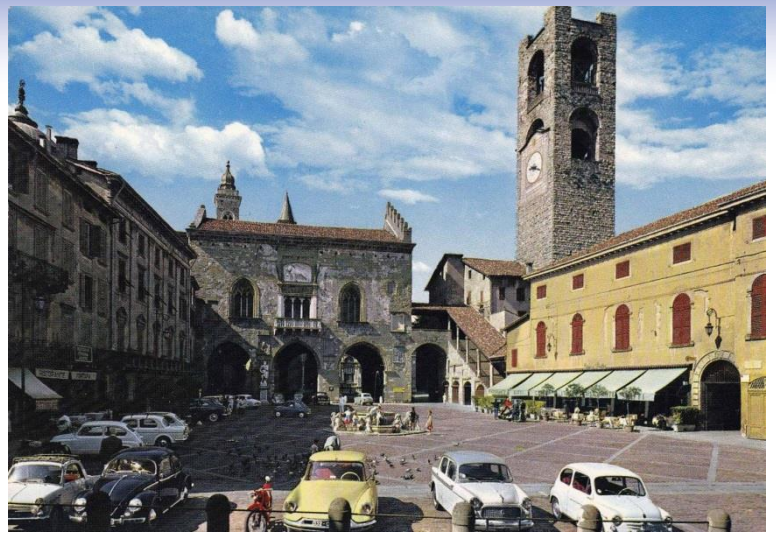
Osteoporosis and cardiovascular diseases



- Prof Dr Willem F Lems
- Department of Rheumatology
- EULAR Centre of Excellence:

- VU University medical centre and Reade,
- Amsterdam, the Netherlands

Osteoporosis and cardiovascular diseases

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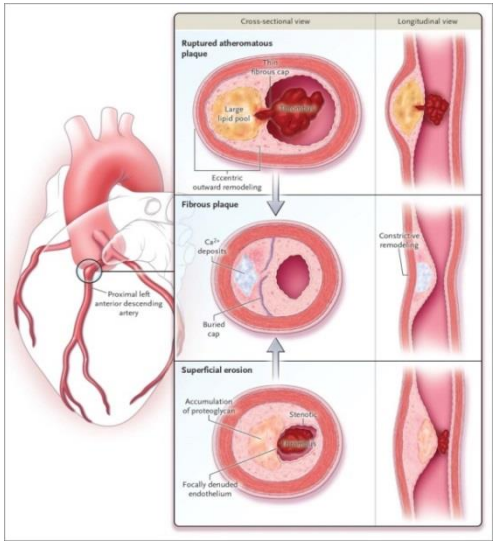
DISCLOSURES

- Speaker’s fee: Amgen, Eli Lilly, Merck.
- Advisory boards: Amgen, Eli Lilly, Merck.
-
-
-

Association between Osteoporosis and Cardiovascular Diseases? Fact or Fiction?

- Part 1: Is fracture risk elevated in patients with CVD?
- Part 2: Is CVD-risk elevated in osteoporotic patients?
- Part 3: Osteoporosis and CHD in rheumatic diseases
- Part 4: Pathogenesis
- Part 5: Consequences for daily practice



The NEW ENGLAND JOURNAL of MEDICINE

Risk Factors Cardiovasculair Events and Osteoporotic Fractures (1)

	Cardiovascular events	Osteoporotic Fractures
Age	+++	+++
Hypercholesterolaemia	+	-
Hypertension	+	-
Familiary	(+)	(+)
Smoking		
Diabetes Mellitus		
Immobility		
Fall events		
Vitamin D deficiency		
Postmenopausal status		
Low Grade inflammation		

Risk Factors Cardiovasculair Events and Osteoporotic Fractures (2)

	Cardiovascular events	Osteoporotic Fractures
Age	+++	+++
Hypercholesterolaemia	+	-
Hypertension	+	-
Familiary	(+)	(+)
Smoking	+	+
Diabetes Mellitus	+	+ (!)
Immobility	+	+
Fall events		
Vitamin D deficiency		
Postmenopausal status		
Low Grade inflammation		

Risk Factors Cardiovasculair Events and Osteoporotic Fractures (3)

	Cardiovascular events	Osteoporotic Fractures
Age	+++	+++
Hypercholesterolaemia	+	-
Hypertension	+	-
Familiary	(+)	(+)
Smoking	+	+
Diabetes Mellitus	+	+ (!)
Immobility	+	+
Fall events	-	+
Vitamin D deficiency	?	+
Postmenopausal status	+	+
Low Grade inflammation	++	++

Original Investigation | December 11/25, 2006

High-Sensitivity C-Reactive Protein and Risk of Nontraumatic Fractures in the Bruneck Study FREE

Georg Schett, MD; Stefan Kiechl, MD; Siegfried Weger, MD; Angelo Pederiva, MD; Agnes Mayr, MD; Manuele Petrangeli, MD; Friedrich Oberhollenzer, MD; Rolando Lorenzini, MD; Kurt Redlich, MD; Roland Axmann, MD; Jochen Zwerina, MD; Johann Willeit, MD

Arch Int Med

Published in final edited form as:
Am J Cardiol. 2007 June 1; 99(11): 1500–1503.

Comparison of Characteristics of Future Myocardial Infarctions in Women with Baseline High versus Baseline Low Levels of High-Sensitivity C-Reactive Protein

Sandeep Bansal, MD and **Paul M. Ridker, MD, MPH**
Center for Cardiovascular Disease Prevention, Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Table 3. Incidence of Nontraumatic Fractures According to Tertile Group for hs-CRP Level*

Variable	Tertile Group for hs-CRP Level		
	1 (Low)	2 (Medium)	3 (High)
hs-CRP level, median (range), mg/L	0.70 (0.10-1.08)	1.70 (1.09-2.52)	4.60 (2.53-89.80)
No. of nontraumatic fractures	5	14	50
Follow-up, person-years*	3947	3726	3589
Incidence, events per 1000 person-years	1.3	3.8	13.9

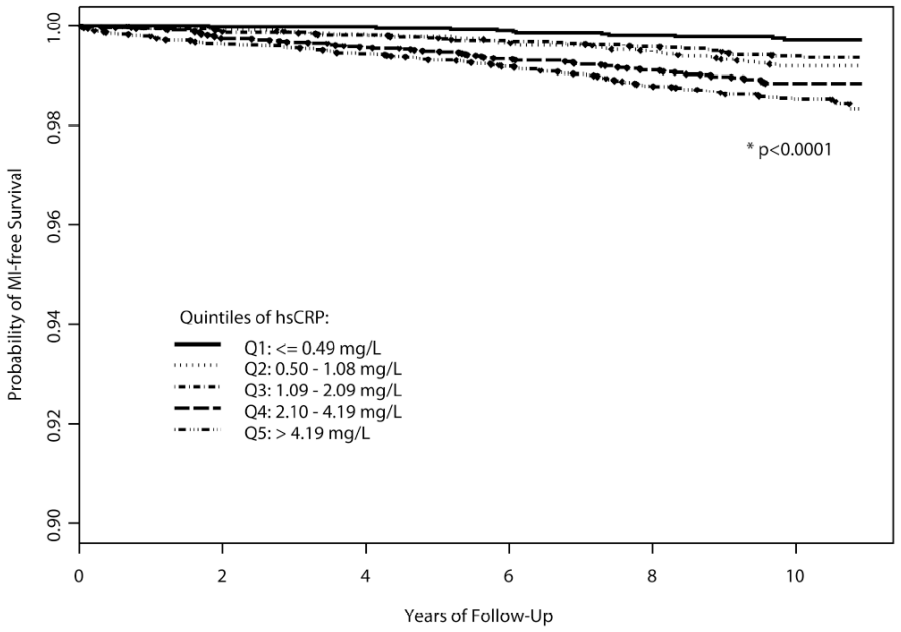


Figure.
MI-free Survival According to Quintile of Baseline hsCRP

VU university medical center

arthritis research&therapy

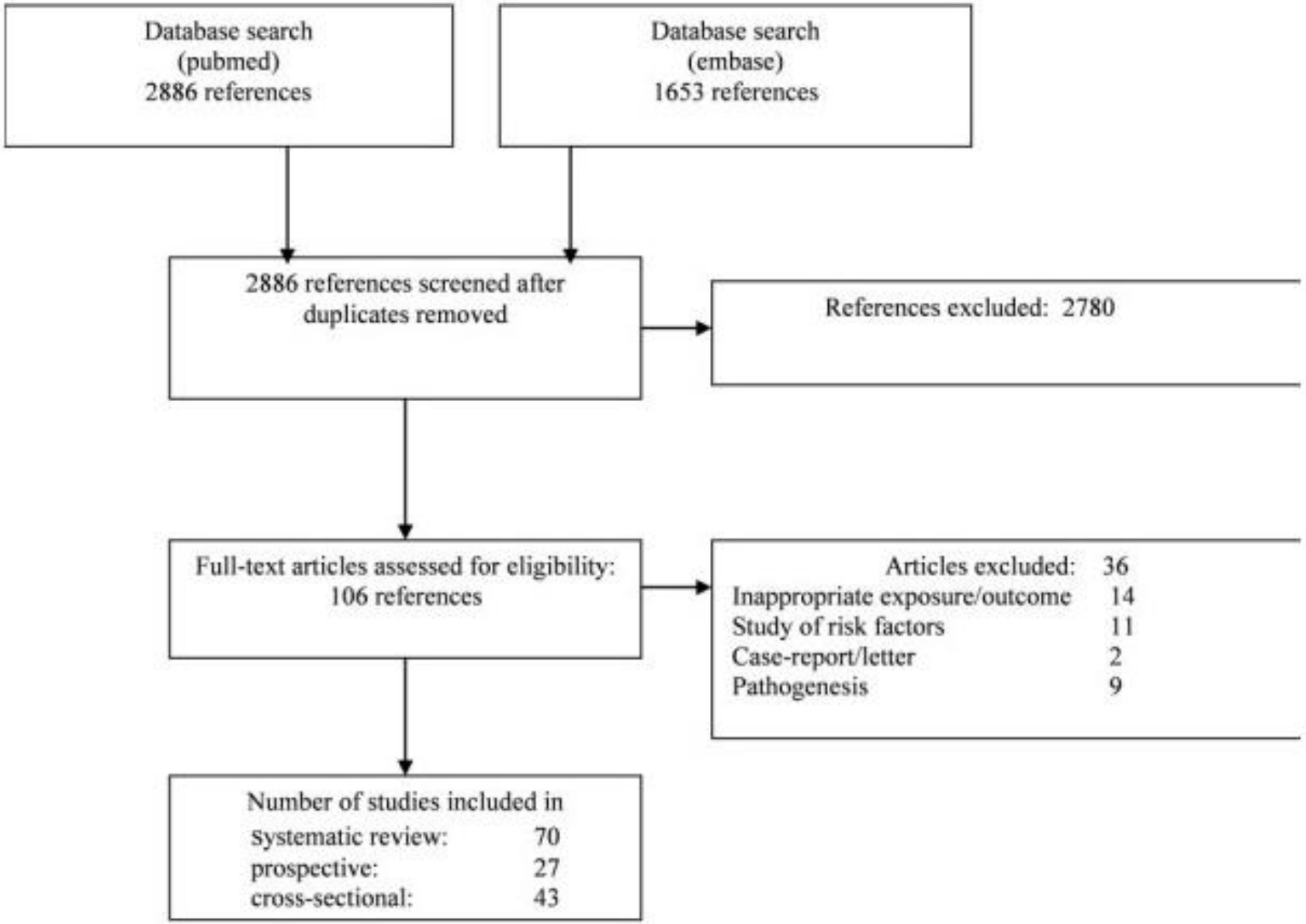
RESEARCH ARTICLE Open Access

(Sub)clinical cardiovascular disease is associated with increased bone loss and fracture risk; a systematic review of the association between cardiovascular disease and osteoporosis

Debby den Uyl[1], Mike T Nurmohamed[2,3*], Lilian HD van Tuyl[1], Hennie G Raterman[1], Willem F Lems[1,3]

den Uyl *et al. Arthritis Research & Therapy* 2011, **13**:R5
http://arthritis-research.com/content/13/1/R5

Figure 1


Database search
(pubmed)
2886 references
Database search
(embase)
1653 references
2886 references screened after
duplicates removed
References excluded: 2780
Full-text articles assessed for eligibility:
106 references
Articles excluded: 36
Inappropriate exposure/outcome 14
Study of risk factors 11
Case-report/letter 2
Pathogenesis 9
Number of studies included in
systematic review: 70
prospective: 27
cross-sectional: 43

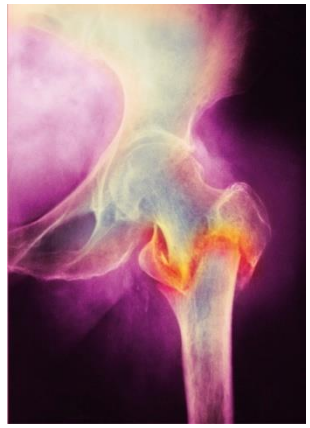
Systematic review

- Review of the current literature association between CVD and a) osteoporotic fractures and b) low BMD
- 2886 papers.

- Finally, 70 articles:
  - Prospective studies: 27
  - Cross-sectional studies: 43

  - *Due to a large heterogeneity in study population, design and outcome measures a formal meta-analysis was not possible.*

Patients with Cardiovascular Disease: elevated fracture risk? (1)



- Population based cohort studies: n=7
- In 4 studies an increased risk of incident fractures:
  Risk Rates ranging from 1.2 to 6.7;
  - Vertebral fractures and hip fractures
  - In women and in men
  - Some studies small with short follow-up
  - Different subgroups CVD:
    - Little information
    - Mostly Aortic Calcification and PAD

Patients with CVD: elevated fracture risk? (2)

- 15.968 twins, inclusion at age of 50
- Follow-up: 20 years
- Excluded: CVD at age of 50;

- Primary Outcome: time to hip# after diagnosis, or death
- Results for 4 subcategories:
  - Heart failure
  - Stroke
  - Peripheral Vascular Disease
  - Ischemic Heart Disease

From: **Cardiovascular Diseases and Risk of Hip Fracture**

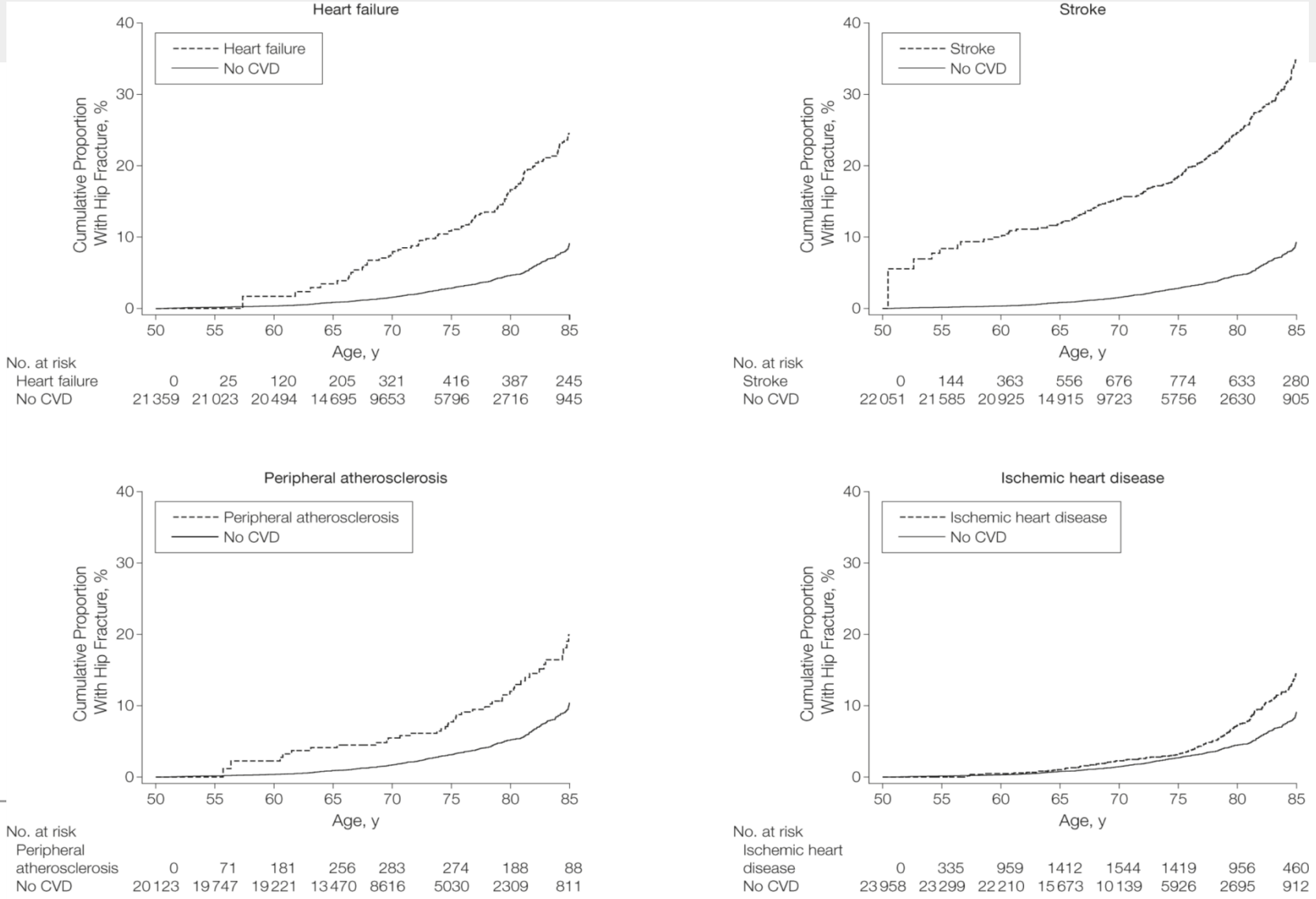


Figure Legend:

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

JAMA. 2009;302(15):1666-1673. doi:10.1001/jama.2009.1463

Risk of Hip/Femur Fracture After Stroke

A Population-Based Case-Control Study

Sander Pouwels, PharmD; Arief Lalmohamed, BSc; Bert Leufkens, PhD;
Anthonius de Boer, MD, PhD; Cyrus Cooper, MD, FMedSci;
Tjeerd van Staa, MD, PhD; Frank de Vries, PhD

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)

Risk of Hip/Femur Fracture After Stroke

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Undefined stroke§	97	159	2.44 (1.89–3.15)	2.10 (1.61–2.73)

*Adjusted for: the use of benzodiazepines with the 3 months before the index date; use of inhaled corticosteroids, oral corticosteroids, antipsychotics, antidepressants, beta-blockers, opioids, antiepileptics, ≥2 dispensing occurrences of a nonsteroidal antiinflammatory drug, disease-modifying antirheumatic drugs, nitrates, antidiabetics, calcium-channel blockers, bisphosphonates, hormone replacement therapy, antiarrhythmics (excluding digoxin) within the 6 months before the index date; a diagnosis of anemia, mental disorder, skin, or subcutaneous disease within the year before the index date; a diagnosis of malignant neoplasm, endocrine disorder, obstructive airways disease, inflammatory bowel disease, or musculoskeletal and connective tissue diseases at any time before the index date.

CVD and fracture risk

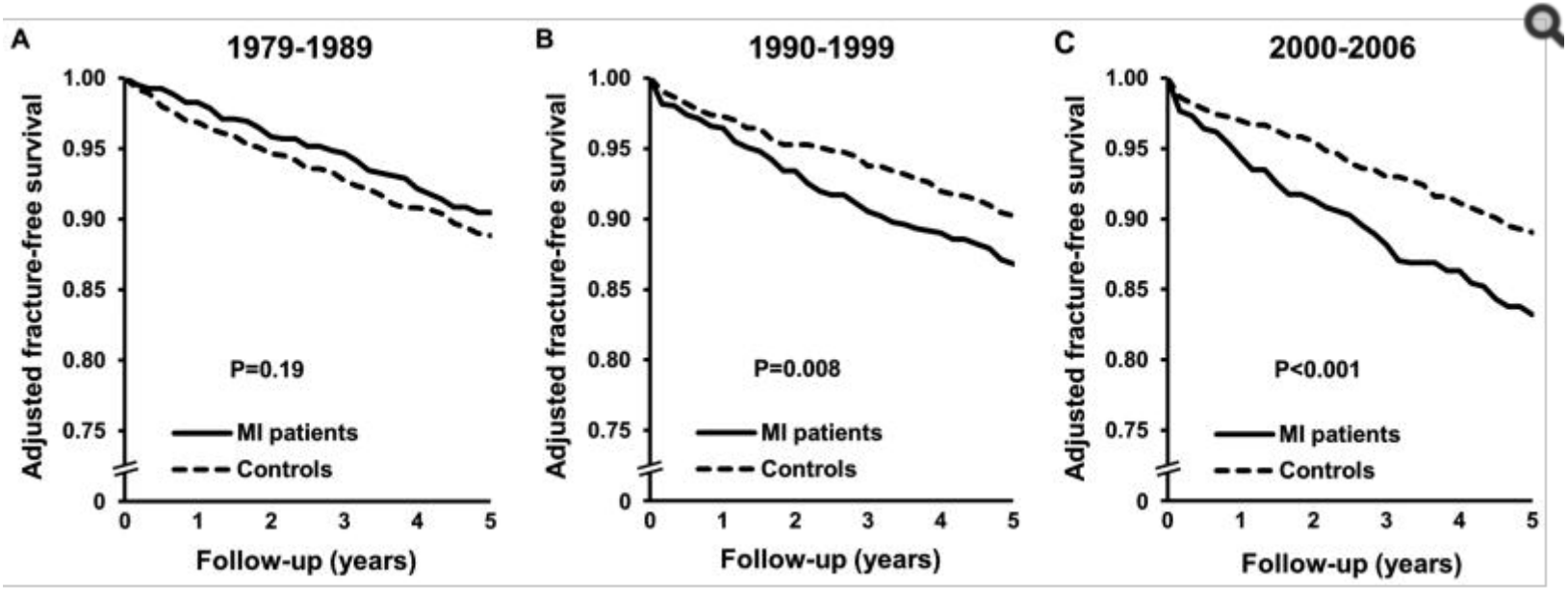
- Follow-up 4 years, 3321 cases (incident myocardial infarction=MI) vs 3321 controls;
- Age 67.4 (14.2), excluded prior MI
- Outcome: fracture after MI

- Results:
  - Overall: HR 1.32 (95% CI 1.12-1.56)
  - Women: HR 1.45 (95% CI 1.17-1.79)
  - Men: HR 1.25 (95% CI 0.86-1.48)

Gerber Circulation 2011;124:297-303

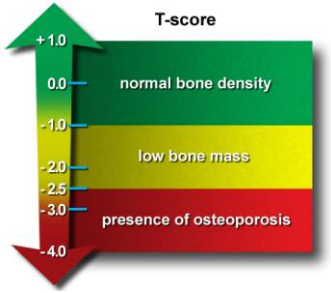
Association Between Myocardial Infarction and Fractures: An Emerging Phenomenon

Yariv Gerber, PhD, L. Joseph Melton, III, MD, MPH, Susan A. Weston, MS, and Véronique L. Roger, MD, MPH

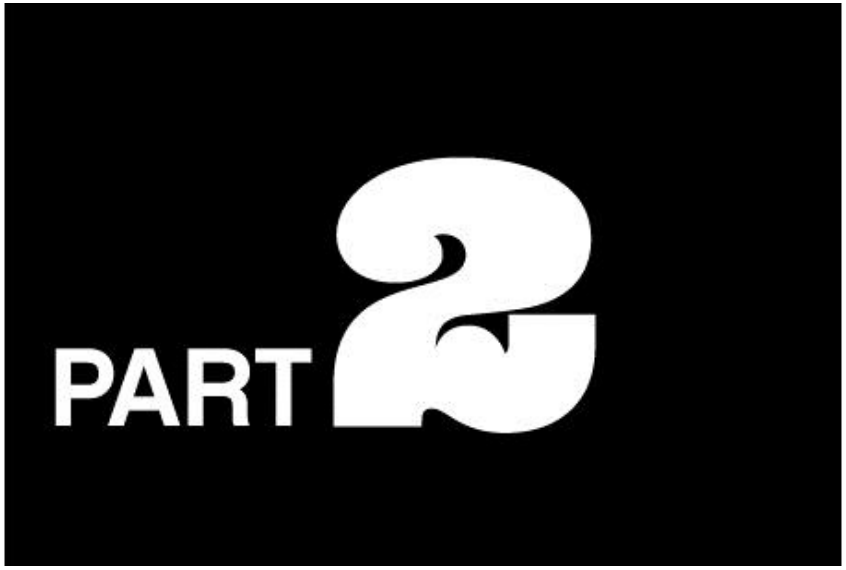


Circulation 2011

Are cardiologists screening for osteoporosis in their patients after a cardiovascular event?



Is cardiovascular risk elevated in osteoporotic patients?



RESEARCH ARTICLE

Decreased Bone Mineral Density Is an Independent Predictor for the Development of Atherosclerosis: A Systematic Review and Meta-Analysis

Chenyi Ye[1], Mingyuan Xu[2], Shengdong Wang[1], Shuai Jiang[1], Xi Chen[1], Xiaoyu Zhou[1], Rongxin He[1]*

1 Department of Orthopedics, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, People's Republic of China, **2** Department of Plastic Surgery, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, People's Republic of China

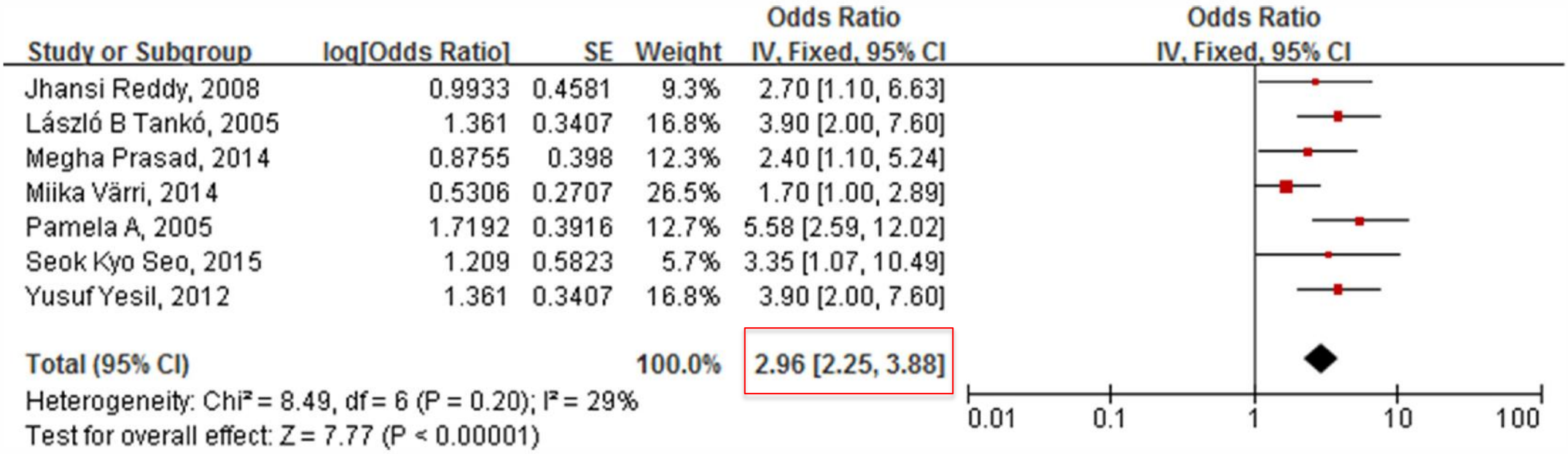


Fig 6. Forest plot shows that the incidence of atherosclerotic vascular abnormalities is significantly higher in individuals with low BMD than those with normal BMD, after adjusting for age, gender, BMI, hypertension, and other vascular risk factors.

Atherosclerotic Vascular abnormalities in individuals with low BMD versus normal BMD

RESEARCH ARTICLE

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1 Department of Orthopedics, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, People's Republic of China, **2** Department of Plastic Surgery, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, People's Republic of China

Study or Subgroup	Osteoporosis Events	Osteoporosis Total	Non-osteoporosis Events	Non-osteoporosis Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ihsane Hmamouchi, 2009	19	40	16	32	11.9%	0.90 [0.36, 2.29]
Jhansi Reddy, 2008	42	65	48	163	12.4%	4.38 [2.38, 8.05]
Liliana C Bajew, 2011	6	16	5	45	2.1%	4.80 [1.21, 18.97]
Megha Prasad, 2014	3	39	12	155	5.7%	0.99 [0.27, 3.71]
Miika Värri, 2014	17	20	158	270	4.2%	4.02 [1.15, 14.03]
P. Pennisia, 2010	27	40	25	52	9.0%	2.24 [0.95, 5.28]
Pamela A, 2005	50	67	60	142	12.4%	4.02 [2.11, 7.65]
Raja Varma, 2007	40	53	85	145	14.2%	2.17 [1.07, 4.41]
S. Beer, 2011	60	65	498	558	10.2%	1.45 [0.56, 3.74]
Seok Kyo Seo, 2009	5	31	7	121	3.1%	3.13 [0.92, 10.65]
Shokoofeh Hajsadeghi, 2011	34	55	33	64	14.9%	1.52 [0.73, 3.16]
Total (95% CI)		**491**		**1747**	**100.0%**	**2.45 [1.90, 3.17]**
Total events	303		947			

Heterogeneity: Chi² = 16.60, df = 10 (P = 0.08); I² = 40%

Test for overall effect: Z = 6.89 (P < 0.00001)

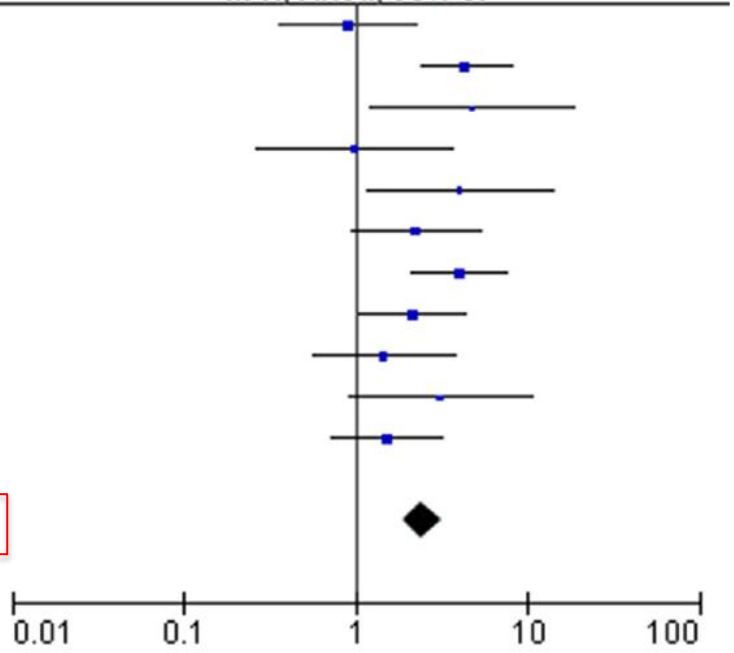

Fig 3. Forest plot shows that the incidence of atherosclerotic vascular abnormalities is significantly higher in individuals (including male and female) with osteoporosis than those without osteoporosis.

Atherosclerotic vascular abnormalities in individuals with osteoporosis versus without osteoporosis

May 5, 2016

RESEARCH ARTICLE

Decreased Bone Mineral Density Is an Independent Predictor for the Development of Atherosclerosis: A Systematic Review and Meta-Analysis

Chenyi Ye[1], Mingyuan Xu[2], Shengdong Wang[1], Shuai Jiang[1], Xi Chen[1], Xiaoyu Zhou[1], Rongxin He[1]*

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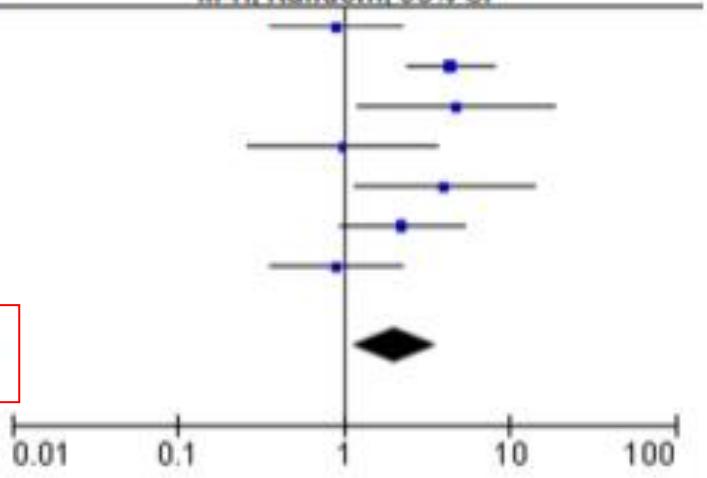
Seok Kyo Seo, 2009	19	40	16	32	15.3%	0.90 [0.36, 2.29]
Total (95% CI)		260		749	**100.0%**	**2.05 [1.13, 3.72]**
Total events	133		280			

Heterogeneity: $Tau^2 = 0.38$; $Chi^2 = 15.41$, df = 6 (P = 0.02); $I^2 = 61\%$

Test for overall effect: Z = 2.37 (P = 0.02)



Atherosclerotic vascular abnormalities in postmenopausal women with osteoporosis versus without osteoporosis

May 5, 2016

Research Article

Cardiovascular Risk Factor Analysis in Patients with a Recent Clinical Fracture at the Fracture Liaison Service

Caroline E. Wyers,[1,2] Lisanne Vranken,[1,2] Robert Y. van der Velde,[1] Piet P. M. M. Geusens,[3,4] Heinrich M. J. Janzing,[5] J. Wim Morrenhof,[6] and Joop P. W. van den Bergh[1,2,4]

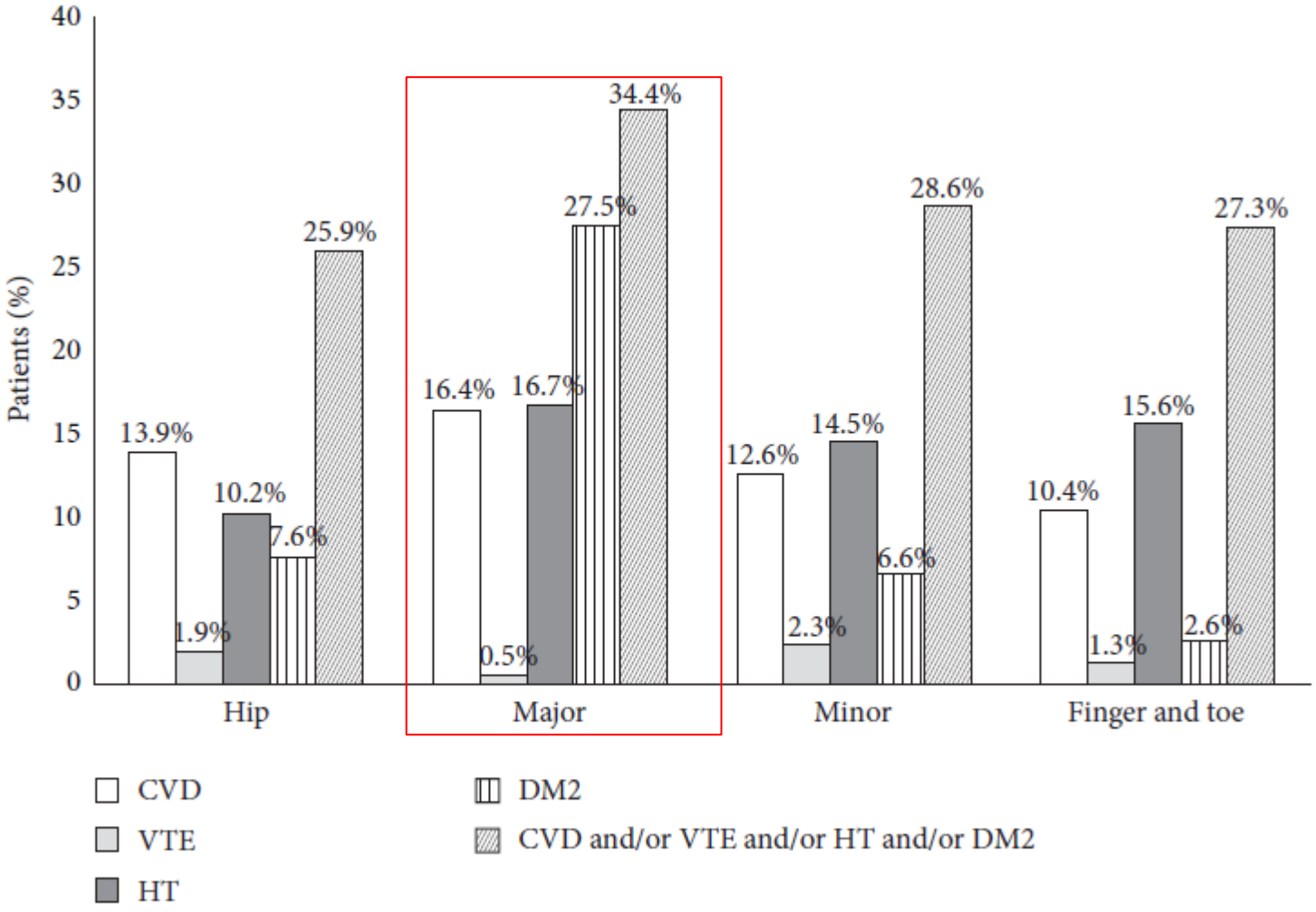
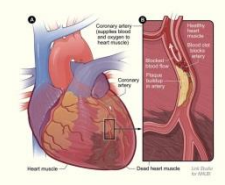
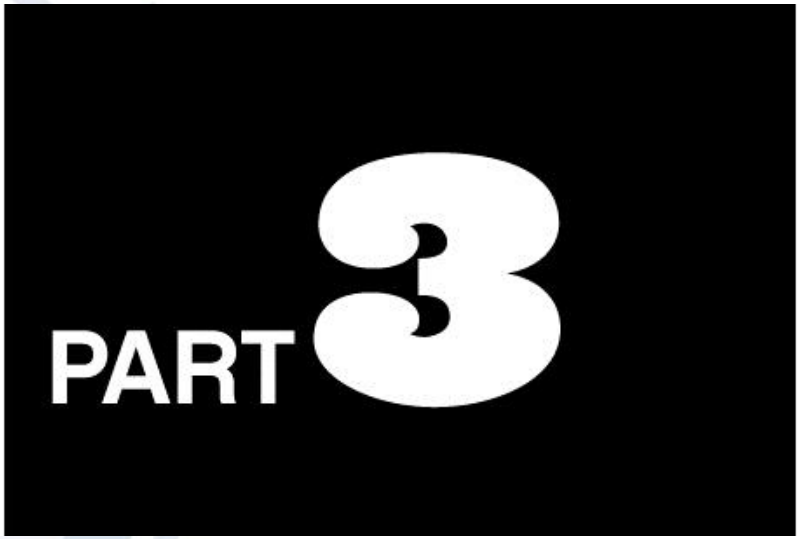


FIGURE 1: Prevalence of cardiovascular risk factors and diabetes mellitus type 2 according to the center classification.

Is Cardiovascular Risk Management a substantial part in the work-up of patients with a recent osteoporotic fracture, at the Fracture Liaison Service?

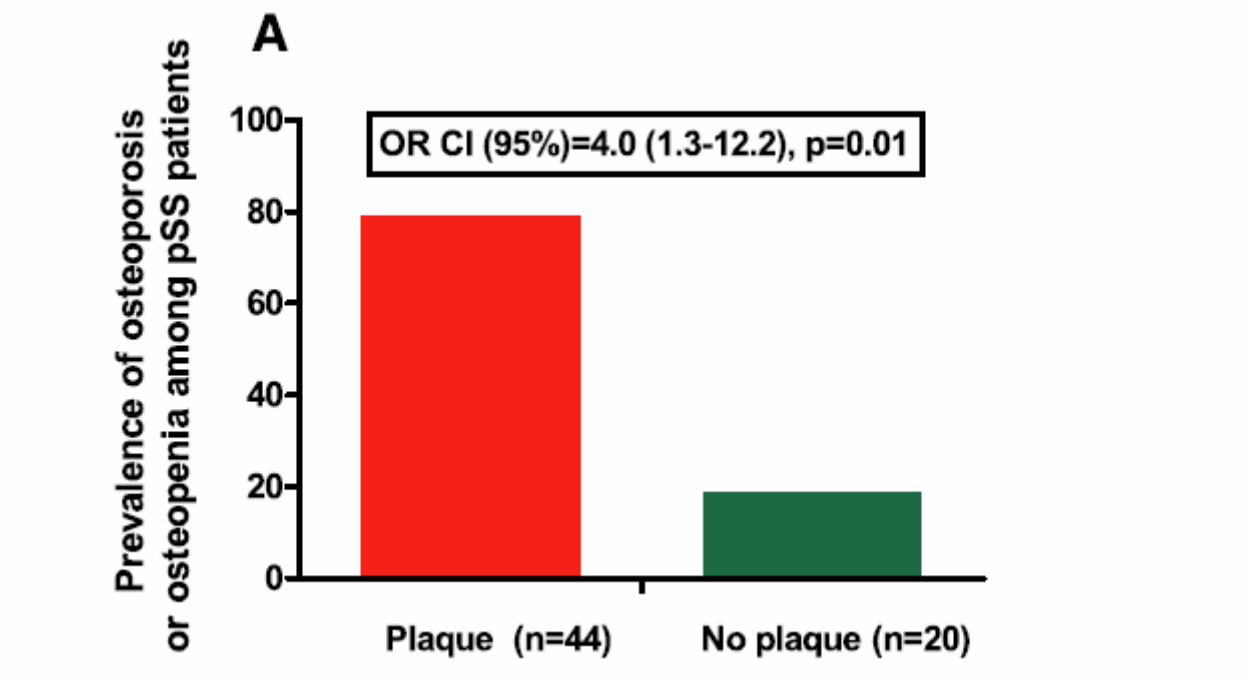


Cardiovascular events and osteoporotic fractures in patients with rheumatic diseases.



Subclinical atherosclerosis and impaired bone health in patients with primary Sjogren's syndrome: prevalence, clinical and laboratory associations

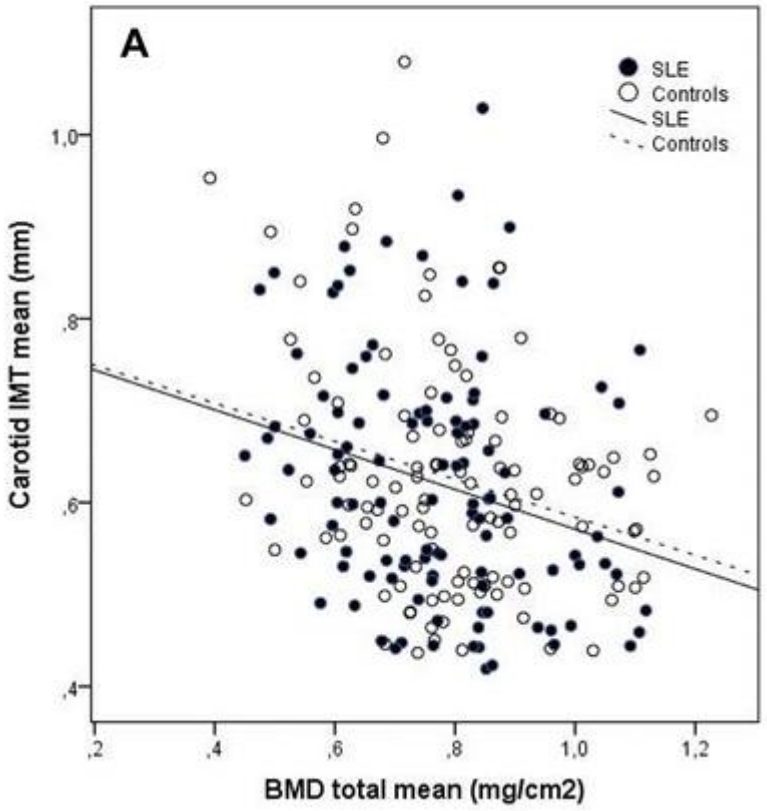
Fotini Gravani[1,2], Ioanna Papadaki[1], Eleni Antypa[3], Andrianos Nezos[4], Kyriaki Masselou[5], Dimitrios Ioakeimidis[1], Michael Koutsilieris[4], Haralampos M Moutsopoulos[2] and Clio P Mavragani[2,4*]



Bone mineral density and carotid atherosclerosis in systemic lupus erythematosus: a controlled cross-sectional study

Sofia Ajeganova[1*], Thomas Gustafsson[2], Tomas Jogestrand[2], Johan Frostegård[3] and Ingiäld Hafström[1]

Figure 1



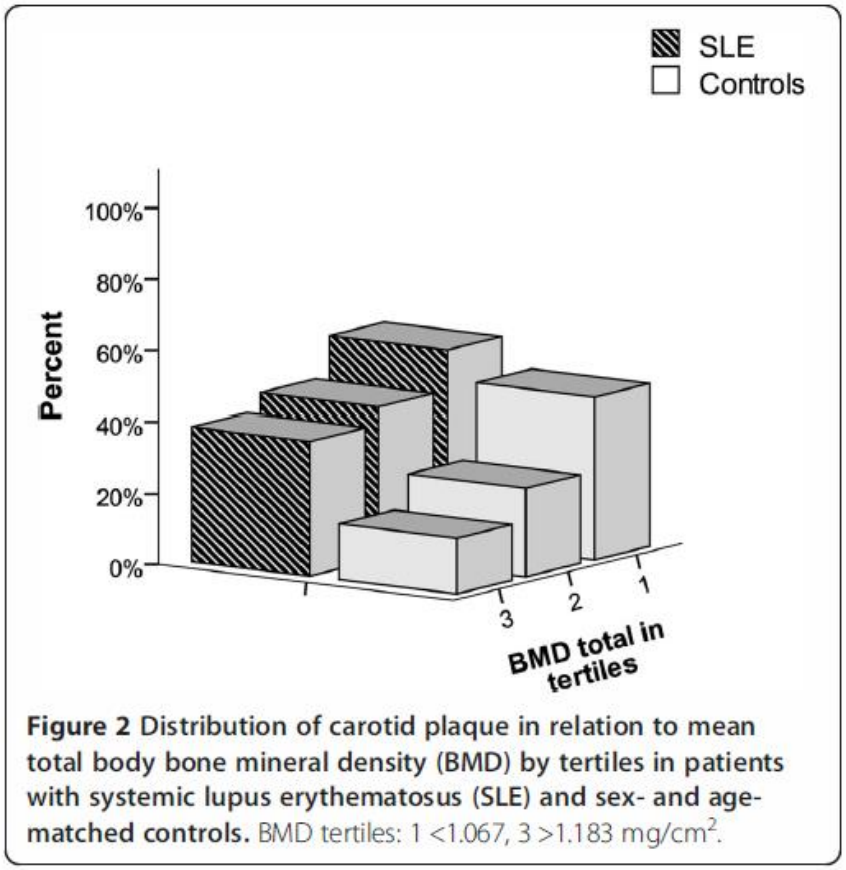
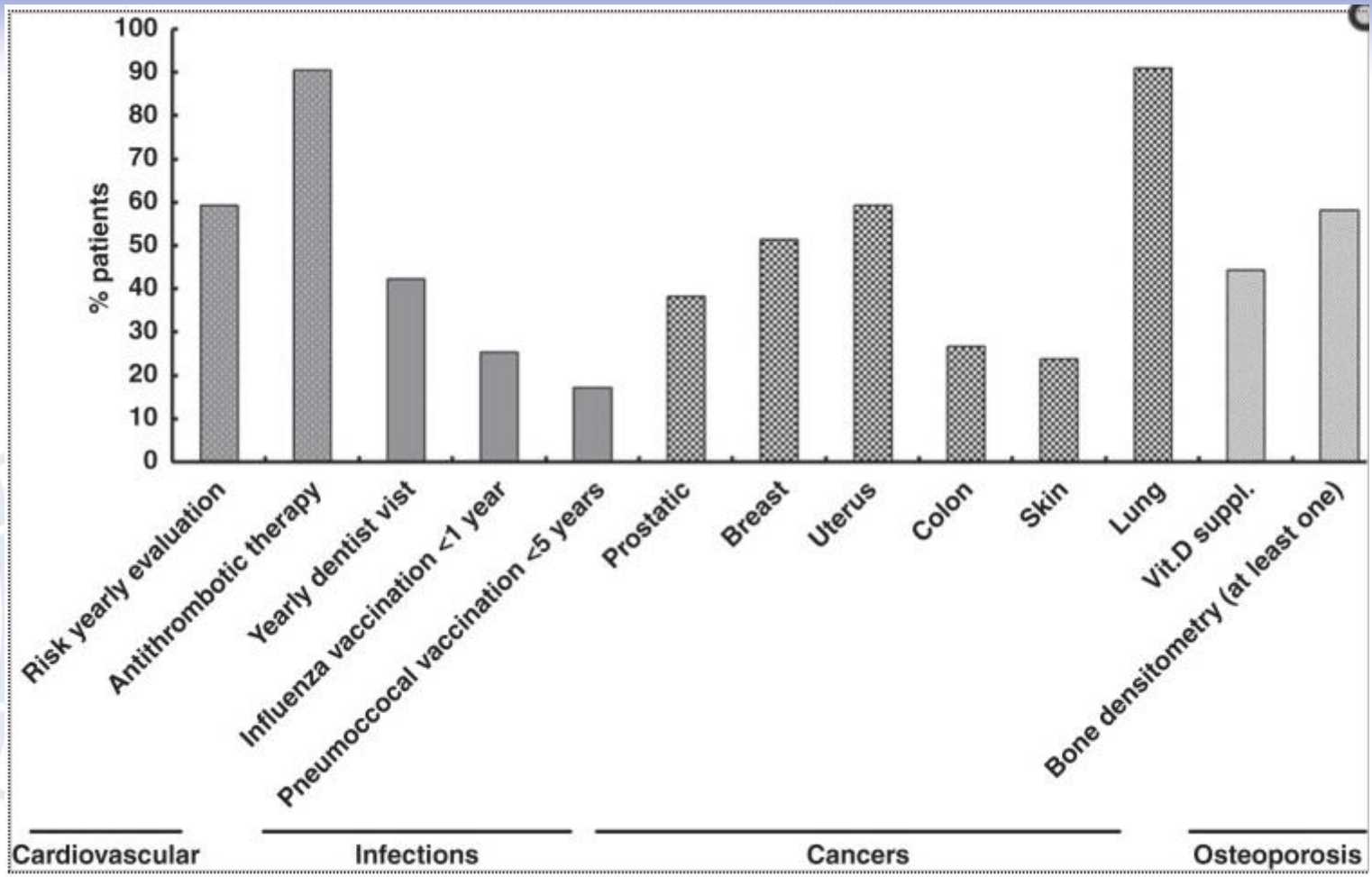


Figure 2 Distribution of carotid plaque in relation to mean total body bone mineral density (BMD) by tertiles in patients with systemic lupus erythematosus (SLE) and sex- and age-matched controls. BMD tertiles: 1 <1.067, 3 >1.183 mg/cm^2.

EXTENDED REPORT

Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA)

Maxime Dougados,[1,2] Martin Soubrier,[3] Anna Antunez,[4] Peter Balint,[5] Alejandro Balsa,[6] Maya H Buch,[7,8] Gustavo Casado,[9] Jacqueline Detert,[10] Bassel El-zorkany,[11] Paul Emery,[7,8] Najia Hajjaj-Hassouni,[12] Masayoshi Harigai,[13] Shue-Fen Luo,[14] Reka Kurucz,[5] Gabriel Maciel,[15] Emilio Martin Mola,[16] Carlo Maurizio Montecucco,[17] Iain McInnes,[18] Helga Radner,[19] Josef S Smolen,[19] Yeong-Wook Song,[20] Harald Erwin Vonkeman,[21] Kevin Winthrop,[22] Jonathan Kay[23]



Clin Calcium. 2015 May;25(5):655-60. doi: CliCa1505655660.

[Vascular Calcification - Pathological Mechanism and Clinical Application - . Vascular calcification as a clinical manifestation of bone-vascular axis].

[Article in Japanese]

Yamamoto M[1].

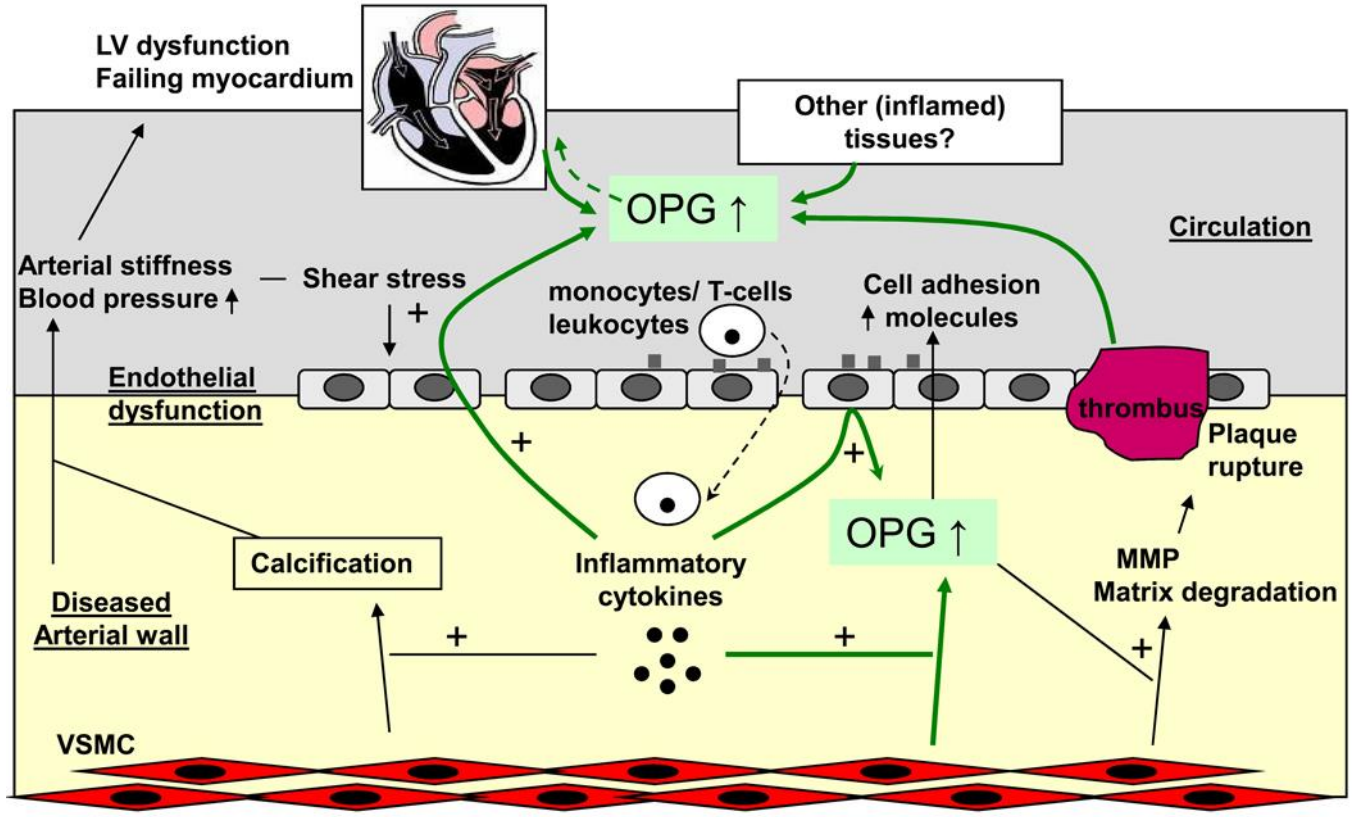
Abstract

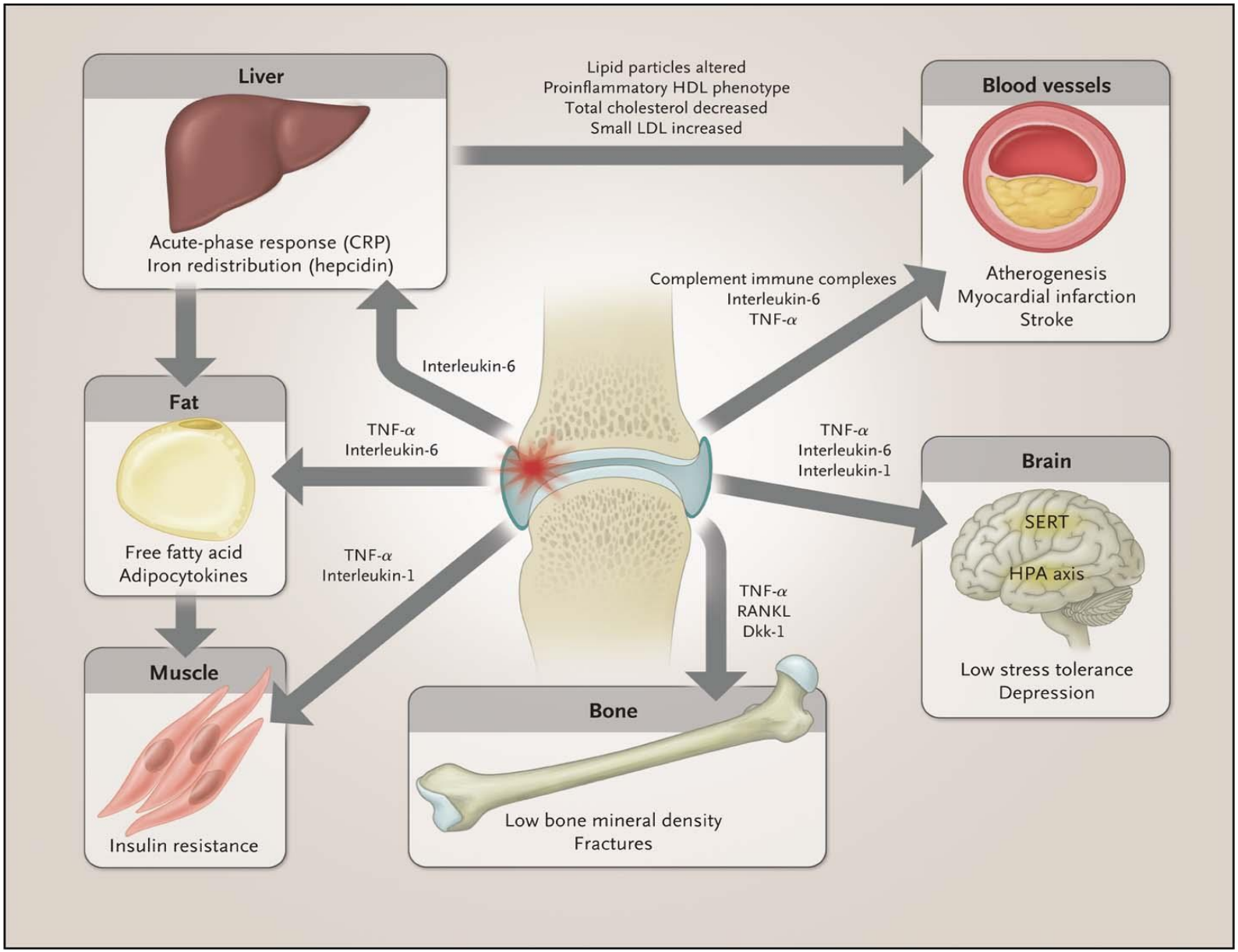
Several clinical studies has been shown the close relationship between osteoporosis and arteriosclerosis, and basic researches confirmed the reasonability of this association by the findings that organized molecular mechanism of bone formation in bone tissue was also observed in the lesion of vascular calcification, RANK/RANKL/OPG axis is one of potent and explainable molecular mechanism for bone-vascular association. However, one recent clinical intervetion study using RANKL antibody for post menopauisal women with primary osteoporosis could not validate that relationship. Further examinations are needed to improve understanding of the precise mechanism in this area.

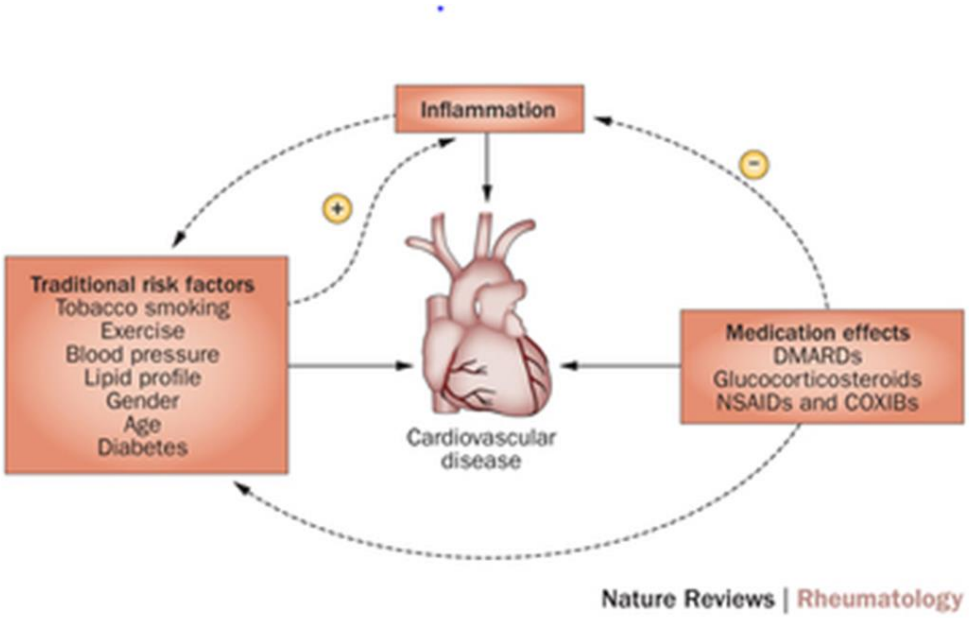
Atherosclerosis. 2009 June ; 204(2): 321–329. doi:10.1016/j.atherosclerosis.2008.09.033.

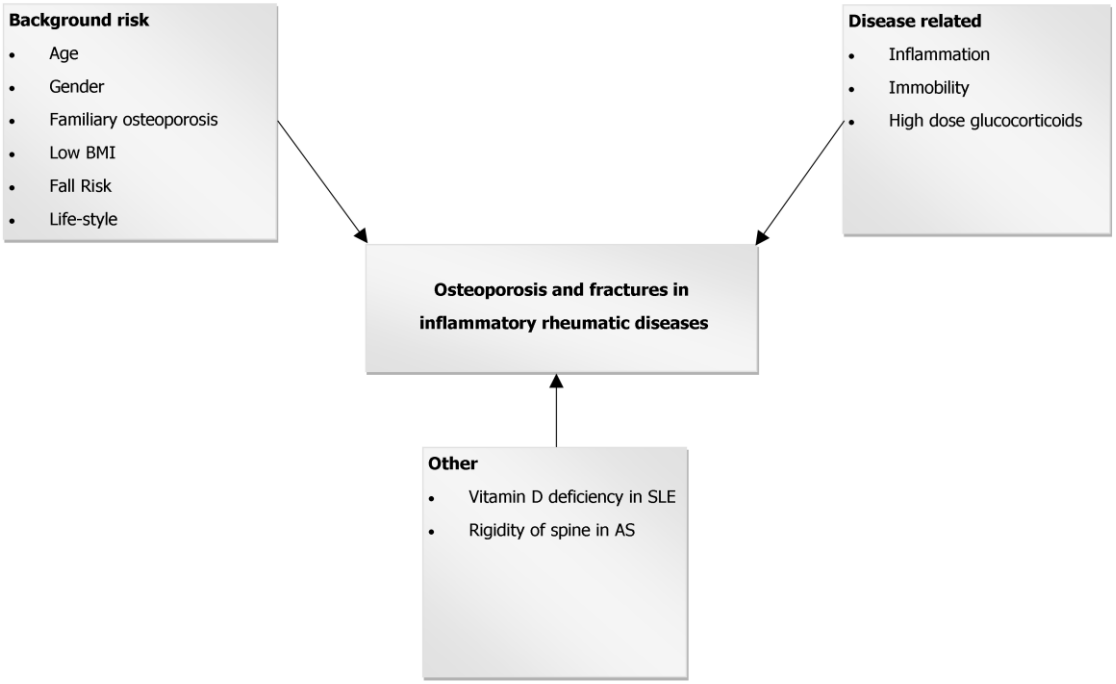
Osteoprotegerin, vascular calcification and atherosclerosis

Ann Van Campenhout, PhD and **Jonathan Golledge, MChir**
Vascular Biology Unit, School of Medicine, James Cook University, Townsville QLD 4811, Australia.









Nurmohamed 2012

Bultink, Lems 2012

Cardiovascular events and osteoporotic fractures

-Fracture risk in elevated in patients with cardiovascular disases, particularly after stroke;
- Atherosclerotic manifestations occur more often in patients with osteoporosis.

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Cardiovascular events and osteoporotic fractures

-Several common risk factors for CVD and osteoporosis, particularly systemic inflammation;
- Co-occurrence of CVD and osteoporosis may occur in patients with systemic inflammatory rheumatic diseases.


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Thank you for attention!

The Unrecognized Burden of Osteoporosis-Related Vertebral Fractures in Patients With Heart Failure

Kristin J. Lyons, Sumit R. Majumdar and Justin A. Ezekowitz

Circ Heart Fail. 2011;4:419-424; originally published online May 10, 2011;

Table 3. Independent Correlates of the Presence of 1 or More Moderate to Severe Vertebral Fractures Versus Multiple Moderate to Severe Vertebral Fractures

	One or More Fractures (n=77)			Multiple Fractures (n=42)		
Characteristic	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age, per year	1.01	0.98–1.03	0.67	1.02	0.98–1.05	0.27
Female	1.15	0.61–2.14	0.67	1.37	0.61–3.09	0.41
Atrial fibrillation	2.07	1.19–3.59	0.009	1.75	0.84–3.86	0.14
Weight, per kg	0.98	0.97–1.0	0.01	0.98	0.96–1.0	0.02
Lipid-lowering agents	0.22	0.05–0.95	0.04	0.22	0.03–1.67	0.14
Bisphosphonate	6.12	2.14–17.5	<0.001	7.03	2.12–23.34	0.001