La stenosi aortica degenerativa è un'epidemia?

Ruolo della terapia medica nel ritardare il momento della sostituzione.

E' davvero possibile incidere con i farmaci nel ritardare la progressione della malattia?

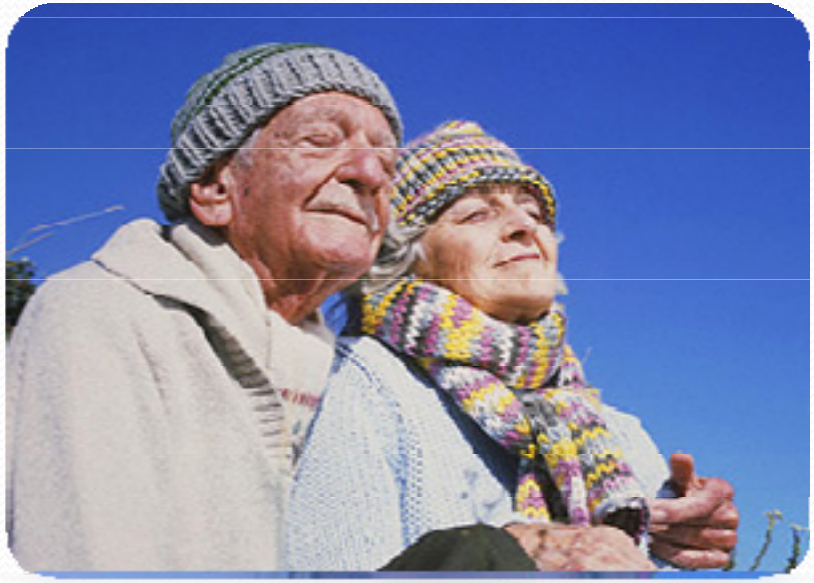
Alessandro Parolari MD PhD

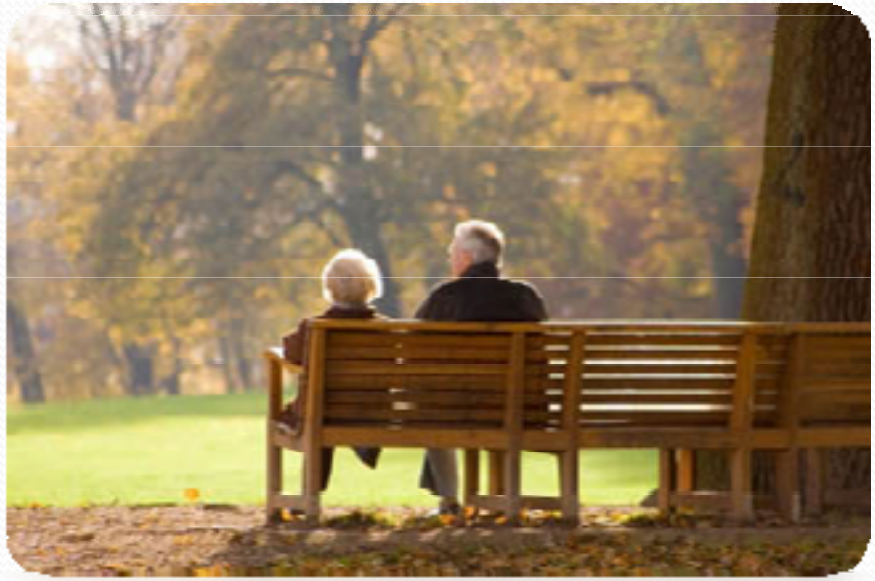
Centro Cardiologico Monzino IRCCS

Università di Milano – Dipartimento di Scienze Cardiovascolari

Disclosure: no conflict of interest

Aortic valve stenosis = elderly





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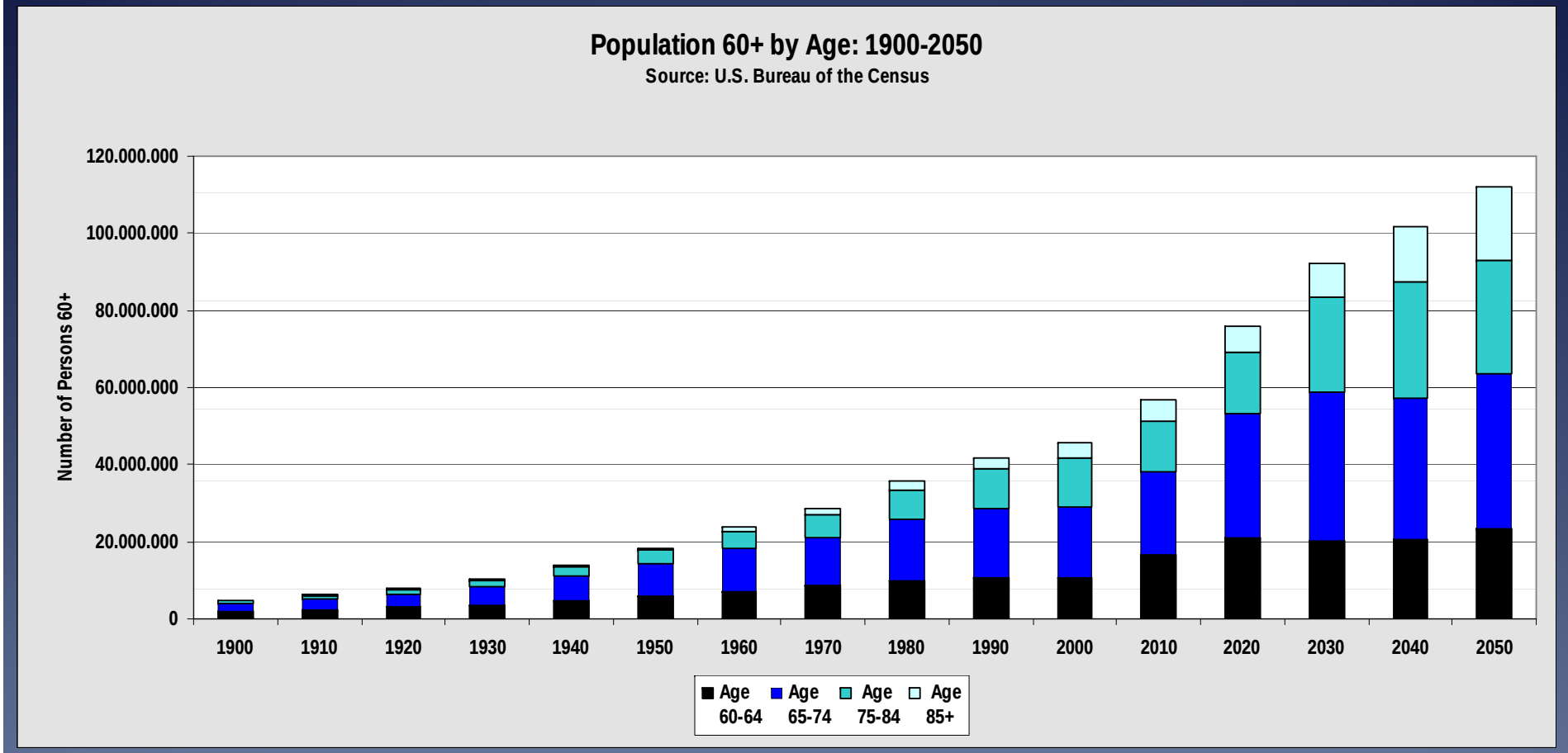
USA increase in the population 60 and older.

From 4.9 million people in 1900 to 45.8 million in 2000.
Projection: 92.2 million in 2030 and 112 million in 2050.



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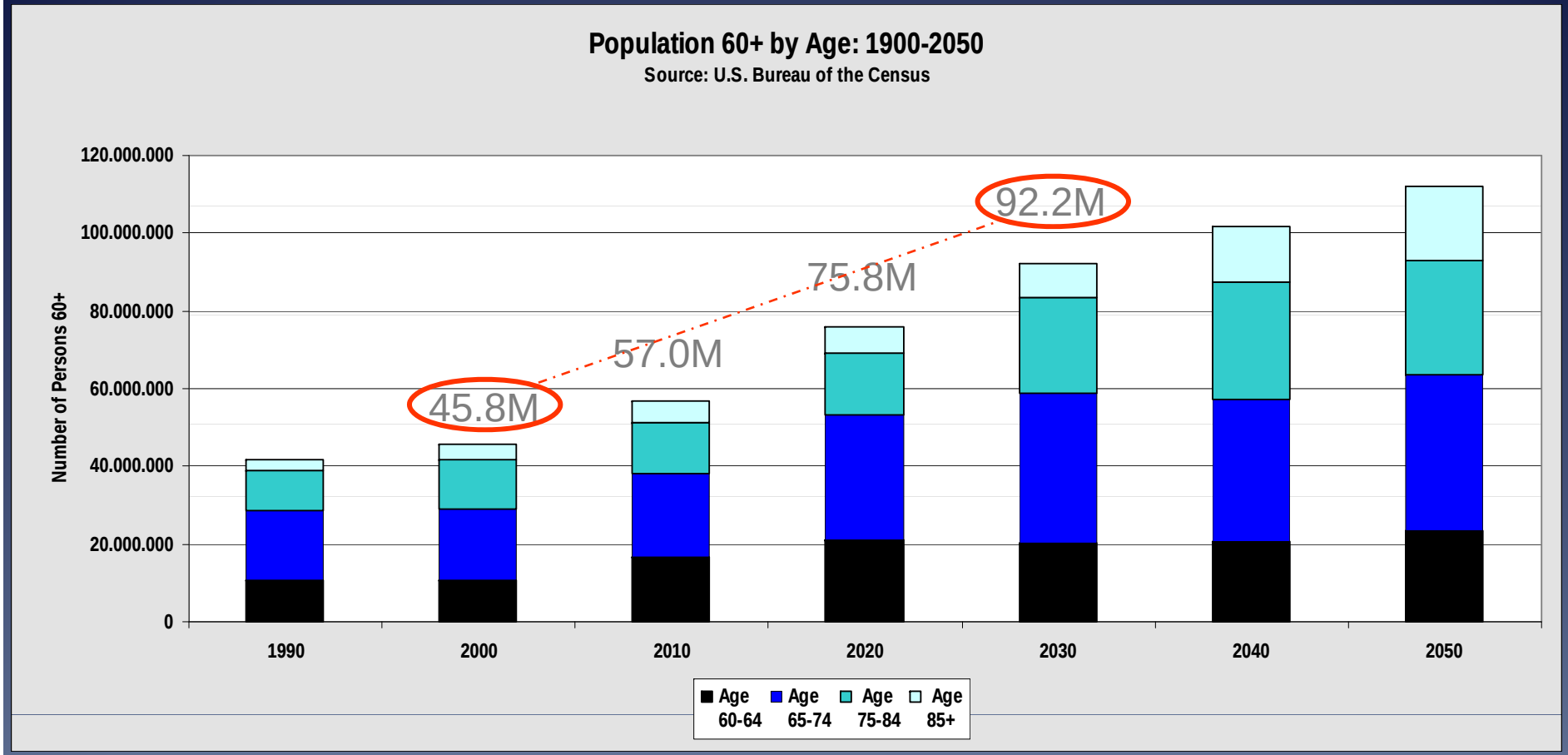
AOA Administration on Aging

Doubling of the population 60 and older in 30 years!



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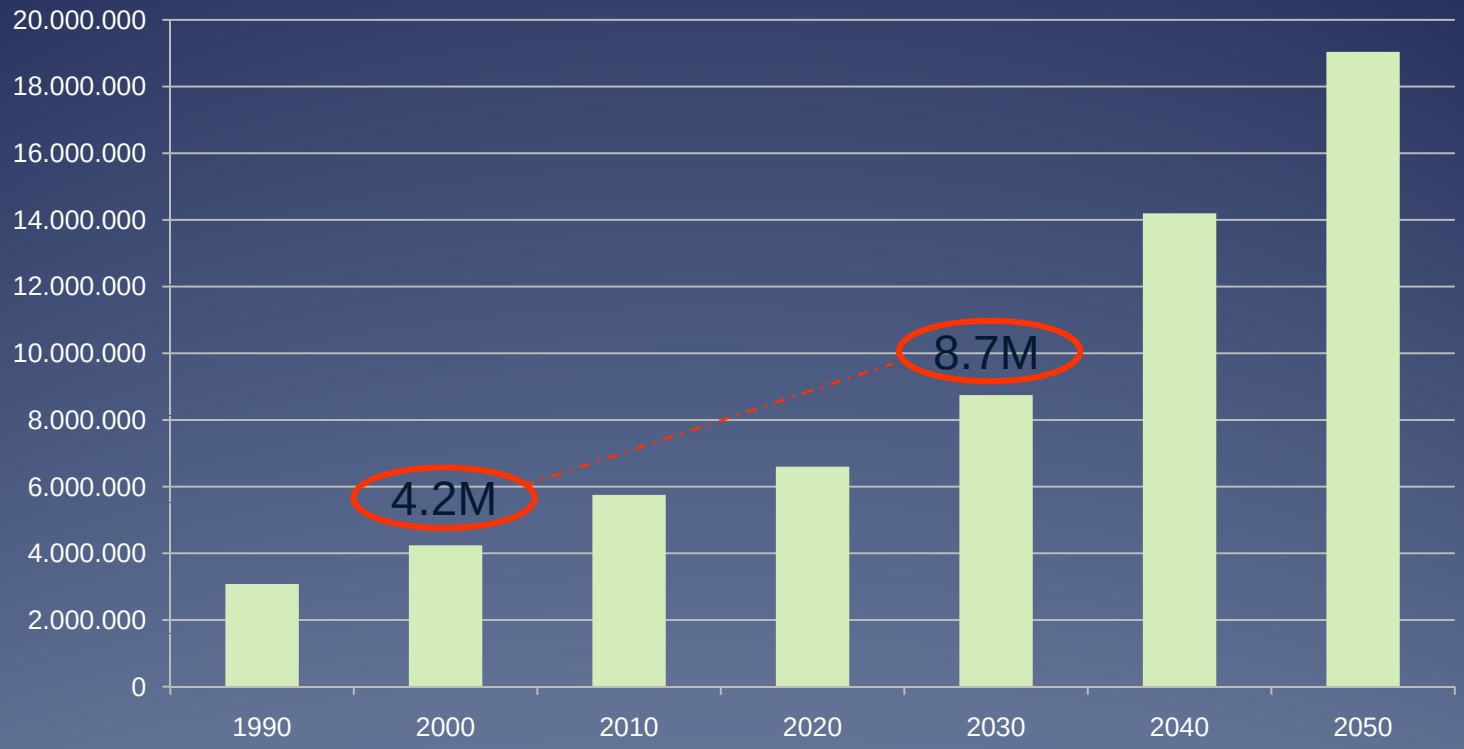
AOA Administration on Aging

Doubling of the population 85 and older in 30 years!



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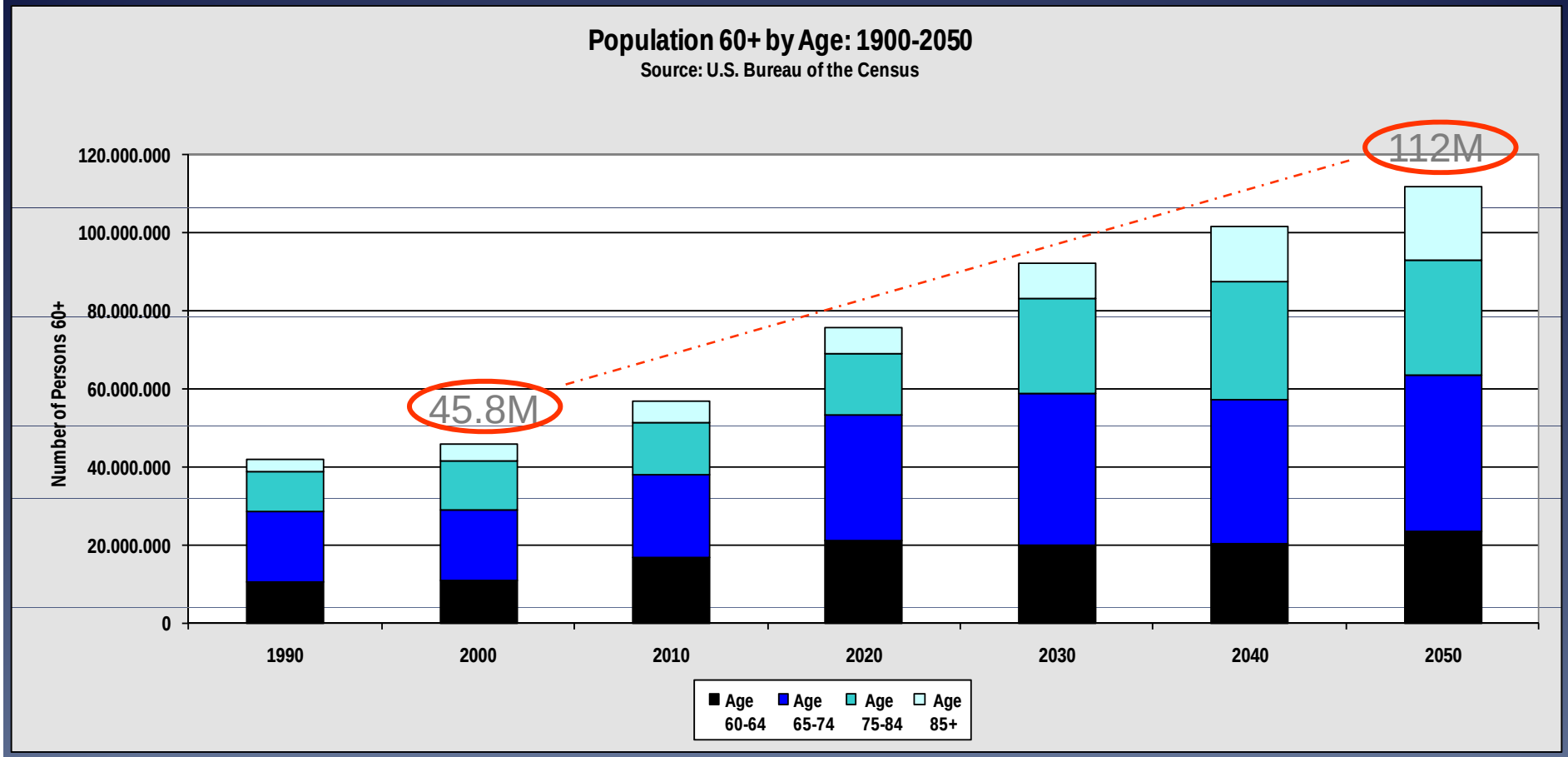
AOA Administration on Aging

2.45X increase of the population 60 and older in 50 years!



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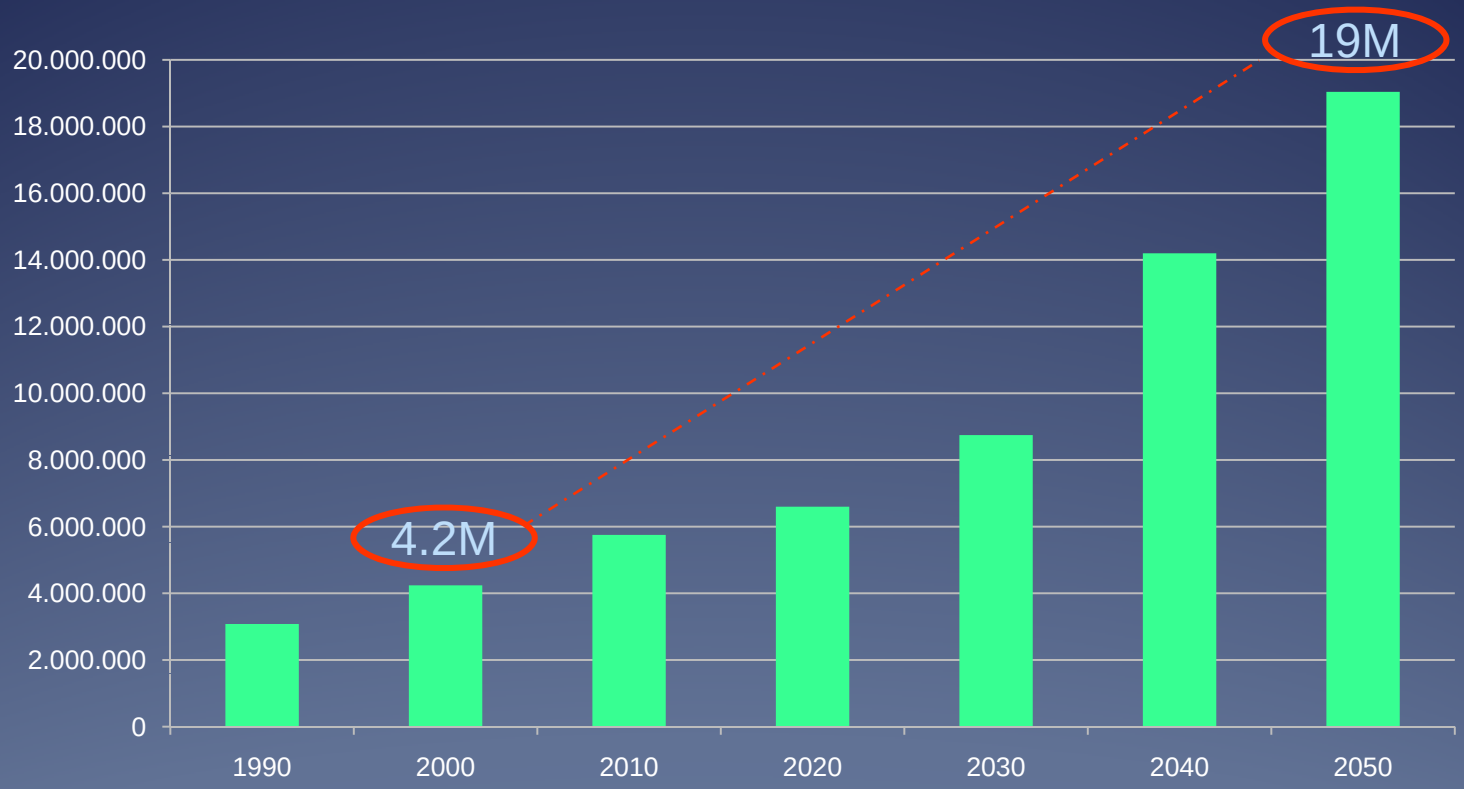
AOA Administration on Aging

4.5X increase of the population 85 and older in 50 years!



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AOA Administration on Aging

Population increase in minorities

Census Year	Total Population - All Ages	Total - All Persons 85 and older	Hispanic Persons 85 and older	Non-Hispanic White Persons 85 and older	Non-Hispanic Black Persons 85 and older	Non-Hispanic American Indians and Alaskan Native Persons 85 and older	Non-Hispanic Asian Persons 85 and older	Non-Hispanic Native Hawaiian and Pacific Islander Persons 85 and older	Non-Hispanic Persons 85 and older with Two or More Races
2000	282.158.336	4.295.943	153.531	3.733.647	314.355	11.512	63.900	1.660	17.338
2010	310.232.863	5.751.299	304.702	4.901.877	387.090	17.300	111.819	2.525	25.986
2020	341.386.665	6.597.019	531.391	5.324.331	481.571	28.272	188.705	4.722	38.027
2030	373.503.674	8.744.986	867.605	6.731.390	671.931	50.134	351.021	8.863	64.042
2040	405.655.295	14.197.701	1.644.694	10.381.395	1.228.782	93.471	713.875	17.248	118.236
2050	439.010.253	19.041.041	2.871.224	12.825.427	1.880.860	133.826	1.127.644	27.916	174.144
	1.6X	4.5X	18.7X				17.6X		

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AOA Administration on Aging

Cardiovascular Health Study (pts ≥ 65 y)

Prevalence of Aortic Valve Abnormalities by Echocardiography

	None	Sclerosis	Stenosis (>2.5 m/s)
All subjects	3,736 (72%)	1,329 (26%)	88 (2%)
Women	2,249 (76%)	641 (22%)	43 (1.5%)
Men	1,487 (67%)	688 (31%)	45 (2%)
65–74 years old	2,684 (78%)	697 (20%)	43 (1.3%)
Women	1,654 (82%)	344 (17%)	20 (1.0%)
Men	1,030 (73%)	353 (25%)	23 (1.6%)
75–84 years old	962 (62%)	542 (35%)	37 (2.4%)
Women	546 (66%)	259 (31%)	22 (2.7%)
Men	416 (58%)	283 (39%)	15 (2.1%)
85+ years old	90 (48%)	90 (48%)	8 (4%)
Women	49 (56%)	38 (43%)	1 (1%)
Men	41 (41%)	52 (52%)	7 (7%)

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Clinical Factors Associated With Calcific Aortic Valve Disease

B. FENDLEY STEWART, MD, FACC, DAVID SISCOVICK, MD, MPH, BONNIE K. LIND, MS, JULIUS M. GARDIN, MD, FACC,* JOHN S. GOTTDIENER, MD, FACC,† VIVIENNE E. SMITH, MD,‡ DALANE W. KITZMAN, MD, FACC,§ CATHERINE M. OTTO, MD, FACC, FOR THE CARDIOVASCULAR HEALTH STUDY‖

JACC Vol. 29, No. 3
March 1, 1997:630–4

Both aortic sclerosis and aortic stenosis are associated to an increased risk of death and of cardiovascular events

EVENT F-UP: 5 Y	NORMAL AORTIC VALVES (N=3919, 70%)	AORTIC SCLEROSIS (N=1610, 29%)	AORTIC STENOSIS (N=92, 1%)	P VALUE
Death from any cause	583 (14.9)	353 (21.9)	38 (41.3)	<0.001
Death from CV causes	238 (6.1)	162 (10.1)	18 (19.6)	<0.001
Myocardial Infarction	217 (6.0)	123 (8.6)	9 (11.3)	<0.001
Angina	358 (11.0)	160 (13.0)	17 (24.3)	0.001
Congestive heart failure	337 (8.9)	192 (12.6)	21 (24.7)	<0.001
Stroke	238 (6.3)	122 (8.0)	10 (11.6)	0.003

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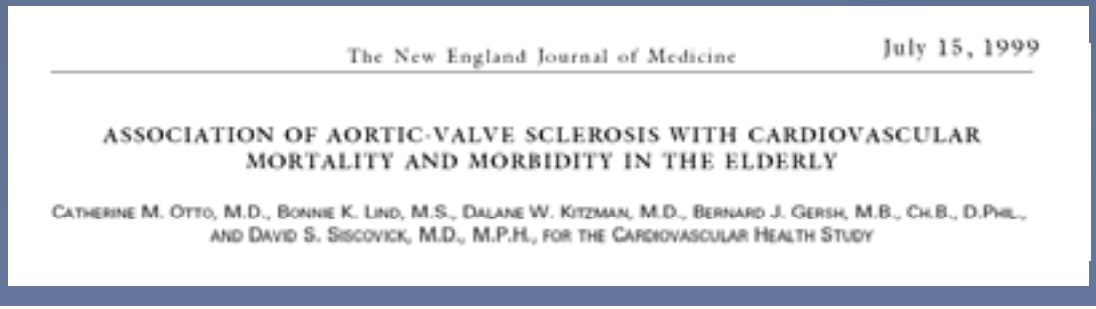
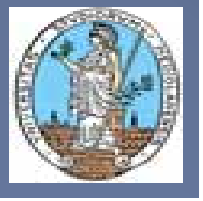


The New England Journal of Medicine July 15, 1999

ASSOCIATION OF AORTIC-VALVE SCLEROSIS WITH CARDIOVASCULAR MORTALITY AND MORBIDITY IN THE ELDERLY

CATHERINE M. OTTO, M.D., BONNIE K. LIND, M.S., DALANE W. KITZMAN, M.D., BERNARD J. GERSH, M.B., CH.B., D.PHIL., AND DAVID S. SISCOVICK, M.D., M.P.H., FOR THE CARDIOVASCULAR HEALTH STUDY



Cardiovascular Health Study

Clinical Factors Associated With Aortic Stenosis or Sclerosis

Stepwise Multiple Logistic Regression

Variable	p Value	OR	95%CIs
Age	<0.001	2.18 (10y)	2.15, 2.20
Male gender	<0.001	2.03	1.7, 2.5
Lp(a)	<0.001	1.23 (10U)	1.14, 1.32
Height (cm)	0.001	0.84 (25/75%)	0.75, 0.93
History of hypertension	0.002	1.23	1.1, 1.4
Present smoking	0.006	1.35	1.1, 1.7
LDLc (mg/dl)	0.008	1.12 (25/75%)	1.03, 1.23

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Clinical Factors Associated With Calcific Aortic Valve Disease

B. FENDLEY STEWART, MD, FACC, DAVID SISCOVICK, MD, MPH, BONNIE K. LIND, MS, JULIUS M. GARDIN, MD, FACC,* JOHN S. GOTTDIENER, MD, FACC,† VIVIENNE E. SMITH, MD,‡ DALANE W. KITZMAN, MD, FACC,§ CATHERINE M. OTTO, MD, FACC, FOR THE CARDIOVASCULAR HEALTH STUDY‖

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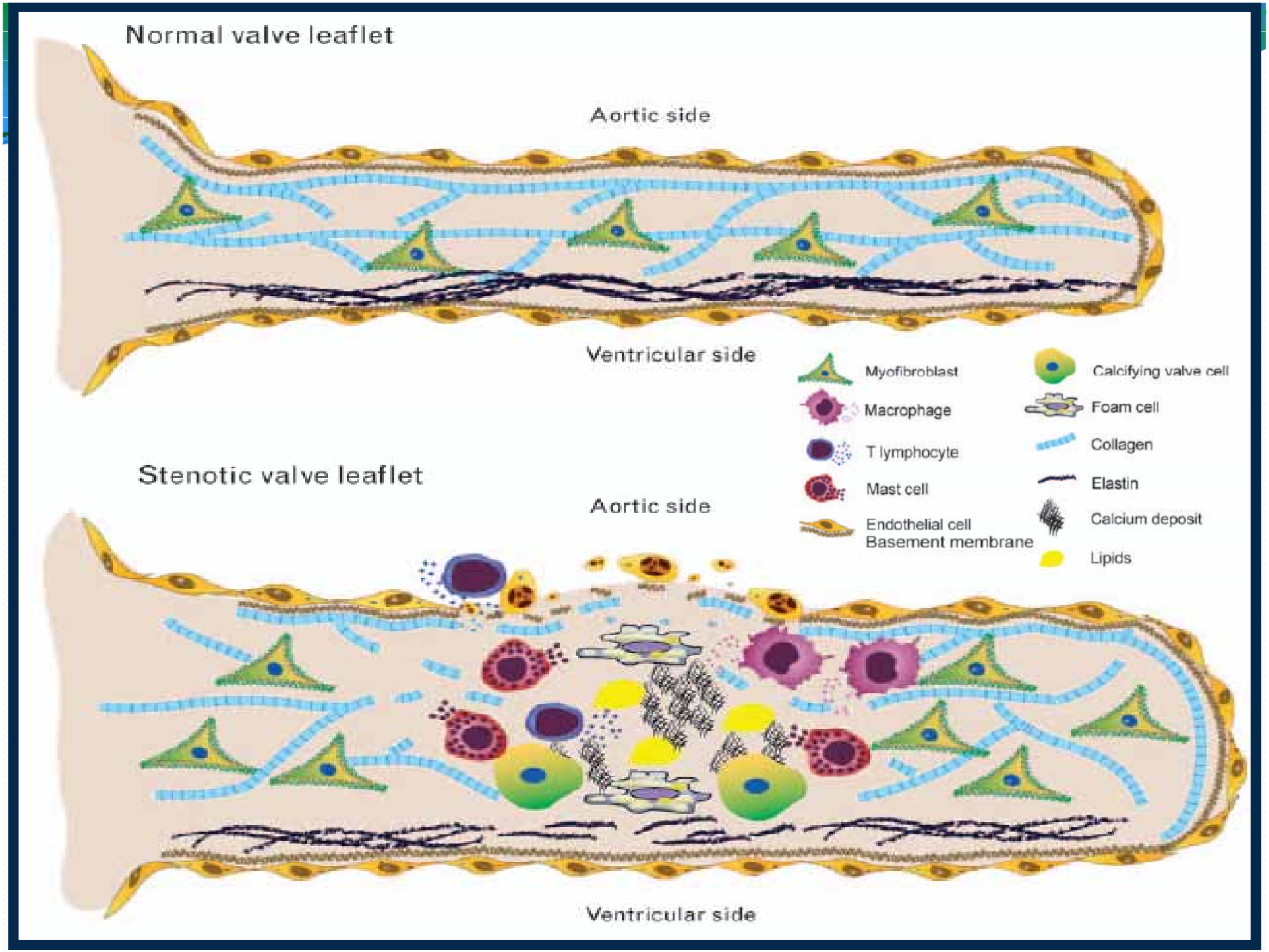
Normal valve leaflet
Aortic side
Ventricular side
Myofibroblast
Macrophage
T lymphocyte
Mast cell
Endothelial cell
Basement membrane
Calcifying valve cell
Foam cell
Collagen
Elastin
Calcium deposit
Lipids
Stenotic valve leaflet
Aortic side
Ventricular side

Nonrheumatic calcific aortic stenosis: an overview from basic science to pharmacological prevention☆

European Journal of Cardio-thoracic Surgery 35 (2009) 493–504

Alessandro Parolari[a,*], Claudia Loardi[a], Luciana Mussoni[b], Laura Cavallotti[a], Marina Camera[a,b], Paolo Biglioli[a], Elena Tremoli[a,b], Francesco Alamanni[a]

...Taken together, current evidence suggests that **the progression of calcific aortic stenosis is a multi-factorial process**; the multitude of the mechanisms potentially involved in aortic valve stenosis indicates that drug therapy aimed at reducing its progression is necessarily multi-factorial and should address the earliest stages of the disease, as it is now evident that pharmacological treatment administered in more advanced stages of the disease may be ineffective or, at best, much less effective.

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Potential mechanisms of aortic valve stenosis at which pharmacological treatment could be targeted, the potential drugs, and their desirable effects

Target processes in valves	Drug	Desirable effects in valves
Endothelial injury	Statins	Endothelial dysfunction ↓
	AT-1R antagonists	Endothelial integrity ↑
Accumulation and deposition of lipoprotein-derived lipids	Statins	Blood lipids ↓, leading to lipoprotein influx ↓
Angiotensin II–mediated actions	ACE inhibitors/AT-1R antagonists	Blocking ACE/AT-1R in valves
NEP activity	NEP inhibitors	Blocking NEP in valves
Accumulation and activation of inflammatory cells	Statins	Number of inflammatory cells in valves ↓
		C-reactive protein in valves ↓
	AT-1R antagonists	Valvular macrophages ↓
Extracellular matrix remodeling	Statins	MMP-secreting inflammatory cells ↓
	ACE inhibitors/AT-1R antagonists	Angiotensin II-mediated fibrosis ↓
	MMP inhibitors?	MMP activity in valves ↓
	Cathepsin inhibitors?	Cathepsin activity ↓
Neovascularization	Statins	Neovessels in valves ↓
Calcification of the valve	Statins	Calcification-inducing lipids in valves ↓, calcification ↓
	ACE inhibitors	Calcification ↓
	AT-1R antagonists,	Osteoblastic differentiation ↓
	specific inhibitors of calcification?	Calcification ↓

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ACE, angiotensin-converting enzyme; AT-1R, angiotensin II type 1 receptor; MMP, matrix metalloproteinase; NEP, neutral endopeptidase.

Statins on aortic valve stenosis: why a meta-analysis?

Several studies have indicated that aortic stenosis progression is due to an active process sharing several features with atherosclerosis.

Many trials have assessed the role of statins in delaying such progression, but with conflicting results.

Since 2001, several studies, mainly observational, suggested that statin *therapy delays the progression of calcific non-rheumatic aortic* stenosis, assessed by echocardiography or computed tomography.

These findings were not confirmed by three recent prospective randomized trials.

For this reason, the role of statins in these patients is an open question.

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Meta-Analysis January 2009

Statins and Nonrheumatic Calcific Aortic Stenosis: A Meta-analysis on Outcomes and Disease Progression

Alessandro Pamlari, Elena Tremoli, Laura Cavallotti, Matteo Trezzi, Claudia Leardi, Ilaria Crippa, Fabrizio Veglia, Cntr Cardiologico Monzino, 20138, Italy; Davide Pacini, Ospedale S. Orsola-Malpighi, 40138, Italy; Francesco Alamanni; Cntr Cardiologico Monzino, 20138, Italy

BACKGROUND: whether statin treatment improves hard outcomes and reduces aortic stenosis progression in nonrheumatic calcific aortic stenosis is unclear. METHODS AND RESULTS: We undertook a meta-analysis of prospective and retrospective trials reporting the effect of statin therapy on the hard outcomes (all-cause mortality, cardiovascular mortality and need of aortic valve surgery at follow-up) and on valve stenosis progression (annualized rates of jet velocity progression and of aortic valve area decrease) in patients affected by calcific nonrheumatic aortic stenosis. Electronic bibliographic databases, key journals and reference lists of reviews and articles were searched to identify studies for inclusion. Data were analyzed using both fixed and random-effects models. Heterogeneity among trials was examined using the Q statistic and I^2 methods. A predefined subgroup analysis assessed the effect of statin treatment on prospective and retrospective trials. We selected 7 trials (3 prospective, 4 retrospective) involving 3107 participants (2037 non statin-treated and 1430 statin-treated). No significant differences were found for all-cause mortality (OR 0.98; 95% CI 0.74, 1.30), cardiovascular mortality (OR 0.83; 95% CI 0.56, 1.22), and for the need of aortic valve surgery (OR 0.90; 95% CI 0.75, 1.09) at follow-up. Aortic valve stenosis progression was significantly reduced by statin treatment, being the mean annual difference of jet velocity progression (-0.07 m/s/y; 95%CI -0.12, -0.02; p=0.003) and the mean annual difference in aortic valve area decrease (-0.03 cm2/y; 95%CI -0.05, 0.00; p=0.04) both in favor of statin treatment. These results were, however, weakened by substantial heterogeneity in the models for both variables, and by publication bias at funnel plots. Finally, subgroup analysis showed that statin effect was evident only in retrospective but not in prospective trials. CONCLUSIONS: currently available data weakly support statin use to reduce disease progression in nonrheumatic calcific aortic valve stenosis.

CONCLUSIONS: currently available data weakly support statin use to reduce disease progression in nonrheumatic calcific aortic valve stenosis

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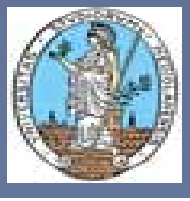
American Heart Association | SCIENTIFIC SESSIONS 2009

Exhibits: November 15-17 | Sessions: November 14-18 | Orlando, Florida



Meta-analysis of prospective and retrospec-tive trials reporting the effect of statin therapy:

on the hard outcomes

on valve stenosis progression

Patients affected by calcific nonrheumatic aortic stenosis.

Data analysis using both fixed and random-effects models.

Heterogeneity analysis with the Q statistic and I2 methods.

Subgroup analysis on the effect of statin treatment on prospective and retrospective trials.

Seven studies were selected for meta-analysis; of these, 3 were prospective and 4 retrospective. A total of 3467 participants (2037 non statin-treated and 1430 statin-treated) provided data for this meta-analysis.

754 Citations identified and filtered by title

735 Excluded

19 Citations filtered by abstract

6 were not focused on statins as drug therapy

American Heart Association | SCIENTIFIC SESSIONS 2009

Exhibits November 15-17 | Sessions November 14-18 | Orlando, Florida

13 Citations filtered by full-text article

6 Excluded

2 no extractable data reported

2 overlap from 100 patients enrolled

1 involved on rheumatic aortic valve disease

1 duplicate publication

7 Eligible studies

3 Prospective studies

4 Retrospective studies

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2009 Meta-Analysis results – Summary

Hard outcomes	n (N)	Events		OR (95% CI)	Heterogeneity		p for overall effect
		Statins	No statins		p value	I^2	
Death from any cause at follow-up	2149 (3)	109/1082 (10.1%)	109/1067 (10.2%)	0.98 (0.74, 1.30)	0.33	9%	0.91
Death from cardiovascular causes at follow-up	2297 (3)	52/1155 (4.9%)	59/1007 (5.9%)	0.83 (0.56, 1.22)	0.80	0%	0.34
Aortic valve surgery at follow-up	2149 (3)	283/1082 (26.1%)	300/1067 (28.1%)	0.90 (0.75, 1.09)	0.28	20%	0.30

Aortic valve stenosis progression	n (N)	Mean difference (95% CI)	Heterogeneity		p for overall effect
			p value	I^2	
Jet velocity progression (m/s/y)	3092 (6)	-0.07 (-0.12, -0.02)	<0.00001	83%	0.003
Aortic valve area decrease (sq cm/y)	2278 (5)	-0.03 (-0.05, 0.00)	0.11	48%	0.04

Centro Cardiologico Monzino

Meta-Analysis January 2010

Meta-analysis of prospective and retrospective trials reporting the effect of statin therapy:

on the hard outcomes

mortality, CV mortality, aortic valve surgery

on valve stenosis progression

Jet velocity, AVA, peak and mean gradient

Subgroup analysis on the effect of statin treatment on prospective and retrospective and on randomized and non-randomized trials.

Ten studies were selected for meta-analysis; of these, 5 were prospective and 5 retrospective (3 randomized and 7 non-randomized).

A total of 3822 participants (2214 non statin-treated and 1608 statin-treated) provided data for this meta-analysis.

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Prospective papers selected for Meta-Analysis

(January 2010)

Study	Year	Study design	Treatment groups	No. of pts.	Age (y)	LDL chol. (mg/dL)	Diabetes	Aortic jet velocity (m/sec)	Aortic valve area (cm^2)	Transaortic pressure gradient (mmHg)	Follow-up
Chan (ASTRONOMER)	2010	Prospective randomized	Placebo Rosuvastatin 40 mg/d	135 134	58±14 58±13	122±29 124±25	n.a. n.a.	3.19±0.42 3.16±0.42	1.56±0.70 1.49±0.71	Mean:23±8 Mean:23±8	Median 3.5 (2.1-4.5) years
Cowell (SALTIRE)	2005	Prospective randomized	Placebo Atorvastatin 80 mg/d	78 77	68±10 68±10	133±30 137±34	4 (5%) 3 (4%)	3.45±0.67 3.39±0.62	1.02±0.41 1.03±0.40	Peak:50±20 Peak:48±17	Median: 25 (7-36) months
Rossebo (SEAS)	2008	Prospective randomized	Placebo Simvastatin (40-80 mg/d) + ezetimibe	929 944	67±10 68±9	139±35 140±36	n.a. n.a.	3.10±0.54 3.09±0.55	1.27±0.46 1.29±0.48	Mean:23.0±8.7 Mean:22.7±8.8	Median: 52.2 months
Mohler	2007	Prospective observational	No statins Statins	22 31	64±10 70±10	n.a. n.a.	3 (14%) 7 (18%)	n.a. n.a.	1.22±0.25 1.13±0.27	n.a. n.a.	12 months
Moura (RAAVE)	2007	Prospective open label	No treatment Rosuvastatin 20 mg/d	60 61	74±9 73±9	117±21 158±32	13 (22%) 26 (43%)	3.62±0.61 3.65±0.64	1.20±0.35 1.23±0.43	Mean:36±13 Mean:35±13	Mean: 73±24 weeks

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Retrospective papers selected for Meta-Analysis

(January 2010)

Study	Year	Study design	Treatment groups	No. of pts.	Age (y)	LDL chol. (mg/dL)	Diabetes	Aortic jet velocity (m/sec)	Aortic valve area (cm^2)	Transaortic pressure gradient (mmHg)	Follow-up
Antonini-Canterin	2008	Retrosp.	No statins: mild aortic stenosis	360	71±8	n.a.	82 (23%)	2.3±0.2	n.a.	Mean:13.1±3.2	Mean: 5.6±3.2 years
			Statins: mild aortic stenosis	141	71±7	n.a.	50 (36%)	2.3±0.2	n.a.	Mean:12.7±3.1	
			No statins: moderate aortic stenosis	214	72±8	n.a.	42 (20%)	3.3±0.2	n.a.	Mean:26.1±5.1	
			Statins: moderate aortic stenosis	62	70±8	n.a.	14 (23%)	3.3±0.2	n.a.	Mean:26.0±5.0	
Bellamy	2002	Retrosp.	No statins	118	78±12	137±43	28 (24%)	3.0±0.8	1.20±0.35	Mean:22±12	Mean: 3.7±2.3 years
			Statins	38	73±11	164±49	9 (24%)	2.8±0.5	1.32±0.29	Mean:18±7	
Kuwabara	2006	Retrosp.	No statins Statins	20 13	75±5 74±5	n.a. n.a.	3 (15%) 6 (46%)	}3.1±1.0	n.a n.a.	}Mean:42±29	31±23 months 30±20 months
Novaro	2001	Retrosp.	No statins	117	67±13	131(112-143)	23 (20%)	n.a.	1.2(1.0-1.4)	Mean:15(12-22)	Mean:21 months
			Statins	57	71±9	128(94-146)	20 (35%)	n.a.	1.2(1.0-1.4)	Mean:15(12-22)	
Rosenhek	2004	Retrosp.	No statins	161	69±11	141±39	32 (20%)	3.92±0.86	0.84±0.23	Mean:42±20	Median: 24±18 months
			Statins	50	72±8	145±38	11 (22%)	4.08±0.86	0.82±0.23	Mean:42±18	

2010 Meta-Analysis results – Summary

Subgroup analysis: prospective vs. retrospective trials

Hard outcomes	n (N)	Events		OR (95% CI)	p for overall effect	Heterogeneity		Egger's test p value
		Statins	No statins			p value	I^2	
Death from any cause	2149 (3)	109/1082 (10.1%)	109/1067 (10.2%)	0.98 (0.74, 1.30)	0.91	0.33	9%	0.15
Death from cardiovascular causes	2297 (7)	52/1155 (4.5%)	64/1142 (5.6 %)	0.79 (0.54, 1.15)	0.22	0.67	0%	0.70
Aortic valve surgery	2418 (4)	311/1216 (25.6%)	327/1202 (27.2%)	0.92 (0.76, 1.10)	0.35	0.43	0%	0.99

Aortic valve stenosis progression	n (N)	Mean difference (95% CI)	p for overall effect	Heterogeneity		Egger's test p value
				p value	I^2	
Jet velocity progression (m/s/y)	3125 (7)	-0.08 (-0.13, -0.03)	0.0007	<0.00001	82%	0.02
Prospective studies	1948 (3)	-0.05 (-0.13, 0.03)	0.22	0.01	78%	
Retrospective studies	1177 (4)	-0.11 (-0.17, -0.04)	0.002	0.0002	82%	
Aortic valve area decrease (sq cm/y)	2608 (7)	-0.02 (-0.03, 0.00)	0.02	0.24	25%	0.21
Prospective studies	2278 (5)	-0.01 (-0.03, 0.00)	0.15	0.29	19%	
Retrospective studies	330 (2)	-0.05 (-0.09, -0.01)	0.01	1.00	0%	
Peak aortic gradient progression (mm Hg/y)	731 (5)	-1.76 (-3.73, 0.21)	0.08	0.05	57%	0.03
Prospective studies	524 (3)	-0.67 (-2.89, 1.54)	0.55	0.15	47%	
Retrospective studies	207 (2)	-3.08 (-5.22, -0.94)	0.005	0.34	0%	
Mean aortic gradient progression (mm Hg/y)	2413 (5)	-0.99 (-2.04, 0.07)	0.07	0.008	71%	0.04
Prospective studies	2083 (3)	-0.36 (-1.25, 0.53)	0.43	0.12	53%	
Retrospective studies	330 (2)	-1.92 (-3.55, -0.29)	0.02	0.22	35%	

2010 Meta-Analysis results – Summary

Subgroup analysis: randomized vs. non-randomized trials

Hard outcomes	n (N)	Events		OR (95% CI)	p for overall effect	Heterogeneity		Egger's test p value
		Statins	No statins			p value	I^2	
Death from any cause	2149 (3)	109/1082 (10.1%)	109/1067 (10.2%)	0.98 (0.74, 1.30)	0.91	0.33	9%	0.15
Randomized studies	2028 (2)	108/1021 (10.6%)	105/1007 (10.4%)	1.01 (0.76, 1.35)	0.92	0.46	0%	
Non-randomized studies	121 (1)	1/61 (1.6%)	4/60 (6.7%)	0.23 (0.03, 2.15)	0.20	n.a.	n.a.	
Death from cardio-vascular causes	2297 (3)	52/1155 (4.5%)	64/1142 (5.6 %)	0.79 (0.54, 1.15)	0.22	0.67	0%	0.70
Aortic valve surgery	2418 (4)	311/1216 (25.6%)	327/1202 (27.2%)	0.92 (0.76, 1.10)	0.35	0.43	0%	0.99
Randomized studies	2297 (3)	306/1155 (26.5%)	324/1142 (28.4%)	0.91 (0.76, 1.09)	0.30	0.35	4%	
Non-randomized studies	121 (1)	5/61 (8.2%)	3/60 (5.0%)	1.70 (0.39, 7.44)	0.48	n.a.	n.a.	

Aortic valve stenosis progression	n (N)	Mean difference (95% CI)	p for overall effect	Heterogeneity p value	Heterogeneity I^2	Egger's test p value
Jet velocity progression (m/s/y)	3125 (7)	-0.08 (-0.13, -0.03)	0.0007	<0.0001	82%	0.02
Randomized studies	1827 (2)	-0.01 (-0.03, 0.02)	0.48	0.88	0%	
Non-randomized studies	1298(5)	-0.12 (-0.18, -0.06)	0.0002	<0.0001	81%	
Aortic valve area decrease (sq cm/y)	2608 (7)	-0.02 (-0.03, 0.00)	0.02	0.24	25%	0.21
Randomized studies	2096 (3)	0.00 (-0.02, 0.02)	0.75	0.93	0%	
Non-randomized studies	512 (4)	-0.05 (-0.07, -0.02)	0.0004	0.90	0%	
Peak aortic gradient progression (mm Hg/y)	731 (5)	-1.76 (-3.73, 0.21)	0.08	0.05	57%	0.03
Randomized studies	403 (2)	0.10 (-1.36, 1.56)	0.89	0.86	0%	
Non-randomized studies	328 (3)	-3.40 (-5.39, -1.41)	0.0008	0.46	0%	
Mean aortic gradient progression (mm Hg/y)	2413 (5)	-0.99 (-2.04, 0.07)	0.07	0.008	71%	0.04
Randomized studies	1962 (2)	-0.10 (-0.36, 0.16)	0.46	1.00	0%	
Non-randomized studies	451 (3)	-2.19 (-3.35, -1.03)	0.0002	0.38	0%	

Note for the next slides

Green: sample size estimation from **prospective studies**

Yellow: sample size estimation from **randomized studies**

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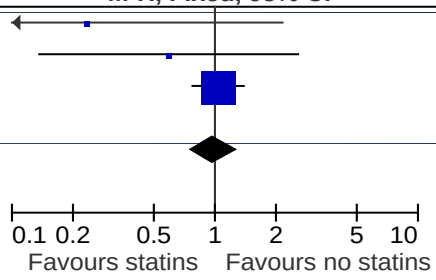
Total mortality

Randomize?

Study or Subgroup	Statins Events	Statins Total	No statins Events	No statins Total	Weight	Odds Ratio M-H, Fixed, 95% CI
RAAVE 2007	1	61	4	60	4.0%	0.23 [0.03, 2.15]
SALTIRE 2005	3	77	5	78	4.9%	0.59 [0.14, 2.57]
SEAS 2008	105	944	100	929	91.1%	1.04 [0.78, 1.39]
Total (95% CI)		**1082**		**1067**	**100.0%**	**0.98 [0.74, 1.30]**
Total events	109		109			

Heterogeneity: Chi² = 2.20, df = 2 (P = 0.33); I² = 9%

Test for overall effect: Z = 0.12 (P = 0.91)



>700.000 pts

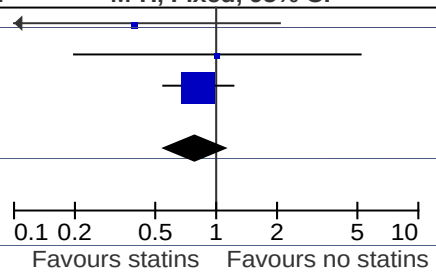
n.a. (OR 1.01)

Mortality from CV causes

Study or Subgroup	Statins Events	Statins Total	No statins Events	No statins Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ASTRONOMER 2010	2	134	5	135	8.0%	0.39 [0.08, 2.07]
SALTIRE 2005	3	77	3	78	4.7%	1.01 [0.20, 5.18]
SEAS 2008	47	944	56	929	87.3%	0.82 [0.55, 1.22]
Total (95% CI)		**1155**		**1142**	**100.0%**	**0.79 [0.54, 1.15]**
Total events	52		64			

Heterogeneity: Chi² = 0.79, df = 2 (P = 0.67); I² = 0%

Test for overall effect: Z = 1.21 (P = 0.22)



13.500 pts

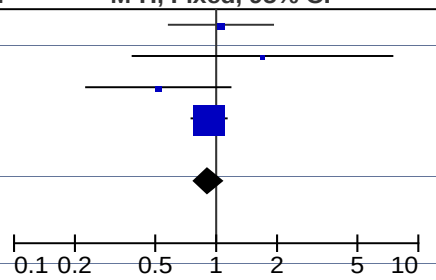
13.500 pts

Aortic valve surgery

Study or Subgroup	Statins Events	Statins Total	No statins Events	No statins Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ASTRONOMER 2010	28	134	27	135	8.8%	1.06 [0.58, 1.91]
RAAVE 2007	5	61	3	60	1.2%	1.70 [0.39, 7.44]
SALTIRE 2005	11	77	19	78	6.7%	0.52 [0.23, 1.18]
SEAS 2008	267	944	278	929	83.3%	0.92 [0.76, 1.13]
Total (95% CI)		**1216**		**1202**	**100.0%**	**0.92 [0.76, 1.10]**
Total events	311		327			

Heterogeneity: Chi² = 2.75, df = 3 (P = 0.43); I² = 0%

Test for overall effect: Z = 0.93 (P = 0.35)



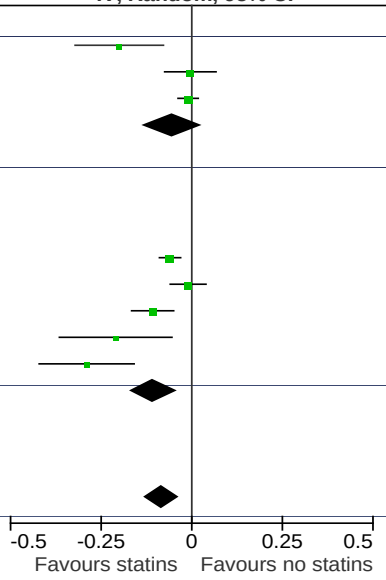
13.500 pts

15.500 pts

Jet velocity progression (m/sec/y)

Randomize?

Study or Subgroup	Statins Mean	SD	Total	No statins Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 Prospective studies								
RAAVE 2007	0.04	0.38	61	0.24	0.3	60	8.4%	-0.20 [-0.32, -0.08]
SALTIRE 2005	0.199	0.21	65	0.203	0.208	69	13.1%	-0.00 [-0.07, 0.07]
SEAS 2008	0.15	0.293	859	0.16	0.288	834	17.4%	-0.01 [-0.04, 0.02]
Subtotal (95% CI)			**985**			**963**	**38.9%**	**-0.05 [-0.13, 0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 9.03, df = 2 (P = 0.01); I² = 78%								
Test for overall effect: Z = 1.21 (P = 0.22)								
1.4.2 Retrospective studies								
Antonini mild AS	0.09	0.15	141	0.15	0.15	360	17.3%	-0.06 [-0.09, -0.03]
Antonini moderate AS	0.21	0.18	62	0.22	0.15	214	15.4%	-0.01 [-0.06, 0.04]
Bellamy 2002	0.135	0.135	38	0.243	0.216	118	14.5%	-0.11 [-0.17, -0.05]
Kubawara 2006	0.01	0.21	13	0.22	0.24	20	6.2%	-0.21 [-0.37, -0.05]
Rosenhek 2004	0.1	0.41	50	0.39	0.42	161	7.7%	-0.29 [-0.42, -0.16]
Subtotal (95% CI)			**304**			**873**	**61.1%**	**-0.11 [-0.17, -0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 21.73, df = 4 (P = 0.0002); I² = 82%								
Test for overall effect: Z = 3.16 (P = 0.002)								
Total (95% CI)			**1289**			**1836**	**100.0%**	**-0.08 [-0.13, -0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 38.95, df = 7 (P < 0.00001); I² = 82%								
Test for overall effect: Z = 3.38 (P = 0.0007)								

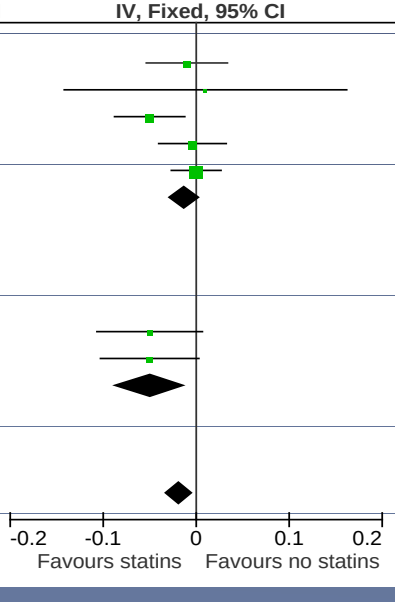


4.000 pts

20.000 pts

Aortic valve area decrease (cm ^{2} /y)

Study or Subgroup	Statins Mean	SD	Total	No statins Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.5.1 Prospective studies								
ASTRONOMER 2010	0.07	0.15	134	0.08	0.21	135	12.8%	-0.01 [-0.05, 0.03]
Mohler 2007	0.07	0.17	39	0.06	0.34	22	1.1%	0.01 [-0.14, 0.16]
RAAVE 2007	0.05	0.12	61	0.1	0.09	60	17.1%	-0.05 [-0.09, -0.01]
SALTIRE 2005	0.079	0.107	65	0.083	0.107	69	18.5%	-0.00 [-0.04, 0.03]
SEAS 2008	0.03	0.28	859	0.03	0.28	834	34.2%	0.00 [-0.03, 0.03]
Subtotal (95% CI)			**1158**			**1120**	**83.7%**	**-0.01 [-0.03, 0.00]**
Heterogeneity: Chi² = 4.94, df = 4 (P = 0.29); I² = 19%								
Test for overall effect: Z = 1.44 (P = 0.15)								
1.5.2 Retrospective studies								
Bellamy 2002	0.04	0.15	38	0.09	0.17	118	7.6%	-0.05 [-0.11, 0.01]
Novaro 2001	0.06	0.16	57	0.11	0.18	117	8.7%	-0.05 [-0.10, 0.00]
Subtotal (95% CI)			**95**			**235**	**16.3%**	**-0.05 [-0.09, -0.01]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%								
Test for overall effect: Z = 2.54 (P = 0.01)								
Total (95% CI)			**1253**			**1355**	**100.0%**	**-0.02 [-0.03, -0.00]**
Heterogeneity: Chi² = 7.97, df = 6 (P = 0.24); I² = 25%								
Test for overall effect: Z = 2.34 (P = 0.02)								
Test for subgroup differences: Chi² = 3.03, df = 1 (P = 0.08), I² = 67.0%								

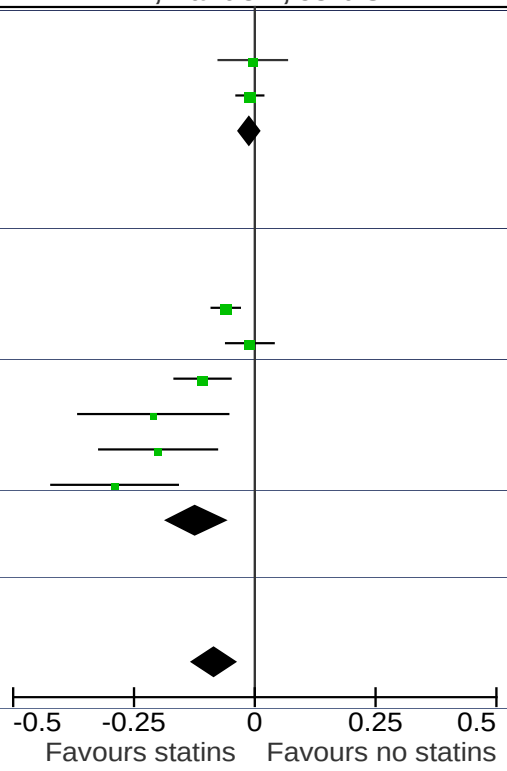


>300.000 pts

n.a. mean diff=0.00

Jet velocity progression (m/sec/y) by random vs. nonrandom studies

Study or Subgroup	Statins Mean	Statins SD	Statins Total	No statins Mean	No statins SD	No statins Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 Randomized studies								
SALTIRE 2005	0.199	0.21	65	0.203	0.208	69	13.1%	-0.00 [-0.07, 0.07]
SEAS 2008	0.15	0.293	859	0.16	0.288	834	17.4%	-0.01 [-0.04, 0.02]
Subtotal (95% CI)			**924**			**903**	**30.5%**	**-0.01 [-0.03, 0.02]**
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%								
Test for overall effect: Z = 0.70 (P = 0.48)								
1.4.2 Non-randomized studies								
Antonini mild AS	0.09	0.15	141	0.15	0.15	360	17.3%	-0.06 [-0.09, -0.03]
Antonini moderate AS	0.21	0.18	62	0.22	0.15	214	15.4%	-0.01 [-0.06, 0.04]
Bellamy 2002	0.135	0.135	38	0.243	0.216	118	14.5%	-0.11 [-0.17, -0.05]
Kubawara 2006	0.01	0.21	13	0.22	0.24	20	6.2%	-0.21 [-0.37, -0.05]
RAAVE 2007	0.04	0.38	61	0.24	0.3	60	8.4%	-0.20 [-0.32, -0.08]
Rosenhek 2004	0.1	0.41	50	0.39	0.42	161	7.7%	-0.29 [-0.42, -0.16]
Subtotal (95% CI)			**365**			**933**	**69.5%**	**-0.12 [-0.18, -0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 26.18, df = 5 (P < 0.0001); I² = 81%								
Test for overall effect: Z = 3.67 (P = 0.0002)								
Total (95% CI)			**1289**			**1836**	**100.0%**	**-0.08 [-0.13, -0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 38.95, df = 7 (P < 0.00001); I² = 82%								
Test for overall effect: Z = 3.38 (P = 0.0007)								

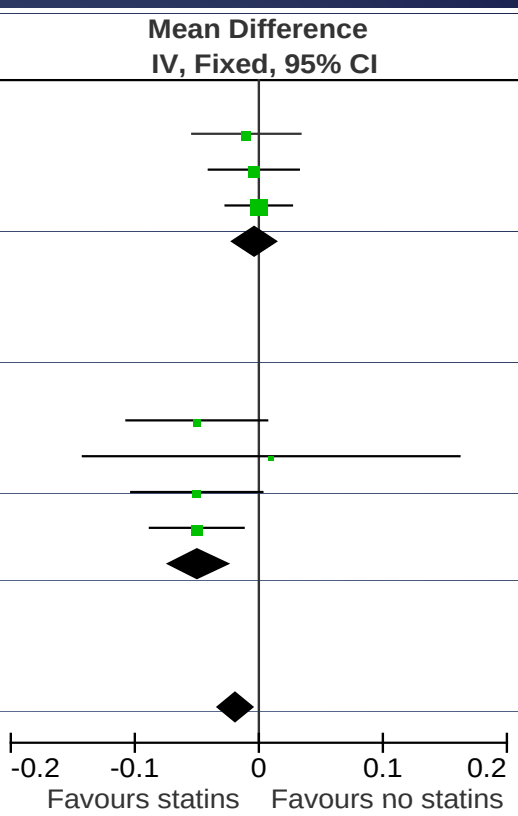


Randomize?

20.000 pts

Aortic valve area decrease (cm^2/y) by random vs. nonrandom studies

Study or Subgroup	Statins Mean	SD	Total	No statins Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.5.1 Randomized studies								
ASTRONOMER 2010	0.07	0.15	134	0.08	0.21	135	12.8%	-0.01 [-0.05, 0.03]
SALTIRE 2005	0.079	0.107	65	0.083	0.107	69	18.5%	-0.00 [-0.04, 0.03]
SEAS 2008	0.03	0.28	859	0.03	0.28	834	34.2%	0.00 [-0.03, 0.03]
Subtotal (95% CI)			**1058**			**1038**	**65.6%**	**-0.00 [-0.02, 0.02]**
Heterogeneity: Chi² = 0.15, df = 2 (P = 0.93); I² = 0%								
Test for overall effect: Z = 0.31 (P = 0.75)								
1.5.2 Non-randomized studies								
Bellamy 2002	0.04	0.15	38	0.09	0.17	118	7.6%	-0.05 [-0.11, 0.01]
Mohler 2007	0.07	0.17	39	0.06	0.34	22	1.1%	0.01 [-0.14, 0.16]
Novaro 2001	0.06	0.16	57	0.11	0.18	117	8.7%	-0.05 [-0.10, 0.00]
RAAVE 2007	0.05	0.12	61	0.1	0.09	60	17.1%	-0.05 [-0.09, -0.01]
Subtotal (95% CI)			**195**			**317**	**34.4%**	**-0.05 [-0.07, -0.02]**
Heterogeneity: Chi² = 0.58, df = 3 (P = 0.90); I² = 0%								
Test for overall effect: Z = 3.55 (P = 0.0004)								
Total (95% CI)			**1253**			**1355**	**100.0%**	**-0.02 [-0.03, -0.00]**
Heterogeneity: Chi² = 7.97, df = 6 (P = 0.24); I² = 25%								
Test for overall effect: Z = 2.34 (P = 0.02)								
Test for subgroup differences: Chi² = 7.24, df = 1 (P = 0.007), I² = 86.2%								

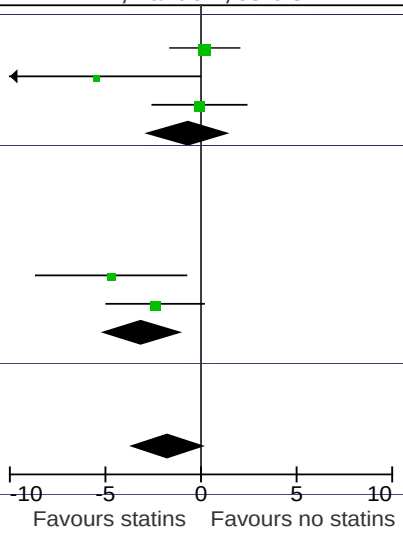


Randomize?

??????

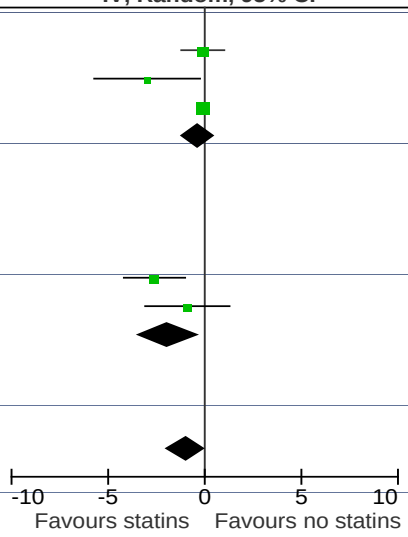
Peak aortic gradient progression (mmHg/y)

Study or Subgroup	Statins Mean	SD	Total	No statins Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.6.1 Prospective studies								
ASTRONOMER 2010	6.3	6.9	134	6.1	8.2	135	28.5%	0.20 [-1.61, 2.01]
RAAVE 2007	2.13	19.21	61	7.57	9.62	60	9.8%	-5.44 [-10.84, -0.04]
SALTIRE 2005	6.48	7.43	65	6.56	7.1	69	23.6%	-0.08 [-2.54, 2.38]
Subtotal (95% CI)			**260**			**264**	**61.9%**	**-0.67 [-2.89, 1.54]**
Heterogeneity: Tau² = 1.78; Chi² = 3.80, df = 2 (P = 0.15); I² = 47%								
Test for overall effect: Z = 0.60 (P = 0.55)								
1.6.2 Retrospective studies								
Kubawara 2006	1.3	5.3	13	6	6.1	20	15.0%	-4.70 [-8.63, -0.77]
Novaro 2001	3	8.6	57	5.4	6.8	117	23.0%	-2.40 [-4.95, 0.15]
Subtotal (95% CI)			**70**			**137**	**38.1%**	**-3.08 [-5.22, -0.94]**
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.34); I² = 0%								
Test for overall effect: Z = 2.82 (P = 0.005)								
Total (95% CI)			**330**			**401**	**100.0%**	**-1.76 [-3.73, 0.21]**
Heterogeneity: Tau² = 2.69; Chi² = 9.34, df = 4 (P = 0.05); I² = 57%								
Test for overall effect: Z = 1.75 (P = 0.08)								
Test for subgroup differences: Chi² = 4.61, df = 1 (P = 0.03), I² = 78.3%								



Mean aortic gradient progression (mmHg/y)

Study or Subgroup	Statins Mean	SD	Total	No statins Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.7.1 Prospective studies								
ASTRONOMER 2010	3.8	4.4	134	3.9	4.9	135	24.3%	-0.10 [-1.21, 1.01]
RAAVE 2007	2.08	8.15	61	5.06	7.17	60	10.3%	-2.98 [-5.71, -0.25]
SEAS 2008	2.7	2.9	859	2.8	2.8	834	32.5%	-0.10 [-0.37, 0.17]
Subtotal (95% CI)			**1054**			**1029**	**67.1%**	**-0.36 [-1.25, 0.53]**
Heterogeneity: Tau² = 0.33; Chi² = 4.22, df = 2 (P = 0.12); I² = 53%								
Test for overall effect: Z = 0.79 (P = 0.43)								
1.7.2 Retrospective studies								
Bellamy 2002	2.9	3.4	38	5.5	6.4	118	19.1%	-2.60 [-4.18, -1.02]
Novaro 2001	2.4	7.6	57	3.3	5.1	117	13.8%	-0.90 [-3.08, 1.28]
Subtotal (95% CI)			**95**			**235**	**32.9%**	**-1.92 [-3.55, -0.29]**
Heterogeneity: Tau² = 0.50; Chi² = 1.53, df = 1 (P = 0.22); I² = 35%								
Test for overall effect: Z = 2.31 (P = 0.02)								
Total (95% CI)			**1149**			**1264**	**100.0%**	**-0.99 [-2.04, 0.07]**
Heterogeneity: Tau² = 0.88; Chi² = 13.76, df = 4 (P = 0.008); I² = 71%								
Test for overall effect: Z = 1.82 (P = 0.07)								
Test for subgroup differences: Chi² = 8.01, df = 1 (P = 0.005), I² = 87.5%								



Statins in aortic stenosis

Unfortunately, data currently available do not support any role of statins in the progression of aortic stenosis for stages from moderate (mild?) to severe.

Also, the effect of statins on hard outcomes is very controversial for these patients

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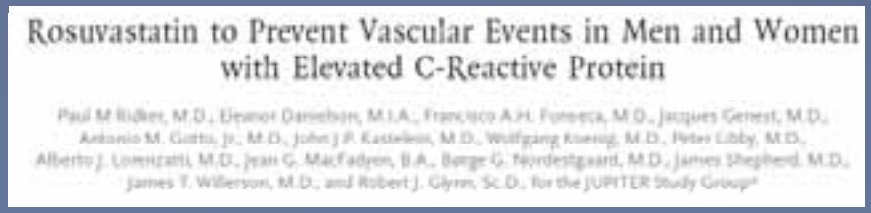
JUPITER study:
Change in LDL cholesterol and CRP levels

Measure	Baseline	12 mo	24 mo	36 mo	48 mo
LDL cholesterol (mg/dL)					
•Rosuvastatin 20 mg	108	55	54	53	55
•Placebo	108	110	108	106	109
High-sensitivity CRP (mg/L)					
•Rosuvastatin 20 mg	4.2	2.2	2.2	2.0	1.8
•Placebo	4.3	3.5	3.5	3.5	3.3

p<0.001 for all between-group comparisons

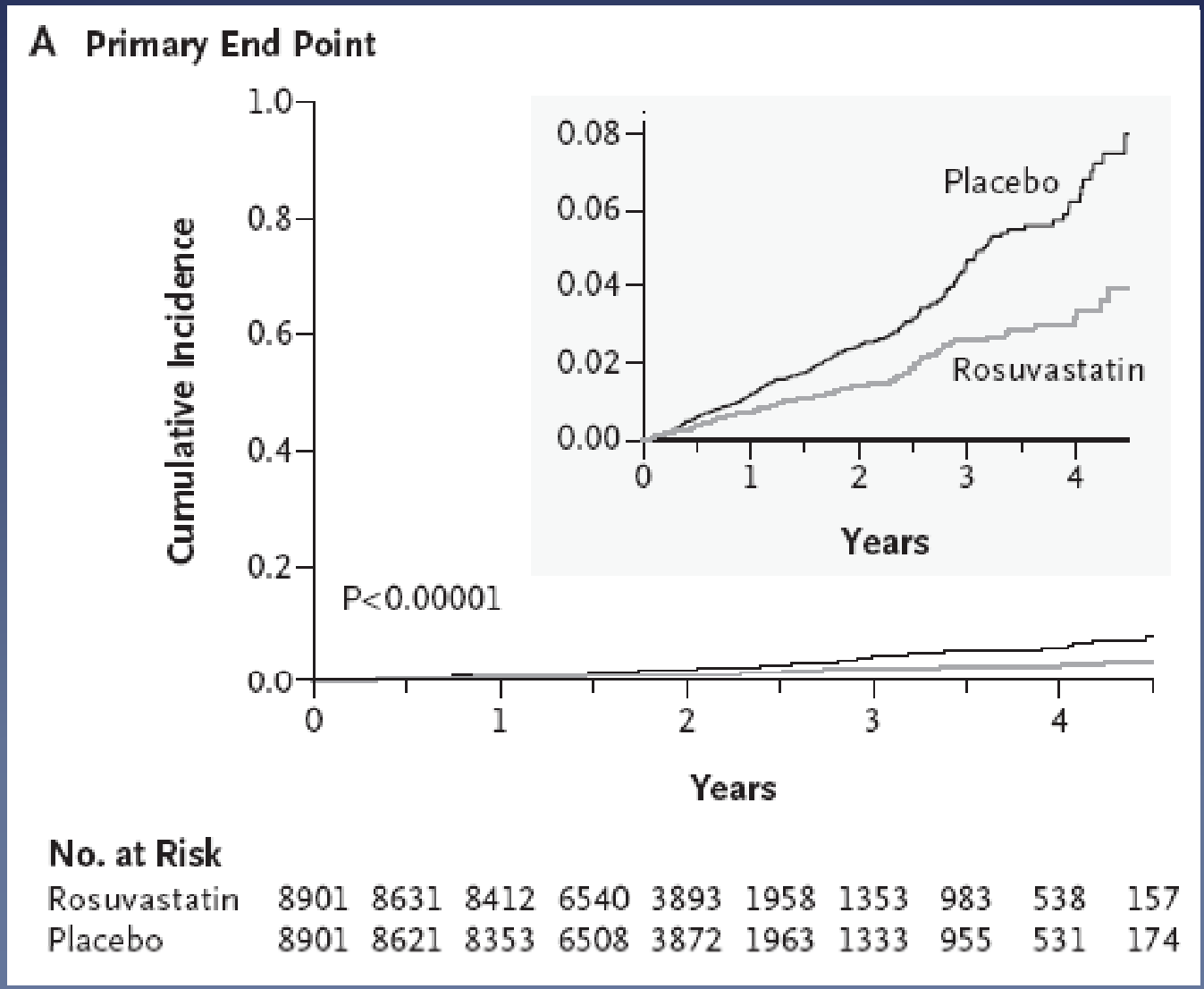


JUPITER study: Outcomes according to study group

End point	Patients with event, rosuvastatin (n=8901), n	Patients with event, placebo (n=8901), n	Hazard ratio (95% CI)
Primary end point*	**142**	**251**	**0.56 (0.46–0.69)**
•Nonfatal MI	22	62	0.35 (0.22–0.58)
•Any MI	31	68	0.46 (0.30–0.70)
•Nonfatal stroke	30	58	0.52 (0.33–0.80)
•Any stroke	33	64	0.52 (0.34–0.79)
•Revascularization	71	131	0.54 (0.41–0.72)
•Hospitalization for unstable angina	16	27	0.59 (0.32–1.10)
•Revascularization or hospitalization for unstable angina	76	143	0.53 (0.40–0.70)
•MI, stroke, or death from CV causes	83	157	0.53 (0.40–0.69)
•Death on any known date	190	235	0.81 (0.67–0.98)
•Any death	198	247	0.80 (0.67–0.97)

*Primary end point: composite of nonfatal MI, nonfatal stroke, hospitalization for unstable angina, revascularization, and confirmed death from cardiovascular causes

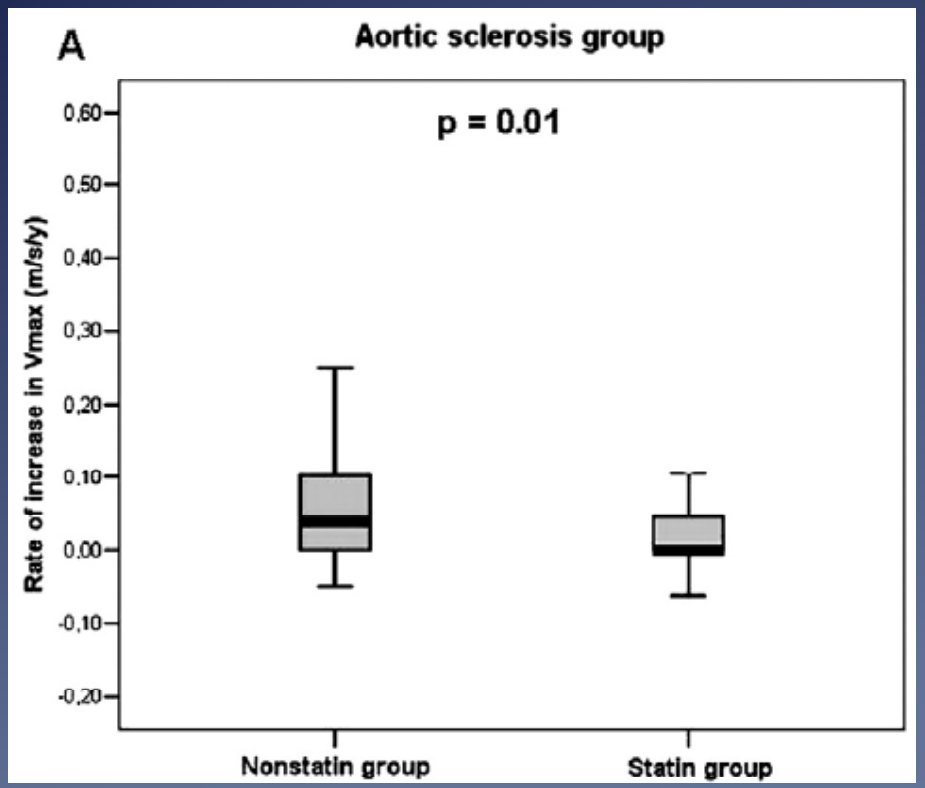
JUPITER was designed as a four-year study but was stopped by AstraZeneca after just 1.9 years based on recommendations from an independent data monitoring board and the JUPITER steering committee.

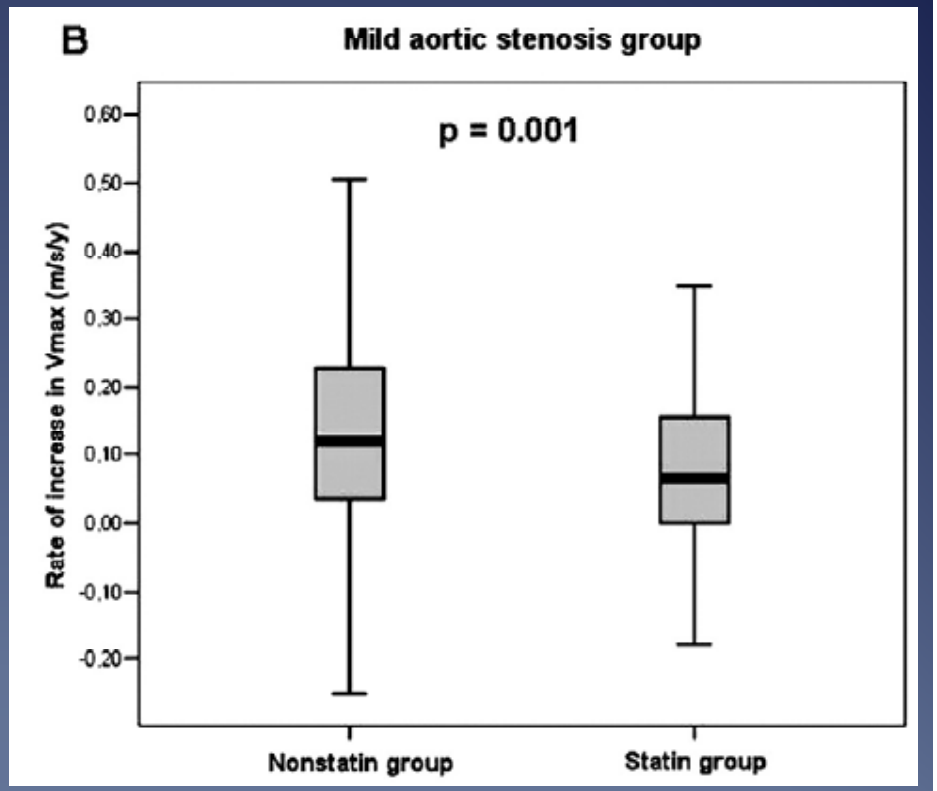


Stage-Related Effect of Statin Treatment on the Progression of Aortic Valve Sclerosis and Stenosis

Am J Cardiol 2008;102:738–742

Francesco Antonini-Canterin, MD[a,*], Monica Hîrşu, MD[b], Bogdan Alexandru Popescu, MD, PhD[b], Elisa Leiballi, MD[a], Rita Piazza, MD[a], Daniela Pavan, MD[a], Carmen Ginghină, MD, PhD[b], and Gian Luigi Nicolosi, MD[a]





Avg jet velocity: 1.6 m/s

Avg jet velocity: 2.3 m/s

Avg peak gradient: 23 mmHg

Avg mean gradient: 12 mmHg

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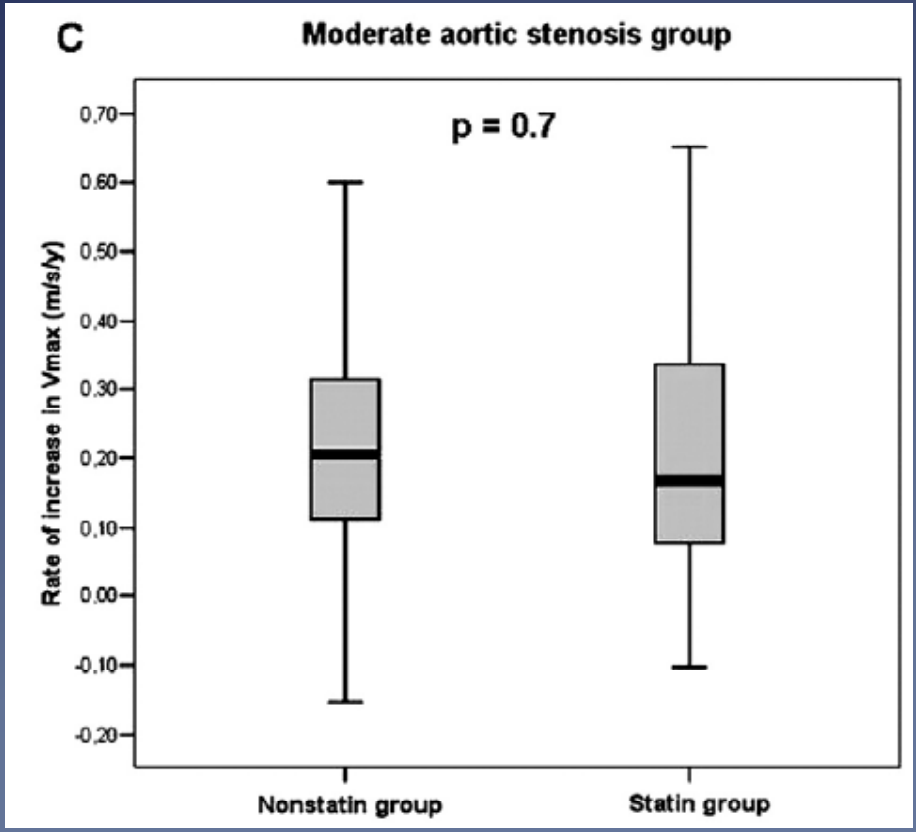

Avg jet velocity: 3.3 m/s

Avg peak gradient: 44 mmHg

Avg mean gradient: 24 mmHg

New perspectives ?
New hopes?

Statins administration at earlier stages of the disease

(cost-effective?)

New classes of drugs?

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Statins administration at earlier stages of the disease: cost-effective?

	Cost (€)
One-year statin therapy	
Simvastatin 20 mg	200
Rosuvastatin 5 mg	325
Atorvastatin 20 mg	550
Aortic valve replacement	17500-22500
TAVI	“no more than standard AVR”

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Potential mechanisms of aortic valve stenosis at which pharmacological treatment could be targeted, the potential drugs, and their desirable effects

Target processes in valves	Drug	Desirable effects in valves
Endothelial injury	Statins	Endothelial dysfunction ↓
	AT-1R antagonists	Endothelial integrity ↑
Accumulation and deposition of lipoprotein-derived lipids	Statins	Blood lipids ↓, leading to lipoprotein influx ↓
Angiotensin II–mediated actions	ACE inhibitors/AT-1R antagonists	Blocking ACE/AT-1R in valves
NEP activity	NEP inhibitors	Blocking NEP in valves
Accumulation and activation of inflammatory cells	Statins	Number of inflammatory cells in valves ↓
		C-reactive protein in valves ↓
	AT-1R antagonists	Valvular macrophages ↓
Extracellular matrix remodeling	Statins	MMP-secreting inflammatory cells ↓
	ACE inhibitors/AT-1R antagonists	Angiotensin II-mediated fibrosis ↓
	MMP inhibitors?	MMP activity in valves ↓
	Cathepsin inhibitors?	Cathepsin activity ↓
Neovascularization	Statins	Neovessels in valves ↓
Calcification of the valve	Statins	Calcification-inducing lipids in valves ↓, calcification ↓
	ACE inhibitors	Calcification ↓
	AT-1R antagonists,	Osteoblastic differentiation ↓
	specific inhibitors of calcification?	Calcification ↓
	Estrogen receptor modulation (raloxifene)	Calcification ↓

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ACE, angiotensin-converting enzyme; AT-1R, angiotensin II type 1 receptor; MMP, matrix metalloproteinase; NEP, neutral endopeptidase.

Phases necessary for the myofibroblast cell to differentiate to form bone

1) Activation of cell proliferation

2) Extracellular matrix synthesis

3) Mineralization of the bone formation

4) Final step: apoptosis

The presence of apoptosis is critical for bone mineralization.

Apoptosis is the final common pathway necessary for the transition of the osteoblasts to mineralized bone.

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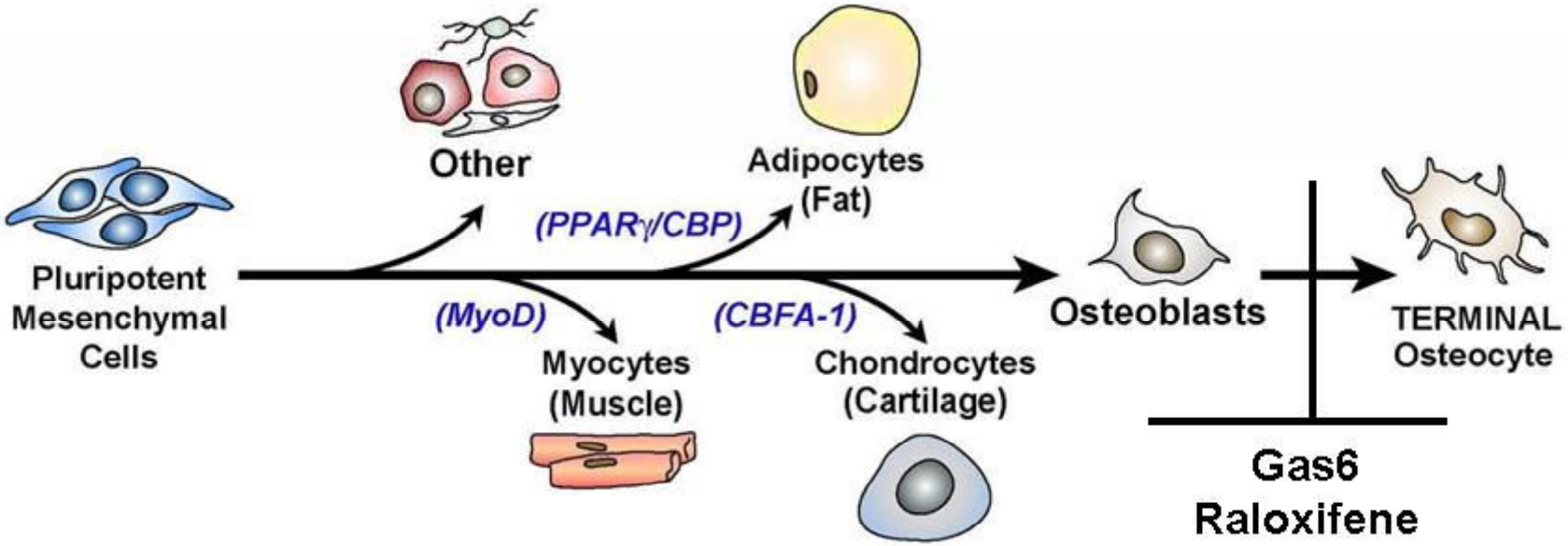
Myofibroblast Ontogeny

Mesenchymal Stem Cell Derivation of Osteoblast Cells



Phase I — **Cell Proliferation**

Phase II — **Extracellular Matrix**

Phase III — **Mineralization**
Apoptosis

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Rationale of estrogen receptor modulation

To date, there is no effective therapy to prevent cardiovascular calcification.

The association of osteoporosis and vascular calcification has been reported, suggesting that osteoporosis may increase vascular calcification ("bone vascular paradox“)

It has been suggested that antiosteoporosis medications might actually reduce vascular calcification.

Raloxifene is a mixed estrogen receptor agonist and antagonist; it exerts different effects on apoptosis in different tissues and has been shown to have a protective effect against osteoblast cell death.

Its potential role in valvular calcification is yet unknown.

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Diapo scartate

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The Society of Thoracic Surgeons National Database - 2007

No. of isolated coronary artery bypass procedures	154188
No. of aortic valve procedures	17592
No. of mitral valve procedures	4251
Unadjusted isolated coronary artery bypass operative mortality rate	2%
Unadjusted aortic valve operative mortality rate	3%
Unadjusted mitral valve operative mortality rate	6%
Mean postprocedure length of stay for isolated coronary artery bypass procedures	7.0 days
Mean postprocedure length of stay for aortic valve procedures	8.1 days
Mean postprocedure length of stay for mitral valve procedures	10.6 days

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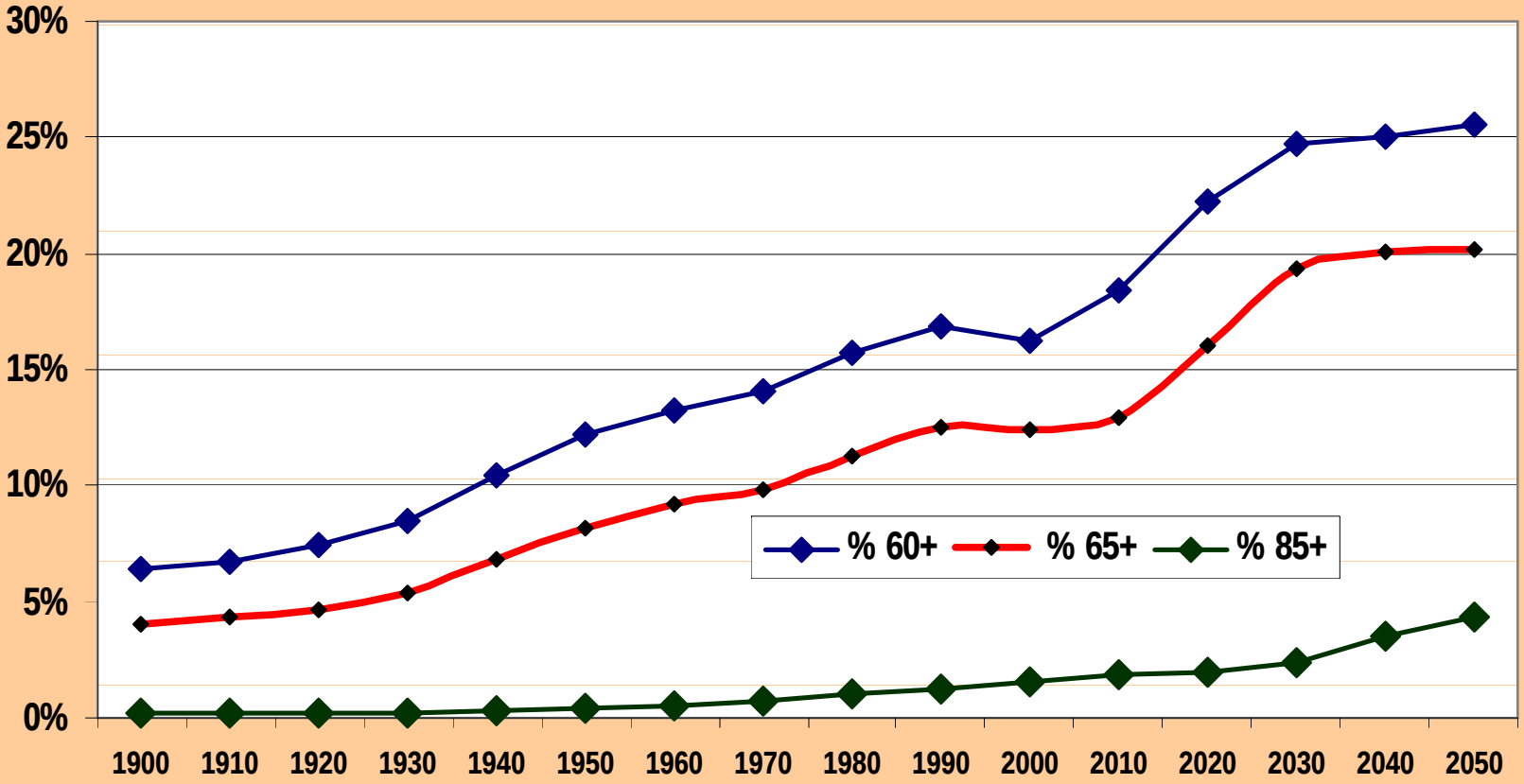
Older Population by Age: 1900-2050 - Percent 60+, Percent 65+, and 85+



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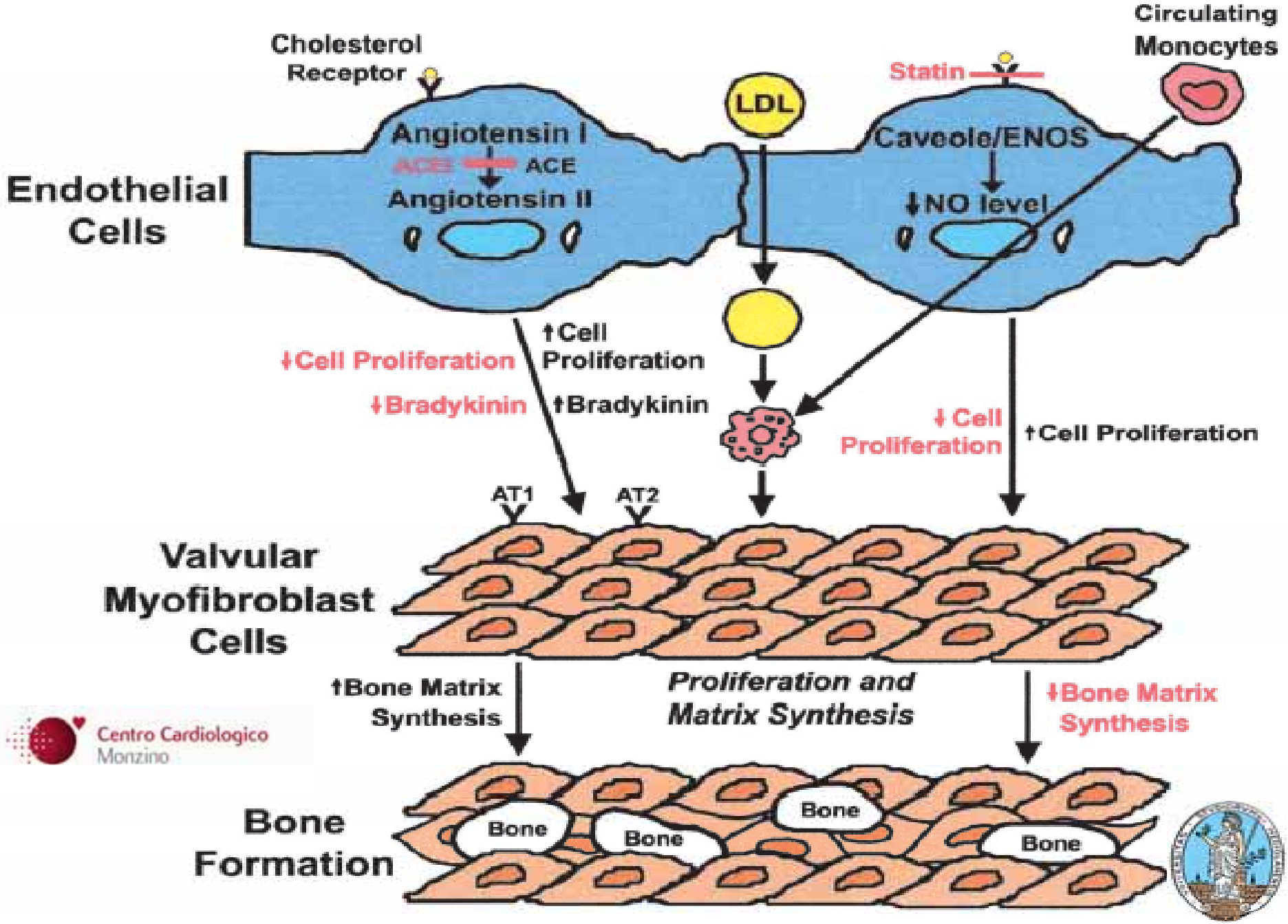
AOA Administration on Aging


Circulating
Monocytes
Cholesterol
Receptor
Statin
LDL
Angiotensin I
ACE
ACE
Angiotensin II
Caveole/ENOS
↓NO level
Endothelial
Cells
↓Cell Proliferation
↑Cell
Proliferation
↓Bradykinin
↑Bradykinin
↓ Cell
Proliferation
↑Cell Proliferation
AT1
AT2
Valvular
Myofibroblast
Cells
↑Bone Matrix
Synthesis
Proliferation and
Matrix Synthesis
↓Bone Matrix
Synthesis
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Bone
Formation
Bone
Bone
Bone
Bone

New perspectives ?
New hopes?

Statins administration at earlier stages of the disease (probably still cost-.effective)

New classes of drugs?

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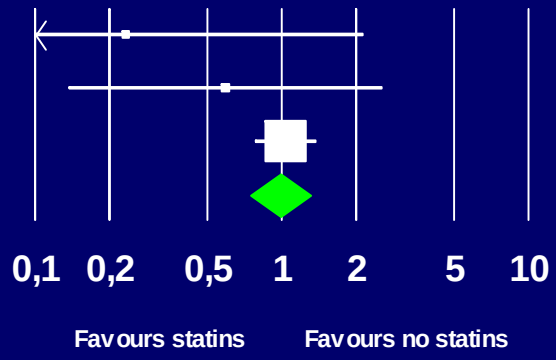
INCLUDED TRIALS

Study	Year	Study design	Treatment groups	N° of pts.	Age (y)	LDL cholesterol (mg/dL)	Diabetes	Aortic jet velocity (m/sec)	Aortic valve area (cm^2)	Transaortic pressure gradient (mmHg)	Follow-up
Cowell (SALTIRE)	2005	Prospective randomized	Placebo	78	68±10	133±30	4 (5%)	3.45±0.67	1.02±0.41	Peak:50±20	Median: 25 (7-36) months
			Atorvastatin 80 mg/d	77	68±10	137±34	3 (4%)	3.39±0.62	1.03±0.4	Peak:48±17	
Moura (RAAVE)	2007	Prospective open label	No treatment	60	74±9	117±21	13 (22%)	3.62±0.61	1.20±0.35	Mean:36±13	Mean: 73±24 weeks
			Rosuvastatin 20 mg/d	61	73±9	158±32	26 (43%)	3.65±0.64	1.23±0.43	Mean:35±13	
Rossebo (SEAS)	2008	Prospective randomized	Placebo	929	67±10	139±35	n.a.	3.10±0.54	1.27±0.46	Mean:23.0±8.7	Median: 52.2 months
			Simvastatin (40-80 mg/d) plus ezetimibe	944	68±9	140±36	n.a.	3.09±0.55	1.29±0.48	Mean:22.7±8.8	
Antonini-Canterin	2008	Retrospective	No statins: mild aortic stenosis	360	71±8	n.a.	82 (23%)	2.3±0.2	n.a.	Mean:13.1±3.2	Mean: 5.6±3.2 years
			Statins: mild aortic stenosis	141	71±7	n.a.	50 (36%)	2.3±0.2	n.a.	Mean:12.7±3.1	
			No statins: moderate aortic stenosis	214	72±8	n.a.	42 (20%)	3.3±0.2	n.a.	Mean:26.1±5.1	
			Statins: moderate aortic stenosis	62	70±8	n.a.	14 (23%)	3.3±0.2	n.a.	Mean:26.0±5.0	
Bellamy	2002	Retrospective	No statins	118	78±12	137±43	28 (24%)	3.0±0.8	1.20±0.35	Mean:22±12	Mean: 3.7±2.3 years
			Statins	38	73±11	164±49	9 (24%)	2.8±0.5	1.32±0.29	Mean:18±7	
Novaro	2001	Retrospective	No statins	117	67±13	131(112-143)	23 (20%)	n.a.	1.2(1.0-1.4)	Mean:15(12-22)	Mean:21 months
			Statins	57	71±9	128(94-146)	20 (35%)	n.a.	1.2(1.0-1.4)	Mean:15(12-22)	
Rosenhek	2004	Retrospective	No statins	161	69±11	141±39	32 (20%)	3.92±0.86	0.84±0.23	Mean:42±20	Median: 24±18 months
			Statins	50	72±8	145±38	11 (22%)	4.08±0.86	0.82±0.23	Mean:42±18	

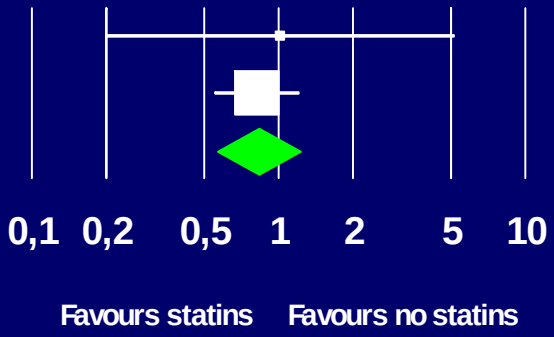
All cause mortality

Study name	Events / Total		MH odds ratio and 95% CI	
	Statins	No statins	MH odds ratio	p-Value
RAAVE	1 / 61	4 / 60	0,233	0,199
SALTIRE	3 / 77	5 / 78	0,592	0,484
SEAS	105 / 944	100 / 929	1,037	0,804
			0,983	0,907



Cardiovascular mortality

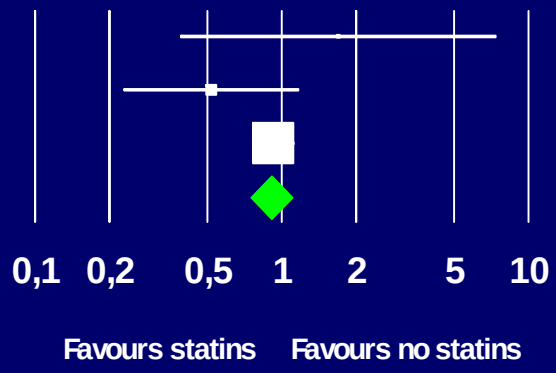
Study name	Events / Total		MH odds ratio	p-Value
	Statins	No statins		
SALTIRE	3 / 77	3 / 78	1,014	0,987
SEAS	47 / 944	56 / 929	0,817	0,320
			0,827	0,336



About 5% of patients died for CV causes at follow-up.
Statins may reduce the incidence of this complication by 15%-20%.
A sample size of 12309 (15% reduction) or 6745 (20% reduction) patients for each treatment arm (alpha=0.8, p=0.05) is needed.

Aortic valve surgery

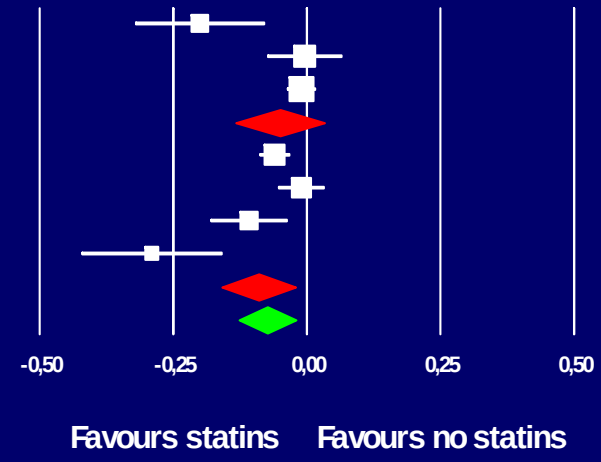
Study name	Events / Total			
	Statins	No statins	MH odds ratio	p-Value
RAAVE	5 / 61	3 / 60	1,696	0,483
SALTIRE	11 / 77	19 / 78	0,518	0,116
SEAS	267 / 944	278 / 929	0,924	0,434
			0,903	0,299



About 27% of patients needed aortic valve surgery at follow-up.
Statins may reduce the need of this intervention by 10%.
A sample size of 4106 patients for each treatment arm (alpha=0.8, p=0.05) is needed.

Jet velocity progression (m/s/y)

Group by Subgroup within study	Studyname	Subgroup within study	Statistics for each study: Difference in means	Standard error	p-Value
Prospective	RAAVE	Prospective	-0,200	0,062	0,001
Prospective	SALTIRE	Prospective	-0,004	0,036	0,912
Prospective	SEAS	Prospective	-0,010	0,014	0,479
Prospective			-0,051	0,042	0,225
Retrospective	Antonini mild AS	Retrospective	-0,060	0,015	0,000
Retrospective	Antonini mod. AS	Retrospective	-0,010	0,023	0,659
Retrospective	Bellamy	Retrospective	-0,108	0,037	0,004
Retrospective	Rosenhek	Retrospective	-0,290	0,068	0,000
Retrospective			-0,091	0,035	0,009
Overall			-0,075	0,027	0,006



Aortic valve area decrease (cm2/y)

Group by Subgroup within study	Study name	Subgroup within study	Difference in means	Standard error	p-Value
Prospective	RAAVE	Prospective	-0,050	0,019	0,010
Prospective	SALTIRE	Prospective	-0,004	0,018	0,829
Prospective	SEAS	Prospective	0,000	0,014	1,000
Prospective			-0,016	0,015	0,290
Retrospective	Bellamy	Retrospective	-0,050	0,031	0,105
Retrospective	Novaro	Retrospective	-0,050	0,028	0,075
Retrospective			-0,050	0,021	0,016
Overall			-0,028	0,012	0,023