From AV Sclerosis to AV Stenosis

: Is It Possible to Delay the Progression?

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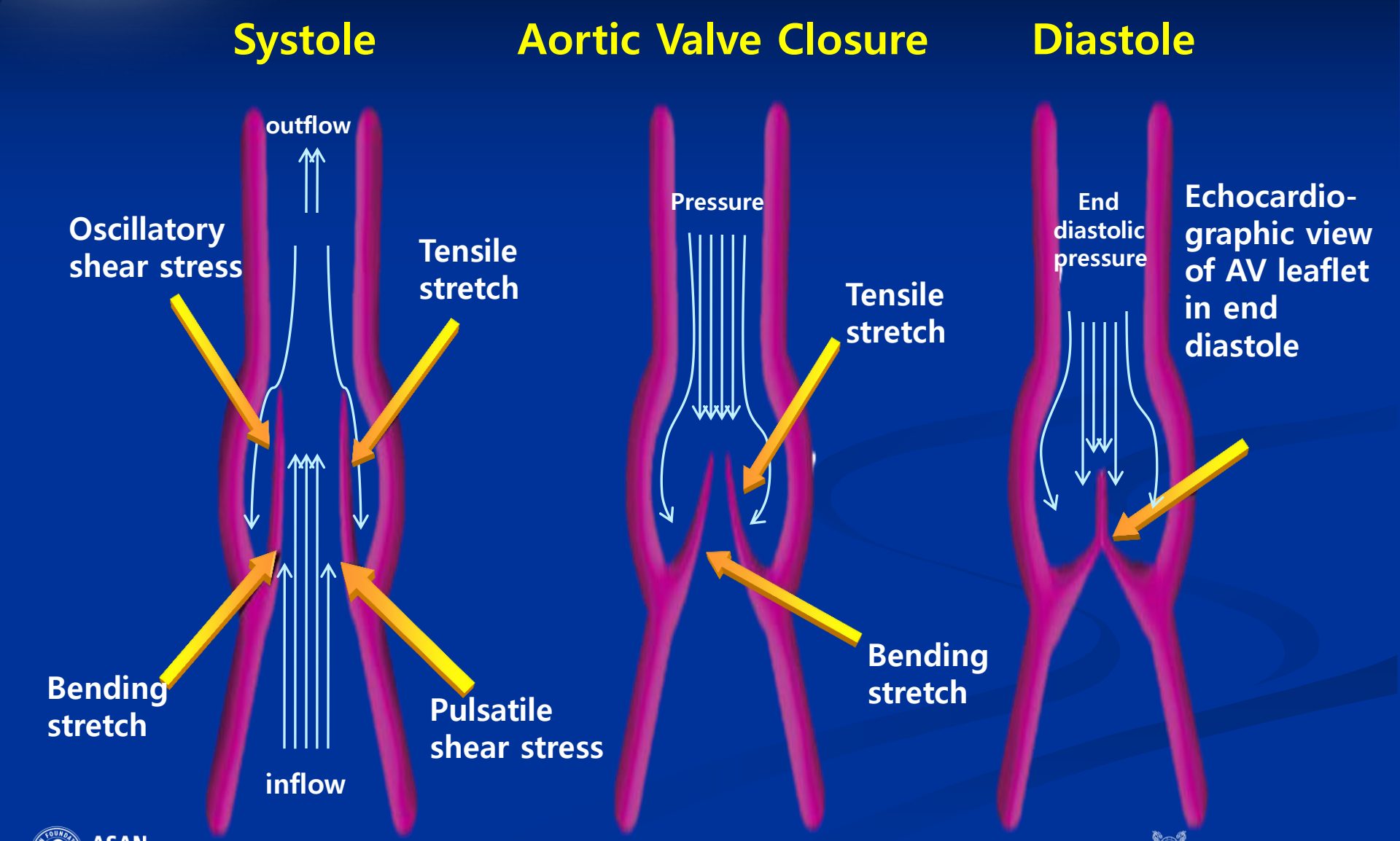
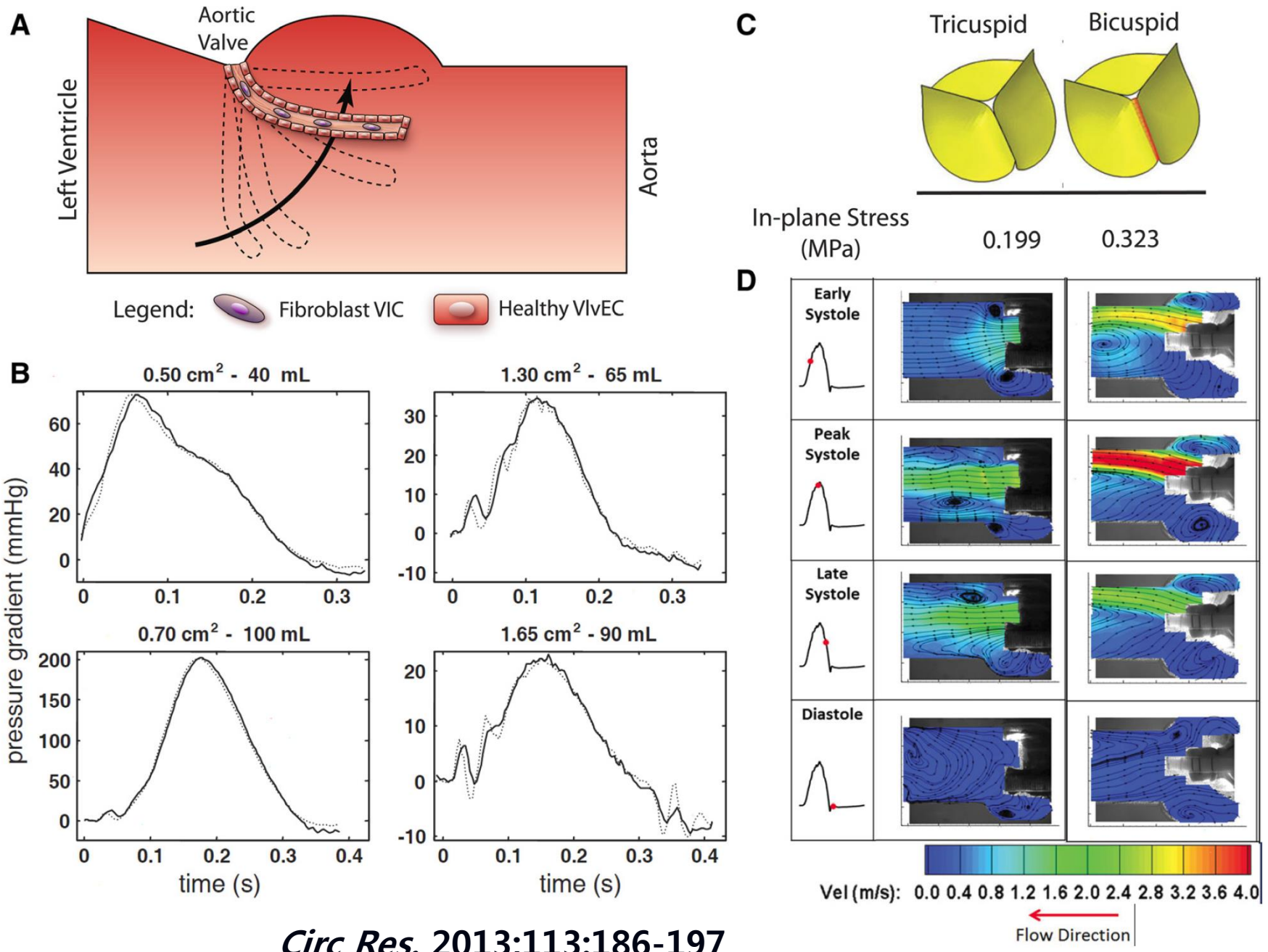
Valve sclerosis

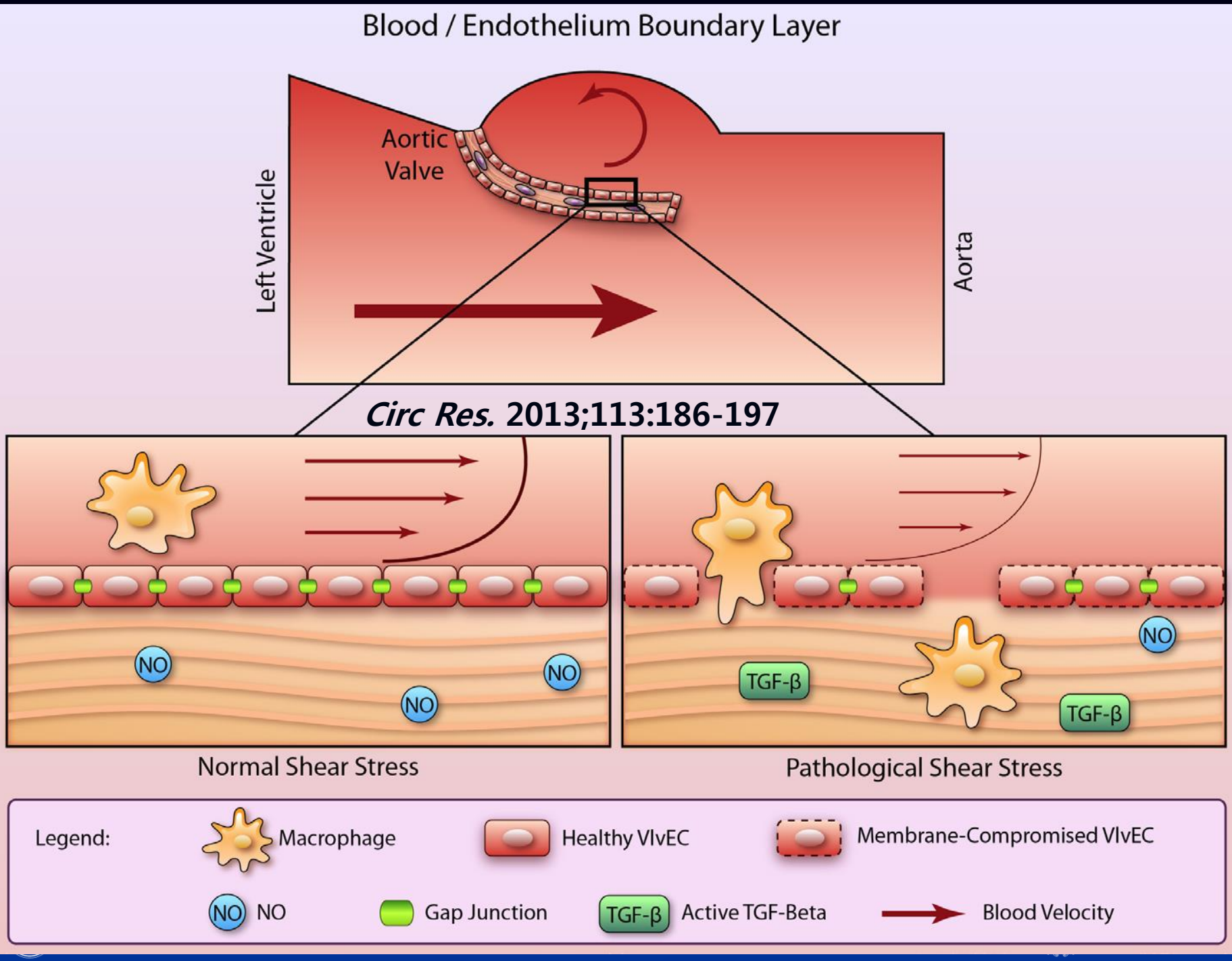
- **Aortic valve sclerosis (AVS) & Mitral annlus calcification (MAC)**
  - AVS related to thickening of the aortic cusps without obstruction to left ventricular outflow
  - MAC is a chronic degenerative non-inflammatory process characterized by calcification of the surrounding fibrous support of the mitral valve
  - Clinical precursors of atherosclerosis are also risk factors for MAC and AV sclerosis
  - 2 conditions often exist concurrently
- **Right side valve sclerosis ???**

Hemodynamic stress across AV



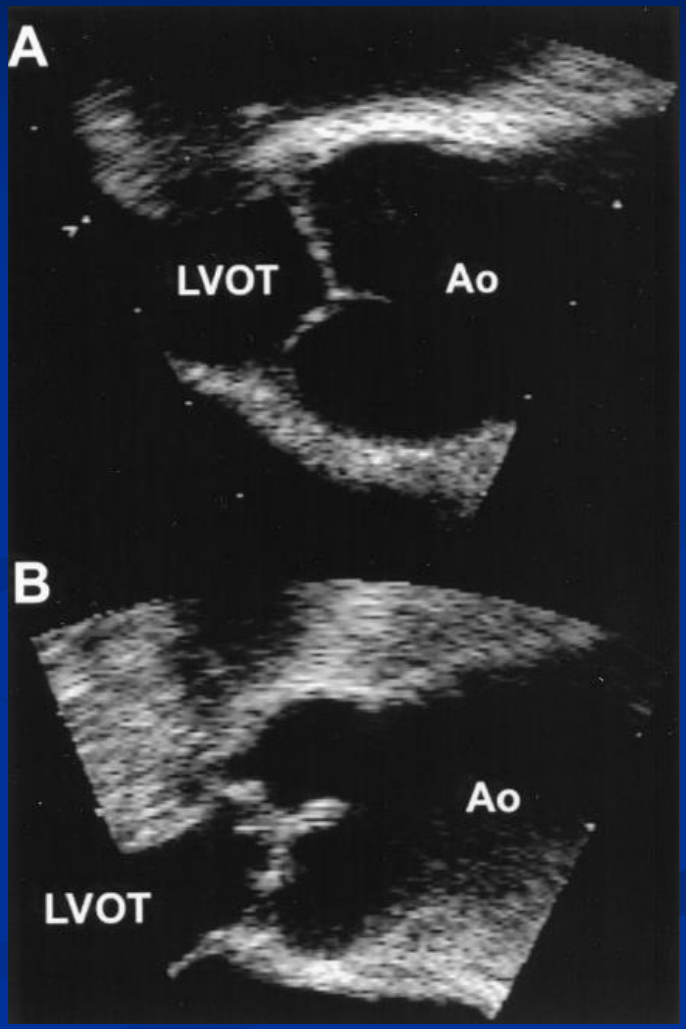


Circ Res. 2013;113:186-197

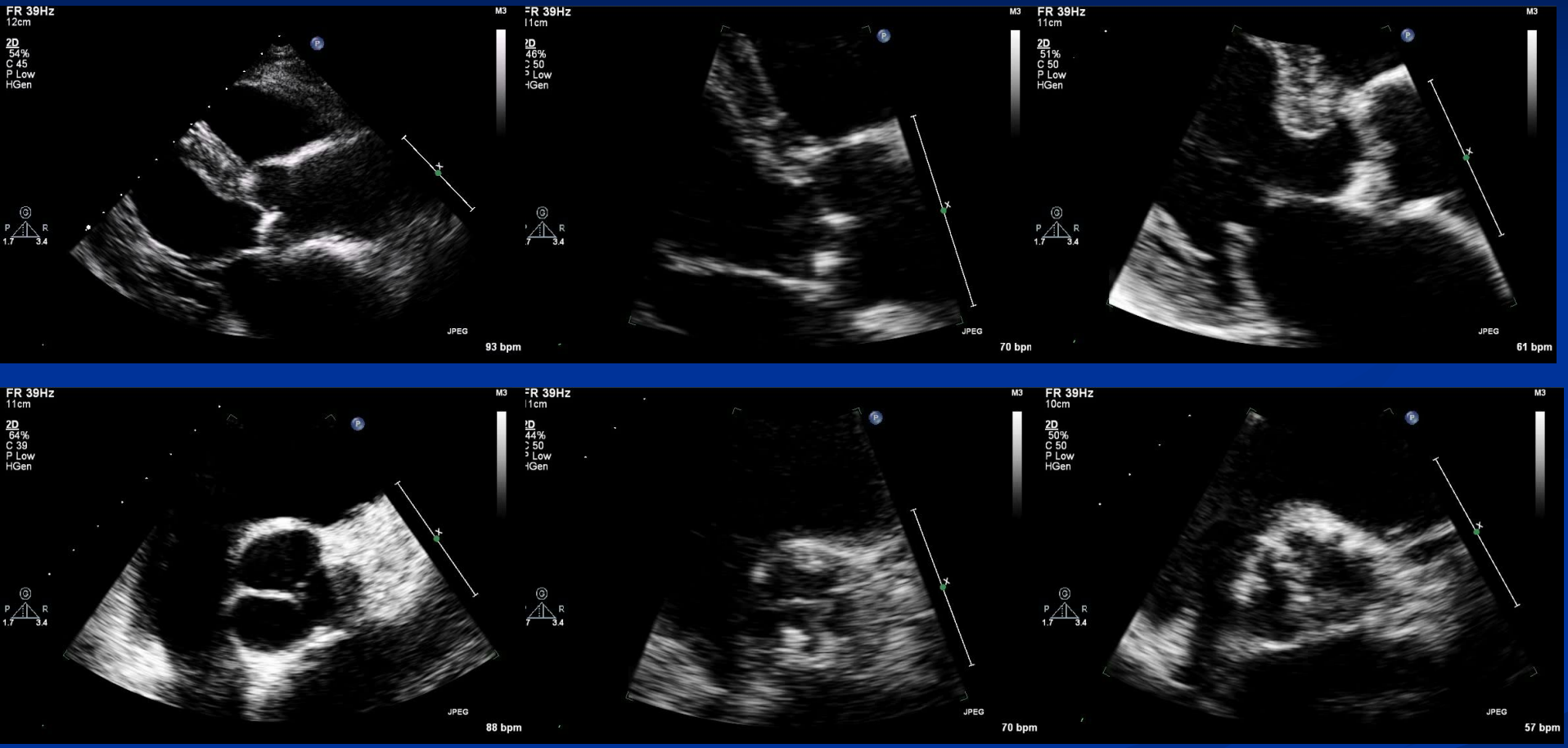

Blood / Endothelium Boundary Layer
Aortic Valve
Left Ventricle
Aorta
Circ Res. 2013;113:186-197
NO
NO
NO
TGF-β
TGF-β
NO
Normal Shear Stress
Pathological Shear Stress
Legend:
Macrophage
Healthy VIvEC
Membrane-Compromised VIvEC
NO
NO
Gap Junction
TGF-β
Active TGF-Beta
Blood Velocity

AV sclerosis

- Thickening of the aortic cusps without obstruction
  : AV V_{max} ≤2.5m/s
- 25%-30% :65 years of age
- Up to 40% : 75 years of age



AV sclerosis



Mild **Moderate** **Severe**

AV sclerosis

EVENT	Normal (N=3919)	Aortic Sclerosis (N=1610)	Aortic stenosis (N=92)	P VALUE
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.

Otto et al .NEJM 1999

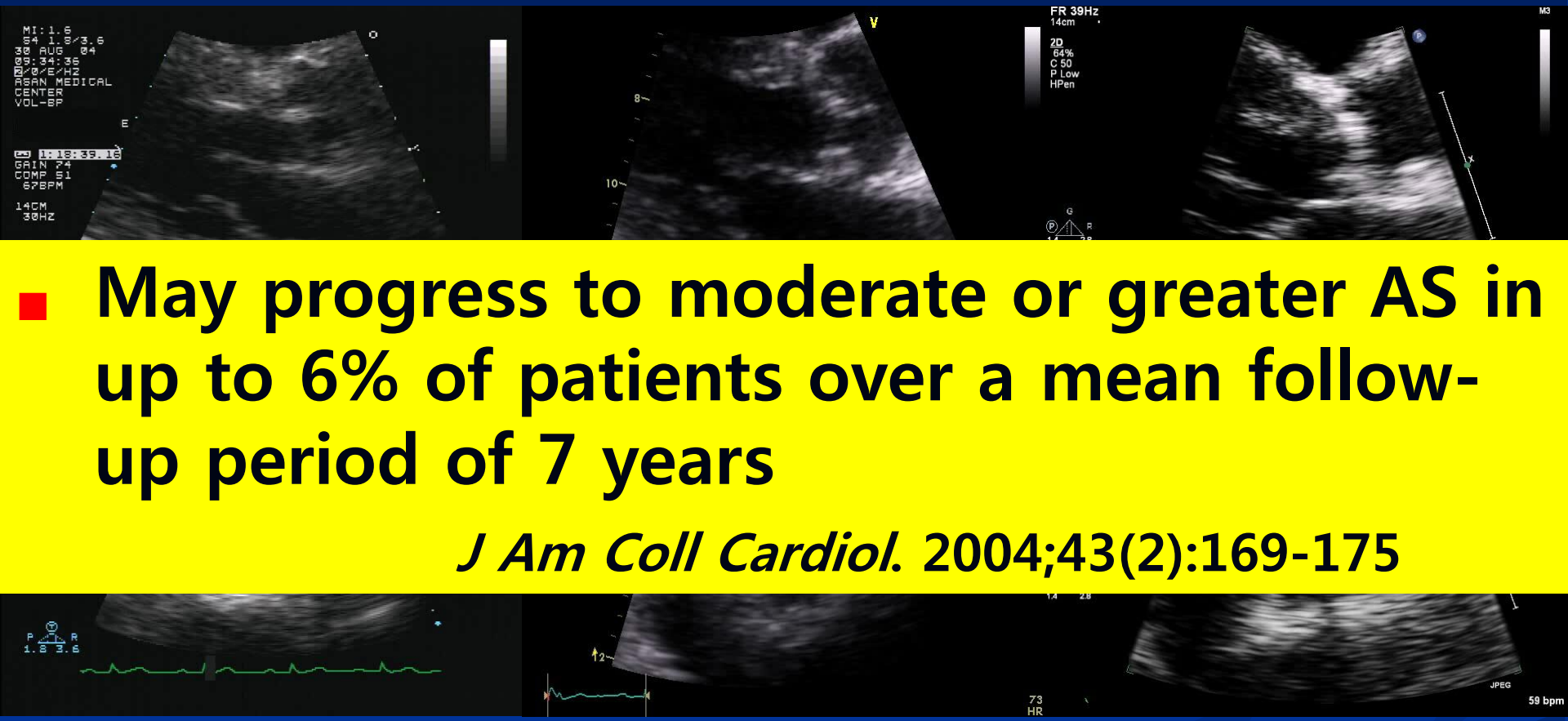
AV sclerosis

	VARIABLE	TOTAL NO. OF SUBJECTS	RATE/1000 PERSON-YR	RELATIVE RISK (95% CI)
CAD (-)	Death from any cause			1.42 (1.19.1.70)
	Normal aortic valves	2958	19	
	Aortic sclerosis	1115	37	
	Death from cardiovascular causes			1.66 (1.23.2.23)
	Normal aortic valves	2958	6	
	Aortic sclerosis	1115	14	
CAD(+)	Death from any cause			1.16 (0.94-1.43)
	Normal aortic valves	961	45	
	Aortic sclerosis	495	61	
	Death from cardiovascular causes			1.25 (0.94.1.65)
	Normal aortic valves	961	25	
	Aortic sclerosis	495	35	

Otto et al .NEJM 1999

AV sclerosis
Progression

65 YO Male



- **May progress to moderate or greater AS in up to 6% of patients over a mean follow-up period of 7 years**

  J Am Coll Cardiol. **2004;43(2):169-175**

2004
AV V max = 1.9 m/s

2008
AV V max = 2.3 m/s

2011
AV V max = 3.4 m/s

Aortic Valve sclerosis

Sclerosis

Stenosis

Lesion formation

Progressive calcification

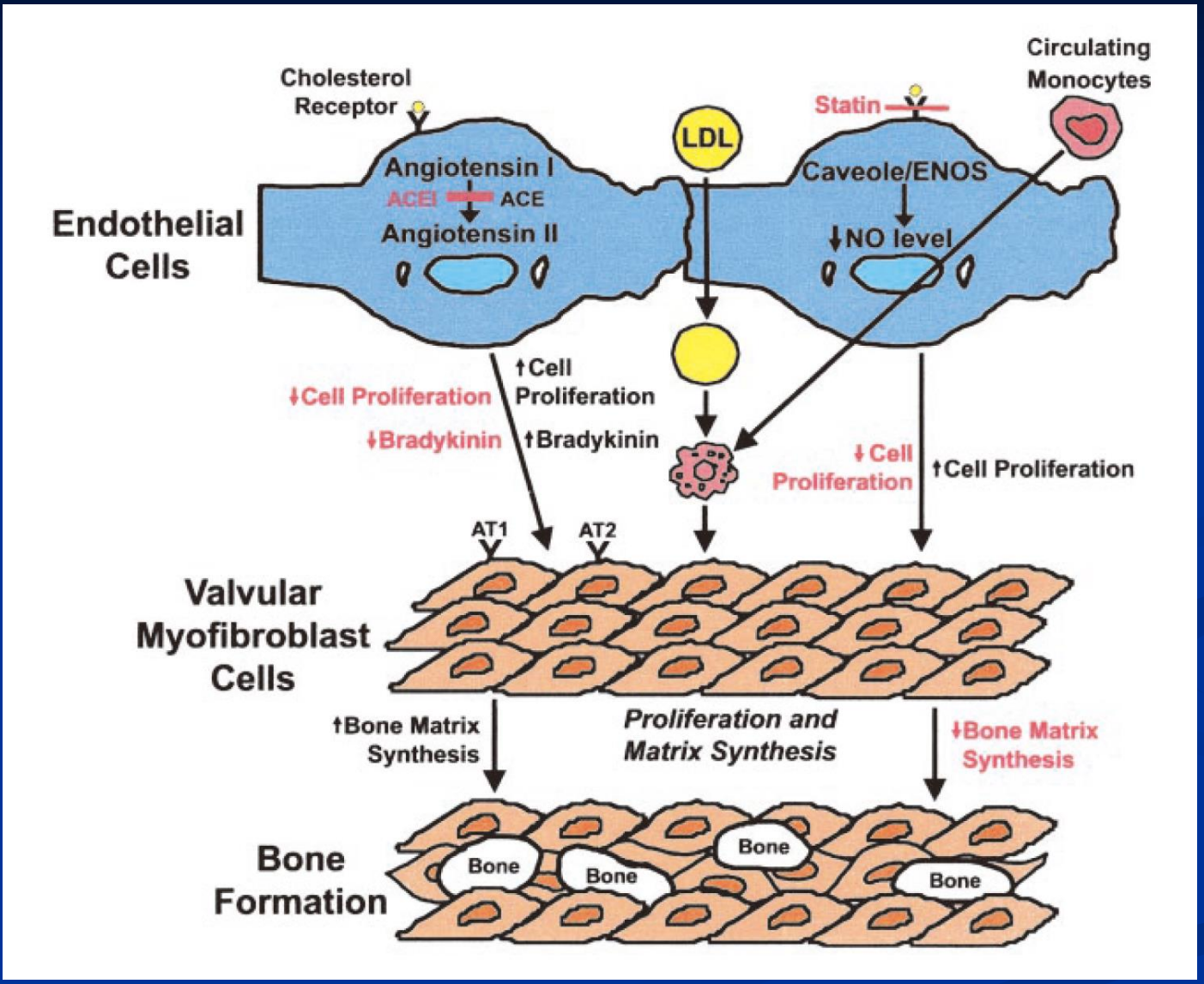
Age
Gender
Dyslipidemia
Diabetes/MetS
Hypertension
Smoking
Height

Myofibroblast differentiation

Oxidative stress
Nos uncoupling
Wnt, Runx2, Msx2
Osteoblast regulation
Osteochondrogenesis
Calcium homeostasis
Epitaxial calcium deposition

Genetics/Valve Morphology/Shear Stress

Important cellular pathway



Circulation. 2004;110:1180-1182

Factors associated with calcific AS progression

- Gene
- Age
- Aortic valve area
- Aortic valve calcification
- C-reactive protein
- Coronary artery disease
- Calcium: Elevated serum values
- Diabetes mellitus
- Dyslipidemia
- Hypertension
- Left ventricular mass index
- Left ventricular outflow tract velocity
- Mitral annular calcification
- Obesity
- Renal failure and elevated serum creatinine
- Sex (male)
- Smoking
- Valve structure

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Genetic Associations with Valvular Calcification and Aortic Stenosis

Table 1. Baseline Characteristics of Participants in the Discovery and Replication Cohorts.*

Characteristic	Discovery Cohorts						Replication Cohorts		
	FHS	AGES-RS	MESA		MESA		HNR	MDCS	CCHS
	White European	*White European*	*White European*	*African American*	*Hispanic American*	*Chinese American*	*White European*	*White European*	*White European*
Genotyping platform	Affymetrix, version 5.0	Illumina Hu370CNV	Affymetrix, version 6.0	Affymetrix, version 6.0	Affymetrix, version 6.0	Affymetrix, version 6.0	Illumina HumanOmni1-Quad	LifeSciences ABI 7900HT	LifeSciences ABI 7900HT
Imputation software	MACH	MACH, version 1.0.16	IMPUTE, version 2.1.1	IMPUTE, version 2.1.1	IMPUTE, version 2.1.1	IMPUTE, version 2.1.1	IMPUTE, version 2.1.2	NA	NA
Country of origin	United States	Iceland	United States	United States	United States	United States	Germany	Sweden	Denmark
No. of participants	1298	3120	2527	2497	2027	774	745	28,193	10,400
Age — yr	60±9	76±5	63±10	61±10	61±10	62±10	60±8	58±8	56±16
Female sex — no. (%)	616 (47)	1811 (58)	1321 (52)	1395 (56)	1094 (54)	394 (51)	379 (51)	17,008 (60)	5796 (56)
Presence of aortic-valve calcium — no. (%)	510 (39)	1338 (43)	397 (16)	263 (11)	243 (12)	67 (9)	91 (12)	308 (1)†	192 (2)†
Presence of mitral annular calcium — no. (%)	259 (20)	NA	309 (12)	175 (7)	197 (10)	37 (5)	18 (2)	NA	NA

* Plus–minus values are means ±SD. AGES-RS denotes Age, Gene/Environment Susceptibility–Reykjavik Study, CCHS Copenhagen City Heart Study, FHS Framingham Heart Study, HNR Heinz Nixdorf Recall Study, MDCS Malmö Diet and Cancer Study, MESA Multi-Ethnic Study of Atherosclerosis, and NA not applicable.

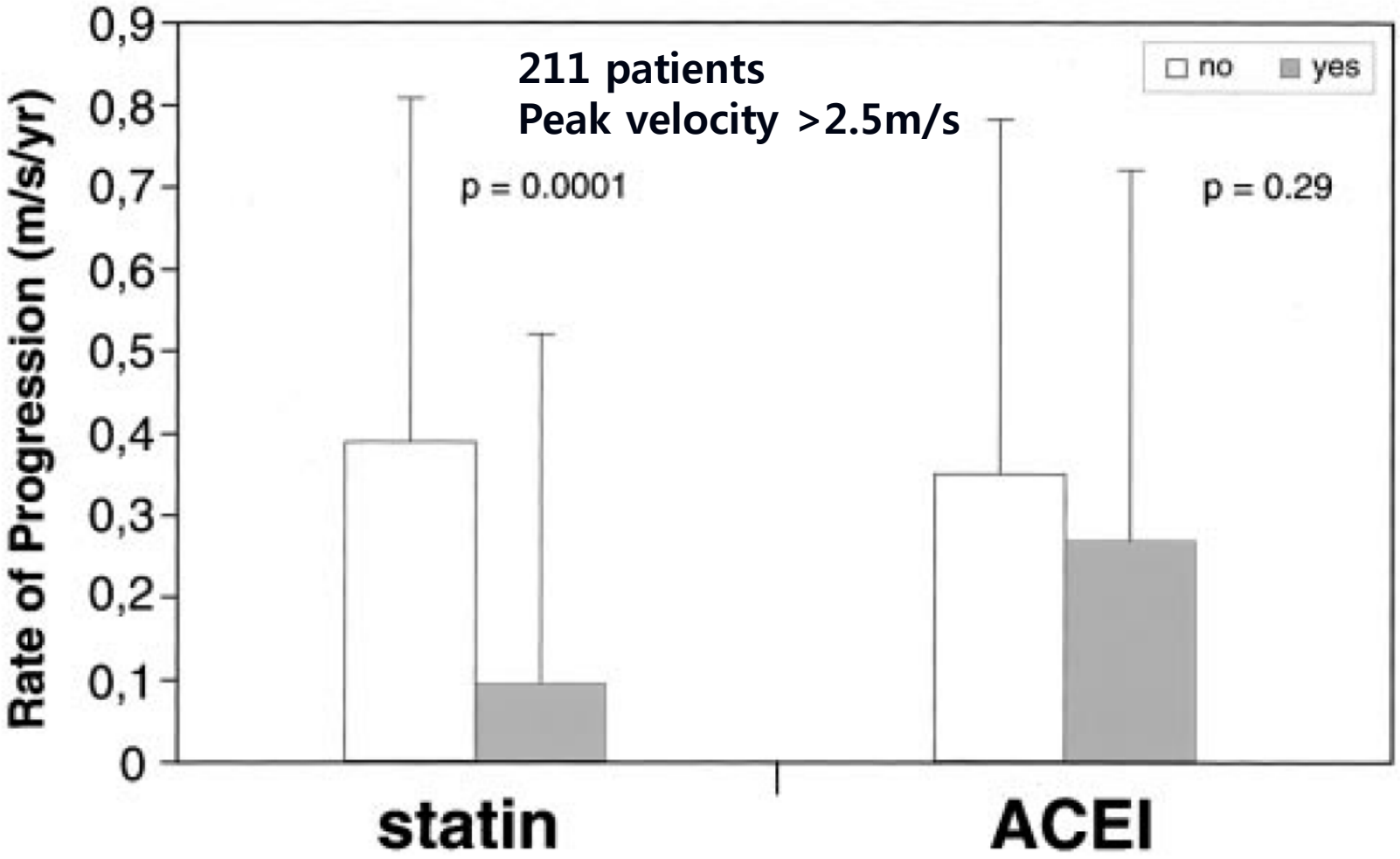
† Included are data from participants with incident aortic stenosis over a median follow-up period of 14 years in the MDCS and 17 years in the CCHS.

Genetics

SNP	Phenotype	Chr.	Minor Allele	MAF	OR (95% CI)	P Value	Nearest Gene
rs10455872	AV calcification	6	G	0.07	2.05 (1.63–2.57)	9.0×10^{-10}	LPA
rs17659543	MAC	2	T	0.16	1.66 (1.39–1.98)	1.5×10^{-8}	IL1F9
rs13415097	MAC	2	C	0.16	1.66 (1.39–1.98)	1.8×10^{-8}	IL1F9

N Engl J Med 2013;368:503-12.

Medical Treatment for AS Progression Delay



Rosenhek et al. Circulation. 2004;110:1291-1295

Nonrandomized Retrospective Studies

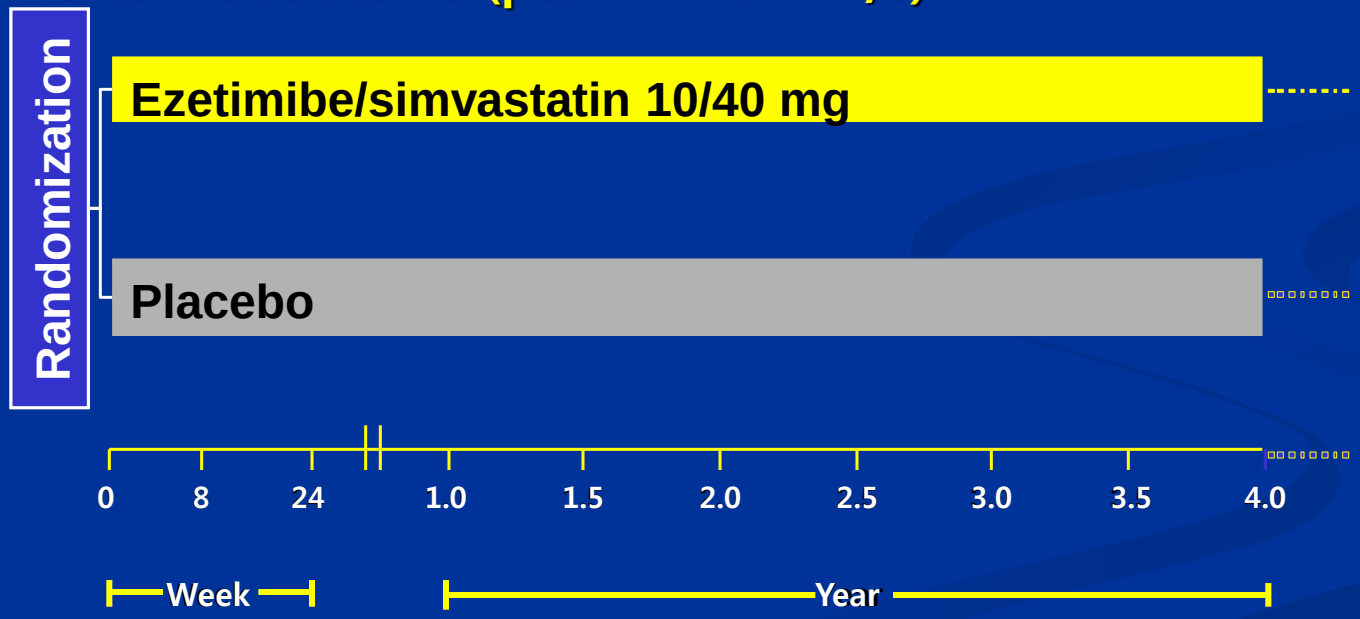
EBT calcium						
Pohle 2001[11]	104	65 y (86)	1.25 y		Increase in valve calcium (per year)	
Echocardiography						
Aronow 2001[14]	180	82 y (31)	2.8 y		Increase in peak gradient (mm Hg/y)	
				LDL ≥125 mg/dL, not on statin	6.3±1.4	<0.0001
				LDL ≥125 mg/dL, on statin	3.4±1.0	
				LDL <125 mg/dL, not on statin	3.1±1.1	
Novaro 2001[15]	174	68 y (44)	1.8 y		Decrease in valve area (cm^2/y)	0.03
				Statin therapy (33%)	0.06±0.16	
				No statin therapy	0.11±0.18	
Bellamy 2002[13]	156	77 y (58)	3.7 y		Decrease in valve area (cm^2/y)	0.04
				Statin therapy (24%)	0.04±0.15	
				No statin therapy	0.09±0.17	

Prospective Studies on Lipid Lowering in AS

	RAAVE*	SALTIRE	TASS	SEAS	ASTRONOMER
Sample size, n	121	155	47	1873	269
Active treatment, mg/d	Rosuvastatin 20	Atorvastatin 80	Atorvastatin 20	Simvastatin 40 plus ezetimibe 10	Rosuvastatin 40
Age, y	73.7±8.9	68±10	67±11	68±10	58.1±13.6
Men, n (%)	57 (47.1)	108 (70)	28 (60)	1150 (61)	167 (61)
Hypertension, n (%)	77 (64)	102 (66)	23 (49)	953 (51)	75 (28)
Diabetes, n (%)	39 (32)	7 (5)	6 (12)	0	0
Smoker, n (%)	4 (3)	43 (28)	5 (10)	360 (19)	28 (10)
Total cholesterol, mg/dL	212±50	220±38†	220±46‡	222±39	205±35
HDL-C, mg/dL	54±13		63±18‡	58±17	61±19
LDL-C, mg/dL	138±40	137±34†	140±39‡	139±36	131±39
Peak AS velocity	3.63±0.62	3.39±0.62	3.3±0.2‡	3.09±0.54	3.18±0.42
BAV, n (%)	0	5 (3)	?	85 (4.5)	133 (49)

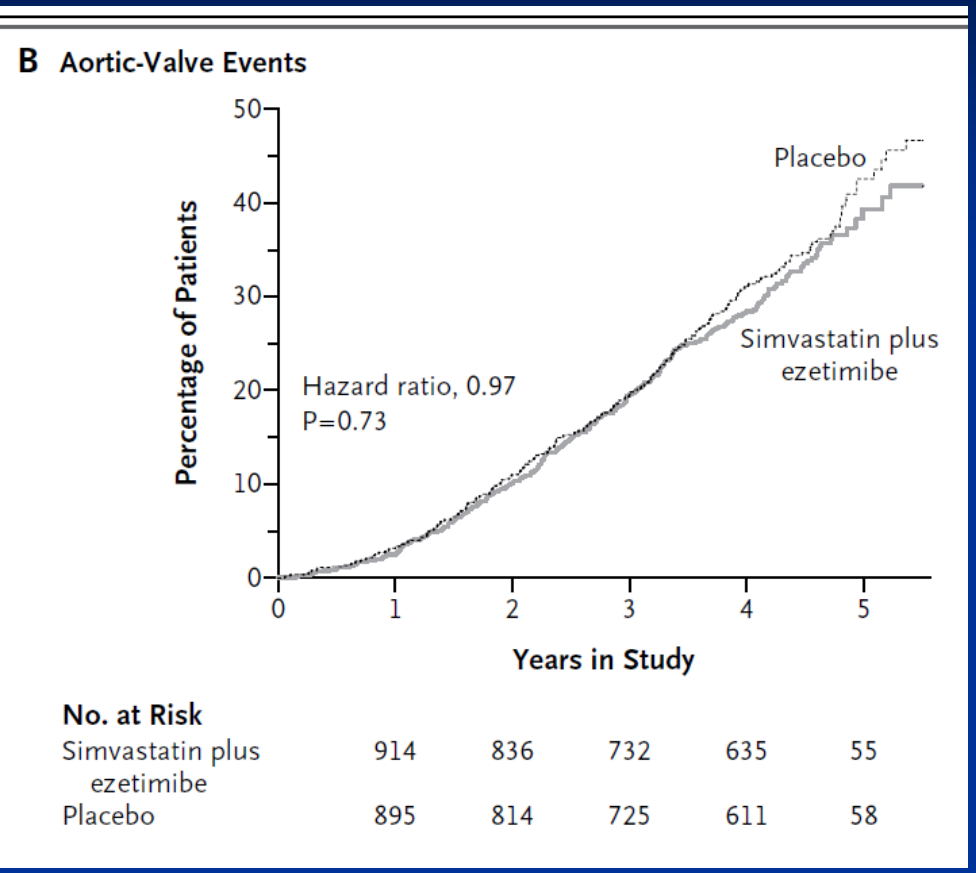
New Aspects From the SEAS Study

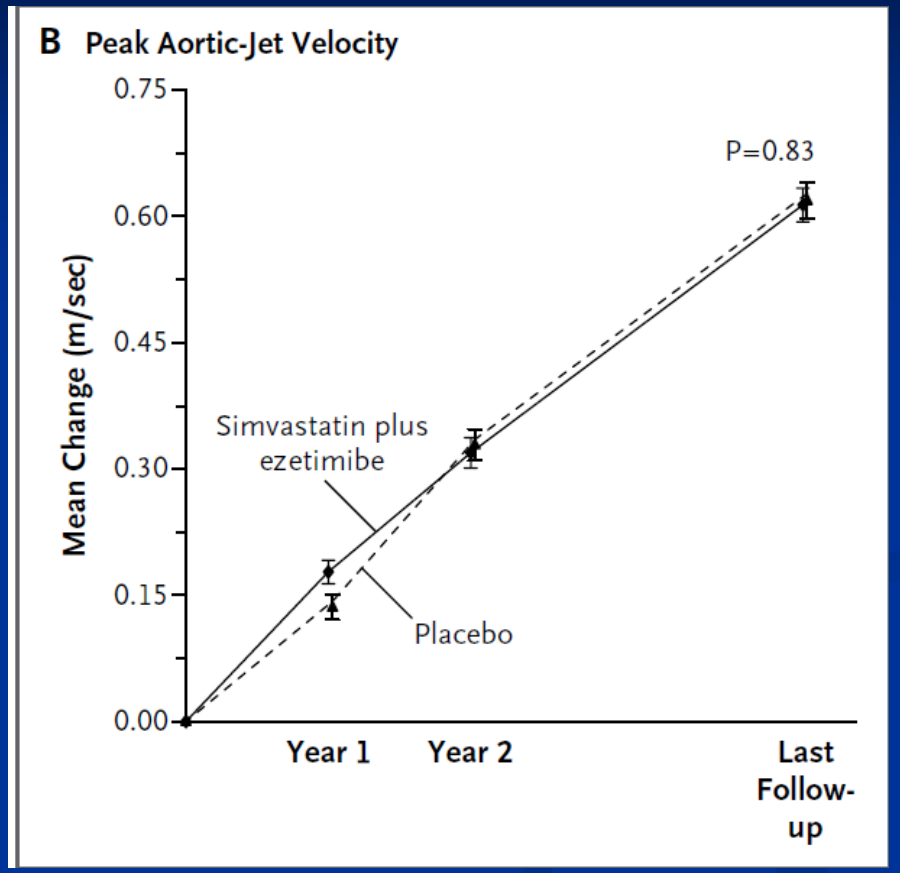
- Randomized, double blind, placebo controlled, multicenter
- 173 centers: Norway, Sweden, Denmark, Finland, Germany, UK, Ireland
- 4-Week placebo/diet run-in
- 1873 patients (Minimum follow-up: 4 years) with asymptomatic mild to moderate AS (peak V: 2.5 -4m/s)



Rossebø AB et al.N Engl J Med. 2008;359(13):1343-56

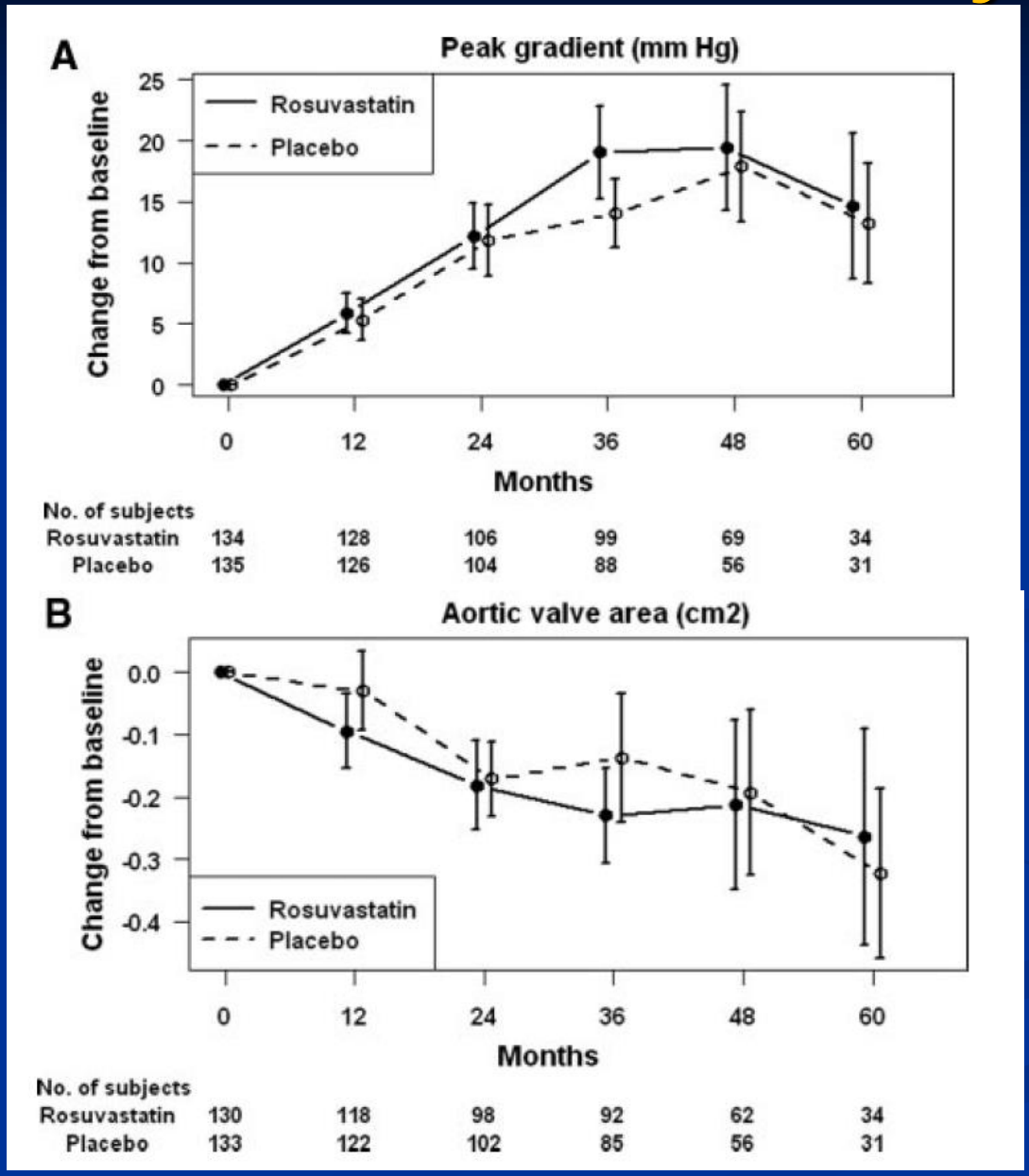
New Aspects From the SEAS Study



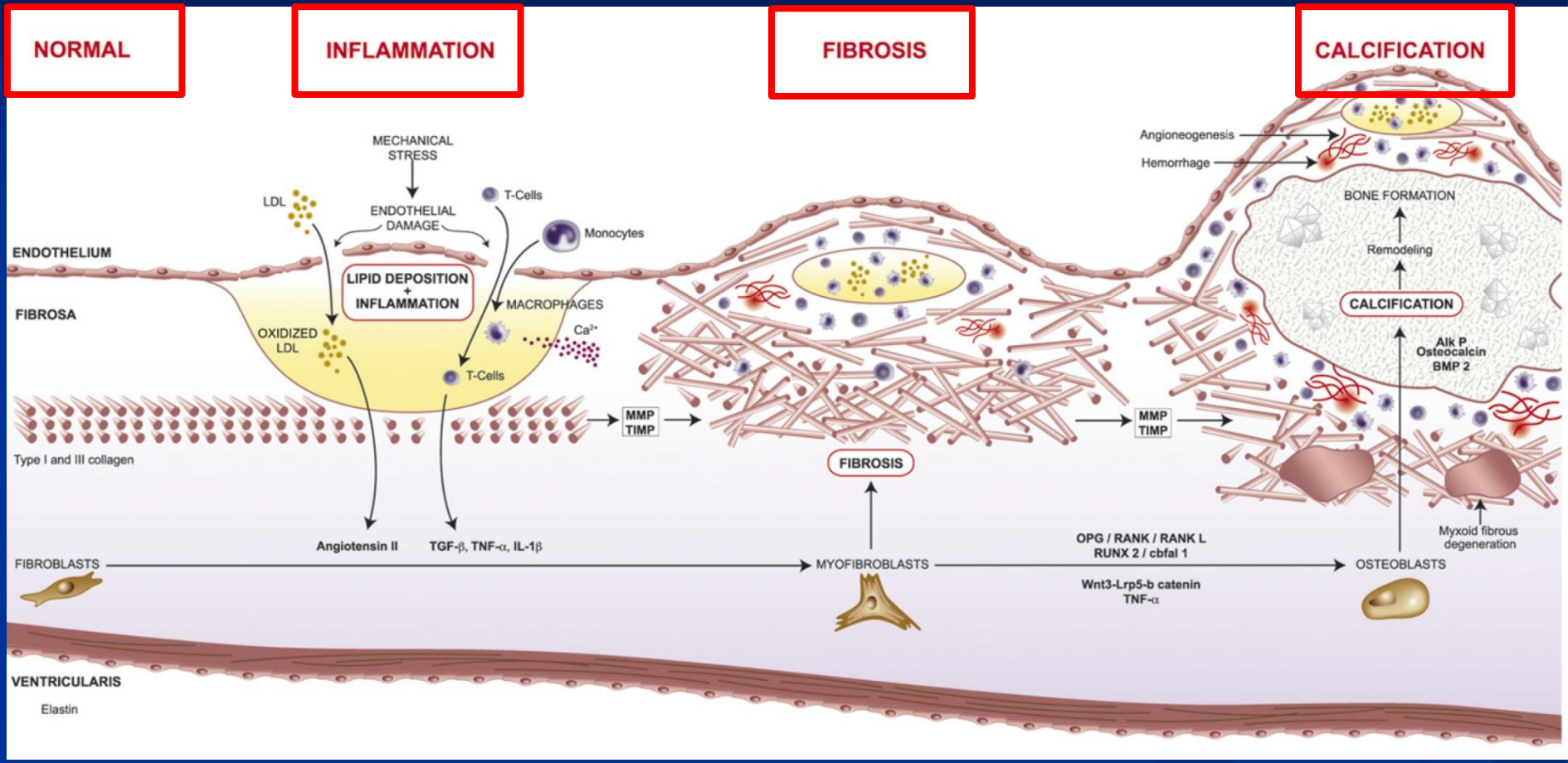


Rossebø AB et al.N Engl J Med. 2008;359(13):1343-56

ASTRONOMER study



Calcific Aortic Stenosis



Fibroblast **Myofibroblast** **Osteoblast**

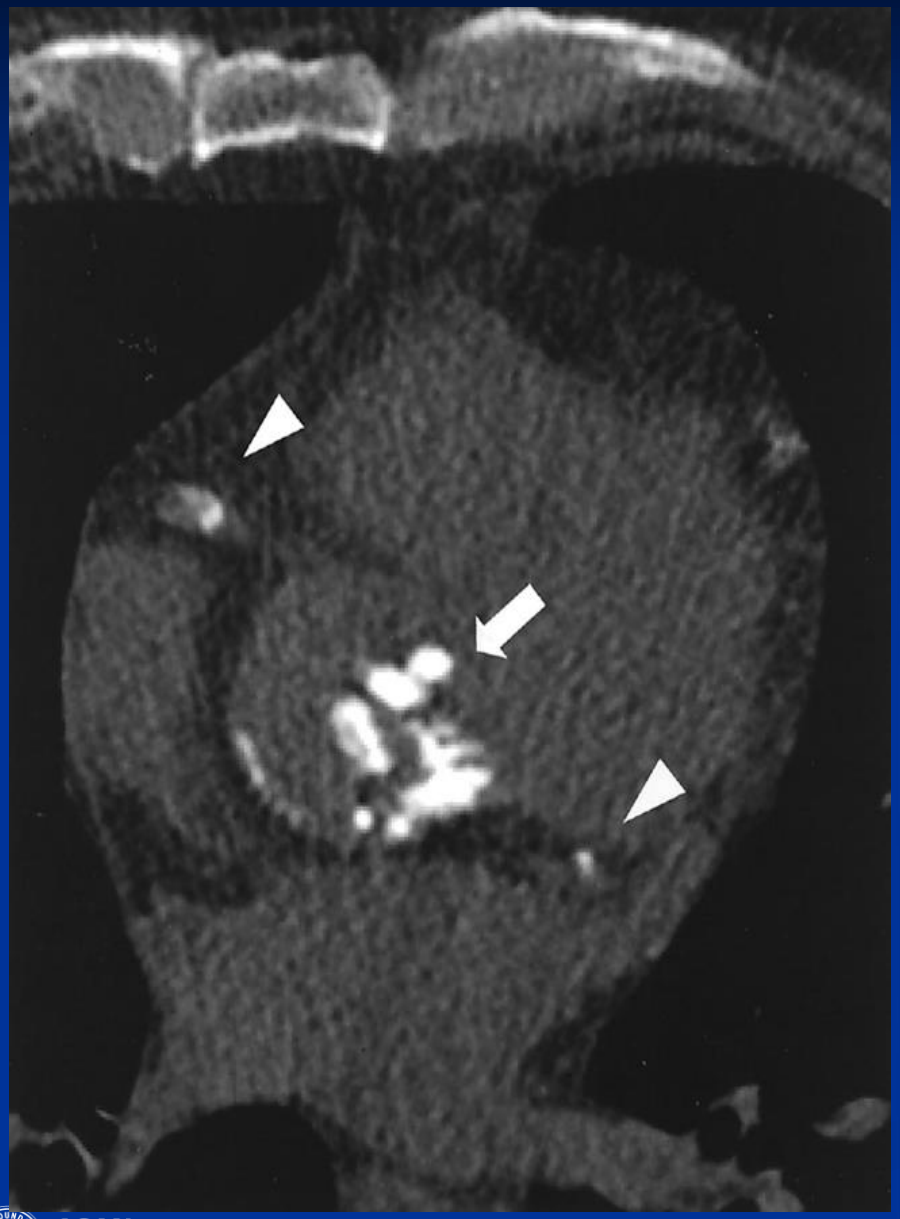
AV sclerosis
Progression

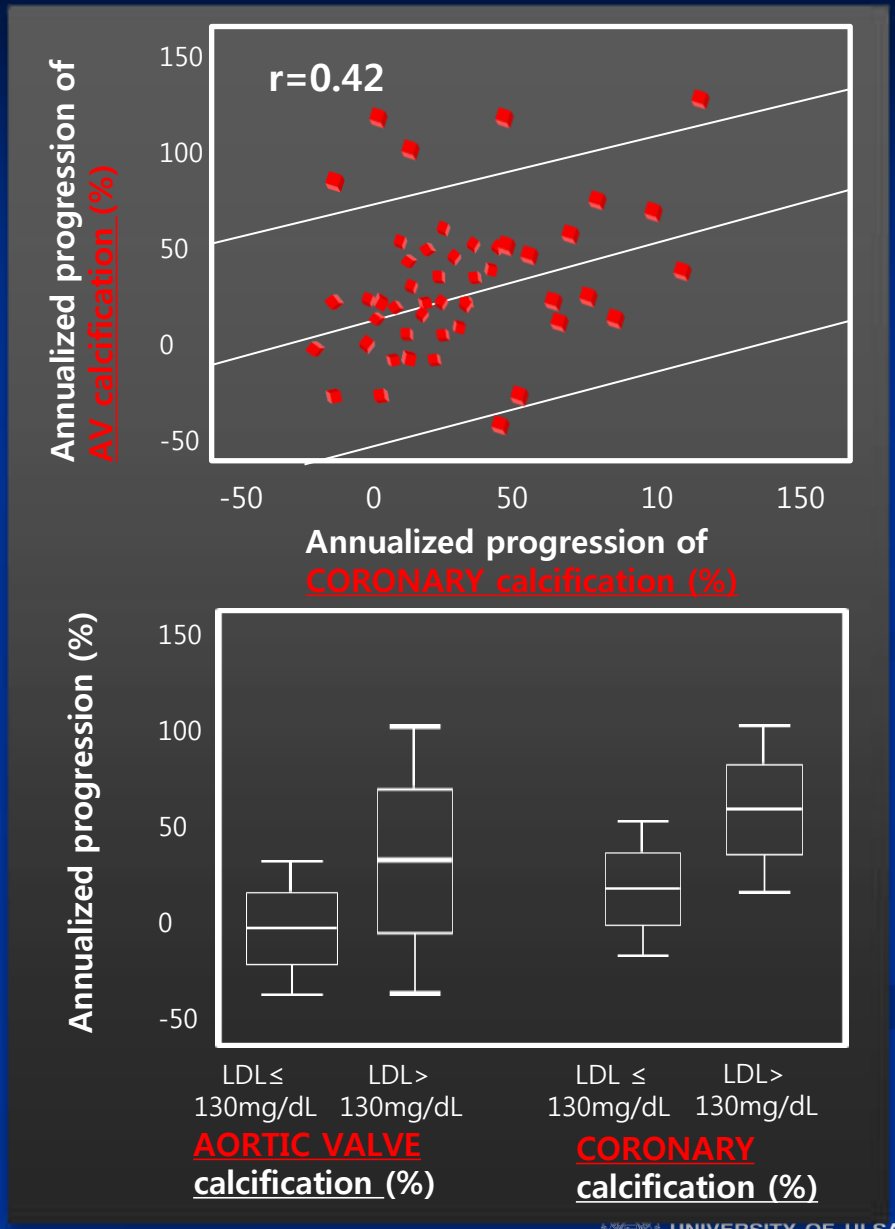
	Statin (+) (N=309)	Statin (-) (N=737)	P VALUE
AV sclerosis	0.04±0.09	0.07±0.10m/s/year	0.01
Mild AS	0.09±0.15	0.15±0.15m/s/year	0.001
Moderate AS	0.21±0.18	0.22±0.15	0.70

Am J Cardiol 2008;102:738 –742

Method of Early Detection

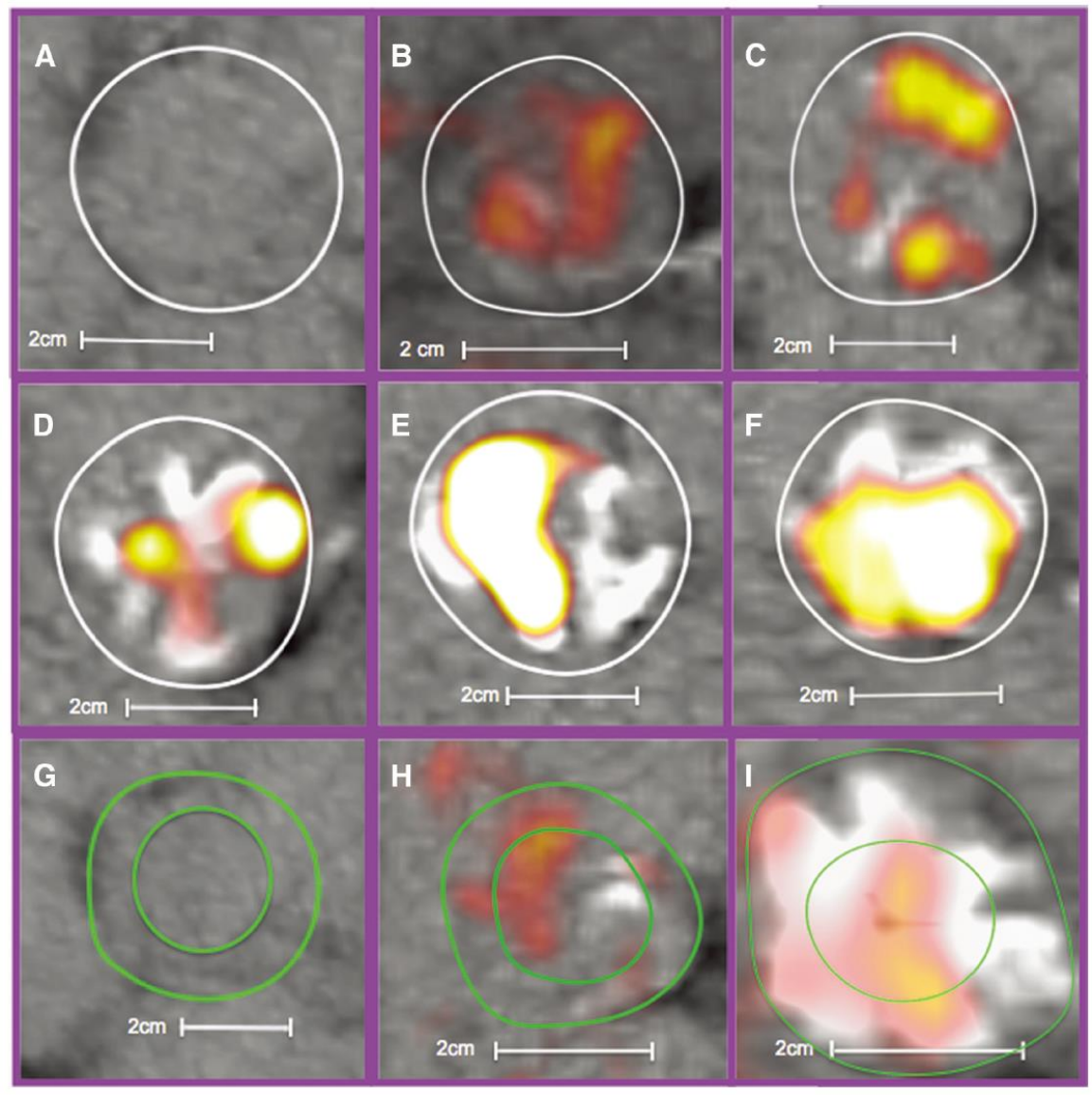
AV sclerosis





Pohle et al. Circulation 2001

Assessment of Valvular Calcification and Inflammation

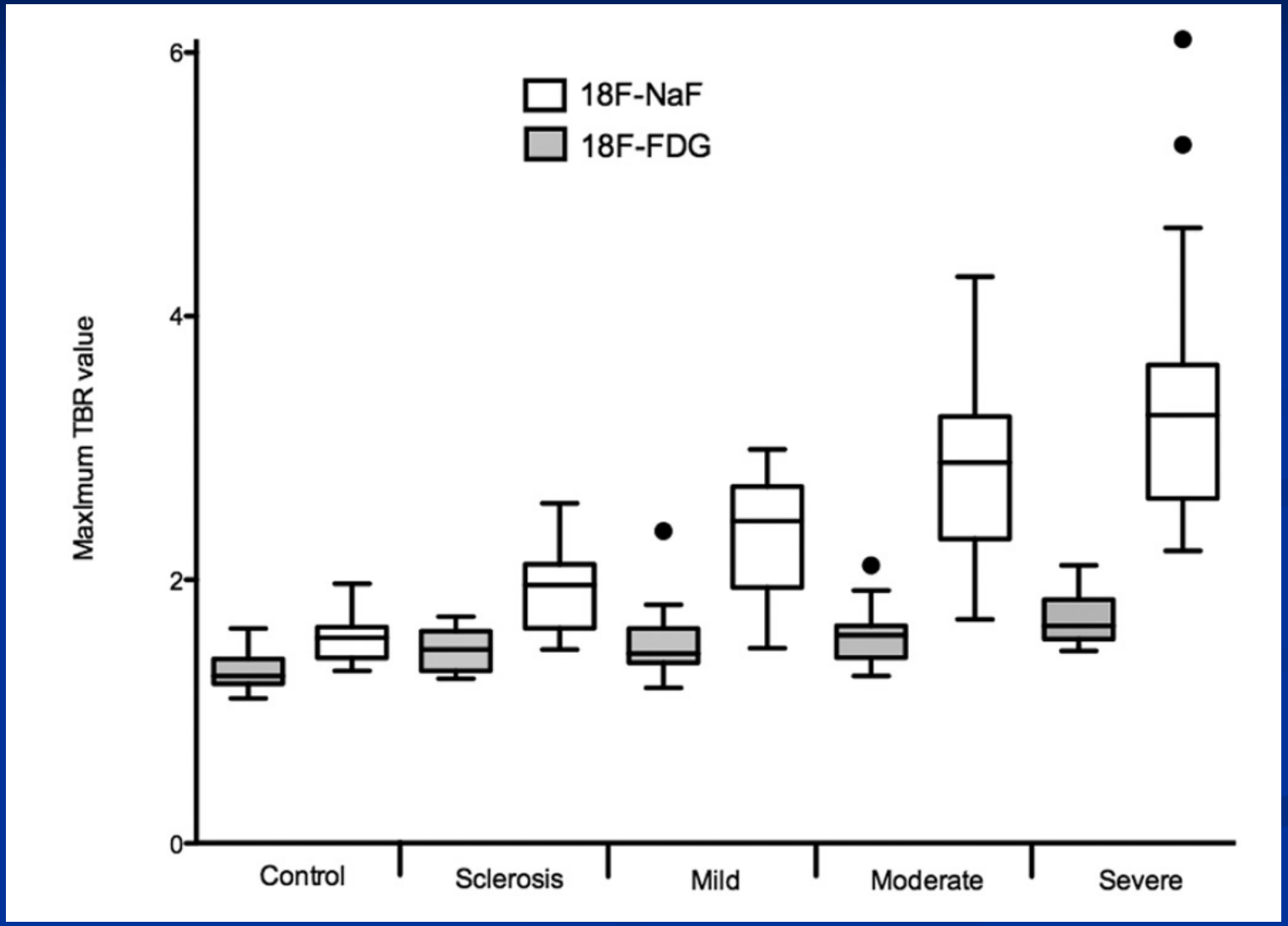


18F-NaF

18F-FDG

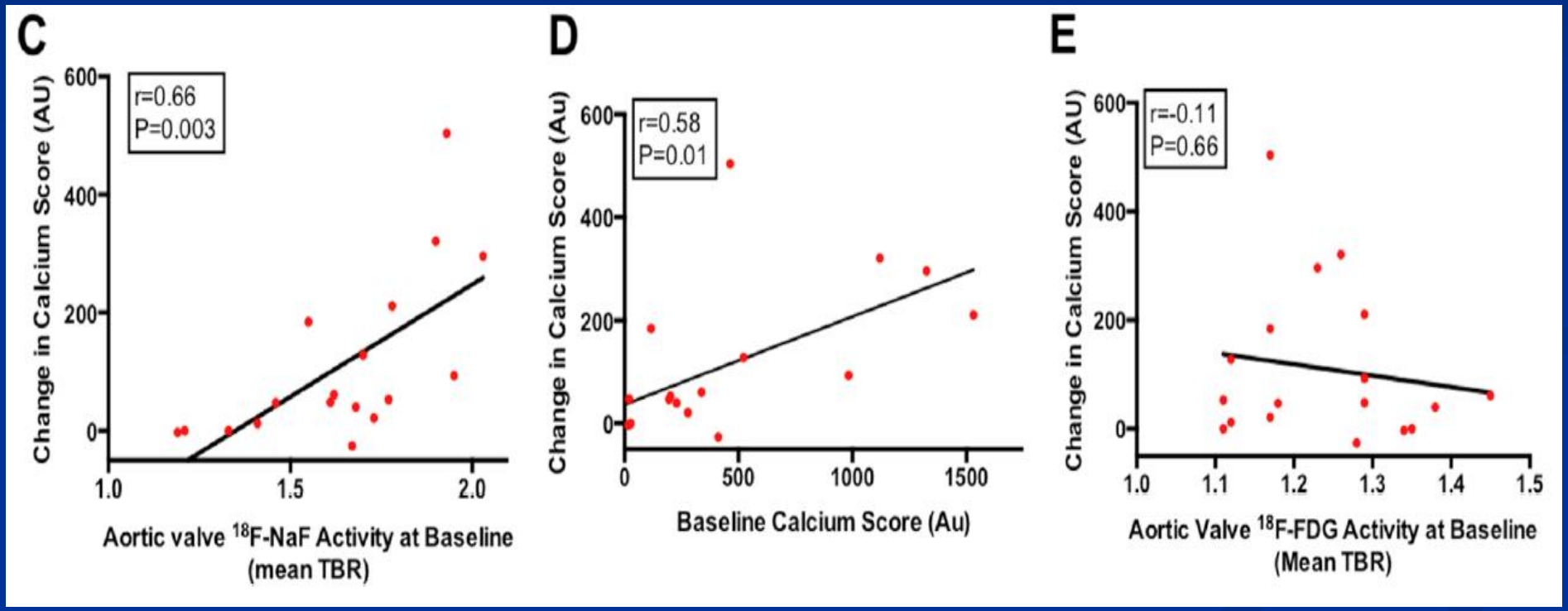
Dweck et al. Circulation. 2012;125:76-86

Assessment of Valvular Calcification and Inflammation



Dweck et al. Circulation. 2012;125:76-86

Progression of calcium score

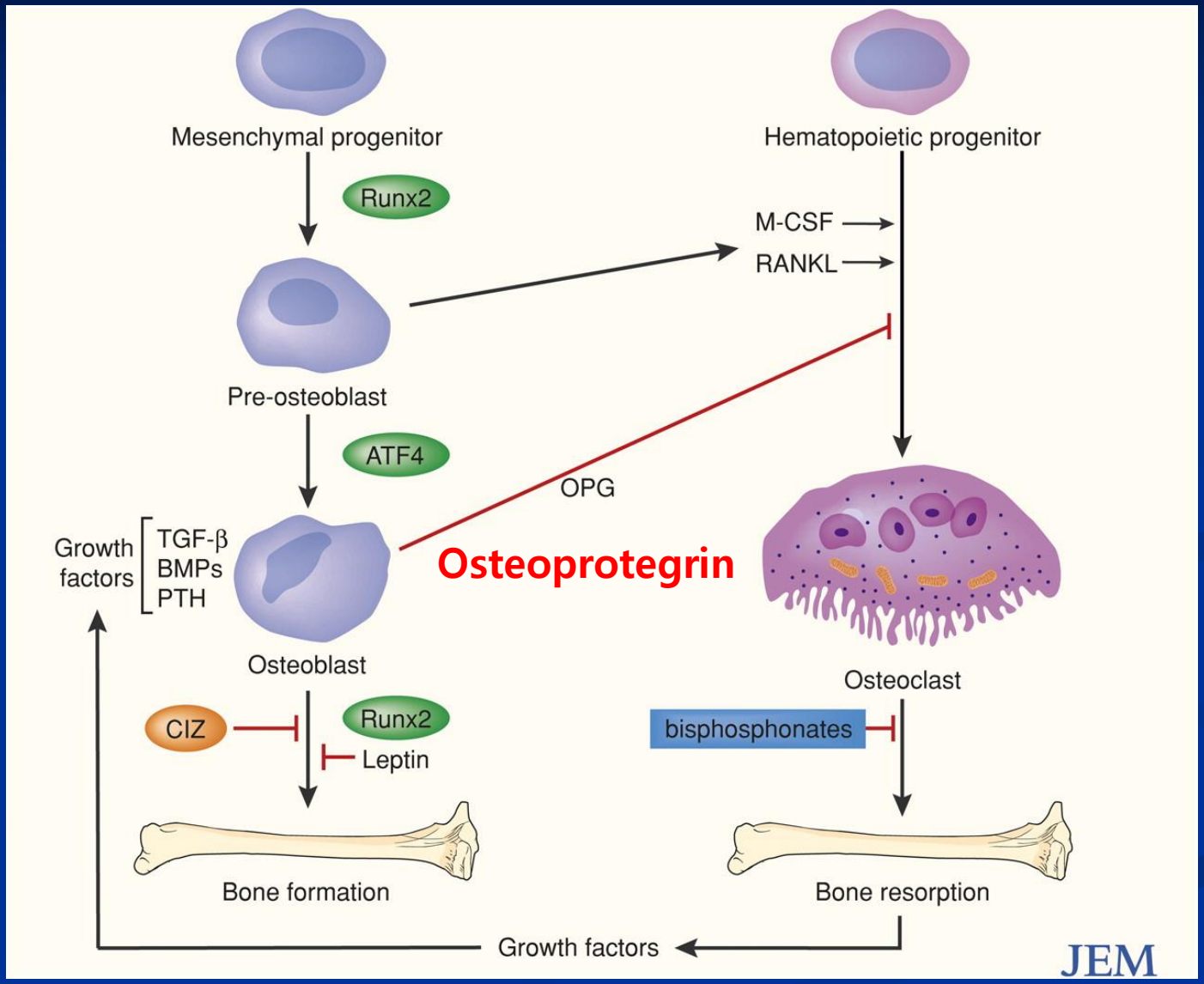


Dweck et al. Circ Cardiovasc Imaging. 2014;7:371-378

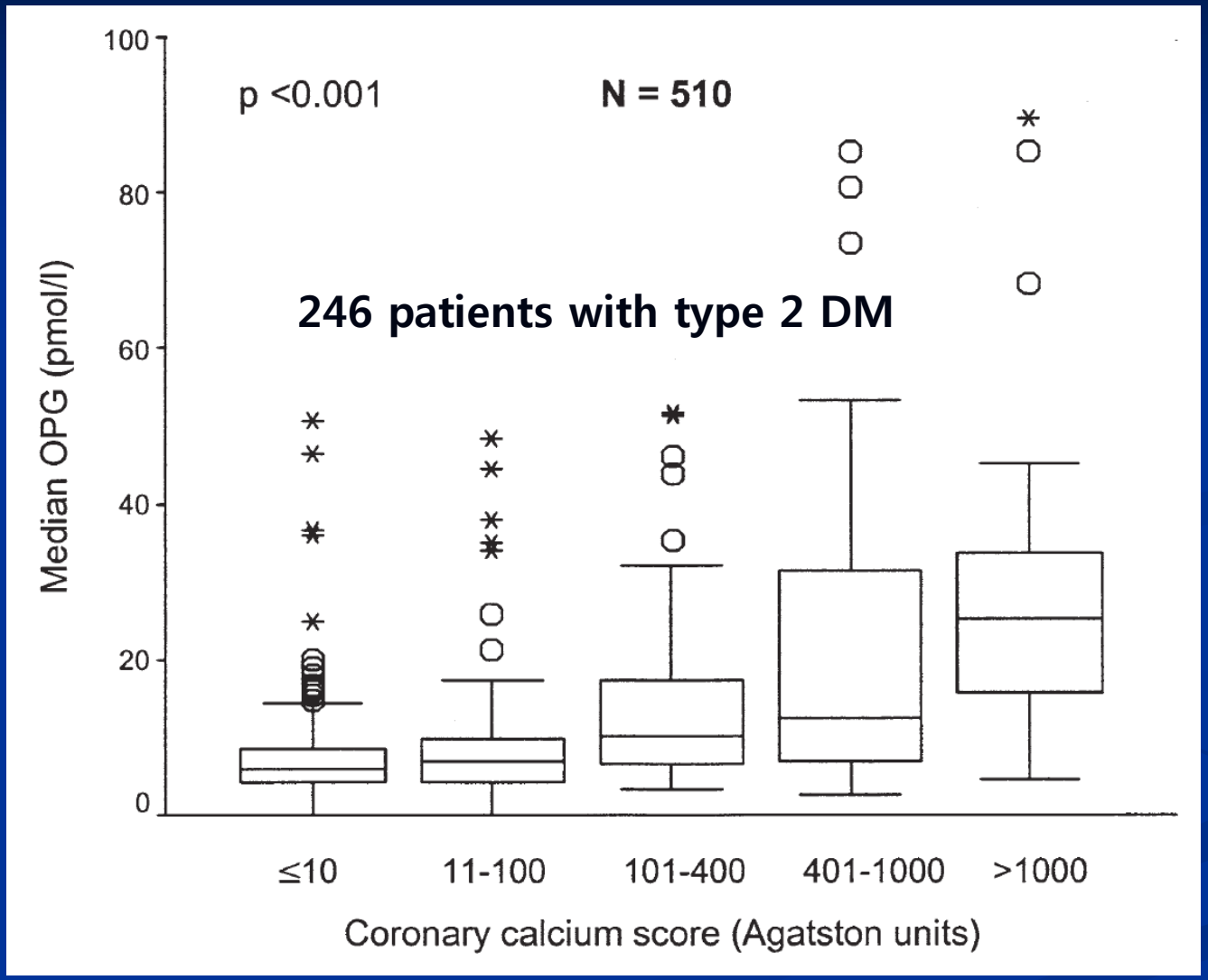
Imaging for early detection

- CT : calcium scoring
- PET imaging
  - 18F-NaF – Osteoblastic activity
  - 18F-FDG – Inflammation

New Biomarker



Osteoprotegrin (OPG)



J Am Coll Cardiol 2006;47:1850–7

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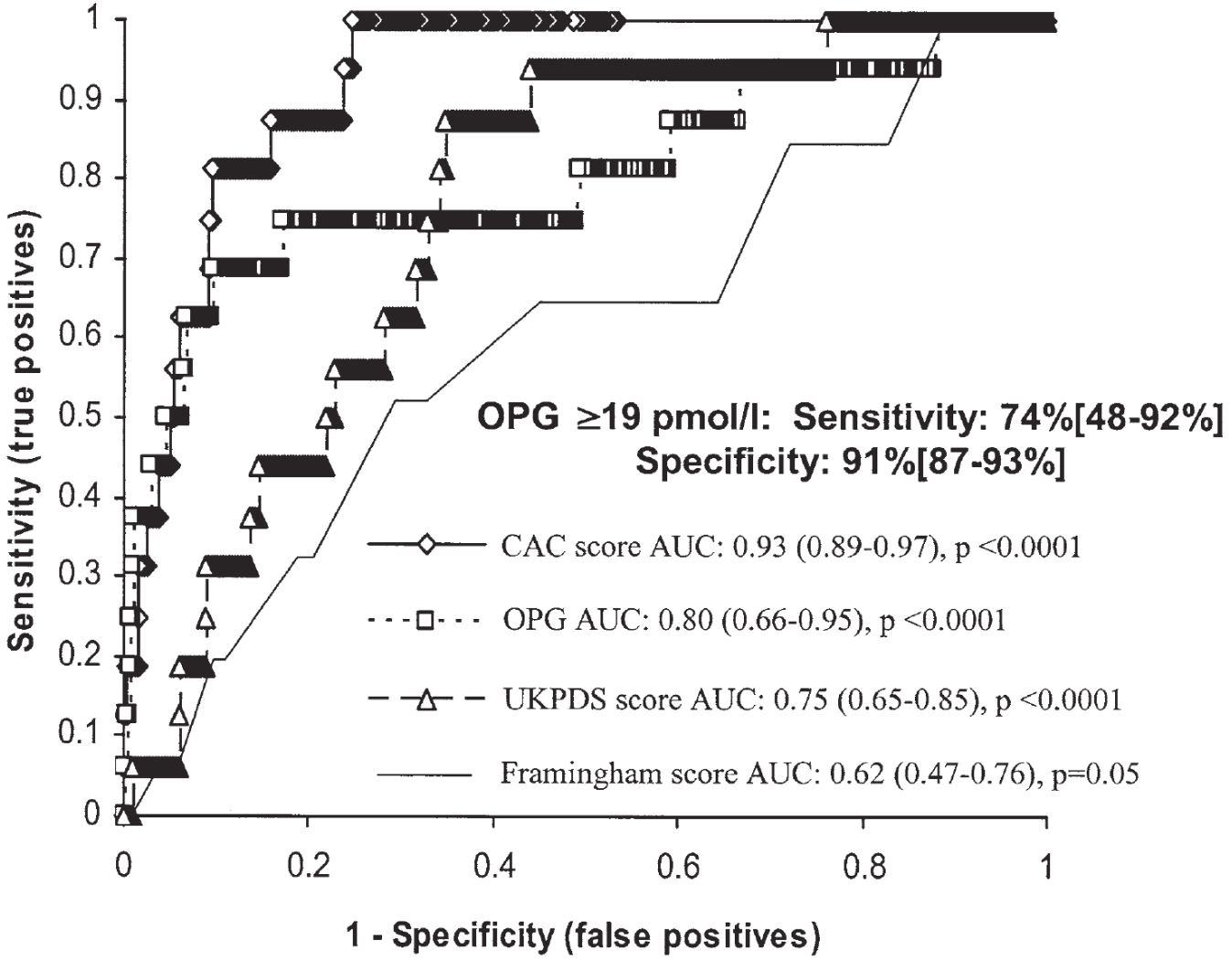
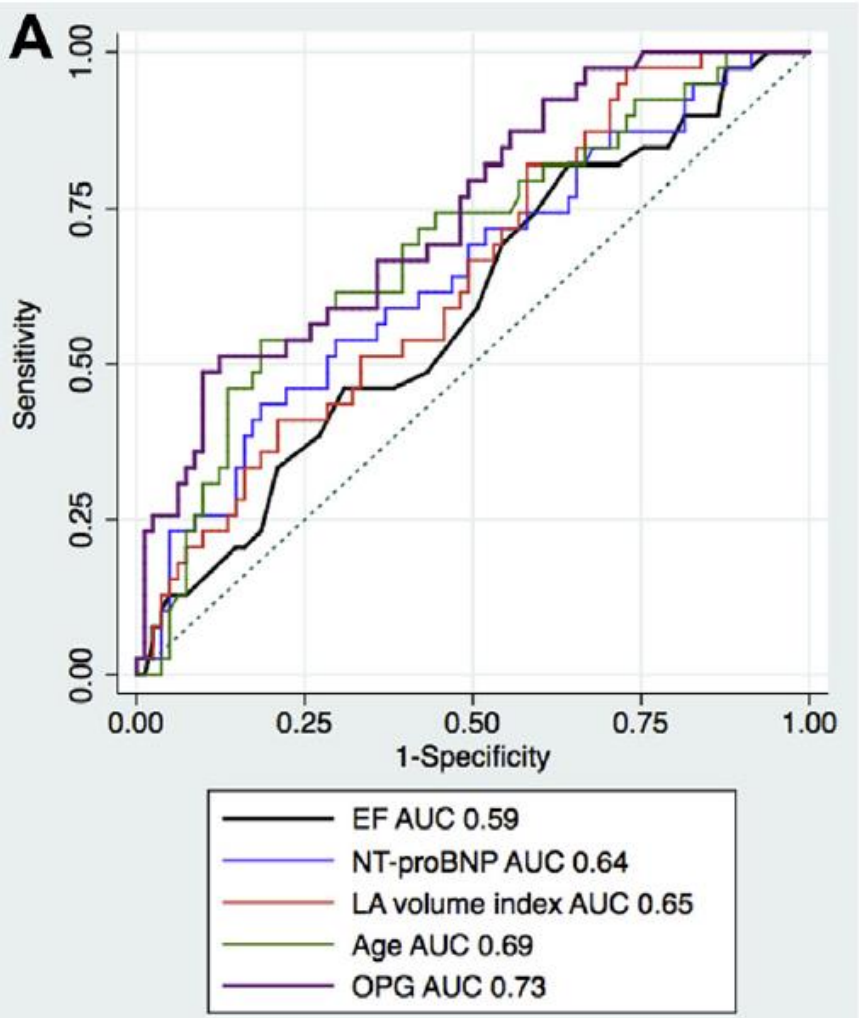
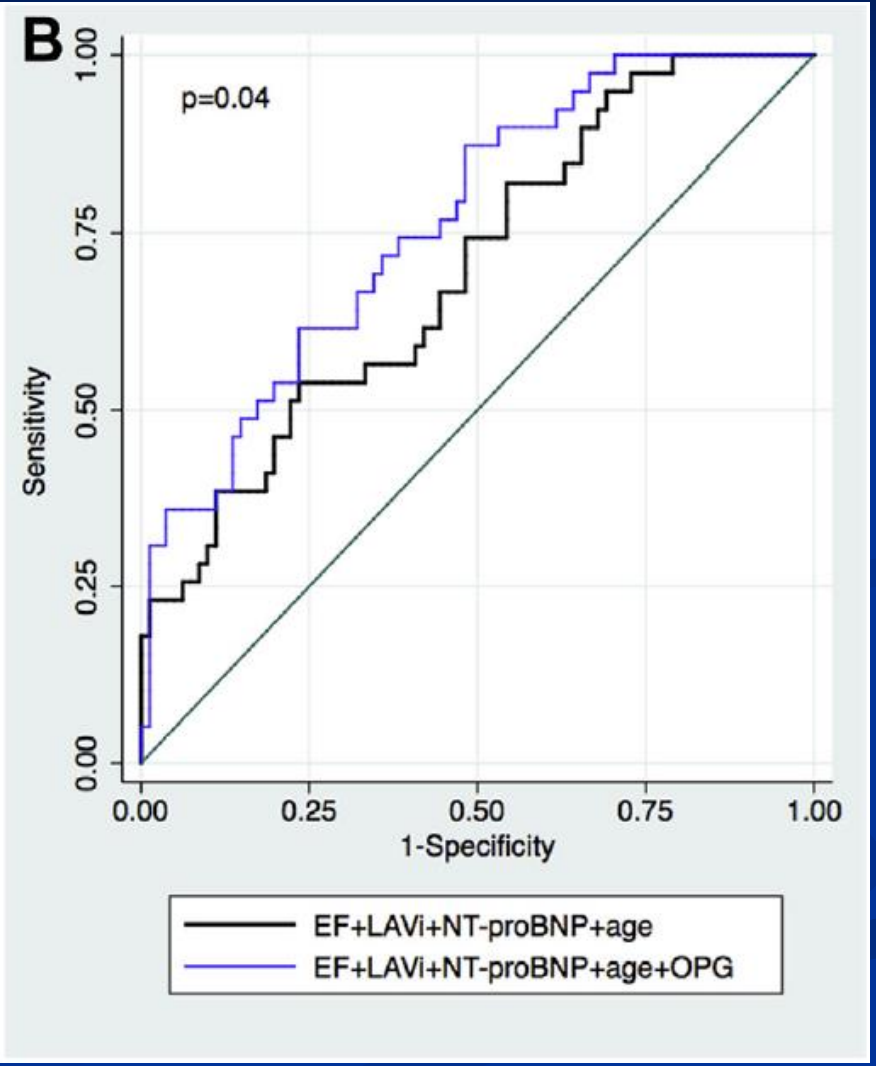


J Am Coll Cardiol 2006;47:1850–7

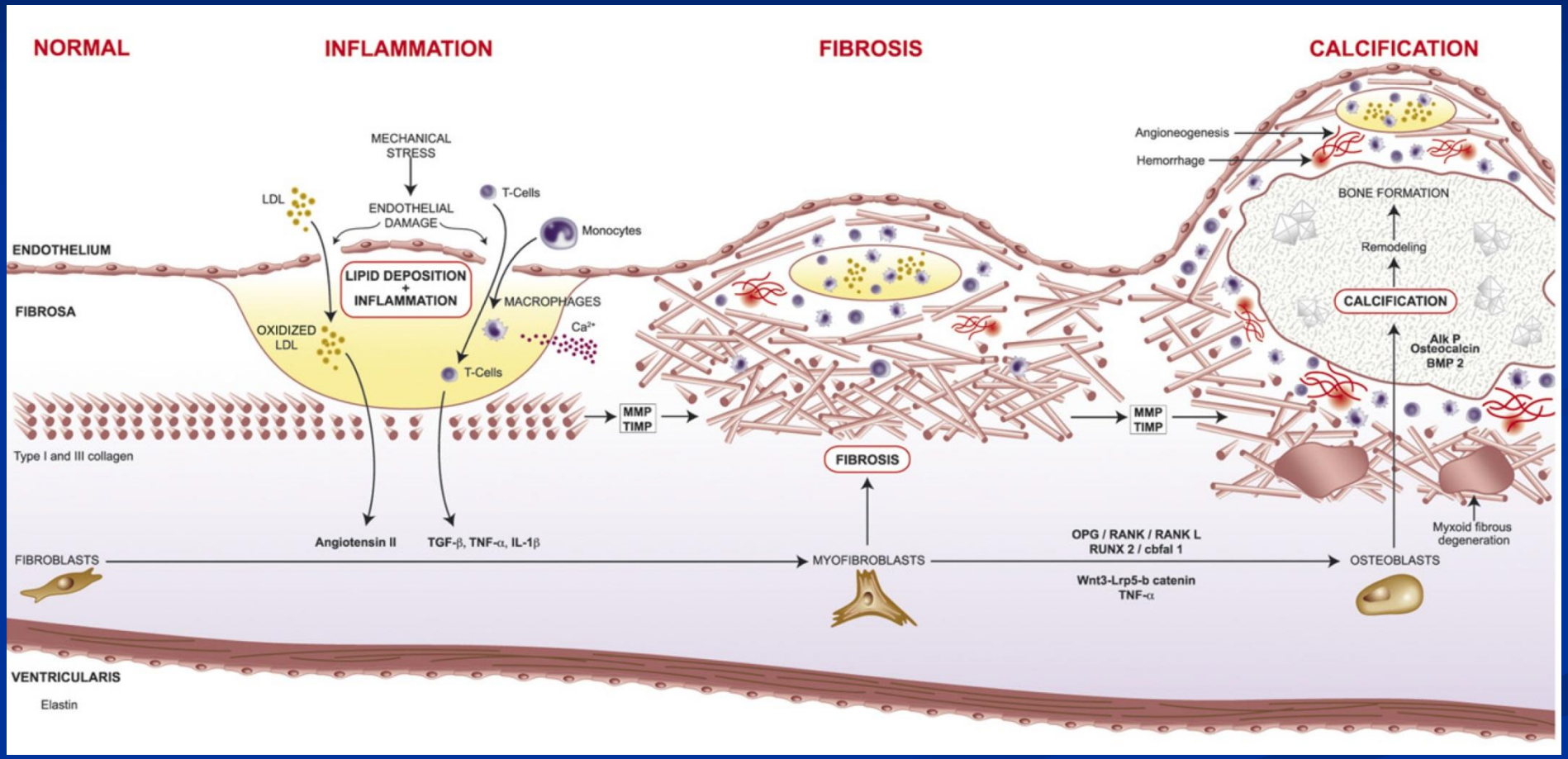
Osteoprotegrin (OPG)
Aortic stenosis





Am J Cardiol 2013;112:1433e1438

New Therapeutic Target



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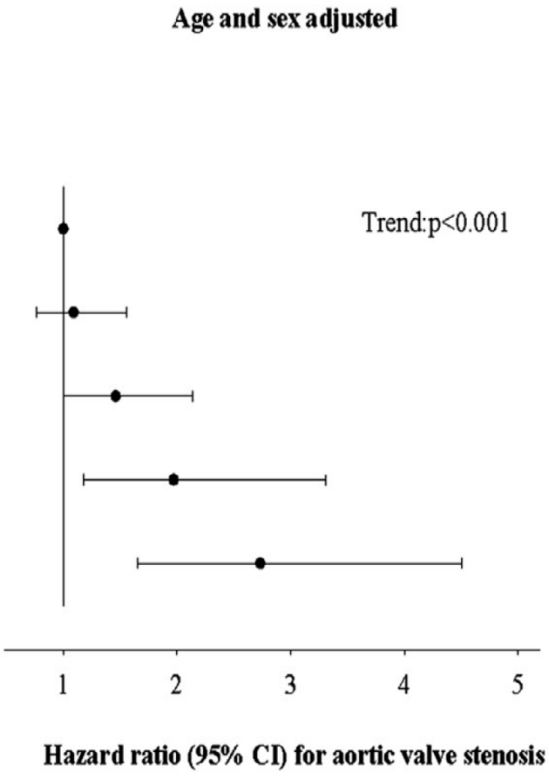
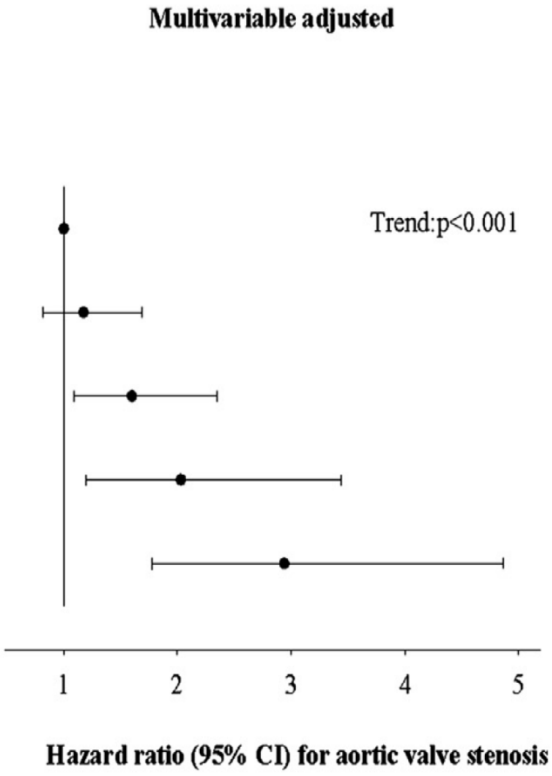
rs13415097	MAC	2	C	0.16	1.66 (1.39–1.98)	1.8×10^{-8}	IL1F9

N Engl J Med 2013;368:503-12.

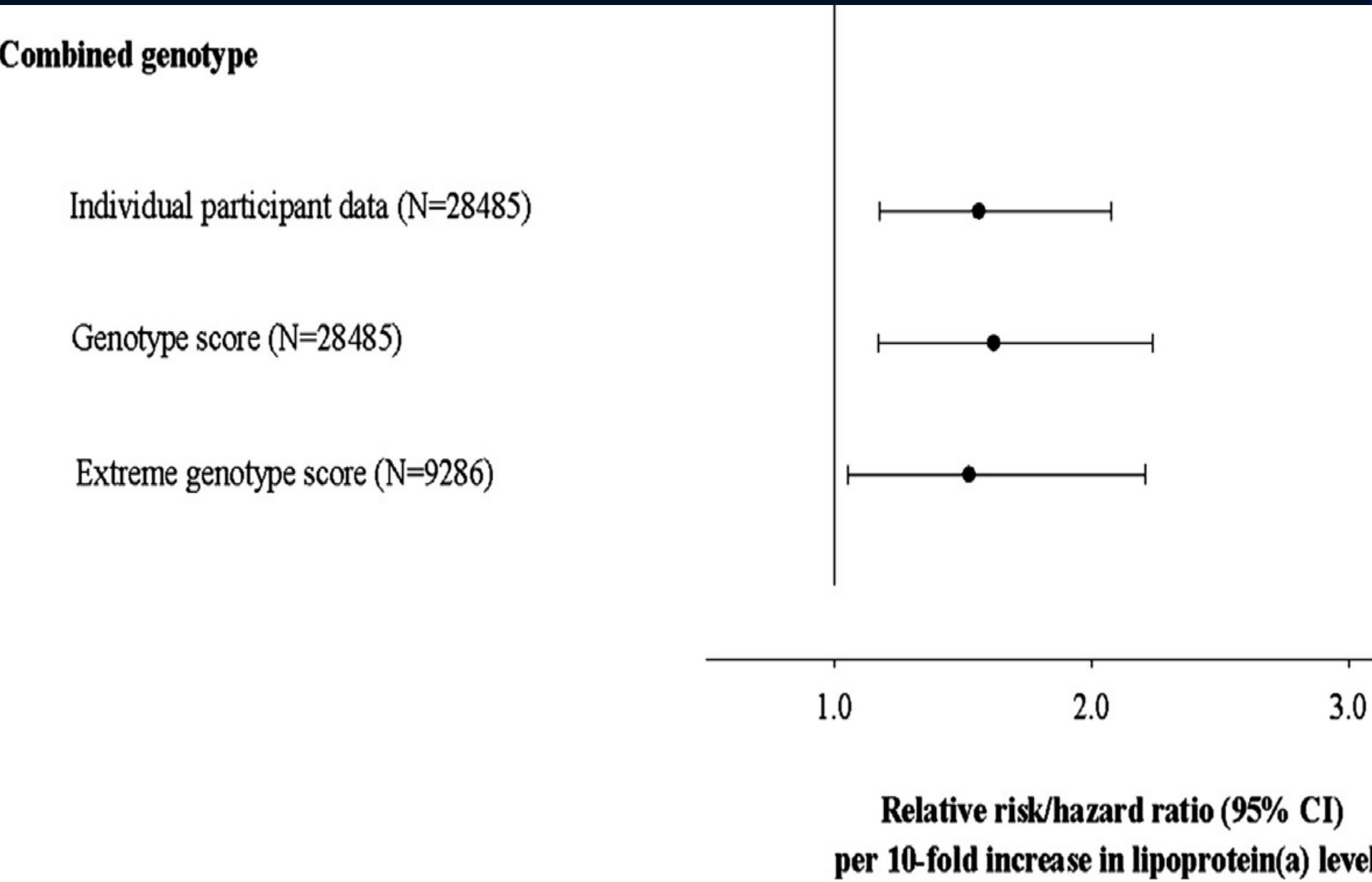
Lipoprotein(a)

Lipoprotein(a) percentile	mg/dL	Participants N	Events N
<22	3(2-4)	6123	53
22-66	11(7-17)	13053	127
67-89	40(30-51)	6677	87
90-95	80(63-95)	1728	27
>95	124(104-148)	1435	30





J Am Coll Cardiol 2014;63:470–7


Combined genotype
Individual participant data (N=28485)
Genotype score (N=28485)
Extreme genotype score (N=9286)
1.0
2.0
3.0
Relative risk/hazard ratio (95% CI)
per 10-fold increase in lipoprotein(a) level

percentile

Elevated Expression of Lipoprotein-Associated Phospholipase A2 in Calcific Aortic Valve Disease

Implications for Valve Mineralization

Ablajan Mahmut, MD, MSc,* Marie-Chloé Boulanger, PhD,* Diala El Husseini, MS

Together, these results demonstrated that Lp-PLA2 is highly
mineralization of valve interstitial cells. Further work is neces
considered as a novel target in CAVD. (J Am Coll Cardiol 20
Cardiology Foundation

Results Transcriptomic analyses of CAVD and control nonmineralized aortic valves revealed tha
4.2-fold in mineralized aortic valves. Higher expression of Lp-PLA2 in stenotic aortic va
quantitative polymerase chain reaction, immunohistochemistry, and enzymatic Lp-PLA
Lp-PLA2 transcripts correlated with several indexes of tissue remodeling. In vitro, lysoph
the expression of alkaline phosphatase, the ectonucleotide pyrophosphatase/phospho
sodium-dependent phosphate cotransporter 1 (encoded by the *SLC20A1* gene), and os
that lysophosphatidylcholine-induced mineralization involved ectonucleotidase enzyme a
a protein-kinase-A-dependent pathway.

Conclusions Together, these results demonstrated that Lp-PLA2 is highly expressed in CAVD, and it
mineralization of valve interstitial cells. Further work is necessary to document whethe
considered as a novel target in CAVD. (J Am Coll Cardiol 2014;63:460–9) © 2014 b
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EDITORIAL COMMENT

New Therapeutic Targets for Calcific Aortic Valve Stenosis

The Lipoprotein(a)-Lipoprotein-Associated Phospholipase A_2-Oxidized Phospholipid Axis*

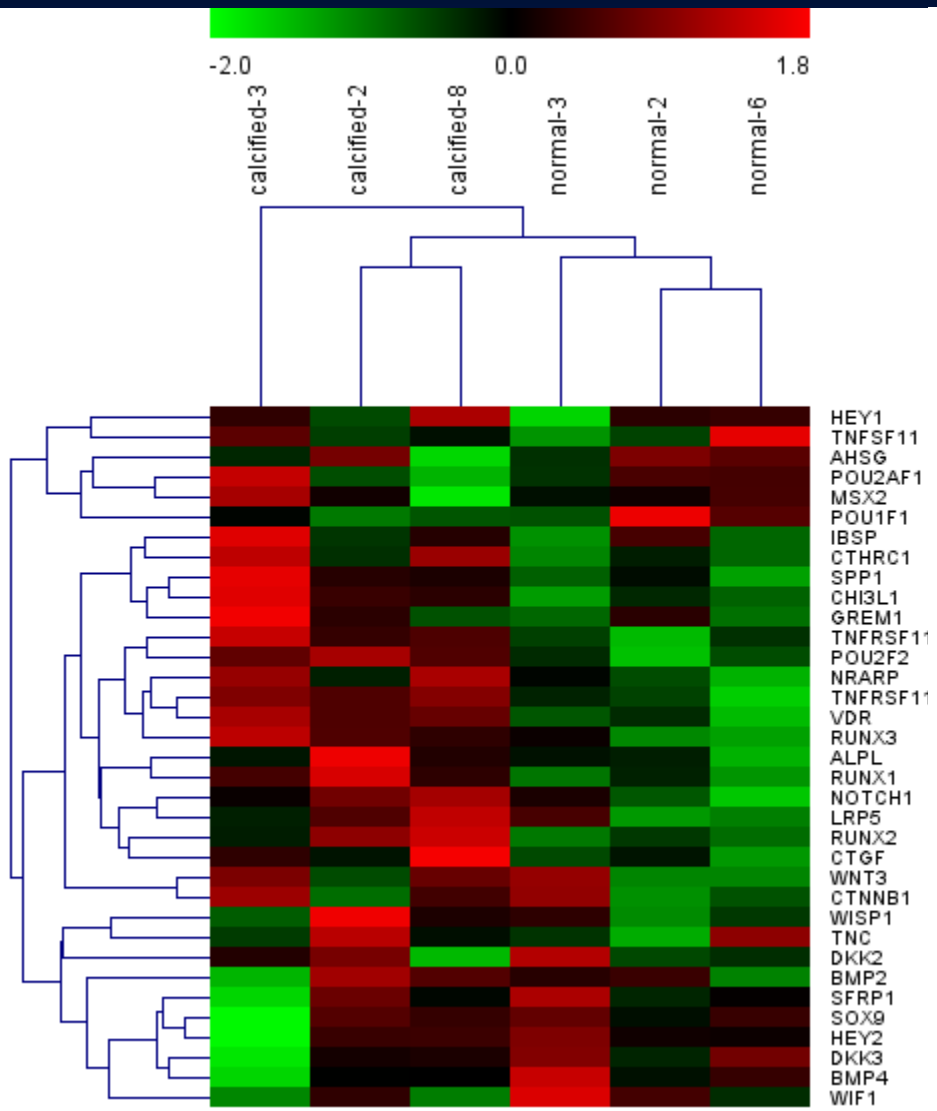
Ming-Yow Hung, MD,†‡§ Joseph L. Witztum, MD,§ Sotirios Tsimikas, MD§

New Taipei City and Taipei, Taiwan; and La Jolla, California

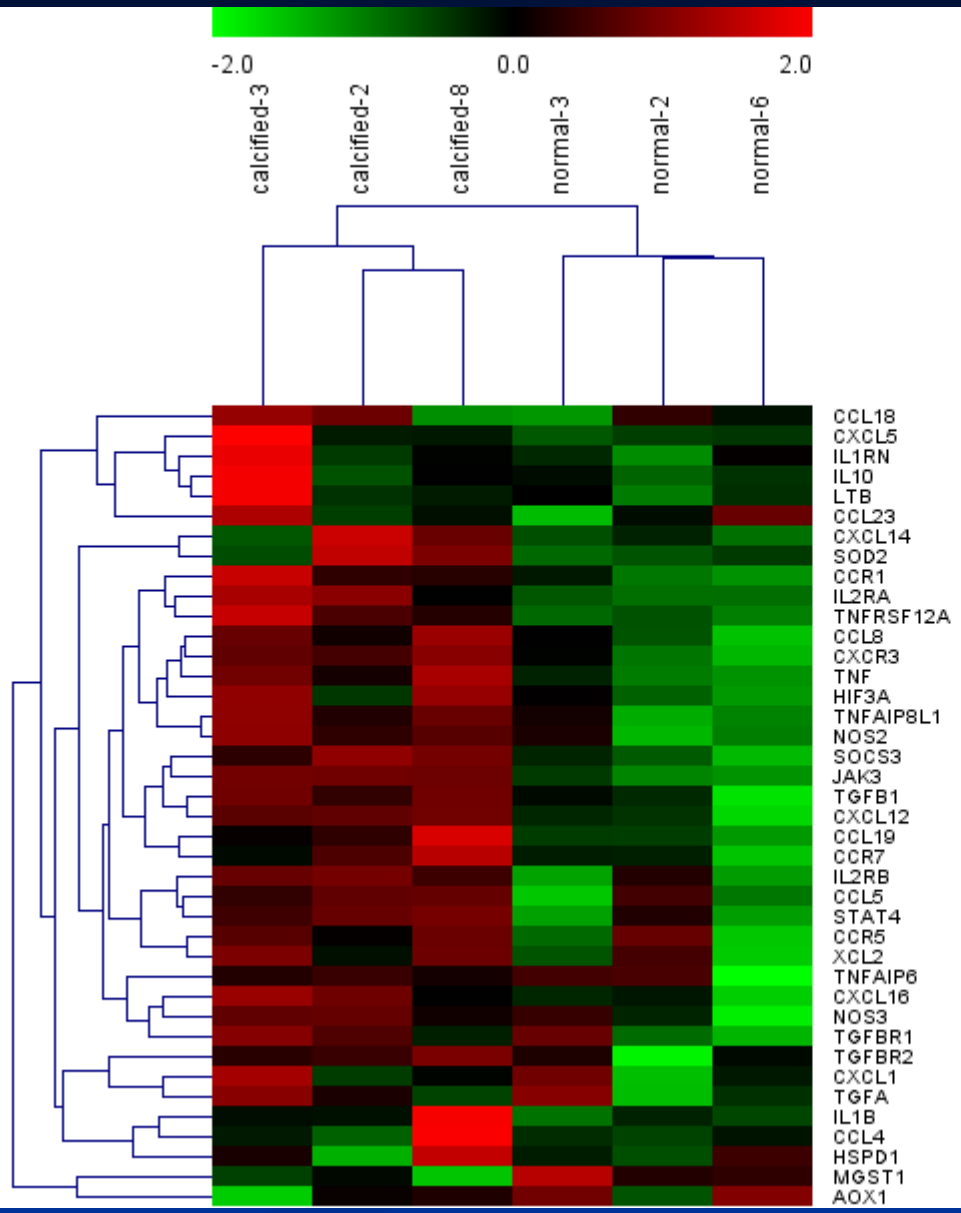
Calcific aortic valve stenosis (CAVS) is the most common form of acquired valvular heart disease, present in 3% of the population more than 75 years of age (1). Although risk factors are similar for CAVS and atherosclerosis, ~50% of patients with CAVS do not have clinically significant cardiovascular disease (CVD), suggesting related, but unique, pathophysiology (1). Although surgical aortic valve replacement remains the gold standard treatment for most patients, at least one-third of symptomatic patients with CAVS may not undergo surgical aortic valve replacement.

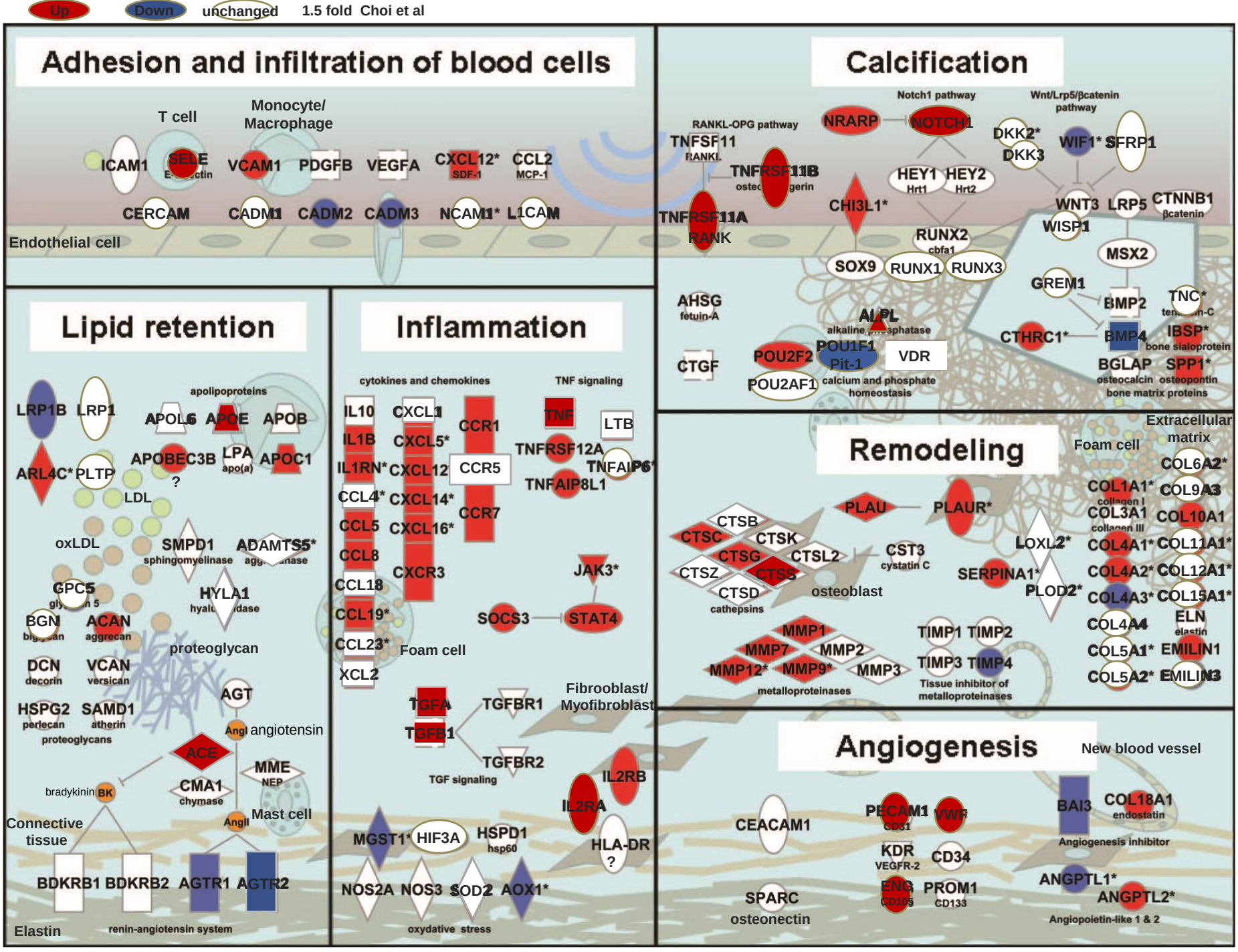
See pages 460 and 470

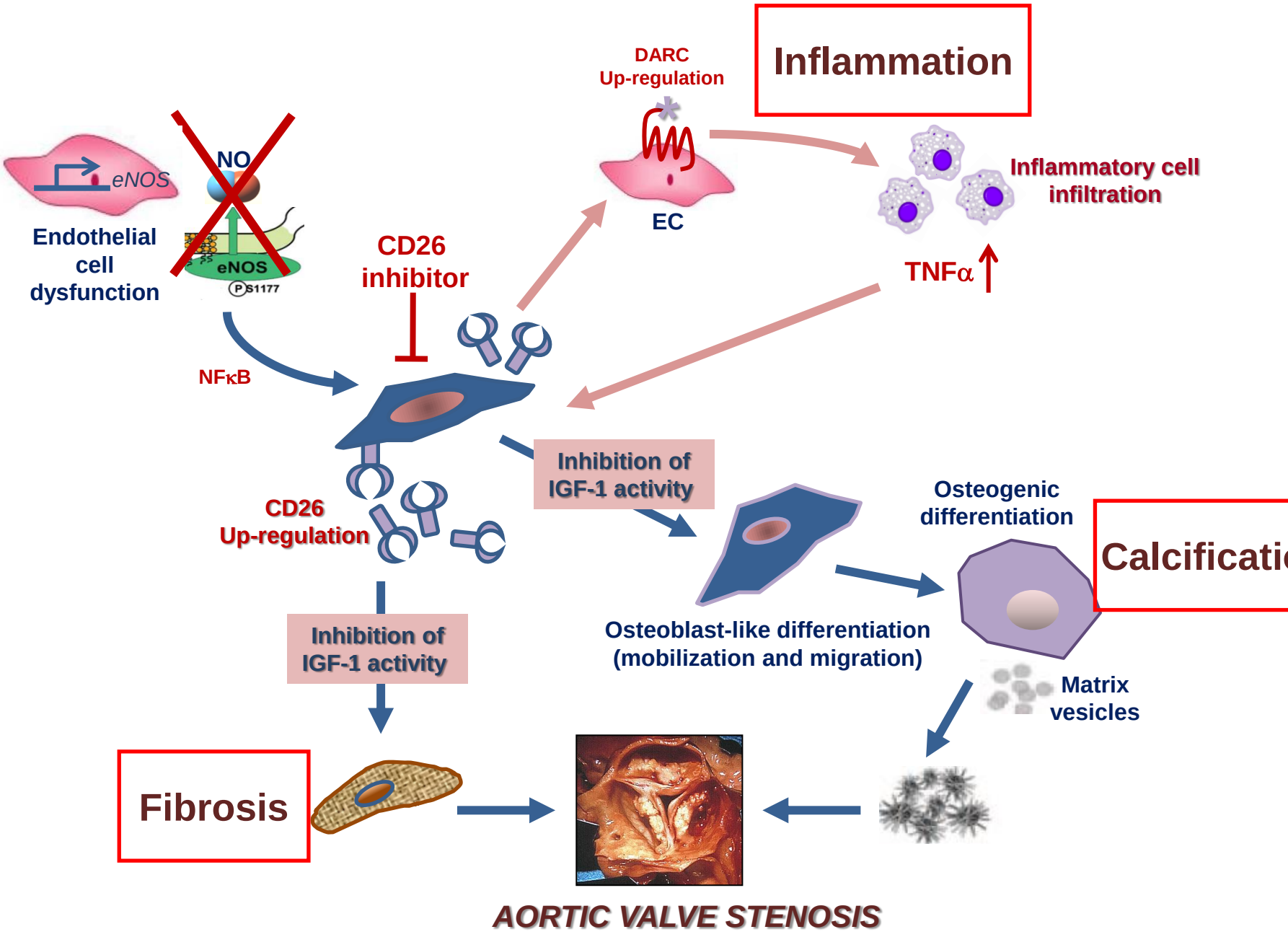
Calcification



Inflammation

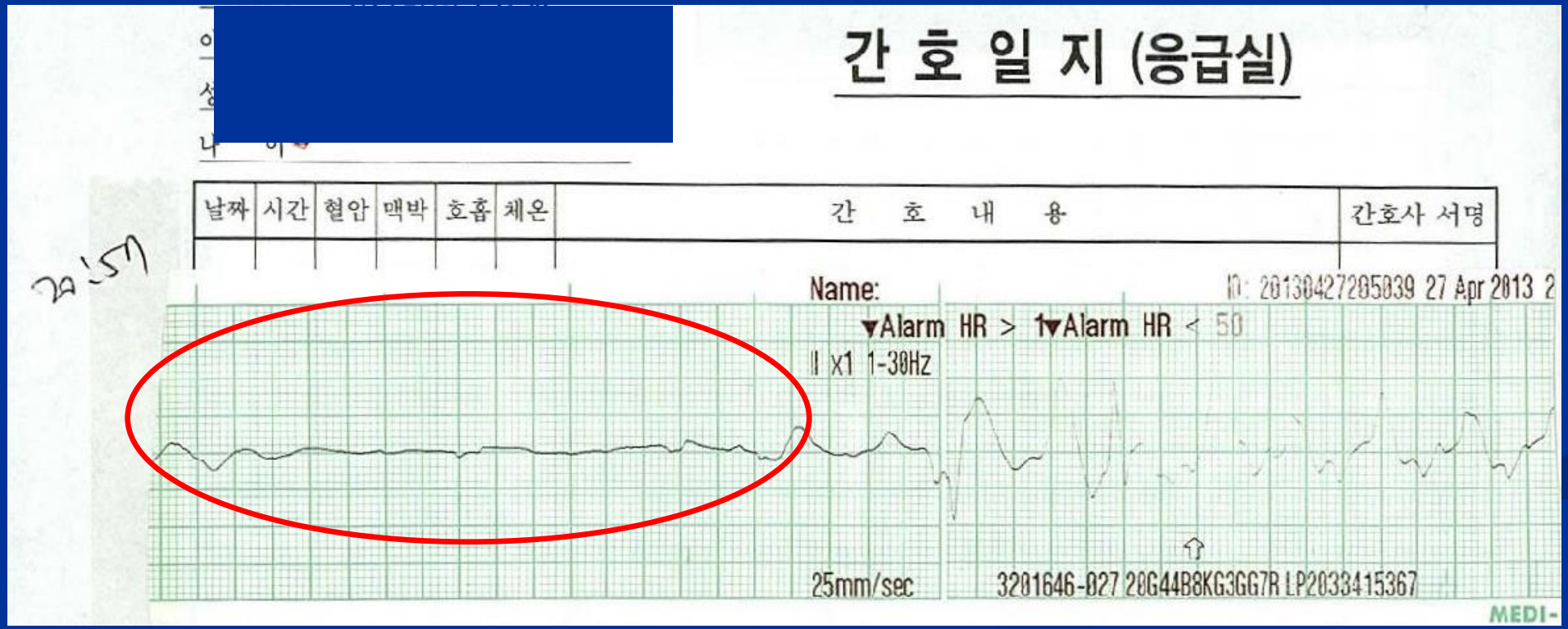



Up
Down
unchanged
1.5 fold Choi et al
Adhesion and infiltration of blood cells
T cell
Monocyte/ Macrophage
ICAM1
SELE
VCAM1
PDGFB
VEGFA
CXCL12*
SDF-1
CCL2
MCP-1
CERCAM
CADM1
CADM2
CADM3
NCAM1*
L1CAM
Endothelial cell
Calcification
Notch1 pathway
Wnt/Lrp5/βcatenin pathway
RANKL-OPG pathway
NRARP
NOTCH1
DKK2*
DKK3
WIF1*
SFRP1
TNFSF11
RANKL
HEY1
Hrt1
HEY2
Hrt2
CHI3L1*
WNT3
LRP5
CTNNB1
βcatenin
WISP1
TNFRSF11A
RANK
RUNX2
cbfa1
MSX2
SOX9
RUNX1
RUNX3
GREM1
AHSG
fetuin-A
BMP2
TNC*
ALPL
alkaline phosphatase
CTHRC1*
BMP4
IBSP*
bone sialoprotein
POU2F2
POU1F1
Pit-1
VDR
BGLAP
osteocalcin
SPP1*
osteopontin
CTGF
POU2AF1
calcium and phosphate homeostasis
bone matrix proteins
Lipid retention
apolipoproteins
LRP1B
LRP1
APOL6
APOE
APOB
APOBEC3B
?
LPA
apo(a)
APOC1
ARL4C*
PLTP
LDL
oxLDL
SMPD1
sphingomyelinase
ADAMTS5*
HYLA1
GPC5
BGN
biglycan
ACAN
aggrecan
proteoglycan
DCN
decorin
VCAN
versican
HSPG2
perlecan
SAMD1
atherin
proteoglycans
AGT
Angl
angiotensin
ACE
MME
NEP
CMA1
chymase
bradykinin
BK
Angll
Mast cell
Connective tissue
BDKRB1
BDKRB2
AGTR1
AGTR2
Elastin
renin-angiotensin system
Inflammation
cytokines and chemokines
TNF signaling
IL10
CXCL1
CCR1
TNF
LTB
IL1B
CXCL5*
TNFRSF12A
TNFAIP6*
IL1RN*
CXCL12
CCR5
TNFAIP8L1
CCL4*
CXCL14*
CCR7
CCL5
CXCL16*
CCL8
CXCR3
JAK3*
CCL18
CCL19*
SOCS3
STAT4
CCL23*
Foam cell
XCL2
TGFA
TGFBR1
Fibrooblast/ Myofibroblast
TGFB1
TGFBR2
TGF signaling
IL2RB
IL2RA
HLA-DR
?
MGST1*
HIF3A
HSPD1
hsp60
NOS2A
NOS3
SOD2
AOX1*
oxydative stress
Remodeling
Foam cell
Extracellular matrix
PLAU
PLAUR*
COL6A2*
COL1A1*
collagen I
COL9A3
CTSB
COL3A1
collagen III
COL10A1
CTSC
CTSK
LOXL2*
COL4A1*
COL11A1*
CTSG
CTSL2
CST3
cystatin C
CTSZ
CTSS
SERPINA1*
COL4A2*
COL12A1*
osteoblast
PLOD2*
CTSD
cathepsins
COL4A3*
COL15A1*
MMP1
TIMP1
TIMP2
ELN
elastin
MMP7
MMP2
COL4A4
MMP12*
MMP9*
MMP3
TIMP3
TIMP4
COL5A1*
EMILIN1
metalloproteinases
Tissue inhibitor of metalloproteinases
COL5A2*
EMILIN3
Angiogenesis
New blood vessel
CEACAM1
PECAM1
CD31
VWF
BAI3
COL18A1
endostatin
KDR
VEGFR-2
CD34
Angiogenesis inhibitor
ANGPTL1*
ENG
CD105
PROM1
CD133
ANGPTL2*
SPARC
osteonectin
Angiopoietin-like 1 & 2

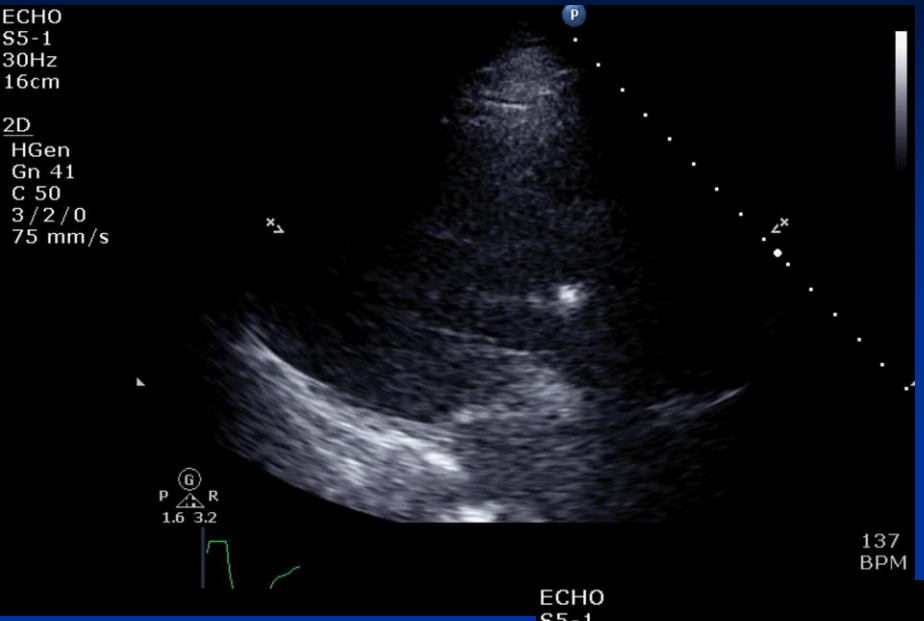

Inflammation
DARC
Up-regulation
eNOS
NO
eNOS
P S1177
Endothelial cell dysfunction
EC
Inflammatory cell infiltration
TNFα
CD26 inhibitor
NFκB
CD26
Up-regulation
Inhibition of IGF-1 activity
Osteogenic differentiation
Calcification
Osteoblast-like differentiation (mobilization and migration)
Matrix vesicles
Inhibition of IGF-1 activity
Fibrosis
AORTIC VALVE STENOSIS

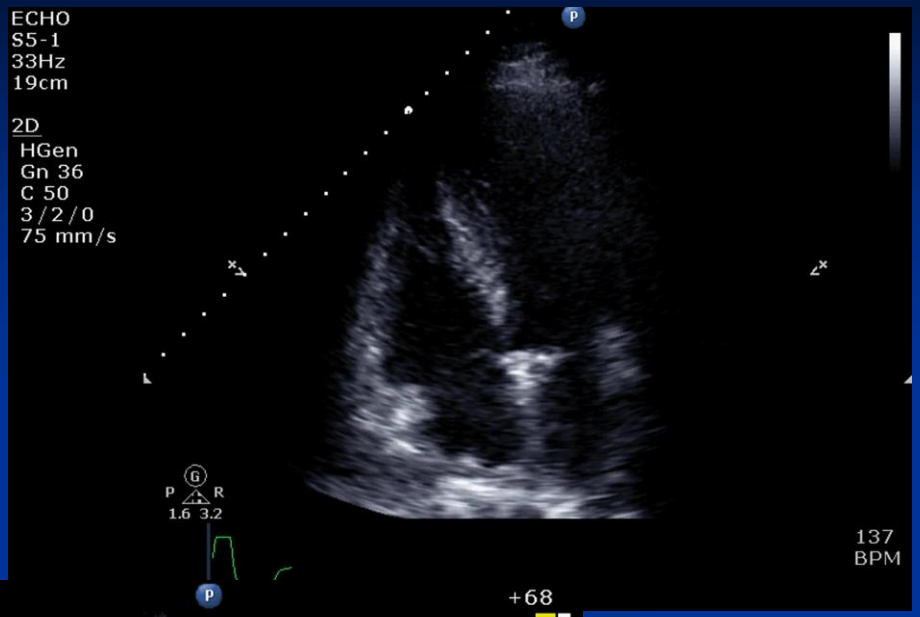
New Therapeutic Target for the Calcification Would Be Enough ???

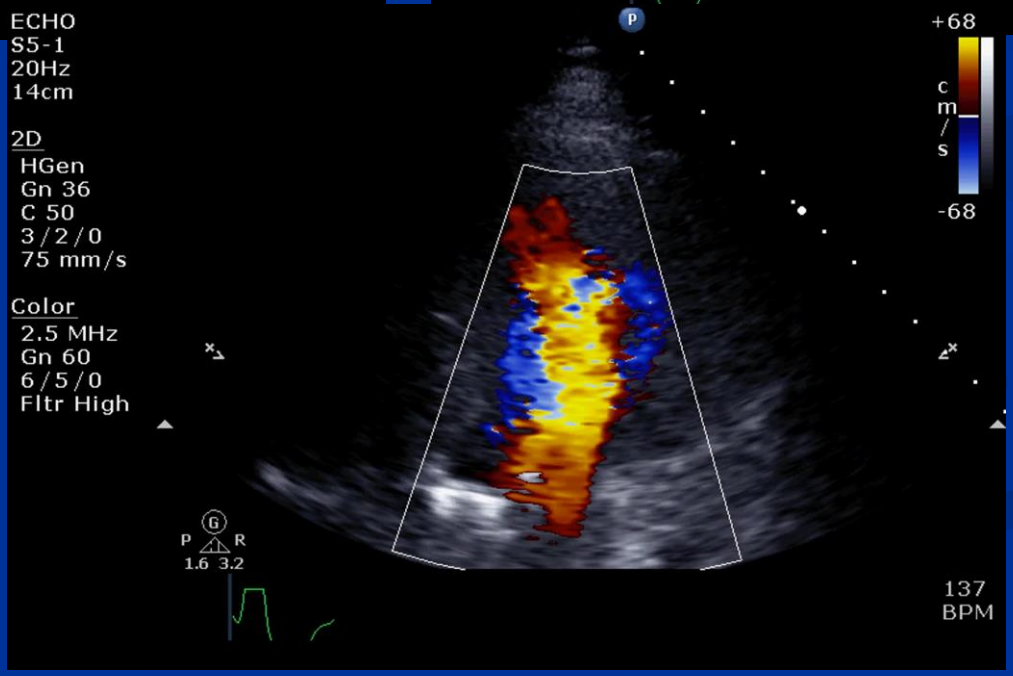
62/F
4YA HTN on MX
10MA AVR
PreOP CAG: mild CAD



Portable echocardiography







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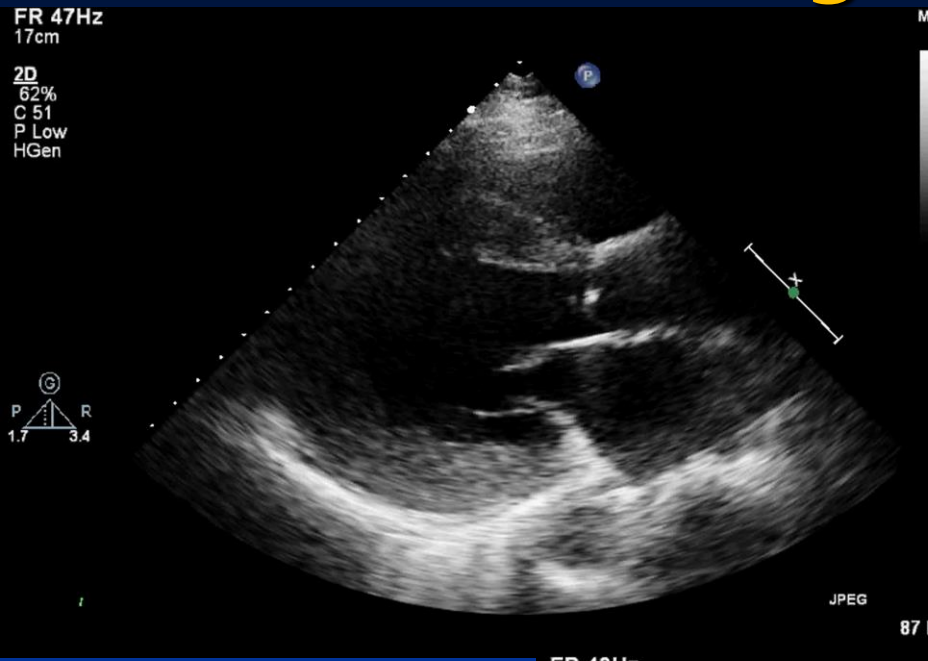
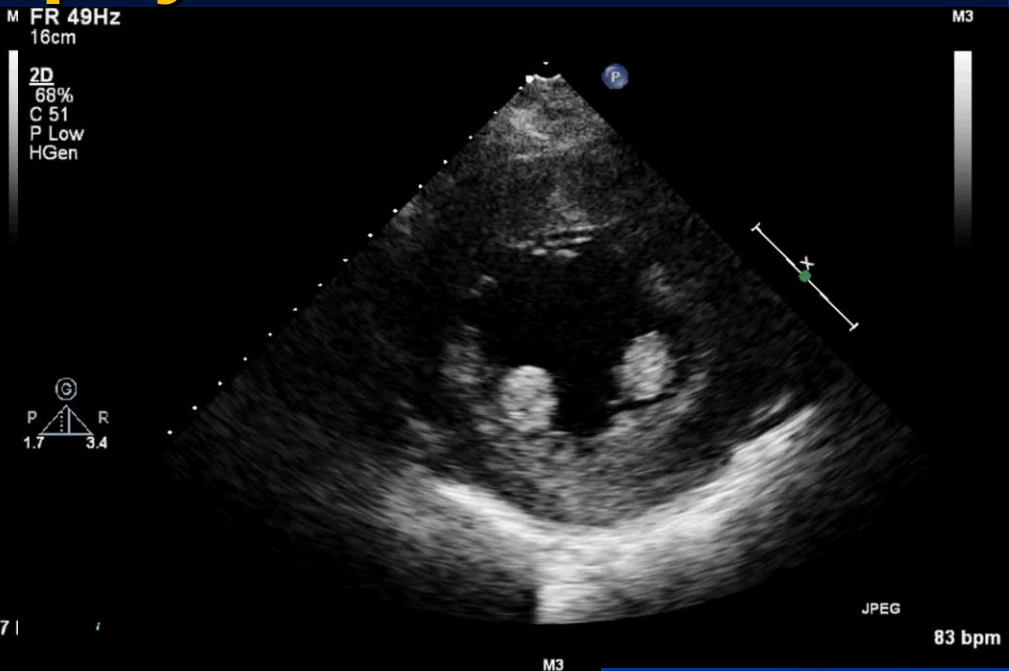
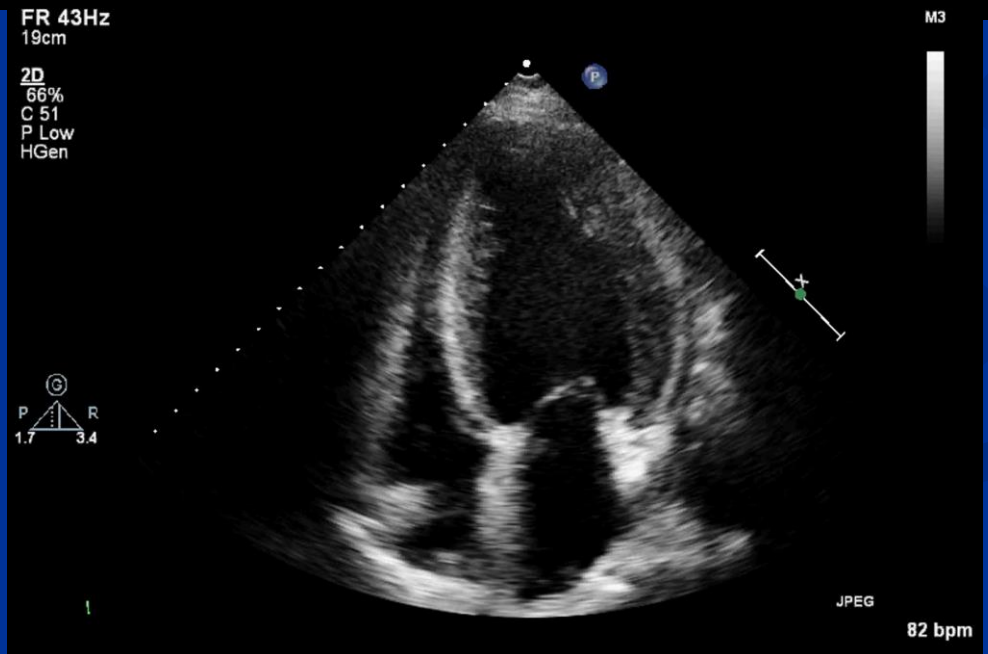
Echocardiography before OP







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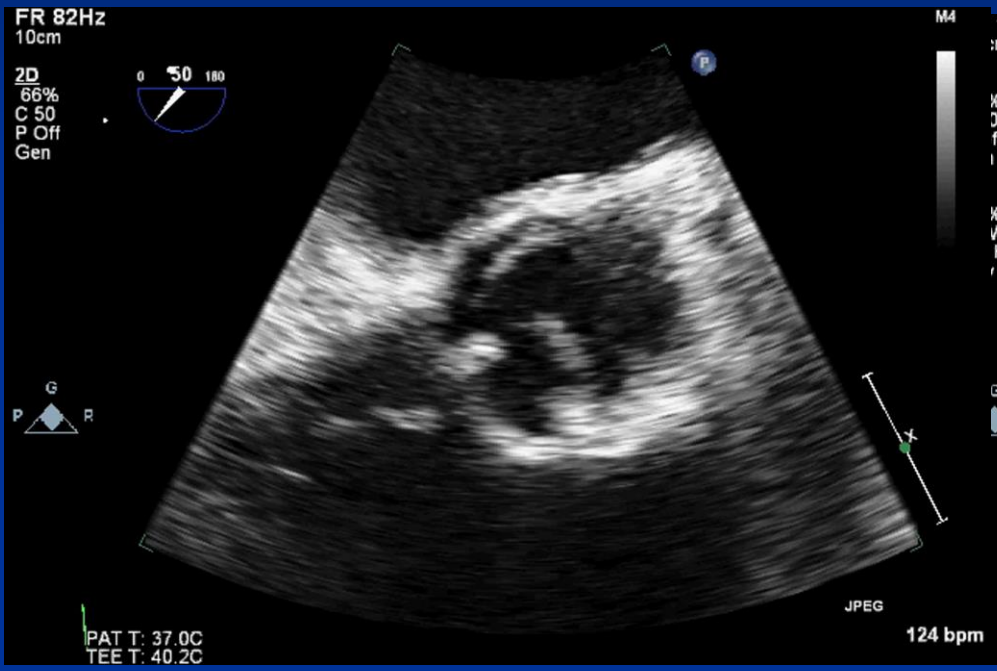
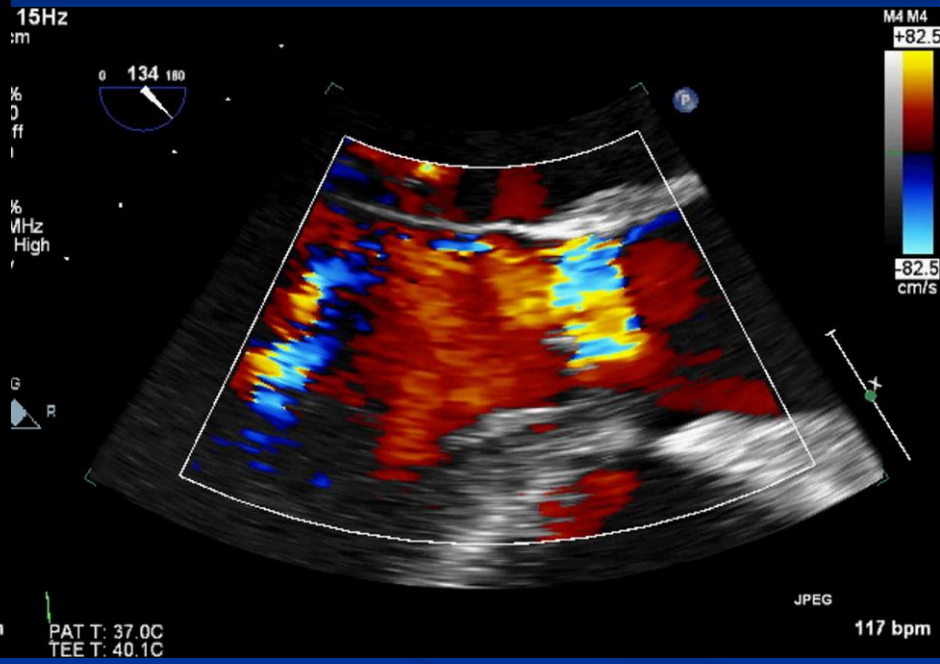
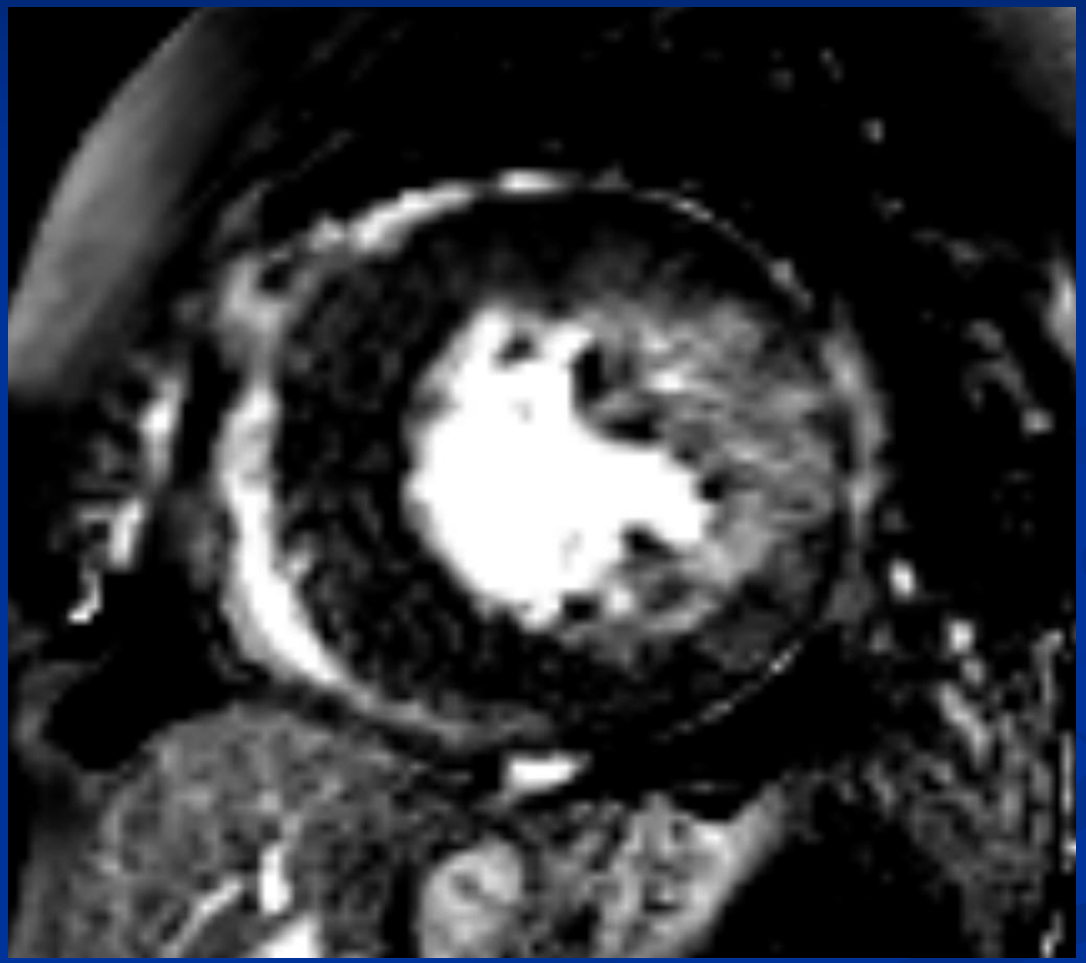
Echocardiography before OP





Cardiac MRI before OP



Prognostic Significance of Myocardial Fibrosis Quantification by Histopathology and Magnetic Resonance Imaging in Patients With Severe Aortic Valve Disease

Clerio F. Azevedo, MD, Marcelo Nigri, MD, Maria L. Higuchi, MD, Pablo M. Pomerantzeff, MD, Guilherme S. Spina, MD, Roney O. Sampaio, MD, Flávio Tarasoutchi, MD, Max Grinberg, MD, Carlos Eduardo Rochitte, MD

São Paulo, Brazil

Table 1 Pre-Operative Characteristics of the 54 Patients

	All (n = 54)	Aortic Regurgitation (n = 26)	Aortic Stenosis (n = 28)	p Value
Sex				
Male	42 (78%)	24 (92%)	18 (64%)	0.02
Female	12 (22%)	2 (8%)	10 (36%)	
Age (yrs)	46.8 ± 13.7	46.5 ± 14.2	47.2 ± 13.5	0.85
Etiology				
Rheumatic disease	27 (50%)	20 (77%)	7 (25%)	<0.001
Bicuspid aortic valve	18 (33%)	3 (11.5%)	15 (54%)	
Degenerative/calcification	6 (11%)	0	6 (21%)	
Other	3 (6%)	3 (11.5%)	0	
NYHA functional class				
I	3 (5%)	2 (8%)	1 (4%)	0.79
II	22 (41%)	10 (38%)	12 (43%)	
III	29 (54%)	14 (54%)	15 (53%)	
Angina	13 (24%)	3 (12%)	10 (36%)	0.04
Syncope	5 (9%)	1 (4%)	4 (14%)	0.18
Pressure gradient (mm Hg)				
Peak	—	—	97 ± 27	—
Mean	—	—	63 ± 20	—
Hypertension	0	0	0	—
Diabetes	0	0	0	—
Hypercholesterolemia	0	0	0	—
Smoking	2 (4%)	1 (4%)	1 (4%)	1.0
Family history of CAD	0	0	0	—
LV EDV (ml)	244 ± 92	318 ± 68	175 ± 43	<0.001
LV ESV (ml)	124 ± 67	169 ± 67	83 ± 30	<0.001
LV mass (g)	272 ± 47	280 ± 44	266 ± 50	0.27
LVEF (%)	51 ± 11	48 ± 11	53 ± 9	0.09
MF by histopathology (%)	24.6 ± 9.8	25.8 ± 10.3	23.4 ± 9.3	0.37
MF by ce-MRI (%)	3.72 ± 2.17	4.35 ± 2.32	3.15 ± 1.87	0.04
MF by qualitative analysis				
Present	35 (65%)	18 (69%)	17 (61%)	0.51
Absent	19 (35%)	8 (31%)	11 (39%)	

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Midwall Fibrosis Is an Independent Predictor of Mortality in Patients With Aortic Stenosis

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London and Edinburgh, United Kingdom

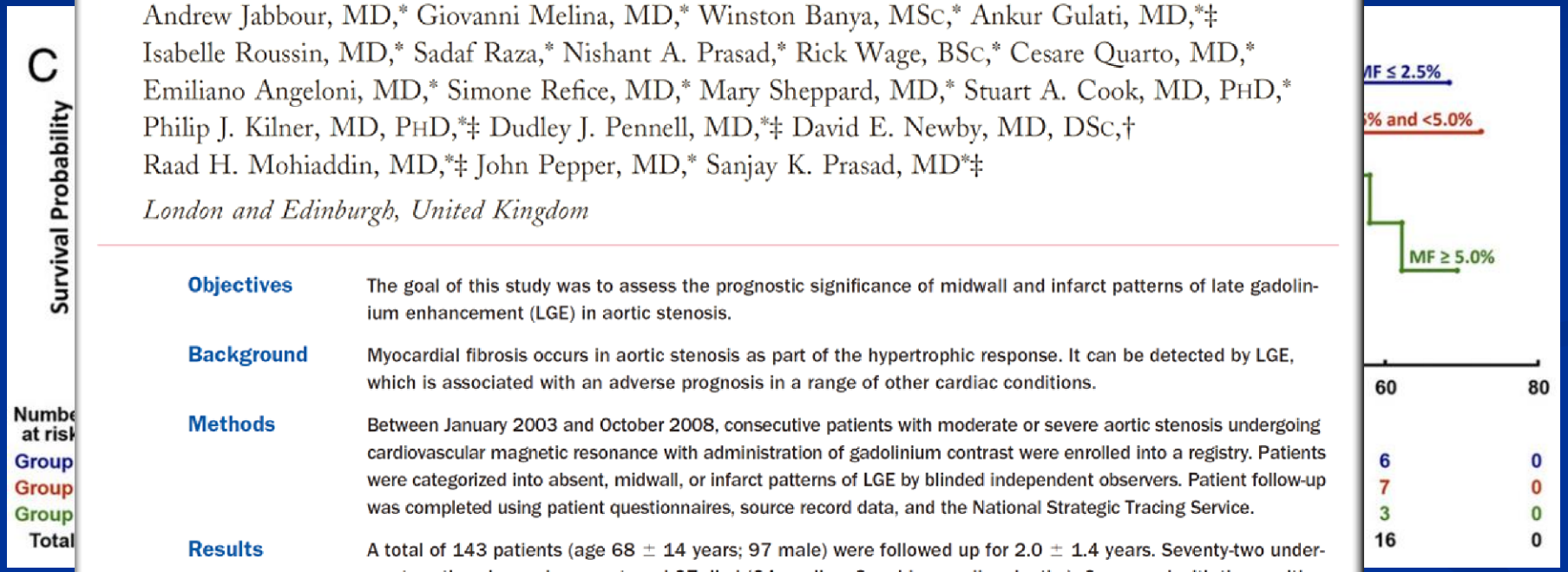
Objectives The goal of this study was to assess the prognostic significance of midwall and infarct patterns of late gadolinium enhancement (LGE) in aortic stenosis.

Background Myocardial fibrosis occurs in aortic stenosis as part of the hypertrophic response. It can be detected by LGE, which is associated with an adverse prognosis in a range of other cardiac conditions.

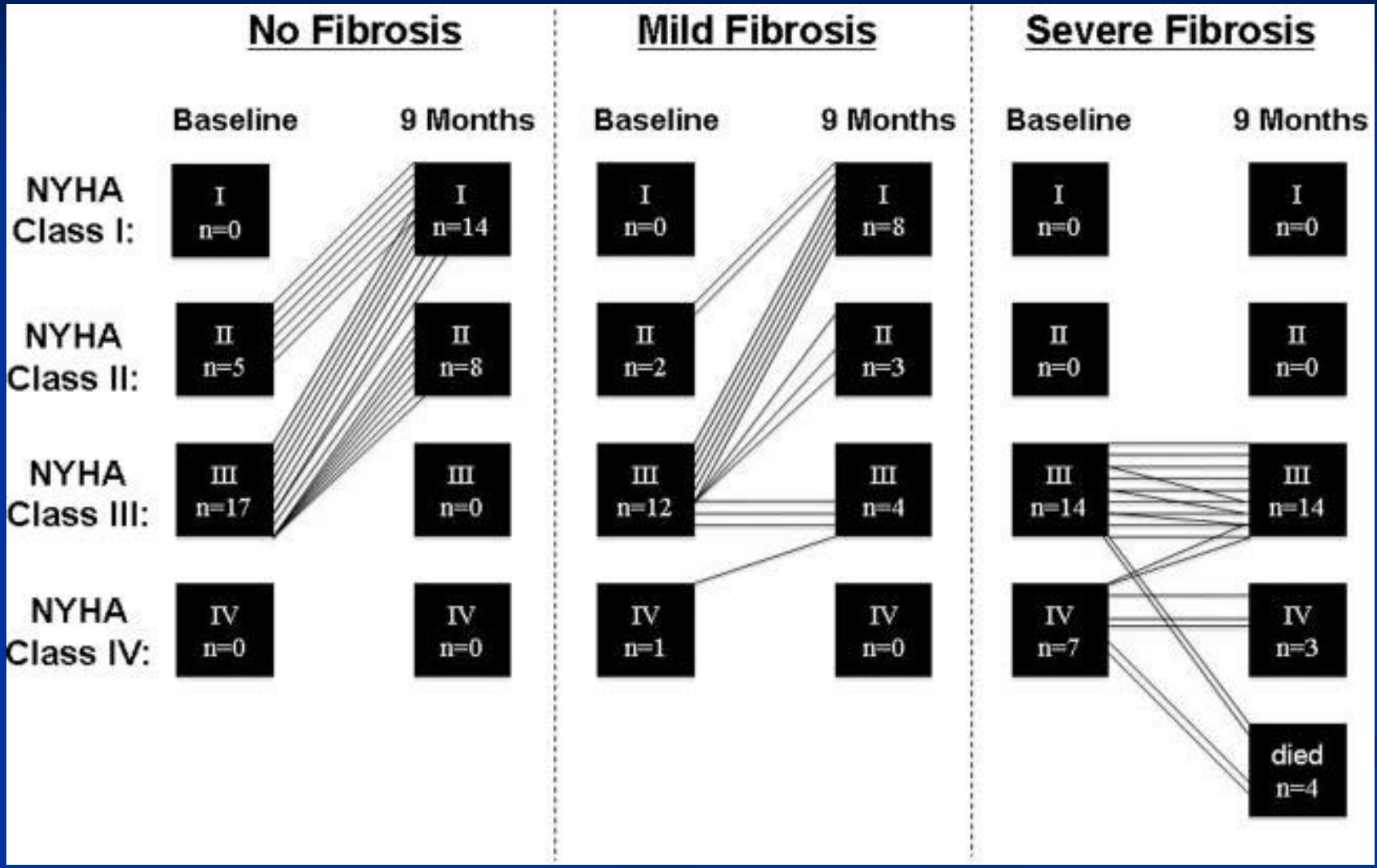
Methods Between January 2003 and October 2008, consecutive patients with moderate or severe aortic stenosis undergoing cardiovascular magnetic resonance with administration of gadolinium contrast were enrolled into a registry. Patients were categorized into absent, midwall, or infarct patterns of LGE by blinded independent observers. Patient follow-up was completed using patient questionnaires, source record data, and the National Strategic Tracing Service.

Results A total of 143 patients (age 68 ± 14 years; 97 male) were followed up for 2.0 ± 1.4 years. Seventy-two underwent aortic valve replacement, and 27 died (24 cardiac, 3 sudden cardiac deaths). Compared with those with no LGE (n = 49), univariate analysis revealed that patients with midwall fibrosis (n = 54) had an 8-fold increase in all-cause mortality despite similar aortic stenosis severity and coronary artery disease burden. Patients with an infarct pattern (n = 40) had a 6-fold increase. Midwall fibrosis (hazard ratio: 5.35; 95% confidence interval: 1.16 to 24.56; p = 0.03) and ejection fraction (hazard ratio: 0.96; 95% confidence interval: 0.94 to 0.99; p = 0.01) were independent predictors of all-cause mortality by multivariate analysis.

Conclusions Midwall fibrosis was an independent predictor of mortality in patients with moderate and severe aortic stenosis. It has incremental prognostic value to ejection fraction and may provide a useful method of risk stratification. (The Prognostic Significance of Fibrosis Detection in Cardiomyopathy; NCT00930735) (J Am Coll Cardiol 2011; 58:1271–9) © 2011 by the American College of Cardiology Foundation



Functional capacity recovery after AVR



Circulation. 2009;120:577-584

Calcific aortic stenosis

A Disease of the Valve and the Myocardium

Summary

- **Aortic valve sclerosis**
  - Clinical precursors of degenerative AS
  - Related with cardiovascular mortality and morbidity
- **Calcific aortic stenosis**
  - Precursor
  - Pathologic cellular mechanism
  - Early detection & intervention
  - New therapeutic target : calcification
  - A disease of the valve and the myocardium

Dream Therapeutic Target