Clinical Outcome in Patients with Aortic Stenosis

Is the Prognosis Worse in Patients with Low-Gradient Severe Aortic Stenosis?

Yoel Angel BSc, **Shemy Carasso MD, Diab Mutlak MD,**

Jonathan Lessick MD Dsc, Izhak Kehat MD PhD, Doron Aronson MD

Shimon A. Reisner MD, Yoram Agmon MD

Echocardiography Laboratory and Heart Valves Clinic

Rambam Health Care Campus

Technion – Israel Institute of Technology

Haifa

Conflicts of interest – **none** (all coauthors)

Background

- Trans-aortic pressure gradients (ΔP) – typically high in pts with

  - Severe aortic stenosis (AS) *and*

  - Preserved left ventricular ejection fraction (LVEF)

- ΔP – occasionally low despite severe AS (per calculated AVA)

  "Low-gradient / low-output, preserved-LVEF AS"

- Frequency of low-gradient / low-output preserved-LVEF AS

  - High?[1,2]

  - Not so high[3]

- Questionable prognosis[2,4]

  - Similar to / worse than high-gradient severe AS?[2,5]

  - Similar to moderate AS?[4]

[1]Minners J et al, *Eur Heart J* 2008;29:1043-8

[2]Hachica Z et al, *Circulation* 2007;115:2856-64

[3]Angel Y et al, Israel Heart Society Annual Scientific Meeting 2012

[4]Jander N et al, *Circulation* 2011;123:887-95

[5]Clavel MA et al, *JACC* 2012;60:1259-67
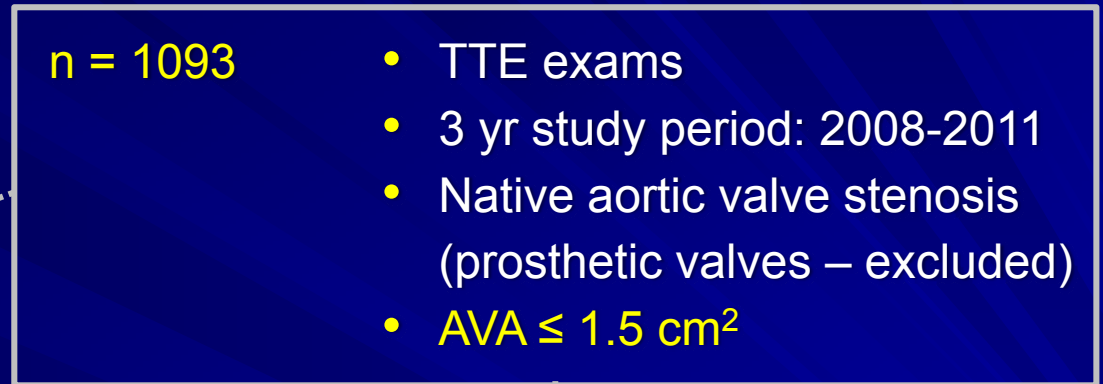
Objectives

Primary objective

- To determine the survival of pts with AS in relation to

  - AS severity – moderate or severe (per AVA)

  - ΔP – high or low

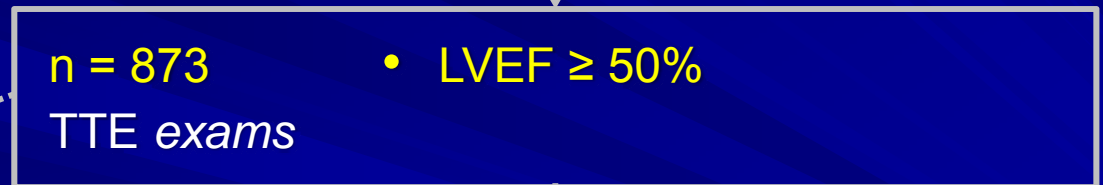   combinations

Secondary objective

- To examine the pattern of referral to aortic valve replacement (AVR) according to AVA / ΔP combinations

Methods
Patient Population

n = 1093
- TTE exams
- 3 yr study period: 2008-2011
- Native aortic valve stenosis (prosthetic valves – excluded)
- AVA ≤ 1.5 cm^2

- LVEF < 50% *excluded*

n = 873 TTE *exams*
- LVEF ≥ 50%

- Repeat exams *excluded* (1st exam analyzed)

n = 618 *patients*

AVA (1.0 cm^2)

Mean trans-aortic ΔP (40 mmHg)

Data Collection and Statistical Analysis

- Data sources

  - Echocardiography laboratory database

  - Clinical data (baseline) – hospital records @ RMC

    - 368 pts (hospitalized during index echo exam)

  - AVR during follow-up – RMC clinical database & inter-institutional database (Clalit – "Ofek")

  - Mortality – Ministry of Interior database

- Statistical methods – survival / referral to AVR

  - Kaplan-Meier (Log-rank statistics)

  - Multivariate Cox proportional hazards model

Results
Patient Subgroups – by AVA & ∆P (Mean)
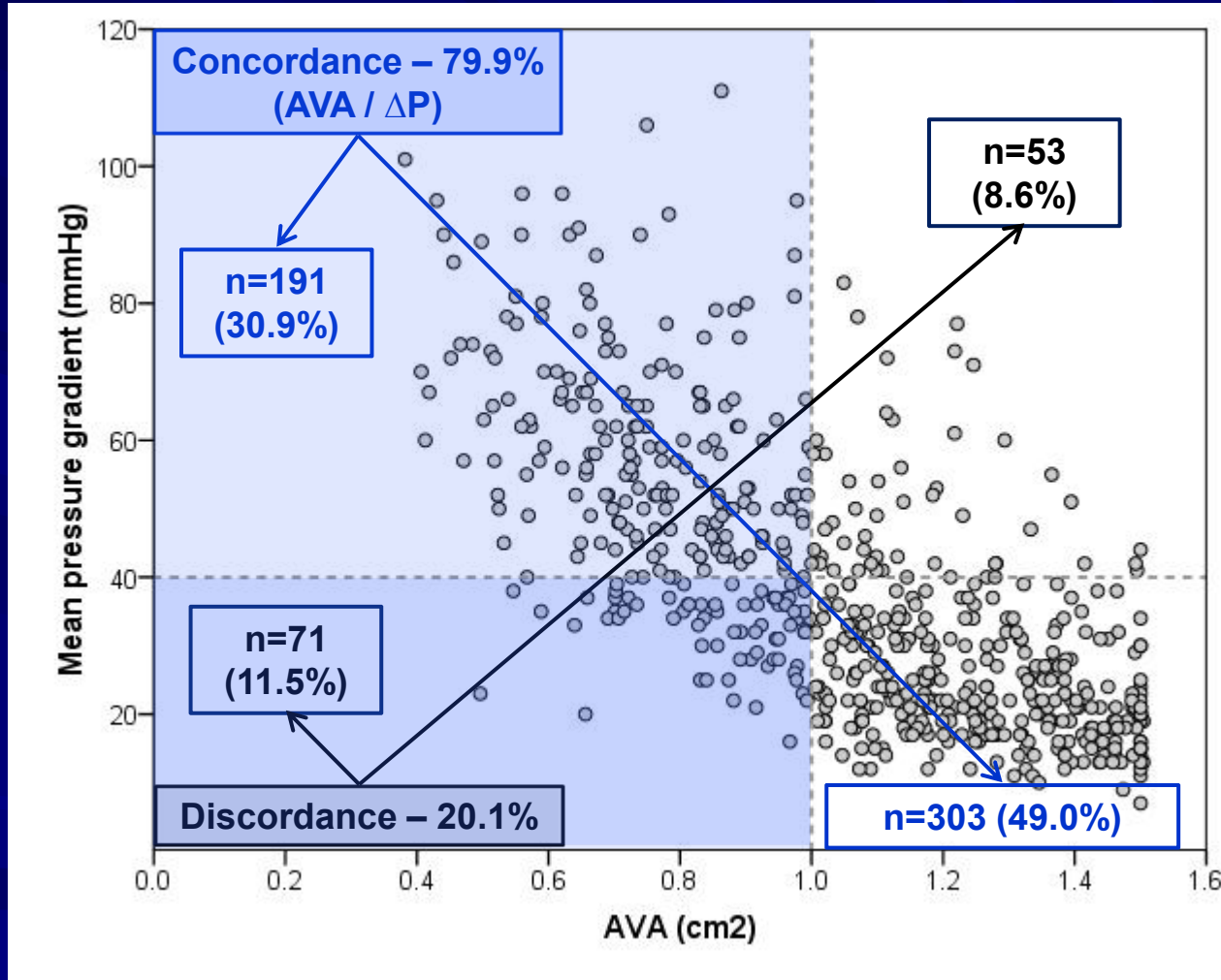
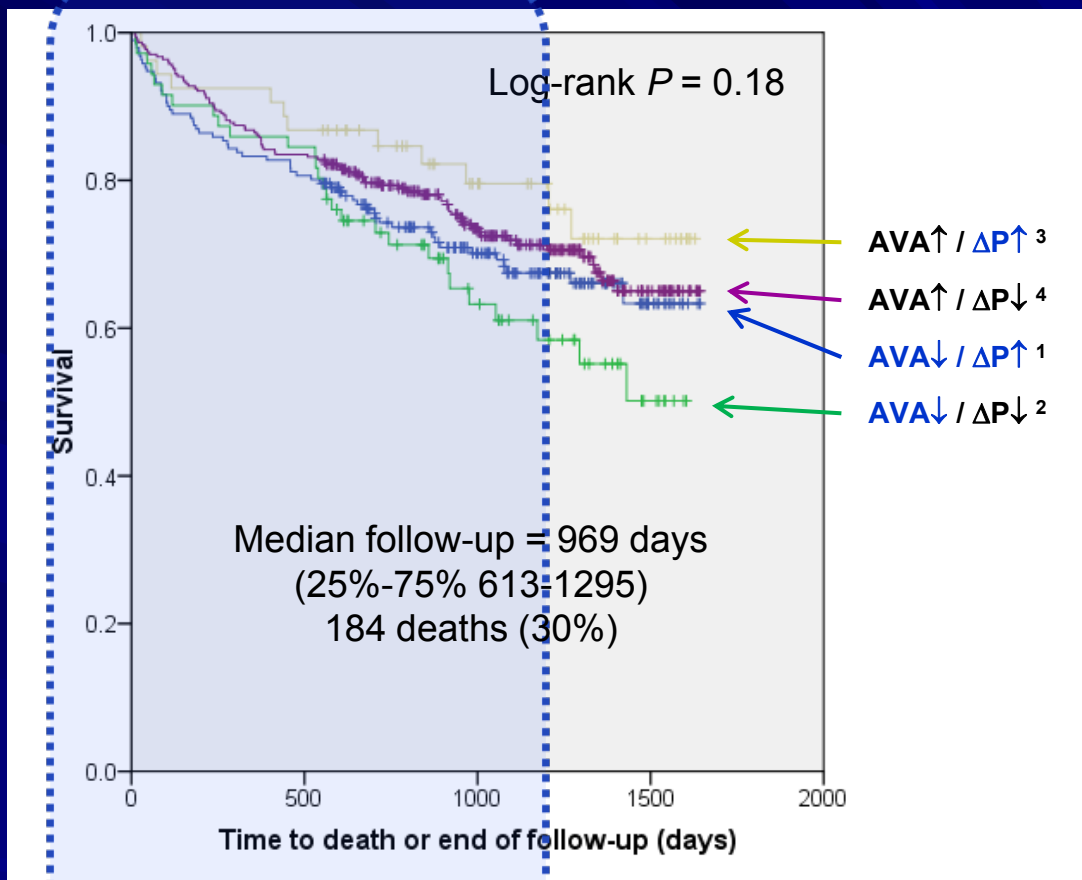Low-∆P severe AS
27% of pts with severe AS

Patient Characteristics – by Subgroups

	AVA↓ / ∆P↑ (n=191)	AVA↓ / ∆P↓ (n=71)	AVA↑ / ∆P↑ (n=53)	AVA↑ / ∆P↓ (n=303)	P
Age, yrs	76±11	80±10	75±11	76±12	0.06
Male, n (%)	65 (34)	22 (31)	36 (68)	127 (42)	<0.001
AVA, cm^2	0.74±0.15	0.86±0.12	1.16±0.14	1.27±0.15	<0.001
Mean ∆P, mmHg	60±15	32±5	51±11	23±7	<0.001
LVEF, %	64±4	64±4	64±4	64±4	0.59
Indexed SV, ml/m^2	51±10	46±8	67±12	51±11	<0.001
CAD, n (%)*	41 (32)	22 (46)	5 (22)	60 (35)	0.20
Angina pectoris, n (%)*	54 (43)	17 (35)	9 (39)	63 (37)	0.76
Functional class (NYHA)*	2.3±1.2	2.3±1.4	1.7±1.1	2.3±1.3	0.24
Syncope (per Hx), n (%)*	25 (20)	3 (6)	4 (17)	22 (13)	0.12
Charlson index ≥3, n (%)*	32 (25)	20 (42)	3 (13)	63 (37)	0.03

ANOVA *P* value; * Data in hospitalized patients (n=368:127/48/23/170)
AVA = aortic valve area; ∆P = pressure gradient; LVEF = left ventricular ejection fraction; SV = stroke volume;
CAD = coronary artery disease (previous MI / CABG / PCI); Charlson index 3 = 75% percentile (all pts)
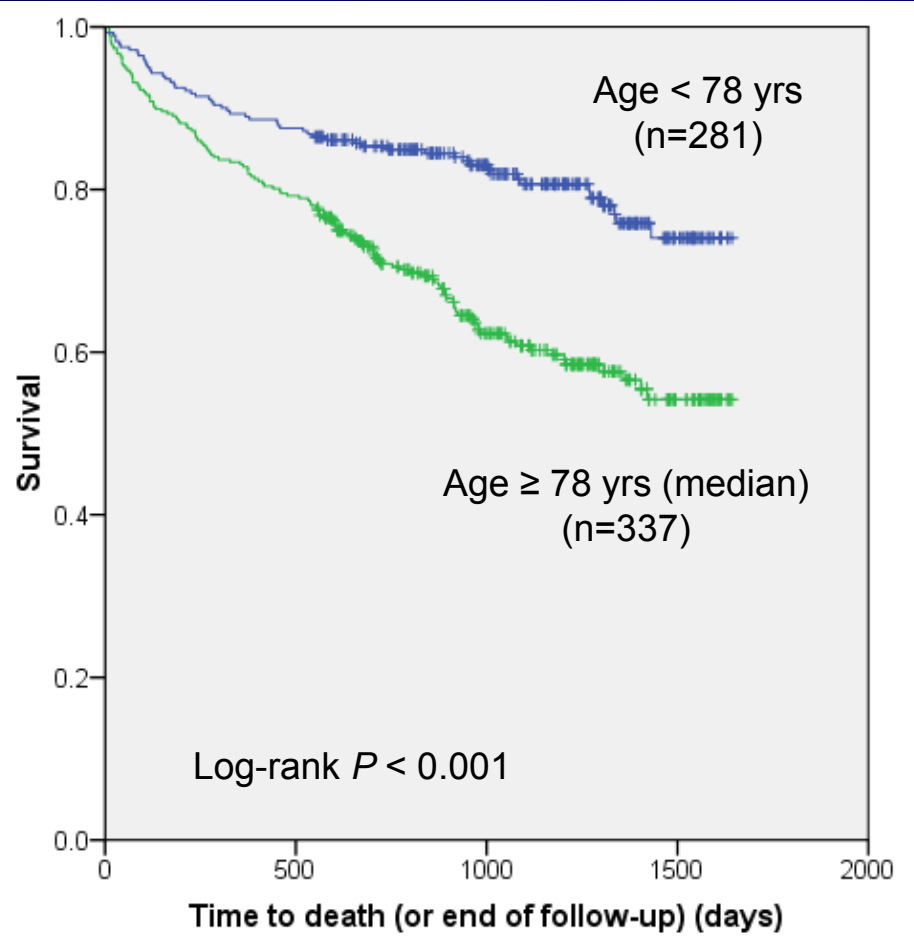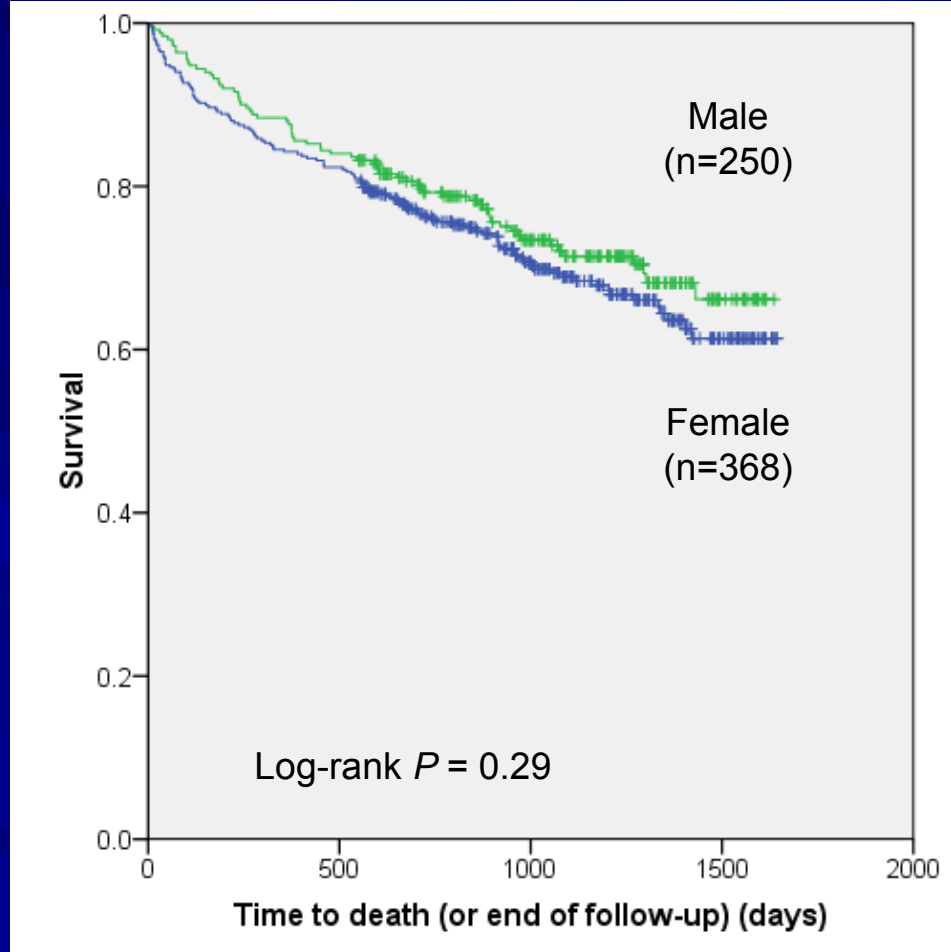
Overall Survival – by AVA / ΔP Subgroups

Log-rank *P* = 0.18

AVA↑ / ΔP↑ [3]
AVA↑ / ΔP↓ [4]
AVA↓ / ΔP↑ [1]
AVA↓ / ΔP↓ [2]

Median follow-up = 969 days
(25%-75% 613-1295)
184 deaths (30%)

Survival

Time to death or end of follow-up (days)

No. at risk					
191	154	88	14	(1)
71	60	30	7	(2)
53	46	28	9	(3)
303	253	147	29	(4)

Age, Gender → Survival

Age

Age < 78 yrs
(n=281)

Age ≥ 78 yrs (median)
(n=337)

Log-rank $P < 0.001$

Gender

Male
(n=250)

Female
(n=368)

Log-rank $P = 0.29$

Hospitalization, Comorbidity → Survival

Hospitalization status

Non-hospitalized (n=250)

Hospitalized (n=368)

Log-rank *P* < 0.001

Survival

Time to death (or end of follow-up) (days)
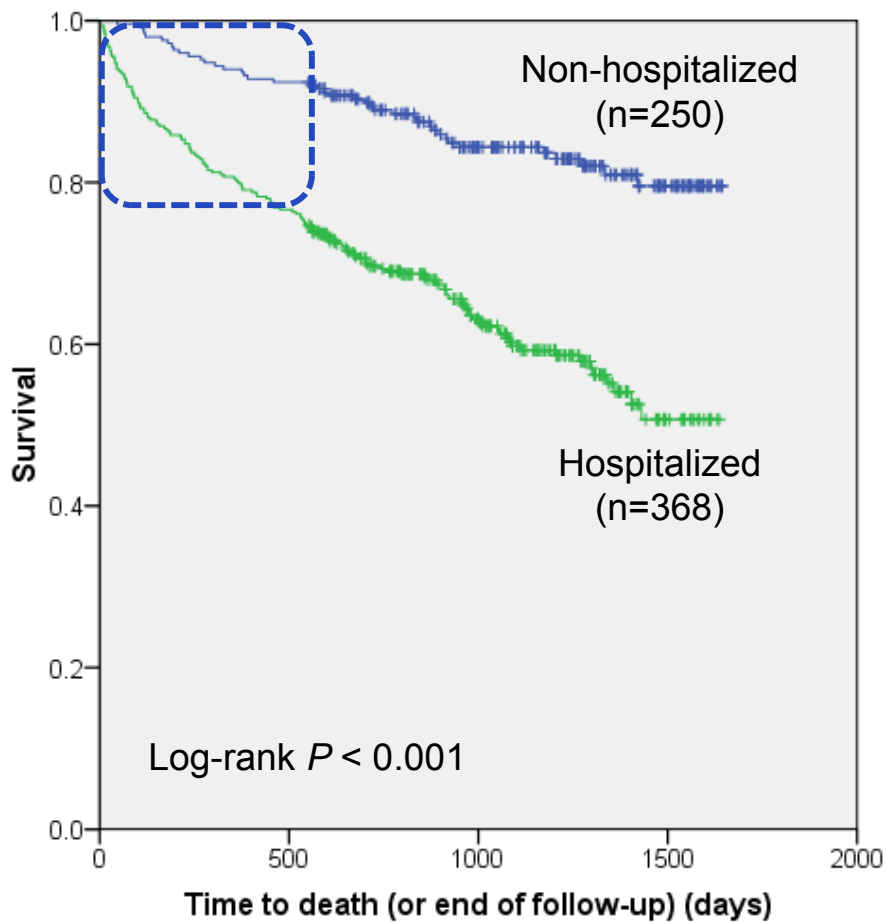
Charlson comorbidity index

Low (0-1) (n=186)

Interm (2-3) (n=112)

High (≥ 4) (n=70)

Log-rank *P* < 0.001

Survival

Time to death (or end of follow-up) (days)
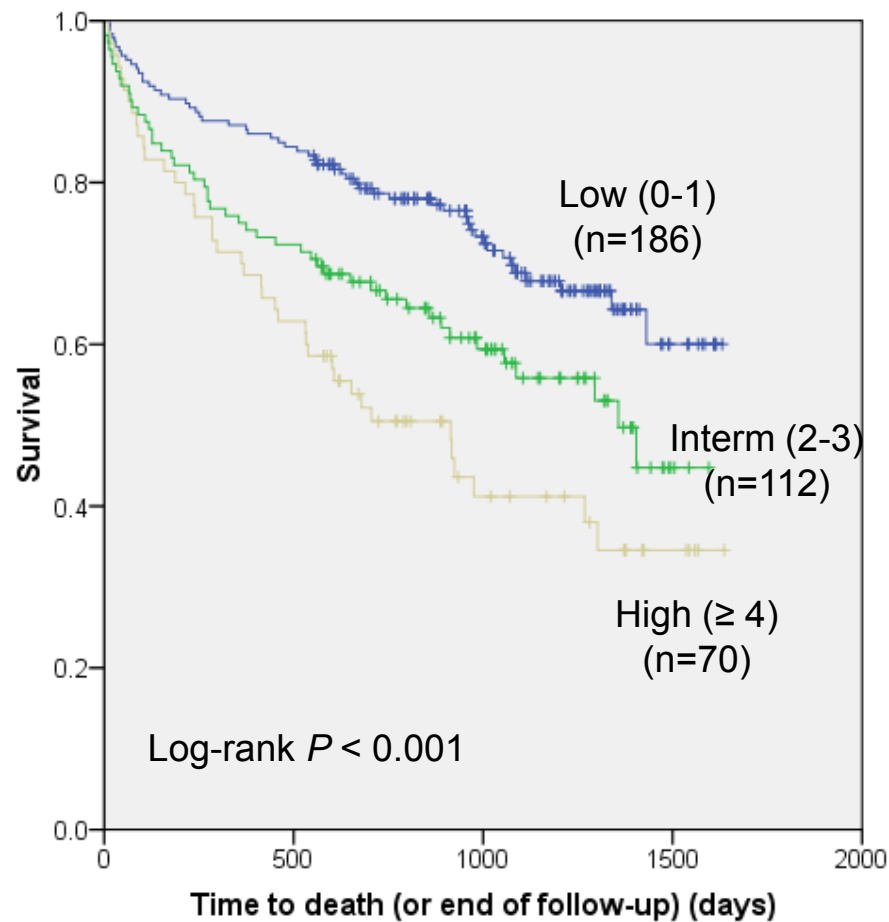
Hemodynamics → Survival (III)

Stroke volume (indexed)

SVi > 51 ml/m² (median)
(n=272)

SVi ≤ 51 ml/m² (median)
(n=261)

SVi ≤ 35 ml/m²
n=25

Log-rank P = 0.06
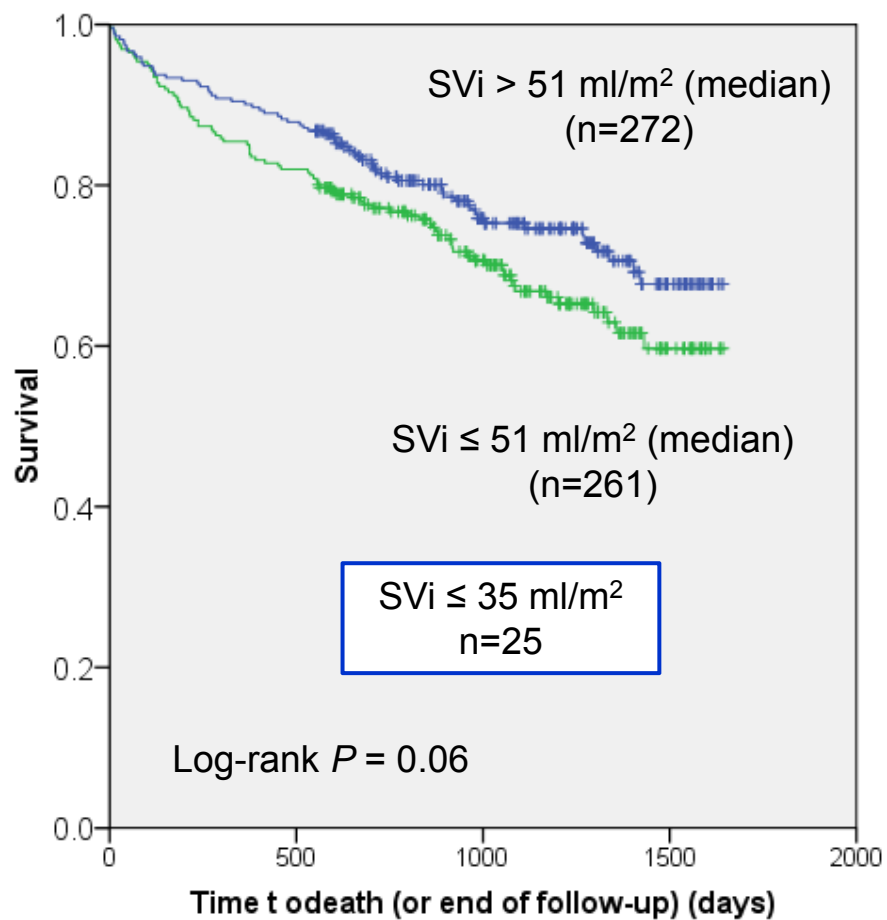
Valvulo-arterial impedance

VAI < 3.4 mmHg/ml/m² (median)
(n=149)

VAI ≥ 3.4 mmHg/ml/m² (median)
(n=149)

Log-rank P = 0.16
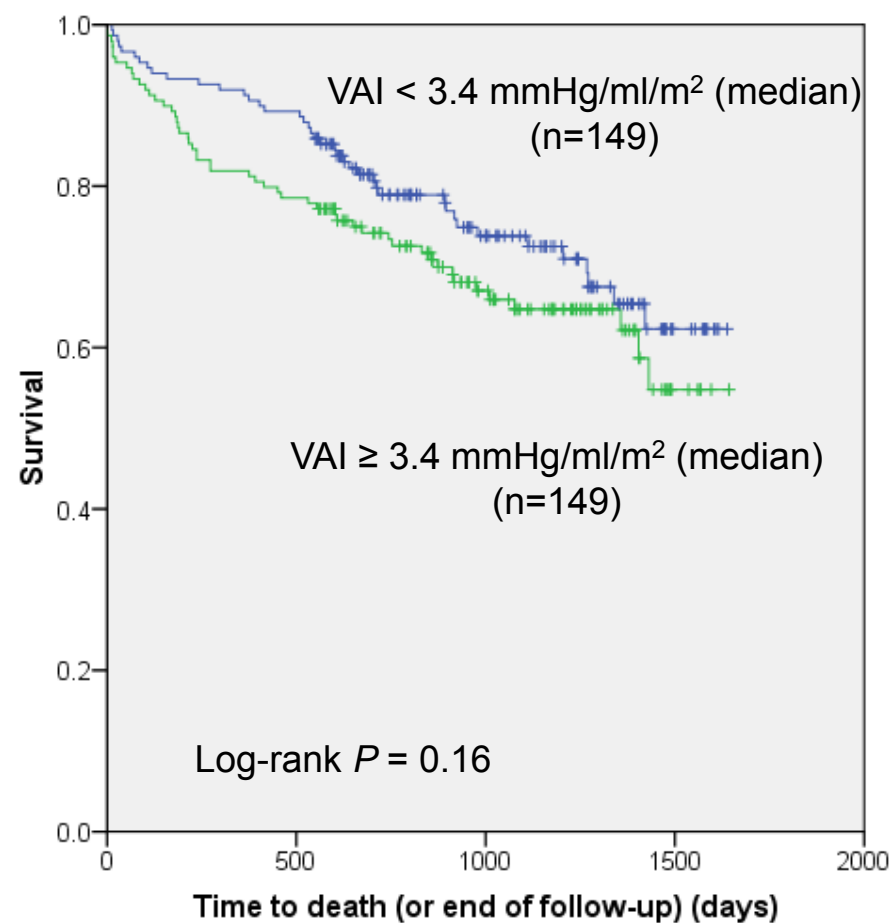
Predictors of Mortality
Multivariate Cox Regression (Total Study Population)

	HR	95% CI	*P*
• Age, per 10 yrs	1.77	1.48-2.11	<0.001
• Male gender	1.06	0.78-1.43	0.72
• Hospitalized pts	2.69	1.89-3.81	<0.001
• AVA / ΔP subgroup			0.78
AVA↓ / ΔP↑	1.10	0.79-1.54	
AVA↓ / ΔP↓	1.12	0.73-1.73	
AVA↑ / ΔP↑	0.82	0.45-1.52	
AVA↑ / ΔP↓	reference		
• SVi, per 10 ml/m²*	0.86	0.74-1.02	0.08
• VA impedance†	1.21	0.97-1.50	0.09

* Data available in 533 pts (86%)

† Data available in 298 pts (48%); HR per 1 mmHg/ml*m²

Predictors of Mortality
Subgroup Analyses

	HR	95% CI	*P*
I. Hospitalized pts (n=368)			
• Age, per 10 yrs	1.76	1.43-2.16	<0.001
• AVA / ∆P subgroup			0.55
• Charlson index			<0.001
Low (0-1)	reference		
Intermediate (2-3)	1.64	1.11-2.43	
High (>=4)	2.50	1.65-3.77	
II. Severe AS (AVA < 1.0 cm^2; n = 262)			
• Age, per 10 yrs	1.65	1.28-2.14	<0.001
• Hospitalized pts	2.44	1.45-4.12	0.001
• ∆P↑ (vs. ∆P↓)	0.95	0.60-1.51	0.95

Referral to Aortic Valve Replacement (AVR)

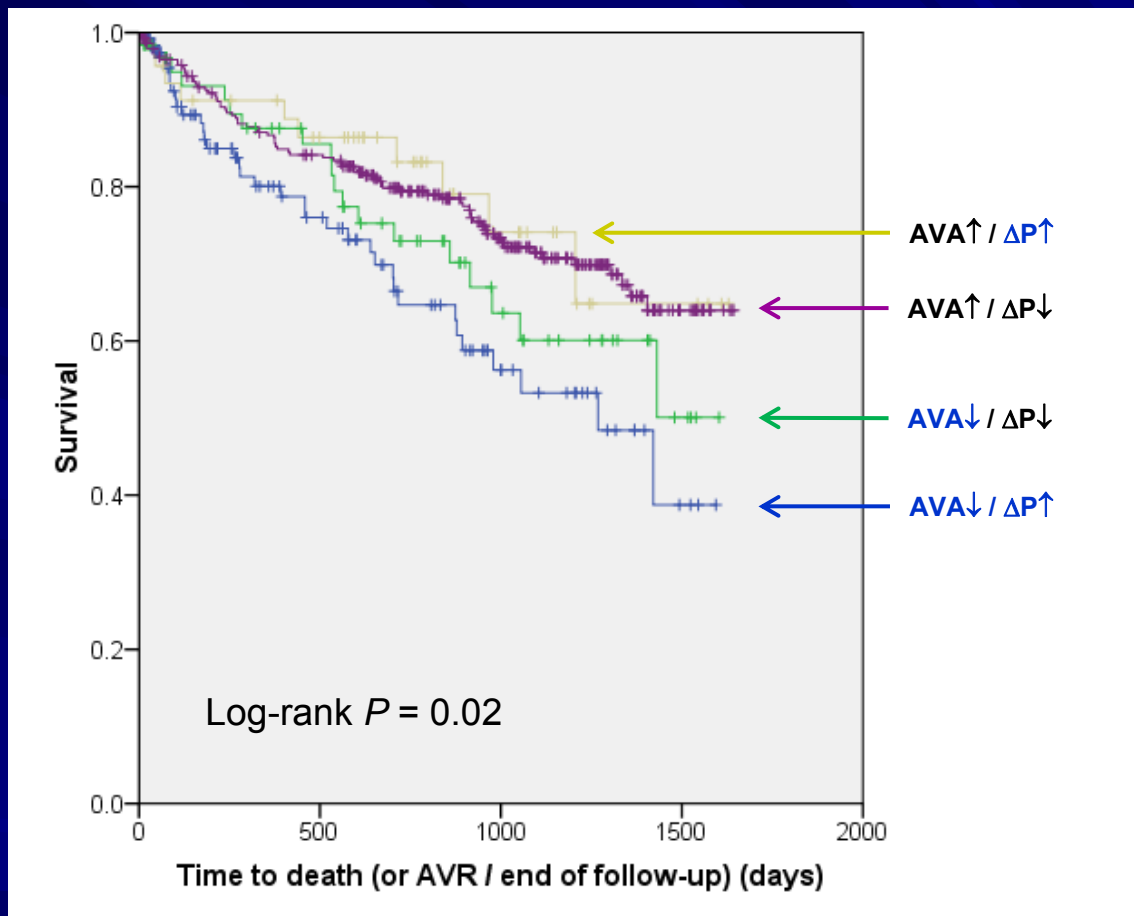**All patients**
n=618; AVR – 212 pts (34%)

**Excluding 71 pts (12%)
hospitalized in *cardiac surgery***
n=547; AVR - 154 (28%)
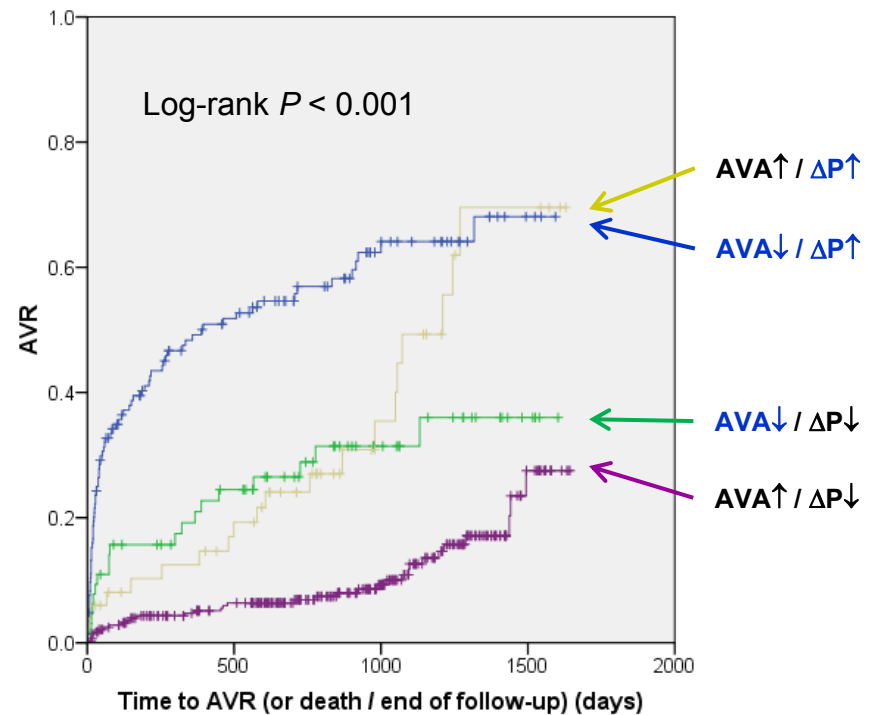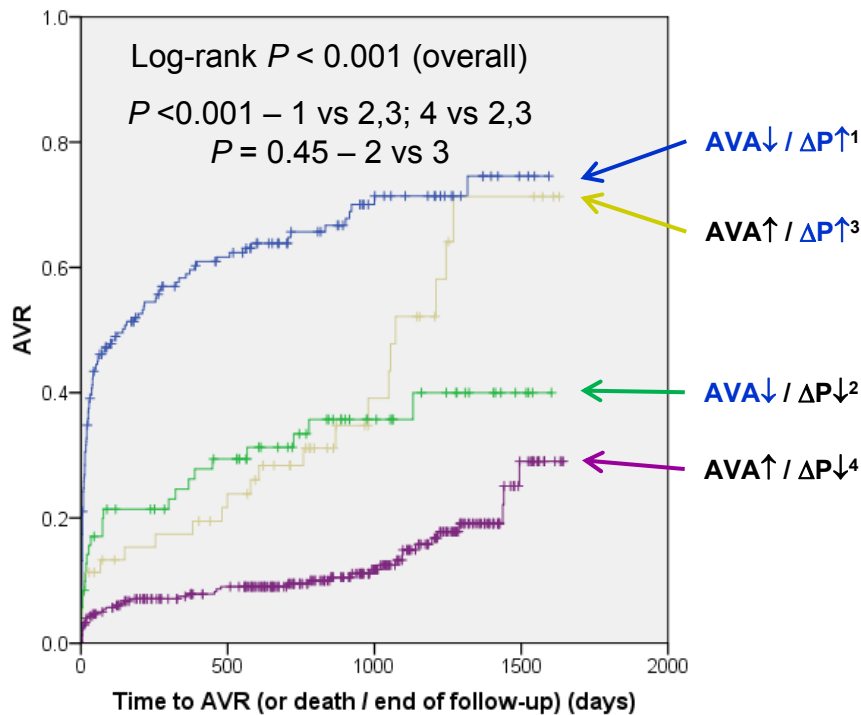
Predictors of referral to AVR:

- Age ↓, male gender, hospitalization, Charlson index < 4 (multivariate Cox)
- AVA↓ / ΔP↑ >> AVA↓ / ΔP ↓ ≈ AVA ↑ / ΔP↑ > AVA ↑ / ΔP↓

Survival with Medical Rx (without AVR)

- Endpoint = death
- Censoring @ AVR / end of F/U

Conclusions

- The frequency of low-gradient preserved-LVEF severe AS appears to be lower than previously reported

- Patients with low-gradient severe AS (compared to high-gradient AS):

    - Older

    - More comorbidity

    - Less frequently referred to AVR

    - All-cause mortality is *not higher* in these pts despite older age, higher comorbidity & lower referral rate to AVR

Backup slides

Study Limitations

- Selection bias (tertiary medical center)

- Retrospective pt selection (via echocardiography database)

  - Prospective follow-up (death / AVR)

- Retrospective collection of clinical & echocardiographic data

- Clinical data – subgroup of hospitalized pts

- Analysis of all-cause mortality (± cardiac)

- Limited follow-up duration (intermediate-term survival)

Charlson Weighted Index of Comorbidity

1 point	2 Points	3 Points	6 points
Myocardial Infarction	Hemiplegia	Mod. / Sev. Liver Disease	Metastatic Solid Tumor
Congestive Heart Disease	Mod. / Sev. Renal Disease *		AIDS
Diabetes (no end organ damage)	DM + end organ damage		
CVA	Any Tumor		
Connective Tissue Disease	Leukemia		
Dementia	Lymphoma		
Chronic Pulmonary Disease			
Ulcer Disease			
Mild Liver Disease			
Peripheral Vascular Disease			

* Cr > 2 or diagnosis of chronic renal disease

Charlson M et al, J Chron Dis 1987: 40(5); 373-383