TAVR Clinical Trials

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Disclosure Statement of Financial Interest

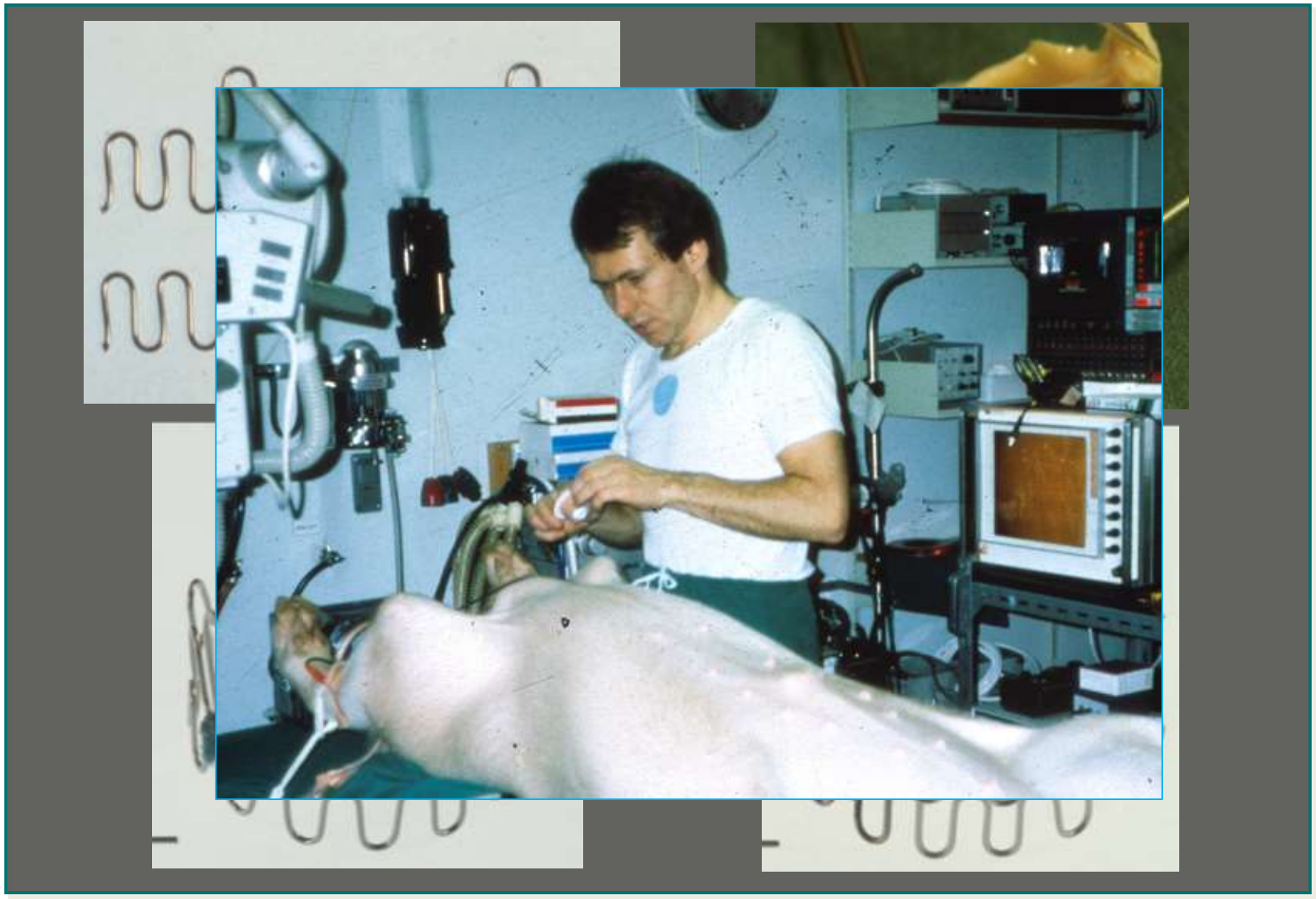
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Edwards Lifesciences, Abbott
• Scientific Advisory Board	• Medtronic, Abbott
• Executive Physician Council	• Boston Scientific Corp

TAVR Clinical Evidence in 8 min

- The beginning….
- Clinical Trial Data for benchmarking
- What is hot?

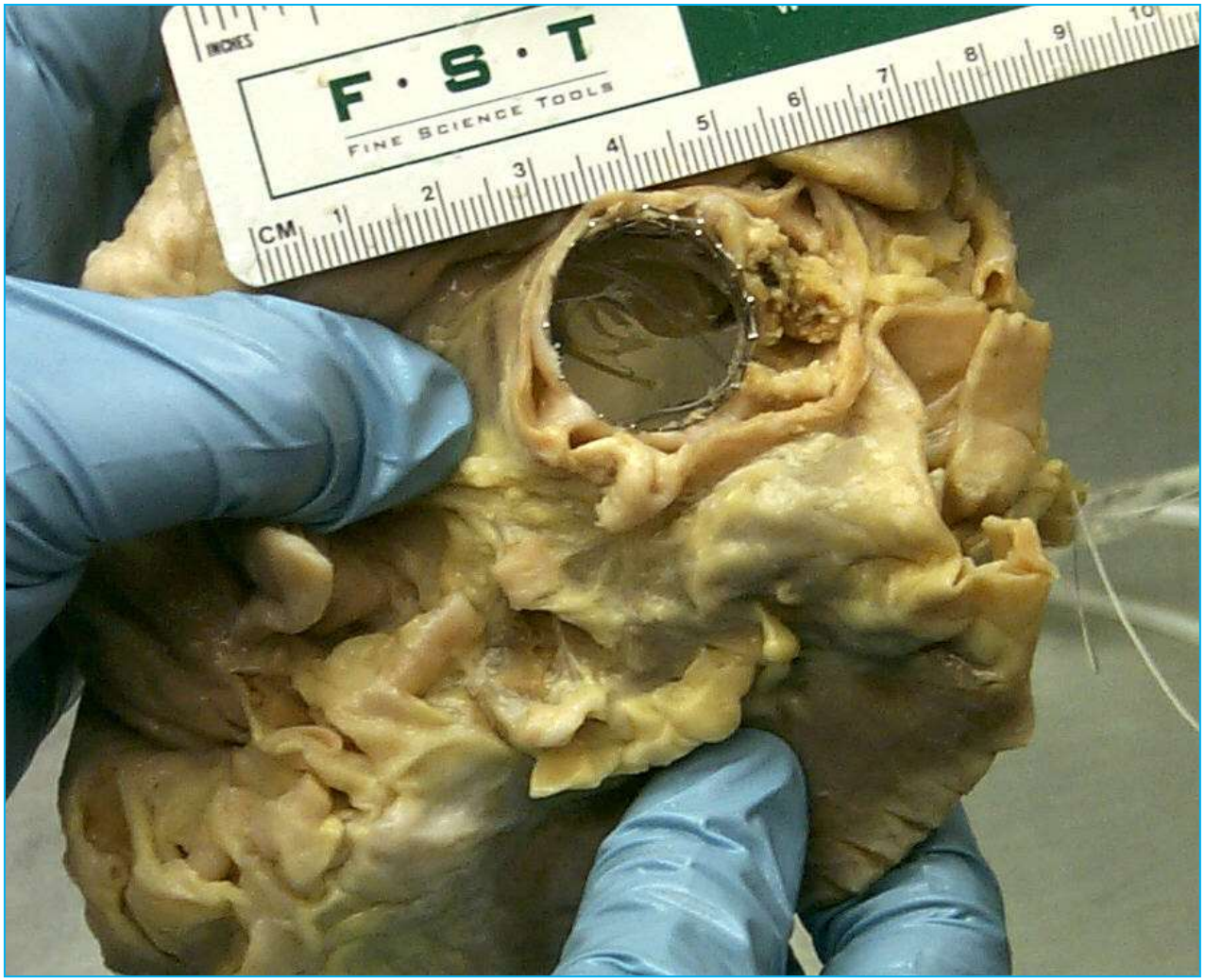
The Andersen Stent-Valve (1989)



2000-2002: The Sheep Era

CERA (Centre d’ Experimentation et de Recherche Appliquée)
Institut Monsouris, Paris, France

PVT - Cadaver Heart Study at AFIP



Dr. Alain Cribier
First-in-Man PIONEER

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association.
Learn and Live.

Percutaneous Transcatheter Implantation of an Aortic Valve Prosthesis for Calcific Aortic Stenosis

First Human Case Description

Alain Cribier, MD; Helene Eltchaninoff, MD; Assaf Bash, PhD; Nicolas Borenstein, MD; Christophe Tron, MD; Fabrice Bauer, MD; Genevieve Derumeaux, MD; Frederic Anselme, MD; François Laborde, MD; Martin B. Leon, MD

Conclusions— *Nonsurgical implantation of a prosthetic heart valve can be successfully achieved with immediate and midterm hemodynamic and clinical improvement.*

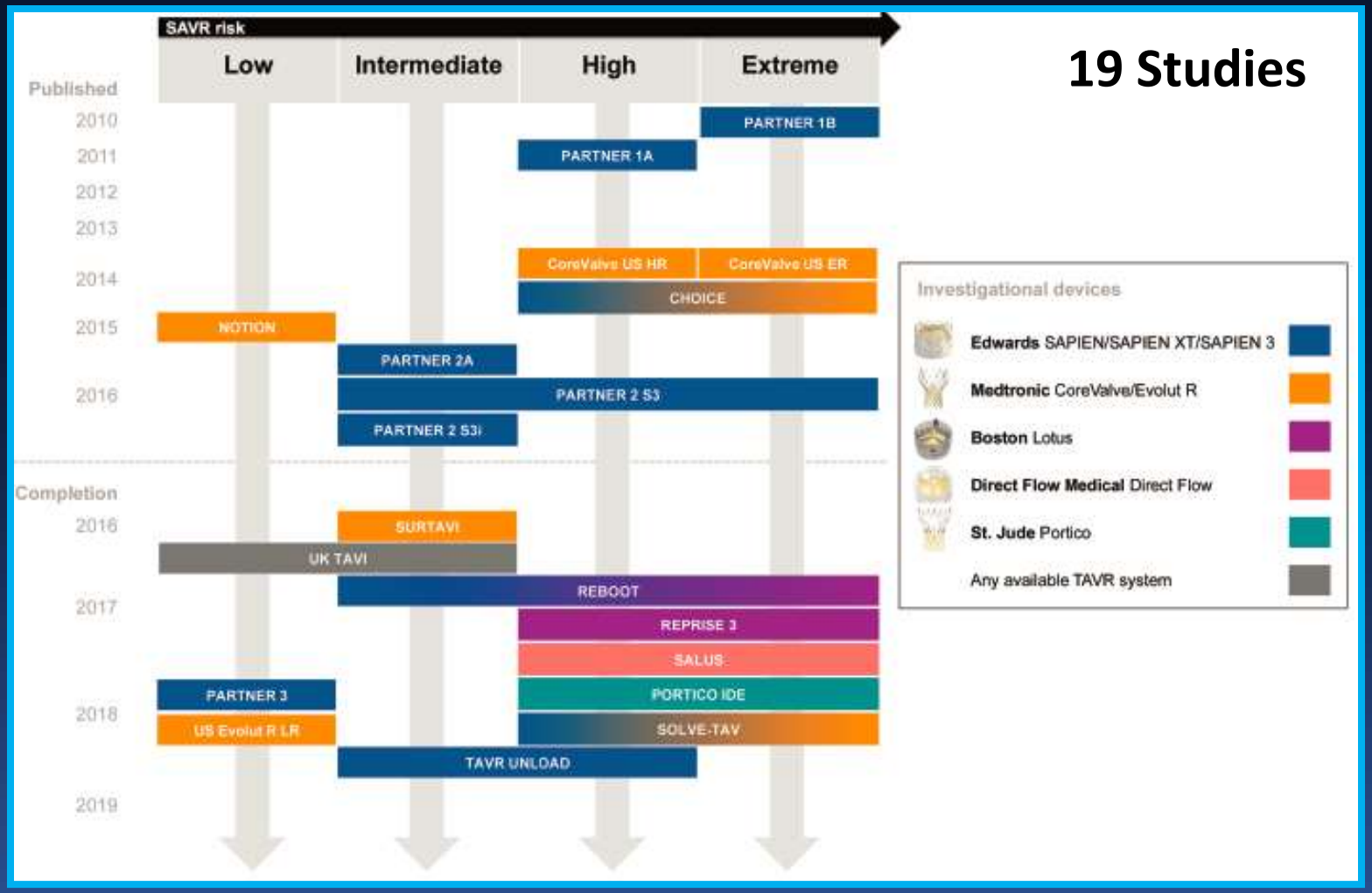
April 16, 2002

TAVR – The Early Skeptics

- Strokes
- Aortic rupture
- Coronary occlusion
- Mitral valve injury
- Valve instability – embolization
- Para-valvular regurgitation
- Vascular complications
- Valve durability
- Technical challenges insurmountable

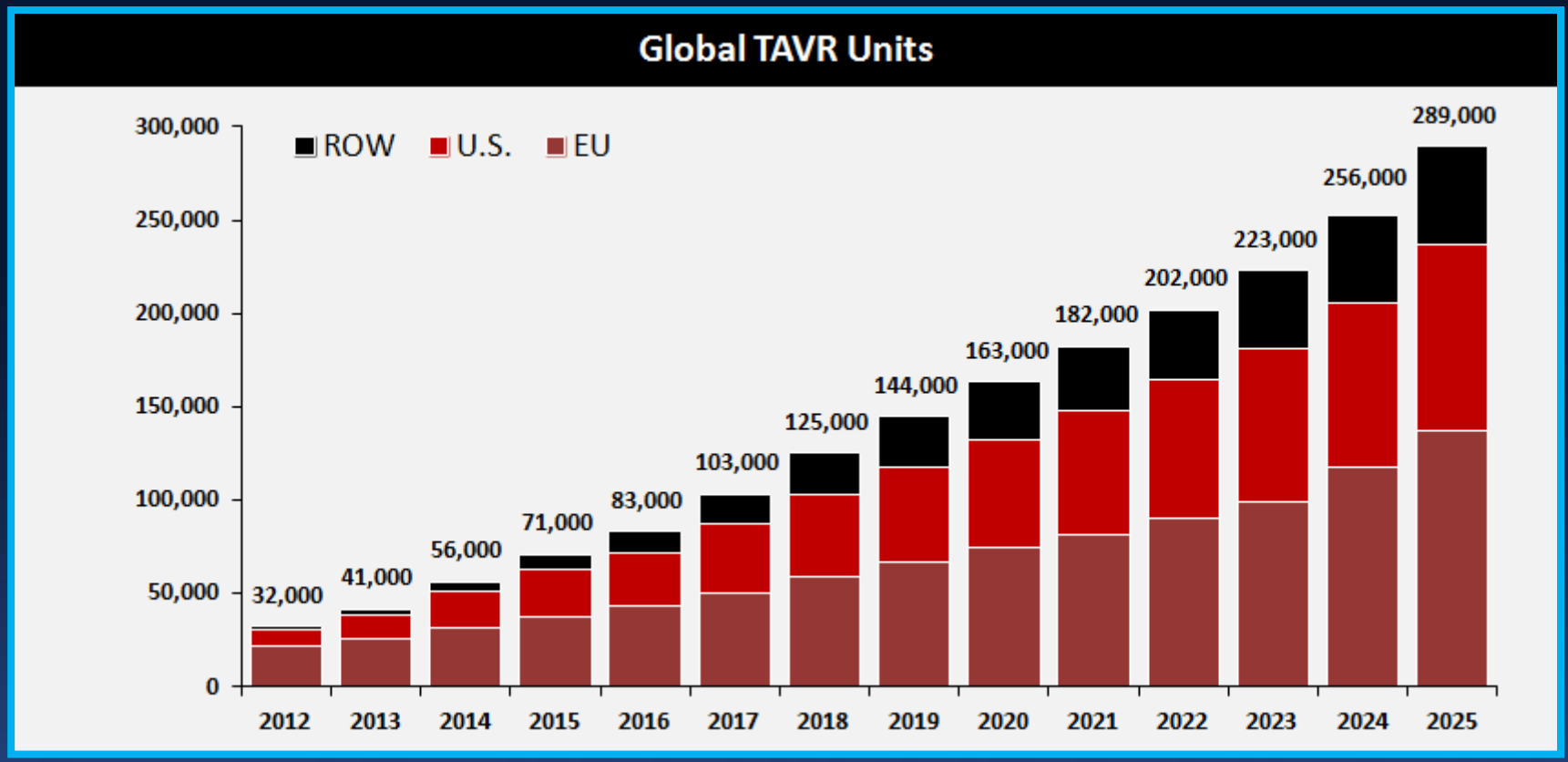
This is a crazy project that will fail!

TAVR Clinical Evidence



Capodanno D and Leon MB. EuroIntervention 2016;12:Y1-Y5.

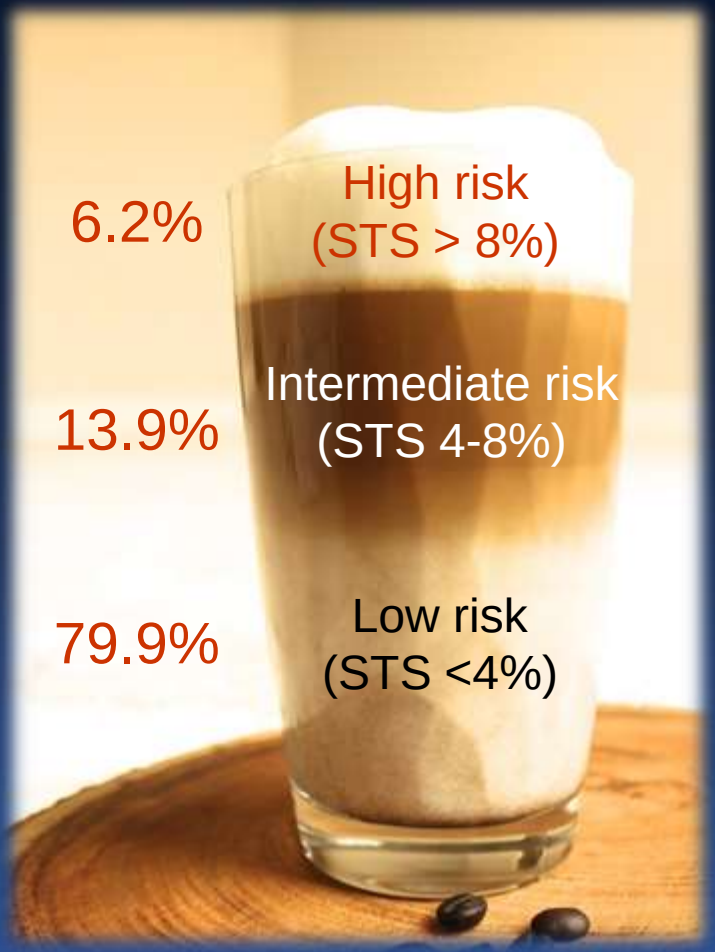
Estimated Global TAVR Growth



SOURCE: Credit Suisse TAVI Comment –January 8, 2015. ASP assumption for 2024 and 2025 based on analyst model. Revenue split assumption in 2025 is 45% U.S., 35% EU, 10% Japan, 10% ROW

In the next 10 years, TAVR growth will increase X4!

STS database 2002-2010 (141,905 pts)



Since 2007, in the U.S., >15,000 patients have been enrolled in FDA studies (including 6 RCTs) with multiple generations of two TAVR systems!

PARTNER 5-year FU in Lancet (March, 2015)

5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial

Samir R Kapadia, Martin B Leon, Raj R Makkar, E Murat Tuzcu, Lars G Svensson, Susheel Kodali, John G Webb, Michael J Mack, Pamela S Douglas, Vinod H Thourani, Vasilis C Babaliaros, Howard C Herrmann, Wilson Y Szeto, Augusto D Pichard, Mathew R Williams, Gregory P Fontana, D Craig Miller, William N Anderson, Jodi J Akin, Michael J Davidson†, Craig R Smith, for the PARTNER trial investigators*

5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial

Michael J Mack, Martin B Leon, Craig R Smith, D Craig Miller, Jeffrey W Moses, E Murat Tuzcu, John G Webb, Pamela S Douglas, William N Anderson, Eugene H Blackstone, Susheel K Kodali, Raj R Makkar, Gregory P Fontana, Samir Kapadia, Joseph Bavaria, Rebecca T Hahn, Vinod H Thourani, Vasilis Babaliaros, Augusto Pichard, Howard C Herrmann, David L Brown, Mathew Williams, Jodi Akin, Michael J Davidson†, Lars G Svensson, for the PARTNER 1 trial investigators*

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The risk of all-cause mortality at 5 years was 71·8% in the TAVR group versus 93·6% in the standard treatment group (hazard ratio 0·50, 95% CI 0·39–0·65; p<0·0001).

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5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial

At 5 years, risk of death was 67·8% in the TAVR group compared with 62·4% in the SAVR group (hazard ratio 1·04, 95% CI 0·86–1·24; p=0·76).

Evolution of the Edwards Balloon-Expandable Transcatheter Valves

Cribier-Edwards

2002

SAPIEN

2006

SAPIEN XT

2009

SAPIEN 3

2013

Baseline Patient Characteristics

S3HR Patients (n=583 at 29 sites)

THE PARTNER II TRIAL

Average STS =

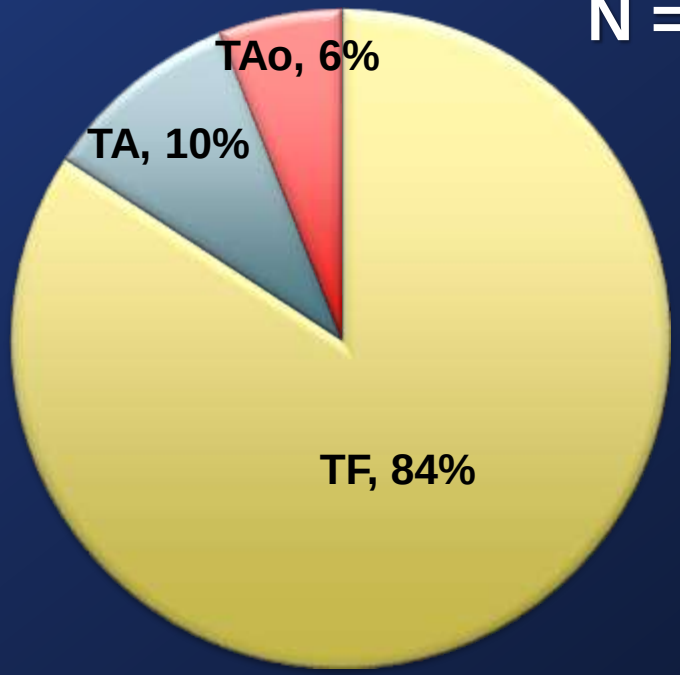
8.6%

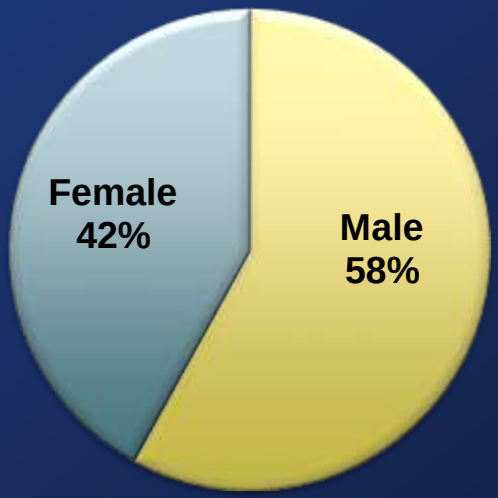
(Median 8.4%)

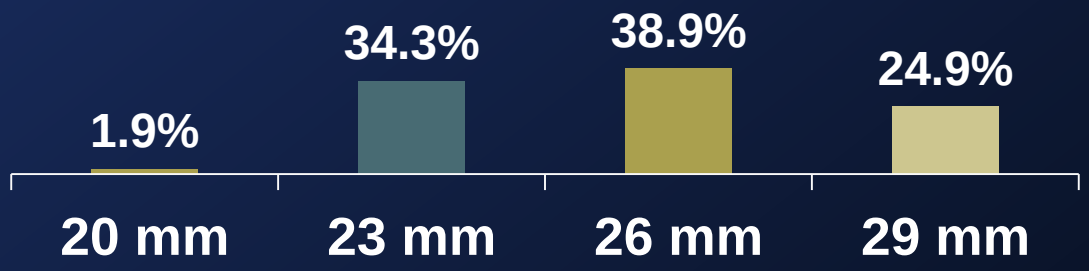
Average Age =

82.6yrs

N = 583





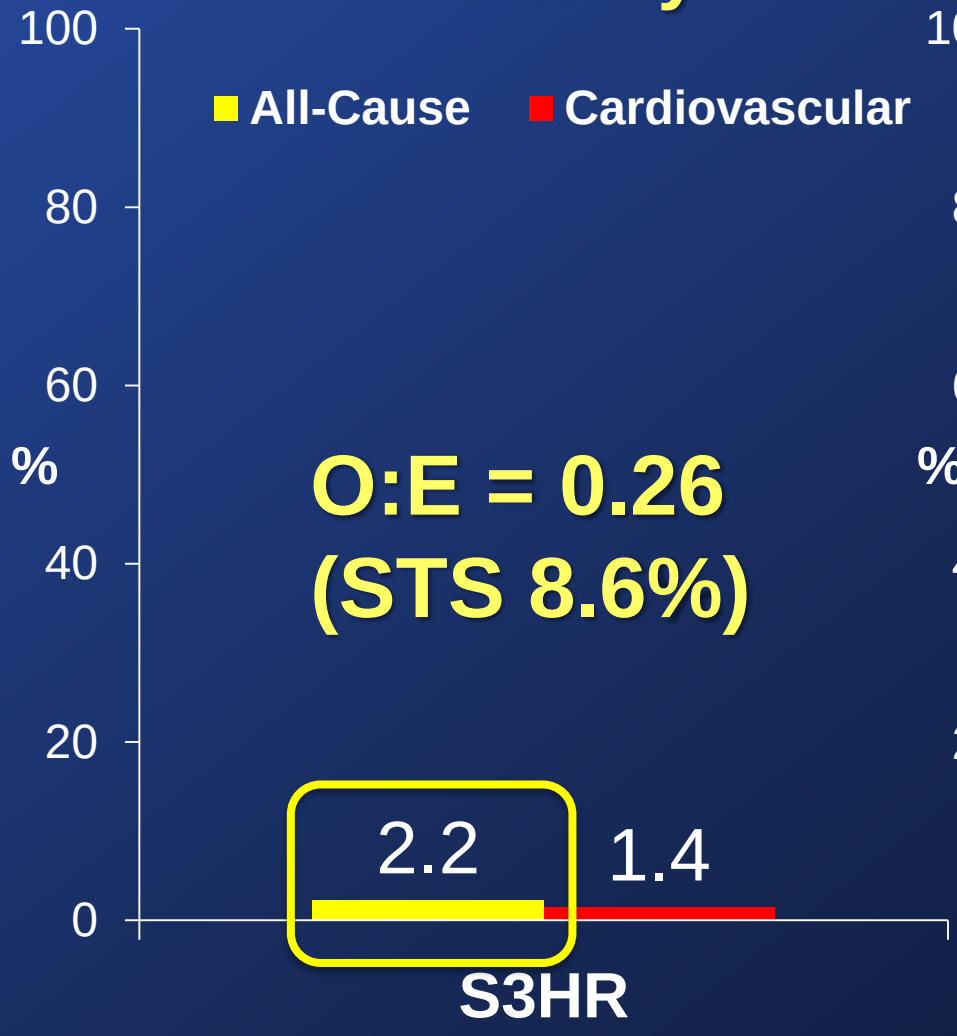


Mortality and Stroke: S3HR

At 30 Days (As Treated Patients)

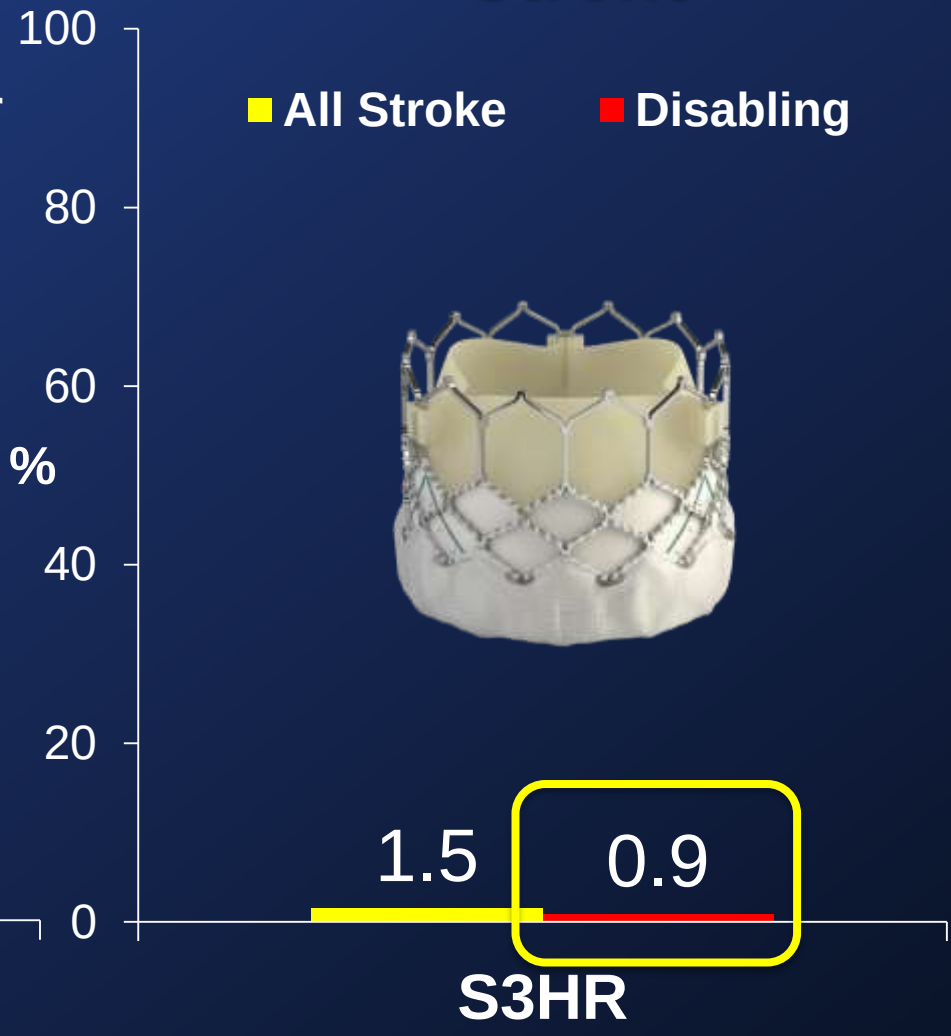
THE PARTNER II TRIAL

Mortality



O:E = 0.26
(STS 8.6%)

Stroke



Baseline Patient Characteristics

S3i Patients (n=1076 at 51 sites)

THE PARTNER II TRIAL

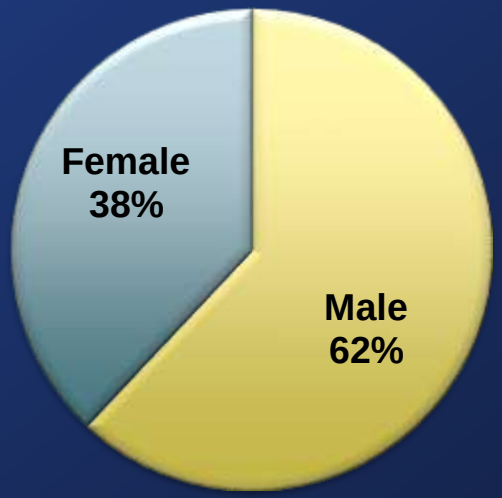
Average STS =

5.3%

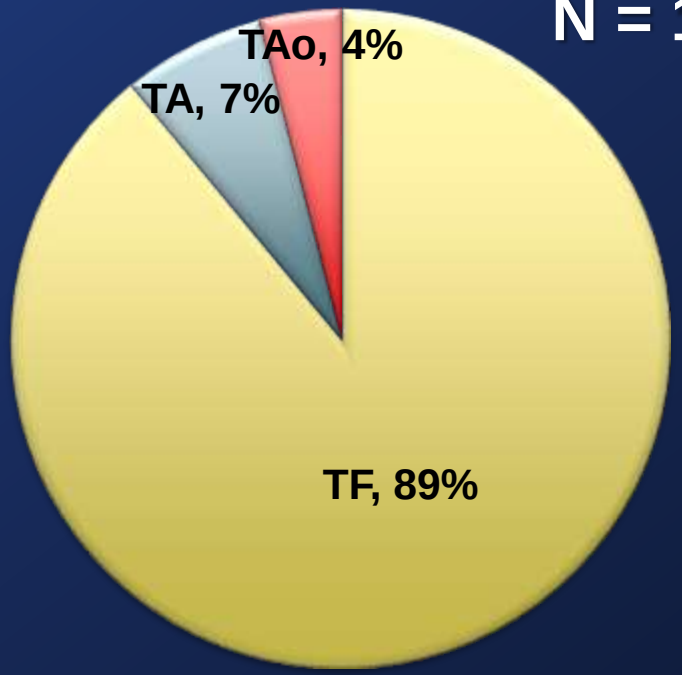
(Median 5.2%)

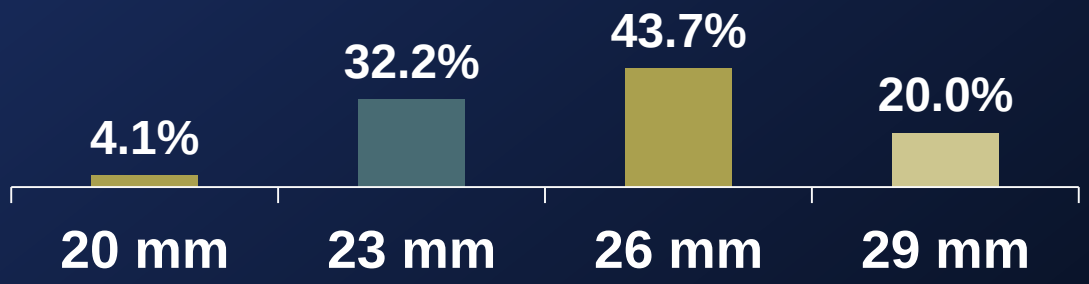
Average Age =

81.9yrs



N = 1076



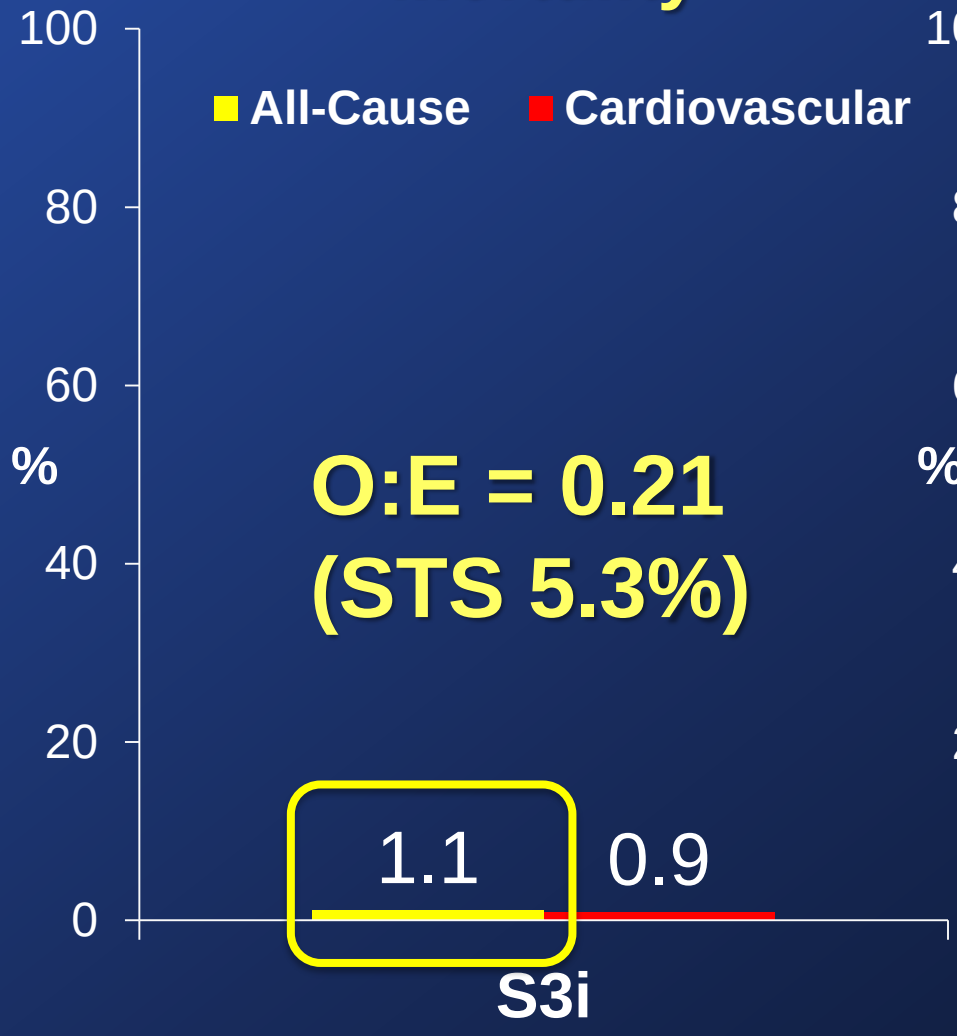


Mortality and Stroke: S3i

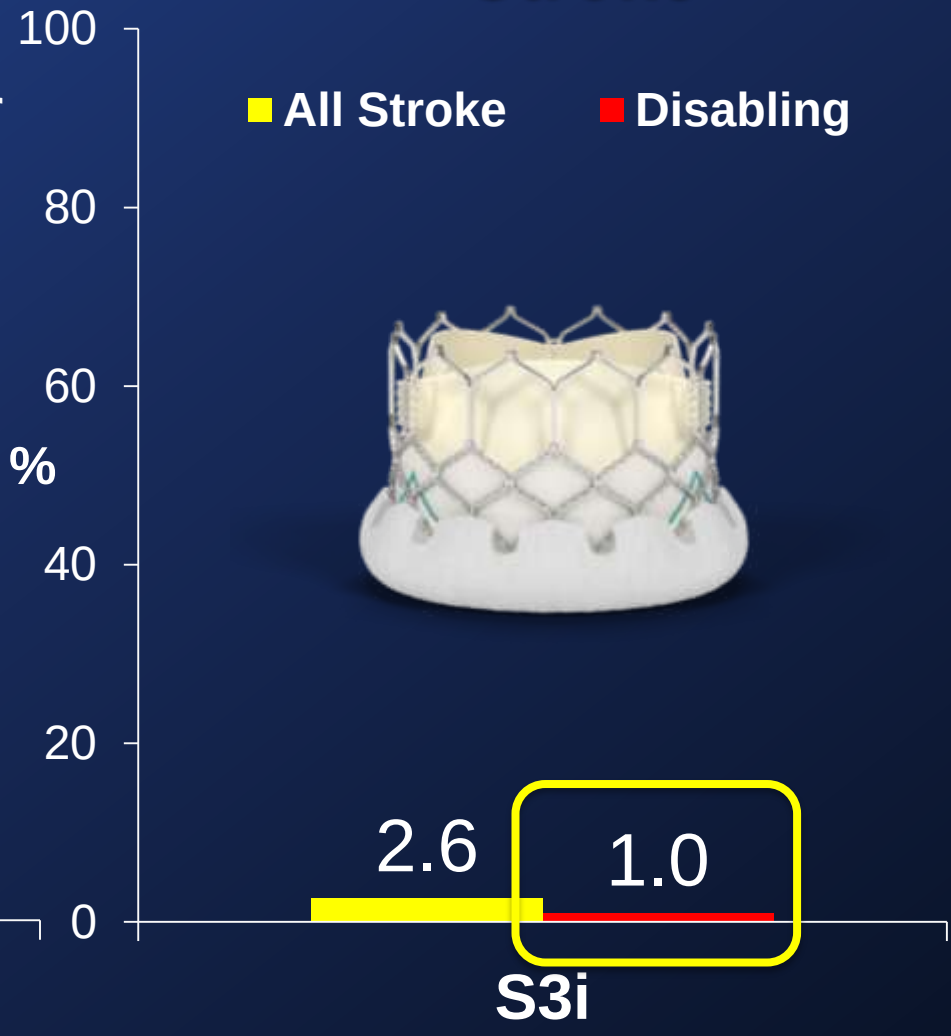
At 30 Days (As Treated Patients)

THE PARTNER II TRIAL

Mortality



Stroke

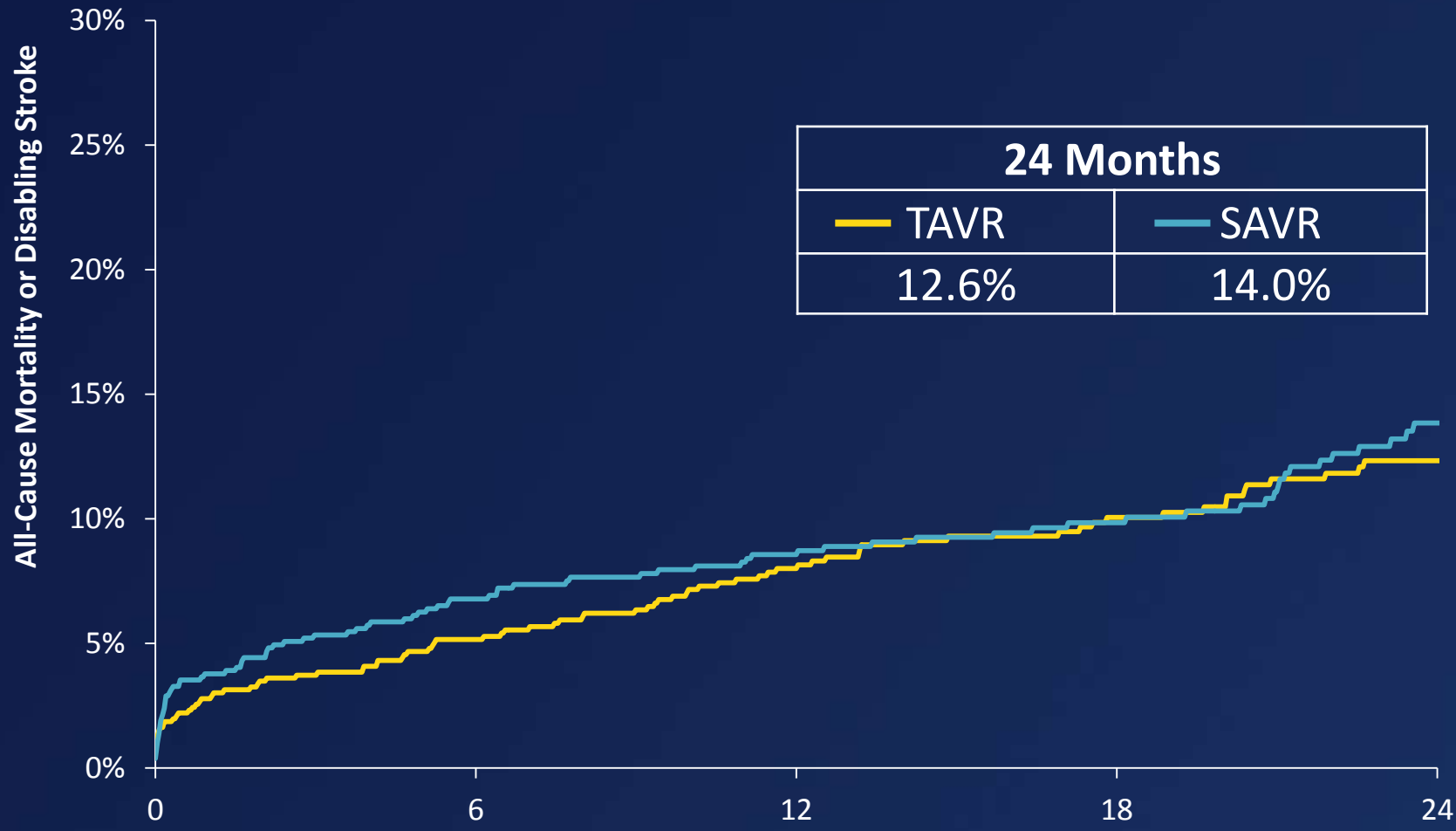


Transcatheter Aortic Valve Replacement with a Self-Expanding Prosthesis or Surgical Aortic Valve Replacement in Intermediate-Risk Patients: First Results from the SURTAVI Clinical Trial

Michael J. Reardon, MD

For the SURTAVI Investigators

All-Cause Mortality or Disabling Stroke



No. at Risk					
SAVR	796	674	555	407	241
TAVR	864	755	612	456	272

30-Day Safety and Procedure-related Complications

	TAVR (N=864)	SAVR (N=796)	95% CI for Difference
All-cause mortality or disabling stroke	2.8	3.9	-2.8, 0.7
All-cause mortality	2.2	1.7	-0.9, 1.8
Disabling stroke	1.2	2.5	-2.6, 0.1
All stroke	3.4	5.6	-4.2, -0.2
Overt life-threatening or major bleeding	12.2	9.3	-0.1, 5.9
Transfusion of PRBCs* - n (%)			
0 units	756 (87.5)	469 (58.9)	24.4, 32.5
2 – 4 units	48 (5.6)	136 (17.1)	-14.5, -8.5
≥ 4 units	31 (3.6)	101 (12.7)	-11.7, -6.5
Acute kidney injury, stage 2-3	1.7	4.4	-4.4, -1.0
Major vascular complication	6.0	1.1	3.2, 6.7
Cardiac perforation	1.7	0.9	-0.2, 2.0
Cardiogenic shock	1.1	3.8	-4.2, -1.1
Permanent pacemaker implant	25.9	6.6	15.9, 22.7
Atrial fibrillation	12.9	43.4	-34.7, -26.4

*Percentage rates, all others are Bayesian rates

TAVR Clinical Evidence

Upcoming TAVI trials: rationale, design and impact on clinical practice

Davide Capodanno[1]*, MD, PhD; Martin B. Leon[2], MD

1. Cardio-Thoracic-Vascular Department, Ferrarotto Hospital, University of Catania, Catania, Italy; 2. Columbia University Medical Center and Cardiovascular Research Foundation, New York, NY, USA

19 Additional Studies!

Simplifying TAVR

DIRECT
EASY TAVI

Expanding Indications

NOTION 2
EARLY TAVR

Optimizing Outcomes

ACTIVATION
REDUCE AKI
SENTINEL
REFLECT

Capodanno D and Leon MB. EuroIntervention 2016;12:Y1-Y5.

TAVR Clinical Evidence

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19 Additional Studies!

Anti-thrombotic Therapy

ARTE
POPULAR TAVI
AUREA
AVATAR
GALILEO
ATLANTIS

Valve Leaflet Thickening/ Thrombosis

RESOLVE
SAVORY
EVOLUT R Low Risk
PARTNER 3
PORTICO IDE

Capodanno D and Leon MB. EuroIntervention 2016;12:Y1-Y5.

Transcatheter aortic valve implantation for failed surgical aortic bioprostheses using a self-expanding device: early results from the prospective VIVA post-market study

Prof. Ran Kornowski, Rabin Medical Center, Petah Tikva, Israel

Dr. Didier Tchétché, Clinique Pasteur, Toulouse, France

Prof. Jean-Philippe Verhoye, CHU Rennes, Rennes, France

Dr. Bernard Chevalier, Institut Cardio-vasculaire Paris-Sud, Massy, France

and on behalf of the VIVA Investigators

Baseline Characteristics

Characteristic	All (N=202)
Age (yrs)	79.9 ± 7.2
Men	47.0
Height (cm)	164.3 ± 9.1
Weight (kg)	73.7 ± 16.3
BMI (kg/m^2)	27.2 ± 5.4
BSA (m^2)	1.8 ± 0.2
LogEuroSCORE (%)	25.0 ± 14.3
STS score (%)	6.6 ± 5.1
Diabetes mellitus	26.2
Peripheral vascular disease	13.9
Chronic renal replacement therapy	1.5
Previous stroke	5.0
NYHA III/IV	70.7
LVEF %	61.0 ± 12.0
(n)	(157)

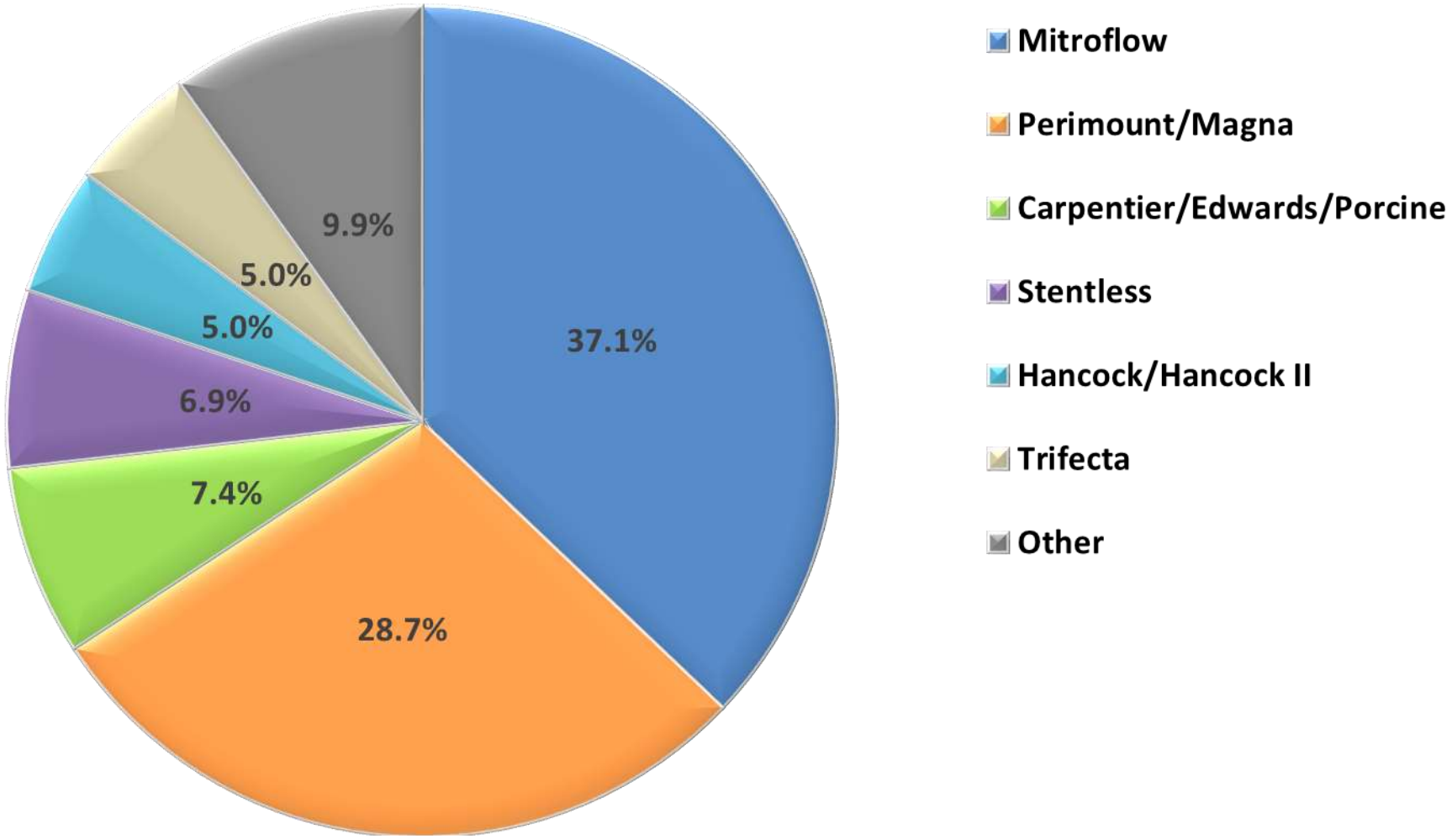
Values are mean ± SD or %.

Devices Utilized

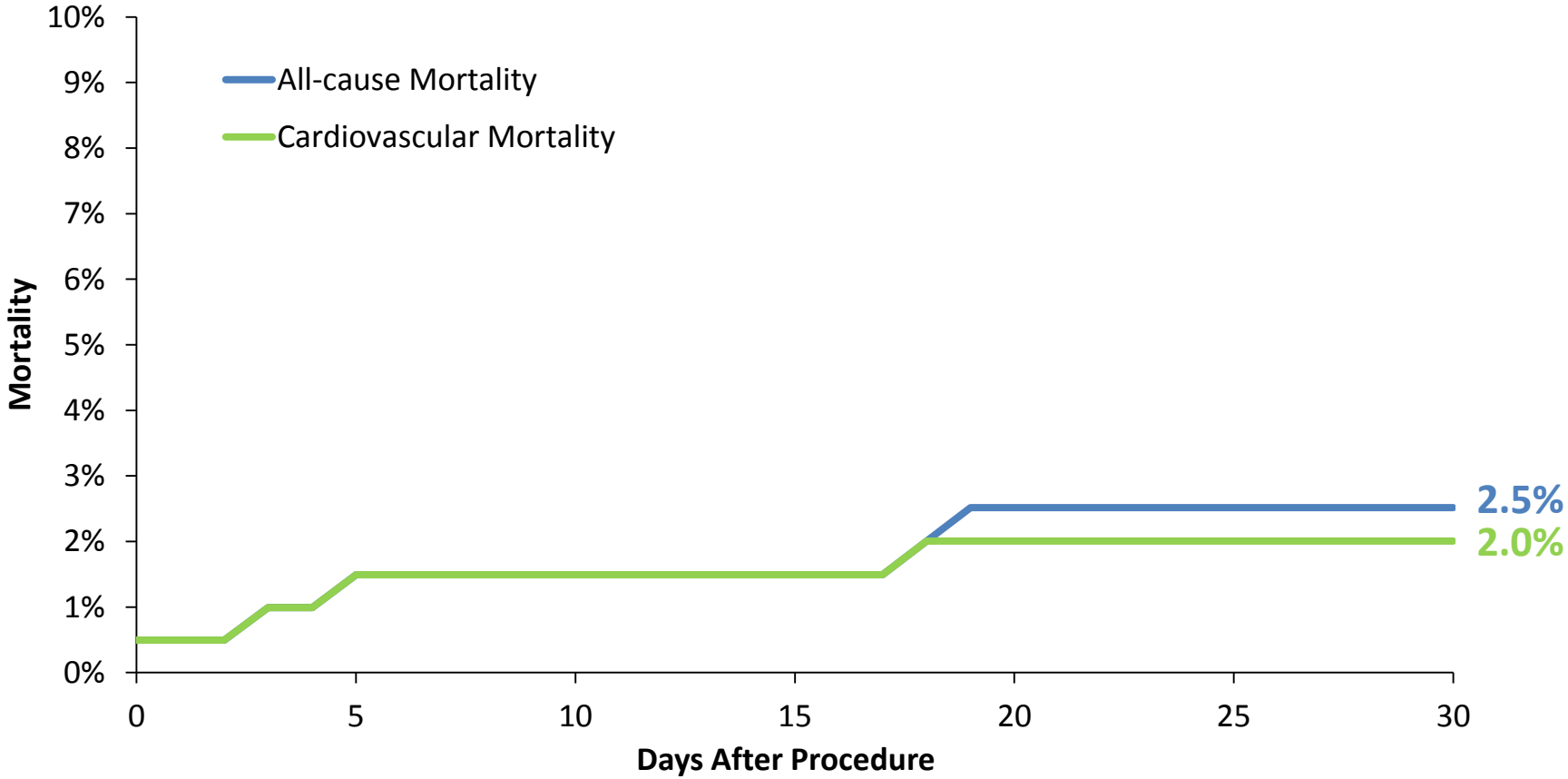
CoreValve
Enrolled: n=19

Evolut R
Enrolled: n=183

Surgical Valve Types



Primary Endpoint: Cardiovascular Mortality at 30 Days



No. at risk:

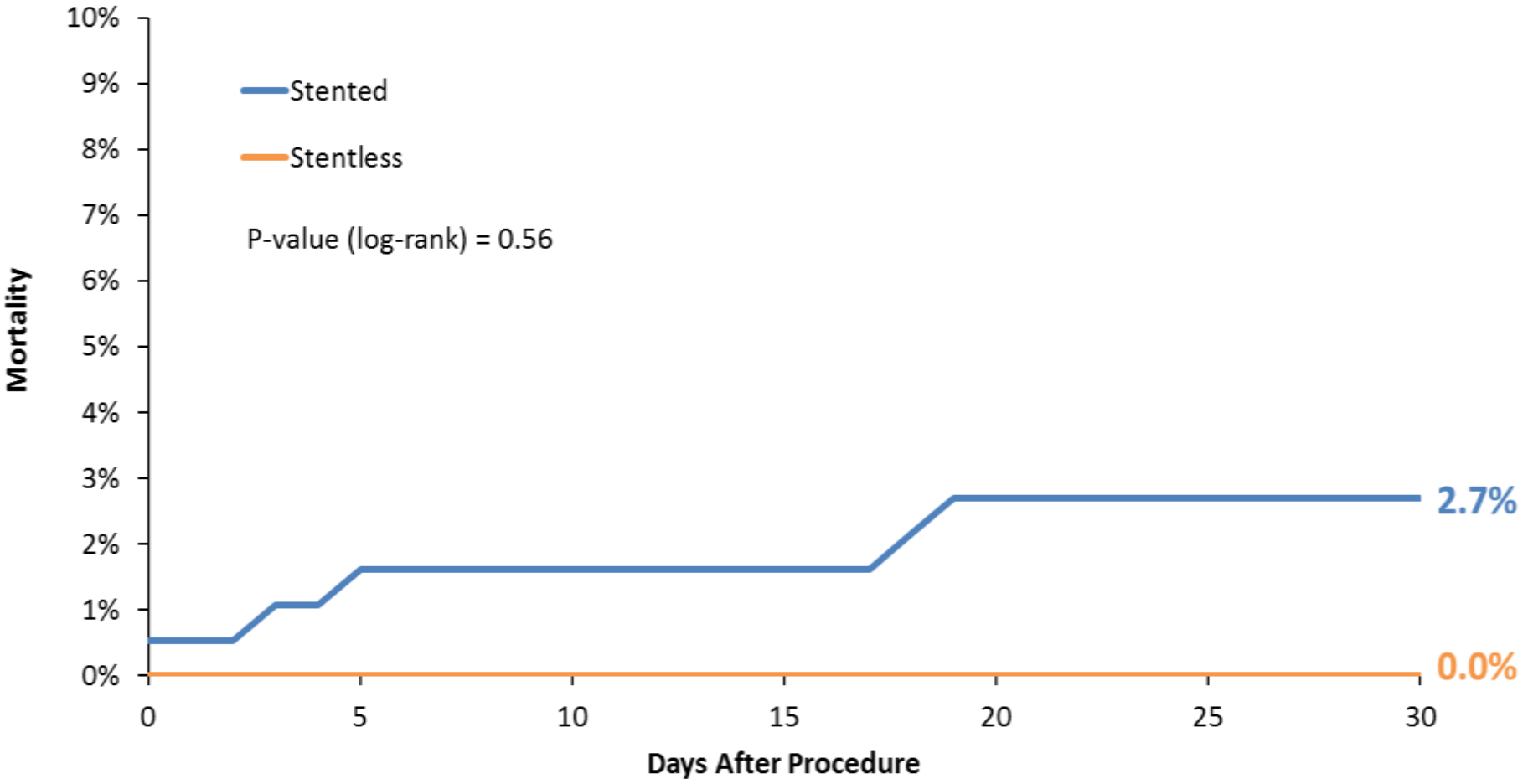
202						180

Other Clinical Outcomes at 30 Days

Endpoint	All (N=202)
Duration of hospital stay, days (mean ± SD)	7.4 ± 6.1
All stroke (%)	3.0
Disabling (%)	0.0
Major vascular complication (%)*	6.5
Bleeding (%)*	14.9
Life-threatening	0.0
Major	7.0
Minor	7.9
Acute kidney injury (%)*	0.5
Stage I	0.5
Stage II or III	0.0
Permanent pacemaker implantation (%) £	7.0

Kaplan-Meier event rates.
*According to the Valve Academic Research Consortium 2 (VARC-2) definition
£Baseline pacemaker included

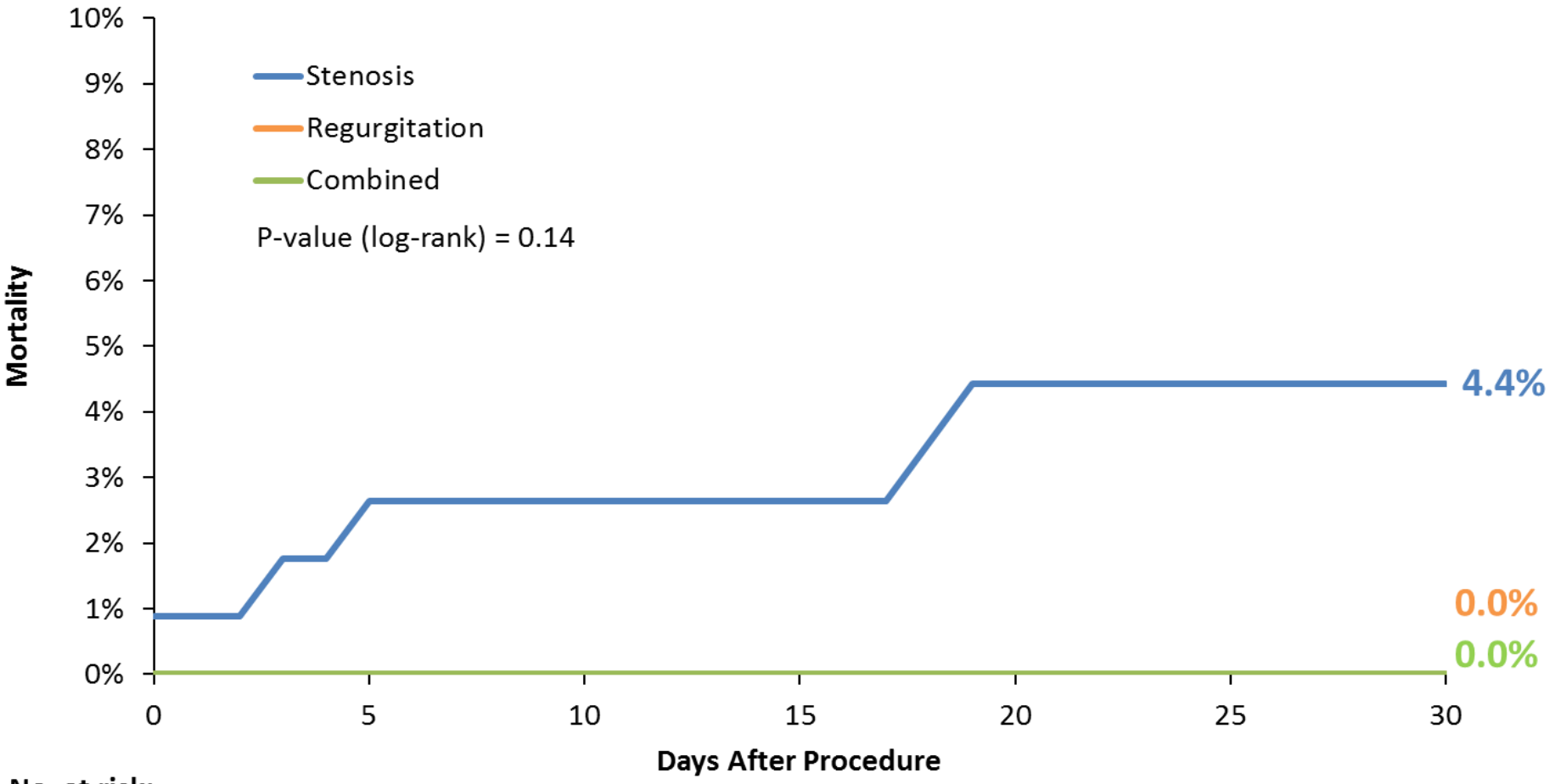
Mortality by Surgical Valve Type



No. at risk:

188						170
14						10

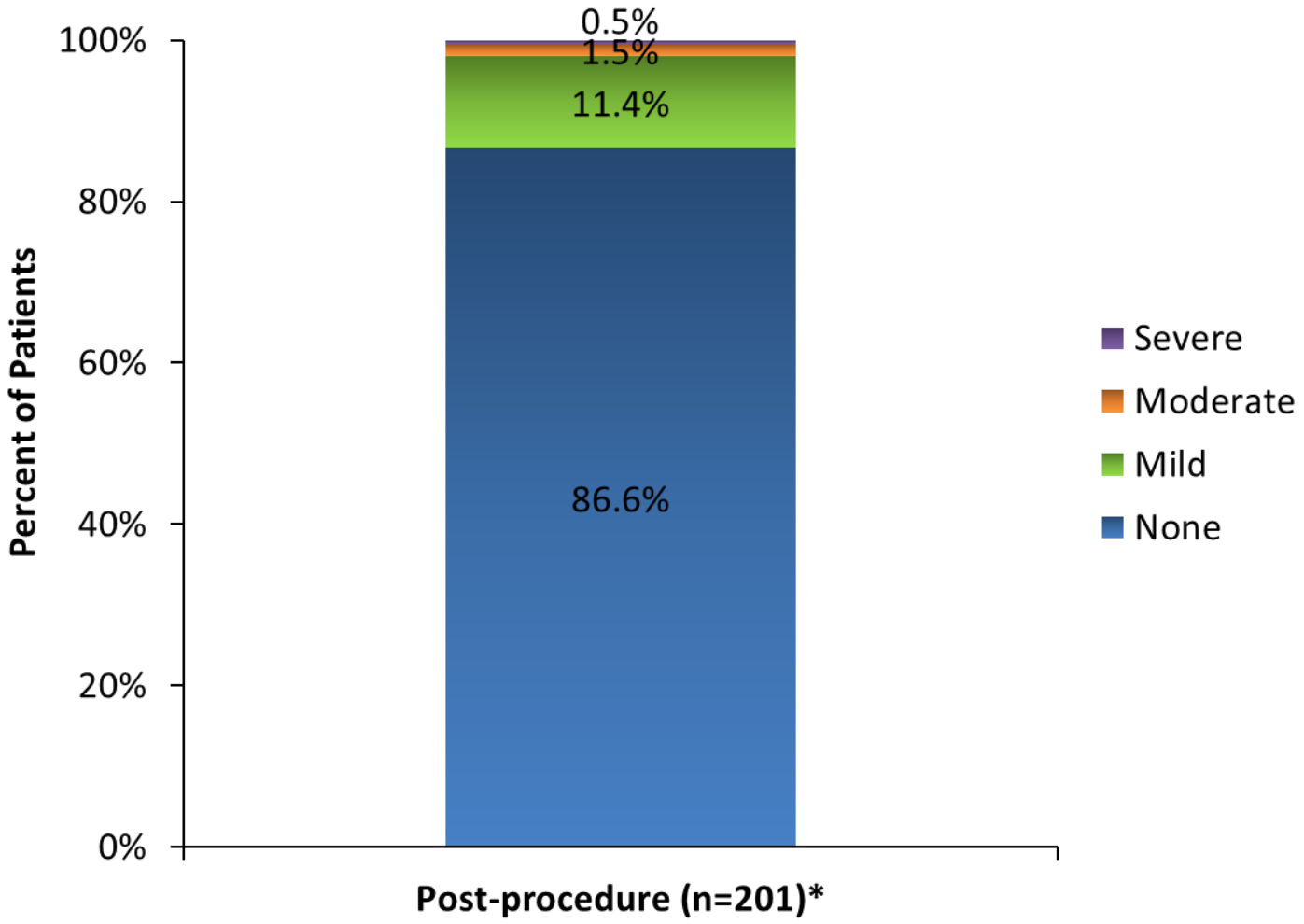
Mortality by Failure Mode



No. at risk:

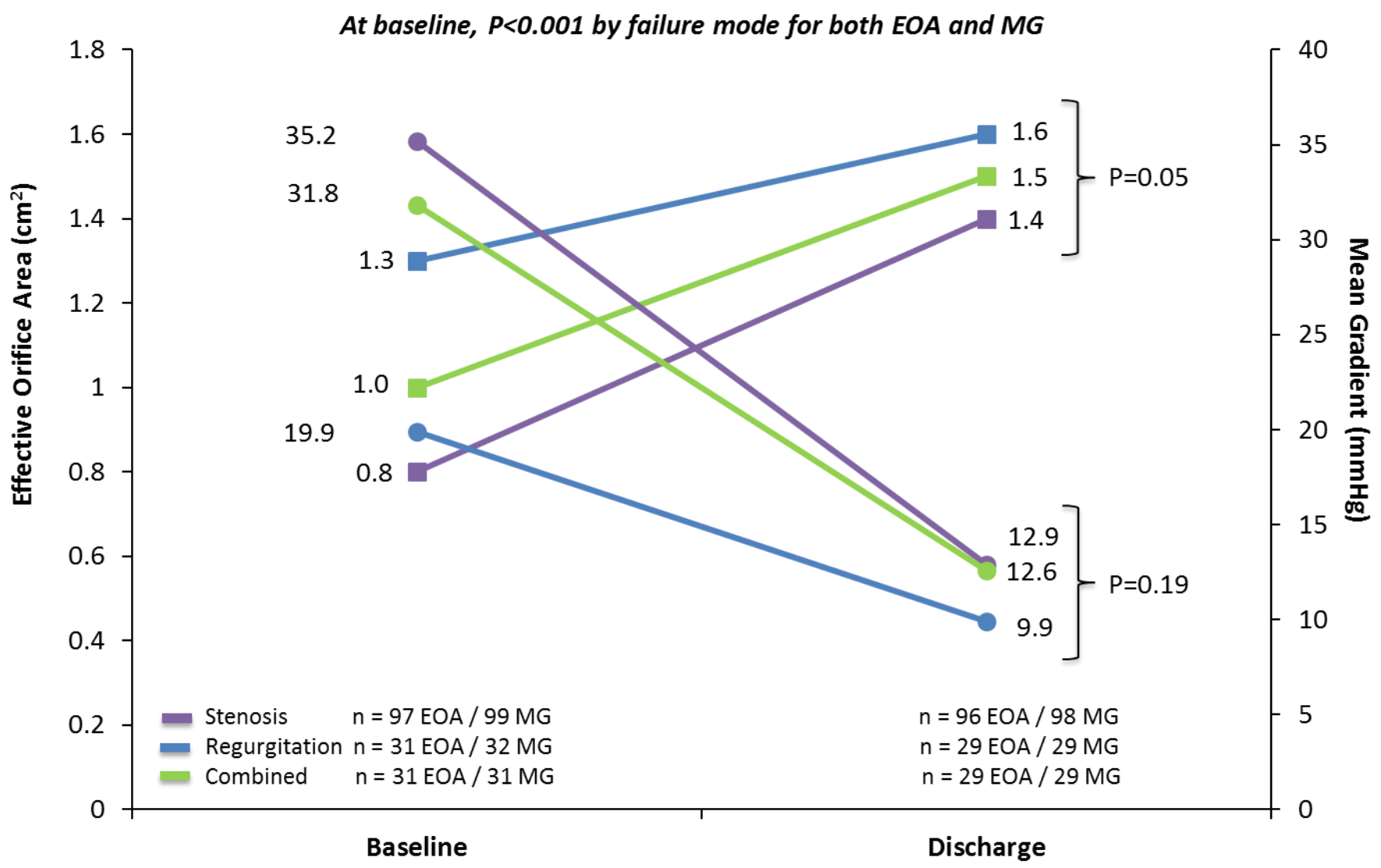
114						99
46						42
42						39

Paravalvular Regurgitation



Official assessments based on site post-procedure aortography data ; core lab data pending
*Unable to assess PVL in 1 subject

Echocardiographic Findings by Failure Mode



Echo Core Lab confirmed data

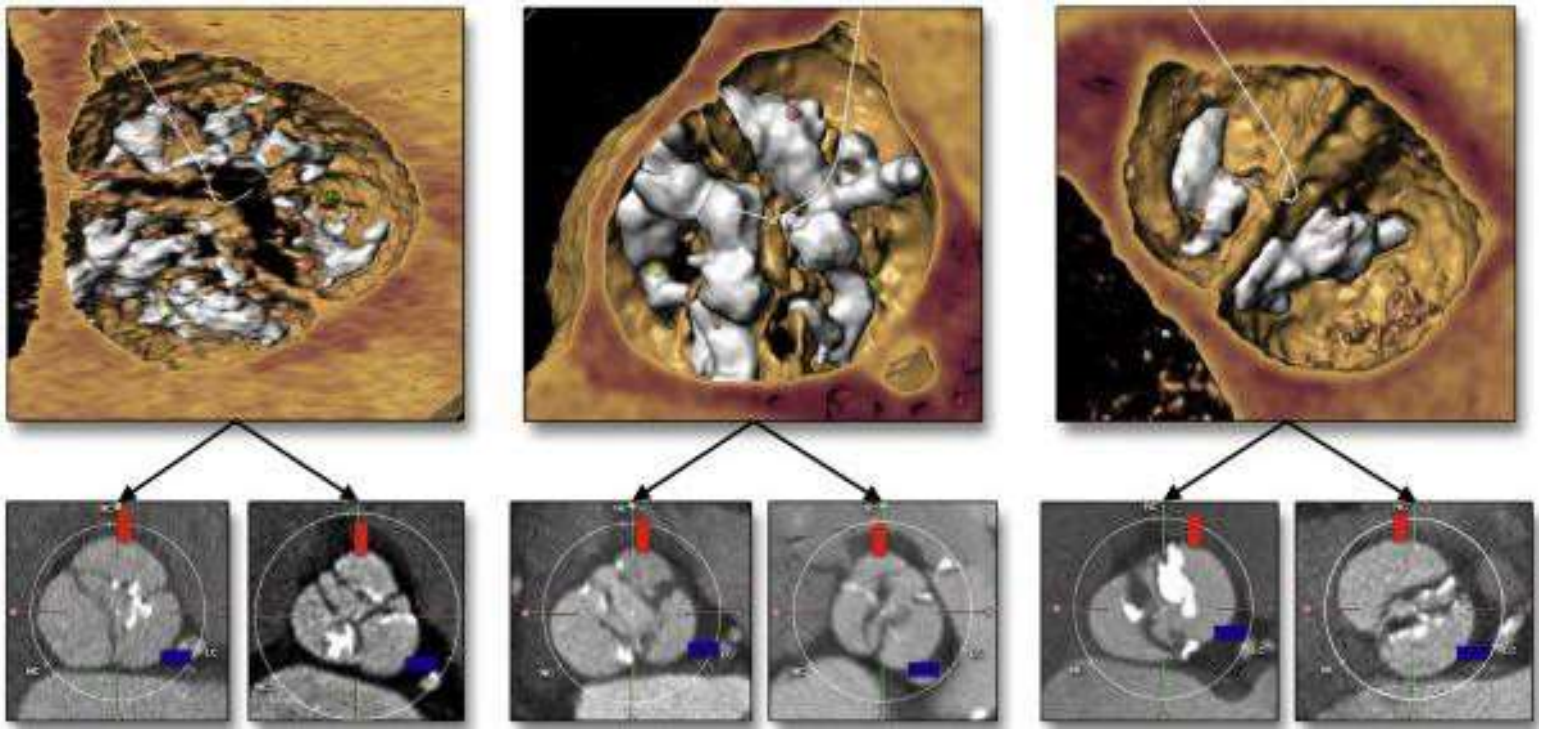
The Impact of Bicuspid Aortic Valve Morphology on Outcomes After TAVI

Sung-Han Yoon, MD

On Behalf of Bicuspid AS TAVR Registry

CEDARS-SINAI

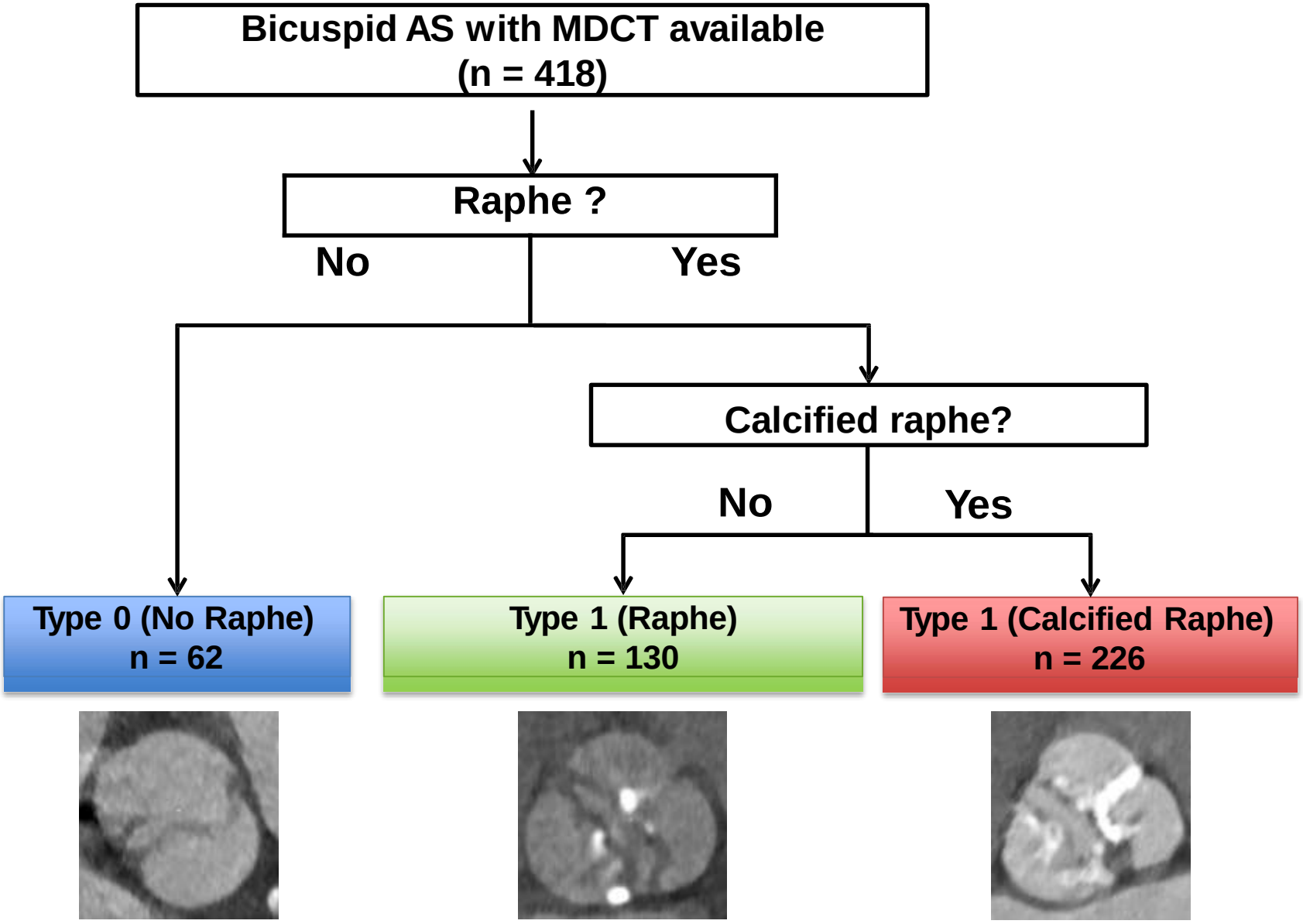
Bicuspid AV Morphology



Hasan Jilaihawi et al; JACC: Cardiovascular Imaging, Volume 9, Issue 10, 2016, 1145–1158

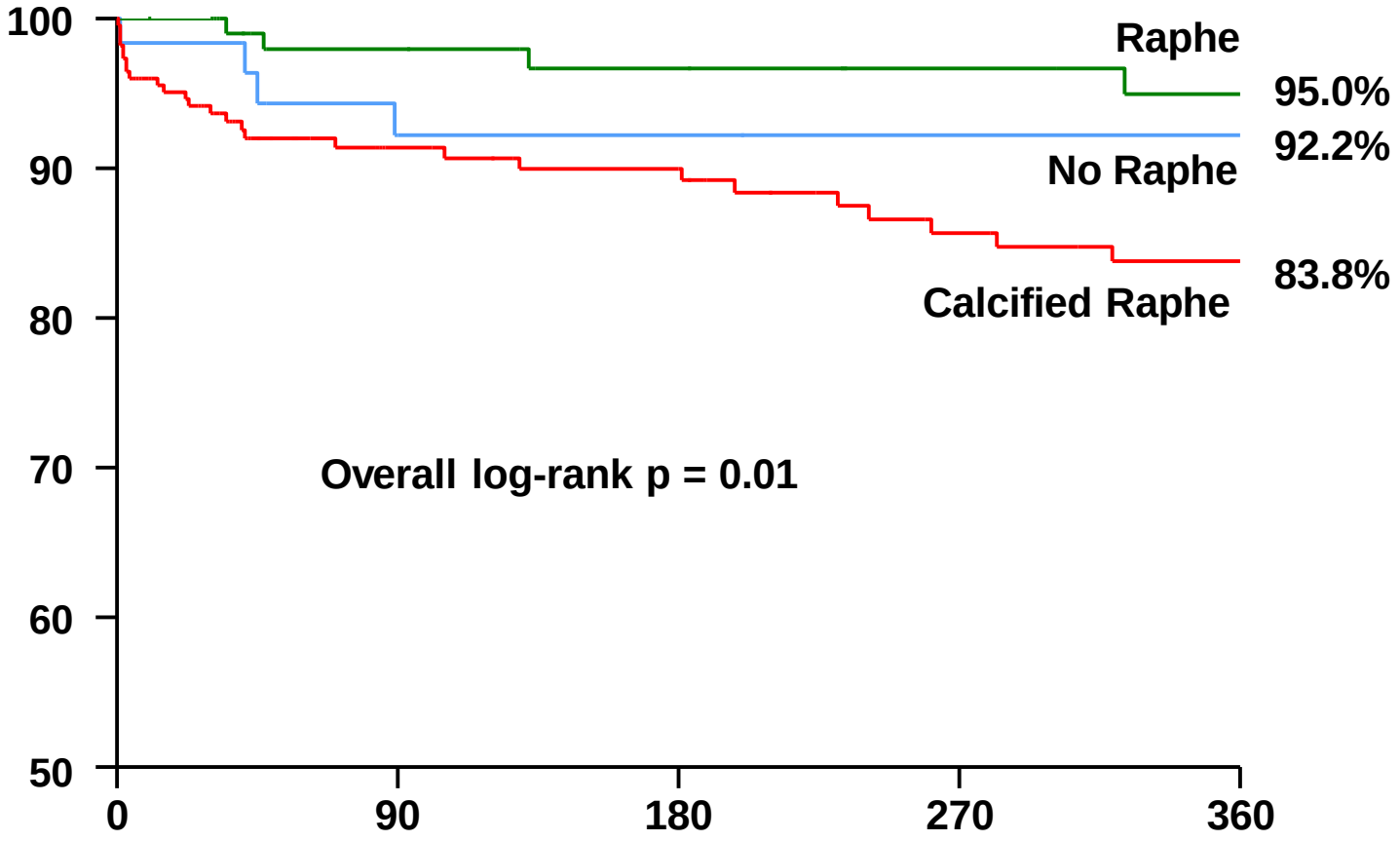
We aimed to investigate the association between Bicuspid AS morphology and clinical outcomes after TAVI

Study Design



Cumulative Survival at 1 Year

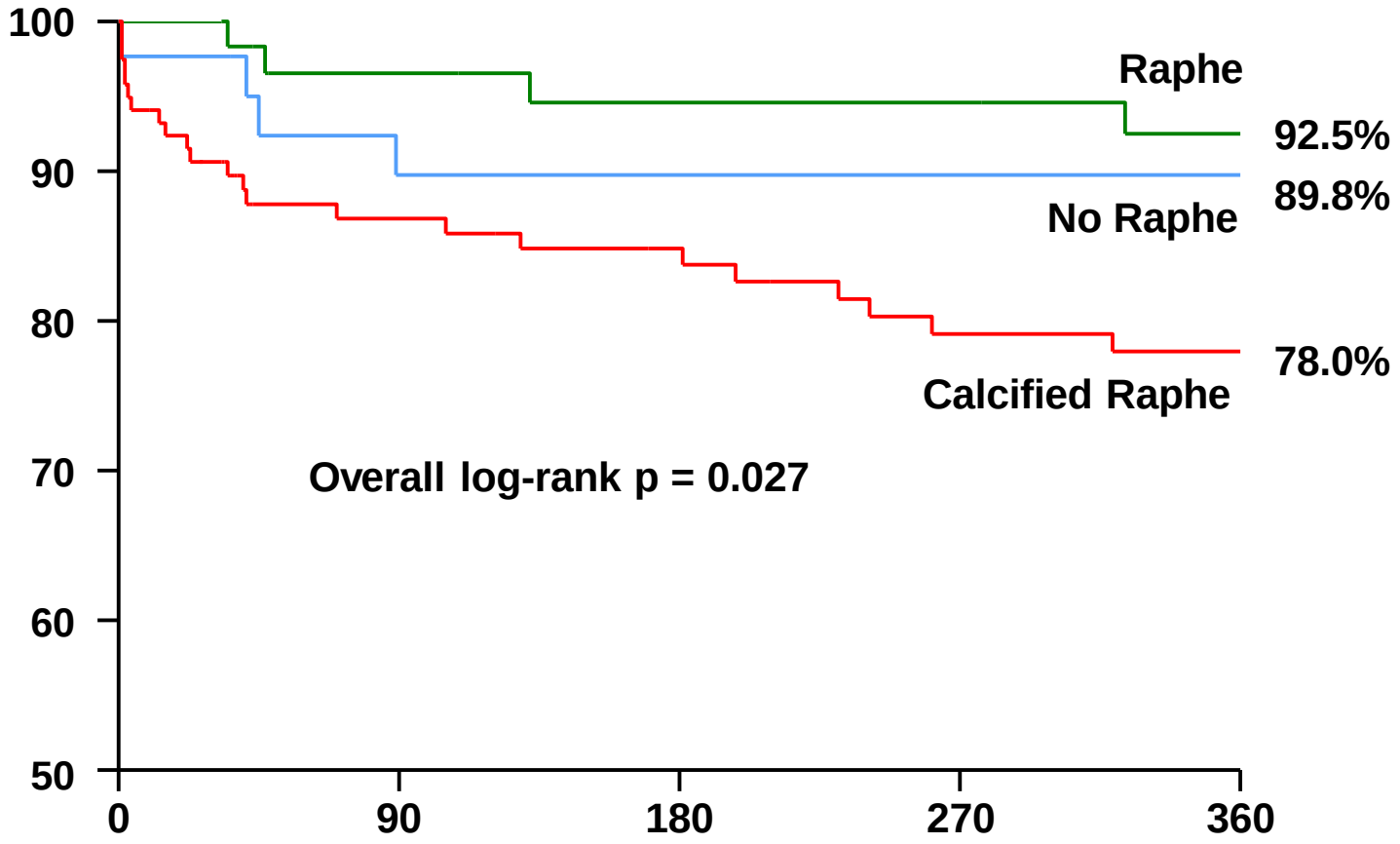
Overall Cohort



No. at Risk			
	62	Day s 42	35
No Raphe			
Raphe	130	73	52
Calcified Raphe			

Cumulative Survival at 1 Year

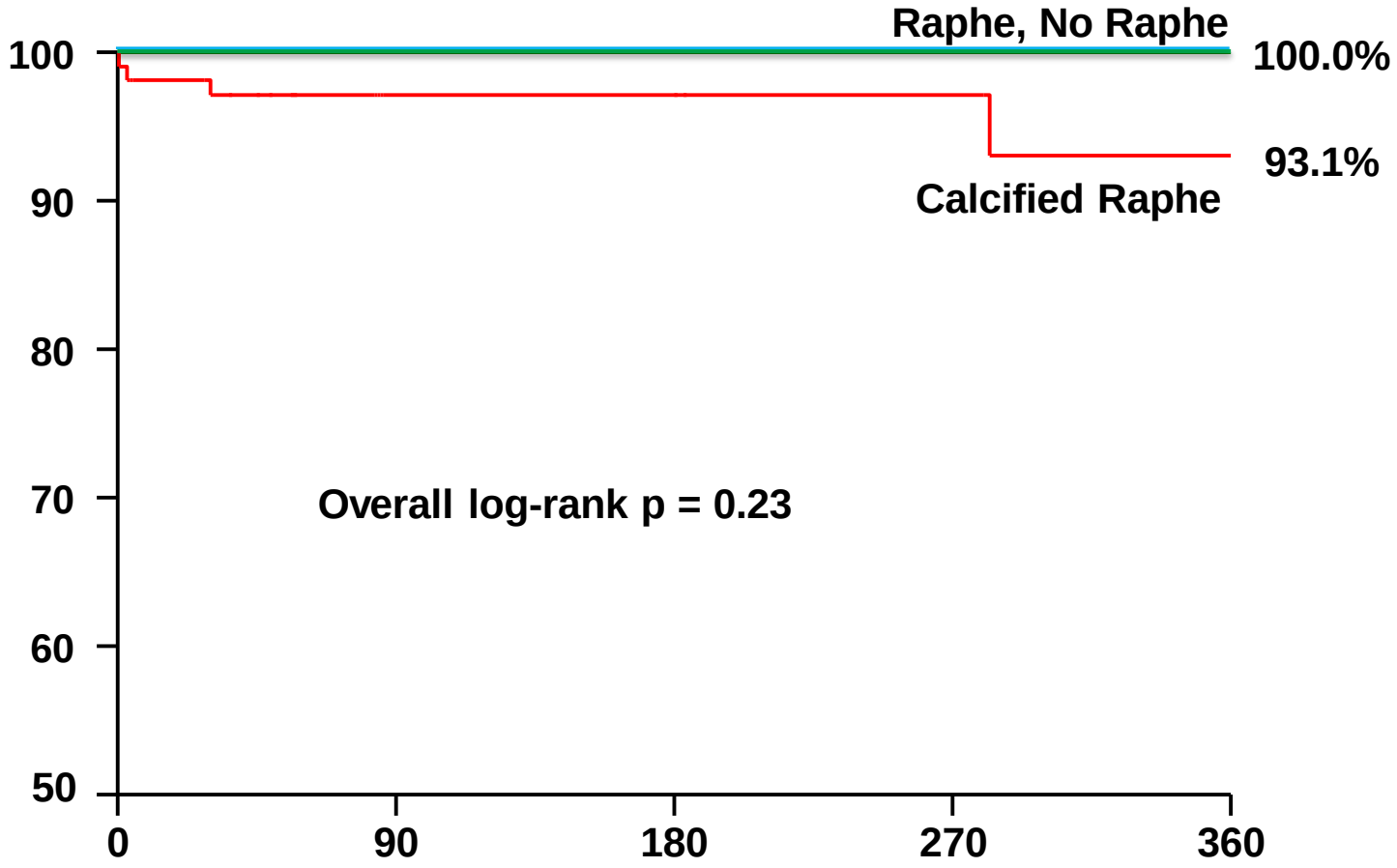
Early-generation Devices



No. at Risk No Raphe	43	Day s 32	27
Raphe	65	48	42

Cumulative Survival at 1 Year

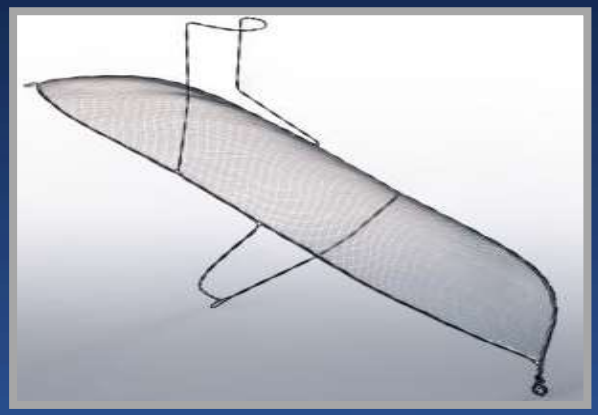
New-generation Devices



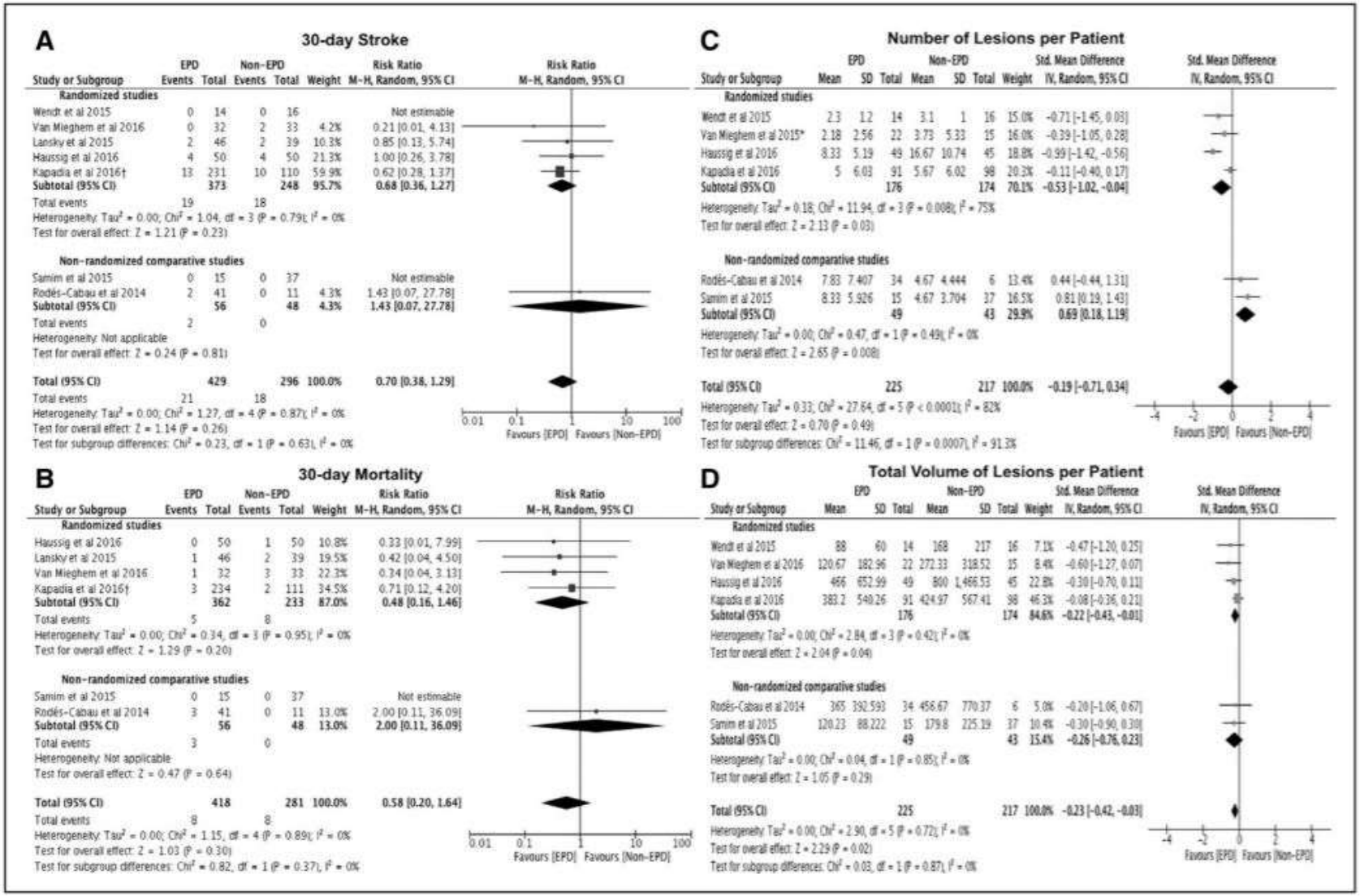
No. at Risk		Days	
No Raphe	19		8
Raphe	65	25	10

Cerebral Embolic Protection Devices

TriGuard™ Cerebral	Embrella™	Claret Sentinel™
Deflector	Deflector	Dual Filter
Femoral Access	Radial Access	Radial Access
9F Sheath (7F Delivery)	6F Shuttle Sheath	6F Radial Sheath



EPD in TAVR: Meta-Analysis



Bagur, R et al: Stroke. 2017;48:1306-1315

The PARTNER 3 Trial
Study Design

Symptomatic Severe Calcific Aortic Stenosis

Low Risk ASSESSMENT by Heart Team
(STS < 4%, TF only)

1:1 Randomization
(n=1,228)

TF - TAVR (SAPIEN 3)	Surgery (Bioprosthetic Valve)
CT Imaging Sub-Study (n=200)	CT Imaging Sub-Study (n=200)
Actigraphy/QoL Sub-Study	Actigraphy/QoL Sub-Study

PARTNER 3 Registries

- Alternative Access (n=100) (TA/TAo/Subclavian)
- Bicuspid Valves (n=50)
- Aortic ViV (n=100)
- Mitral ViV or ViR (n=100)

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

Follow-up: 30 days, 6 mos, 1 year and annually through 10 years

TAVR UNLOAD Trial

Study Design

(600 patients, 1:1 Randomized)

TAVR UNLOAD Trial

International Multicenter Randomized

Heart Failure
LVEF < 50%
NYHA ≥ 2
Optimal HF therapy (OHFT)
Moderate AS

R

TAVR + OHFT

OHFT Alone

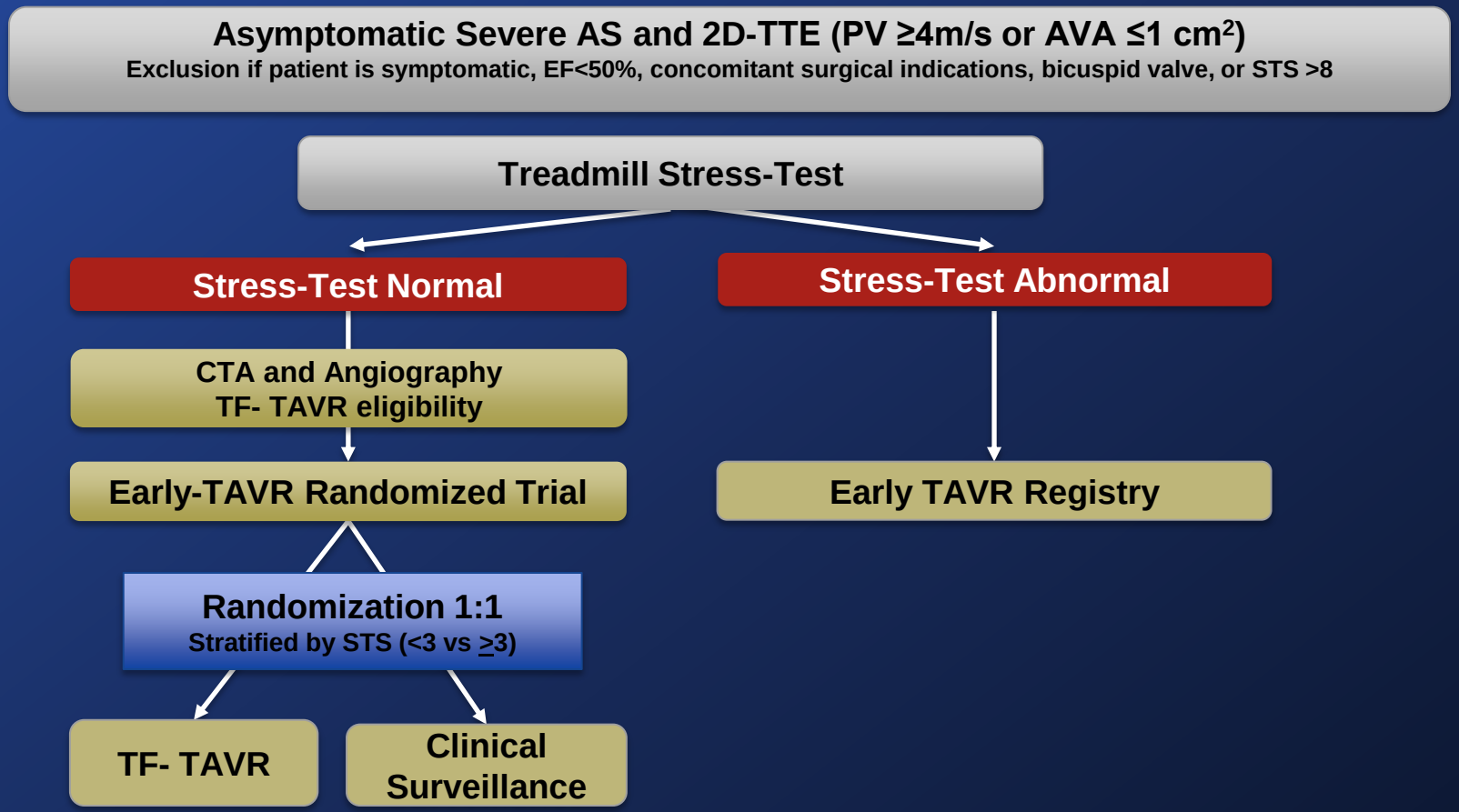
Follow-up:
1 month
6 months
1 year

Clinical endpoints
Symptoms
Echo
QoL

Primary Endpoint
Hierarchical occurrence of:
- **All-cause death**
- **Disabling stroke**
- **Hospitalizations for HF, aortic valve disease**
- **Change in KCCQ**

Reduced AFTERLOAD
Improved LV systolic and diastolic function

EARLY TAVR Trial
Study Flow



Primary Endpoint (superiority): 2-year composite of all-cause mortality, all strokes, and repeat hospitalizations (CV)