Systematic Review and Meta-Analysis on Management Strategies for Asymptomatic Severe Aortic Stenosis

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Disclosure Statement of Financial Interest

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

- **Edwards LifeSciences**
  - **Consultant, Speaker Fees, Proctor**

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 trial

Transthoracic echocardiography as the initial diagnostic modality	I, B	-
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

Asymptomatic Severe AS
MG≥40mmhg, AVA≤ 1.0 cm2 and EF >50%

PV ≥5m/s **(ACC/AHA)** or ≥5.5m/s **(ESC): Class IIa**
PV progression≥0.3m/s/year: **ACC/AHA IIb and ESC Class IIa**
Severe LVH**: ESC Class IIb**
Repeatedly markedly elevated BNP: **ESC Class IIb**

Exercise Testing **(ACC/AHA Class IIa)**

\+ | \+ | -

Limiting Symptoms
Angina
Syncope
Dyspnea

Decrease exercise tolerance

Abnormal SBP response (drop or <20mmhg rise)

Exercise Imaging **(ACC/AHA class IIa)**

Increase in MG with exercise by >20 mm Hg

ACC/AHA Class I
ESC Class I

ACC/AHA Class IIa
ESC Class IIa

ESC Class IIb

If Stress test and Stress Echo normal:
Clinical and Echo follow-up 6-12 months ACC/AHA Class I

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

Why Early AVR In Asymptomatic Severe AS is Rarely Performed?

Sudden Death with Asymptomatic AS:

~1%/year

Peri-operative Mortality

SAVR: ~2-3%?

Asymptomatic Severe AS: Rationale for Early AVR

Pros

- Reduce irreversible myocardial damage and subsequent consequences
- Decreased operative risk for asymptomatic patients
- Presence of latent symptoms; AS progression highly variable; potential for a very rapid deterioration
- Risk of late (or too late) symptoms reporting
- Increase of STS with time…
- Death on waiting list
- Sudden death without preceding symptoms

Cons

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

Practical Issues with *"Watchful Waiting" Strategy*

- **Clinicians still have a fear of stress test 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 are frequent**
- **Many sudden deaths occurred in Asx patients with no Class I indication of AVR and no preceding symptoms**
- ***"Wishful Thinking"* Strategy…**

What is the Prevalence of Asymptomatic Severe AS?

- ***~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 National Projections.

What is the Prognosis of Asx Severe AS Patients?

STATE-OF-THE-ART REVIEW

Natural History, Diagnostic Approaches, and Therapeutic Strategies for Patients With Asymptomatic Severe Aortic Stenosis

Philippe Généreux, MD,[a,b,c] Gregg W. Stone, MD,[a,b] Patrick T. O'Gara, MD,[d] Guillaume Marquis-Gravel, MD,[c] Björn Redfors, MD, PhD,[b,e] Gennaro Giustino, MD,[f] Philippe Pibarot, DVM, PhD,[g] Jeroen J. Bax, MD, PhD,[h] Robert O. Bonow, MD,[i] Martin B. Leon, MD[a,b]

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 observational studies pertinent identified**
- ***4 studies* with observational comparison *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

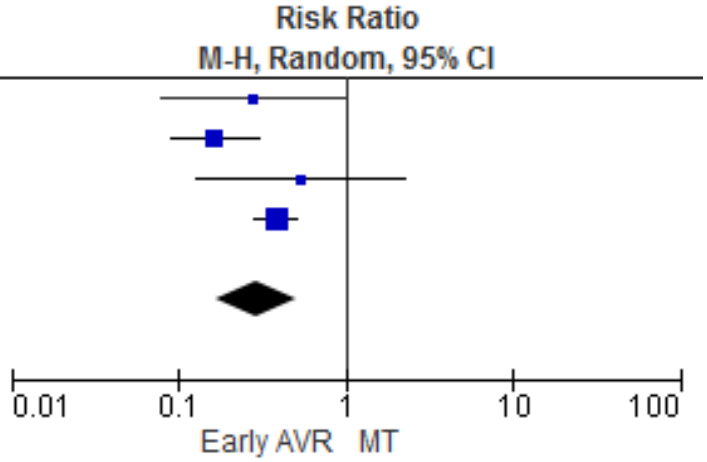
Généreux et al. J Am Coll Cardiol 2016;67:2263–88

All-Cause Mortality AVR vs. Medical Therapy in Asymptomatic Severe AS

Study or Subgroup	Early AVR Events	Early AVR Total	MT Events	MT Total	Weight	Risk Ratio M-H, Random, 95% CI
Kang et al	3	102	10	95	13.9%	0.28 [0.08, 0.98]
Pai et al	10	99	147	239	31.4%	0.16 [0.09, 0.30]
Pellikka et al	2	30	14	113	11.5%	0.54 [0.13, 2.24]
Taniguchi et al	40	291	542	1517	43.2%	0.38 [0.29, 0.52]
Total (95% CI)		**522**		**1964**	**100.0%**	**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

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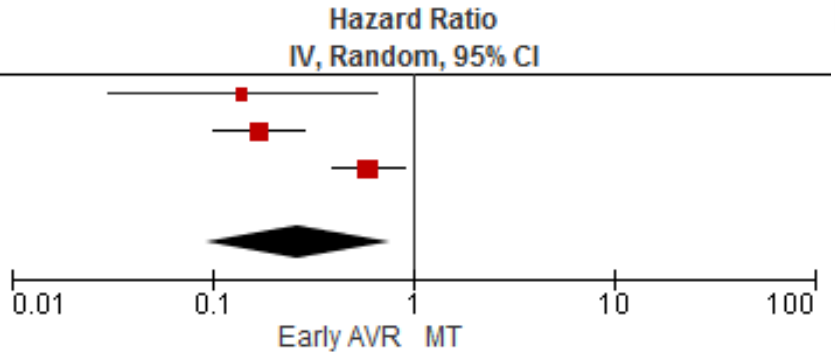
All-Cause Mortality
AVR vs. Medical Therapy in Asymptomatic Severe AS

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Kang et al	-1.9661	0.786	22.1%	0.14 [0.03, 0.65]
Pai et al	-1.772	0.2707	38.2%	0.17 [0.10, 0.29]
Taniguchi et al	-0.5108	0.2069	39.8%	0.60 [0.40, 0.90]
Total (95% CI)			**100.0%**	**0.27 [0.09, 0.77]**

Heterogeneity: $Tau^2 = 0.67$; $Chi^2 = 15.22$, df = 2 (P = 0.0005); $I^2 = 87\%$
Test for overall effect: Z = 2.46 (P = 0.01)



Adjusted: ~3.7 fold increase in all-cause Mortality

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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***

~1% sudden death/year

~Among all the sudden deaths, 73% (32/44) had No preceding AS Symptoms

Saito et al. 2012; n=103	***6***	***4***	***2***
Yingchoncharoen et al.; 2012; n=79	1	-	-
Levy et al. 2014; n=43	0		

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

Stress Test in Severe Asymptomatic AS?

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…"

Lung et al. Eur Heart J 2003; 24, 1231–1243

What % of Severe Asx AS will have Abnormal Stress Test?

Usual criteria for Abnormal stress test:

1) ***Limiting*** **symptoms (Angina-dyspnea-severe dizziness-syncope)**

2) **Fall or no increase (<20mmhg) in SBP during exercise**

3) **Significant ventricular arrhythmias (>3 consecutive ventricular premature beats)**

4) **>2 mm (or 5mm?) ST-segment depression**

ESC Guidelines Eur Heart J (2002) 23, 1253–1266

Abnormal Stress Test in Asx AS

Studies	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			

Overall: Range: 26-67%

~Pooled 40-50% Abnormal Stress Test

Lancellotti et al. 2008				47%	60	128
Lafitte et al. 2009				65%	39	60
Marechaux et al. 2010	27%	51	186			
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%***	

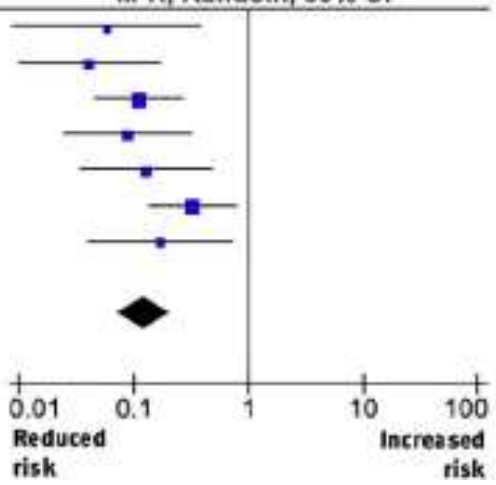
Généreux et al. J Am Coll Cardiol 2016;67:2263–88

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

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)

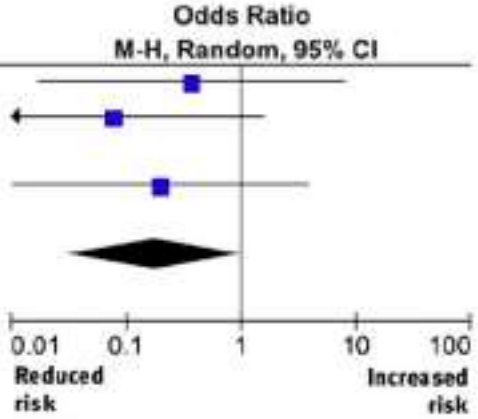


Figure 3. Pooled outcome estimates of risk for sudden cardiac death. None of the patients with normal stress test results experienced sudden death. *Squares* represent effect sizes; *extended lines* indicate 95% CIs; *diamond* represents total effect size.

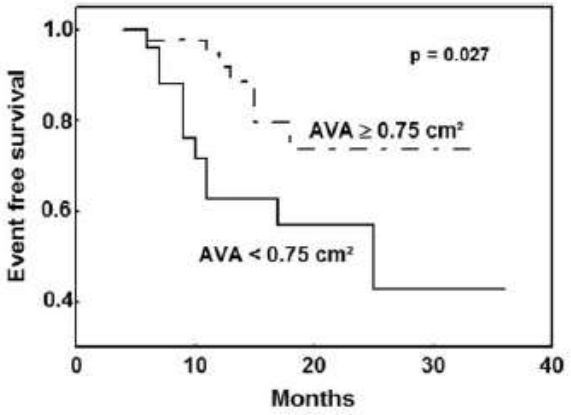
Abnormal stress test associated with ~6 fold increase in Cardiac Death

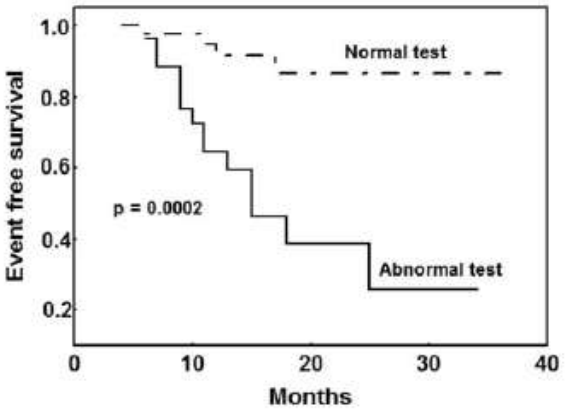
Rafique et al. Am J Cardiol 2009;104:972–977

Prognostic Importance of Quantitative Exercise Doppler Echocardiography in Asymptomatic Valvular Aortic Stenosis

Patrizio Lancellotti, MD, PhD; Florence Lebois, MD; Marc Simon, MD; Christophe Tombeux, MD; Christophe Chauvel, MD; Luc A. Pierard, MD, PhD, FESC

Adverse Event: Cardiac death, AVR, hospitalization for HF, Onset symptoms





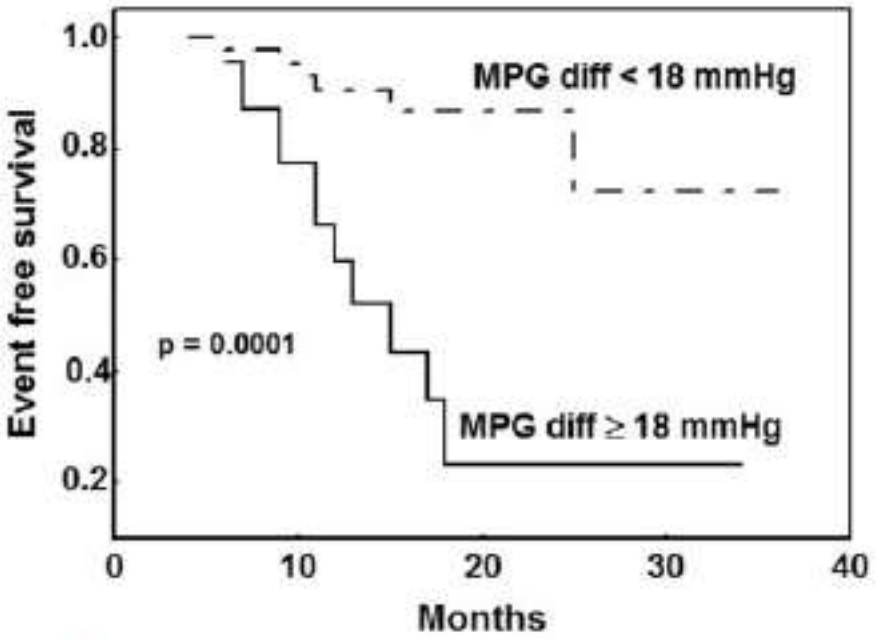


Figure 2. Survival curves according to exercise-induced changes in mean transaortic pressure gradient (MPG). Diff indicates difference exercise-rest.

Lancellotti et al. Circulation. 2005;112 [suppl I]:I-377–I-382

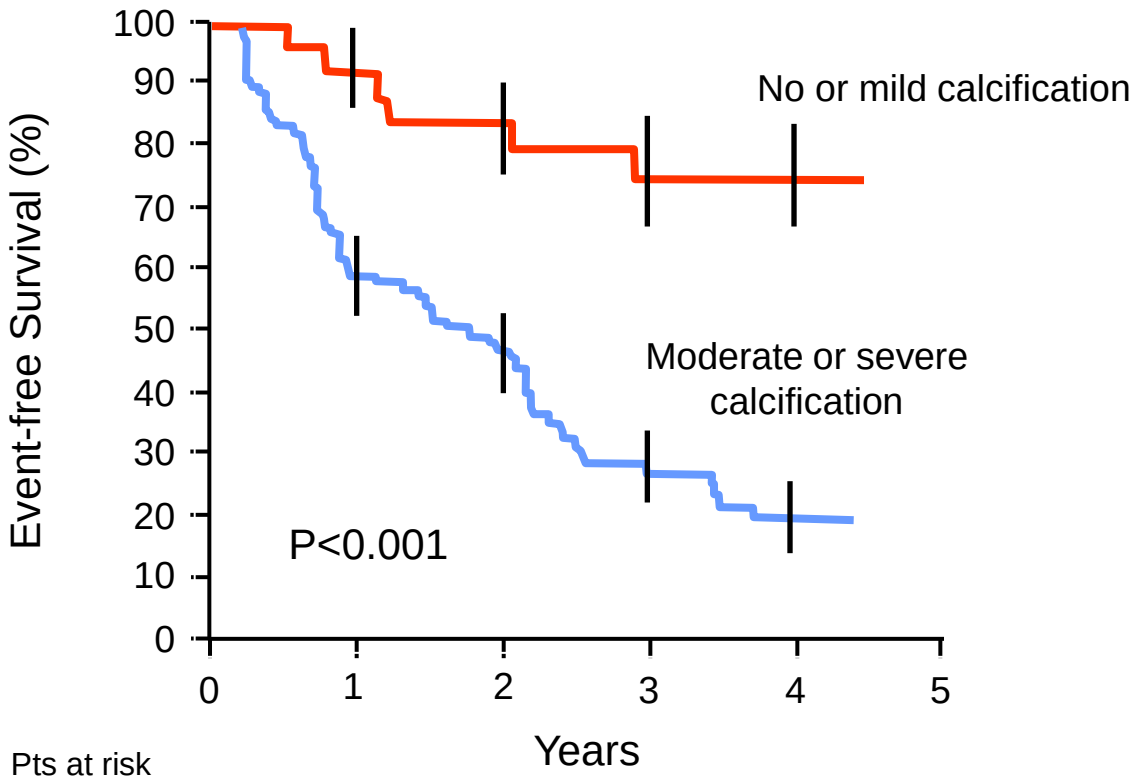
Predictors of Adverse Events In Asymptomatic Severe Aortic Stenosis

Predictor of Adverse Events in Patients with Asymptomatic Severe Aortic Stenosis

Echocardiographic	Stress Imaging
Peak velocity (>4m/s; >5m/s; >5.5m/s)	Increase in MG during exercise (>18mmhg or >20mmhg)
Rates of progression of PV (>0.3m/s/year)	Decrease in LVEF at peak exercise
AVA or IAVA (<0.7cm^2 or<0.6cm^2/m^2)	Exercise induced pulmonary hypertension (best cut-off SPAP >60mm Hg)
Mean Gradient	Peak VO2 ≤14 mL/kg/min, VE/VCO2 slope >34
Calcification severity	
Left ventricle hypertrophy or LVMI	
LVEF or LVEF<50%	
LVEDV	
Mitral regurgitation 3 or 4	
Left atrial area	
LV strain	
Valvuloarterial impedance (Zva) (especially>4.5)	
Low stroke volume (<35cc/m^2)	
Pressure drop / flow slope	

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

Valve Calcification



Pts at risk					
No or mild calcification	25	23	20	17	9
Moderate or severe calcification:	101	48	38	21	7

Rosenheck et al. N Engl J Med 2000; 343:611-7

What about the “truly” 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%)**

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

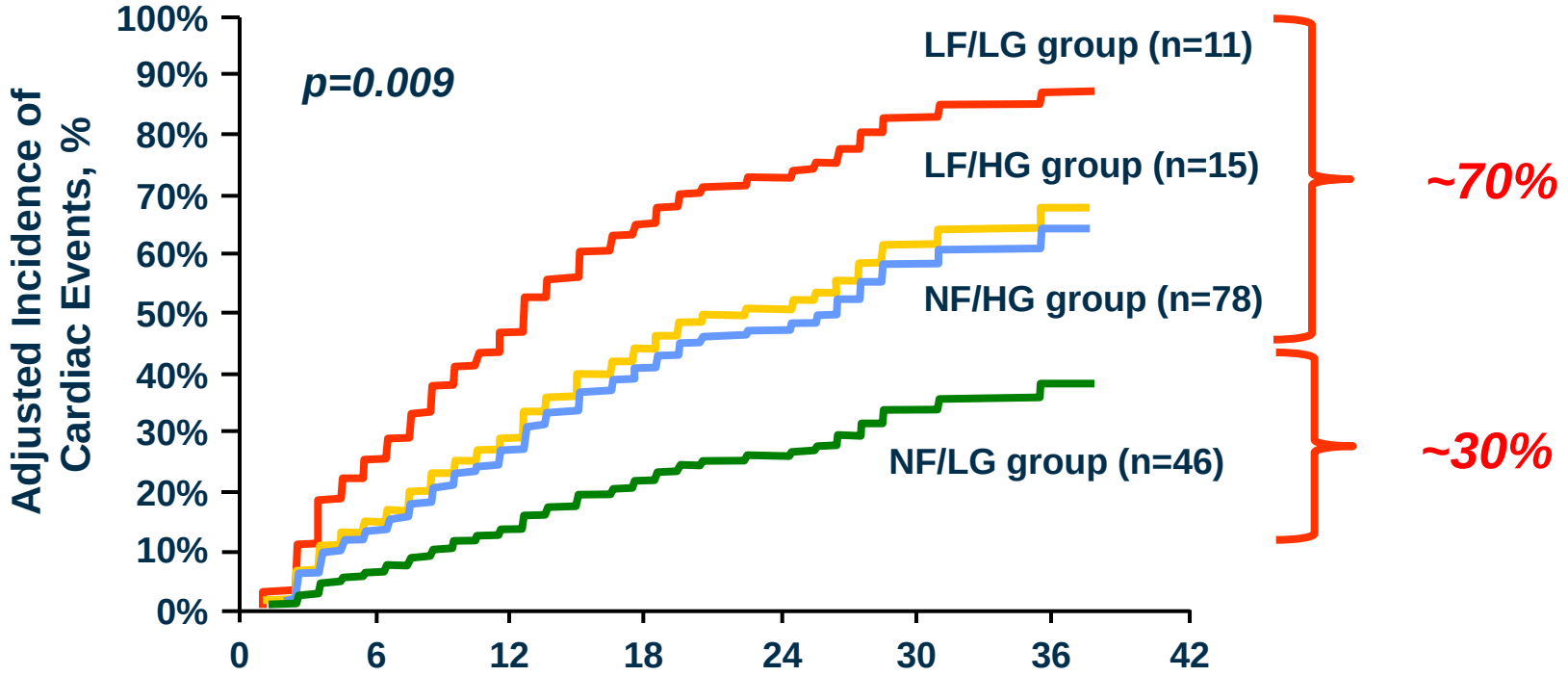
Clinical Outcome in Asymptomatic Severe Aortic Stenosis

Insights From the New Proposed Aortic Stenosis Grading Classification

CV events 29% at 1-year FU
49% at 2-year FU
60% at 3-year FU

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

Adjusted Incidence of CV events among patients with Normal Stress Test: n=150

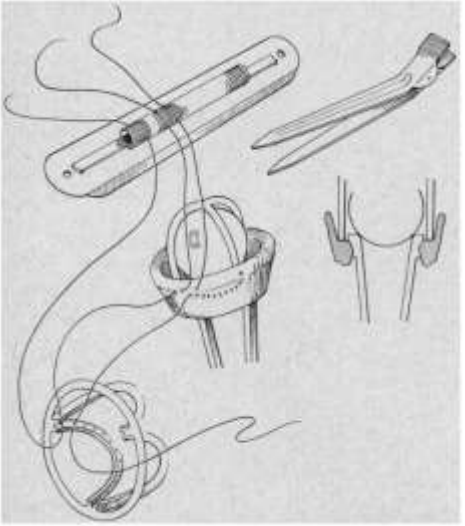


Among the subset of patients with Asymptomatic Severe AS AND Normal stress test, ~70% of patients have at least 50% chance to have adverse CV events at 2 years

LF= indexed stroke volume <35cc/m²
LG= MG <40mmhg

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

Should and could we recommend an early intervention strategy for "truly" Asymptomatic Severe Aortic Stenosis patients?



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

"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."

McGoon DC, Pestana C, Moffitt EA. Arch Surg.1965;Nov,91:779-86.

Aortic Stenosis Spectrum: Functional Classification

Mild AS	Moderate AS Symptoms -	Moderate AS Symptoms +	Severe AS Symptoms -	Severe AS Symptoms +
		TAVI-UNLOAD	?	PARTNERs

Conclusions

- **Asymptomatic Severe AS *is frequent,* representing ~50% of the Severe AS referred to echo lab**
- ***Stress tests* are abnormal in *~40-50%* of the patients, and are associated with *high rates of adverse cardiac events* at follow-up**
- **Rate of *sudden death are ~1.0%/year*, with high proportion of sudden death occurring without preceding symptoms**

Conclusions

- **Many Echographic predictors (such as peak velocity, peak velocity progression, degree of valve calcification, Zva, LV stroke volume, LVH, etc.) have been identified and can help better stratify patients**
- ***Better level of evidences (randomized trial) is clearly needed* to improve level of recommendations**