



Vascular  
Research  
Clinic

# Mechanisms of Vascular Ageing

**Professor John Cockcroft**

**Professor of Cardiology**

**Wales Heart Research Institute**

**University Hospital**

**CARDIFF UK**



**The Wellcome Trust**



**British Heart  
Foundation**



“Every man wants to live long but  
no man desires to grow old”.

*Johnathan Swift 1667-1745*



“In extreme old age, the arteries themselves, the grand instrument of the circulation, by continual apposition of earth, become hard, and as it were bony, till, having lost the power of contracting themselves they can no longer propel the blood, even through the largest channels, in consequence of which death naturally ensues”

*John Wesley 1703-1791*

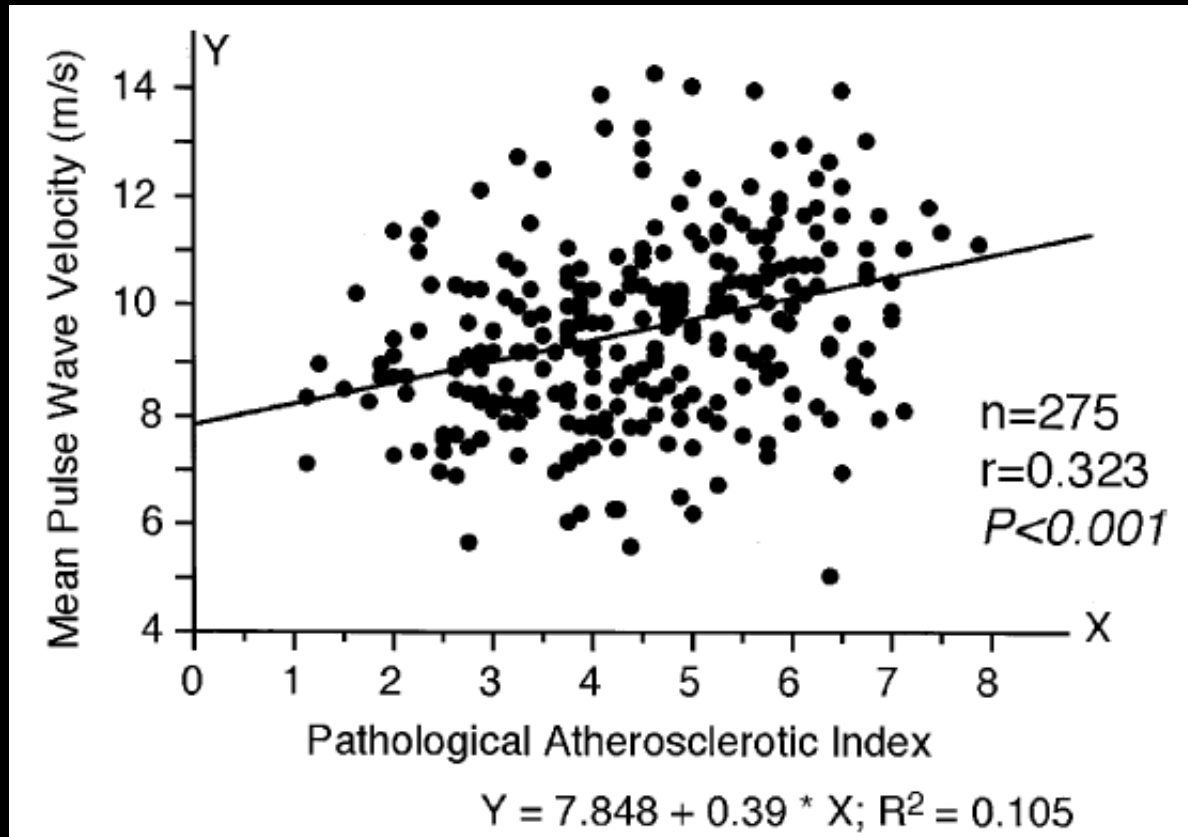
## *Atherosclerosis*

A degenerative disease of the arteries characterised by patchy thickening of the inner lining of the artery walls, caused by deposits of fatty material; **a form of arteriosclerosis**

## *Arteriosclerosis*

A common disorder characterised by thickening loss of elasticity and calcification of arterial walls. The condition develops with aging, hypertension, nephrosclerosis, diabetes and hyperlipidaemia. **Also called hardening of the arteries.**

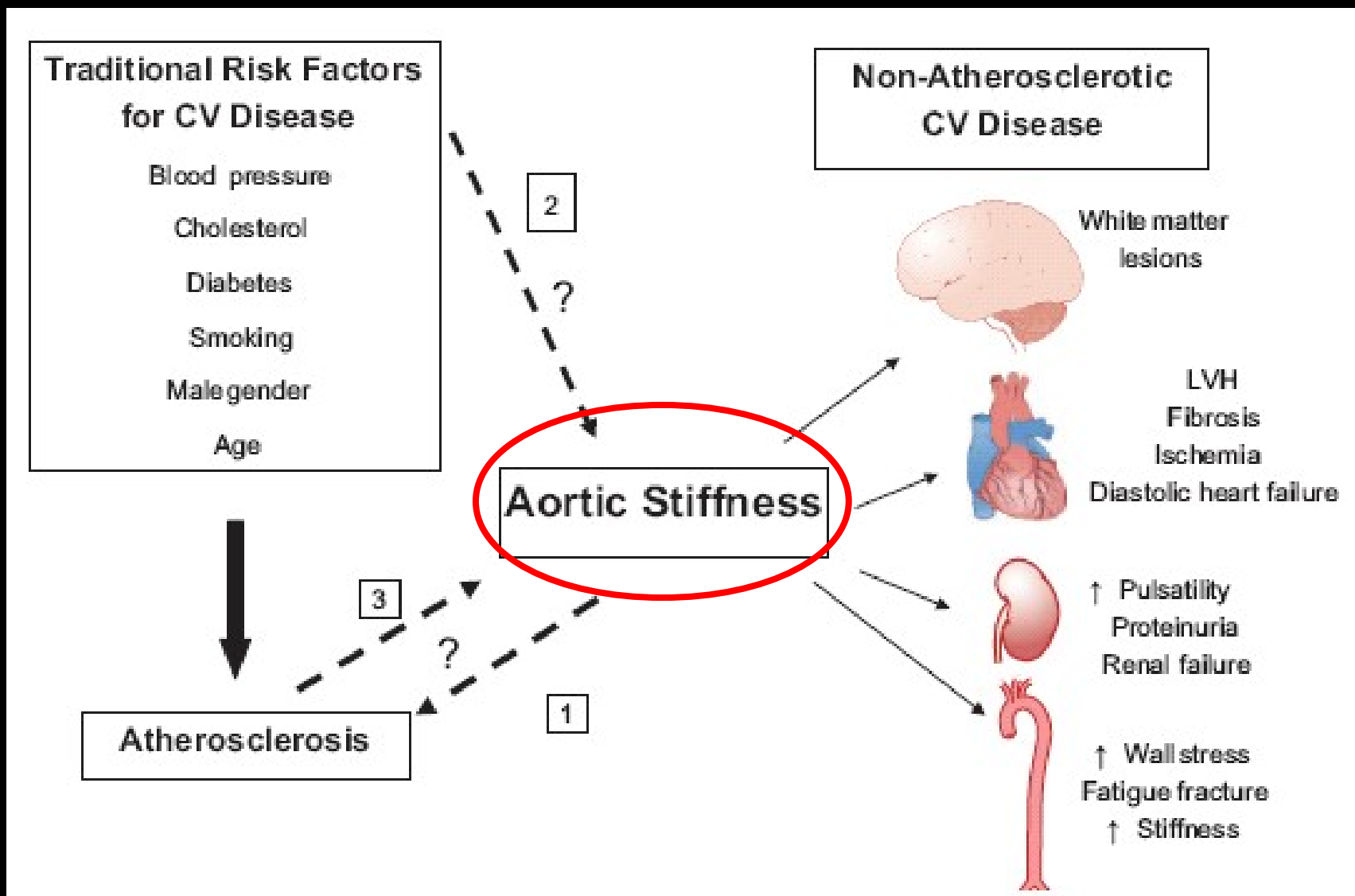
# Aortic PWV and Atherosclerosis Post-Mortem Data



## *Arteriosclerosis*

A common disorder characterised by thickening loss of elasticity and calcification of arterial walls. The condition develops with aging, hypertension, nephrosclerosis, **diabetes and hyperlipidaemia**. Also called hardening of the arteries.

# Proposed Mechanisms Linking Aortic Stiffness with Atherosclerotic and Nonatherosclerotic Cardiovascular Disease





## Aortic Pulse Wave Velocity Improves Cardiovascular Event Prediction

An Individual Participant Meta-Analysis of Prospective Observational Data From 17,635 Subjects

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**Table 1**

Pooled Adjusted Hazard Ratios (95% CIs) of a 1-SD Increase in Log<sub>e</sub>-Transformed aPWV for All-Cause Mortality, CVD Mortality, CHD Events, Stroke Events, and CVD Events

	Model 1*	Model 2*	Model 3*
CHD events (n = 1,195)	1.35 (1.22-1.50)	1.32 (1.18-1.48)	1.23 (1.11-1.35)
CVD events (n = 1,785)	1.45 (1.30-1.61)	1.37 (1.23-1.52)	1.30 (1.18-1.43)
Stroke events (n = 641)	1.54 (1.34-1.78)	1.37 (1.21-1.54)	1.28 (1.16-1.42)
CVD mortality (n = 395)	1.41 (1.27-1.56)	1.35 (1.20-1.53)	1.28 (1.15-1.43)
All-cause mortality (n = 2,041)	1.22 (1.16-1.27)	1.20 (1.15-1.26)	1.17 (1.11-1.22)

**Table 1****Pooled Adjusted Hazard Ratios (95% CIs) of a 1-SD Increase in Log<sub>e</sub>-Transformed aPWV for All-Cause Mortality, CVD Mortality, CHD Events, Stroke Events, and CVD Events**

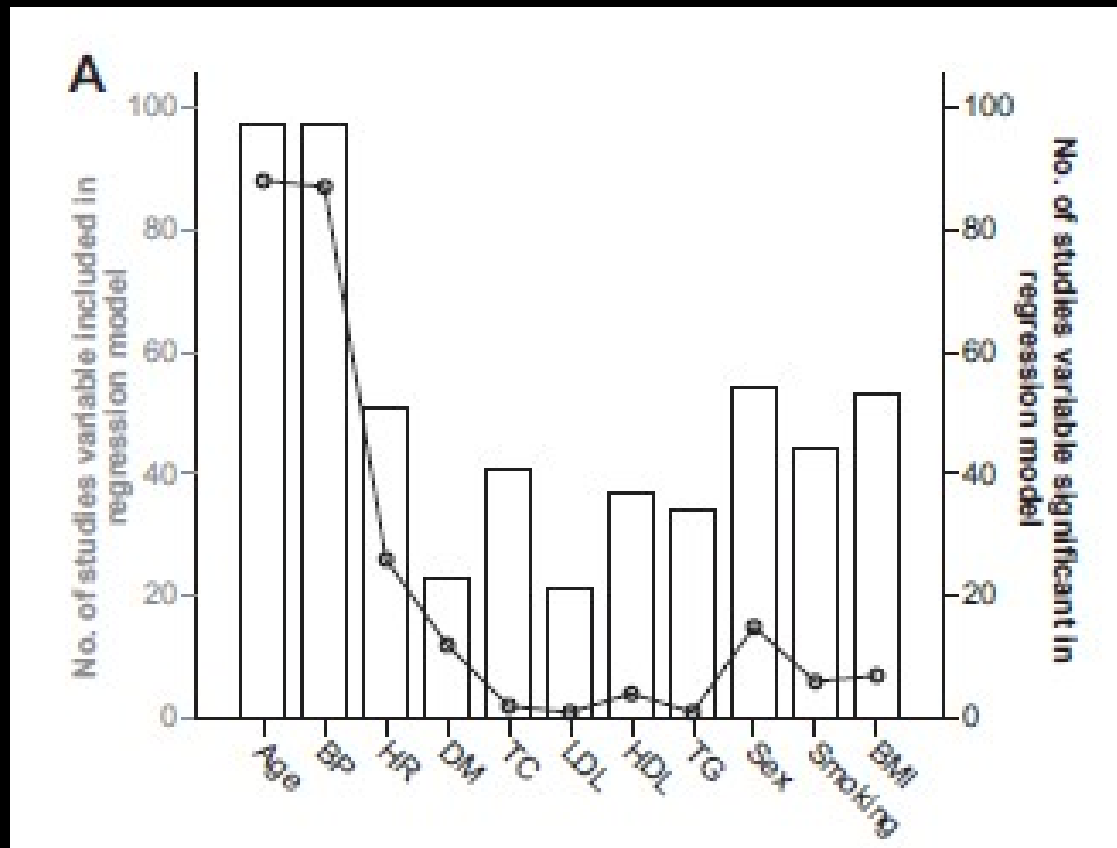
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13% of intermediate risk individuals were reclassified into higher or lower quartiles of risk

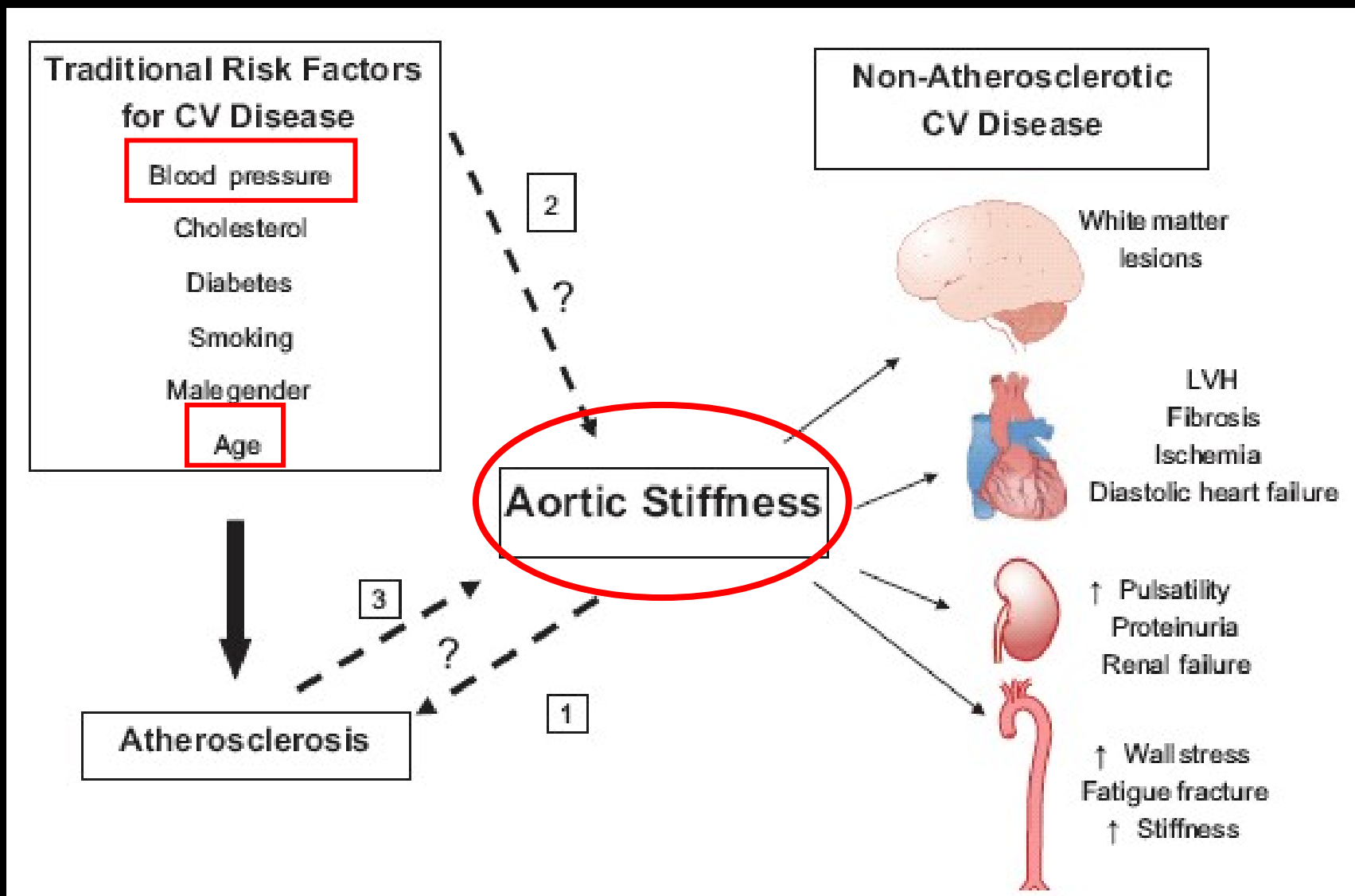
**Dissociation of Aortic Pulse Wave Velocity With Risk  
Factors for Cardiovascular Disease Other  
Than Hypertension  
A Systematic Review**

Marina Cecelja, Philip Chowienczyk

Studies in Which Classical Risk Factors and Heart Rate Were Included in Which the Risk Factor was Significantly Independently Associated with PWV (All Studies)



# Proposed Mechanisms Linking Aortic Stiffness with Atherosclerotic and Nonatherosclerotic Cardiovascular Disease



# Arterial Stiffness and Hypertension : The FHS

ORIGINAL CONTRIBUTION

**JAMA** The Journal of the  
American Medical Association



Scan for Author  
Video Interview

## Aortic Stiffness, Blood Pressure Progression, and Incident Hypertension

Bernhard M. Kaess, MD

Jian Rong, PhD

Martin C. Larson, ScD

Naomi M. Hamburg, MD

Joseph A. Vita, MD

Daniel Levy, MD

Emelia J. Benjamin, MD, ScM

Ramachandran S. Vasan, MD

Gary F. Mitchell, MD

**V**ASCULAR STIFFNESS INCREASES with advancing age and is a major risk factor for age-related morbidity and mortality.<sup>1</sup> A compliant aorta pro-

**Context** Vascular stiffness increases with advancing age and is a major risk factor for age-related morbidity and mortality. Vascular stiffness and blood pressure pulsatility are related; however, temporal relationships between vascular stiffening and blood pressure elevation have not been fully delineated.

**Objective** To examine temporal relationships among vascular stiffness, central hemodynamics, microvascular function, and blood pressure progression.

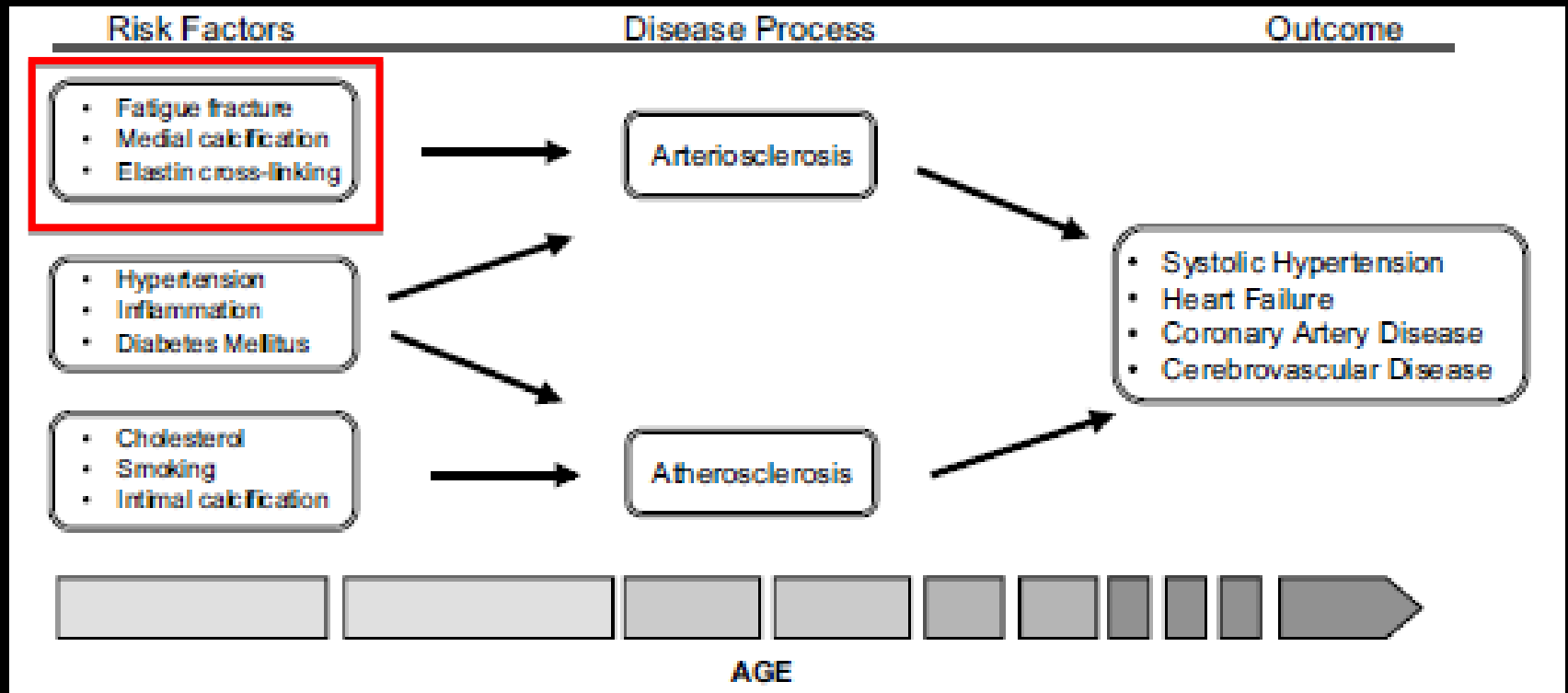
**Design, Setting, and Participants** Longitudinal community-based cohort study conducted in Framingham, Massachusetts. The present investigation is based on the 2 latest examination cycles (cycle 7: 1998-2001; cycle 8: 2005-2008 [last visit: January 25, 2008]) of the Framingham Offspring study (recruited: 1971-1975). Temporal relationships among blood pressure and 3 measures of vascular stiffness and pressure pulsatility derived from arterial tonometry (carotid-femoral pulse wave velocity [CFPWV], forward wave amplitude [FWA], and augmentation index) were examined over a 7-year period in 1759 participants (mean [SD] age: 60 [9] years; 974 women).

**Main Outcome Measures** The primary outcomes were blood pressure and incident hypertension during examination cycle 8. The secondary outcomes were CFPWV, FWA, and augmentation index during examination cycle 8.

## Framingham Offspring Study

- N = 1759
- 60±9 years
- 55% women
- 7 years
- 338 cases of incident HTN
- Does BP predict aortic stiffening or does stiffness predict incident HTN?

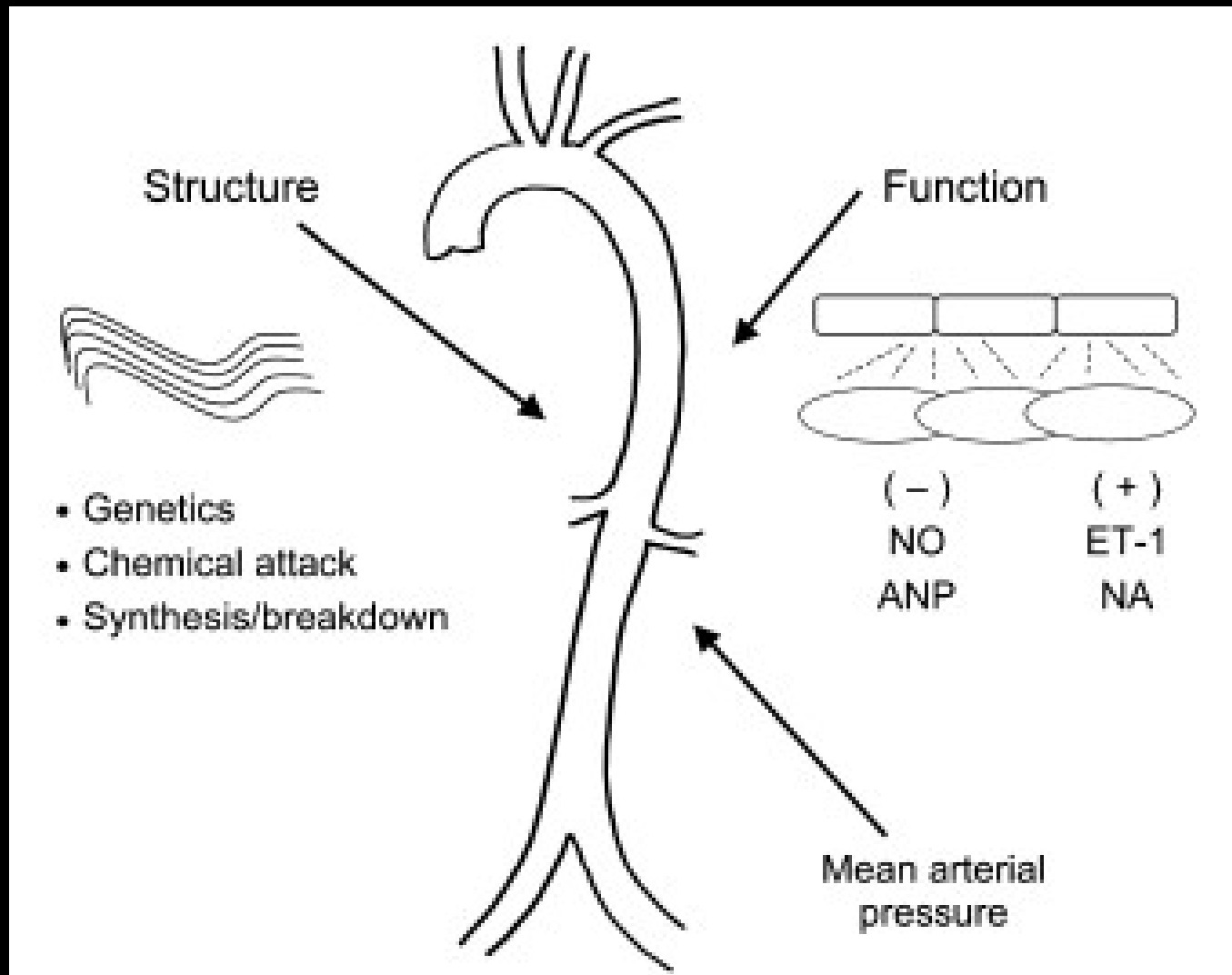
# Arteriosclerosis and Atherosclerosis are Separate Pathological Entities, Which are Largely Driven by Different Mechanisms



Mechanisms of Increased Aortic PWV.....?



# Major Determinants of Arterial Stiffness



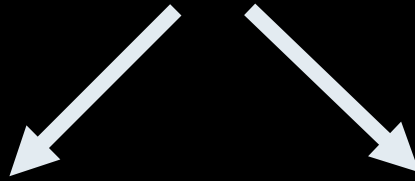
YOUNG

OLD



McDonald's Blood Flow in Arteries

# Elastin Fatigue



Number of cycles     $\times$     Cyclical stress

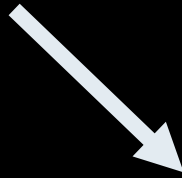
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Heart rate

$\times$

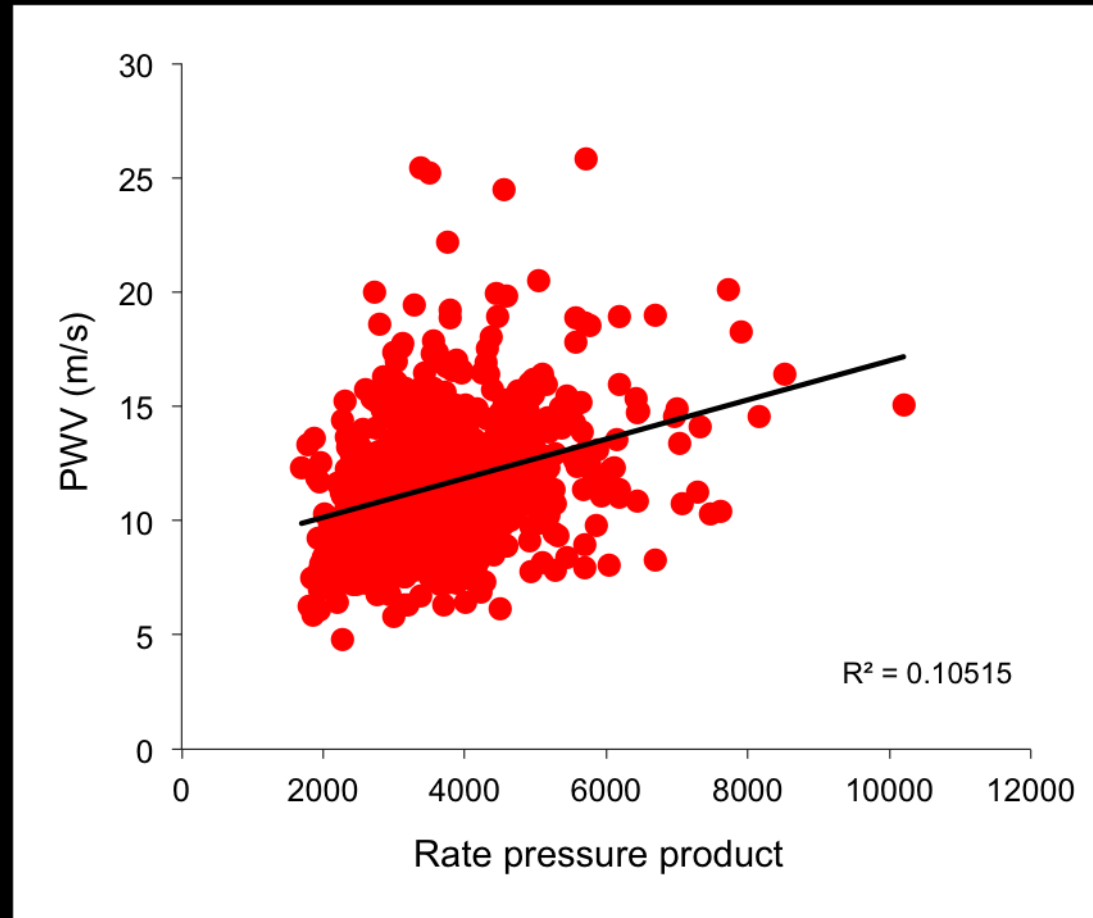
Pulse pressure



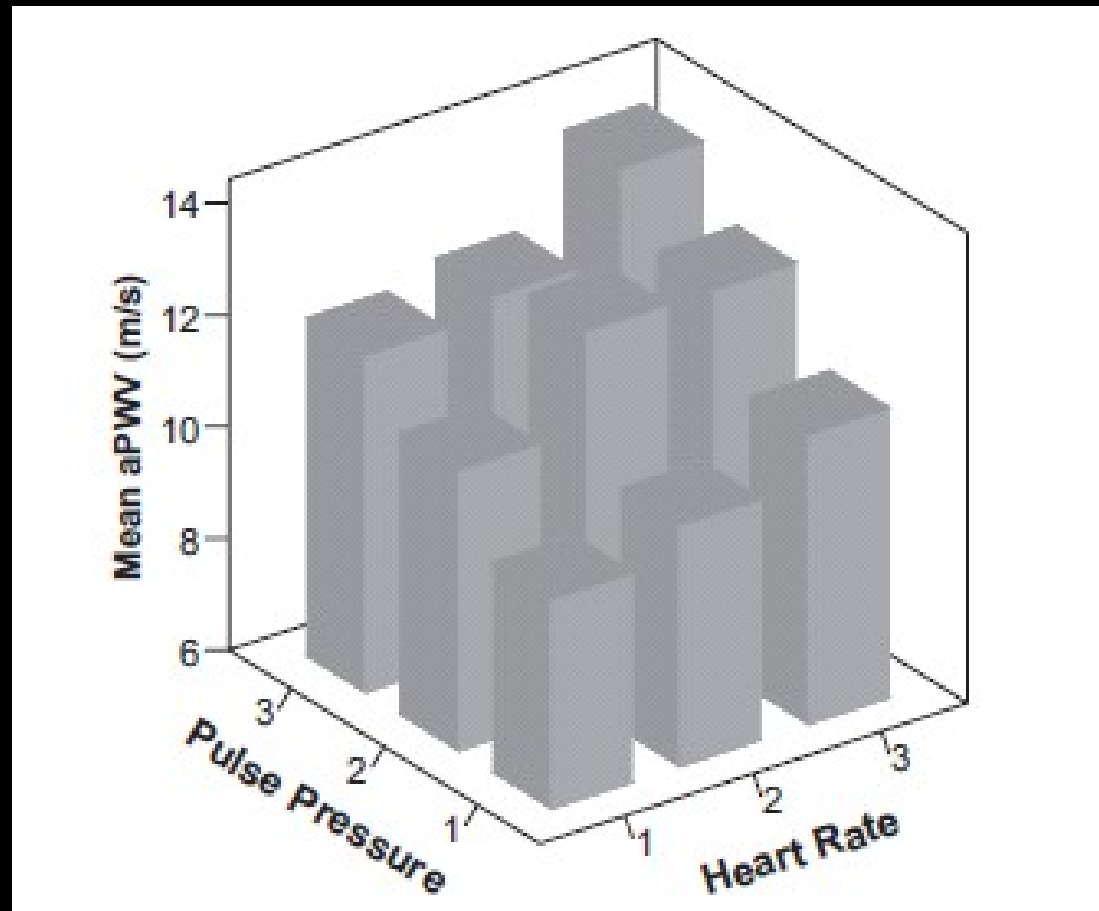
## Arterial Stiffening



# Relationship Between Rate Pressure Product and aPWV in the Caerphilly Study

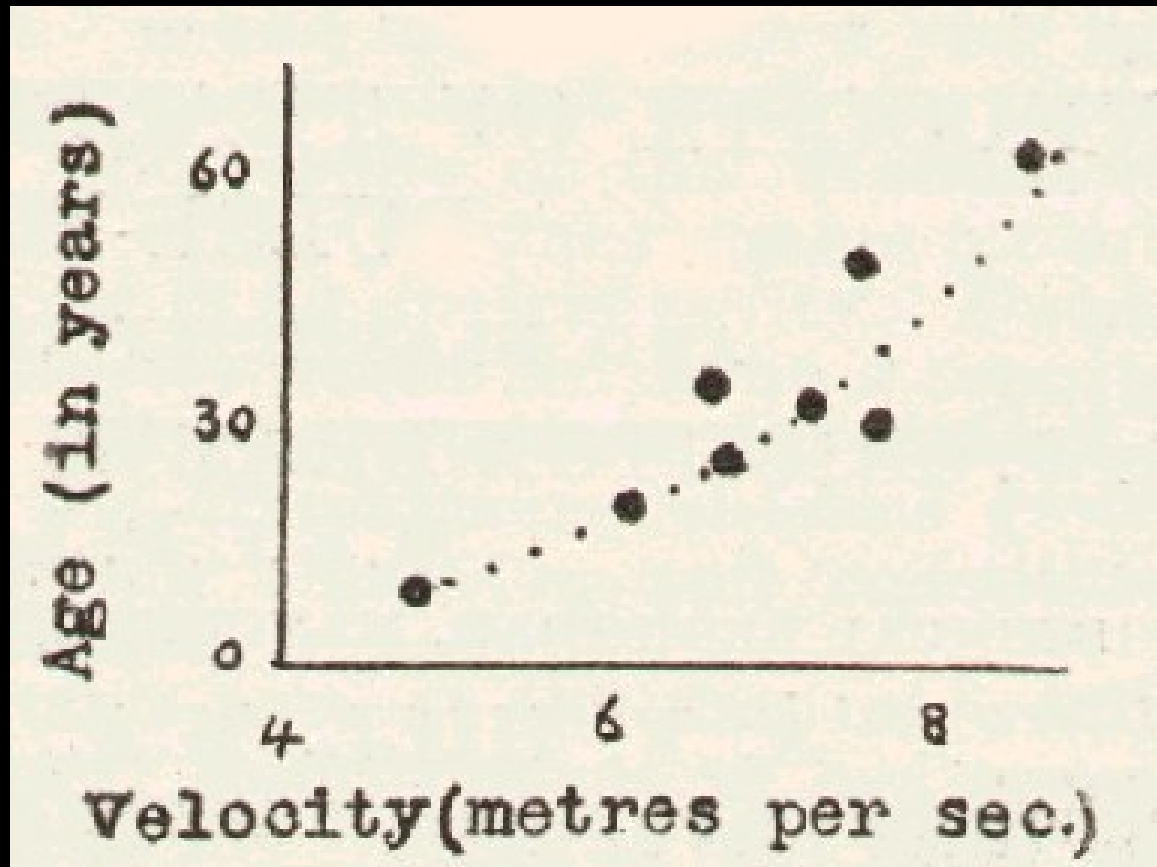


# Integrated Heart Rate and Pulse Pressure Tertiles Across 20 Years and Their Association with aPWV in Later Life

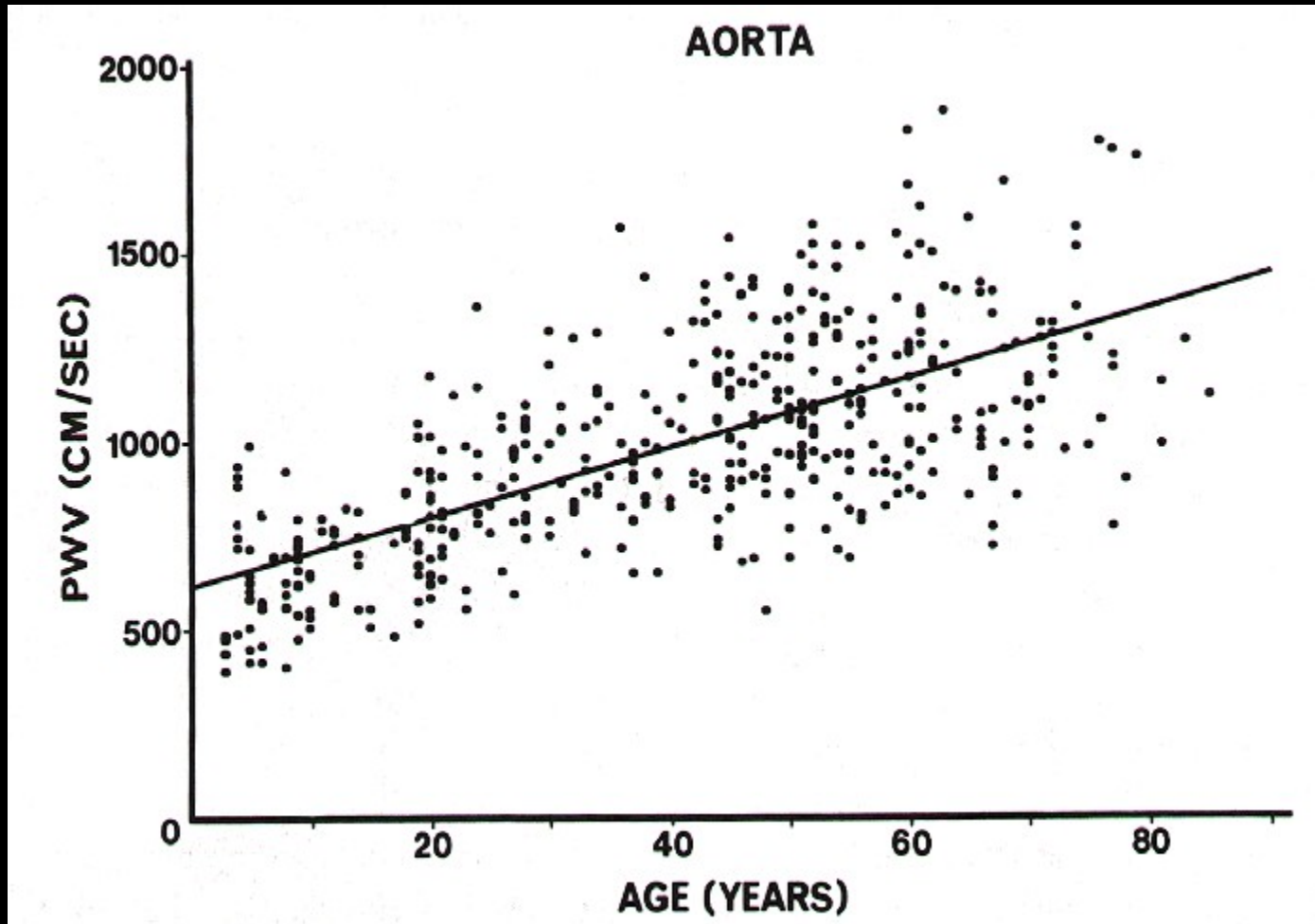


*Aortic PWV & Age.....*

## Age and Aortic Pulse Wave Velocity



# Aortic PWV and Age





Normal Vascular Aging: Differential Effects  
on Wave Reflection and Aortic Pulse Wave Velocity

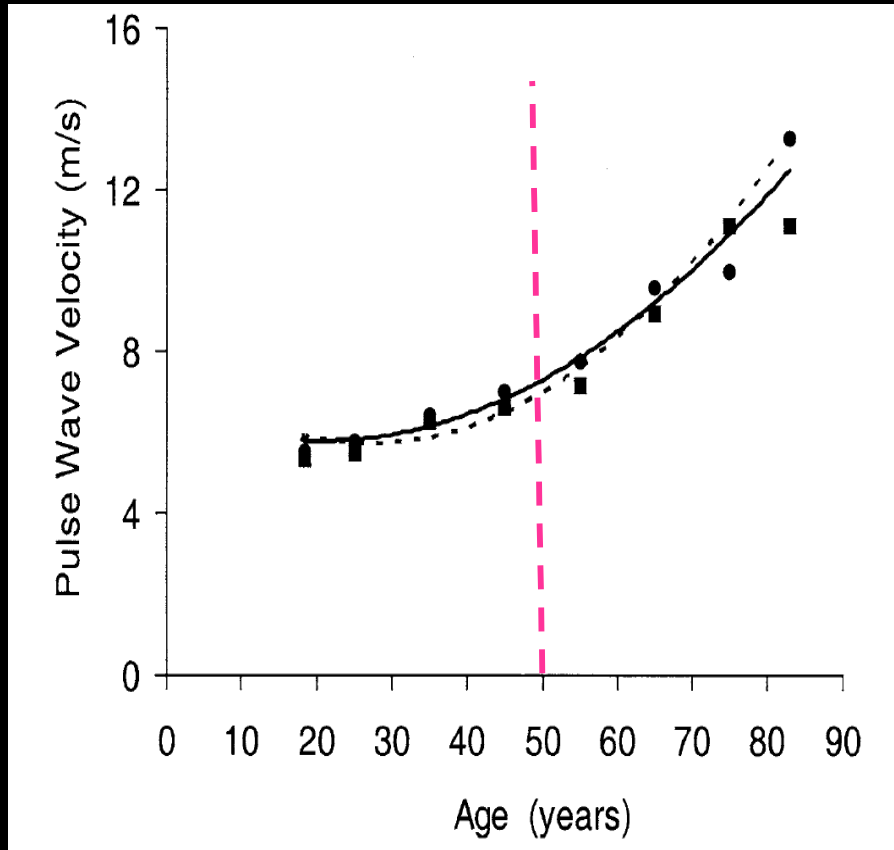
The Anglo-Cardiff Collaborative Trial (ACCT)

Carmel M. McEniery, PhD,\* Yasmin, PhD,\* Ian R. Hall, MB, MRCP,† Ahmad Qasem, PhD,‡  
Ian B. Wilkinson, MA, DM, MRCP,\* John R. Cockcroft, BSc, MB, FRCP†, on behalf of the  
ACCT Investigators

*Cambridge and Cardiff, United Kingdom; and Sydney, Australia*

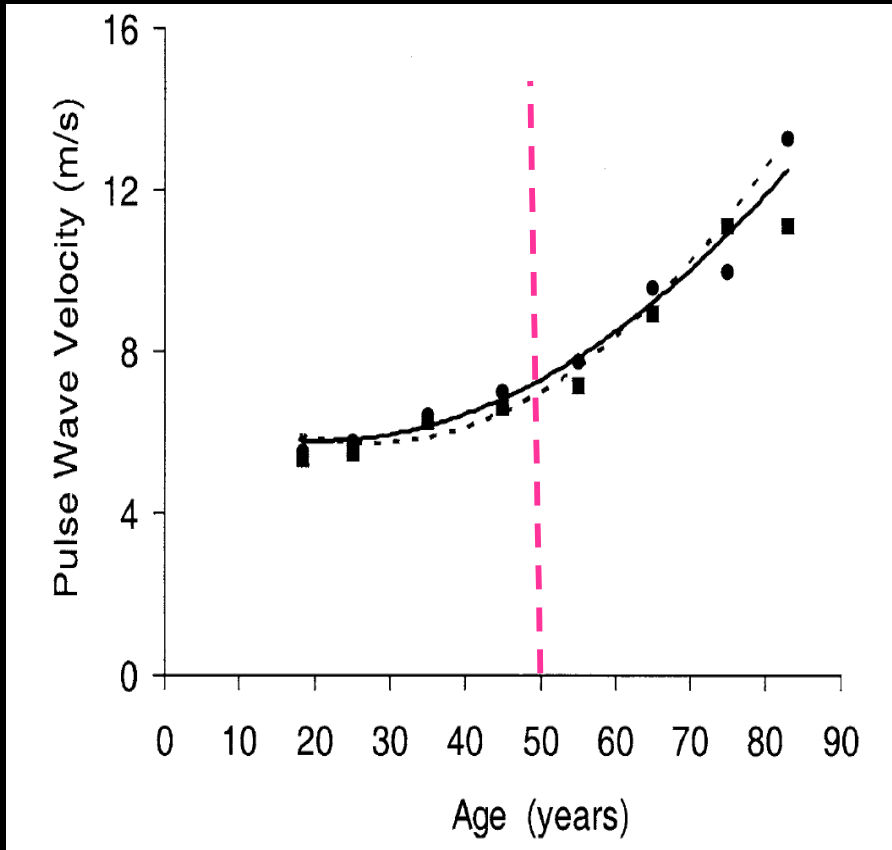
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## Age and PWV: UK



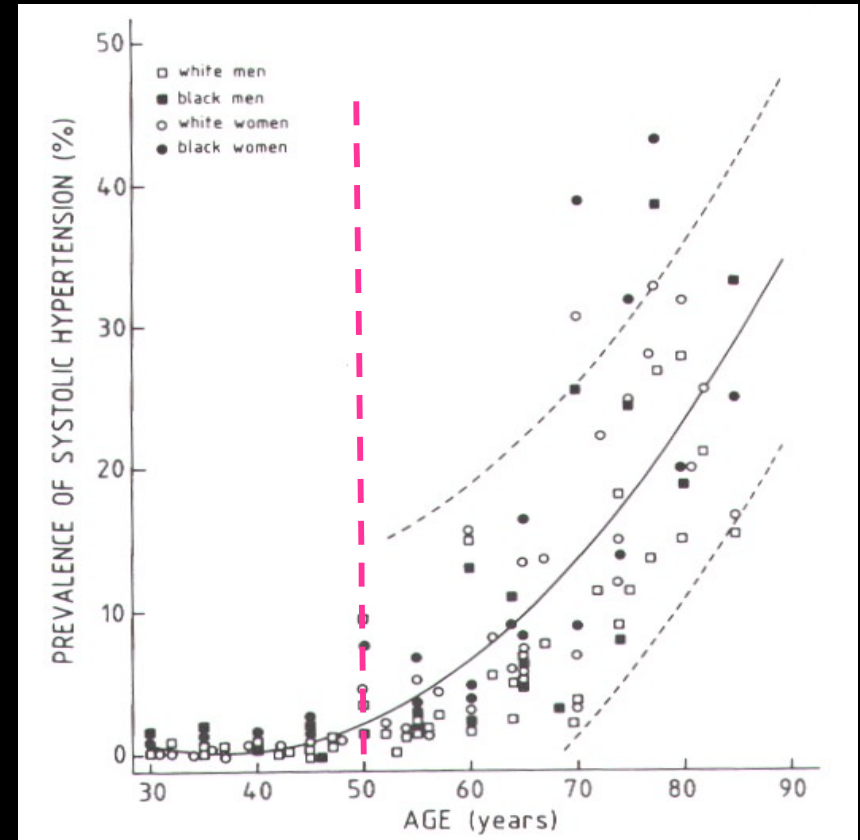
McEniery et al *JACC* 2005;46:1753

## Age and PWV: UK



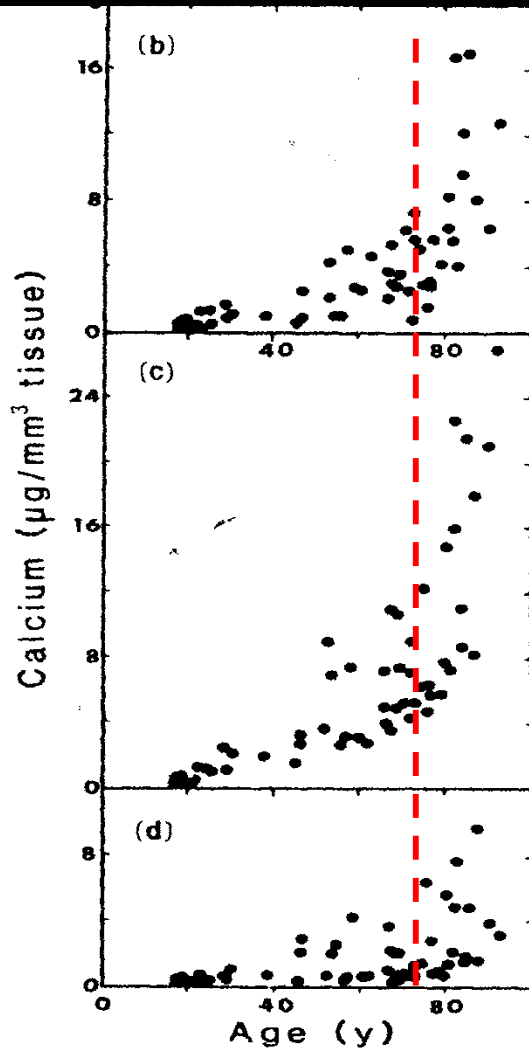
McEniery et al *JACC* 2005;46:1753

## Isolated Systolic Hypertension



Staessen et al. *J Hypertens* 1990;8:393

# Relationship Between Age and Thoracic Aortic Calcium Content in Man

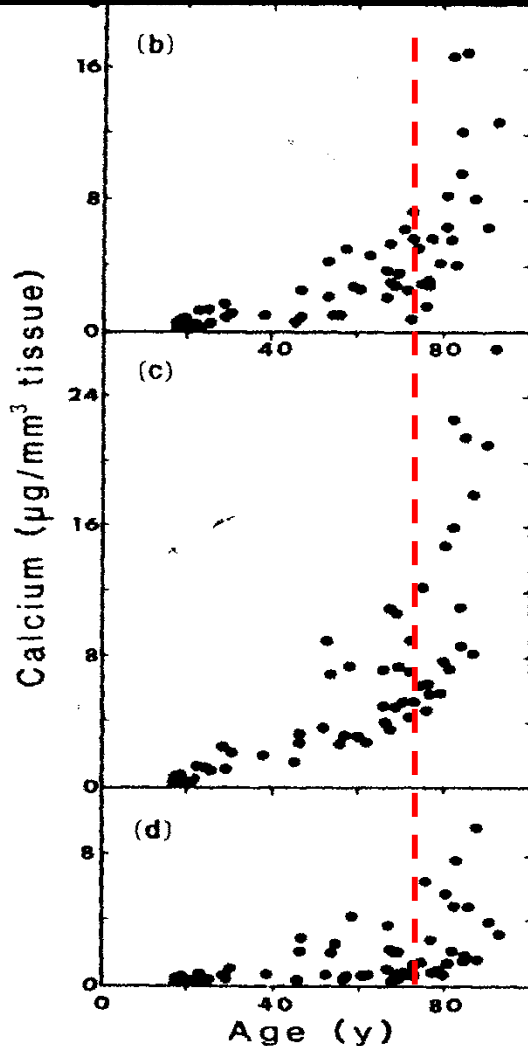


Media

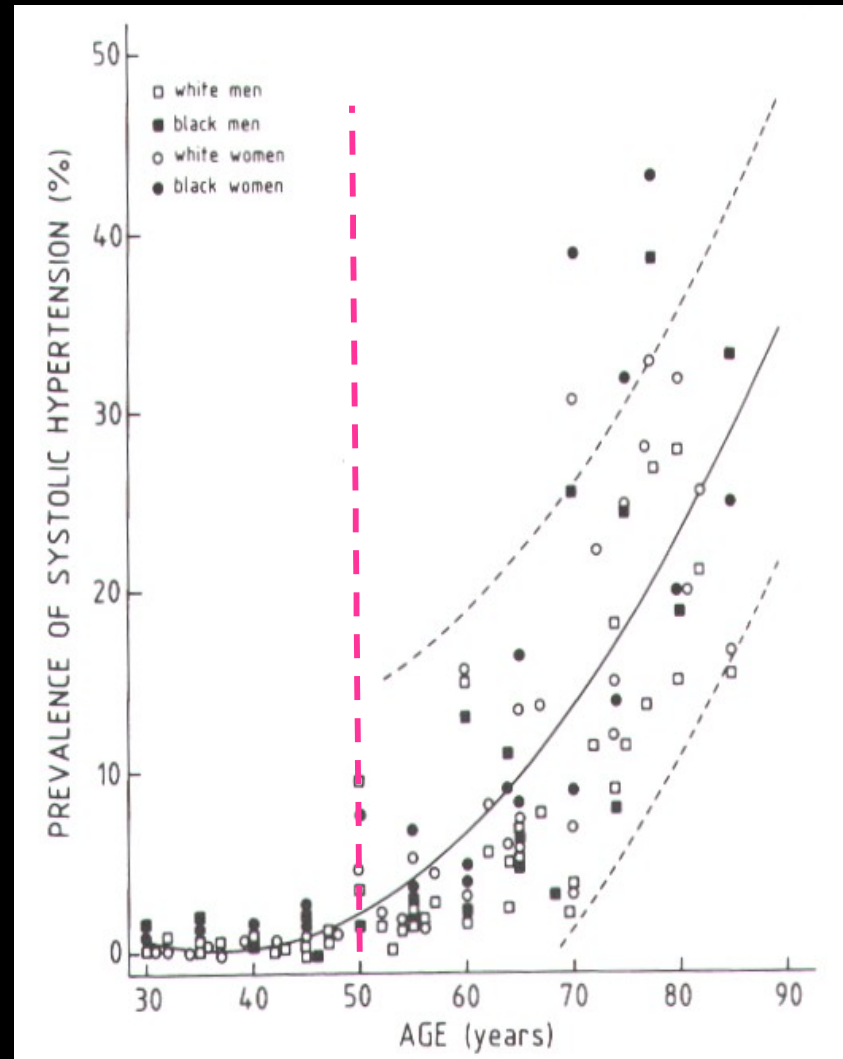
Adventitia

# Relationship Between Age and Thoracic Aortic Calcium Content in Man

Media



Adventitia



# **Aortic Calcification Is Associated With Aortic Stiffness and Isolated Systolic Hypertension in Healthy Individuals**

Carmel M. McEniery, Barry J. McDonnell, Alvin So, Sri Aitken, Charlotte E. Bolton, Margaret Munnery, Stacey S. Hickson, Yasmin, Kaisa M. Maki-Petaja, John R. Cockcroft, Adrian K. Dixon, Ian B. Wilkinson; on behalf of the Anglo-Cardiff Collaboration Trial Investigators



# Non-invasive Assessment of Aortic Calcification Using 64-Slice Spiral CT

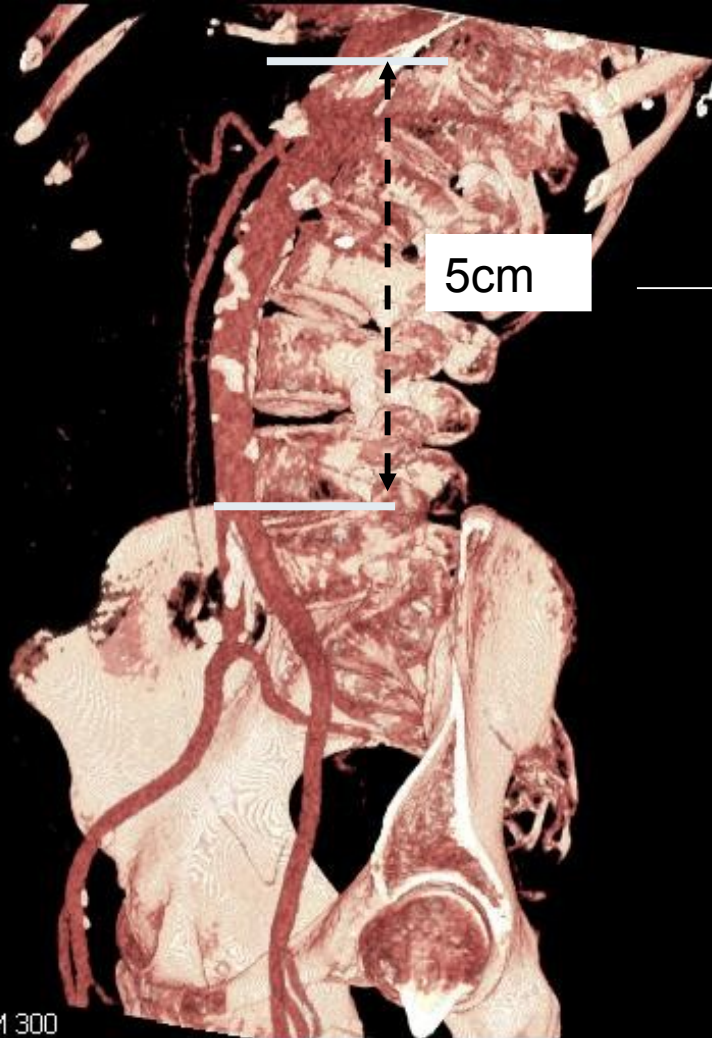




# Aortic Calcium

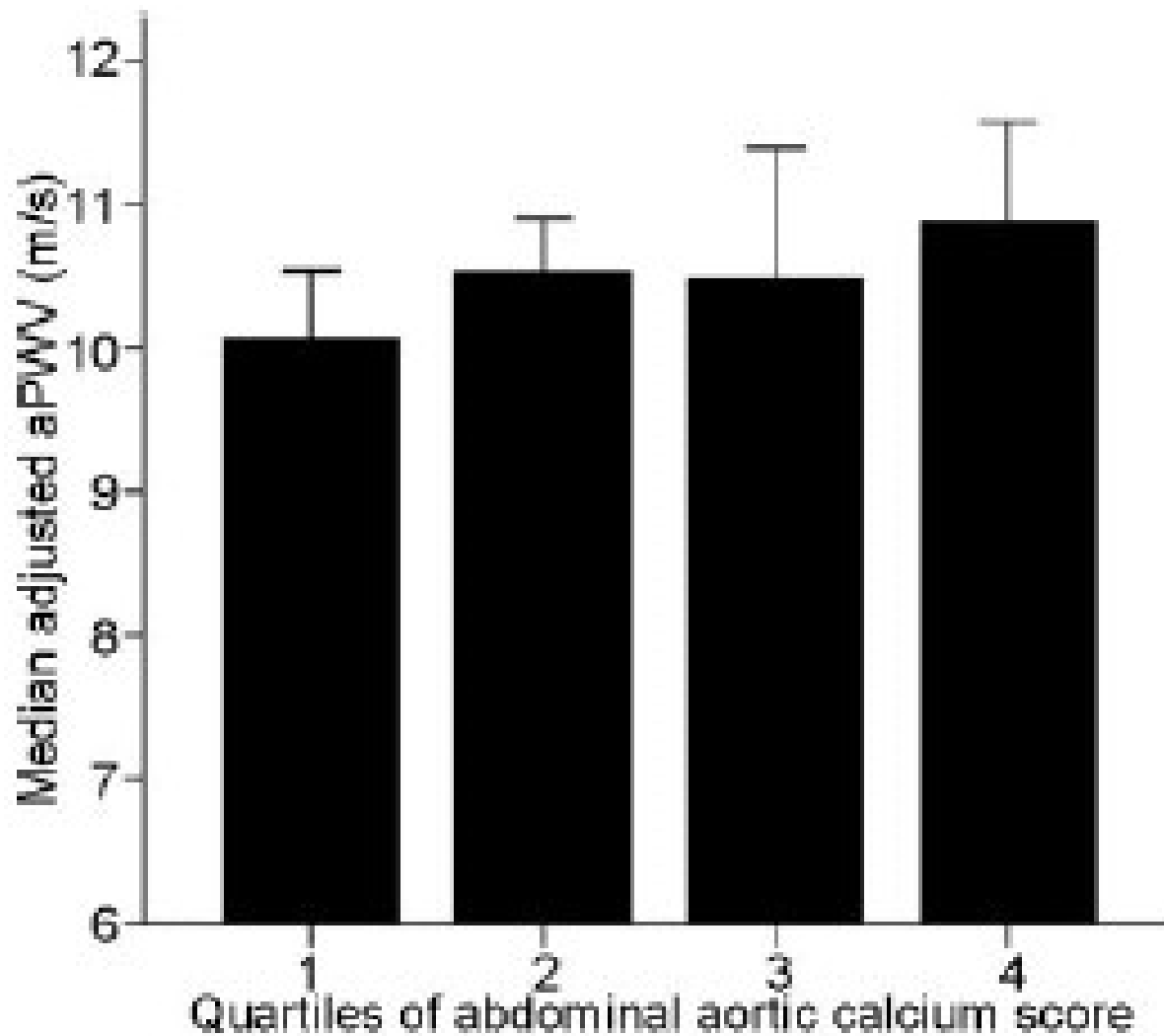


# Quantification of Calcium Load

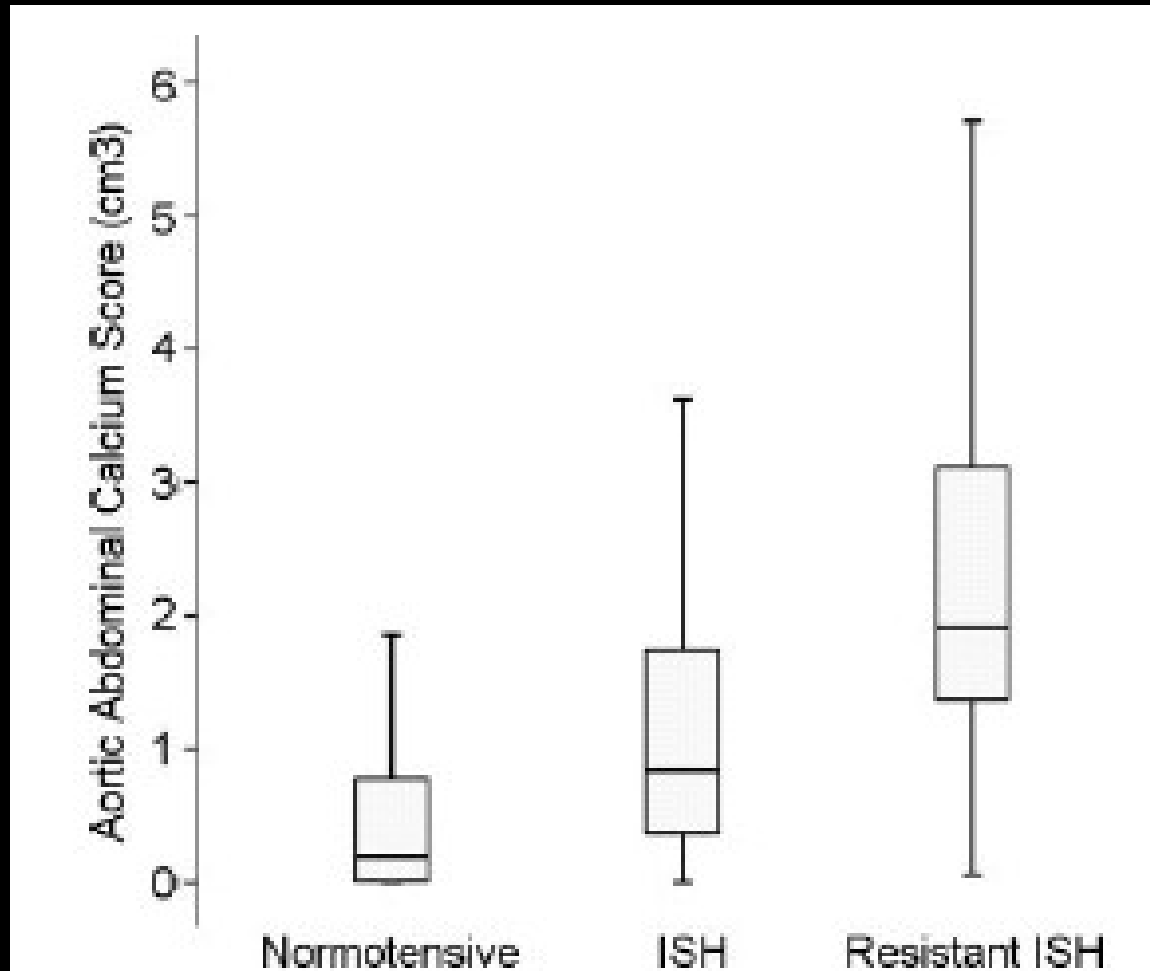


Identify all voxals  $>130\text{HU}$   
 $\text{Ca}^{2+} = \text{no voxals} \times 1\text{mm}^3$

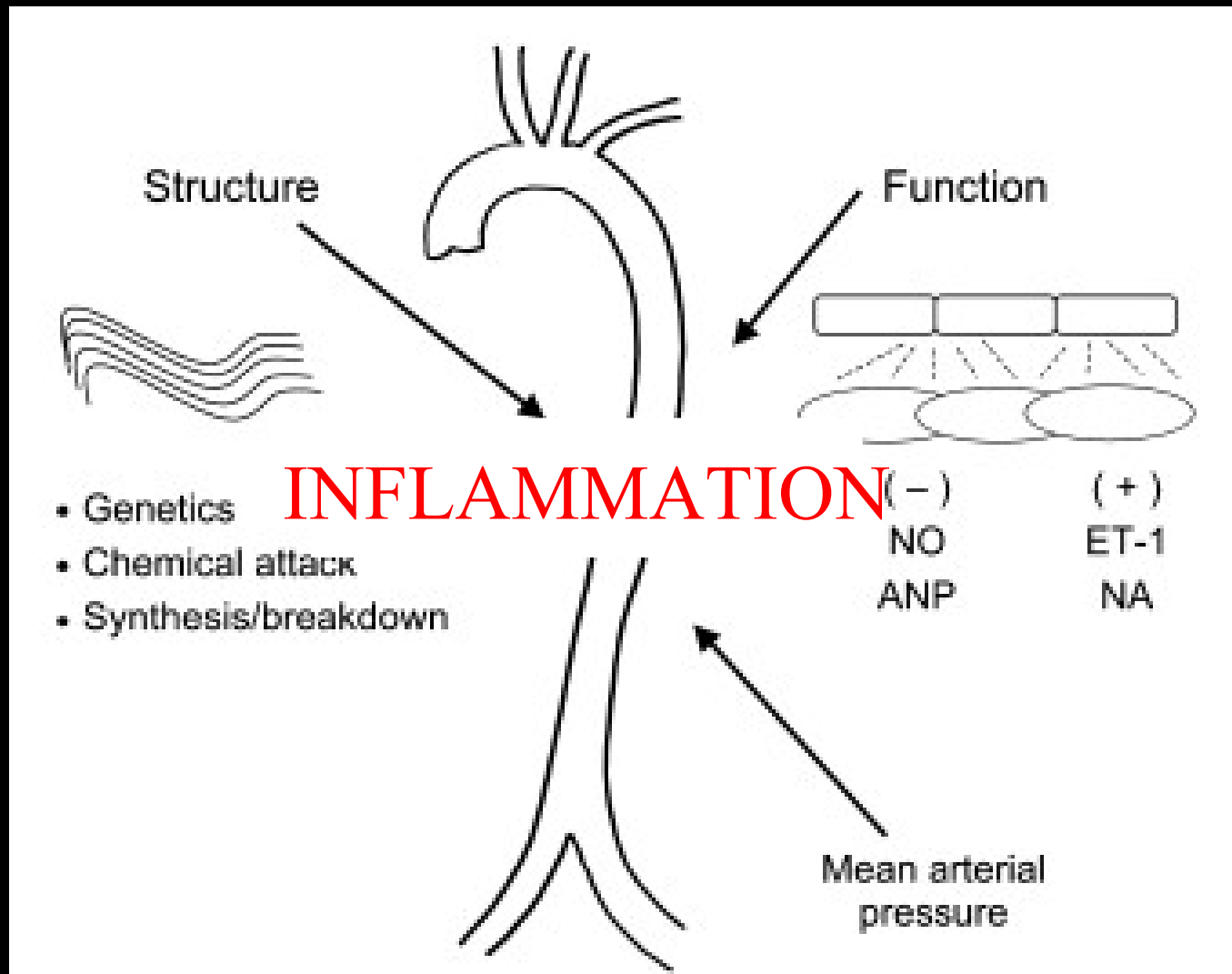
# Aortic Calcification and Pulse Wave Velocity



# Abdominal Aortic Calcification Score in Normotensive and Hypertensive Individuals



# Major Determinants of Arterial Stiffness

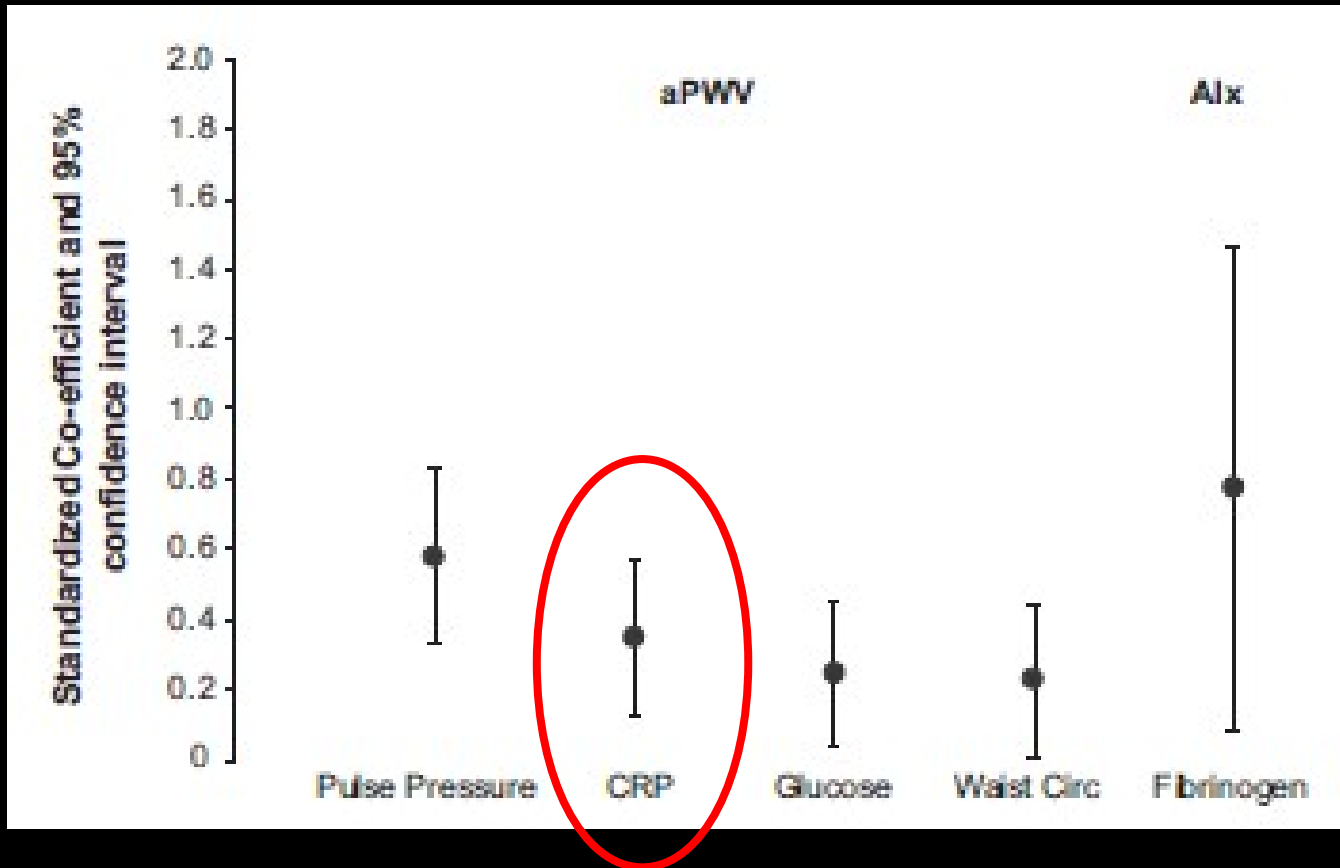


# **An Analysis of Prospective Risk Factors for Aortic Stiffness in Men**

## **20-Year Follow-Up From the Caerphilly Prospective Study**

Carmel M. McEniery, Michael Spratt, Margaret Munnerly, John Yarnell, Gordon D. Lowe,  
Ann Rumley, John Gallacher, Yoav Ben-Shlomo, John R. Cockcroft, Ian B. Wilkinson

# Independent Predictors of aPWV and AIx from 20 years Before



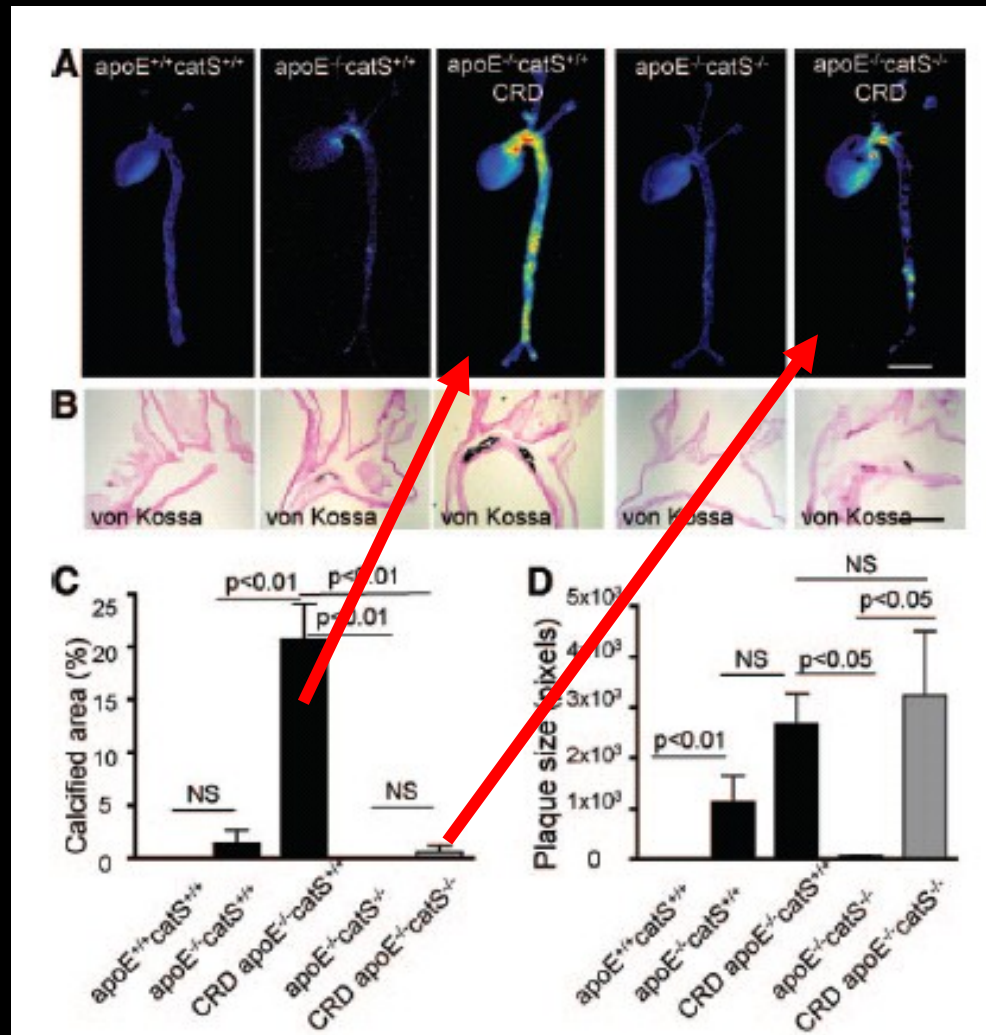
Inflammation and calcification....



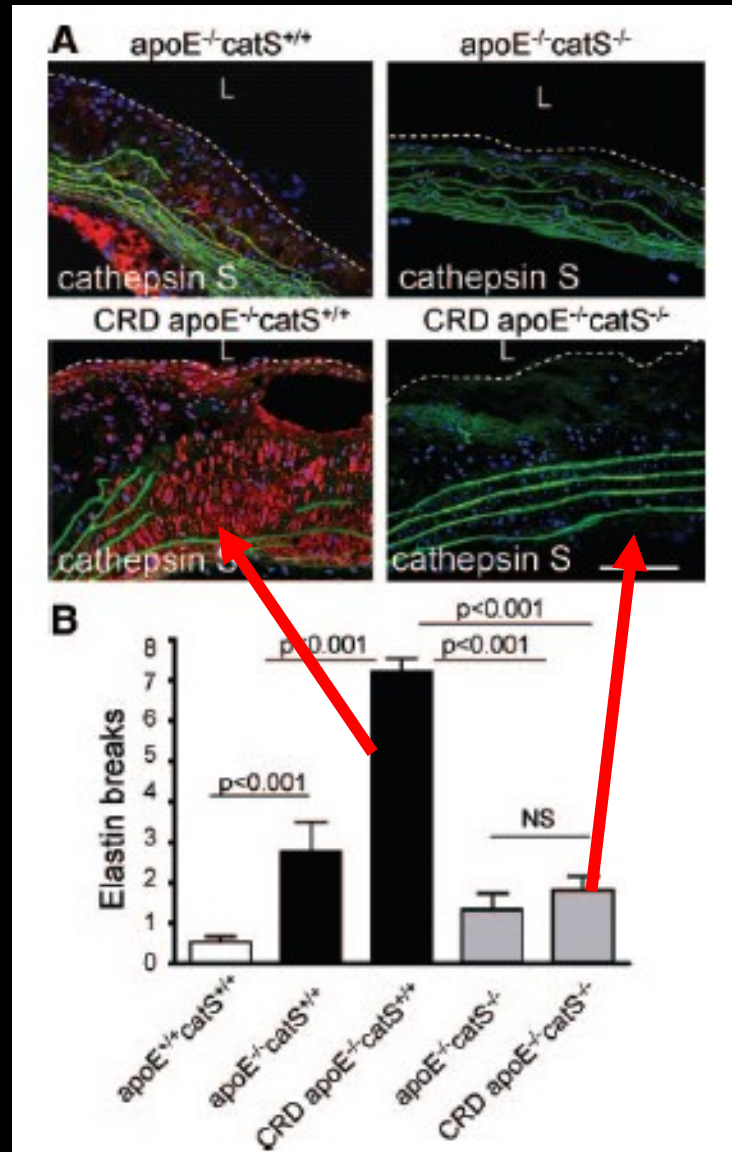
# **Arterial and Aortic Valve Calcification Abolished by Elastolytic Cathepsin S Deficiency in Chronic Renal Disease**

Elena Aikawa, MD, PhD; Masanori Aikawa, MD, PhD; Peter Libby, MD; Jose-Luiz Figueiredo, MD; Gabriel Rusanescu, PhD; Yoshiko Iwamoto, BS; Daiju Fukuda, MD, PhD; Rainer H. Kohler, PhD; Guo-Ping Shi, DSc; Farouc A. Jaffer, MD, PhD; Ralph Weissleder, MD, PhD

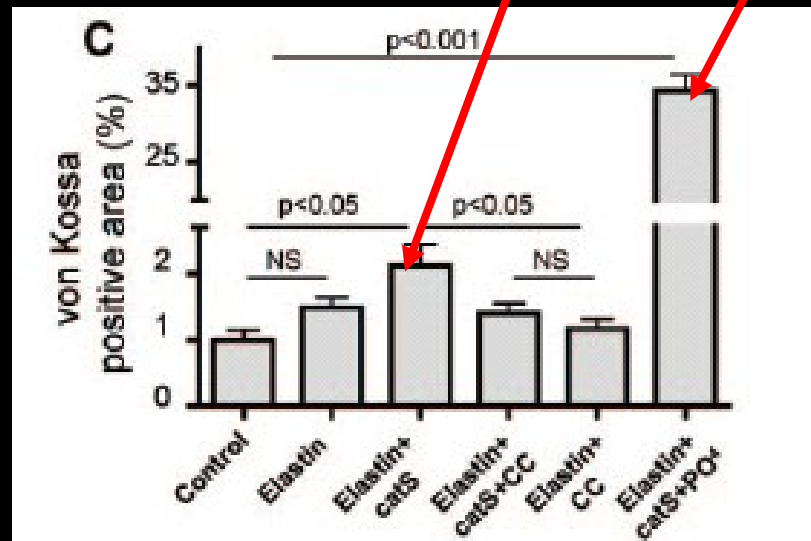
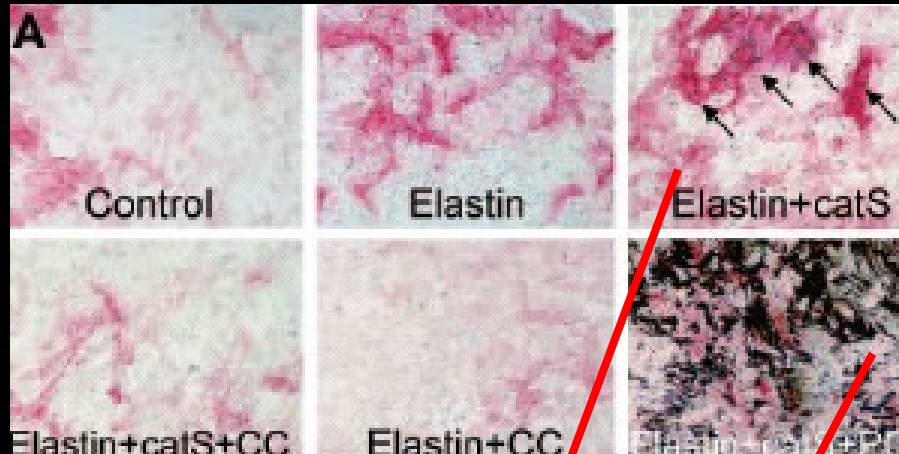
# Effect of Cathepsin S Deficiency on Aortic Calcification in CRD Mice



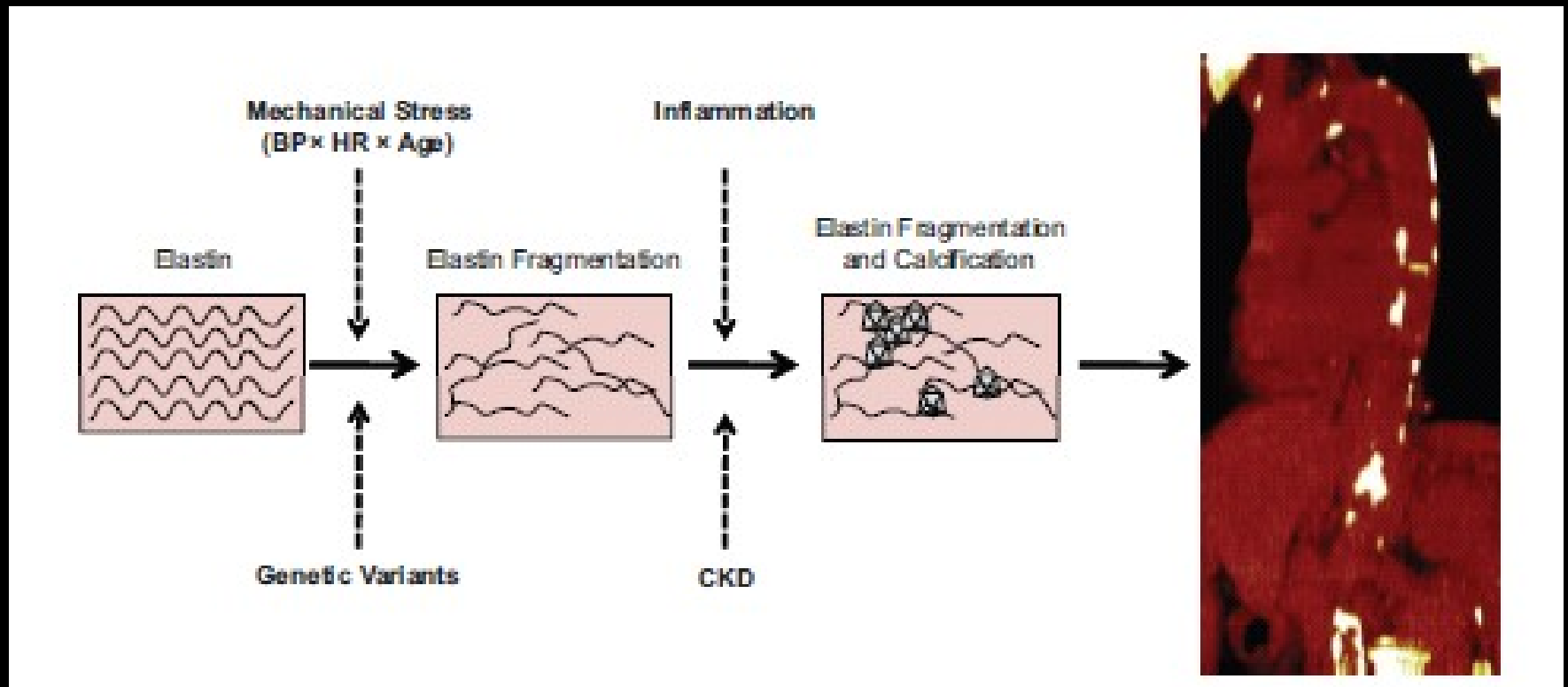
# Effect of Cathepsin S Deficiency on Elastin Fragmentation in CRD Mice



# Effect of Elastin Peptides and High Phosphate Levels on Calcification of Human Vascular SMC

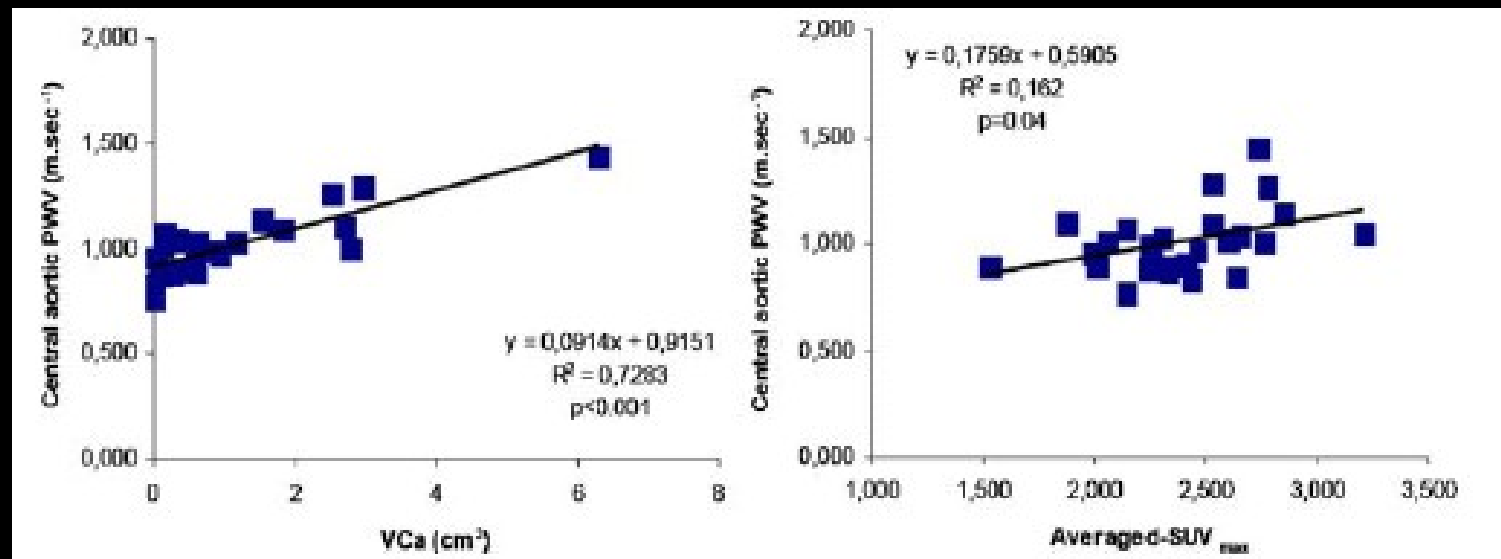


# Potential Mechanisms of Aortic Calcification

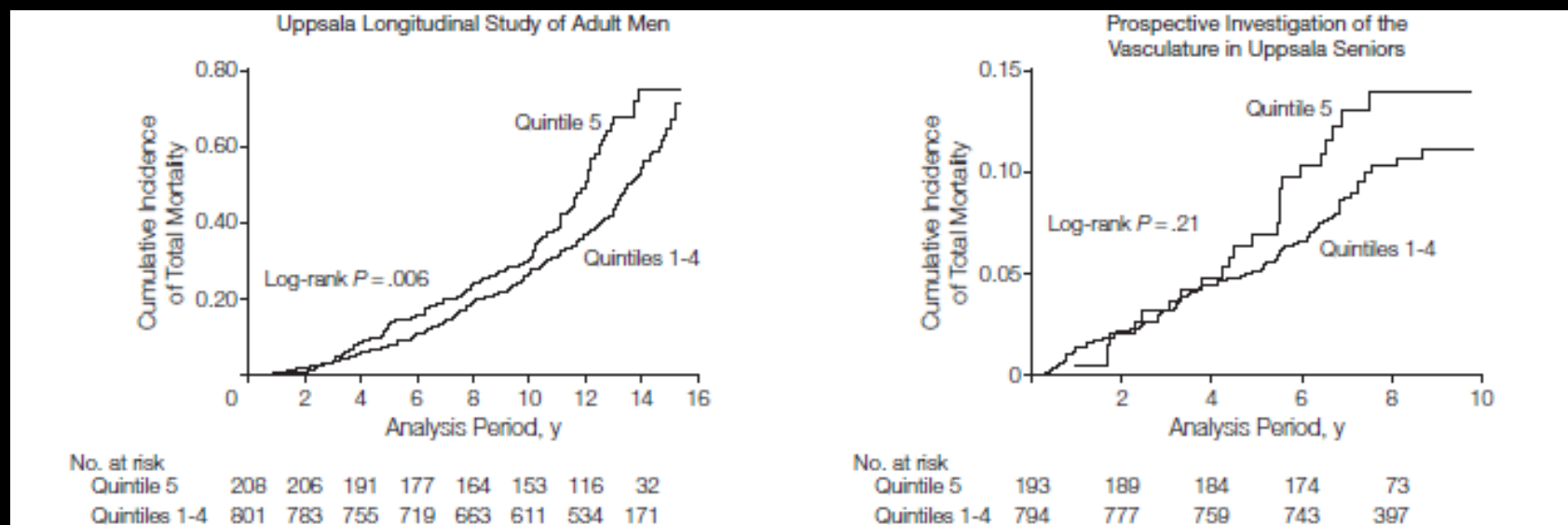


# Aortic inflammation, as assessed by hybrid FDG-PET/CT imaging, is associated with enhanced aortic stiffness in addition to concurrent calcification

Laure Joly • Wassila Djaballah • Gregory Koehl •  
Damien Mandry • Gilles Dolivet • Pierre-Yves Marie •  
Athanas Benetos



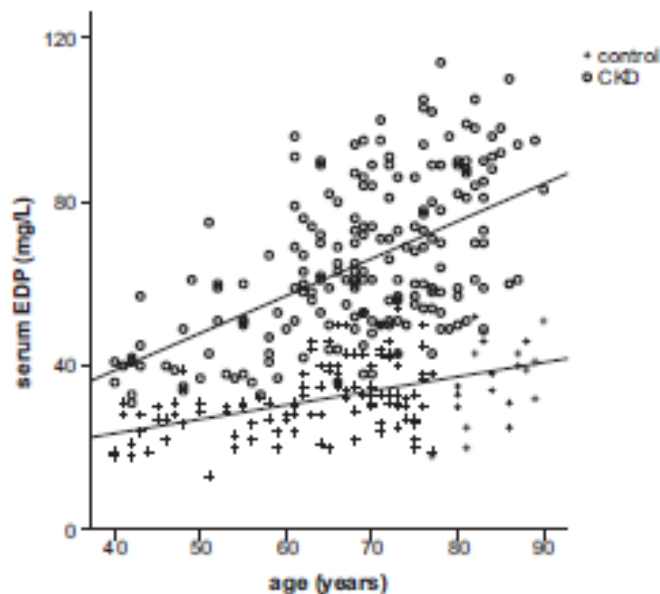
# Association Between Serum Cathepsin S and Mortality in Older Adults



# Kidney

## Elastin Degradation Is Associated With Progressive Aortic Stiffening and All-Cause Mortality in Predialysis Chronic Kidney Disease

Edward R. Smith, Laurie A. Tomlinson, Martin L. Ford, Lawrence P. McMahon, Chakravarthi Rajkumar, Stephen G. Holt



**Table 1. Longitudinal Determinants of Aortic Pulse Wave Velocity in Patients With Stage 3 and 4 Chronic Kidney Disease (n=65)**

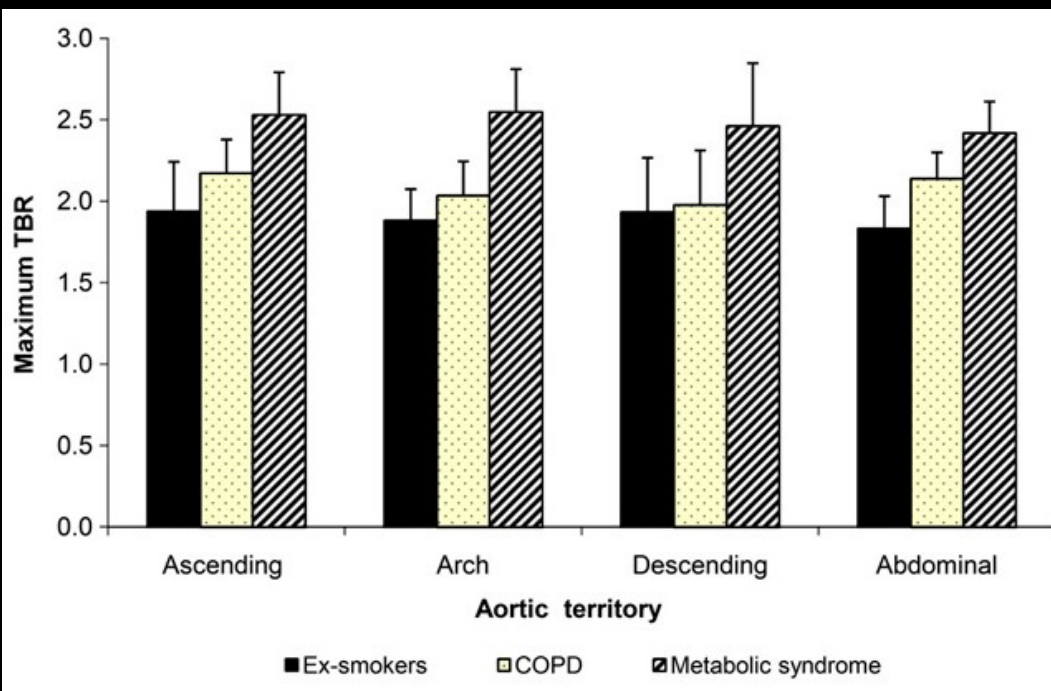
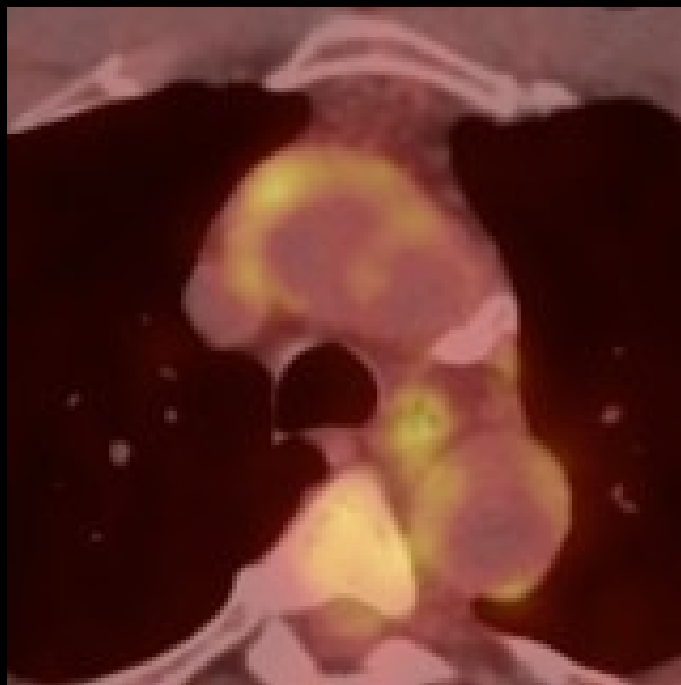
Parameter	Coefficient (95% CI)	P
Age	0.97 (0.49 to 1.46)	<0.001
MAP	0.005 (-0.014 to 0.009)	0.345
eGFR	-0.21 (-0.47 to 0.06)	0.021
hsCRP	1.25 (0.60-1.90)	<0.001
MMP-2	0.15 (0.08-0.32)	0.009
Cathepsin S	0.09 (0.04-0.22)	0.016
EDP	0.61 (0.38-0.99)	<0.001



# Excessive Aortic Inflammation in Chronic Obstructive Pulmonary Disease: An $^{18}\text{F}$ -FDG PET Pilot Study

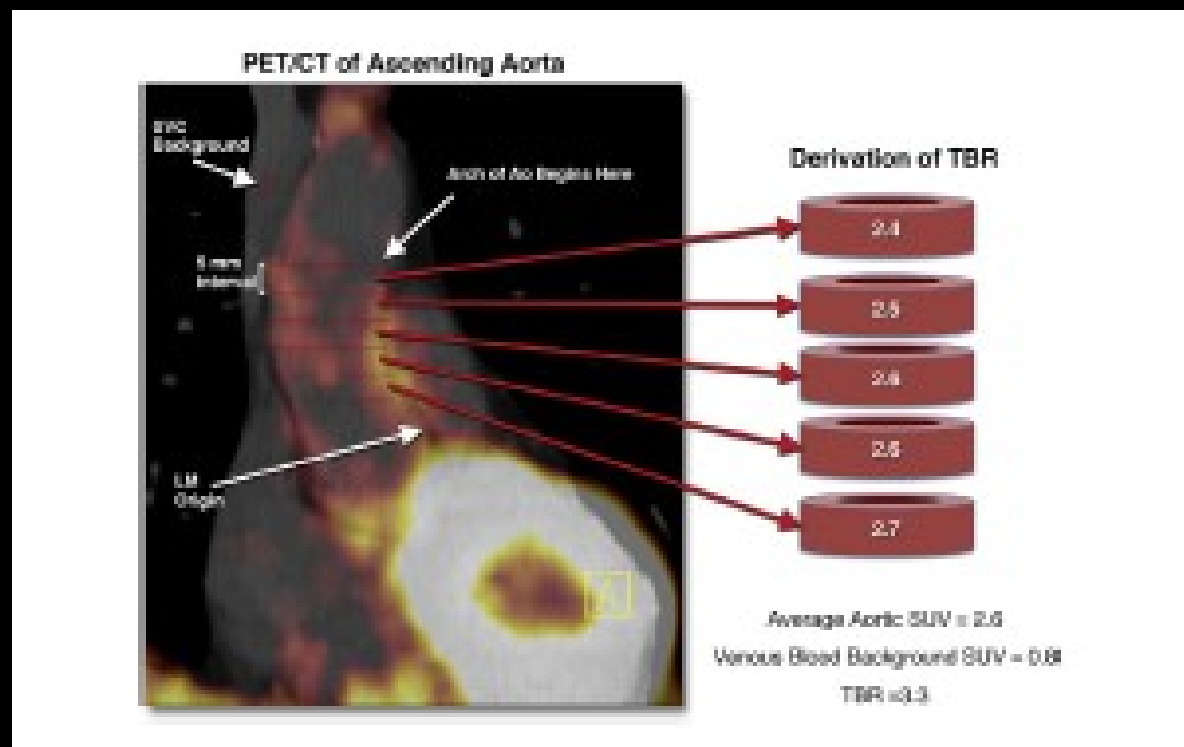
James M. Coulson<sup>1</sup>, James H.F. Rudd<sup>2</sup>, James M. Duckers<sup>1</sup>, John I.S. Rees<sup>3</sup>, Dennis J. Shale<sup>1</sup>, Charlotte E. Bolton<sup>1,4</sup>, and John R. Cockcroft<sup>1</sup>

<sup>1</sup>Wales Heart Research Institute, School of Medicine, Cardiff University, Cardiff, Wales, United Kingdom; <sup>2</sup>Division of Cardiovascular Medicine, University of Cambridge, Cambridge, United Kingdom; <sup>3</sup>Department of Radiology, University Hospital of Wales, Cardiff, Wales, United Kingdom; and <sup>4</sup>Nottingham Respiratory Biomedical Research Unit, University of Nottingham, Nottingham, United Kingdom

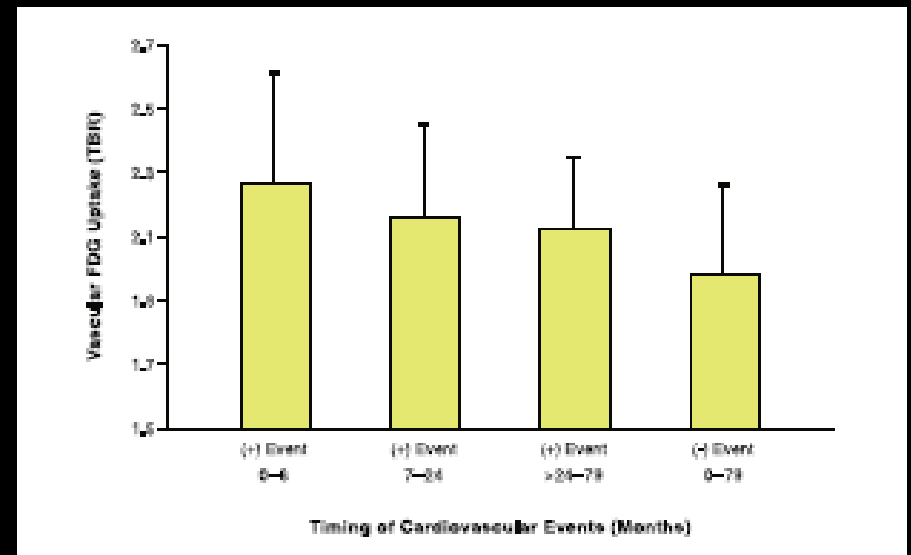
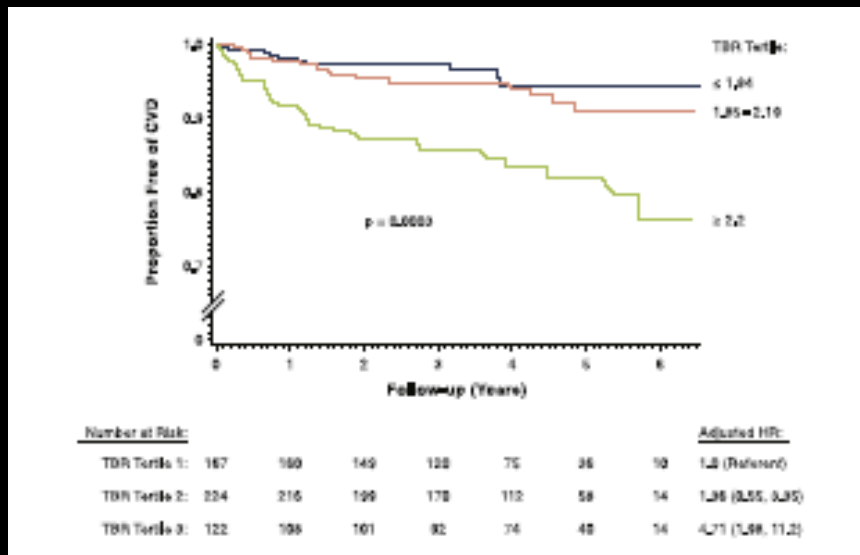


# Measurement of Arterial Activity on Routine FDG PET/CT Images Improves Prediction of Risk of Future CV Events

Amparo L. Figueroa, MD, MPH,\* Amr Abdelbaky, MD,\* Quynh A. Truong, MD, MPH,\*†  
Erin Corsini, BS,\* Megan H. MacNabb, BA,\* Zachary R. Lavender, BA,\*  
Meredith A. Lawler, BA,\* Steven K. Grinspoon, MD,†‡ Thomas J. Brady, MD,\*  
Khurram Nasir, MD, MPH,§|| Udo Hoffmann, MD, MPH,\* Ahmed Tawakol, MD\*†  
*Boston, Massachusetts; Miami, Florida; and Baltimore, Maryland*



# Effect of Aortic Inflammation on CV Events and Timing of CV Events

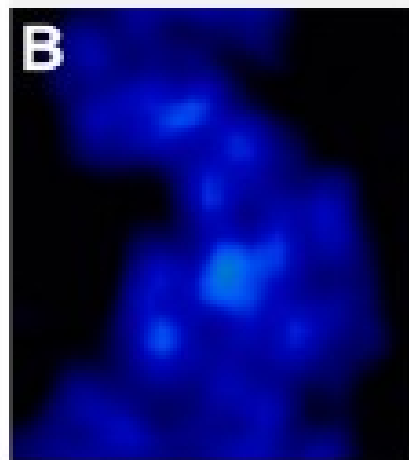


# Correlation of Inflammation Assessed by $^{18}\text{F}$ -FDG PET, Active Mineral Deposition Assessed by $^{18}\text{F}$ -Fluoride PET, and Vascular Calcification in Atherosclerotic Plaque: A Dual-Tracer PET/CT Study

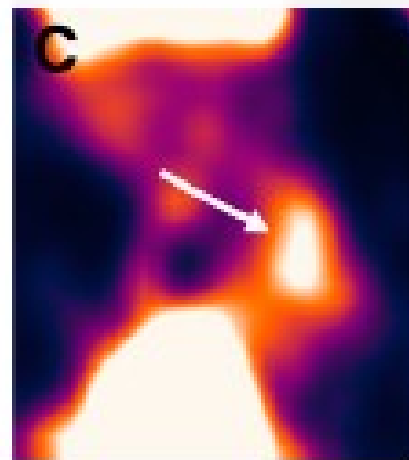
Thorsten Derlin<sup>1</sup>, Zoltán Tóth<sup>2</sup>, László Papp<sup>3</sup>, Christian Wisotzki<sup>1</sup>, Ivayla Apostolova<sup>4</sup>, Christian R. Habermann<sup>5</sup>, Janos Mester<sup>1</sup>, and Susanne Klutmann<sup>1</sup>



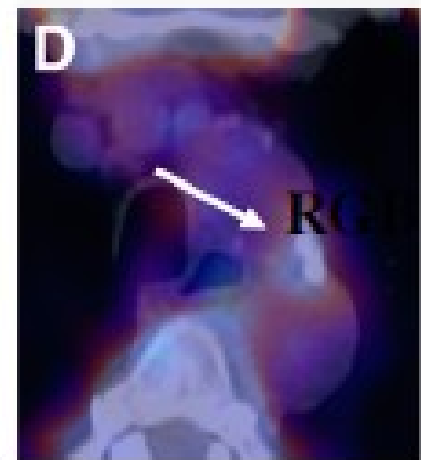
CT Image



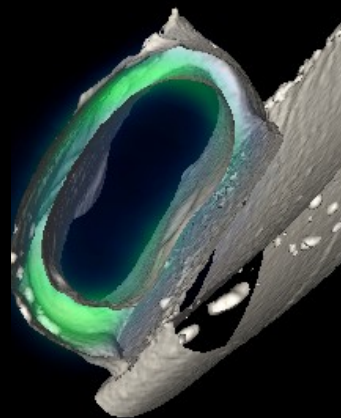
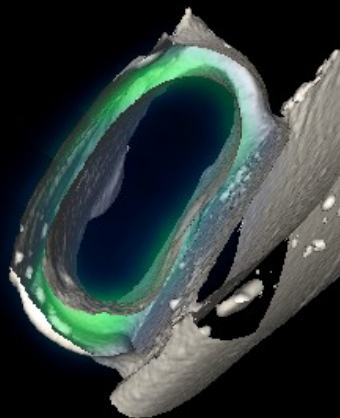
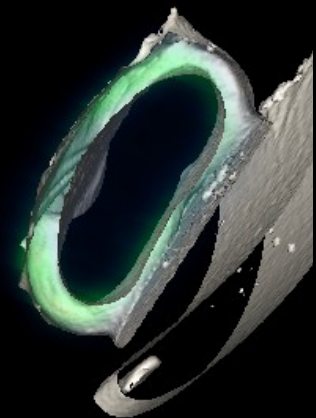
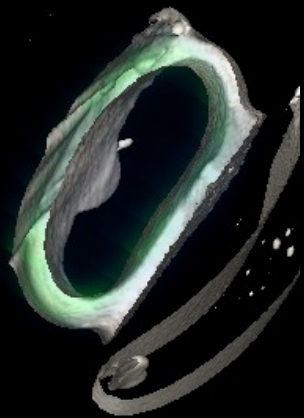
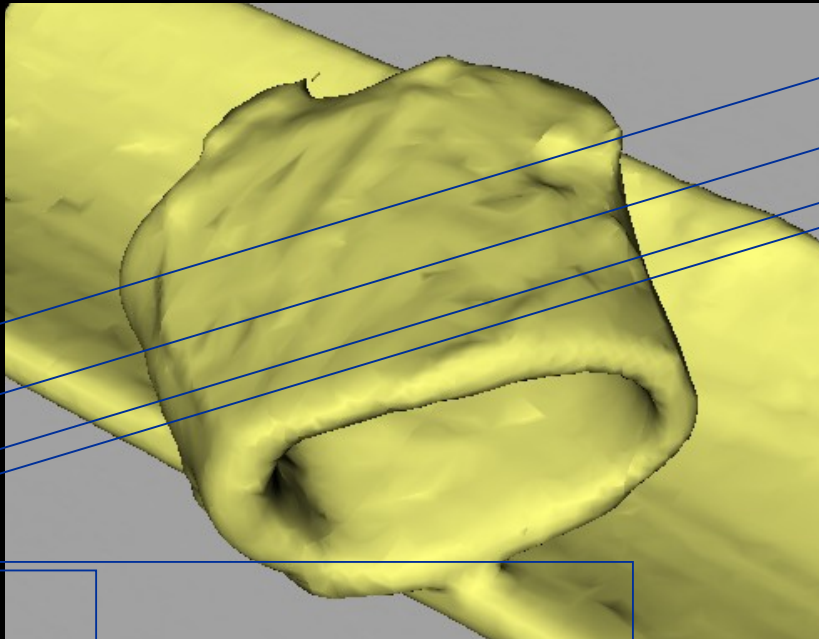
$^{18}\text{F}$ -FDG PET



$^{18}\text{F}$ -fluoride PET



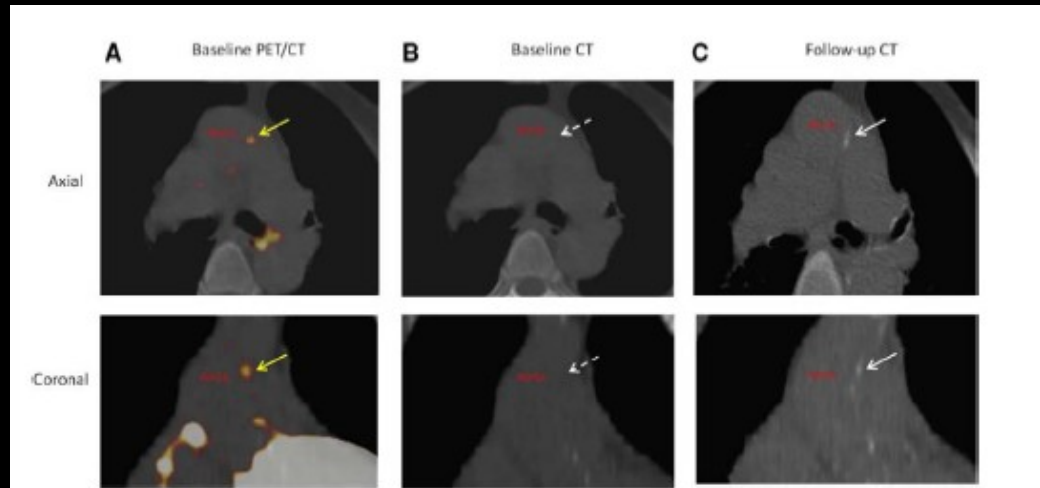
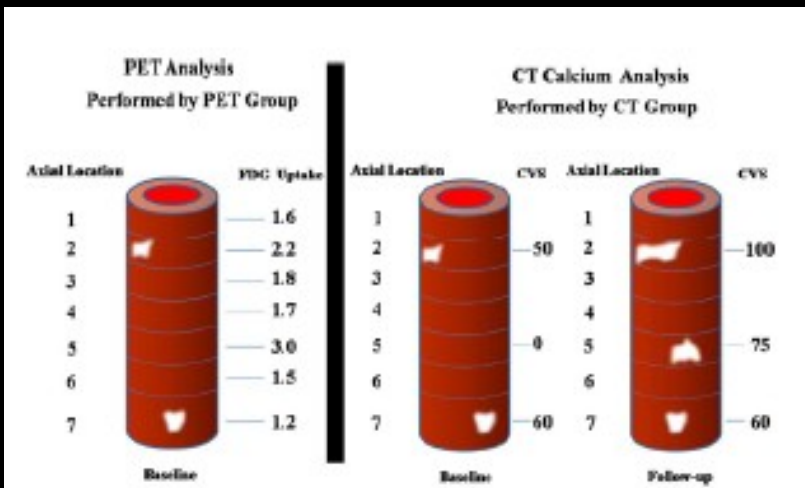
$^{18}\text{F}$ -FDG PET  
 $^{18}\text{F}$ -fluoride PET/  
CT Image



# Focal Arterial Inflammation Precedes Subsequent Calcification in the Same Location

## A Longitudinal FDG-PET/CT Study

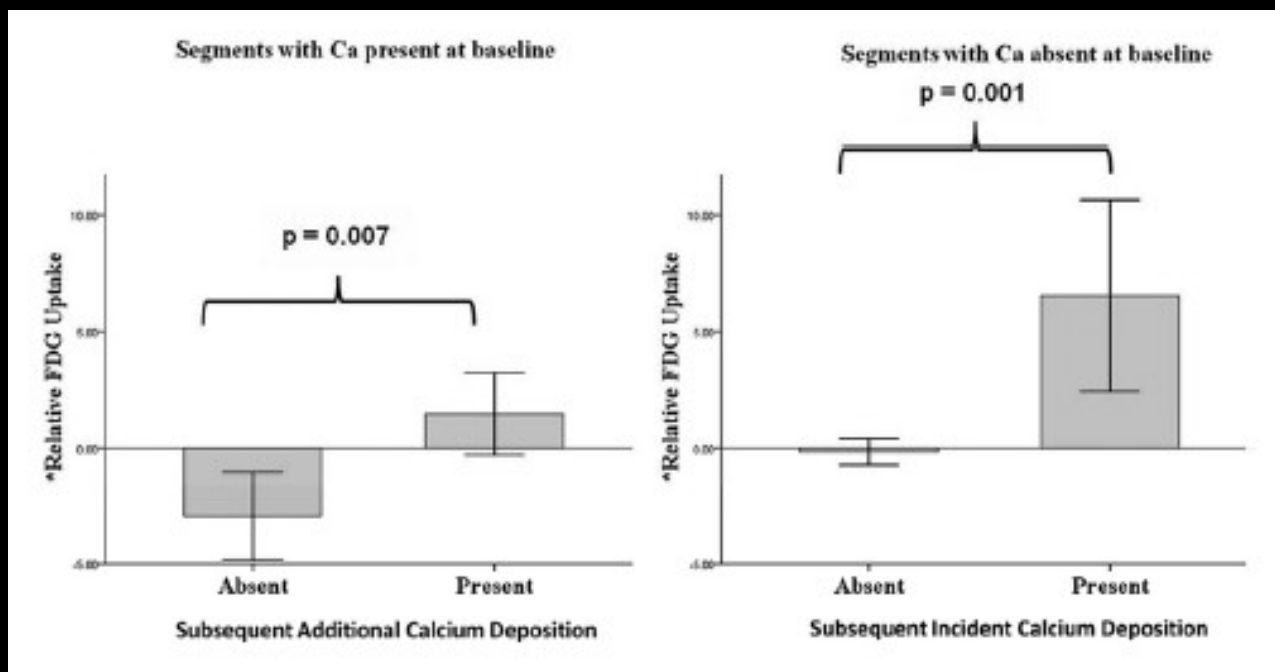
Amr Abdelbaky, MD; Erin Corsini, BS; Amparo L. Figueroa, MD, MPH; Sara Fontanez, BA; Sharath Subramanian, MD; Maros Ferencik, MD, PhD; Thomas J. Brady, MD; Udo Hoffmann, MD, MPH; Ahmed Tawakol MD



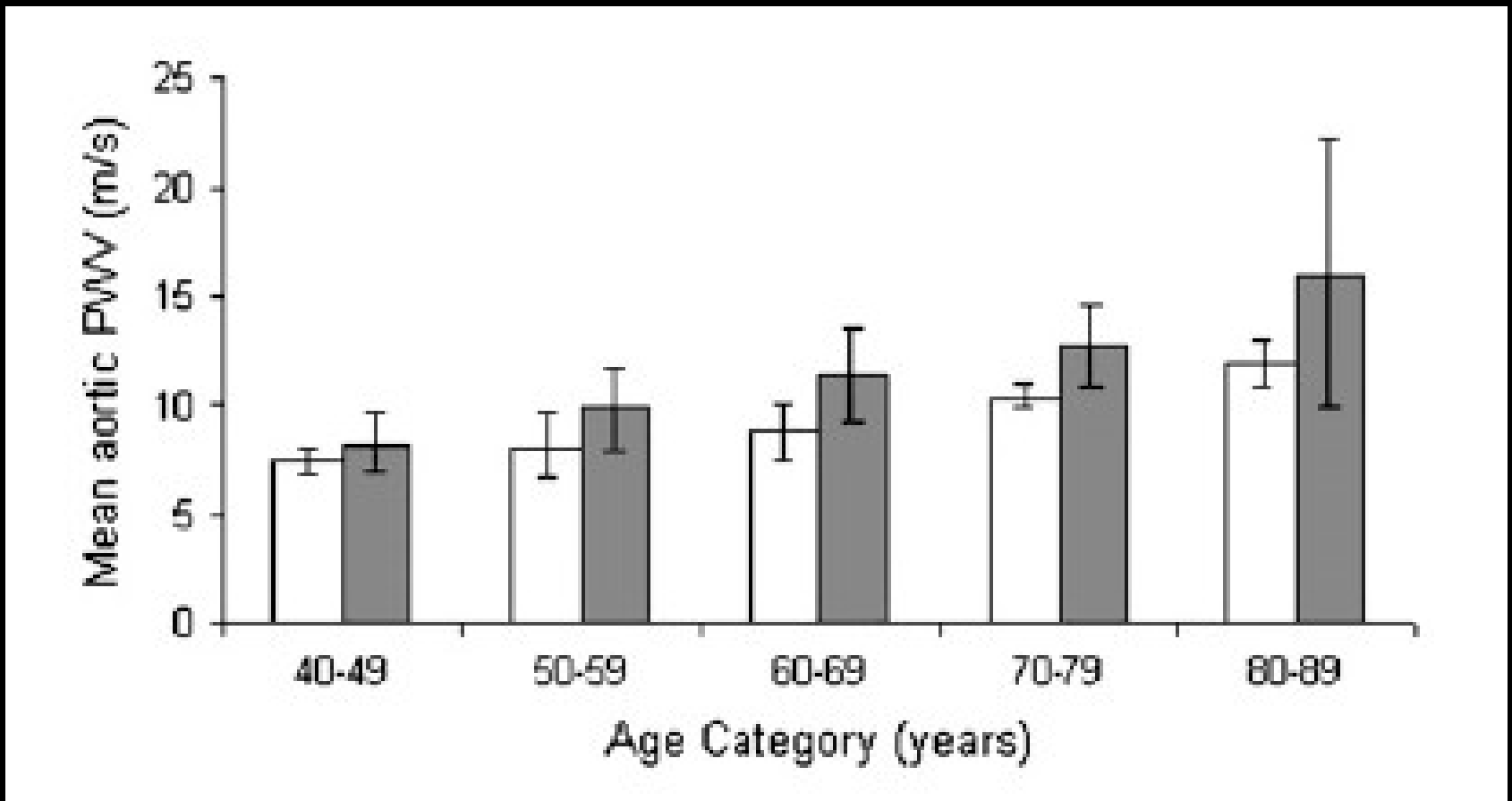
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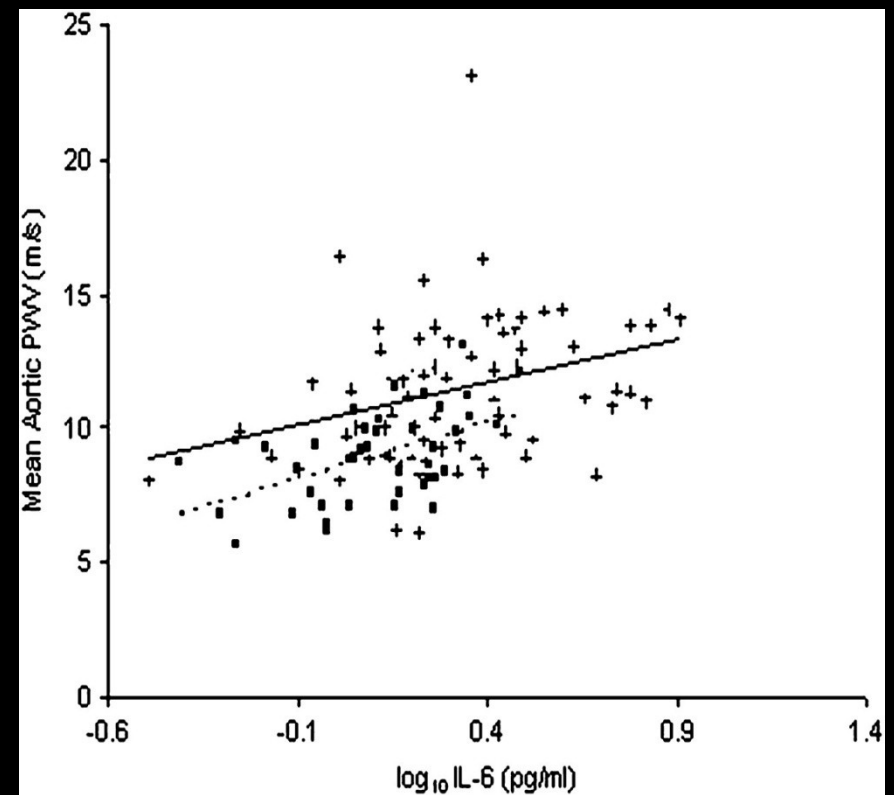
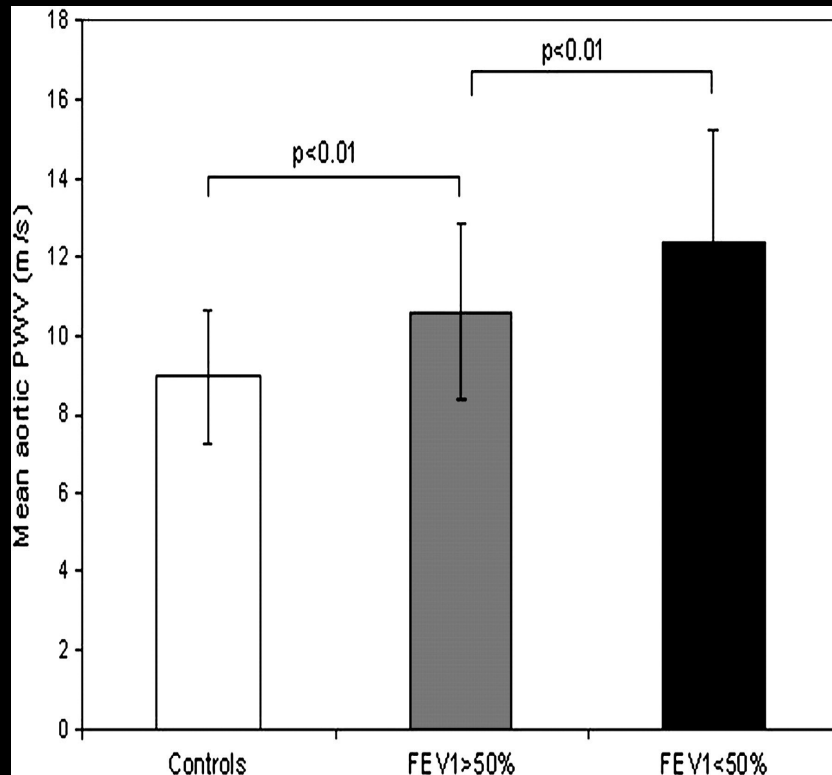
# Age and Aortic PWV in Subjects with COPD and Controls



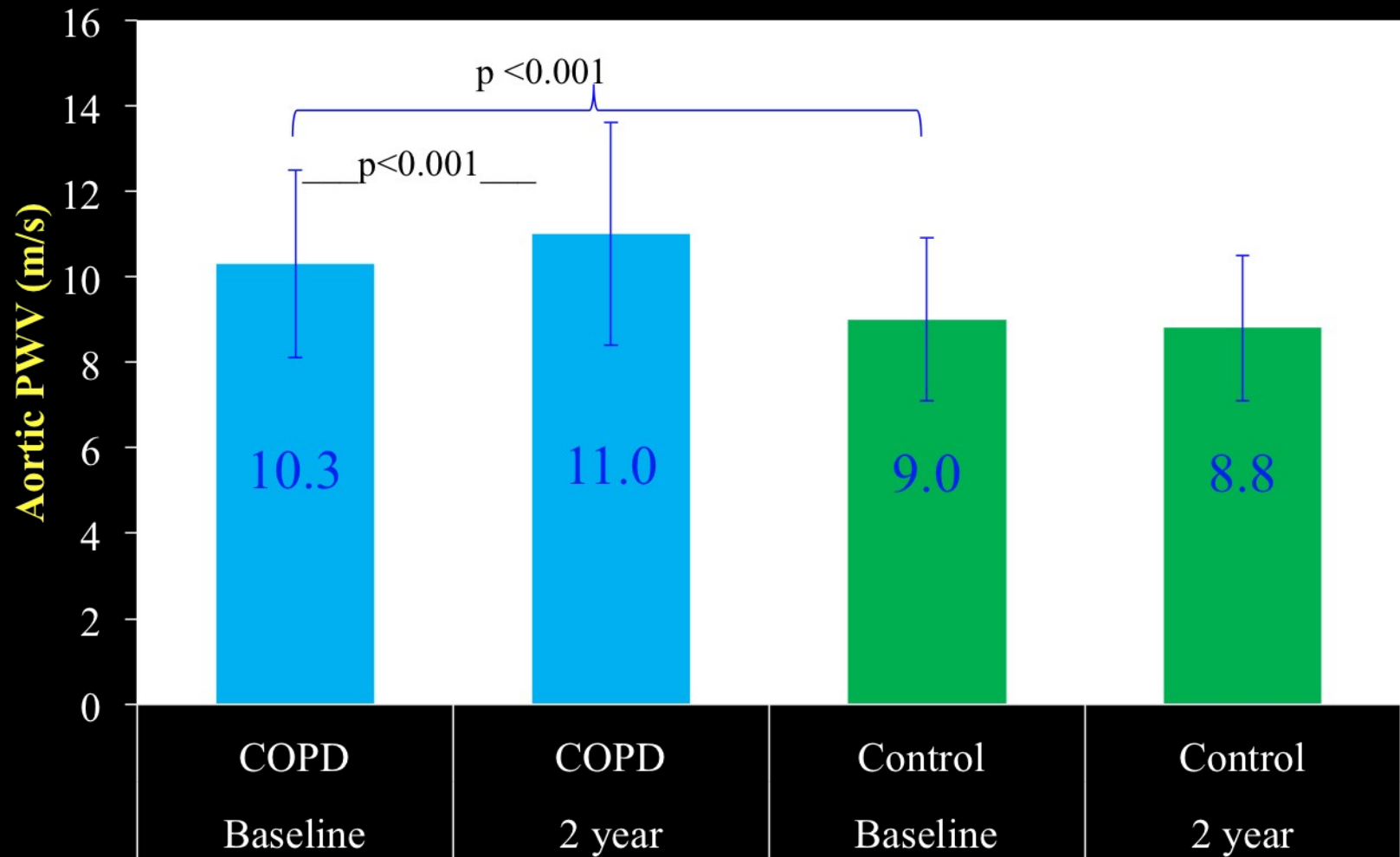


# Arterial Stiffness and Osteoporosis in Chronic Obstructive Pulmonary Disease

Ramsey Sabit<sup>1</sup>, Charlotte E. Bolton<sup>1</sup>, Peter H. Edwards<sup>2</sup>, Rebecca J. Pettit<sup>3</sup>, William D. Evans<sup>3</sup>, Carmel M. McEniery<sup>4</sup>, Ian B. Wilkinson<sup>4</sup>, John R. Cockcroft<sup>5</sup>, and Dennis J. Shale<sup>1</sup>



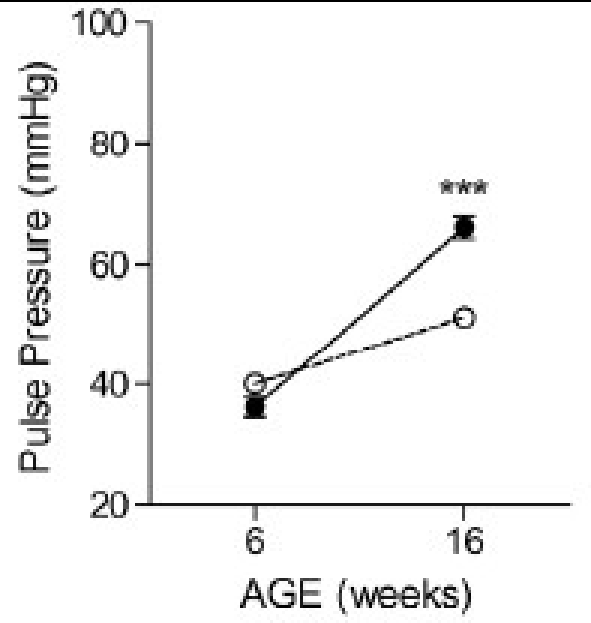
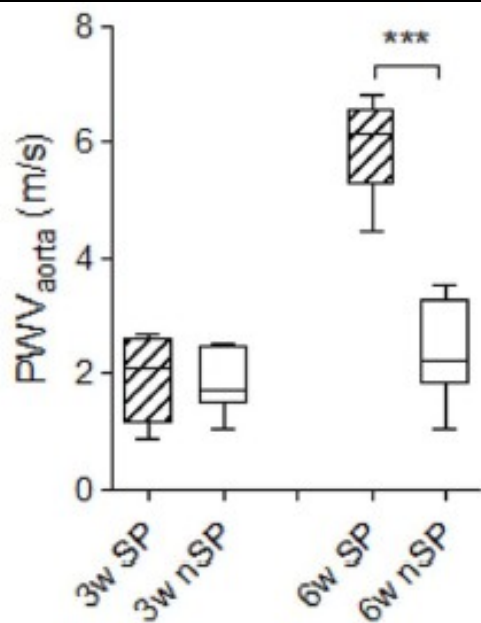
# Change in Aortic Stiffness



# Aortic and Carotid Arterial Stiffness and Epigenetic Regulator Gene Expression Changes Precede Blood Pressure Rise in Stroke-Prone Dahl Salt-Sensitive Hypertensive Rats

Victoria L. Herrera, Julius L. Decano, Nicholas Giordano, Ann Marie Moran, Nelson Ruiz-Opazo\*

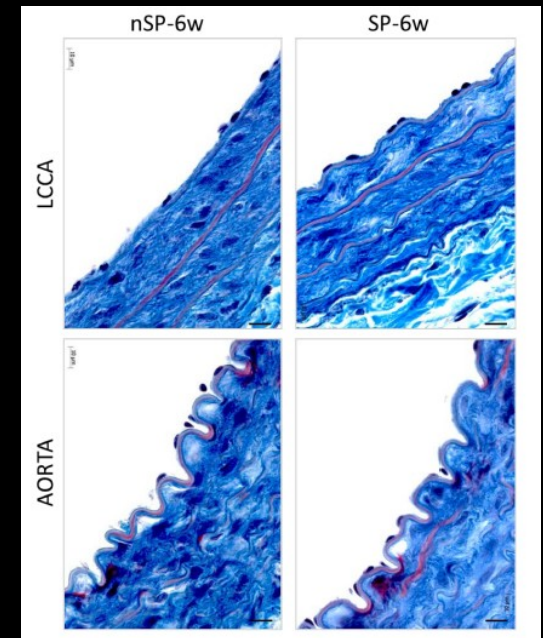
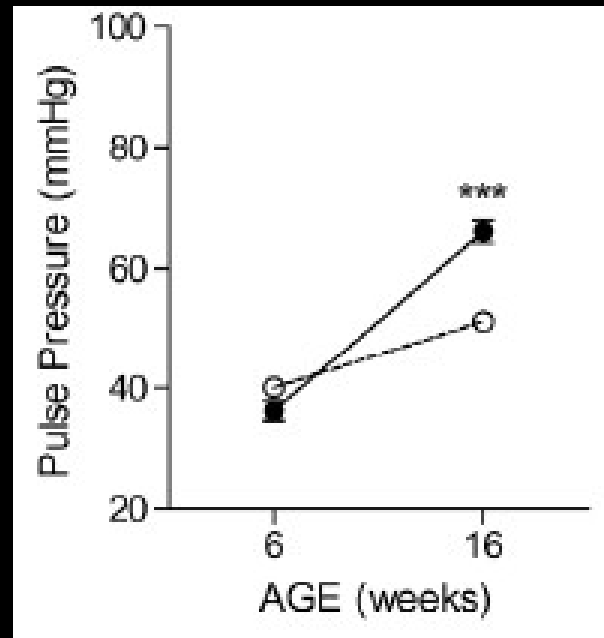
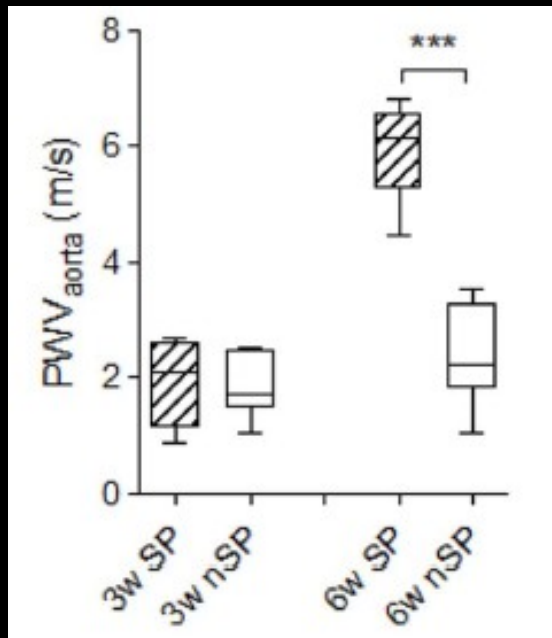
Whitaker Cardiovascular Institute, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, United States of America



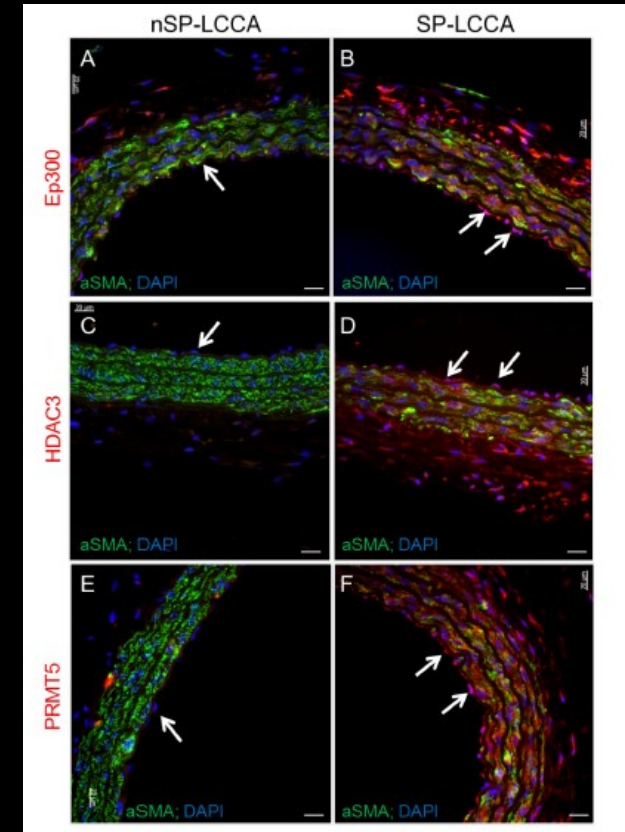
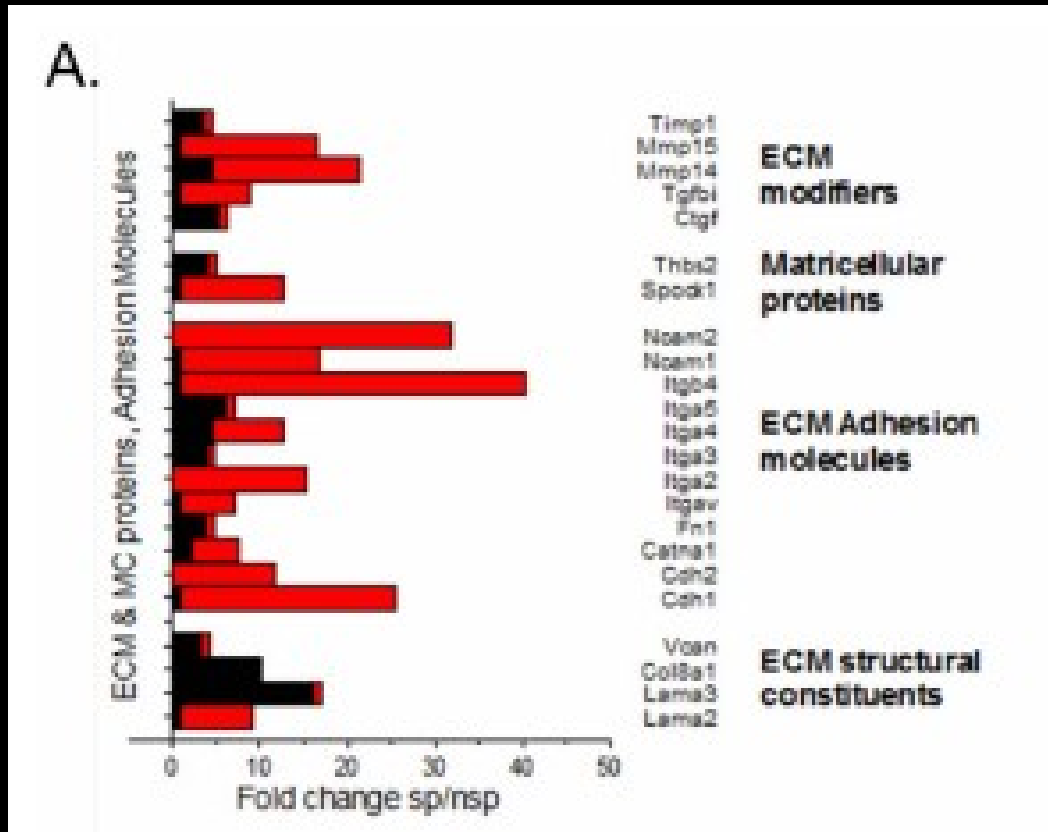
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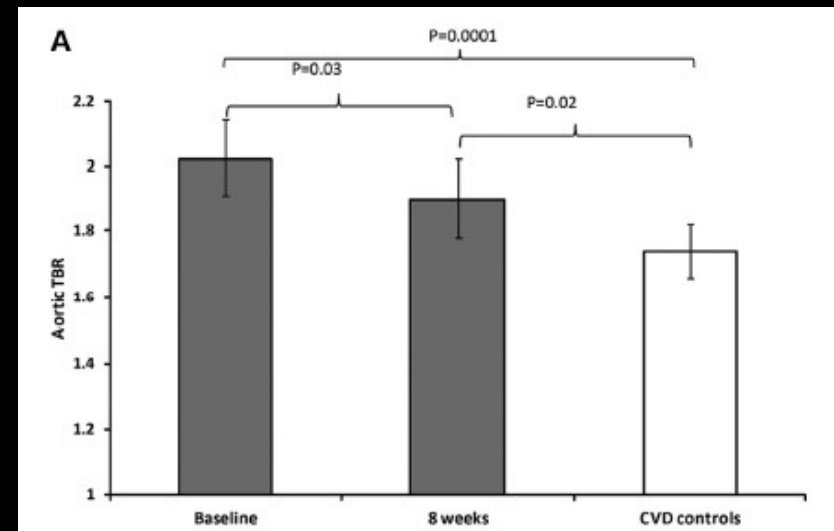
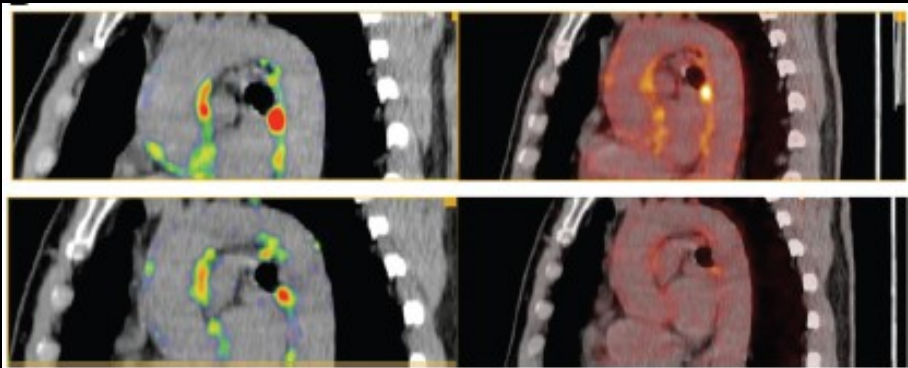
# RT-PCR Array Profiling in Aortas and Left Common Carotid Artery (LCCA) in SP and nSP Dahl Rats



Therapy.....

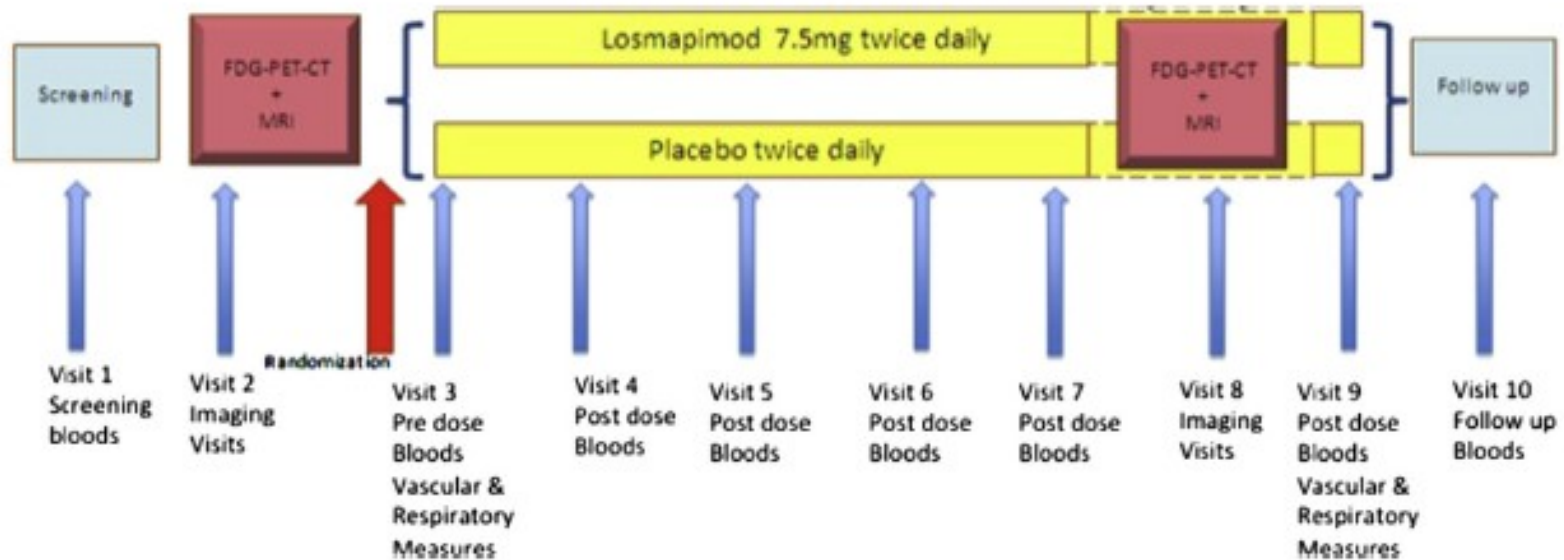
# Anti-Tumor Necrosis Factor- $\alpha$ Therapy Reduces Aortic Inflammation and Stiffness in Patients With Rheumatoid Arthritis

Kaisa M. Mäki-Petäjä, PhD; Maysoon Elkhawad, MRCS; Joseph Cheriyan, FRCP; Francis R. Joshi, MRCP; Andrew J.K. Östör, MBBS, FRACP; Frances C. Hall, FRCP, DPhil; James H.F. Rudd, PhD, MRCP; Ian B. Wilkinson, FRCP, DM



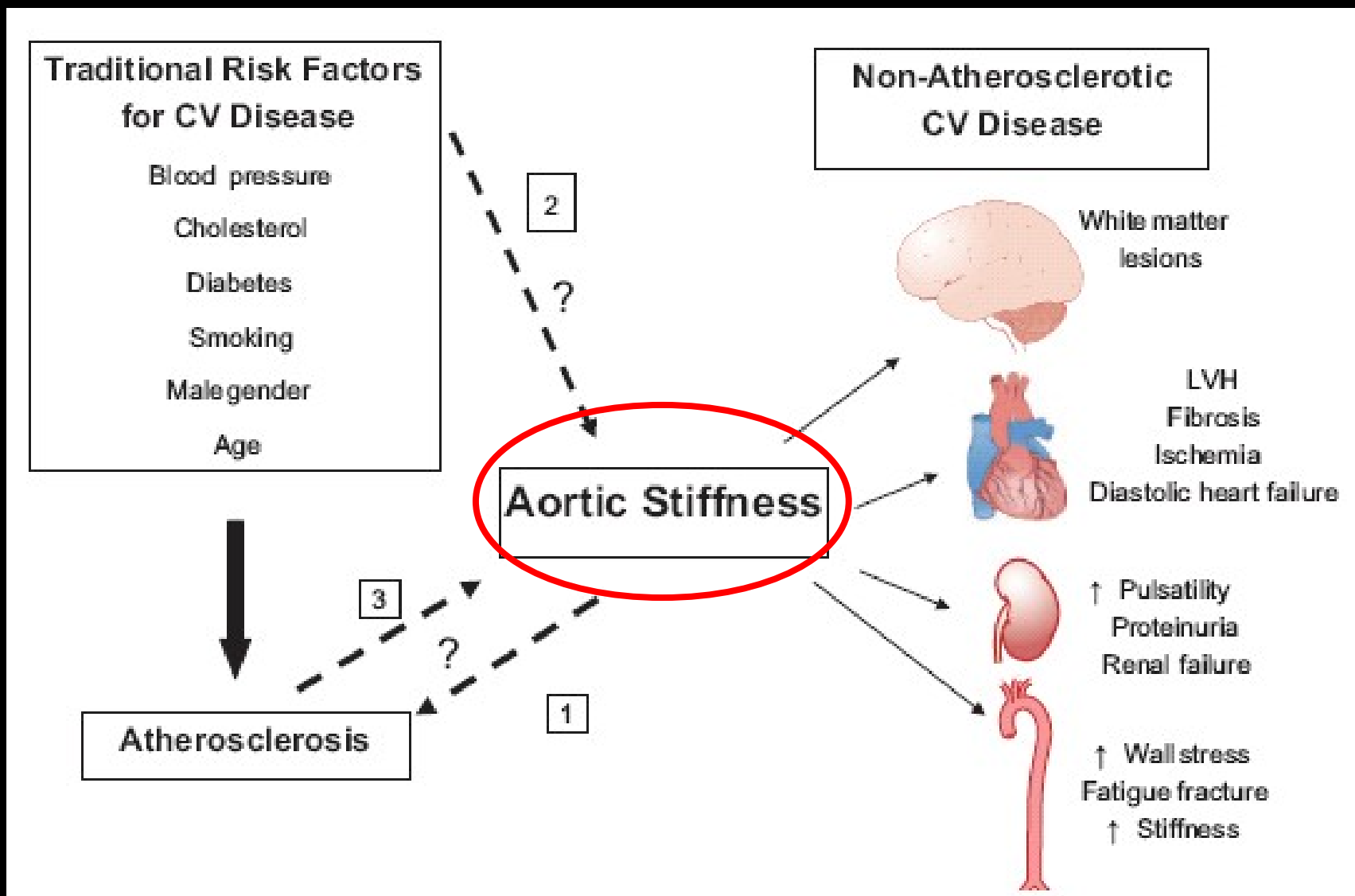
# Evaluation of losmapimod in patients with chronic obstructive pulmonary disease (COPD) with systemic inflammation stratified using fibrinogen ('EVOLUTION'): Rationale and protocol

M. Fisk<sup>a,f</sup>, D. Mohan<sup>b,f</sup>, J. Cheriyan<sup>a,e,\*,f</sup>, L. Yang<sup>a</sup>, J. Fuld<sup>c</sup>, C.M. McEnery<sup>a</sup>, R. Tal-Singer<sup>d</sup>, M.I. Polkey<sup>b</sup>, I.B. Wilkinson<sup>a,e</sup>

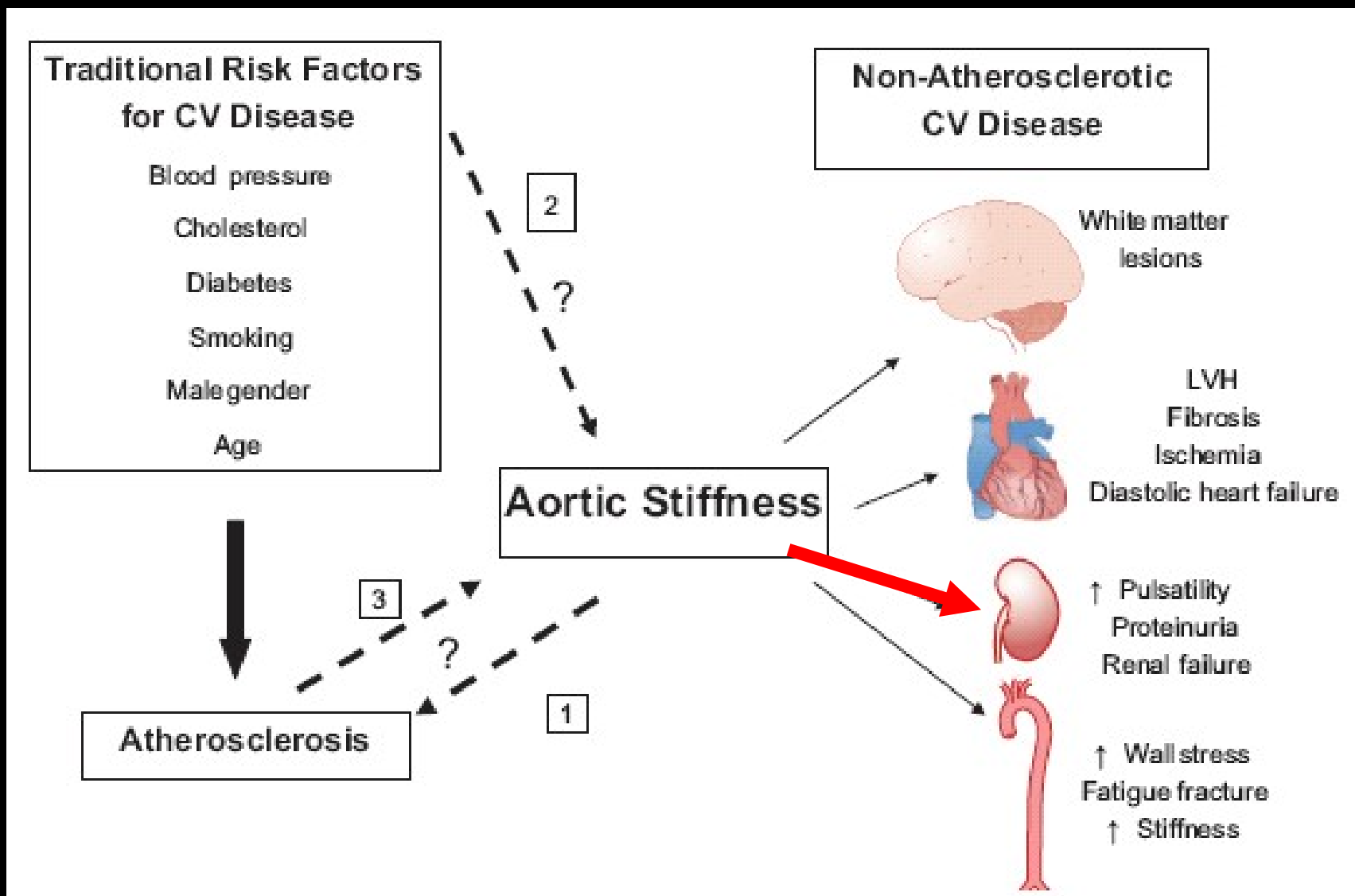




# Proposed Mechanisms Linking Aortic Stiffness with Atherosclerotic and Nonatherosclerotic Cardiovascular Disease

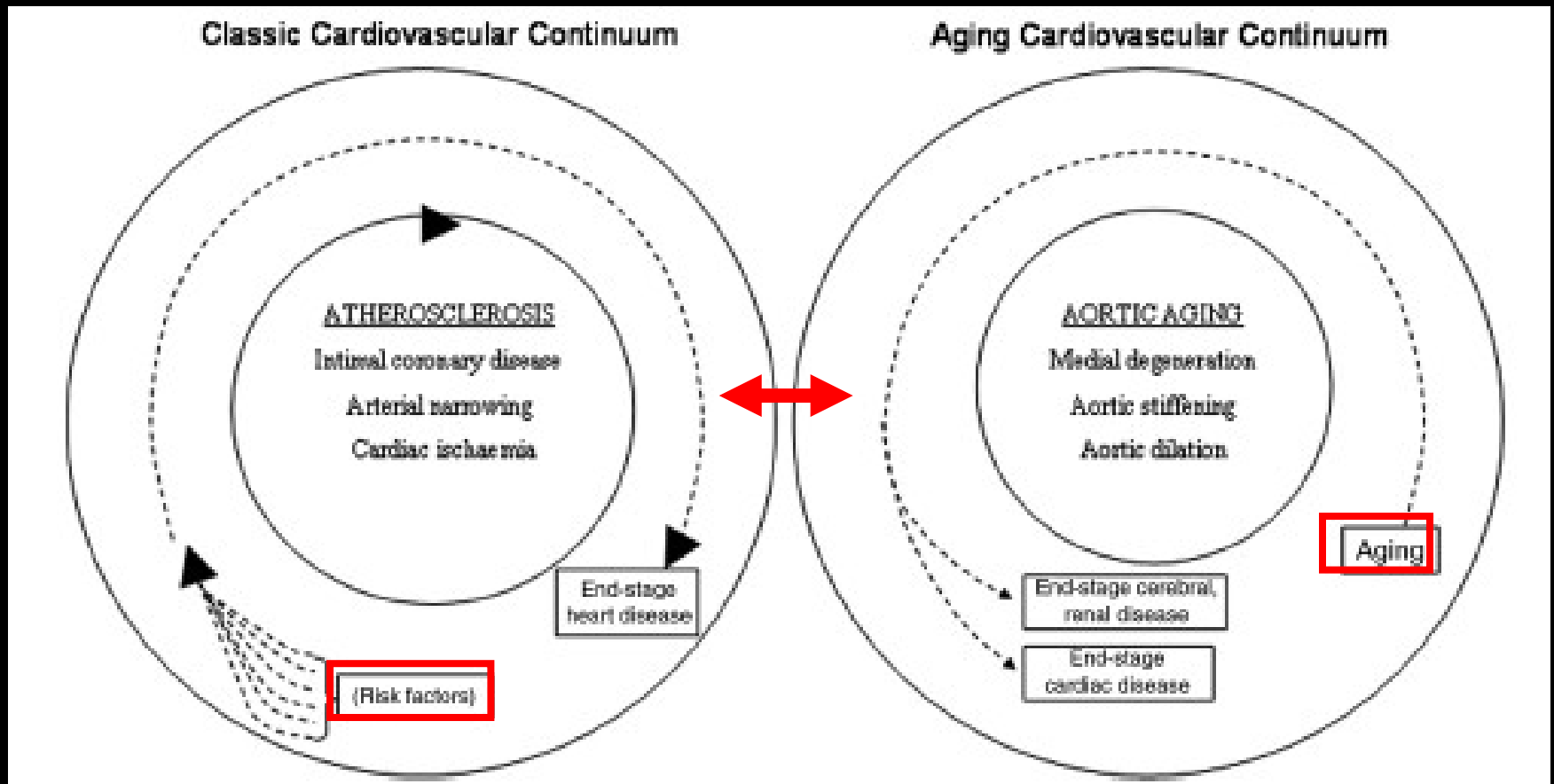


# Proposed Mechanisms Linking Aortic Stiffness with Atherosclerotic and Nonatherosclerotic Cardiovascular Disease



## Atherosclerosis

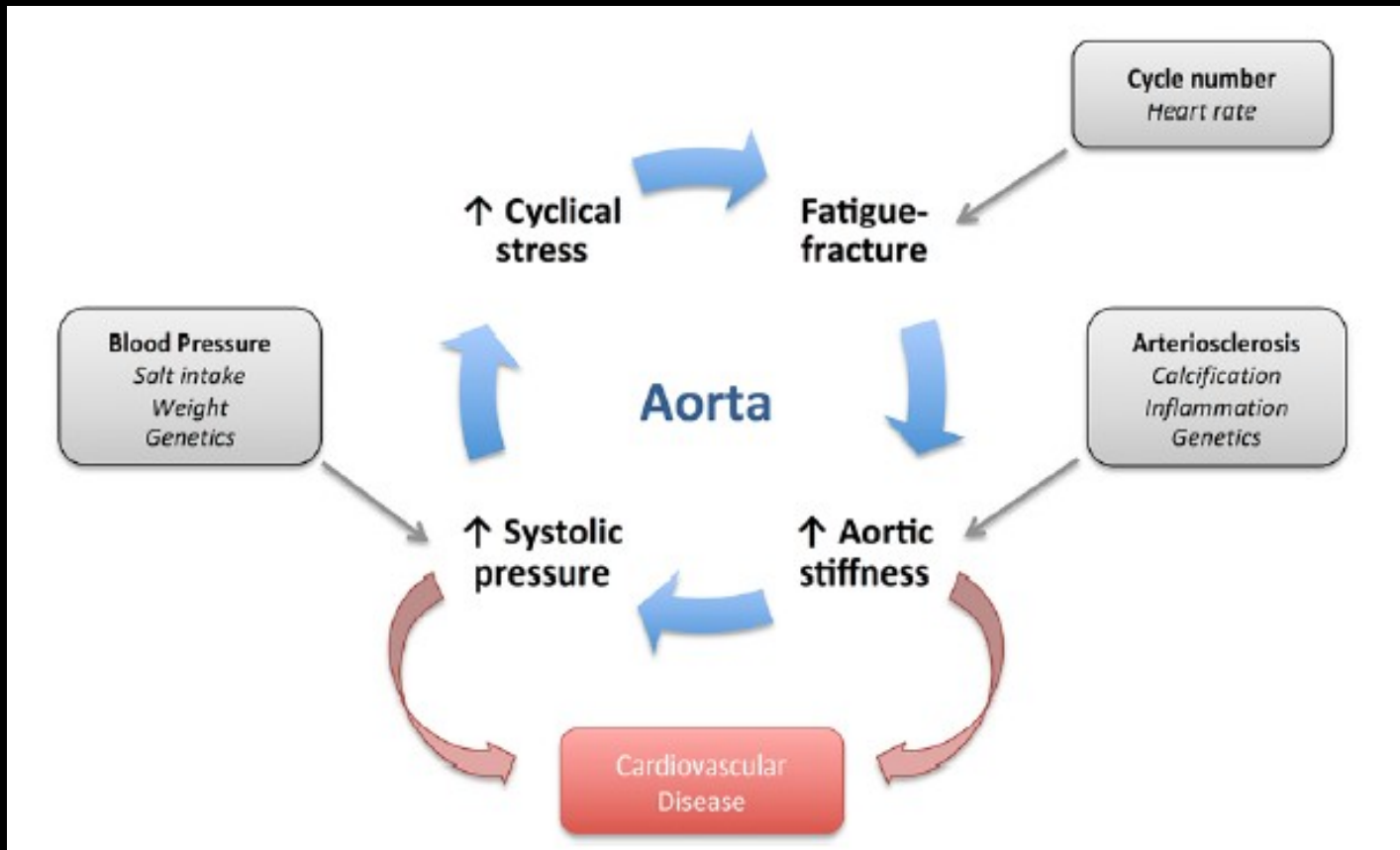
## Arteriosclerosis



# Editorial Commentary

## The Pressures of Aging

Carmel M. McEniery, Ian B. Wilkinson



You can't help  
getting older,  
but you don't have  
to get **old.**

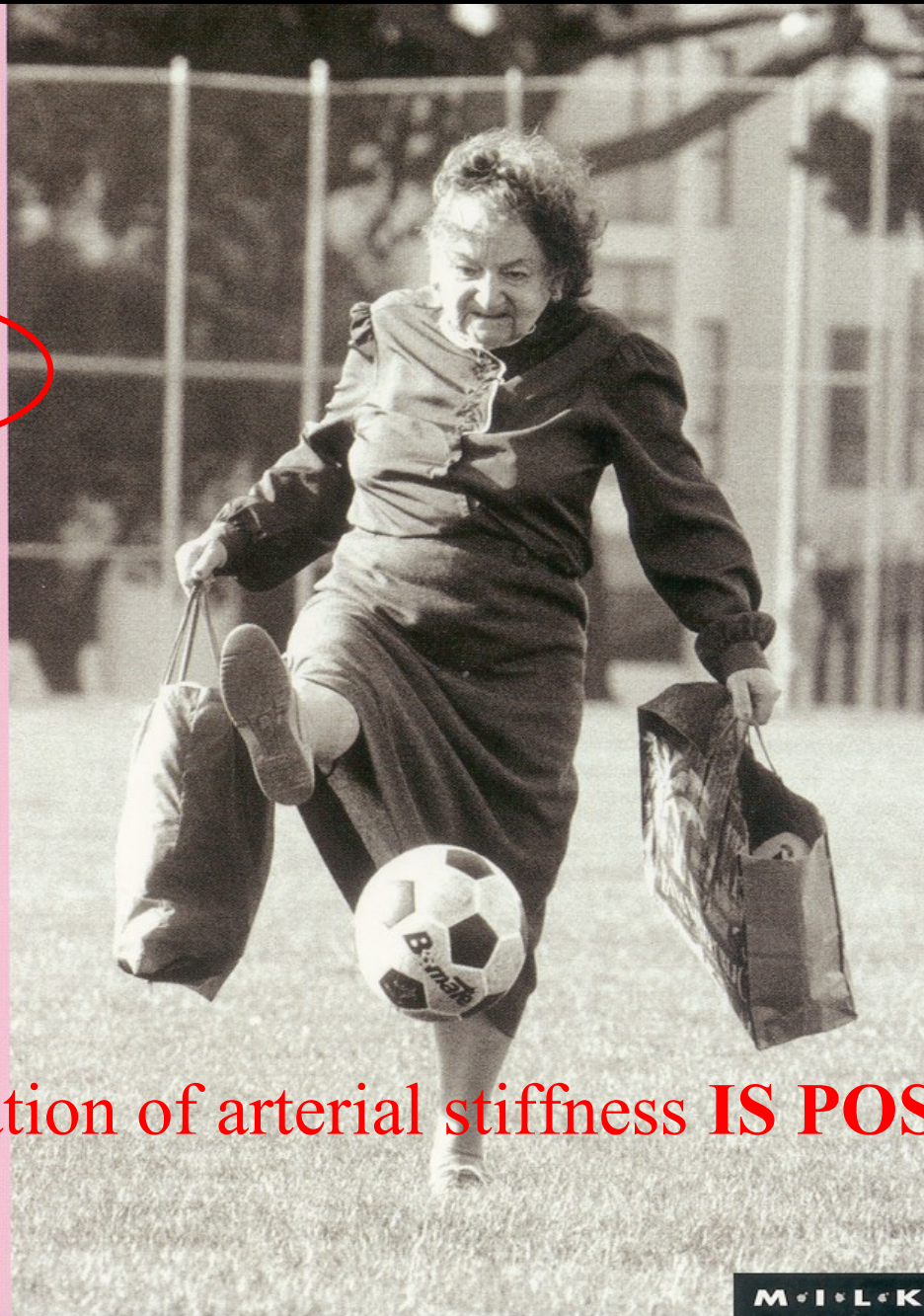
[GEORGE BURNS]



M • I • L • K

You can't help  
getting older,  
but you don't have  
to get old.

[GEORGE BURNS]



Therapeutic modulation of arterial stiffness **IS POSSIBLE**

M•I•L•K

# ARTERY

# 14



THURSDAY 9 – SATURDAY 11 OCTOBER 2014  
MECC, MAASTRICHT, THE NETHERLANDS







## Brief Reviews

### Arterial Aging

#### Is It an Immutable Cardiovascular Risk Factor?

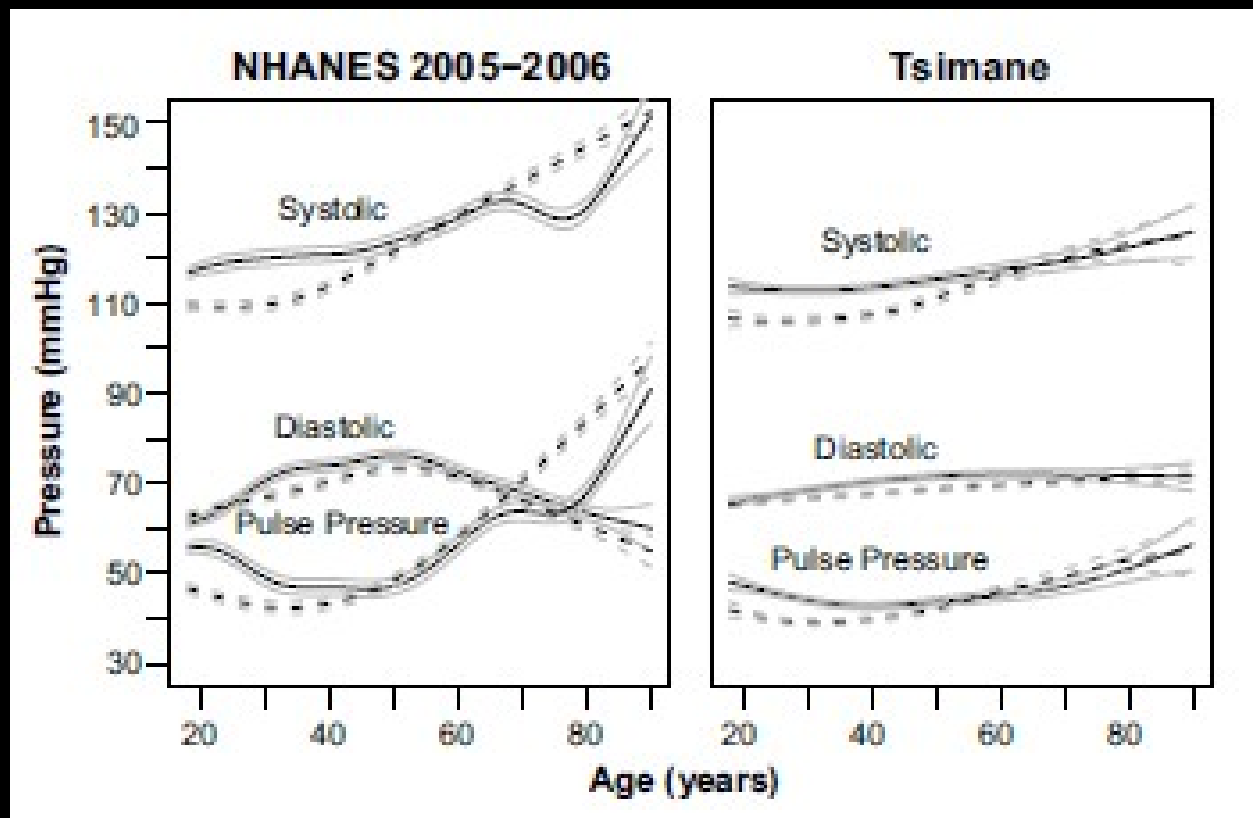
Samer S. Najjar, Angelo Scuteri, Edward G. Lakatta

Is arteriosclerosis inevitable....?

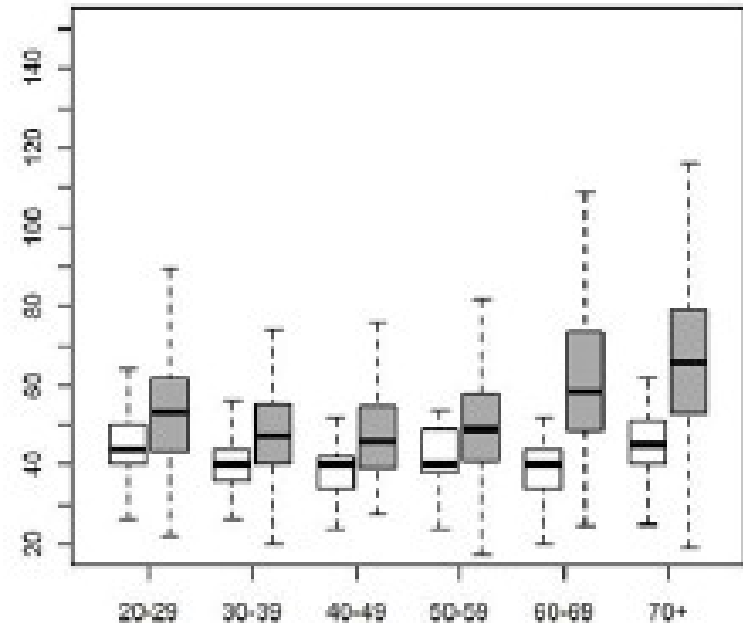
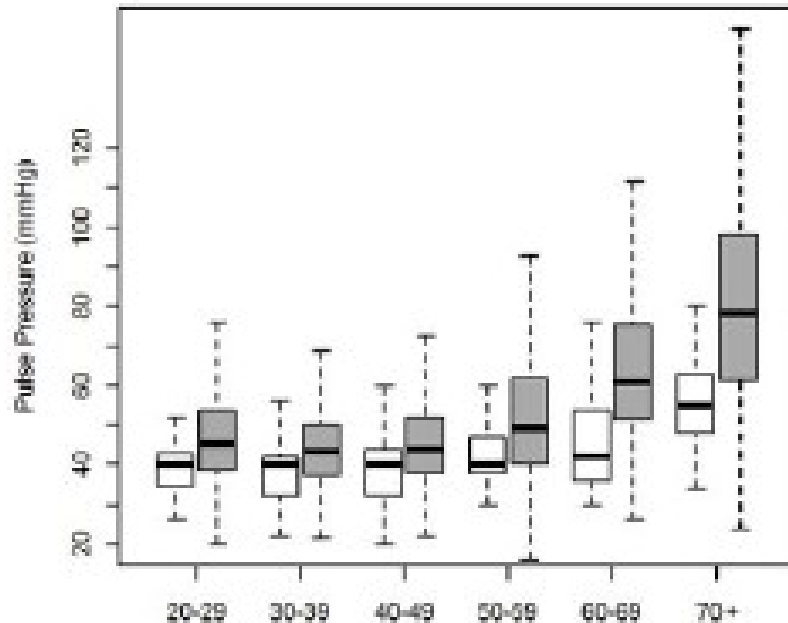
# Does Blood Pressure Inevitably Rise With Age?

## Longitudinal Evidence Among Forager-Horticulturalists

Michael Gurven, Aaron D. Blackwell, Daniel Eid Rodríguez, Jonathan Stieglitz, Hillard Kaplan



# PP for Last Tsimane Medical Round (Oct 2008-2009) and NHANES 2005-2006



# Editorial Commentary

## Arteriosclerosis Inevitable or Self-Inflicted?

Ian B. Wilkinson, Carmel M. McEniery

