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# TAVI for Severe Asymptomatic Aortic Stenosis

Horst Sievert,

Ilona Hofmann, Laura Vaskelyte, Sameer Gafoor, Stefan Bertog, Predrag  
Matić, Markus Reinartz, Bojan Jovanovic, Kolja Sievert, Nalan Schnelle  
CardioVascular Center Frankfurt - CVC,  
Frankfurt, Germany

# Disclosures

Physician name	Company	Relationship
Horst Sievert	Abbott, Ablative Solutions, Acoredis, Atrium, Biosense Webster, Bioventrix, Boston Scientific, Carag, Cardiac Dimensions, CardioKinetix, Celonova, Cibiem, CGuard, Coherex, Comed B.V., Contego, CSI, CVRx, ev3, FlowCardia, Gardia, Gore, GTIMD Medical, Guided Delivery Systems, Hemoteq, InspireMD, Kona Medical, Lumen Biomedical, Lifetech, Medtronic, Occlutech, pfm Medical, Recor, SentreHeart, Svelte Medical Systems, Terumo, Trivascular, Valtech, Vascular Dynamics, Venus Medical, Veryan	Consulting fees, Travel expenses, Study honoraria
	Cardiokinetix, Access Closure, Coherex, SMT	Stock options

# What is the problem?

- Patients with asymptomatic aortic stenosis ...
  - ... are frequent
  - ... are rarely diagnosed
- Many believe the prognosis is good in asymptomatic patients
- Therefore, asymptomatic patients are usually not referred to surgery
- They had been excluded from TAVI trials
- But they may die from sudden death

# Incidence

- 25-50% of all patients with severe aortic stenosis are asymptomatic
- $\approx$  500,000 pts in the US

# Patients with asymptomatic aortic stenosis are rarely diagnosed

- Patients: "Don't go to the doctor, if you do not feel sick"
- In many places, auscultation is not part of a routine examination anymore
- A systolic murmur especially in the elderly is often classified as "functional" and not always triggering further evaluation

"The prognosis is good"

Not true!

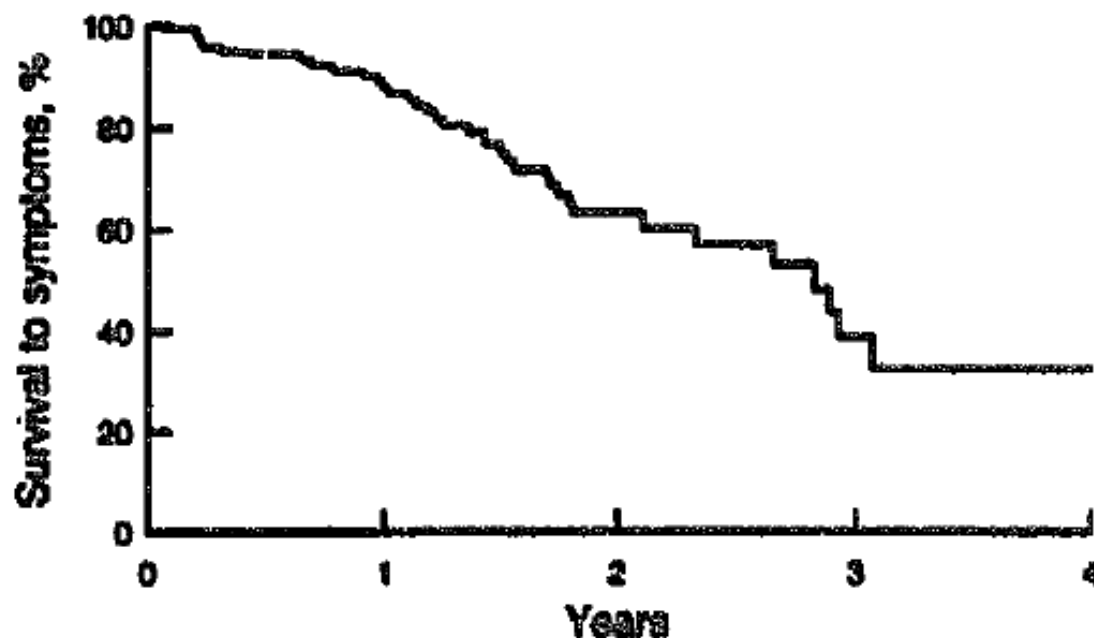
Most of the patients are becoming  
symptomatic very soon ...

... and sudden death  
may occur

# The Natural History of Adults With Asymptomatic, Hemodynamically Significant Aortic Stenosis

PATRICIA A. PELLIKKA, MD, RICK A. NISHIMURA, MD, FACC, KENT R. BAILEY, PhD,  
A. JAMIL TAJIK, MD, FACC

*Rochester, Minnesota*



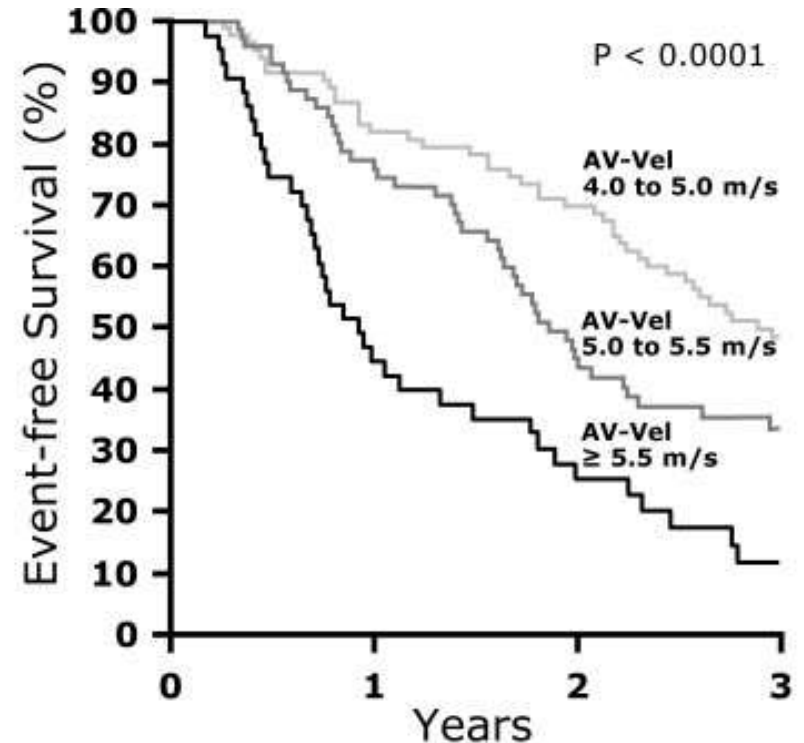
**Figure 1.** Survival free of development of symptoms for 113 patients with asymptomatic aortic stenosis who did not receive early intervention (group 2).

**JACC Vol. 15, No. 5  
April 1990:1012-7**

# Asymptomatic Severe Aortic Stenosis

Event-free survival (indication for aortic valve replacement, cardiac death)

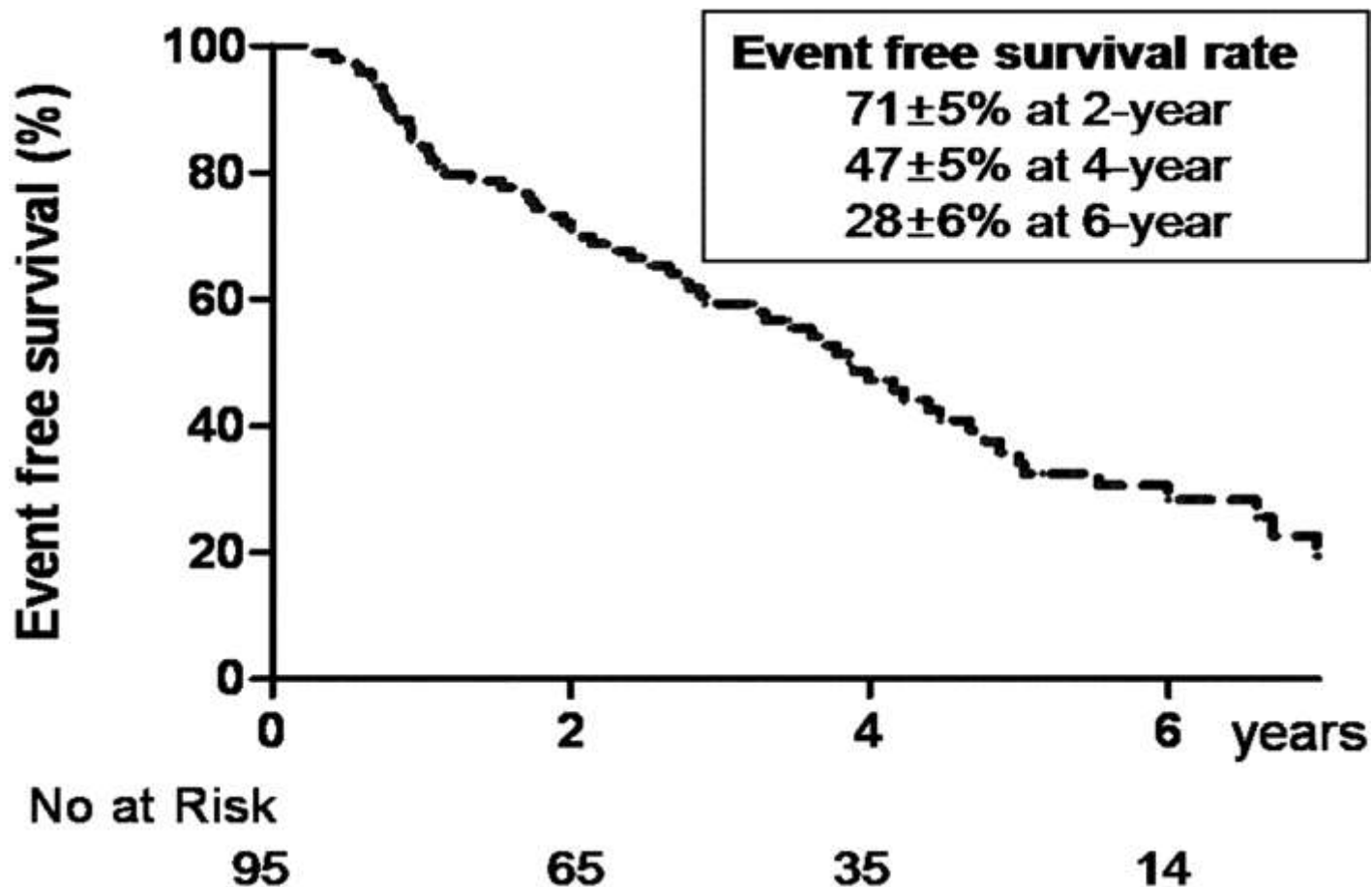
- N = 116, age  $67 \pm 16$  yrs
- Severe aortic stenosis
- Median follow-up: 41 mo
- Poor prognosis!
  - Event-free survival was low and clearly depending on severity of aortic stenosis
  - 6 cardiac deaths occurred in previously asymptomatic patients



<b>Patients with AV-Vel from 4.0 to 5.0 m/s</b>				
Pts. at risk:	82	69	59	38
<b>Patients with AV-Vel from 5.0 to 5.5 m/s</b>				
Pts. at risk:	72	53	29	18
<b>Patients with AV-Vel <math>\geq 5.5</math> m/s</b>				
Pts. at risk:	44	20	11	5



# Survival free of cardiac death or surgery in patients with asymptomatic aortic stenosis



"In asymptomatic patients we could just wait until they become symptomatic"

However, it would be bad if the first symptom is sudden death

Therefore, one of the key questions is **how frequent is sudden death** in these patients?

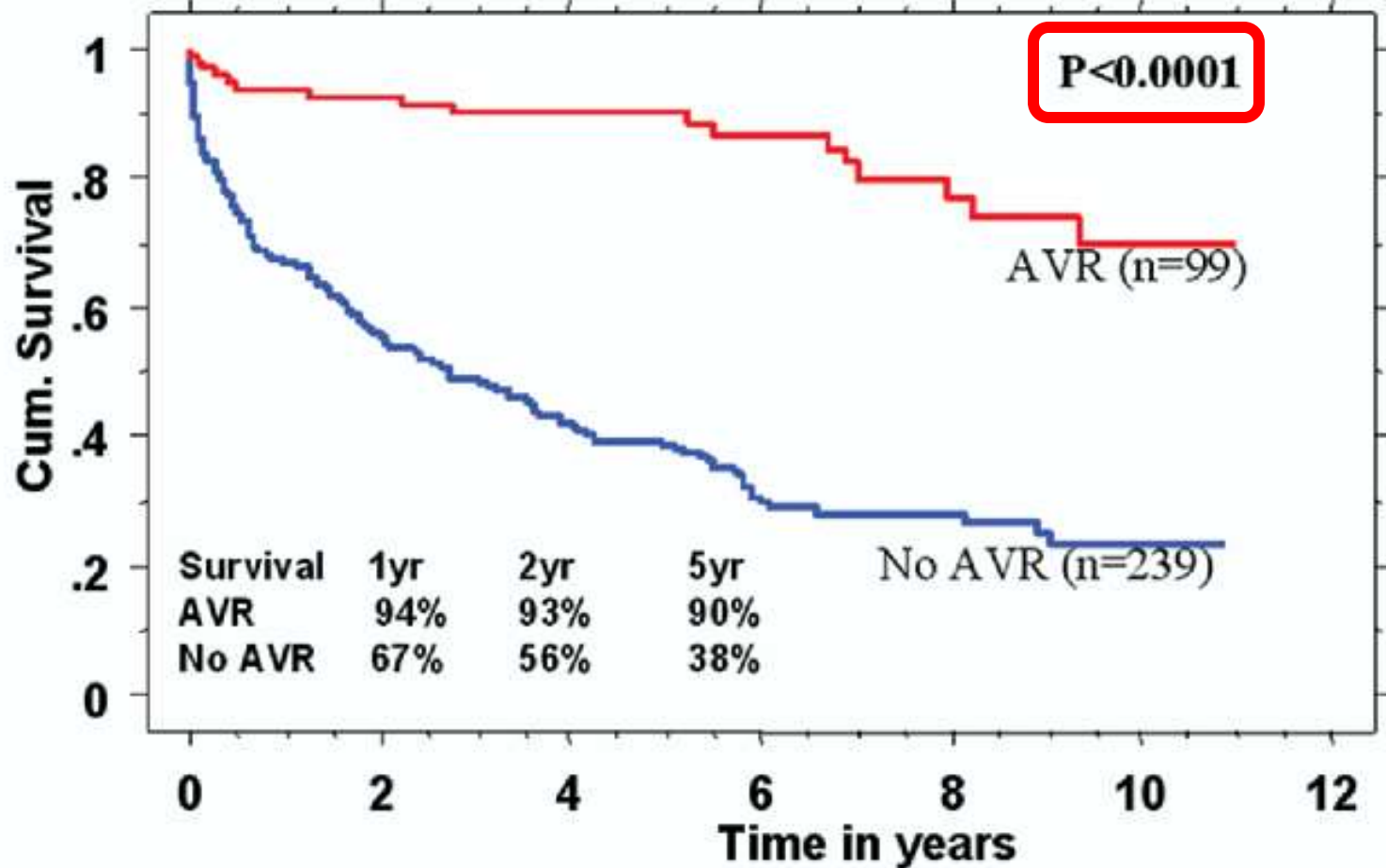
# Sudden death in asymptomatic severe aortic stenosis is rare but usually not preceded by symptoms

Studies	Sudden death (n)	Preceded by symptoms (n)	Not preceded by symptoms (n)
<i>Pellikka et al. 1990</i>	3/143	3	0
Rosenheck et al. 2000	1/128	-	-
<i>Amato et al. 2001</i>	4/66	-	4
Lancellotti et al 2005	2/69	-	-
<i>Pellikka et al. 2005</i>	11/622	0	11
<i>Avakian et al. 2008</i>	7/133	3	4
Monin et al. 2009	2/107	-	-
Cioffi et al. 2009	2/218	-	-
<i>Kang et al. 2010</i>	9/197	2	7
<i>Lancellotti et al. 2010</i>	3/163	0	3
<i>Rosenheck et al. 2010</i>	1/113	0	1
Stewart et al. 2010	4/183	-	-
<i>Saito et al. 2012</i>	6/103	4	2
Yingchoncharoen et al.; 2012	1/79	-	-
	<b>1% per year</b>	<b>27%</b>	<b>73%</b>

What are the results of surgical  
aortic valve replacement in  
asymptomatic patients?

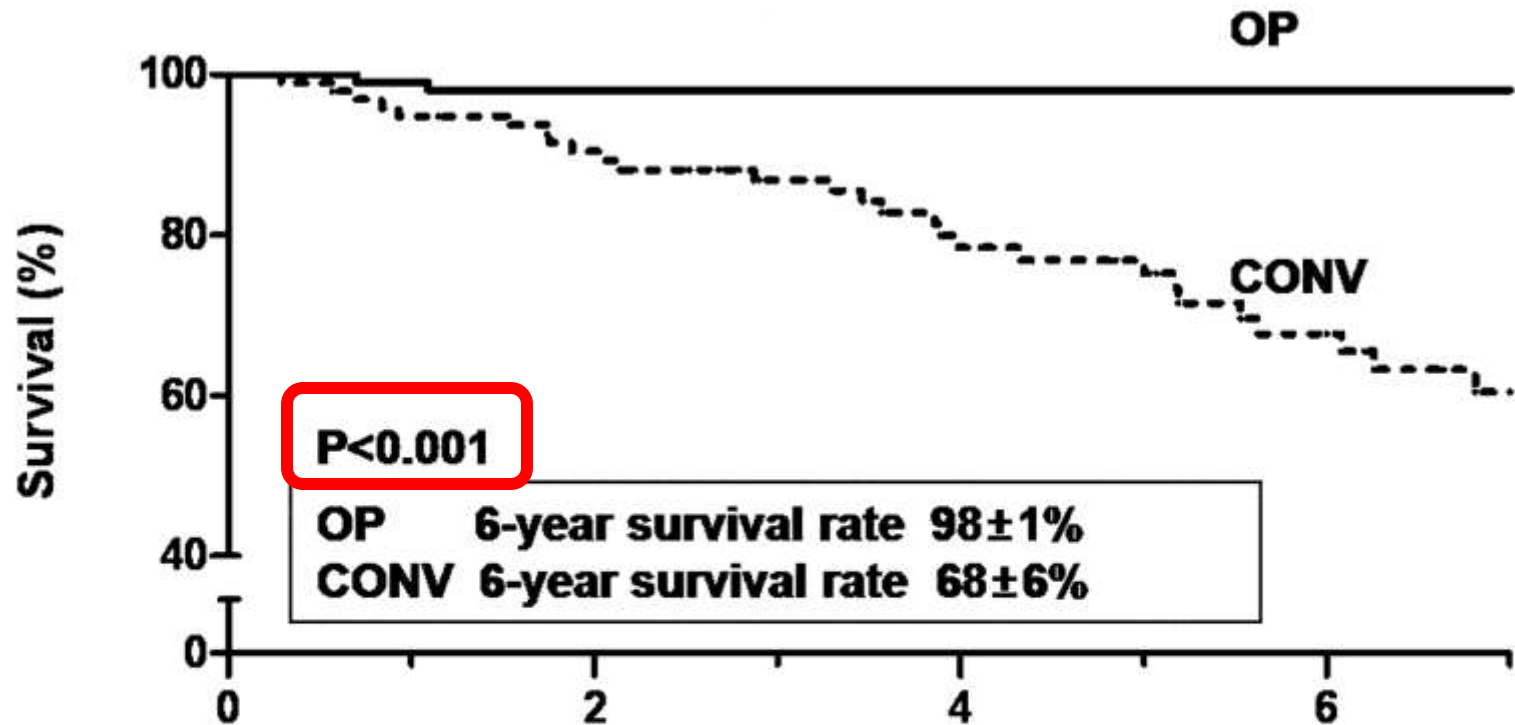
Observational studies only,  
no randomized trials

# Survival in asymptomatic severe aortic stenosis patients with and without aortic valve replacement (AVR)



No at risk	0	2	4	6	8	10	11	(AVR)
	99	87	78	71	64	55	46	35
	239	140	104	86	68	57	38	28
								18
								14
								6
								(no AVR)

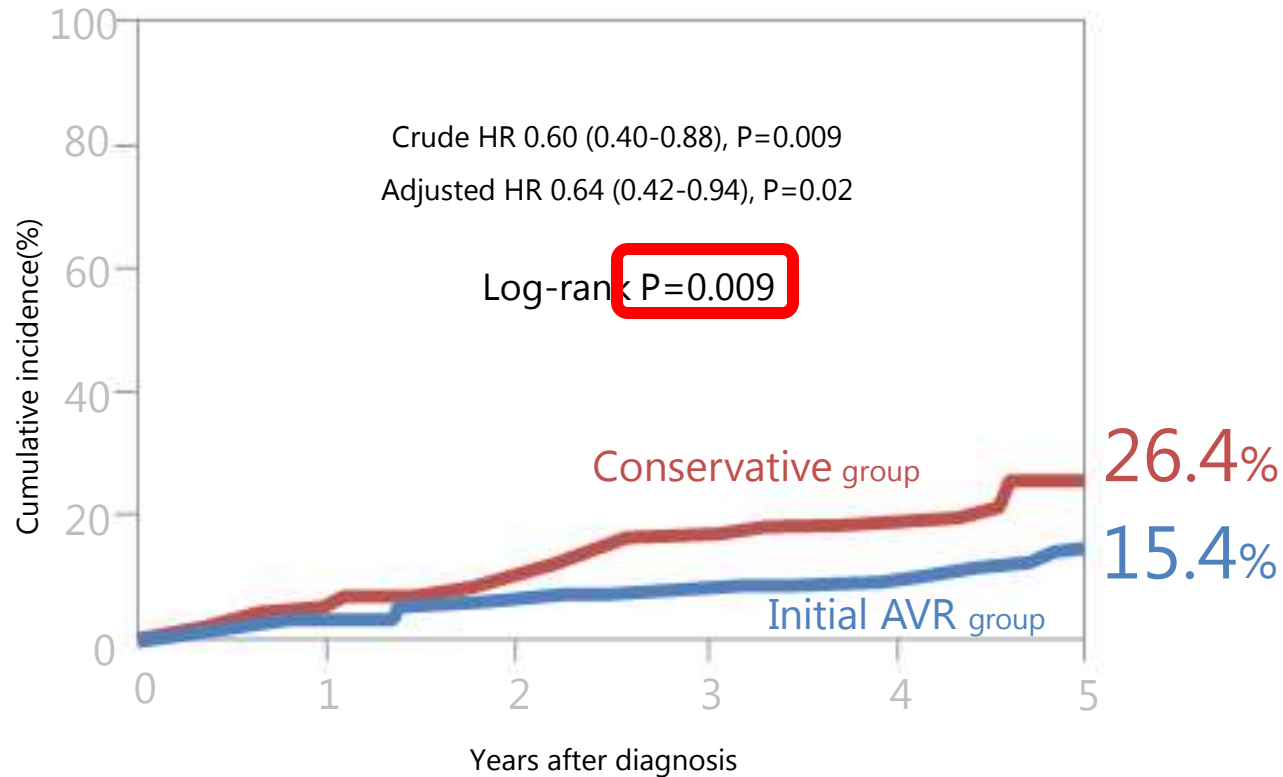
# Comparison of overall survival between the early surgery (OP) and conventional treatment (CONV) groups



No at Risk

OP	102	96	48	29
CONV	95	82	54	32

# All-cause death



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

# Metaanalysis: Surgical aortic valve replacement vs. observation in asymptomatic severe AS patients;

N=2,486

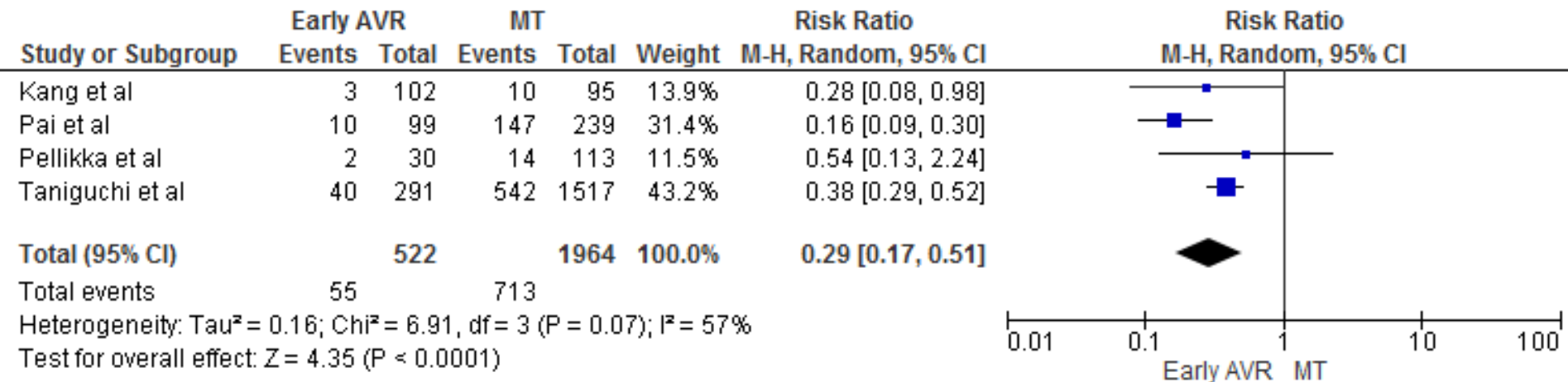
Authors	AS definition	N	Age	Female	Follow-up (median)
<b>Pellikka et al.1990</b>	Severe AS; Doppler PV $\geq 4$ m/s	143 30 AVR 113 Medical	72 (mean) 40 to 94	38%	AVR 21 m Medical 20 m
<b>Pai et al. 2006</b>	Severe AS AVA $< 0.8$ cm <sup>2</sup>	338 99 AVR 239 Medical	71 $\pm$ 15	49%	3.5 y
<b>Kang et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



# Metaanalysis: Surgical aortic valve replacement vs. observation in asymptomatic severe AS patients;

N=2,486

## All-Cause Mortality



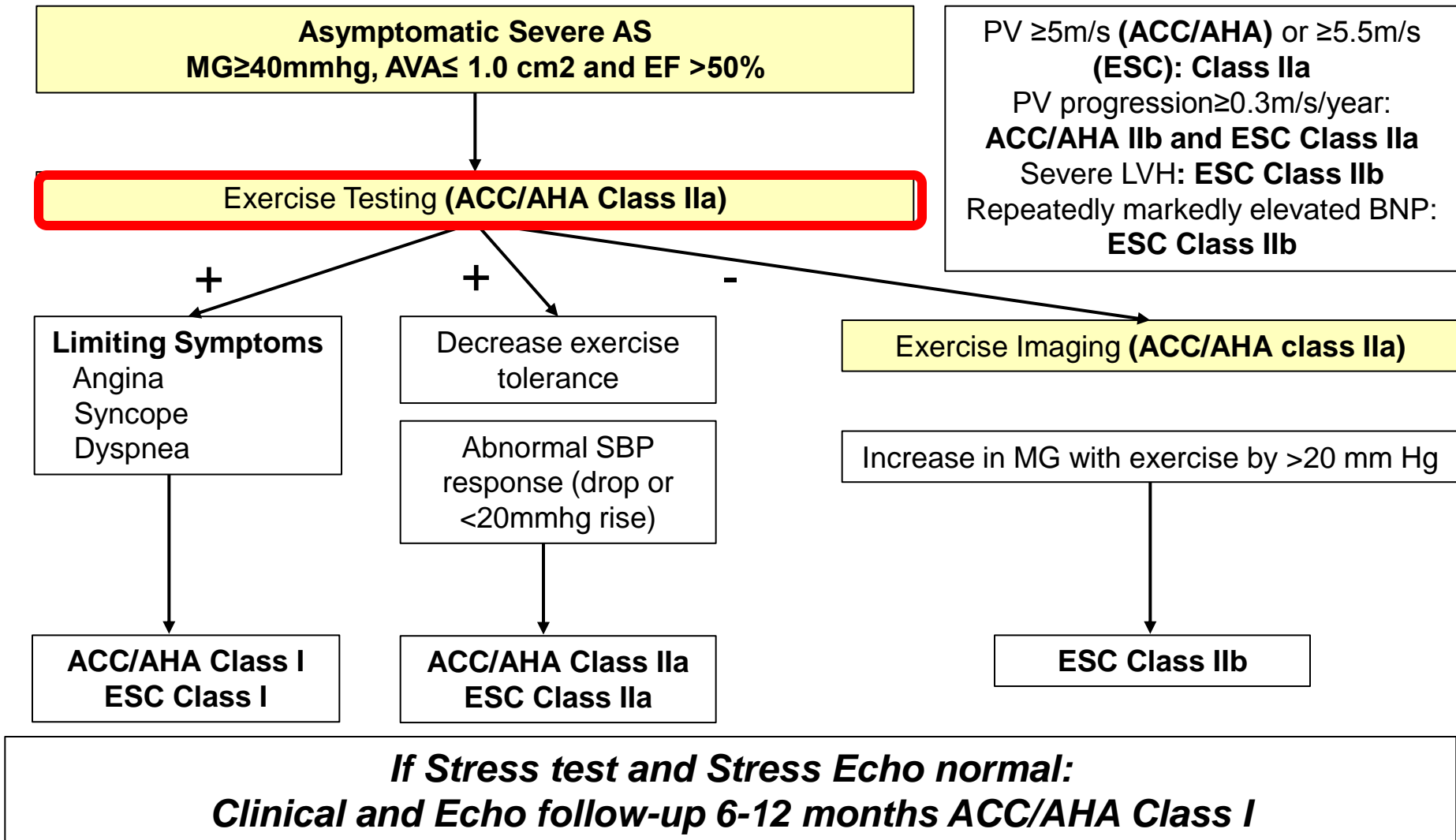
***~3.5 fold higher all-cause Mortality  
if treated medically***

# According to guidelines, aortic valve replacement is recommended in many subgroups of asymptomatic patients

	ACC/AHA	ESC/EACTS
<b><i>Indications for aortic valve replacement</i></b>		
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 $\geq$ 5.0 m/s [ACC]; >5.5m/s [ESC] and low surgical risk	IIa, B	IIa, C
Rate of PV progression $\geq$ 0.3 m/s per year and low surgical risk	IIb, C	IIa, C
Repeatedly markedly elevated natriuretic peptide and low surgical risk	-	IIb, C
Increase of MG with exercise by >20 mmHg and low surgical risk	-	IIb, C
Excessive LVH in the absence of hypertension and low surgical risk	-	IIb, C

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

# ACC/AHA and ESC/EACTS Guidelines



# Why is a stress test important?

- Symptoms are subjective
- Symptoms depend upon patient's life style
  - No exertion → no exertional dyspnea
- Stress test is positive in 50% of patients with severe aortic stenosis
- A positive stress test has a huge impact on prognosis

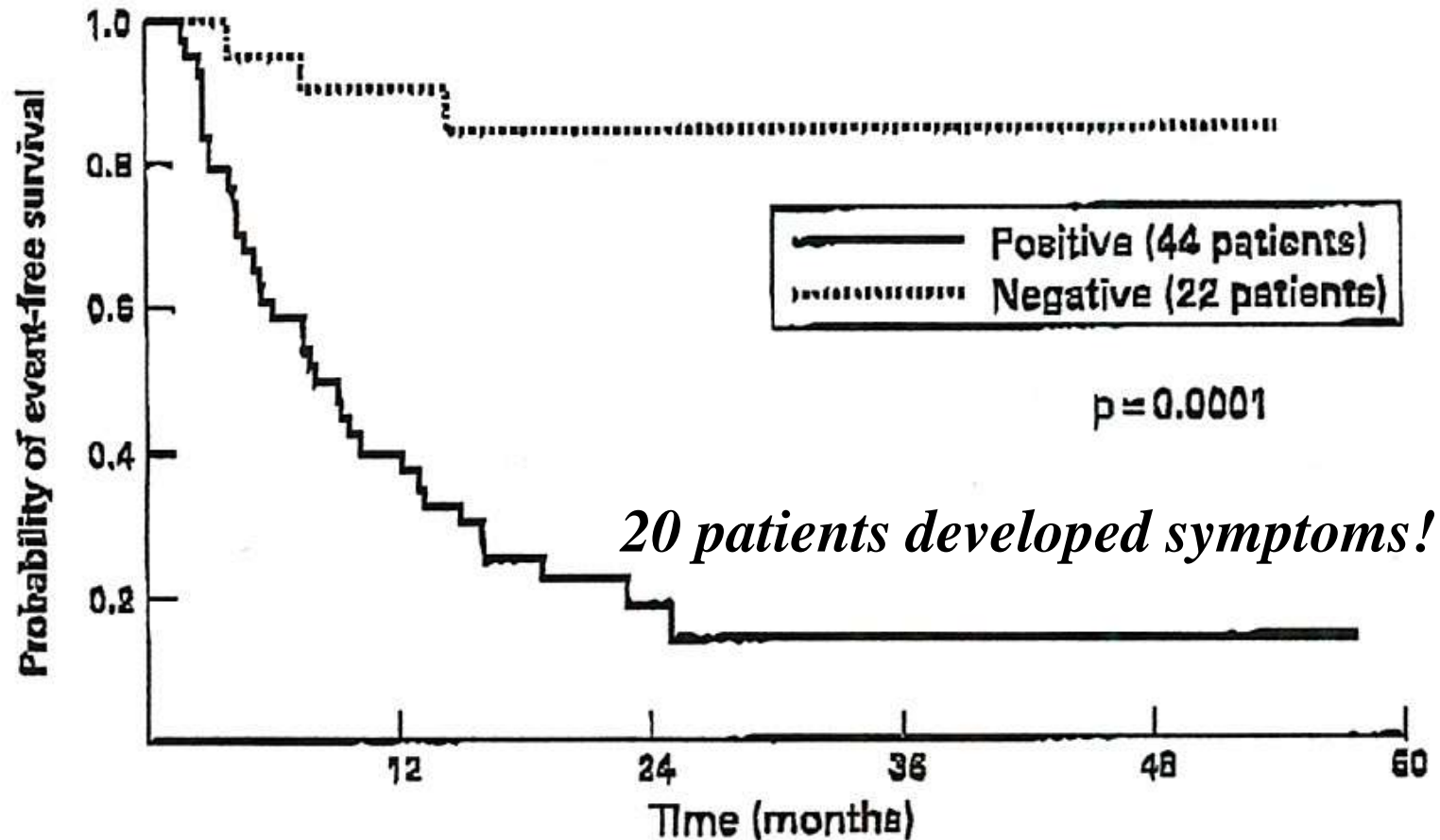
# Important stress test parameters

- Symptoms
- Decreased exercise tolerance
- Systolic blood pressure
  - drop or
  - $<20$  mmHg rise
- Increase in mean gradient by  $>20$  mm Hg

# How often is the stress test abnormal in asymptomatic severe aortic stenosis?

<b>Studies</b>	<b>% Abnormal Stress Test</b>	<b>n</b>	<b>n</b>
Amato et al. 2001	67%	44	66
Lancellotti et al. 2005	38%	26	69
Marechaux et al. 2007	48%	24	50
Lancellotti et al. 2008	47%	60	128
Lafitte et al. 2009	65%	39	60
Rajani et al. 2010	39%	7	18
Levy et al. 2014	28%	12	43
<b>Total</b>		<b>212</b>	<b>434</b>
<b>% abnormal stress test</b>	<b>Range: 28-67%</b>	<b>Pooled: 48.8%</b>	

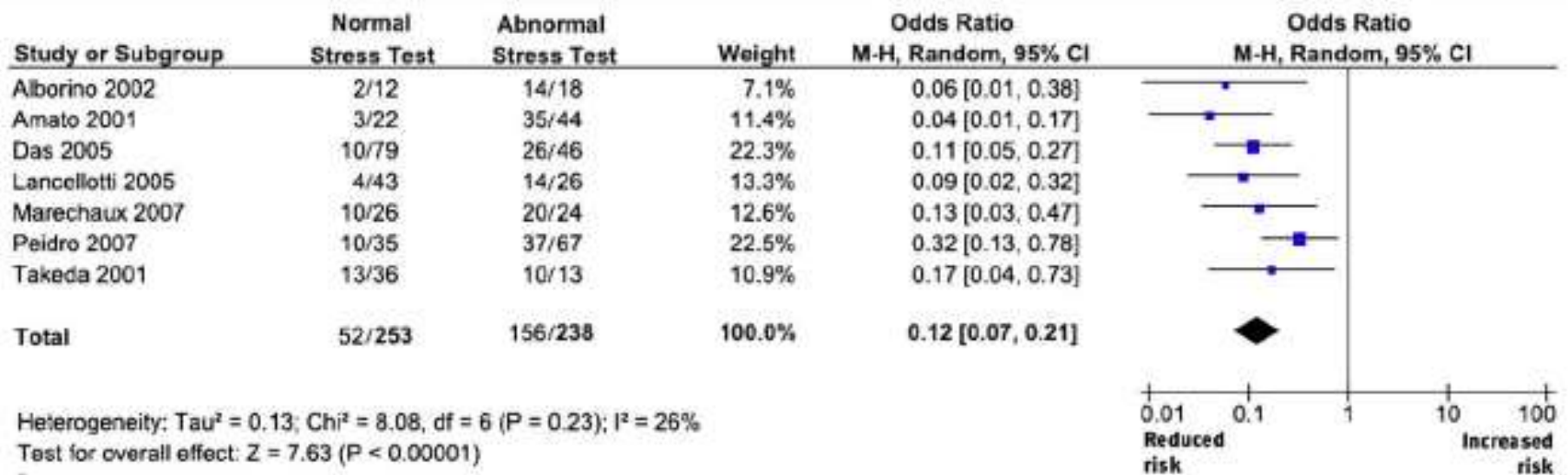
# A positive exercise test in asymptomatic aortic stenosis patients dramatically reduces event-free survival



Probability of event-free survival over 60 month for patients with asymptomatic severe aortic stenosis according to positive or negative results of exercise testing

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

Asim M. Rafique, MD<sup>a</sup>, Simon Biner, MD<sup>a,b</sup>, Indraneil Ray, MD<sup>a</sup>, James S. Forrester, MD<sup>a</sup>, Kirsten Tolstrup, MD<sup>a</sup>, and Robert J. Siegel, MD<sup>a,\*</sup>



***Abnormal stress test:  
 ~8 fold increase in CV Events***



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

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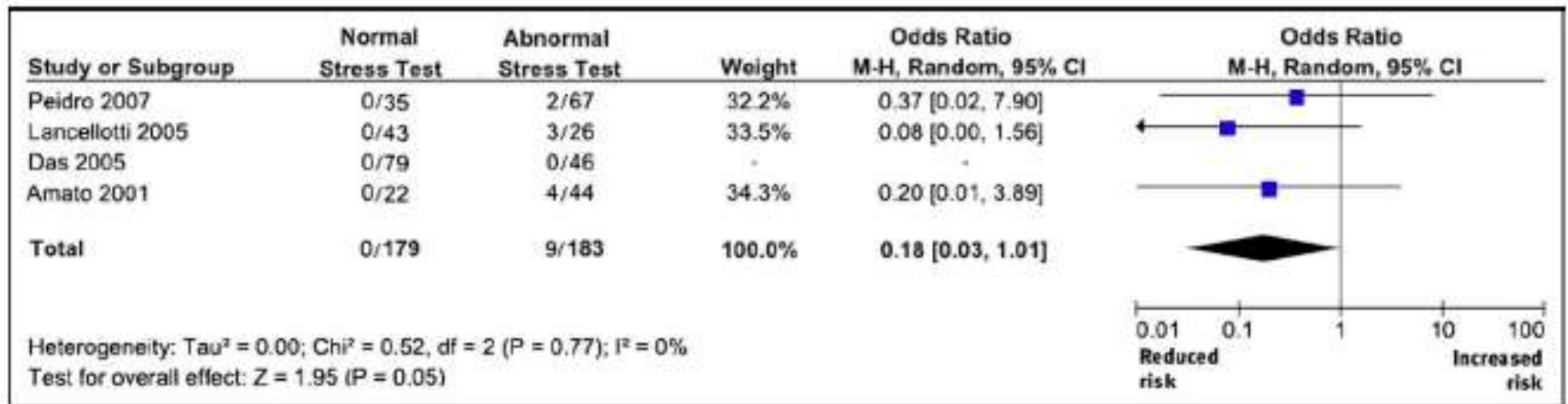


Figure 3. Pooled outcome estimates of risk for sudden cardiac death. None of the patients with normal stress test results experienced sudden death. *Squares* represent effect sizes; *extended lines* indicate 95% CIs; *diamond* represents total effect size.

***Abnormal stress test:  
 ~6 fold increase in Cardiac Death***

Are patients treated  
according guidelines?

Rarely!



ELSEVIER



EUROPEAN  
SOCIETY OF  
CARDIOLOGY

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

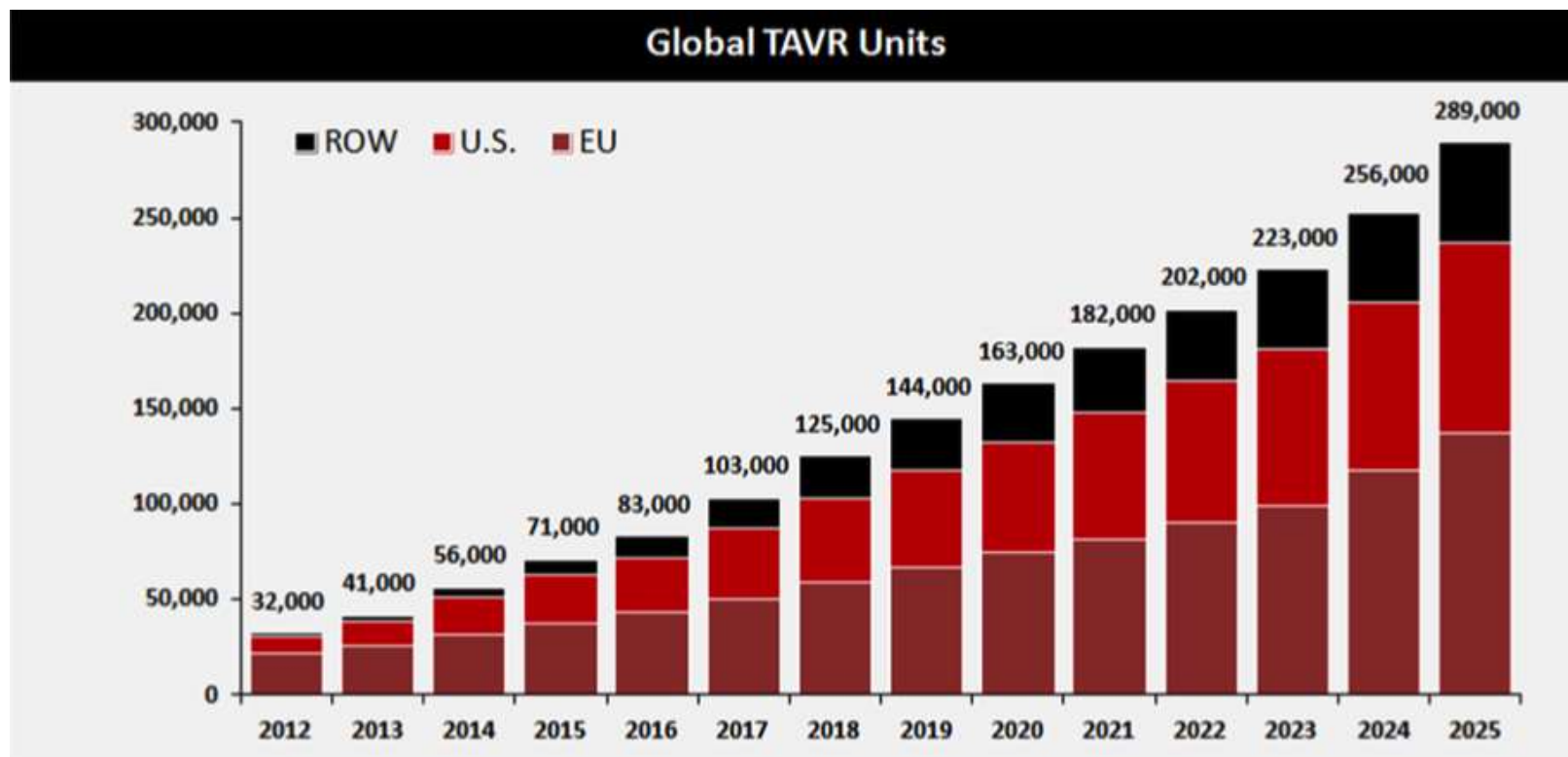
Bernard Lung<sup>a\*</sup>, Gabriel Baron<sup>b</sup>, Eric G. Butchart<sup>c</sup>, François Delahaye<sup>d</sup>, Christa Gohlke-Bärwolf<sup>e</sup>, Olaf W. Levang<sup>f</sup>, Pilar Tornos<sup>g</sup>, Jean-Louis Vanoverschelde<sup>h</sup>, Frank Vermeer<sup>i</sup>, Eric Boersma<sup>j</sup>, Philippe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

“In severe AS, an exercise test was performed in only 5.7% of patients with no symptoms...”

# Why is a stress test rarely performed in patients with aortic stenosis?

- It is widely assumed to be contra-indicated
  - not true according to guidelines
- It requires a specific expertise and infrastructure
  - often not available in smaller institutions

What will happen if all patients with asymptomatic severe aortic stenosis are diagnosed properly and then referred to either surgery or TAVI?



SOURCE: Credit Suisse TAVI Comment ~January 8, 2015. ASP assumption for 2024 and 2025 based on analyst model. Revenue split assumption in 2025 is 45% U.S., 35% EU, 10% Japan, 10% ROW

**The predicted number of TAVIs will have to be doubled**

Sometimes patients are asymptomatic just because they do not exercise in daily life

The stress test just uncovers the symptomatic status

What is the prognosis in patients who remain asymptomatic even during the stress test?

# Prognosis in truly asymptomatic aortic stenosis

Lanzelotti P et al

J Am Coll Cardiol 2012;59:235–43

- N=150
- AVA <1cm<sup>2</sup>
- Negative stress test
- No other indication for valve replacement
- Mean FU 27 months
- Endpoint: CV death or need for valve replacement
- Results:
  - 51% (76/150) events (indication for valve replacement according to guidelines or death)

# What to do with "truly" asymptomatic patients?

There are no retrospective studies  
because these patients currently are not  
operated according to guidelines

There is clearly a need  
for prospective randomized trials



# If valve replacement is indicated:

- It seems to be unlikely that peri-operative complications or long-term results depend upon symptomatic/asymptomatic baseline status.
- Therefore, it seems reasonable to make the decision TAVI vs surgery according to established recommendations for symptomatic patients
- For a definite answer a randomized trial TAVI vs surgery would be necessary
  - The question is whether we need this trial in this group of patients

# Conclusions

- Asymptomatic aortic stenosis is frequent
- It is under-diagnosed
- In many of these patients stress test is positive
- In patients with positive stress test
  - sudden death occurs in 1% per year
  - valve replacement is indicated
  - TAVI should be considered according to the same rules as established for symptomatic patients
- Randomized trials are needed for the "truly" asymptomatic patients with negative stress test