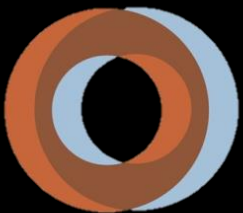


Aortic Valve Stenosis: Medical Treatment, Still in the Pipeline?

Philippe Pibarot, DVM, PhD, FACC, FAHA, FESC, FASE
Research Group in Valvular Heart Diseases
Canada Research Chair in Valvular Heart Diseases



**Institut Universitaire de Cardiologie
et de Pneumologie de Québec /
Québec Heart & Lung Institute**



**Université
LAVAL**

Disclosure: Philippe Pibarot

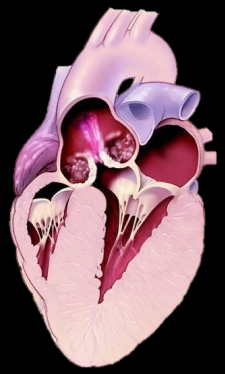
Financial relationship with industry:

- **Edwards Lifesciences: Echo CoreLab for PARTNER 2– SAPIEN 3, PARTNER 3, TAVR-UNLOAD, EARLY-TAVR trials**
- **V-Wave Ltd: Echo CoreLab for FIM Study**
- **Cardiac Phoenix: Echo CoreLab for BACE FIM Study**
- **Ionis Pharmaceuticals**

Other financial disclosure

- **Foundation Grant, Canadian Institutes of Health Research**

Off label Use: None



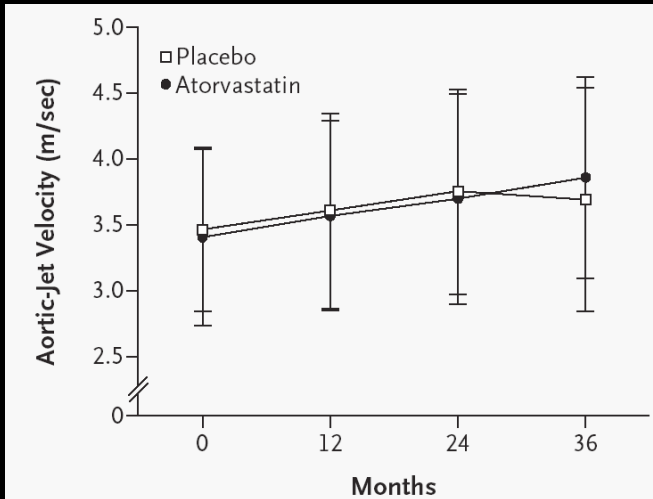
The Changing Face of Aortic Stenosis

- **“Degenerative” process as a result of wear and tear?**
- **AS shares many similarities (risk factors, mechanisms) with atherosclerosis**
- **AS: a potentially modifiable atherosclerotic disease?**
- **Hope for pharmacotherapy in AS: Statins!**



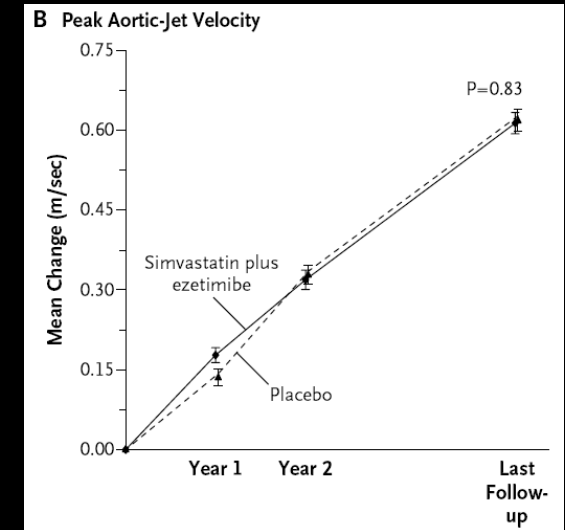
Effect of Statins on AS Progression: Randomized Trials

SALTIRE



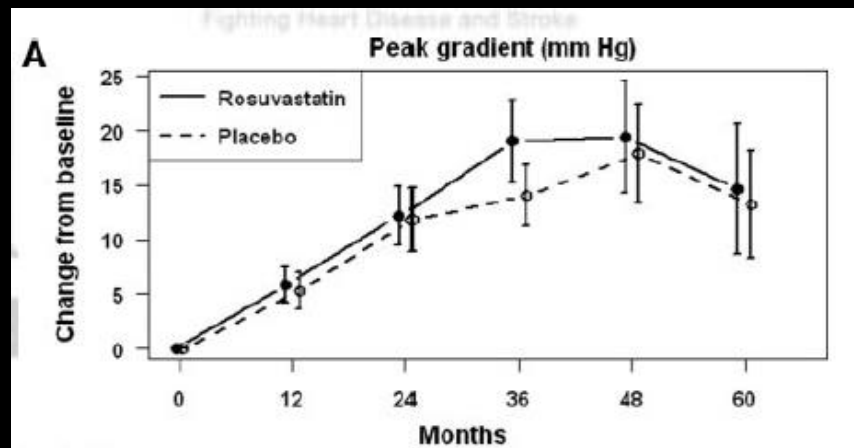
Cowell, NEJM,
352:2389-97,2005

SEAS



Rossebo NEJM,
359:1343-56, 2008

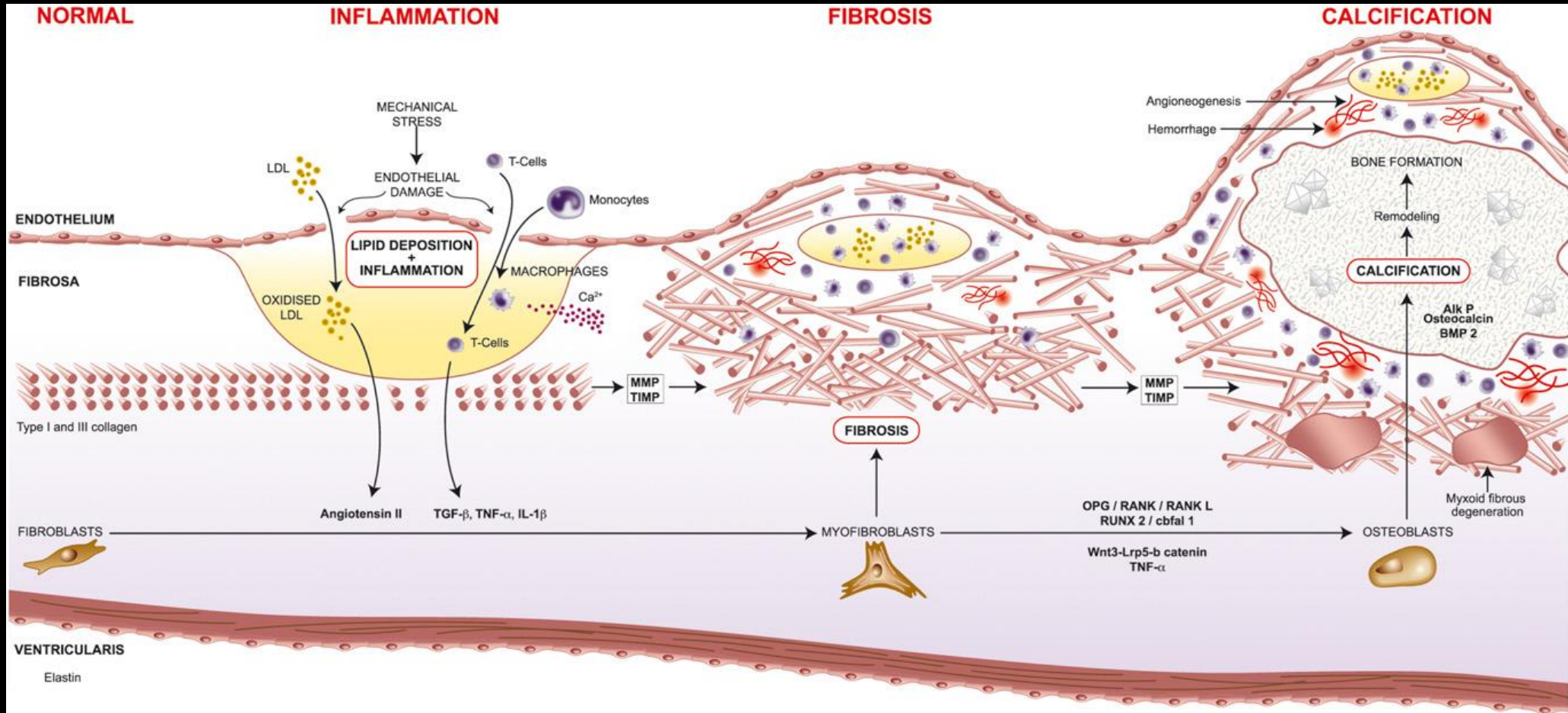
ASTRONOMER



Chan Circulation
121:306-314, 2010

Calcific AS has *some similarities and some dissimilarities* with atherosclerosis

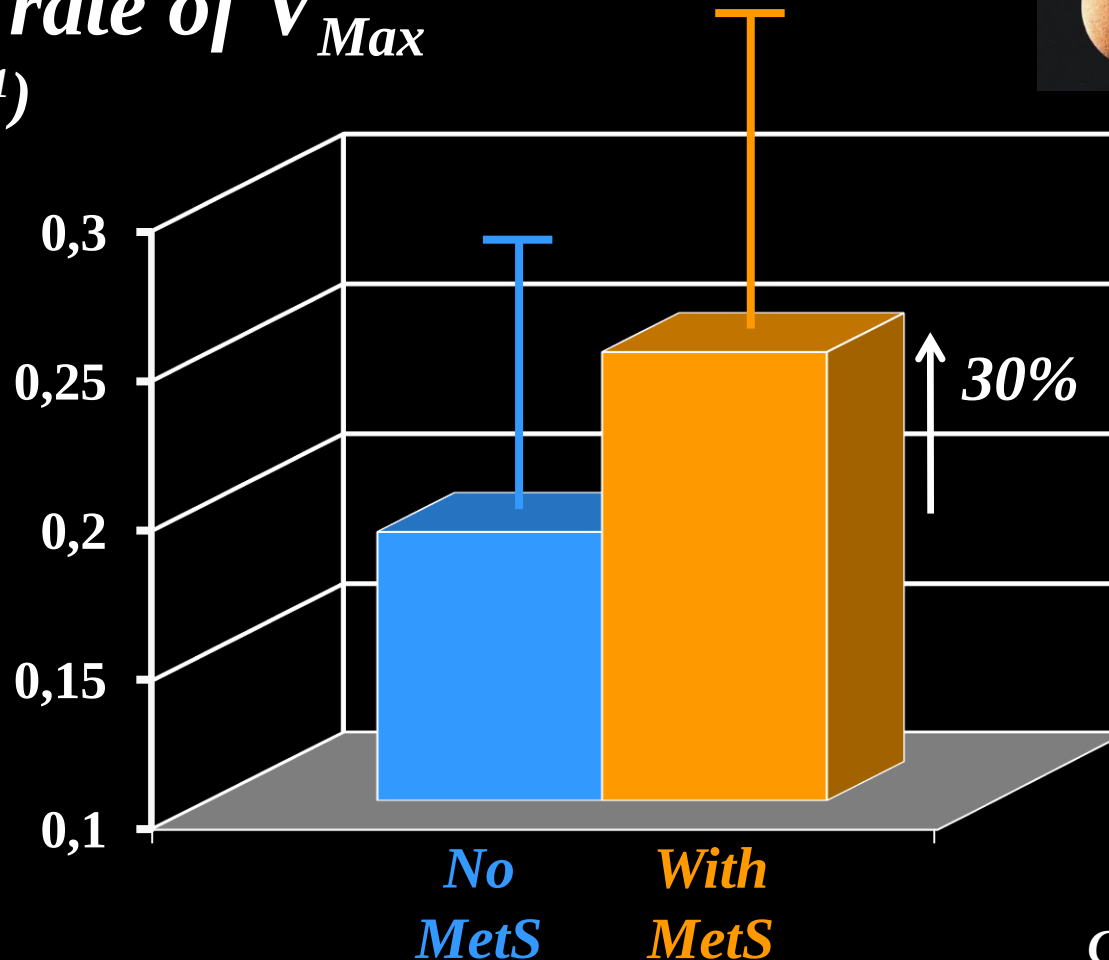
C Otto Circulation 1994



Dweck et al . JACC 2012

MetS is a Predictor of Faster Stenosis Progression: A Substudy of the ASTRONOMER Trial

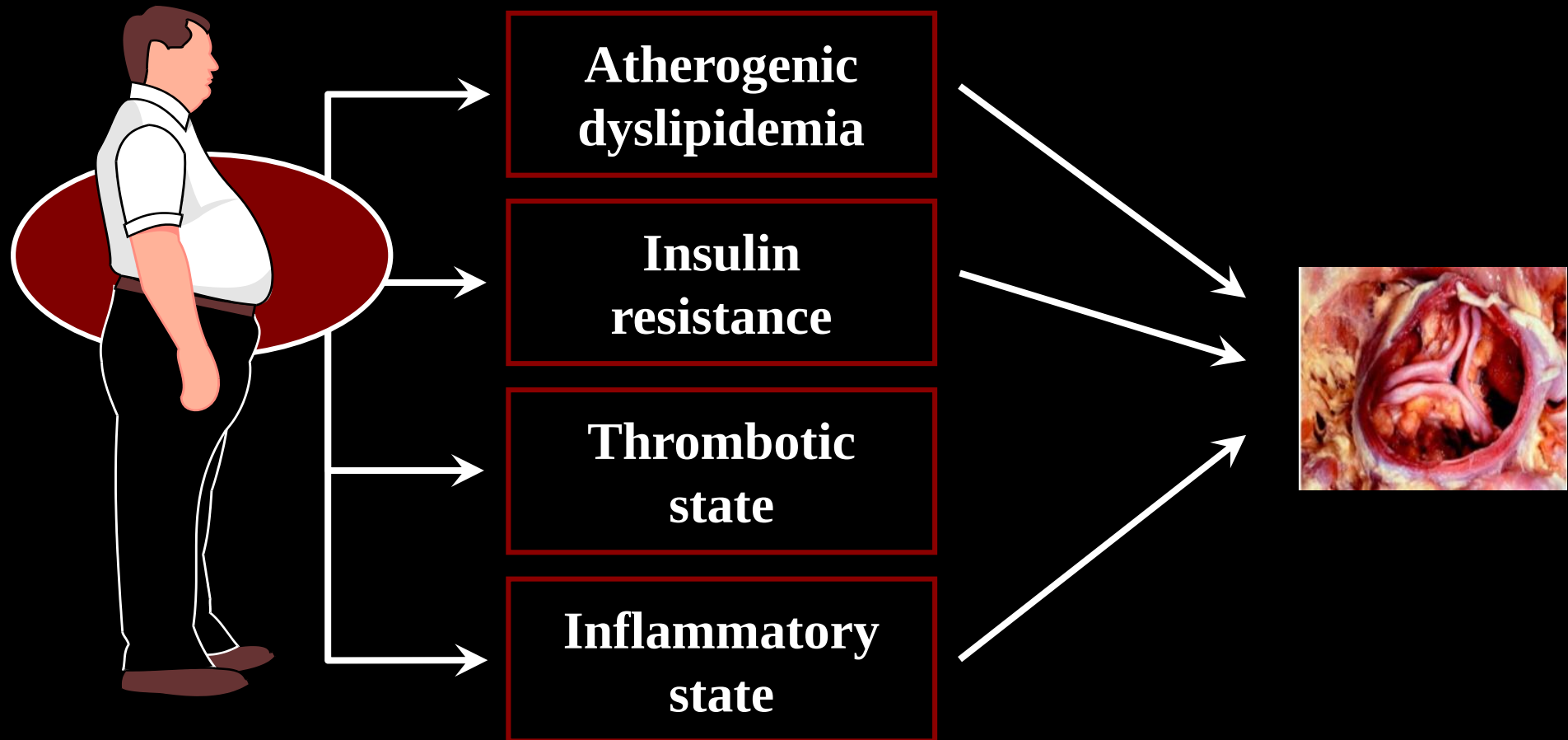
*Progression rate of V_{Max}
($m.s^{-1}.yr^{-1}$)*



$p = 0.03$

*Capoulade et al.
JACC 2012 ;60:216-23*

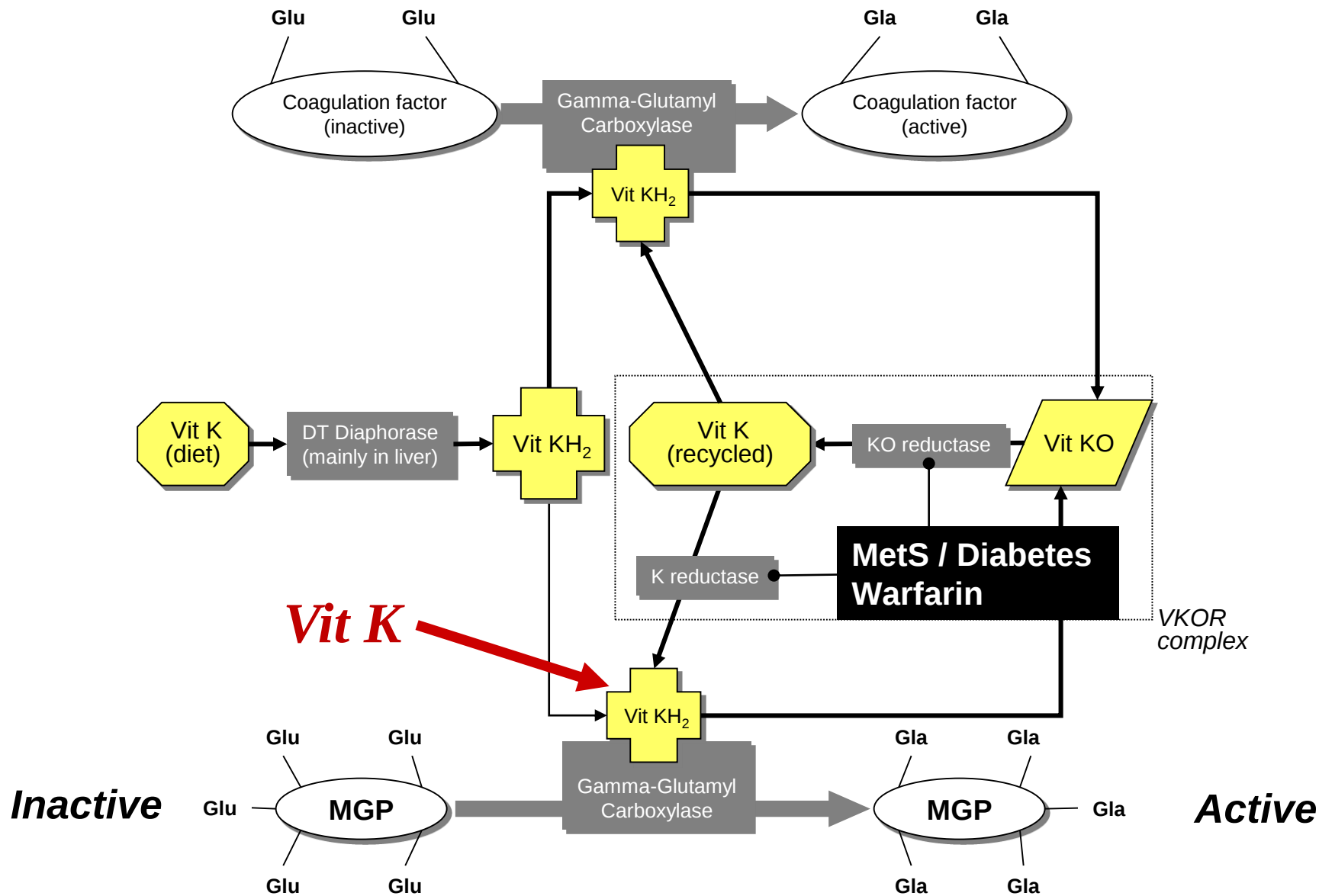
Metabolic Abnormalities Linked to Visceral Obesity Predispose to Initiation and Progression of calcific AS



Lifestyle Improvement Strategies

From JAMA (2001) 285 :2486-2497

Matrix Gla Protein Protects Against Ectopic Calcification: Effect of Diabetes



Slower Progress of Aortic Valve Calcification With Vitamin K Supplementation

Results From a Prospective Interventional Proof-of-Concept Study

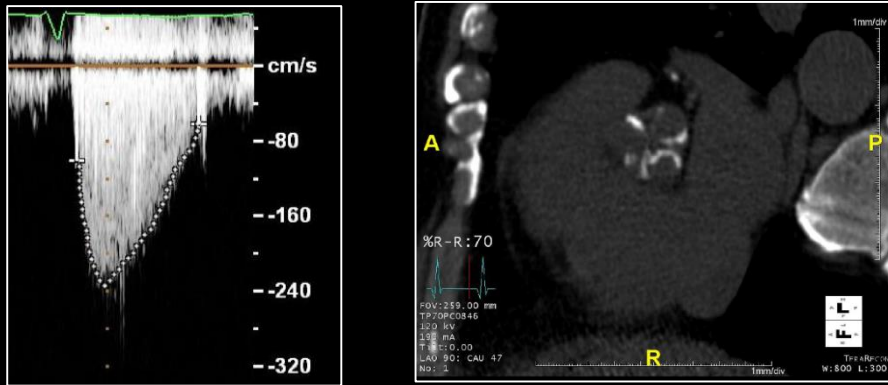
Patients with aortic sclerosis or mild/moderate AS were randomized to 2 mg VitK1 vs. placebo

	Vitamin K Group (n=38)					Placebo Group (n=34)				
	t0		t12			t0		t12		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Age, y	69.3	10.1						68.9	7.9	
Calcification volume, mL	793	742	871	791	0.006*	836	856	1017	939	<0.001†
Mean valvular gradient, mm Hg	17	6	17	7	0.63*	18	8	21	11	0.03†
Peak flow velocity, m/s	2.70	0.44	2.63	0.56	0.42*	2.82	0.62	2.95	0.70	0.24†

Patient with Mild AS and Rapid Progression during FU (B Stage)

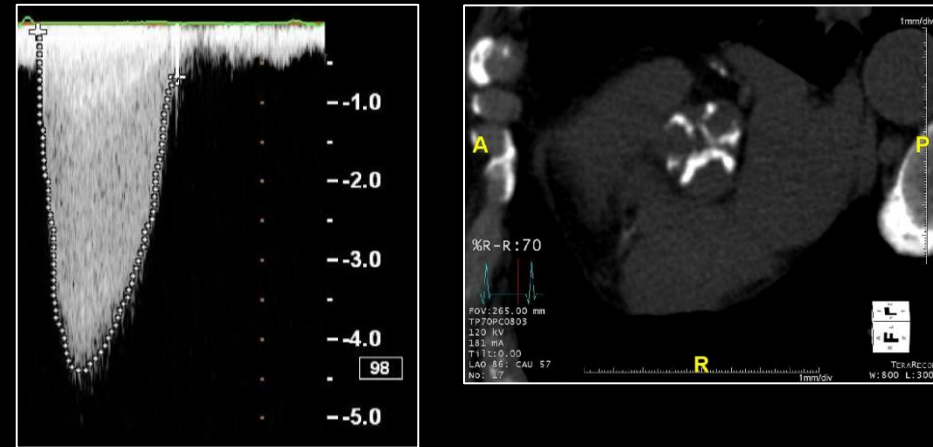
57 y.o. man with mild calcific AS

Baseline



- V_{Peak} : 2.3 m/s
- Peak/mean gradients: 22/12 mmHg
- AVA: 1.6 cm²
- Calcium score: 901 AU

2.5 years later



- V_{Peak} : 4.4 m/s (progression 0.8 m/s/yr)
- Peak/mean gradients: 77/44 mmHg
- AVA: 0.88 cm²
- Calcium score: 2007 AU

Lipoprotein (a) level: 147 mg/dl

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

FEBRUARY 7, 2013

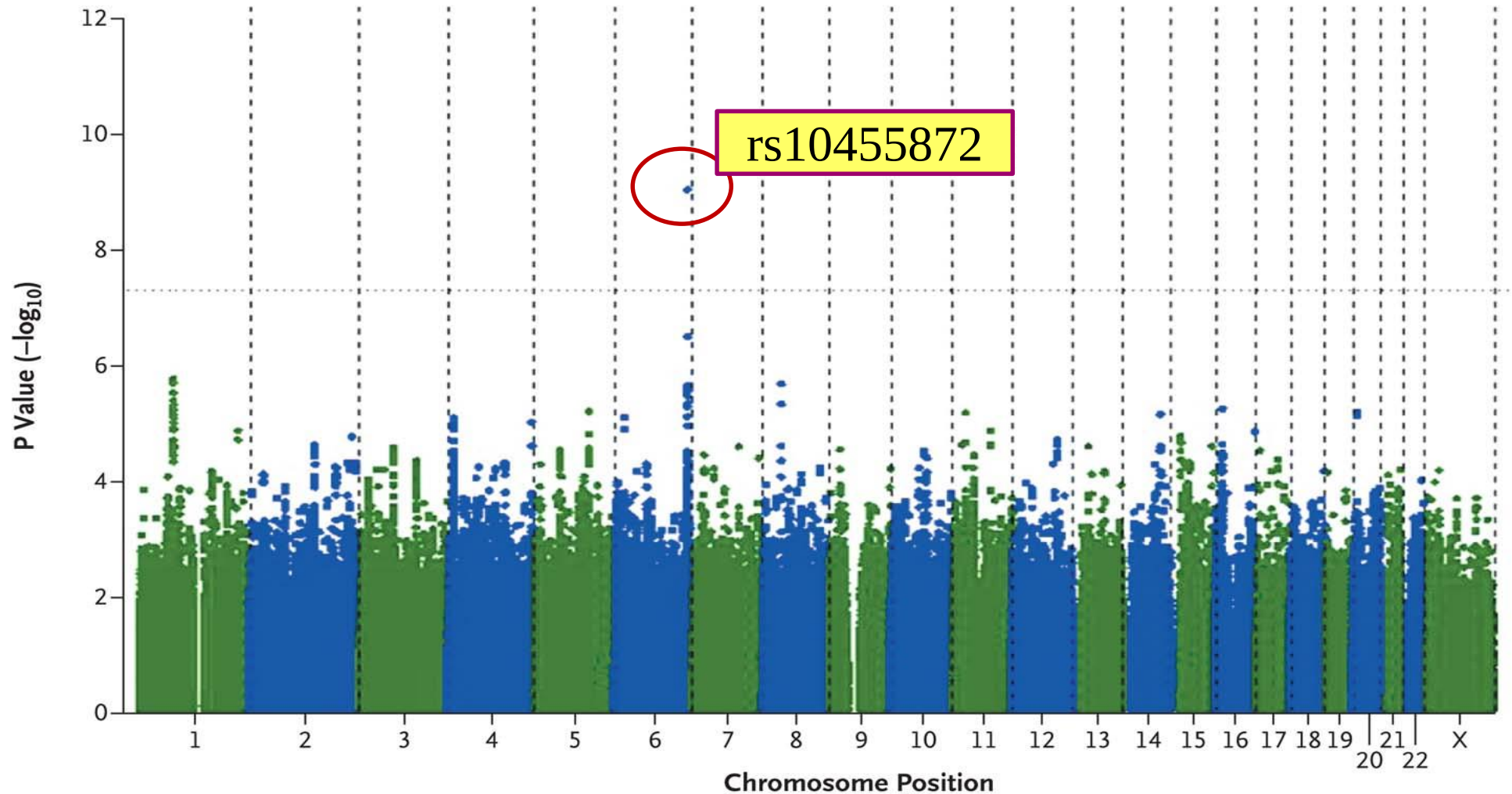
VOL. 368 NO. 6

Genetic Associations with Valvular Calcification and Aortic Stenosis

George Thanassoulis, M.D., Catherine Y. Campbell, M.D., David S. Owens, M.D., J. Gustav Smith, M.D., Ph.D., Albert V. Smith, Ph.D., Gina M. Peloso, Ph.D., Kathleen F. Kerr, Ph.D., Sonali Pechlivanis, Ph.D., Matthew J. Budoff, M.D., Tamara B. Harris, M.D., Rajeev Malhotra, M.D., Kevin D. O'Brien, M.D., Pia R. Kamstrup, M.D., Ph.D., Børge G. Nordestgaard, M.D., D.M.Sc., Anne Tybjaerg-Hansen, M.D., D.M.Sc., Matthew A. Allison, M.D., M.P.H., Thor Aspelund, Ph.D., Michael H. Criqui, M.D., M.P.H., Susan R. Heckbert, M.D., Ph.D., Shih-Jen Hwang, Ph.D., Yongmei Liu, Ph.D., Marketa Sjogren, Ph.D., Jesper van der Pals, M.D., Ph.D., Hagen Kälisch, M.D., Thomas W. Mühleisen, Ph.D., Markus M. Nöthen, M.D., L. Adrienne Cupples, Ph.D., Muriel Caslake, Ph.D., Emanuele Di Angelantonio, M.D., Ph.D., John Danesh, F.R.C.P., Jerome I. Rotter, M.D., Sigurdur Sigurdsson, M.Sc., Quenna Wong, M.S., Raimund Erbel, M.D., Sekar Kathiresan, M.D., Olle Melander, M.D., Ph.D., Vilmundur Gudnason, M.D., Ph.D., Christopher J. O'Donnell, M.D., M.P.H., and Wendy S. Post, M.D.,
for the CHARGE Extracoronary Calcium Working Group

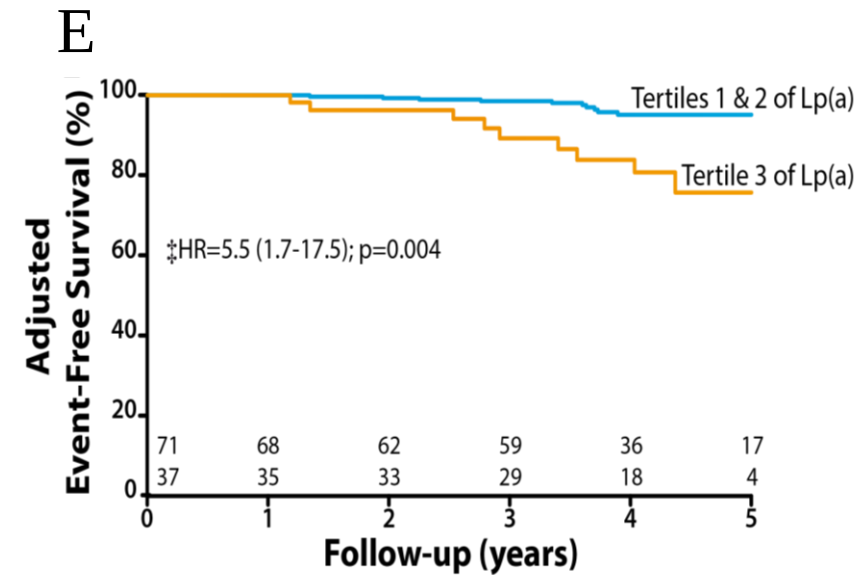
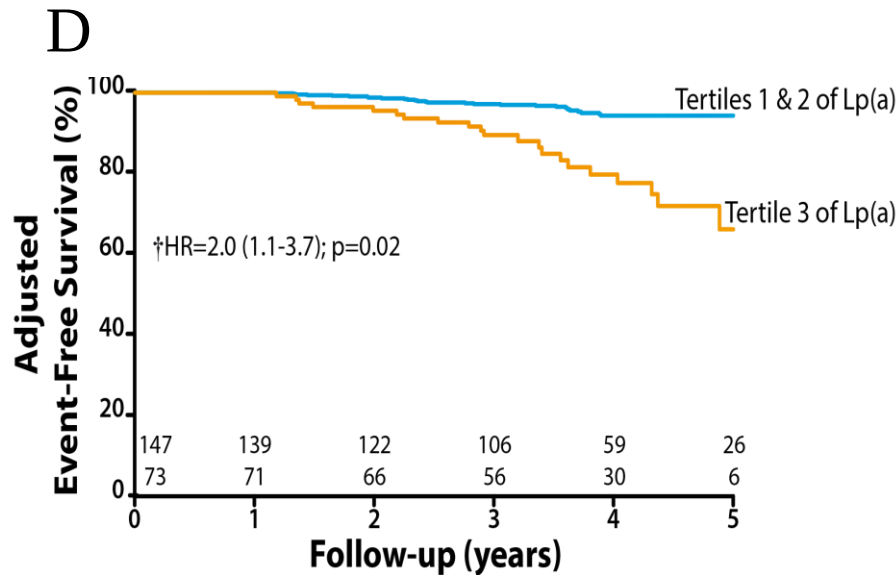
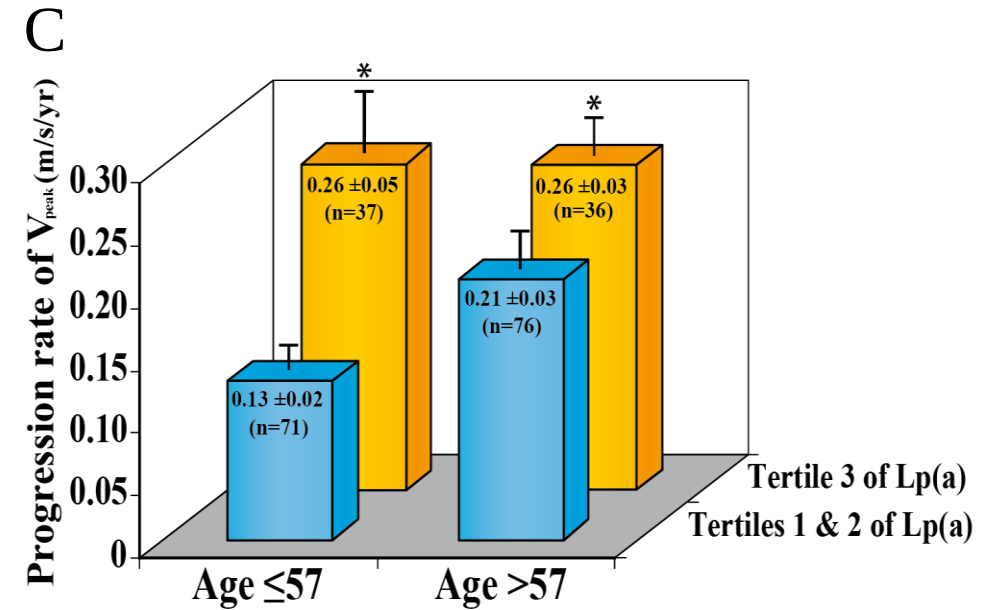
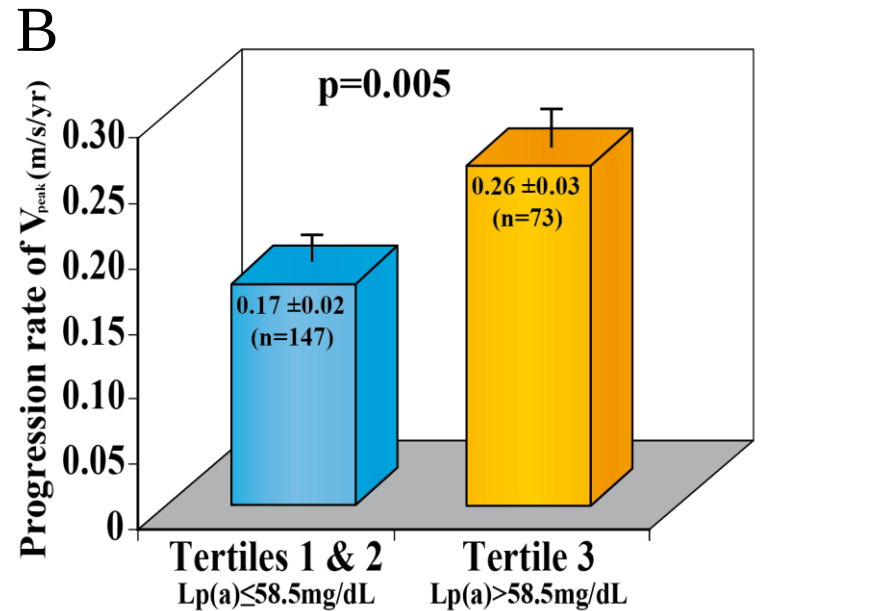
Association between LPA and Aortic Valve Calcification

A SNP Associations with Aortic-Valve Calcium

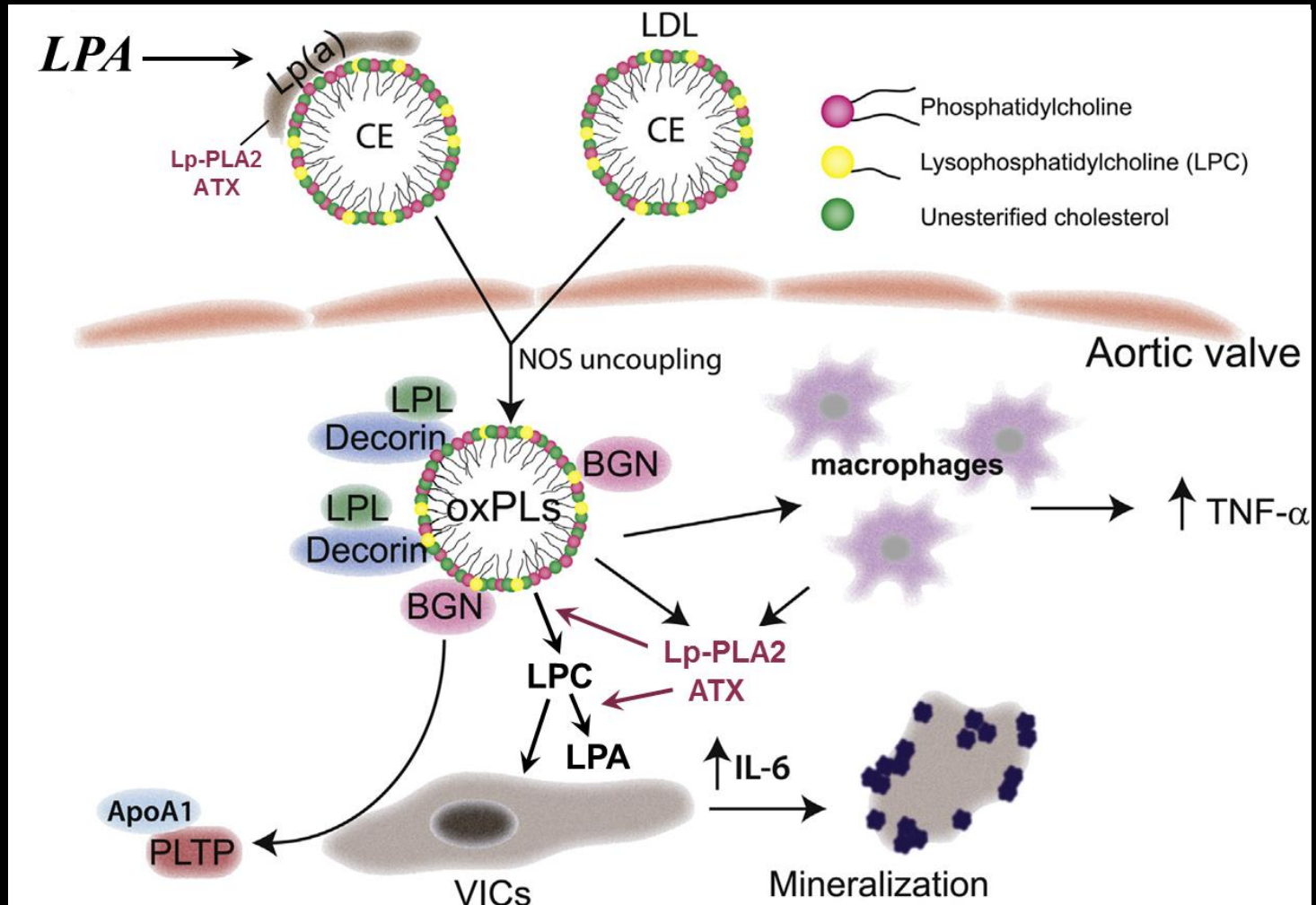


Genomewide significance prespecified = $P < 5.0 \times 10^{-8}$

Lipoprotein(a) and AS Progression: Astronomer Trial

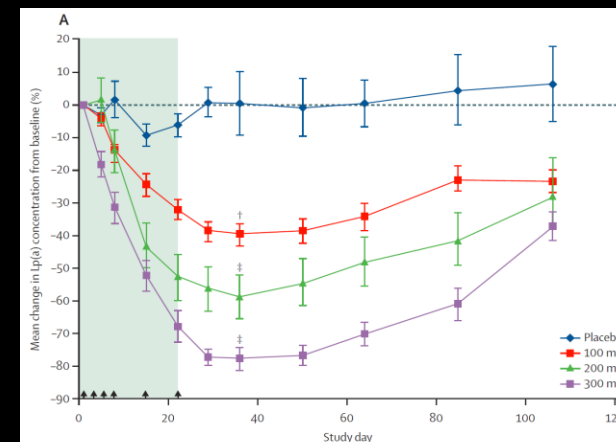
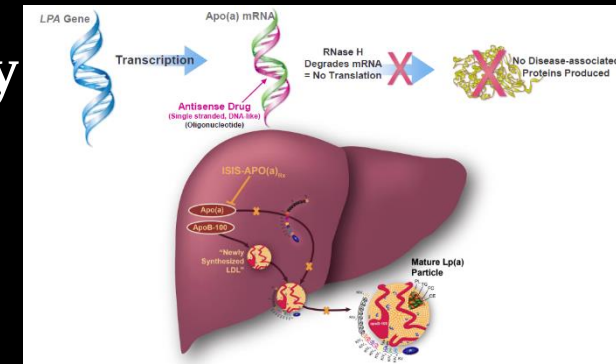
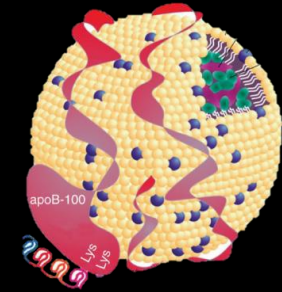


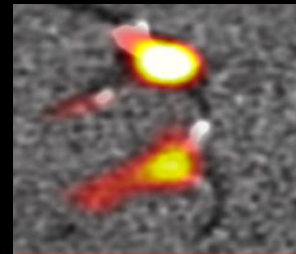
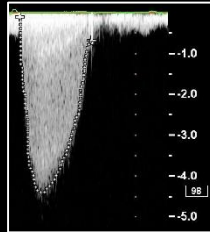
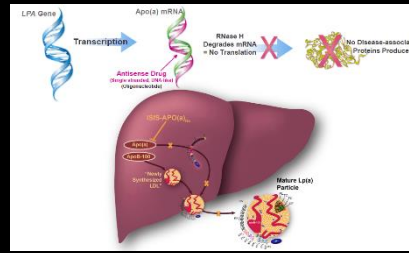
Lipoprotein(a) – Oxidized Phospholipids and Calcific Aortic Stenosis



Rationale for Lipoprotein(a) Lowering in AS

- About 20% of the general population (65 Million people in North America) have elevated Lp(a)
- Lp(a) circulating levels are determined genetically and currently available drugs (Niacin) only achieve modest reduction in Lp(a) and have significant side effects
- Phase I and II trials report that oligonucleotide antisense directed to Apo(a), reduces Lp(a) levels by >80% with minimal side effects
- 1 in 7 cases of severe AS could be prevented by marked lowering of Lp(a)





**Randomized
Trial**

**International
Multicenter
Randomized**

**n=460
Asymptomatic
Patients with
mild/mod AS
(V_{peak} 2.5-3.5)
Lp(a)>50 mg/dL**

R

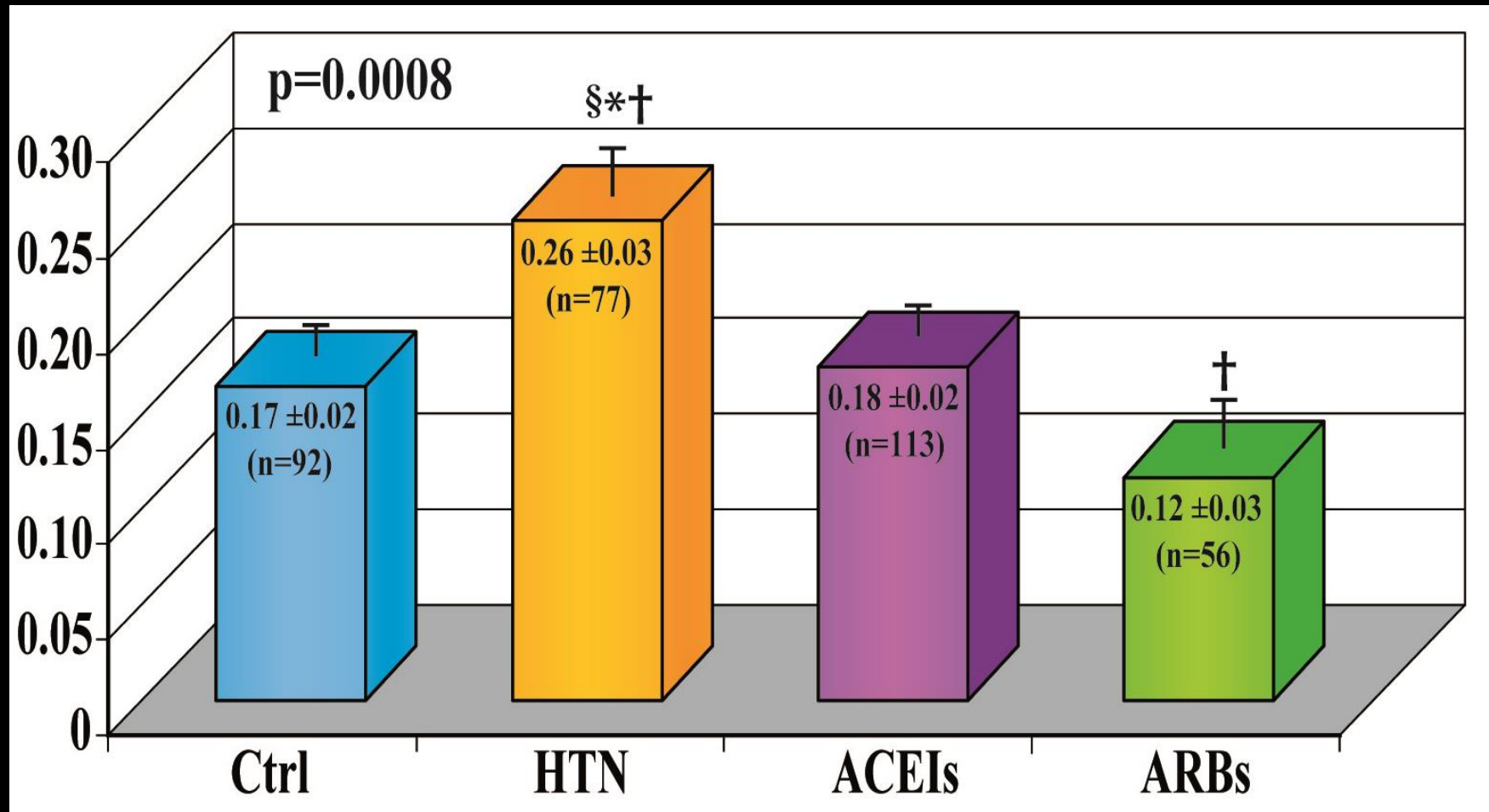
**ApoA OAS
40 mg/ month
SC**

Placebo

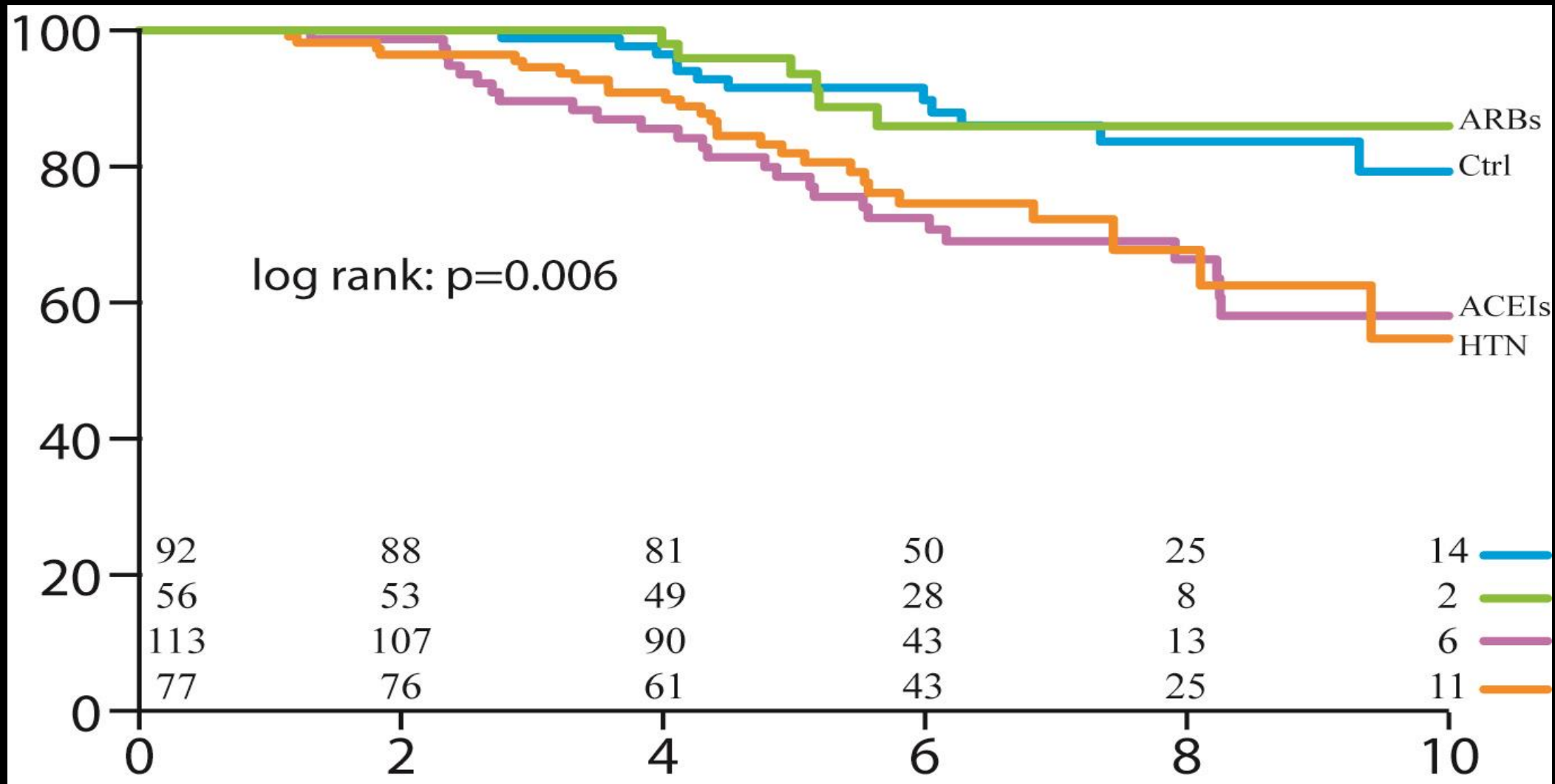
**Progression of
AS & AoV Ca
by TTE, CT, and
PET-CT (NaF)
at 3 years**

Impact of ACEi and ARBs on AS Progression Rate

Progression rate of Vmax
($m.s^{-1}.yr^{-1}$)

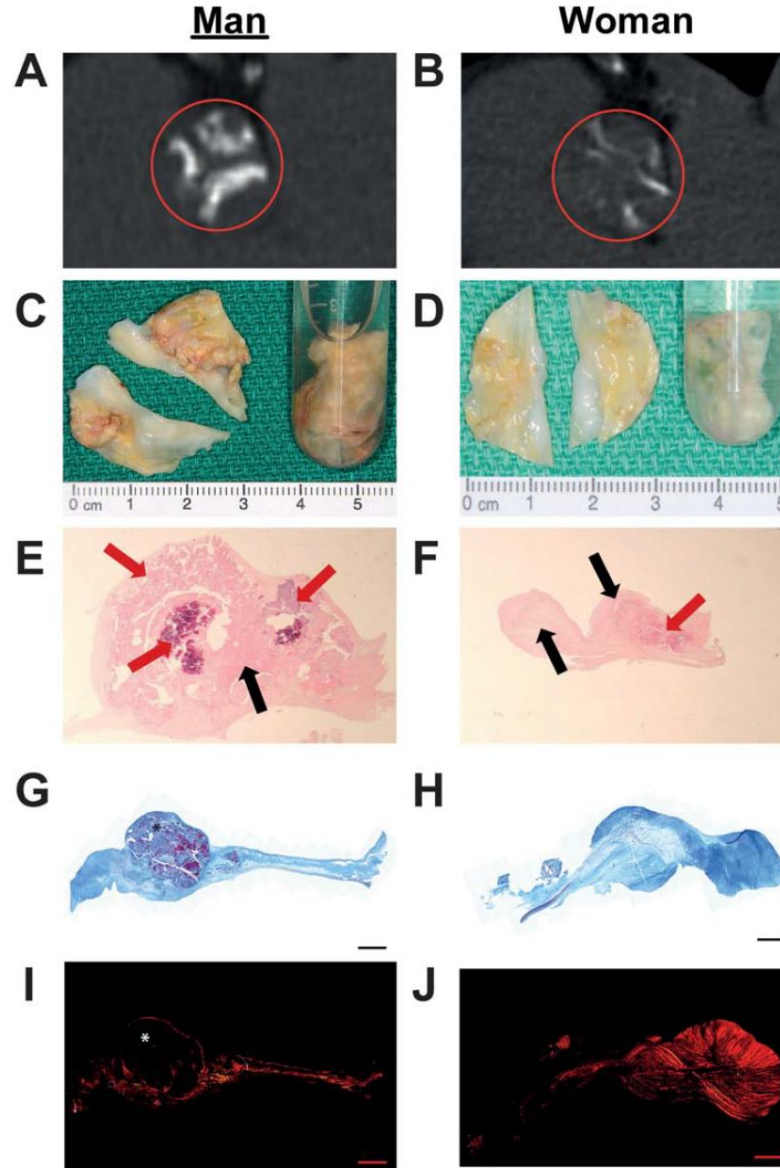
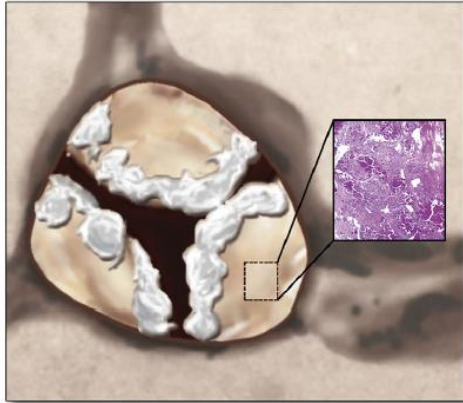


Impact of ACEi and ARBs on All-Cause Mortality

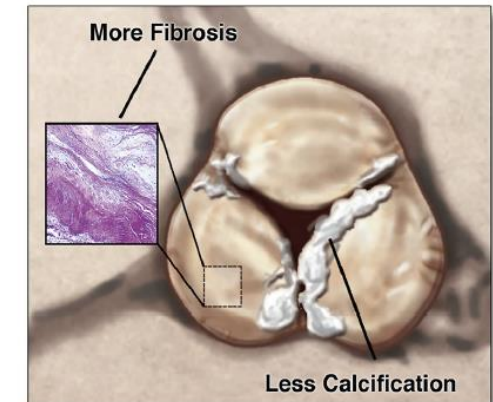


Women have less AoV calcification but more fibrosis compared to men

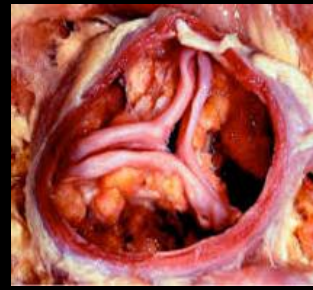
Men



Women



*Simard et al.
Circ Res 2016*



Breaking News!

ARTICLE

DOI: 10.1038/s41467-018-03260-6

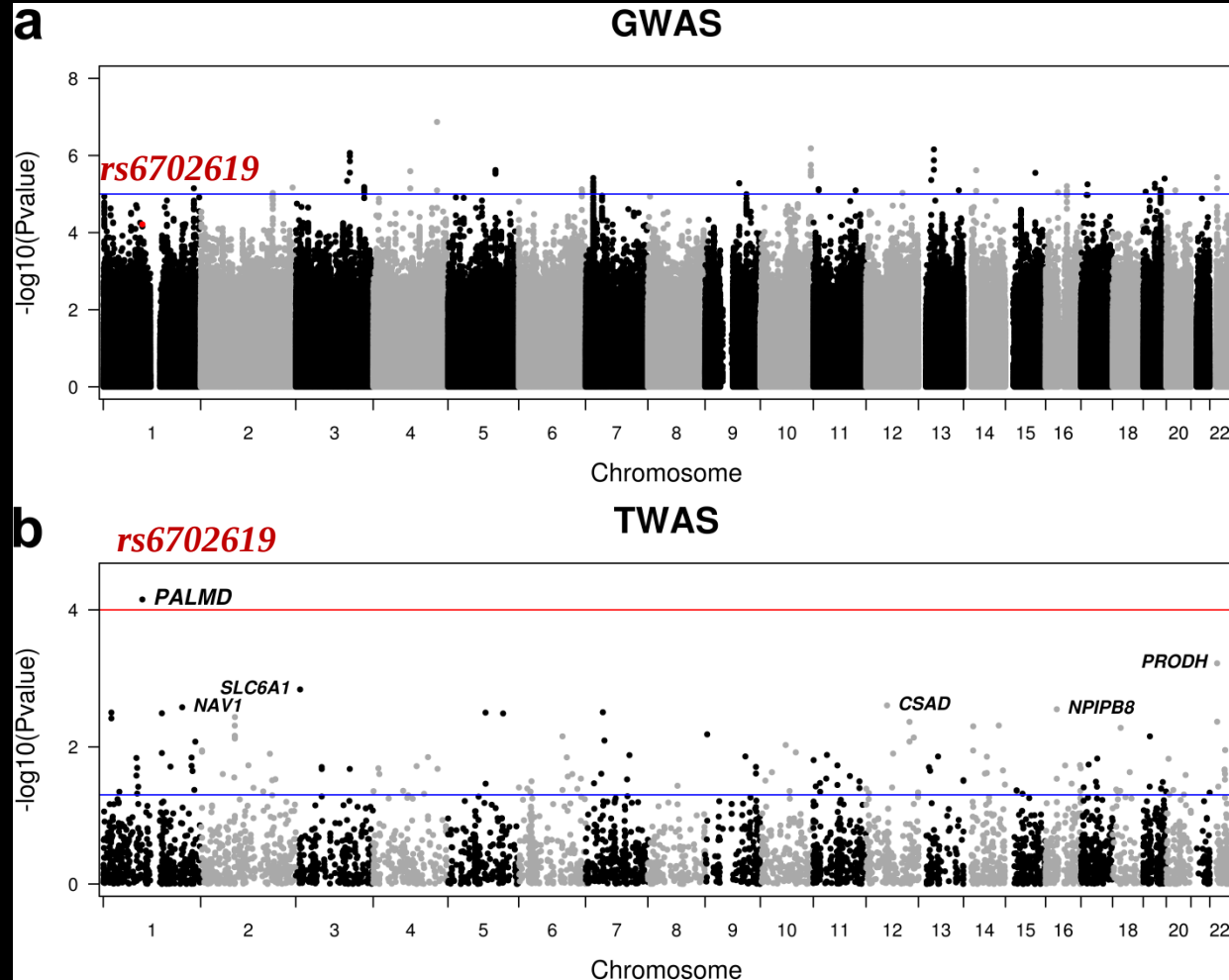
OPEN

A transcriptome-wide association study identifies *PALMD* as a susceptibility gene for calcific aortic valve stenosis

Sébastien Thériault^{1,2}, Nathalie Gaudreault¹, Maxime Lamontagne¹, Mickael Rosa¹, Marie-Chloé Boulanger¹, David Messika-Zeitoun^{3,4}, Marie-Annick Clavel¹, Romain Capoulade¹, François Dagenais¹, Philippe Pibarot¹, Patrick Mathieu¹ & Yohan Bossé^{1,5}

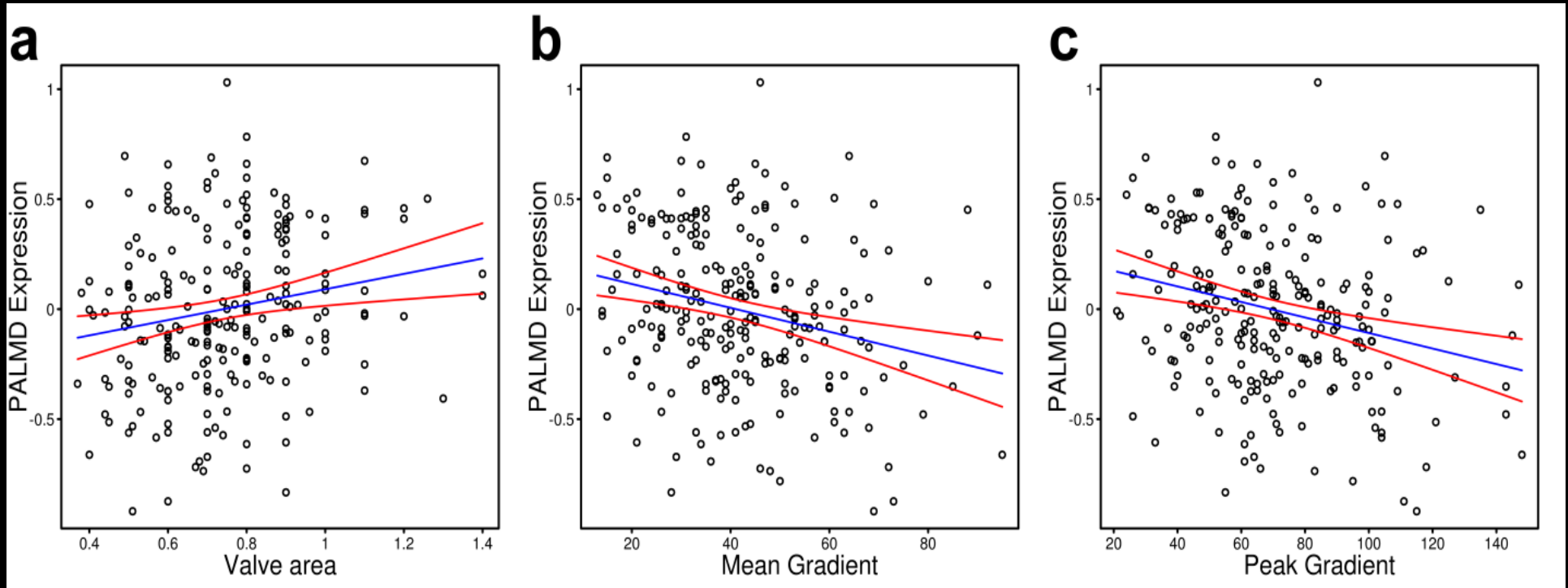
Thériault S. Nature Comm. March 2018

A transcriptome-wide association study identifies PALMD (Palmdelphin) as a susceptibility gene for calcific AS



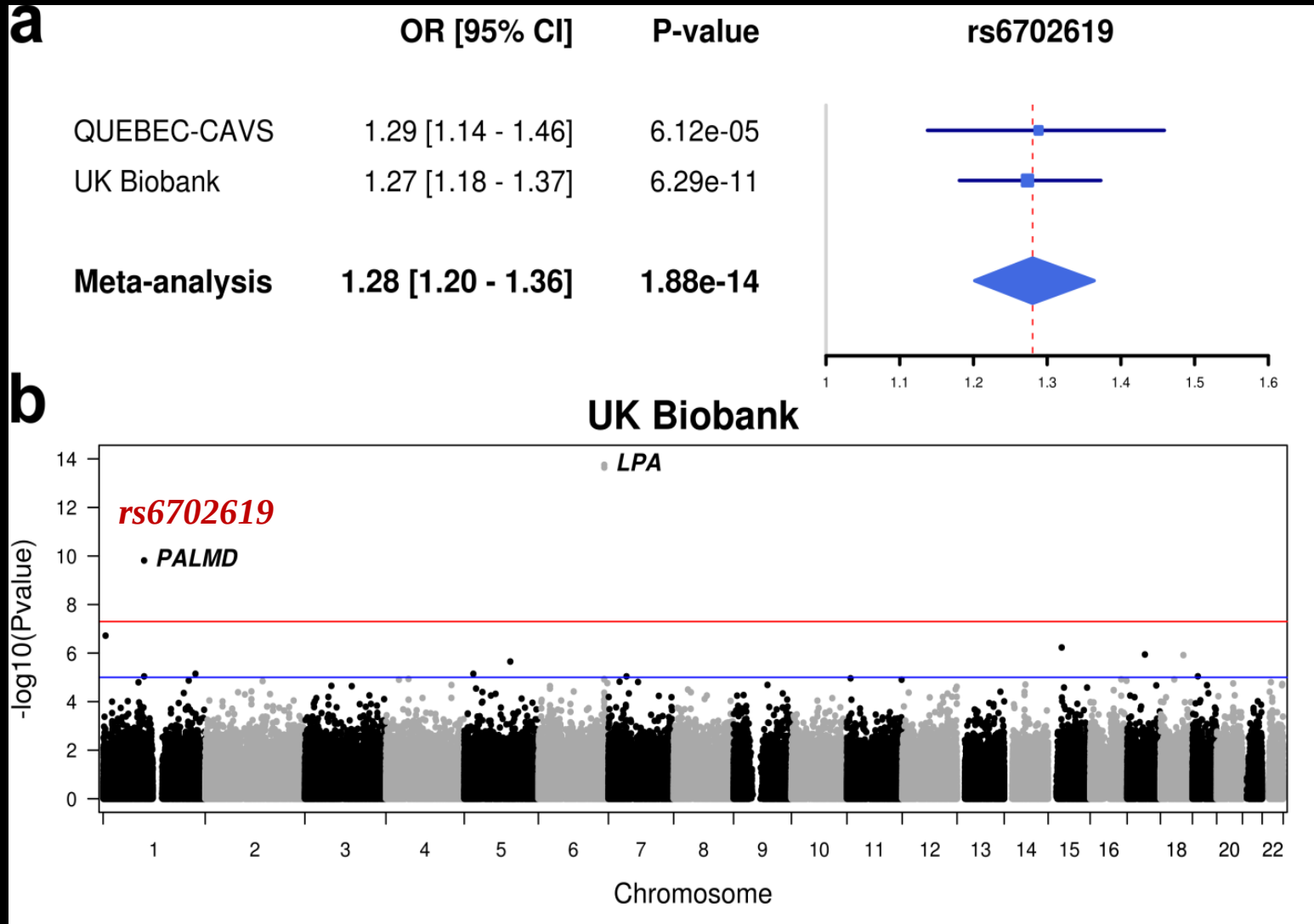
Thériault S. Nature Comm. March 2018

PALMD mRNA expression levels in aortic valve tissues according to AS severity



Thériault S. Nature Comm. March 2018

Replication in UK Biobank



1,391 cases
352,195 Controls

ARTICLE

DOI: 10.1038/s41467-018-03252-6

OPEN

Genome-wide analysis yields new loci associating with aortic valve stenosis

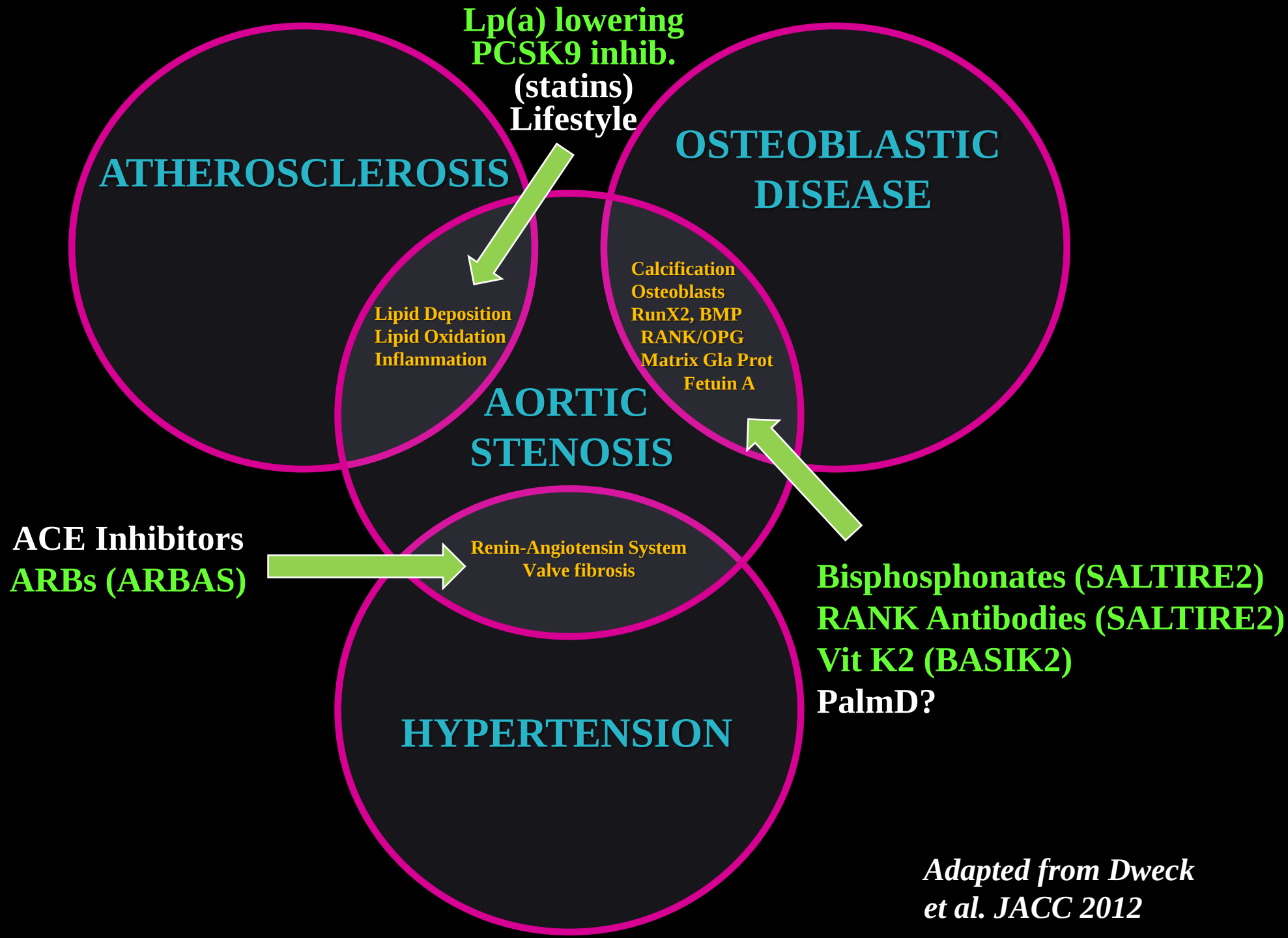
Anna Helgadottir 

- **GWAS: 7,307 AS cases and 801,073 controls.**
- **Two new AS loci**
 - on chromosome 1p21 near **PALMD** (rs7543130; OR=1.20, $P=1.2 \times 10^{-22}$)
 - on chromosome 2q22 in **TEX41** (rs1830321; OR=1.15, $P=1.8 \times 10^{-13}$)

Helgadottir et al. Nature Comm. March 2018

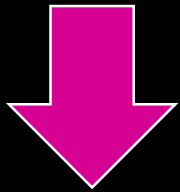
PALMD: A New Susceptibility Gene in AS

- *A new AS susceptibility gene, PALMD, was identified by 2 independent TWAS/GWAS studies*
- *The identified variants act by decreasing the expression of PALMD.*
- *PALMD is a mainly cytosolic protein, localized predominantly in actin filaments, and may be implicated in plasma membrane dynamics and cell shape control.*
- **PALMD is specific to AS and could be involved in the later stages of the disease**



*Adapted from Dweck
et al. JACC 2012*

Pharmacological Therapy for AS?



- Not yet but several promising targets have been identified and several RCTs are ongoing
- The « One drug fits all » will not work for AS
- Need to tailor therapy according to age, sex, and AS severity

**Lp(a) lowering
PCSK9i**



**Younger patients
Mild AS**

**ARBs
Anti-fibrotic therapy**



Women

**Bisphosphonates
RANK Antibodies
Vitamin K**



**Older patients
Men**

The Team!

