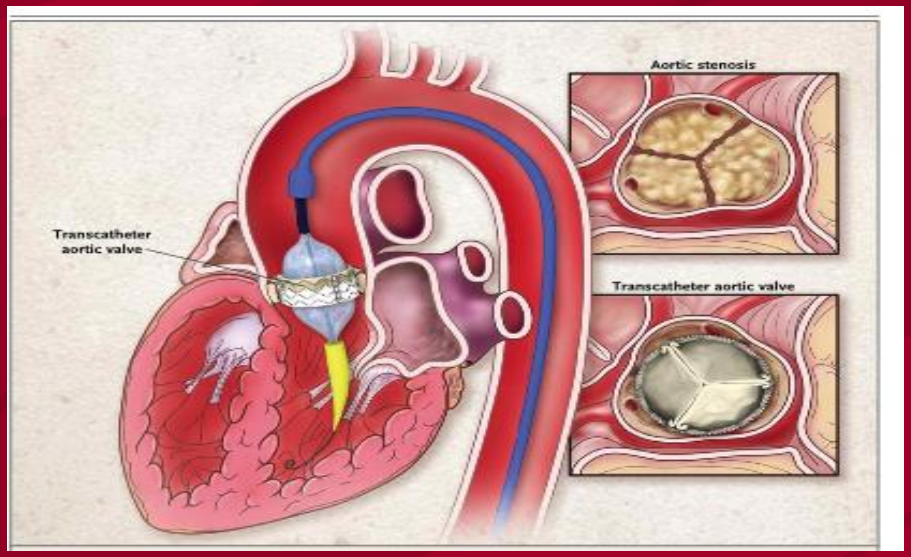
Transcatheter Aortic Valve Replacement



Deepak P. Vivek, MD

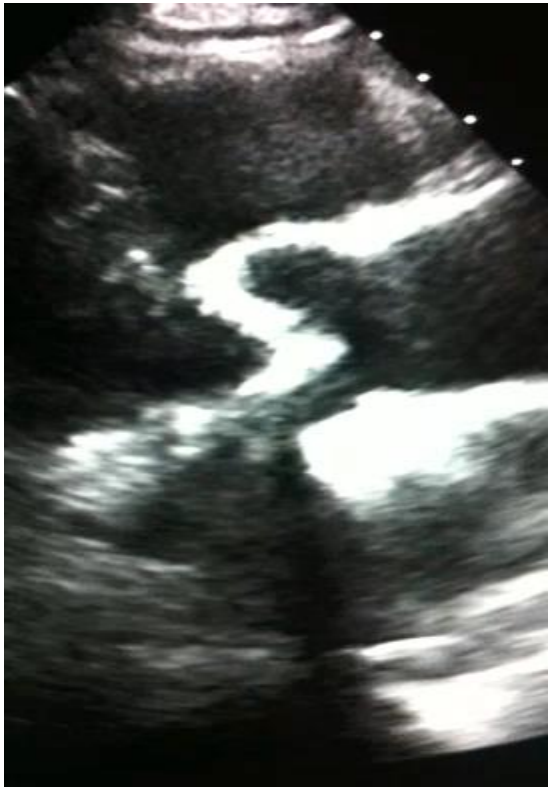
October 7, 2017

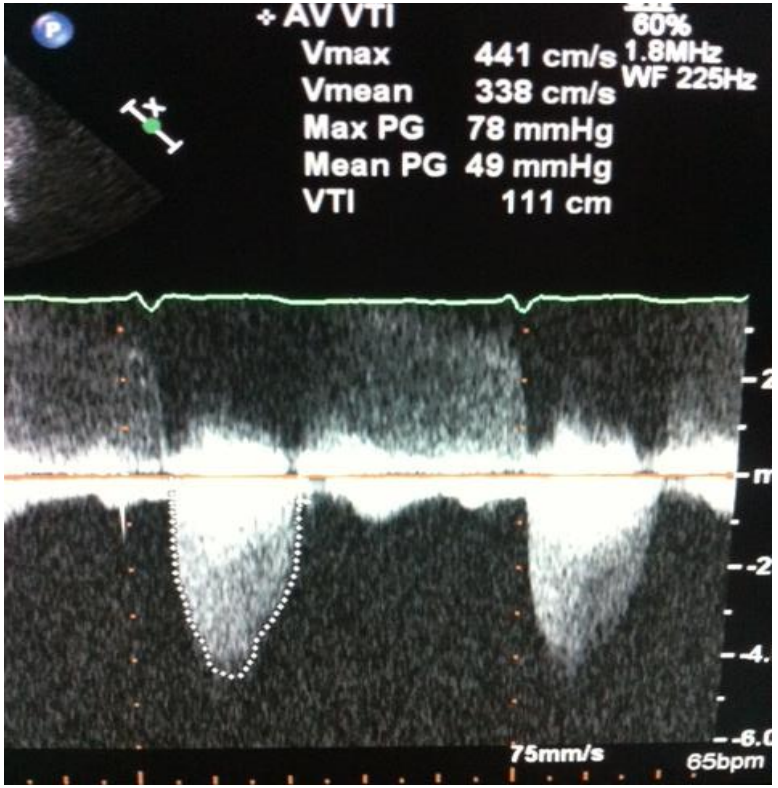
ORLANDO HEALTH®

Patient Case

- 75 year old male with previous 3V CABG 2009
- Develops sxs of DOE over past 6 months
- On exam, diminished carotid upstroke
  - II/VI harsh late peaking systolic murmur; soft S2
  - Radiation of murmur to neck
  - Diminished carotid upstroke

2D echo

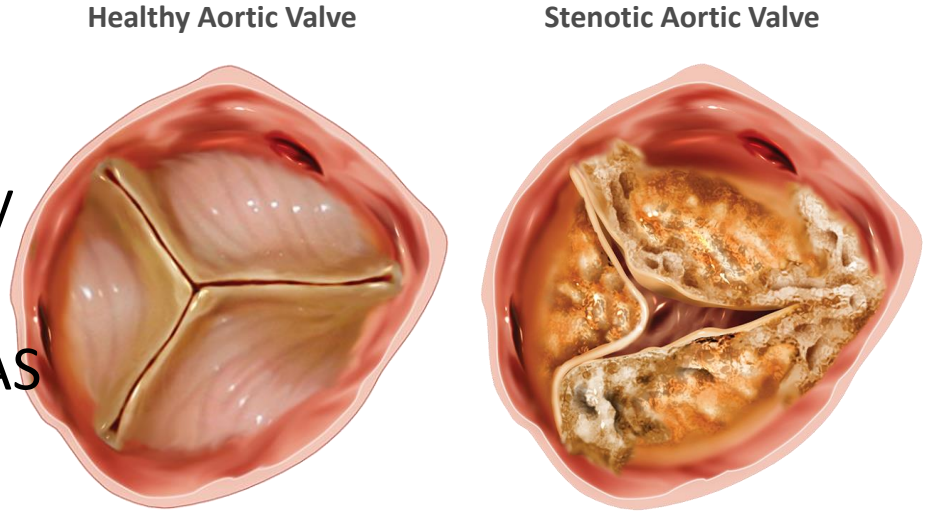



AV VTI
Vmax 441 cm/s
Vmean 338 cm/s
Max PG 78 mmHg
Mean PG 49 mmHg
VTI 111 cm
60%
1.8MHz
WF 225Hz
75mm/s
65bpm

Etiology: Calcific Aortic Stenosis (AS)

Mechanism of Stenosis is Similar to Atherosclerosis[1]

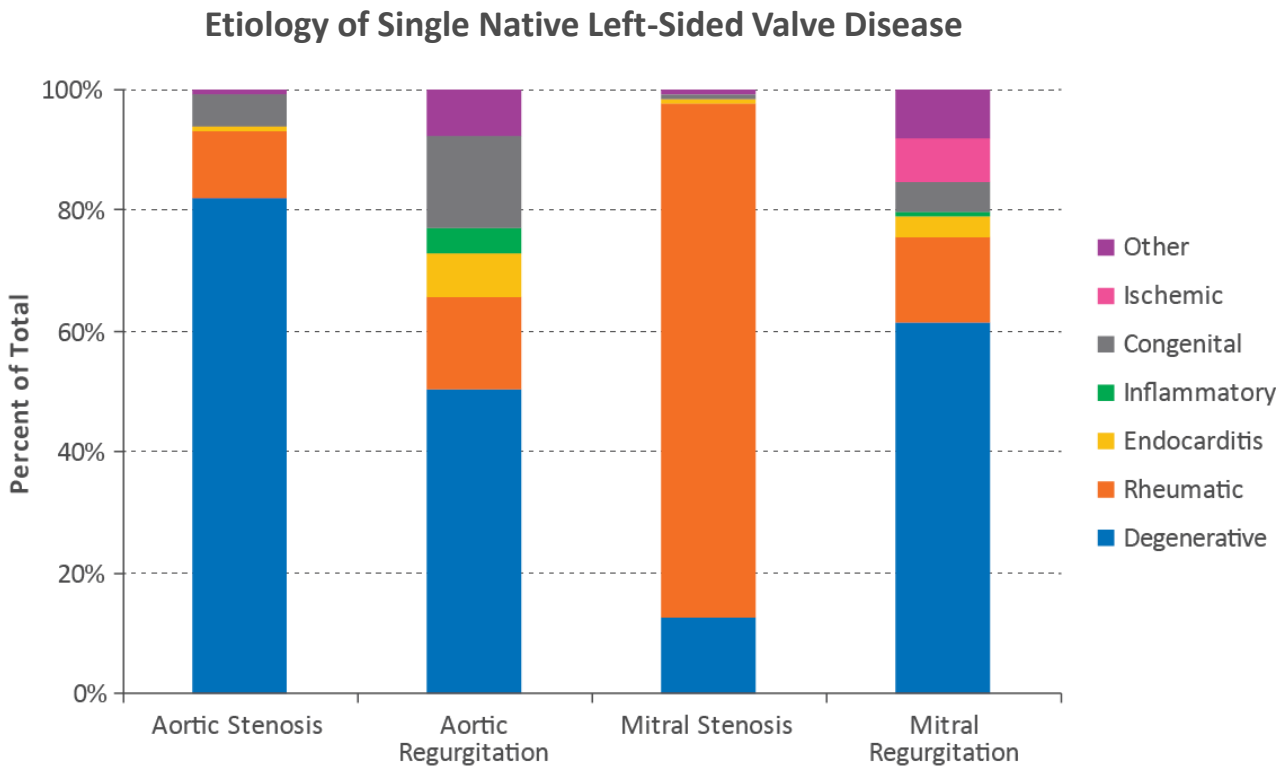
- Mainly solid calcium deposits within the valve cusps
- Similar risk factors to Coronary Artery Disease (CAD)
- High coincidence of CAD and AS in same individual[2]
- 6th, 7th, and 8th decades of life
- Calcific AS is leading cause of aortic valve replacement



1. Otto. *Circulation.* 1994;90:844-853.
2. Otto. *NEJM.* 1999;341:142-147.

Disease Etiology

Aortic Stenosis is Predominantly a Degenerative Disease

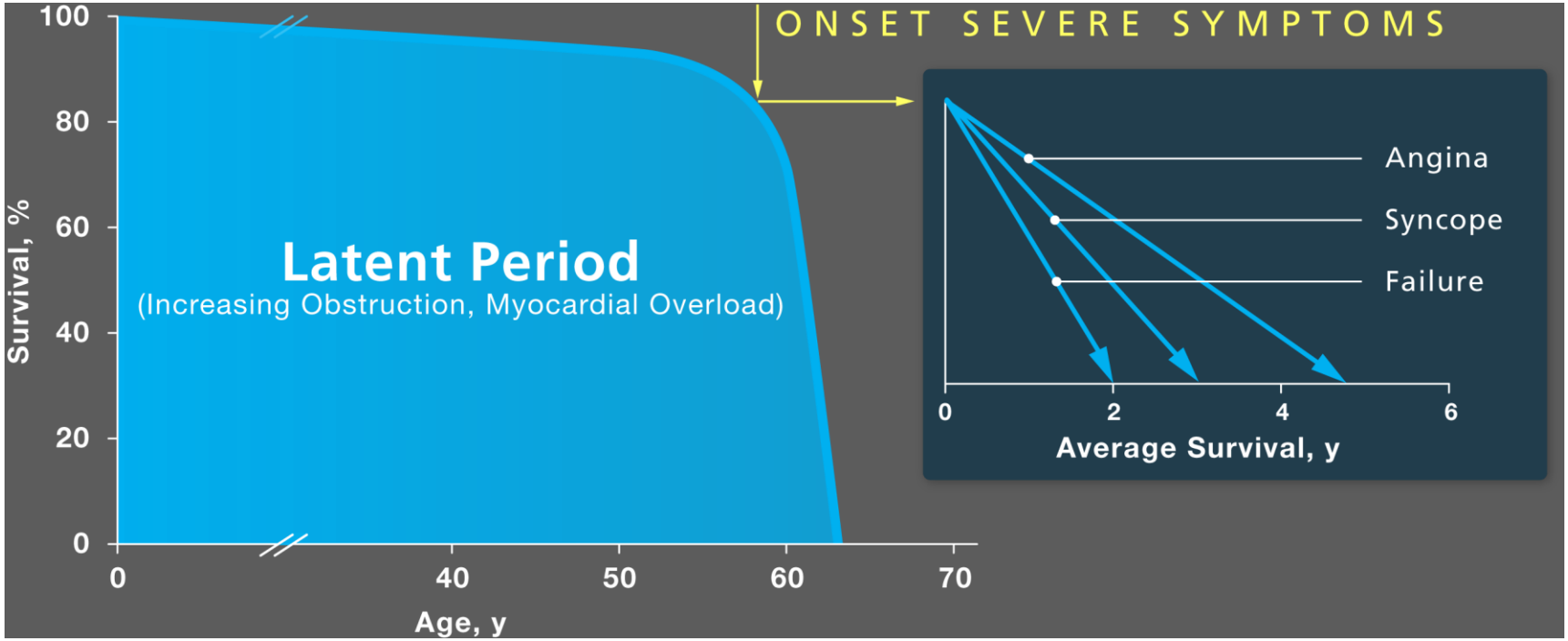


lung B, Baron G, Butchart E, et al. *Eur Heart J.* 2003;24:1244-1253.

Triad of Symptoms

- Angina
- - Increased oxygen demand due to LV hypertrophy
- - Reduced coronary flow reserve
- - Subendocardial ischemia
- Syncope
- - Arrhythmias (AFIB, NSVT, transient AV block)
- - Vasodepressor reflexes
- CHF
- - Afterload mismatch; diastolic dysfunction

Prognosis



- Survival after onset of symptoms is 50% at 2 years and 20% at 5 years[2]
- Intervention for severe aortic stenosis should be performed promptly once even minor symptoms occur[2]

Aortic Stenosis Severity Classification

AHA/ACC Guidelines 2014
Guidelines

Indicator	Stage A: At Risk	Stage B: Progressive (Mild)	Stage B: Progressive (Moderate)	Stage C: Asymptomatic (Severe)	Stage D: Symptomatic (Severe)
Jet Velocity *(m/s)*	< 2.0	2.0 - 2.9	3.0 – 3.9	≥ 4.0	≥ 4.0
Mean Gradient *(mmHg)*		< 20	20 – 39	≥ 40	≥ 40
Valve Area *(cm^2)*				≤ 1.0	≤ 1.0
Valve Area Index *(cm^2/m^2)*				≤ 0.6	≤ 0.6

Nishimura RA, et al. *Circulation*. 2014;129.

Timing of Aortic Valve Replacement (AVR)

ACC/AHA 2014 Guideliines

Recommendations	COR	LOE	References
AVR is recommended with severe high-gradient AS who have symptoms by history or on exercise testing (stage D1)	I	B	(10, 57-59)
AVR is recommended for asymptomatic patients with severe AS (stage C2) and LVEF <50%	I	B	(61, 62)
AVR is indicated for patients with severe AS (stage C or D) when undergoing other cardiac surgery	I	B	(63, 64)
AVR is reasonable for asymptomatic patients with very severe AS (stage C1, aortic velocity $\geq$ 5.0 m/s) and low surgical risk	IIa	B	(65, 66)
AVR is reasonable in asymptomatic patients (stage C1) with severe AS and decreased exercise tolerance or an exercise fall in BP	IIa	B	(27, 38)
AVR is reasonable in symptomatic patients with low-flow/low-gradient severe AS with reduced LVEF (stage D2) with a low-dose dobutamine stress study that shows an aortic velocity $\geq$ 4.0 m/s (or mean pressure gradient $\geq$ 40 mm Hg) with a valve area $\leq$ 1.0 cm^2 at any dobutamine dose	IIa	B	(67-69)
AVR is reasonable in symptomatic patients who have low-flow/low-gradient severe AS (stage D3) who are normotensive and have an LVEF $\geq$ 50% if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms	IIa	C	N/A
AVR is reasonable for patients with moderate AS (stage B) (aortic velocity 3.0–3.9 m/s) who are undergoing other cardiac surgery	IIa	C	N/A
AVR may be considered for asymptomatic patients with severe AS (stage C1) and rapid disease progression and low surgical risk	IIb	C	N/A

AS=aortic stenosis; AVR=aortic valve replacement by either surgical or transcatheter approach; BP=blood pressure; COR= Class of Recommendation; LOE=Level of Evidence; LVEF=left ventricular ejection fraction; N/A=not applicable.

Nishimura RA, et al. *Circulation*. 2014;129.

- Surgical aortic valve replacement has been the standard of care and treatment of choice in patients with severe AS.

- However, over 30% of patients are not candidates for surgical AVR due to comorbidities (LV dysfunction, advanced age, COPD, etc).

Risk Stratification of Severe, Symptomatic Aortic Stenosis Patients

AHA/ACC 2014 Guidelines

	Low Operative Risk (Must Meet ALL Criteria in This Column)	**Intermediate Operative Risk** (Any 1 Criterion in This Column)	**High Operative Risk** (Any 1 Criterion in This Column)	**Prohibitive Operative Risk** (Any 1 Criterion in This Column)
STS PROM[1]	< 3% AND	3% to 8% OR	> 8% OR	Prohibited risk with surgery of death or major morbidity (all-cause) > 50% at 1 year OR
Frailty[2]	None AND	1 Index (mild) OR	≥ 2 Indices (moderate to severe) OR	
Major organ system compromise not to be improved postoperatively[3]	None AND	1 organ system OR	No more than 2 organ systems OR	≥ 3 organ systems OR
Procedure specific impediment[4]	None	Possible procedure-specific impediment	Possible procedure-specific impediment	Severe procedure-specific impediment

1. Use of the STS PROM to predict risk in a given institution with reasonable reliability is appropriate only if institutional outcomes are within 1 standard deviation of STS average observed/expected ratio for the procedure in question.
2. Seven frailty indices: Katz Activities of Daily Living (independence in feeding, bathing, dressing, transferring, toileting, and urinary continence) and independence in ambulation (no walking aid or assist required or 5-meter walk in <6 s). Other scoring systems can be applied to calculate no, mild-, or moderate-to-severe frailty.
3. Examples of major organ system compromise: Cardiac—severe LV systolic or diastolic dysfunction or RV dysfunction, fixed pulmonary hypertension; CKD stage 3 or worse; pulmonary dysfunction with FEV1 <50% or DLCO2 <50% of predicted; CNS dysfunction (dementia, Alzheimer's disease, Parkinson's disease, CVA with persistent physical limitation); GI dysfunction—Crohn's disease, ulcerative colitis, nutritional impairment, or serum albumin <3.0; cancer—active malignancy; and liver—any history of cirrhosis, variceal bleeding, or elevated INR in the absence of VKA therapy.
4. Examples: tracheostomy present, heavily calcified ascending aorta, chest malformation, arterial coronary graft adherent to posterior chest wall, or radiation damage.

Nishimura RA, et al. *Circulation*. 2014;129.

The Eyeball Test

TAVR Patient Selection
Includes Careful Frailty Assessment

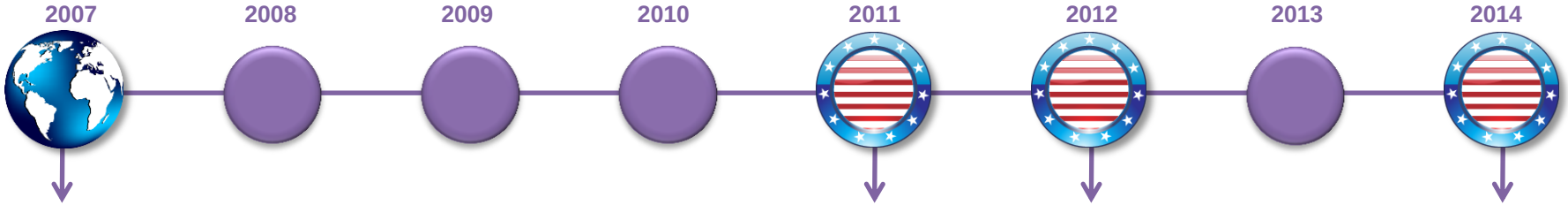
Patient A *vs.* *Patient B*

Same age and predicted risk
One passes the "eyeball test" – one does not

Frailty is being studied systematically as part of the PARTNER U.S. IDE study

Transcatheter Aortic Valve Replacement Global Timeline

- More than 100,000 TAVR implants globally since 1st introduced commercially in 2007
- More than 60 countries



CoreValve® Device 1st TAVR Platform Approved in 2007

SAPIEN US FDA Approval Extreme Risk Iliofemoral November 2011

SAPIEN US FDA Approval High Risk October 2012

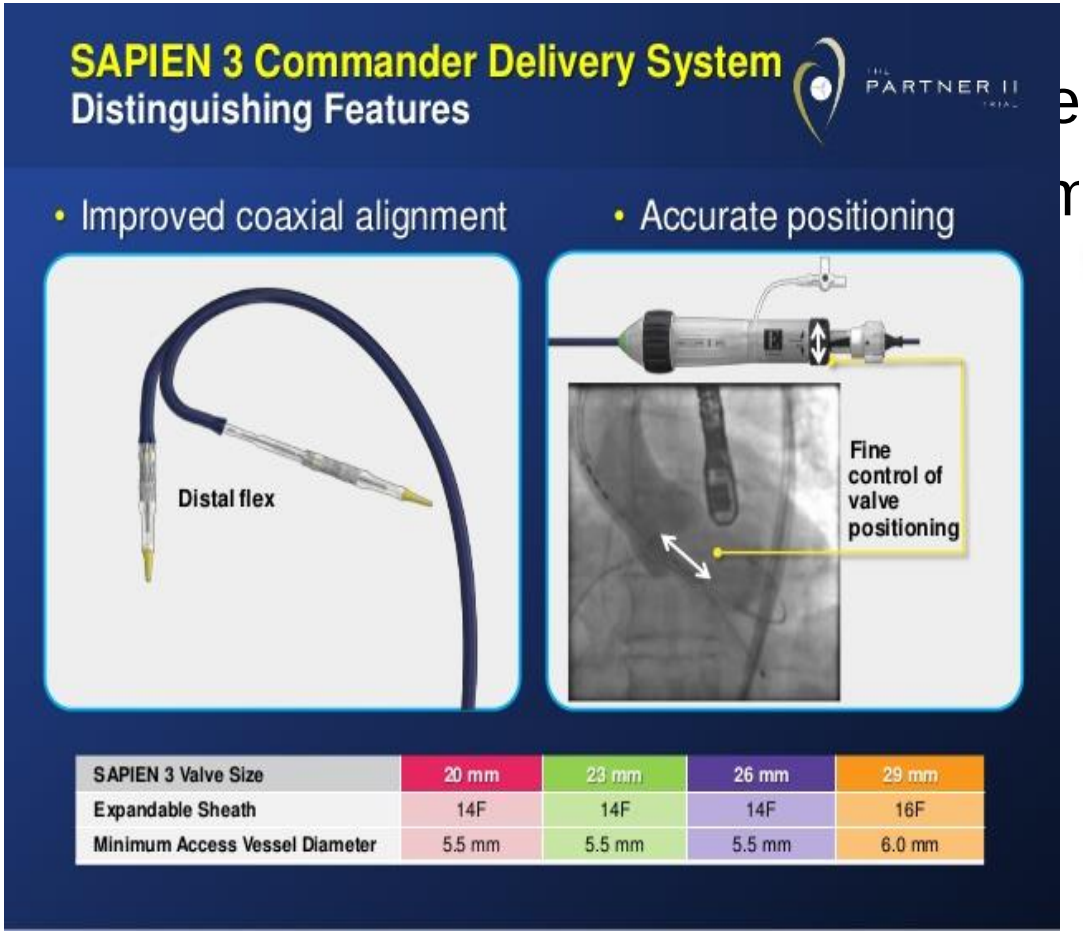
CoreValve US FDA Approval Extreme Risk January 2014

CoreValve US FDA Approval High Risk June 2014

Significant body of TAVR evidence with 4 large U.S. trials and 5 NEJM publications.

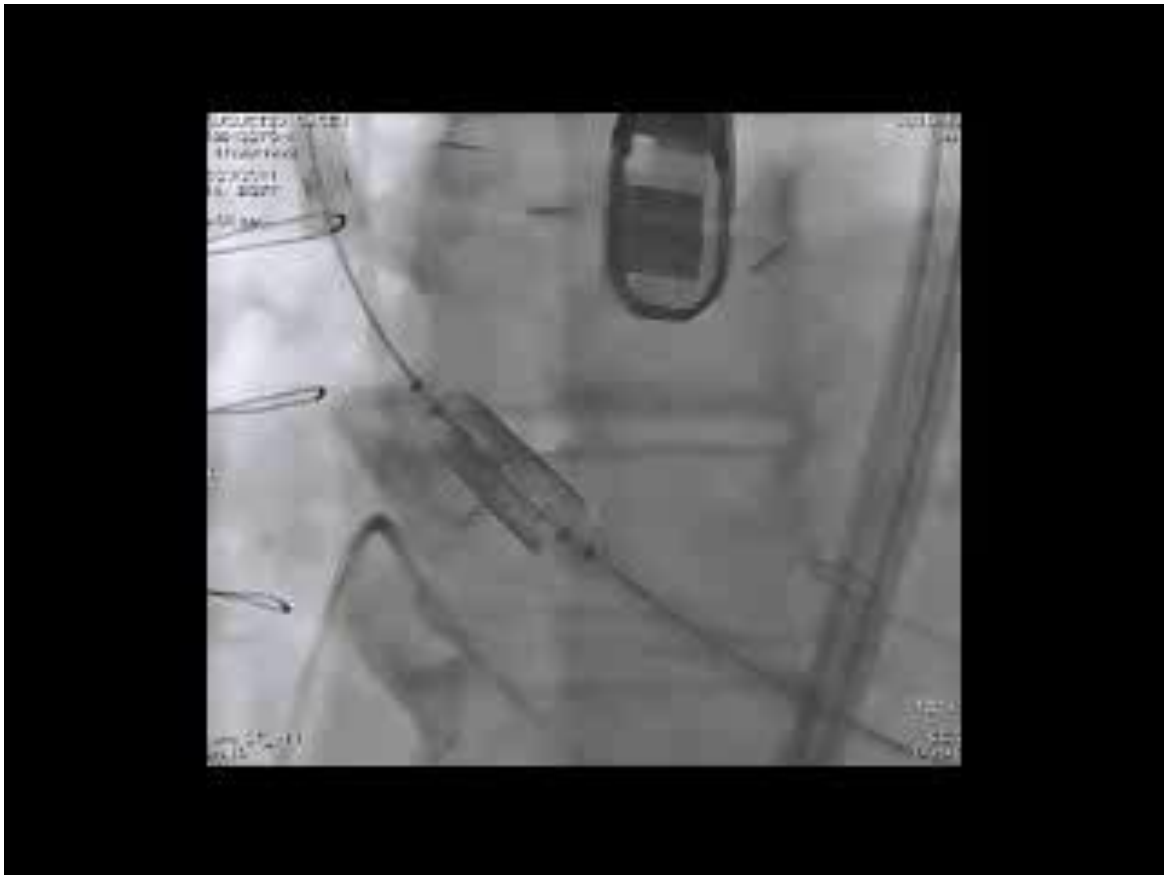
To view the complete CoreValve Instructions for Use visit: *manuals.medtronic.com*

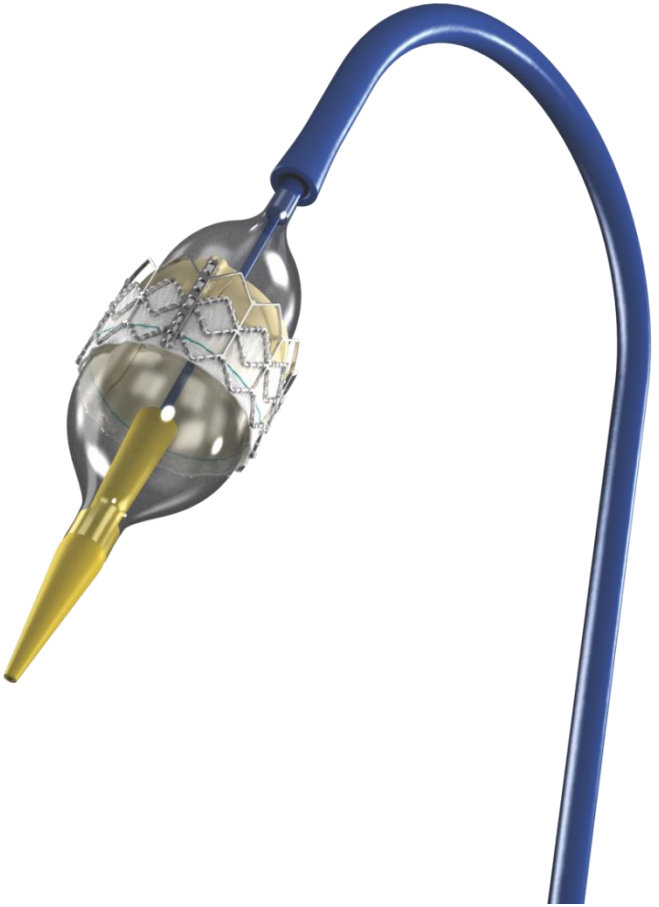
Edwards Sapien 3



- Tri-leaflet bovine pericardial tissue
- Balloon expandable cobalt chromium frame
- Needs rapid pacing for deployment
- TF, TA, TAo deployment

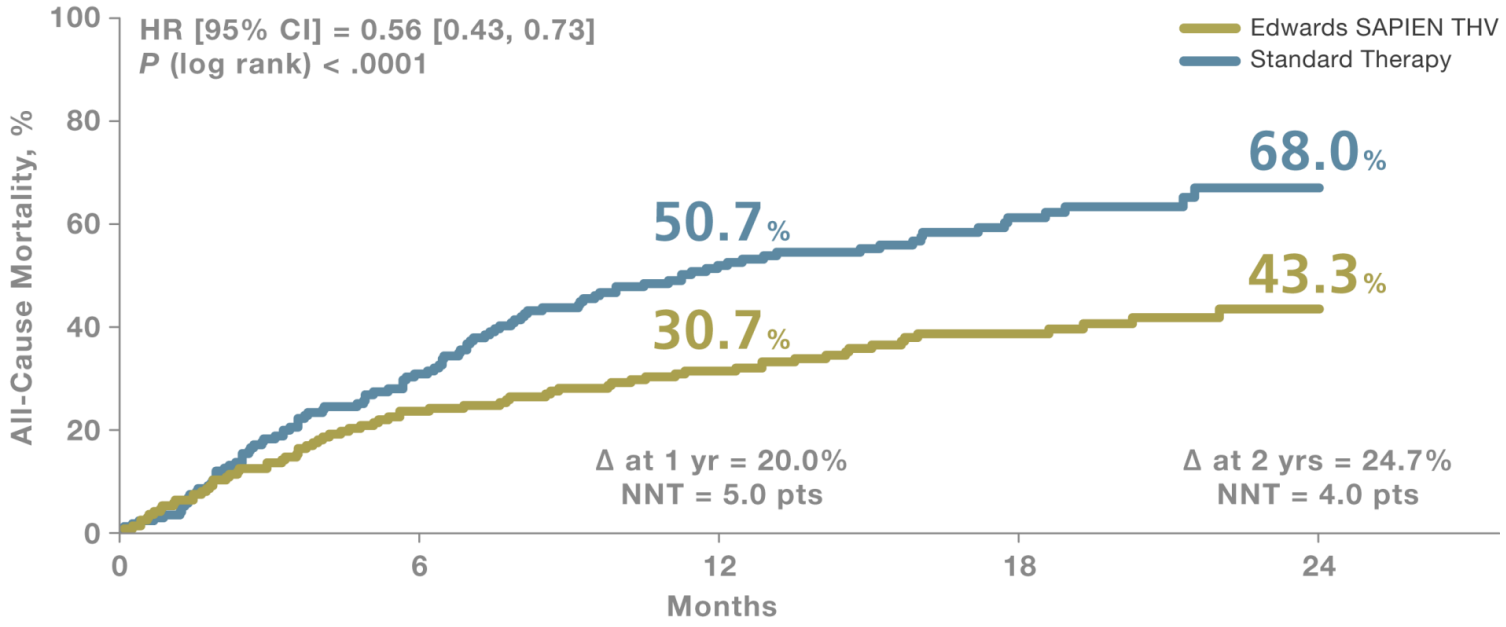
Edwards SAPIEN Transcatheter Heart Valve Deployment





PARTNER TRIAL: Cohort B

ALL-CAUSE MORTALITY AT 1 YEAR AND 2 YEARS



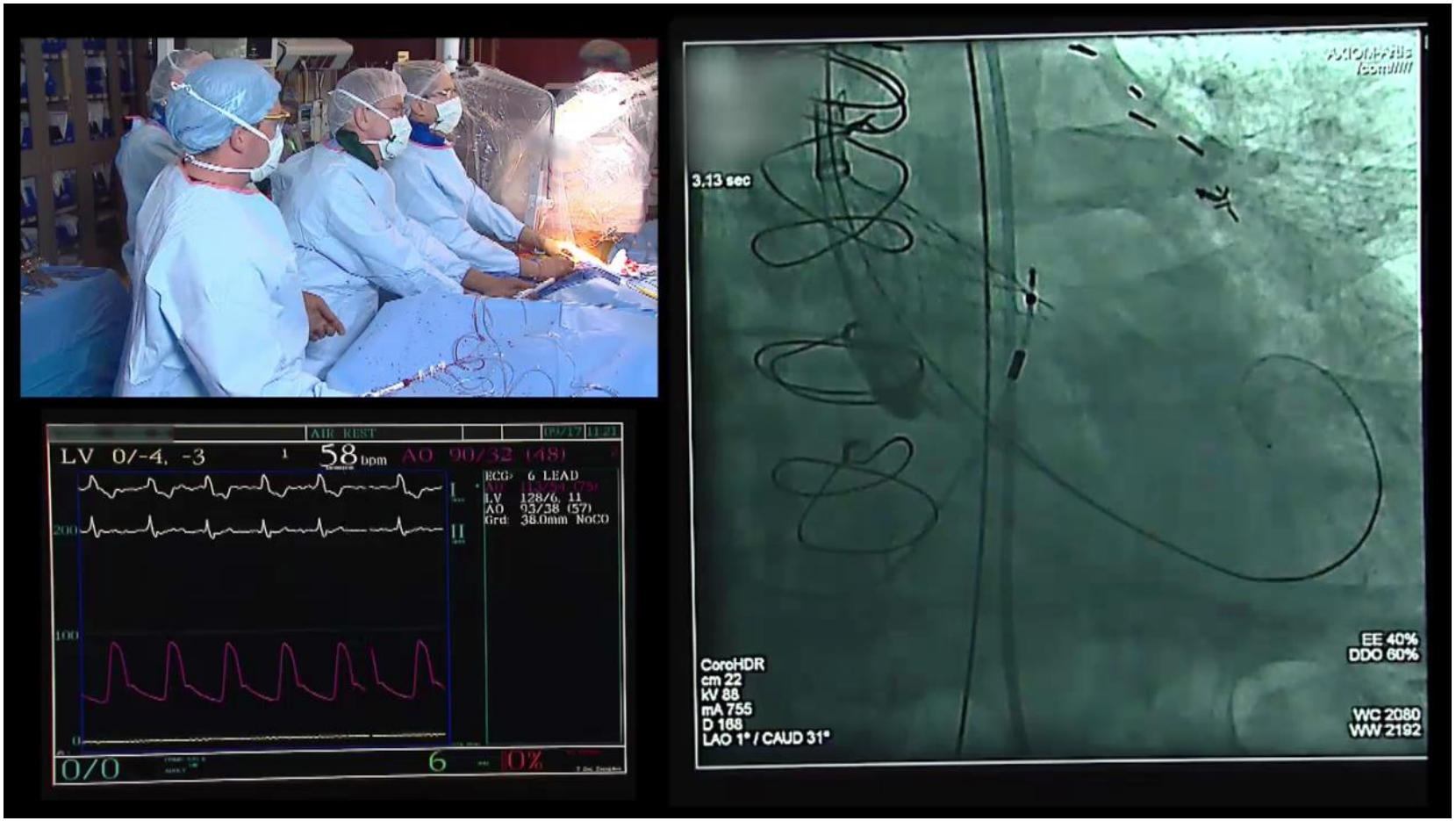
Numbers at Risk

Edwards SAPIEN THV	179	138	124	110	83
Standard Therapy	179	121	85	62	42

Medtronic Evolut R

ORMC first in Central Florida to deploy this valve
14 French equivalent
First recapturable and repositionable device on the market

- *self expanding nitinol frame*
- pacemaker requirement
- 23mm, 26, 29,31mm devices

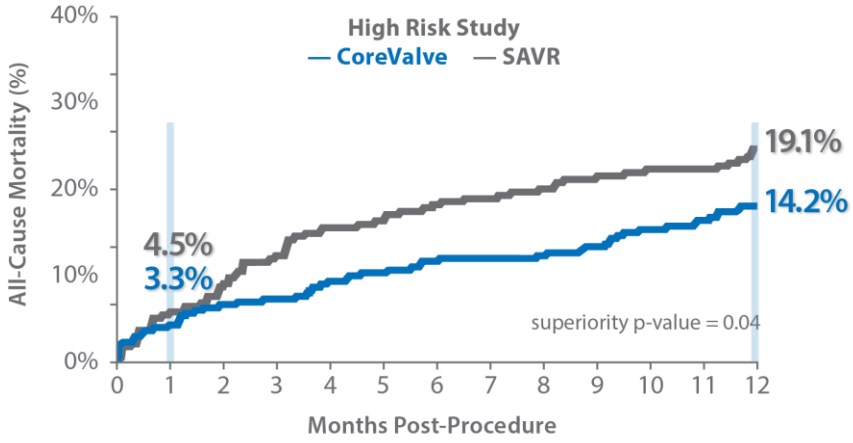

3.13 sec
CoroHDR
cm 22
kV 88
mA 755
D 168
LAO 1° / CAUD 31°
EE 40%
DDO 60%
WC 2080
WW 2192
LV 0/-4, -3
58 bpm
AO 90/32 (48)
ECG 6 LEAD
LV 128/6, 11
AO 93/38 (57)
Grd: 38.0mm NoCO
0/0
6
0%

CoreValve U.S. Pivotal Trial High Risk Study Optimal TAVR Outcomes

The Proof:

High Survival

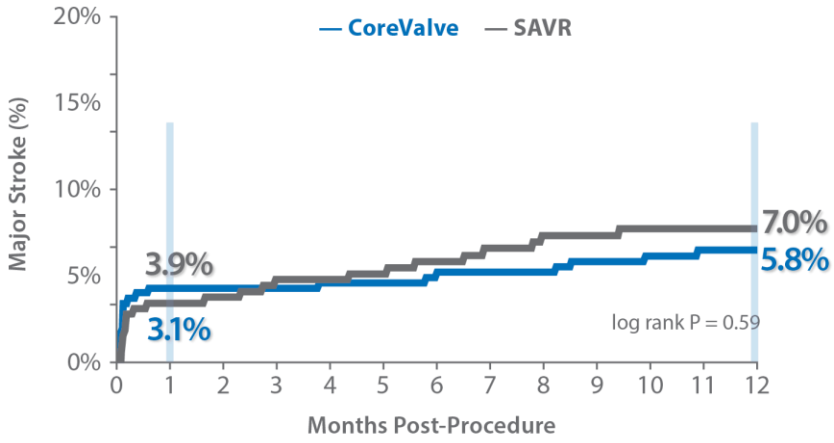
The CoreValve Platform demonstrates high survival rates that outperform the standard of care at one year.



One year survival significantly outperforms surgical valve replacement in high risk patients

Low and Stable Major Stroke Rate

The CoreValve Platform demonstrates a low stroke rate out to one year.



Using a prospective assessment of stroke in high risk patients, the major stroke rate is comparable to surgical valve replacement.

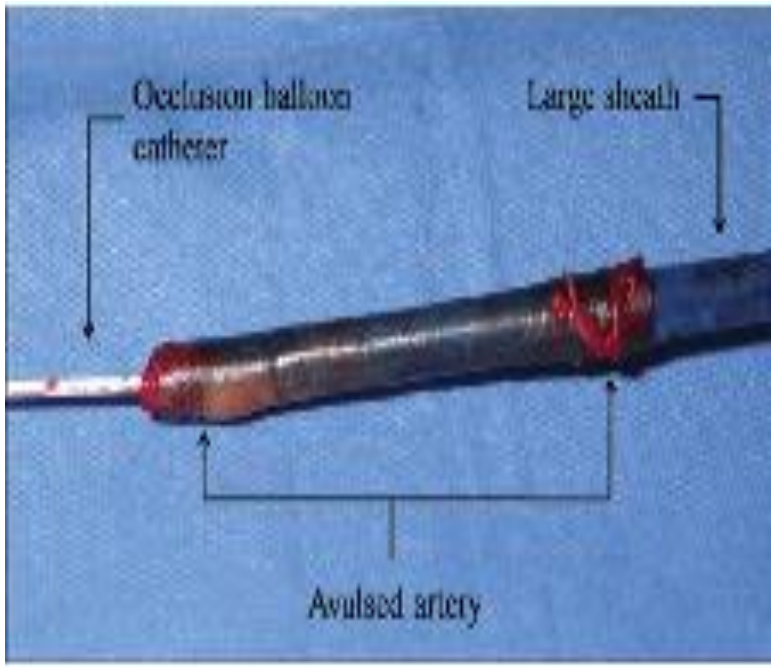
~20-25% needed new pacemakers post-TAVR vs 10% with surgery

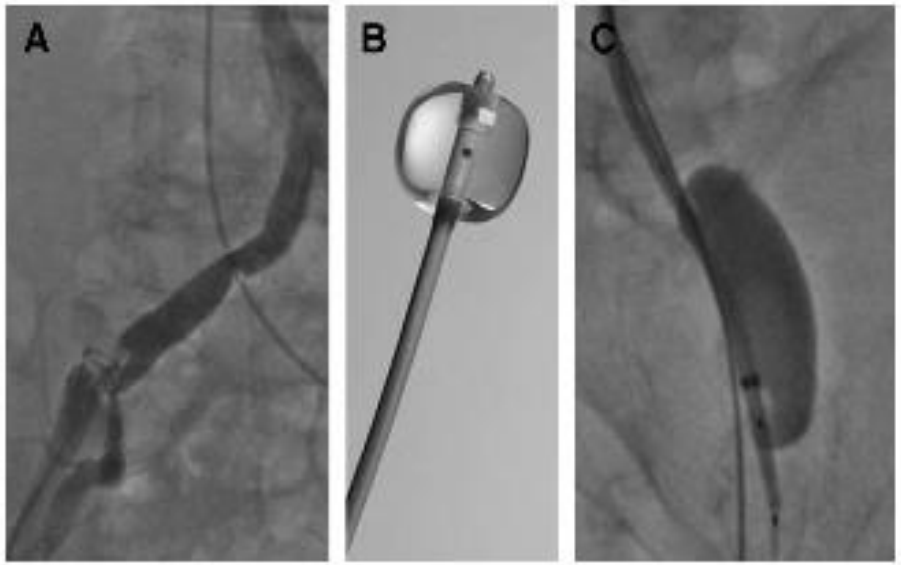
Adams DH, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Prosthesis *N Engl J Med.* 2014;8;370:1790-8.

To view the complete CoreValve Instructions for Use visit: *manuals.medtronic.com*

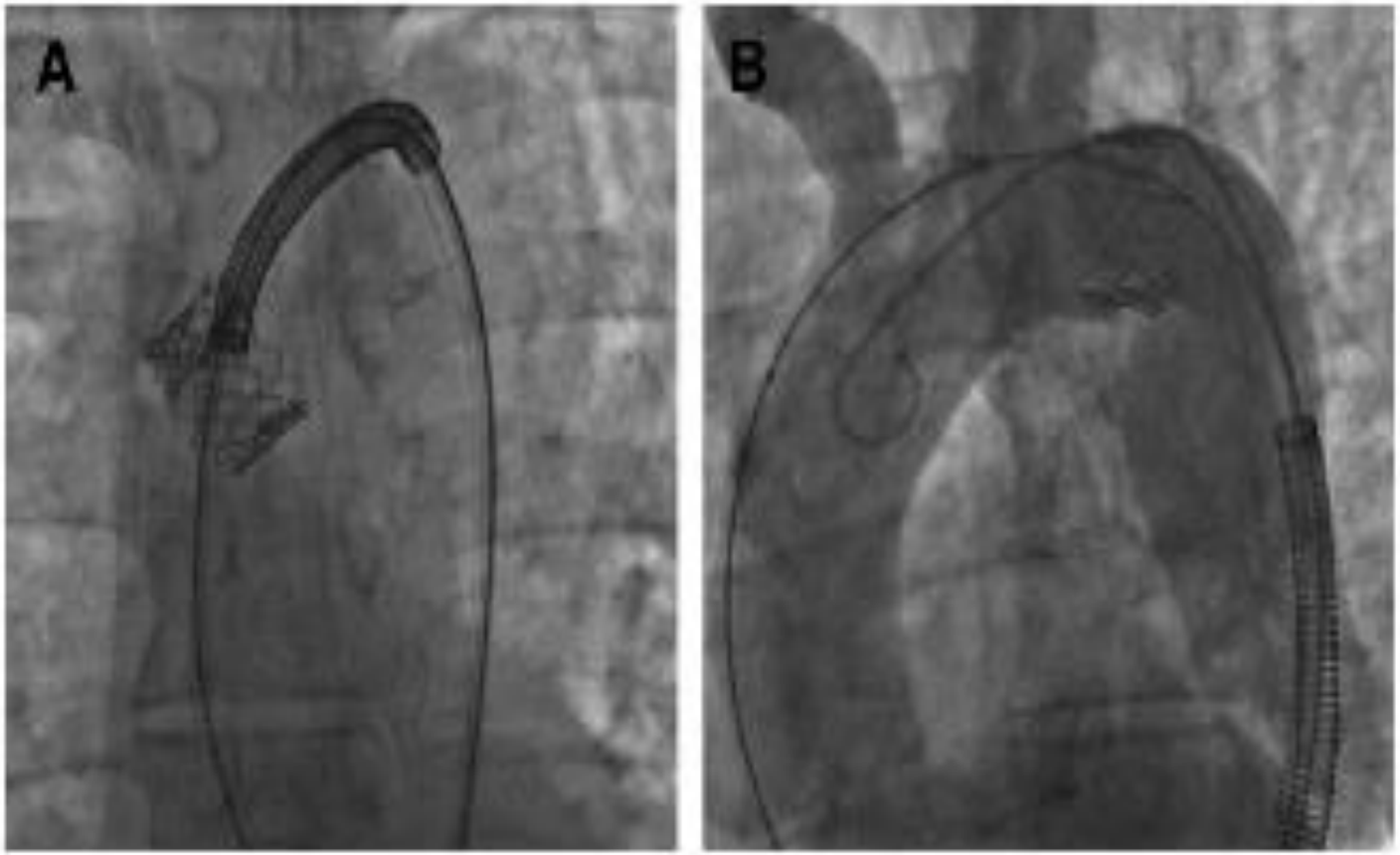
TAVR Mayhem

- “Iliac on a stick”



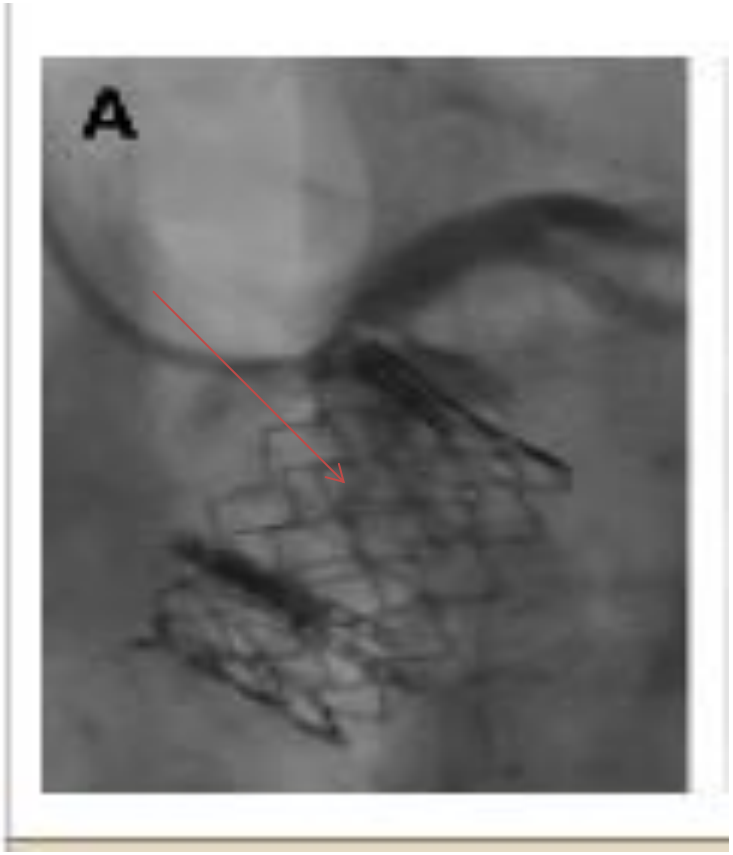


Valve Embolization

- 

Valve Embolization

Coronary occlusion



Heart Valve Team

Patient Evaluation at Heart Valve Clinic

Example of Testing Conducted at a Heart Valve Clinic

- CT Scan
- Echo
- Labs
- EKG
- Physical Exam
- STS Score
- Independent Living
- Gait Test/Grip Strength
- MMSE2
- NY Heart Failure Class
- Catheterization

Hybrid Operating Room

Growth of TAVR at ORMC

Fiscal Year	Number of TAVRs
2013	26
2014	31
2015	50
2016	73
2017	90 (*and counting!*)

Statistics (N = 270)

	ORMC (%)	National Average(%)
30 day/discharge mortality	1.85	7
One year mortality	12.6	23.7
Stroke	3	4.1
Permanent pacemaker	14	17
Vascular complications	4	8-15 (Meta)

Hospital Course

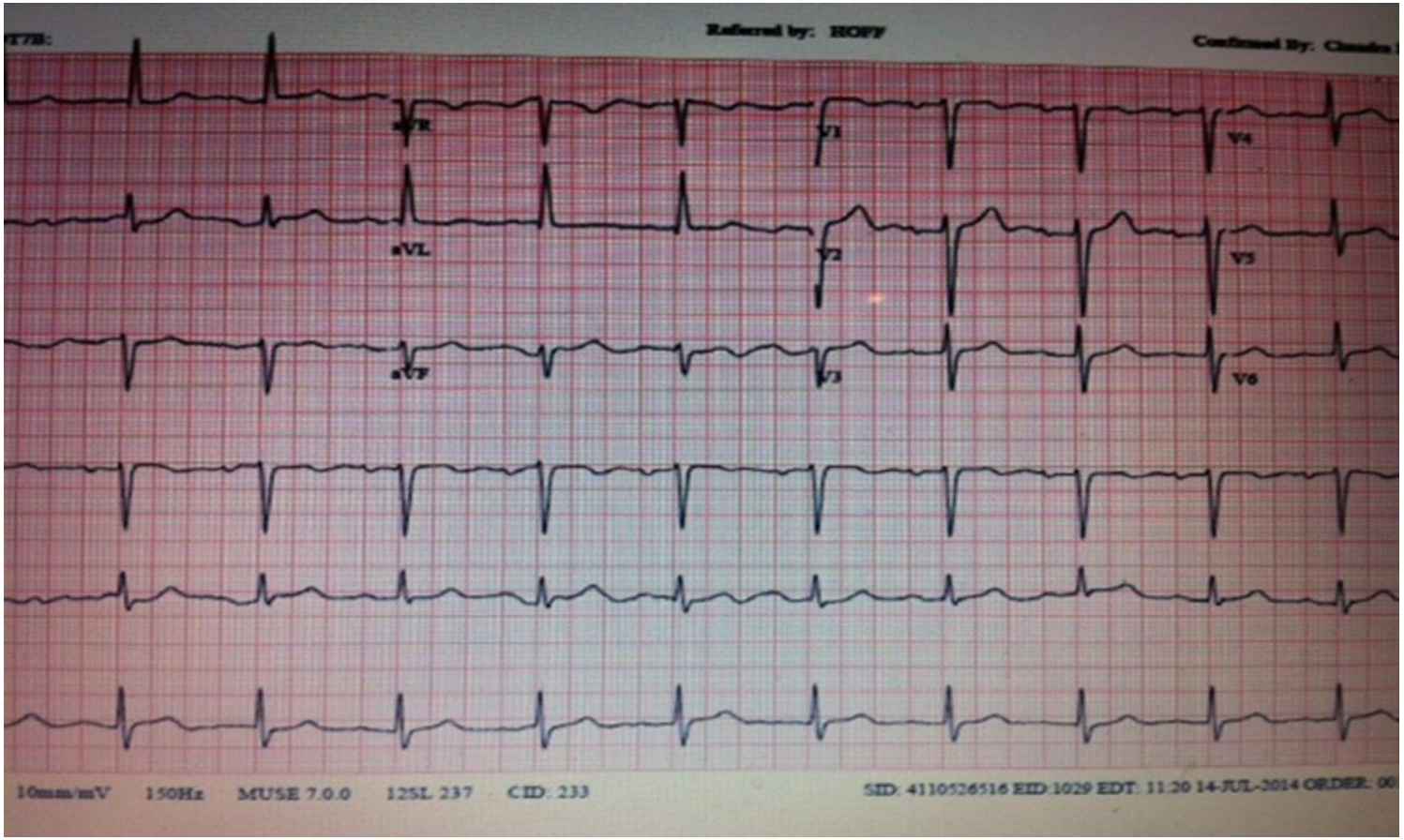
- Calculated STS score ~ 7.5
- Much debate on best approach

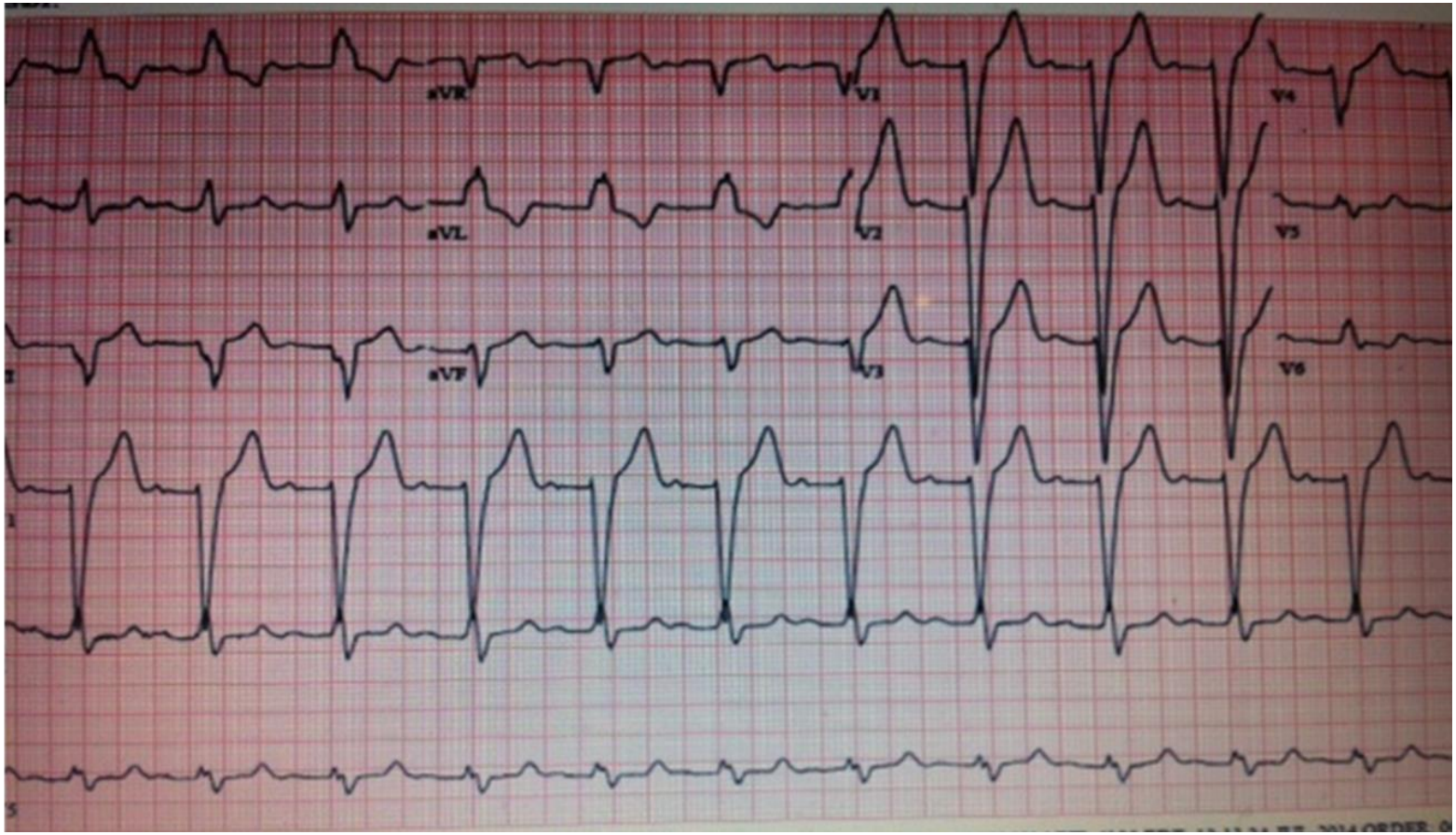
- Pt underwent successful TAVR with 29mm Corevalve from transfemoral approach.

Post-operative Course

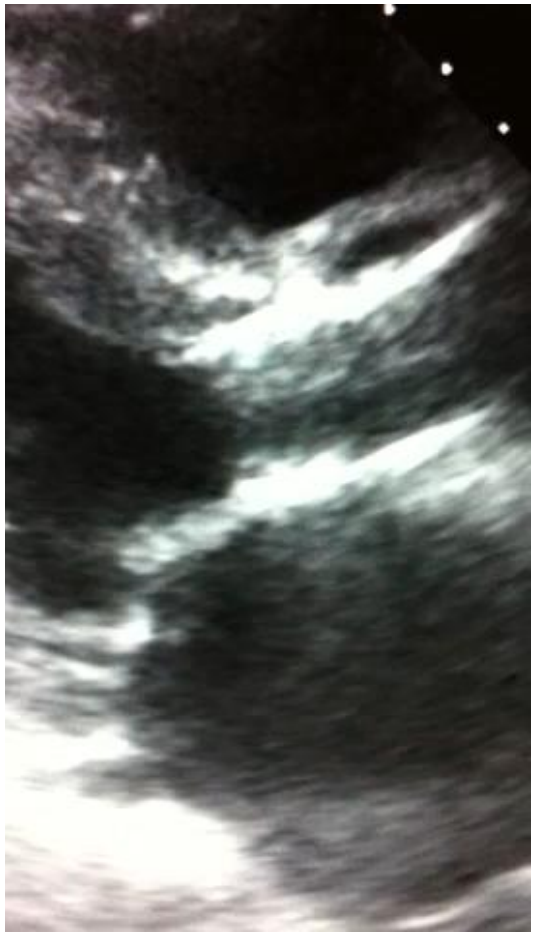
- Seen at 30-day follow-up. Echo gradients significantly improved. Mean gradient 7 mmHg. Trivial AI.

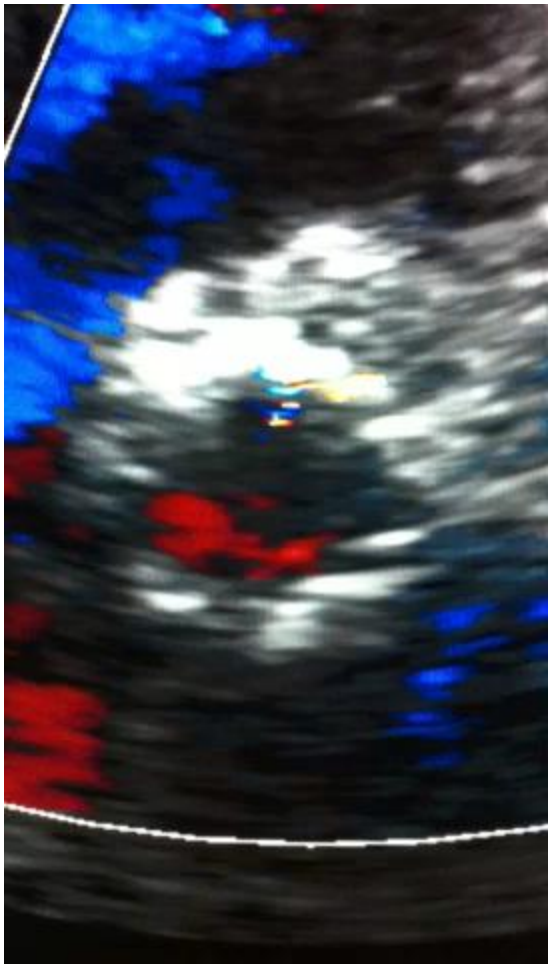
- Sxs of dyspnea on exertion significantly improved.

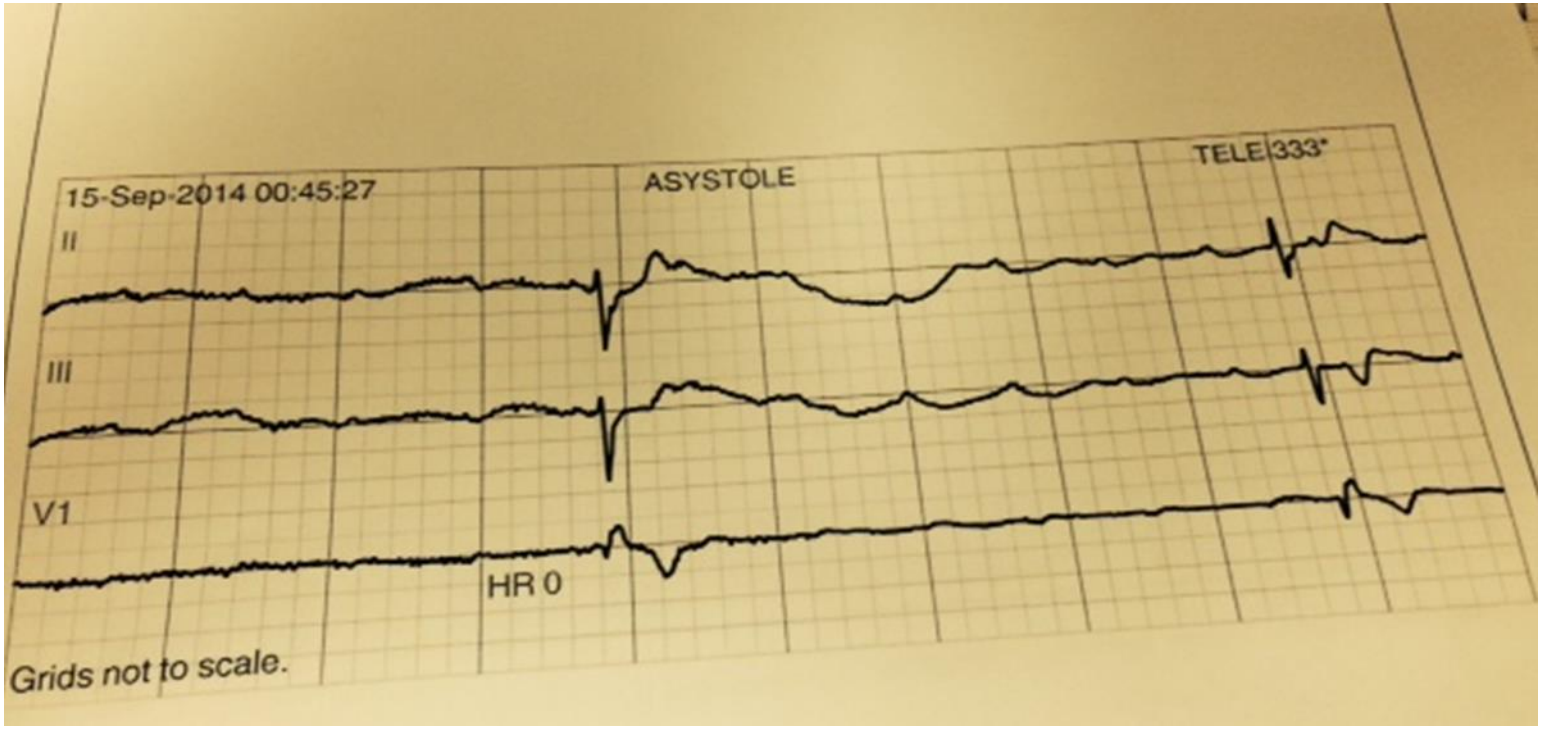

Referred by: HOFF
aVR
V1
V4
aVL
V2
V5
aVF
V3
V6
10mm/mV 150Hz MUSE 7.0.0 12SL 237 CID: 233
SID: 4110526516 EID:1029 EDT: 11:20 14-JUL-2014


aVR
V1
V4
aVL
V2
V5
aVF
V3
V6

Post-TAVR echo






15-Sep-2014 00:45:27
ASYSTOLE
TELE 333*
II
III
V1
HR 0
Grids not to scale.

Conclusions

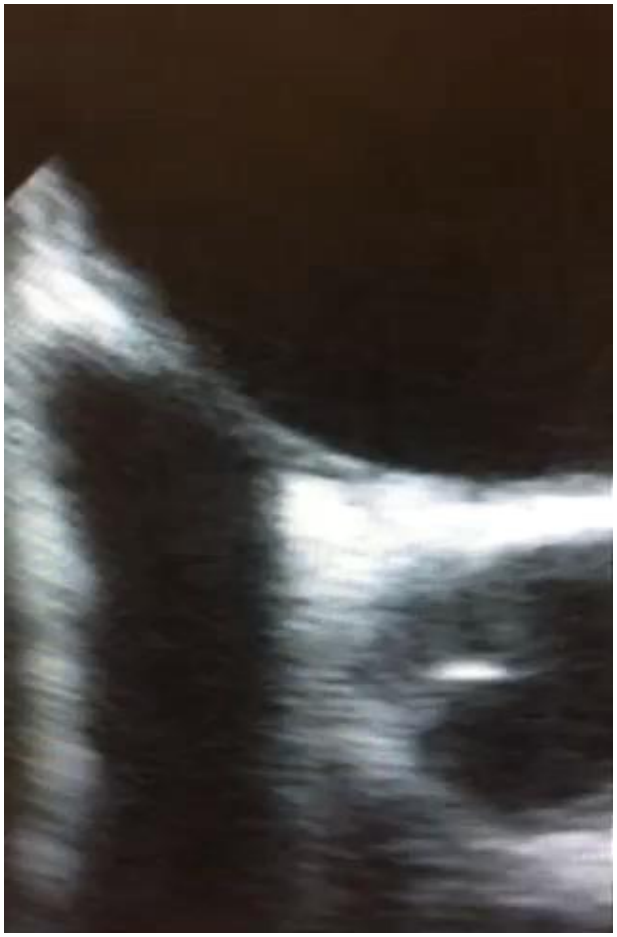
- TAVR has become the standard of care in patients with severe AS who are deemed inoperable or high risk for standard AVR
- TAVR is now approved for use in intermediate risk patients (STS score 3 -8).
- Successful implementation of TAVR requires a cohesive team of cardiologists and surgeons, state-of-the-art infrastructure and a supportive hospital administration.

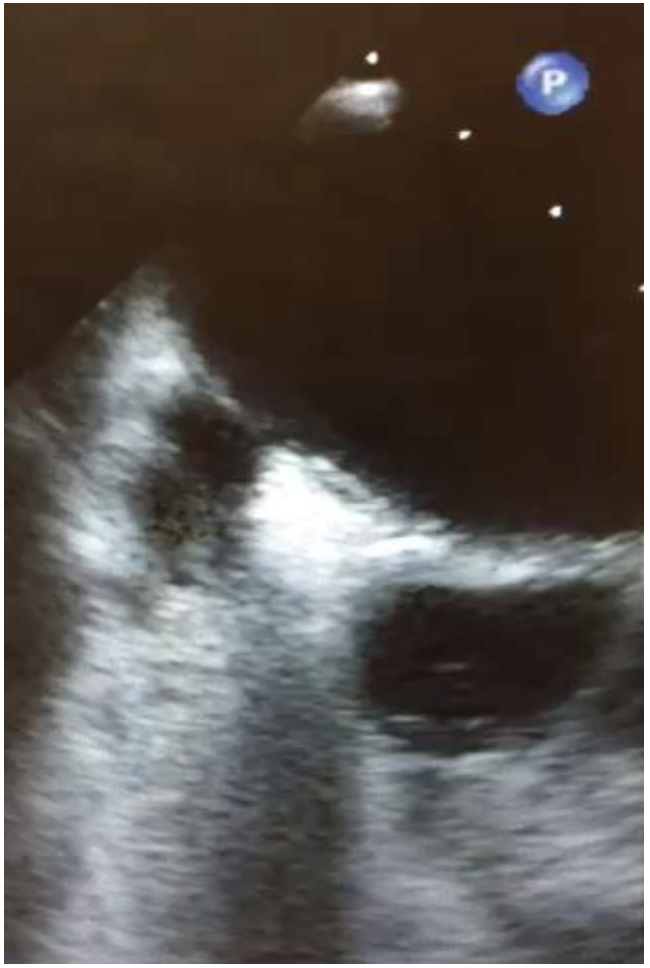
Case Presentation

- 49 year old male with no previous cardiac history
- Presented with left sided weakness and aphasia
- non-smoker; non-drinker
- On no medications
- CT brain – no hemorrhage
- CTA showed R MCA clot; TPA initiated with subsequent right M1 embolectomy by interventional Neurosurgery

- Symptoms completely resolved
- 2D echo (no bubble study) – unremarkable
- MRV pelvic veins – unremarkble
- MRA carotid/brain – unremarkable
- Hypercoag workup unremarkable
- TCD – Grade V shunting
- Pt started on empiric Eliquis
- Cardiology consult obtained for TEE:

TEE Findings:



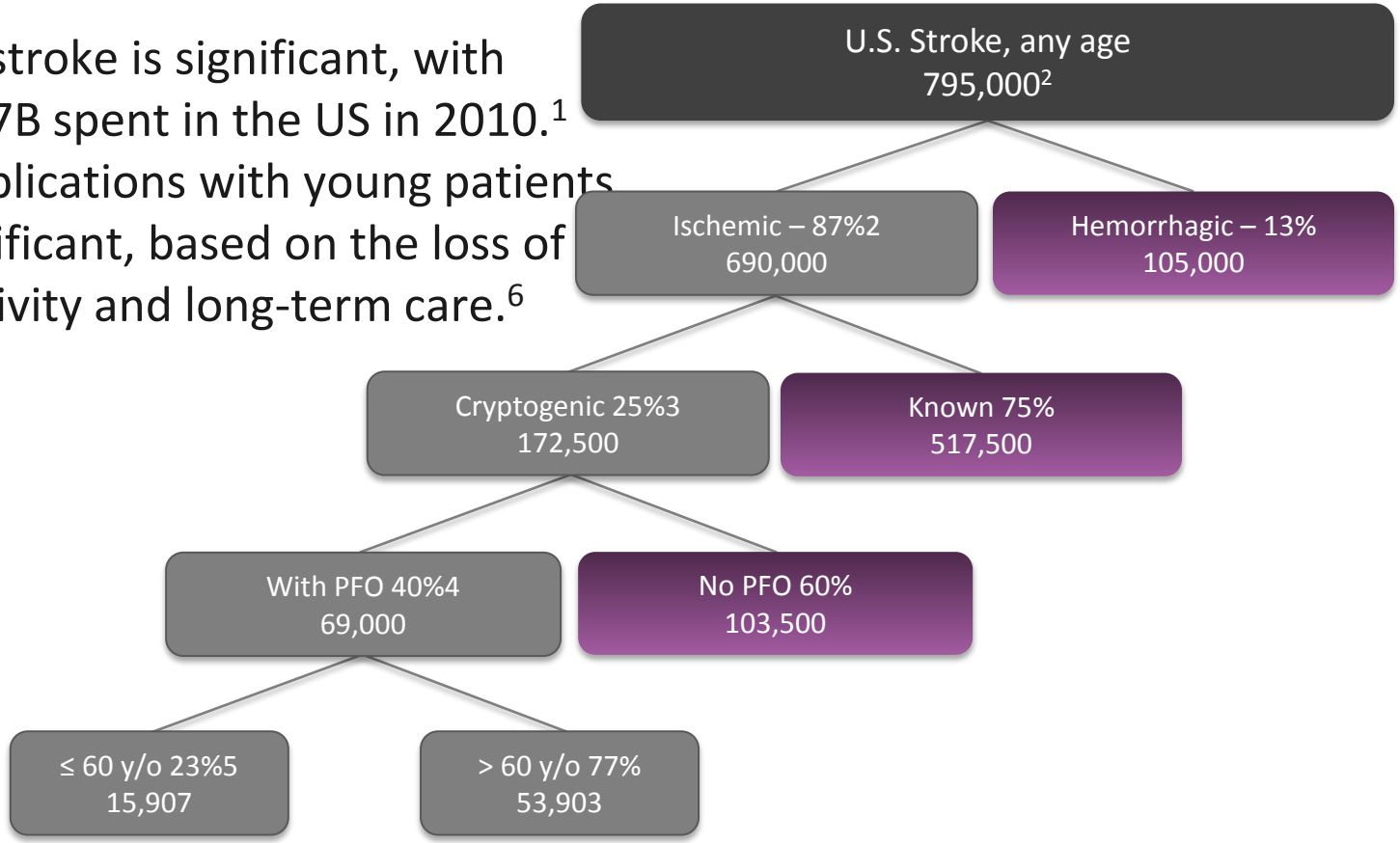


- Normal LV/RV size and function
- Atrial septal aneurysm with patent foramen ovale (PFO) with positive bubble study
- What is the data for PFO closure in cryptogenic stroke?

Is the PFO an innocent bystander?

U.S. PFO Incidence

- Cost of stroke is significant, with over $37B spent in the US in 2010.[1] Cost implications with young patients are significant, based on the loss of productivity and long-term care.[6]



1. Roger et al Circulation 2014:129(3): e28-e292
2. AHA Statistical Update: Heart Disease and Stroke Statistics
3. Hart, R. G., Diener, H. C., Coutts, S. B., Easton, J. D., Granger, C. B., O'Donnell, M. J., . . . Connolly SJ. (2014). Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurology, 13*, 429-438.
4. Handke, M., Harloff, A., Olschewski, M., Hetzel, A., & Geibel, A. (2007). Patent foramen ovale and cryptogenic stroke in older patients. *The New England Journal of Medicine, 357*(22), 2262-2268.
5. Fonarow, G. C., Reeves, M. J., Zhao, X., Olson, D. M., Smith, E. E., Saver, J. L., & Schwamm, L. H. (2010). Age-related differences in characteristics, performance measures, treatment trends, and outcomes in patients with ischemic stroke. *Circulation, 121*, 879-891.
6. Mozzafarian, D., et al. (2015). Heart disease and stroke statistics-2015 update: A report from the American Heart Association. Circulation, 131(4), e180, e189.

RESPECT Trial

- Randomized, event-driven, open-label trial with blinded endpoint adjudication
- Patients randomized 1:1 to AMPLATZER™ PFO Occluder (device) vs. guideline-directed medical management (MM)
- 980 subjects enrolled from 2003 to 2011
- 69 sites in U.S. and Canada

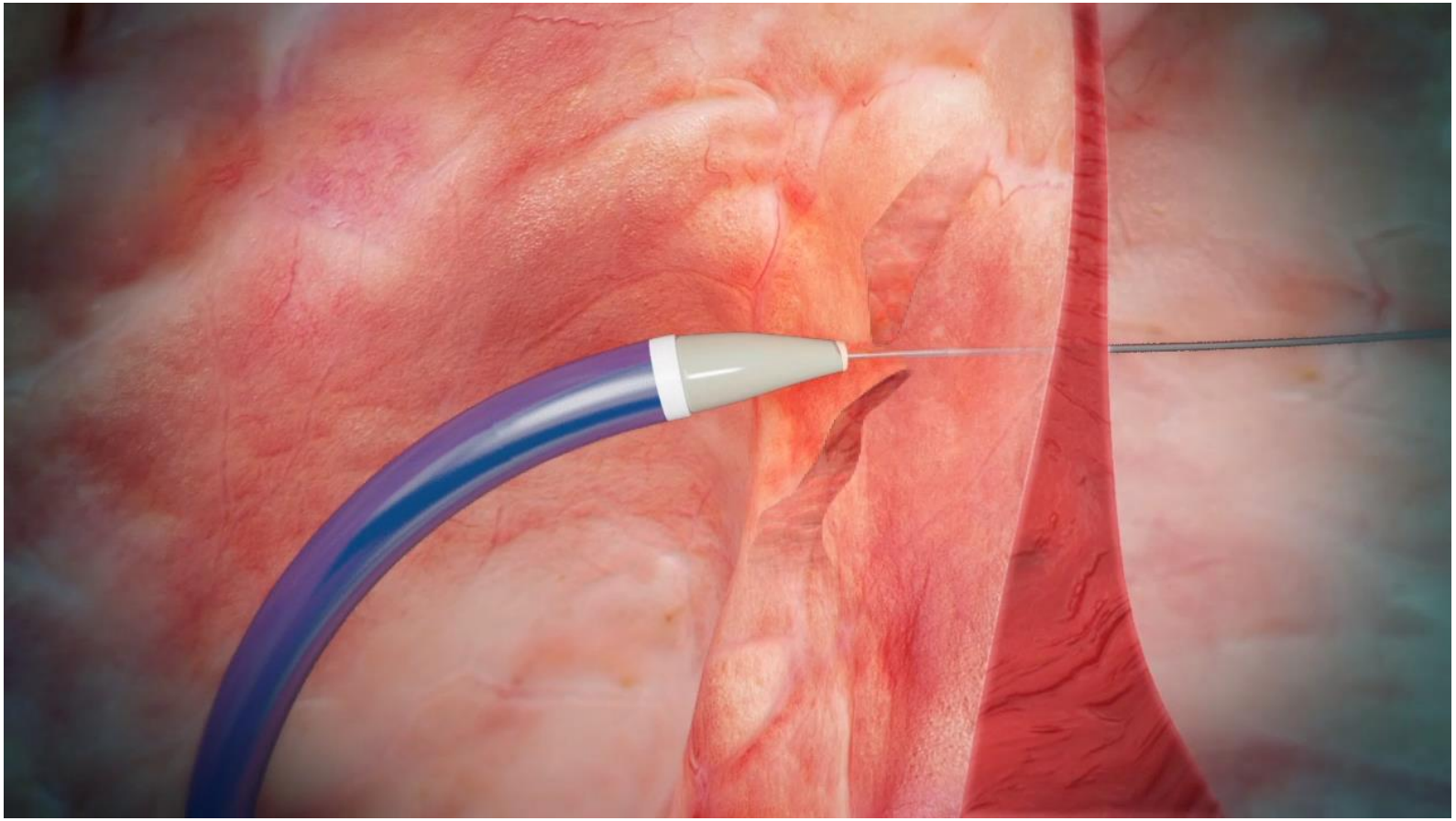
Amplatzer PFO occluder

Technology

- **Self-expandable double disc device** lined with **thin polyester fabric** and linked together by a short connecting **waist**
- **Nitinol** wire mesh
- **Recapturable, repositionable**
- **Self-centering**
- Distal and proximal **radiopaque marker** bands
- **MR conditional**
- **End screw** to facilitate optimal handling

- Current status:
  - Initial **CE-Mark in 1998**; currently available in > 80 countries worldwide
  - **FDA Approval** October 2016

Deployment



Enrollment Criteria

Key Inclusion Criteria

- **Cryptogenic stroke within last 9 months**
- **TEE-confirmed PFO**
- **18-60 years**
  - Patients > 60 at higher risk of recurrent stroke from non-PFO mechanisms

Key Exclusion Criteria

- **Stroke due to identified cause such as:**
  - Large vessel atherosclerosis (e.g., carotid stenosis)
  - Atrial fibrillation
  - Intrinsic small vessel disease (lacunar infarcts)
  - 11 other specific etiologies
- **Inability to discontinue anticoagulation**

Baseline Characteristics Balanced Between Groups

Characteristic	AMPLATZER™ PFO Occluder (N=499)	Medical Management (N=481)
Age (yr), mean ± SD	48 ± 10	46 ± 10
Male	54%	56%
Hypercholesterolemia	39%	41%
Family h/o CAD	33%	33%
Hypertension	32%	32%
COPD	0.8%	1.5%
Congestive heart failure	0.6%	0%
History of DVT	4.0%	3.1%
Atrial septal aneurysm	36%	35%
Substantial shunt	50%	48%

Procedural Results and Follow-up

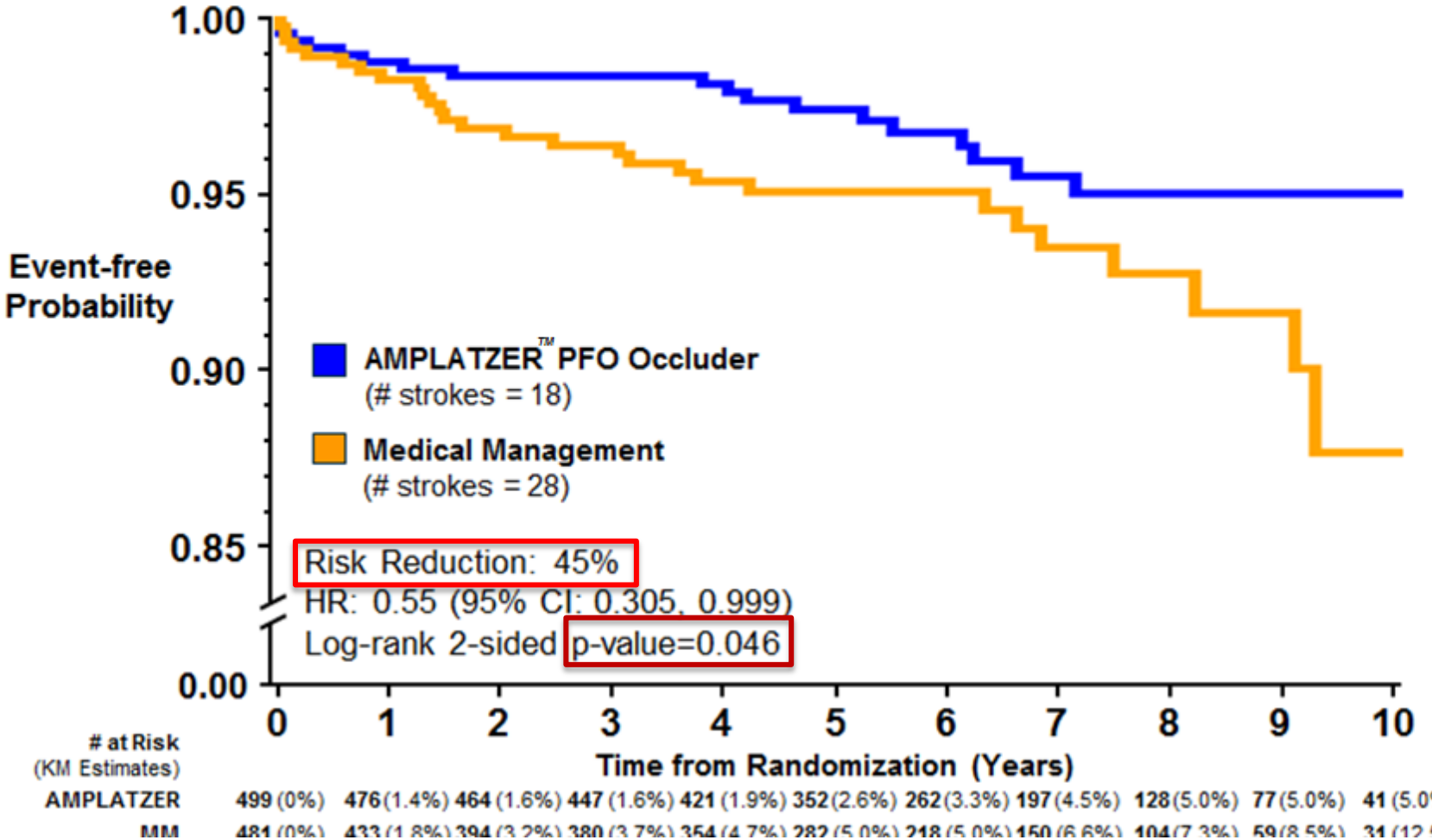
- **Technical Success*** **99.1%**
- **Procedural Success**** **96.1%**
- **Mean Follow-up:** **5.9 years (0-12 years)**
  - Device
    - Mean 6.3 years; Total 3141 patient-years
  - Medical Management
    - Mean 5.5 years; Total 2669 patient-years

*Delivery and release of the device

**Implantation without in-hospital SAE

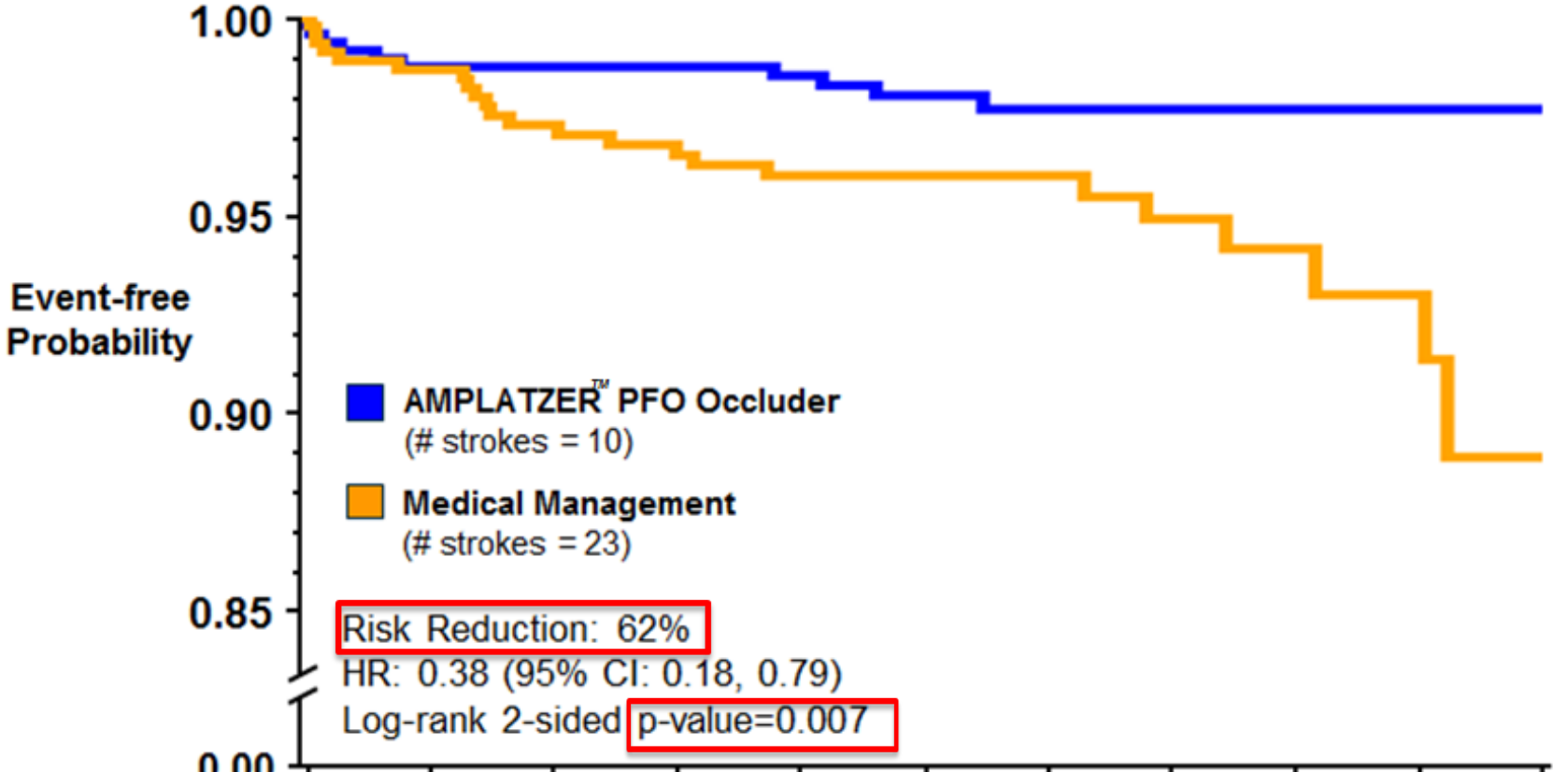
RESPECT Final Results

Freedom from Recurrent Ischemic Stroke (Intention to Treat)



RESPECT Final Results

Freedom from Recurrent Ischemic Stroke of Unknown Mechanism (Intention to Treat)



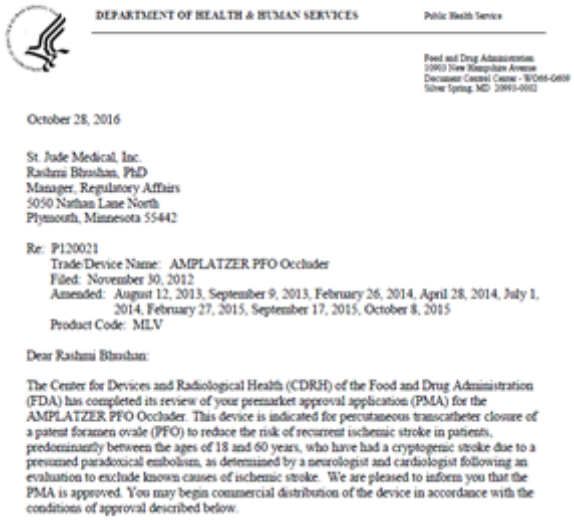
# at Risk (KM Estimates)										
AMPLATZER	499 (0%)	476 (1.2%)	464 (1.2%)	447 (1.2%)	421 (1.5%)	352 (2.0%)	262 (2.3%)	197 (2.3%)	128 (2.3%)	77 (2.3%)	41 (2.3%)
MM	481 (0%)	433 (1.3%)	394 (2.7%)	380 (3.5%)	354 (4.0%)	282 (4.0%)	218 (4.0%)	150 (5.1%)	104 (5.8%)	59 (7.0%)	31 (11.1%)

DSMB Adjudicated Procedure or Device Related SAEs

- No intra-procedural strokes
- No device embolization
- No device thrombosis
- No device erosion
- Major vascular complications (0.9%) and device explants (0.4%)

FDA Approval 10/28/16

The AMPLATZER™ PFO Occluder is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.



DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

October 28, 2016

St. Jude Medical, Inc.
Rashmi Bhushan, PhD
Manager, Regulatory Affairs
5050 Nathan Lane North
Plymouth, Minnesota 55442

Re: P120021
Trade/Device Name: AMPLATZER PFO Occluder
Filed: November 30, 2012
Amended: August 12, 2013, September 9, 2013, February 26, 2014, April 28, 2014, July 1, 2014, February 27, 2015, September 17, 2015, October 8, 2015
Product Code: MLV

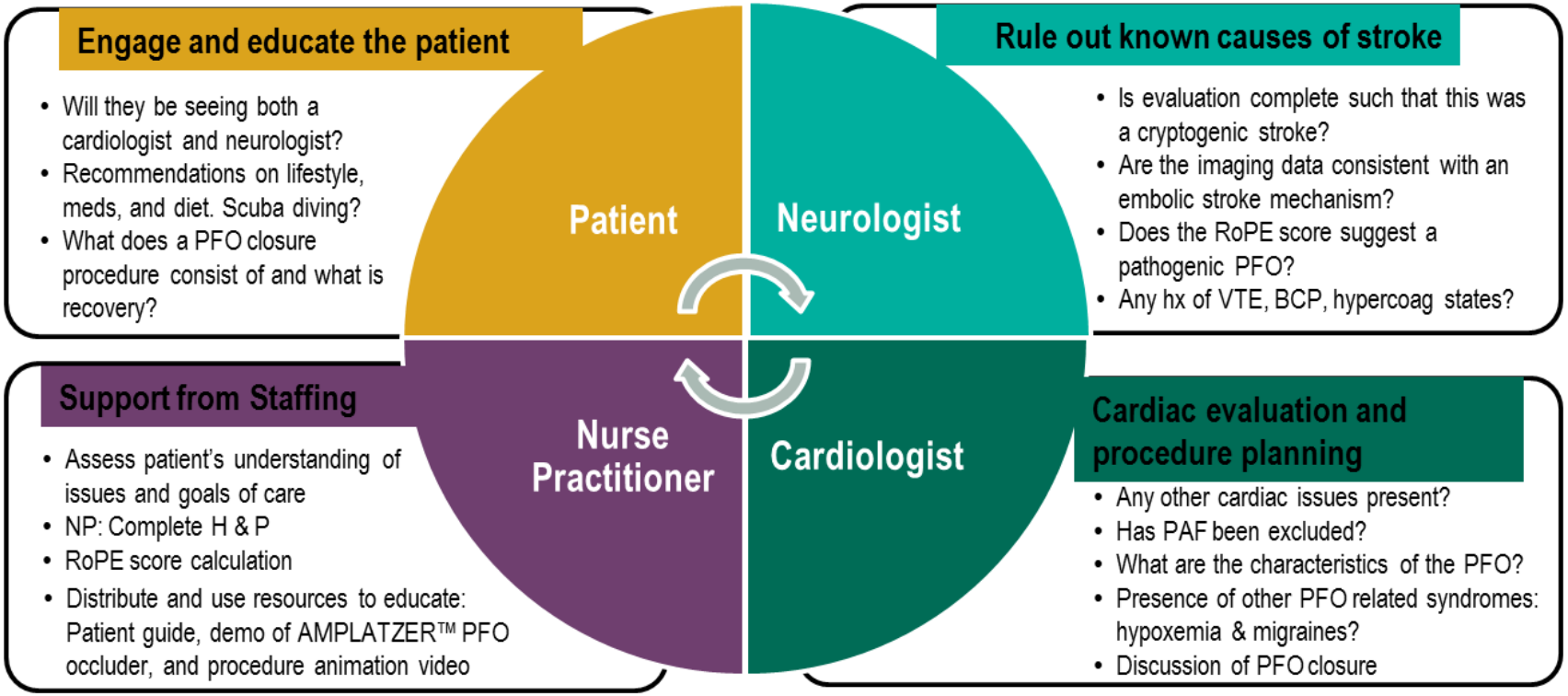
Dear Rashmi Bhushan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the AMPLATZER PFO Occluder. This device is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

Best Practice: A PFO Clinic*
Fulfilling the goal of shared decision-making

Heart-Brain Team

- **Prior to seeing Patient:** Review brain imaging and TTE/TEE to share key findings with each other
- **Discussion with Patient and Family:** Provide a joint consultation as a multidisciplinary team with both clinicians providing their assessment, recommendations, and answering questions and concerns



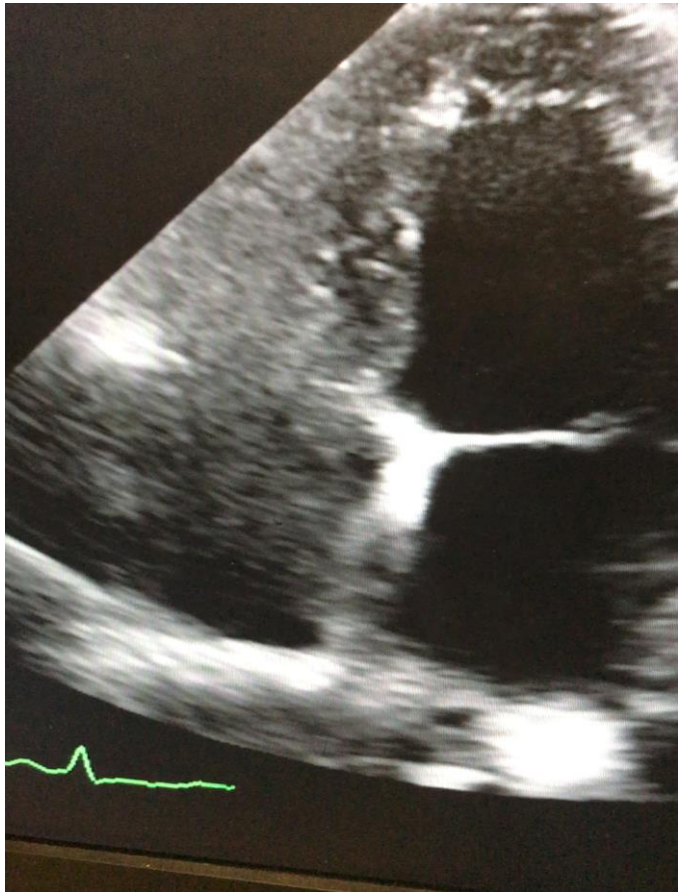
** Compliments of John Carroll MD, University of Colorado Hospital*

RoPE Score

(Risk of paraxodical embolism) Score

TABLE 1. RoPE SCORE CALCULATOR		
Characteristic	**Points**	**Score**
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Age (y)		
18–29	5	
30–39	4	
40–49	3	
50–59	2	
60–69	1	
≥ 70	0	
Total score (sum of individual points)		
Maximum score (a patient < 30 y without vascular risk factors, no history of stroke or TIA, and cortical infarct)		10
Minimum score (a patient ≥ 70 y with vascular risk factors, prior stroke, and no cortical infarct)		0

Post Closure Echo



- Pt treated with ASA and Plavix post-procedure. Eliquis discontinued.

- PFO closure is now FDA approved for the prevention of recurrent stroke in patients with cryptogenic stroke from presumed paradoxical embolism.

- Careful decision making by the heart brain team is necessary to achieve the most optimal results

Thank you!