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## LA STENOSI AORTICA: UNA NUOVA SINDROME GERIATRICA

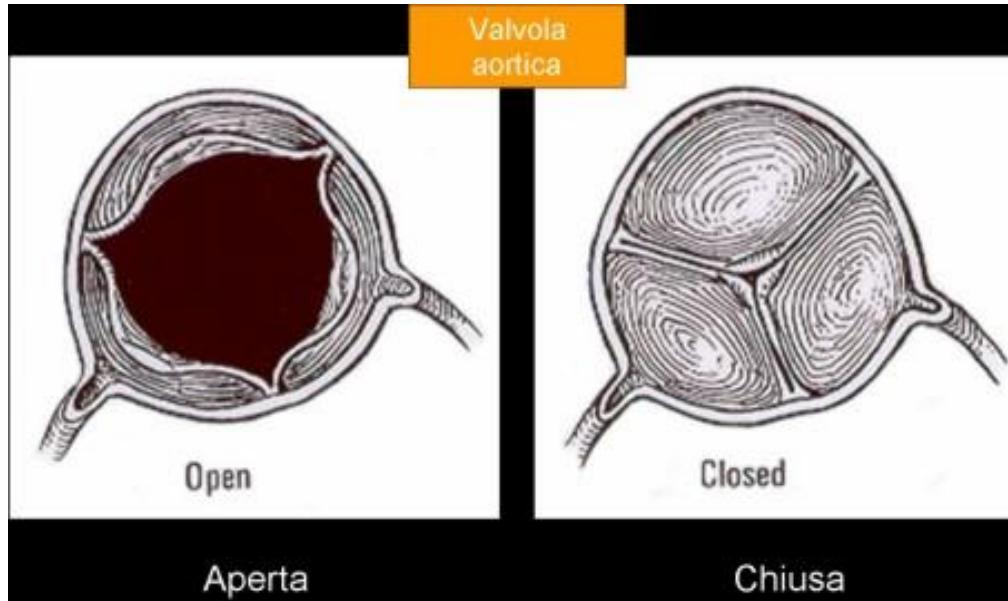
### *Infiammazione e aterosclerosi nell'etiopatogenesi*

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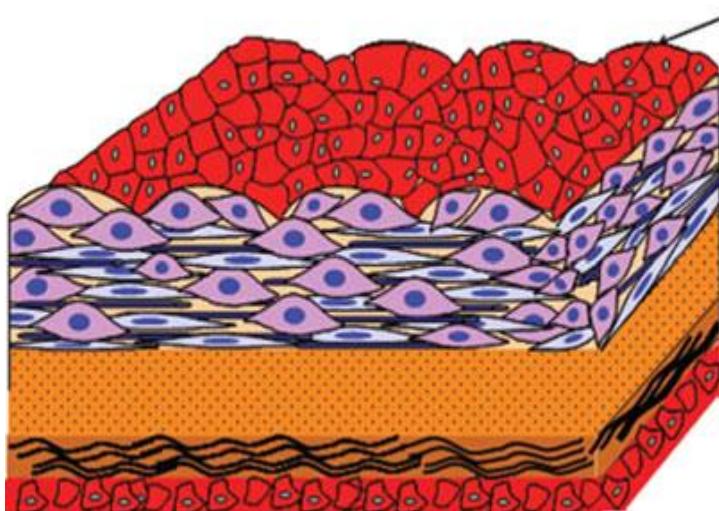
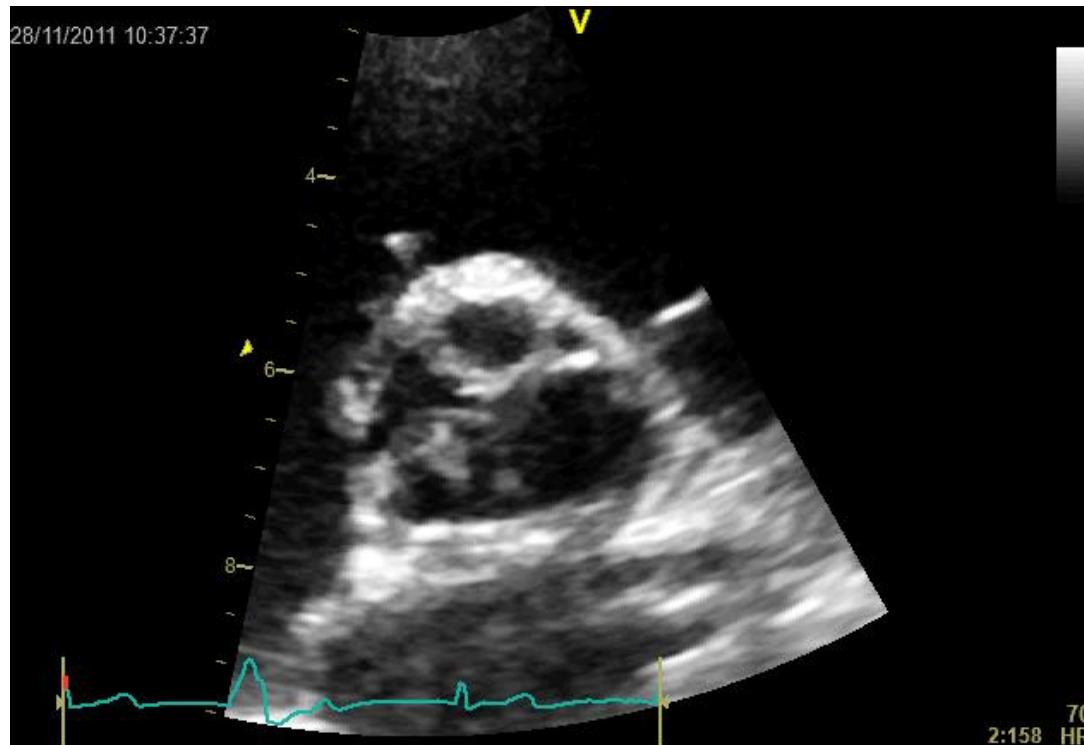
**Valentina Parisi, MD, PhD**  
*Dipartimento di Scienze Mediche Traslazionali*  
*Università degli Studi di Napoli 'Federico II'*

# The living aortic valve



- La valvola aortica ha funzioni estremamente complicate
- Queste dipendono strettamente da specifiche caratteristiche strutturali e funzionali delle sue componenti “viventi”.

# The living aortic valve



FIBROSA

→ PRESSIONE

SPONGIOSA

→ ELASTICITA'

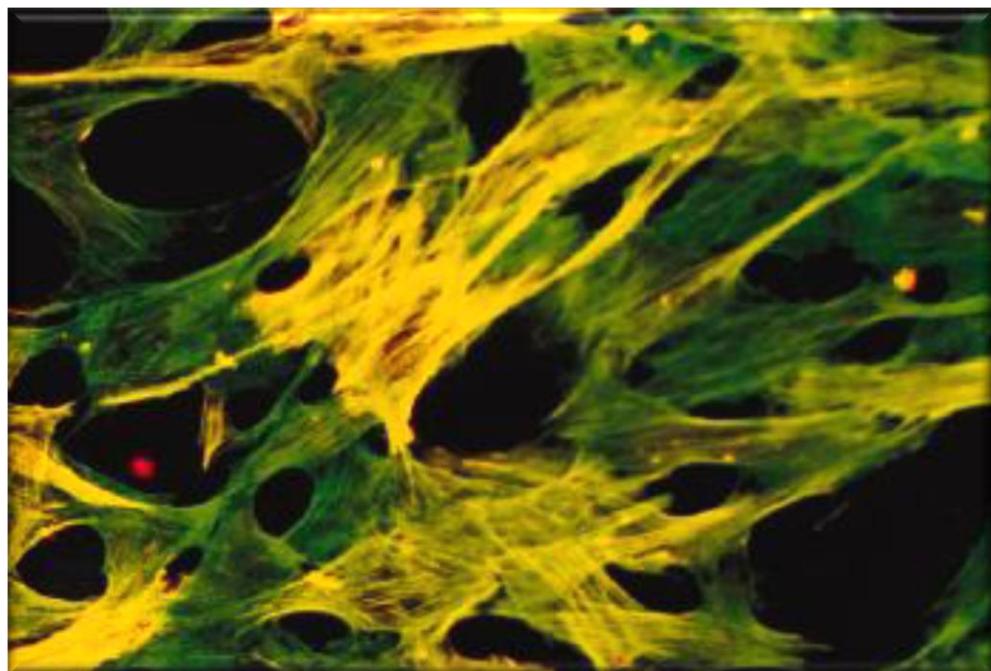
VENTRICULARIS

→ FORMA

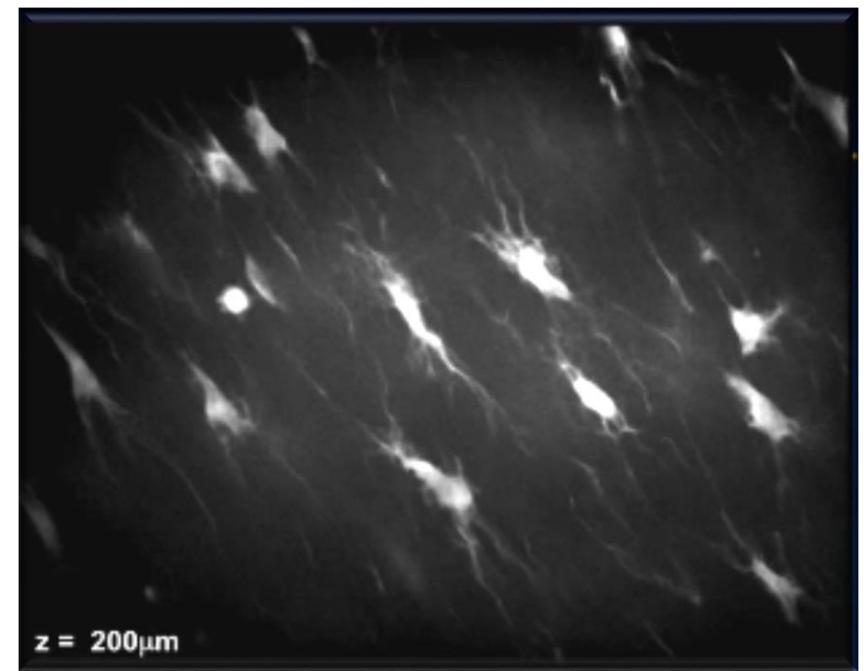
# The living aortic valve

Active dynamism:

Critical role of specific cells



Smooth Muscle Cells



Valvular Interstitial Cells (VICs)

$z = 200\mu\text{m}$

# nature

## ON THE WING

'Morphing' gives the swift exquisite flight control

### ANTIBODY THERAPY

Clinical trials and tribulations

### TIPPING THE SCALES

Weighing single nanoparticles

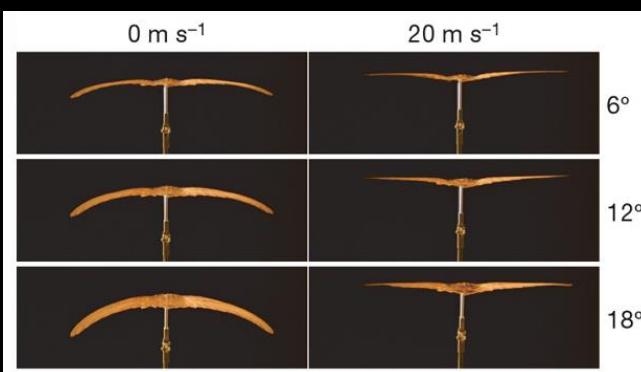
### THE OCEAN CARBON CYCLE

Iron as a natural fertilizer

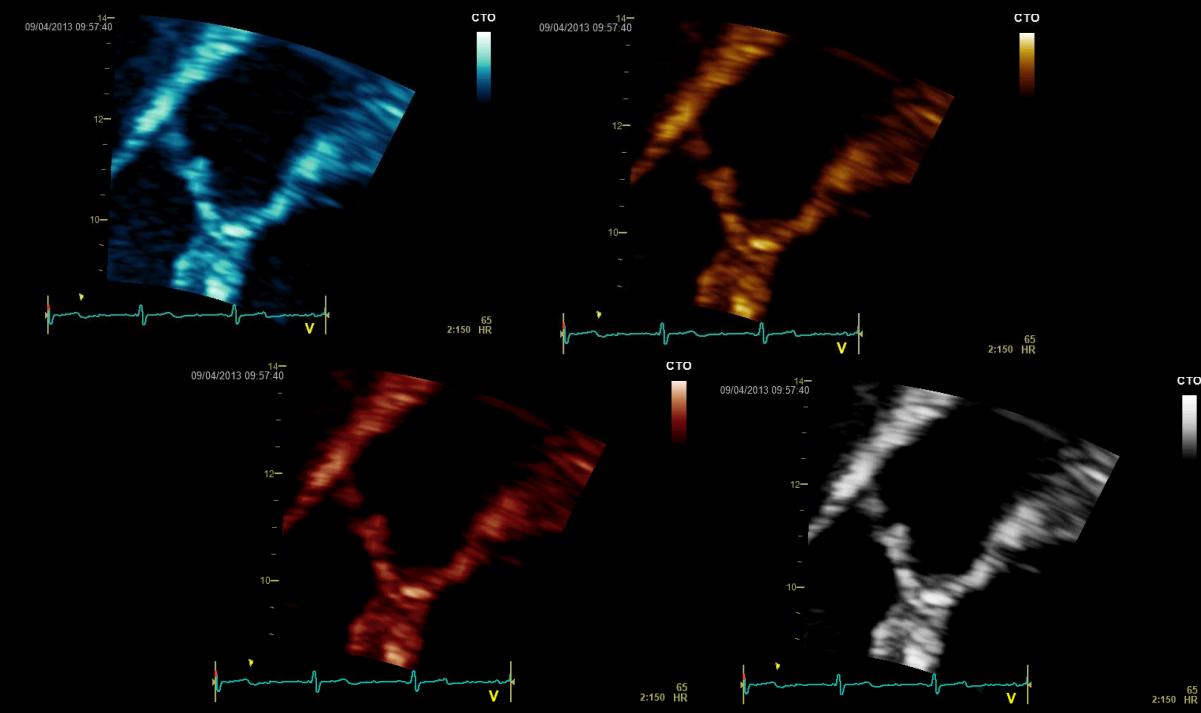
NATUREJOBS  
Spotlight on Florida



© Getty Images



Lentink et al, Nature 2007



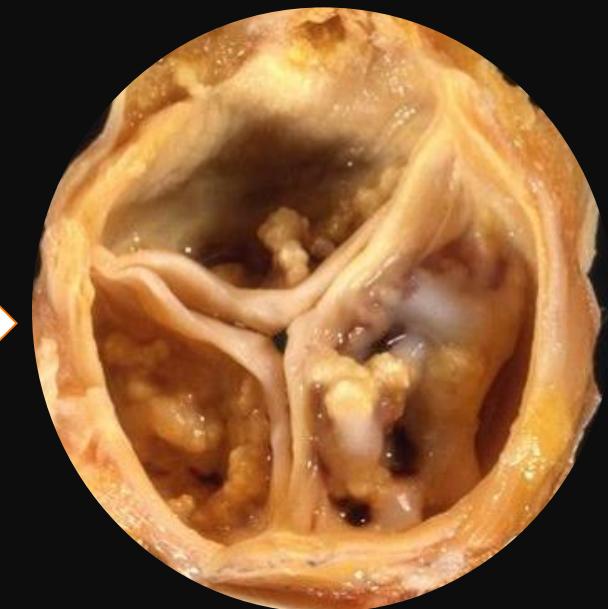
# Stenosi aortica calcifica: degenerazione valvolare ATTIVA



Normale

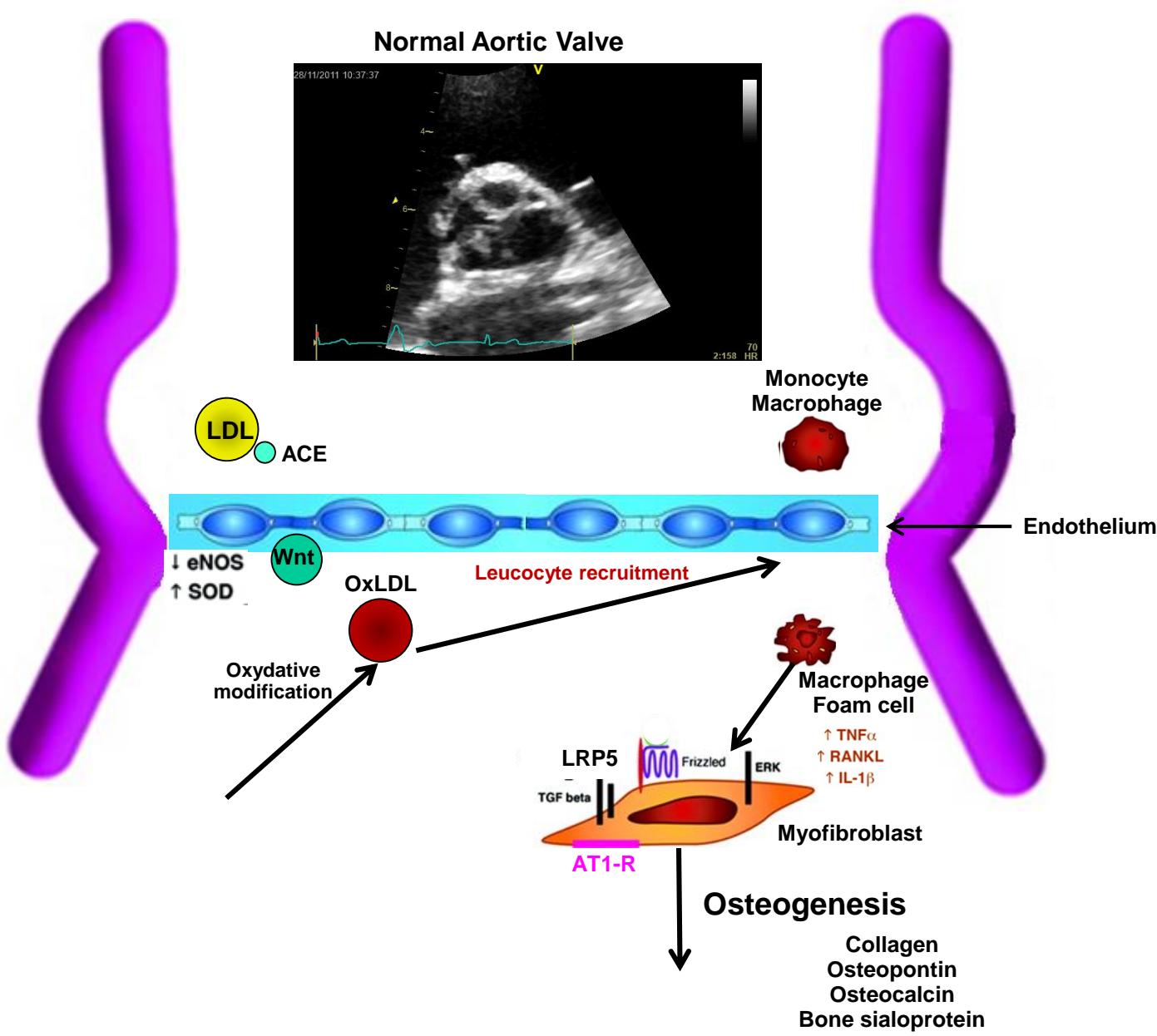
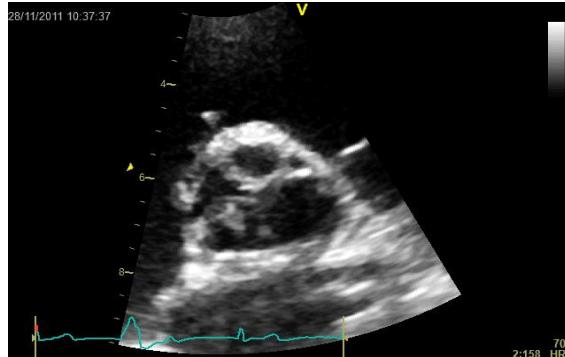


Sclerosi

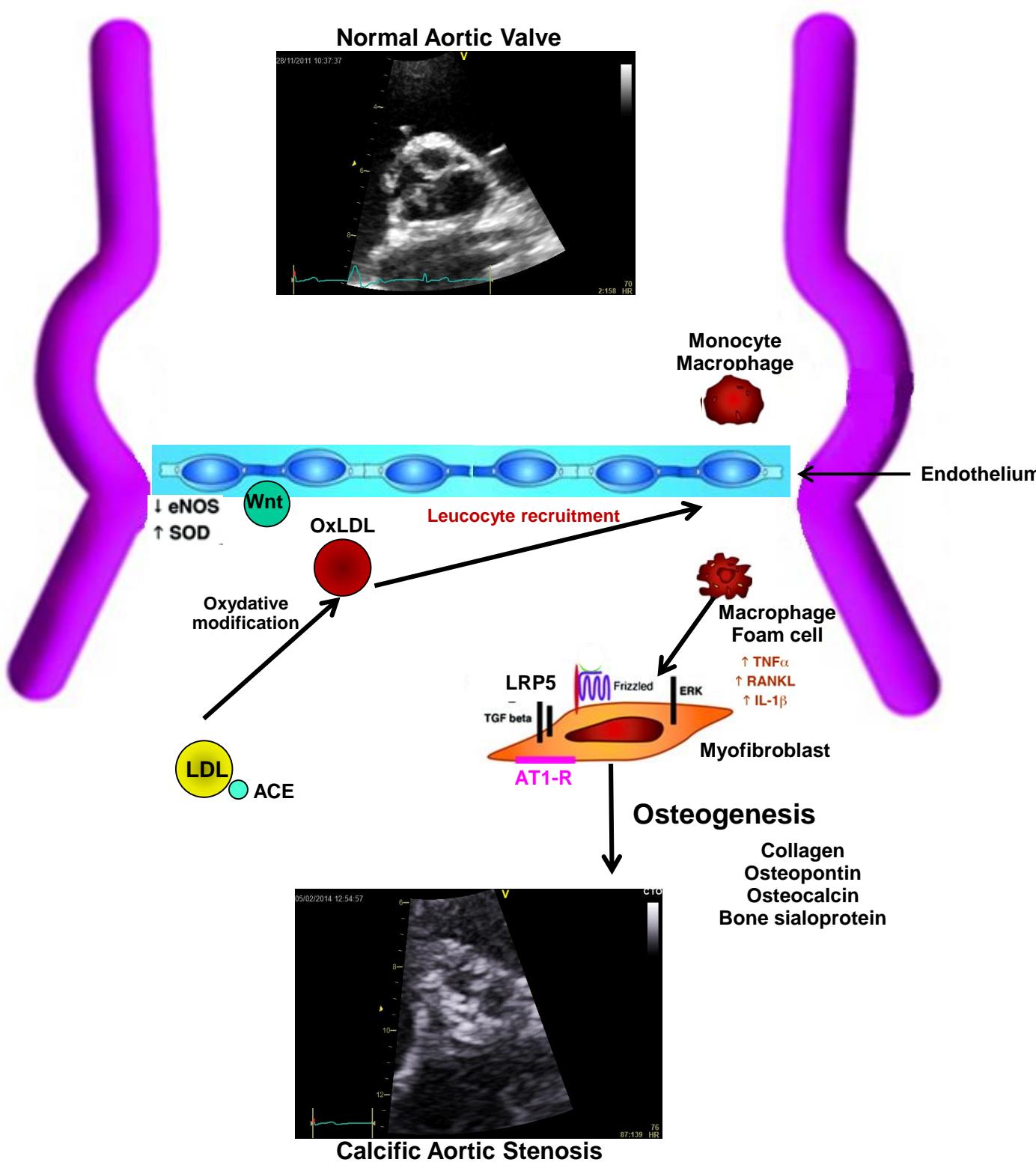
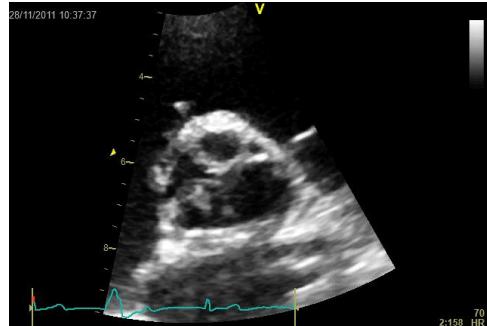


Stenosi

## Normal Aortic Valve



## Normal Aortic Valve



# Calcific Aortic Stenosis

## Epidemiology: Risk Factors

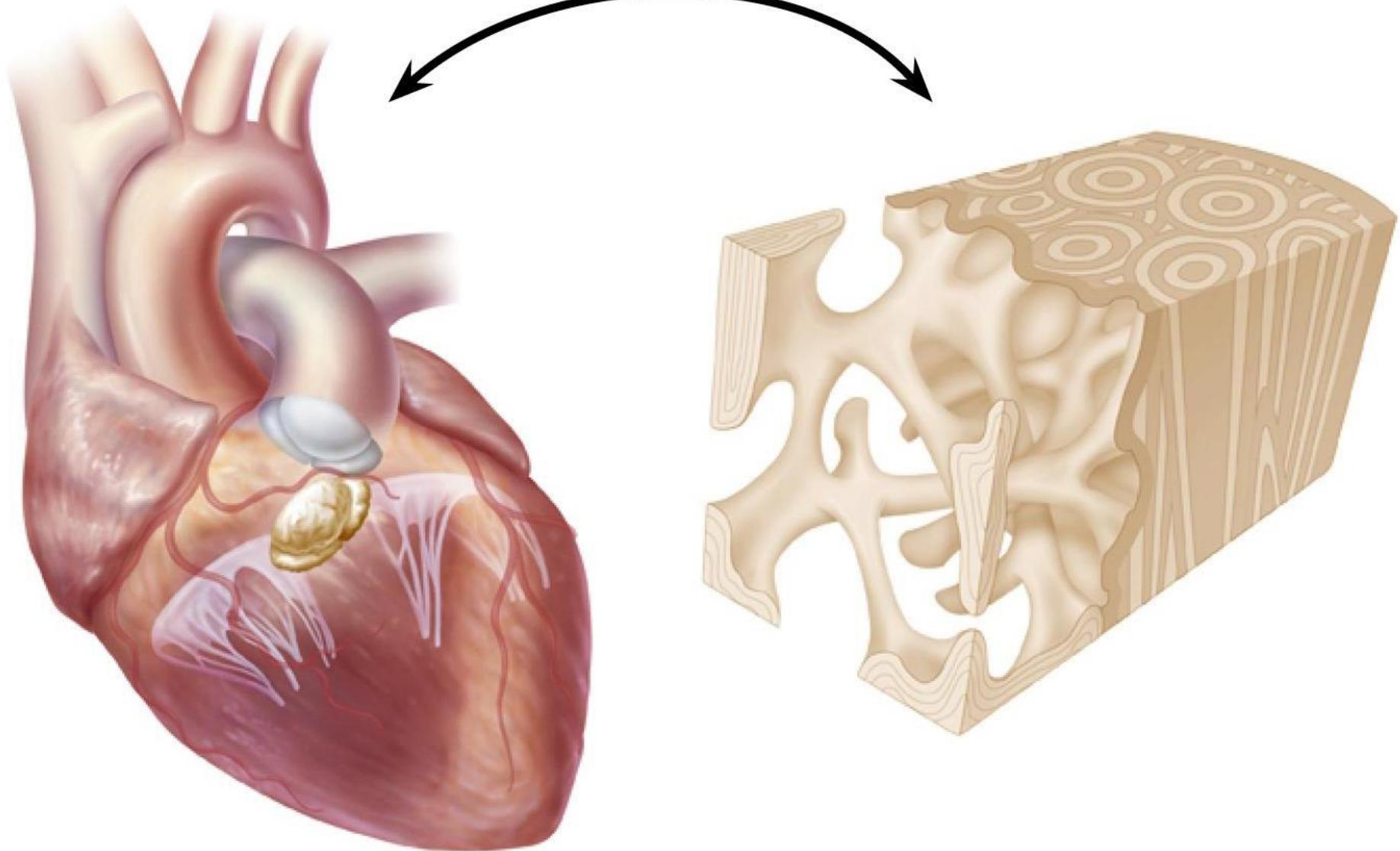


- Età
- Ipertensione
- Insufficienza renale
- Osteoporosi
- Dislipidemia
- Stress ossidativo

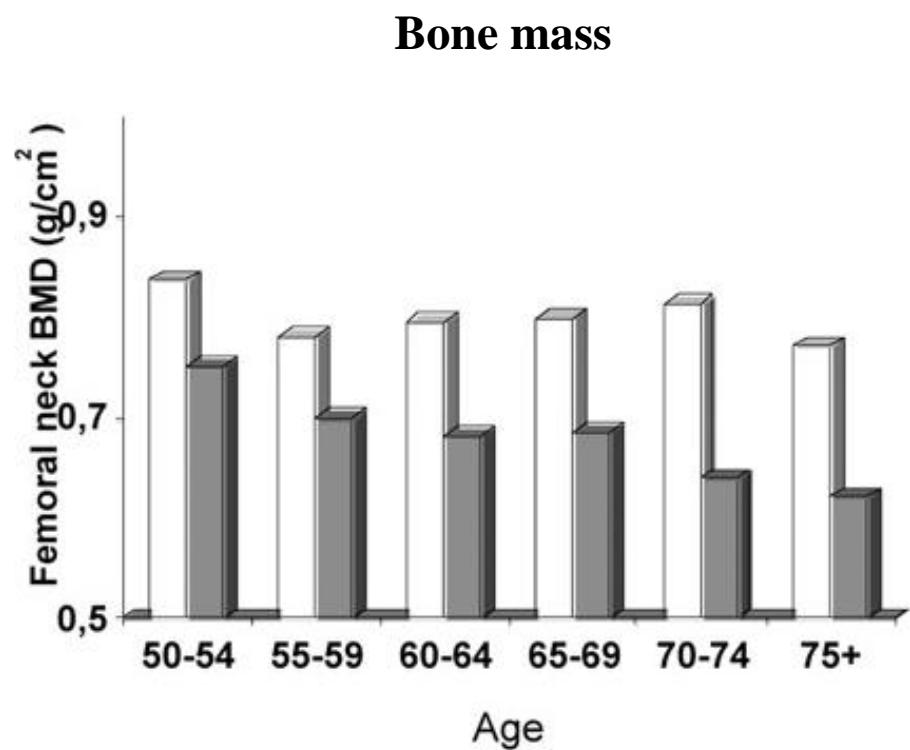
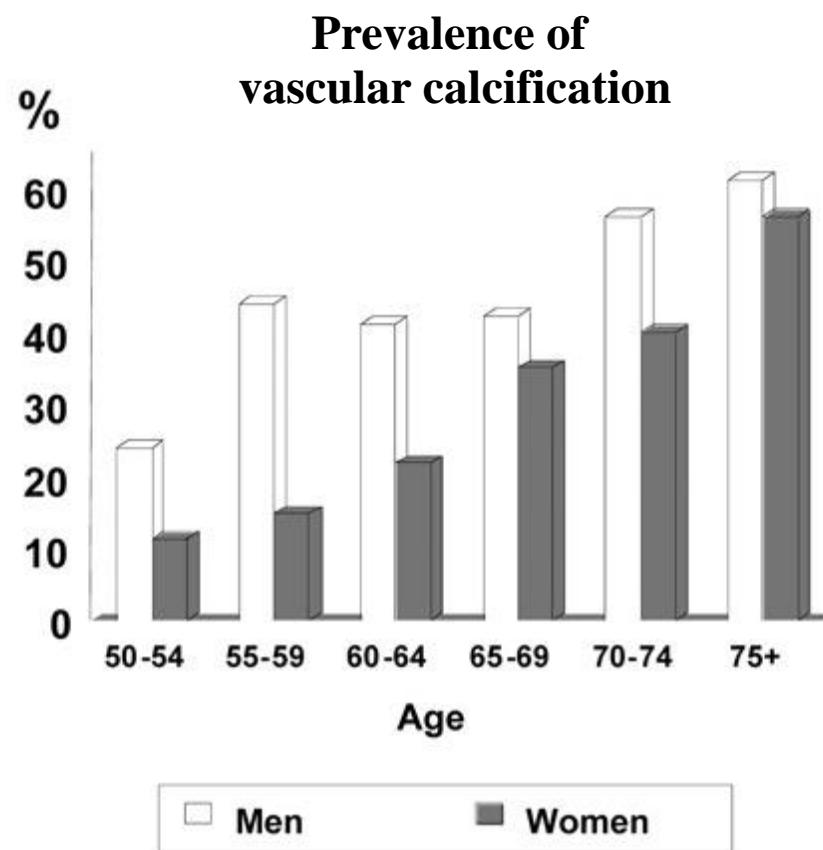


# The Bone Paradox

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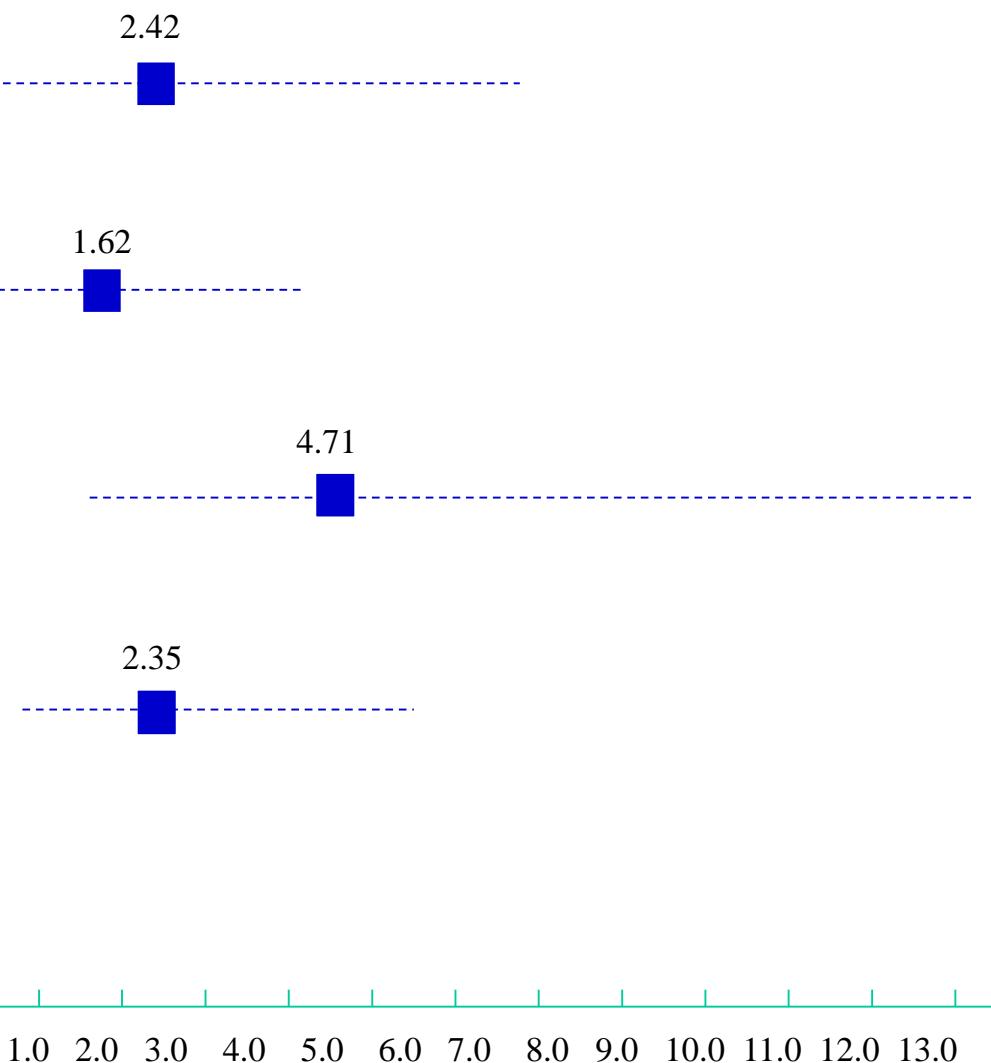


# European Vertebral Osteoporosis Study (EVOS)



# ORs of Ca<sup>++</sup> nei distretti arteriosi in presenza di ridotta BMD

Carotid Arteries

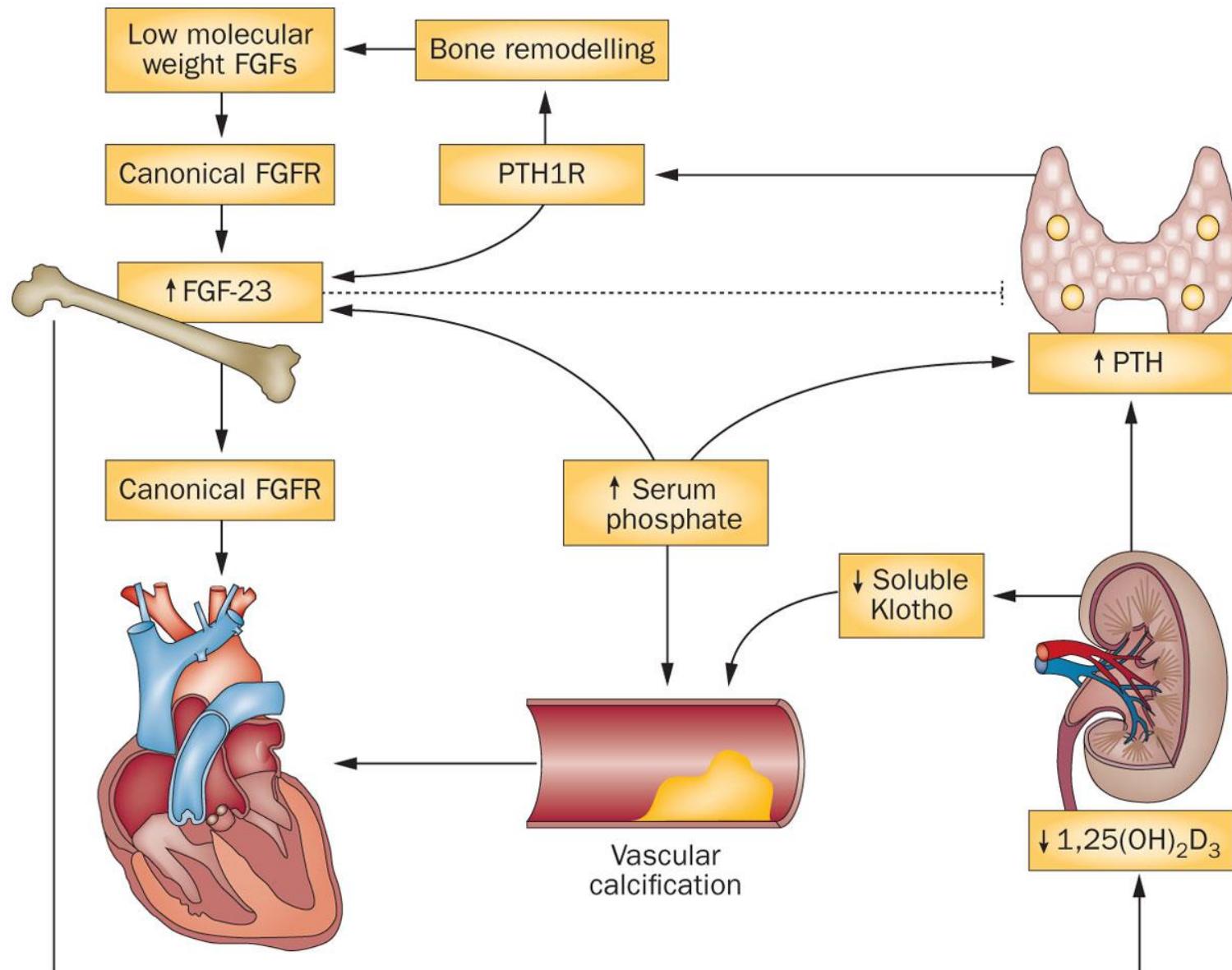


Coronary Arteries

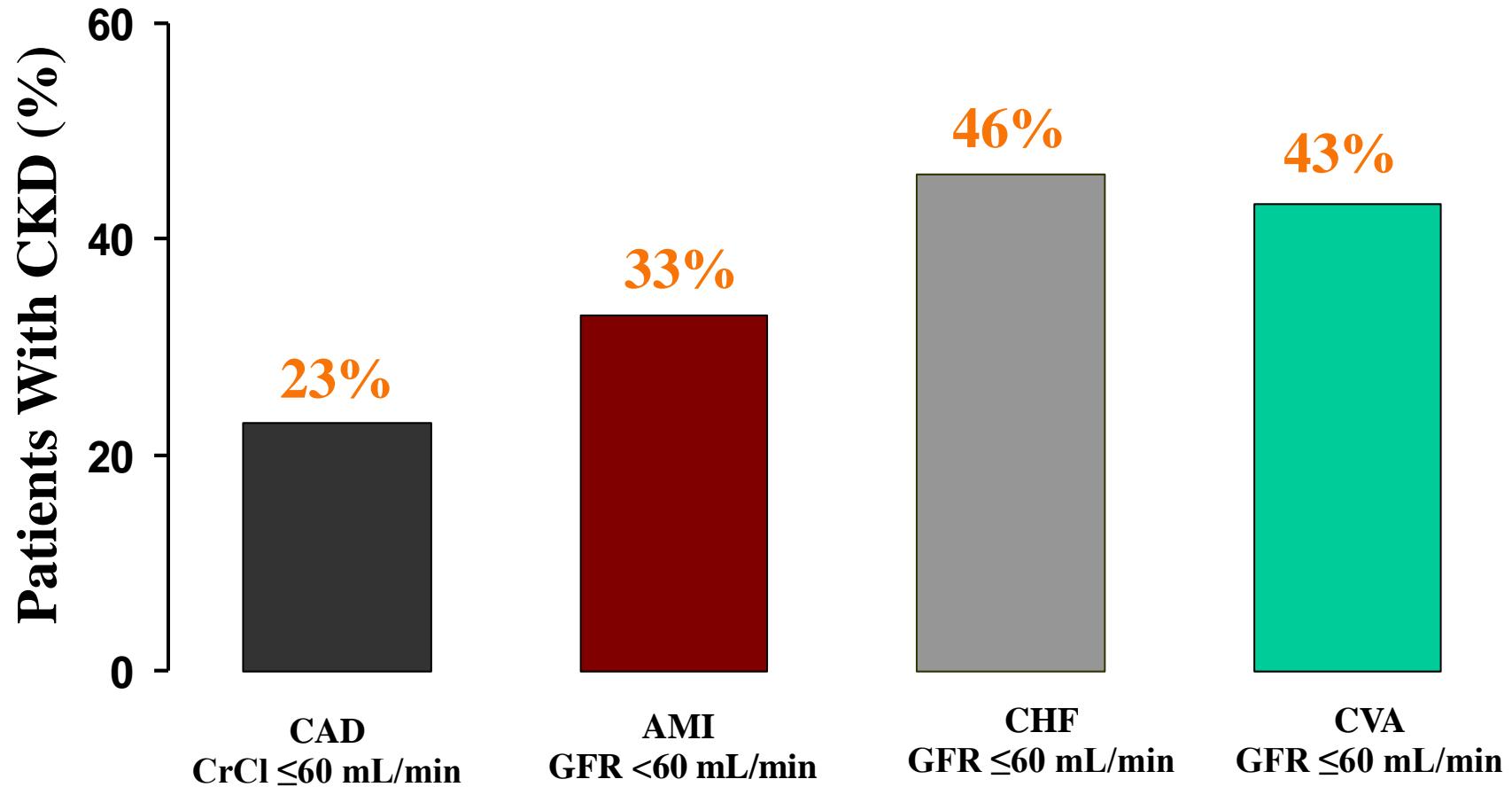
Aorta

Iliac Arteries

# The bone paradox in CKD

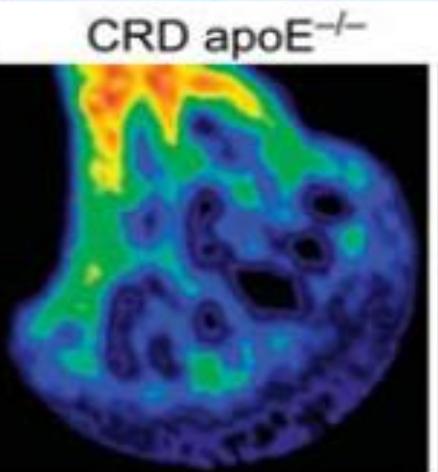
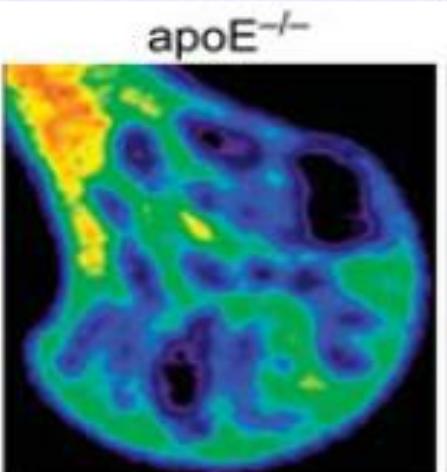
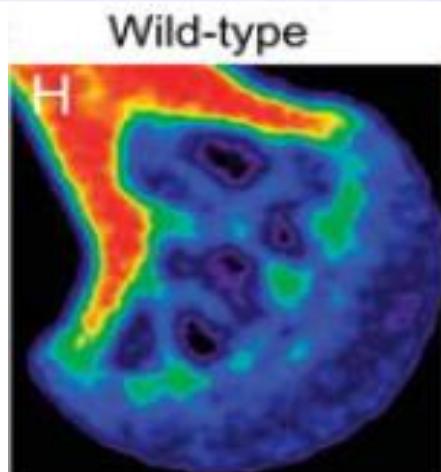
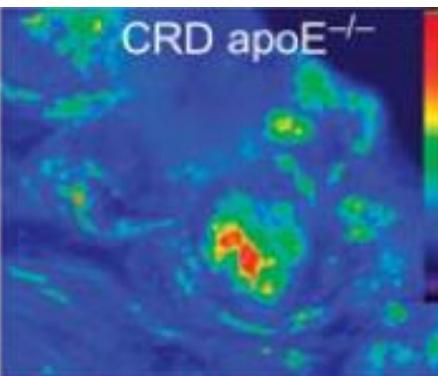
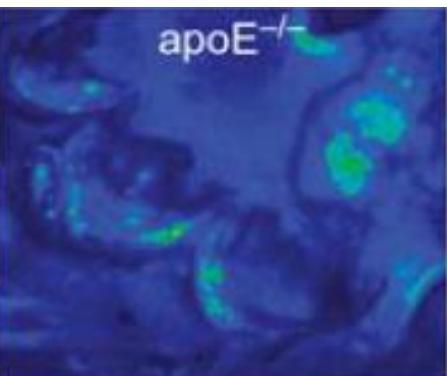
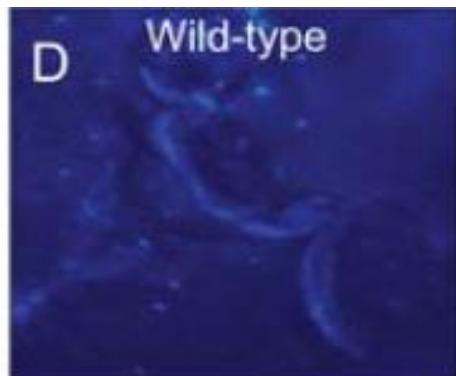
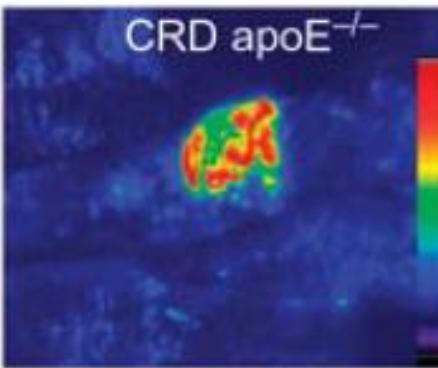
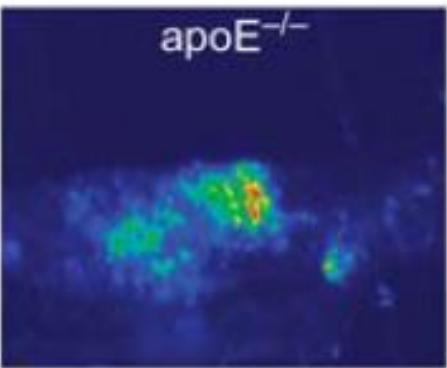


# CKD E PATOLOGIA CARDIOVASCOLARE



*Ix, et al., 2003; Anavekar, et al., 2004; Shlipak, et al., 2004, McClellan et al, 2006.*

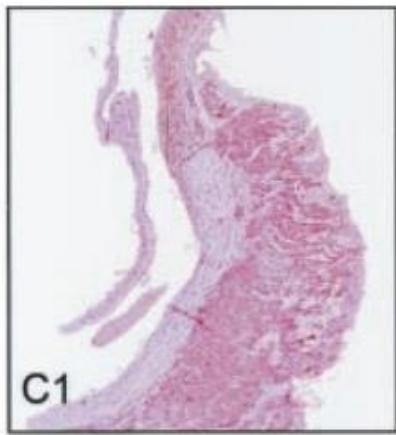
# Le calcificazioni arteriose e valvolari correlano inversamente con il rimodellamento osseo in senso osteoporotico



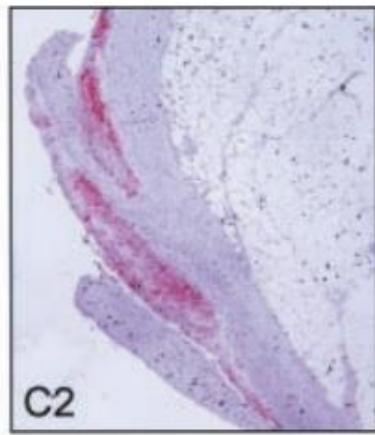
# Stenosi aortica: dislipidemia-infiammazione-calcificazione

## Macrophage Marker

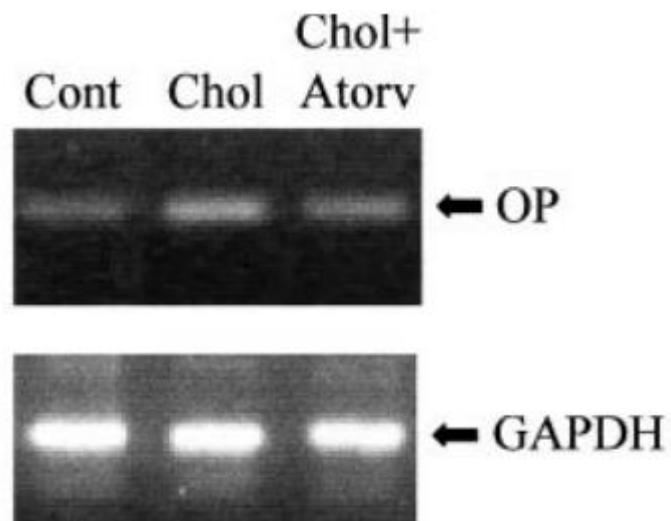
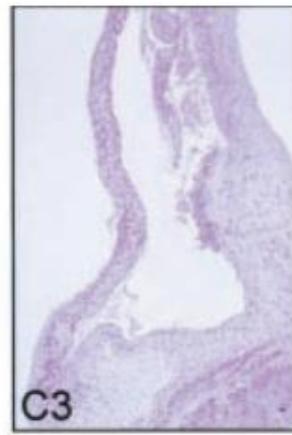
1. Control Diet



2. Cholesterol  
Diet

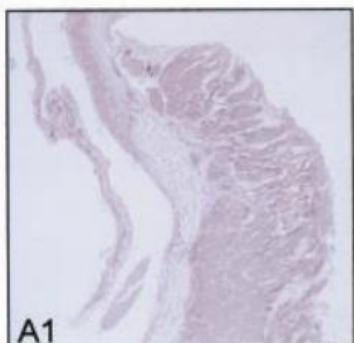


3. Cholesterol +  
Atorvastatin

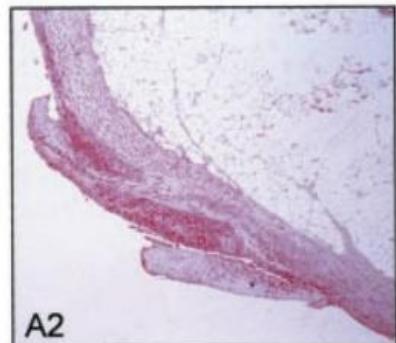


## Osteopontin bone marker

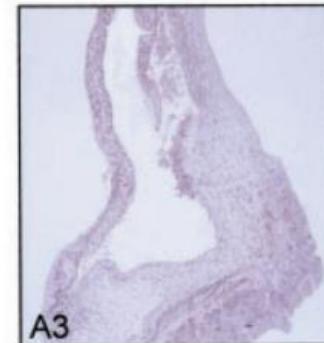
1. Control Diet



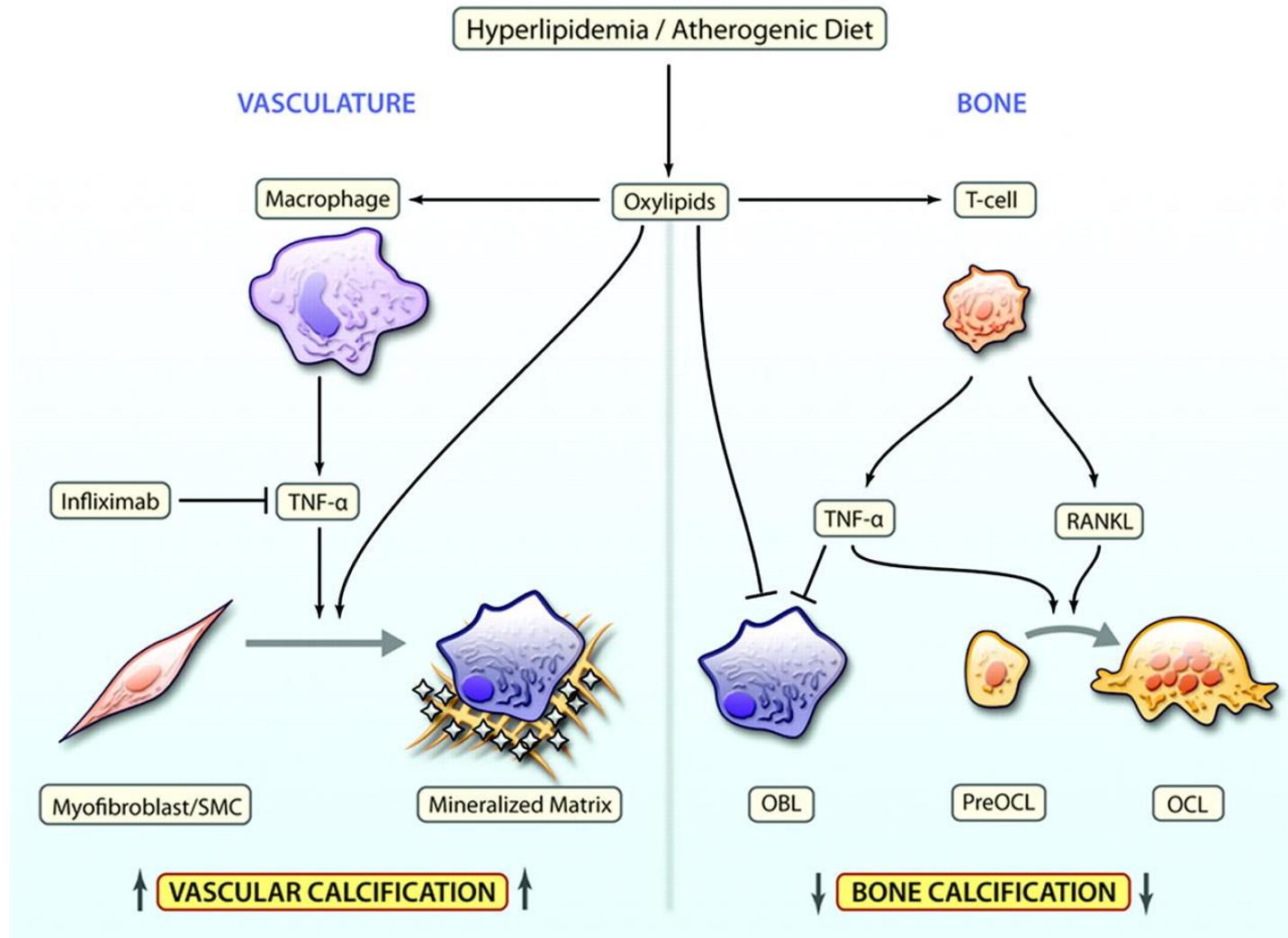
2. Cholesterol  
Diet



3. Cholesterol +  
Atorvastatin

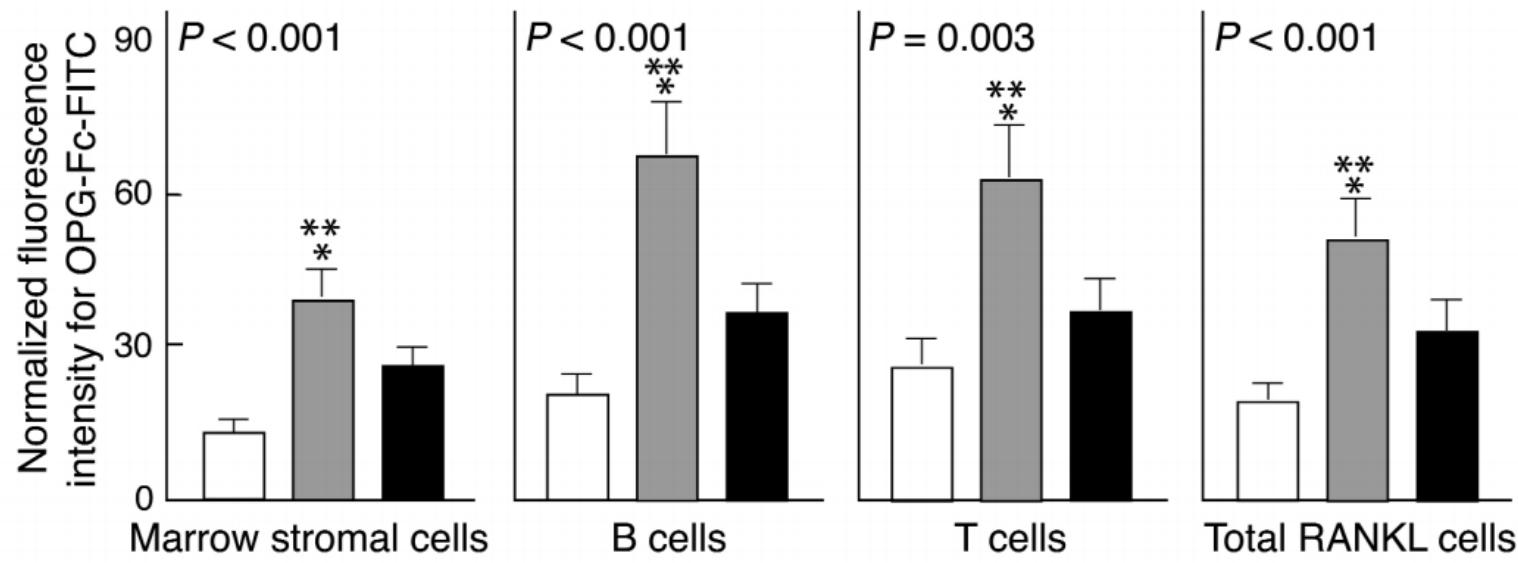


# The bone paradox and the lipid theory



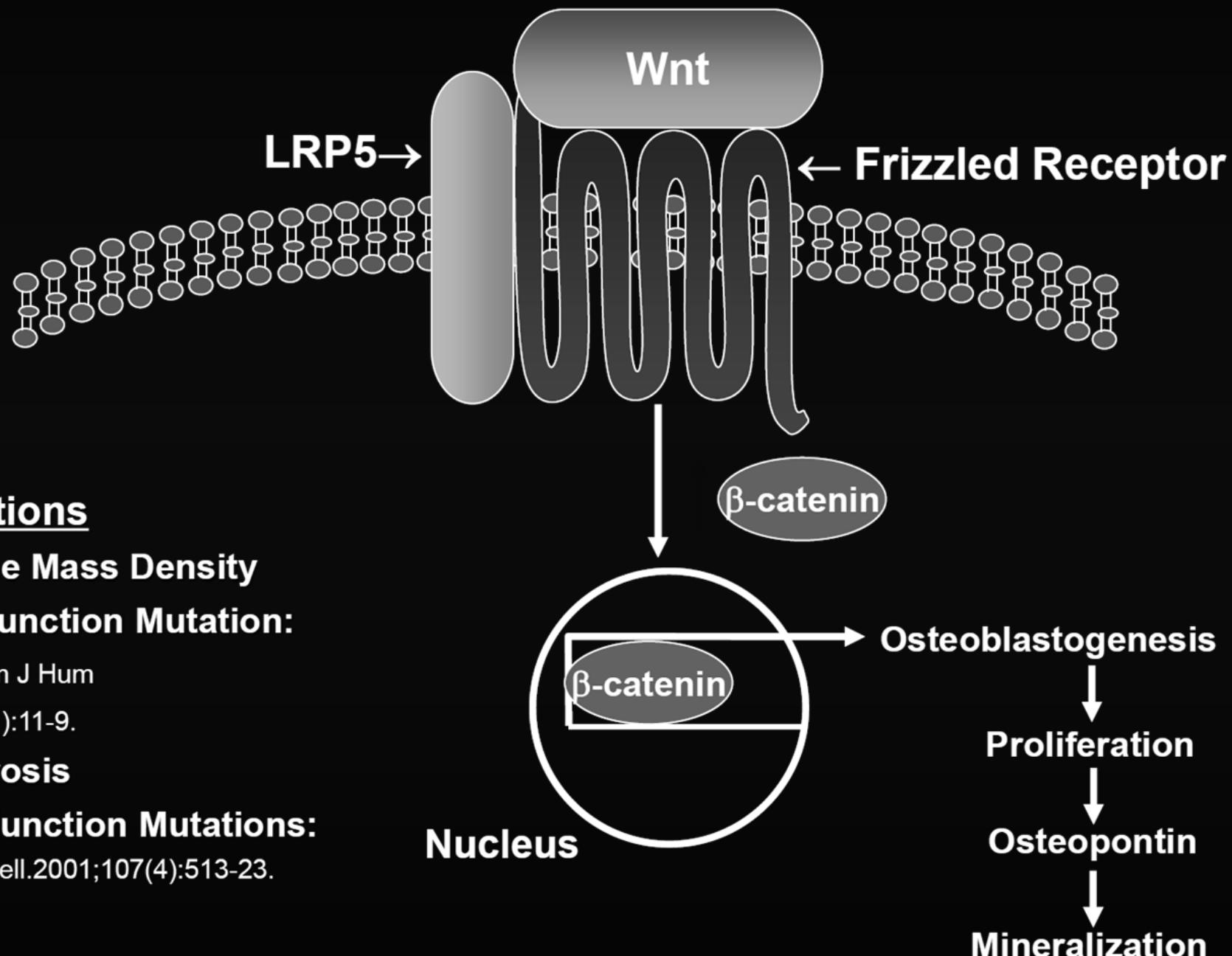
# Role of RANK ligand in mediating increased bone resorption in postmenopausal women

## RANKL expression on cell surface

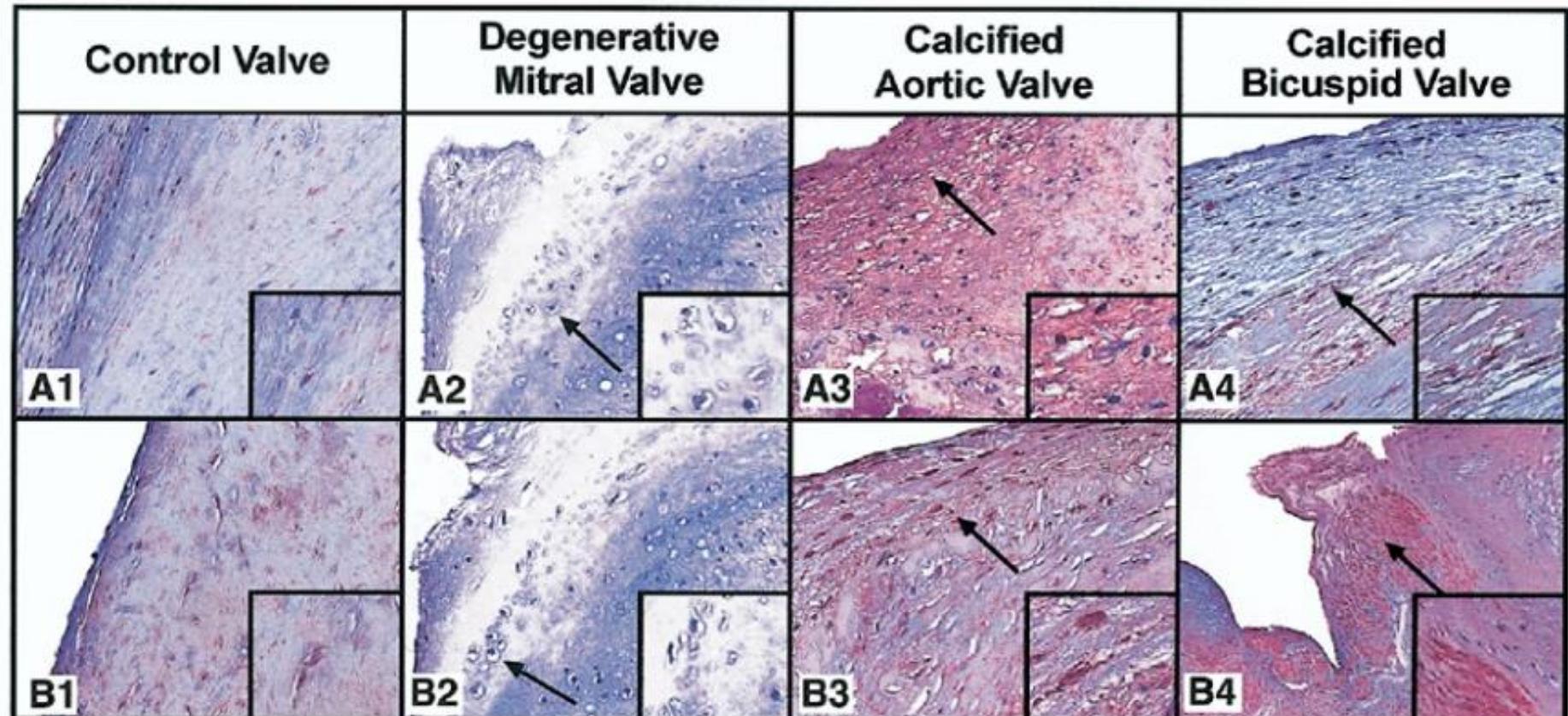


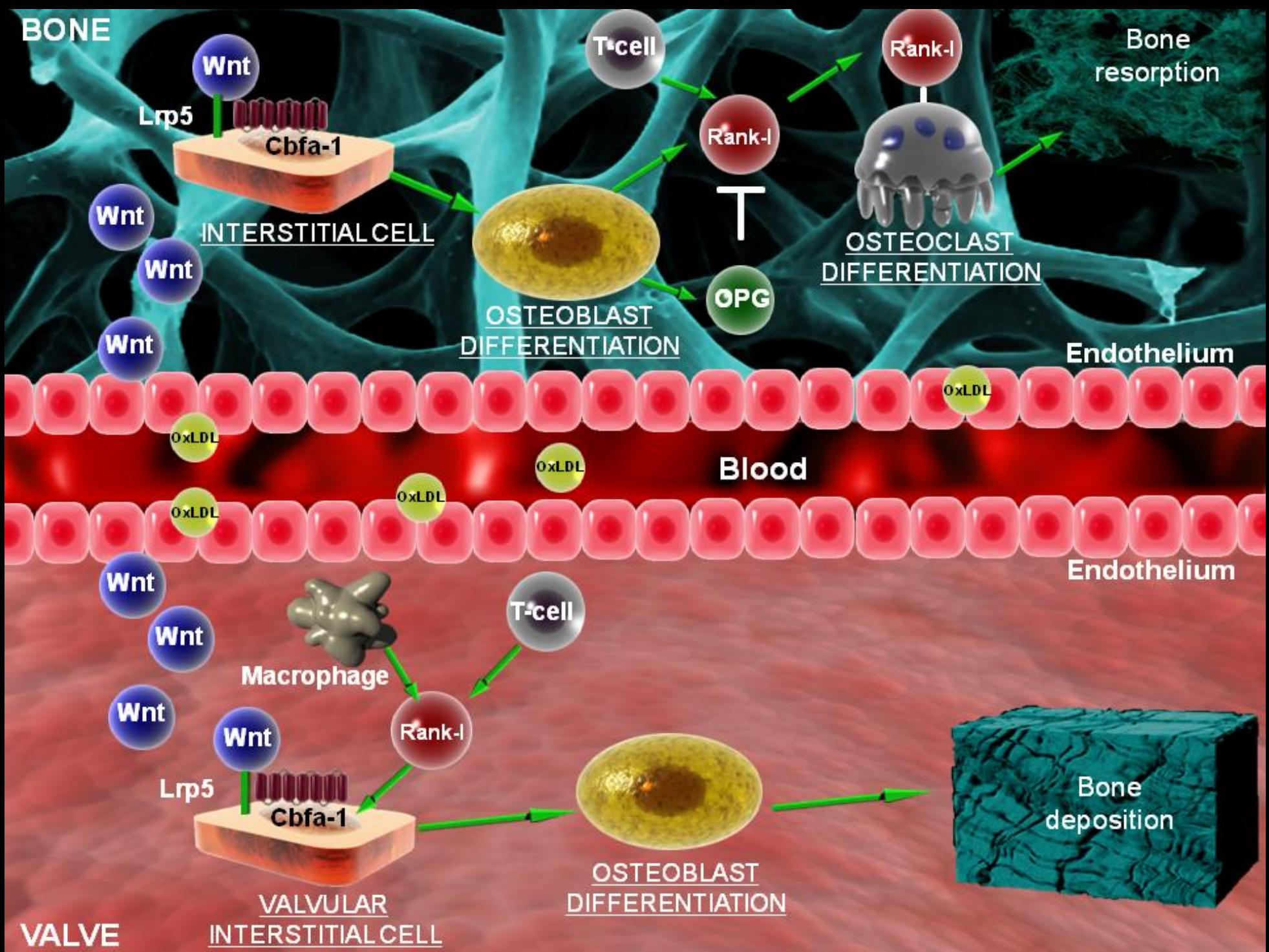
- Pre-menopausal women
- Untreated Post-menopausal women
- Estrogen Treated Post-menopausal women

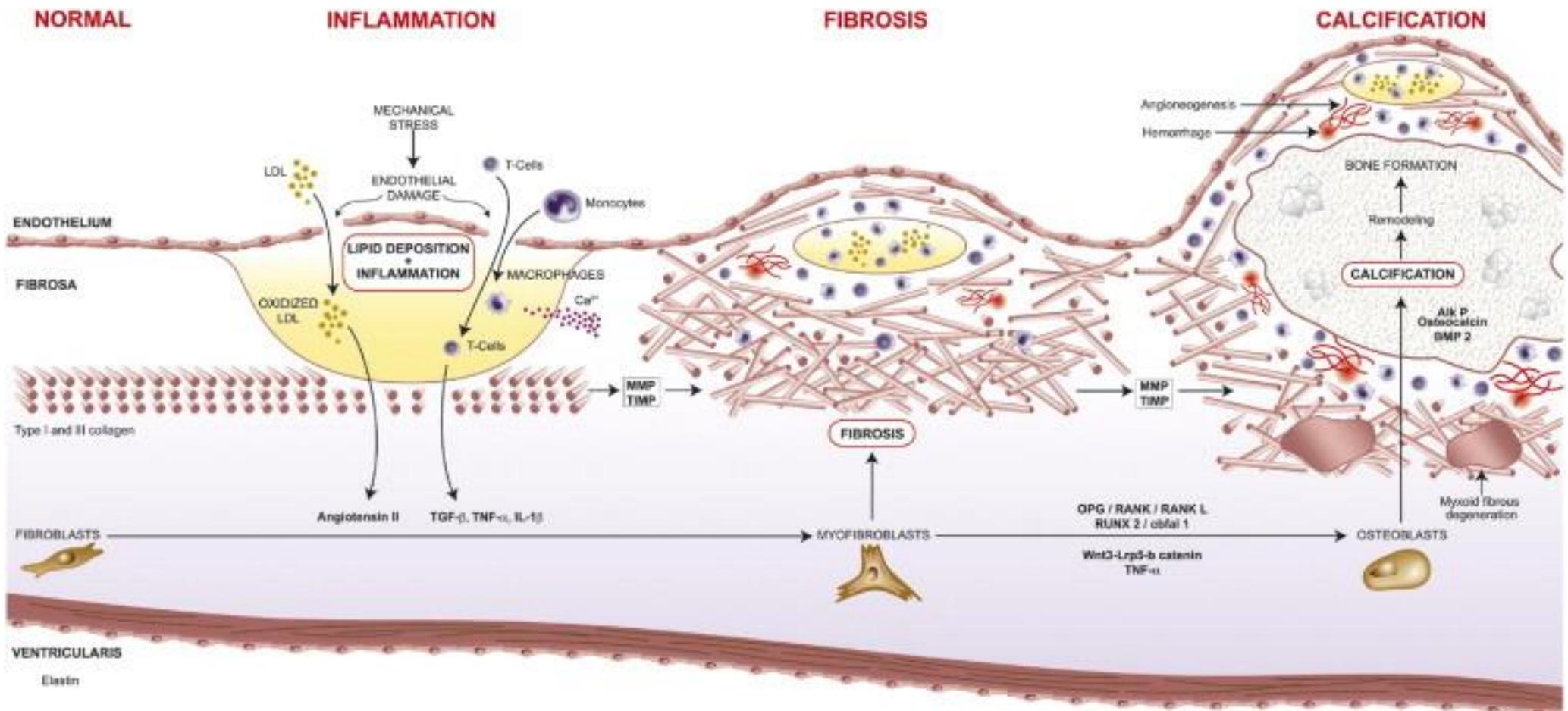
# Lrp5/WNT Regulation of Osteoblastogenesis



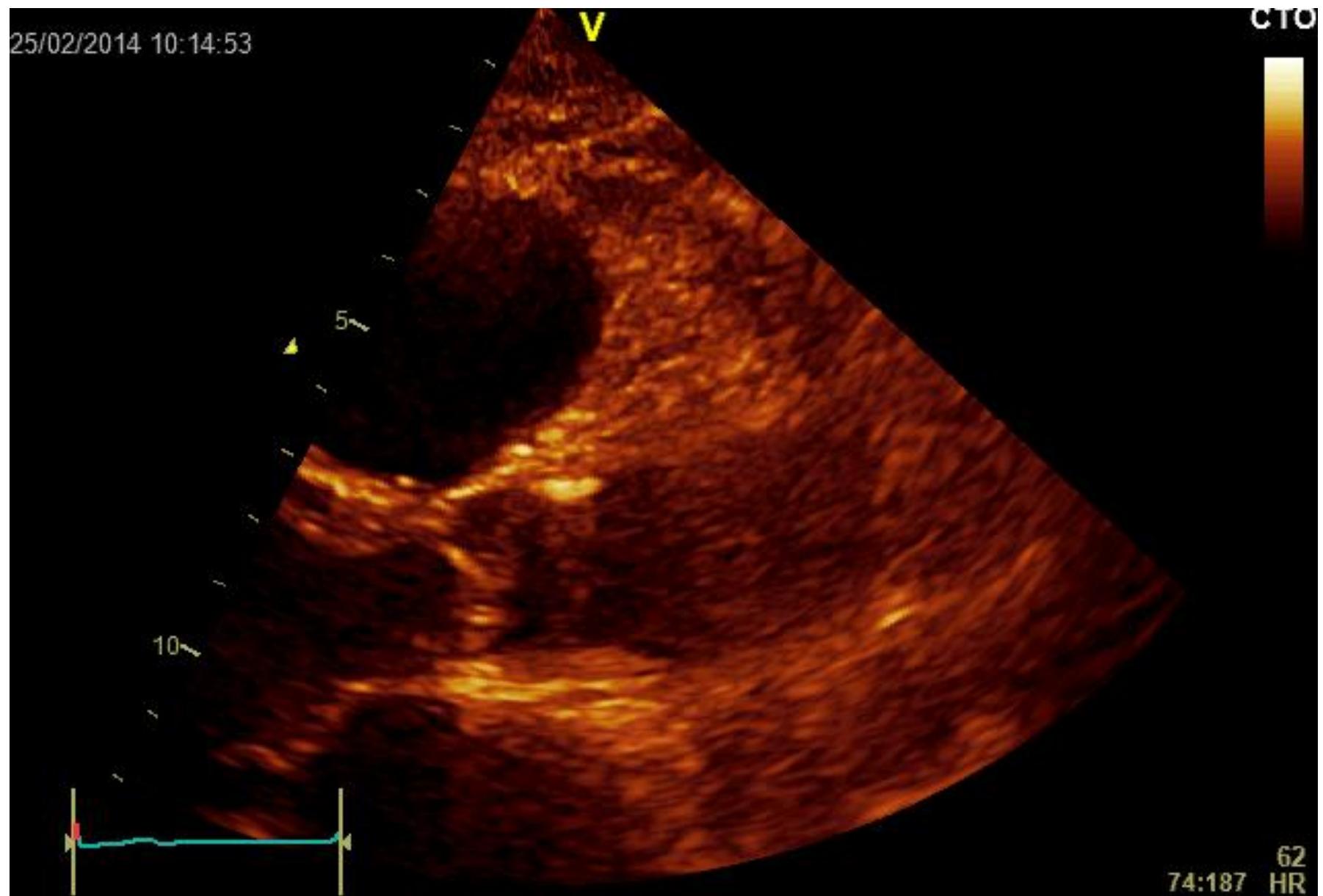
# Lrp5 Signaling in Human Valvular Heart Disease







# Epicardial adipose tissue



# Epicardial adipose tissue

Il tessuto adiposo epicardico è il deposito di grasso viscerale cardiaco → nuovo marker di rischio cardiometabolico

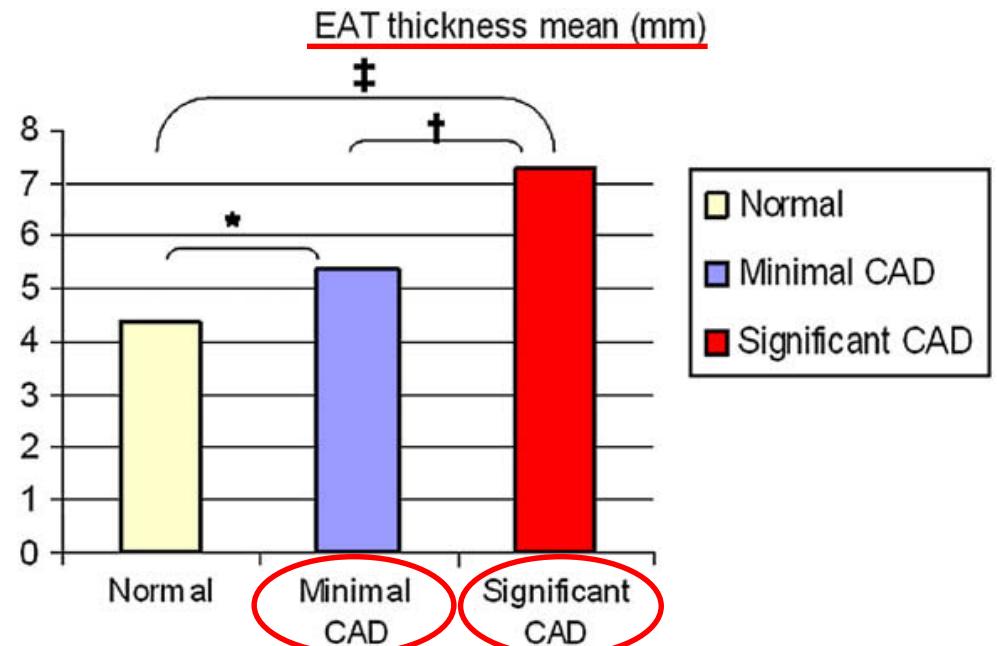
## In condizioni fisiologiche

- Risorsa energetica per il miocardio
- Fonte di adipochine anti-infiammatorie ed anti-aterogeniche

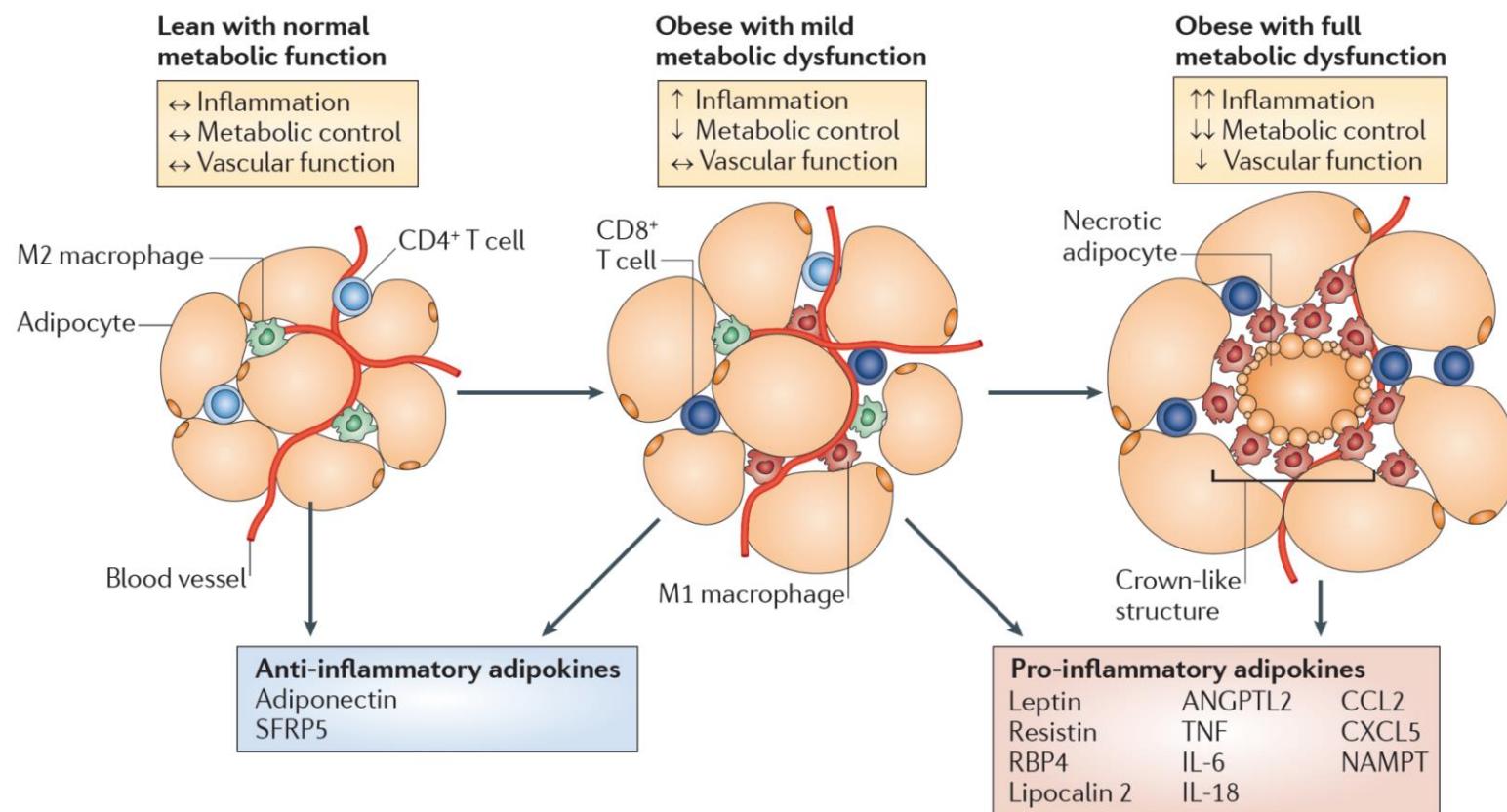
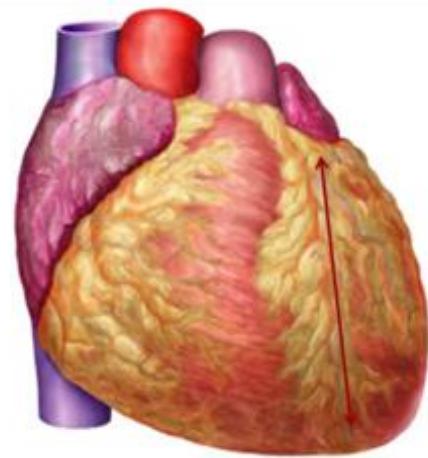
## In condizioni patologiche

- Stato infiammatorio intrinseco
- Produzione e secrezione di citochine proaterogeniche e proinfiammatorie
- Relazione con:

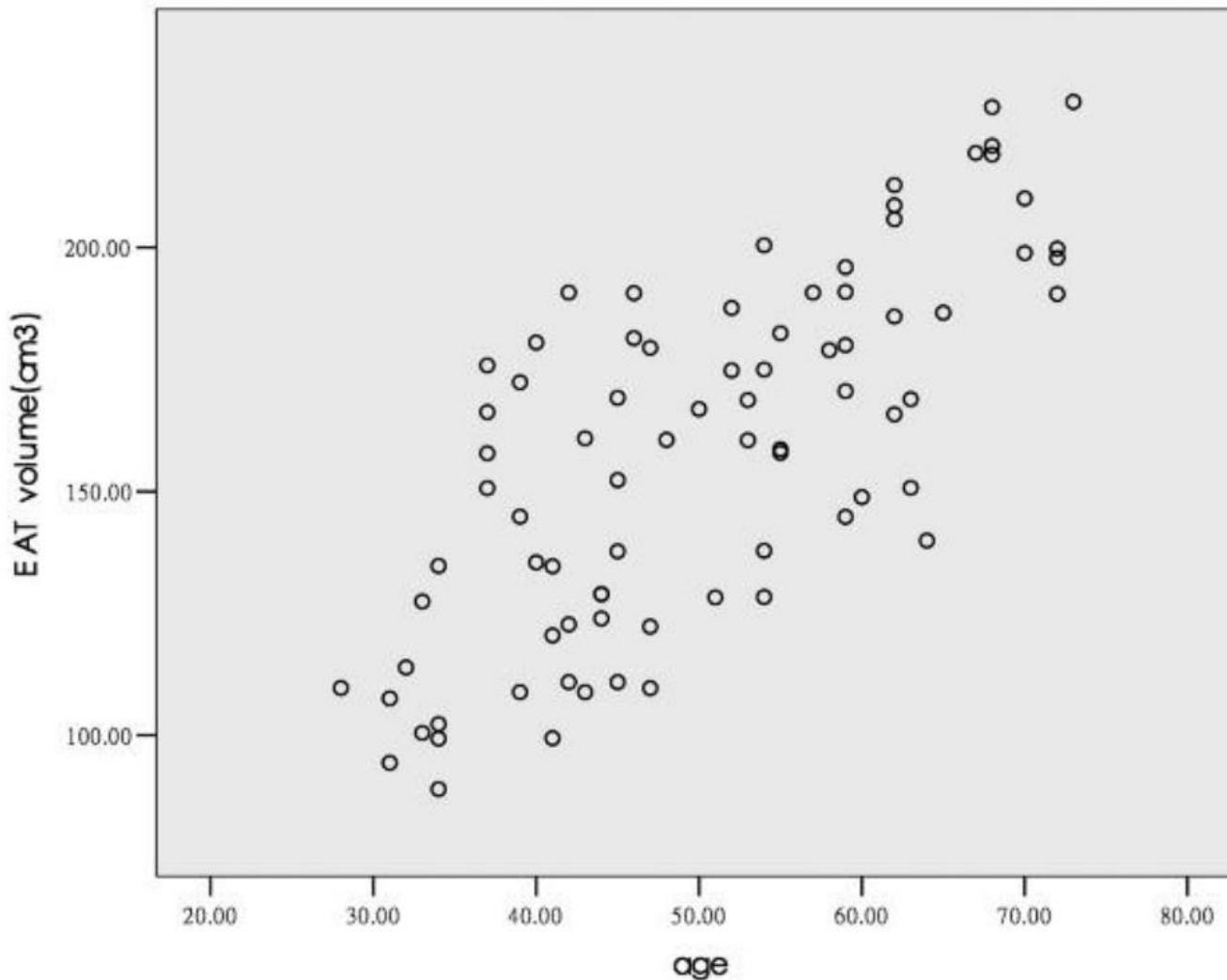
- CAD
- Ipertrofia LV
- Disfunzione diastolica
- Scompenso cardiaco
- Fibrillazione atriale



# Physiological, pathophysiological mechanisms and vasocrine/paracrine pathways of epicardial fat

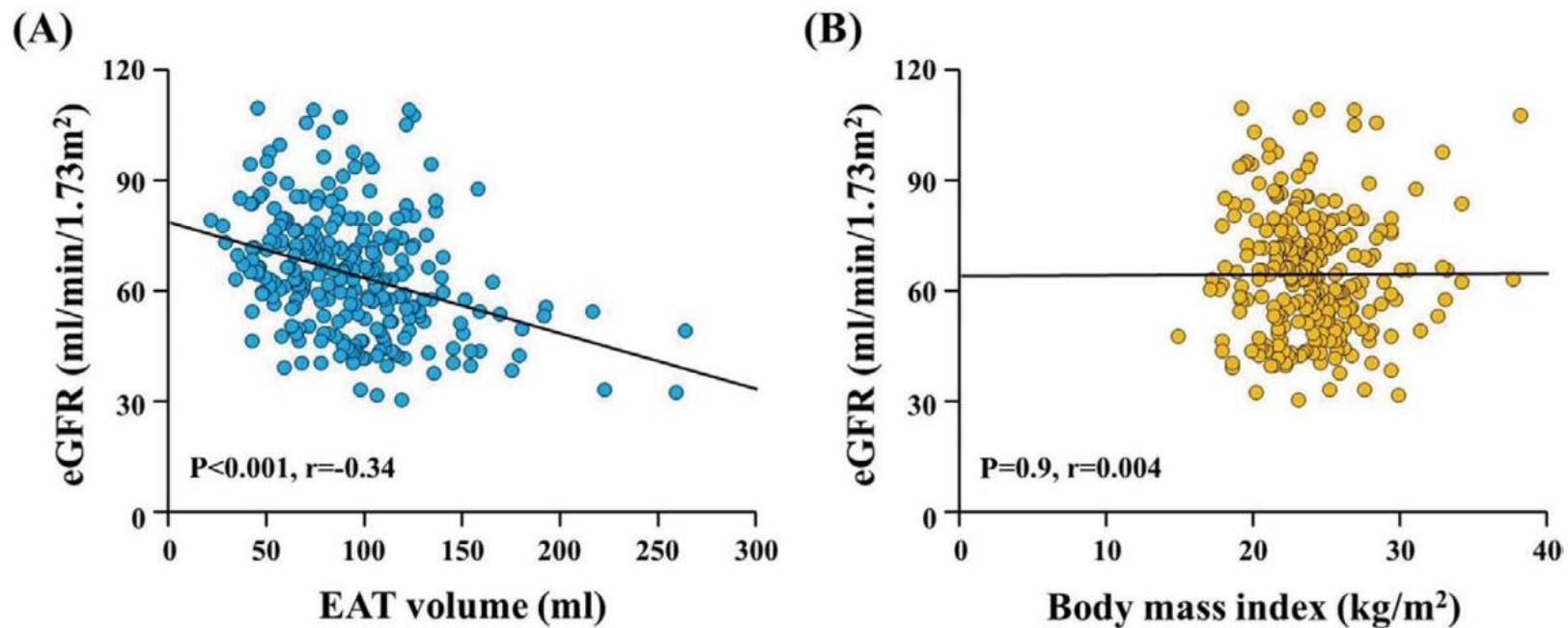


# Epicardial adipose tissue



**EAT volume aumenta con l'età**

# Epicardial adipose tissue- CKD- CAD

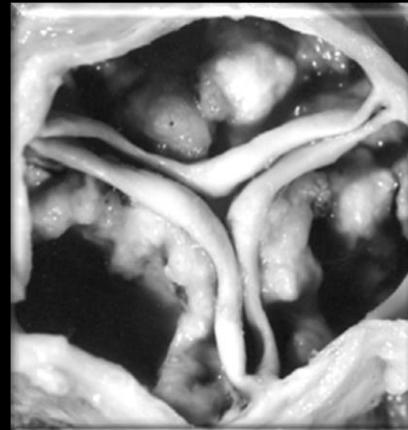
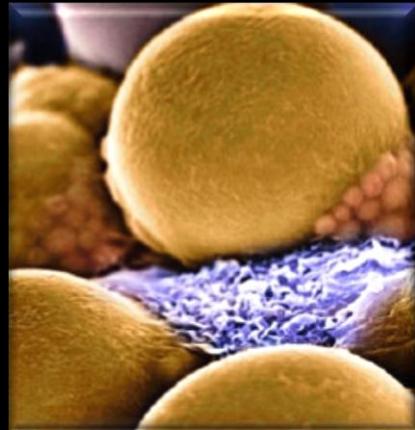


**EAT volume associato con la presenza di placche ad alto rischio indipendentemente dai fattori di rischio aterosclerotici tradizionali**

Nakanishi K, Circ J 2015

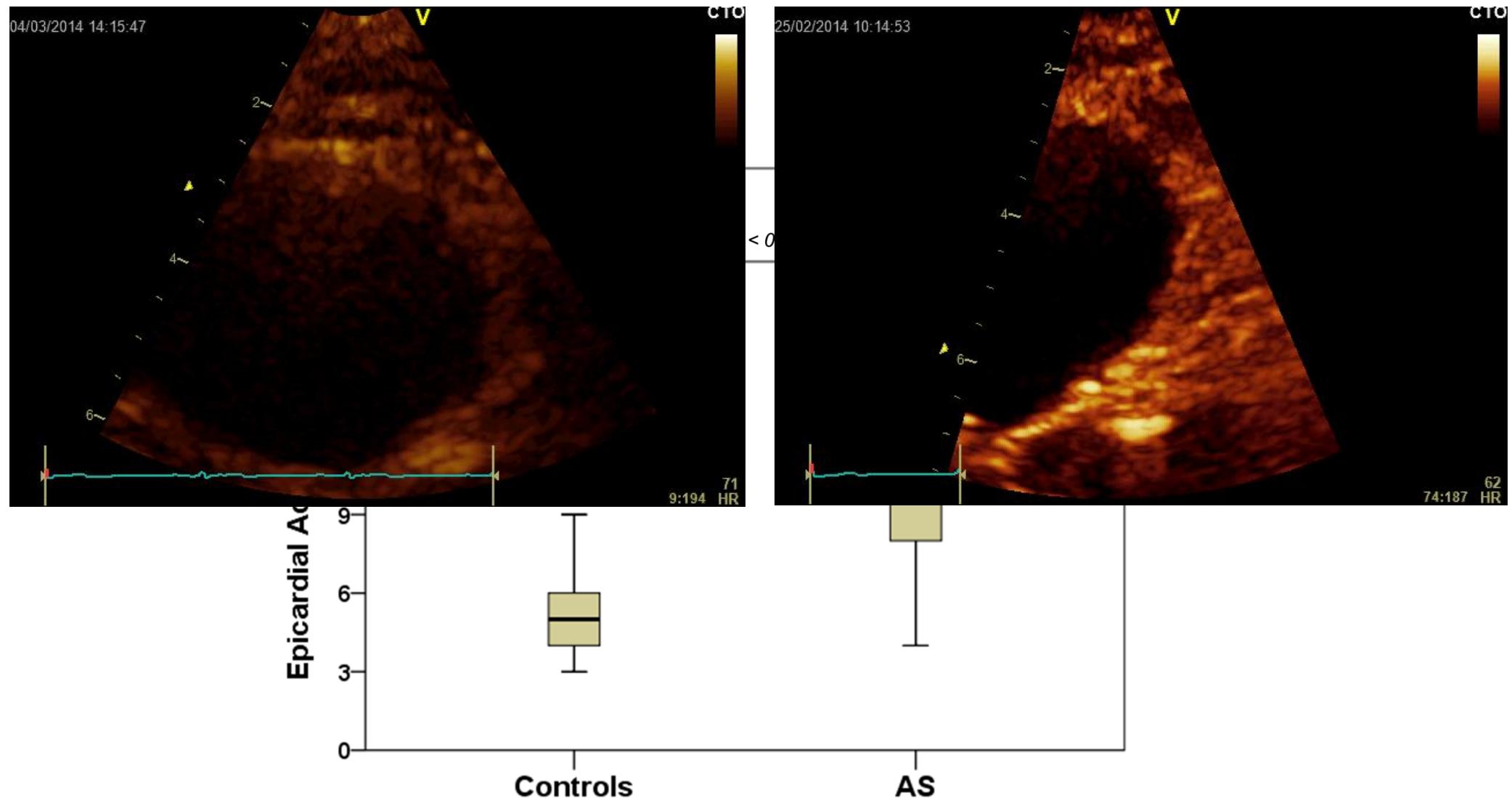
**EAT volume aumenta nei pz in dialisi e correla con l'aumento di mediatori infiammatori e calcificazioni coronariche indipendentemente dall'adiposità generale**

Graham-Brown MP, Curr Opin Nephrol Hypertens. 2015



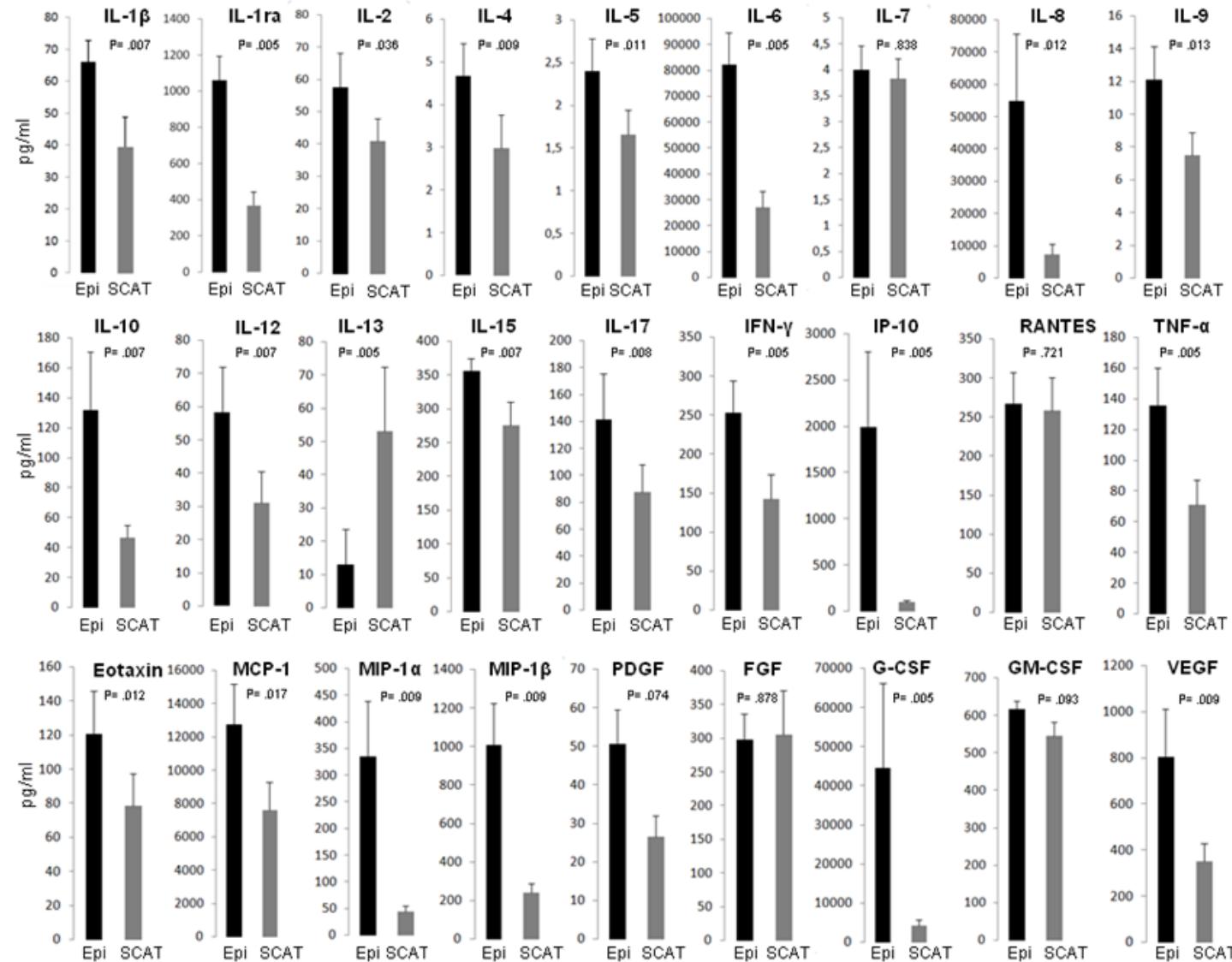
# Tessuto adiposo epicardico: Un ruolo nelle calcificazioni valvolari?

# Epicardial adipose tissue is increased in pts with calcific aortic stenosis





# Epicardial adipose tissue is increased in pts with calcific aortic stenosis



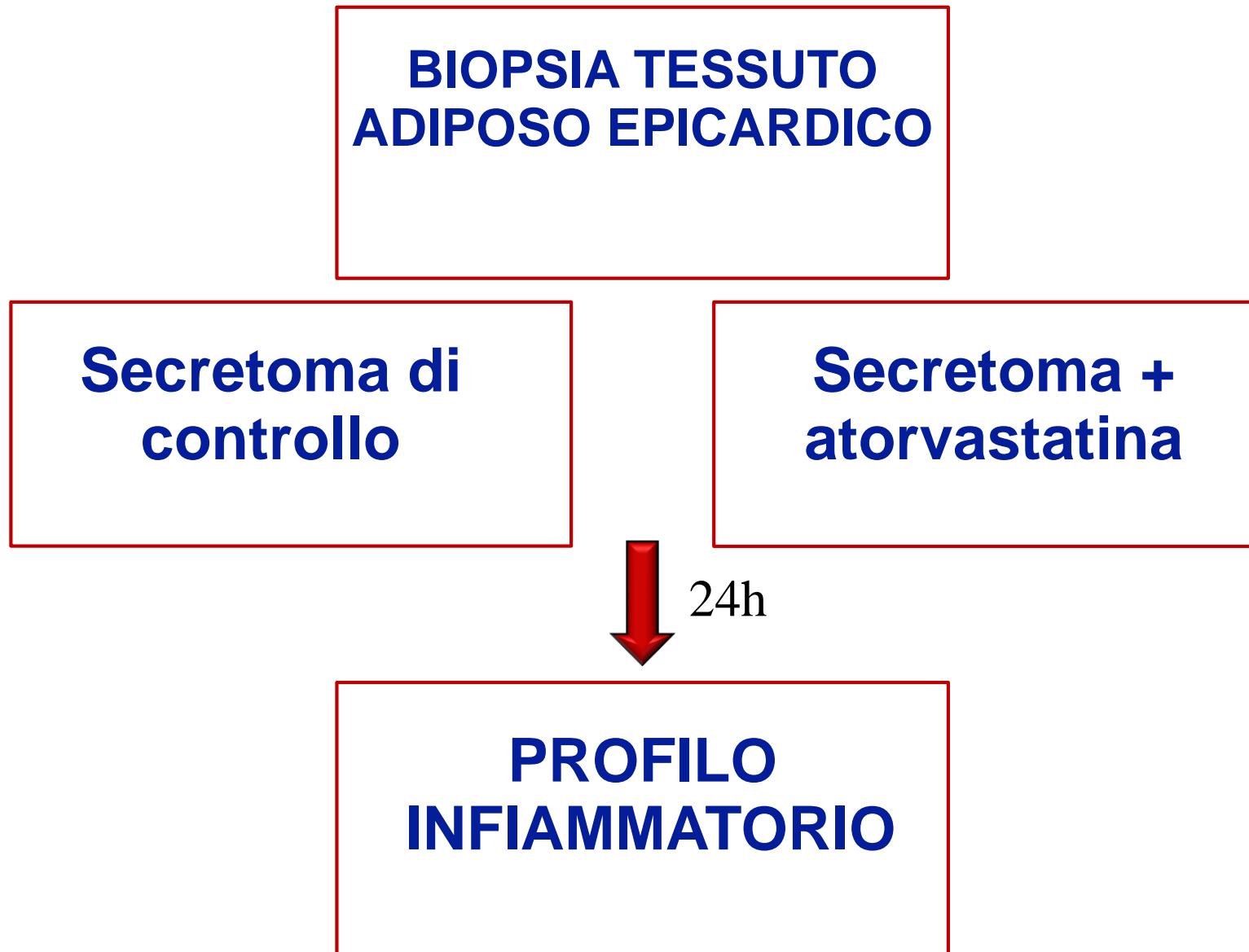
# Correlazione tra spessore EAT e secrezione di mediatori infiammatori

	Epicardial fat	
	Spearman	p value
PDGF	.728*	.017
IL-1 $\beta$	.887**	.001
IL-1ra	.936**	.000
IL-2	.790*	.020
IL-4	.801**	.005
IL-5	.954**	.000
IL-6	.691*	.027
IL-7	.991**	.000
IL-8	.837**	.010
IL-9	.911**	.000
IL-10	.960**	.000
IL-12	.636*	.048
IL-13	.110	.762
IL-15	.538	.108
IL-17	.838**	.002
Eotaxin	.850**	.007
FGF basic	.917**	.000
G-CSF	.813**	.004
GM-CSF	.275	.441
IFN- $\gamma$	.813**	.004
IP-10	.881**	.001
MCP-1	.711*	.048
MIP-1 $\alpha$	.813**	.004
MIP-1 $\beta$	.869**	.001
RANTES	.575	.082
TNF- $\alpha$	.869**	.001
VEGF	.569	.086

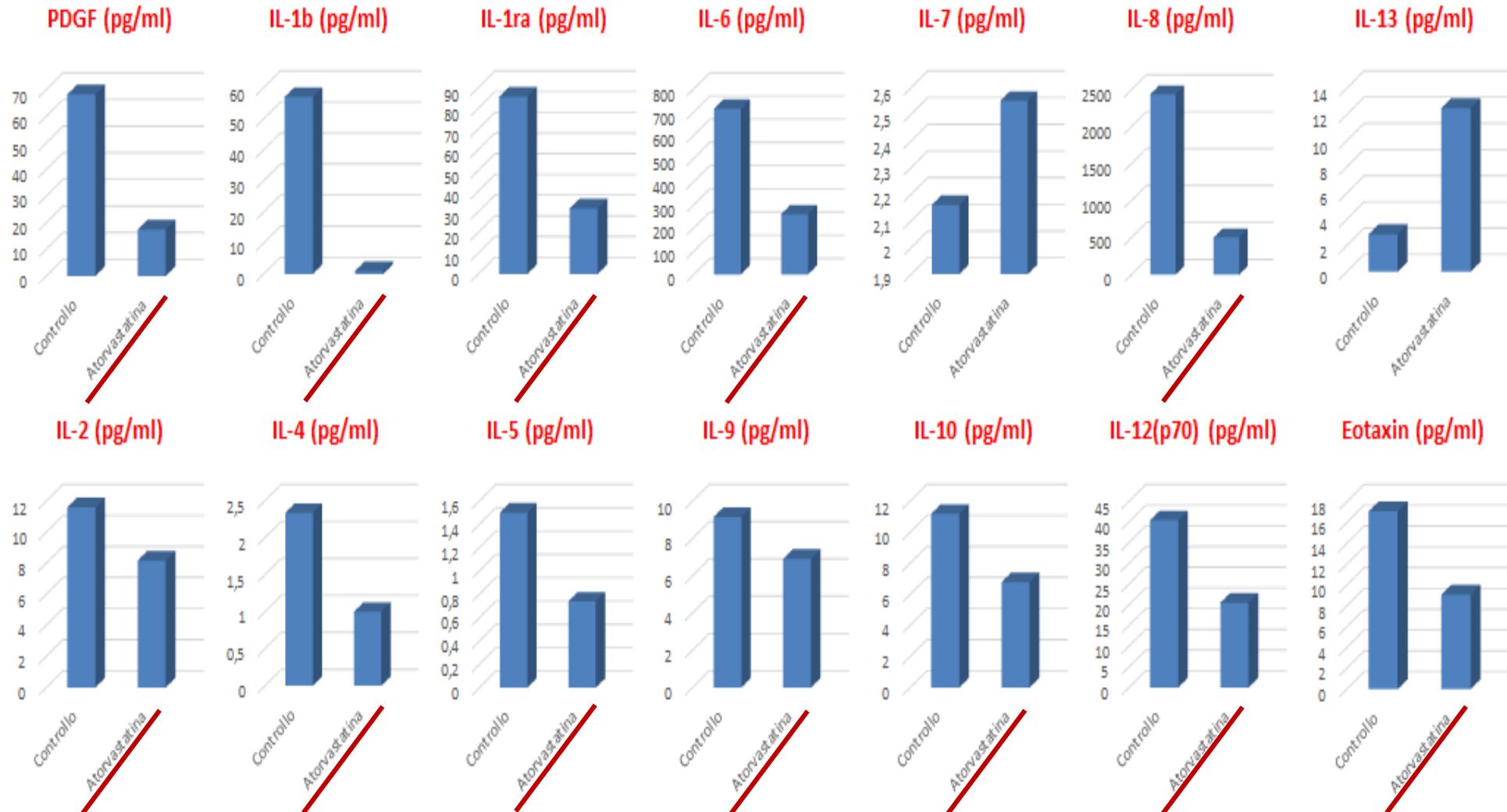
# Epicardial adipose tissue: statin vs no statin therapy

Plasma	P value	EAT secretome	P value
PDGF	.994	PDGF	.056
IL-1 $\beta$	.366	IL-1 $\beta$	.000
IL-1ra	.962	IL-1ra	.000
IL-2	.251	IL-2	.000
IL-4	.503	IL-4	.000
IL-5	.532	IL-5	.010
IL-6	.021	IL-6	.004
IL-7	.812	IL-7	.000
IL-8	.414	IL-8	.000
IL-9	.723	IL-9	.000
IL-10	.145	IL-10	.002
IL-12	.499	IL-12	.048
IL-13	.721	IL-13	.792
IL-15	.511	IL-15	.008
IL-17	.753	IL-17	.000
Eotaxin	.761	Eotaxin	.000
FGF basic	.613	FGF basic	.006
G-CSF	.583	G-CSF	.054
GM-CSF	.930	GM-CSF	.0864
IFN- $\gamma$	.369	IFN- $\gamma$	.000
IP-10	.592	IP-10	.014
MCP-1	.679	MCP-1	.000
MIP-1 $\alpha$	.011	MIP-1 $\alpha$	.000
MIP-1 $\beta$	.108	MIP-1 $\beta$	.000
RANTES	.631	RANTES	.423
TNF- $\alpha$	.091	TNF- $\alpha$	.000
VEGF	.004	VEGF	.105

# Azione diretta delle statine sul tessuto adiposo epicardico:



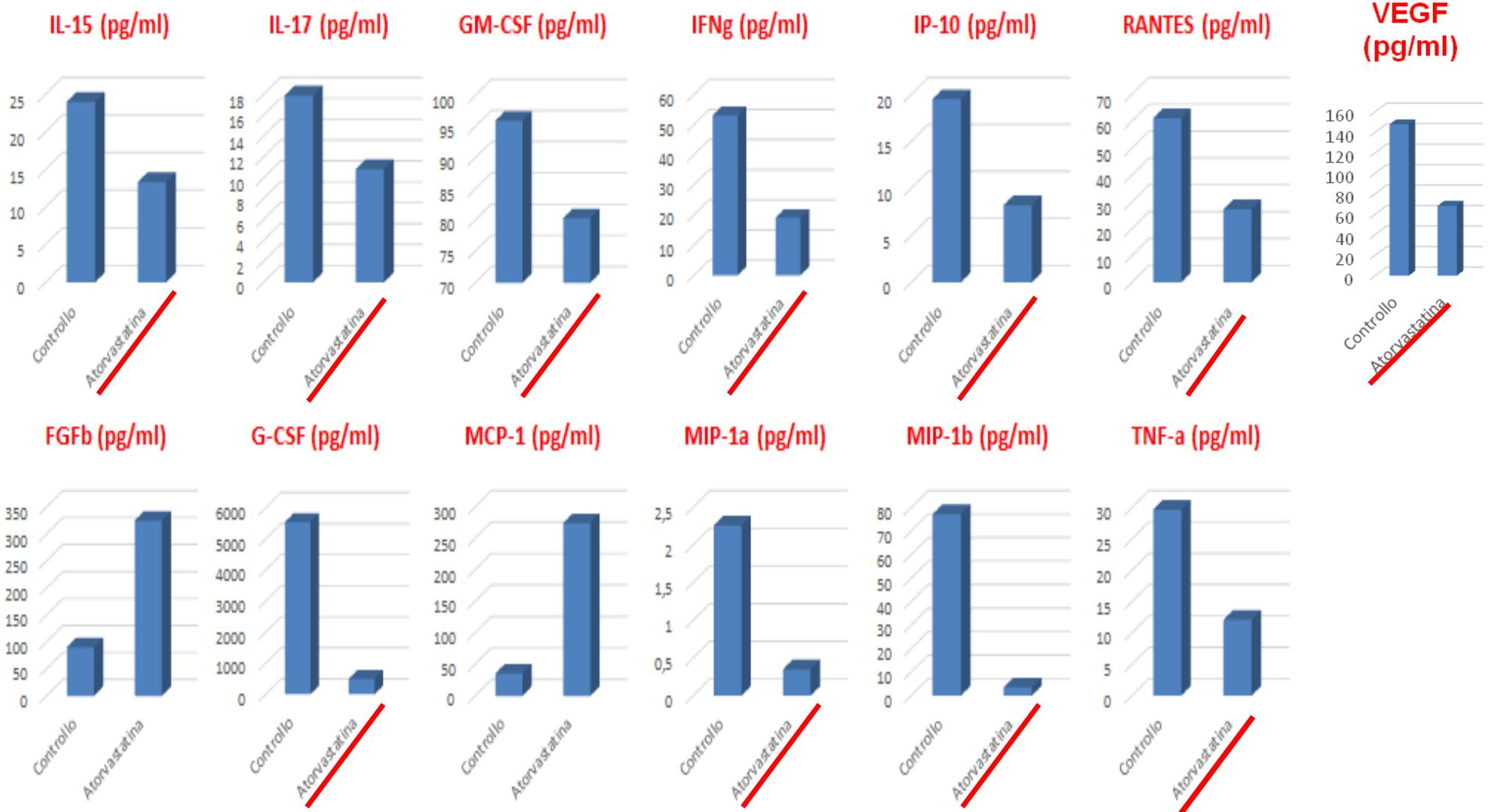
# Livelli di citochine infiammatorie nel secretoma di EAT con e senza Statina



$p < 0.05$

Parisi V et al, data in progress

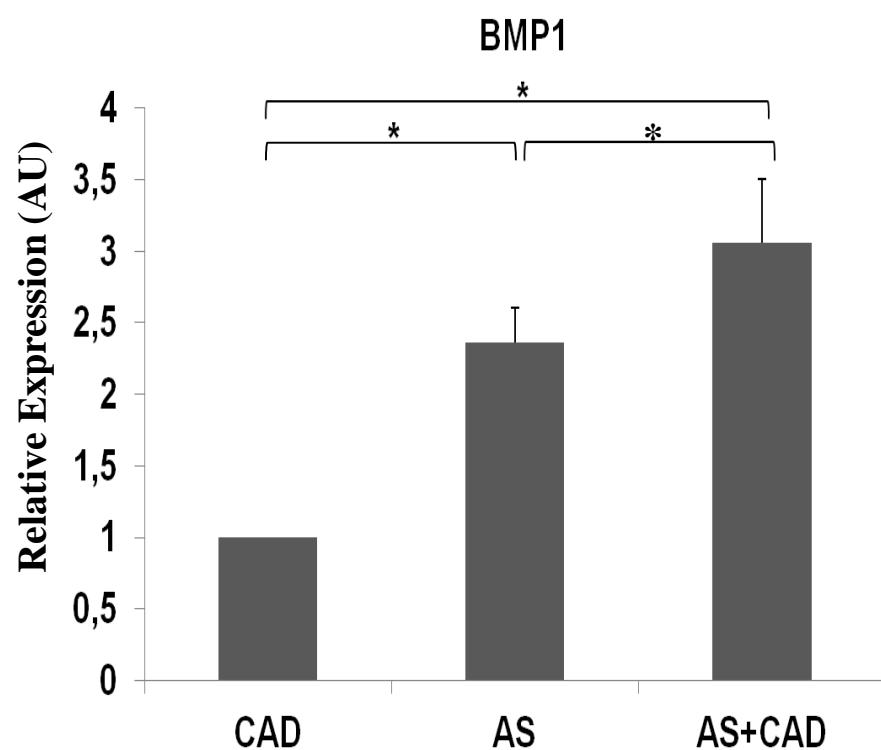
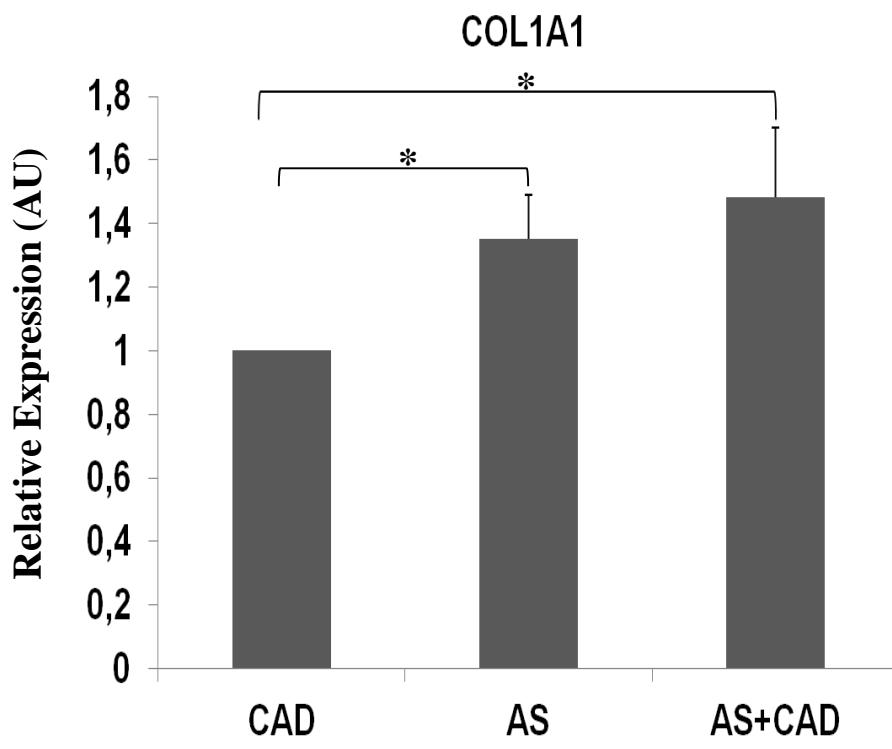
# Livelli di citochine infiammatorie nel secretoma di EAT con e senza Statina



$p < 0.05$

Parisi V et al, data in progress

# Expression of osteogenic markers in EAT of pts with calcific AS



*Personal in progress data*

# CONCLUSIONI

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- Infiammazione ed aterosclerosi determinanti nella degenerazione ed ossificazione della valvola aortica
- La demineralizzazione ossea e le calcificazioni valvolari sono regolati da processi biologici ATTIVI ed OPPOSTI modulati da: dislipidemia, insufficienza renale ed infiammazione
- Il tessuto adiposo epicardico è fonte di citokine pro-infimmatorie e pro-calcifiche che verosimilmente condizionano l'aterogenesi vascolare e valvolare



## LA STENOSI AORTICA: UNA NUOVA SINDROME GERIATRICA

### *Infiammazione e aterosclerosi nell'etiopatogenesi*



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*Dipartimento di Scienze Mediche Traslazionali*  
*Università degli Studi di Napoli 'Federico II'*