Aterosclerosi e osteoporosi: due facce della stessa medaglia?

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REGIONE SICILIA

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Il sottoscritto Agostino Gaudio

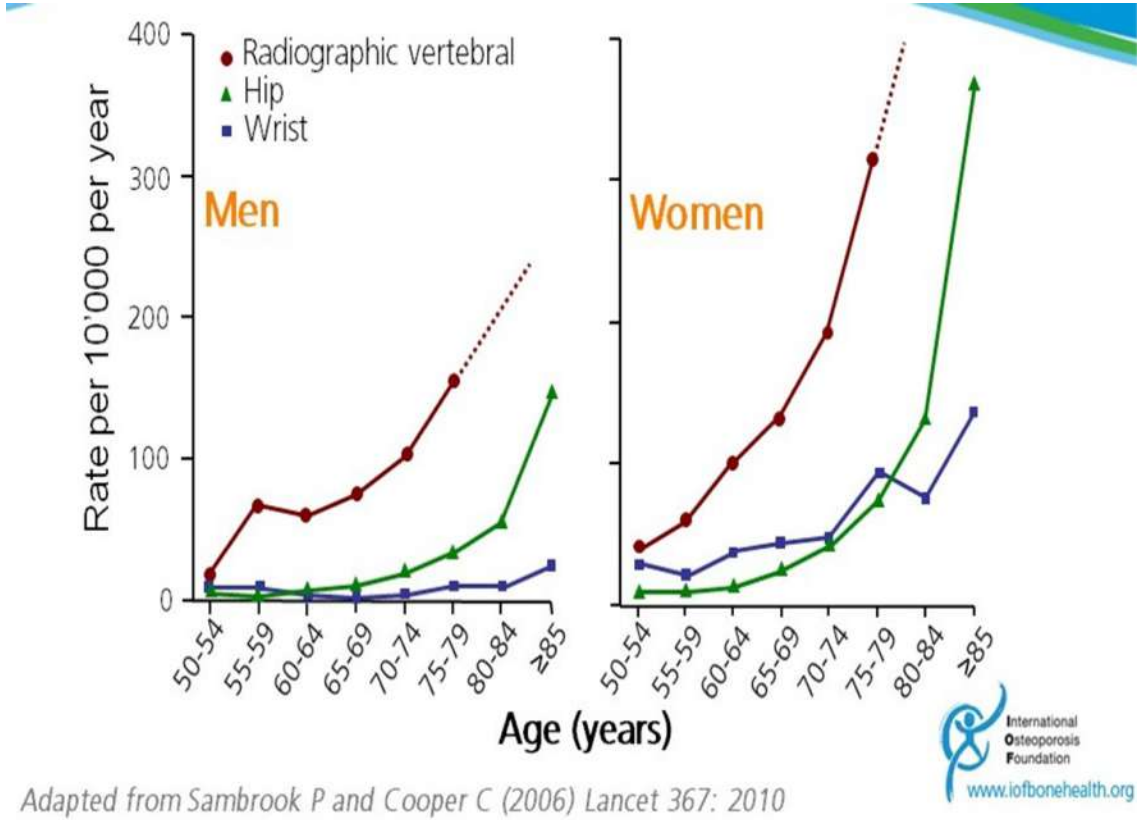
ai sensi dell’art. 76, comma 4 dell’Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara che

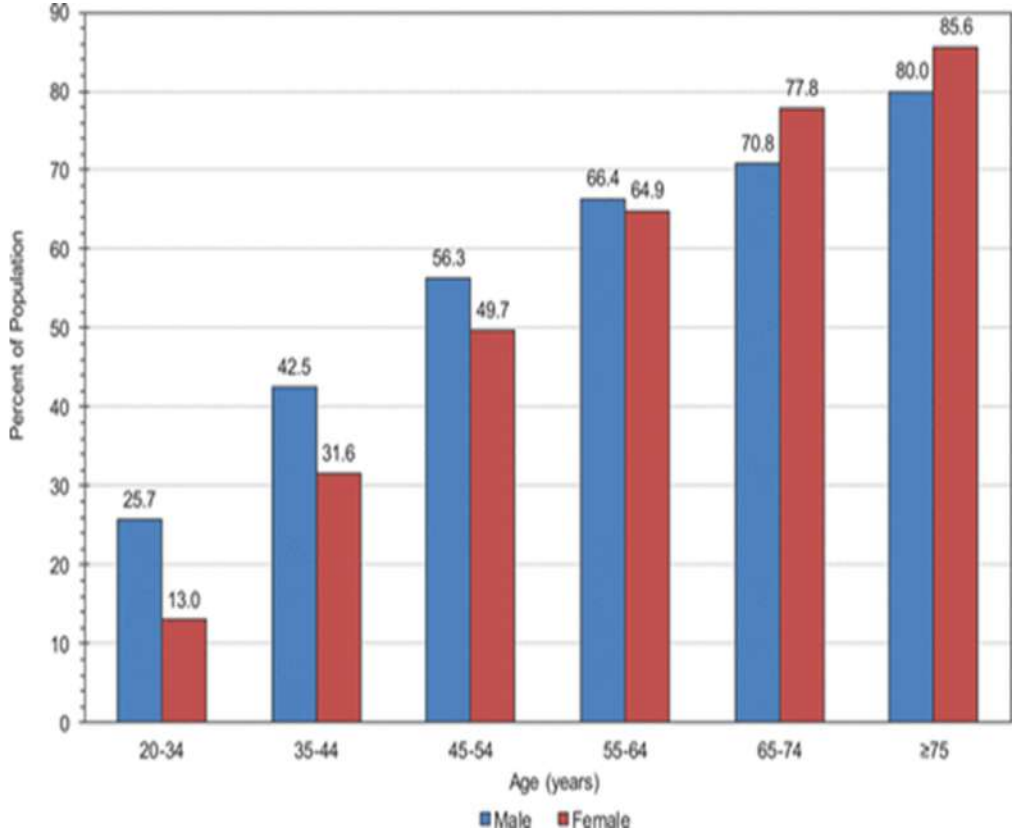
negli ultimi due anni ha avuto i seguenti rapporti con soggetti portatori di interessi commerciali in ambito sanitario

UCB, Theramex e Lilly

L’incidenza delle fratture e delle malattie cardiovascolari aumenta con l’età sia negli uomini che nelle donne



Adapted from Sambrook P and Cooper C (2006) Lancet 367: 2010



Virani SS, et al. Circulation. 2020

Studies associating osteoporosis (BMD) and atherosclerosis

Table 1 Studies associating osteoporosis (represented by bone mineral density) with atherosclerosis

Studies	Associated vascular condition	Year of publication	Number of patients
Von der Recke et al. [6]	Cardiovascular mortality	1999	1063
Kado et al. [7]	Cardiovascular mortality	2000	6046
Browner et al. [8]	Cardiovascular mortality	1991	9704
Marcovitz et al. [9]	Coronary artery disease	2005	209
Sennerby et al. [11]	Cardiovascular disease	2007	4497
Kiel et al. [12]	Aortic calcification	2001	554
Schultz et al. [13]	Aortic calcification	2004	228
Hyder et al. [14]	Aortic calcification	2007	365
Mangiafico et al. [15]	Augmentation index and central aortic systolic pressure	2008	342
Barengolts [16]	Coronary calcification	1998	45
Uyama et al. [17]	Carotid atherosclerosis	1997	30
Jorgensen et al. [18]	Carotid atherosclerosis	2006	2733
Shaffer et al. [19]	Carotid atherosclerosis	2007	870
Jorgensen et al. [24]	Carotid atherosclerosis	2004	5269
Van der Klift et al. [20]	Peripheral artery disease	2002	5268
Farhat [25]	Peripheral and coronary artery disease	2006	3075
Jorgensen et al. [21]	Stroke	2001	63
Browner et al. [22]	Stroke	1993	4024
Johansson [26]	Survival	1998	1924

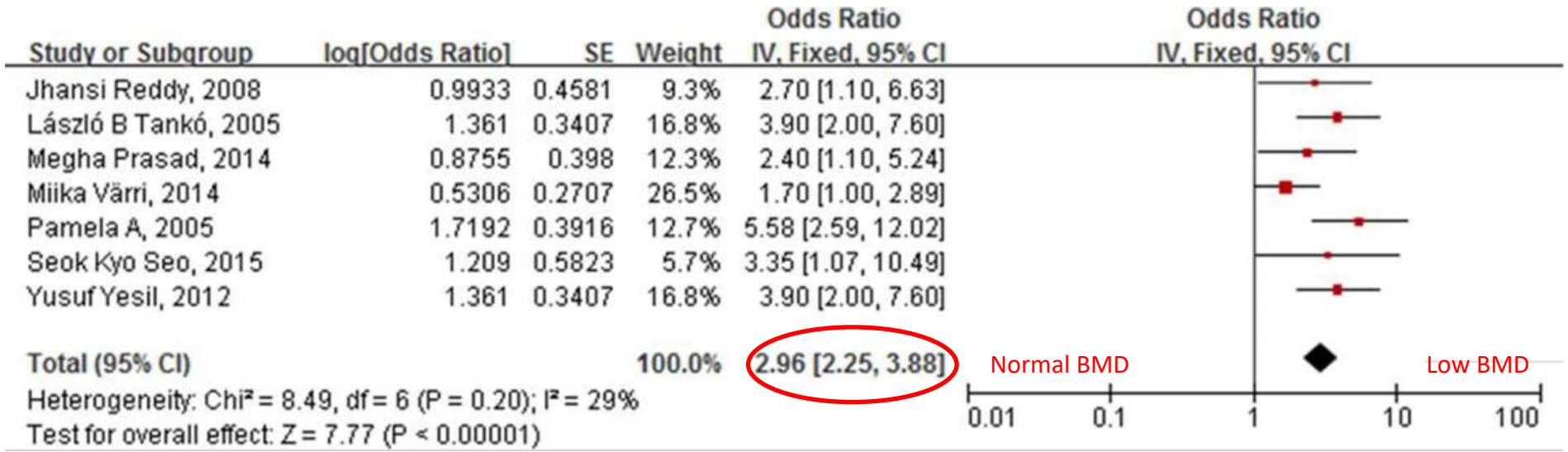
Anagnostis P, et al. Osteoporos Int. 2009

Malattie età-correlate o rapporto di causalità?

Aterosclerosi/Arteriosclerosi

Osteoporosi

L'incidenza di qualsiasi patologia vascolare su base aterosclerotica è risultata significativamente aumentata nei soggetti con bassa BMD rispetto a quelli con BMD normale (odds ratio (OR) 2.96), dopo aggiustamento per età, sesso, BMI, ipertensione e altri fattori di rischio cardiovascolare.



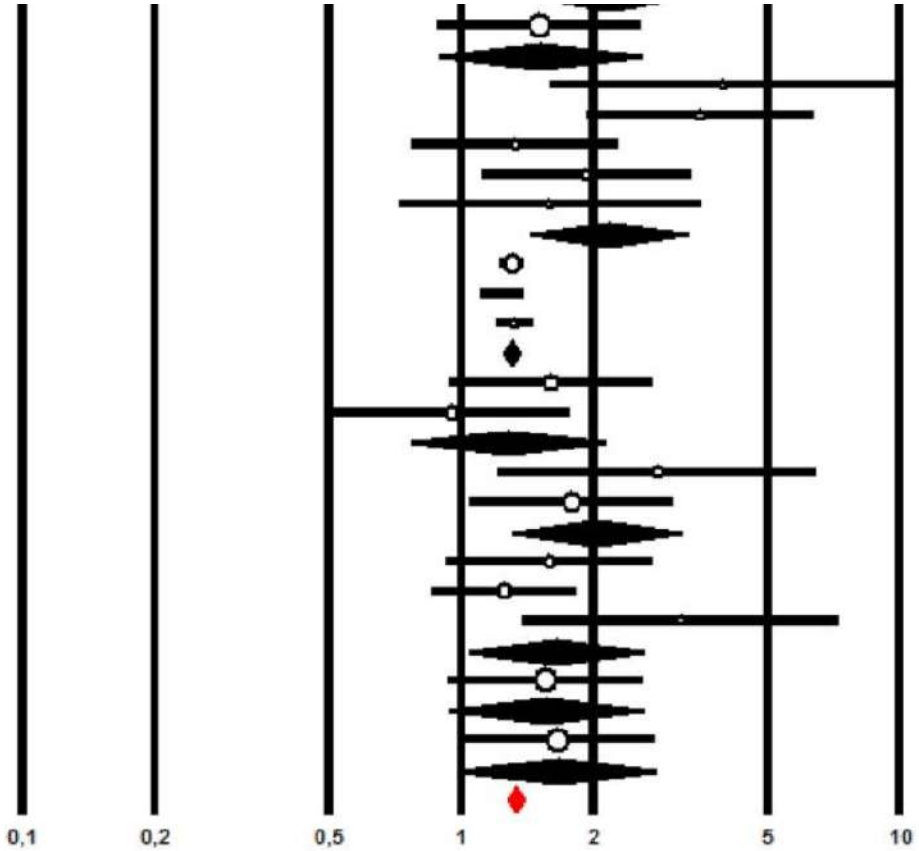
Meta-analisi di 25 studi con 10.299 pazienti.

Patologia vascolare su base aterosclerotica: carotid artery calcification (CAC); cardiovascular disease (CVD); and coronary artery disease (CAD).

Ye C, et al. PLoS One 2016

Le persone con bassa BMD hanno un aumentato rischio di sviluppare una malattia cardiovascolare (CVD) durante il follow-up con un hazard ratio (HR) di 1,33.

Szulc et al., 2009 (distal radius)	1,510	0,887	2,570	1,518	0,129
	1,510	0,887	2,570	1,518	0,129
Zhou et al., 2015	3,940	1,604	9,680	2,990	0,003
Shen et al., 2012	3,510	1,940	6,350	4,151	0,000
Szulc et al., 2009 (femoral neck)	1,330	0,775	2,284	1,034	0,301
Nordstrom et al., 2010	1,920	1,114	3,311	2,347	0,019
Domiciano et al., 2016 (femoral neck)	1,590	0,722	3,501	1,152	0,249
	2,153	1,424	3,256	3,633	0,000
Chen et al., 2015	1,300	1,227	1,377	8,938	0,000
Lin et al., 2014	1,240	1,108	1,388	3,749	0,000
Yu et al., 2015	1,320	1,201	1,451	5,751	0,000
	1,295	1,238	1,354	11,237	0,000
Szulc et al., 2009 (spine)	1,600	0,941	2,722	1,734	0,083
Domiciano et al., 2016 (lumbar)	0,950	0,510	1,770	-0,162	0,872
	1,266	0,761	2,104	0,908	0,364
Matsubara et al., 2008	2,800	1,222	6,416	2,434	0,015
Szulc et al., 2009 (whole body)	1,780	1,048	3,024	2,133	0,033
	2,030	1,299	3,172	3,108	0,002
Szulc et al., 2009 (total hip)	1,590	0,926	2,729	1,682	0,093
Mussolino et al., 2007	1,250	0,862	1,813	1,175	0,240
Domiciano et al., 2016 (total hip)	3,170	1,389	7,235	2,740	0,006
	1,645	1,043	2,594	2,143	0,032
Szulc et al., 2009 (trochanter)	1,560	0,938	2,594	1,713	0,087
	1,560	0,938	2,594	1,713	0,087
Szulc et al., 2009 (ultradistal radius)	1,650	0,990	2,750	1,921	0,055
	1,650	0,990	2,750	1,921	0,055
	1,325	1,268	1,383	12,689	0,000



Meta-analisi di 11 studi

Veronese N, et al. J Bone Miner Res. 2017

Analysis	Number of studies	Meta-analysis				Heterogeneity
		HR	95% CI		P-value	I^2
CHD						
Femoral neck	**1**	**1.43**	**1.21**	**1.69**	**<0.0001**	-
Total hip	**1**	**1.48**	**1.10**	**2.00**	**<0.0001**	-
Overall	**1**	**1.44**	**1.25**	**1.66**	**<0.0001**	0
Stroke + TIA						
Calcaneus	1	**1.31**	**1.03**	**1.67**	**0.03**	-
Femoral neck	**1**	**1.69**	**1.48**	**1.93**	**<0.0001**	-
Radiographic	1	1.03	0.92	1.16	0.62	-
Overall	**3**	**1.28**	**1.18**	**1.39**	**<0.0001**	93
Death for CVD						
Calcaneus	1	0.99	0.78	1.26	0.94	-
Distal radius	2	1.15	0.71	1.87	0.58	66
Femoral neck	**2**	**1.67**	**1.46**	**1.90**	**<0.0001**	0
Proximal radius	1	1.17	0.91	1.50	0.21	-
Radiographic	1	1.09	0.99	1.20	0.08	-
Spine	1	1.37	0.79	2.39	0.27	-
Total hip	1	1.08	0.90	1.30	0.30	-
Trochanter	1	1.31	0.79	2.18	0.30	-
Overall	**7**	**1.22**	**1.14**	**1.30**	**<0.0001**	77

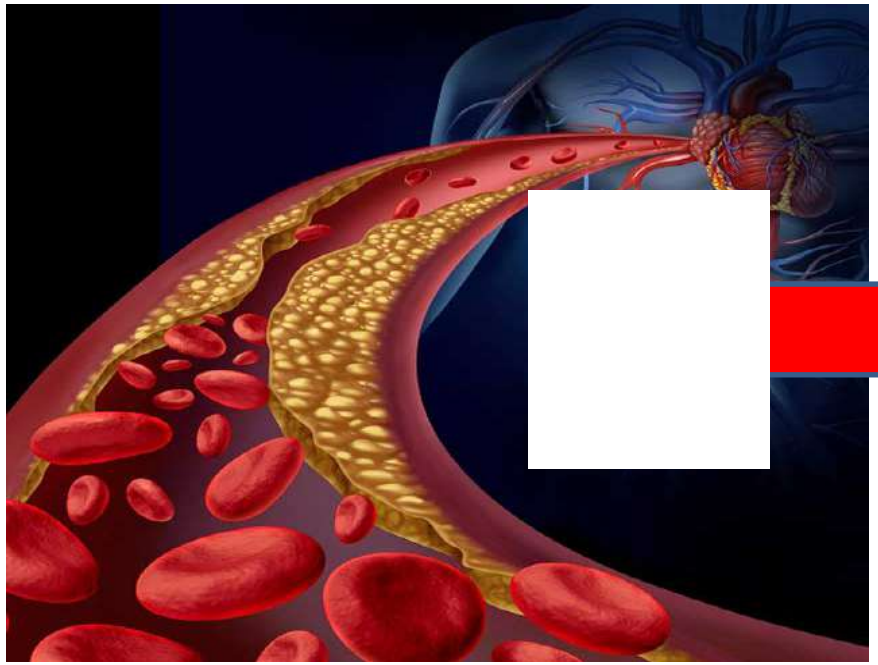
La riduzione di una DS della BMD si traduceva nell'incremento del:

- 44% di malattia cardiovascolare
- 28% di malattia cerebrovascolare
- 22% di morte per eventi cardiovascolari.

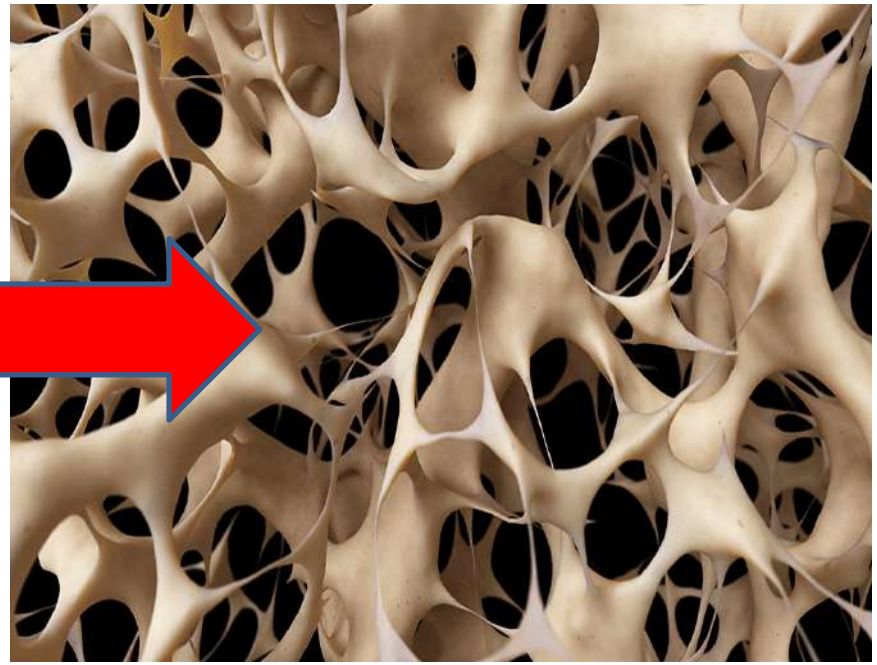
In conclusione, c'è un aumento del rischio di aterosclerosi e malattie cardiovascolari in soggetti con osteoporosi.

Veronese N, et al. J Bone Miner Res. 2017

Malattie età-correlate o rapporto di causalità?

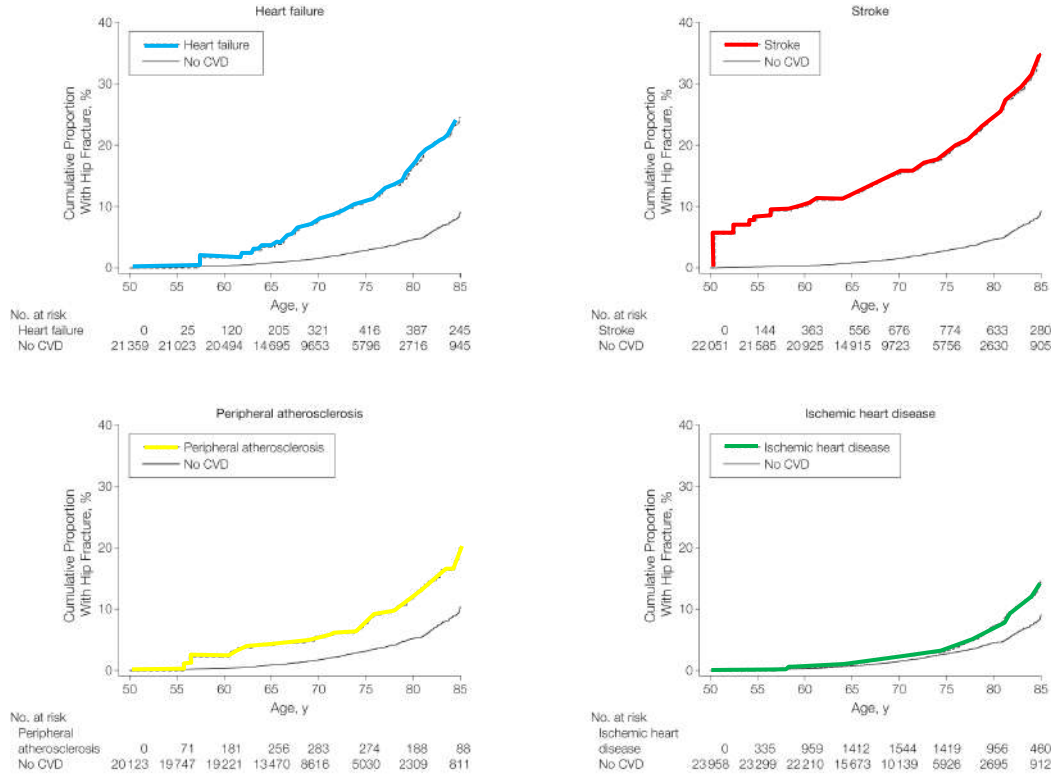


Aterosclerosi/Arteriosclerosi



Osteoporosi

Kaplan-Meier curves of hip fracture for twins with and without cardiovascular disease (CVD)



Hazard Ratios of Hip Fracture Associated With Different Cardiovascular Diseases

	Heart Failure	Stroke	Peripheral Atherosclerosis	Ischemic Heart Disease
No. of hip fracture cases with CVD	113	218	45	185
Exposed, person-years	8931	17 313	6828	35 935
No CVD, person-years	430 041	437 461	396 356	464 172
Sex-adjusted model, HR (95% CI)	3.04 (2.42-3.81)	3.86 (3.25-4.59)	2.04 (1.50-2.79)	1.85 (1.54-2.21)
Multivariable model, HR (95% CI)[b]	4.40 (3.43-5.63)	5.09 (4.18-6.20)	3.20 (2.28-4.50)	2.32 (1.91-2.84)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.
[a] No CVD group was used as reference group (includes 526 twins with hip fracture).
[b] Adjusted for sex, endocrine disorder, neurologic disease, psychiatric disorder, respiratory disease, musculoskeletal disorder, hyperlipidemia, diabetes mellitus, heart failure, stroke, peripheral atherosclerosis, ischemic heart disease, and hypertension (all dichotomous).

32.000 gemelli svedesi seguiti dall'età di 50 anni per un periodo medio di follow-up di 20 anni. Il principale outcome era il tempo di frattura dell'anca dopo la diagnosi di CVD.

Sennerby U, et al. JAMA 2009

Table 2. Risk of Hip/Femur Fracture and Type of Stroke

	Cases (n=6763)	Controls (n=26 341)	Crude OR (95% CI)	Adjusted OR (95% CI)*
Never experienced stroke	6538	25 934	1.00	1.00
Ever experienced stroke	225	407	2.22 (1.88–2.62)	1.96 (1.65–2.33)
Hemorrhagic stroke†	35	66	2.14 (1.41–3.22)	1.94 (1.27–2.96)
Ischemic stroke‡	93	182	2.06 (1.60–2.65)	1.85 (1.42–2.39)
Undefined stroke§	97	159	2.44 (1.89–3.15)	2.10 (1.61–2.73)

Table 3. Risk of Hip/Femur Fracture and Strokes Stratified by Sex and Age

	Cases (n=6763)	Controls (n=26 341)	Crude OR (95% CI)	Adjusted OR (95% CI)*
Never experienced stroke	6538	25 934	1.00	1.00
Ever experienced stroke	225	407	2.22 (1.88–2.62)	1.96 (1.65–2.33)
Male	57	126	1.82 (1.32–2.51)	1.63 (1.17–2.28)
Female	168	281	2.40 (1.97–2.91)	2.12 (1.73–2.59)
Male and female				
18–70 years	41	28	6.31 (3.83–10.39)	5.12 (3.00–8.75)
71–80 years	91	152	2.44 (1.87–3.18)	2.07 (1.57–2.73)
Older than 80 years	93	227	1.61 (1.26–2.06)	1.51 (1.18–1.94)

Case-control study using the Dutch PHARMO Record Linkage System database. Cases (n=6763) were patients with a first hip/femur fracture; controls were matched by age, sex, and region.

Lo stroke aumentava di circa 2 volte il rischio di una successiva frattura di femore.
Il rischio era più elevato tra i pazienti di sesso femminile, al di sotto dei 71 anni di età, e in quelle che avevano avuto l'ictus più recente.

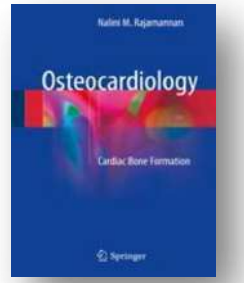
In conclusione, c'è un aumentato rischio di perdita ossea, osteoporosi e fratture da fragilità in pazienti con CVD.

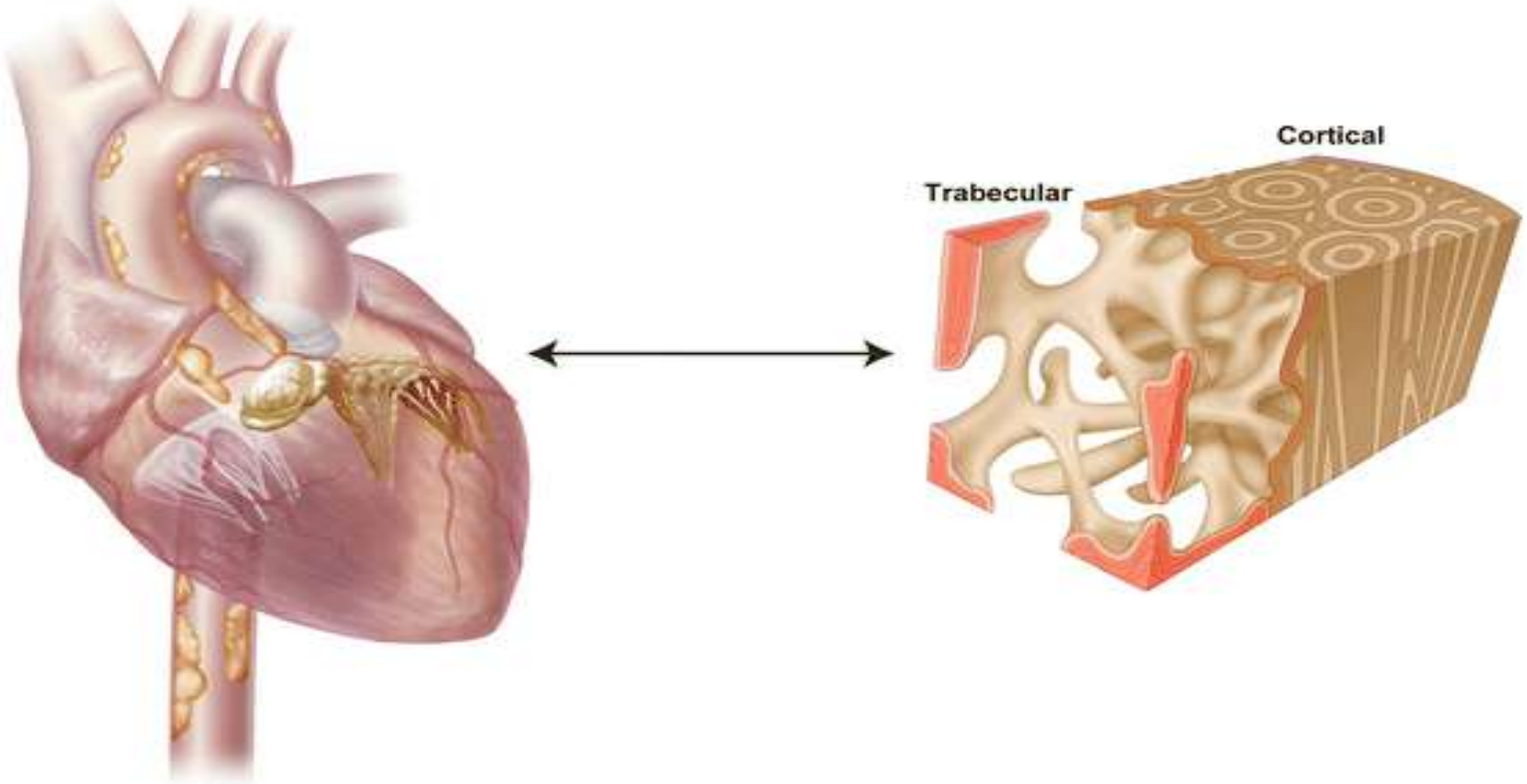
Pouwels S, et al. Stroke 2009

Aterosclerosi e osteoporosi condividono comuni fattori di rischio:

- Età
- Diabete Mellito
- Fumo
- Abuso di alcool
- Ridotta attività fisica
- Menopausa (donne)

The heart-bone paradox



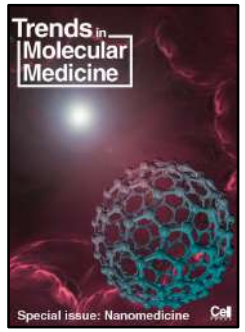


"As bone formation decreases in the skeleton, it increases in the heart"

Rajamannan N.M. (2018). In: Osteocardiology. Springer,

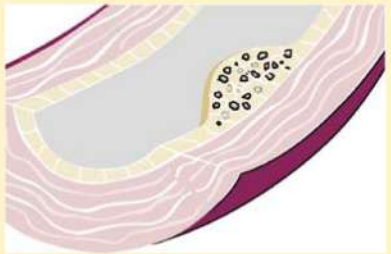
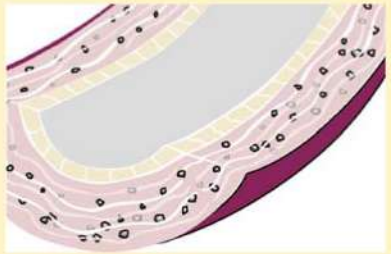
Vascular calcification and bone disease: the calcification paradox

Veerle Persy and Patrick D'Haese

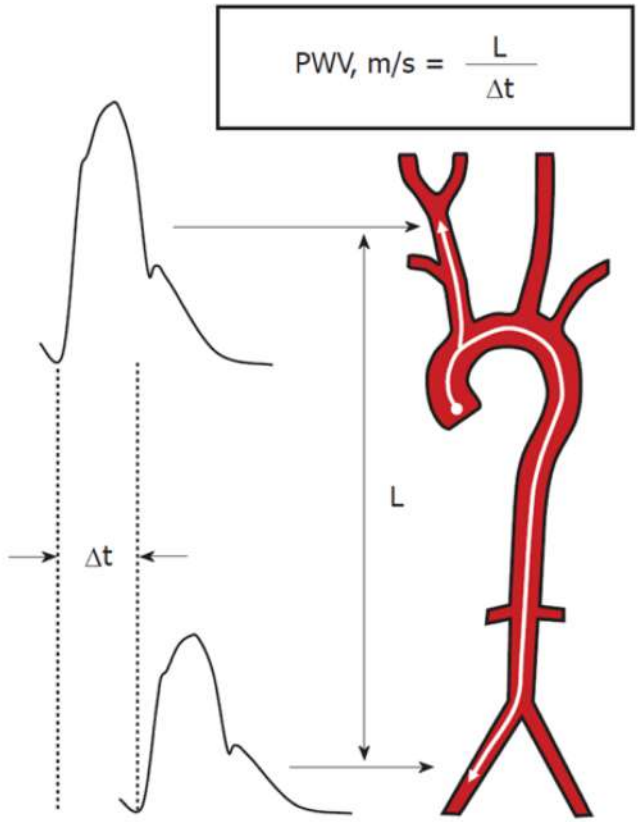


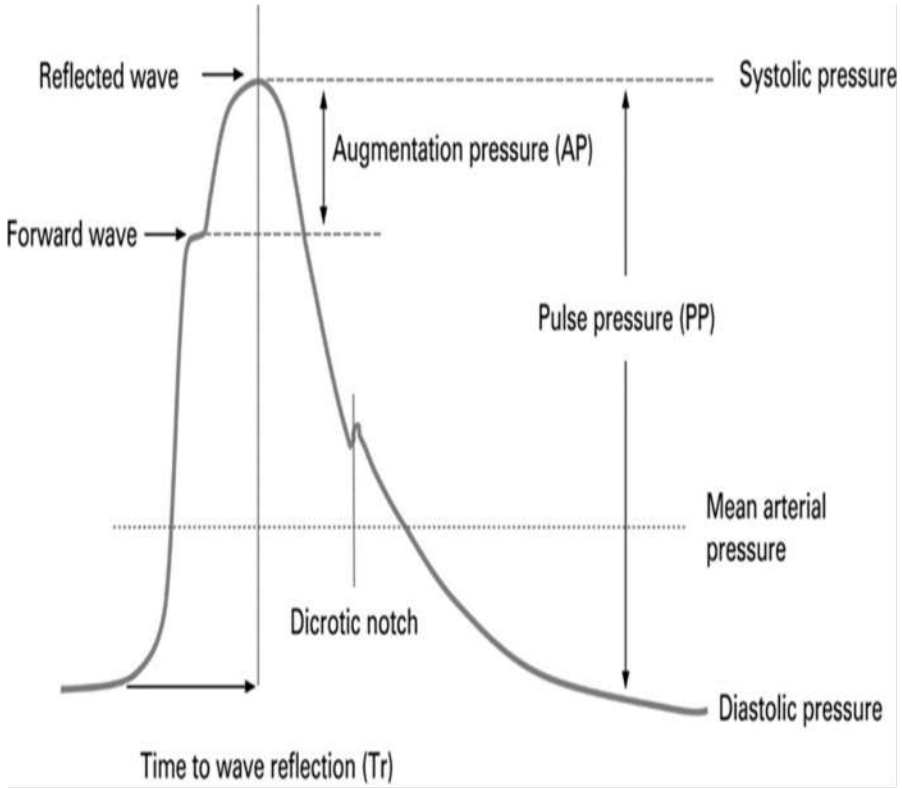
Trends Mol Med. 2009 Sep;15(9):405-16

Box 1. Intima versus media calcification

	Intima calcification	Media calcification
	Atherosclerosis	Arteriosclerosis or Mönckeberg's sclerosis
Calcification pattern	Focal, in plaques	Generalized
		
Risk factors	Dyslipidemia, hypercholesterolemia	Aging, diabetes, renal failure, osteoporosis, hypertension
Molecular mechanisms	Lipid accumulation Foam cell formation Inflammation Oxidative stress Apoptosis	Transdifferentiation of VSMCs into bone-like cells (osteoblast-chondrocyte and osteoclast-like cells) Ca, P, vitamin D metabolism Loss of calcification inhibitors (pyrophosphate, MGP, fetuin)
Consequences	Plaque formation: stenosis Plaque calcification: controversial effect on plaque stability, possibly relating to the localization of calcification [117]	Arterial stiffening: increased pulse pressure, elevated pulse wave velocity
Complications	Ischemia, infarction	Systolic hypertension, left ventricular hypertrophy

Arterial stiffness



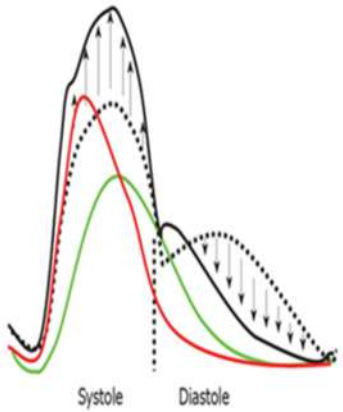


AIx= Augmentation pressure/Pulse pressure

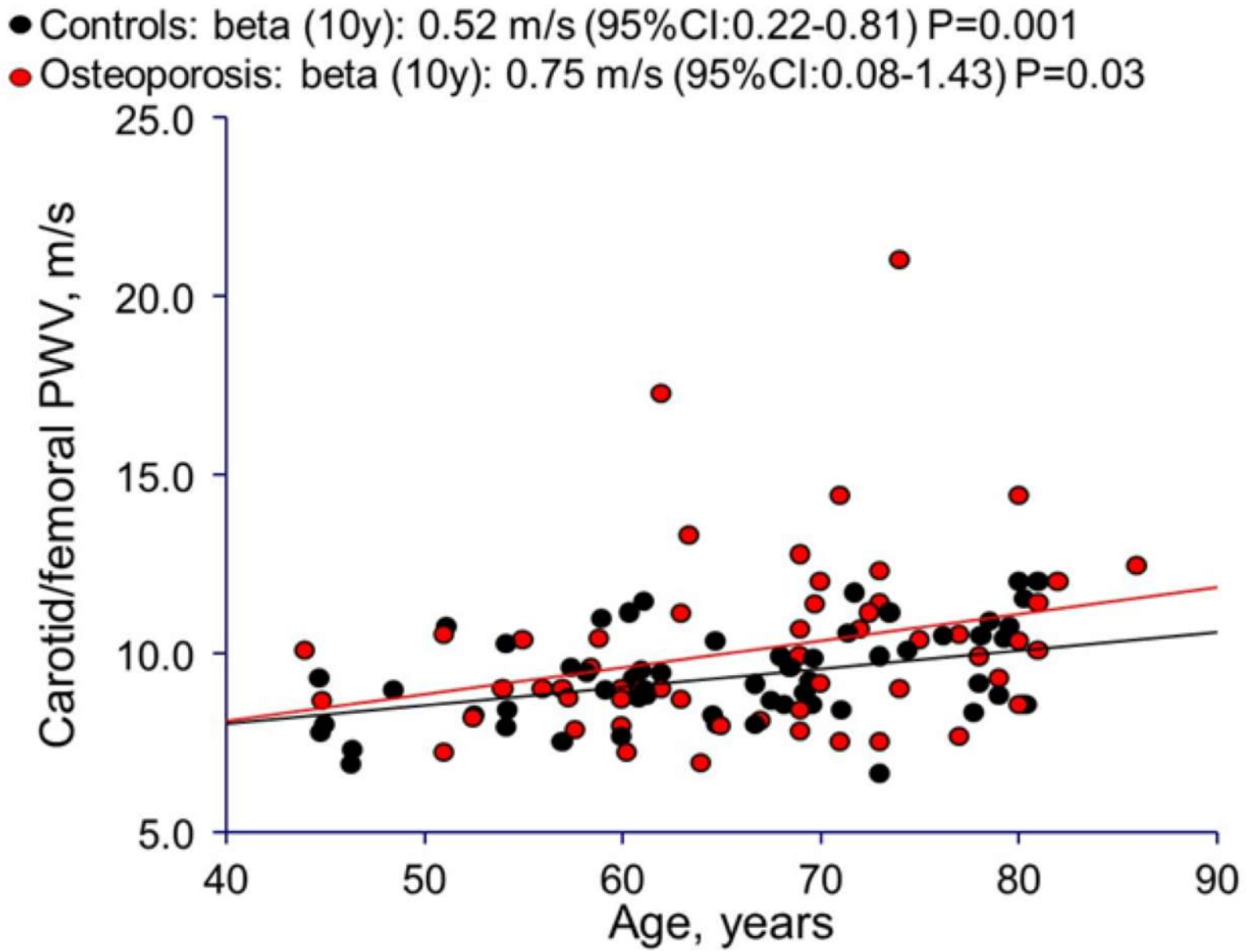
PWV e AIx rappresentano due markers riconosciuti di rischio cardiovascolare.

Parametri vascolari dei pazienti e dei controlli

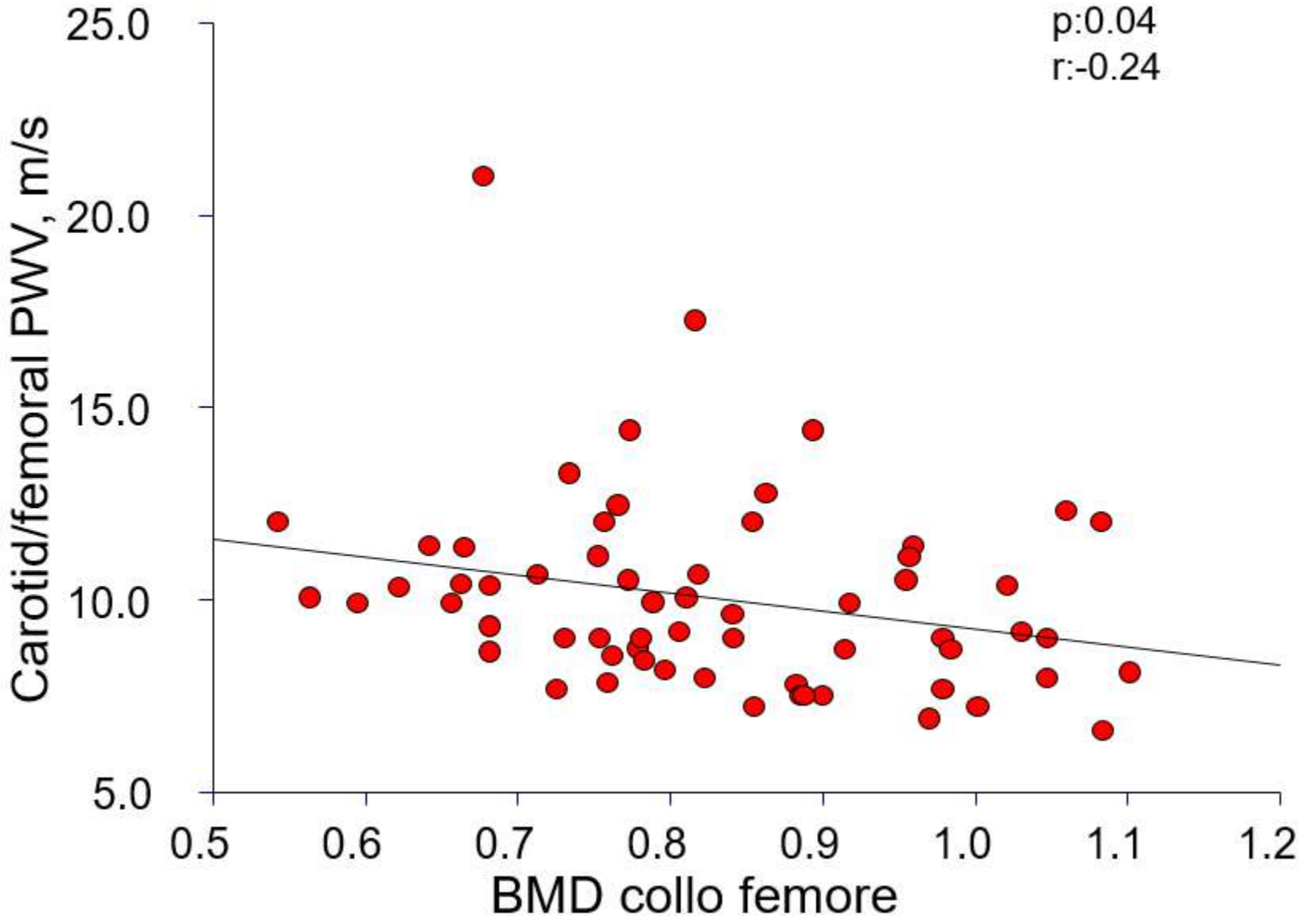
	Controlli n=58	Osteoporosi n=58	P-value
PWV, m/s	9.3±1.3	10.1±2.6	**0.045**
IMT, µm	710±146	904±197	**<0.001**
AIx, %	30±13	40±11	**<0.001**



Gaudio A, et al. Sci Rep. 2020

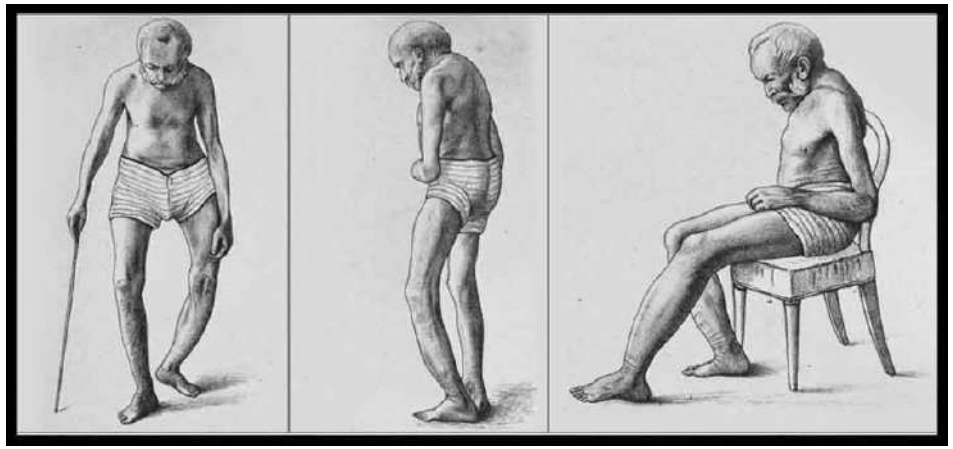


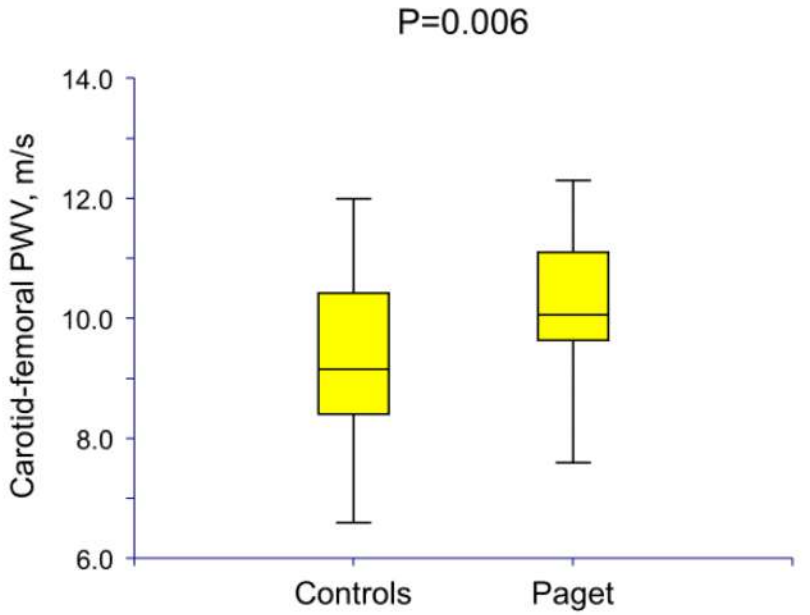
Gaudio A, et al. Sci Rep. 2020

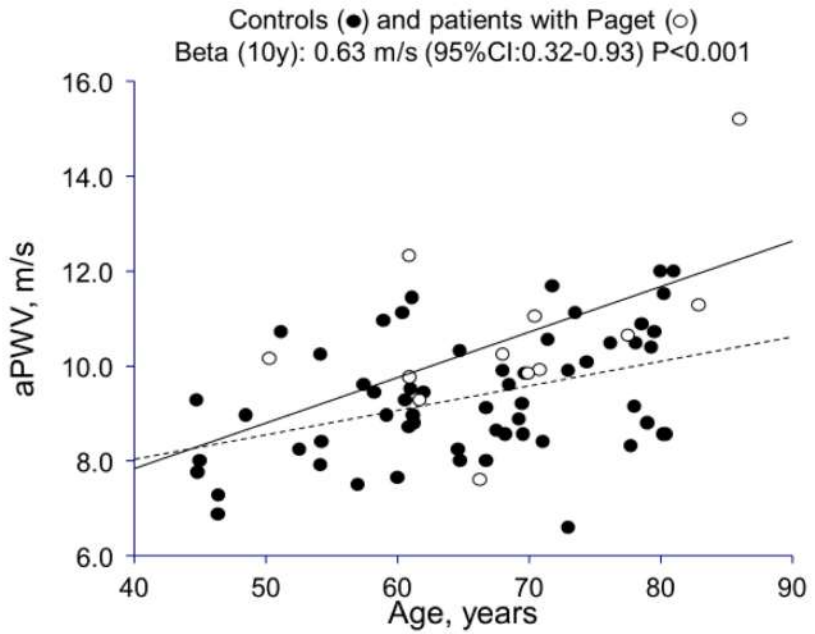


Gaudio A, et al. Sci Rep. 2020

Malattia ossea di Paget e rischio cardiovascolare

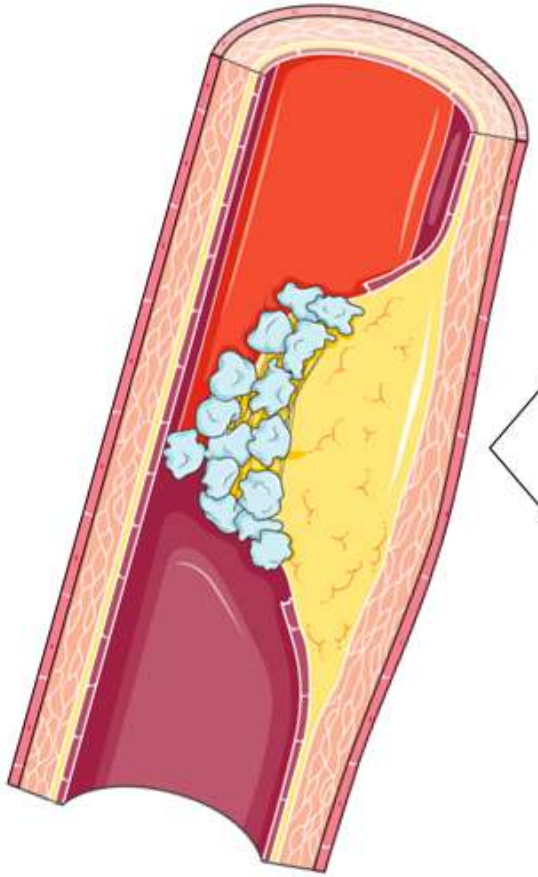






Gaudio A, et al. Curr Vasc Pharmacol. 2021

Potenziali comuni meccanismi patogenetici



Omocisteina

Deficit estrogenico

Flogosi/citochine

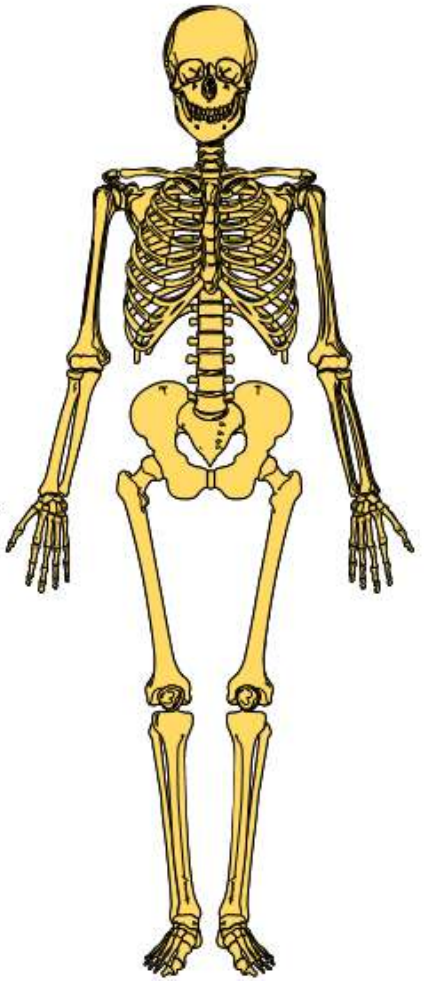
Osteocalcina

Vitamina D/Vitamina K

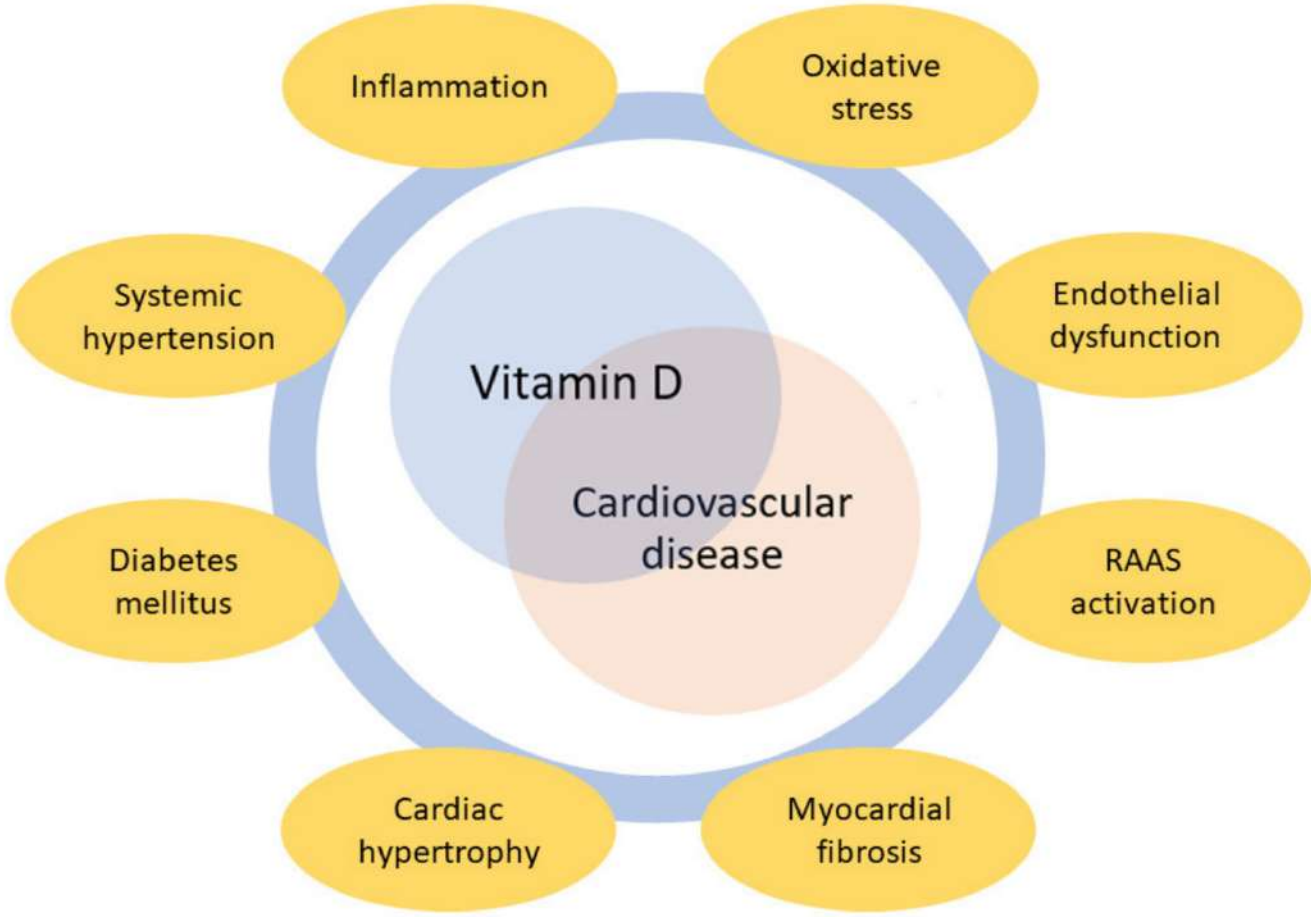
Ossidazione lipidica

Fetuina-A

FGF-23

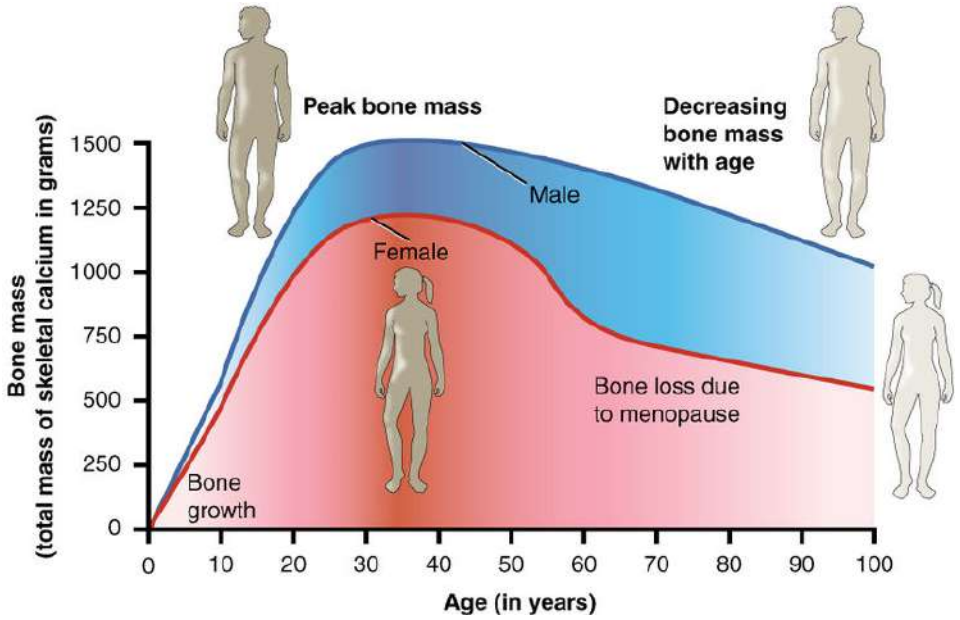


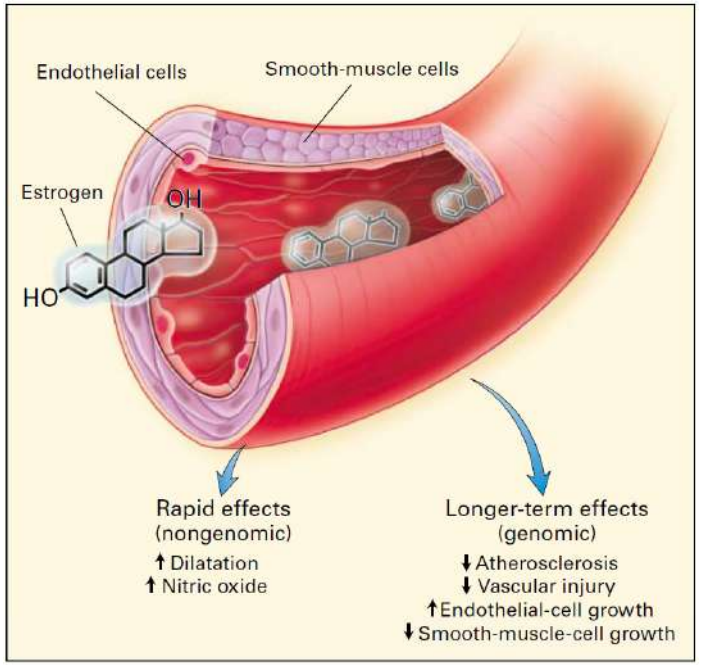
Vitamin D and cardiovascular disease

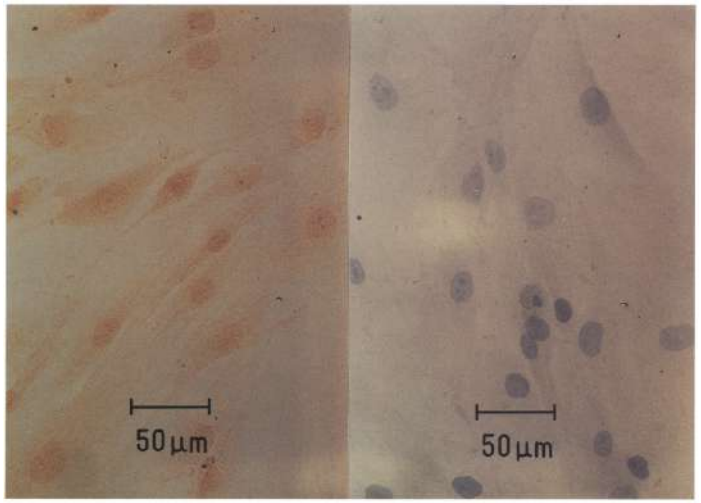


Cosentino N, et al. Nutrients. 2021

Estrogens



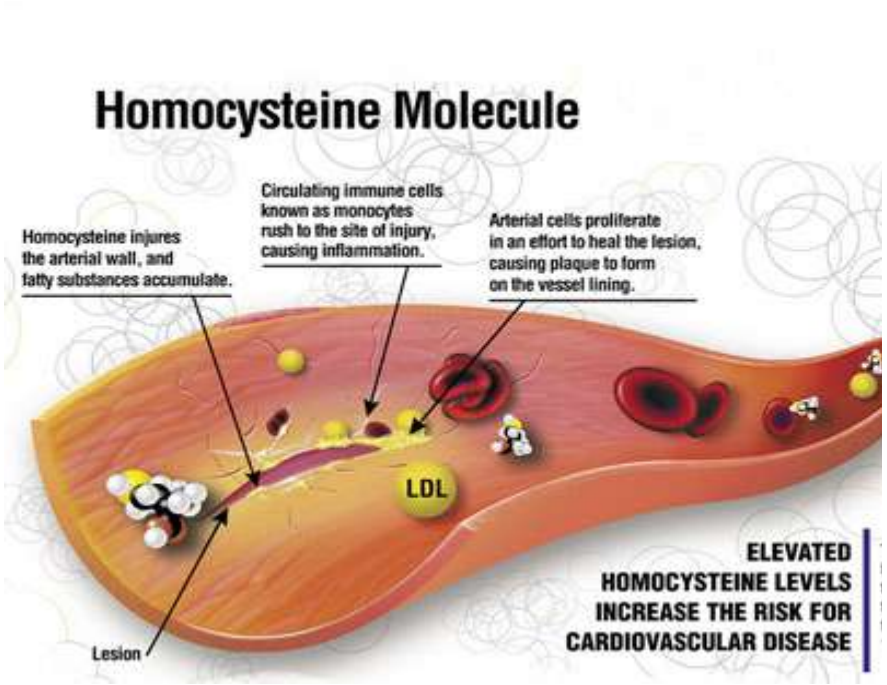


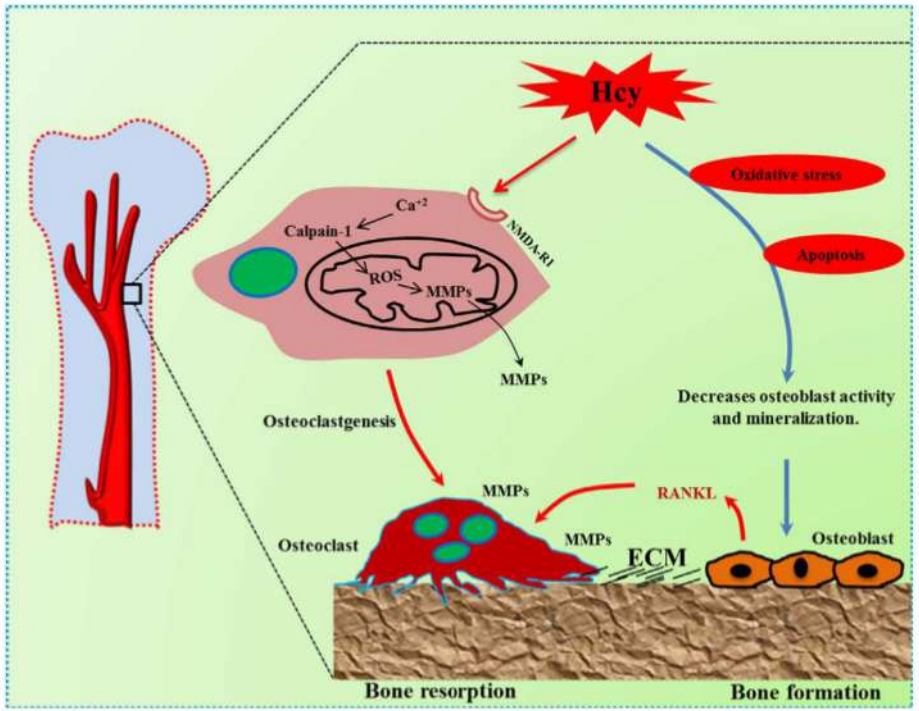


Both bone and coronary arteries are target organs for estrogens. Estrogen receptors have been detected on osteoblasts, osteoclasts and coronary artery smooth muscle cells.

Losordo et al. Circulation 1994

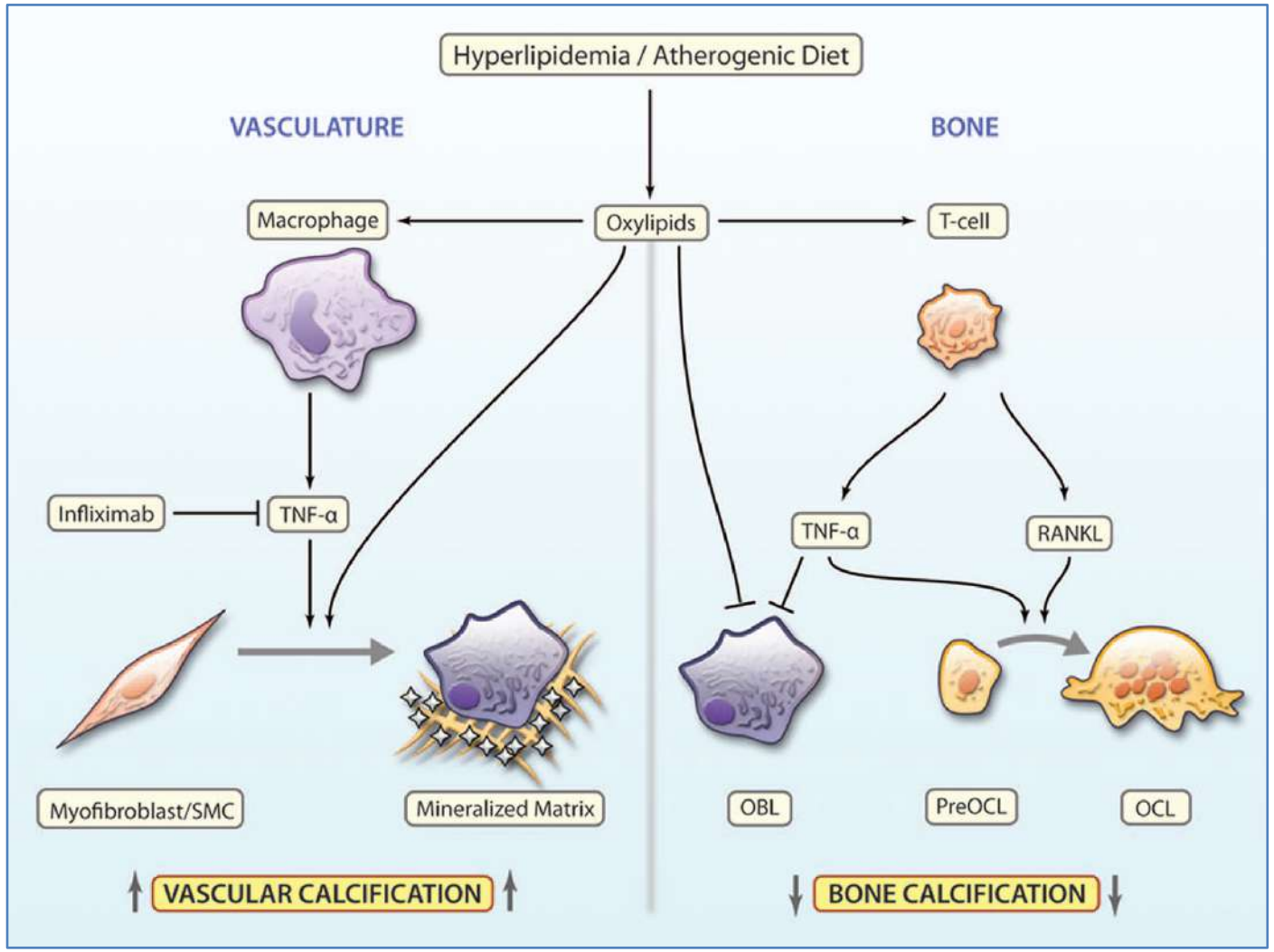
Homocysteine





Behera et al. J Cell Physiol 2016

Lipid oxidation products



Demer L et al. Circulation Research 2011

Inflammatory process

It is well-known that atherosclerosis includes an ongoing inflammatory process. Markers of inflammation such as interleukin-6 (IL-6) and C-reactive protein (CRP) have been associated with cardiovascular mortality in both sexes.

Table 3. Relative Risks of Coronary Heart Disease during Follow-up, According to the Quintile of Plasma Levels of Inflammatory Markers at Baseline.*

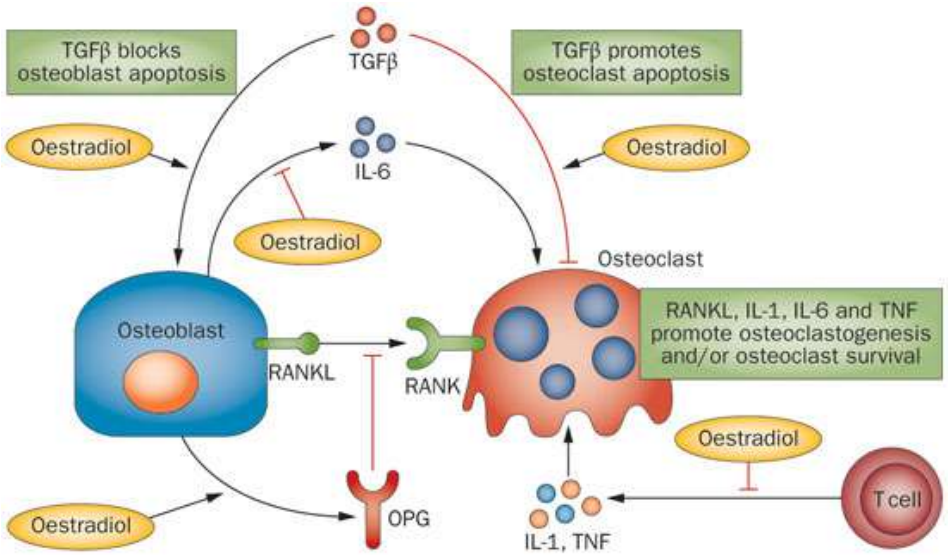
Variable†	Quintile of Plasma Level					P for Trend‡
	1	2	3	4	5	
	relative risk (95 percent confidence interval)					
Women						
Interleukin-6§						
Median — pg/ml	0.82	1.23	1.65	2.37	4.15	
Quintile value — pg/ml	<1.08	1.08–1.44	1.45–1.91	1.92–2.91	≥2.92	
Model 1 (matching factors)	1.0	1.42 (0.81–2.51)	1.15 (0.65–2.05)	1.98 (1.16–3.40)	1.92 (1.11–3.31)	0.01
Model 2 (multivariable)	1.0	1.16 (0.63–2.13)	0.96 (0.51–1.79)	1.32 (0.72–2.40)	1.33 (0.73–2.43)	0.30
Model 3 (model 2+diabetes and hypertension)	1.0	1.08 (0.58–2.03)	0.81 (0.42–1.55)	1.01 (0.54–1.89)	1.05 (0.56–1.97)	0.79
C-reactive protein						
Median — mg/liter	0.50	1.18	2.20	4.02	9.14	
Quintile value — mg/liter	<0.80	0.80–1.70	1.71–2.91	2.92–5.96	≥5.97	
Model 1 (matching factors)	1.0	1.28 (0.74–2.23)	1.03 (0.59–1.81)	1.54 (0.91–2.63)	2.18 (1.30–3.64)	<0.001
Model 2 (multivariable)	1.0	1.17 (0.64–2.14)	0.81 (0.43–1.52)	1.17 (0.64–2.14)	1.86 (1.00–3.46)	0.008
Model 3 (model 2+diabetes and hypertension)	1.0	1.23 (0.66–2.32)	0.89 (0.46–1.72)	1.22 (0.65–2.30)	1.61 (0.84–3.07)	0.08

Table 3. (Continued.)

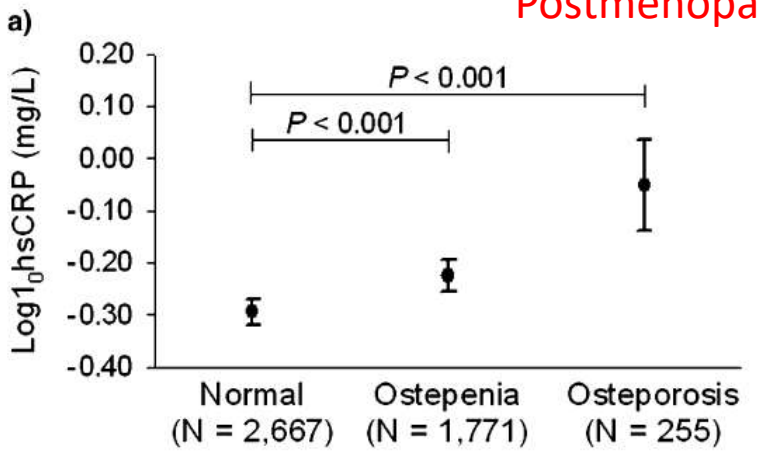
Variable†	Quintile of Plasma Level					P for Trend‡
	1	2	3	4	5	
	relative risk (95 percent confidence interval)					
Men						
Interleukin-6						
Median — pg/ml	0.69	1.09	1.53	2.43	5.73	
Quintile value — pg/ml	<0.88	0.88–1.29	1.30–1.89	1.90–3.15	≥3.16	
Model 1 (matching factors)	1.0	1.09 (0.66–1.81)	1.19 (0.72–1.98)	1.52 (0.93–2.48)	1.57 (0.95–2.57)	0.06
Model 2 (multivariable)	1.0	0.94 (0.55–1.60)	0.99 (0.59–1.69)	1.25 (0.74–2.10)	1.31 (0.78–2.21)	0.17
Model 3 (model 2+diabetes and hypertension)	1.0	0.97 (0.57–1.65)	0.98 (0.58–1.68)	1.24 (0.73–2.09)	1.31 (0.77–2.22)	0.19
C-reactive protein						
Median — mg/liter	0.27	0.60	1.08	2.05	5.24	
Quintile value — mg/liter	<0.44	0.44–0.80	0.81–1.49	1.50–2.78	≥2.79	
Model 1 (matching factors)	1.0	1.81 (1.04–3.17)	2.00 (1.15–3.50)	2.74 (1.59–4.71)	3.29 (1.91–5.65)	<0.001
Model 2 (multivariable)	1.0	1.75 (0.97–3.14)	1.83 (1.02–3.30)	2.27 (1.26–4.09)	2.73 (1.51–4.96)	0.007
Model 3 (model 2+diabetes and hypertension)	1.0	1.75 (0.97–3.16)	1.74 (0.96–3.15)	2.14 (1.18–3.88)	2.55 (1.40–4.65)	0.02

Pai J K et al. N Engl J Med 2004

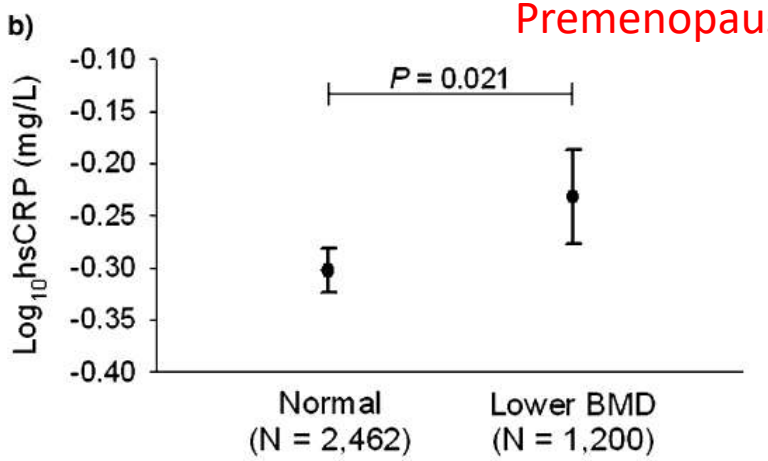
IL-6 and CRP and osteoporosis



Postmenopausal

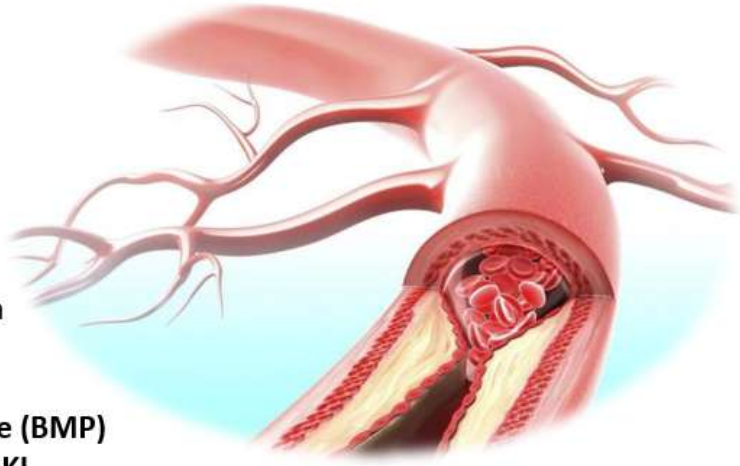


Premenopausal

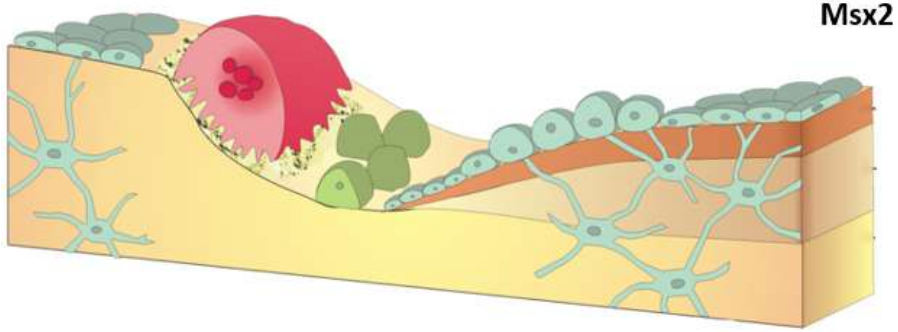


Koh JM, et al Osteoporos Int (2005)

Mineralizzazione ossea e calcificazione vascolare: due facce della stessa medaglia



Fosfatasi alcalina ossea
Proteine GLA
Osteopontina
Proteine morfogenetiche ossee (BMP)
Sistema OPG/RANK/RANKL
Segnale WNT/beta catenina
Cbfa1
Runx2
Msx2



Vascular calcification and bone mineralization processes

- Vascular calcification appears to share some common characteristics with bone mineralization.
- In particular
  - hydroxyapatite, the basic component of the mineral phase of bone, is also present in calcium deposits in atherosclerotic lesions;
  - cells with osteoblastic or osteoclastic potential have been observed in the arterial wall;
  - different proteins produced by bone cells, such as osteocalcin, osteopontin, osteoprotegerin (OPG), receptor activator of nuclear factor kappa-ligand (RANKL), and bone morphogenetic proteins (BMPs) are found in atherosclerotic lesions.

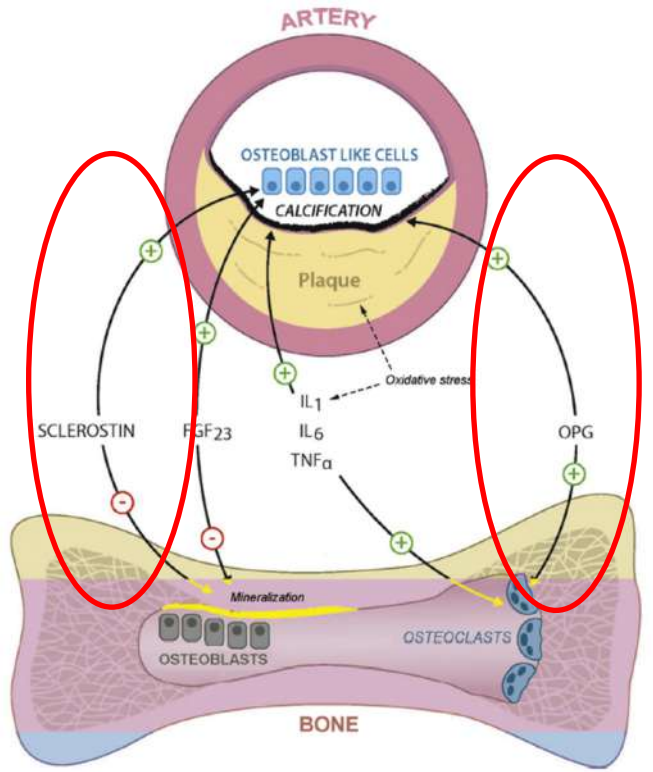
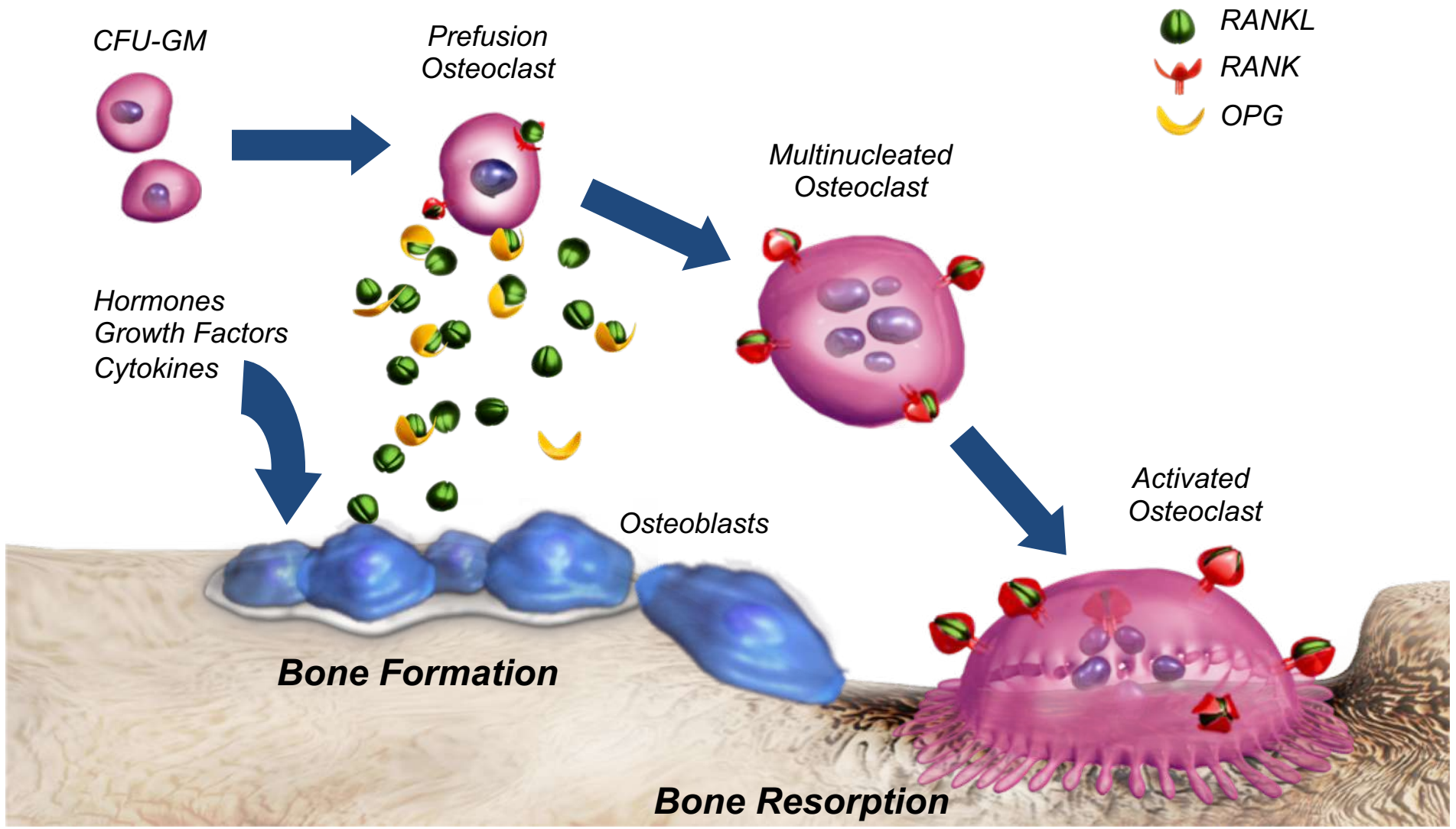


Fig. 1. Cytokines and growth factors involved in bone turnover and in calcified vascular plaque formation.

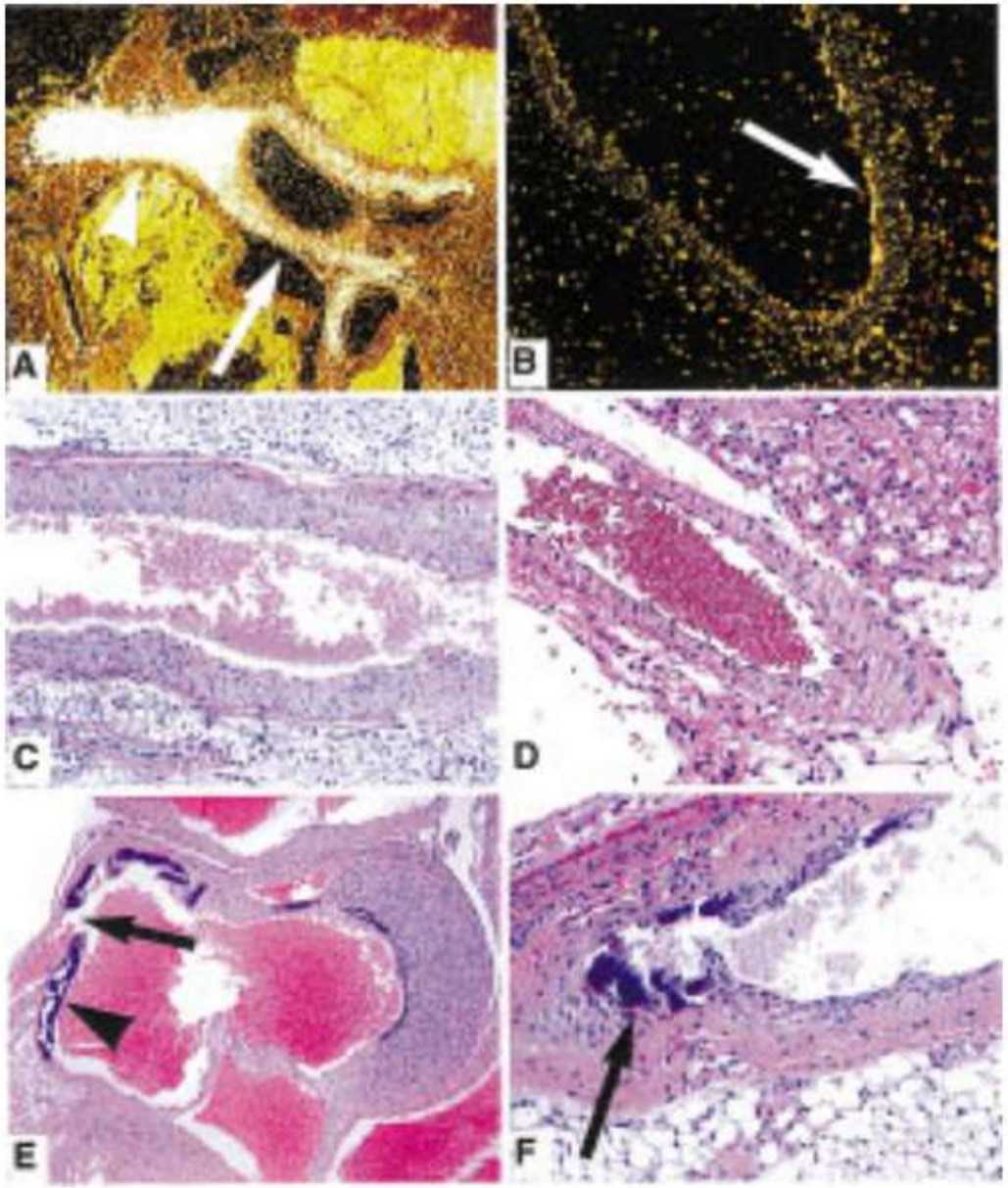
Laroche M, et al. Joint Bone Spine. 2017

OPG/RANK/RANKL system



Adapted from: Boyle WJ, et al. Nature. 2003;423:337-342.

OPG



Adolescent and adult $OPG^{-/-}$ mice exhibit a decrease in total bone density characterized by severe trabecular and cortical bone porosity, marked thinning of the parietal bones of the skull, and a high incidence of fractures.

OPG-deficient mice also exhibit medial calcification of the aorta and renal arteries.

Bucay N, et. Genes Dev. 1998

Serum Levels of OPG and Cardiovascular Disease

In humans, cardiovascular disease correlates **positively** with serum levels of OPG and **negatively** with serum levels of RANKL, the opposite of that expected from animal studies.

OPG was measured in 6265 subjects recruited from a general population without a prior myocardial infarction and ischemic stroke (the Tromsø Study). Incident myocardial infarction, ischemic stroke and mortality were registered during follow-up.

Serum OPG levels were associated with an increased risk of a myocardial infarction(1.20; 1.11–1.31), ischemic stroke (1.32; 1.18–1.47), total mortality (1.34; 1.26–1.42), death because of ischemic heart disease, (1.35; 1.18–1.54) after adjustment for age, gender, current smoking, systolic blood pressure, body mass index, high density lipoprotein cholesterol, total cholesterol, creatinine, high sensitivity C-reactive protein (CRP) and diabetes mellitus or HbA1c > 6.1%

Table 2 Hazard ratios with 95% confidence intervals (HR, 95% CI) of myocardial infarction (n = 6264), ischemic stroke (n = 6260) and total mortality (n = 6265) calculated for osteoprotegerin (OPG) tertile groups and per SD (1.13 ng mL^{-1}) increase in OPG levels. The Tromsø Study

	OPG levels					
	Tertile 1	Tertile 2	Tertile 3	P (trend)	SD OPG	P-value
Incident myocardial infarction						
Events	n = 130	n = 200	n = 311		n = 641	
Unadjusted	1.0	1.58 (1.26–1.97)	2.67 (2.17–3.28)	< 0.001	1.25 (1.21–1.29)	< 0.001
Model 1	1.0	1.14 (0.91–1.44)	1.59 (1.25–2.02)	< 0.001	1.24 (1.17–1.31)	< 0.001
Model 2*	1.0	1.03 (0.80–1.31)	1.36 (1.05–1.76)	0.008	1.20 (1.11–1.31)	< 0.001
Incident ischemic stroke						
Events	n = 41	n = 105	n = 171		n = 317	
Unadjusted	1.0	2.65 (1.85–3.80)	4.72 (3.35–6.63)	< 0.001	1.28 (1.24–1.33)	< 0.001
Model 1	1.0	1.76 (1.21–2.56)	2.39 (1.62–3.52)	< 0.001	1.30 (1.21–1.40)	< 0.001
Model 2†	1.0	1.55 (1.04–2.30)	2.03 (1.35–3.06)	0.001	1.32 (1.18–1.47)	< 0.001
Total mortality						
Events	n = 124	n = 255	n = 531		n = 910	
Unadjusted	1.0	2.09 (1.69–2.59)	4.69 (3.86–5.71)	< 0.001	1.30 (1.28–1.33)	< 0.001
Model 1	1.0	1.28 (1.02–1.60)	2.06 (1.65–2.58)	< 0.001	1.35 (1.30–1.40)	< 0.001
Model 2‡	1.0	1.18 (0.94–1.49)	1.63 (1.28–2.06)	< 0.001	1.34 (1.26–1.42)	< 0.001

Model 1: Adjusted for age and gender. Model 2: Adjusted for age, gender, current smoking, systolic blood pressure, body mass index, high-density lipoprotein cholesterol, total cholesterol, creatinine, diabetes mellitus or HbA1C > 6.1% and high sensitive C-reactive protein. *n = 5699, events 575. †n = 5696, events 284. ‡n = 5700, events 824.

However, it has not been elucidated yet whether elevation of serum OPG levels in different cardiovascular conditions represents a compensatory mechanism to prevent vascular damage or is responsible for such damage.

Vik A, et al. J Thromb Haemost. 2011

Maturitas. 2010 Dec;67(4):358-62. doi: 10.1016/j.maturitas.2010.07.013. Epub 2010 Aug 19.

The association between carotid or femoral atherosclerosis and low bone mass in postmenopausal women referred for osteoporosis screening. Does osteoprotegerin play a role?

Pennisi P[1], Russo E, Gaudio A, Veca R, D'Amico F, Mangiafico RA, Laspina M, Tringali G, Signorelli SS, Fiore CE.

Table 2
Number of femoral and carotid atherosclerotic plaques and plaques/patients ratio in normal, osteopenic and osteoporotic patients.

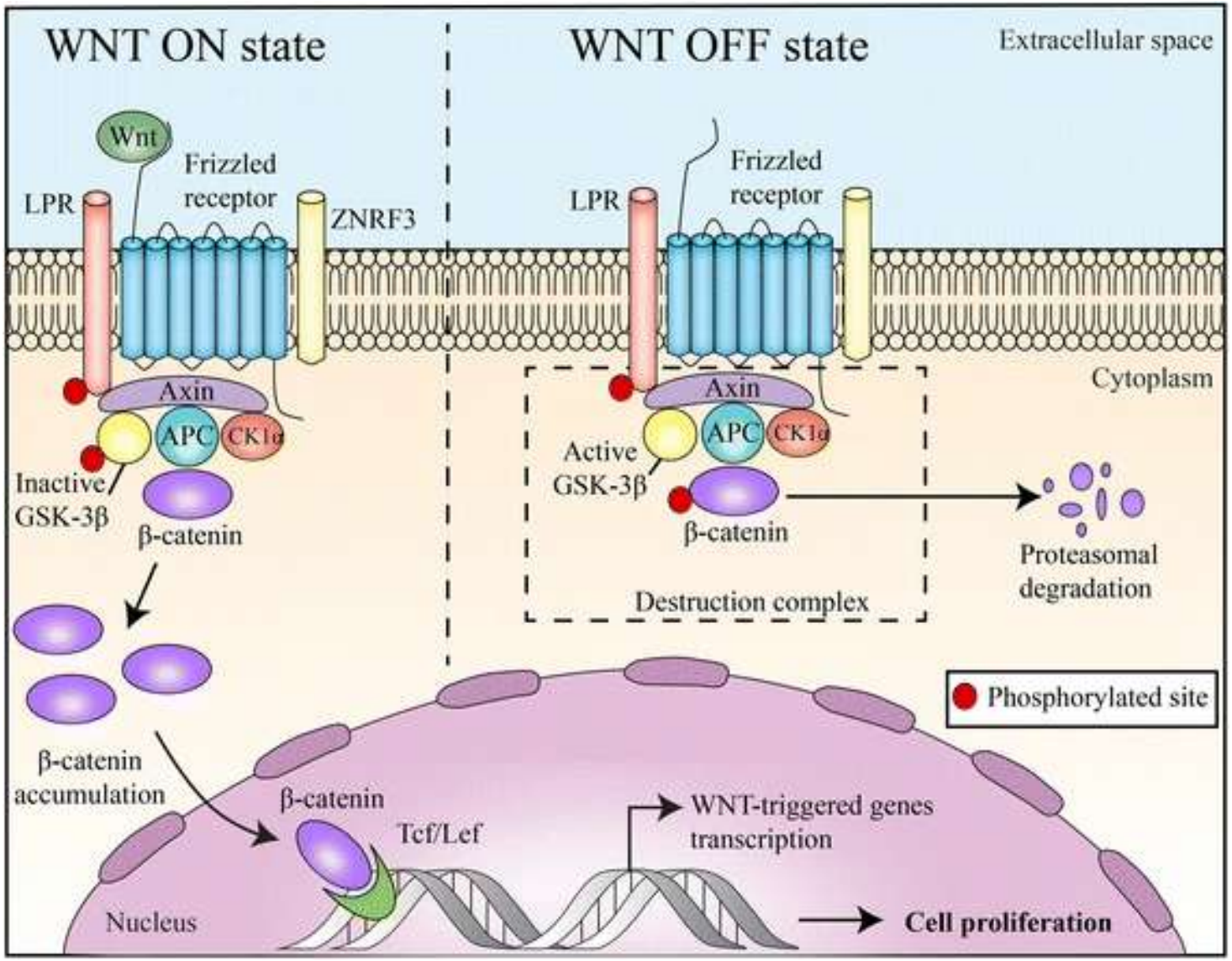
	No. of plaques	No. of patients	Total plaques	Plaques/patients ratio (mean ± SD)
Group A (normal)	1	3	3	
	2	5	10	
	3	1	3	
	4	1	4	
Total		*10*	*20*	*2.00 ± 0.94*
Group B (osteopenic)	1	1	1	
	2	2	4	
	3	2	6	
	4	8	32	
	5	0	0	
	6	2	12	
Total		*15*	*55*	*3.66 ± 1.16**
Group C (osteoporotic)	1	1	1	
	2	8	16	
	3	4	12	
	4	7	28	
	5	1	5	
	6	5	30	
	7	1	7	
Total		*27*	*99*	*3.66 ± 1.66**

* $p < 0.001$ vs Group A.

Patients with atherosclerotic plaques in both carotid and femoral districts showed a significant association between OPG serum levels and the number of plaques ($r^2 = 0.758$; $p < 0.0001$).

Our results would suggest that OPG could be useful in refining cardiovascular risk prediction in postmenopausal women.

Wnt/beta catenin signalling



Pai SG. J Hematol Oncol 2017

Table 1. Association Between Circulating Concentrations of Sclerostin and Carotid Artery Intima Media Ratio

Reference	Population	No. of patients	Overnight fasting before blood collection	Findings	Correlation coefficient (*P* value)
Positive association					
Wahlin et al[33]*	Patients with rheumatoid arthritis	54	NR	Serum sost was significantly predictive of right common carotid artery IMT severity 11 y later	NR
Shalash et al[34]†	Patients with type 2 diabetes	50	Yes	Patients with serum sost above median had significantly greater IMT	NR
Popovic et al[35]‡	Obese patients	50	Yes	Serum sost levels correlated positively with carotid artery IMT	NR
Gaudio et al[36]§	Adults >50 y assessed for metabolic bone disease	67	Yes	Serum sost levels correlated positively with carotid artery IMT	0.314 (0.03)
Kirkpantur et al[37]‖	ESRF on HD	122	Yes	Serum sost levels correlated positively with carotid artery IMT	0.459 (<0.01)
Ghardashi-Afousi et al[39]†	Diabetes	74	Yes	Decrease in serum sost in response to high intensity interval training correlated with decrease in carotid artery IMT after 12 wk	NR
Morales-Santana et al[38]†	Type 2 diabetes	78	Yes	Serum sost positively correlation with IMT	0.522 (<0.01)
Negative association					
Gaudio et al[40]†¶	Type 2 diabetes postmenopausal women	40	Yes	Serum sost inversely correlated with carotid artery IMT	−0.42 (0.006)
No association					
Fayed et al[41]*	Rheumatoid arthritis	100	Yes	No significant association between serum sost and carotid artery IMT	NR
Figurek et al[42]§	CKD	88	Yes	No association between serum sost and carotid artery IMT	NR
Genre et al[43]#	Patients with AS	163	Yes	No association between serum sost and carotid artery IMT	NR

Golledge J, et al. Arterioscler Thromb Vasc Biol. 2022

Table 3. Association Between Circulating Concentrations of Sclerostin and Arterial Stiffness or Severe Atherosclerosis

Reference	Population	No. of patients	Overnight fasting before blood collection	Finding	Correlation coefficient (*P* value)/ OR (95% CI)
Positive association					
Del Toro et al[56]*	Patients having elective coronary angiography	80	Yes	Significantly higher serum sost in patients with advanced atherosclerosis (critical coronary [≥70%] and carotid stenosis [≥50%])	NR
Zhao et al[57]†	Stage 3–5 CKD	140	Yes	Serum sost independently associated with carotid atherosclerosis	1.03 (1.00–1.05)
Teng et al[58]‡	People aged >65 y	68	Yes	Higher serum sost independently associated with significantly higher risk of PAD	1.05 (1.01–1.09)
Kim et al[59]*	Patients who underwent CABG compared with age and sex matched controls	124	NR	Serum sost levels significantly higher in patients with CHD compared with controls	NR
Fehervari et al[64]*	Heart failure	78	Yes	Serum sost correlated with aortic PWV	0.291 (0.010)
Stavrinou et al[63]†	ESRF on HD	80	Yes	Serum sost significantly higher in patients with aortic PWV >9.5 m/s	NR
Chang et al[62]§	Patients with hypertension	105	Yes	Serum sost independently associated with higher aortic PWV	1.04 (1.02–1.07)
Lin et al[61]†	ESRF having peritoneal dialysis	75	Yes	Serum sost correlated with AI	0.363 (0.001)
Yang et al[65]‖	Type 2 diabetes	125	Yes	Serum sost independently associated with higher aortic PWV	1.01 (1.00–1.10)
Jin et al[66]†	ESRF on HD	154	Yes	Serum sost correlated with and independently associated with aortic PWV	NR
Hsu et al[60]†	ESRF having renal transplants	68	Yes	Serum sost independently associated with a stiff aorta	1.05 (1.01–1.10)
Hampson et al[48]¶	Postmenopausal women	146	Yes	Participants with PWV >9 m/s significantly higher serum sost	NR
Negative association					
Milovanova et al[67]†	ESRF on HD	42	NR	Inverse correlation between serum sost and symptoms of CHD	NR
No association					
Thambiah et al[68]#	CKD	77	No	No significant association of serum sost with PWV	NR

Golledge J, et al. Arterioscler Thromb Vasc Biol. 2022

Table 4. Association Between Circulating Concentrations of Sclerostin and Cardiovascular Events

Reference	Population	No. of patients	Overnight fasting before blood collection	Finding	Hazard ratio, 95% CI
Positive association					
Kern et al[70]*	Patients having elective coronary angiography with renal impairment	205	Yes	Serum sost above median associated with a higher risk of MACE	1.75 (1.10–2.10)
Stavrinou et al[63]†	ESRF on HD	80	Yes	Tertile 3 of serum sost, for death, MI, stroke, coronary revascularization or admission	3.85 (1.50–9.85)
Mayer et al[71]*	CHD	945	Yes	Serum sost ≥589 ng/L for cardiovascular death	1.52 (1.01–2.27)
He et al[72]*	Patients who had a recent ischemic stroke compared with healthy controls	184	Yes	Significantly higher serum sost in patients with ischemic stroke	NR
Negative association					
He et al[73]*	Stable CHD undergoing percutaneous coronary intervention	310	Yes	Risk of major adverse cardiovascular and cerebrovascular events (including all-cause death, stroke, MI and repeat revascularization) for above median compared with below median serum sost	0.46 (0.25–0.85)
No association					
Ueland et al [77]‡§	Pulmonary hypertension	106	NR	No significant association with risk of death	NR
Klingenschmid et al[78]*	Random community population	706	Yes	No significant association with risk of ischemic or hemorrhagic stroke, transient ischemic attack, myocardial infarction, angina pectoris, peripheral vascular disease, and revascularization procedures	0.92 (0.78–1.08) per SD
Szulc et al[74]*	Community population of men aged ≥ 50 y	710	Yes	No significant association between serum sost and MACE	0.96 (0.79–1.16) per SD
Ress et al[75]*	Healthy community population of men aged 40 to 60 y and women aged 50 to 70 y	264	Yes	No significant association with cardiovascular events including MI or acute coronary syndrome, coronary angioplasty or bypass surgery, stroke, angioplasty, stenting or bypass surgery for PAD, carotid endarterectomy or carotid artery stenting	NR

Golledge J, et al. Arterioscler Thromb Vasc Biol. 2022

ARCH: adverse events

Table 2. Adverse Events.

Event	Month 12: Double-Blind Period		Primary Analysis: Double-Blind and Open-Label Period*	
	Alendronate (N=2014)	Romosozumab (N=2040)	Alendronate to Alendronate (N=2014)	Romosozumab to Alendronate (N=2040)
	number of patients (percent)			
Adverse event during treatment	1584 (78.6)	1544 (75.7)	1784 (88.6)	1766 (86.6)
Back pain†	228 (11.3)	186 (9.1)	393 (19.5)	329 (16.1)
Nasopharyngitis†	218 (10.8)	213 (10.4)	373 (18.5)	363 (17.8)
Serious adverse event	278 (13.8)	262 (12.8)	605 (30.0)	586 (28.7)
Adjudicated serious cardiovascular event‡	38 (1.9)	50 (2.5)	122 (6.1)	133 (6.5)
Cardiac ischemic event	6 (0.3)	16 (0.8)	20 (1.0)	30 (1.5)
Cerebrovascular event	7 (0.3)	16 (0.8)	27 (1.3)	45 (2.2)
Heart failure	8 (0.4)	4 (0.2)	23 (1.1)	12 (0.6)
Death	12 (0.6)	17 (0.8)	55 (2.7)	58 (2.8)
Noncoronary revascularization	5 (0.2)	3 (0.1)	10 (0.5)	6 (0.3)
Peripheral vascular ischemic event not requiring revascularization	2 (<0.1)	0	5 (0.2)	2 (<0.1)
Death	21 (1.0)§	30 (1.5)	90 (4.5)§	90 (4.4)
Event leading to discontinuation of trial regimen	64 (3.2)	70 (3.4)	146 (7.2)	133 (6.5)
Event leading to discontinuation of trial participation	27 (1.3)	30 (1.5)	43 (2.1)	47 (2.3)
Event of interest¶				
Osteoarthritis‖	146 (7.2)	138 (6.8)	268 (13.3)	247 (12.1)
Hypersensitivity	118 (5.9)	122 (6.0)	185 (9.2)	205 (10.0)
Injection-site reaction**	53 (2.6)	90 (4.4)	53 (2.6)	90 (4.4)
Cancer	28 (1.4)	31 (1.5)	85 (4.2)	84 (4.1)
Hyperostosis††	12 (0.6)	2 (<0.1)	27 (1.3)	23 (1.1)
Hypocalcemia	1 (<0.1)	1 (<0.1)	1 (<0.1)	4 (0.2)
Atypical femoral fracture‡	0	0	4 (0.2)	2 (<0.1)
Osteonecrosis of the jaw‡	0	0	1 (<0.1)	1 (<0.1)

Saag KG, et al. N Engl J Med 2017

Abstract: Background: Cardiovascular safety concerns for major cardiovascular events (MACE) were raised during the clinical trials of romosozumab. We aimed to evaluate the cardiovascular safety profile of romosozumab in a large pharmacovigilance database. **Methods:** All cases reported between January 2019 and December 2020 where romosozumab was reported were extracted from the Food and Drug Administration Adverse Event Reporting System (FAERS). The outcome of interest was MACE (myocardial infarction (MI), stroke, or cardiovascular death). A disproportionality analysis was conducted by estimating the reporting odds ratios (RORs) and 95% confidence intervals. Disproportionality analyses were stratified by sex and reporting region (US, Japan, other). **Results:** Of the 1995 eligible cases with romosozumab, the majority (*N* = 1188; 59.5%) originated from Japan. Overall, 206 suspected MACE reports were identified, of which the majority (n = 164; 13.8%) were from Japan, and 41 (5.2%) were from the United States (US). Among Japanese reports, patients were older and more frequently male than reports from the US. Similarly, cases with a reported MACE were older and had higher reports of cardioprotective drugs than those without cardiovascular events. Elevated reports for MACE (ROR 4.07, 95% CI: 2.39–6.93) was identified overall, which was primarily driven by the significant disproportionality measures in the Japanese reports. **Conclusions:** The current pharmacovigilance study identified a potential signal for elevated MACE, particularly in Japan. The results support the current safety warnings from the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to avoid use in high-risk patients.

Journal of *Clinical Medicine*

Article

Cardiovascular Safety Profile of Romosozumab: A Pharmacovigilance Analysis of the US Food and Drug Administration Adverse Event Reporting System (FAERS)

Annika Vestergaard Kvist [1,†], Junaid Faruque [2,†], Enriqueta Vallejo-Yagüe [1], Stefan Weiler [1,3], Elizabeth M. Winter [4] and Andrea M. Burden [1,*]

	Romosozumab	Romosozumab	All other Drugs	All other Drugs	
	Event	No Event	Event	No Event	ROR (95% CI)
MACE	206	1789	84,723	2,996,511	4.07 (2.39–6.93)
Myocardial infarction	42	1953	21,253	3,059,981	3.10 (1.43–6.72)
Stroke	84	1911	38,489	3,042,745	3.47 (1.81–6.69)
Cardiovascular death	86	1909	28,070	3,053,164	4.90 (2.55–9.40)
Other cardiovascular event	58	1937	56,239	3,024,995	1.61 (0.79–3.29)
General cardiac events	16	1979	16,880	3,064,354	1.47 (0.55–3.92)
Bleeding	19	1976	20,699	3,060,535	1.42 (0.55–3.64)
Thrombosis	23	1972	19,753	3,061,481	1.81 (0.74–4.44)

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4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

EVENITY è indicato per il trattamento dell'osteoporosi severa in donne in post-menopausa ad alto rischio di frattura (vedere paragrafo 5.1).

4.2 Posologia e modo di somministrazione

Il trattamento deve essere iniziato e monitorato da medici specialisti con esperienza nella gestione dell'osteoporosi.

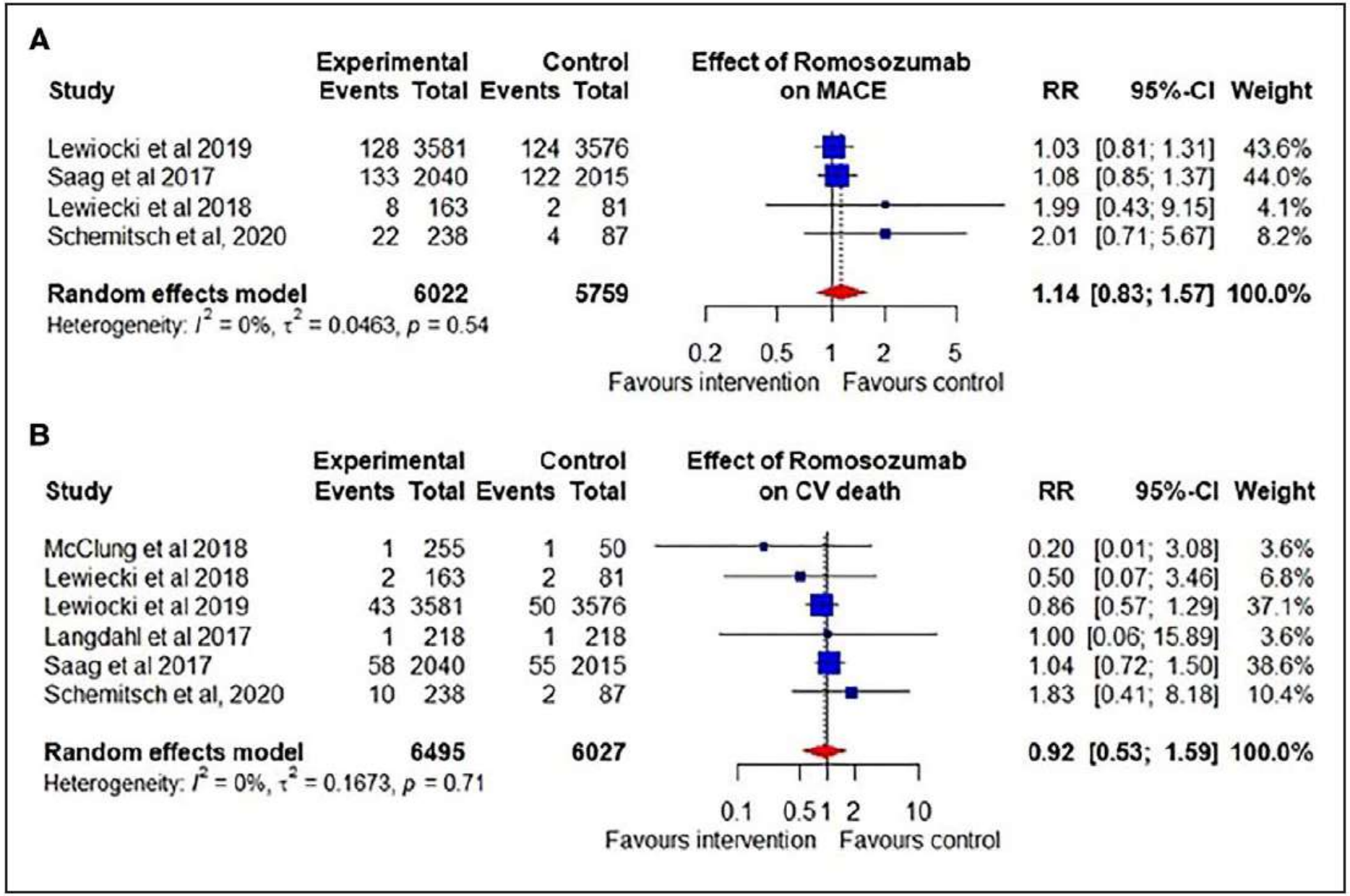
Posologia

La dose raccomandata è di 210 mg di romosozumab (somministrati come due iniezioni sottocutanee da 105 mg ciascuna) una volta al mese per 12 mesi.

Le pazienti devono assumere un'adeguata integrazione di calcio e vitamina D prima e durante il trattamento (vedere paragrafi 4.3 e 4.4).

4.3 Controindicazioni

- Ipersensibilità al principio attivo o ad uno qualsiasi degli eccipienti elencati al paragrafo 6.1 (vedere paragrafo 4.4)
- Ipocalcemia (vedere paragrafo 4.4)
- Anamnesi di infarto miocardico o ictus (vedere paragrafo 4.4)

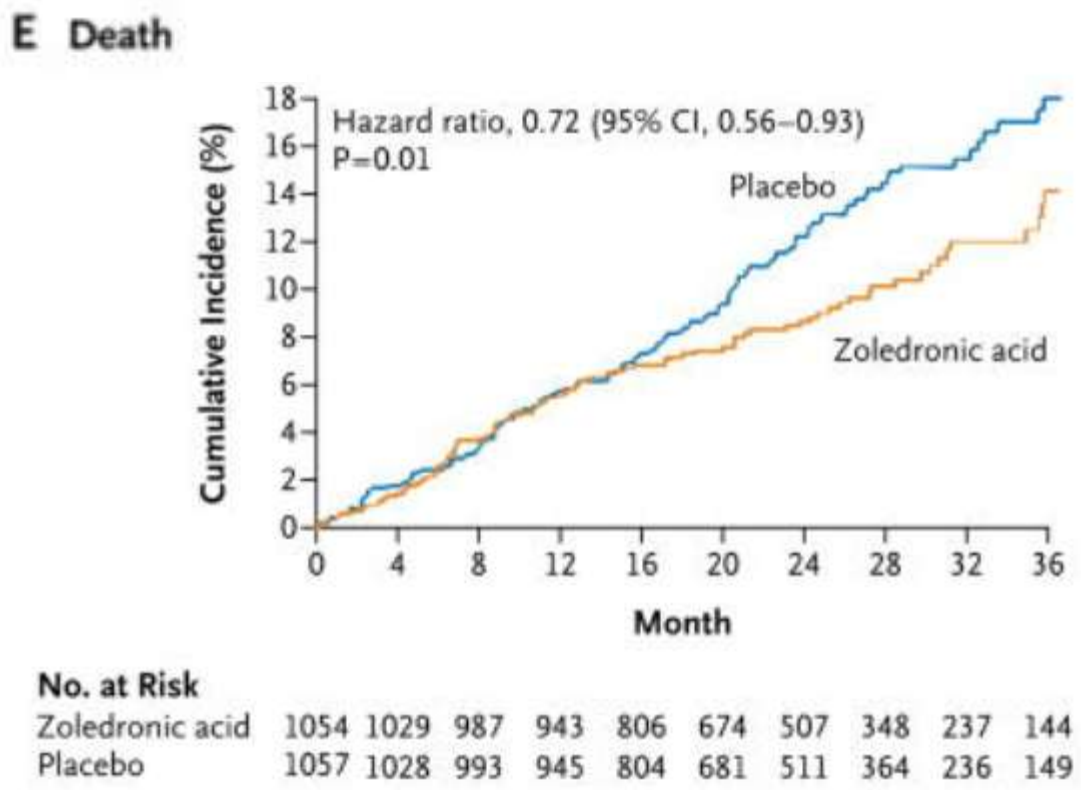


Golledge J, et al. Arterioscler Thromb Vasc Biol. 2022

Zoledronic acid and mortality

In this randomized, double-blind, placebo-controlled trial (HORIZON), 1065 patients were assigned to receive yearly intravenous zoledronic acid (at a dose of 5 mg), and 1062 patients were assigned to receive placebo.

In the safety analysis, 101 of 1054 patients in the zoledronic acid group (9.6%) and 141 of 1057 patients in the placebo group (13.3%) died, a reduction of 28% in deaths from any cause in the zoledronic-acid group (P = 0.01).



Lyles KW, et al. N Engl J Med. 2007

Hazard ratio 0.60 (95% CI, 0.36 to 1.00)

Adverse event data from that a 6 –year study, double-blind trial of 2000 osteopenic women aged >65 years They were randomly assigned to receive four infusions of either zoledronate 5 mg or normal saline at 18-month intervals. Supplements of vitamin D, but not calcium, were provided.

Hazard ratio 0.76 (95% CI,0.53 to 1.08)

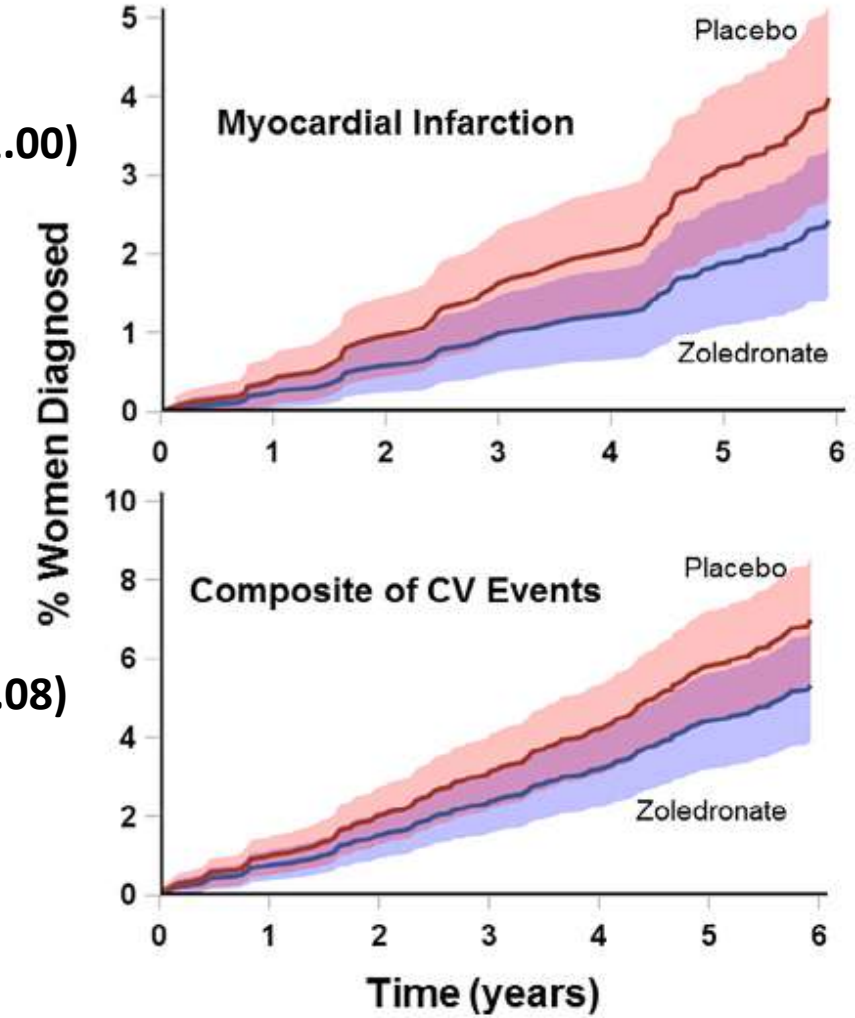


Fig. 2. (Upper panel) Cox proportional hazard function of time to first myocardial infarction in osteopenic women randomized to zoledronate or placebo. Shaded areas indicate 95% confidence intervals. Hazard ratio 0.60 (95% CI, 0.36 to 1.00); rate ratio 0.58 (95% CI, 0.35 to 0.94). (Lower panel) Cox proportional hazard function of time to first event of a composite CV endpoint (consisting of sudden death, myocardial infarction, coronary artery revascularization, or stroke. Hazard ratio 0.76 (95% CI, 0.53 to 1.08); rate ratio 0.72 (95% CI, 0.53 to 0.98). CV = cardiovascular.

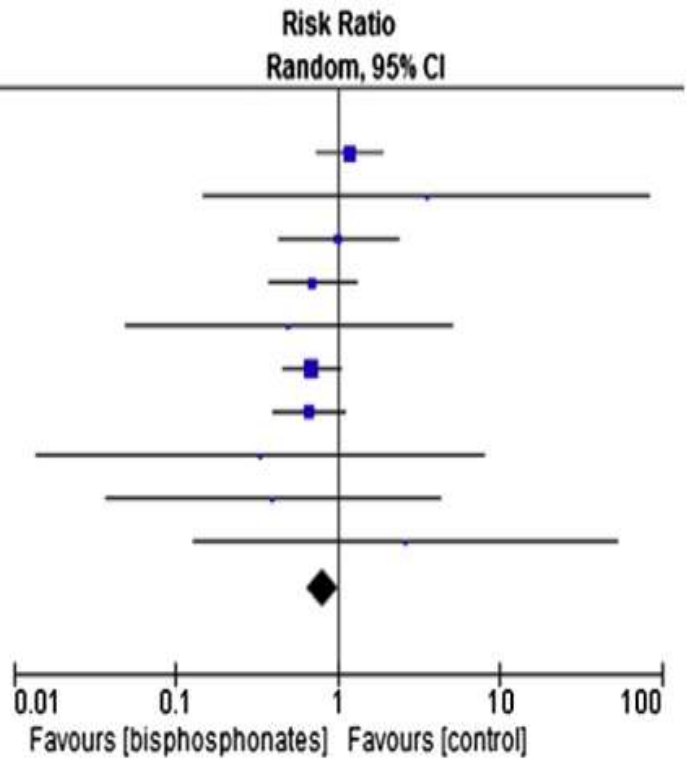
Reid IR, et al. J Bone Miner Res. 2020

61 trials reporting the effects of bisphosphonates on the outcomes of interest were included.

Cardiovascular mortality

	Bisphosphonates Events	Total	Control Events	Total	Weight	Risk Ratio Random, 95% CI
Cardiovascular mortality						
Black 2007	39	3862	33	3852	24.8%	1.18 [0.74, 1.87]
Chailurkit 2003	1	32	0	38	0.5%	3.55 [0.15, 84.14]
Dearnaley 2003	10	155	10	156	7.4%	1.01 [0.43, 2.35]
Denham 2014	16	536	23	537	13.5%	0.70 [0.37, 1.30]
Kraj 2004	1	23	2	23	1.0%	0.50 [0.05, 5.14]
Lyles 2007	36	1054	52	1057	30.5%	0.69 [0.46, 1.05]
Mason 2007	22	254	33	254	20.3%	0.67 [0.40, 1.11]
Palomba 2008	0	45	1	45	0.5%	0.33 [0.01, 7.97]
Ravn 1996	2	150	1	30	0.9%	0.40 [0.04, 4.27]
Stoch 2009	2	114	0	59	0.6%	2.61 [0.13, 53.47]
Total (95% CI)		6225		6051	100.0%	0.81 [0.64, 1.02]
Total events	129		155			

Heterogeneity: Tau² = 0.00; Chi² = 6.32, df = 9 (P = 0.71); I² = 0%
Test for overall effect: Z = 1.79 (P = 0.07)
Test for subgroup differences: Not applicable



No effect of bisphosphonate treatment on cardiovascular events was found (pooled RR of 20 trials 1.03; 95%CI 0.91-1.17), while a lower risk for cardiovascular mortality was observed in patients treated with bisphosphonates (pooled RR of 10 trials 0.81; 95% CI 0.64-1.02) although not statistically significant.

Kranenburg G, et al. Atherosclerosis. 2016

Retrospective population-based study of patients with hip fracture.
A total of 4594 treated patients were matched with 13,568 non treated patients.

Results of Cox regression analysis revealed that alendronate was associated with a significantly lower risk of 1-year cardiovascular mortality (HR 0.33; 95% CI, 0.17 to 0.65) and incident myocardial infarction (HR 0.55; 95% CI, 0.34 to 0.89), whereas marginally significant reduction in risk of stroke was observed at 5 years and 10 years.

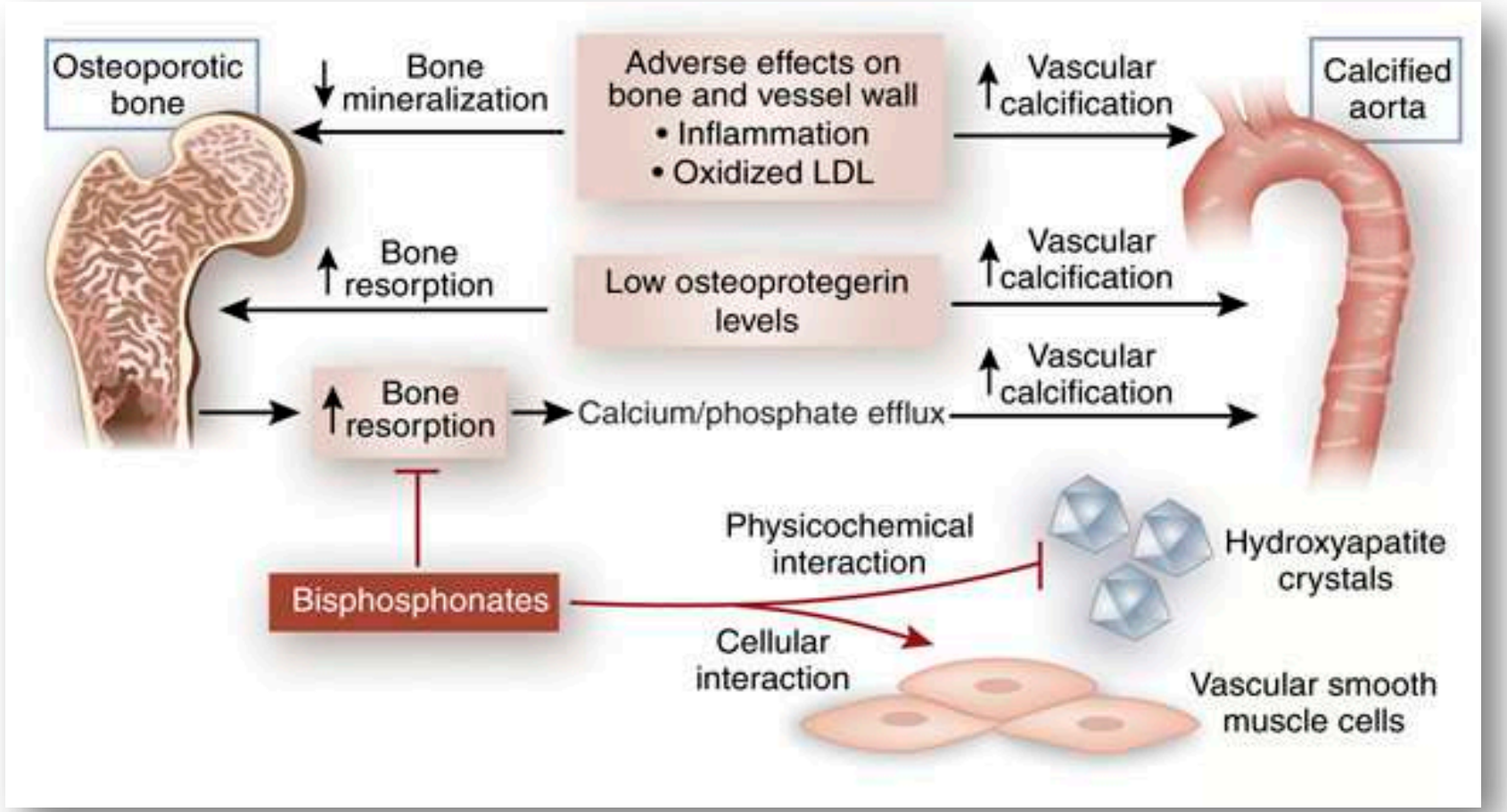
Sing CW, et al. J Bone Miner Res. 2018.

Table 2. Risk of CVE with N-BPs

Group	Subjects (*n*)	Events (*n*)	Mortality/incidence rate, per 10,000 person-years	Hazard ratio (95% CI)	*p*
1-Year follow-up					
Cardiovascular mortality					
Non-exposed	13,568	130	108.9 (91–129.3)	1	–
Alendronate	3081	10	34.7 (16.6–63.7)	0.33 (0.17–0.65)	0.001
All N-BPs	3778	13	37 (19.7–63.2)	0.35 (0.20–0.63)	<0.001
Incident myocardial infarction					
Non-exposed	12,708	151	135.3 (114.5–158.6)	1	–
Alendronate	2998	20	71.4 (43.6–110.3)	0.55 (0.34–0.89)	0.014
All N-BPs	3679	22	64.4 (40.3–97.4)	0.51 (0.32–0.81)	0.004
Incident stroke					
Non-exposed	10,188	229	257.1 (224.9–292.7)	1	–
Alendronate	2696	49	194.6 (144–257.3)	0.78 (0.56–1.08)	0.133
All N-BPs	3299	56	182.8 (138.1–237.4)	0.70 (0.52–0.95)	0.022
3-Year follow-up					
Cardiovascular mortality					
Non-exposed	13,568	301	102.7 (91.4–115)	1	–
Alendronate	3081	36	47.3 (33.1–65.4)	0.48 (0.33–0.69)	<0.001
All N-BPs	3778	45	48.4 (35.3–64.8)	0.47 (0.34–0.66)	<0.001
Incident myocardial infarction					
Non-exposed	12,708	364	132.9 (119.6–147.3)	1	–
Alendronate	2998	57	77.2 (58.5–100.1)	0.63 (0.47–0.85)	0.002
All N-BPs	3679	64	71.1 (54.7–90.8)	0.58 (0.44–0.76)	<0.001
Incident stroke					
Non-exposed	10,188	526	242.5 (222.2–264.1)	1	–
Alendronate	2696	132	199.7 (167.1–236.9)	0.88 (0.71–1.09)	0.226
All N-BPs	3299	152	189.3 (160.4–221.9)	0.80 (0.66–0.98)	0.027
5-Year follow-up					
Cardiovascular mortality					
Non-exposed	13,568	386	99 (89.4–109.4)	1	–
Alendronate	3081	56	53.3 (40.3–69.2)	0.55 (0.40–0.75)	<0.001
All N-BPs	3778	69	53.5 (41.6–67.7)	0.54 (0.41–0.72)	<0.001
Incident myocardial infarction					
Non-exposed	12,708	506	139 (127.2–151.7)	1	–
Alendronate	2998	100	98.4 (80–119.6)	0.70 (0.55–0.90)	0.005
All N-BPs	3679	121	96.9 (80.4–115.8)	0.69 (0.55–0.86)	0.001
Incident stroke					
Non-exposed	10,188	647	225.3 (208.3–243.4)	1	–
Alendronate	2696	168	185.1 (158.2–215.3)	0.82 (0.67–1.00)	0.049
All N-BPs	3299	198	178.5 (154.5–205.2)	0.77 (0.65–0.93)	0.006
10-Year follow-up					
Cardiovascular mortality					
Non-exposed	13,568	429	96.3 (87.4–105.8)	1	–
Alendronate	3081	78	63.9 (50.5–79.7)	0.59 (0.44–0.79)	<0.001
All N-BPs	3778	92	60.8 (49–74.5)	0.58 (0.44–0.75)	<0.001
Incident myocardial infarction					
Non-exposed	12,708	580	139.6 (128.5–151.5)	1	–
Alendronate	2998	123	104.2 (86.6–124.3)	0.71 (0.56–0.89)	0.004
All N-BPs	3679	145	99.1 (83.6–116.6)	0.67 (0.54–0.83)	<0.001
Incident stroke					
Non-exposed	10,188	694	212 (196.5–228.4)	1	–
Alendronate	2696	183	173.9 (149.6–200.9)	0.83 (0.69–1.01)	0.065
All N-BPs	3299	220	169.6 (147.9–193.5)	0.79 (0.66–0.94)	0.008

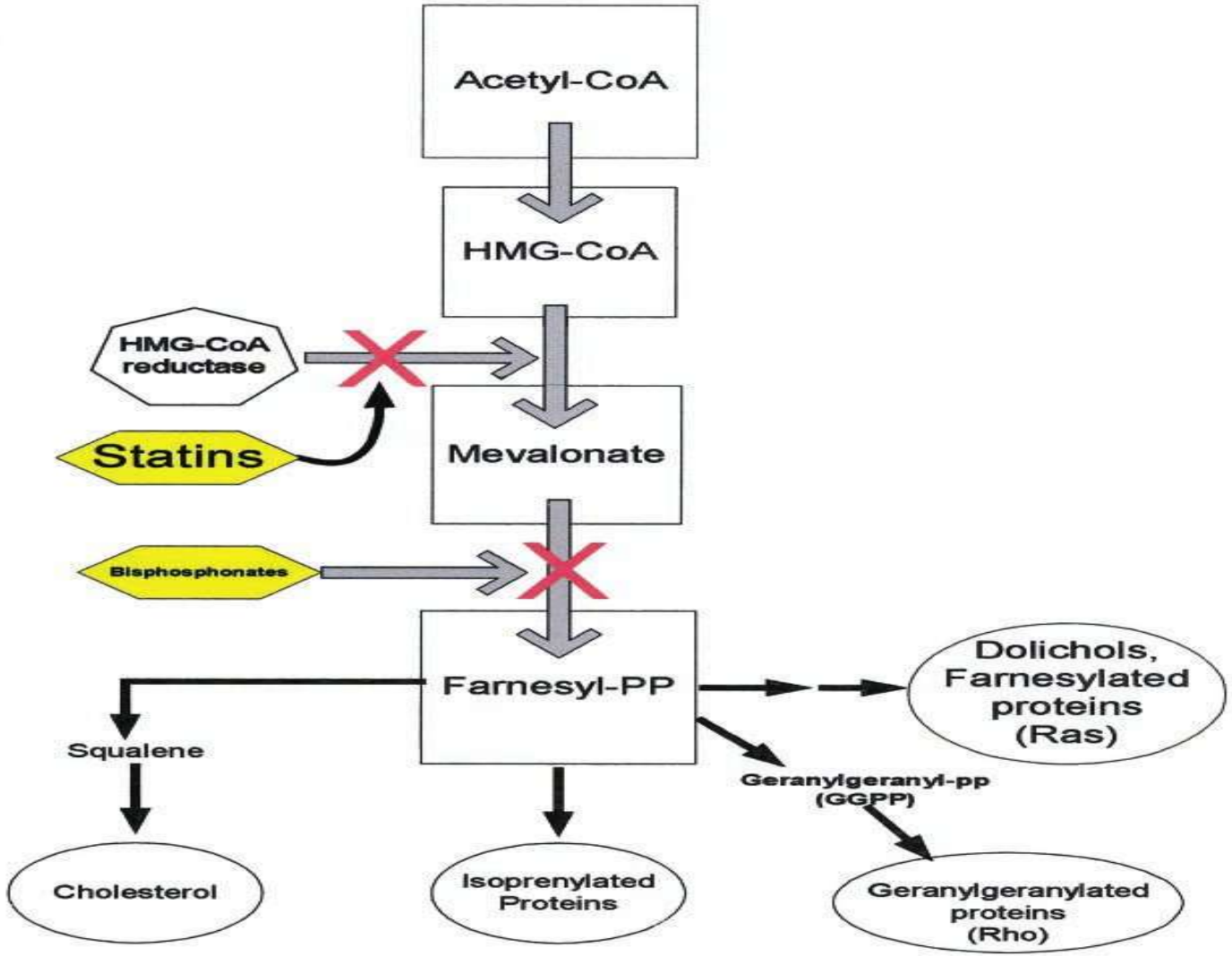
Prevention of vascular calcification with bisphosphonates without affecting bone mineralization: a new challenge?

Ellen G. Neven[1], Marc E. De Broe[1] and Patrick C. D'Haese[1]



Kidney International 2009

Bisphosphonates and lipids

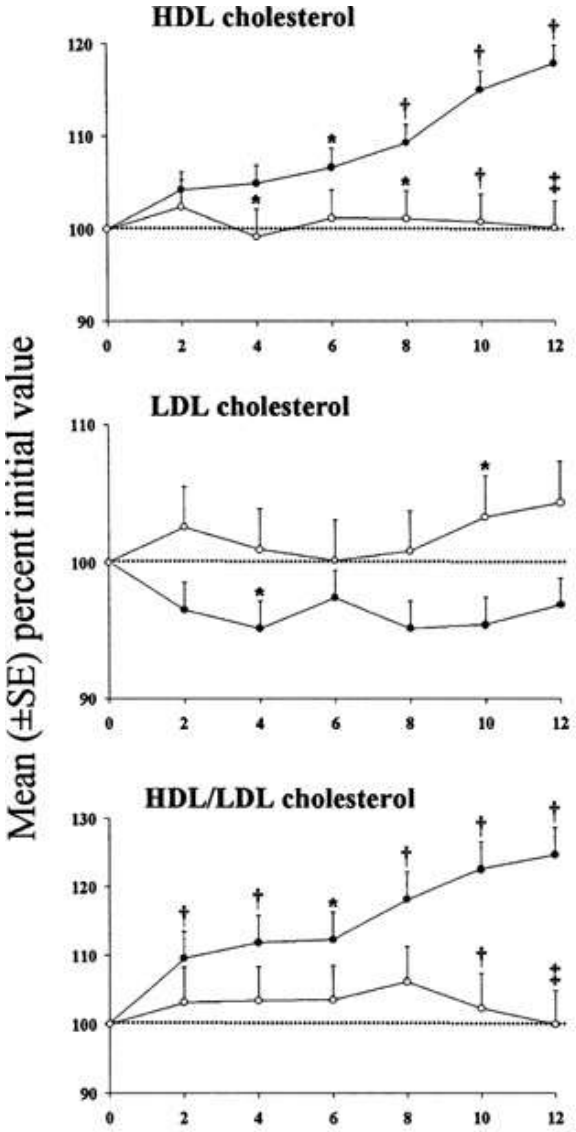


McFarlane SI, et al. J Clin Endocrinol Metab. 2002

Bisphosphonates and lipids

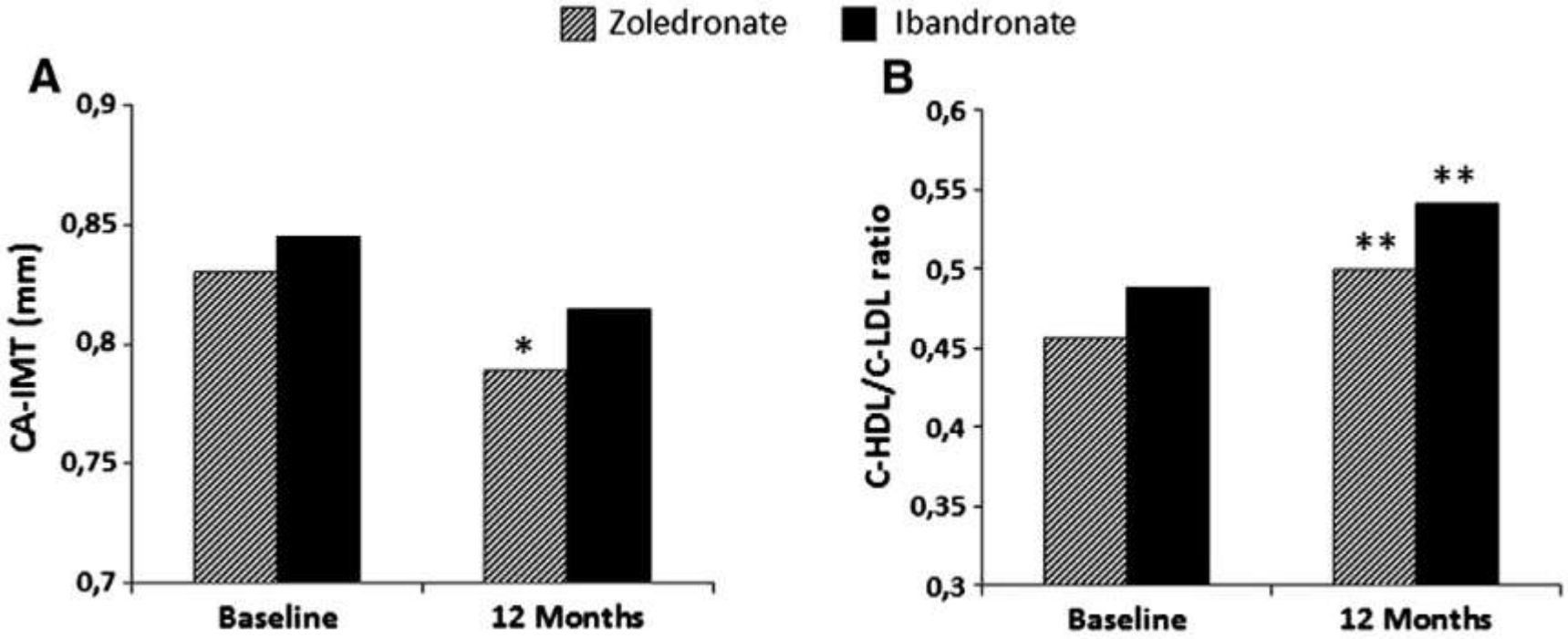
The study includes 87 postmenopausal women with moderate to severe osteoporosis. The patients were randomly assigned to intravenous (iv) infusion of 50 mg of the aminobisphosphonate Neridronate dissolved in 100 ml of saline solution every 2 months for a year.

In these patients serum total cholesterol and serum triglycerides showed marginal decreases, which were occasionally significant. LDL-C and Apo B fell by 5-6% and these changes were statistically significant at most time points. Apo A-I and HDL-C rose progressively with time. At the 12th month, HDL-C rose 17-18% ($p < 0.0001$) above the baseline values



Adami S, et al. J Bone Miner Res. 2000

Sixty postmenopausal osteoporotic women were randomly assigned to 1-year treatment with zoledronate 5 mg i.v. annually or ibandronate 3 mg i.v. every 3 months.



The osteoporotic women treated with zoledronate showed a greater reduction in CA-IMT than those treated with ibandronate. HDL-C and HDL-C/LDL-C ratio showed a significant ($p < 0.01$) increase in the 2 groups, whereas, LDL-C showed a reduction in the two groups which, however, reached statistical significance ($p < 0.05$) only in the zoledronate group.

Gonnelli S, et al. Bone. 2014

Conclusioni

- Osteoporosi e aterosclerosi sono due importanti problemi di salute pubblica.
- Numerosi dati supportano un link causale tra queste due condizioni patologiche.
- La comprensione dei meccanismi fisiopatologici condivisi da aterosclerosi e osteoporosi può potenzialmente influenzare la ricerca di molecole/farmaci per la prevenzione e il trattamento di queste due condizioni cliniche molto comuni.

Grazie per la vostra attenzione