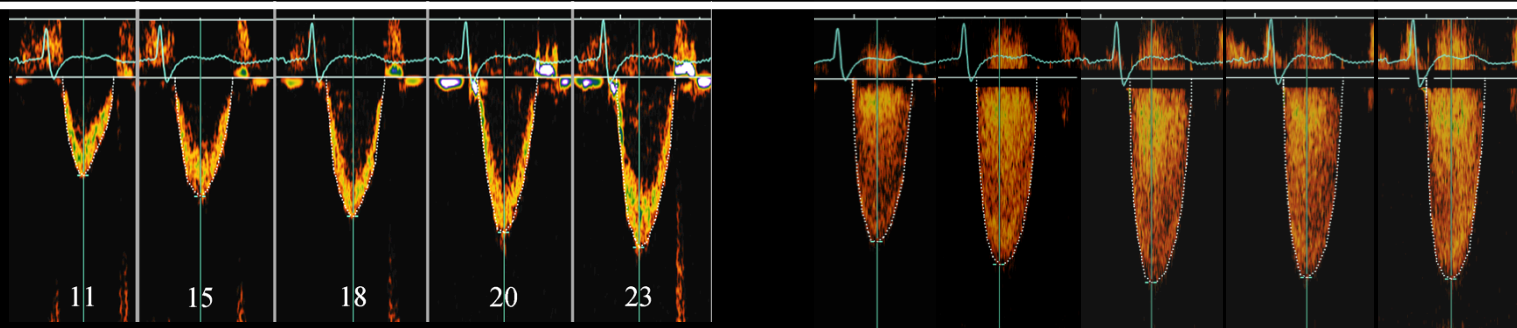


Henri Mondor



# Low Gradient Aortic Stenosis with depressed LV ejection fraction



Réunion scientifique ECHOSUD  
Nice, 05 janvier 2010

J-L. MONIN, MD, PhD. *Henri Mondor University Hospital*  
Créteil, FRANCE



# What is Low-Flow/ Low-gradient AS ?

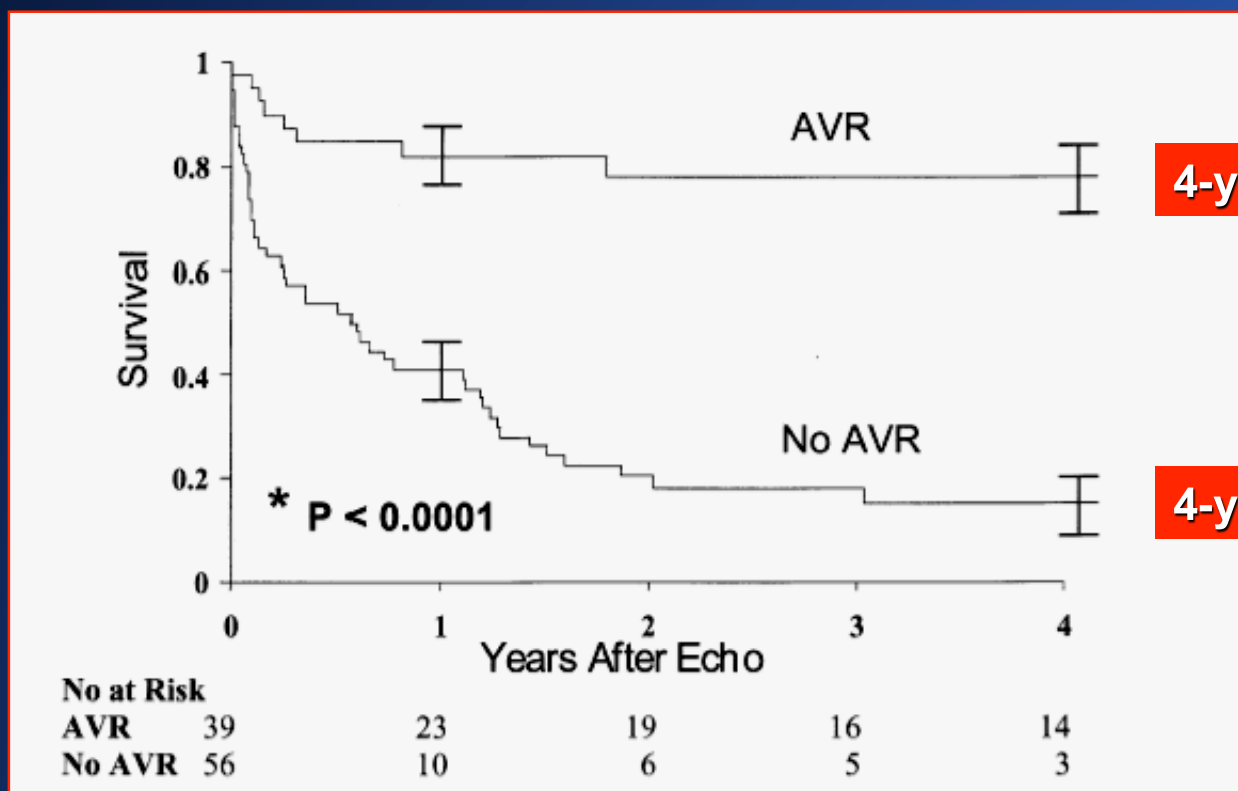
---

**Severe AS :  $AVA < 1.0 \text{ cm}^2$  ( $< 0.6 \text{ cm}^2/\text{m}^2$ )**  
**with LV systolic dysfunction (LVEF  $< 40\%$ )**  
**and Mean Pressure Gradient  $< 40 \text{ mm Hg}$**



## Low-flow / Low-gradient AS : Dismal prognosis under conservative TT

95 patients, AVA <0.75 cm<sup>2</sup>, LVEF <35%, MPG <30 mm Hg



4-year Survival = 78%

4-year Survival = 15%

Pereira et al. *J Am Coll Cardiol.* 2002;39: 1356-63



## Low transaortic pressure gradient = High operative risk

Author (year)	Patients (n)	Mean PG (mm Hg)	Deaths (D 30)
Brogan (1993)	18	< 30	33%
Connolly (2000)	52	< 30	21%
Pereira (2002)	68	$\leq 30$	8%
<b>Nishimura (2002)</b>	<b>32</b>	<b><math>\leq 40</math></b>	<b>14%</b>
<b>Monin (2007)</b>	<b>152</b>	<b><math>\leq 40</math></b>	<b>12%</b>
<b>Clavel (2008)</b>	<b>44</b>	<b><math>\leq 40</math></b>	<b>18%</b>

Standard operative risk for AVR: 3- 6% according to STS/ EuroHeart Survey





# **Low-flow / Low-gradient aortic stenosis : The clinical challenge**

---

- **Small subset of patients : 5-7% of all patients with AS**
- **The 3 main issues to consider :**
  - **Dismal prognosis under medical therapy**
  - **Relatively high operative risk**
  - **Uncertainty regarding the real severity of AS**



## Low Gradient Aortic Stenosis with depressed LV ejection fraction

---

- Does LV contractile reserve matter ?
- Does pseudo-severe AS matter ?
- Does BNP serum level matter ?
- Does Prosthesis-patient mismatch matter ?



# Low Gradient Aortic Stenosis with depressed LV ejection fraction

---

- Does LV contractile reserve matter ?
- Does pseudo-severe AS matter ?
- Does BNP serum level matter ?
- Does Prosthesis-patient mismatch matter ?



## Dobutamine ( $\mu\text{g/kg/min}$ )

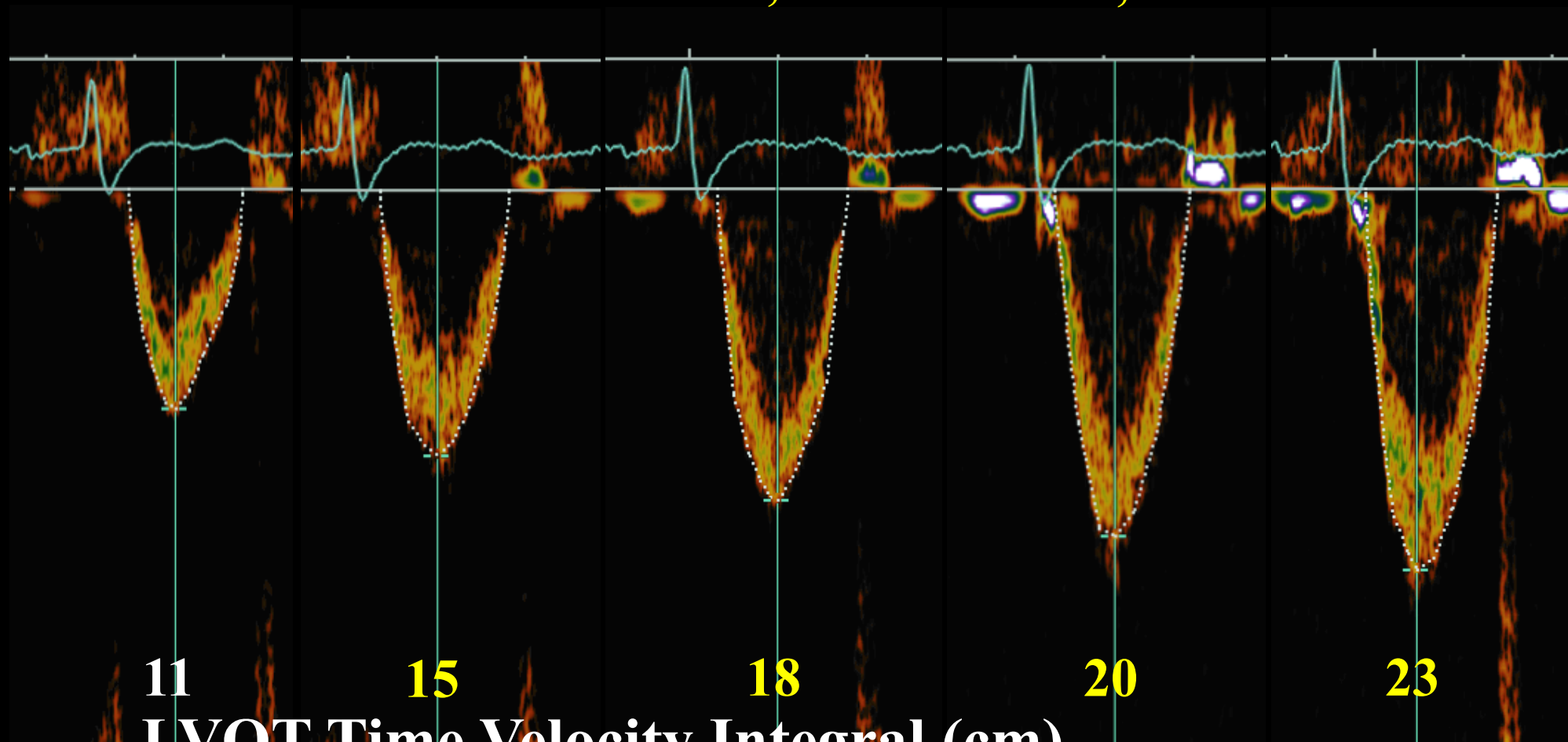
Baseline

5

7,5

12,5

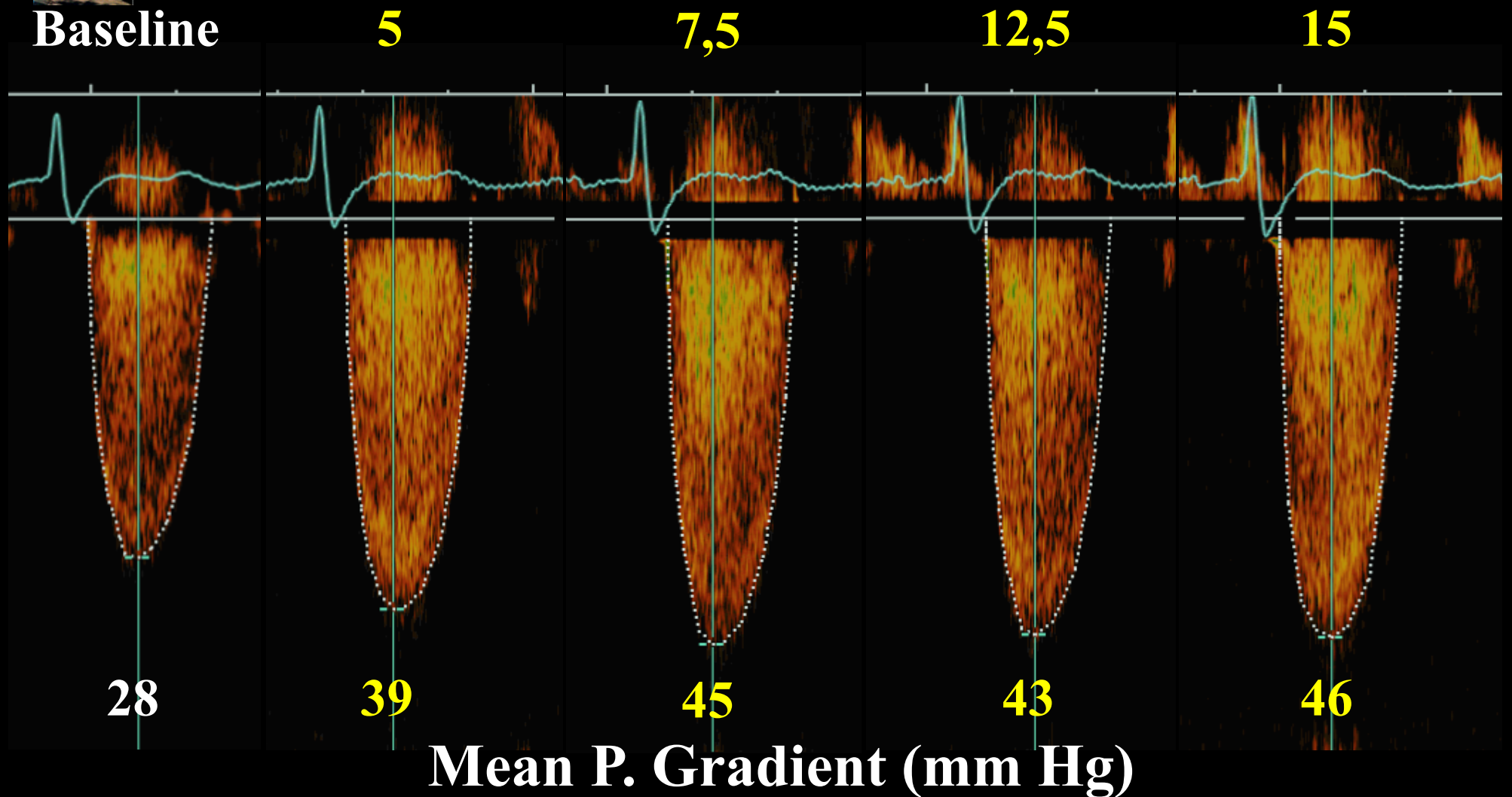
15



LVOT Time Velocity Integral (cm)



## Dobutamine ( $\mu\text{g/kg/min}$ )





**LV Contractile Reserve =  $\uparrow$  Stroke Volume  $> 20\%$**

**Contractile Reserve  
n= 92 (68%)**

- AVR : 64 patients (70%)
- Deaths (D30) n= 3 (5%)
- Associated CABG (n= 19):  
Deaths (D 30) n=2 (11%)
- NYHA I-II: 54/64 patients (84%)

**Exhausted Reserve  
n= 44 (32%)**

- AVR : 31 patients (70%)
- Deaths (D 30) n= 10 (32%)\*
- Associated CABG (n= 8):  
Deaths (D 30) n=5 (68%)\*
- NYHA I-II: 14/31 patients (45%)\*



# Dobutamine Challenge in the Cath. Lab.

**Low-flow / Low-gradient AS (n=21)**

**Contractile Reserve, n=15 (71%)**



**1 periop. death (7%)**



**2 late deaths  
(noncardiac)**



**NYHA class I-II  
12 patients**

**Exhausted Reserve, n=6 (29%)**



**2 periop. death (33%)**



**2 late deaths  
(CHF)**



**NYHA class I-II  
2 patients**





# Independent predictors of long-term survival after aortic valve replacement

152 consecutive patients with Low-flow/ Low-gradient AS undergoing AVR 1994 – 2005, median FU: 44 months (range 24–67)



## Independent predictors of survival

(Cox Prop. Hazard model) :

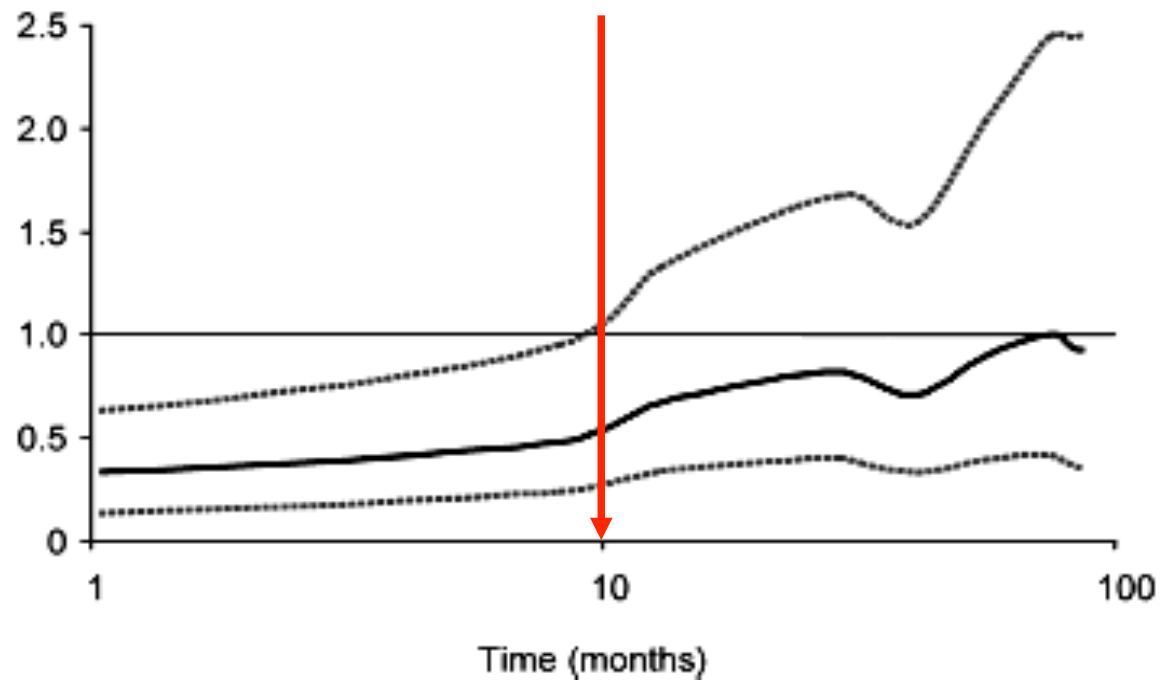
- LV contractile reserve:  $p = 0.002$
- Associated CABG:  $p = 0.003$
- Baseline MPG:  $p = 0.02$
- Logistic EuroSCORE:  $p = 0.04$
- Previous cancer:  $p = 0.04$





# LV contractile reserve impacts Early postoperative outcome (< 10 months)

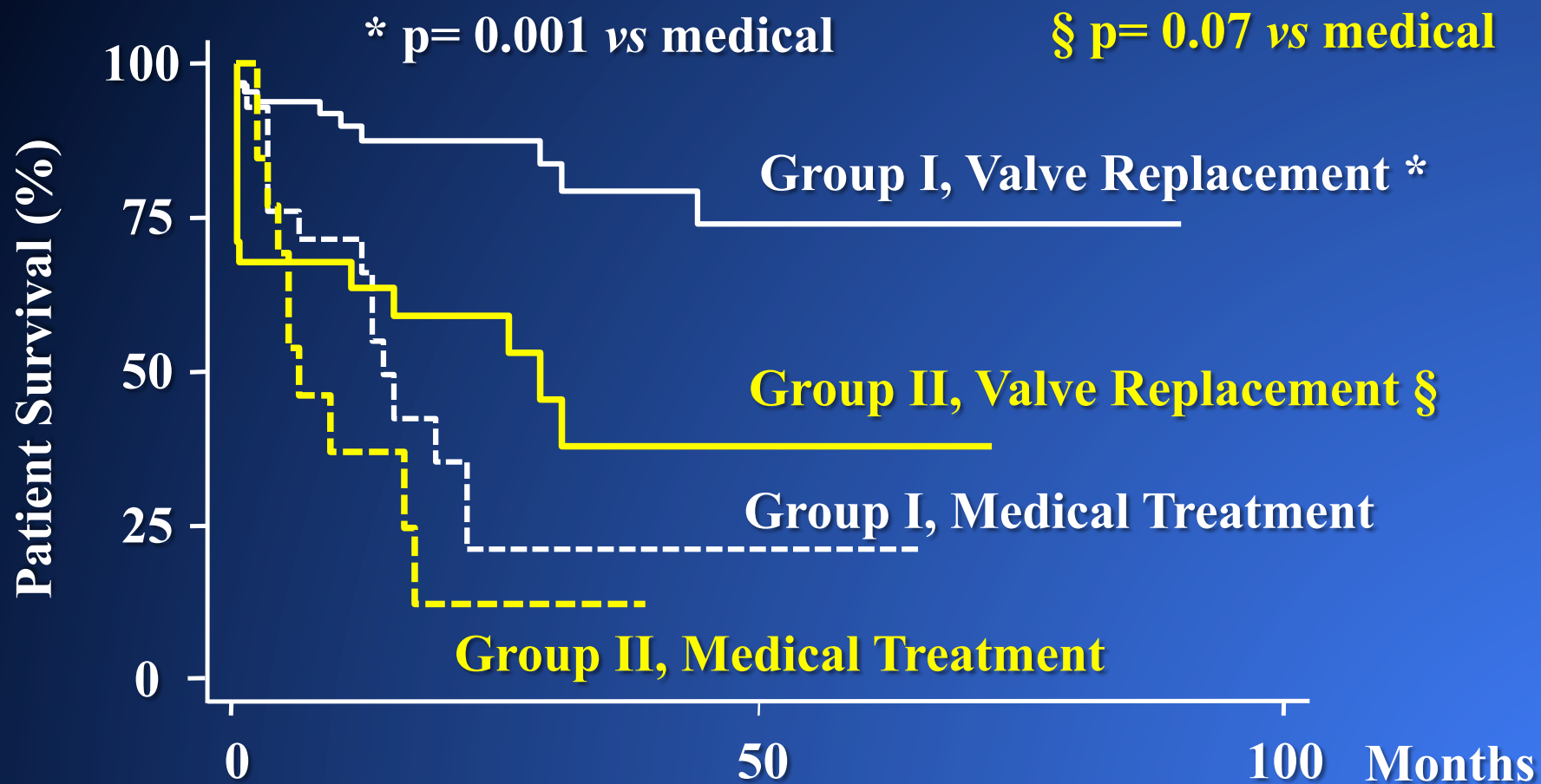
Effect of LV contractile reserve:  
hazard ratio for mortality  
(95% confidence intervals)



Monin et al. *Eur Heart J.* 2007; 28: 2620-6



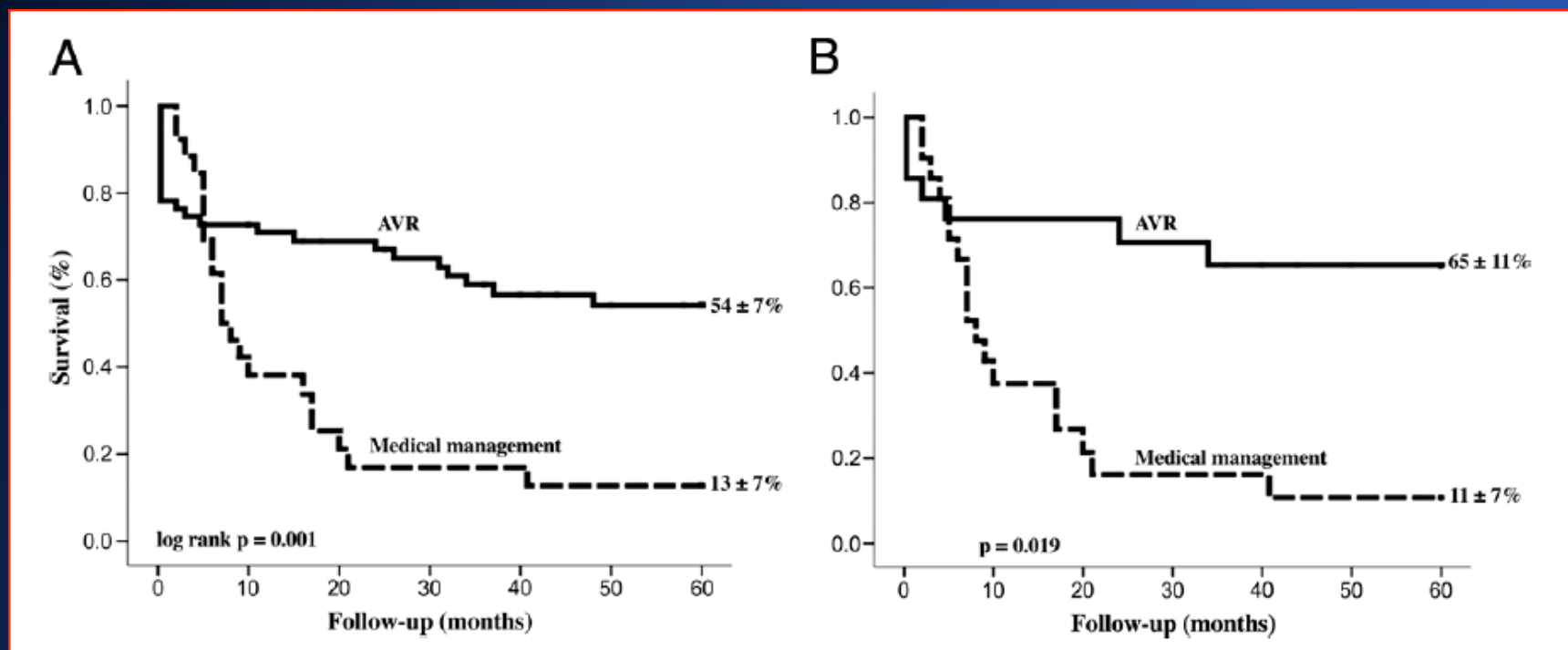
## Interaction of LV contractile reserve and aortic valve replacement (n= 136)





# Substantial benefit of AVR in Patients without contractile reserve

Multicenter Registry: 81 consecutive patients with Low-flow/ Low-gradient AS and without contractile reserve, median FU: 37 $\pm$  41 months



Whole cohort, n= 81

Matched patients, n= 42

Tribouilloy et al. *J Am Coll cardiol.* 2009;53: 1865-73



# LV Contractile Reserve is NOT related to postoperative LV ejection fraction

Patients should not be denied surgery on the sole basis of exhausted CR

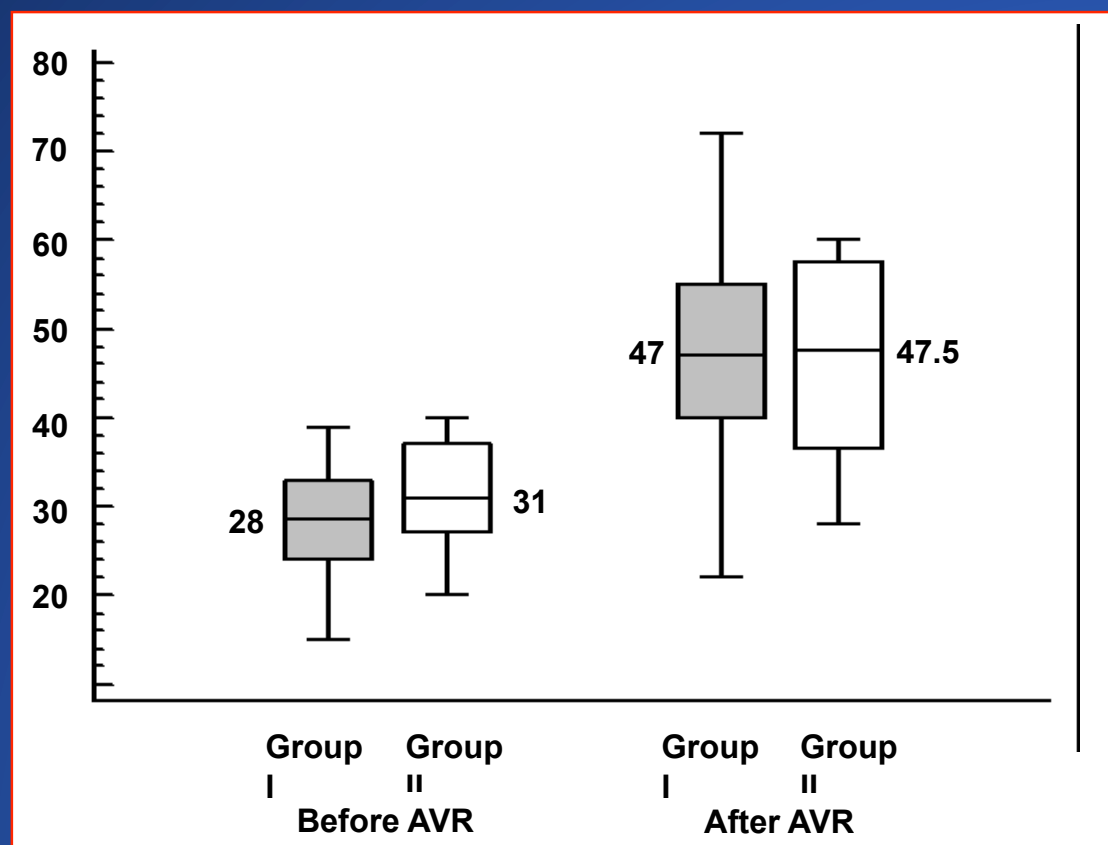
## Postop. LVEF related to:

- Multi-vessel CAD ( $p=0.05$ )
- Baseline MPG ( $p=0.01$ )

NOT to LV contractile reserve

## Limitation:

Exclusion of the patients who died postoperatively may underestimate the influence of CR on postop. LVEF

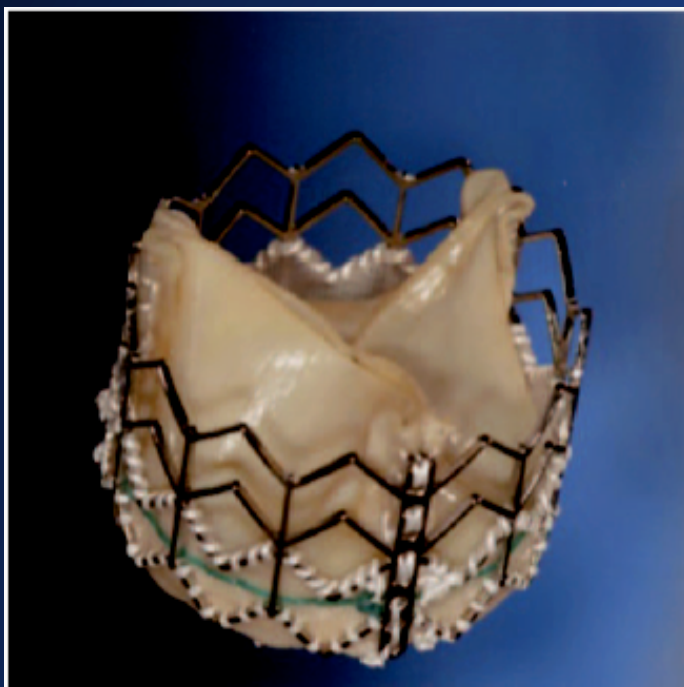


Quéré et al. *Circulation*. 2006; 113; 1738-44

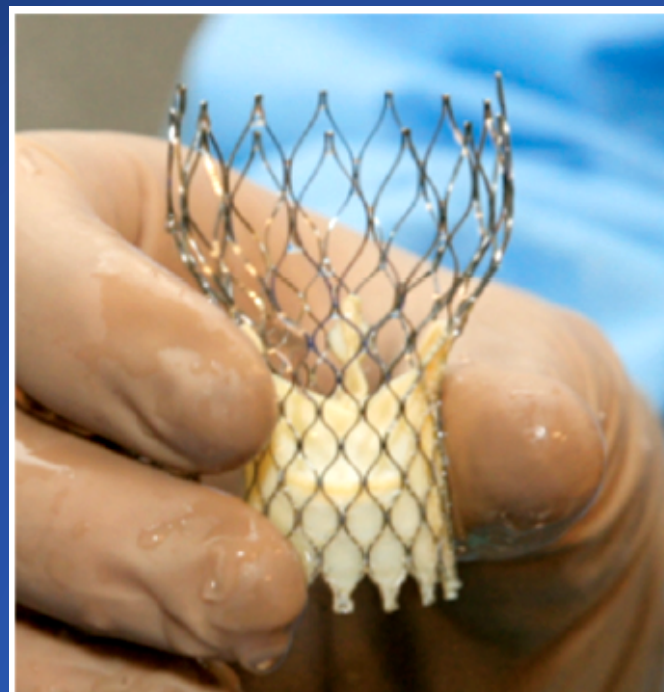


# Alternative Strategies for High-risk Patients: Percutaneous Valve Implantation ?

---



**Edwards SAPIEN<sup>TM</sup>  
Aortic Bioprosthesis**



**CoreValve Revalving<sup>TM</sup>  
System (CRS)**





# ACC-AHA/ ESC Guidelines

---

## Class IIa:

**Dobutamine Stress-Echo is reasonable to evaluate patients with Low-Gradient AS and left ventricular dysfunction**

**Bonow et al. *J. Am. Coll. Cardiol.* 2006;48: e1-148**

## Indications for Valve Replacement in Aortic Stenosis:

**AS with low gradient (<40 mmHg) and LV Dysfunction:**

- With contractile reserve **IIa**
- Without contractile reserve **IIb**

**Vahanian et al. *Eur Heart J.* 2007;28: 230-68**



# Low Gradient Aortic Stenosis with depressed LV ejection fraction

---

- Does LV contractile reserve matter ?
- Does pseudo-severe AS matter ?
- Does BNP serum level matter ?
- Does Prosthesis-patient mismatch matter ?

# **Usefulness of Dobutamine Echocardiography in Distinguishing Severe from Nonsevere Valvular Aortic Stenosis in Patients with Depressed Left Ventricular Function and Low Transvalvular Gradients**

Christopher R. deFilippi, MD, DuWayne L. Willett, MD, M. Elizabeth Brickner, MD, Christopher P. Appleton, MD, Clyde W. Yancy, MD, Eric J. Eichhorn, MD, and Paul A. Grayburn, MD

**I**n adults with aortic stenosis (AS), valve replacement is recommended if symptoms are accompanied by severely reduced aortic orifice area.<sup>1-5</sup> In such patients, valve replacement improves symptoms and life expectancy, even in the setting of left ventricular (LV) dysfunction. LV dysfunction in severe AS is usually due to afterload mismatch, to the extent that valve replacement relieves the afterload excess imposed by the stenotic valve and improves LV performance.<sup>6,7</sup> However, a subset of patients with severe AS, LV dysfunction, and low transvalvular gradients have a high operative mortality.<sup>7-9</sup> Accurate assessment of aortic valve area in such patients is difficult<sup>10</sup> because calculated valve area is directly proportional to cardiac output<sup>11-13</sup> and the Gorlin constant varies at low flow states.<sup>14-16</sup> Cannon et al<sup>17</sup> showed that some patients with LV dysfunction and low mean gradients have Gorlin valve areas indicating critical AS when the valve is only moderately diseased at surgery. This study was performed to determine whether dobutamine echocardiography, which enables aortic valve area calculation at 2 different flow conditions

cal, suprasternal, and right parasternal views using spectral and audio signals to identify the maximal aortic flow velocity.

Heart rate, blood pressure, rhythm, and wall motion were monitored throughout the procedure. Intravenous dobutamine was started at 5  $\mu\text{g/kg/min}$  and increased by 5  $\mu\text{g/kg/min}$  every 3 minutes until a maximal dose of 20  $\mu\text{g/kg/min}$  was obtained. The protocol was stopped at lower doses for wall motion abnormalities, hypotension, or significant adverse side effects. The last stage was continued for 6 minutes to acquire final echocardiographic and Doppler data, which were obtained from the same transducer position as at baseline.

LV ejection fraction was assessed by biplane Simpson's rule at baseline and after dobutamine. Regional wall motion was assessed on a quad screen display using the 16-segment model in which each segment was graded as 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic.<sup>19</sup> Wall motion score was calculated at baseline and peak dobutamine as described previously.<sup>19,20</sup> LV contractile reserve was defined as  $\geq 20\%$  improve-





# deFilippi: n=18 patients, 3 Groups

	LVEF	Gradient	AVA
Group IA	↗	↗	→
Group IB	↗	→	↗
Group II	→	→	?

"Pseudo-severe AS": Favorable outcome (1 year) under medical TT (4/5)

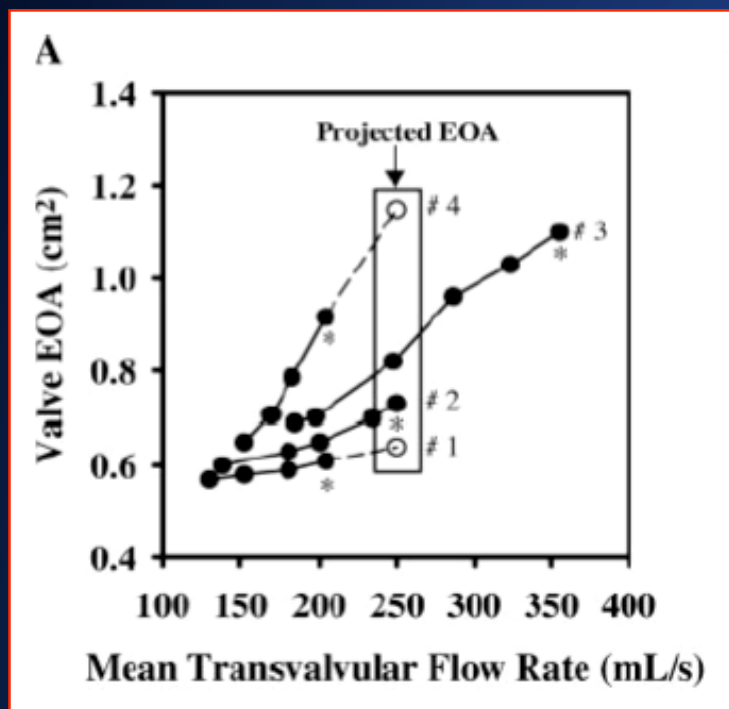
deFilippi et al. *Am J Cardiol* 1995;75: 191



## Interest of the projected AVA : TOPAS Multicenter Group

46 consecutive patients (2002-2004, Canada/ Austria)

AVA  $\leq 1.2 \text{ cm}^2$  / LVEF  $\leq 40\%$  / MPG  $< 40 \text{ mm Hg}$



Slope of the regression line of AVA plotted  
against flow at each dobutamine stage

Projected Valve Area :

AVA at a standardized flow rate of 250 mL/s

In 23 operated patients:

Fairly concordant with surgical valve  
inspection. Limitation: no outcome data

Blais et al. *Circulation*. 2006;113: 711-721



# Pseudo-severe Aortic Stenosis : Prevalence / Clinical Outcome

Author (year)	Criteria for Pseudo-severe AS	Incidence	Follow-up (months)	Mortality
deFilipi (1995)	$\Delta$ EOA $>0.3$ cm <sup>2</sup>	5/18 (28%)	12	20%
Schwammenthal (2001)	$\Delta$ EOA $>0.3$ cm <sup>2</sup> ; final EOA $>1$ cm <sup>2</sup>	8/24 (30%)	11	25%
Nishimura (2002)	Final EOA $>1.2$ cm <sup>2</sup> ; final MPG $<30$ mm Hg	7/32 (22%)	32	57–100%
Monin (2003)	$\Delta$ EOA $>0.3$ cm <sup>2</sup> ; final EOA $>1$ cm <sup>2</sup>	7/136 (5%)	19	50%
Zuppiroli (2003)	$\Delta$ EOA $>0.25$ cm <sup>2</sup>	10/48 (21%)	24	70%
<i>Pooled</i>		<i>37/258 (14%)</i>	<i>20</i>	<i>48–57%</i>

**Bermejo & Yotti. Heart. 2007;93: 298-302**



## **Low-flow / Low-gradient AS : 3 Major issues to consider**

---

- 1/ Valve calcification (« Look at the valve »)**
- 2/ LV contractile reserve: perhaps most important, rather than precise distinction between fixed and pseudo-AS**
- 3/ Pseudo-severe AS: remains to be tested in large groups, against clinical outcome**



# Outcomes under Conservative Treatment in Low-Gradient AS: Focus on Pseudo-Severe AS

---

- European Multicenter Registry for Low-gradient AS : 8 Medical centers (Belgium, France) including 250 patients
- Present study: 84 consecutive patients followed under conservative TT
- Baseline characteristics : **Age: 76 years [69-81]**, 61 males (73%), **AVA: 0.8 cm<sup>2</sup> [0.6-0.9]**, MPG: 22 mmHg [17-27], **LVEF: 30% [23-35]**

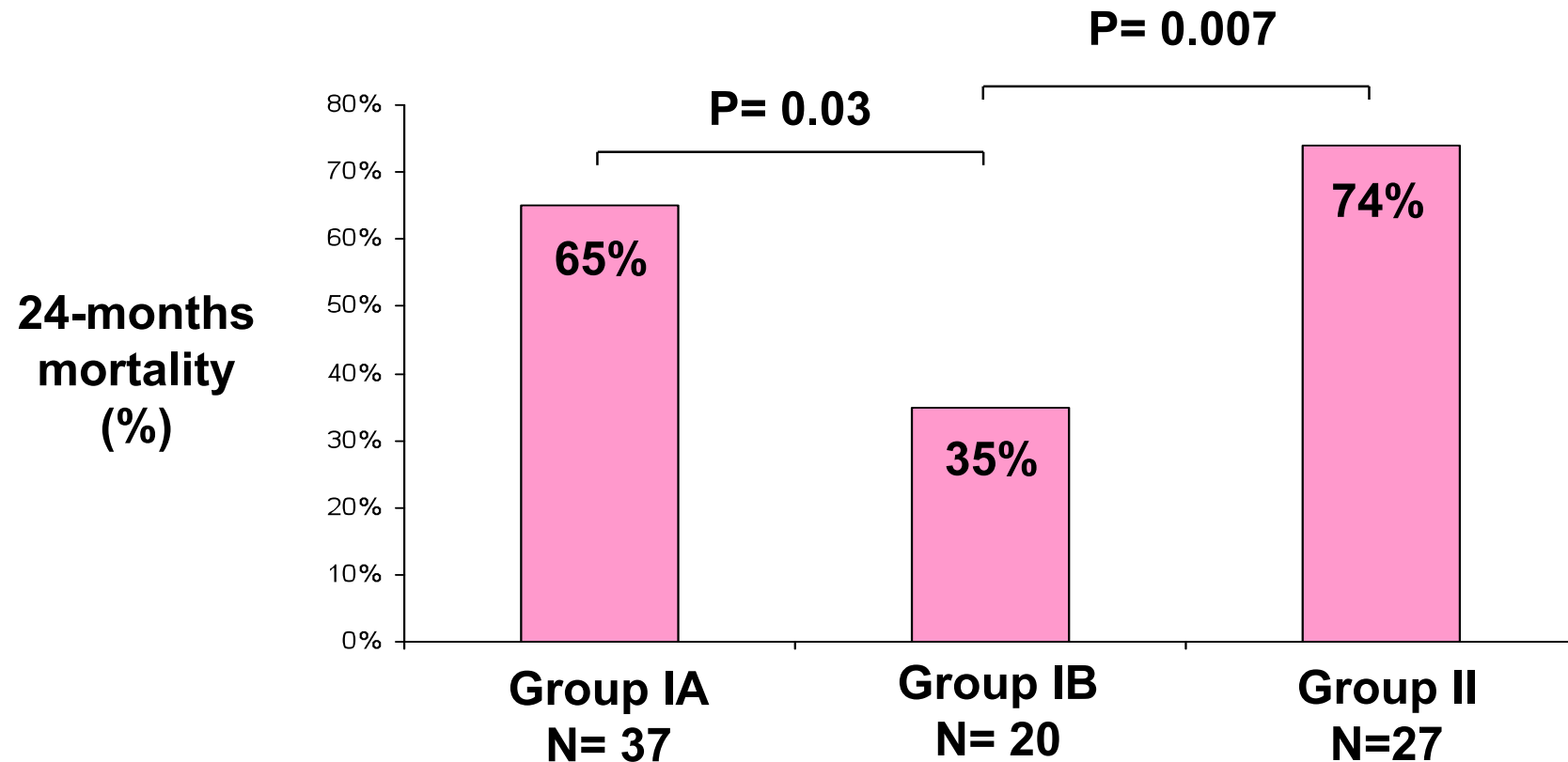
## According to deFillipi et al :

- Group IA: 37 patients with True-severe AS (LV contractile reserve +)
- **Group IB: 20 patients with Pseudo-severe AS, defined by a Dobutamine AVA  $\geq 1.2$  cm<sup>2</sup> with peak MPG <40 mm Hg**
- Group II: 27 patients without LV contractile reserve

*E. Fougères et al. Submitted.*



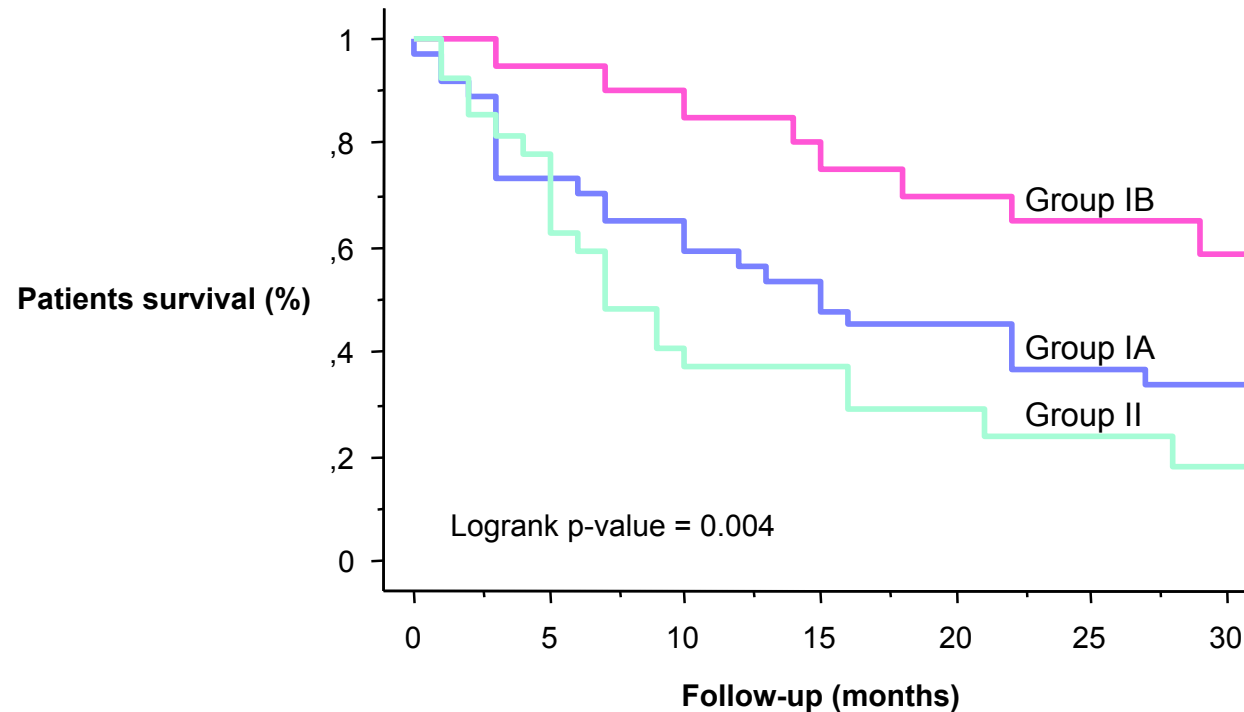
## Outcomes in Low-gradient AS under conservative treatment : European registry



E. Fougères et al. *Submitted.*



# Outcomes in Low-gradient AS under conservative treatment : European registry



Number of patients

	0	5	10	15	20	25	30
Group IA	37	22	16	12			
Group IB	20	17	14	9			
Group II	27	10	6	3			

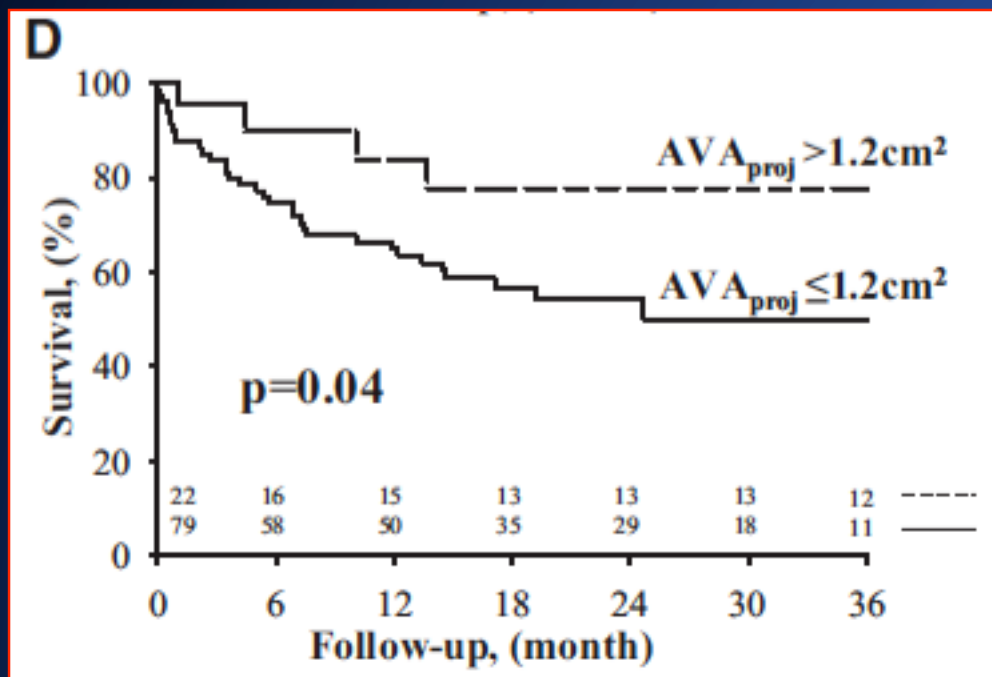
E. Fougères et al. *Submitted.*





## Clinical relevance of Pseudo-severe AS : TOPAS Multicenter Group

Multicenter Group: 101 consecutive patients with Low-gradient AS :  
 $AVA \leq 1.2 \text{ cm}^2$ ,  $LVEF \leq 40\%$ ,  $MPG \leq 40 \text{ mm Hg}$



**Projected AVA was an independent predictor of survival, only in the subgroup treated conservatively**





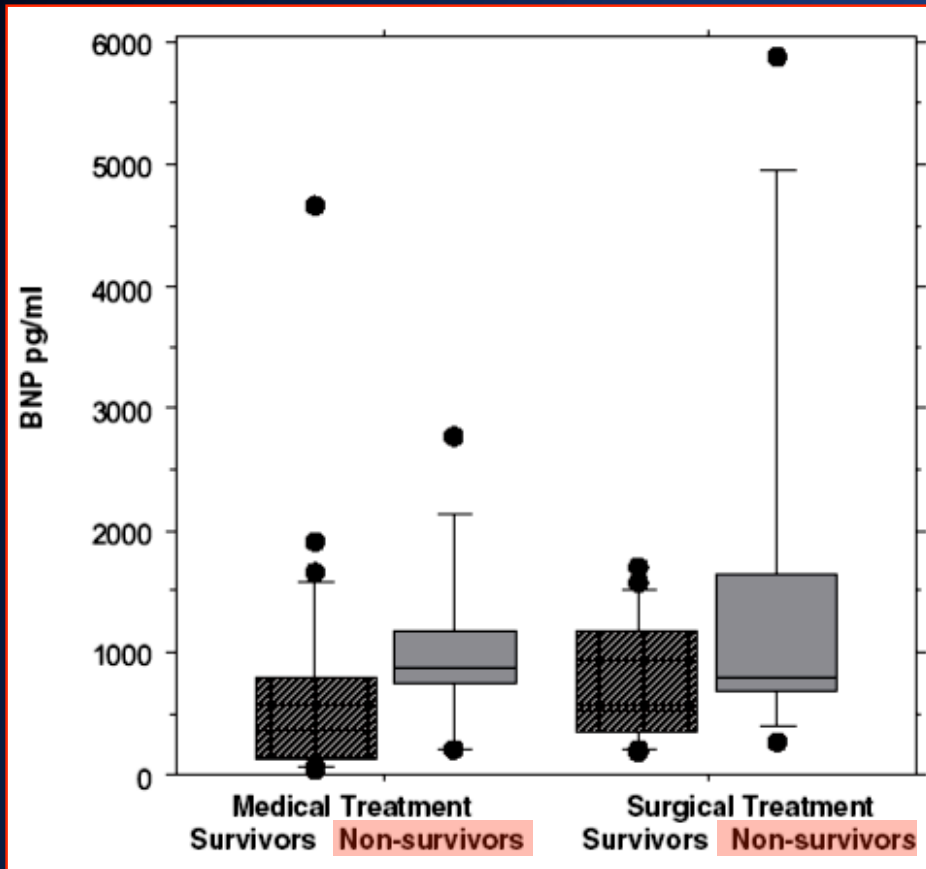
# Low Gradient Aortic Stenosis with depressed LV ejection fraction

---

- Does LV contractile reserve matter ?
- Does pseudo-severe AS matter ?
- Does BNP serum level matter ?
- Does Prosthesis-patient mismatch matter ?



# BNP in Low-gradient AS: Results from the TOPAS study



Prospective Multicenter study:

Quebec, Ottawa, Vienna

**69 patients with low-gradient AS**

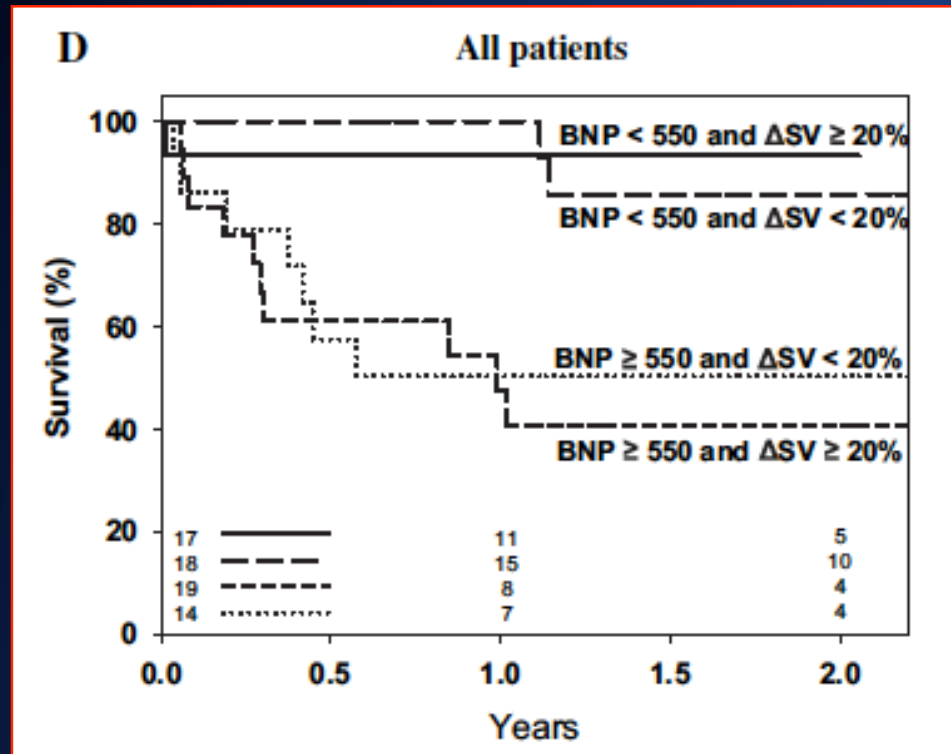
(Indexed EOA  $\leq 0.6$  cm<sup>2</sup>/m<sup>2</sup>, LVEF  $\leq 40\%$  and  
MPG  $\leq 40$  mm Hg)

**RESULTS:**

- Trend towards higher BNP in patients who died after AVR
- However it didn't reach statistical significance



## BNP in Low-gradient AS: Results from the TOPAS study



### All patients:

- BNP level has a significant impact on survival, whatever the presence of contractile reserve
- **However: most patients (40/69) were medically treated : Incremental value of BNP for operative risk stratification is unknown**
- BNP might add to risk stratification in group II



# Low Gradient Aortic Stenosis with depressed LV ejection fraction

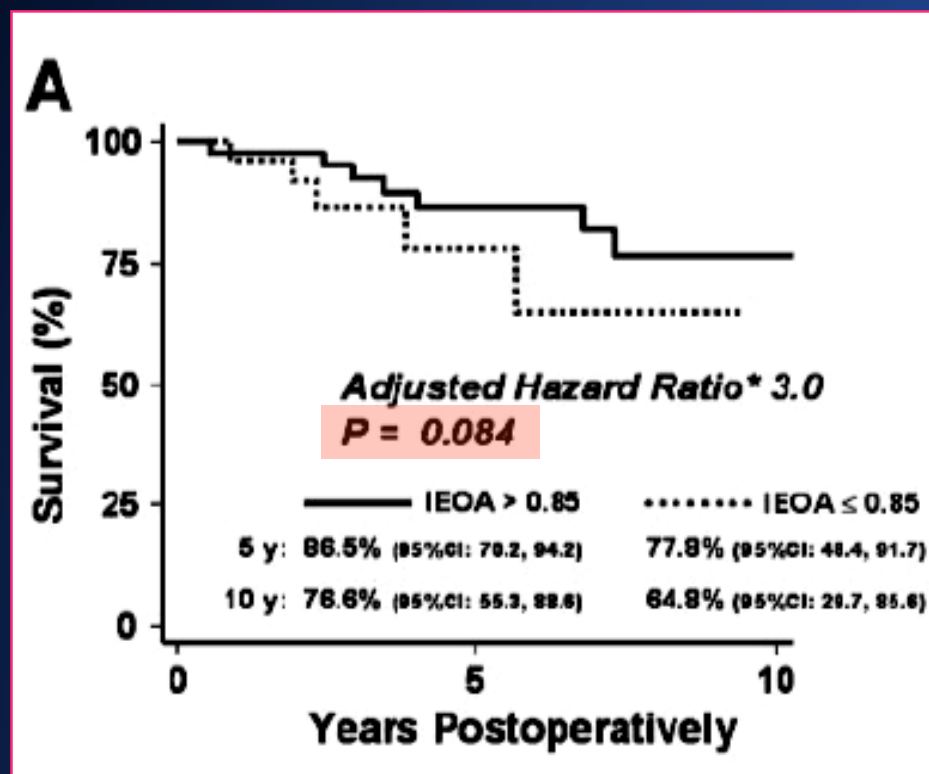
---

- Does LV contractile reserve matter ?
- Does pseudo-severe AS matter ?
- Does BNP serum level matter ?
- Does Prosthesis-patient mismatch matter ?



# Impact of mismatch after AVR in Low-gradient aortic stenosis

Prospective study: Ottawa Heart Institute, Canada  
79 patients undergoing AVR for Low-gradient AS (1990-2002)  
(AVA <1.2 cm<sup>2</sup>, LVEF <50% and MPG <40 mm Hg)



**Results: Trend toward  
increased late mortality in case  
of PPM (p= 0.08)**



## (Lack of) impact of PPM after AVR in Low-gradient aortic stenosis

---

Multicenter registry for Low-flow/ Low-gradient AS :  
AVA <1.0 cm<sup>2</sup>, LVEF <40% and MPG <40 mm Hg

**152 consecutive patients undergoing AVR 1994 - 2005**

- PPM in 79 patients (52%), moderate in 72 (47%) and severe in 7 (5%).

### Patients with PPM:

- Significantly older, higher EuroSCORE and a higher prevalence of stented bioprosthetic valves
- Otherwise, no significant difference in BMI, sex ratio, NYHA functional class, **prevalence of LV contractile reserve** or extra-cardiac comorbidities

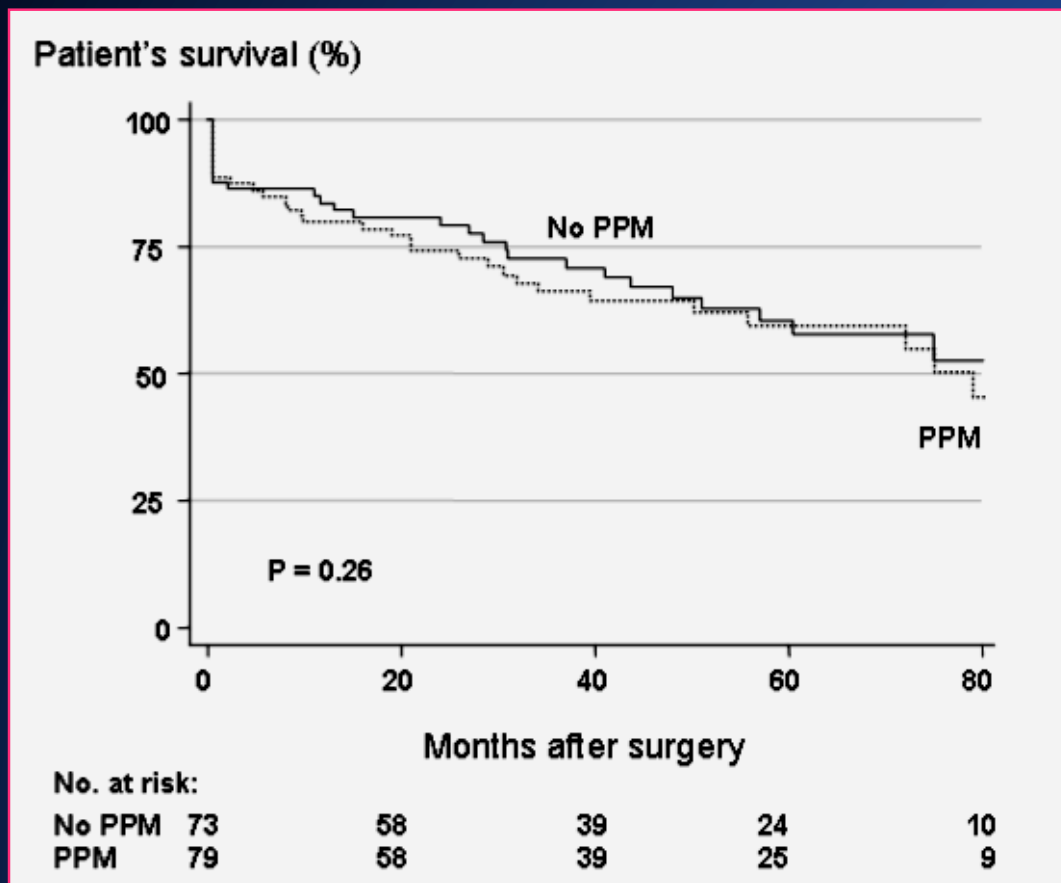
**Monin et al. Eur Heart J. 2007; 28: 2620-6**





## (Lack of) impact of PPM after AVR in Low-gradient aortic stenosis

**PPM, moderate in most cases, was not predictive of survival**



**(Cox Prop. Hazard model) :**

- EOA:  $p = 0.11$
- Indexed EOA (continuous variable):  $p = 0.24$
- PPM (dichotomous variable, EOA Index  $< 0.85 \text{ cm}^2/\text{m}^2$ ):  $p = 0.34$

Monin et al. *Eur Heart J.* 2007; 28: 2620-6



# Take-Home messages

---

- Low-Gradient Aortic Stenosis: 5-7% of all patients with AS, still remains a common medical challenge
- LV contractile reserve has a strong impact on mid-term postoperative outcome, thus it is useful for risk stratification
- Patients without contractile reserve: high operative mortality but significant clinical/ hemodynamic benefit in survivors
- Lack of CR in itself IS NOT a contraindication to valve replacement (or transcatheter implantation ?)





## Take-Home messages (2)

---

- Patients with pseudo-severe AS may benefit from initial conservative treatment at mid-term
- Further studies are needed to assess the potential of BNP for risk stratification
- Moderate PPM seems to have no significant impact on postoperative survival in this setting
- Transcatheter aortic valve implantation may be an alternative to surgery for high-risk patients

# Henri Mondor

