Transcatheter Aortic Valve Replacement

June 2, 2015
6:00-7:00
UVM Community Medical School Series

Harold Dauerman, MD
Professor of Medicine and Surgery
Director, Cardiovascular Services
University of Vermont Medical Center

Disclosures

- Research grants from Medtronic (Corevalve Trials and Registries), Abbott Vascular
- Consulting for Medtronic, Edwards, Boston Scientific

- Contact Information:

harold.dauerman@uvmhealth.org

802-847-3602

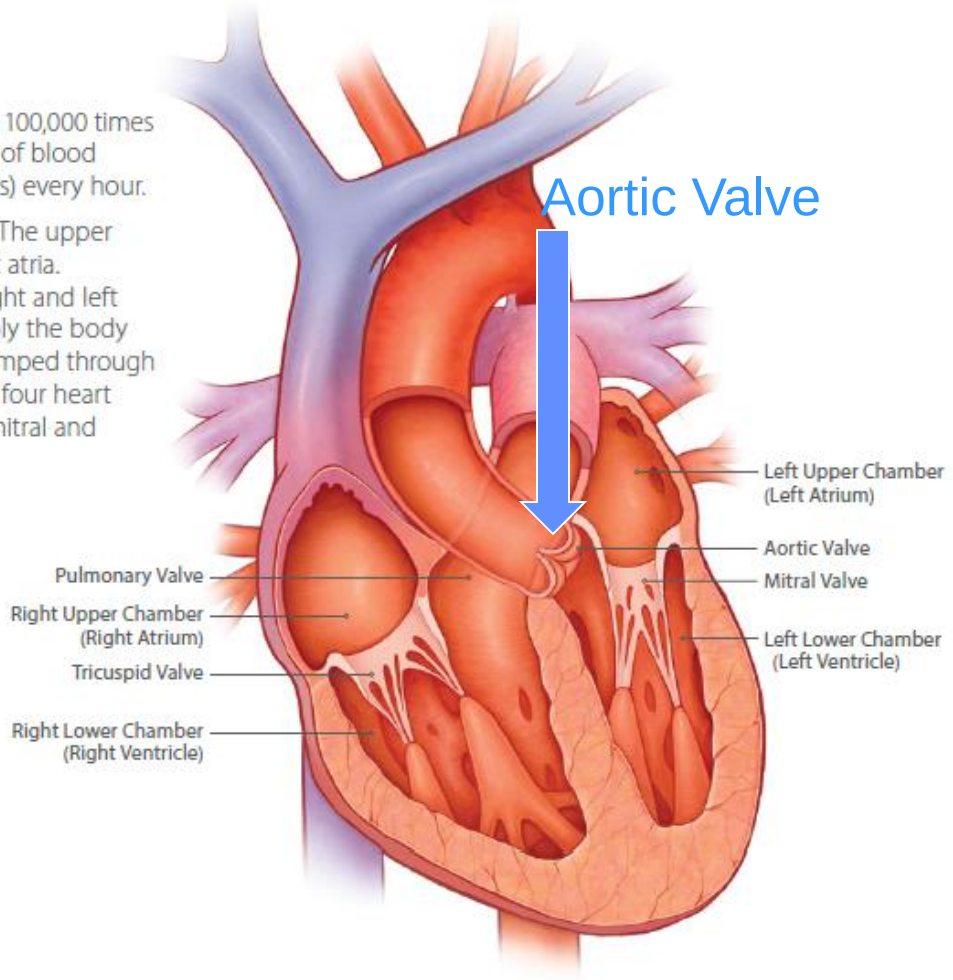
Aortic Stenosis is a Disease of A Heart Valve

About the Heart

How the Heart Works

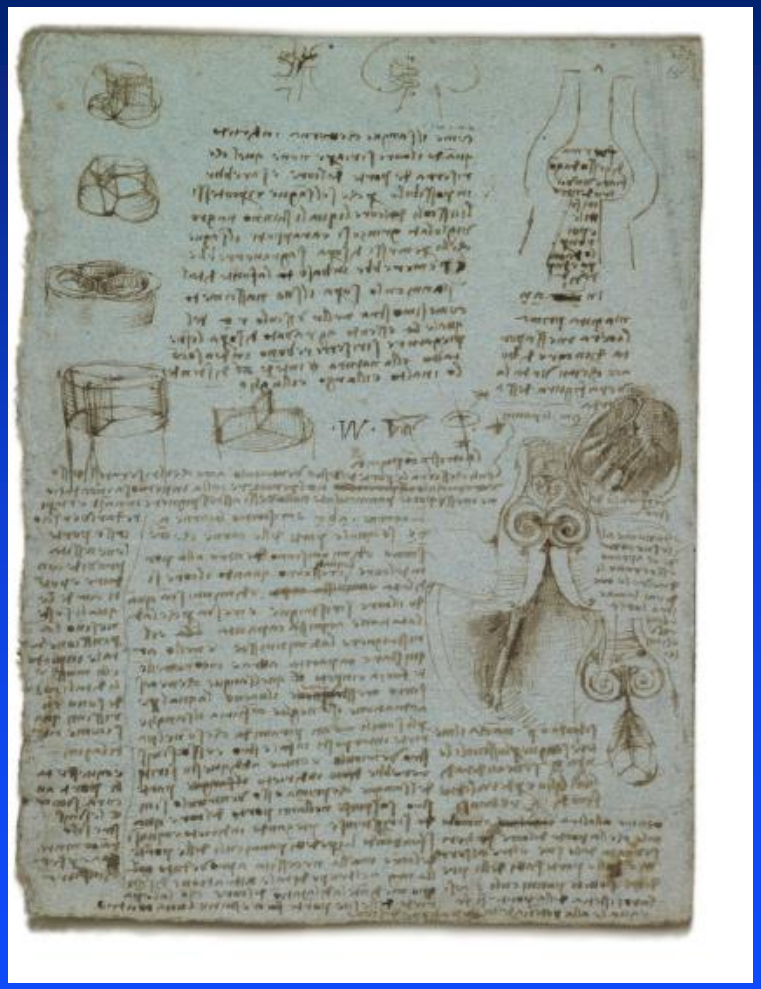
A healthy heart beats approximately 100,000 times a day and pumps about five quarts of blood each minute, or 75 gallons (284 liters) every hour.

A normal heart has four chambers. The upper two chambers are the right and left atria. The lower two chambers are the right and left ventricles. The heart's job is to supply the body with oxygen-rich blood. Blood is pumped through the four chambers with the help of four heart valves—the tricuspid, pulmonary, mitral and aortic valves.

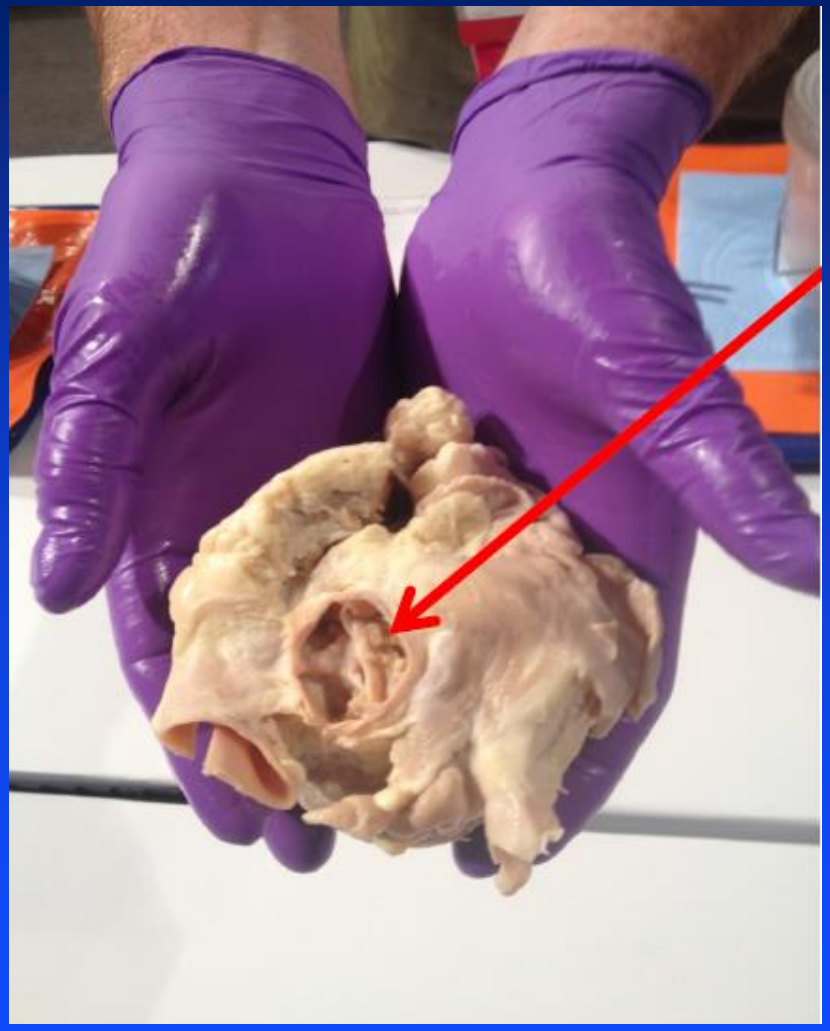


1

Aortic Stenosis is not a New Disease: Leonardo Da Vinci



Aortic Stenosis is a Blockage of A Heart Valve which Limits Blood Flow to Your Body



Symptoms of Severe AS

Signs and symptoms of severe AS can include:

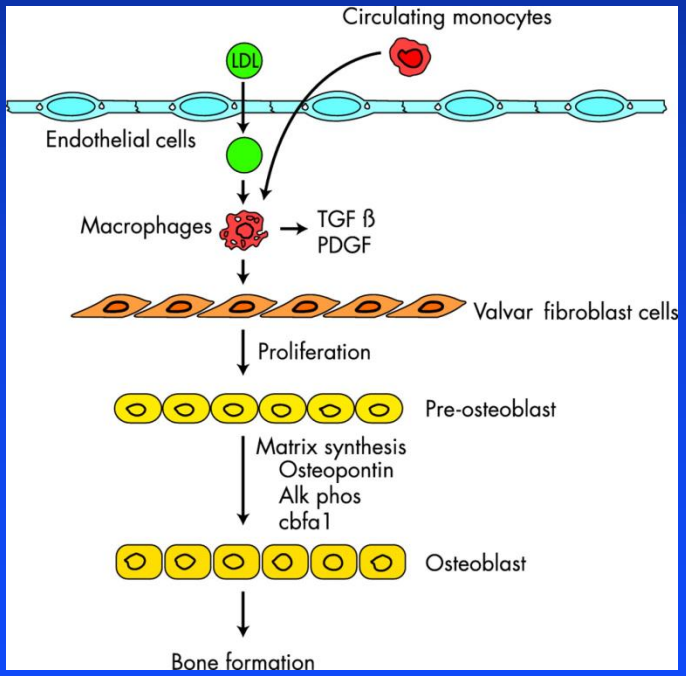
- Chest pain or tightness
- Feeling faint or fainting with activity
- Dizziness
- Fatigue
- Shortness of breath
- Irregular heart beat (palpitations)
- Unusual sound heard during a heartbeat (murmur)

Normal Valve

Stenotic Valve

Calcific Aortic Stenosis is a Disease of the Elderly

- 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



[1]Otto CM, Lind BK, et al. Circulation 1994; 90: 844-53.

[2]Otto CM, Lind BK, et al. New Eng J Med 1999; 341: 142-147.

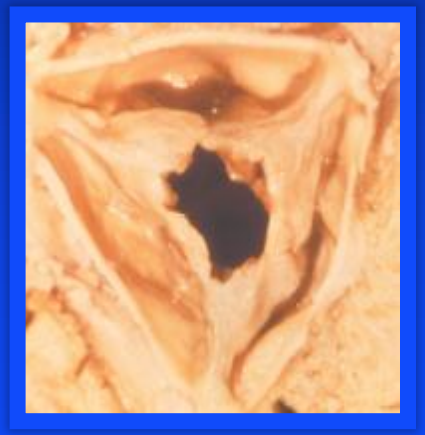
What Causes Aortic Stenosis in Adults

Less Common

More Common

Congenital Abnormality

Rheumatic Fever



Age-Related Calcific Aortic Stenosis

Images courtesy of John Webb, MD at St. Paul's Hospital and Renu Virmani, MD at the CVPath Institute

Aortic Stenosis Prevalence

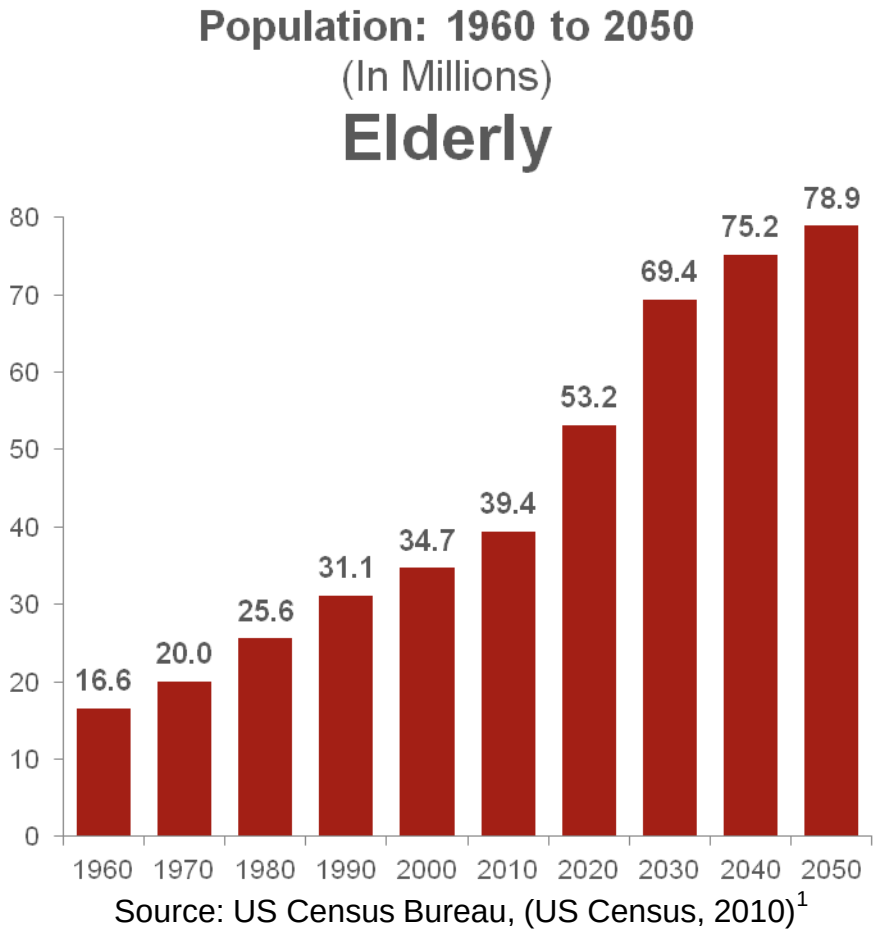
- Aortic Stenosis (AS) is the most prevalent native valve disease[1]
- Prevalence:[2]
  - 2% of people over 65
  - 3% of people over 75
  - 4% of people over 85
- Over 100,000 people in the U.S. are diagnosed with severe aortic stenosis each year[3]
- Prevalence of AS and co-morbidities that increase the risk of surgical valve replacement, increase with age[1]

1. lung B, *Eur Heart J.* 2003;24:1231-1243.
2. Stewart BF. J Am Coll Cardiol. 1997;29:630-634.
3. Medtronic Data on File.

Population at Risk for Aortic Stenosis is Increasing

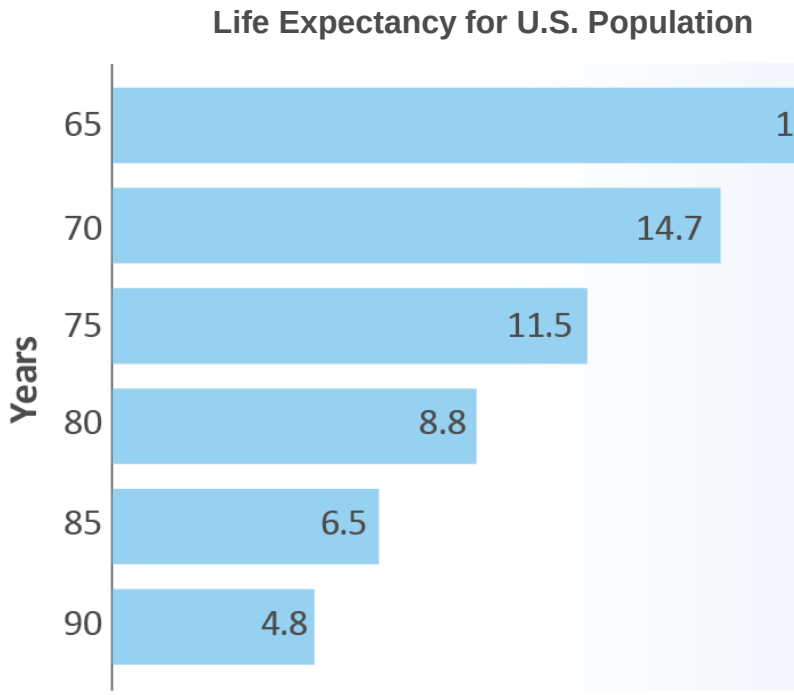
Over 40 Million People in the US Over the Age of 65[1]

- Aortic stenosis is estimated to be prevalent in **up to 7% of the population over the age of 65**[2]
- Between 1990 and 2020, the population from 65 – 74 years will increase 74%
- 80% of adults with symptomatic aortic stenosis are male[3]



Source: US Census Bureau, (US Census, 2010)[1]

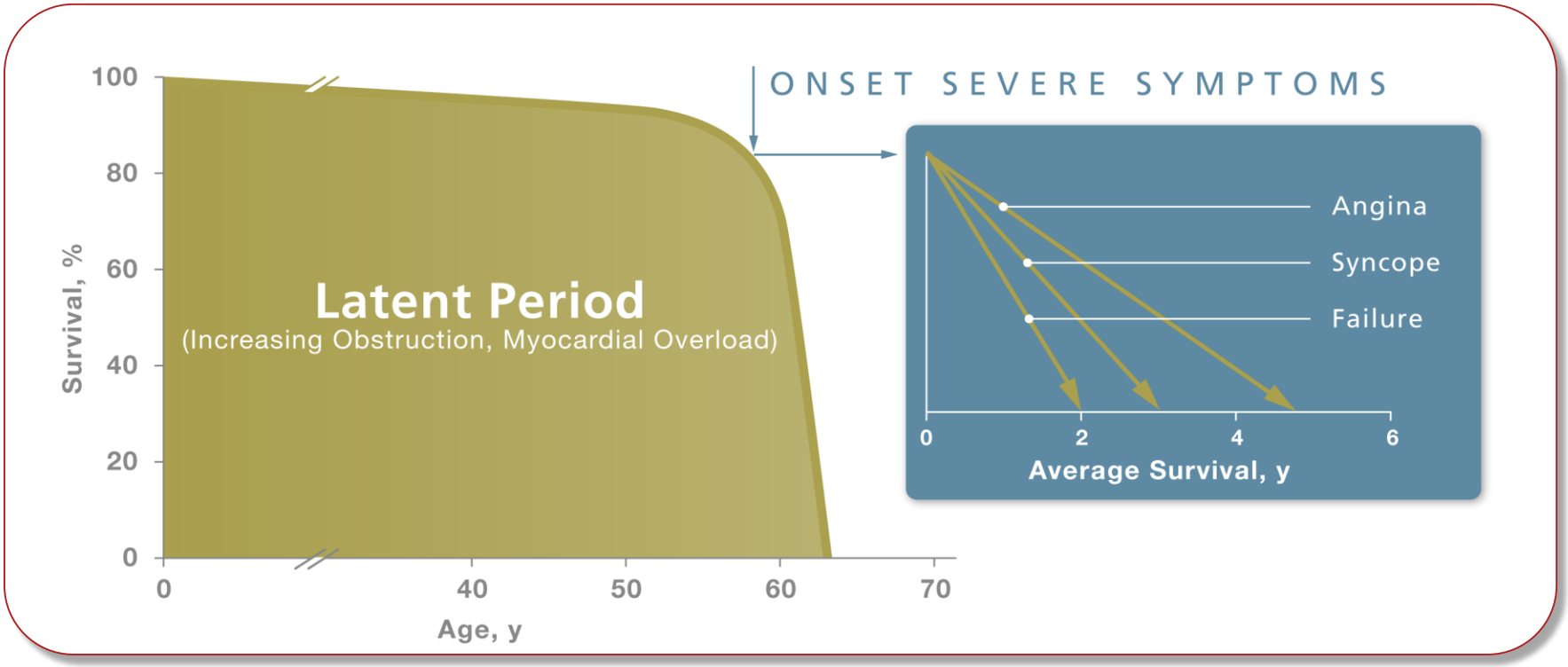
Intervention and Life Expectancy of the Elderly



- Those **expecting to live for more than 1 year** are likely to derive significant benefit from AVR

Hornick, et al. *Clin Geriatr Med.* 2006;22:499-513.

Severe Aortic Stenosis Is Life Threatening and Progresses Rapidly



- After the onset of symptoms, patients with **severe aortic stenosis** have a **survival rate as low as 50% at 2 years and 20% at 5 years** without aortic valve replacement[2]

- The PARTNER Trial demonstrated that **50% of inoperable patients died within 1 year** without a valve replacement

Symptoms of Aortic Stenosis

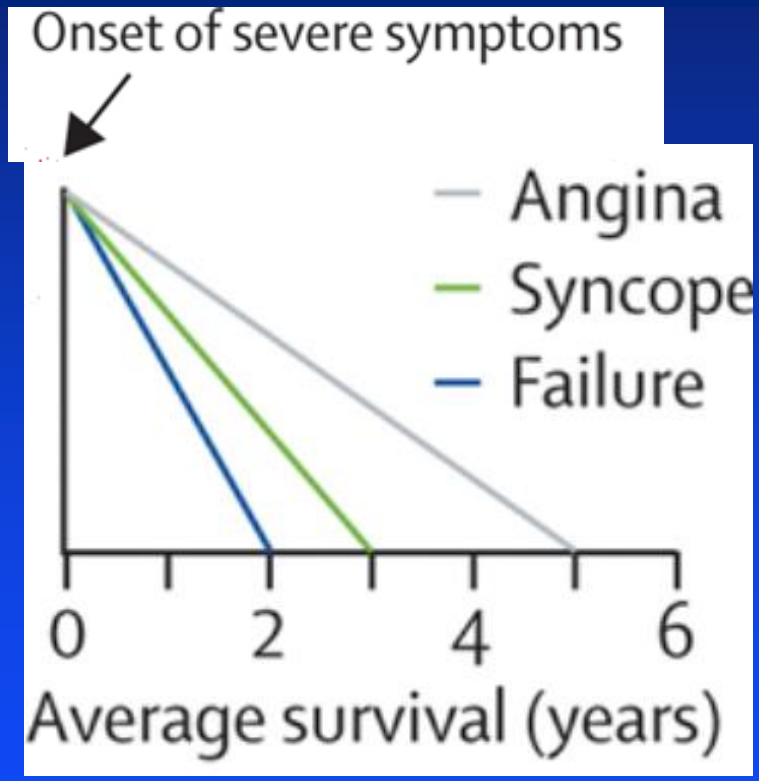
- **Shortness of breath**
- **Angina**
- **Fatigue**
- **Syncope or presyncope**
- Other
  - Rapid or irregular heartbeat
  - Palpitations

Sandy
Actual TAVR Patient
Pre-Procedure
Inoperable

The **symptoms of aortic disease are commonly misunderstood by patients as 'normal' signs of aging**. Many patients initially appear asymptomatic, but **on closer examination up to 37% exhibit symptoms**.

Aortic Stenosis:
Symptoms May Be Subtle in the Elderly

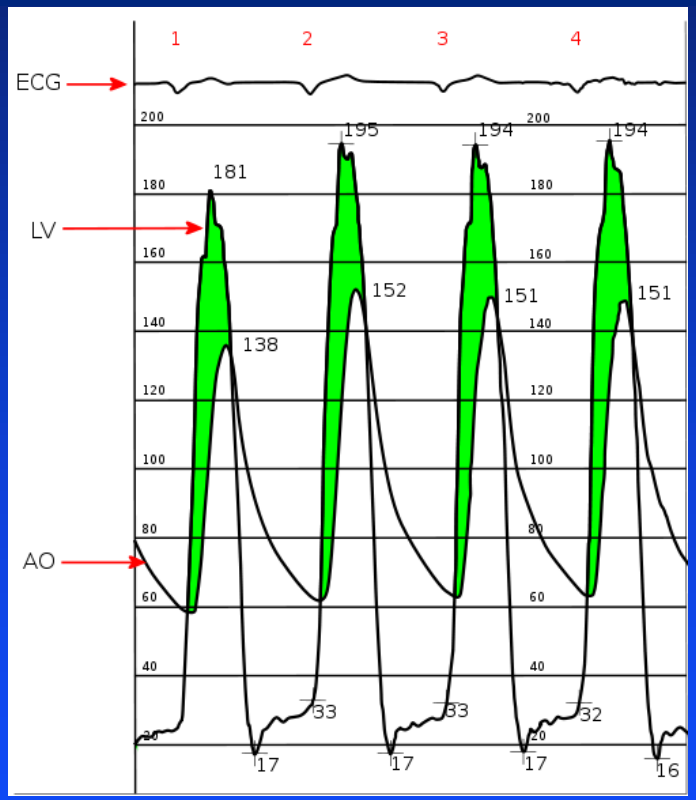
- Angina, Shortness of Breath and Syncope
- Onset of dyspnea and other heart failure symptoms foretell the worst outlook for aortic stenosis patients[1]



[1]Carabello BA, Paulus WJ. Lancet 2009; 373: 956-66.

Ross J, Braunwald E. Circulation 1968; 38: 61-67.

Aortic Stenosis Diagnosis is Not Difficult: Starts with a Heart Murmur on Exam



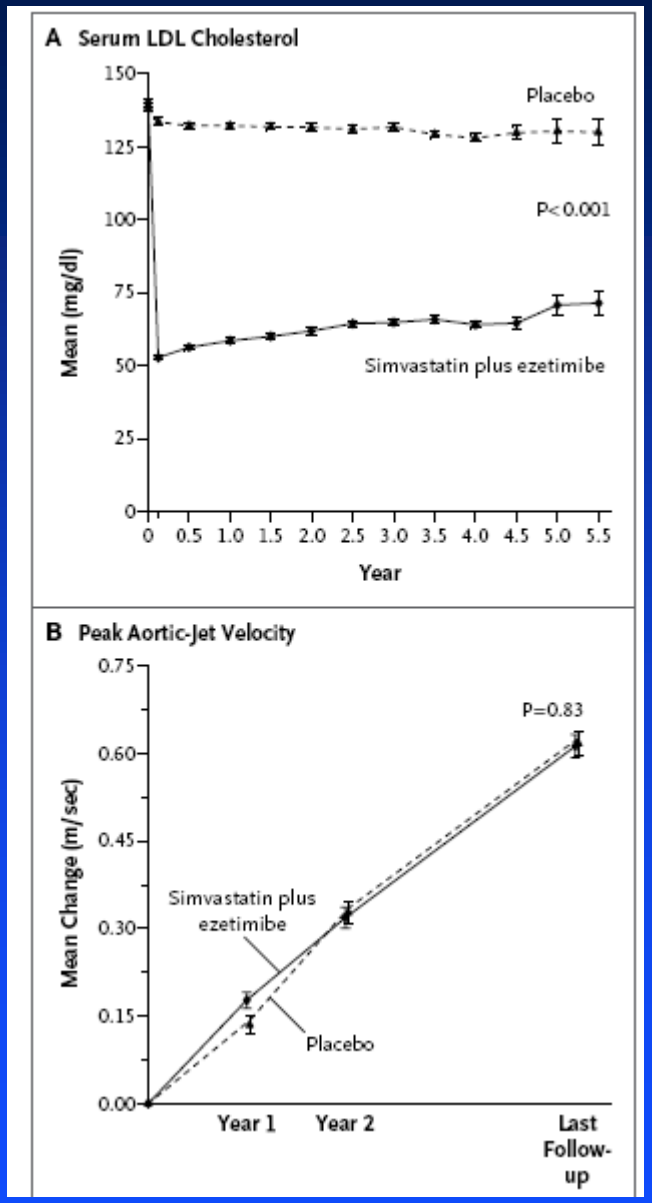
[1]Gorlin R, Gorlin SG. Am Heart J 1951; 41: 1-29.

Aortic Stenosis: Prevention is Unlikely

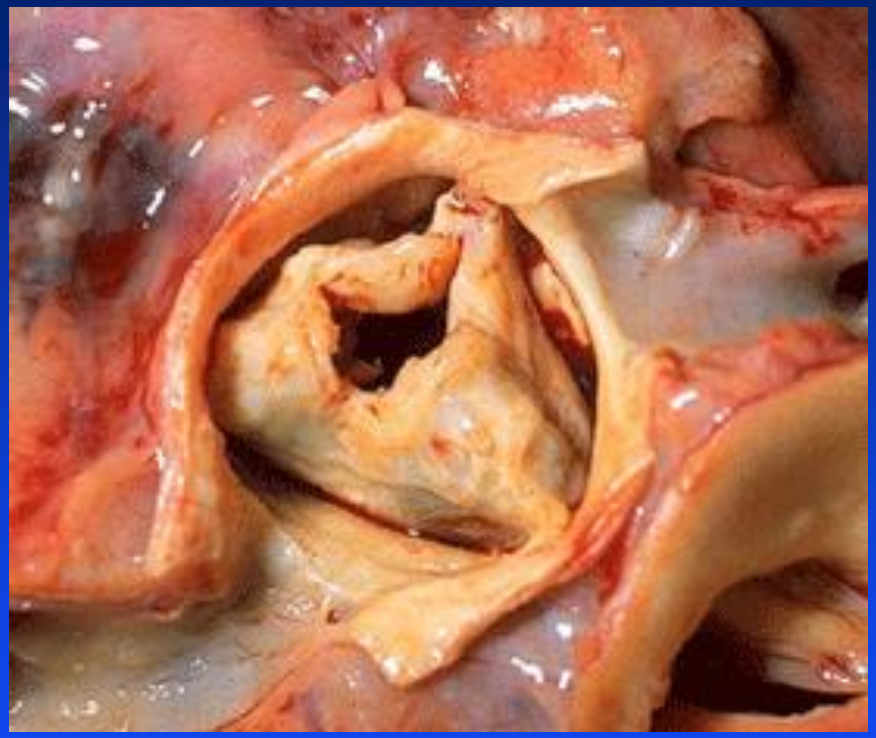
Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis

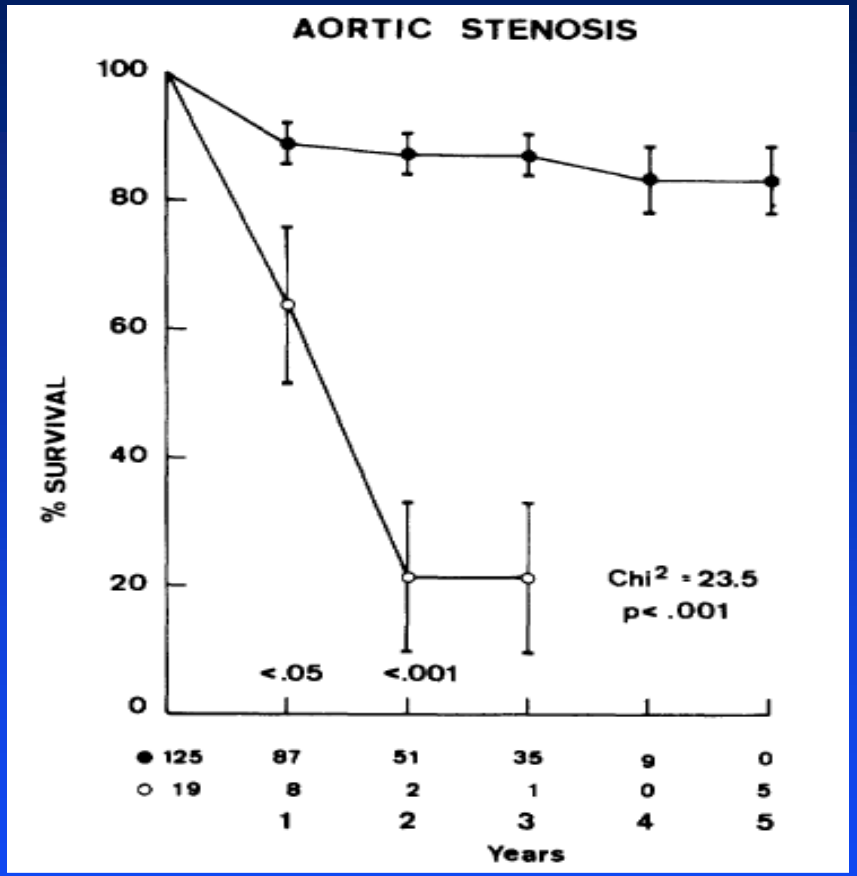
Anne B. Rossebø, M.D., Terje R. Pedersen, M.D., Ph.D., Kurt Boman, M.D., Ph.D., Philippe Brudi, M.D., John B. Chambers, M.D., Kenneth Egstrup, M.D., Ph.D., Eva Gerdts, M.D., Ph.D., Christa Gohlke-Bärwolf, M.D., Ingar Holme, Ph.D., Y. Antero Kesäniemi, M.D., Ph.D., William Malbecq, Ph.D., Christoph A. Nienaber, M.D., Ph.D., Simon Ray, M.D., Terje Skjærpe, M.D., Ph.D., Kristian Wachtell, M.D., Ph.D., and Ronnie Willenheimer, M.D., Ph.D., for the SEAS Investigators*

Rossebo NEJM 2008



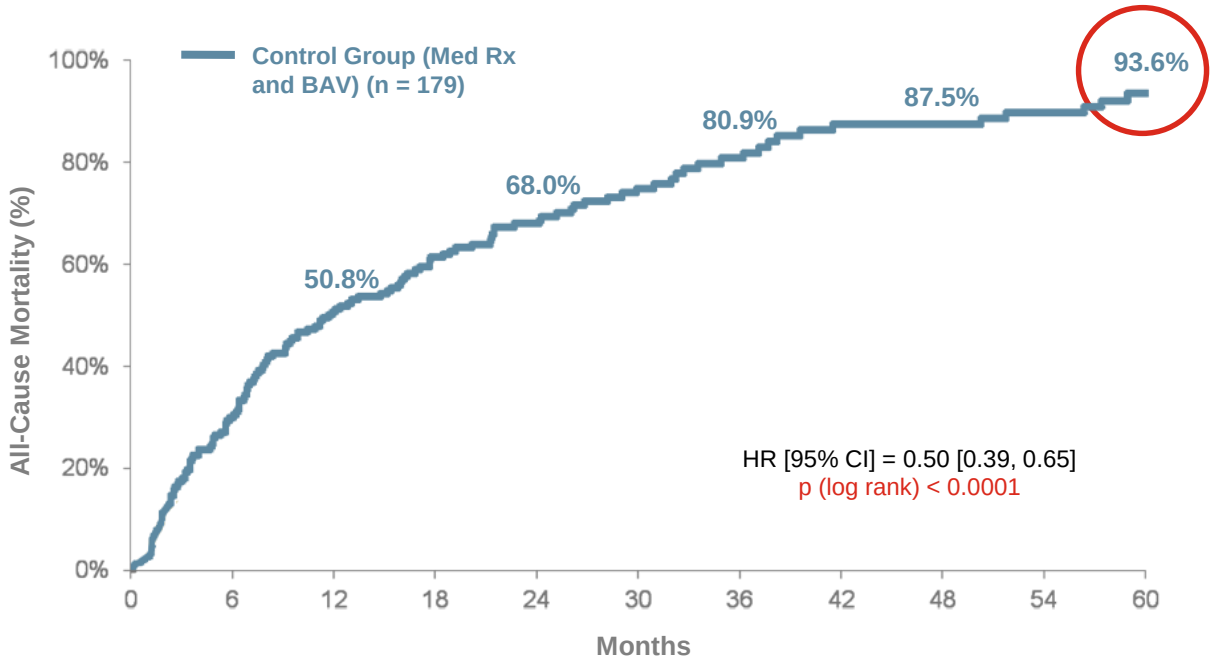
Aortic Valve Surgery: Life Saving Therapy





[1]Schwartz F, Bauman P, et al. Circulation 1982; 66: 1105-10.

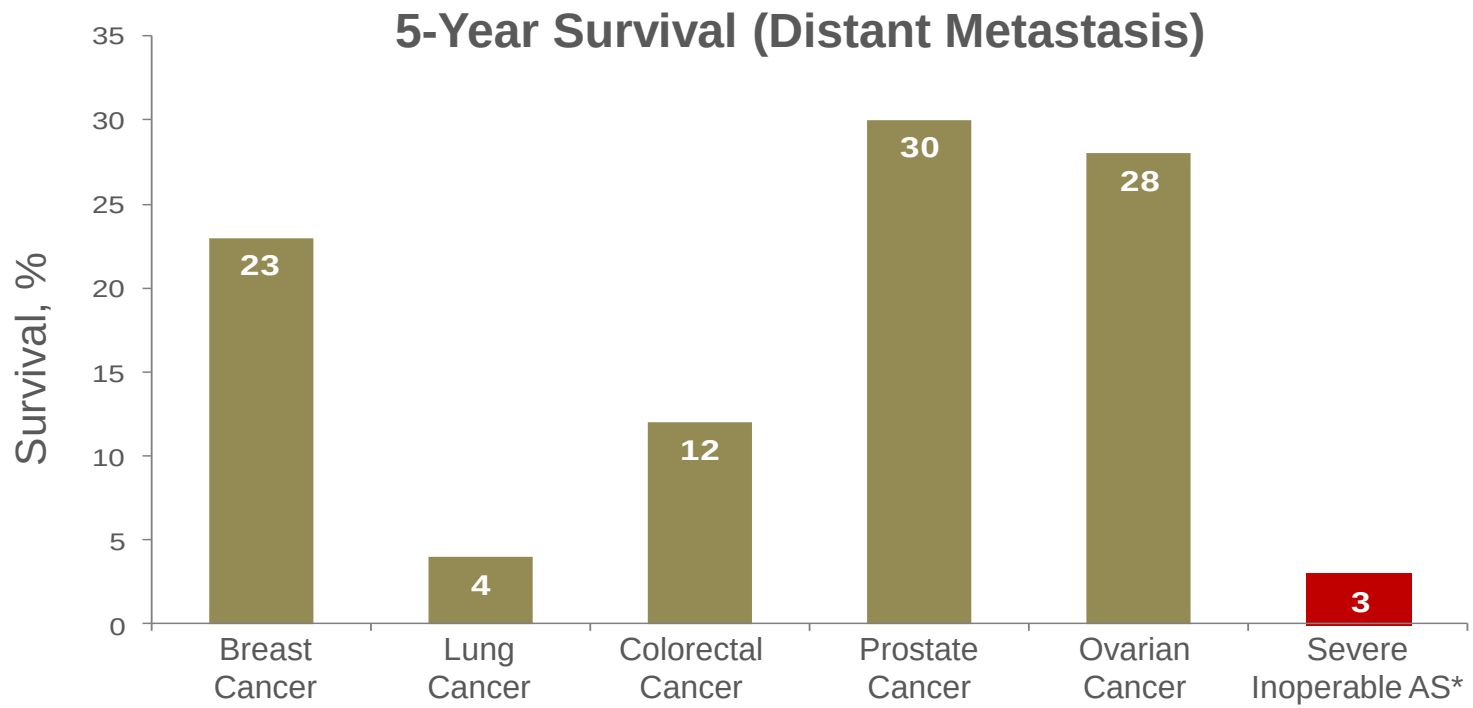
Aortic Stenosis is a Fatal Disease



* In an age and gender matched US population without comorbidities, the mortality at 5 years is 40.5%.

- Despite frequent BAV, **standard therapy did not alter the dismal course of disease for inoperable patients** in The PARTNER Trial
  - 50% died within 1 year
  - 94% died within 5 years

Worse Prognosis than Many Metastatic Cancers

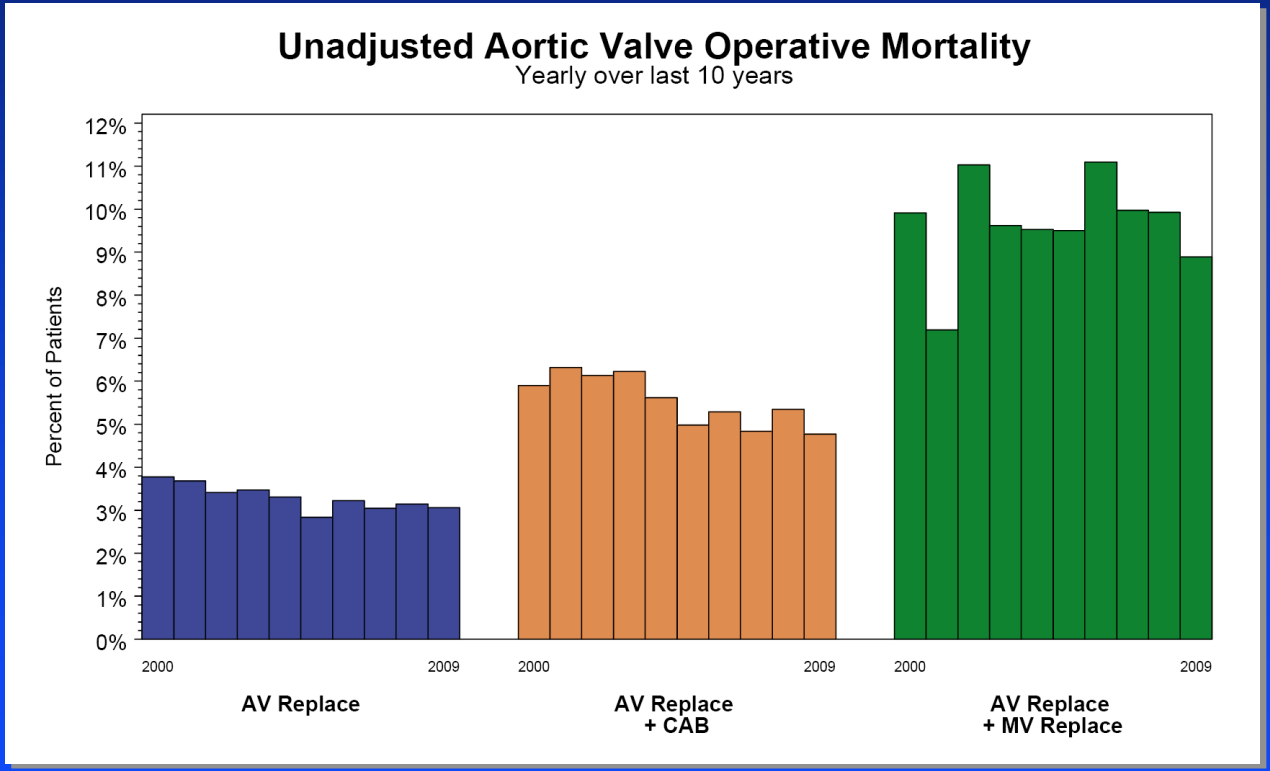


*Using constant hazard ratio. Data on file, Edwards Lifesciences LLC. Analysis courtesy of Murat Tuczu, MD, Cleveland Clinic

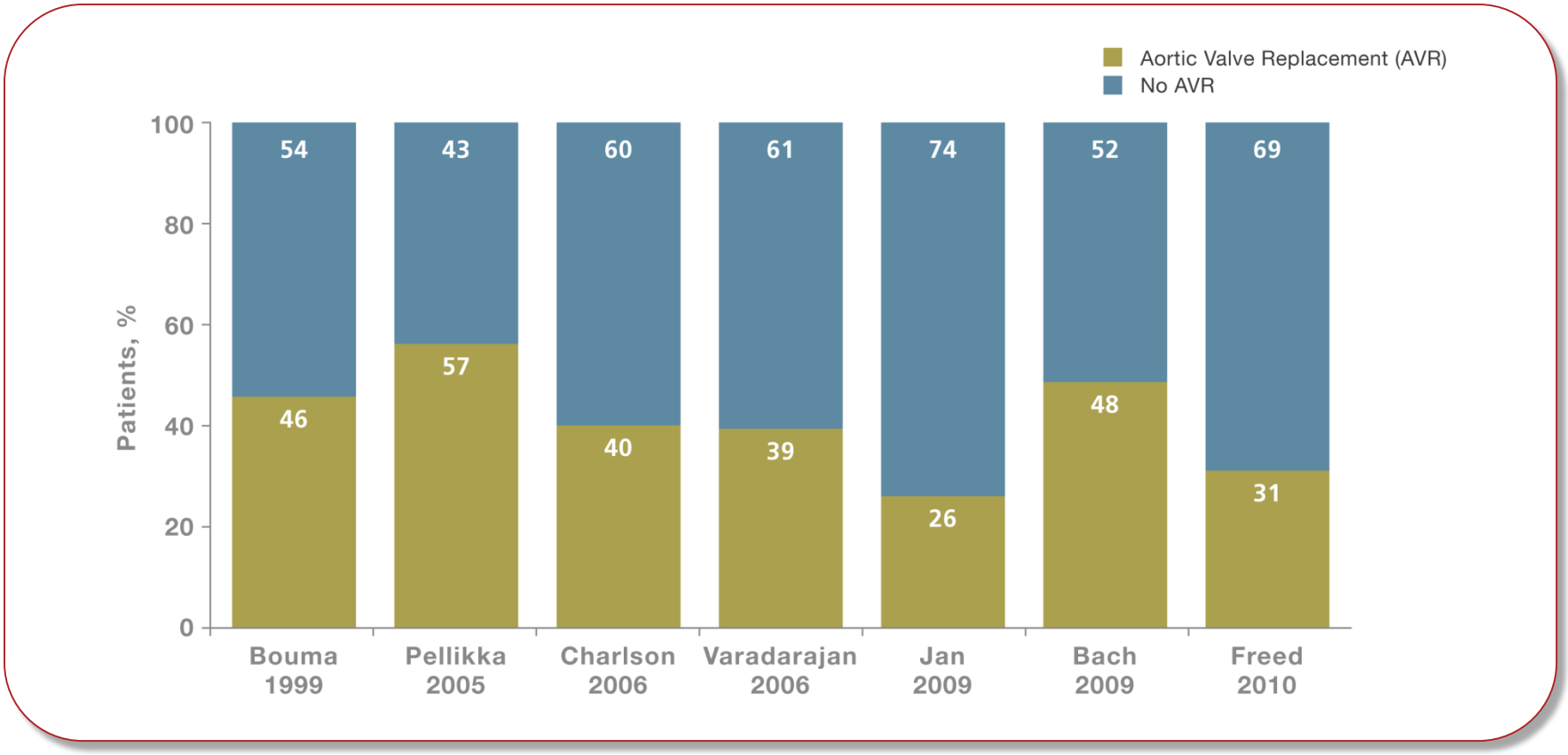
- 5 year survival of breast cancer, lung cancer, prostate cancer, ovarian cancer and severe inoperable aortic stenosis

Treatment: Surgical

Surgical treatment of AS may have operative mortality of less than 5%

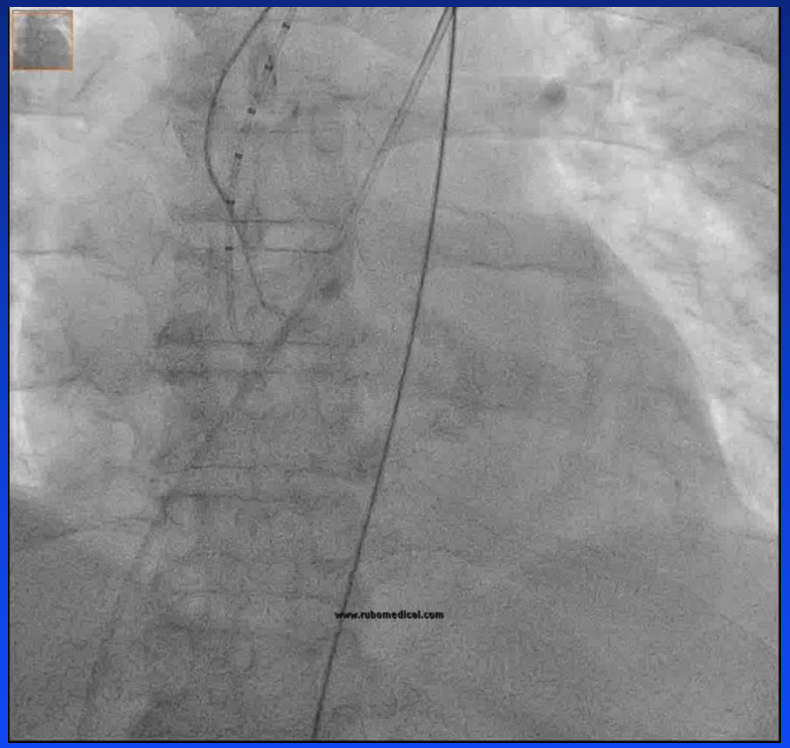


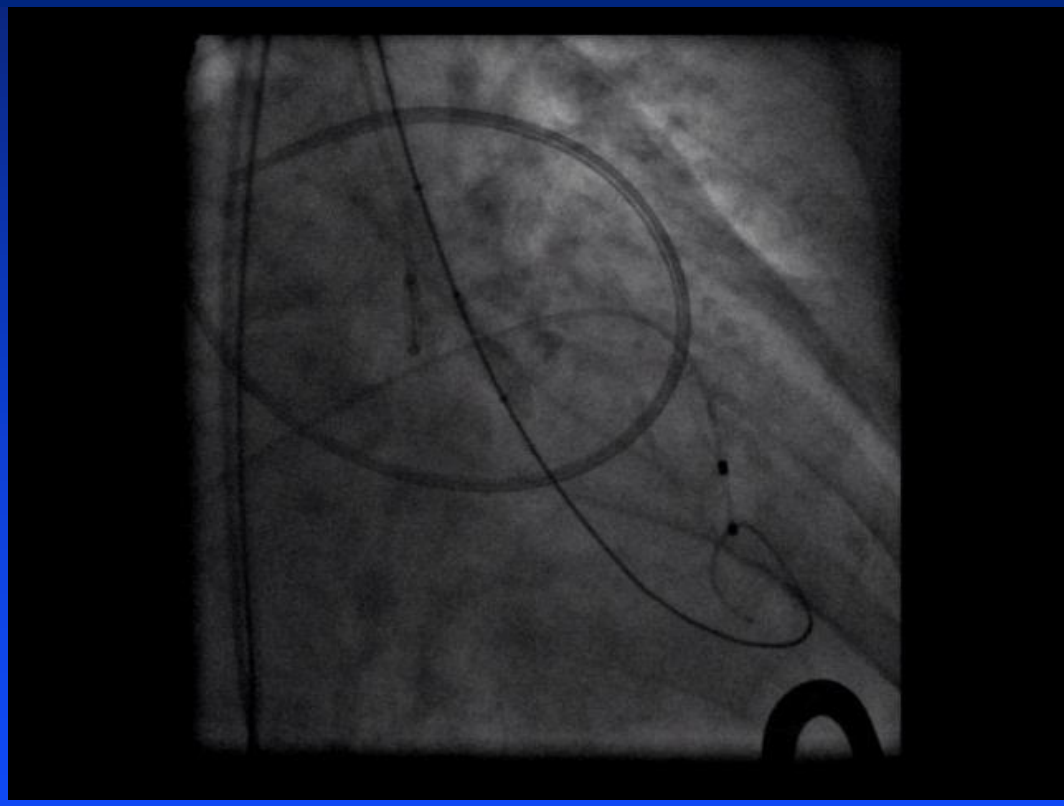
An Under-diagnosed and Under-treated Disease



Studies show at least **40%** of severe aortic stenosis (SAS) patients are not treated with an AVR

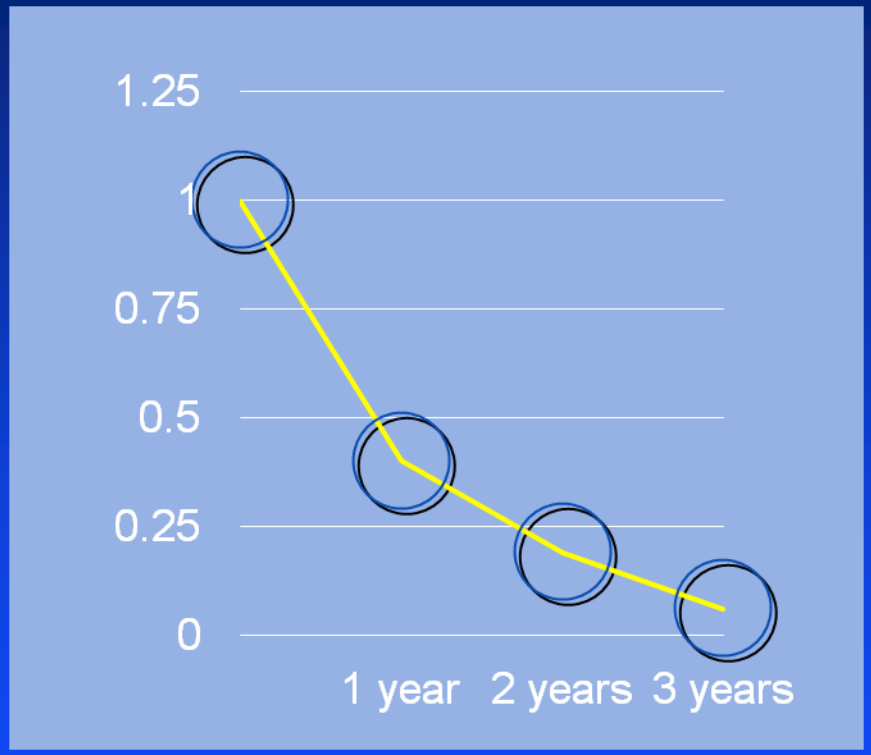
Are There Any Other Options?
Balloon Aortic Valvuloplasty





Aortic Valvuloplasty: Temporary Benefit Only

Event-free Survival, n=165*



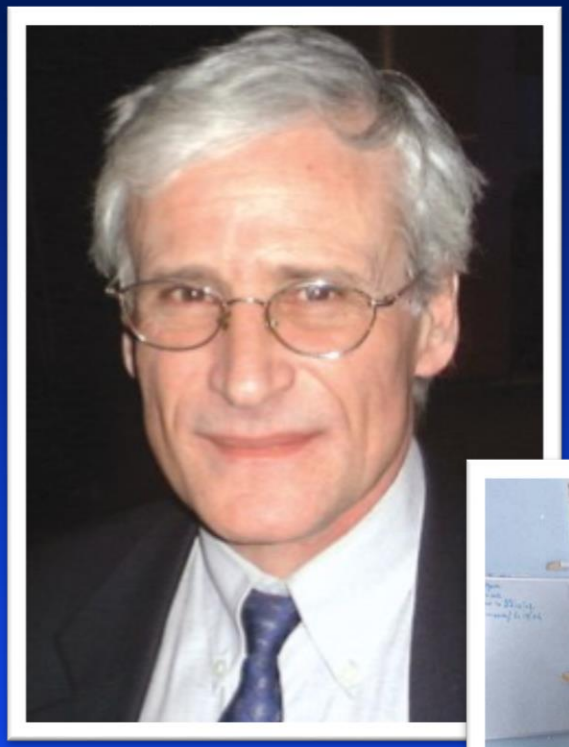
** Freedom from death, AVR, or repeat BAV*

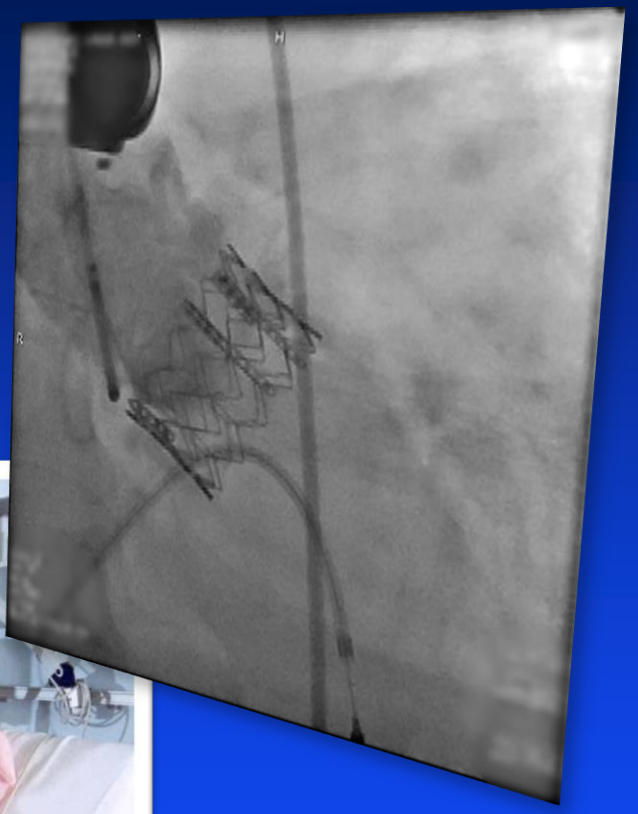
Lieberman, *JACC*, 1994.

What if You Could Implant a New Valve Percutaneously?

The Edwards Sapien Valve

Alain Cribier: First Human Transcatheter Valve Replacement (2002)

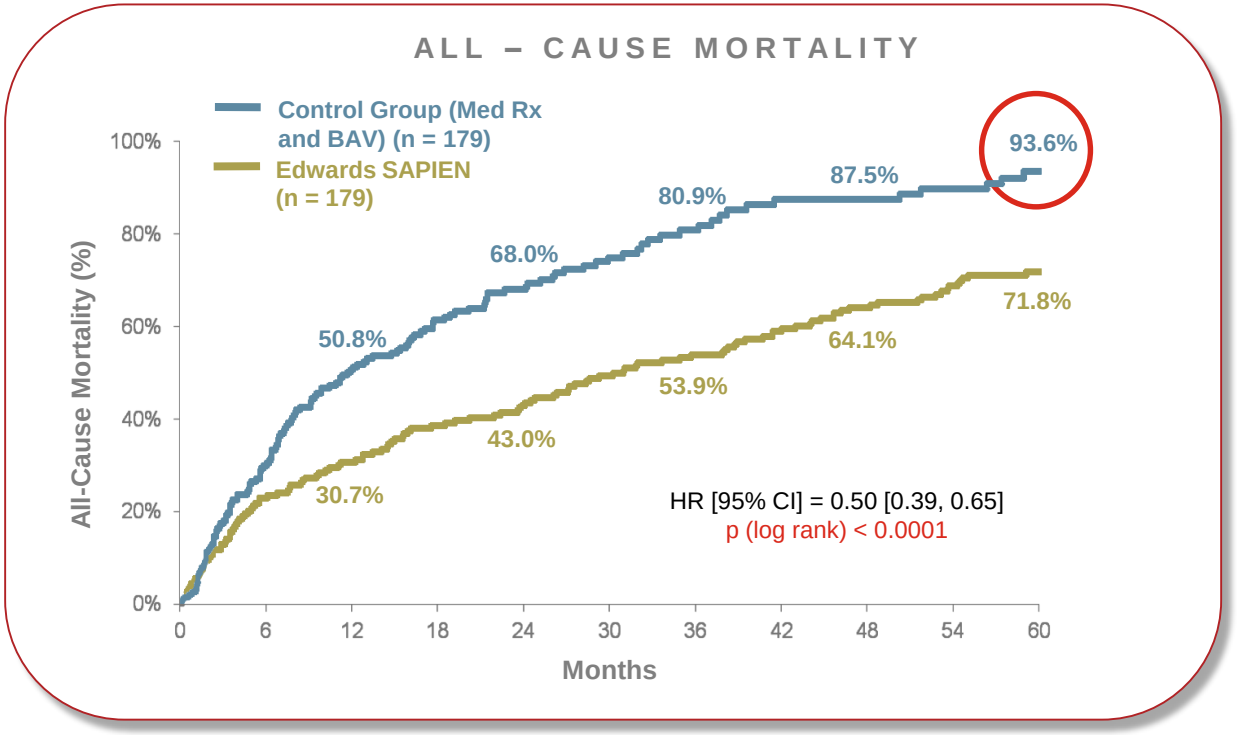




Circulation April 2002

Absolute Reduction in Mortality in Inoperable Patients

The Edwards SAPIEN valve significantly improves survival



21.8% absolute reduction in mortality

Despite expert care and frequent BAV, standard therapy failed to alter the dismal natural course of disease

NEJM 2011

* In an age and gender matched US population without comorbidities, the mortality at 5 years is 40.5%.

TAVR in Extreme Risk Patients: High Death Rate in Both Arms

Table. Interventional Cardiology Trials at the Extreme of Mortality

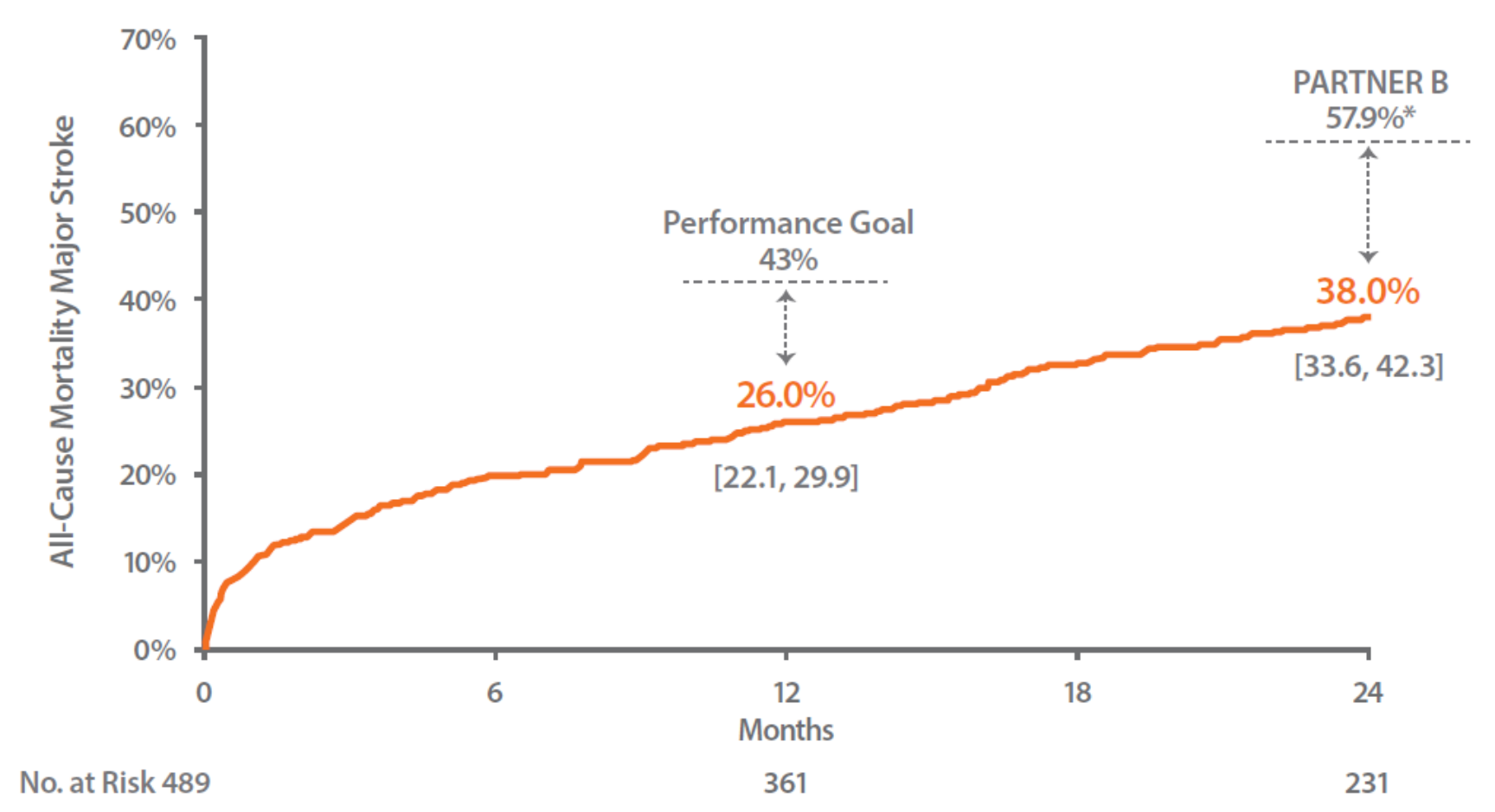
Characteristics	SHOCK[5]	PARTNER B[6]*
Study design	Randomized clinical trial	Randomized clinical trial
Years of enrollment	1993–1998	2007–2009
Randomized sample size, n	302	358
Primary end point	Death at 30 d	Death at 1 y
Expected mortality in control group	75% at 30 d	37.5% at 1 y
Expected impact of novel therapy	20% Absolute reduction in death at 30 d	12.5% Absolute reduction in death at 1 y
Achieved mortality in the novel treatment arm	47% at 30 d	31% at 1 y
Primary end point achieved	No	Yes
Key secondary end point	Significant mortality reduction with early revascularization at 6-mo follow-up	Significant mortality reduction with TAVR persisting for 3 y
Exploratory subgroup analyses	No benefit of early revascularization in the elderly	No benefit of TAVR in patients with STS score > 15%
Subsequent or planned confirmatory trials	No	No

Dauerman HL *Circulation* 2014

Transcatheter Aortic Valve Replacement: Process

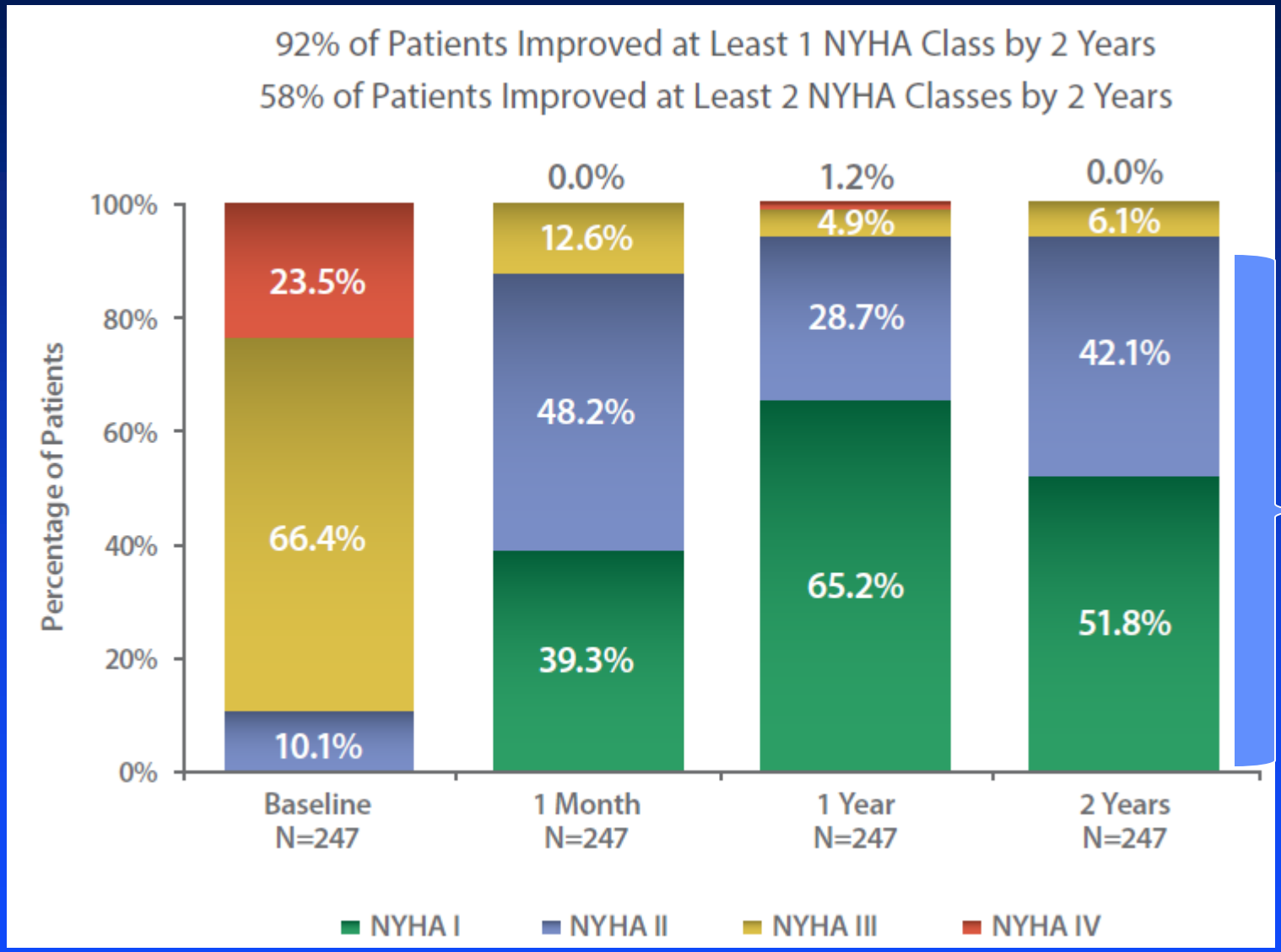
Transcatheter Aortic Valve Replacement: Process

Corevalve:
All Cause Mortality or Major Stroke



** Calculated rate for 117 events in 179 patients (65.4%, lower confidence bound of 57.9% by Exact method) (Makkar RR, et al, New Engl J Med, 2012)*

Quality of Life Improvement 2 Years after Corevalve Extreme Risk TAVR



Corevalve High Risk Trial

As-Treated Population
N=750

Underwent Attempted TAVR
N=391

Underwent Attempted SAVR
N=359

1-Year TAVR
N=323/328
(98.5%)

1-Year SAVR
N=265/281
(94.3%)

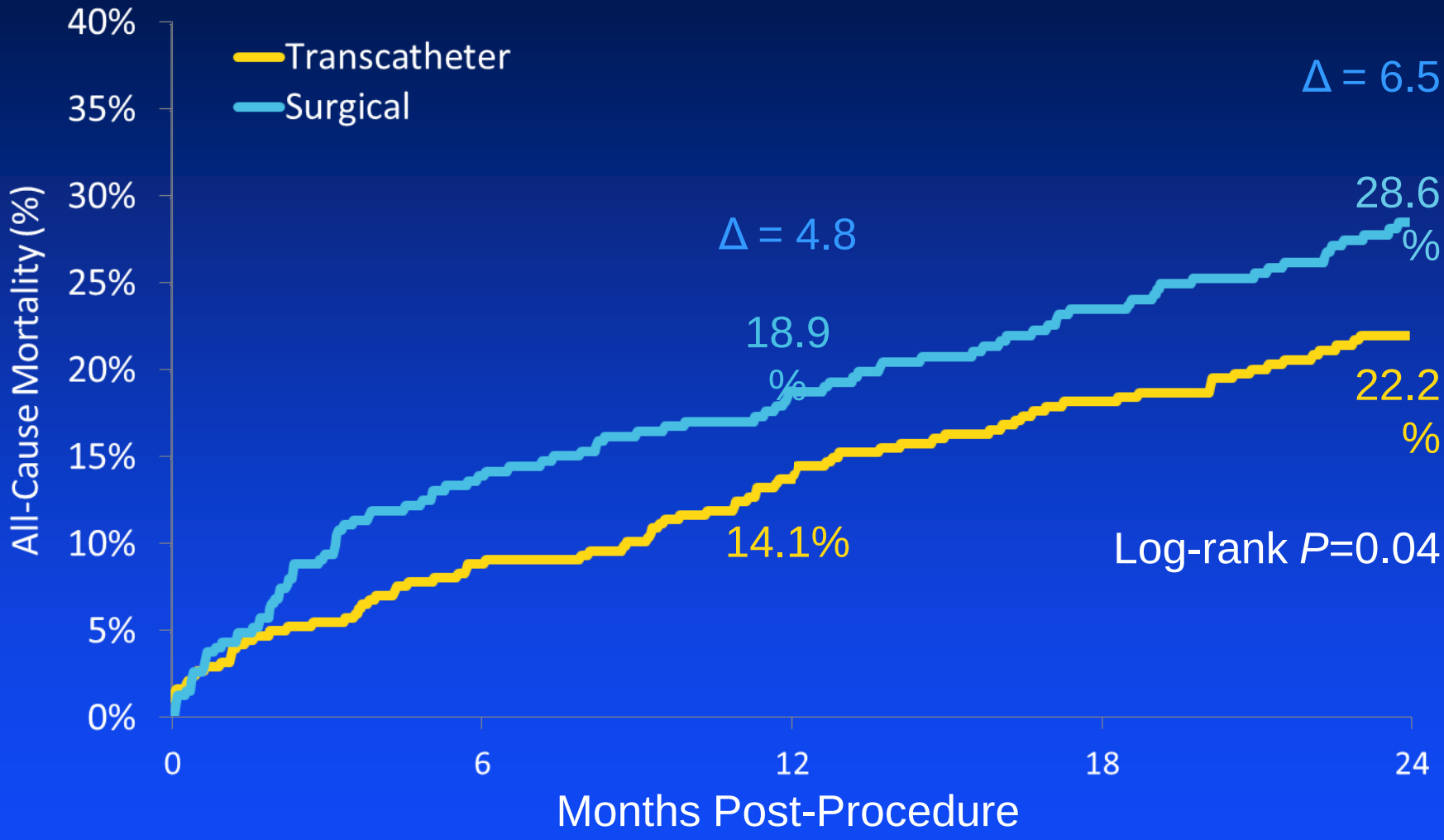
Died-28
Exited-3
Pending follow-up-2

Died-31
Exited-13

2-Year TAVR
N=278/295
(94.2%)

2-Year SAVR
N=221/237
(93.2%)

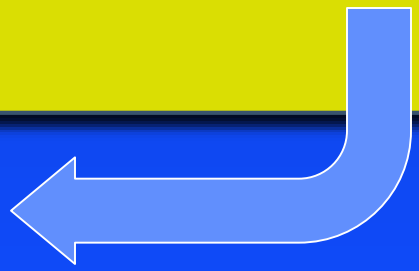
TAVR Superior to Surgical AVR: Corevalve High Risk Trial



Reardon, ACC 2015

Complications Associated with TAVR

- Stroke (major, minor)
- Paravalvular leak
- Conduction System Abnormalities
- Vascular Access Complications
- Valve Embolization and Malposition

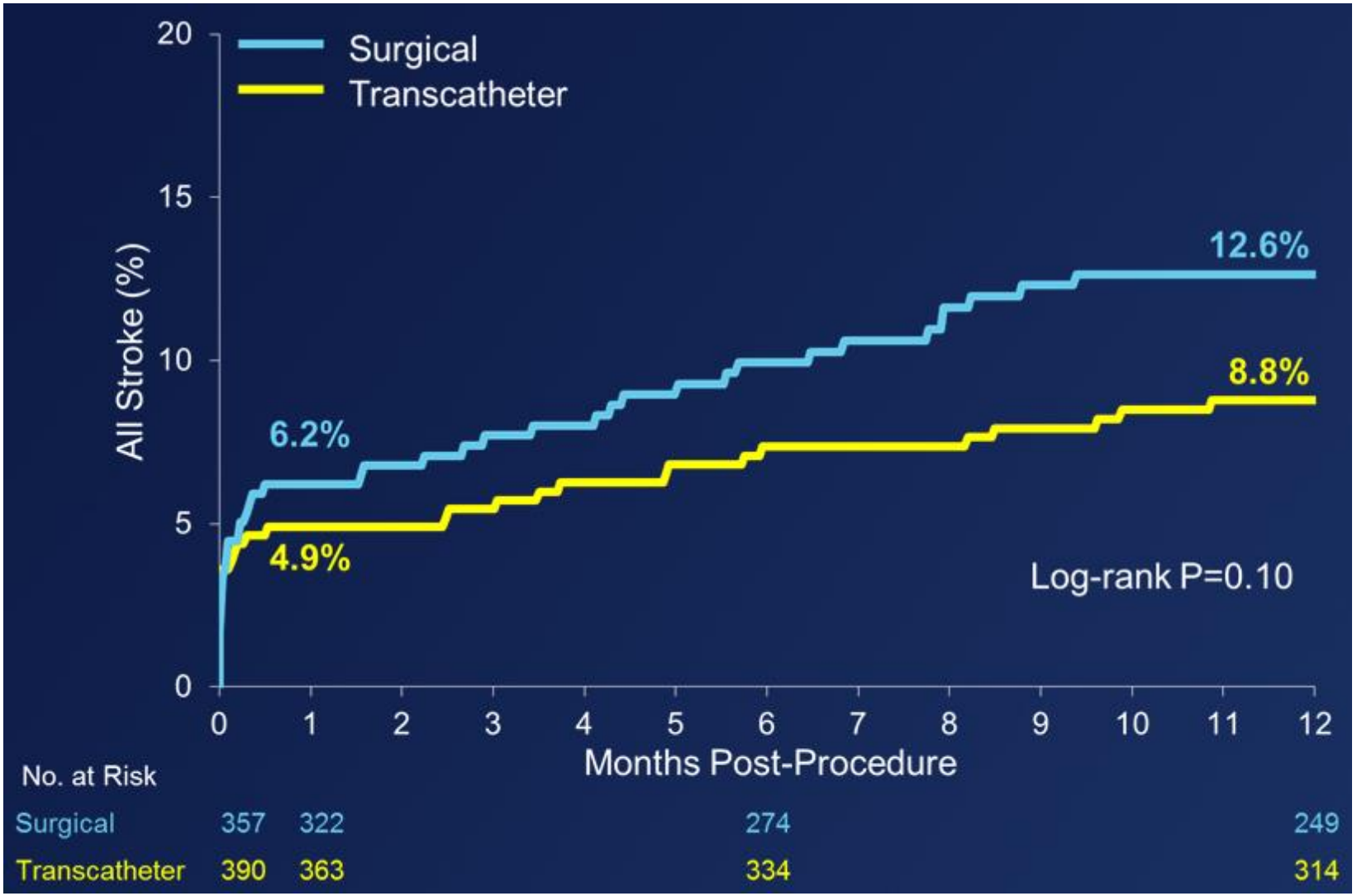


24 Hours SICU Stay

PARTNER High Risk: Stroke

Outcome	30 Days			1 Year		
	TAVR (N = 348)	*AVR (N = 351)*	*p-value*	*TAVR (N = 348)*	*AVR (N = 351)*	*p-value*
All Stroke or TIA – no. (%)	19 (5.5)	8 (2.4)	0.04	27 (8.3)	13 (4.3)	0.04
TIA – no. (%)	3 (0.9)	1 (0.3)	0.33	7 (2.3)	4 (1.5)	0.47
All Stroke – no. (%)	16 (4.6)	8 (2.4)	0.12	20 (6.0)	10 (3.2)	0.08
Major Stroke – no. (%)	13 (3.8)	7 (2.1)	0.20	17 (5.1)	8 (2.4)	0.07
Minor Stroke – no. (%)	3 (0.9)	1 (0.3)	0.34	3 (0.9)	2 (0.7)	0.84
Death/maj stroke – no. (%)	24 (6.9)	28 (8.2)	0.52	92 (26.5)	93 (28.0)	0.68

Corevalve High Risk Trial: Stroke



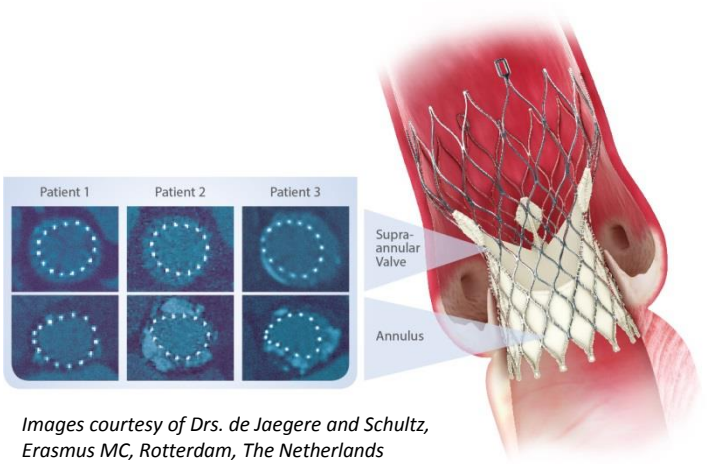
High Risk Study | US Pivotal Trial

CoreValve U.S. Pivotal Trial High Risk Study
Low Rate of Leaky Valve (Paravalvular Leak)

The Product:

Conforming Frame

The CoreValve Nitinol frame conforms and seals to the non-circular annulus

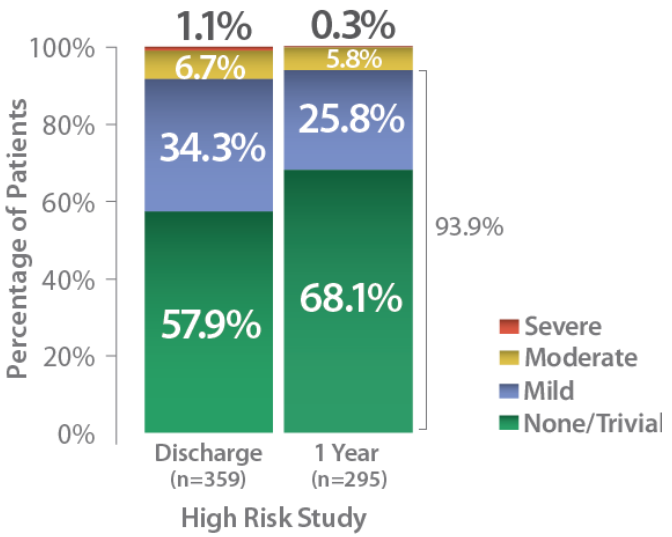


Images courtesy of Drs. de Jaegere and Schultz, Erasmus MC, Rotterdam, The Netherlands

The Proof:

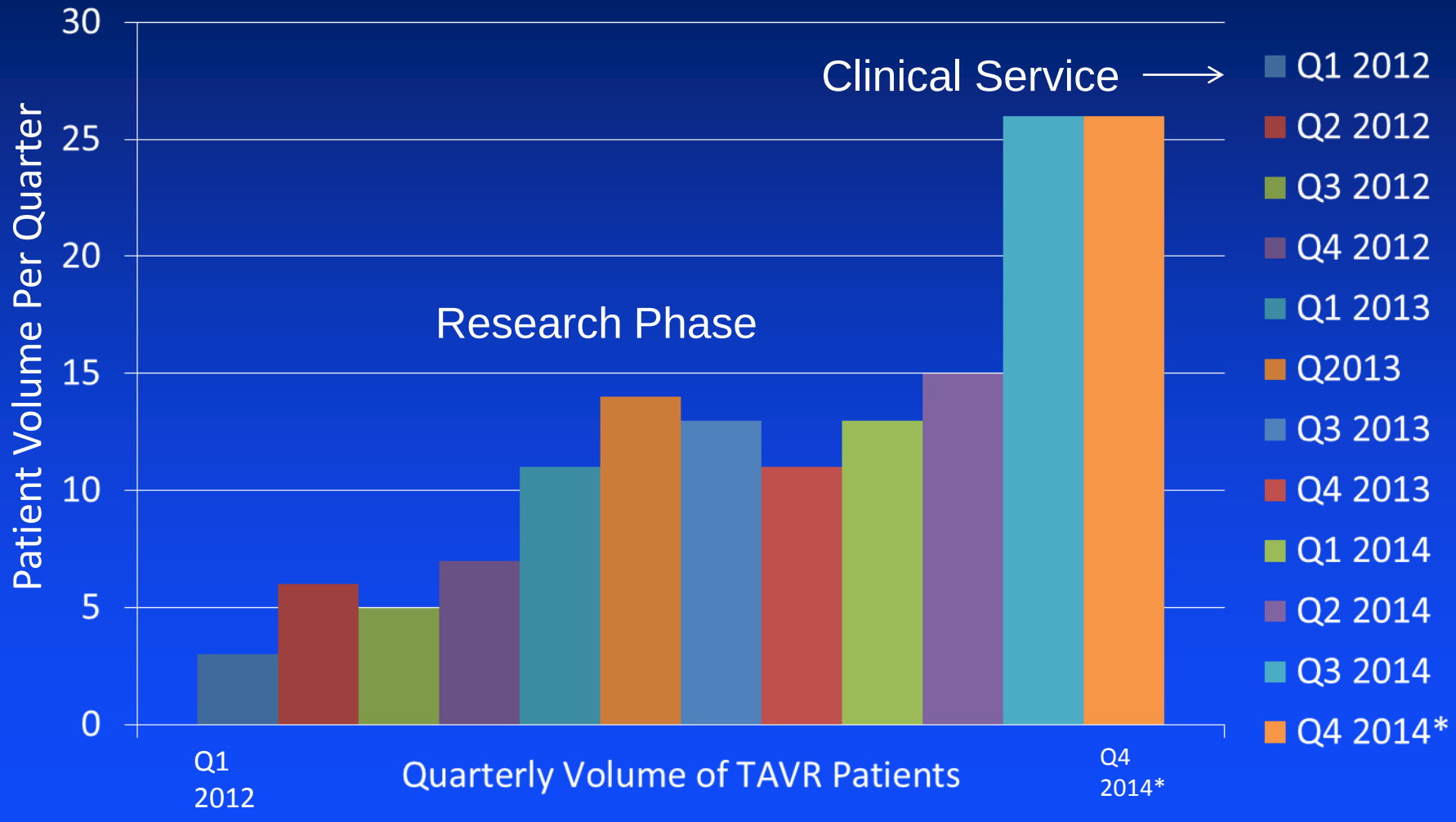
Low Rates of Moderate/Severe PVL[1]

The CoreValve device demonstrates low moderate and severe paravalvular leak rates

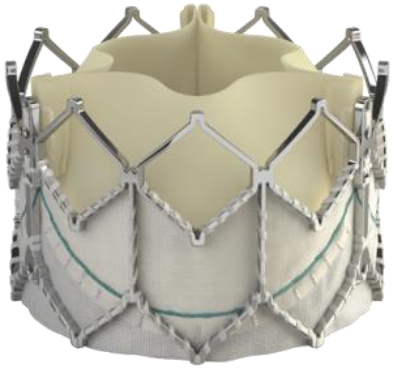


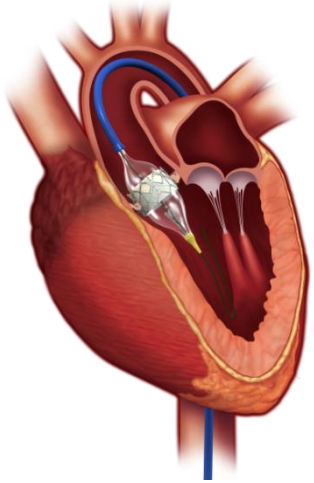
1. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic valve replacement with a self-expanding prosthesis [published online ahead of print March 29, 2014]. New Engl J Med 2014;doi:10.1056/NEJMoa1400590.

UVM Volume Growth of TAVR



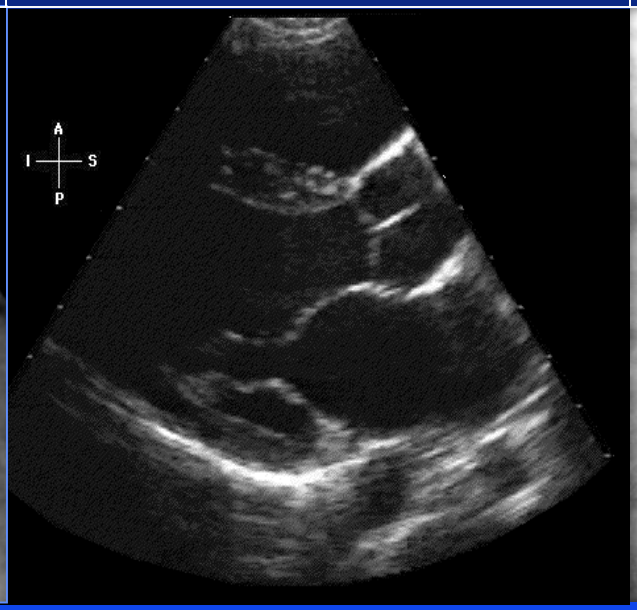
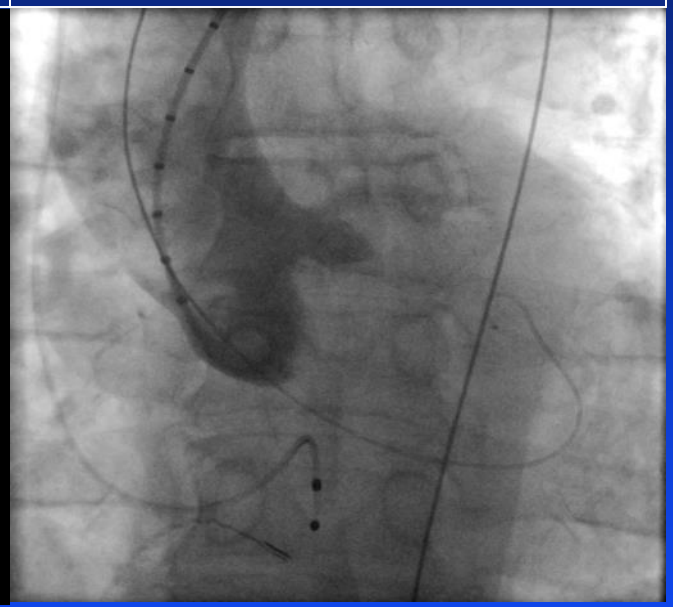
Edwards SAPIEN XT Transcatheter Heart Valve





The Edwards SAPIEN XT Transcatheter Heart Valve, model 9300TFX, systems are indicated for relief of aortic stenosis in patients with **symptomatic heart disease due to severe native calcific aortic stenosis** (aortic valve area ≤ 1.0 cm^2 or aortic valve area index ≤ 0.6 cm^2/m^2, a mean aortic valve gradient of ≥ 40 mmHg, or a peak aortic-jet velocity of ≥ 4.0 m/s), and with native anatomy appropriate for the 23, 26, or 29 mm valve system, who are judged by a heart team, including a cardiac surgeon, to be at **high or greater risk for open surgical therapy** (i.e., Society of Thoracic Surgeons operative risk score ≥ 8% or at a ≥ 15% risk of mortality at 30 days).

Selecting the Right Patients: Aortic Annulus and CT Angio/Echo

Computed Tomography	Echocardiogram	Aortogram
		

Photographs courtesy of Nicolo Piazza, MD

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

Tilley Drive UVM Cardiology

The Art of Selecting Patients For TAVR

- Prevalence of frailty increases with aging; old does not necessarily equal frail
- Elderly patients achieve measurable benefit from cardiac surgery, particularly in terms of:
  - Quality of life
  - Increased survival
  - Prevention of adverse cardiovascular events
- **The "Eyeball Test": Nursing Home, Wheel Chair, Frequent Falls?**

Same age (90) and predicted risk (12%)

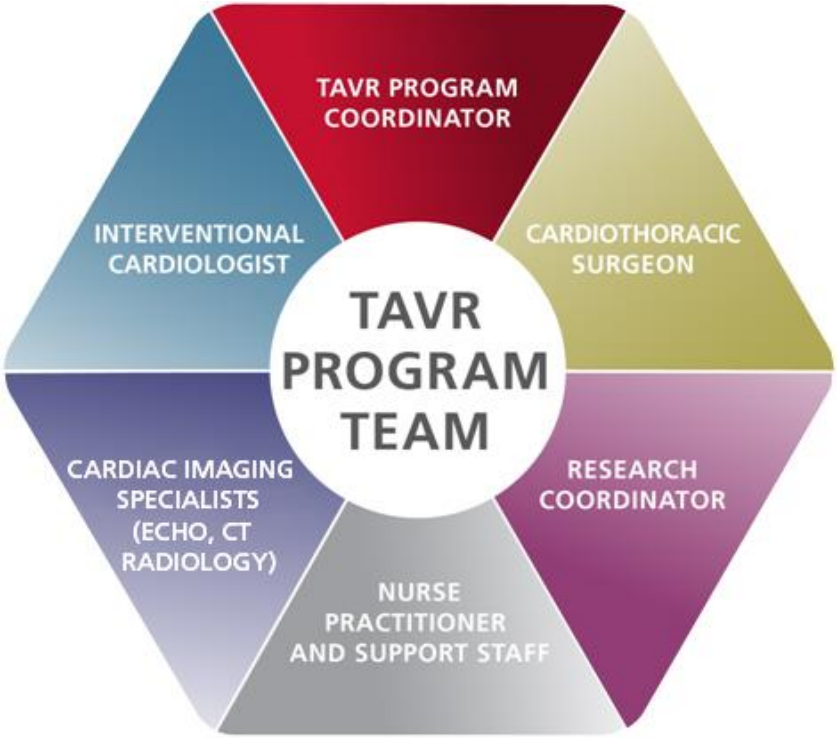
One passes the "eyeball test," one does not

Slide provided courtesy of Todd Dewey, MD, Medical City Dallas

TAVR Heart Team Concept

Multidisciplinary approach ensures:

- Patient centric care
- Thorough assessment by a team of specialists
- Collaborative treatment decision



UVM TAVR Coordinator: Faye Straight, RN
Faye.straight@uvmhealth.org

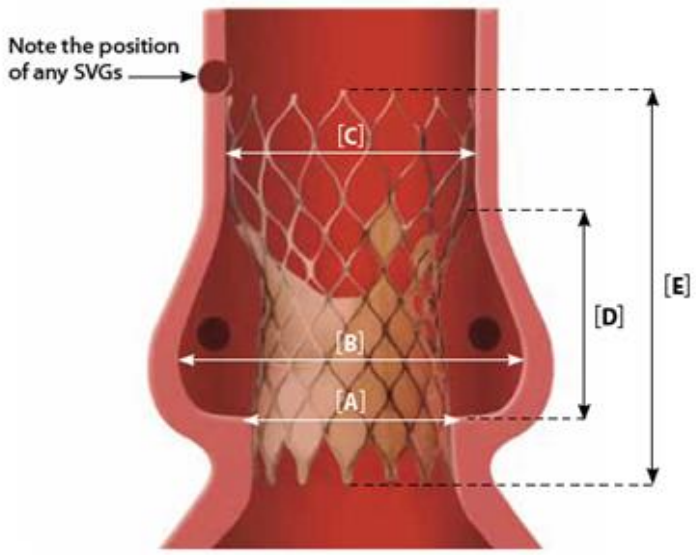
Anatomic Features Important for TAVR Sizing

Primary Features:

- The aortic annulus
- The sinuses of Valsalva
- The ascending aorta

Secondary Features:

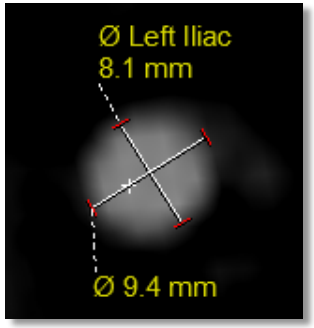
- Coronary artery ostia
- Left ventricular outflow tract (LVOT)

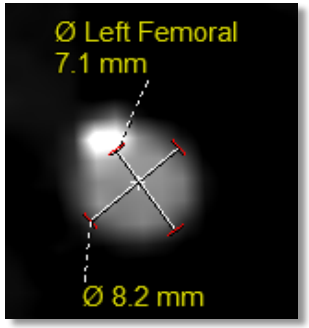


[A] Annulus Diameter
[B] Sinus of Valsalva Width
[C] Ascending Aorta Diameter
[D] Sinus of Valsalva Height
[E] Frame Height (≈ 5 cm)

Dimensional Analysis

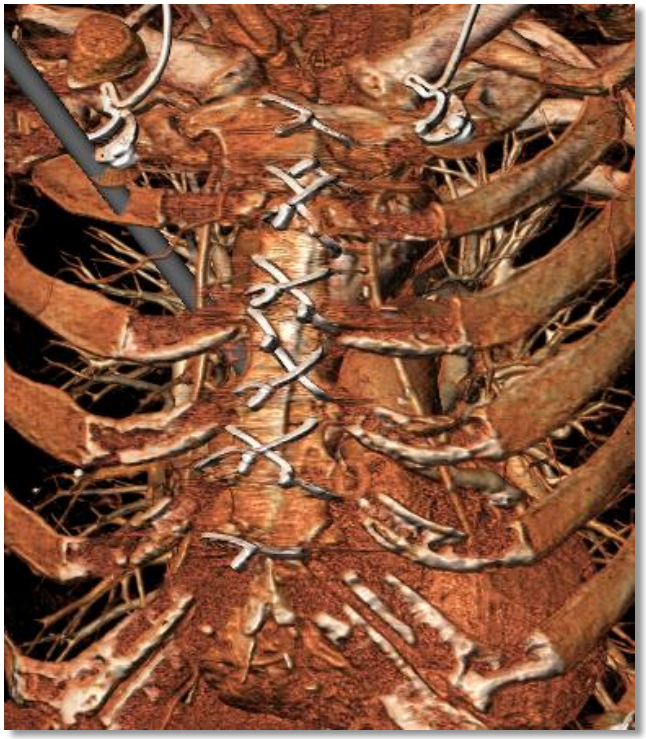
- Measure both left and right iliac and femoral artery axial views to identify minimum diameters
- Measure and record both minimum (minor) and orthogonal (perpendicular) diameters

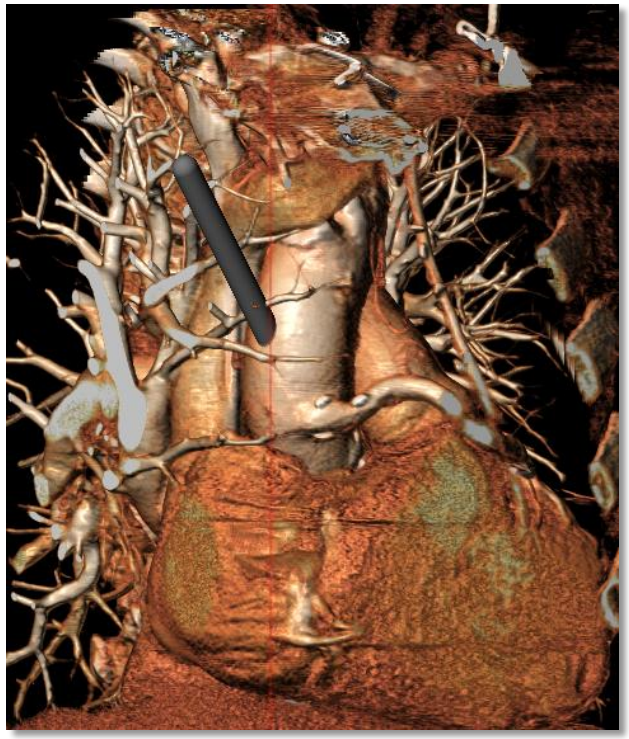


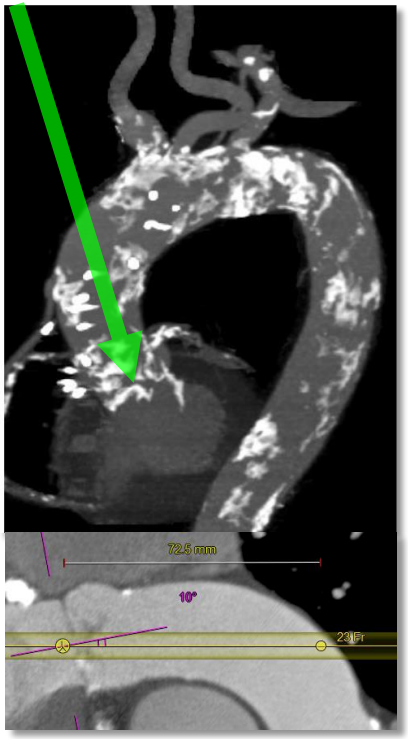


Direct Aortic Approach Delivery Trajectory

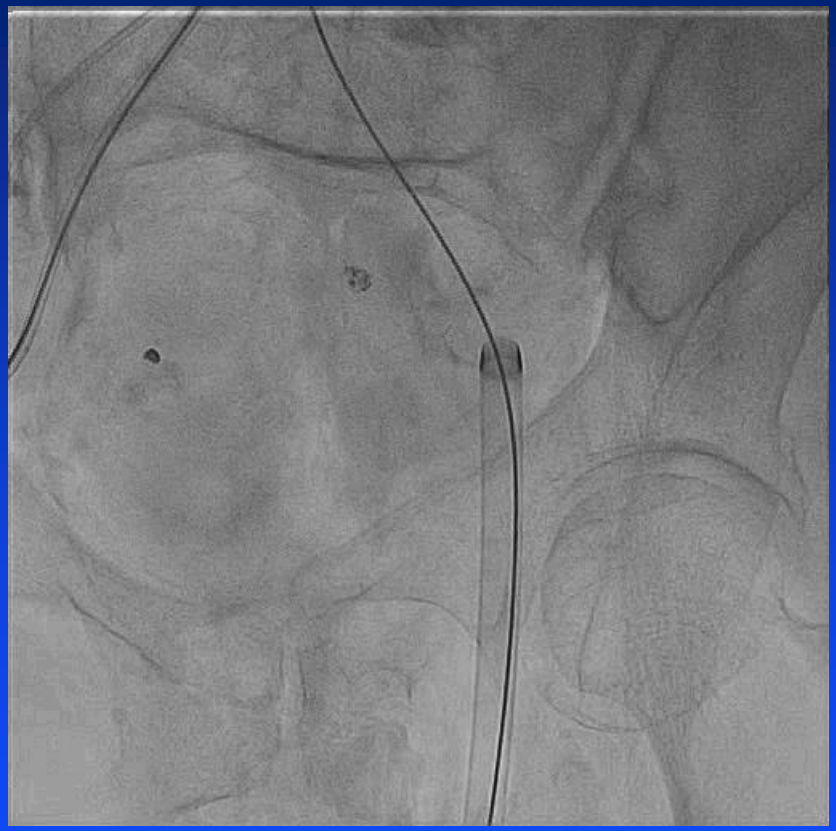
Identify desired access location and pathway

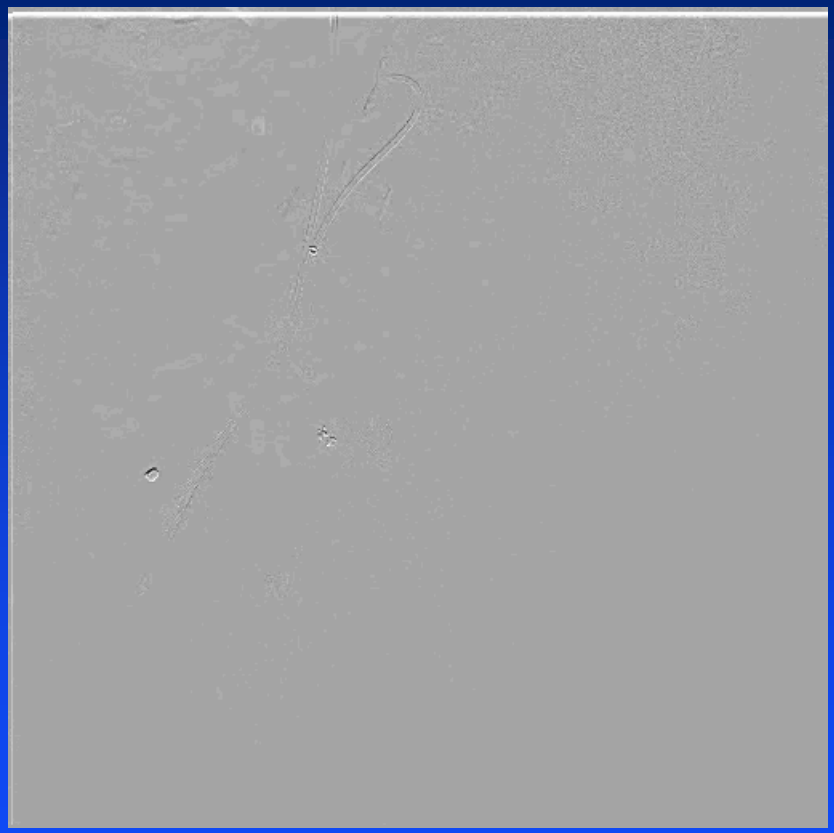






TAVR Has Real Risks

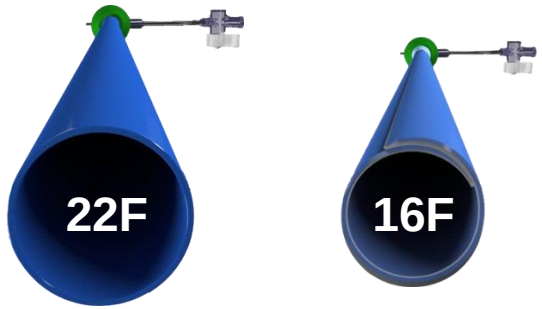




Reduction in Vascular Complications: Next Generation TAVR Devices

Events	SAPIEN (n=271) n	%	SAPIEN XT (n=282) n	%
Vascular:				
Major	43	15.9	32	11.3
Bleeding:				
Disabling	34	12.6	22	7.8

Major vascular complications reduced by 25% with next generation device



RetroFlex 3 Introducer Sheath **eSheath**

Sheath Size Comparison

PARTNER II Trial Cohort B - Incidence data for this figure only contains data from 23 mm and 26 mm valve sizes and does not include 29 mm.

Corevalve Randomized Trial Complications

Events*	1 Month			1 Year		
	TAVR	SAVR	P Value	TAVR	SAVR	P Value
Vascular complications (major), %	5.9	1.7	0.003	6.2	2.0	0.004
Pacemaker implant, %	19.8	7.1	<0.001	22.3	11.3	<0.001
Bleeding (life threatening or disabling), %	13.6	35.0	<0.001	16.6	38.4	<0.001
New onset or worsening atrial fibrillation, %	11.7	30.5	<0.001	15.9	32.7	<0.001
Acute kidney injury, %	6.0	15.1	<0.001	6.0	15.1	<0.001

*Percentages reported are Kaplan-Meier estimates and log-rank P values

Real World SAPIEN Valve Outcomes

30 day STS/ACC TVT Registry Data (Nov 2011 - May 2013):

- **7,710 patients treated at 224 centers**
- **Median Age of 84**
- **Patient Risk Profile**
  - **20% Inoperable / 80% High-Risk**

STS/ACC TVT Registry™

Outcomes (In Hospital)	Overall (n=7,710)
Death (Any Cause)	5.5%
Stroke	2.0%
Moderate or Severe Aortic Insufficiency	8.5%
Major Bleeding (VARC)	3.5%
New Permanent Pacemaker	6.6%
Hospital Duration, Median Days	6

TAVR and Quality Assurance at UVM

Executive Summary

TVT Registry™

The University of Vermont Medical Center (186373) compared to Rolling Four Quarters (R4Q) for US Hospitals ending 2014Q4

Section I: Transcatheter Aortic Valve Replacement (TAVR) Quality Metrics

TAVR Outcome Metrics (In-hospital) - Mortality

Distribution of Hospital Performance

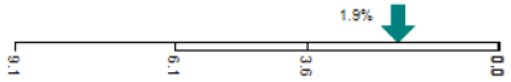
10th percentile — 90th percentile

Better →

2 **Mortality Rate – In Hospital Observed (UNADJUSTED)**

My Hospital	US Hospitals 50th Pctl	US Hospitals 90th Pctl
1.9%	3.6%	0.0%

Your hospital's in-hospital observed, (unadjusted), all-cause mortality rate for all patients. [Detail Line:1500]



TAVR Outcome Metrics (In-hospital)

Distribution of Hospital Performance

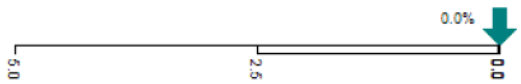
10th percentile — 90th percentile

Better →

5 **Significant Cardiac Event (Procedure Related)**

My Hospital	US Hospitals 50th Pctl	US Hospitals 90th Pctl
0.0%	0.0%	0.0%

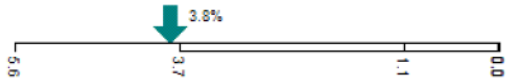
Your hospital's proportion of patients with TAVR with a significant, procedure related, cardiac event post procedure. This includes coronary compression or obstruction, annular dissection, aortic dissection or cardiac perforation. [Detail Line:1323]



6 **Stroke (any)**

My Hospital	US Hospitals 50th Pctl	US Hospitals 90th Pctl
3.8%	1.1%	0.0%

Your hospital's proportion of patients with TAVR with any stroke post procedure. This includes hemorrhagic, ischemic or stroke of undetermined type. [Detail Line:1359]



7 **Acute Kidney Injury (Stage 3)**

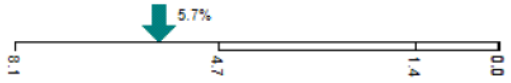
My Hospital	US Hospitals 50th Pctl	US Hospitals 90th Pctl
2.0%	0.0%	0.0%

Your hospital's proportion of patients with acute kidney injury – stage 3 as determined by the Acute Kidney Injury Network (AKIN) RIFLE Criteria. [Detail Line:1370]

8 **Bleeding – Disabling**

My Hospital	US Hospitals 50th Pctl	US Hospitals 90th Pctl
5.7%	1.4%	0.0%

Your hospital's proportion of patients with TAVR with a disabling or life threatening bleeding event. [Detail Line:1387]

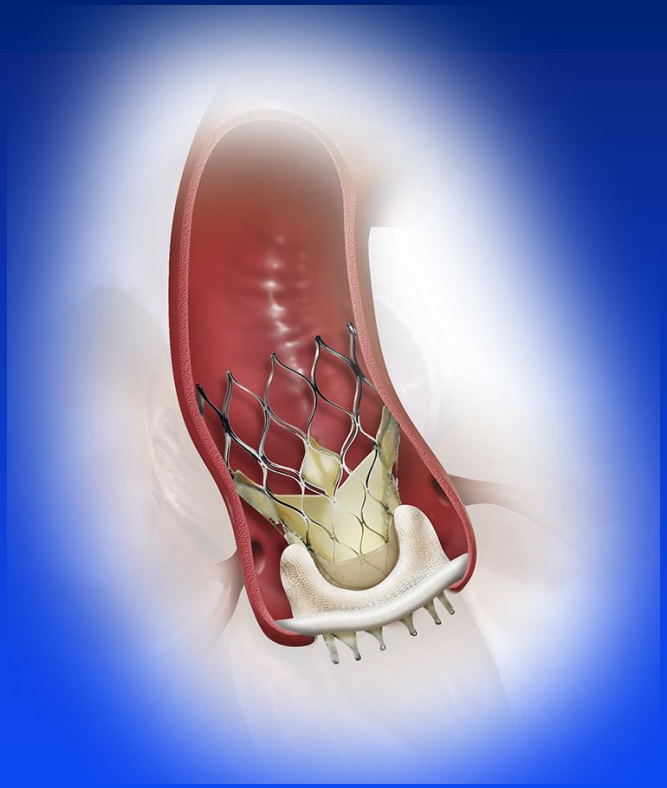


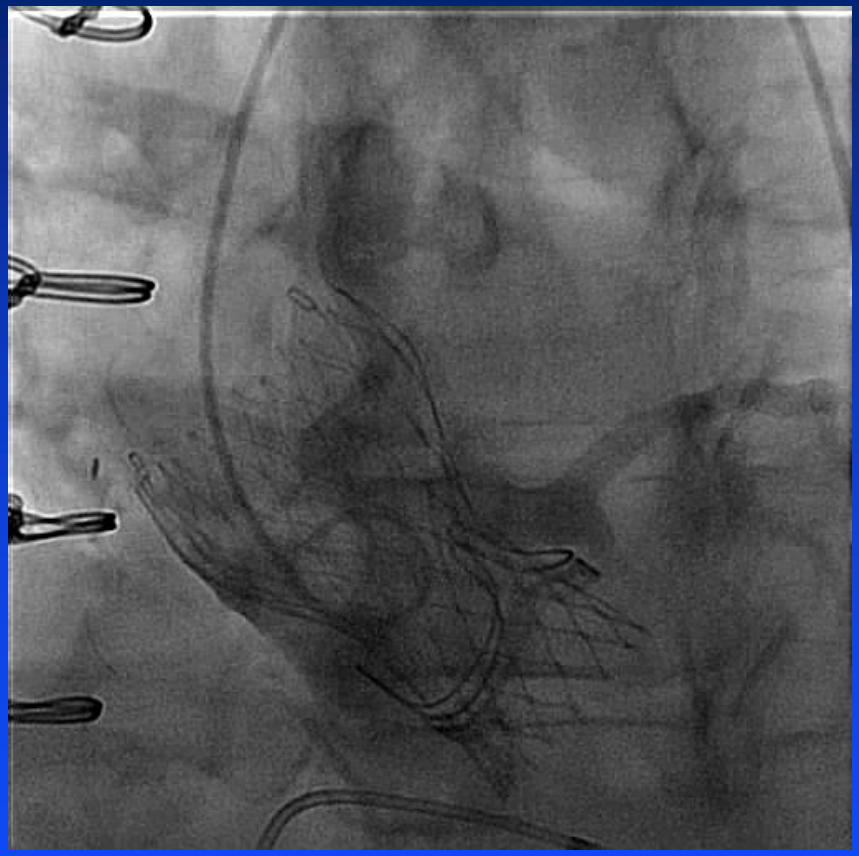
2014 AHA/ACC Valvular Heart Disease Guidelines

- In the absence of serious comorbid conditions, aortic valve replacement (AVR) is **indicated in the majority of symptomatic patients** with severe aortic stenosis
- Because of the risk of sudden death, **AVR should be performed promptly after the onset of symptoms**
- Consultation with or referral to a **Heart Valve Center of Excellence** is reasonable when discussing treatment options for:
  - Asymptomatic patients with severe valvular heart disease
  - Patients with multiple comorbidities for whom valve intervention is considered.
- **Age is not a contraindication to surgery**
- **If surgery is contraindicated, TAVR recommended (extreme risk patients)**
- **If patient is high risk for surgery, TAVR is a reasonable option**

Nishimura RA, Otta CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease. J Am Coll Cardiol. 2014;63:e57-185.

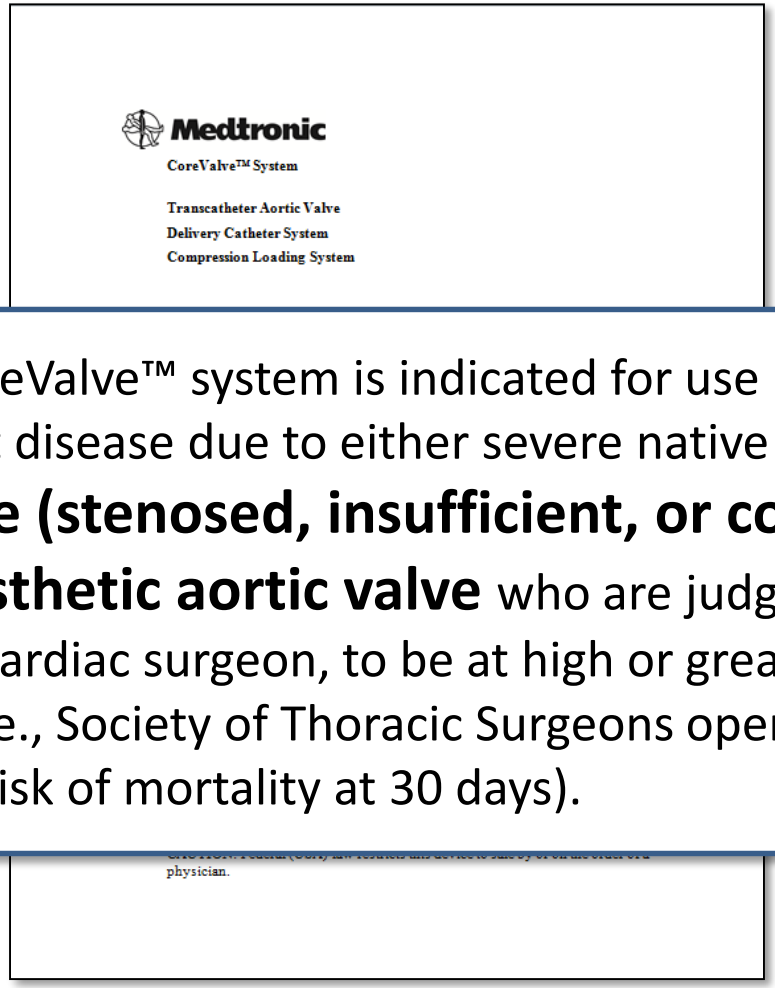
Valve in Valve TAVR: A Growing Indication





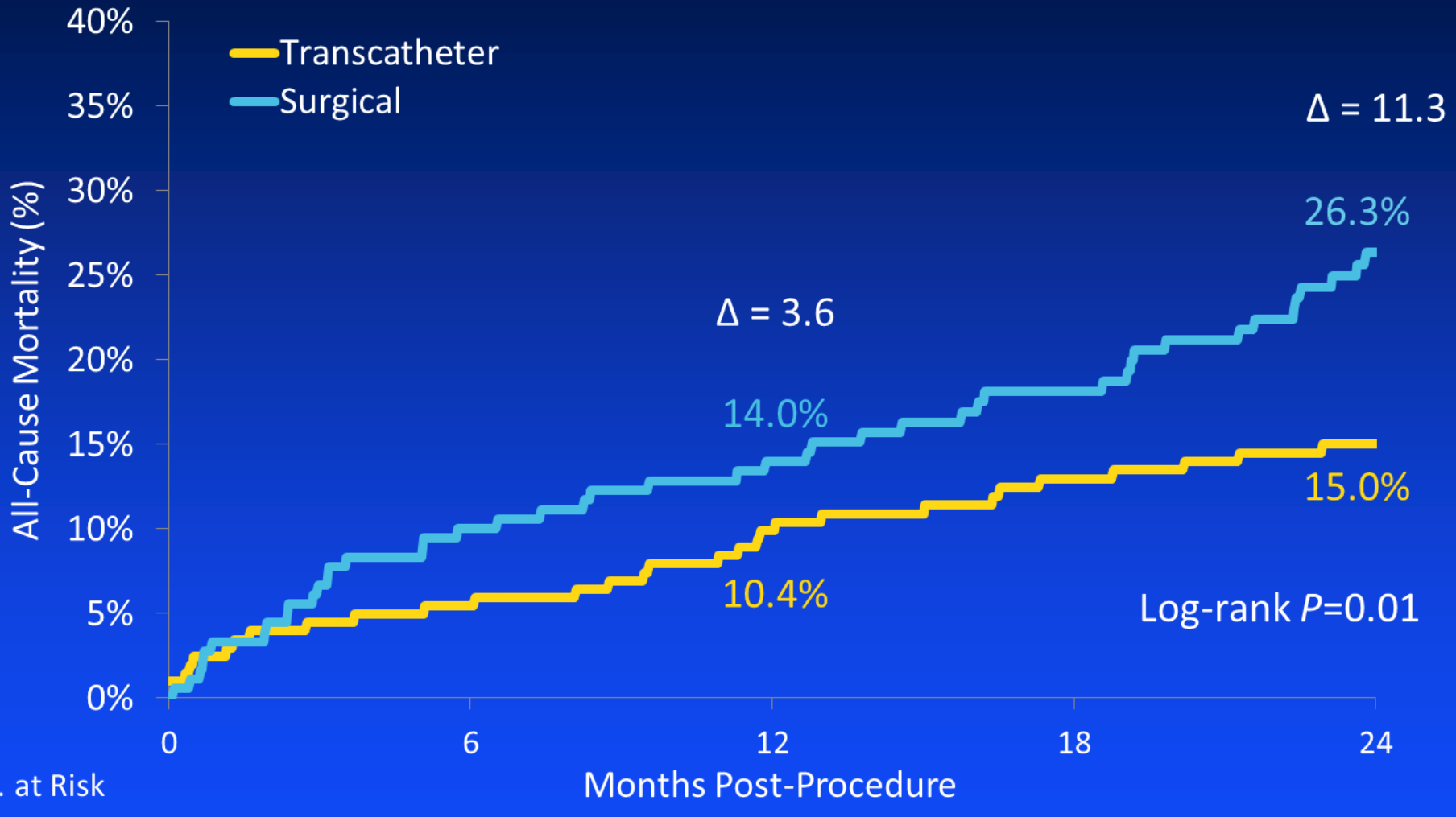
New TAVR Indications: April 2015

CoreValve is Indicated for Symptomatic Patients with a Failed Surgical Bioprosthetic Aortic Valve



The Medtronic CoreValve™ system is indicated for use in patients with symptomatic heart disease due to either severe native calcific aortic stenosis **or failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve** who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥8% or at a ≥15% risk of mortality at 30 days).

Mortality in Lower Risk Patients: STS ≤7%: Corevalve High Risk Trial



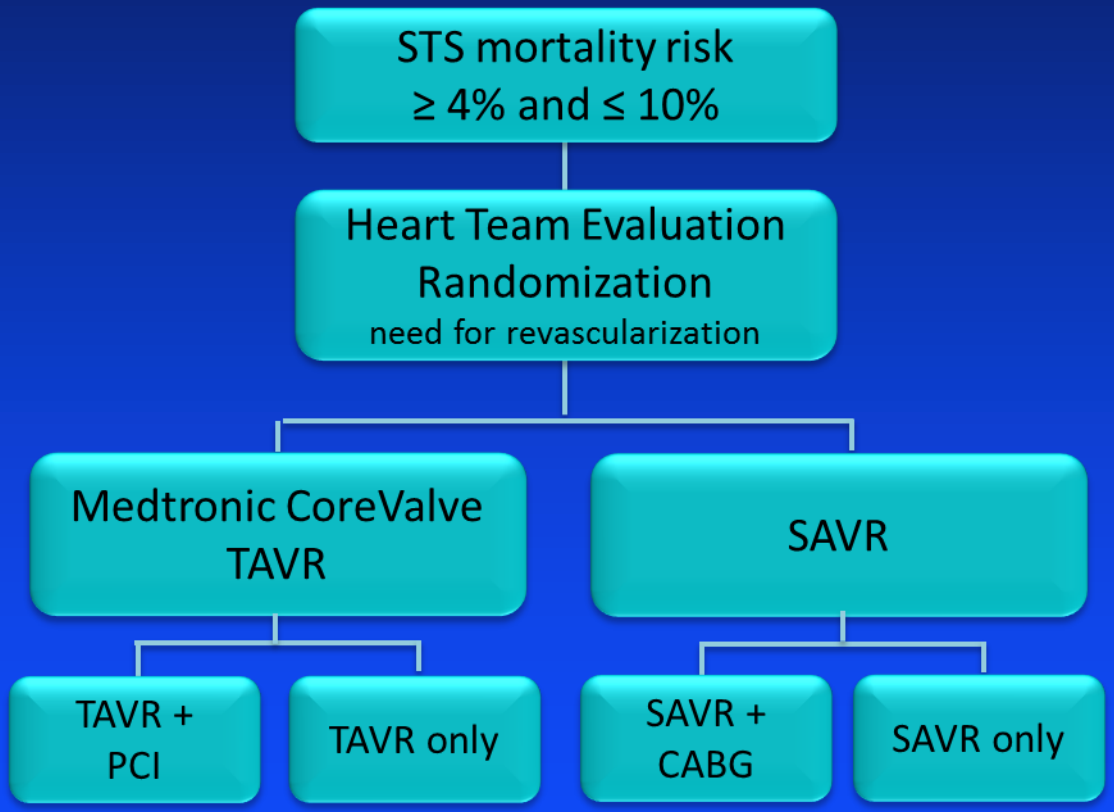
No. at Risk					
Transcatheter	202	197	191	182	128
Surgical	181	174	161	151	93

Ongoing UVM Research: CoreValve® SURTAVI Trial

Revised Enrollment: 3% or higher risk per CT surgeon.

- Evaluate the safety and efficacy of TAVI in Subjects with severe, symptomatic AS at intermediate surgical risk by randomizing Subjects to either SAVR or TAVI with the Medtronic CoreValve® System

- Enrolling approximately 2,500 Subjects randomized 1:1 to TAVI and SAVR in up to 75 European, Canadian, and US centers.

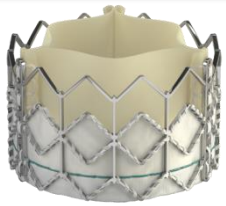


TAVR: A 10 Year Story of Technology and Treatment

2005 — First successful TAVR procedure in US

2007 — Landmark PARTNER clinical trials begin

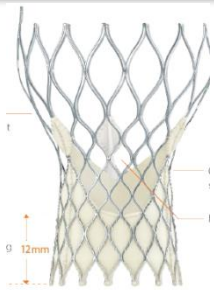
2011 — Edwards SAPIEN heart valve approved for inoperable patients



Edwards SAPIEN Heart Valve

2012 — Edwards SAPIEN heart valve approved for high-risk patients

2014 — Corevalve FDA Approval Extreme and High Risk Patients



Medtronic Corevalve

TAVR Conclusions: Evolution of a Minimally Invasive Option

- Aortic Stenosis is a fatal disease of the elderly
- TAVR saves lives in patients with no surgical option or at high risk for open heart surgery.
- TAVR technology is evolving to address small but real risk of complications including stroke and bleeding.
- Next steps: TAVR in lower risk patients, TAVR in two days.