Asymptomatic Severe Aortic Stenosis

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New York City

Disclosure Statement of Financial Interest

I, Torsten Vahl, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

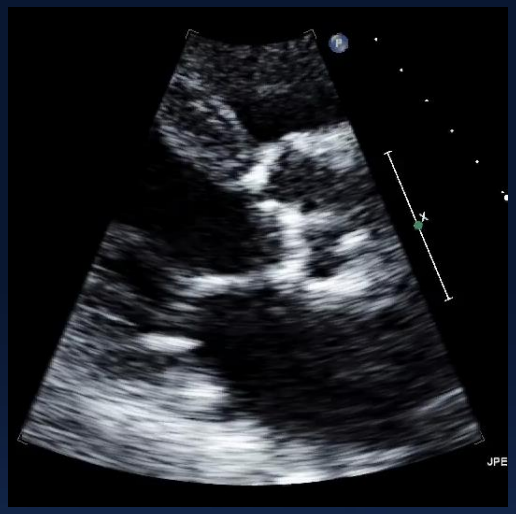
History

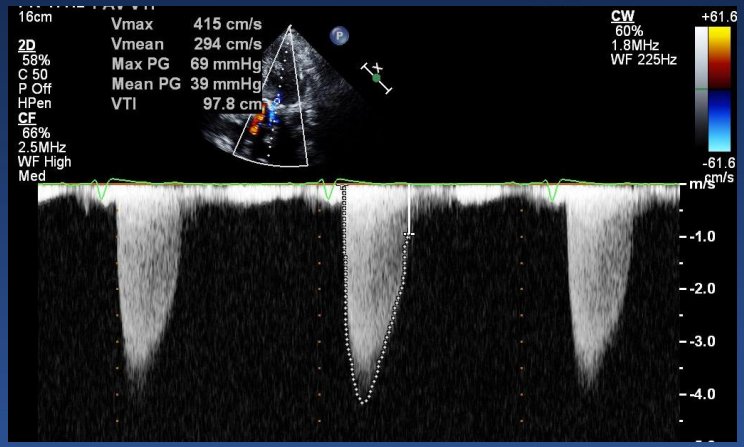
84 yoM with

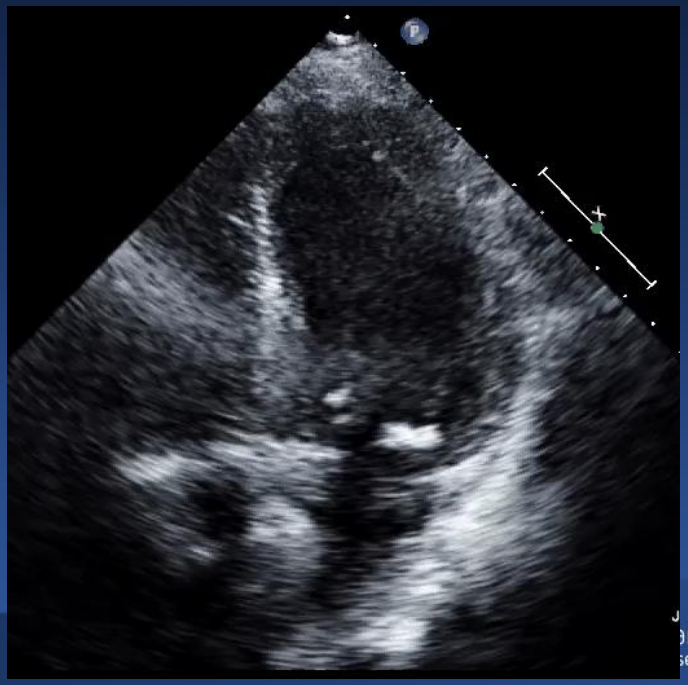
- HTN
- Hodgkins Lymphoma in remission
- CAD s/p 3-vessel CABG 2003
- Severe Aortic Stenosis
  Referred for TAVR evaluation for increase in PV to 4.2 m/s compared with 3.6 m/s 6 months ago. Patient denies any CP, SOB or syncope but family and cardiologist concerned that patient is less active than before.

TTE

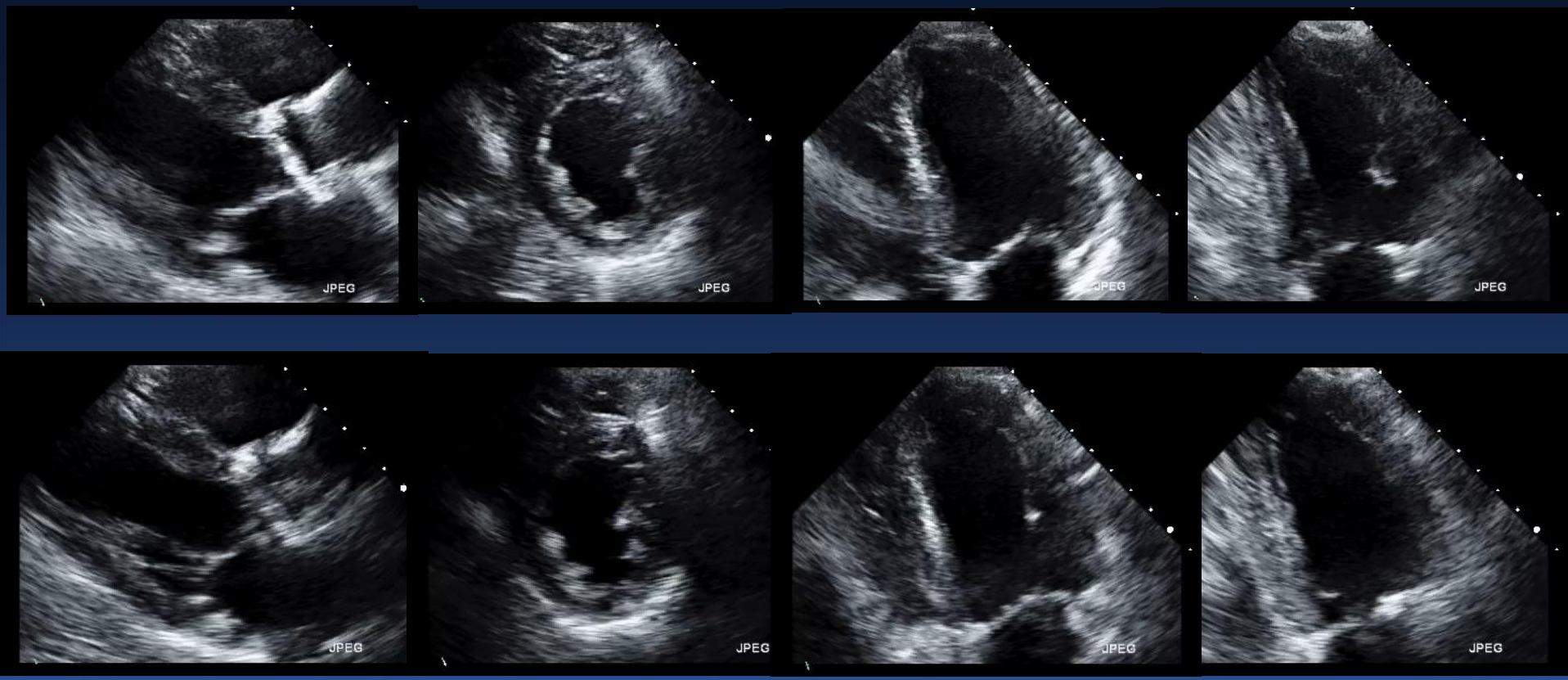
Echo Variable (TTE/TEE)	Measure
Jet Velocity	4.2 m/s
Mean Gradient	40.7 mmHg
Calculated AVA	0.7 cm^2
Calculated AVA index	0.4 cm^2/m^2
TTE/TEE annulus diameter	25.3 mm
Ejection Fraction	60%
Severity of AR	Trace
Severity of MR	Mild



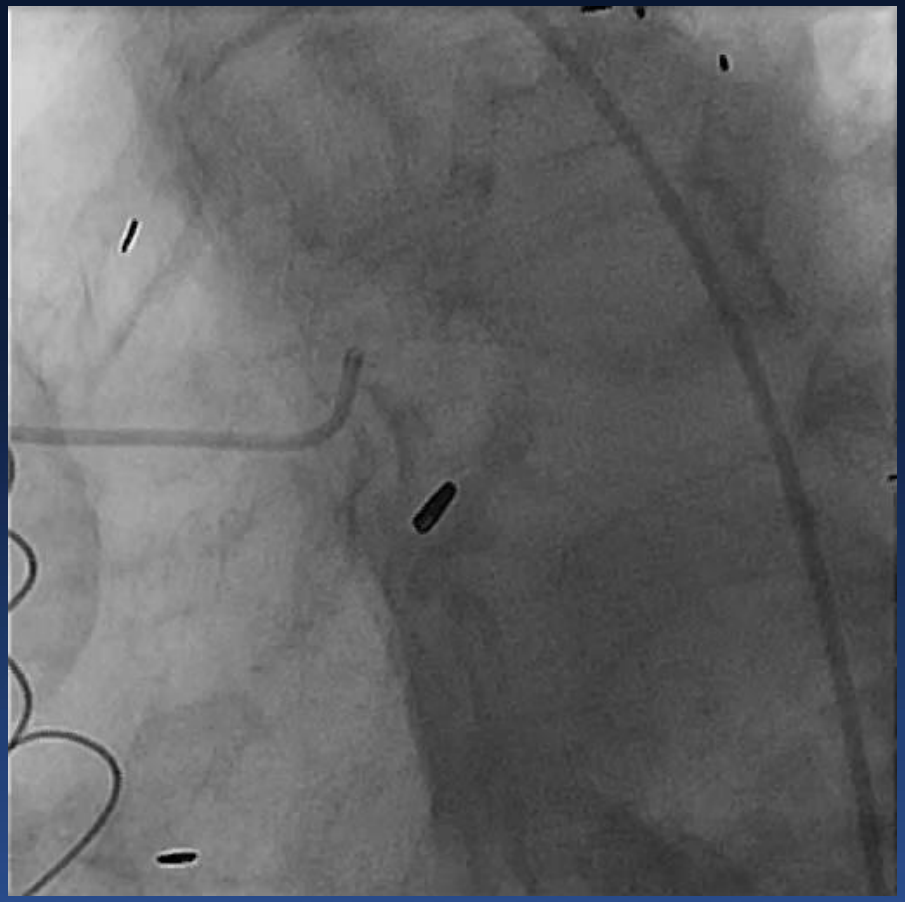


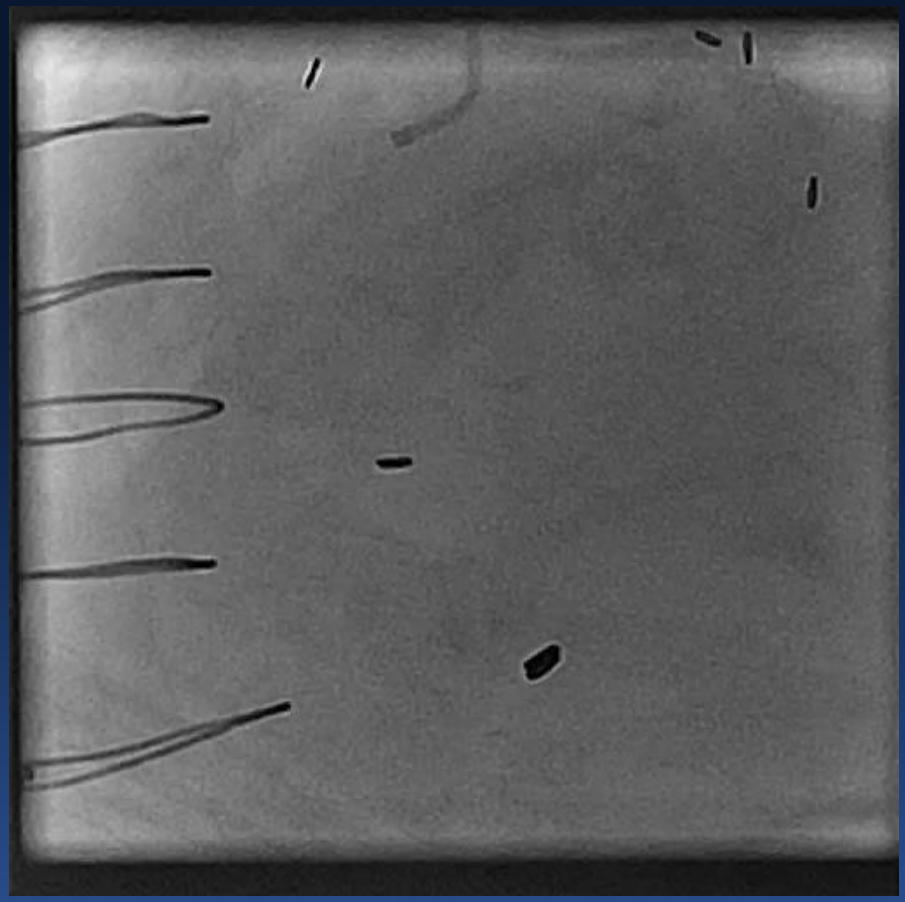


Stress Echo: 3:53 min Bruce protocol (5.6 METS), expected 6:35 min, stopped due to SOB, no CP
Rest BP 134/80, HR 56 Peak BP 154/64 HR 115
Inferior Hypokinesis, no evidence of ischemia

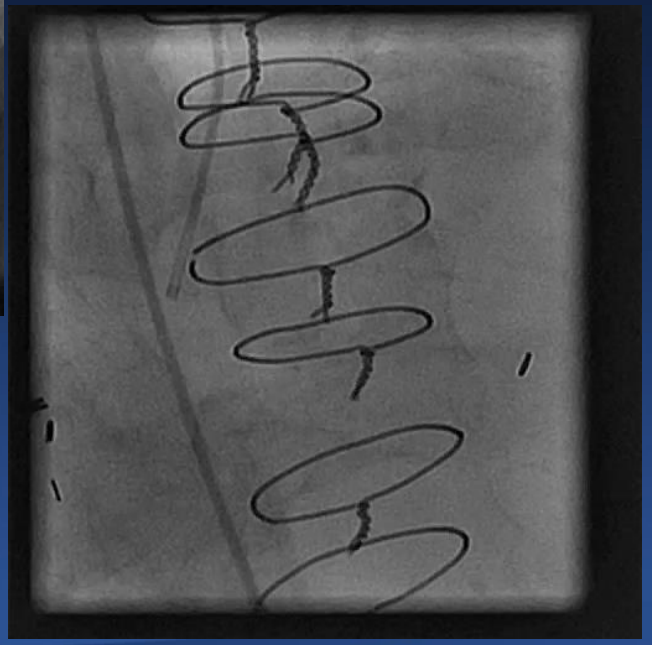


Coronary Angiogram

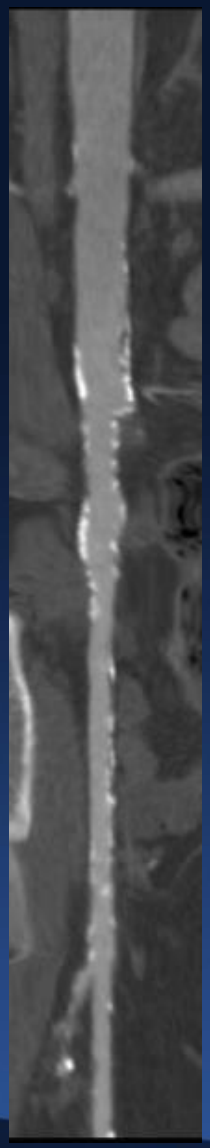




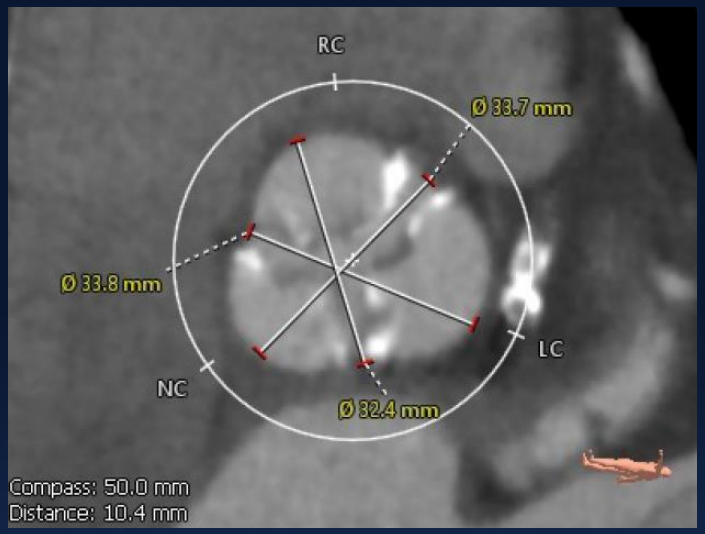
Coronary Angiogram

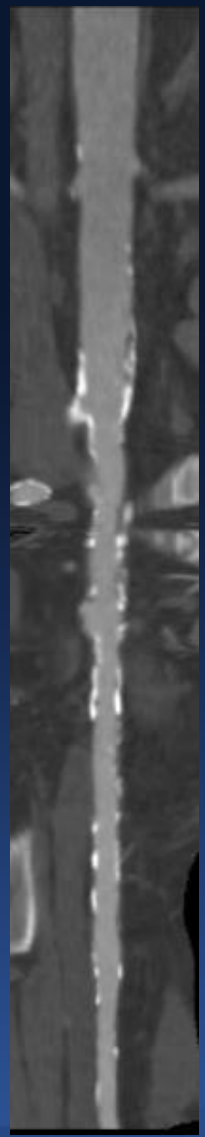


CT Angio




RC
Min. Ø: 22.9 mm
Max. Ø: 30.1 mm
Area derived Ø: 25.8 mm
Perimeter derived Ø: 26
Area: 523.9 mm²
Perimeter: 82.6 mm
LC
NC
Compass: 50.0 mm
Distance: 0.0 mm

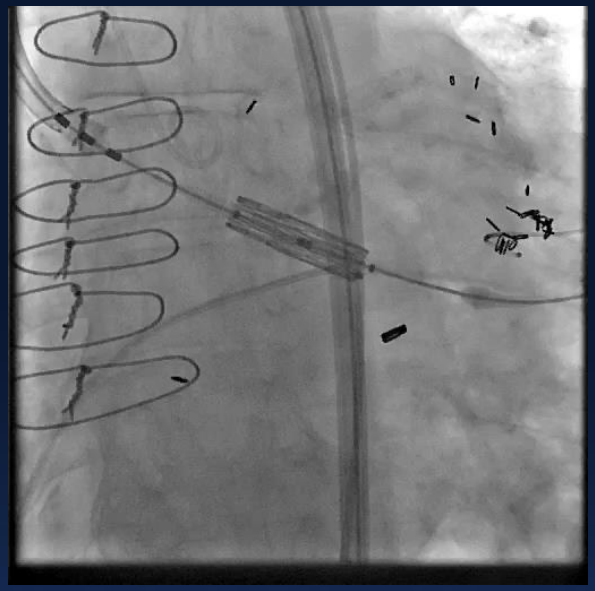

RC
Ø 33.7 mm
Ø 33.8 mm
LC
NC
Ø 32.4 mm
Compass: 50.0 mm
Distance: 10.4 mm

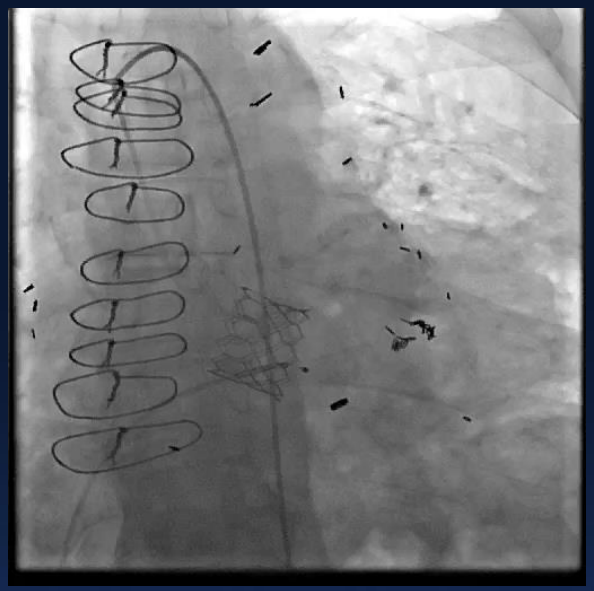


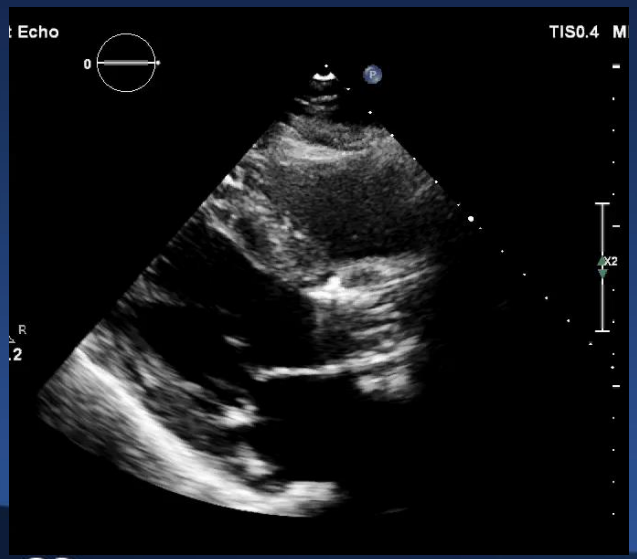

14.0 mm

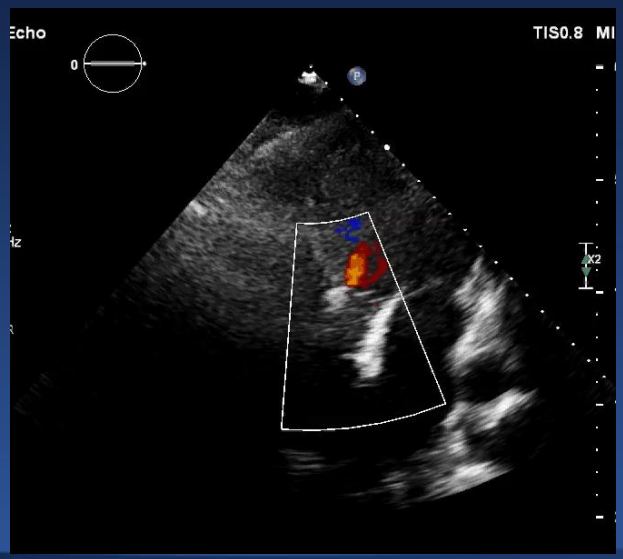

21.9 mm

TAVR with 26 mm Sapien 3 valve









Asymptomatic Severe Aortic Valvular Stenosis: Diagnostic Approaches and Therapeutic Strategies

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AMERICAN COLLEGE of CARDIOLOGY

DECEMBER 9 – 11, 2016
New York Hilton - Midtown

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ACC NY CV, New York City; Dec 9 – 11, 2016

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

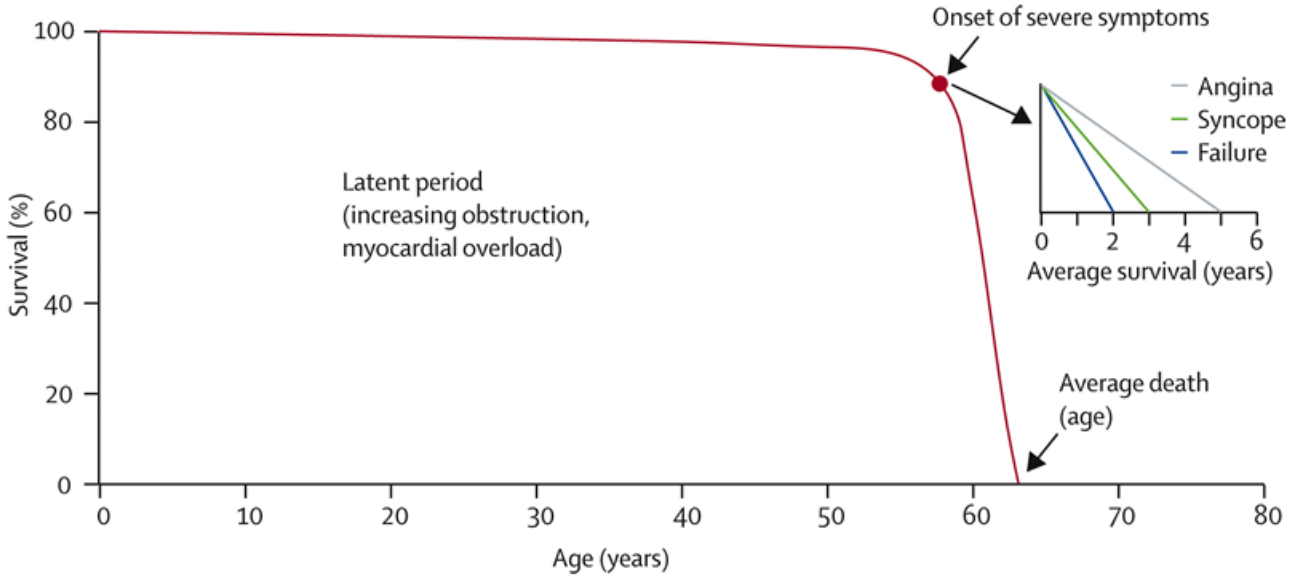
Affiliation / Financial Relationship	*Company*
• Grant / Research Support	Abbott, Boston Scientific, Edwards Lifescience, Medtronic, St. Jude Medical
• Consulting Fees / Honoraria	Abbott, Boston Scientific
• Shareholder / Equity	Claret, Valve Medical

AMERICAN COLLEGE of CARDIOLOGY

Asymptomatic Severe AS

Aortic Stenosis

By John Ross, Jr., M.D. and Eugene Braunwald, M.D.



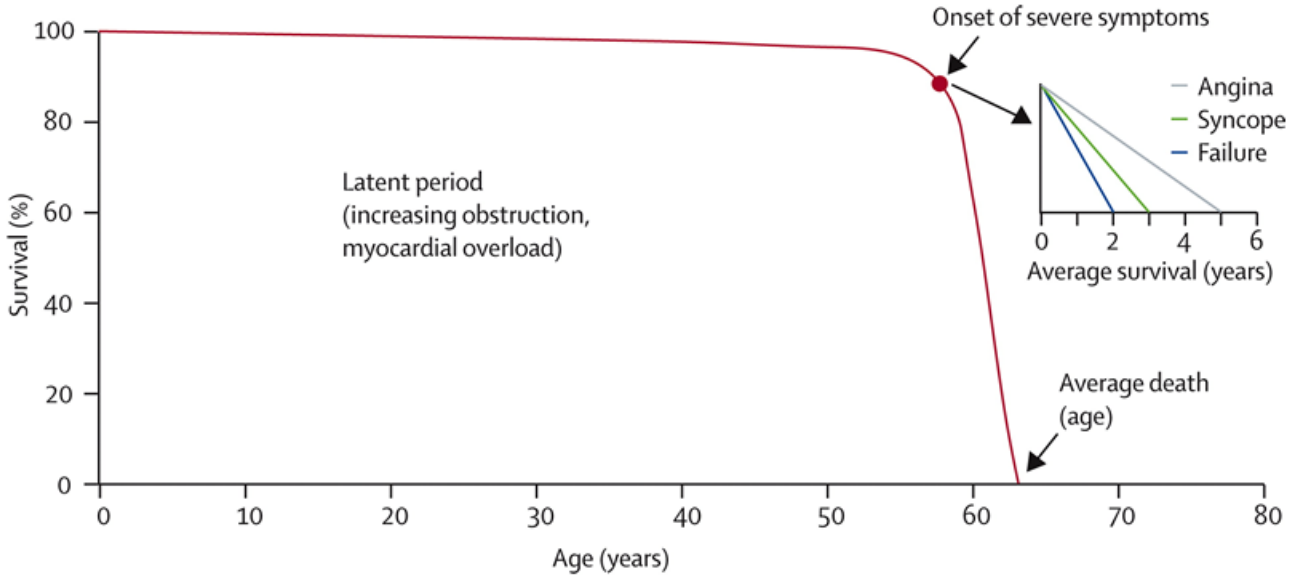
Natural Hx of AS = Medical Dogma!

The most revered and cited image
in all of cardiovascular medicine!

Circulation 1968;38:1S5 V-61-V-67

Aortic Stenosis

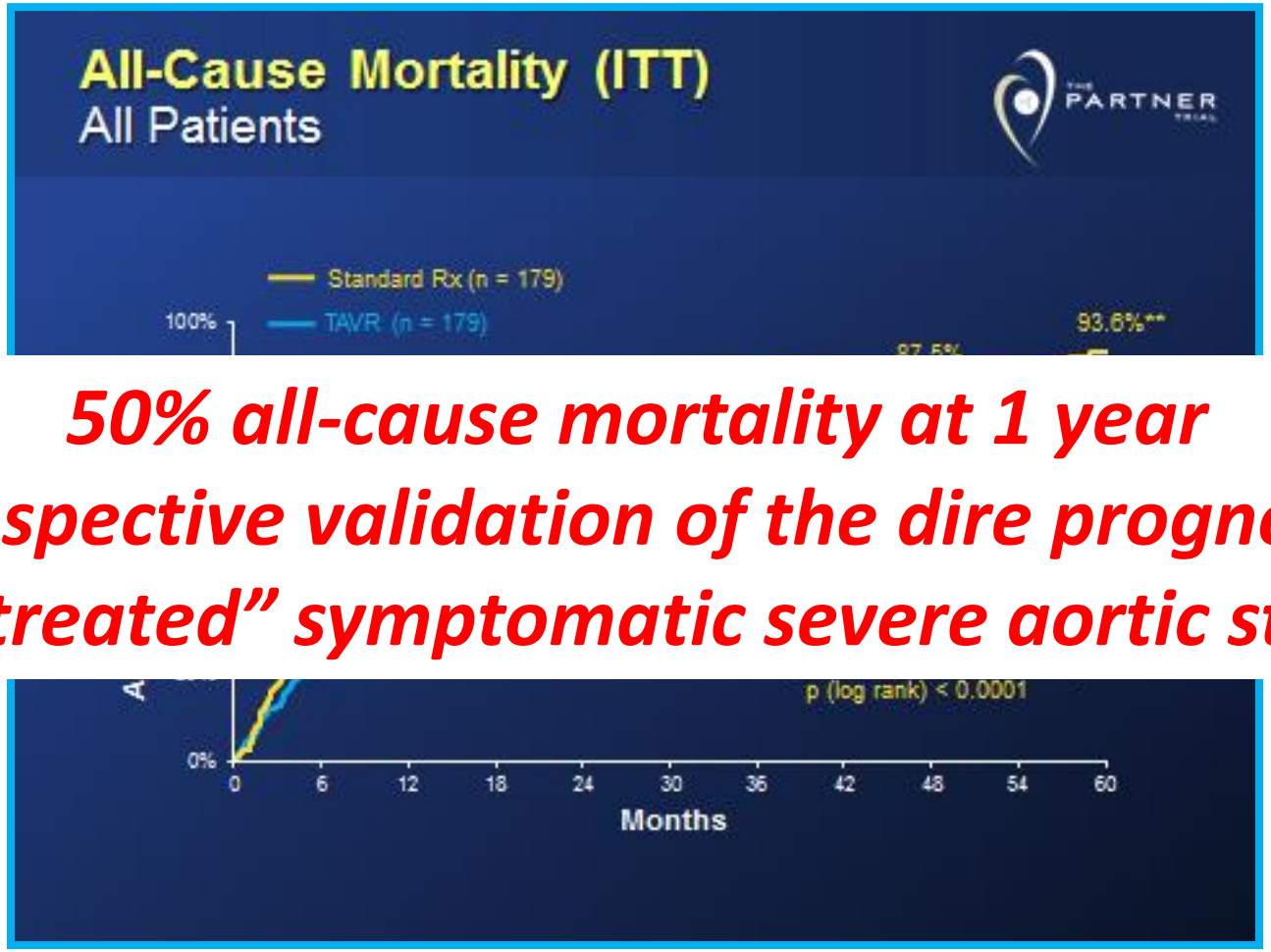
By JOHN ROSS, JR., M.D. AND EUGENE BRAUNWALD, M.D.



Based upon a handful of hastily gathered post-mortem clinical case studies in younger patients with usually rheumatic or congenital valvular aortic stenosis.

Circulation 1968;38:1S5 V-61-V-67

PARTNER 1B – RCT of Symptomatic Severe AS (inoperable patients)
TAVR vs. Standard Medical Therapy (n = 358 patients; 5-year follow-up)

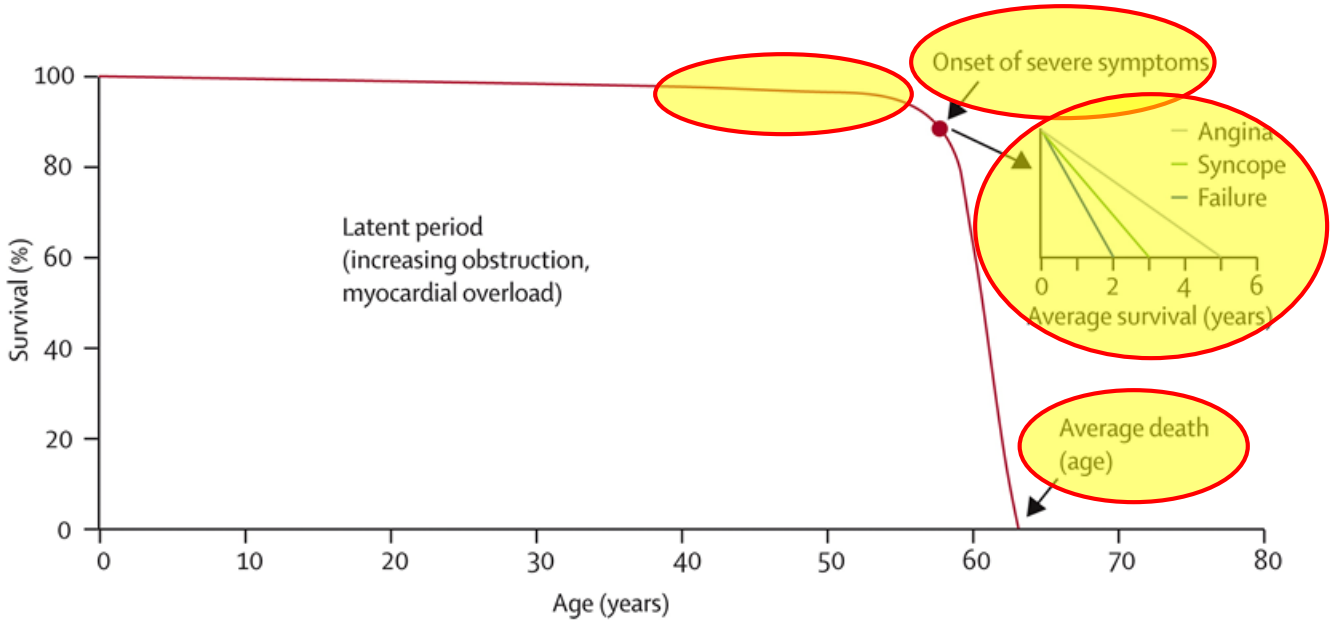


50% all-cause mortality at 1 year
Prospective validation of the dire prognosis
of "untreated" symptomatic severe aortic stenosis

Leon MB, et al. N Engl J Med 2010;363;1597-1607

Aortic Stenosis

By JOHN ROSS, JR., M.D. AND EUGENE BRAUNWALD, M.D.



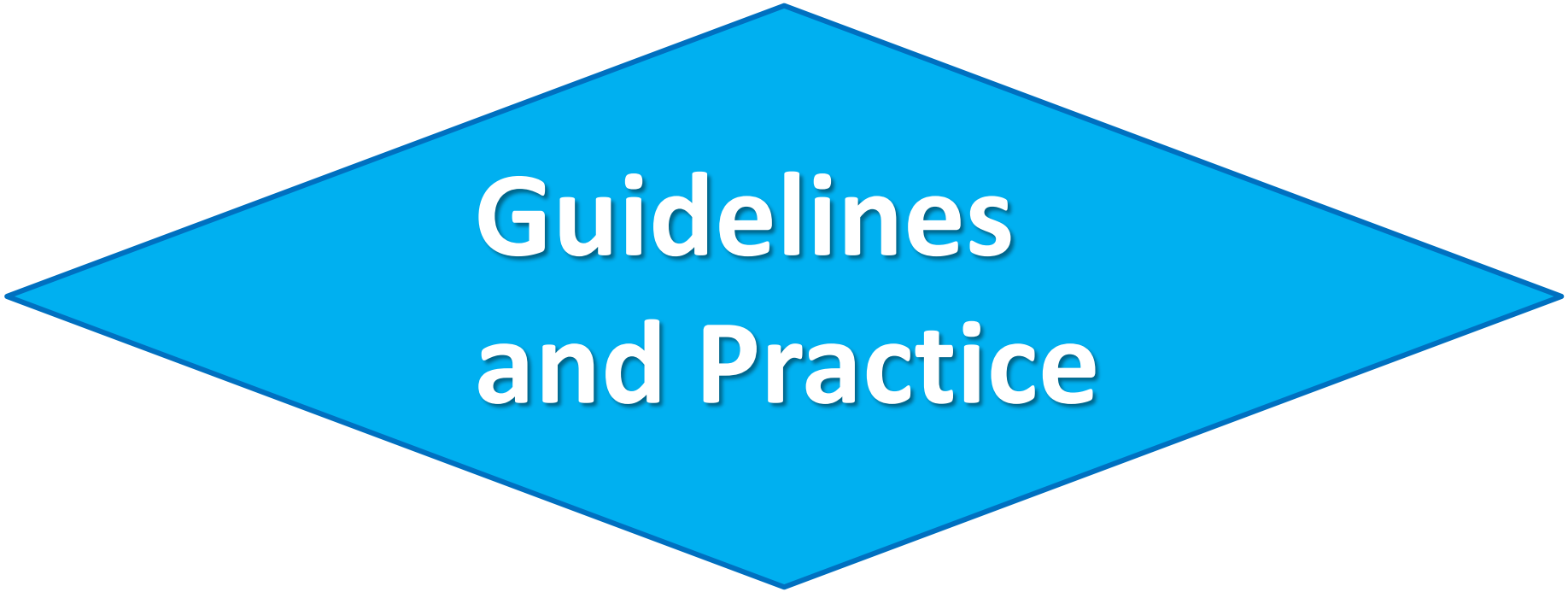
Based upon a handful of hastily gathered post-mortem clinical case studies in younger patients with usually rheumatic or congenital valvular aortic stenosis.

Circulation 1968;38:1S5 V-61-V-67

Currently, the most vexing management issues in caring for AS patients are:

1. Asymptomatic severe AS
2. Low flow – low gradient AS

Asymptomatic Severe AS



Recommendations and Levels of Evidence for Diagnosis, Follow-up, and Timing of Aortic Valve Replacement in Patients With Asymptomatic Severe Aortic Stenosis

	ACC/AHA	ESC/EACTS
Indications for aortic valve replacement		
Left ventricular ejection fraction <50%	I, B	I, C
Undergoing other cardiac surgery	I, B	I, C
Symptoms on exercise test clearly related to aortic stenosis	I, B	I, C
Decreased exercise tolerance	IIa, B	IIa, C
Exercise fall in systolic blood pressure	IIa, B	IIa, C
Very severe AS (PV≥5.0 m/s [ACC]; >5.5m/s [ESC] and low surgical risk	IIa, B	IIa, C

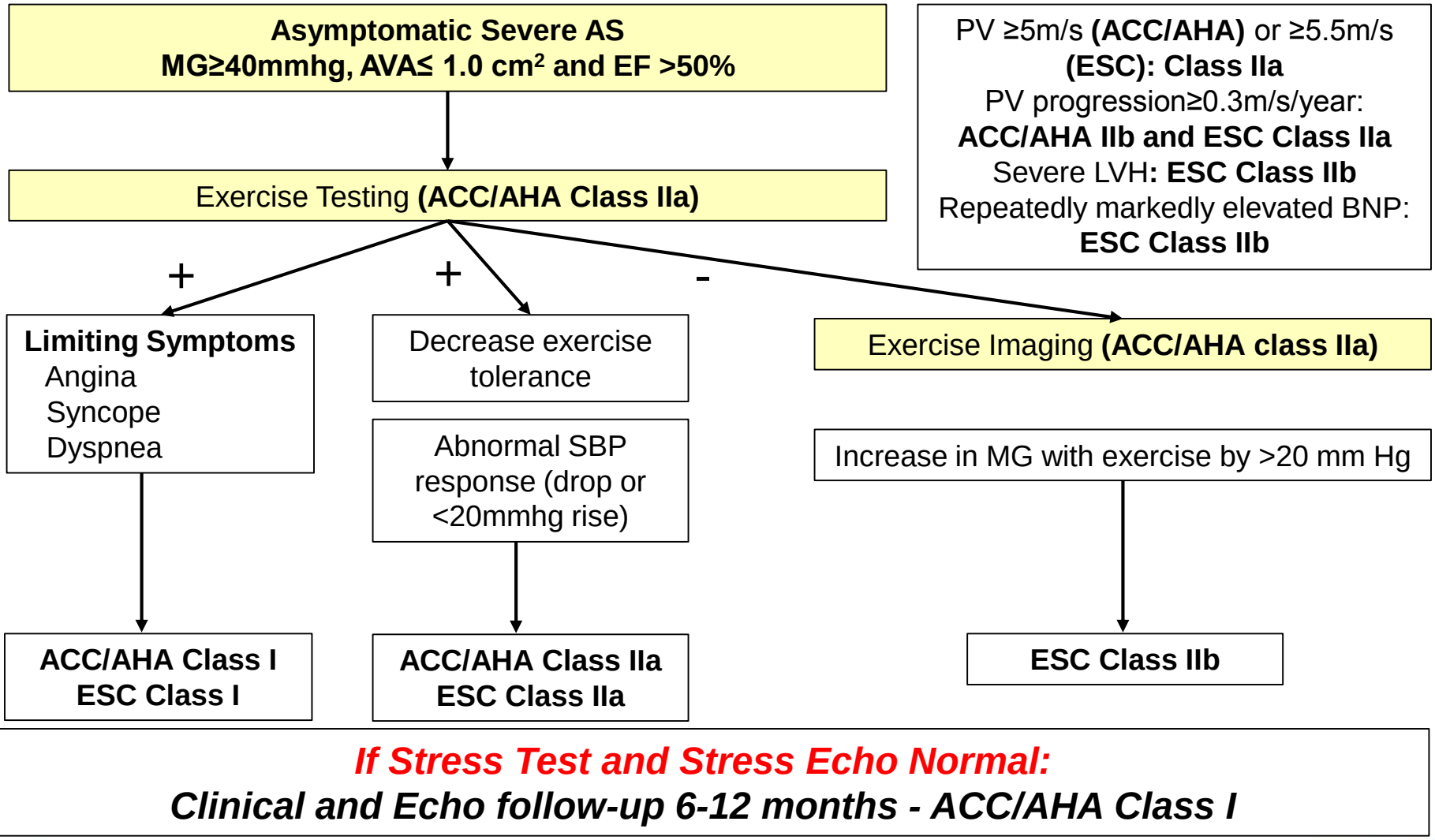
3 Class I indications…3 Class IIa indications…
Level of evidence B or C
No Randomized Trials!

Exercise testing	IIa, B	-
Exercise echocardiography	IIa, B	-
Follow-up		
Echocardiography every 6-12 months	1, C	-

ACC = American College of Cardiology; AHA = American Heart Association; EACTS = European Association for Cardio-Thoracic Surgery; European ESC = European Society of Cardiology

Nishimura et al. J Am Coll Cardiol. 2014; 63(22):e57-185
Vahanian et al. Eur Heart J. 2012; 33(19):2451-96

ACC/AHA and ESC/EACTS Guidelines



Nishimura et al. J Am Coll Cardiol. 2014; 63(22):e57-185
Vahanian et al. Eur Heart J. 2012; 33(19):2451-96

European Heart Journal (2003) 24, 1231–1243

ELSEVIER

EUROPEAN SOCIETY OF CARDIOLOGY

A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease

Bernard Iung[a*], Gabriel Baron[b], Eric G. Butchart[c], François Delahaye[d], Christa Gohlke-Bärwolf[e], Olaf W. Levang[f], Pilar Tornos[g], Jean-Louis Vanoverschelde[h], Frank Vermeer[i], Eric Boersma[j], Philippe Ravaud[b], Alec Vahanian[a]

***"In severe AS, an exercise test was performed in only 5.7%* of patients with no symptoms…"**

"This under-use may be explained by an insufficient implementation of the current guidelines and fear of complications or inexperience in exercise testing…"

Why Early SAVR in Asymptomatic Severe AS is *Rarely Performed?*

Sudden Death with Asymptomatic AS	Peri-operative Mortality with Surgery
~1-2% per year	*~1-5%*

The dominant strategy is watchful waiting (active surveillance)!

Généreux et al. J Am Coll Cardiol 2016;67:2263–88

Practical Issues with *"Watchful Waiting" Strategy*

- Clinicians still fear stress tests with severe AS patients; low penetration and underused
- Stress Imaging requires expertise and specific set-up that most community hospitals don't have
- Sub-optimal follow-up and lost of follow-up is frequent
- Many sudden deaths occurred in Asx patients with no Class I indication of AVR and no preceding symptoms
- ***"Wishful Thinking" Strategy…***

Why Early SAVR in Asymptomatic Severe AS is *Rarely Performed?*

Sudden Death with Asymptomatic AS	Peri-operative Mortality with Surgery
~1-2% per year	*~1-5%*

Is TAVR a better option for asymptomatic patients?

Généreux et al. J Am Coll Cardiol 2016;67:2263–88

Sapien 3 TAVR

European Heart Journal
doi:10.1093/eurheartj/ehw112

Earl … es
after …
repl…
inter… s

Sushee… tt Lim[4],
Kevin L… er[8,9],
Samir … os[2],
Wilson …
Jonatho…
Raj R. N…
Michael…

Asymptomatic Severe AS:
Rationale for Early AVR

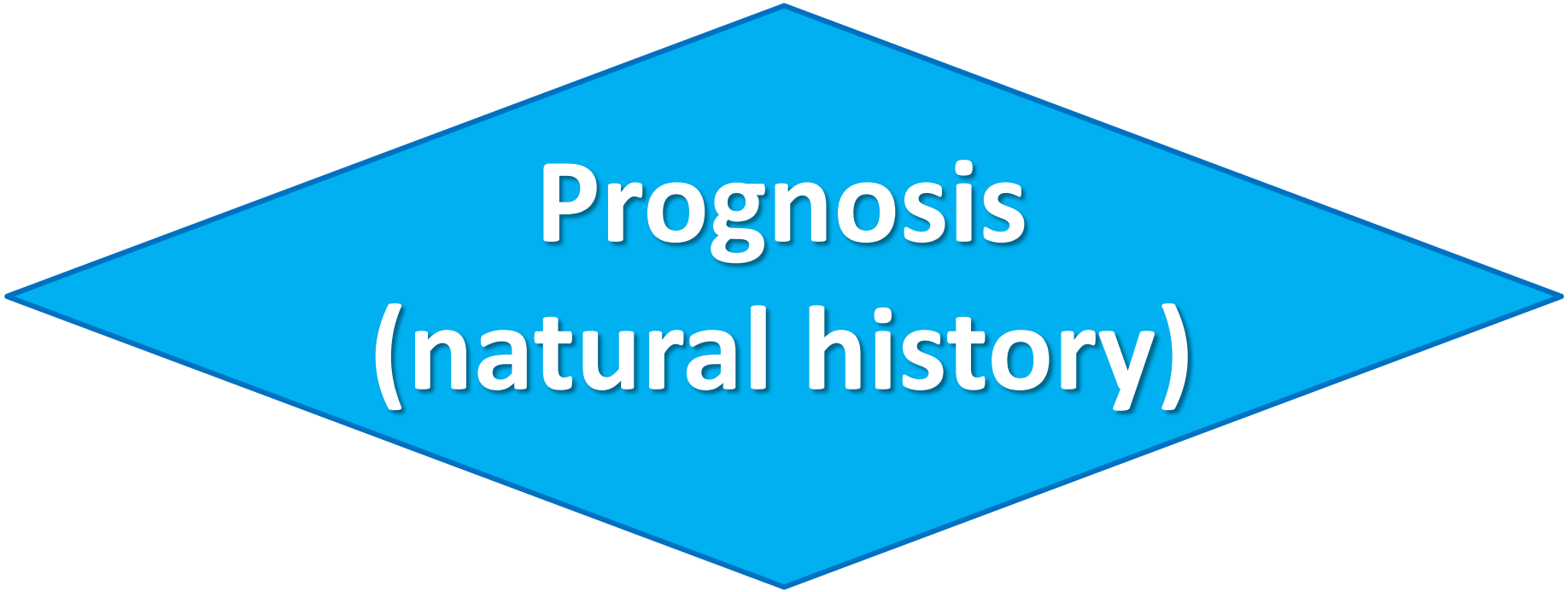
Pros

- Reduces irreversible myocardial dysfunction
- Decreased operative risk for asymptomatic patients
- Presence of latent symptoms; AS progression highly variable; potential for very rapid deterioration; risk of late (or too late) symptom reporting
- Increasing STS with time… increases surgical risk
- Sudden death without preceding symptoms

Cons

- Mortality low among the specific subset of low-risk and truly asymptomatic patients with normal stress test and stress echo
- Frequent follow-up could potentially identify patients ready for AVR in a timely fashion
- Inherent procedural mortality and morbidities of AVR
- Long-term complications of AVR (anticoagulation, need for re-op, endocarditis, thrombosis, etc.)

Asymptomatic Severe AS



What is the Epidemiology of Asx Severe AS Patients?

- ***~40-50%*** *of all severe AS from major echo databases* [1,2,3]
  - ~10-20% are bicuspid
  - ~20-25% have multiple valve disease, clinically significant CAD, prior AVR
- ***Isolated Asymptomatic Severe AS represents ~25-30%*** of all severe AS referred to echo lab
- ~500,000 patients > 65 years old in US[4]

[1]Pellikka et al. Circulation. 2005;111:3290-3295
[2]Pai et al. Ann Thorac Surg 2006;82:2116 –22
[3]Kitai et al. Heart 2011;97:2029e2032
[4]Source U.S. Census Bureau, 2014

Asymptomatic Severe AS

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Natural History, Diagnostic Approaches,

ABSTRACT

Aortic stenosis (AS) is one of the most common valvular diseases encountered in clinical practice. Current guidelines recommend aortic valve replacement (AVR) when the aortic valve is severely stenotic and the patient is symptomatic; however, a substantial proportion of patients with severe AS are asymptomatic at the time of first diagnosis. Although specific morphological valve features, exercise testing, stress imaging, and biomarkers can help to identify patients with asymptomatic severe AS who may benefit from early AVR, the optimal management of these patients remains uncertain and controversial. The current report presents a comprehensive review of the natural history and the diagnostic evaluation of asymptomatic patients with severe AS, and is followed by a meta-analysis from reported studies comparing an early AVR strategy to active surveillance, with an emphasis on the level of evidence substantiating the current guideline recommendations. Finally, perspectives on directions for future investigation are discussed.

(J Am Coll Cardiol 2016;67:2263–88)

What is the Prognosis of Asx Severe AS Patients?

Systematic Review and Meta-Analysis

- MEDLINE, Embase, and Cochrane Central Register of Controlled Trials
- Severe AS asymptomatic patients
- >18 years old and reporting outcomes
- 503 articles
- 27 pertenent observational studies identified
- ***4 studies with observational comparison of AVR vs. Medical treatment; N= 2,486 patients***

Généreux et al. J Am Coll Cardiol 2016;67:2263–88

Studies Comparing AVR vs. Observation in Asymptomatic Severe AS Patients; *N=2,486*

Authors	AS definition	N	Age	Female	Follow-up (median)
Pellikka et al.1990	Severe AS; Doppler PV ≥4m/s	143 30 AVR 113 Medical	72 (mean) 40 to 94	38%	AVR 21 m Medical 20 m
Pai et al. 2006	Severe AS AVA <0.8cm^2	338 99 AVR 239 Medical	71±15	49%	3.5 y
Kang et al. 2010	Very severe AS AVA ≤0.75 cm^2 AND PV ≥4.5 m/s or a MG ≥50 mmHg	197: 102 AVR 95 Medical	63±12	50%	AVR 1265 d Medical 1769 d
Taniguchi et al. 2015	Severe AS AVA: <1cm2 MG: >40mmhg PV: >4m/s	1808: 291 AVR 1517 Medical	AVR 71.6±8.7 Medical 77.8±9.4	60%	1361 d

Sudden Death in Asx Severe AS

Studies	Sudden death (n)	Preceded by symptoms (n)	Not preceded by symptoms (n)
Pellikka et al. 1990 n=143	***3***	***3***	***0***
Rosenheck et al. 2000; n=128	1	-	-
Amato et al. 2001; n=66	***4***	***-***	***4***
Lancellotti et al 2005; n=69	2	-	-
Pellikka et al. 2005; n=622	***11***	***0***	***11***
Avakian et al. 2008; n=133	***7***	***3***	***4***
Levy et al. 2014; n=43	0		

~0.8% pts w Sudden death per year;
Among all the Sudden Deaths,
73% (32/44) pts had
no classical preceding AS symptoms

*6 cardiac deaths occurred: 1 sudden without symptoms and 5 cardiac but with patients asymptomatic at the last follow-up

Abnormal Stress Tests in Asx Severe AS

	Moderate-Severe AS			Severe AS only		
	% Abnormal Stress Test	n	N	% Abnormal Stress Test	n	N
Takeda et al. 2001	27%	13	49			
Amato et al. 2001				67%	44	66
Alborino et al. 2002	60%	18	30			
Das et al. 2003	29%	19	65			
Das et al. 2005	37%	46	125			

Abnormal Stress Test in Asx Severe AS:

Range: 26-67%

~50% pts have Abnormal Stress Test

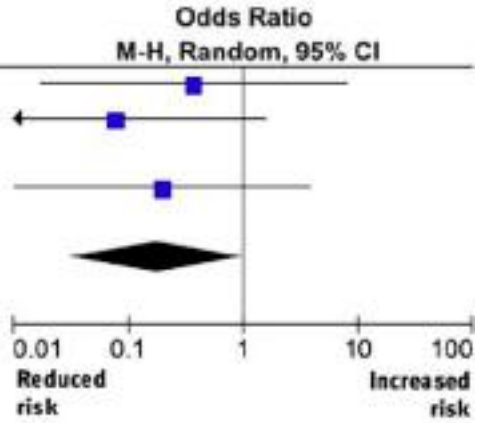
Rajani et al. 2010	15%	3	20	39%	7	18
Donal et al. 2011	33%	69	207			
Levy et al. 2014				28%	12	43
Total		**286**	**784**		**212**	**434**
% Abnormal Stress test	***Range: 15-66%***	***Pooled: 36.5%***		***Range: 28-67%***	***Pooled: 48.8%***	

Meta-Analysis of Prognostic Value of Stress Testing in Patients With Asymptomatic Severe Aortic Stenosis

Asim M. Rafique, MD[a], Simon Biner, MD[a,b], Indraneil Ray, MD[a], James S. Forrester, MD[a], Kirsten Tolstrup, MD[a], and Robert J. Siegel, MD[a,*]

Study or Subgroup	Normal Stress Test	Abnormal Stress Test	Weight	Odds Ratio M-H, Random, 95% CI
Peidro 2007	0/35	2/67	32.2%	0.37 [0.02, 7.90]
Lancellotti 2005	0/43	3/26	33.5%	0.08 [0.00, 1.56]
Das 2005	0/79	0/46	-	-
Amato 2001	0/22	4/44	34.3%	0.20 [0.01, 3.89]
Total	**0/179**	**9/183**	**100.0%**	**0.18 [0.03, 1.01]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.52$, df = 2 (P = 0.77); $I^2 = 0\%$
Test for overall effect: Z = 1.95 (P = 0.05)



Abnormal stress test associated with ~6 fold increase in Cardiac Death

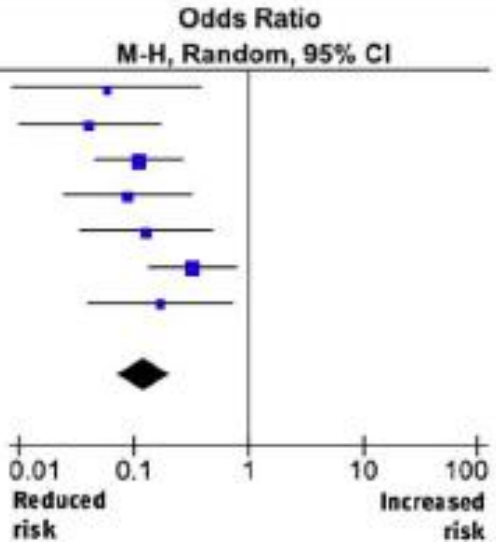
Rafique et al. Am J Cardiol 2009;104:972–977

Meta-Analysis of Prognostic Value of Stress Testing in Patients With Asymptomatic Severe Aortic Stenosis

Asim M. Rafique, MD[a], Simon Biner, MD[a,b], Indraneil Ray, MD[a], James S. Forrester, MD[a], Kirsten Tolstrup, MD[a], and Robert J. Siegel, MD[a,*]

Study or Subgroup	Normal Stress Test	Abnormal Stress Test	Weight	Odds Ratio M-H, Random, 95% CI
Alborino 2002	2/12	14/18	7.1%	0.06 [0.01, 0.38]
Amato 2001	3/22	35/44	11.4%	0.04 [0.01, 0.17]
Das 2005	10/79	26/46	22.3%	0.11 [0.05, 0.27]
Lancellotti 2005	4/43	14/26	13.3%	0.09 [0.02, 0.32]
Marechaux 2007	10/26	20/24	12.6%	0.13 [0.03, 0.47]
Peidro 2007	10/35	37/67	22.5%	0.32 [0.13, 0.78]
Takeda 2001	13/36	10/13	10.9%	0.17 [0.04, 0.73]
Total	**52/253**	**156/238**	**100.0%**	**0.12 [0.07, 0.21]**

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 8.08$, df = 6 (P = 0.23); $I^2 = 26\%$
Test for overall effect: Z = 7.63 (P < 0.00001)



Abnormal stress test associated with ~8 fold increase in CV Events

Rafique et al. Am J Cardiol 2009;104:972–977

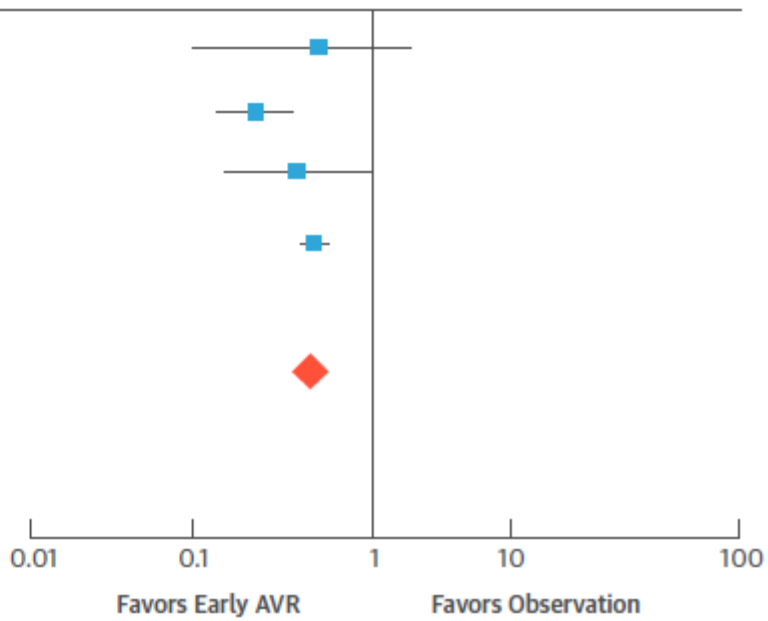
All-Cause Mortality
AVR vs. Medical Therapy in Asymptomatic Severe AS; N=2,486

A

Study	Early AVR Events	Early AVR Total	Observation Events	Observation Total	Weight	Risk Ratio M-H Random, 95% CI
Pellikka et al. (17)	2	30	14	113	11.5%	0.54 [0.13, 2.24]
Pai et al. (19)	10	99	147	239	31.4%	0.16 [0.09, 0.30]
Kang et al. (25)	3	102	10	95	13.9%	0.28 [0.08, 0.98]
Taniguchi et al. (26)	40	291	542	1517	43.2%	0.38 [0.29, 0.52]
Total (95% CI)		**522**		**1964**	**100%**	**0.29 [0.17, 0.51]**
Total events	55		713			

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 6.91$, df = 3 (P=0.07); $I^2 = 57\%$

Test for overall effect: Z = 4.35 (P<0.0001)



Unadjusted: ~3.5 fold increase in All-Cause Mortality

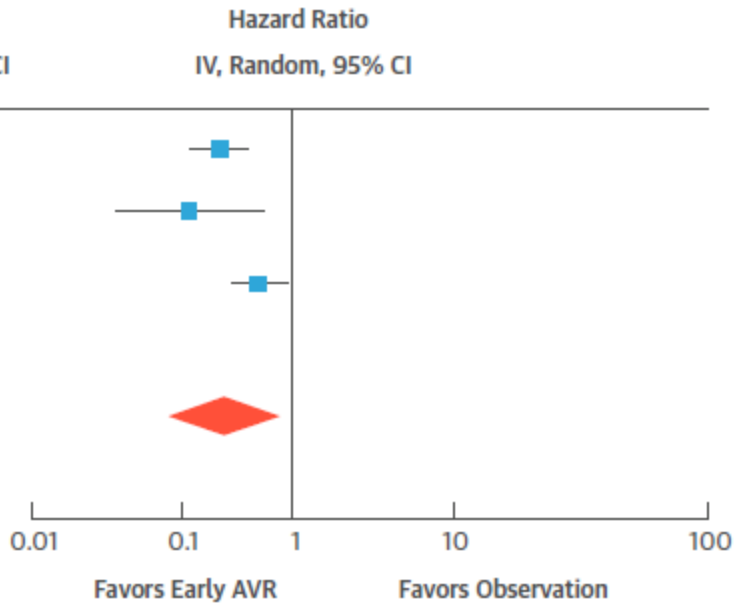
All-Cause Mortality
AVR vs. Medical Therapy in Asymptomatic Severe AS; N=2,486

B

Study	Log [Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Pai et al. (19)	-1.772	0.2707	38.2%	0.17 [0.10, 0.29]
Kang et al. (25)	-1.9661	0.786	22.1%	0.14 [0.03, 0.65]
Taniguchi et al. (26)	-0.5108	0.2069	39.8%	0.60 [0.40, 0.99]
Total (95% CI)			**100%**	**0.27 [0.09, 0.77]**

Heterogeneity: $Tau^2 = 0.67$; $Chi^2 = 15.22$, df = 2 (P=0.005); $I^2 = 87\%$

Test for overall effect: Z = 2.46 (P=0.01)



Adjusted: ~3.7 fold increase in All-Cause Mortality

Evaluation of Initial Surgical Versus Conservative Strategies in Patients With Asymptomatic Severe Aortic Stenosis:

-Results from the CURRENT AS registry-

Tomohiko Taniguchi, MD

Kyoto University Graduate School of Medicine

Takeshi Morimoto, MD, MPH; Hiroki Shiomi, MD; Kenji Ando, MD; Norio Kanamori, MD; Koichiro Murata, MD; Takeshi Kitai, MD; Yuichi Kawase, MD; Chisato Izumi, MD; Makoto Miyake, MD; Hirokazu Mitsuoka, MD; Masashi Kato, MD; Yutaka Hirano, MD; Shintaro Matsuda, MD; Kazuya Nagao, MD; Tsukasa Inada, MD; Tomoyuki Murakami, MD; Yasuyo Takeuchi, MD; Keiichiro Yamane, MD; Mamoru Toyofuku, MD; Mitsuru Ishii, MD; Eri Minamino-Muta, MD; Takao Kato, MD; Moriaki Inoko, MD; Tomoyuki Ikeda, MD ; Akihiro Komasa, MD; Katsuhisa Ishii, MD; Kozo Hotta, MD; Nobuya Higashitani, MD; Yoshihiro Kato, MD; Yasutaka Inuzuka, MD; Chiyo Maeda, MD: Toshikazu Jinnai, MD; Yuko Morikami, MD; Ryuzo Sakata, MD and

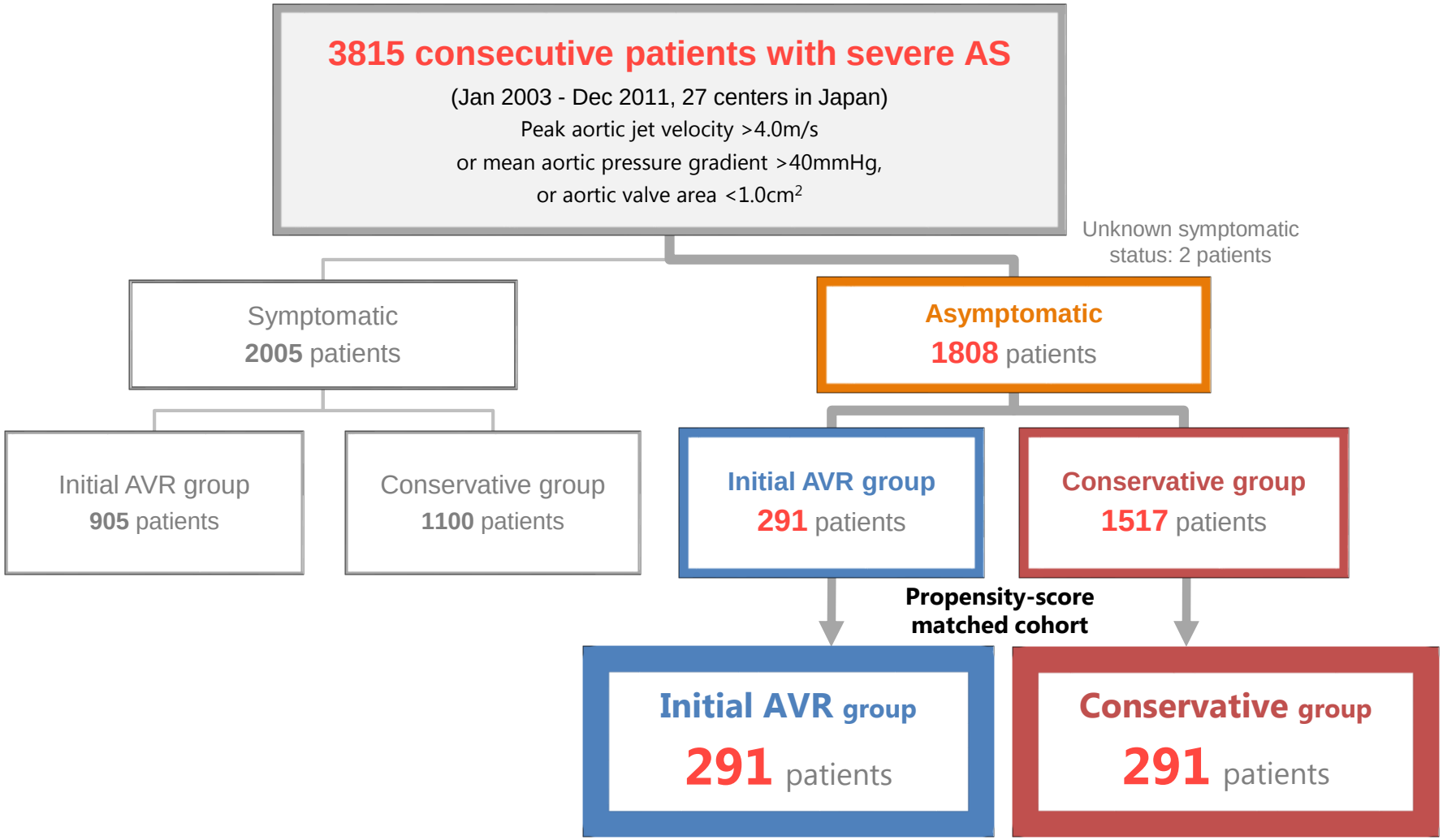
Takeshi Kimura, MD

On behalf of the CURRENT AS registry Investigators

CURRENT AS registry

Main Analysis Set:

Propensity-score Matched Cohort

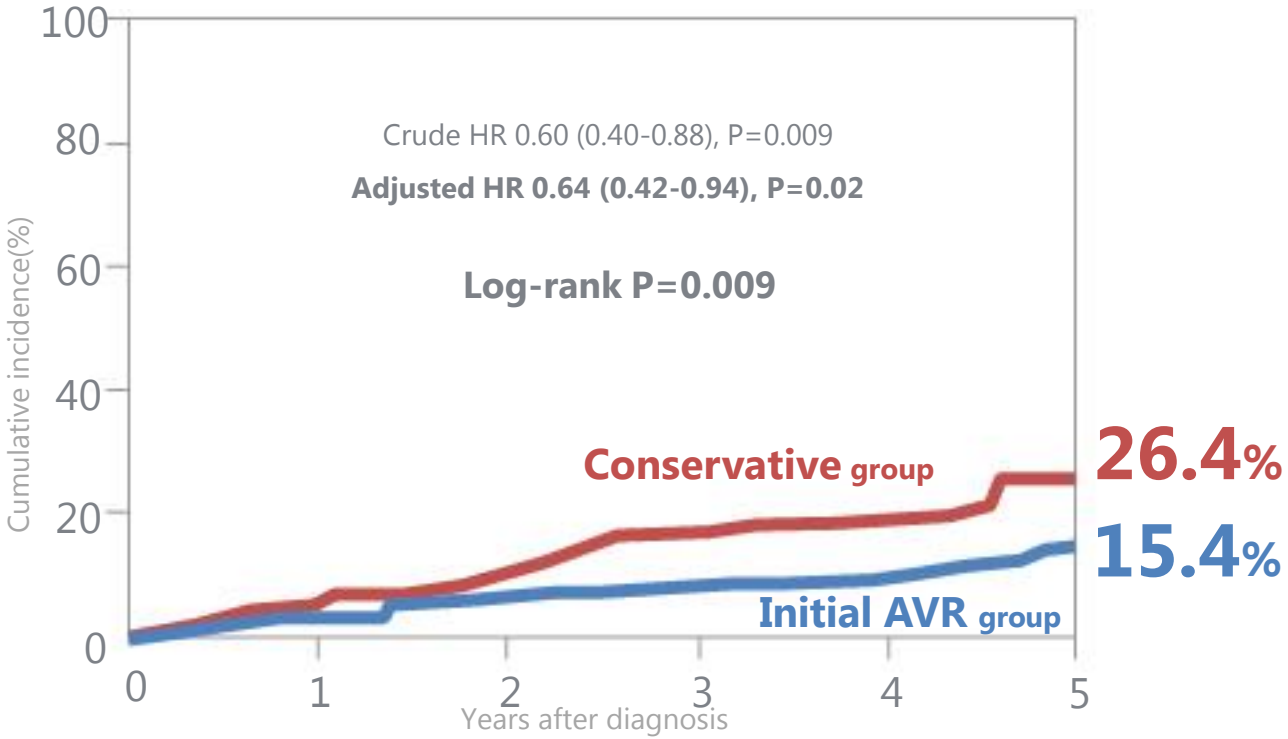


Taniguchi T et al. J Am Coll Cardiol 2015;66:2827-38

CURRENT AS registry

Primary outcome measure

All-cause death

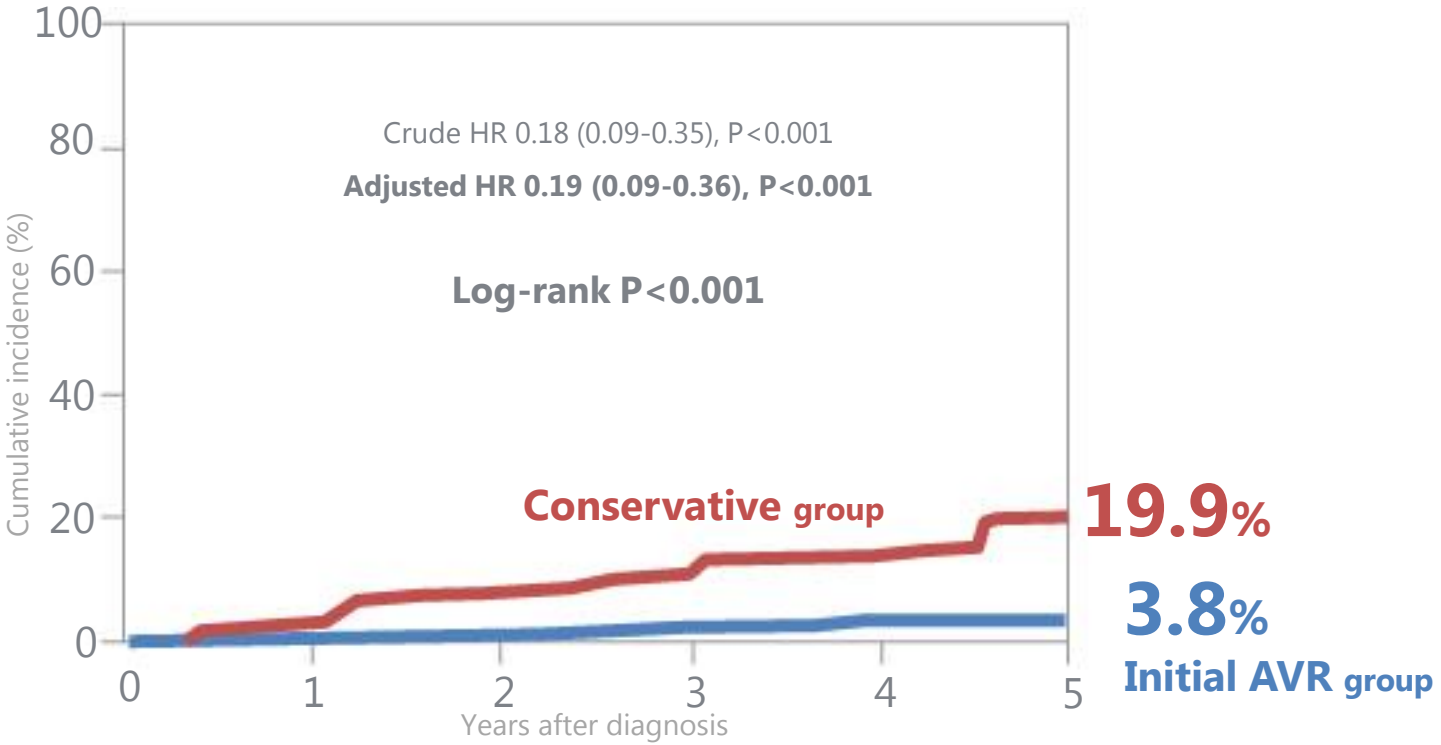


Interval	0d	30d	1y	3y	5y
Conservative group					
N of patients with at least 1 event		3	20	48	60
N of patients at risk	291	279	252	178	72
Cumulative incidence		1.1%	7.2%	17.9%	26.4%
Initial AVR group					
N of patients with at least 1 event		1	14	25	33
N of patients at risk	291	286	266	188	75
Cumulative incidence		0.3%	4.9%	9.0%	15.4%

Taniguchi T et al. J Am Coll Cardiol 2015;66:2827-38

Primary outcome measure

Heart failure hospitalization



Interval	0d	30d	1y	3y	5y
Conservative group					
N of patients with at least 1 event		0	8	31	39
N of patients at risk	291	279	246	161	63
Cumulative incidence		0%	3.0%	13.0%	19.9%
Initial AVR group					
N of patients with at least 1 event		0	3	6	8
N of patients at risk	291	286	264	185	75
Cumulative incidence		0%	1.1%	2.4%	3.8%

The results from the adjusted analysis conducted as a sensitivity analysis were fully consistent with those from the unadjusted analysis.

Taniguchi T et al. J Am Coll Cardiol 2015;66:2827-38

Asymptomatic Severe AS

Clinical Outcome in Asymptomatic Severe Aortic Stenosis

Insights From the New Proposed Aortic Stenosis Grading Classification

Patrizio Lancellotti, MD, PHD,* Julien Magne, PHD,* Erwan Donal, MD, PHD,† Laurent Davin, MD,* Kim O'Connor, MD,*‡ Monica Rosca, MD,* Catherine Szymanski, MD,* Bernard Cosyns, MD, PHD,§ Luc A. Piérard, MD, PHD*

Liège and Brussels, Belgium; Rennes, France; and Quebec, Canada

"Truly" Asymptomatic Severe AS

N=150 with AVA <1cm^2 (no gradient criteria)

Exclusion: **1) LVEF <55%, 2) other moderate-severe valve disease, 3) Atrial Fibrillation, 4) COPD, *5) positive stress test,* 6) incapacity to perform stress test**

Endpoint: **CV death or need for AVR motivated by the development of symptoms or LVEF<50%**

Clinical Outcome in Asymptomatic Severe Aortic Stenosis

Insights From the New Proposed Aortic Stenosis Grading Classification

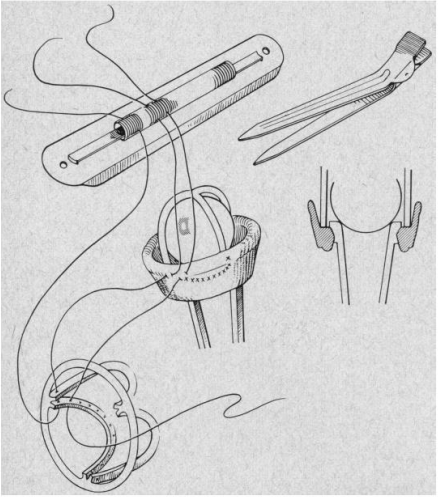
- ***51% (76/150) events*** at a mean follow-up ***27 months***
- ***6% (9/150) deaths;*** 5.3% (8/150) cardiac deaths

CV events at FU: 29% at 1 year,
49% at 2 years,
60% at 3 years

  - Positive stress test during follow-up: 8 (11%)
  - *LVEF <50%: 2 (3%)*

Lancellotti et al. J Am Coll Cardiol 2012;59:235–43

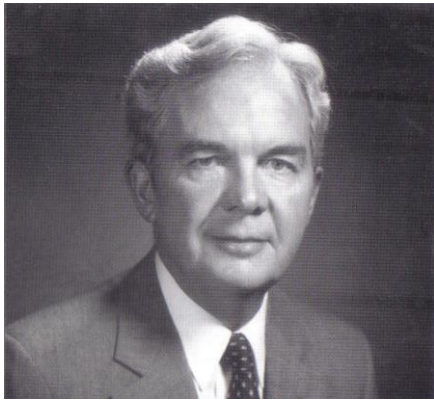
Asymptomatic Severe AS



Arch Surg—Vol 91, Nov 1965

Decreased Risk of Aortic Valve Surgery

DWIGHT C. McGOON, MD; CARLOS PESTANA, MD; AND EMERSON A. MOFFITT, MD, ROCHESTER, MINN



1925-1999

"Low hospital mortality tends to justify a policy of accepting patients for operation earlier in the natural progression of their disability, because it is recognized that there is a definite risk of rapid deterioration or sudden death in the earlier policy of deferring operation patients until their disability had become definite and progressive and until their cardiac reserve was nearly depleted."

EARLY TAVR Trial
Study Flow

THE PARTNER 3 TRIAL

Asymptomatic Severe AS

Ineligible if patient < age 65, has Class 1 AVR indication (e.g. EF<50%), bicuspid valve, or STS ≥ 10

Clinical and Echo Screening

Treadmill Stress-Test

Unable to Perform Stress-Test

Stress-Test Normal

CT Scan and Angiography eligibility

Randomization 1:1
Stratified by STS (<5 vs. ≥5)

N=1,109 pts

TF- TAVR

Clinical Surveillance

Clinical and Echo Follow-up:
30 days (TAVR only), 1, 2, 3 and 5 years

Stress-Test Abnormal

Commercial AVR (TAVR or SAVR), or Low Risk Clinical Trial (P3)

Registry

Telephone Follow-up:
1 year, 2 years, and 5 years

Primary Endpoint (superiority):
2-year composite of all-cause death, all stroke, and repeat cardiovascular hospitalization

Principal Investigators:
Philippe Généreux, MD, Patrick T. O'Gara, MD

Asymptomatic Severe AS

Asx Severe AS - Final Thoughts

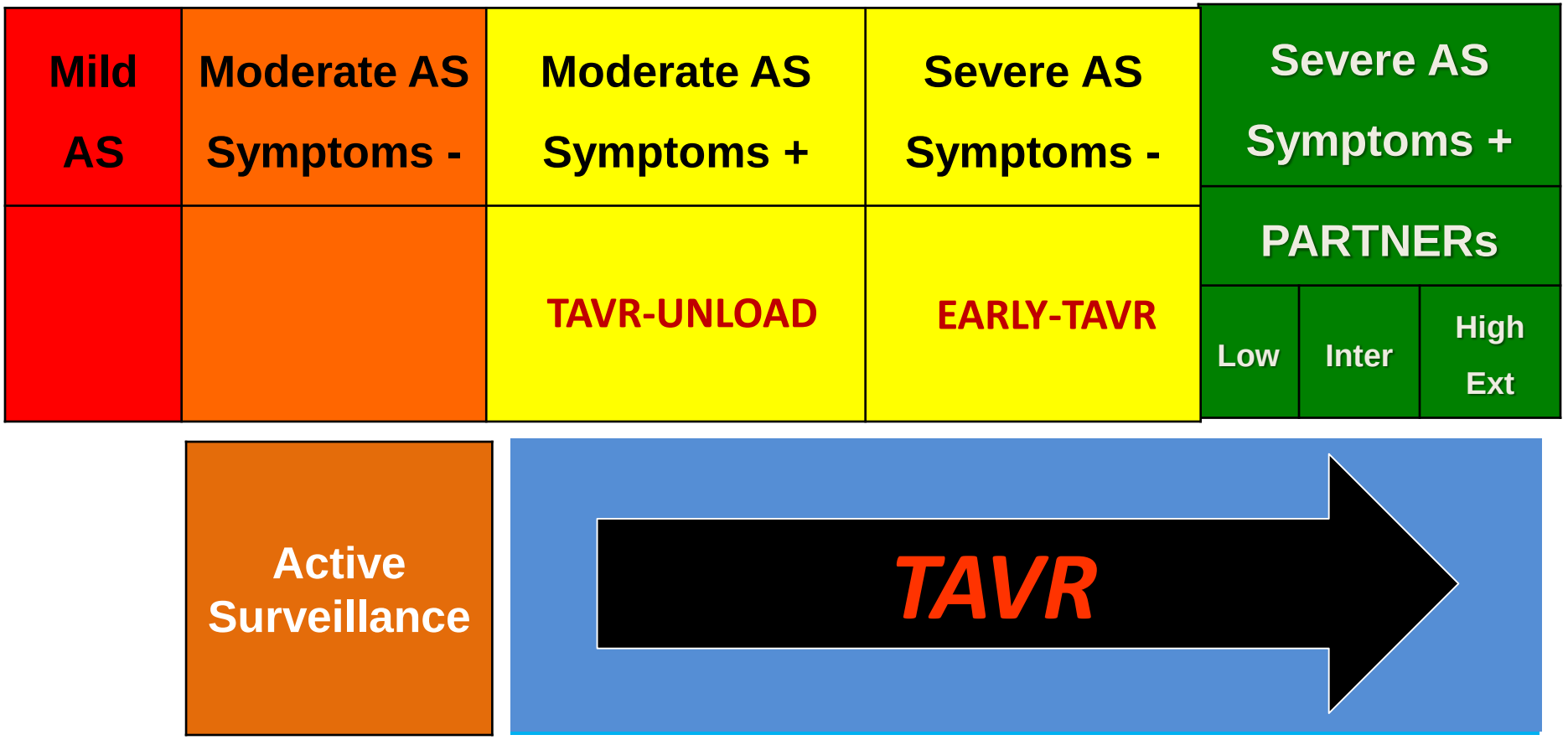
- Asymptomatic severe AS ***is frequent,*** representing ~40-50% of the severe AS referred to the echo lab
- ***Stress tests*** are abnormal in ***~50%*** of the patients, and are associated with ***high rates of adverse cardiac events*** at follow-up
- Rate of ***sudden death are ~1% per year***, with a high proportion of sudden death occurring without preceding symptoms
- Echocardiographic predictors (e.g. PV, PV progression, valve calcification, Zva, LV stroke volume, LVH) and biomarkers can better stratify patients

Asx Severe AS - Final Thoughts

- In “truly” asymptomatic severe AS patients (negative stress tests), the ***CV event rate is ~50% at two years*** with conservative management
- The strategy of ***“watching waiting” is problematic*** resulting in many lost opportunities for optimal outcomes (preservation of LV mechanics, clinical benefits)
- ***In the “modern era” of TAVR (1% mortality, 1% strokes) earlier intervention is now seriously possible, but more robust clinical evidence is clearly needed to support a strong recommendation (randomized trials)!***

Aortic Stenosis Redefined:

Functional Classification



Moderate AS + Heart Failure: Introduction to the UNLOAD Trial

Torsten Vahl, MD and Martin B. Leon, MD

Columbia University Medical Center
Cardiovascular Research Foundation
New York City

Disclosure Statement of Financial Interest

I, Torsten Vahl, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Transcatheter Aortic Valve Replacement to UNLOad the left ventricle in patients with ADvanced heart failure (TAVR UNLOAD)

Nicolas M. Van Mieghem, MD, PhD
Thoraxcenter, Erasmus MC, Rotterdam

and

Martin B. Leon, MD
Columbia University, CRF, New York City

TAVR UNLOAD Trial

Low-Flow, Low-Gradient AS

NORMAL-LVEF
NORMAL-FLOW
HIGH-GRADIENT

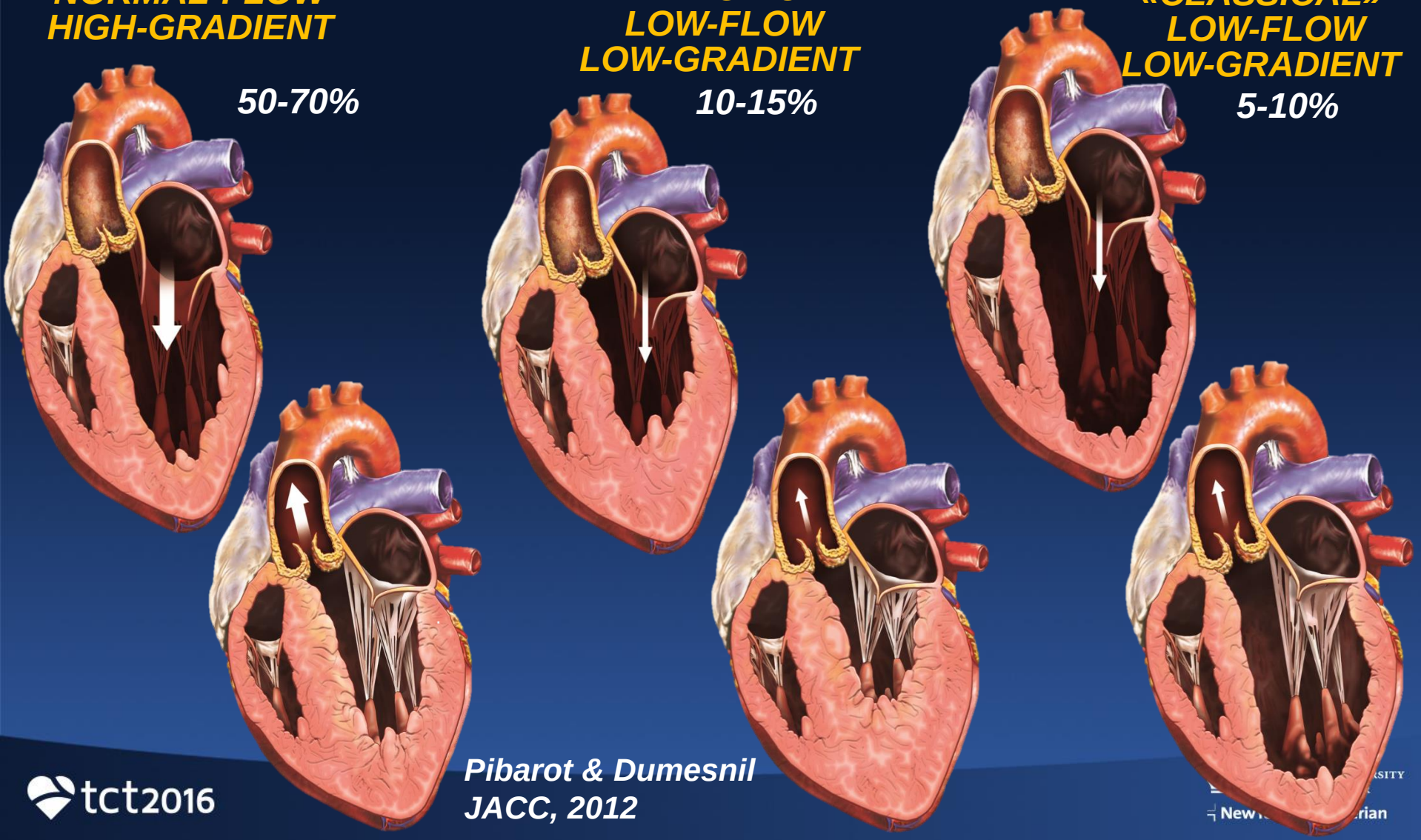
50-70%

NORMAL-LVEF
«PARADOXICAL»
LOW-FLOW
LOW-GRADIENT

10-15%

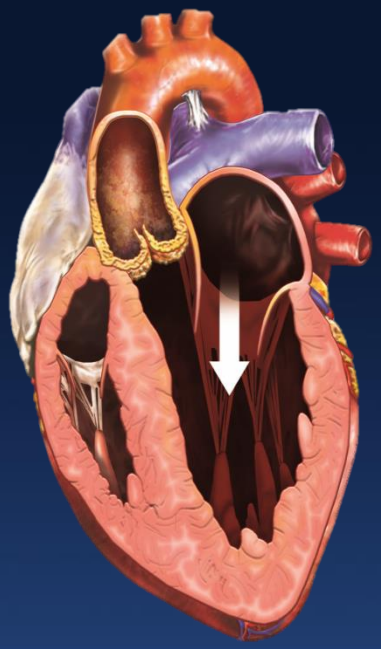
LOW-LVEF
«CLASSICAL»
LOW-FLOW
LOW-GRADIENT

5-10%



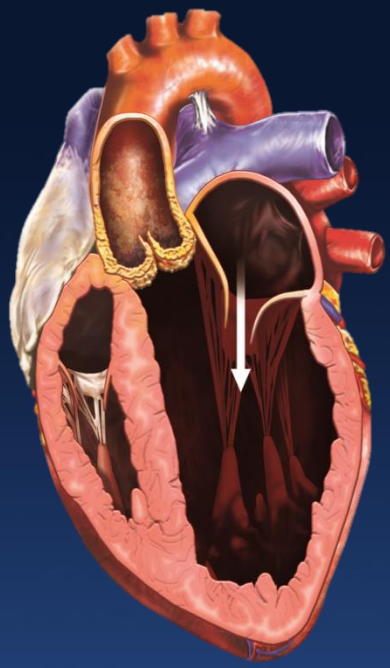
Pibarot & Dumesnil
JACC, 2012

Effect of Moderate AS based on LV function



What may be moderate AS for a normal ventricle

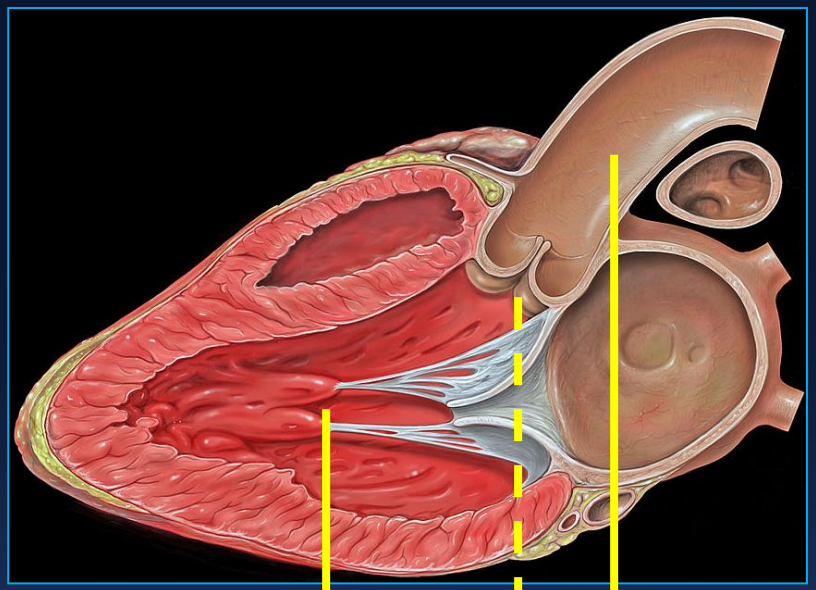
May feel like severe AS to an impaired ventricle



Normal LVEF

Reduced LVEF

Hemodynamic Fundamentals



Elderly with decreased arterial compliance

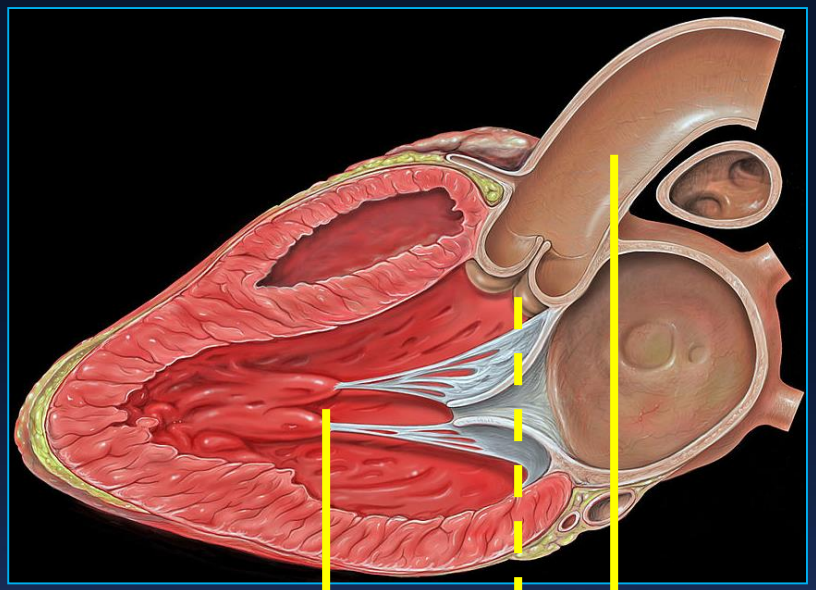
- ✓ **fixed SBP**
- ✓ **no response to vasodilators**

No medical options to reduce the arterial load!

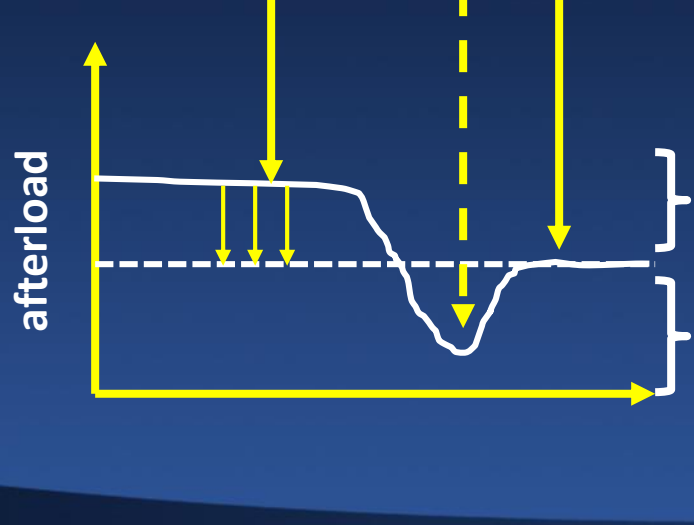
Global Load ≅ Z_{VA} = Transaortic Mean ΔP + SBP / SVi

Fixed

Hemodynamic Fundamentals



TAVR will reduce the valvular load and should improve HF symptoms!

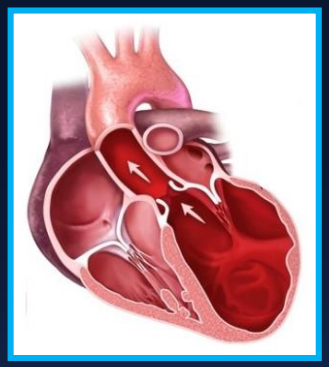


Global Load ≅ Z_{VA} = Transaortic Mean ΔP + SBP / SVi

Aortic Stenosis and Heart Failure

Heart Failure

(Leading cause of hospitalizations)



Increased AFTERLOAD

(*sympathetic activity*)

Impaired LV systolic function

Diastolic dysfunction

Beta-blockers
ACEi/ ARBs
MRAs, Diuretics

Coexistence of Heart Failure and Moderate AS

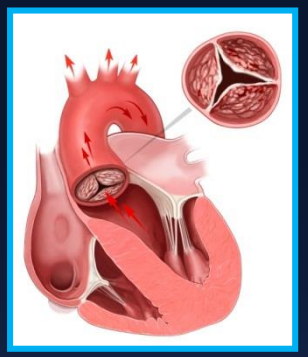
High risk population

Early AVR may be beneficial

TAVR

Aortic Stenosis

(Most frequent valvulopathy)



Increased AFTERLOAD

(*trans-valvular gradient*)

Impaired LV systolic function

Diastolic dysfunction

Moderate AS → **watchful waiting**

Severe AS → **AVR**

TAVR UNLOAD Trial

European Heart Journal Advance Access published January 18, 2016

European Heart Journal
doi:10.1093/eurheartj/ehv701

CLINICAL RESEARCH
Valvular heart disease

Aortic valve surgery and survival in patients with moderate or severe aortic stenosis and left ventricular dysfunction

Zainab Samad[1]*, Amit N. Vora[1,2], Allison Dunning[2], Phillip J. Schulte[2], Linda K. Shaw[2], Fawaz Al-Enezi[1], Mads Ersboll[3], Robert W. McGarrah III[1], John P. Vavalle[1], Svati H. Shah[1,2,4], Joseph Kisslo[1], Donald Glower[1,5], J. Kevin Harrison[1], and Eric J. Velazquez[1,2]

[1]Division of Cardiology, Duke Medicine, Duke University, PO Box 3254, Rm 3347A Duke South, 200 Trent Drive, Durham, NC, USA; [2]Duke Clinical Research Institute, Durham, NC, USA; [3]Department of Cardiology, Rigshospitalet, Copenhagen, Denmark; [4]Duke Molecular Physiology Institute, Durham, NC, USA; and [5]Department of Surgery, Duke University, Durham, NC, USA

- Duke echo database identified 1634 pts with LV systolic dysfunction (EF ≤ 50%) and AS; 1090 (67%) with moderate AS (mean AV gradient ≥ 25-39 mmHg, mean AVA 1.08 cm^2) and 544 (33%) with severe AS (mean AVA 0.72 cm^2)
- Mean age 75yo and major co-morbidities included CAD 61%, DM 33%, and cerebrovascular disease 20%
- Pts followed at least 5 years after the index echo

European Heart Journal Advance Access published January 18, 2016

European Heart Journal
doi:10.1093/eurheartj/ehv701

CLINICAL RESEARCH
Valvular heart disease

Aortic valve surgery and survival in patients with moderate or severe aortic stenosis and left ventricular dysfunction

Zainab Samad[1]*, Amit N. Vora[1,2], Allison Dunning[2], Phillip J. Schulte[2], Linda K. Shaw[2], Fawaz Al-Enezi[1], Mads Ersboll[3], Robert W. McGarrah III[1], John P. Vavalle[1], Svati H. Shah[1,2,4], Joseph Kisslo[1], Donald Glower[1,5], J. Kevin Harrison[1], and Eric J. Velazquez[1,2]

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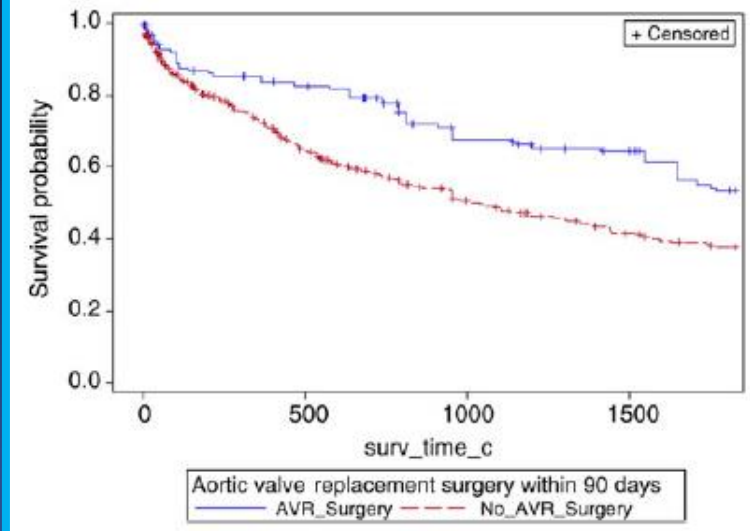


Significant survival benefit in pts with mod AS treated by AVR within 90 days!

Impact of Moderate AS in Patients with Reduced LV Systolic Function

- Retrospective analysis of Doppler-echo and clinical data from 4 large academic medical centers in the Netherlands, Canada, and the U.S.
- 305 patients identified with moderate AS (AVA 1.0 – 1.5 cm^2) and reduced LV systolic function (EF ≤ 50%)
- Av age 73yo, most symptomatic (FC II 42%, FC III/IV 32%), 72% CAD
- Primary endpoint: composite of all-cause mortality, AVR, or HF hospitalization
- Median FU 638 days [IQR 280-1137 days]

Erasmus Medical Center Rotterdam

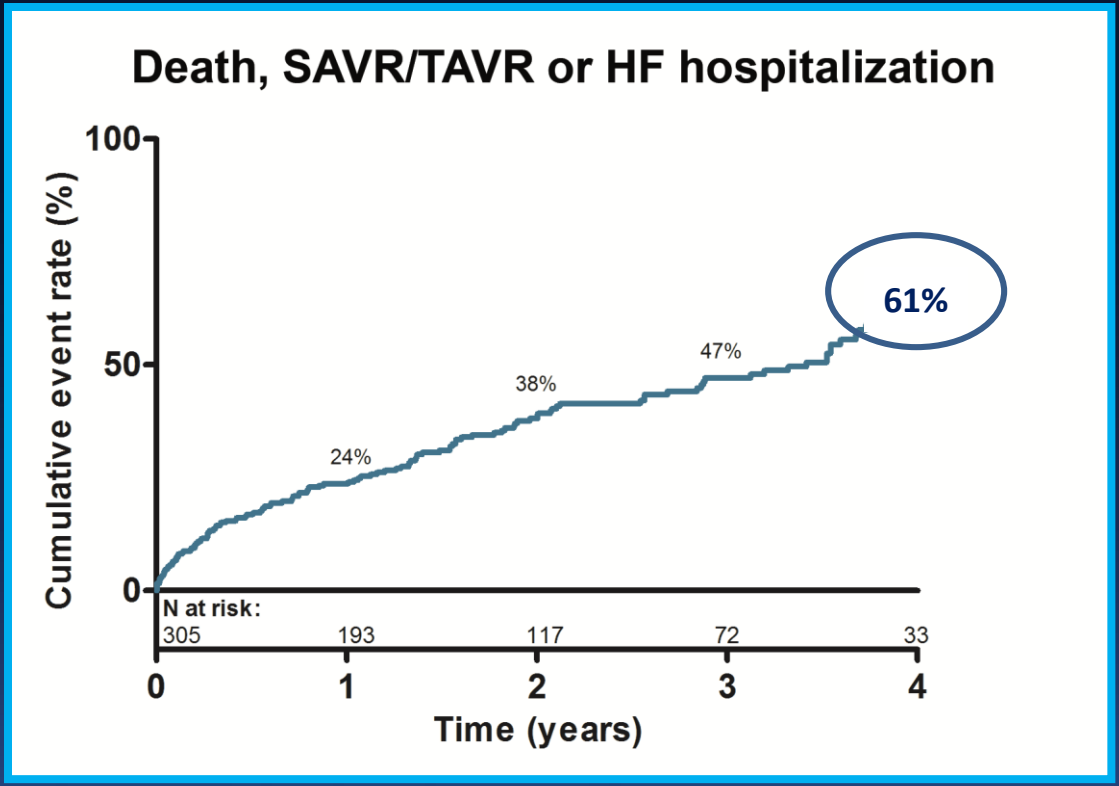
Leiden University Medical Center

Quebec Heart and Lung Institute

Columbia Univ Medical Center, NYC

Courtesy of Lennart van Gils et al; Erasmus, Rotterdam

Impact of Moderate AS in Patients with Reduced LV Systolic Function



- *Composite endpoint in 61% of patients at 4 yrs FU!*
- *All-cause mortality 40%, SAVR/TAVR 29%, HF hosp 34%*

Courtesy of Lennart van Gils et al; Erasmus, Rotterdam

TAVR UNLOAD Trial

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

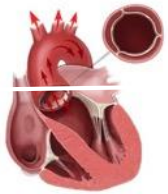
TAVR + OHFT

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

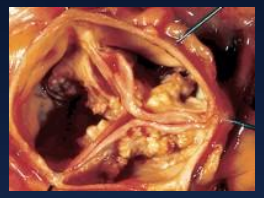
Columbia University Medical Center
NewYork-Presbyterian

TAVR UNLOAD Trial

Heart Team

Multi-disciplinary Heart Team

Heart Failure Specialist



Referring Cardiologist

TAVR UNLOAD

Cardiac Surgeon

Imaging Specialist

Interventional Cardiologist

TAVR UNLOAD Trial
Key Inclusion Criteria

- New York Heart Association Class ≥ 2
- NT-proBNP > 1500 pg/mL or hospitalization for HF within the last year
- Appropriate guideline-directed HF medical therapy (as tolerated) for ≥ 3 months
- LVEF < 50%, but > 20%
- Anatomically suitable for SAPIEN 3 transfemoral TAVR

TAVR UNLOAD Trial
Key Inclusion Criteria

- Moderate AS confirmed by the echo core lab and defined as:
  - Mean transaortic gradient (MG) ≥ 20 mmHg and < 40 mmHg & aortic valve area (AVA) > 1.0 cm^2 and ≤1.5 cm^2 at rest

OR

  - MG ≥ 20 mmHg and < 40 mmHg and AVA ≤ 1.0 cm^2 at rest *AND* MG < 40 mmHg and AVA >1.0 cm^2 with low dose dobutamine stress echo (DSE)

TAVR UNLOAD Trial
Primary Endpoint

- The hierarchical occurrence at 1-year of:
  - all-cause death
  - disabling stroke
  - CV hospitalizations related to heart failure, aortic valve disease (e.g. endocarditis), or non-disabling stroke
  - change in KCCQ from baseline
- Methodology: nonparametric pairwise hierarchical analysis as described by Finklestein-Schoenfeld
- Sample size: 600 patients; randomized 1:1; intention-to-treat analysis population

TAVR UNLOAD Trial

Ready to Go!

Rationale and design of the Transcatheter Aortic Valve Replacement to UNload the Left ventricle in patients with ADvanced heart failure (TAVR UNLOAD) trial

Ernest Spitzer, MD,[a,b] Nicolas M. Van Mieghem, MD, PhD,[a] Philippe Pibarot, DVM,[c] Rebecca T. Hahn, MD,[d,e] Susheel Kodali, MD,[d,e] Mathew S. Maurer, MD,[d] Tamim M. Nazif, MD,[d,e] Josep Rodés-Cabau, MD,[c] Jean-Michel Paradis, MD,[c] Arie-Pieter Kappetein, MD, PhD,[a] Ori Ben-Yehuda, MD,[c] Gerrit-Anne van Es, PhD,[f] Faouzi Kallel, PhD,[g] William N. Anderson, PhD,[h] Jan Tijssen, PhD,[f] and Martin B. Leon, MD[d,e] *Rotterdam, The Netherlands; Québec, Canada; Irvine and Lake Forest, CA*

Spitzer E, Van Mieghem NM, Pibarot P, et al; Am Heart J 2016;182:1-9

- ✓ Site selection completed
- ✓ IDE approved by FDA
- ✓ Reimbursement approved by CMS (U.S.)
- ✓ Enrolled first patient

TAVR UNLOAD Trial

Final Thoughts

Columbia University Medical Center
NewYork-Presbyterian

TAVR UNLOAD Trial

Final thoughts…

- Reduced EF heart failure and moderate AS are both difficult to treat (limited medical alternatives) and associated with frequent clinical events.
- Recent clinical results with TAVR in lower risk patient populations indicate improved safety and efficacy (esp. using transfemoral access).
- The TAVR UNLOAD trial tests the hypothesis that early TAVR in patients with moderate AS, symptoms of HF, and reduced EF will be superior to current strategies of watchful waiting and medical therapy.