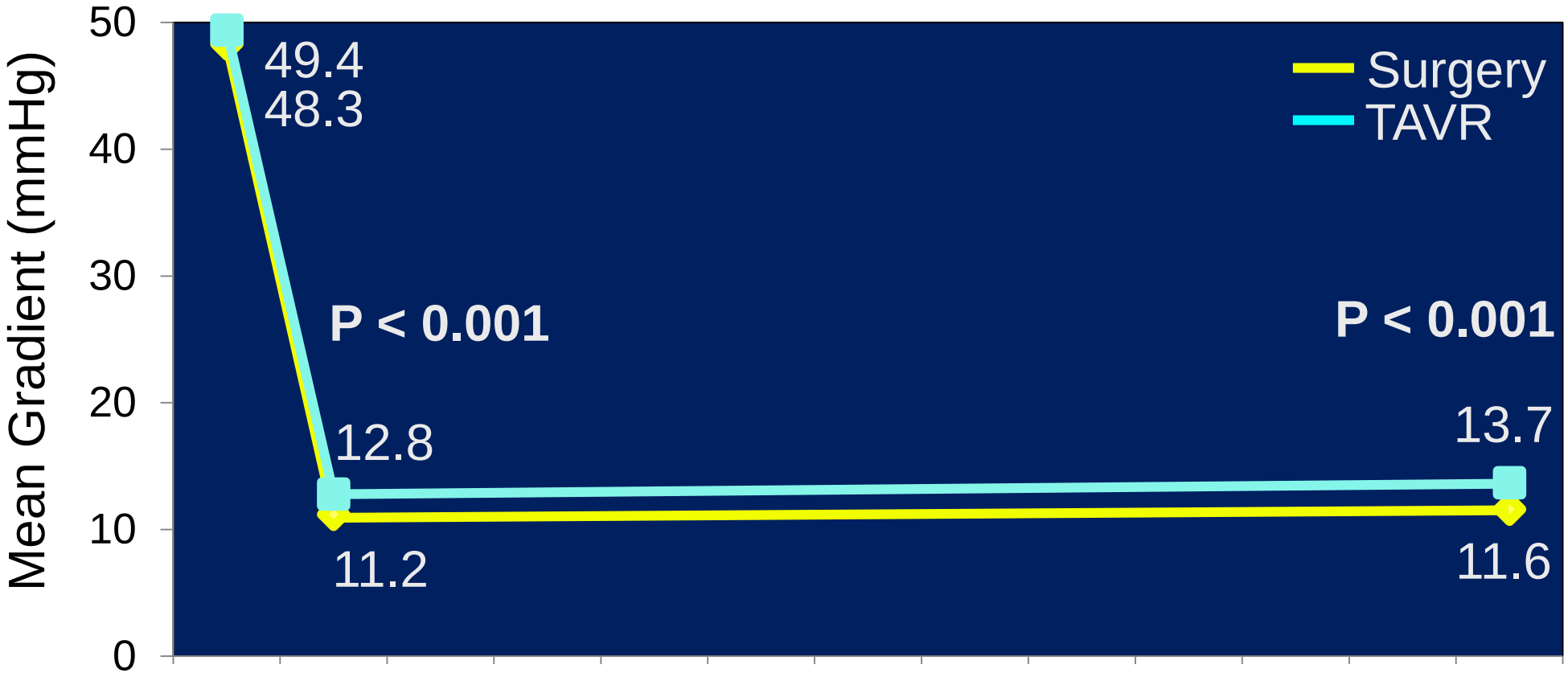
Other Secondary Endpoints

Outcomes	30 Days			1 Year		
	TAVR (N=496)	Surgery (N=454)	P-value	TAVR (N=496)	Surgery (N=454)	P-value
Bleeding - Life-threat/Major	3.6% (18)	24.5% (111)	<0.001	7.7% (38)	25.9% (117)	<0.001
Major Vascular Complics	2.2% (11)	1.5% (7)	0.45	2.8% (14)	1.5% (7)	0.19
AKI - stage 2 or 3*	0.4% (2)	1.8% (8)	0.05	0.4% (2)	1.8% (8)	0.05
New PPM (incl baseline)	6.5% (32)	4.0% (18)	0.09	7.3% (36)	5.4% (24)	0.21
New LBBB	22.0% (106)	8.0% (35)	<0.001	23.7% (114)	8.0% (35)	<0.001
Coronary Obstruction	0.2% (1)	0.7% (3)	0.28	0.2% (1)	0.7% (3)	0.28
AV Re-intervention	0% (0)	0% (0)	NA	0.6% (3)	0.5% (2)	0.76
Endocarditis	0% (0)	0.2% (1)	0.29	0.2% (1)	0.5% (2)	0.49
Asymp Valve Thrombosis	0.2% (1)	0% (0)	0.34	1.0% (5)	0.2% (1)	0.13

Event rates are KM estimates (%) and p-values are based on Log-Rank test

Echocardiography Findings

Mean Gradient



No. of Echos			
Surgery	441	426	390
TAVR	483	490	469

P-values are based on the ANCOVA for TAVR vs Surgery adjusted by baseline.

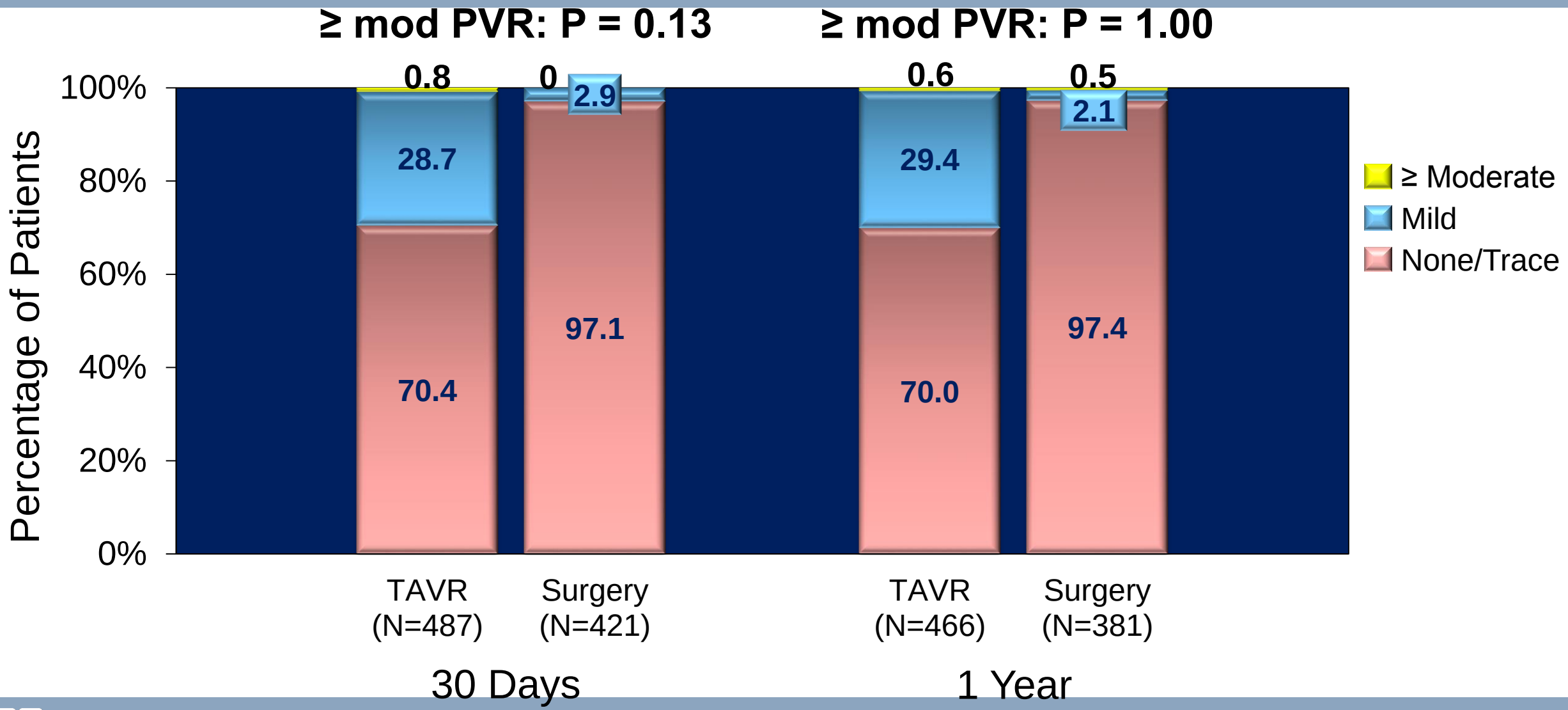
Echocardiography Findings

Aortic Valve Area

No. of Echos			
Surgery	**423**	**395**	**371**
TAVR	**458**	**470**	**446**

P-values are based on the ANCOVA for TAVR vs Surgery adjusted by baseline.

Paravalvular Regurgitation



P values are based on the Wilcoxon rank-sum test.

The PARTNER 3 Trial
Conclusions (1)

In a population of severe symptomatic aortic stenosis patients who were at low surgical risk, TAVR (using the SAPIEN 3 valve) compared to surgery:

- Significantly reduced the primary endpoint of death, stroke, or rehospitalization by 46% at 1-year
  - Components of the primary endpoint favored TAVR, both at 30 days and 1 year
  - Multiple sensitivity analyses confirmed robustness of the primary endpoint findings

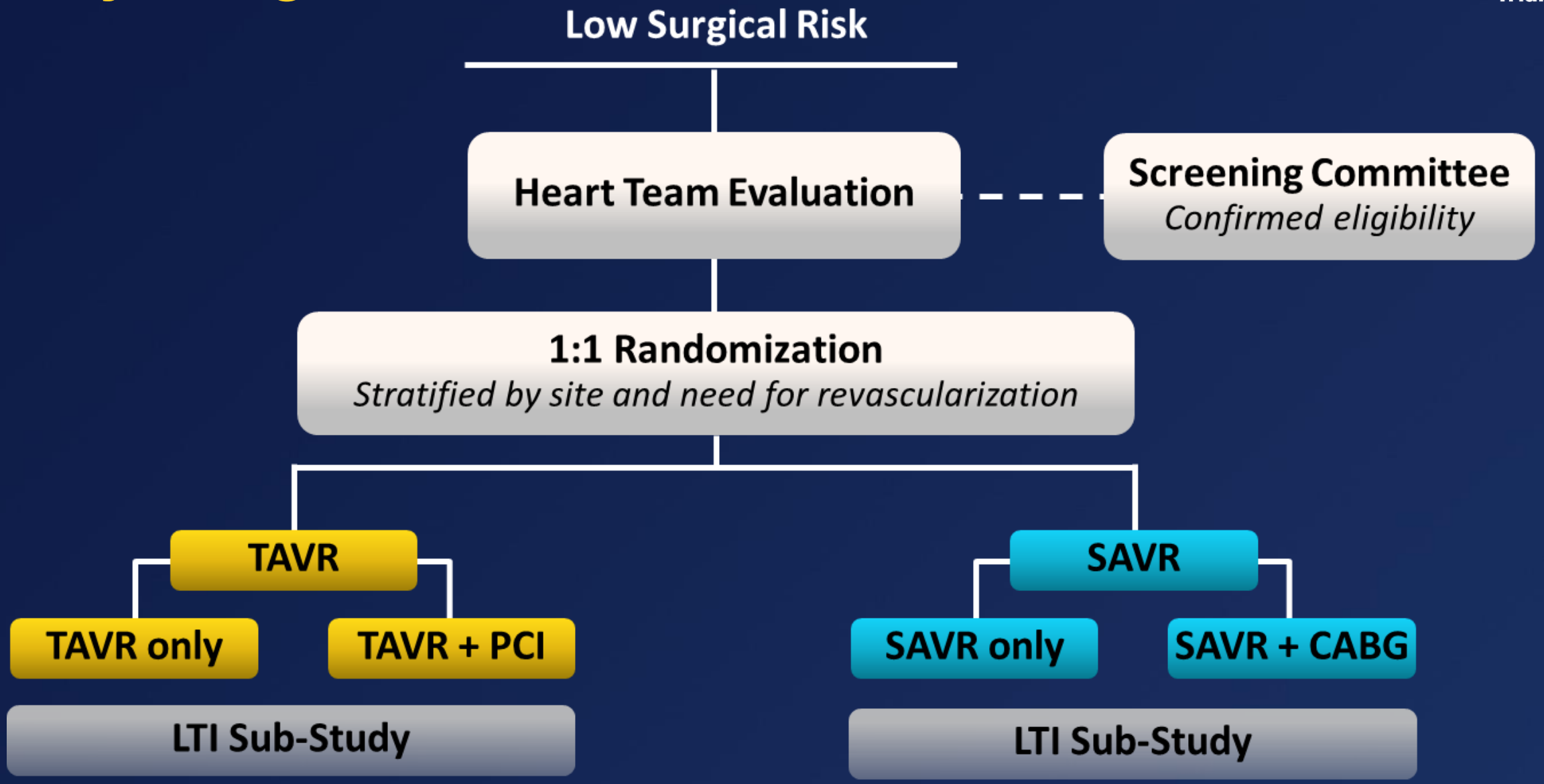
The PARTNER 3 Trial

Clinical Implications

- *Based upon these findings, TAVR, through 1-year, should be considered the preferred therapy in low surgical risk aortic stenosis patients!*
- *PARTNER randomized trials over the past 12 years, clearly indicate that the relative value of TAVR compared with surgery is independent of surgical risk profiles.*
- *The choice of TAVR vs. surgery in aortic stenosis patients should be a shared-decision making process, respecting patient preferences, understanding knowledge gaps (esp. in younger patients), and considering clinical and anatomic factors.*

Study Design

Evolut™ Low Risk Trial



Baseline Characteristics

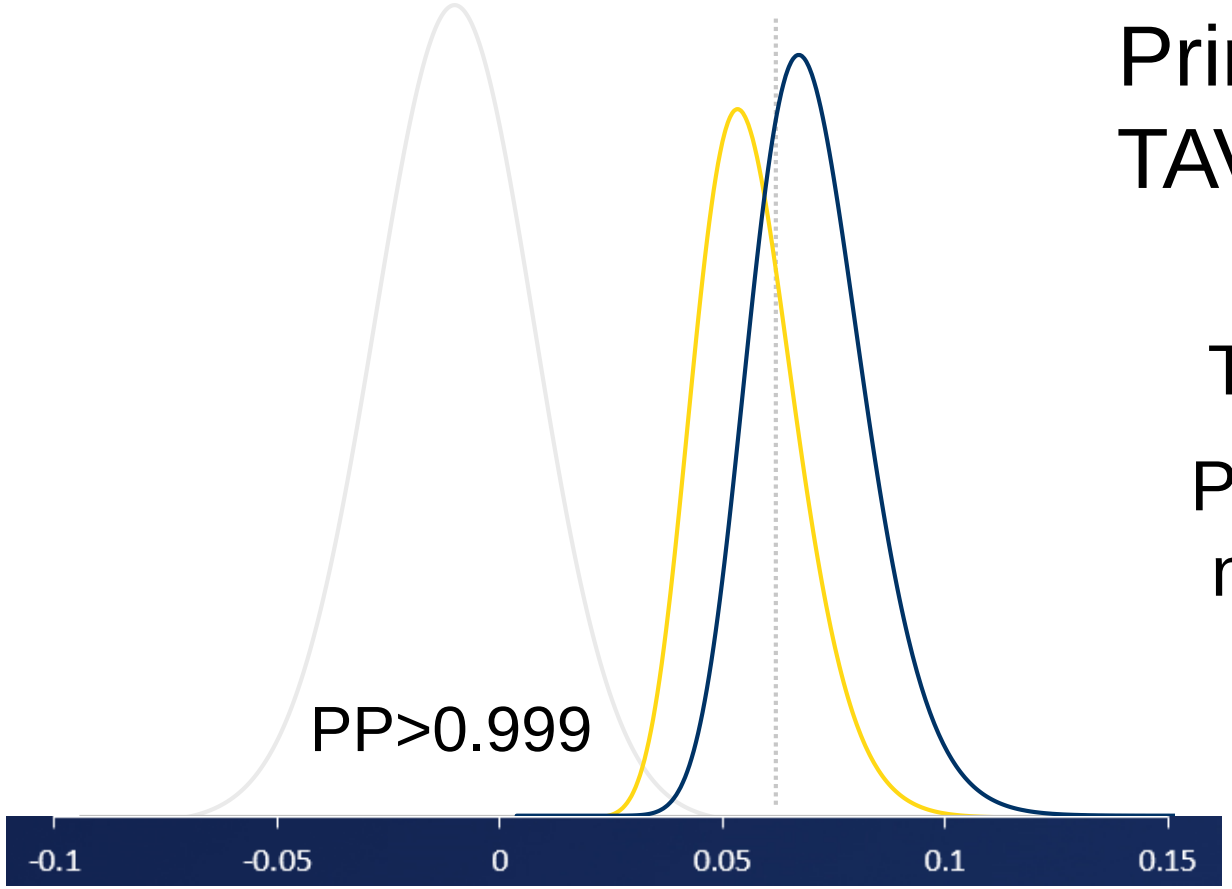
Evolut™ Low Risk Trial

Mean ± SD or %	TAVR (N=725)	SAVR (N=678)
Age, years	74.1 ± 5.8	73.6 ± 5.9
Female sex	36.0	33.8
Body surface area, m^2	2.0 ± 0.2	2.0 ± 0.2
STS PROM, %	1.9 ± 0.7	1.9 ± 0.7
NYHA Class III or IV	25.1	28.5
Hypertension	84.8	82.6
Chronic lung disease (COPD)	15.0	18.0
Cerebrovascular disease	10.2	11.8
Peripheral arterial disease	7.5	8.3

There are no significant differences between groups.

Primary Endpoint

All-Cause Mortality or Disabling Stroke at 2 Years



Primary Endpoint Met
TAVR is noninferior to SAVR

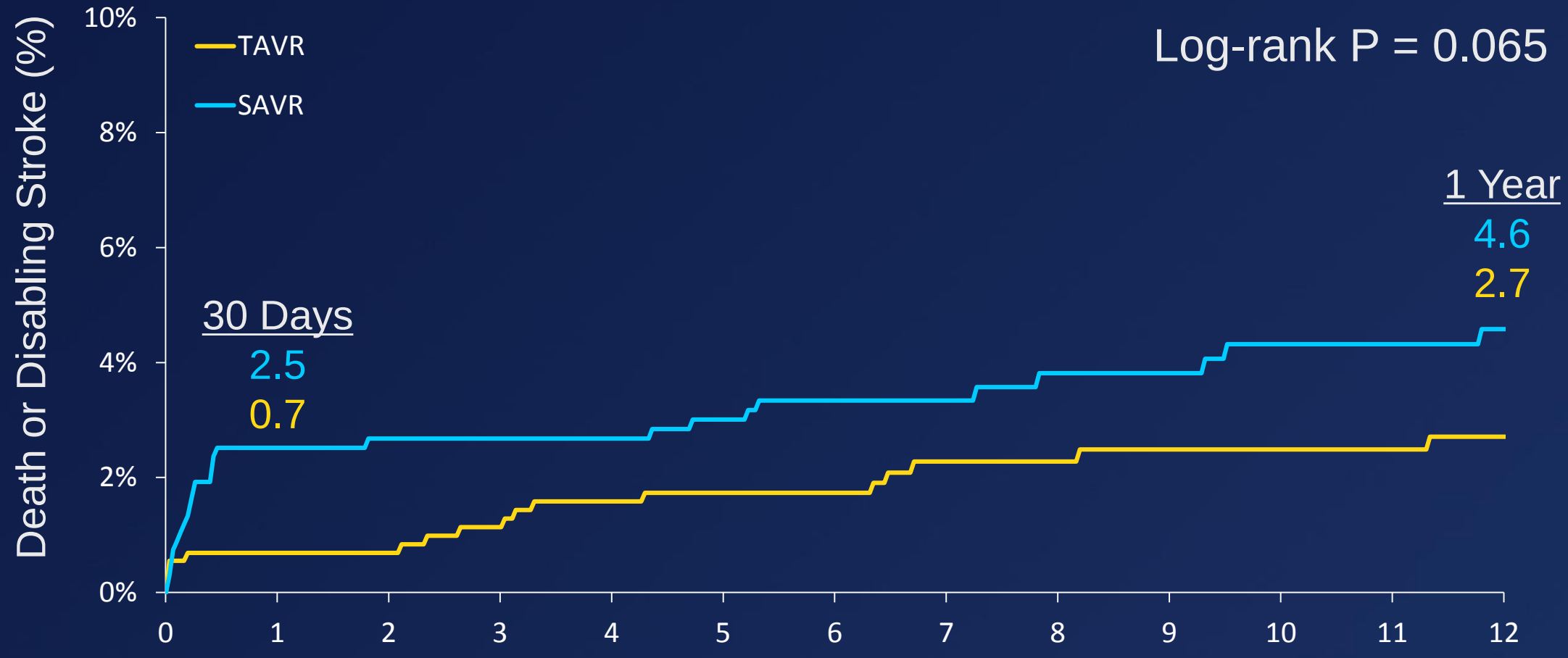
TAVR 5.3% SAVR 6.7%

Posterior probability of noninferiority > 0.999

TAVR –SAVR difference = -1.4% (95% BCI; -4.9, 2.1)

K-M All-Cause Mortality or Disabling Stroke at 1 Year

Evolut™ Low Risk Trial

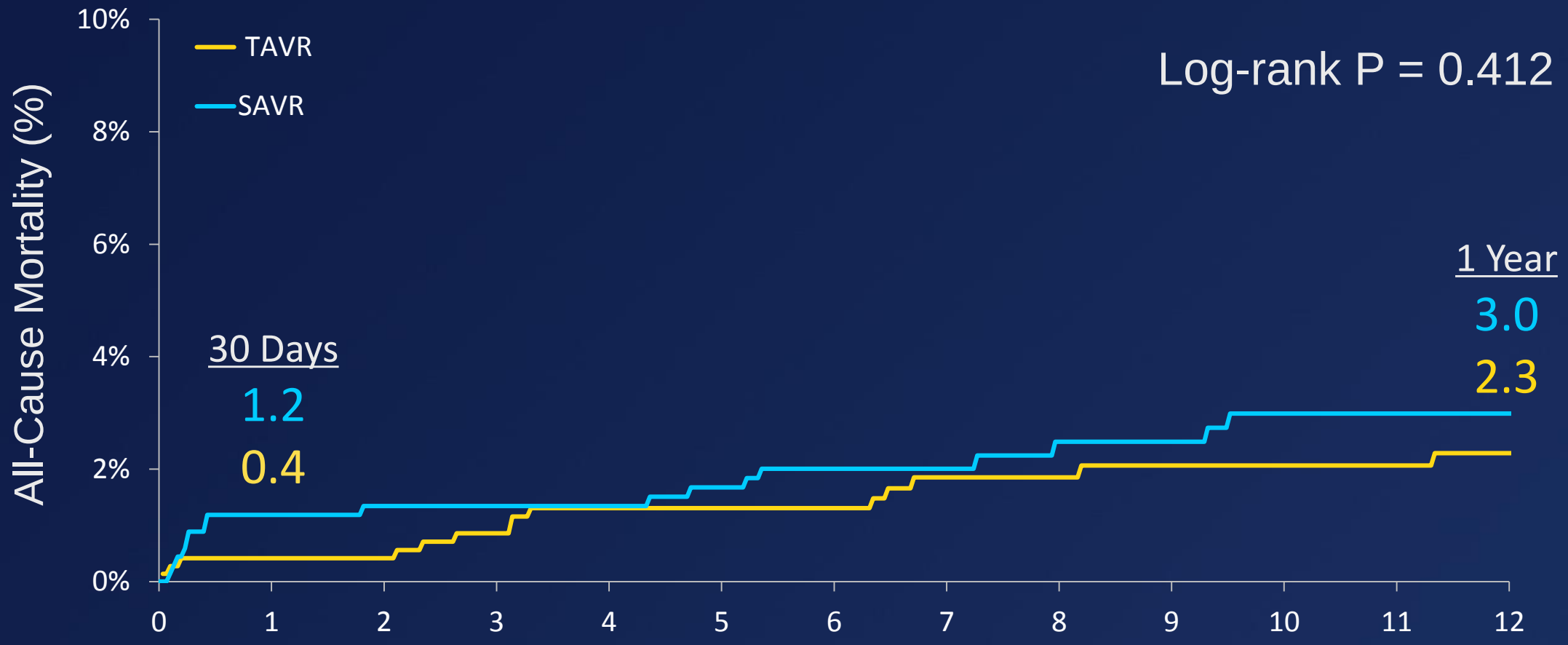


No. at risk

TAVR	725	718	648	435
SAVR	678	656	576	366

K-M Rates of All-Cause Mortality at 1 Year

Evolut™ Low Risk Trial

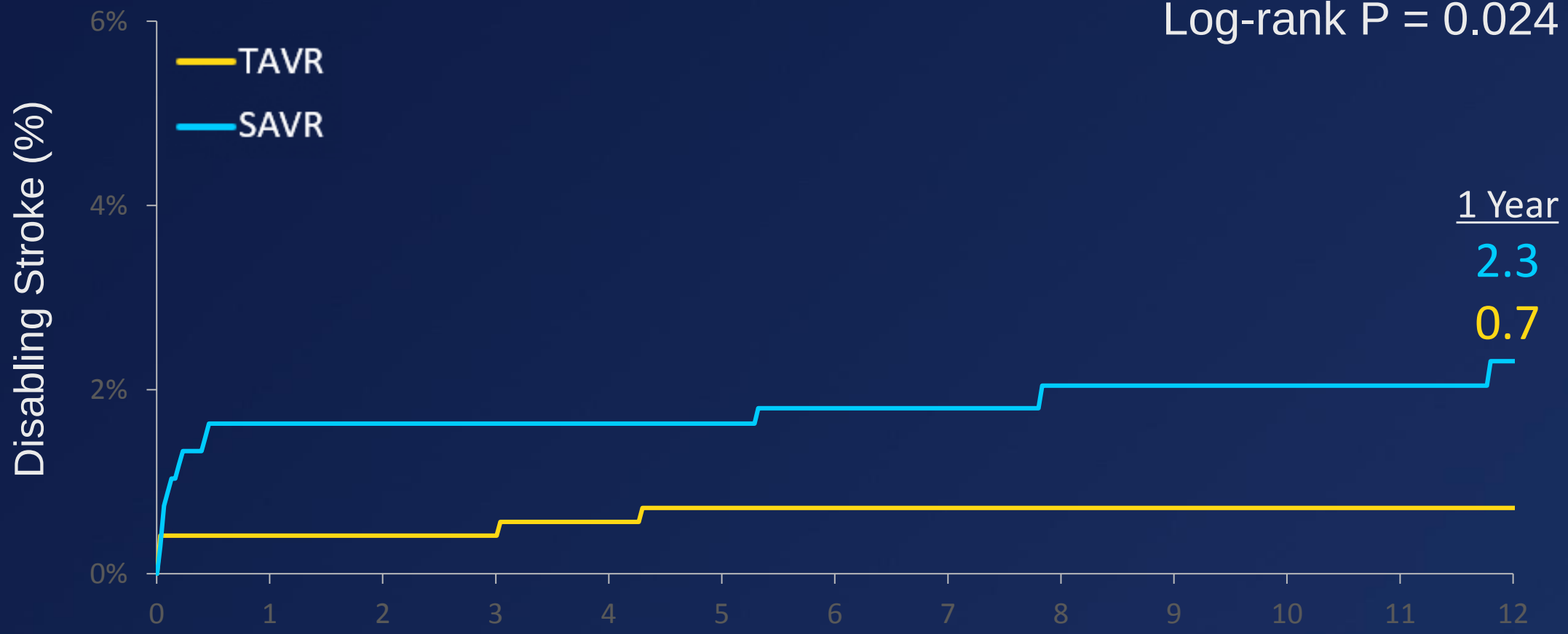


No. at risk

TAVR	725	720	651	435
SAVR	678	665	583	373

K-M Disabling Stroke at 1 Year

Evolut™ Low Risk Trial



No. at risk

TAVR	725	720	648	435
SAVR	678	656	576	366

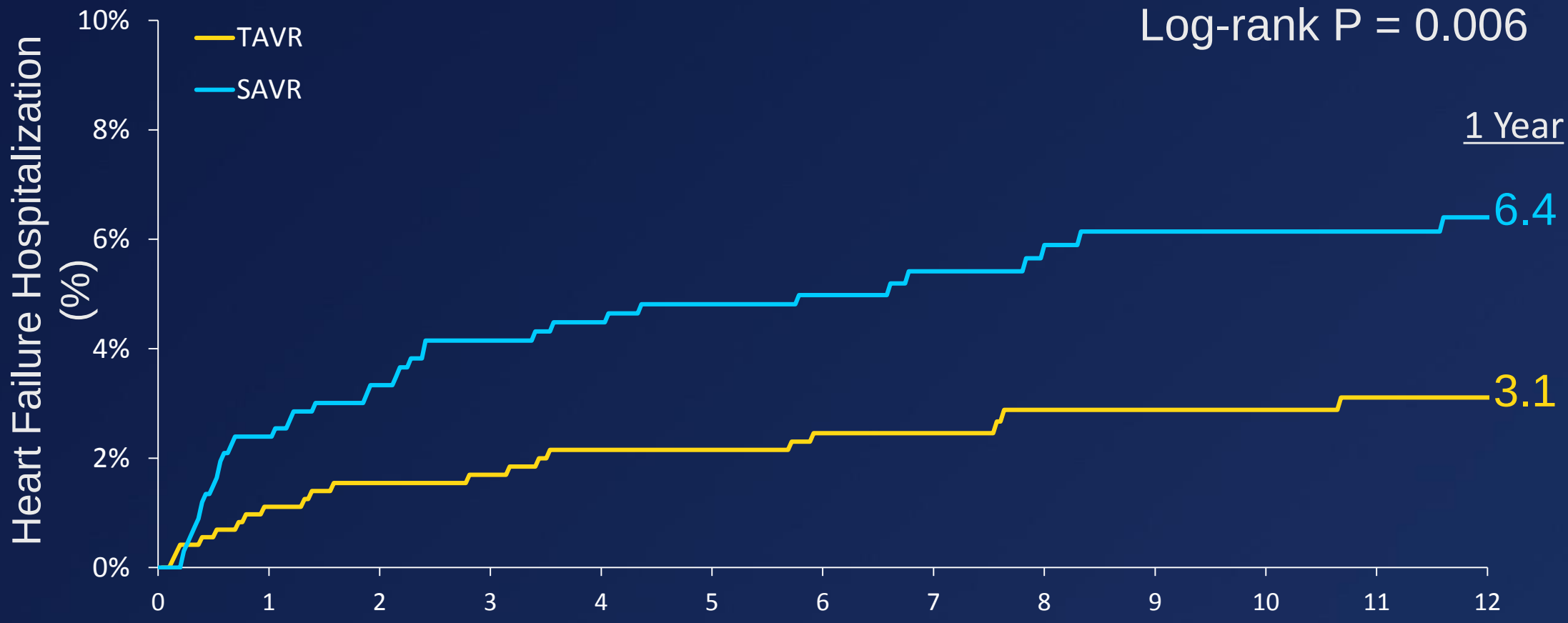
Conclusion

Evolut™ Low Risk Trial

TAVR may be a preferred strategy to surgery in patients with severe aortic stenosis at low risk of surgical mortality.

K-M Heart Failure Hospitalization at 1 Year

Evolut™ Low Risk Trial



No. at risk

TAVR	725	712	636	420
SAVR	678	649	561	358

Cleveland Clinic TAVR Outcomes - 2018

- 2018 = ~495 patients
- 60% High risk, 40% Int risk
- 89% Conscious Sedation

Mortality - 0.2%
Stroke - 0.2%
AR(>=2+) - 0.8%
New PPM - 5%

Question in 2018 - HOW CAN YOU PROVIDE A BETTER TREATMENT OPTION

Isolated SAVR mortality was 0%! – Mostly low risk patients

Unanswered Question(s)

Durability

1. **What is the gold standard?**
2. **What are the predictors? (HALT etc)**
3. **What is the penalty for this?**

Surgical Valve Durability

JAMA Cardiology | Review

Durability Data for Bioprosthetic Surgical Aortic Valve
A Systematic Review

Benish Fatima, MD; Divyanshu Mohananey, MD; Fazal W. Khan, MBBS; Yash Jobanputra, MD; Ramyashree Tummala, MD; Kinjal Banerjee, MD; Amar Krishnaswamy, MD; Stephanie Mick, MD; E. Murat Tuzcu, MD; Eugene Blackstone, MD; Lars Svensson, MD; Samir Kapadia, MD

IMPORTANCE Although several studies have reported data on surgical aortic valve durability, variability in study methodologies and definitions as well as inadequate follow-up make the interpretation of data from these studies difficult to interpret.

OBJECTIVE To review available data on structural valve deterioration (SVD) of surgical bioprosthetic aortic valves by examining the published literature as well as data reported to the US Food and Drug Administration (FDA).

Supplemental cor

Table 1. Definitions of Structural Valve Deterioration (SVD)

Source	Definition
US Food and Drug Administration[5]	SVD is intrinsic and extrinsic mineralization (calcification); leaflet perforation or tear; and leaflet rupture.
Akins et al,[4] 2008 (AATS/STS/EACTS guidelines)	SVD includes dysfunction or deterioration involving the operated valve (exclusive of infection or thrombosis) as determined by reoperation, autopsy, or clinical investigation.
Edmunds et al,[6] 1988	The term *structural deterioration* refers to changes intrinsic to the valve, such as wear, stress fracture, poppet escape, calcification, leaflet tear, stent creep, and disruption or stenosis of a reconstructed valve.
Edmunds et al,[7] 1996	SVD refers to changes intrinsic to the valve, such as wear, fracture, poppet escape, calcification, leaflet tear, stent creep, and suture line disruption of components (eg, leaflets or chordae) of an operated valve.
Khan et al,[8] 1998 (structural failure)	SVD was defined as clinically relevant valvular stenosis or insufficiency as determined by Doppler echocardiography, reoperation, or autopsy.
Gallo et al,[9] 1988 (primary tissue failure)	Primary tissue valve failure was established either at reoperation or autopsy by detection of valve regurgitation or stenosis due to construction failures, cuspal tears, perforation, calcific deposits, or stiffening of the leaflets in the absence of a previous active infective process.
Rizzoli et al,[10] 2006	SVD was defined as every clinical worsening caused by an intrinsic disease of the prosthesis (stenosis or incompetence) exclusive of infection or thrombosis and observed at reoperation, autopsy, or echocardiography.
ISTHMUS Investigators,[11] 2011	SVD is defined according to methodology applied in several recent studies of long-term evaluation of biological prosthetic valves (clinically relevant transprosthetic gradient, confirmed at echocardiography with a mean transprosthetic gradient >40 mm Hg or SVD observed at explant or autopsy).
David et al,[12] 1998 (bioprosthetic valve failure)	Any clinically significant valve stenosis or insufficiency documented by Doppler echocardiography, reoperation, or autopsy.
Le Tourneau et al,[13] 1999 (structural dysfunction)	Dysfunction requiring reoperation (symptoms such as heart failure, syncope, angina, and/or Doppler echocardiographic evidence of aortic valve deterioration with mean transvalvular gradient ≥40 mm Hg or severe aortic regurgitation).
Flameng et al,[14] 2010 (structural valve degeneration)	Structural valve degeneration is stenosis and calcification. Some valves show only rupture of the cusps, whereas others show the combination of leaflet calcification and rupture.

CONCLUSIONS AND RELEVANCE There is considerable variability in reporting SVD of surgical aortic valves, with different definitions and inadequate long-term systematically collected core laboratory data. Rigorously collected long-term data with standardized definitions for surgical valves are needed to provide a benchmark for the durability of rapidly evolving transcatheter valves.

Durability

Research

JAMA Cardiology | Original Investigation

Longitudinal Hemodynamics of Transcatheter and Surgical Aortic Valves in the PARTNER Trial

Pamela S. Douglas, MD; Martin B. Leon, MD; Michael J. Mack, MD; Lars G. Svensson, MD, PhD; John G. Webb, MD; Rebecca T. Hahn, MD; Philippe Pibarot, DVM, PhD; Neil J. Weissman, MD; D. Craig Miller, MD; Samir Kapadia, MD; Howard C. Herrmann, MD; Susheel K. Kodali, MD; Raj R. Makkar, MD; Vinod H. Thourani, MD; Stamatios Lerakis, MD; Ashley M. Lowry, MS; Jeevanantham Rajeswaran, PhD; Matthew T. Finn, MD; Maria C. Alu, MS; Craig R. Smith, MD; Eugene H. Blackstone, MD; for the PARTNER Trial Investigators

IMPORTANCE Use of transcatheter aortic valve replacement (TAVR) for severe aortic stenosis is growing rapidly. However, to our knowledge, the durability of these prostheses is incompletely defined.

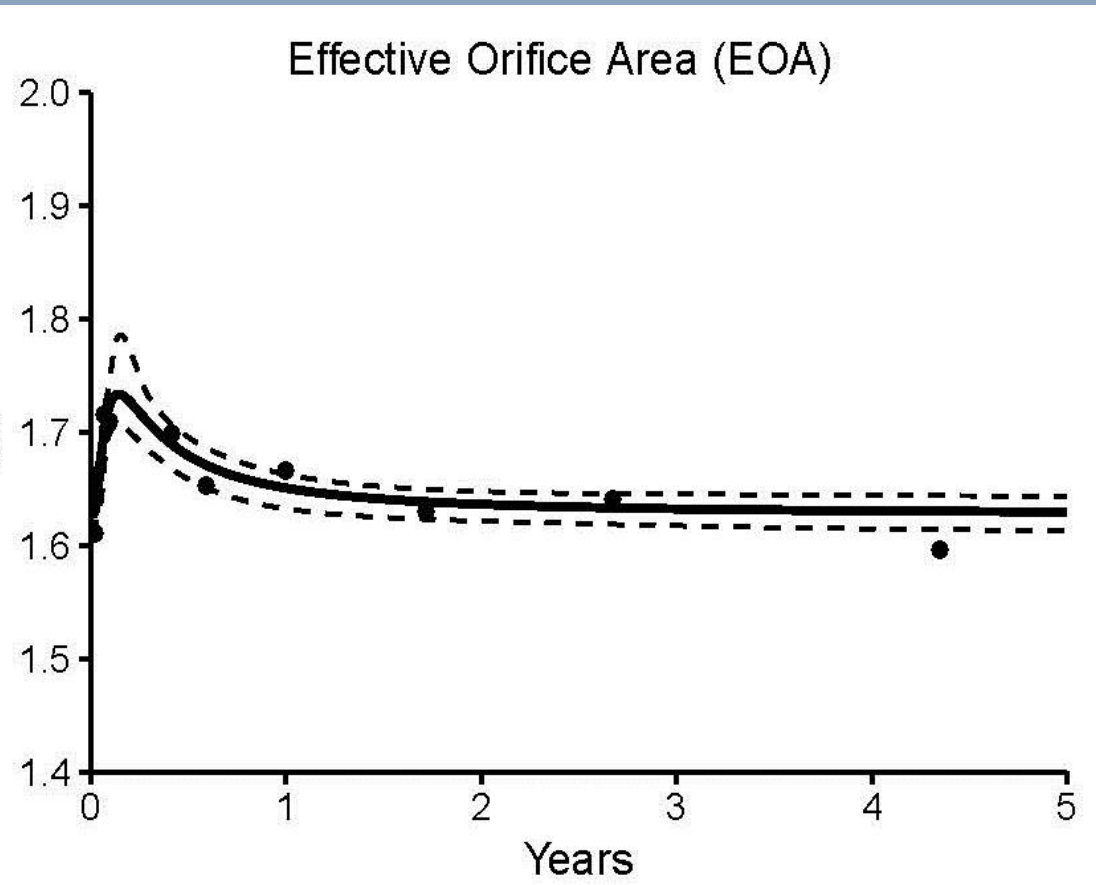
OBJECTIVE To determine the midterm hemodynamic performance of balloon-expandable transcatheter heart valves.

Invited Commentary page 1206

Author Audio Interview

Supplemental content

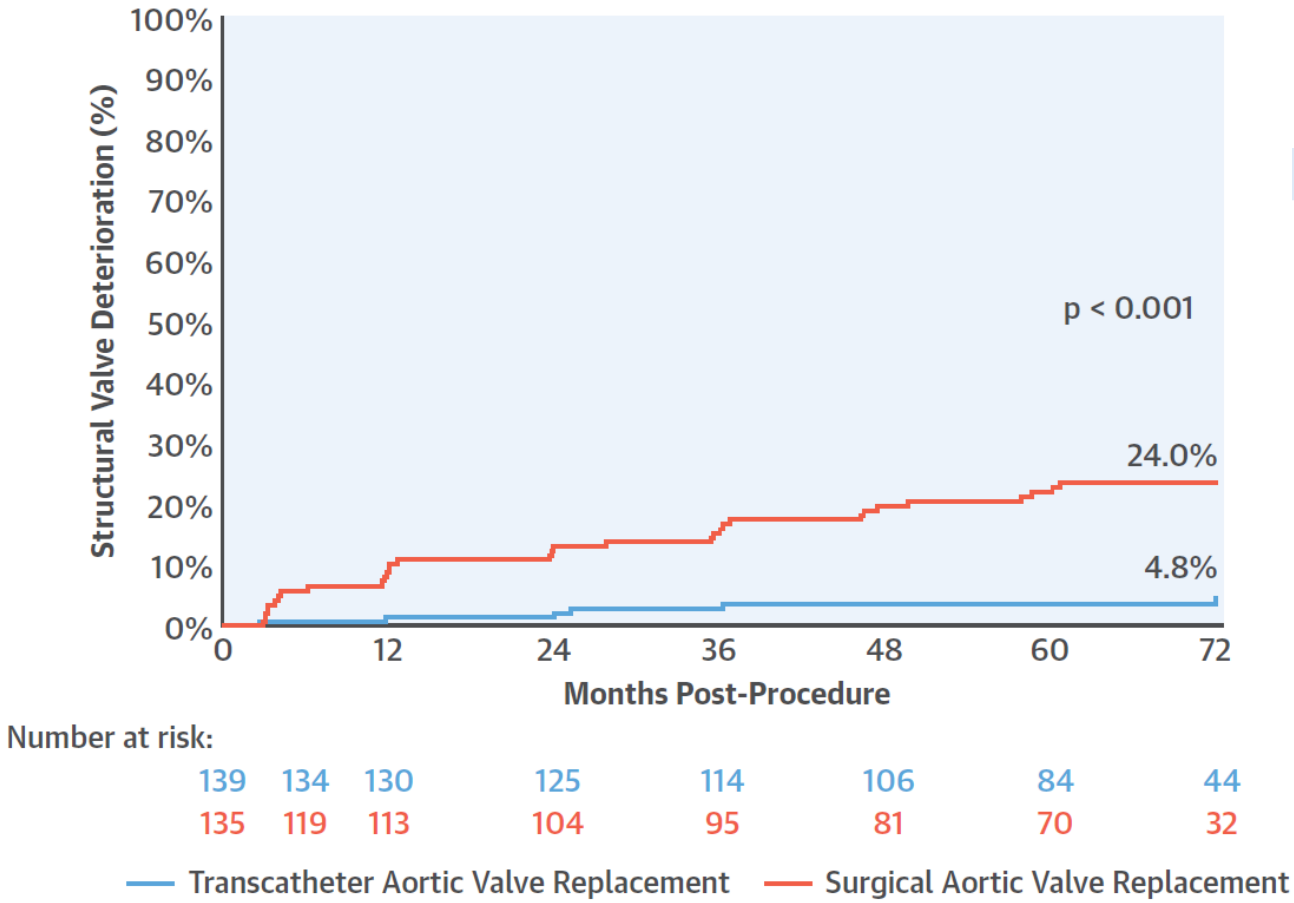
CME Quiz at jamanetwork.com/learning and CME Questions page 1288



CONCLUSIONS AND RELEVANCE This large, core laboratory–based study of transcatheter heart valves revealed excellent durability of the transcatheter heart valves and SAVR. Abnormal findings in individual patients, suggestive of valve thrombosis or structural deterioration, were rare in this protocol-driven database and require further investigation.

Douglas et al, JAMA Cardiol, 2017

Structural Valve Deterioration



	TAVR (n = 139)*	SAVR (n = 135)*
SVD	4.8	24.0
Moderate hemodynamic SVD	3.6	23.7
Mean gradient ≥20 mm Hg	2.9	22.2
Mean gradient ≥10 and <20 mm Hg change from 3 months	1.4	11.1
Moderate central AR	0.0	0.0
Severe hemodynamic SVD	0.7	3.0
Mean gradient ≥40 mm Hg	0.0	1.5
Mean gradient ≥20 mm Hg change from 3 months	0.7	3.0
Severe central AR	0.0	0.0

Søndergaard, L. et al. J Am Coll Cardiol. 2019;73(5):546-53.

ORIGINAL ARTICLE

Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

R.R. Makkar, G. Fontana, H. Jilaihawi, T. Chakravarty, K.F. Kofoed, O. de Backer, F.M. Asch, C.E. Ruiz, N.T. Olsen, A. Trento, J. Friedman, D. Berman, W. Cheng, M. Kashif, V. Jelnin, C.A. Kliger, H. Guo, A.D. Pichard, N.J. Weissman, S. Kapadia, E. Manasse, D.L. Bhatt, M.B. Leon, and L. Søndergaard

ABSTRACT

BACKGROUND

A finding of reduced aortic-valve leaflet motion was noted on computed tomography (CT) in a patient who had a stroke after transcatheter aortic-valve replacement (TAVR) during an ongoing clinical trial. This finding raised a concern about possible subclinical leaflet thrombosis and prompted further investigation.

METHODS

We analyzed data obtained from 55 patients in a clinical trial of TAVR and from two single-center registries that included 132 patients who were undergoing either TAVR or surgical aortic-valve bioprosthesis implantation. We obtained four-dimensional, volume-rendered CT scans along with data on anticoagulation and clinical outcomes (including strokes and transient ischemic attacks [TIAs]).

RESULTS

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. Reduced leaflet motion was detected among patients with multiple bioprosthesis types, including transcatheter and surgical bioprostheses. Therapeutic anticoagulation with warfarin, as compared with dual antiplatelet therapy, was associated with a decreased incidence of reduced leaflet motion (0% and 55%, respectively, P=0.01 in the clinical trial; and 0% and 29%, respectively, P=0.04 in the pooled registries). In patients who were reevaluated with follow-up CT, restoration of leaflet motion was noted in all 11 patients who were receiving anticoagulation and in 1 of 10 patients who were not receiving anticoagulation (P<0.001). There was no significant difference in the incidence of stroke or TIA between patients with reduced leaflet motion and those with normal leaflet motion in the clinical trial (2 of 22 patients and 0 of 33 patients, respectively; P=0.16), although in the pooled registries, a significant difference was detected (3 of 17 patients and 1 of 115 patients, respectively; P=0.007).

CONCLUSIONS

Reduced aortic-valve leaflet motion was shown in patients with bioprosthetic aortic valves. The condition resolved with therapeutic anticoagulation. The effect of this finding on clinical outcomes including stroke needs further investigation. (Funded by St. Jude Medical and Cedars–Sinai Heart Institute; Portico-IDE ClinicalTrials.gov number, NCT02000115; SAVORY registry, NCT02426307; and RESOLVE registry, NCT02318342.)

EDITORIAL

Uncertainty and Possible Subclinical Valve Leaflet Thrombosis

David R. Holmes, M.D., and Michael J. Mack, M.D.

Transcatheter aortic-valve replacement (TAVR) has had a profound effect on the management of bosis Assessed with Four-Dimensional Computed Tomography [SAVORY] registry).

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

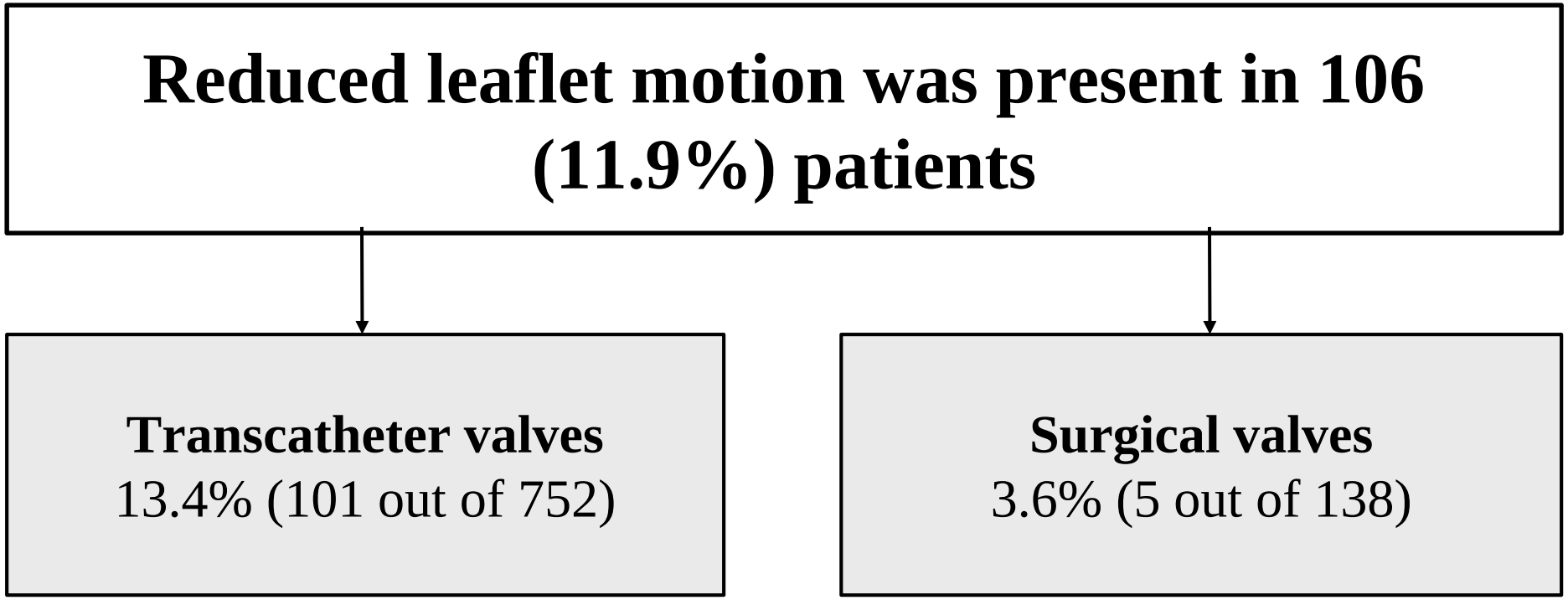
Reduced Leaflet Motion in Bioprosthetic Aortic Valves — The FDA Perspective

John C. Laschinger, M.D., Changfu Wu, Ph.D., Nicole G. Ibrahim, Ph.D., and Jeffrey E. Shuren, M.D., J.D.

Bioprosthetic aortic valves play a critical role in improving the health and quality of life of many patients with severe aortic valve disease. On September 16, 2014, St. Jude Medical publicly disclosed that it had temporarily discontinued article by Makkar et al. now pub- ity from reduced leaflet opening (mild to severe) to complete immobility. Makkar et al. also report that reduced leaflet motion and change in hemodynamic performance were not detected by transthoracic echocardiography,

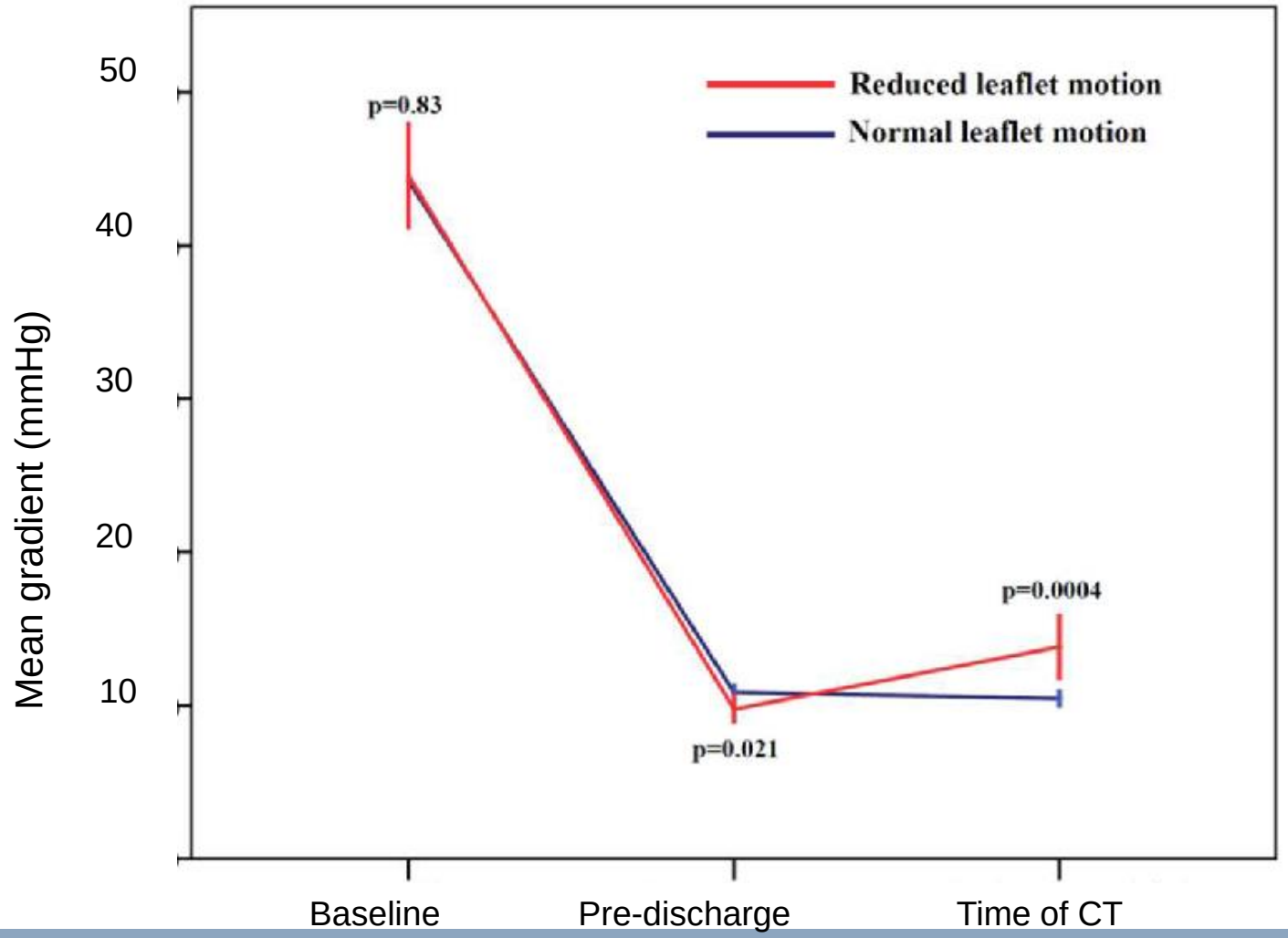
Prevalence of reduced leaflet motion

Transcatheter vs. surgical bioprosthetic aortic valves: p=0.001



Chakravarty et al, Lancet 2017; 389: 2383–92

Reduced Leaflet Motion and Increased Gradients

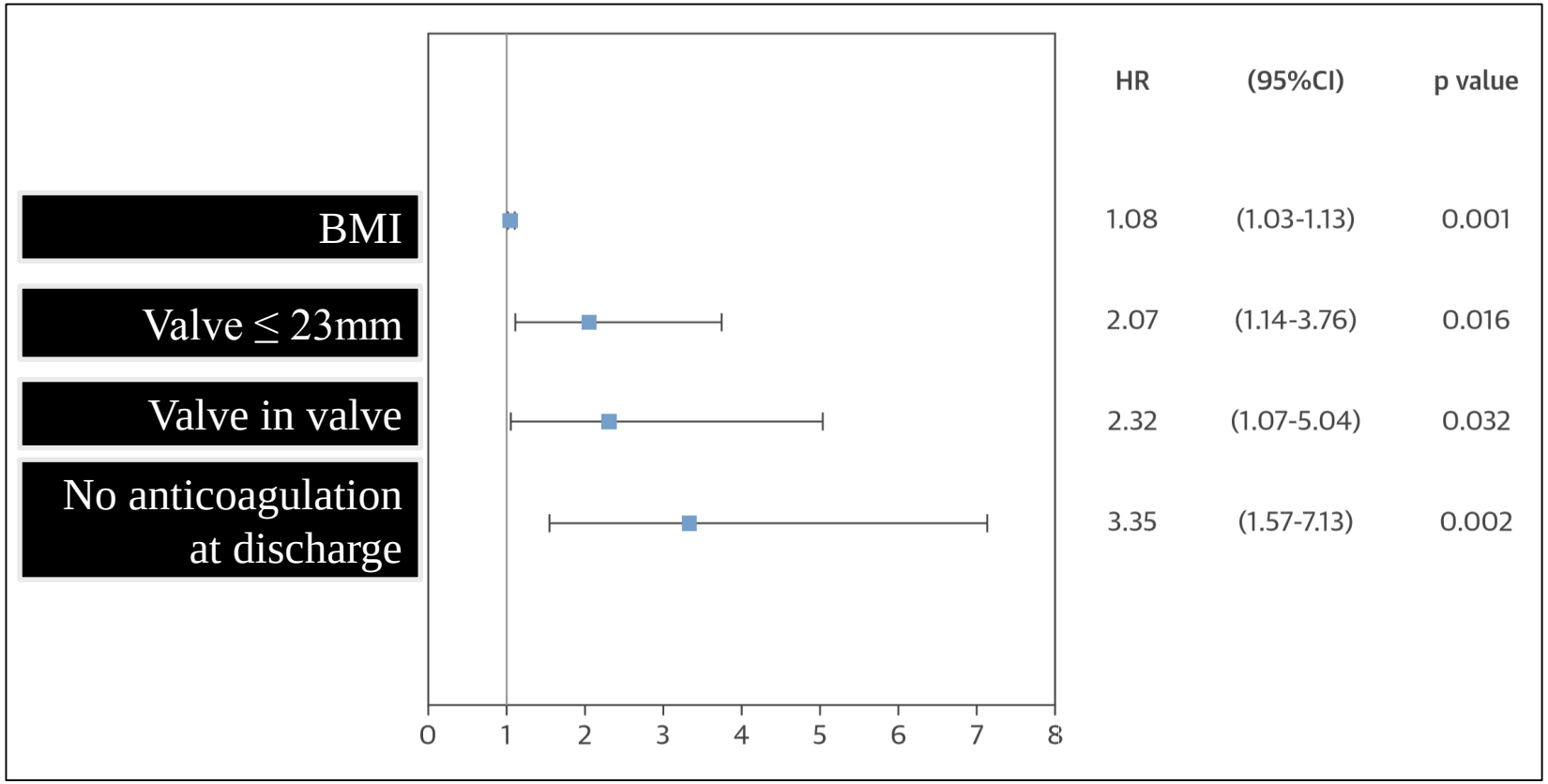


Chakravarty et al, Lancet 2017; 389: 2383–92

Predictors of Valve Hemodynamic Degeneration after TAVR

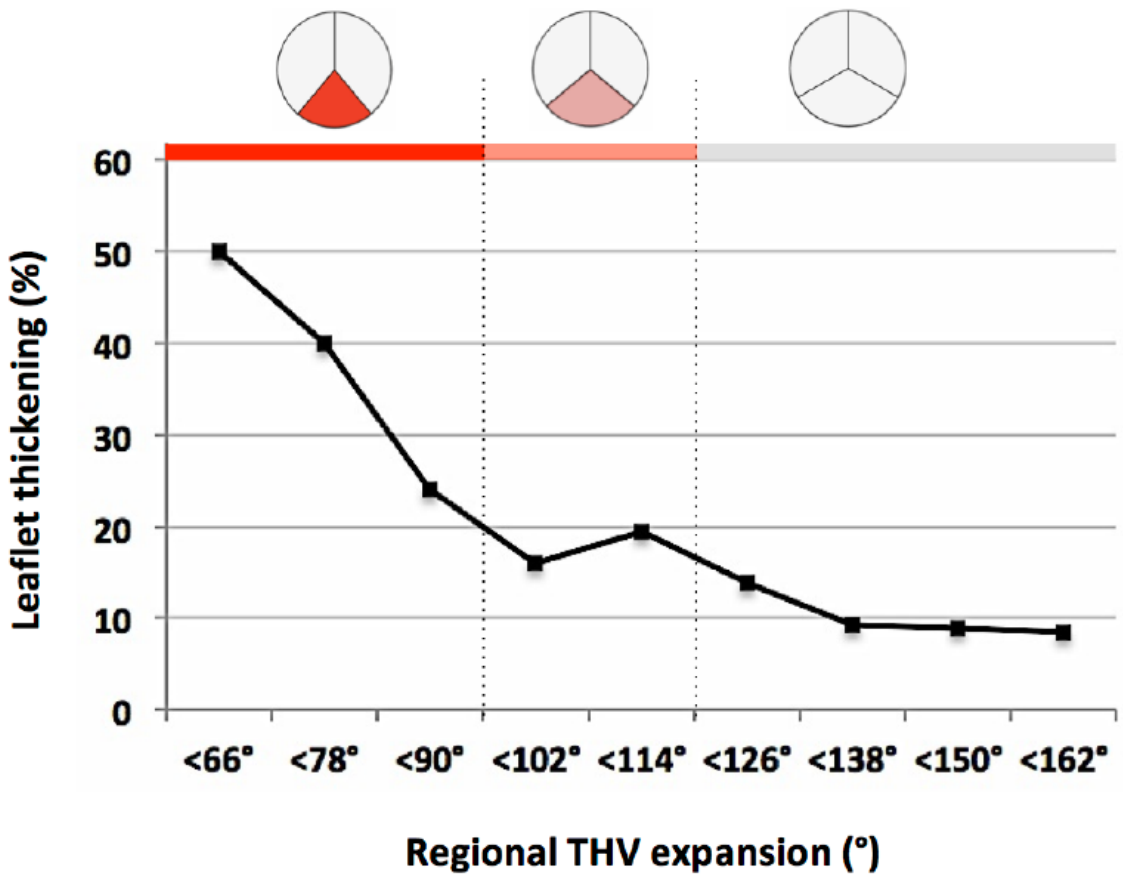
1521 patients undergoing TAVR

Valve hemodynamic degeneration = 10mmHg rise in transvalvular gradients



Del Trigo M. et al. JACC 2016

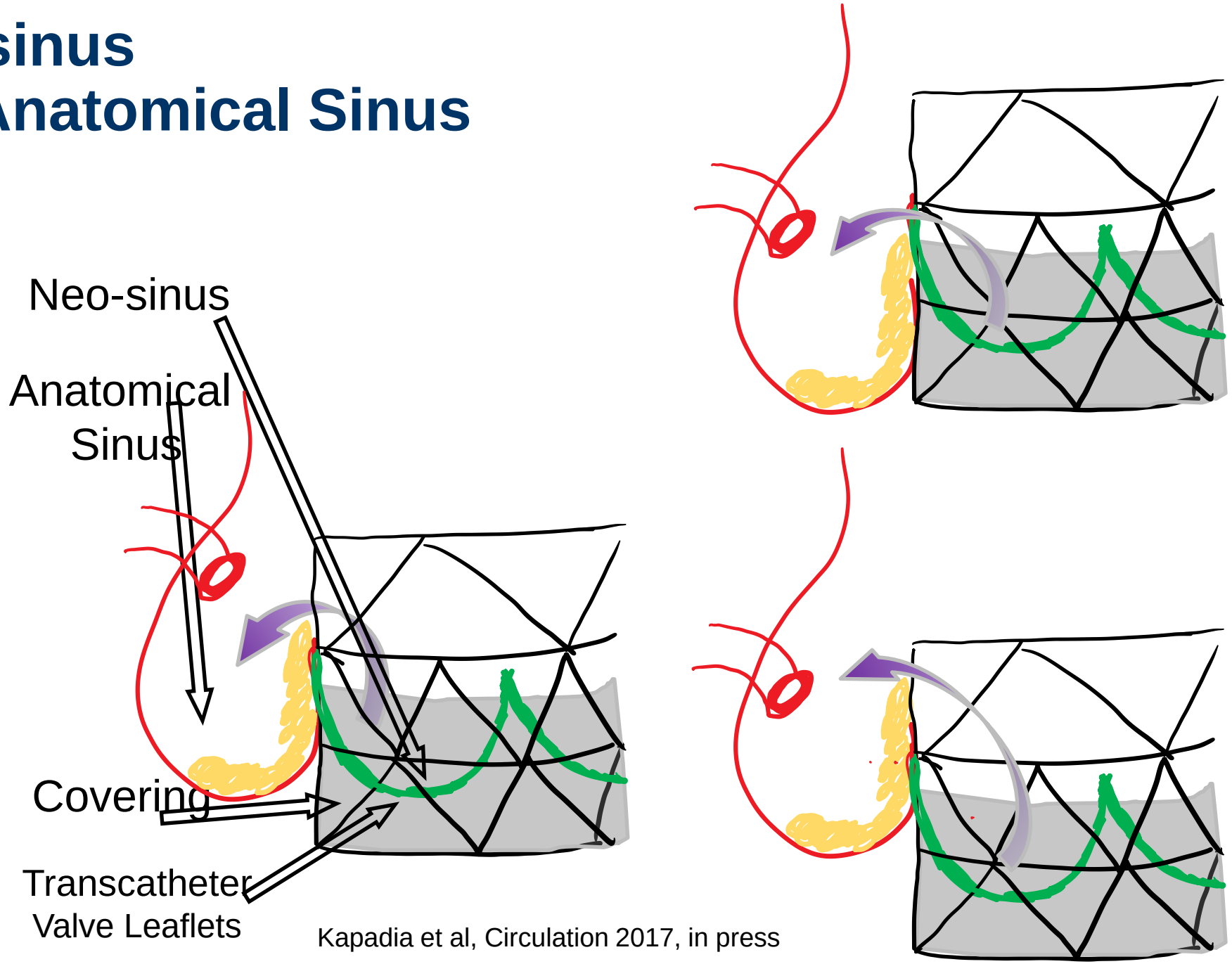
THV expansion and Leaflet Thrombus



# leaflets	4	10	25	50	77	116	184	215	225

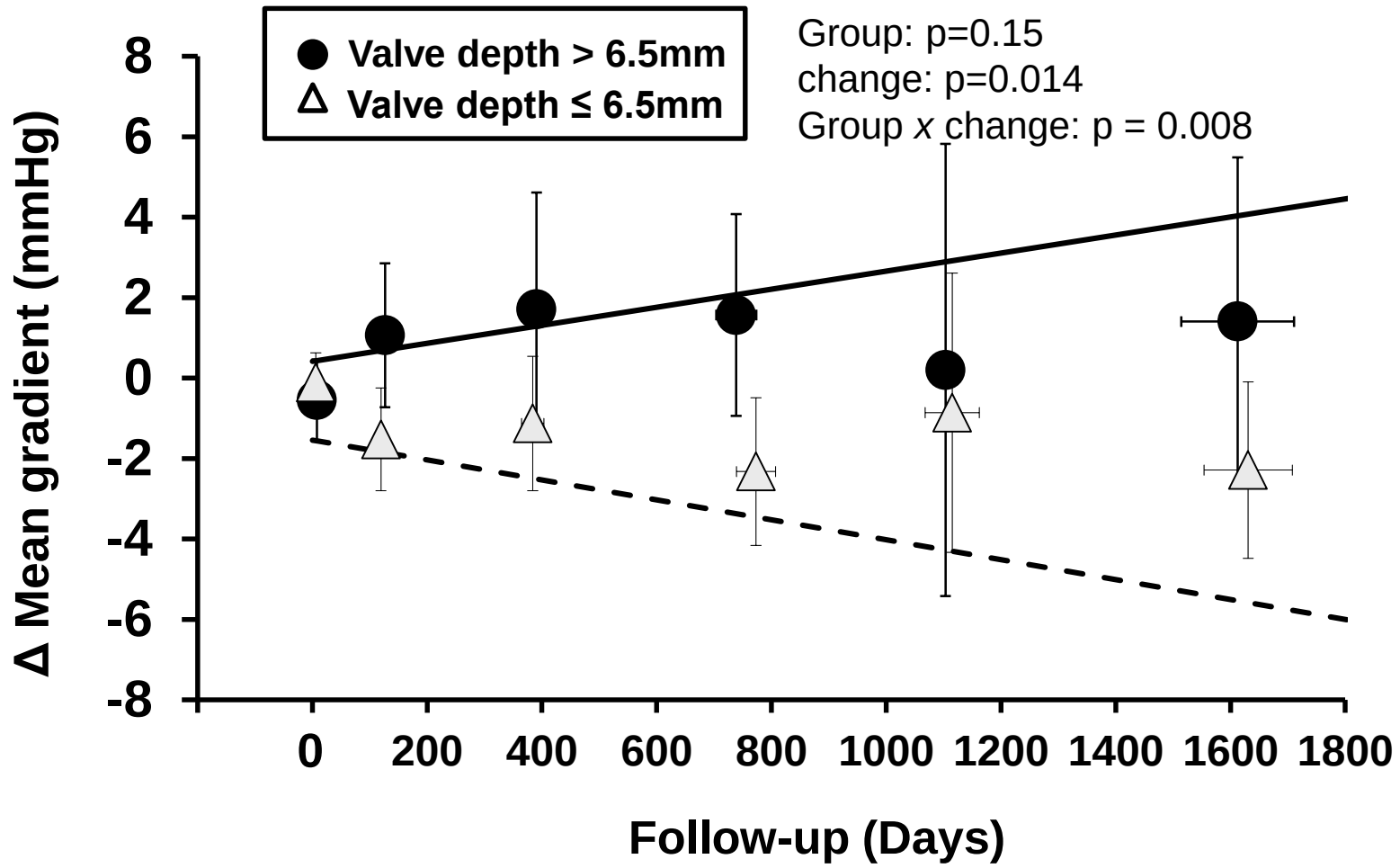
Fuchs et al, Eurointervention, 2017 Jul 25. pii: EIJ-D-17-00373

Neo-sinus and Anatomical Sinus



Kapadia et al, Circulation 2017, in press

Depth of Implant



	0-30	30-300	300-600	600-1000	1000-1400	> 1400 days
Depth > 6.5	28	24	17	14	7	11
Depth ≤ 6.5	83	65	40	34	17	20

What is the correct thinking?

Surgery for low surgical risk patients

OR

TAVR for low TAVR risk patients

Devices Likely to Approved This Year

PORTICO

LOTUS

ACURATE *neo* Aortic Valve

Stabilization Arches

- Axial self-aligning

Upper Crown

- Minimal supra-annular anchoring
- Captures native leaflets and provides coronary clearance

Lower Crown

- Minimal protrusion into LVOT
- Low risk of conduction system interference

Supra-annular Valve

- Porcine pericardium leaflets
- BioFix™ anti-calcification process
- Low gradients

Pericardial Skirt

- Inner and outer anti-leak skirts

Self-expanding Nitinol Frame

- Treats annulus from 21mm to 27mm

ACURATE *neo2* Aortic Valve

ACURATE neo2 maintains key features of the ACURATE neo valve

- Self-expanding nitinol frame with porcine pericardium leaflets
- Supra-annular positioning; two-step top-down deployment
- Treats annuli from 21mm to 27mm

Stabilization Arches

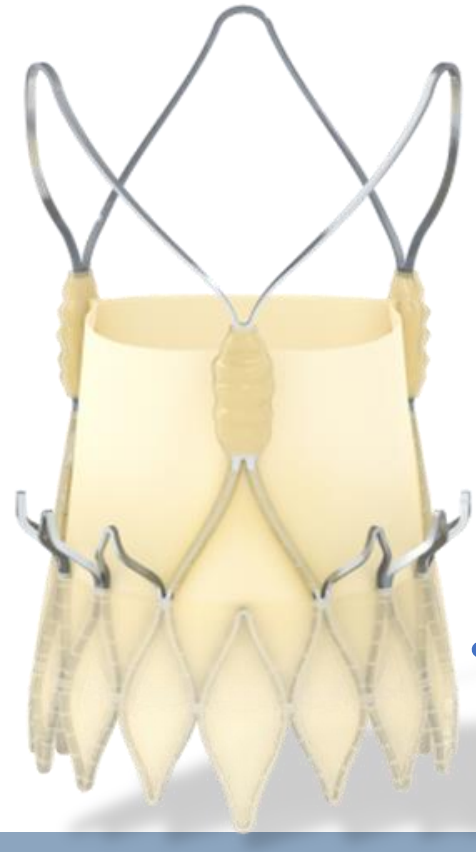
- Axial; self-aligning

Upper Crown

- Captures native leaflets and provides coronary clearance

Lower Crown

- Minimal protrusion into LVOT

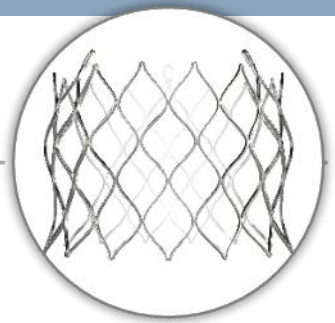


ACURATE neo2 incorporates "Advanced Sealing" technology

- Inner and outer pericardial skirts (outer skirt covers to waist of stent)
- Designed to improve conformability to irregular, calcified anatomy and enhance reduction of PVL

Centera: Self-Expanding TAVR Valve Design

23mm, 26mm, and 29mm valve sizes



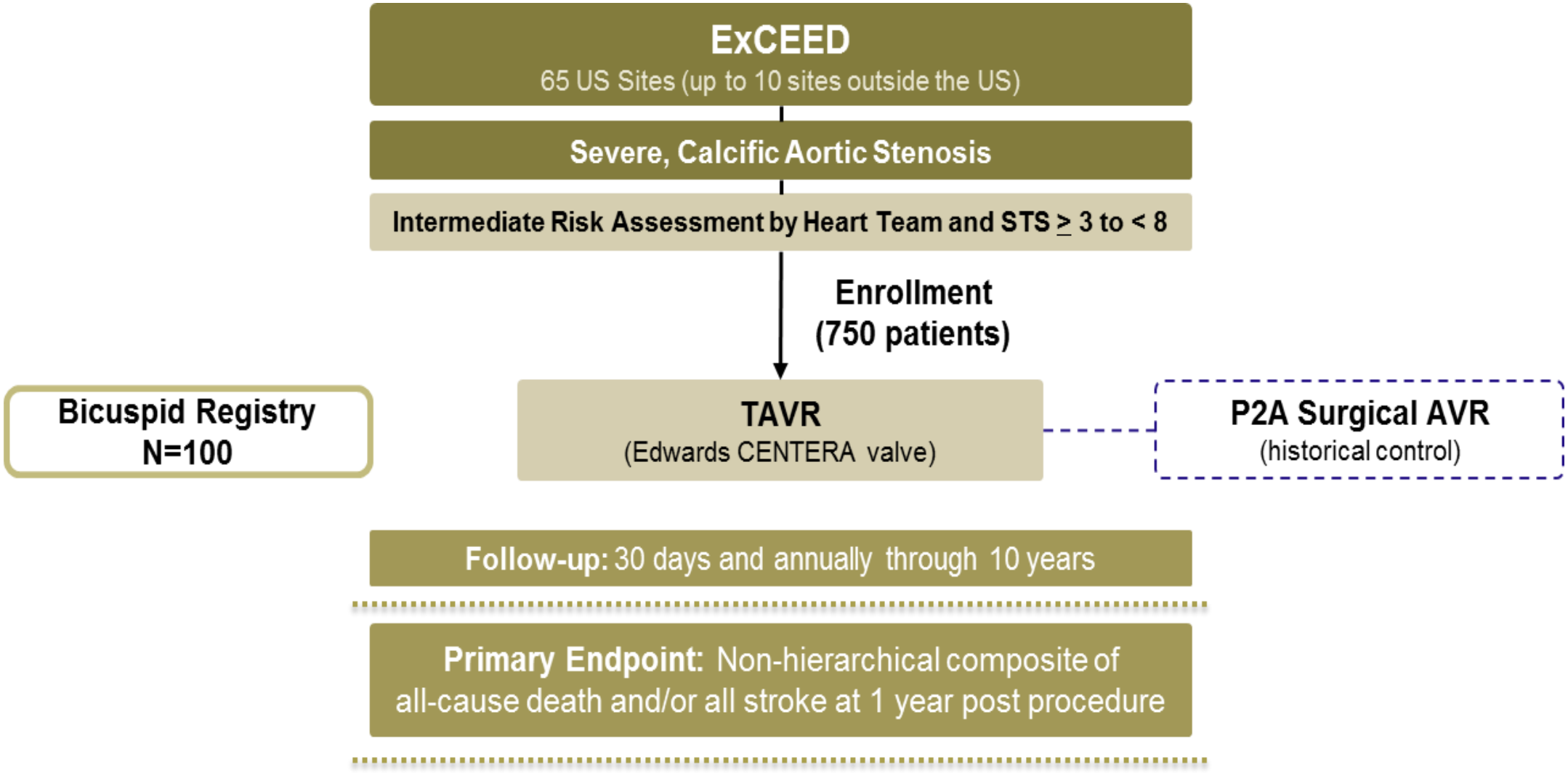
Short frame height designed to respect the cardiac anatomy

- Same **bovine pericardial tissue** as SAPIEN valve family
- **RESILIA tissue technology** allows the valve to be stored dry

Unique contoured frame geometry designed to anchor and seal within the annulus for low PVL rates

Centera Self-Expanding TAVR System

ExCEED U.S. Clinical Trial



Important Areas

- **Early TAVR - Asymptomatic**
- **Bicuspid AS**
- **Valve in Valve**
- **Unload LV – Moderate AS and LV dysfunction**
- **Isolated AR**

EARLY TAVR

Asymptomatic Severe AS and 2D-TTE (PV ≥4m/s or AVA ≤1 cm^2)

Exclusion if patient is symptomatic, EF<50%, concomitant surgical indications, bicuspid valve, or STS >8