Σεμινάριο ομάδων εργασίας ΕΚΕ

Common inflammatory pathways between coronary artery disease and aortic valve stenosis

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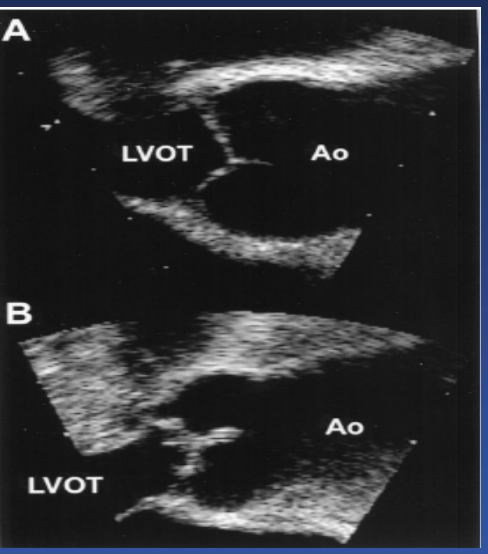
- Acquired nonrheumatic aortic valve stenosis (AVS) is the most common valvular heart disease in the Western world

Cosmi JE, Kort S, Tunick PA, et al. Arch Intern Med 2002;162(20):2345-7

- Considered a passive, age-related degenerative disease
- Recent studies have shown that the pathogenesis of AVS resembles that of atherosclerosis, ranging from endothelial dysfunction to calcification

Yetkin E, Waltenberger J. Int J Cardiol 2009;135(1):4-13.

Hakuno D, Kimura N, Yoshioka M, Fukuda K.. J Mol Med 2009;87(1):17-24.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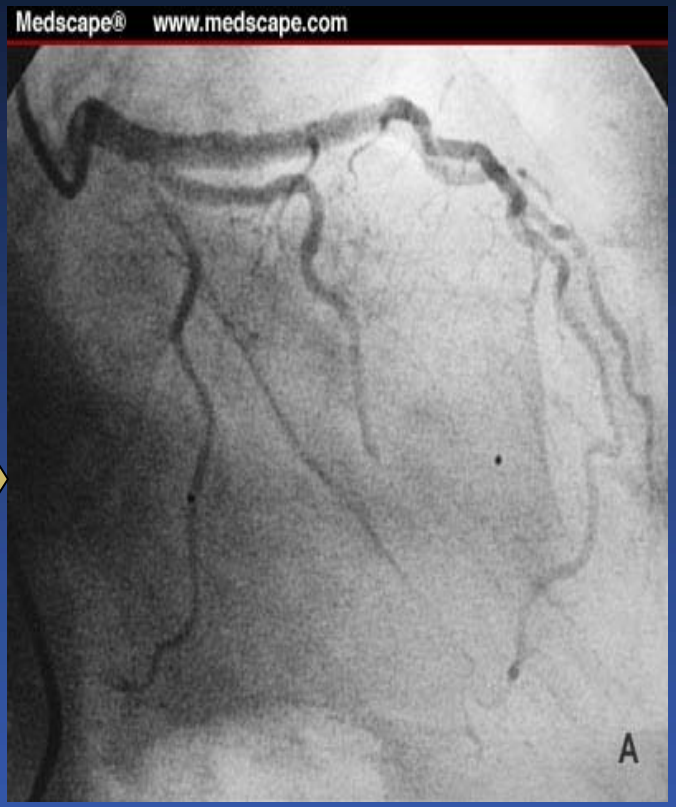
Medscape® www.medscape.com
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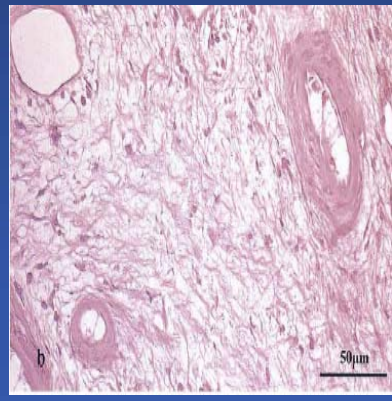

b
50μm

From a clinical point of view, it is of great importance to

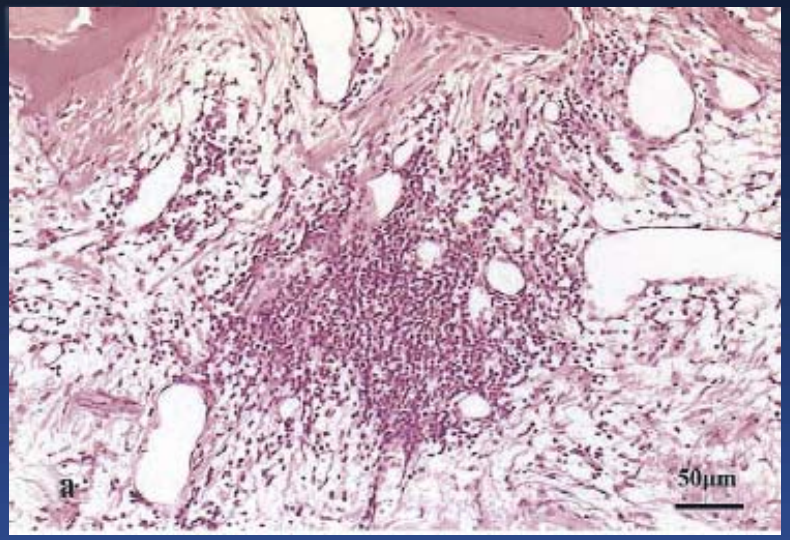
- 1) identify patients with mild or moderate AVS who have increased risk for subclinical coronary atherosclerosis

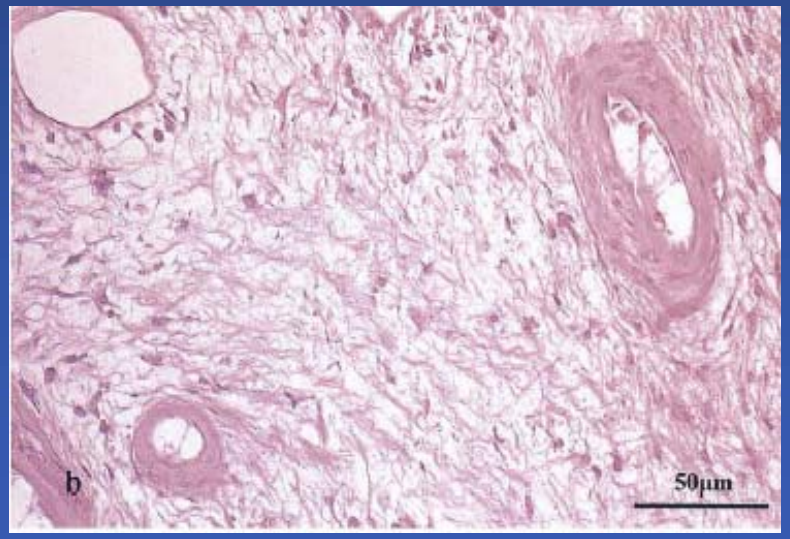
- 2) investigate the effect of atherosclerosis risk factors on the incidence and rate of progression of AVS

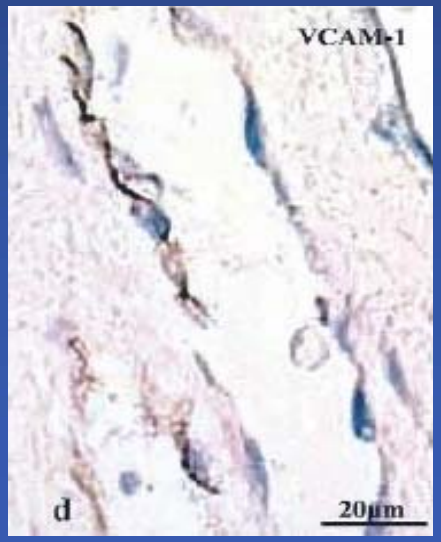
- Common histopathological evidence
- Predisposing factors of progression of aortic valve stenosis
- Aortic valve stenosis and cardiovascular outcome
- Clinical evidence of coronary artery disease in patients with aortic valve stenosis

- **Common histopathological evidence**
- **Predisposing factors of progression of aortic valve stenosis**
- **Aortic valve stenosis and cardiovascular outcome**
- **Clinical evidence of coronary artery disease in patients with aortic valve stenosis**

Φλεγμονή και Στένωση Αορτικής Βαλβίδας







26 ασθενείς στένωση AV

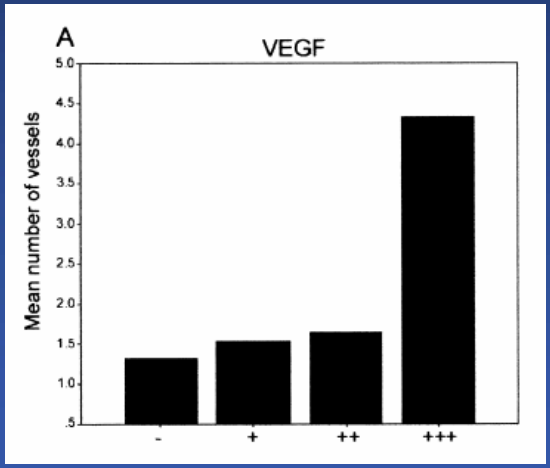
14 ασθενείς ανεπάρκεια AV

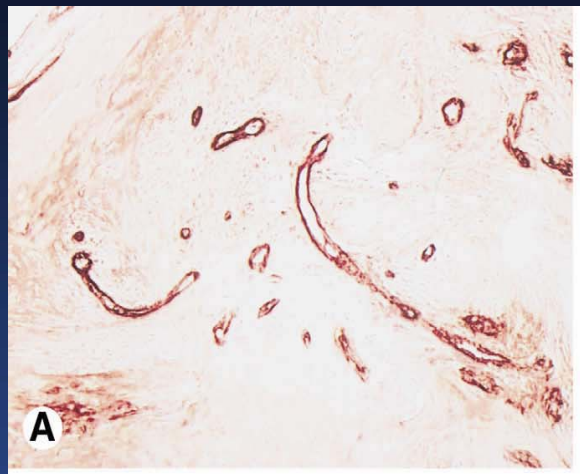
- **Διήθηση λεμφοκυττάρων μακροφάγων, νεοαγγειογένεση σε ασθενείς με στένωση αορτικής βαλβίδας.**
- **Μόρια προσκόλλησης στα ενδοθήλια των νεοαγγείων.**

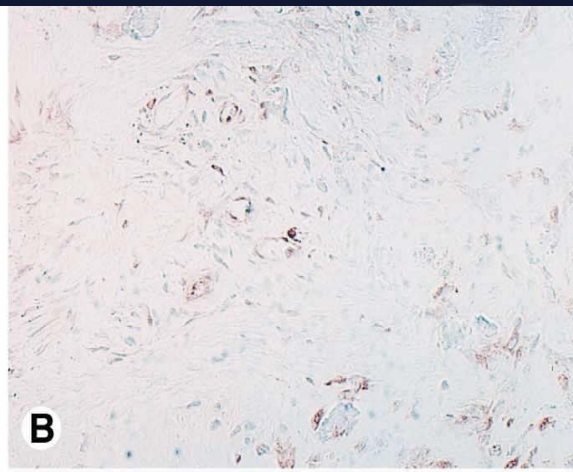
Mazzone et al, J Am Coll Cardiol 2004;43:1670–6

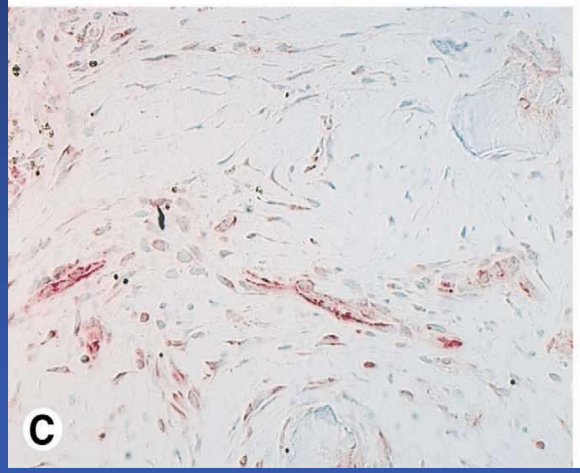
Inflammation and Neoangiogenesis

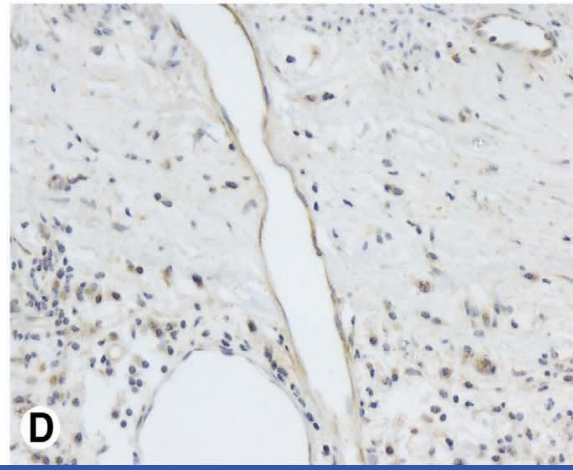
Neoangiogenessis is most intense in moderate forms of AS and is distinctly associated with the inflammatory process, suggesting that the growth factors and cytokines excreted by inflammatory cells contribute to its existence.











The angiogenic process was associated with inflammation, but not with calcification or fibrosis, suggesting the presence of a distinct angiogenic response in the evolution of AVS

Soini Y, et al, Hum Pathol 2003;34(8):756-63

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In Vivo Aortic Valve Thermal Heterogeneity in Patients With Nonrheumatic Aortic Valve Stenosis

The First In Vivo Experience in Humans

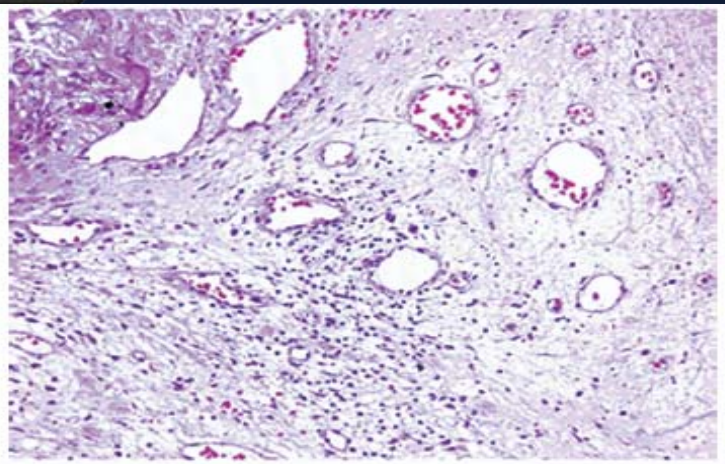
Konstantinos Toutouzas, MD,* Maria Drakopoulou, MD,* Andreas Synetos, MD,* Eleftherios Tsiamis, MD,* George Agrogiannis, MD,† Nikolaos Kavantzas, MD,† Eustratios Patsouris, MD,† Dimitris Iliopoulos, MD,‡ Stergios Theodoropoulos, MD,§ Magdi Yacoub, MD,§‖ Christodoulos Stefanadis, MD*

Athens, Greece; and London, United Kingdom

	AVS (n = 75)				AVI (n = 21)			
Grade	0	1+	2+	3+	0	1+	2+	3+
Histological features, n (%)								
T lymphocytes	0 (0%)	2 (2.6%)	9 (12%)	64 (85.4%)	19 (90.4%)*	2 (9.6%)	0 (0%)*	0 (0%)*
Mast cells	0 (0%)	0 (0%)	10 (14%)	65 (86%)	17 (81%)*	4 (9%)*	0 (0%)*	0 (0%)*
Calcium deposits	0 (0%)	0 (0%)	2 (3%)	73 (97%)	16 (76%)*	5 (23%)*	0 (0%)	0 (0%)*
Immunohistological features, n (%)								
CD3	0 (0%)	1 (1.3%)	8 (10.6%)	66 (88%)	17 (80.9%)*	4 (19.0%)*	0 (0%)	0 (0%)*
TNF-α	0 (0%)	2 (2.7%)	12 (16%)	61 (81.3%)	16 (76.2%)*	5 (23.8%)*	0 (0%)*	0 (0%)*
IL-6	0 (0%)	2 (0%)	13 (17.3%)	60 (80%)	17 (80.9%)*	4 (19.0%)*	0 (0%)*	0 (0%)*

*$p < 0.05$ for comparisons between aortic valve stenosis (AVS) and aortic valve insufficiency (AVI).
CD3 = cluster of differentiation 3; IL = interleukin; TNF = tumor necrosis factor.

- leaflets of AVS had increased inflammatory cell infiltration, calcium deposit, and anti-VEGF expression compared to leaflets of aortic valve insufficiency



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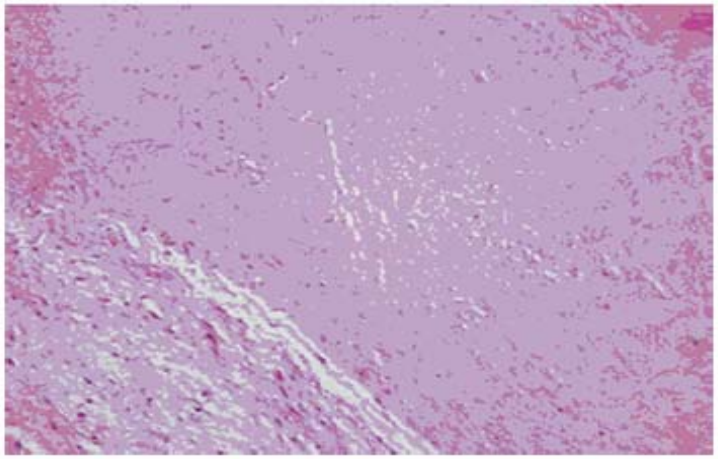

Figure 1 Representative Photomicrographs of HE Staining in Examined Specimens of Aortic Valves

(A) Hematoxylin and eosin (HE) staining in aortic valve stenosis showing intense inflammation (×200). **(B)** The HE staining in aortic valve insufficiency showing normal valvular stroma with sparse cellularity (×200).

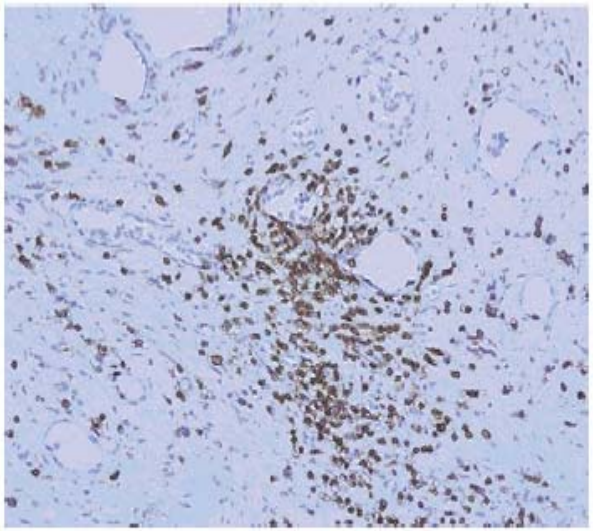

Figure 2 Representative Photomicrograph of CD3-Positive Leukocytes in Examined Specimens of Aortic Valves

Intense expression of cluster of differentiation 3 (CD3)–positive leukocytes in aortic valve stenosis.

Toutouzas K, et al. J Am Coll Cardiol 2008;52(9):758-63.

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Athens, Greece; and London, United Kingdom

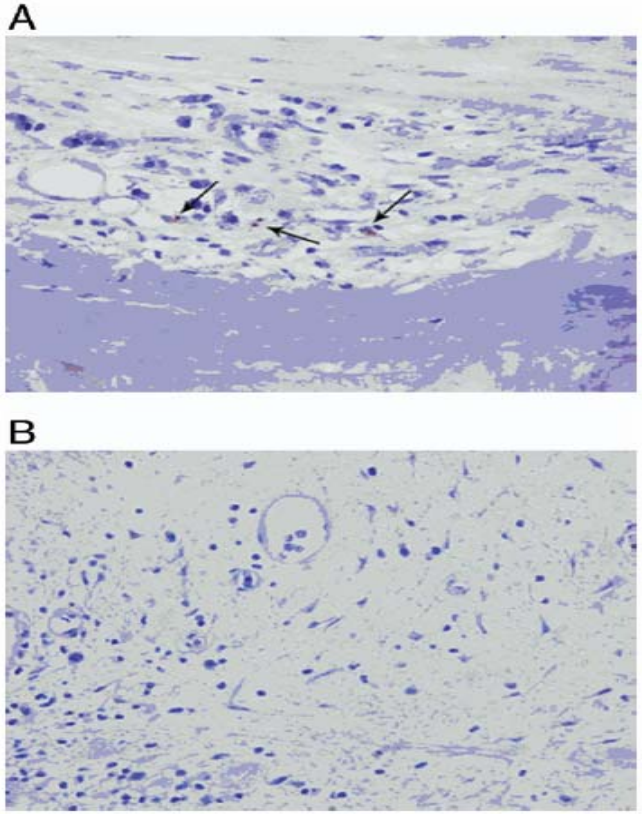

Figure 3 Representative Photomicrographs of Anti–TNF-α Staining in Examined Specimens of Aortic Valves

(A) Anti–tumor necrosis factor (TNF)-α staining in aortic valve stenosis. **Arrows** indicate positivity to anti–TNF-α. **(B)** Anti–TNF-α staining in aortic valve insufficiency showing negative staining for anti–TNF-α (×400).

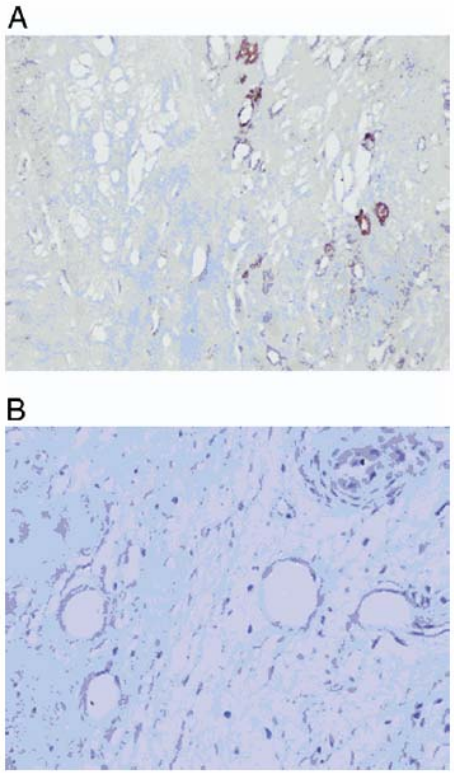

Figure 6 Representative Photomicrographs of VEGF Staining in Examined Specimens of Aortic Valves

(A) Marked vascular endothelial growth factor (VEGF) immunoreactivity in neovessels in severe aortic stenosis (×400). **(B)** Aortic valve insufficiency showing no VEGF immunoreactivity (×400).

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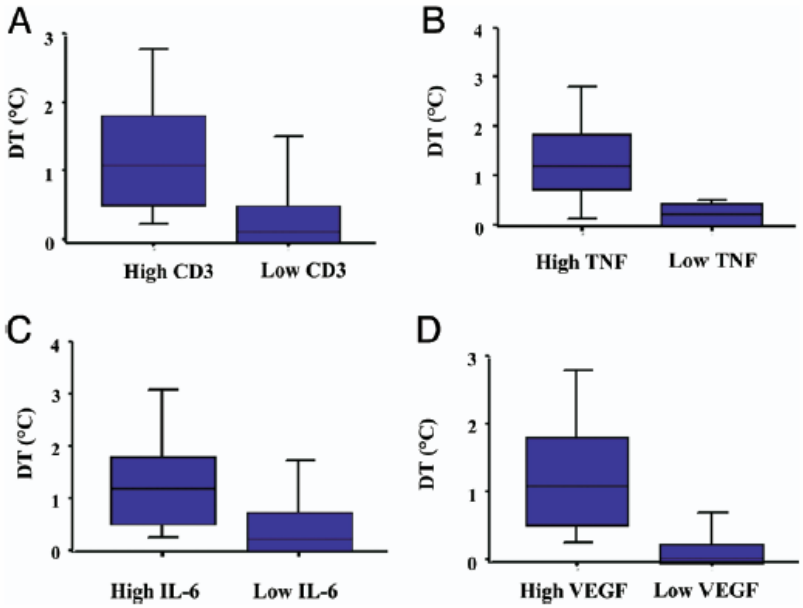
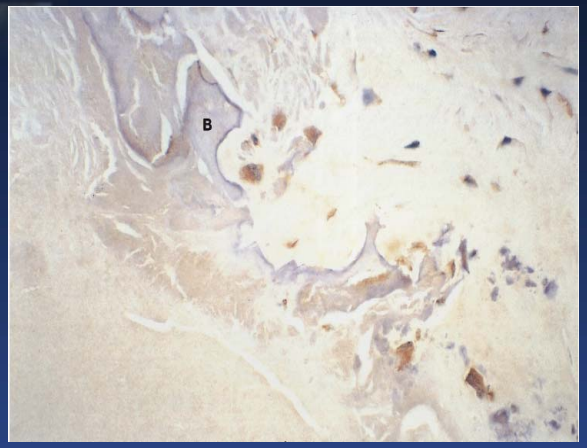
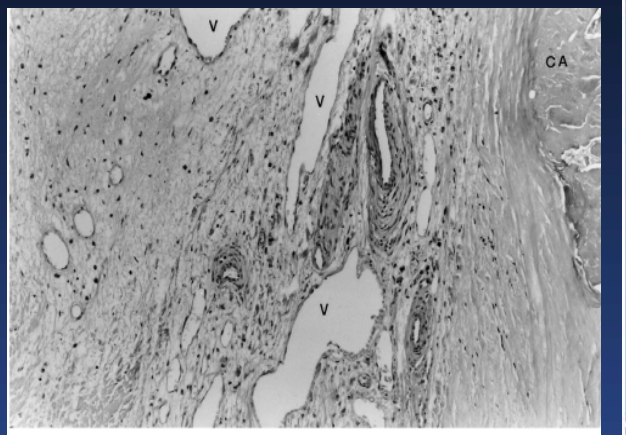


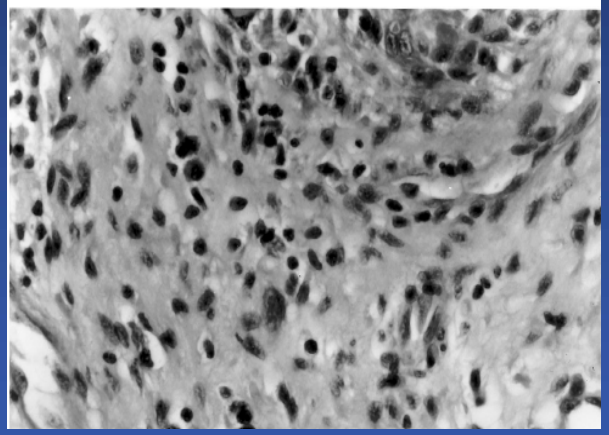
Figure 5 DT in Leaflets With Intense Versus Low Expression of Inflammatory Indexes

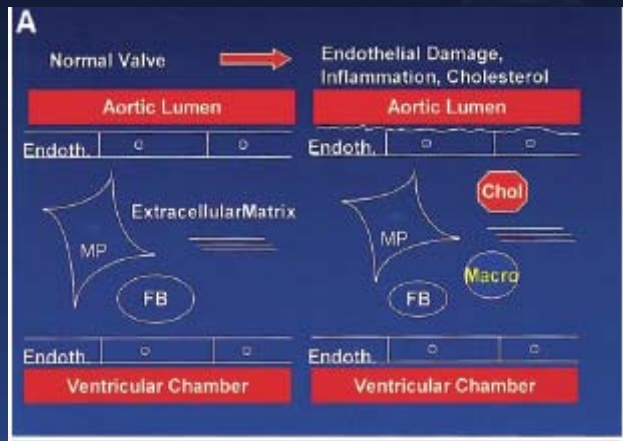
Mean temperature difference (DT) in leaflets with intense versus leaflets with low expression of CD3 **(A)**, TNF-α **(B)**, IL-6 **(C)**, and vascular endothelial growth factor (VEGF) **(D)**. The **bottom of the boxes** represents the first quartile; the **top of the boxes** represents the third quartile, and the **line in the box** represents the median value. Abbreviations as in Figures 2, 3, and 4.

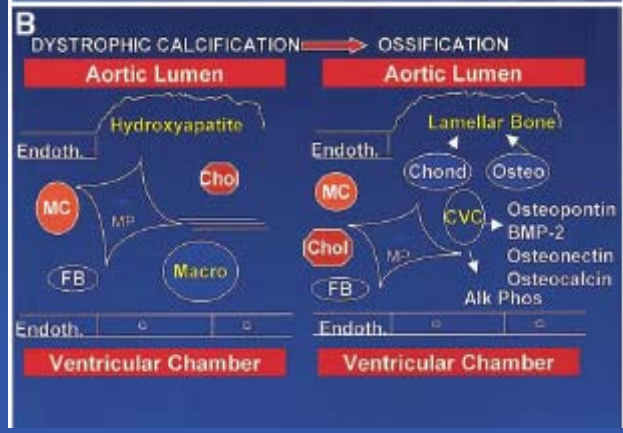
Prevalence and pathology of heterotopic ossification in 347 surgically excised heart valves (256 aortic, 91 mitral) in 324 consecutive patients









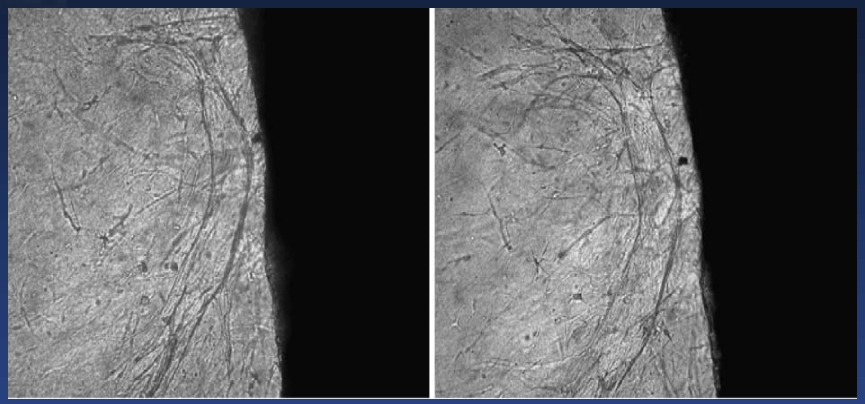


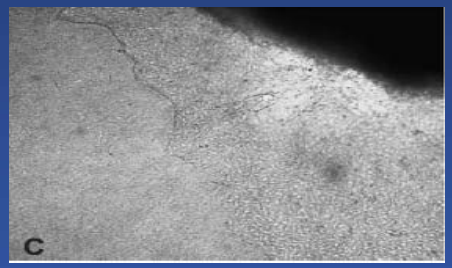
neoangiogenesis
ossification,
lymphocyte and
mast cell

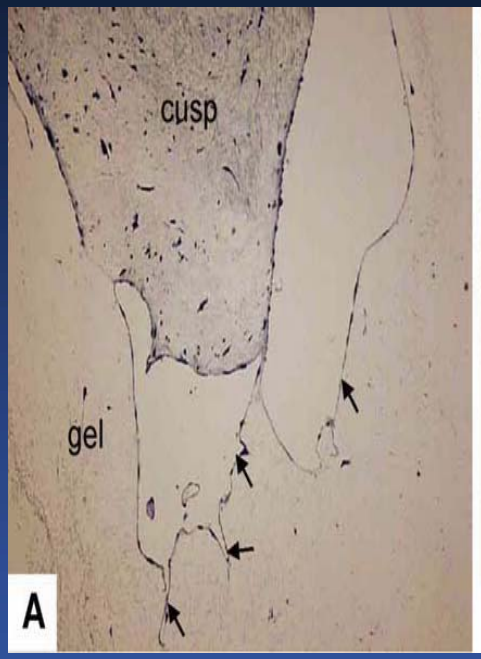
coexist and be
especially prominent in
atheromatous regions of
aortic and mitral valve

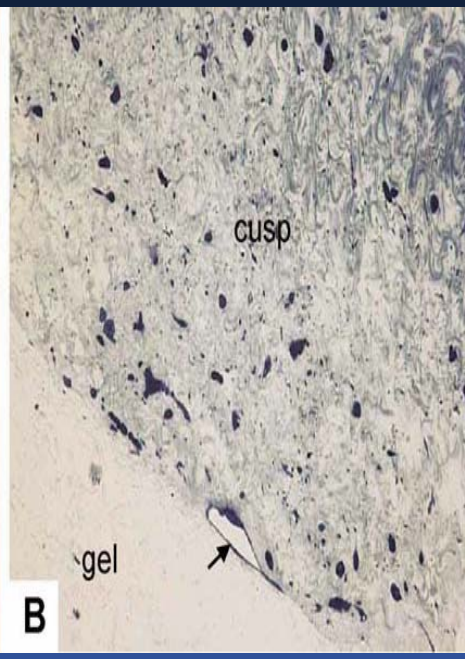
. Mohler et a.l Circulation. 2001 Mar 20;103(11):1522-8.

Higher vascular density in aortic valves with high-grade stenosis compared to the moderate-grade stenosis









Capillary-like sprouts from the at day 10 (A) and day 21 (B) observed with a phase contrast microscope.

ex vivo model

F. Chalajour et al. / Experimental Cell Research 298 (2004) 455–464

Degree of apolipoprotein B deposition in aortic regurgitant and mitral regurgitant valves as compared with aortic stenotic valves and control valves

	Degree of apolipoprotein B deposition							
	0	1+	2+	3+	4+	5+		
AR (n=9)	0	3	4	1	1	0	AR vs. AS	P<.001
							MR vs. AS	P<.001
MR (n=6)	0	2	4	0	0	0	AR vs. MR	P=.601
							AR vs. CV	P=.680
AS (n=29)	0	0	0	5	16	8	MR vs. CV	P=.301
							AS vs. CV	P<.001
CV (n=14)	0	3	8	1	2	0		

Degree of apolipoprotein A-I deposition in aortic regurgitant and mitral regurgitant valves as compared with aortic stenotic valves and control valves

	Degree of apolipoprotein A-I deposition							
	0	1+	2+	3+	4+	5+		
AR (n=9)	0	5	2	1	1	0	AR vs. AS	P<.001
							MR vs. AS	P<.001
MR (n=6)	1	3	2	0	0	0	AR vs. MR	P=.333
							AR vs. CV	P=.321
AS (n=29)	0	0	0	1	12	16	MR vs. CV	P=.049
							AS vs. CV	P<.001
CV (n=14)	1	2	7	3	1	0		

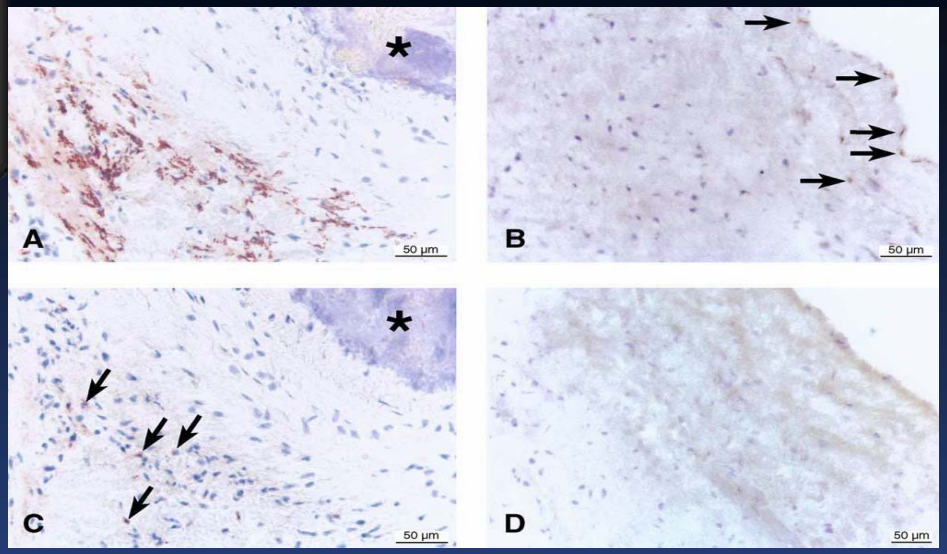
- AR and CNT have lower degree of inflammatory cell infiltrate and apolipoprotein deposition vs AVS

the valves were not subdivided regarding the degree of stenosis

W. Lars et al. / Cardiovascular Pathology 16 (2007) 171–178

• Early lesions of AVS were characterized by accumulation of lipid and infiltration of macrophages and T lymphocytes, whereas,
•late lesions were characterized by formation of calcific plaques, proliferation of fibrous connective tissue and little lipid accumulation

Sui SJ, Ren MY, Xu FY, Zhang Y. Cardiology. 2007;108(4):322-30.

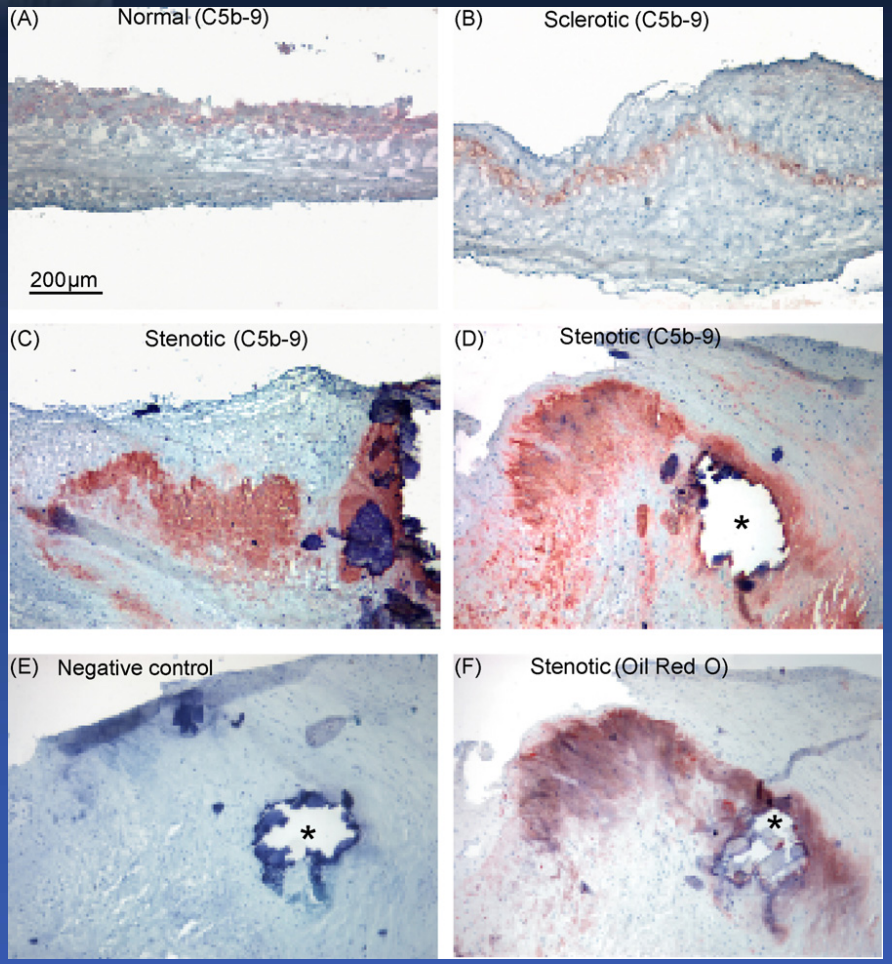


•enhanced expression of MMP-2 and MMP-9 in AVS, confirming the hypothesis of implication of chronic inflammation in AVS

Kaden JJ, Dempfle CE, Grobholz R, et al. . Cardiovasc Pathol 2005;14(2):80-7.
Edep ME, Shirani J, Wolf P, Brown DL. Cardiovasc Pathol 2000;9(5):281-6.

Both inflammation and neoangiogenesis are implicated in the pathogenesis of sclerotic aortic valve leaflets, resembling that of an active or unstable atherosclerotic plaque.

Complement system



- Activation of the complement cascade with ensuing inflammatory response contributes to AVS at its various stages of progression.
- Interestingly, C5b-9 was found already in early aortic valve lesions
- its deposition was augmented in advanced stenotic valves
- suggesting acceleration of the complement activation as the disease advances

S. Helske et al. / Atherosclerosis 196 (2008) 190–200

Infectious Agents

- Stenotic aortic valves have shown a higher density of C. pneumonia in areas with fibrosis and calcification in relation to preserved areas
- calcification is the dominant feature

Pierri H, et al.Int J Cardiol 2006;108(1):43-7

- calcified regions of aortic valve leaflets have features resembling those of arterial atherosclerotic plaques, such as inflammatory infiltrates and lipid content.

- However, calcification during the atherosclerotic process is distinct from the calcification process in a degenerating aortic valve.

Calcification

- Pathogenesis of AVS may additionally involve active bone formation

  Rajamannan NM. Circulation 2006;114(19):2007-9.

- Osteoblast phenotype is associated with AVS

  Rajamannan NM, Circulation 2003;107(17):2181-4.

- Stimulation of human aortic valve interstitial cells by a physiologically relevant bacterial product triggers proinflammatory and proosteogenic gene and protein expression.

  Babu AN, Ann Thorac Surg 2008;86(1):71-6.

- Interestingly, heterotopic ossification, associated with inflammation and neoangiogenesis, has been described, suggesting an unexpected process of tissue repair in endstage calcified heart valves

  Mohler ER, Circulation 2001;103(11):1522-8

Calcification and Lipid deposition

- close association between calcification and lipid deposition, both of which are invariably present in stenotic valves
- Moreover, stenotic aortic valves have a much larger amount of lipids than non-stenotic valves.
- accumulation of three apolipoproteins, in aortic valvular lesions, that have been previously implicated in the pathogenesis of atherosclerosis

O'Brien KD, Arterioscler Thromb Vasc Biol 1996;16(4):523-32

- aortic valves with stenosis contained markedly higher amounts of lipids than healthy valves

Olsson AG.. Curr Atheroscler Rep 2009;11(5):377-83.

- experimental model of acquired AVS in rabbits receiving high-cholesterol diet + supplements of vitamin D2

- animals not receiving vitamin D2 did not display any significant degree of AVS after 12 weeks of treatment

significant role of calcium in the development of AVS
although lipid accumulation is a common finding in both diseases, it seems that its role in the degree of calcification in aortic valve leaflets still needs to be determined,

Drolet MC,. J Heart Valve Dis 2008;17(4):381-7.

- Common histopathological evidence
- Predisposing factors of progression of aortic valve stenosis
- Aortic valve stenosis and cardiovascular outcome
- Clinical evidence of coronary artery disease in patients with aortic valve stenosis

- Clinical risk factors of AVS share considerable overlap with those of coronary artery disease
- older age,
- male gender,
- increased serum low-density lipoprotein (LDL) concentration,
- smoking,
- hypertension,
- diabetes mellitus

Yetkin E, Waltenberger J.Int J Cardiol 2009;135(1):4-13.
Hakuno D, Kimura N, Yoshioka M, Fukuda K. J Mol Med 2009;87(1):17-24.
Mazzone A, Venneri L, Berti S. J Cardiovasc Med (Hagerstown) 2007;8(12):983-9.
Olsson AG. Curr Atheroscler Rep 2009;11(5):377-83.
Adler Y, Vaturi M, Herz I, et al. Atherosclerosis 2002;161(1):193-7

- the factors affecting the progression of AVS have not been extensively investigated.

Factors affecting the progression of AVS

- Age and coexistence of CAD were associated with a more rapid increase in AVS gradient

Peter M.Chest 1993;103(6):1715-9.

A strong influence of LDL cholesterol level on the progression of aortic valve calcification

Pohle K, Circulation 2001;104(16):1927-32.

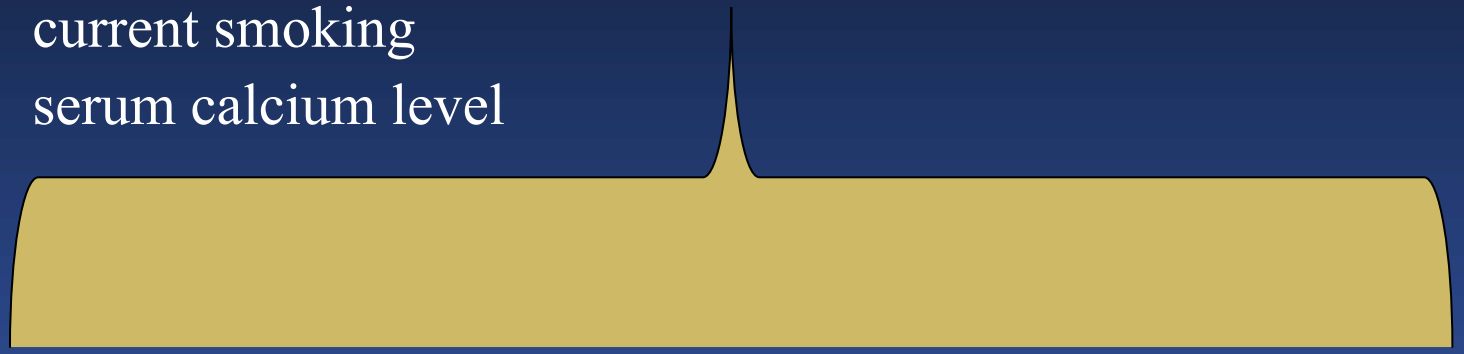
176 asymptomatic patients with mild to moderate AVS

- 5 years
- Patients showed rapid progression of valvular disease,
- 46% developing severe AVS
- Increased mortality
- Significant valve calcification, CAD and rapid progression of aortic jet velocity indicated poor outcome

Rosenhek R. Eur Heart J 2004;25(3):199-205.

170 patients who had paired echocardiograms

- initial AVA,
- current smoking
- serum calcium level



- independent predictors of amount of AVA reduction per year

- Patients with high cholesterol levels had X2 the rate of progression compared with those with lower cholesterol level
- although cholesterol was not an independent predictor in the multiple regression analysis

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Clinical Factors, But Not C-Reactive Protein, Predict Progression of Calcific Aortic-Valve Disease

The Cardiovascular Health Study

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Table 4 Multivariate-Adjusted ORs for Incident Aortic Stenosis in Subjects Who Have Normal Aortic Valves or Aortic Sclerosis at Baseline

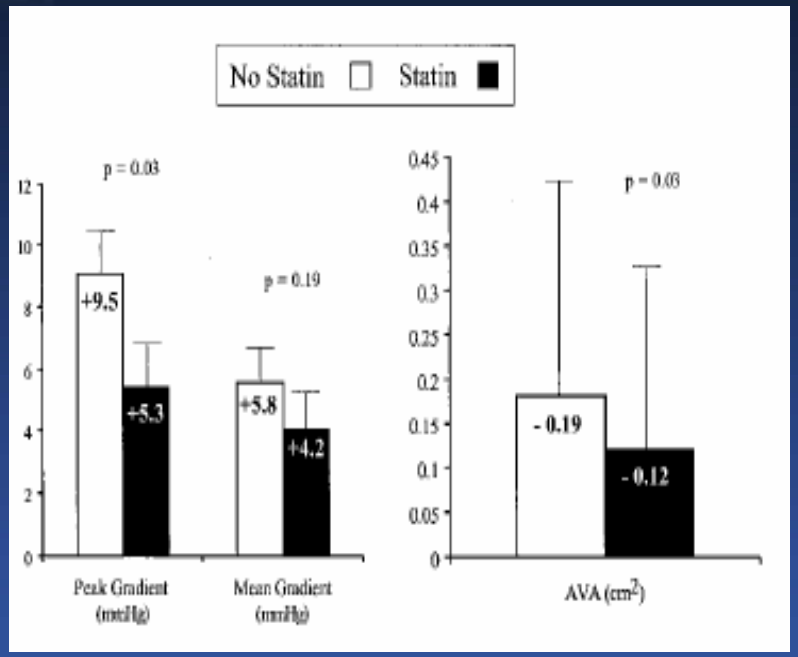
Variable	p Value	OR	95% CI
CRP (log)	0.092	0.85	0.70–1.03
Age	<0.001	1.13	1.09–1.16
Male gender	<0.001	3.05	1.76–5.27
African-American ethnicity	0.035	0.49	0.25–0.95
Diabetes	0.110	1.62	0.90–2.94
Height (cm)	0.013	0.96	0.94–0.99
Renal insufficiency	0.108	1.54	0.91–2.60
LDL cholesterol	0.059	1.01	1.00–1.01

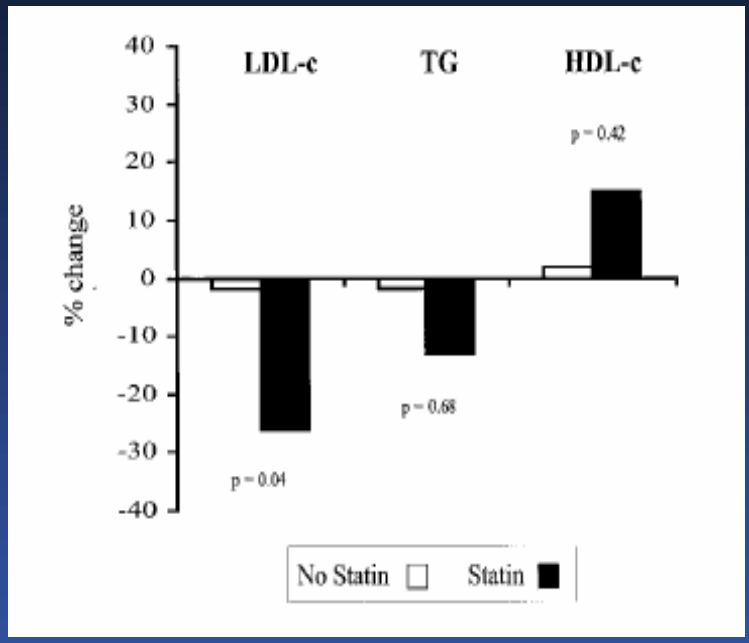
Factors included in the model were current smoking, hypertension, and prevalent coronary heart disease.

- 9% rate of progression from aortic sclerosis to aortic stenosis
- 5-year follow-up period

Novaro GM, J Am Coll Cardiol 2007;50(20):1992-8.

Statins





- retrospective study
- patients treated with statins had reduced AVS progression
- only a modest relationship between the change in LDL cholesterol level and the aortic valve area

Novaro GM, Circulation 2001;104(18):2205-9.

- -echocardiography- none of the atherosclerosis risk factors were associated with AVS progression

Roger VL, Am Heart J 1990;119(2 Pt 1):331-8.

- mitral annular calcification was independently associated with progression to AVS. 15.9% patients developed AVS and almost all patients had aortic sclerosis.

Cosmi et al. Arch Intern Med. 2002 Nov 11;162(20):2345-7

- one-third of the patients with aortic sclerosis developed some degree of AVS in a follow-up of four years confirming the hypothesis that aortic sclerosis may be an important precursor of AVS

Faggiano P, Am J Cardiol 2003;91(1):99-101

confirming the hypothesis that aortic sclerosis may be an important precursor of AVS

- Common histopathological evidence
- Predisposing factors of progression of aortic valve stenosis
- Aortic valve stenosis and cardiovascular outcome
- Clinical evidence of coronary artery disease in patients with aortic valve stenosis

- Aortic valve stenosis has been demonstrated to be an independent predictor of cardiovascular events in recent studies
- the mortality rate is increased in severe symptomatic AVS if untreated
- mild to moderate AVS is associated with increased risk of adverse cardiovascular events.
- The mechanisms involved in this clinical outcome in mild to moderate AVS are not completely defined.
- This risk is attributed to rapid progression of AVS, but also to the presence and progression of subclinical CAD.

Author (year)	Study Population	End-points	Mean follow-up	P value
Aronow(1998)[13]	1797 patients, 165 with mild, 96 with moderate, 301 with severe and 1496 without AVS.	Myocardial infarction, sudden cardiac death.	48±30 months	The incidence of coronary events increased with the degree of stenosis (no AVS:41%, mild:62% moderate:80%, severe:93%, p<0.01).
Aronow(1999)[45]	1980 patients, 981 with mild and 999 without AVS.	Myocardial infarction, sudden cardiac death.	46±28 months	Patients with mild AVS had a 1.8 times higher chance of developing a coronary event than those without AVS.
Otto(1999)[48]	5621 patients, 3919 with normal aortic valves, 1610 with sclerotic valves and 92 with AVS.	Death, cardiovascular events	5 years	Consistent stepwise increase in deaths from any cause and cardiovascular causes with increasing aortic valve abnormality (p<0.001).
Chandra(2004)[47]	425, 203 with mild and moderate AVS. Patients with (peak velocity<2 m/s excluded).	Death, myocardial infarction.	1 year	Higher incidence of cardiovascular events (16.8% vs. 7.1%, p <0.002) and worse event-free survival (normal valves =93%, mild AVS=85%, moderate-severe AVS=77%, p<0.002) in patients with AVS.
Olsen(2005)[16]	960 patients, 388 with aortic valve sclerosis, 557 without AVS.	Cardiovascular death, myocardial infarction, stroke.	60 ±4 months	Composite end points occurred in 15.4% of patients with aortic valve sclerosis compared with 8.3% of patients without aortic valve sclerosis (p<0.001).
Taylor(2005)[49]	2279 patients, 175 with mild AVS, 2104 without AVS.	Myocardial infarction, cardiovascular death, revascularization.	3 years	CAD events incidence rates were >4 times higher for AVS.
Barasch(2006)[46]	3929 patients, 2075 with AVS.	Cardiovascular death, mortality, cardiovascular events.	6.6 years	AVS was associated with incident congestive heart failure and death (HR 1.50, 95%, p<0.05).
Völzke(2009)[50]	2081 patients, 528 with isolated AVS, 35 with isolated mitral annular calcification and 89 with both diseases.	Mortality, cardiovascular death.	8.6 years	Mortality rates were higher for AVS (incidence rate ratio 3.49, p< 0.001).

TABLE 2. EVENT RATES IN THE THREE GROUPS.

EVENT	NORMAL AORTIC VALVES (N=3919)	AORTIC SCLEROSIS (N=1610)	AORTIC STENOSIS (N=92)	P VALUE FOR TREND
	number (percent)			
Death from any cause	583 (14.9)	353 (21.9)*	38 (41.3)*	<0.001
Death from cardiovascular 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

*P<0.001 for the comparison with the group with normal aortic valves.

†The rates were calculated for subjects at risk for new events.

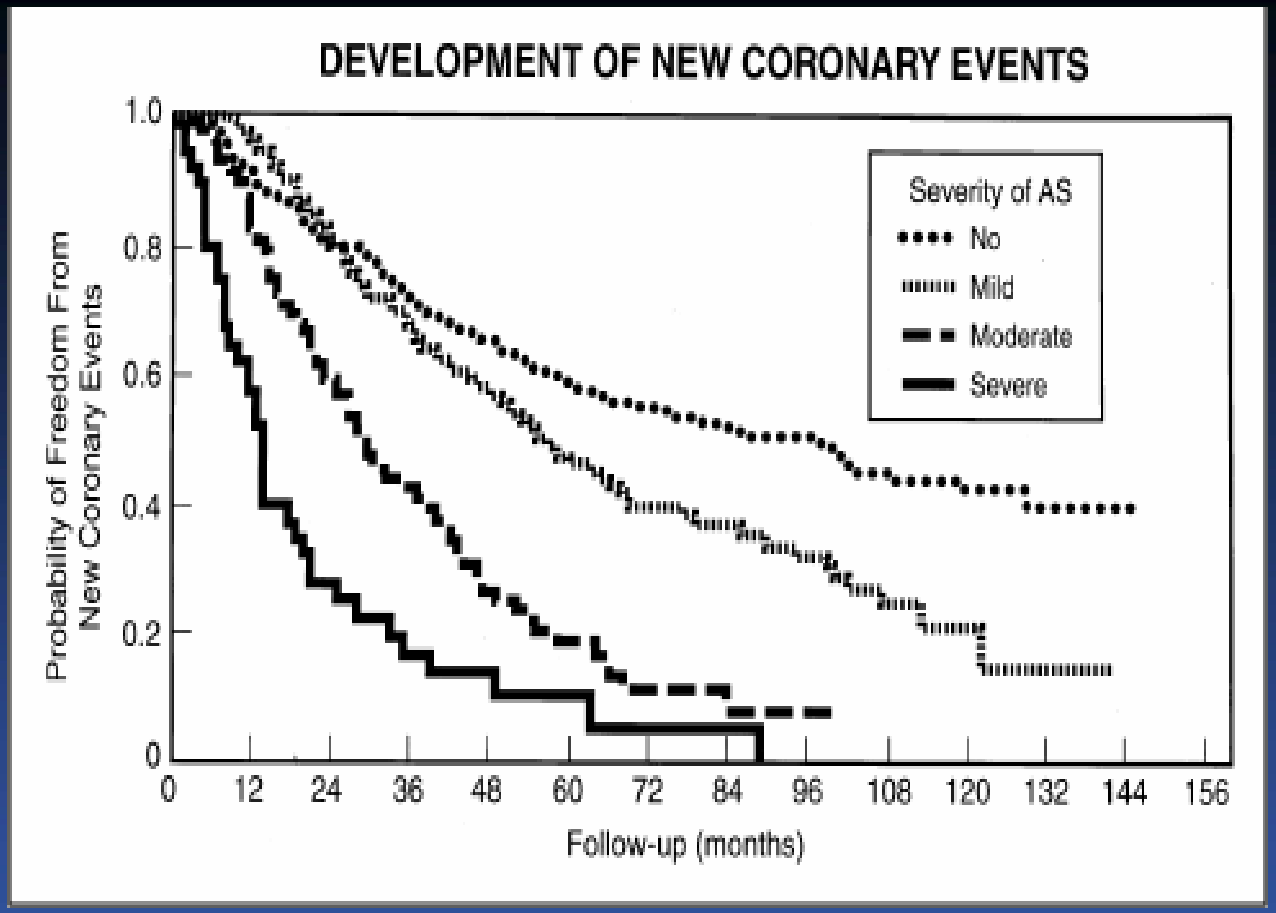
‡P<0.01 for the comparison with the group with normal aortic valves.

§P=0.02 for the comparison with the group with normal aortic valves.

- the presence of mild AVS was associated with a 50% increase in cardiovascular death and myocardial infarction

- stepwise increase in deaths with increasing aortic valve abnormality

Otto CM, N Engl J Med 1999;341(3):142-7.



•the incidence of new coronary events increased with the severity of AVS

•mild AVS had 1.8 times higher risk of developing a new coronary event than those without AVS

Aronow WS, Am J Cardiol 1998;81(5):647-9.

TABLE 3 Hazard Ratio (HR) Estimates for Age-adjusted Simple Models and Multivariable Model for Aortic Valve Sclerosis as a Predictor of Incident Coronary Heart Disease*

Variables	Age-adjusted Simple Models†	Multivariable Model
Aortic valve sclerosis	4.26 (2.15–8.04)	3.82 (1.83–7.97)
Women	0.59 (0.36–0.99)	0.80 (0.41–1.54)
Diabetes mellitus (%)	1.92 (1.13–3.25)	1.80 (0.96–3.38)
Systolic blood pressure (mm Hg)	1.02 (1.01–1.03)	1.02 (1.00–1.03)
Hypertension medication status	2.00 (1.13–3.53)	1.68 (0.85–3.32)
Current smoker status	3.30 (1.78–6.15)	2.65 (1.41–4.97)
High-density lipoprotein (mg/dl)	0.97 (0.96–0.99)	0.99 (0.97–1.01)
Low-density lipoprotein (10 mg/dl)	1.1 (0.99–1.02)	1.1 (0.99–1.01)
Intimal-medial thickness (mm)	4.83 (1.03–22.62)	0.67 (0.01–5.08)
Fibrinogen (10 mg/dl)	1.1 (1.0–1.2)	1.1 (1.0–11.2)
von Willebrand Factor (10%)	1.01 (1.00–1.02)	1.03 (1.00–1.05)

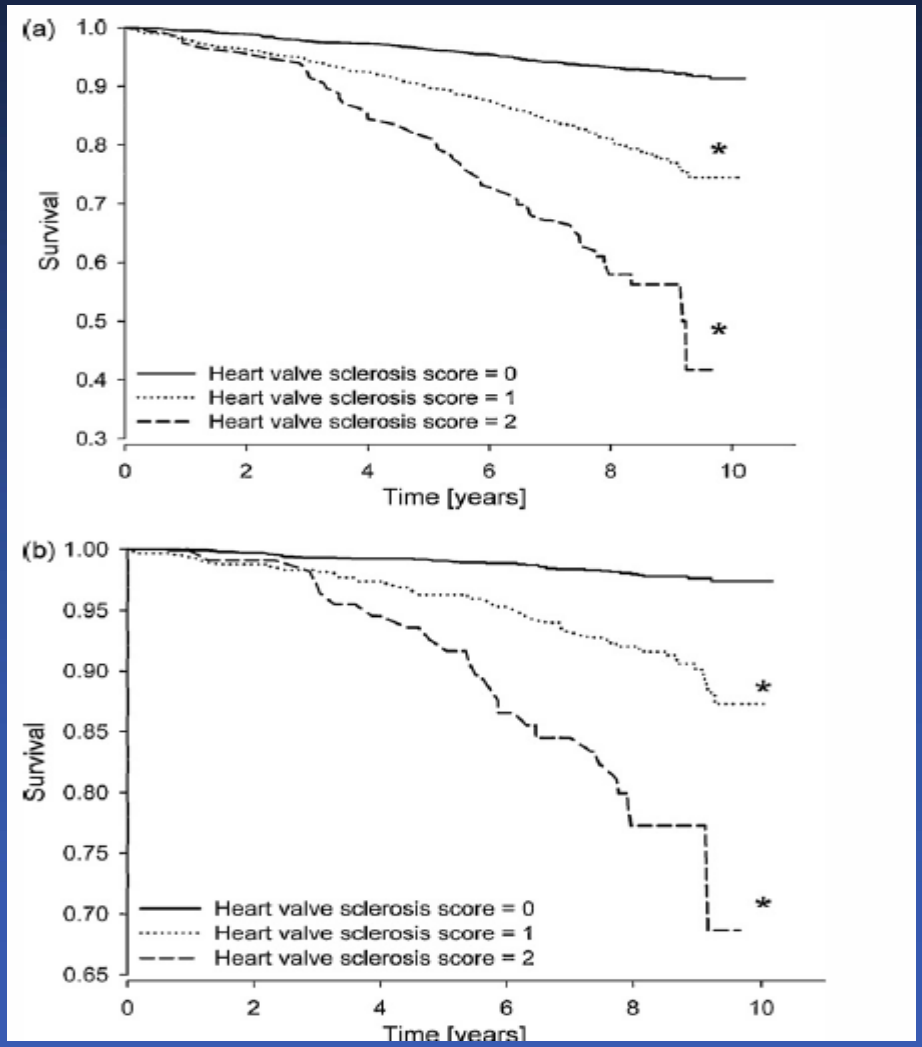
*Hospitalized myocardial infarction or fatal CHD.

†Covariates as major risk factors of CHD are put into the model one at a time, along with the age variable. If a covariate was significant in the simple model, it was put into the multivariable model. Also, variables that have relevant clinical meanings from previous studies, although not significant in the present analyses, are still included in the model.

Values are expressed as hazard ratio (95% confidence interval).

Taylor HA, Jr., Clark BL, Garrison RJ, et al. Am J Cardiol 2005;95(3):401-4.

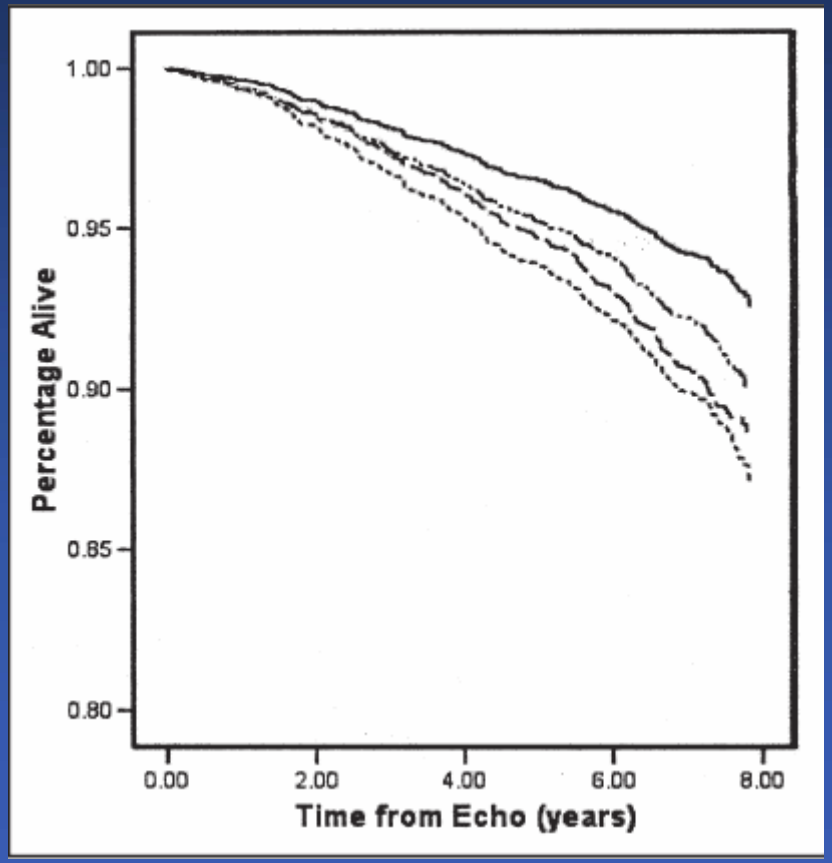
- association of mild to severe with all-cause and cardiovascular Mortality
- 8.6 years follow-up



H. Völzke et al. / Atherosclerosis xxx (2009) xxx–xxx

Incident cardiovascular disease (CVD) for 3,782 participants that was adjusted for age, gender, race, and prevalent CVD

Calcification Category*	MI (n = 275)	Stroke (n = 305)	Angina (n = 419)	CHF (n = 578)
MAC	1.27 (0.93–1.75)	1.13 (0.83–1.53)	1.46 (1.13–1.89)†	1.71 (1.35–2.18)†
AAC	1.14 (0.83–1.56)	1.27 (0.94–1.71)	1.28 (0.99–1.66)	1.62 (1.28–2.06)†
AVS	1.13 (0.83–1.54)	1.09 (0.81–1.46)	1.17 (0.91–1.51)	1.50 (1.19–1.89)†
Any 1 of MAC, AAC, or AVS	1.01 (0.72–1.42)	1.11 (0.80–1.52)	1.19 (0.91–1.56)	1.29 (1.00–1.67)†
Any 2 of MAC, AAC, or AVS	1.09 (0.77–1.54)	1.13 (0.82–1.57)	1.21 (0.92–1.60)	1.47 (1.14–1.90)†
MAC + AAC + AVS	1.39 (0.96–2.01)	1.22 (0.85–1.74)	1.43 (1.05–1.95)†	1.93 (1.48–2.52)†



3929 patients with a follow-up of 6.6 years

AVS was associated with incident congestive heart failure and death

Barasch E, Gottdiener JS, Marino Larsen EK, Chaves PH, Newman AB.). Am J Cardiol 2006;97(9):1281-6.

relationship among AVS- presence of CAD, markers of inflammation, and cardiovascular outcomes

- Patients with AVS had a higher incidence of cardiovascular events and worse event-free survival

- by multivariable analysis AVS
- presence of CAD,
- presentation with acute MI at the time of admission,
- increasing tertiles of C-reactive protein,
- congestive heart failure,
- and age
- were independent predictors of
- adverse cardiovascular outcomes at 1 year follow-up

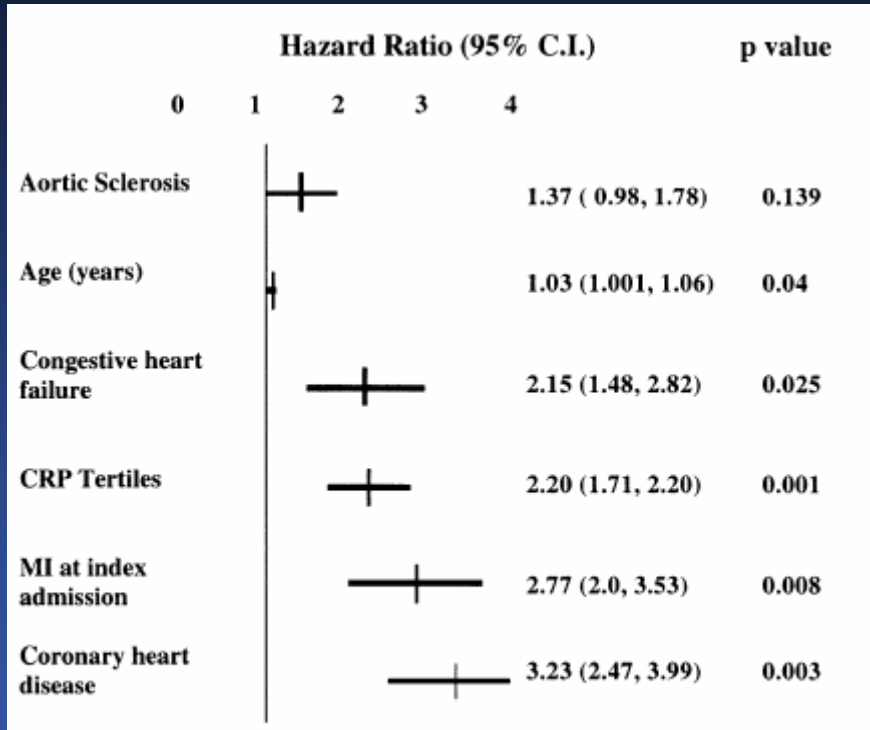


Figure 5. Cox multivariate analysis: one-year outcome of cardiac death and nonfatal myocardial infarction (MI). C.I. = confidence interval; CRP = C-reactive protein. Tertiles <0.32; 0.32 to 1.18; >1.18 (mg/dl).

AVS is not the mediator of adverse outcomes but rather a marker of the presence of CAD

Chandra HR,. J Am Coll Cardiol 2004;43(2):169-75

- The significance of subclinical CAD diagnosis seems to be crucial in this group of patients.

- Although the progression of mild to moderate AVS can be easily evaluated by Doppler examination, the identification of patients with increased risk to present with an adverse cardiovascular event prior to the progression of significant AVS is usually underestimated, as a diagnostic algorithm has not been established.

- Common histopathological evidence
- Predisposing factors of progression of aortic valve stenosis
- Aortic valve stenosis and cardiovascular outcome
- Clinical evidence of coronary artery disease in patients with aortic valve stenosis

93 consecutive patients with chest pain undergoing coronary angiography

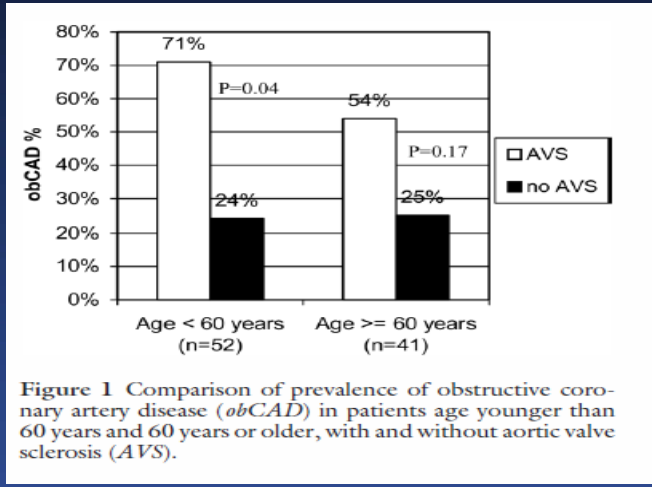


Figure 1 Comparison of prevalence of obstructive coronary artery disease (*obCAD*) in patients age younger than 60 years and 60 years or older, with and without aortic valve sclerosis (*AVS*).

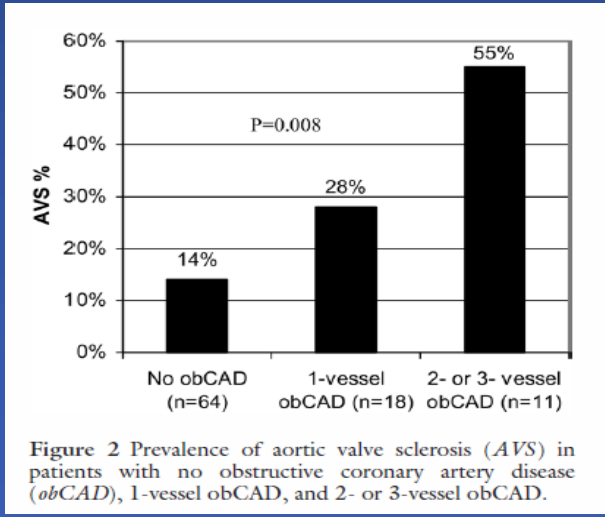


Figure 2 Prevalence of aortic valve sclerosis (*AVS*) in patients with no obstructive coronary artery disease (*obCAD*), 1-vessel obCAD, and 2- or 3-vessel obCAD.

Mild AVS had 38% sensitivity and 86% specificity for the diagnosis of obstructive CAD.

Mild AVS predicted obstructive CAD in patients aged<60 years, it did not reach statistical significance in patients aged>60 years

Patients with a two or three vessel disease had a higher rate of AVS than those with a single-vessel disease or no significant stenosis in the coronary tree

Conte L. J Am Soc Echocardiogr 2007;20(6):703-8.

- Retrospective study
- patients with AVS had a higher positive rate of coronary angiography and multivessel CAD than patients without AVS
- The sensitivity, specificity, positive predictive value and negative predictive value of AVS in diagnosing CAD were 63.8, 71.3, 61.7 and 73.1%

Sui. Cardiology 2007;108(4):322-30

Prevalence and significance of AVS in 357 patients with suspected CAD

- AVS is an independent echocardiographic predictor of significant CAD
- predictive value of AVS for the presence of CAD was more prominent in females and in subjects aged<65 years.

Hsu SY, Int J Clin Pract 2005;59(1):72-7.

Gensini score system

- Association between AVS and the extent of coronary atherosclerosis
- Patients with AVS had higher rate of three vessel disease and higher Gensini score to patients without

Soydinc S Cardiology 2006;106(4):277-82.

- Valvular atherosclerotic changes are strongly analogous with coronary
- atherosclerosis and generalized atherosclerotic processes
- Gensini score was significantly higher in patients with aortic sclerosis

Table 4. Gensini score between groups

Patient characteristics	Valvular atherosclerotic changes (Group 1)	Without valvular atherosclerotic changes (Group 2)	*p* value
Gensini score	26.21 ± 5.31* (SE)	11.16 ± 2.36* (SE)	0.011

*Data are presented as mean ± standard error (SE).

Anvari MS, Arch Med Res 2009;40(2):124-7.

- aortic valve calcification without obstruction detected by echocardiography is a marker of significant CAD in patients undergoing coronary angiography

- the group with mild AVS had a higher prevalence of significant CAD compared with the control group, suggesting that AVS can serve as a window to atherosclerosis of the coronary arteries

Prevalence of coronary artery disease in patients with and without AVC

CAD	AVC group ($n = 388$)	Control group ($n = 320$)	P-value
Significant CAD	351 (90%)	271 (85%)	0.019
Significant LAD	287 (74%)	214 (67%)	0.039
1-Vessel CAD	85 (22%)	76 (24%)	NS
2-Vessel CAD	118 (30%)	90 (28%)	NS
3-Vessel CAD	148 (38%)	105 (33%)	0.14
Left main CAD	49 (13%)	29 (9%)	0.13

AVC, aortic valve calcification; CAD, coronary artery disease; NS, not significant; LAD, left anterior descending.

Adler Y. Atherosclerosis 2002;161(1):193-7

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Cardiac calcification by transthoracic echocardiography in patients with known or suspected coronary artery disease

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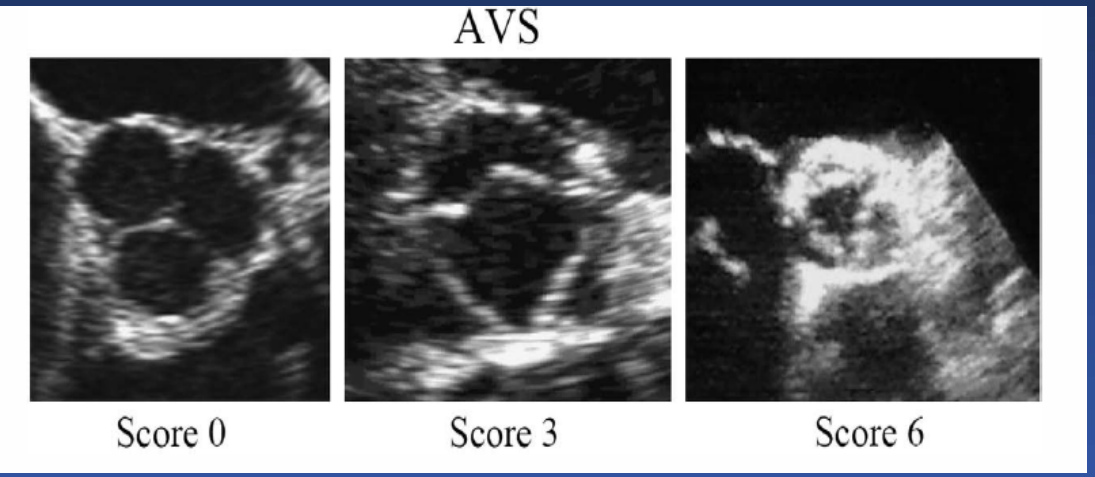

Predictors of CAD

	Univariate			Multivariate		
	OR	95%CI	*p*	OR	95%CI	*p*
Hypercholesterolemia	3.2	1.499–6.831	<0.05	3.74	1.667–8.529	<0.002
Familiarity	0.81	0.416–1.587				
Hypertension	1.46	0.747–2.878				
Smoke history	1.09	0.567–2.101				
Diabetes	3.343	1.379–8.103	<0.05	2.84	1.101–7.717	<0.036
Age	1.01	0.979–1.047				
Gender	0.3	0.152–0.624	<0.05			
CSI	1.26	1.080–1.486	<0.05	1.2	1.010–1.431	<0.038
LVMI	1.1	0.552–2.223				
LA diameter	0.881	0.456–1.705				

- no significant association between the total heart calcification score index, assessed by echocardiography, and angiographically detected CAD

Corciu. Int J Cardiol 2009; in press

Conclusions

- Echocardiographic detection of aortic valve calcification may provide a new surrogate marker of the extent of coronary atherosclerosis

- The presence of mild AVS, may be an indication of underlying significant subclinical CAD------further evaluation and aggressive treatment

- both diseases share common risk factors

- Whether modification of these risk factors reduces equally the incidence and rate of progression of AVS and atherosclerosis is still controversial.