Evolving TAVR Indications: Heart Failure, Asymptomatic AS, AR

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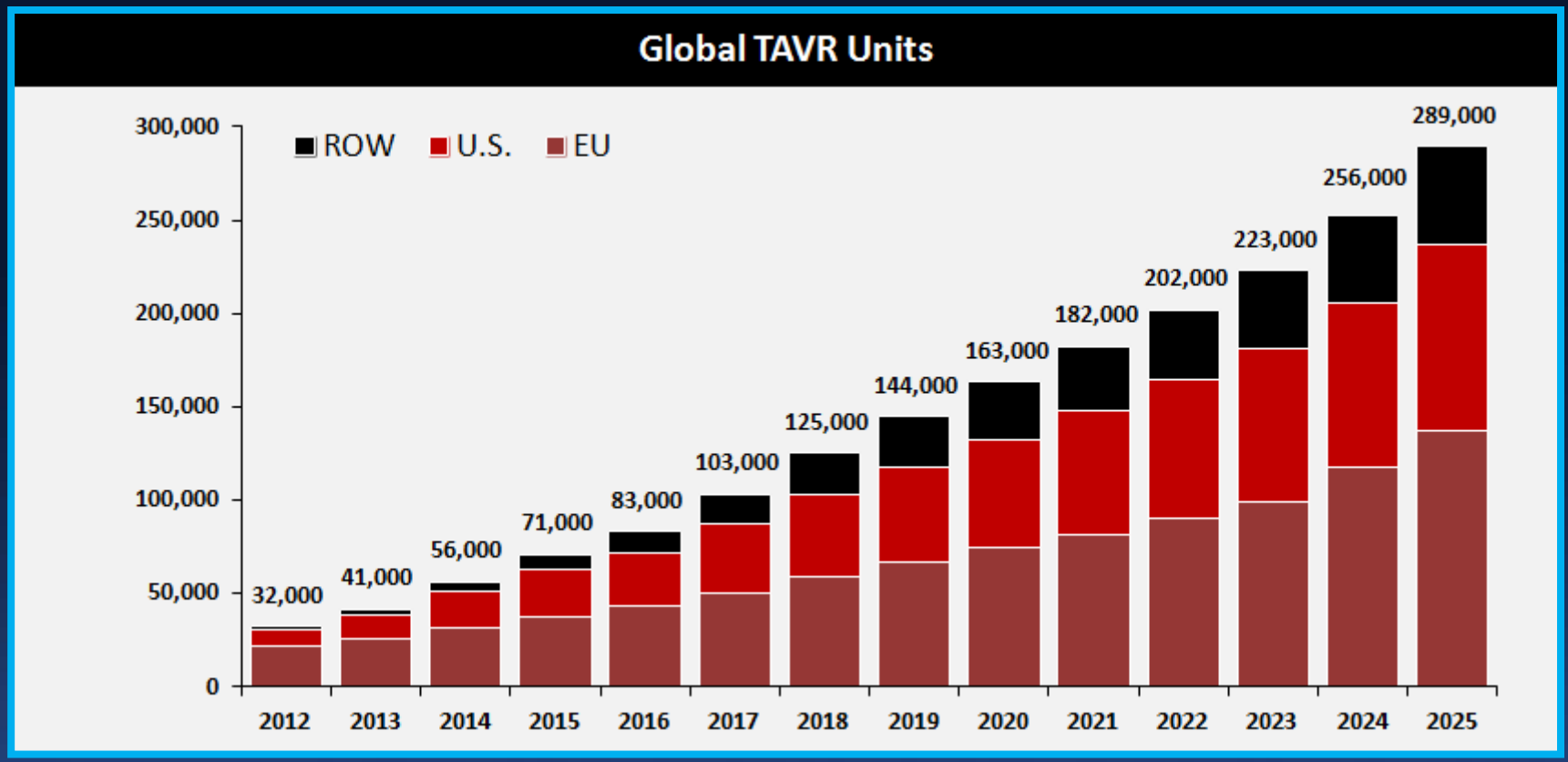
Disclosure Statement of Financial Interest

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

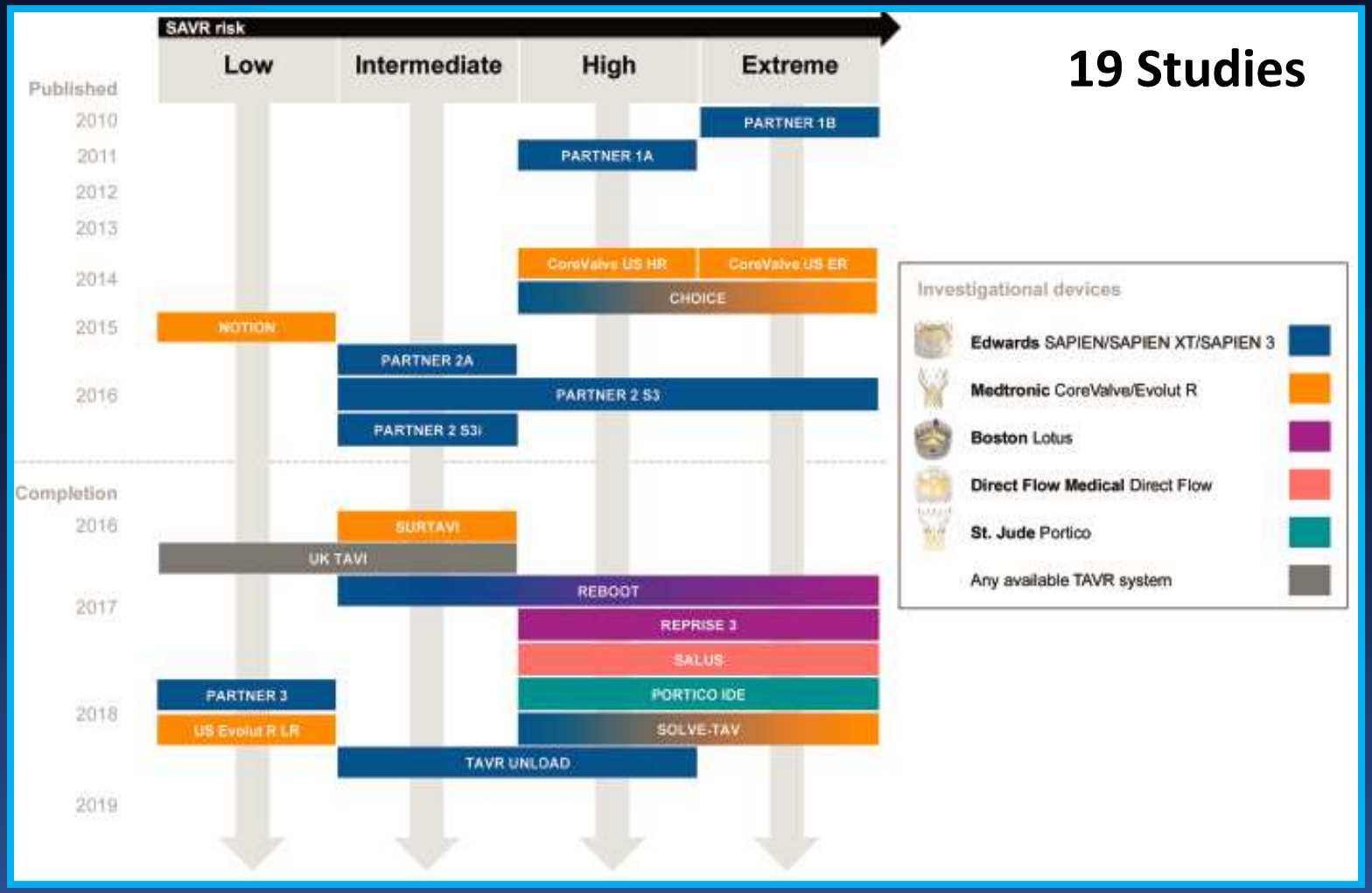
Estimated Global TAVR Growth



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

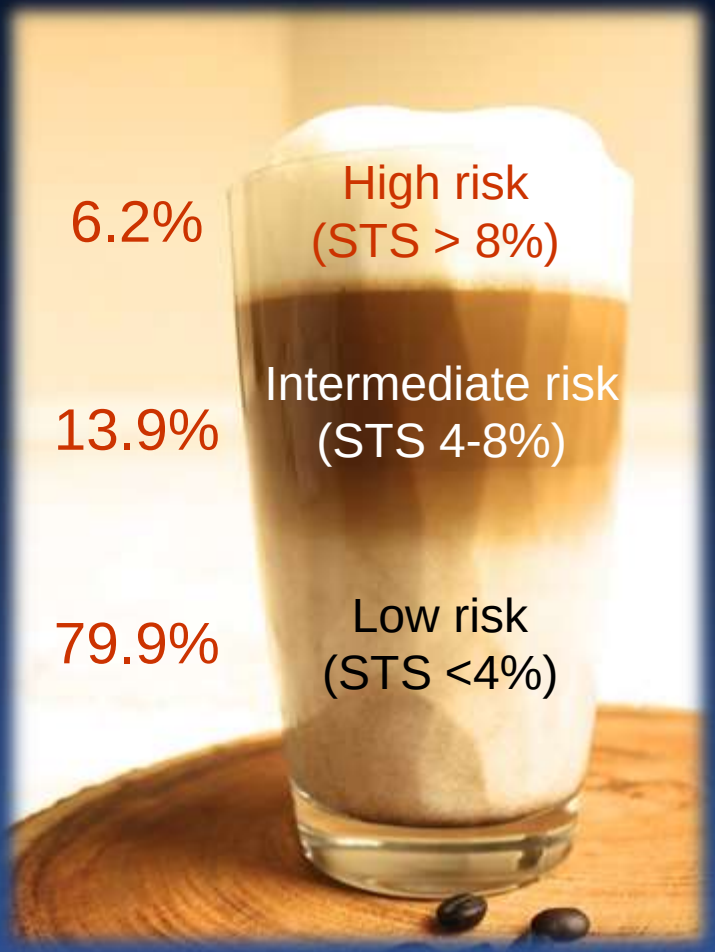
In the next 10 years, TAVR growth will increase X4!

TAVR Clinical Evidence



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

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!

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)
- SAVR orTAVR ViV (n=100/25)
- Mitral ViV or ViR (n=50/50)

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

Expanding TAVR Clinical Indications

A Transformative Technology at the Crossroads?

- Bioprosthetic aortic valve failure
- Low-risk patients (? all-comers)
- Low-flow, low-gradient AS
- Bicuspid AV disease
- AS + concomitant disease (CAD, MR, AF)
- Severe asymptomatic AS
- Moderate AS + CHF
- High-risk AR

Expanding TAVR Clinical Indications

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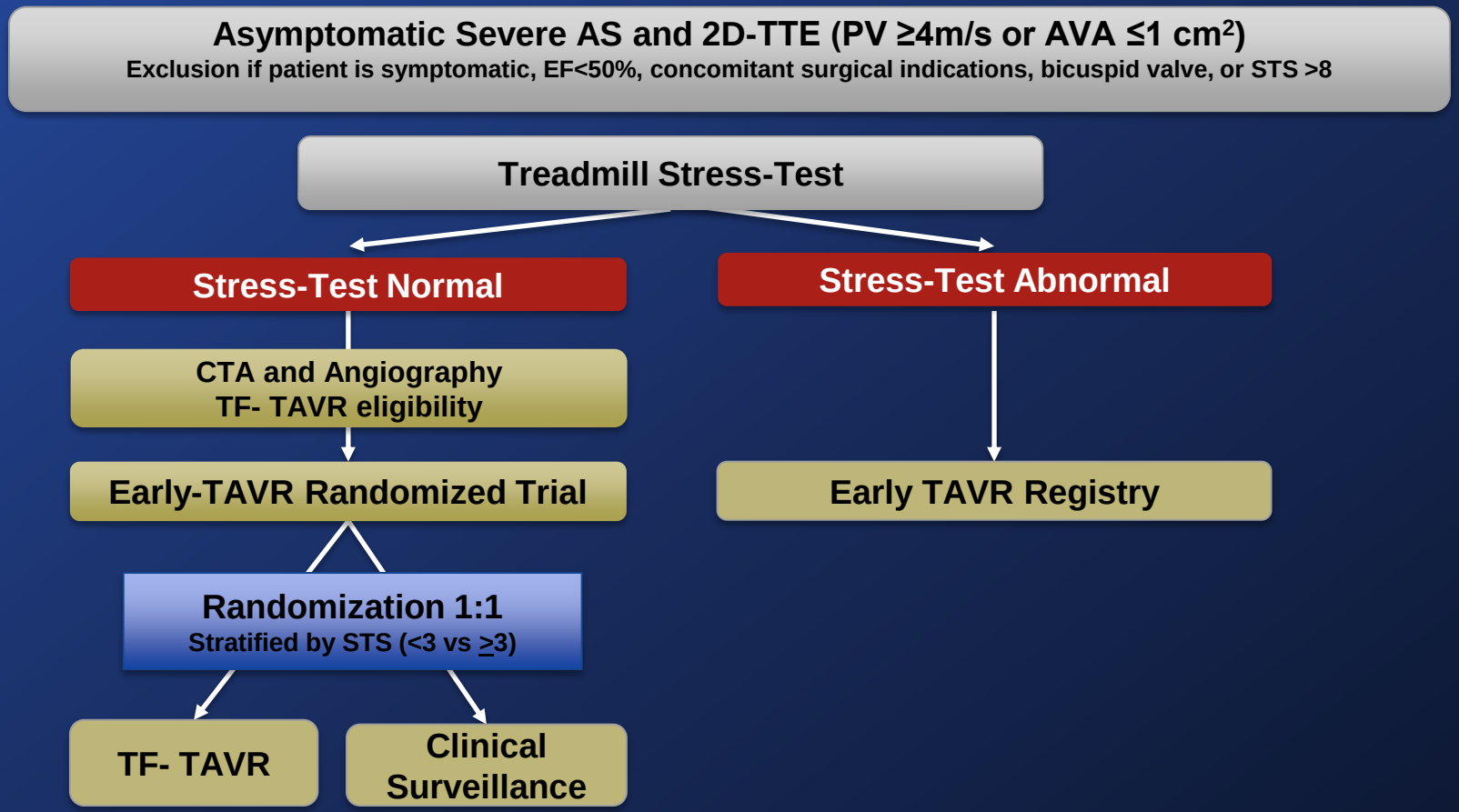
EARLY TAVR Trial
Study Flow



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

The EARLY TAVR Trial

Stanford University Hospital

William Fearon, MD and Michael Fischbein, MD

THE EARLY TAVR TRIAL

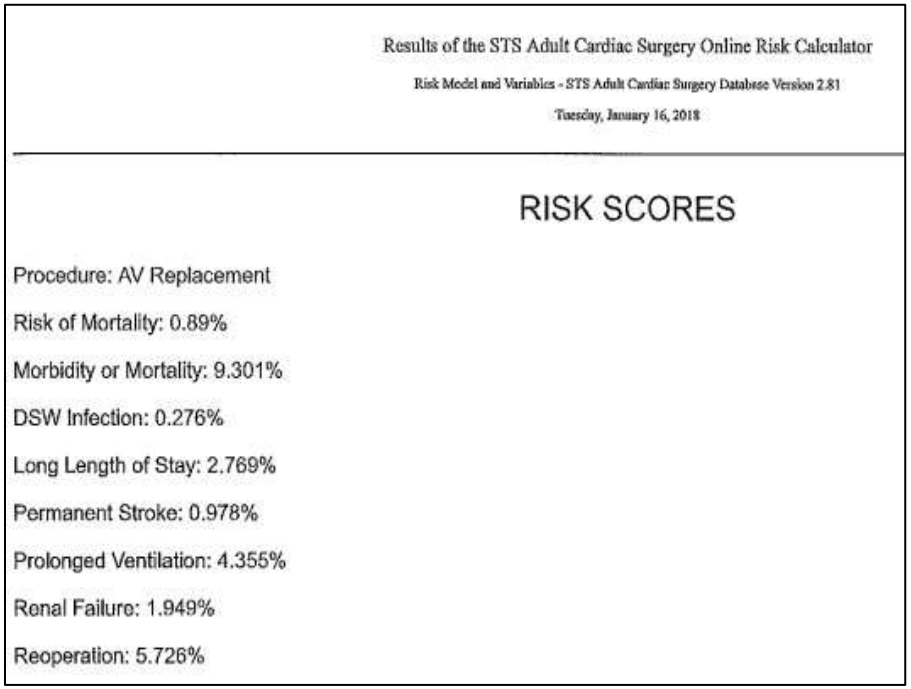
Pt. ID: ETV-0020-004 Pt. Initials: JMB

Patient Information	
Age	73
Gender	M
STS Score	**0.89%**
NYHA Class	I
Height	168.5cm
Weight	103.4 kg
BMI	36.4
GFR	87 mL/min
CR	0.84 mg/dL
HGB	13.0 g/dL
Consent Date	12/7/2017
Planned Procedure Date	1/23/2018

Plan	
Cohort	Asymptomatic
Planned Valve Size	23 mm
Access	Left TF

Relevant History:

- HTN, HLD, CAD



Results of the STS Adult Cardiac Surgery Online Risk Calculator

Risk Model and Variables - STS Adult Cardiac Surgery Database Version 2.81

Tuesday, January 16, 2018

RISK SCORES

Procedure: AV Replacement

Risk of Mortality: 0.89%

Morbidity or Mortality: 9.301%

DSW Infection: 0.276%

Long Length of Stay: 2.769%

Permanent Stroke: 0.978%

Prolonged Ventilation: 4.355%

Renal Failure: 1.949%

Reoperation: 5.726%

THE EARLY TAVR TRIAL

Treadmill Stress Test

Treadmill Stress Test	Response
Treadmill Stress Test performed?	Y
- If No, state reason	
- If No, did physician confirm pt is asymptomatic after thorough assessment?	
Protocol Used (Bruce, Modified Bruce, Naughton, Other)	Modified Bruce
Maximum minutes achieved	5.49 minutes
Maximum METs achieved	3.70 METs
Reason why test was terminated	ST Depression

Treadmill Stress Test	HR (bpm)	SBP (mmHg)	DBP (mmHg)
Baseline	100	140	80
Stage 1	122	163	88
Stage 2	134		
Stage 3			
Stage 4			
Completion			
Recovery 1	91	155	96
Recovery 2	89	132	84

Expected METs	Response
Age	73
Gender	M
60% Expected METs	4.2
100% Expected METs	7.1

Treadmill Stress Test	Response
Syncope/severe dizziness	N
Angina	N
Lack of increase or drop in SBP	N
Significant ventricular arrhythmias (≥ 4 consecutive PVCs)	N

EARLY TAVR TRIAL

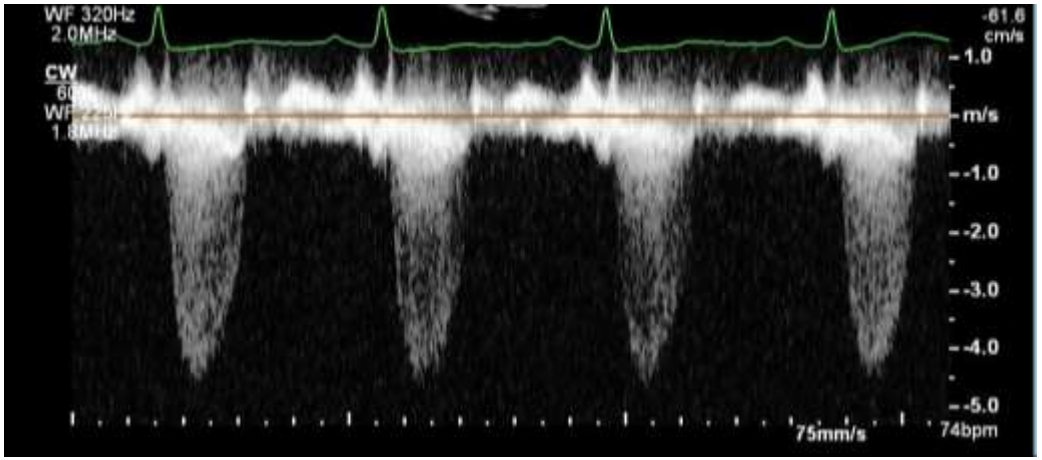
See comments from treadmill committee on next slide

Treadmill Stress Test Committee Comments

- Comments from Dr. Genereux: I am okay calling the pt asymptomatic based on the treadmill results and lack of symptoms.
- Comments from Dr. Schwartz: I am comfortable calling patient asymptomatic, agree that ST changes alone do not count as symptomatic.
- Comments from Dr. Holper: I am okay with it as well.

Echo Analysis: 11/30/2017

Echo Variable (TTE)	Measure
Jet Velocity	4.61 m/s
Mean Gradient	52.8 mmHg
Calculated AVA	0.70 cm^2
Calculated AVA index	0.33 cm^2/m^2
Ejection Fraction	65%
Severity of AR	Trace
Severity of MR	Trace
Severity of Mitral Stenosis (None, Mild, Moderate or Severe)	None
RV Pressure	29.9 mmHg
Is echo within window?	Yes
If OOW, date will be repeated	NA



Comments:

TTE Criteria
Jet Velocity ≥ 4.0 m/s or MG ≥ 40 mmHg AND
AVA ≤ 1.0 cm^2 or AVA index ≤ 0.6 cm^2/m^2

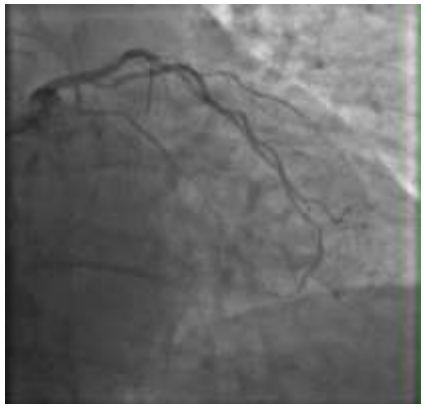
In window TTE = 90 days

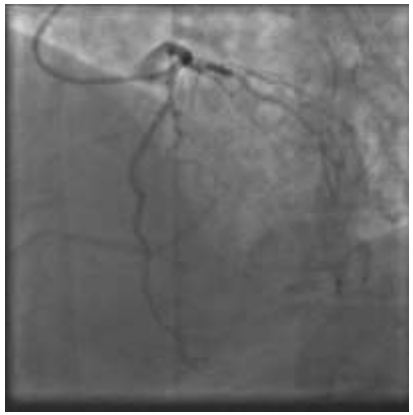
THE EARLY TAVR TRIAL

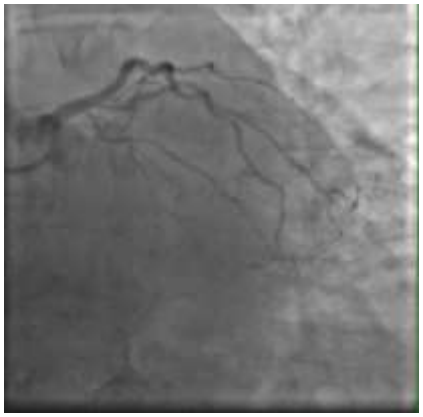
Coronary Evaluation: 12/18/2017

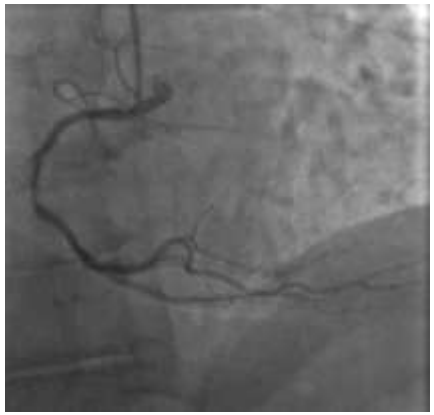
Revascularization Planned?	No
Target PCI vessel(s)	NA

Planned PCI Date	NA
Same Day as TAVR or Staged?	NA









	% stenosis & location (native/graft – prox, mid, distal)
LM	0%
LAD	50% mid, 40% distal, 50% prox D1
LCX	0%
RCA	0%

Syntax Score (N/A for pts w/ prior CABG)	NA

In window Cath = 1 yr

Comments:

THE EARLY TAVR TRIAL

Summary: ETV-0020-004 Pt. Initials: JMB

Patient Information	
Age	73
Gender	M
STS Score	**0.89%**
Cohort	Asymptomatic
Planned Valve Size	23mm
Sizing comments	
Access	Left TF

CT Measurement	Site
Area	411 mm^2
% Oversizing	-1.2%
Planned Valve Size	23 mm

CT Measurement	Core Lab
Area	392.7 mm^2
% Oversizing	+3.4%
Planned Valve Size	23 mm

Clinical Surveillance Arm
(for patients who are now symptomatic)

The following slide should only be completed for patients who are randomized to the Clinical Surveillance arm and are now symptomatic and require TAVR treatment:

- Complete next slide and submit entire presentation to your Clinical Specialist
- Updated presentation will be sent to the Treadmill Stress Test Review Committee for review/confirmation of symptomatic status before proceeding with TAVR treatment

THE EARLY TAVR TRIAL

Pt. ID: ETV-0020-004 Date: 4/12/2018

Patient Assessment	Response
Date originally presented and approved by Case Review Board	1/18/2018
Date randomized to Clinical Surveillance?	1/19/2018
Approximate date pt began having symptoms?	4/8/2018
Does patient have any of the following symptoms:	
- Syncope/Dizziness	Yes
- Angina	No
- SOB	No
- Increased Fatigue	No
- BP Changes (If Y, increase or decrease?)	No
- Arrhythmias	Yes
Planned TAVR Procedure Date	4/13/2018

Patient Assessment

Please describe patient's symptoms below:
73 y/o male from Northern California visiting Newport Beach with history of HTN and severe AS, currently at Hoag for management of his AS in the setting of VT arrest. Briefly, pt was enrolled in Edwards Life Sciences Early TAVR trial Jan/2018. Since then, he has had two syncope episodes.
The initial syncopal episode was on Feb 7, 2018. Stanford team was notified by the patient that he experienced a syncopal episode while exercising at his local gym. CRC called the patient directly to follow-up. He stated that he did not eat much nor hydrated adequately prior to the exercise. He felt this was why he had the syncopal episode. Subsequently, Dr. Fearon spoke to the patient and stated "Spoke with him and let him know he can resume gradual exercise and should he have another episode we will move forward with TAVR."
The most recent syncopal episode occurred the day of admission to Hoag Hospital Newport Beach on 4/8/18 when he had a syncope event while shopping. EMS was called and on route to the hospital, he had a VT arrest that was defibrillated x 1. His initial ECG was NSR with diffuse ST depressions that have normalized and his troponin peaked at 4.8. He had a LHC on 4/9/18 that showed significant stenosis of his LAD and ramus, both of which were stented with DES. His TTE done 4/8/18 showed preserved LV function and normal wall motion, but severe AS (mean AV gradient 56mmhg). He is currently in NSR, CP free without any more VT. Hoag heart team met on 4/12/18 and decided he would be an appropriate TAVR candidate as part of the Early TAVR trial.

Physician who deemed patient symptomatic:
Dr. Castellanos (Hoag)

TAVR UNLOAD Trial

Study Design

(600 patients, 1:1 Randomized)

THE PARTNER 3 TRIAL

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

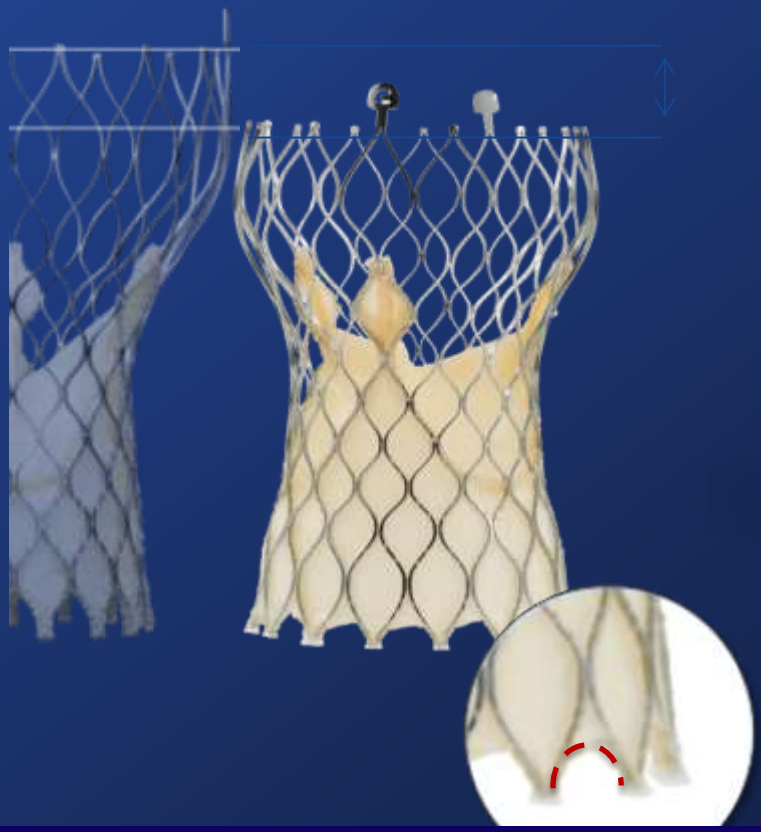
Primary Endpoint
Hierarchical occurrence of:
- **All-cause death**
- **Disabling stroke**
- **Hospitalizations for HF, aortic valve disease**
- **Change in KCCQ**

Reduced AFTERLOAD
Improved LV systolic and diastolic function

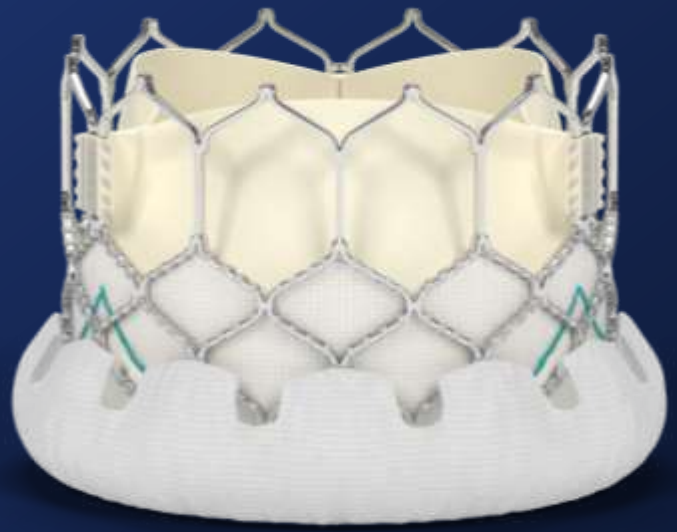
Current "Standards" for TAVR

PARTNER 3 TRIAL

MDT Evolut R (PRO)



Edwards Sapien 3



TAVR in NAVR

- Current device not optimal
- Registry: 254 patients, 56% Core, 12 days in hospital and 20% pacer.

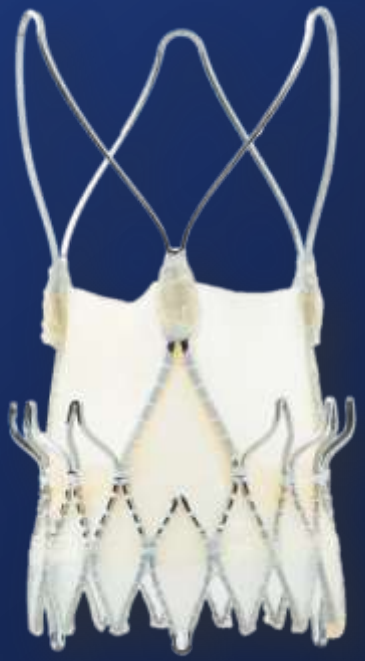
Efficacy Beyond 30 Days Post-TAVR

	First-Generation THV (n = 109)	Newer-Generation THV (n = 145)
Clinical Efficacy	56%	72%
All-Cause Mortality	17%	8%
Cardiac Mortality	12%	7%
Noncardiac Mortality	5%	1%
All Stroke	3%	4%
Valve-Related Dysfunction	29%	10%
Moderate or Severe AR	26%	5%
NYHA Class III or IV	18%	13%

"Next in Line" for TAVR

THE PARTNER 3 TRIAL

LOTUS (Edge) **ACURATE neo** **PORTICO**

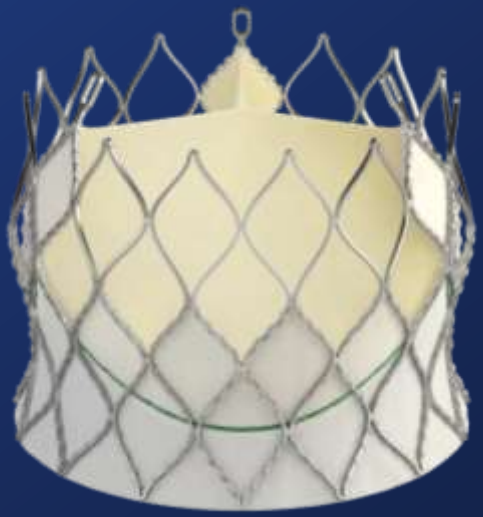


"Rebooting" or Increasing Momentum

THE PARTNER 3 TRIAL

JENA Valve

CENTERA



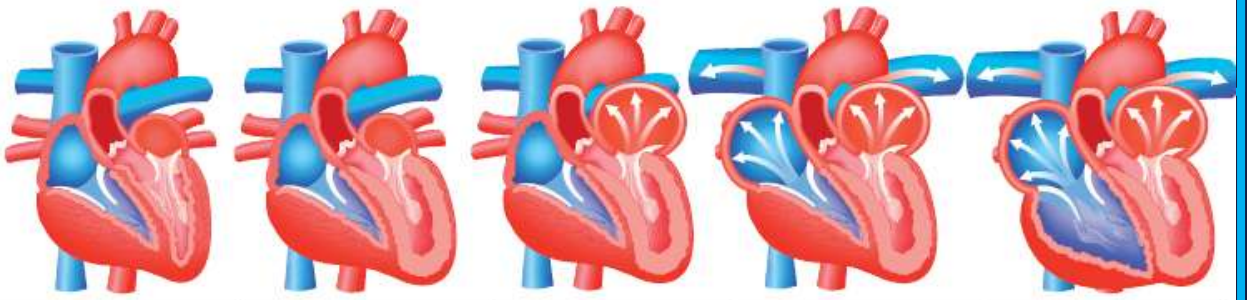
VENUS A Valve

European Heart Journal (2017) **00**, 1–9
doi:10.1093/eurheartj/ehx381

FASTTRACK CLINICAL RESEARCH

Staging classification of aortic stenosis based on the extent of cardiac damage

Philippe Généreux[1,2,3], Philippe Pibarot[4], Björn Redfors[1,5], Michael J. Mack[6], Raj R. Makkar[7], Wael A. Jaber[8], Lars G. Svensson[8], Samir Kapadia[8], E. Murat Tuzcu[8], Vinod H. Thourani[9], Vasilis Babaliaros[9], Howard C. Herrmann[10], Wilson Y. Szeto[10], David J. Cohen[11], Brian R. Lindman[12], Thomas McAndrew[1], Maria C. Alu[13],



Stages/Criteria	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No Cardiac Damage	LV Damage	LA or Mitral Damage	Pulmonary Vasculature or Tricuspid Damage	RV Damage
Echocardiogram		Increased LV Mass Index >115 g/m² (Male) >95 g/m² (Female)	Indexed left atrial volume >34mL/m²	Systolic Pulmonary hypertension ≥60 mmhg	Moderate-Severe right ventricular dysfunction
		E/e' >14	Moderate-Severe mitral regurgitation	Moderate-Severe tricuspid regurgitation	
		LV Ejection Fraction <50%	Atrial Fibrillation		

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Staging classification of aortic stenosis based on the extent of cardiac damage