GISMO 2022

XVIII CONGRESSO NAZIONALE

FRAGILITÀ MUSCOLO-SCHELETRICA
STILI DI VITA E APPROPRIATEZZA TERAPEUTICA
LE SFIDE PER IL FUTURO

Baveno
7 - 8 ottobre 2022

GISMO

Gruppo Italiano Studio
Malattie Metabolismo Osseo

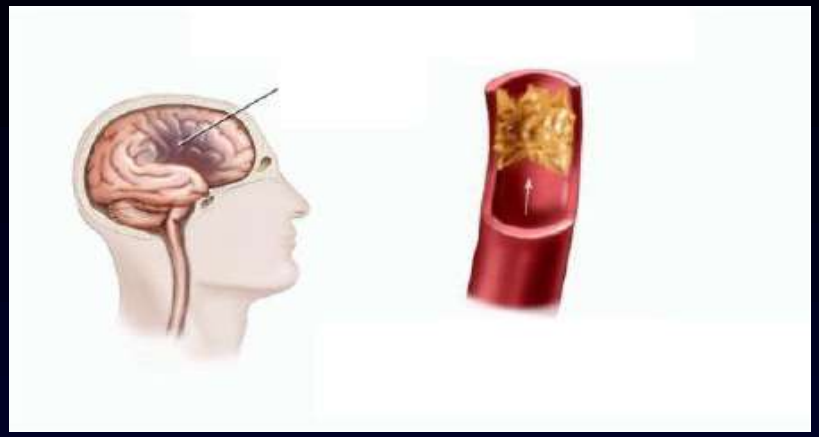
- Osteoporosi
- Malattie Muscolo-Scheletriche
- Malattie Metaboliche
- Dolore
- Nutrizione

Professor Giuseppe Martini

Università degli Studi di Siena

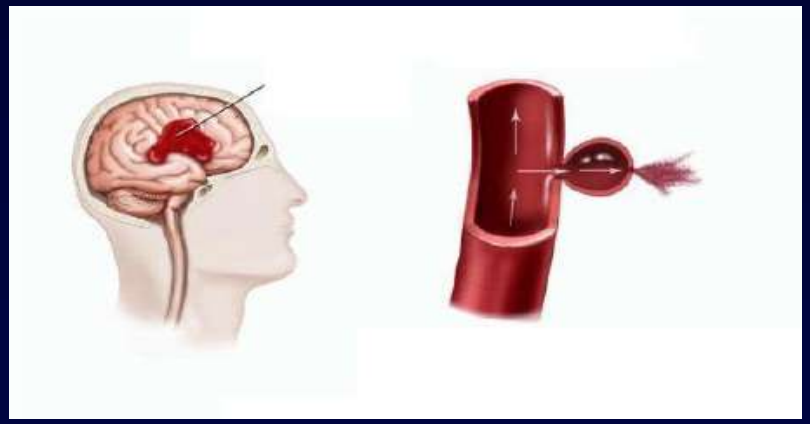
Stroke e Osso

ICTUS ISCHEMICO



Il flusso di sangue è bloccato
da un trombo o da un embolo

ICTUS EMORRAGICO



Il sangue fuoriesce dalla
rottura di un'arteria

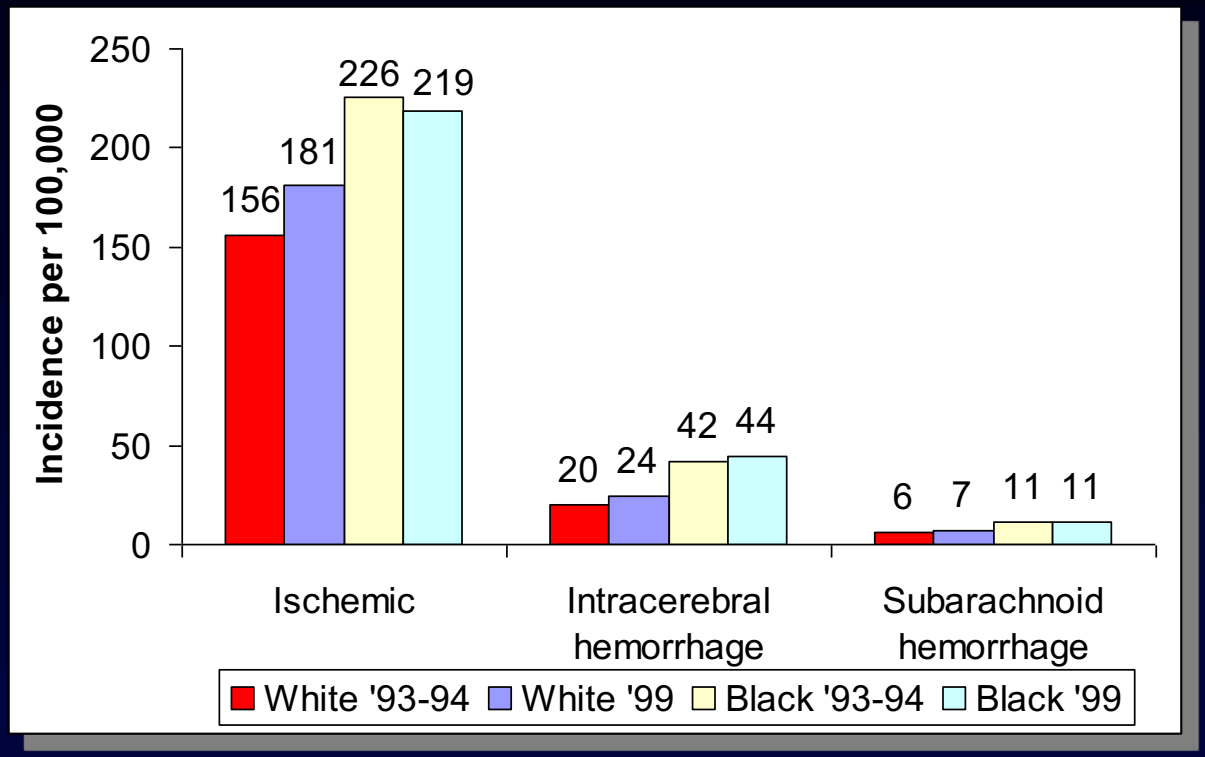
E' il danno cerebrale causato dall'interruzione del flusso di sangue al cervello per

chiusura o rottura di un'arteria cerebrale

STROKE

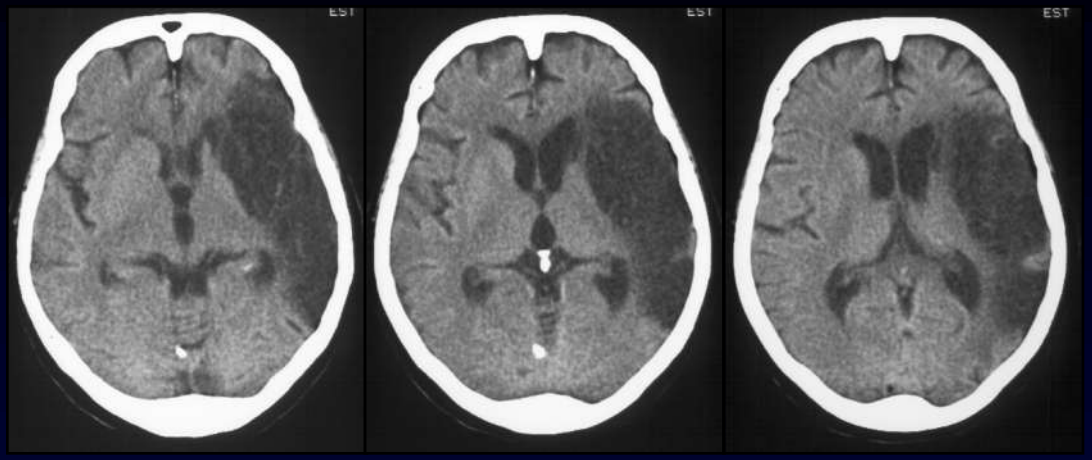
Ischemico
80%-85%

Emorragico
15-20%



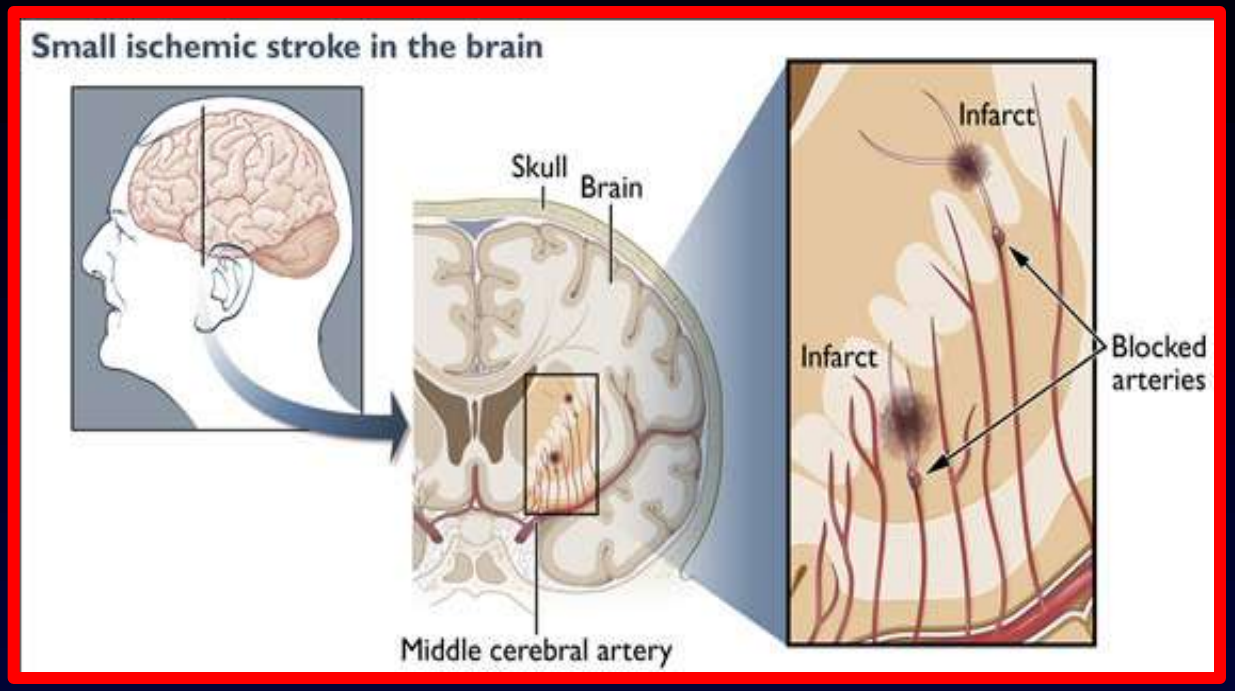
Annual age-adjusted incidence of first-ever stroke, by race. Inpatient plus out-of-hospital ascertainment.
(GCNKSS: 1993-94 and 1999). Source: Stroke 2006;37;2473-2478.

Large vessel disease



Aterotrombosi

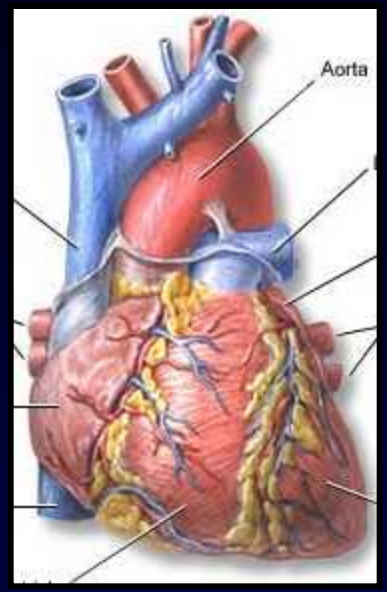
SMALL-VESSEL DISEASE

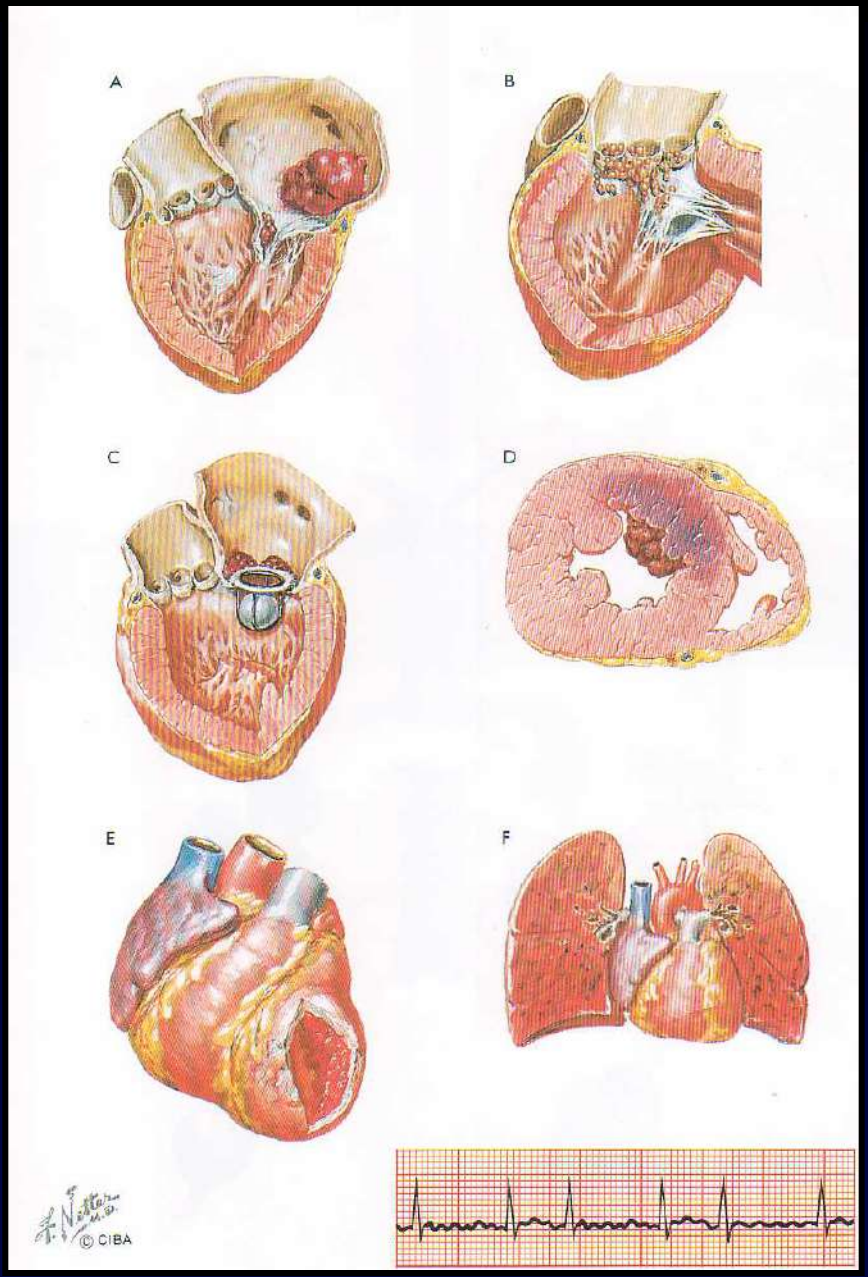


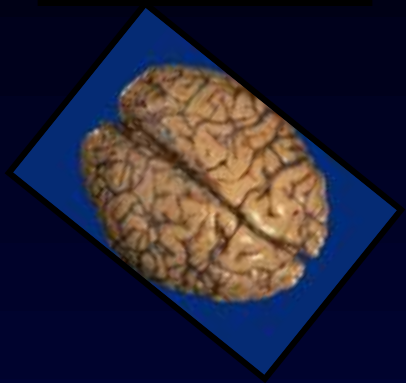
Diabete - Ipertensione

- frequenti lesioni causate dall'occlusione di una singola arteria perforante profonda.
- prognosi migliore degli altri ictus
- la maggior parte delle lacune si verifica nel territorio delle art. lenticolostriate e si ritiene siano spesso silenti; altre in punti strategici come la capsula interna o il ponte producono deficit neurologici estesi.

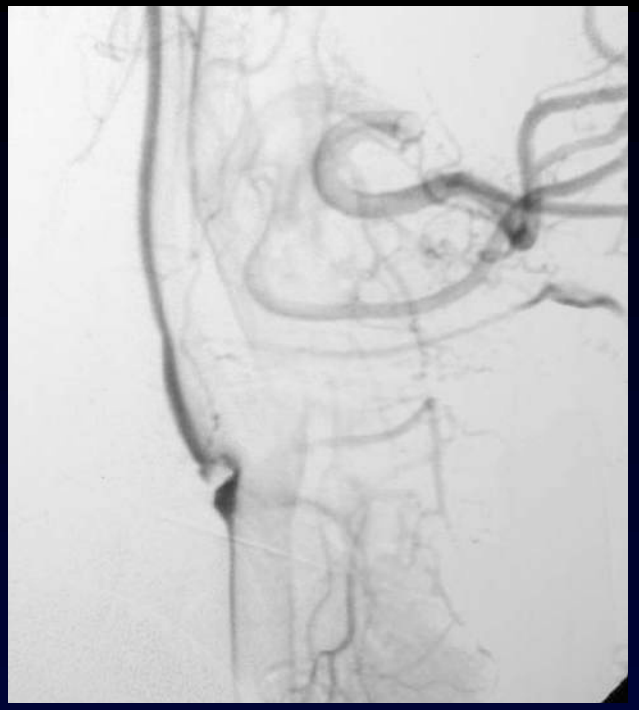
CARDIOEMBOLIC STROKE

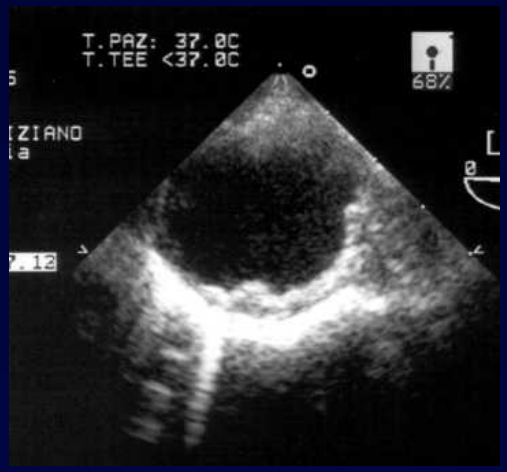


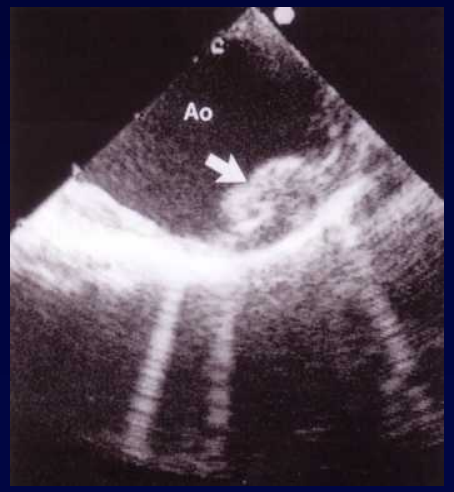


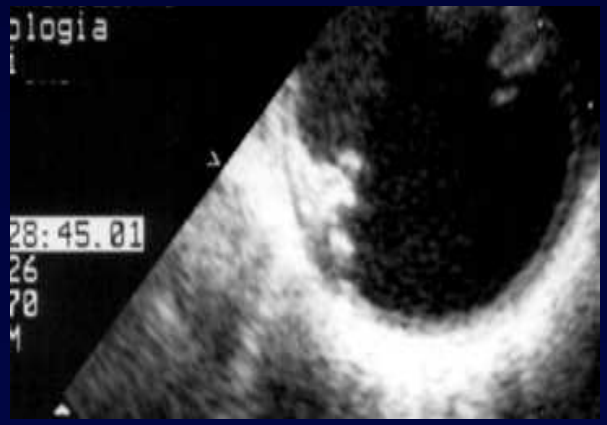


THROMBOEMBOLIC STROKE



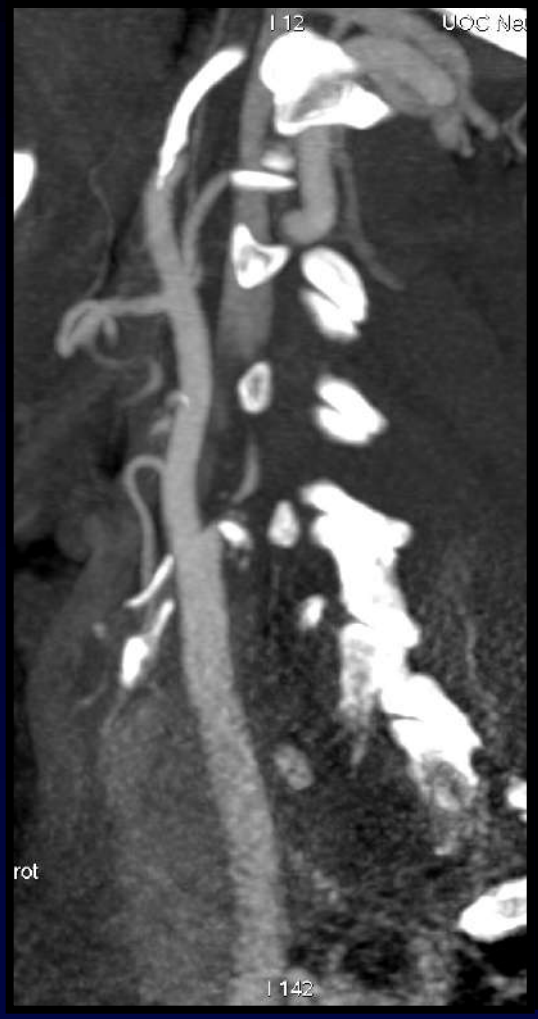


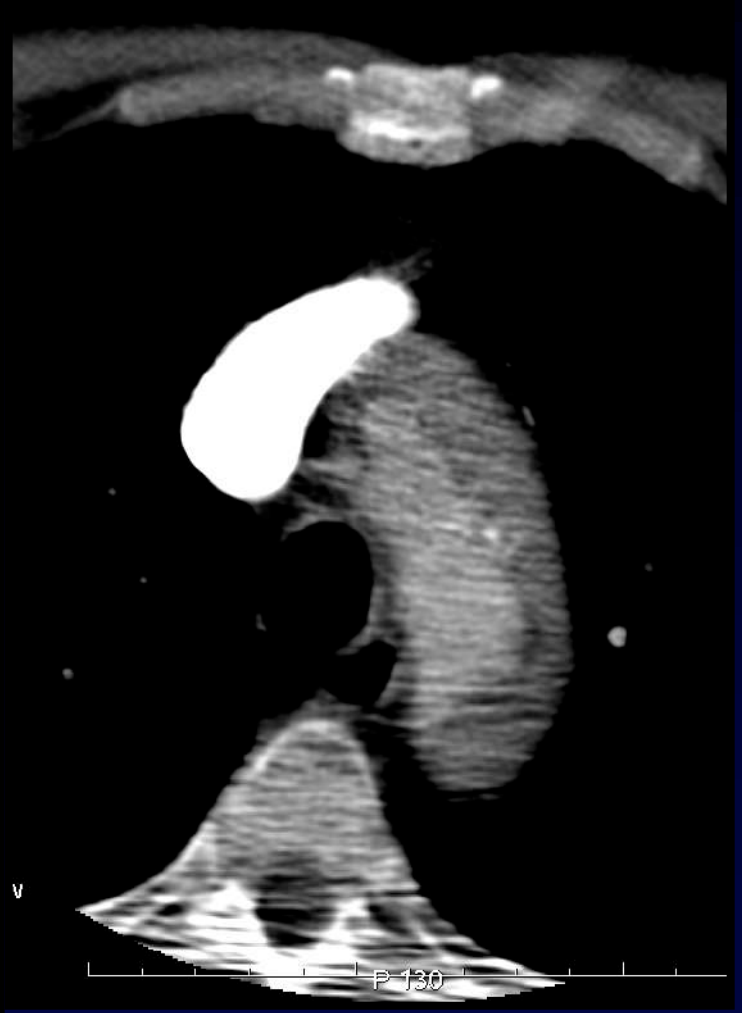




OTHER ETIOLOGY

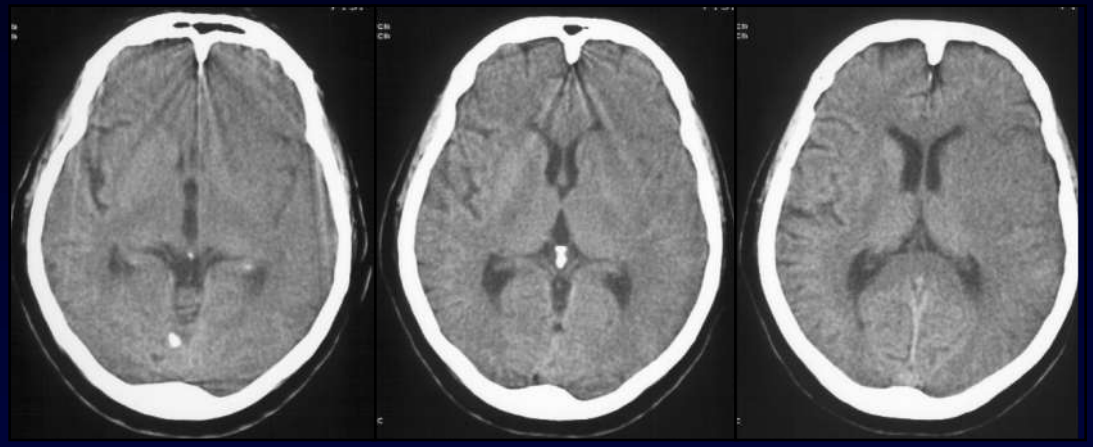
- Prothrombotic States
- Dissections
- Arteritis
- Migraine/Vasospasm
- Drug Abuse
- CADASIL
- Many More





CRYPTOGENIC (Undetermined Etiology)

Nonlacunar cerebral infarction without associated large-artery pathology, clinical heart disease, or chronic inflammatory, infectious or systemic illness



- Two or more causes identified
- Negative evaluation
- Incomplete evaluation

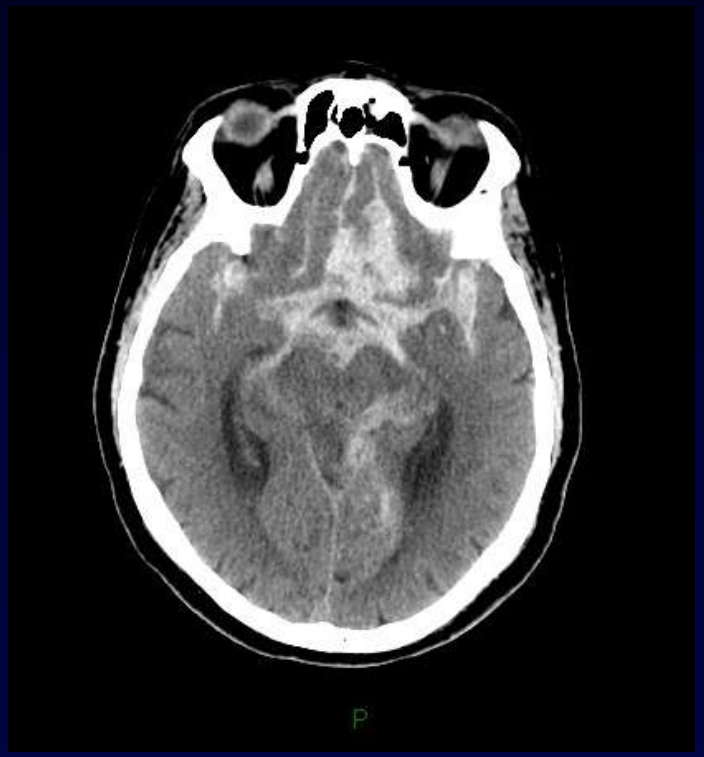
Nel 62% dei pazienti con stroke ischemico fra 15 e i 45 anni la causa è indeterminata.

Leys D et al. Neurology 2002

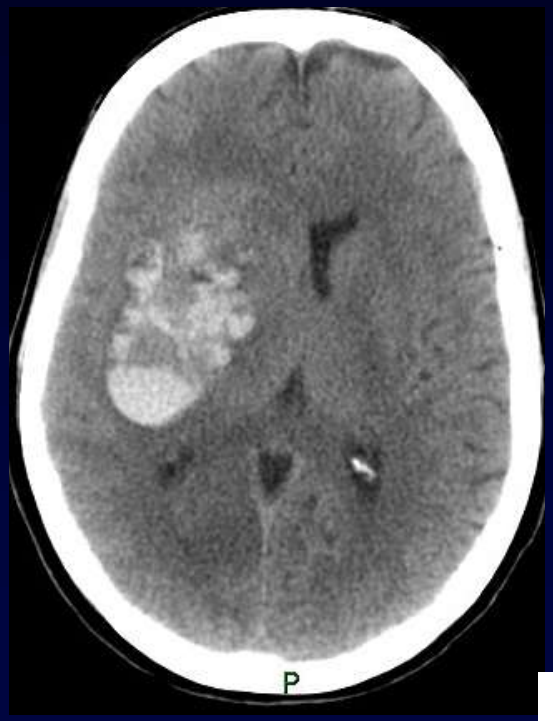
Emorragia cerebrale

Intraparenchimale

Subaracnoidea



Infarcimento emorragico



Prevalenza ed incidenza

- 185.000 nuovi ictus per anno in Italia, di cui il 20% decede entro il primo mese ed il 30% sopravvive con esiti invalidanti.
- di questi 185.00, l'80% sono primi episodi pari a circa 150.000, mentre il 20% sono recidive, pari a 35.000.
- 930.000 persone con pregresso stroke
- 10.000 casi/anno sotto i 54 anni

Mortalità a 30 giorni nei pazienti con stroke

Tabella 4:X – Tassi di letalità per ictus in relazione al tipo di malattia cerebrovascolare

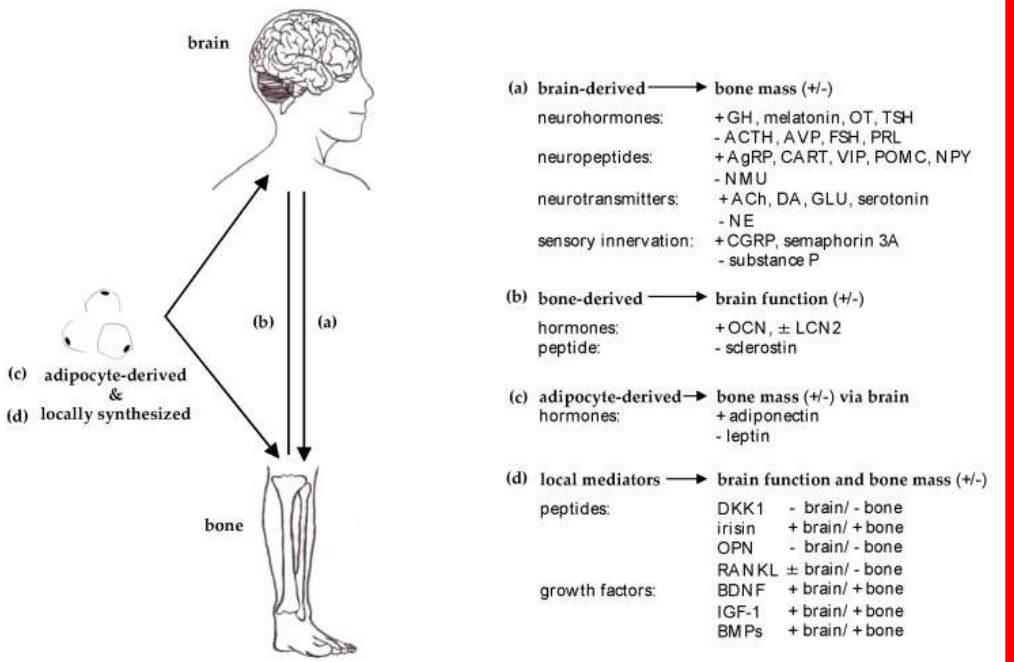
tipo di ictus	numero di casi	decessi	tasso di letalità	IC_{95}
emorragia subaracnoidea	118	41	34,7%	26,2-43,3
emorragia cerebrale	588	283	48,1%	44,1-52,2
ischemia cerebrale	3·594	863	21,2%	19,9-22,6
eventi mal definiti	53	40	75,5%	63,9-87,1
totale	4·353	1·127	25,9%	24,6-27,2

Disability Post Stroke in People > 65 Years at 6 Months

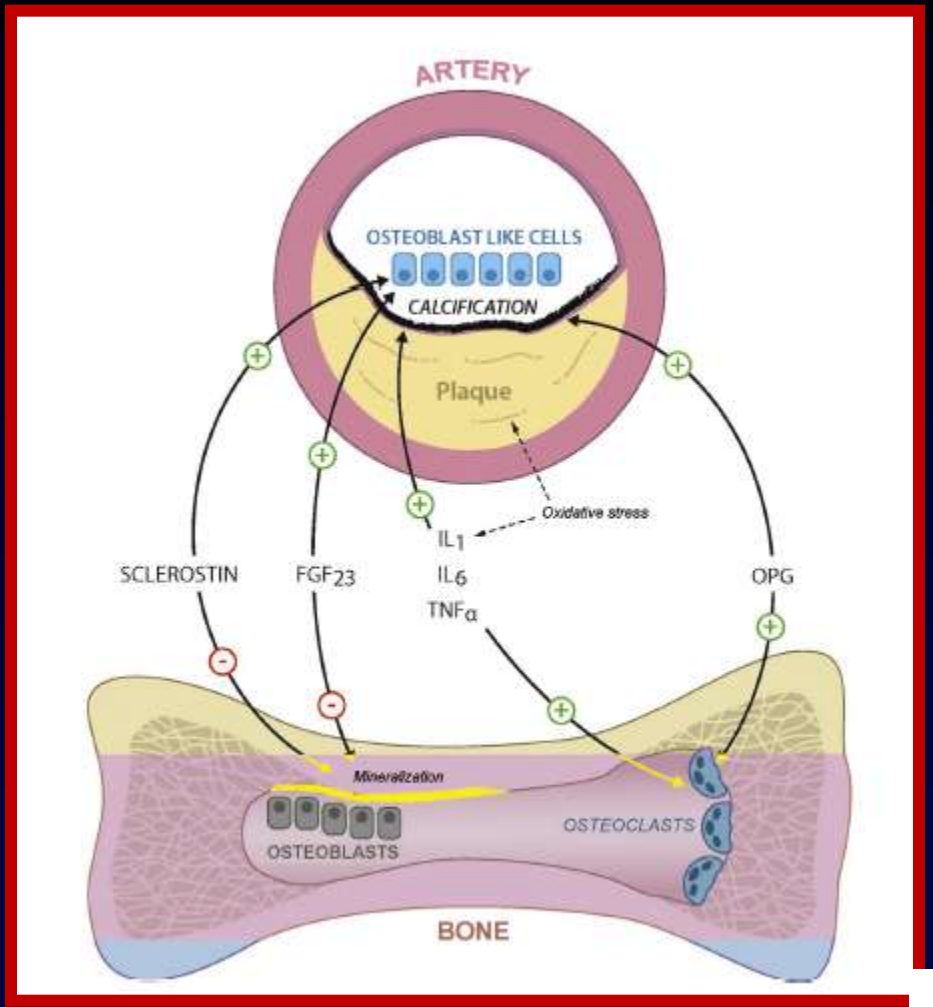
- 50% had some hemiparesis
- 30% were unable to walk without assistance
- 26% were dependent in the activity of daily living
- 19% had aphasia
- 35% had depressive symptoms
- 26% were institutionalized in a nursing home
- **Up to 25% of patients who had a stroke can develop visual field loss**

Cytokine and growth factor involved in bone turnover and in calcified vascular plaque formation

Molecular basis of bone and brain crosstalk

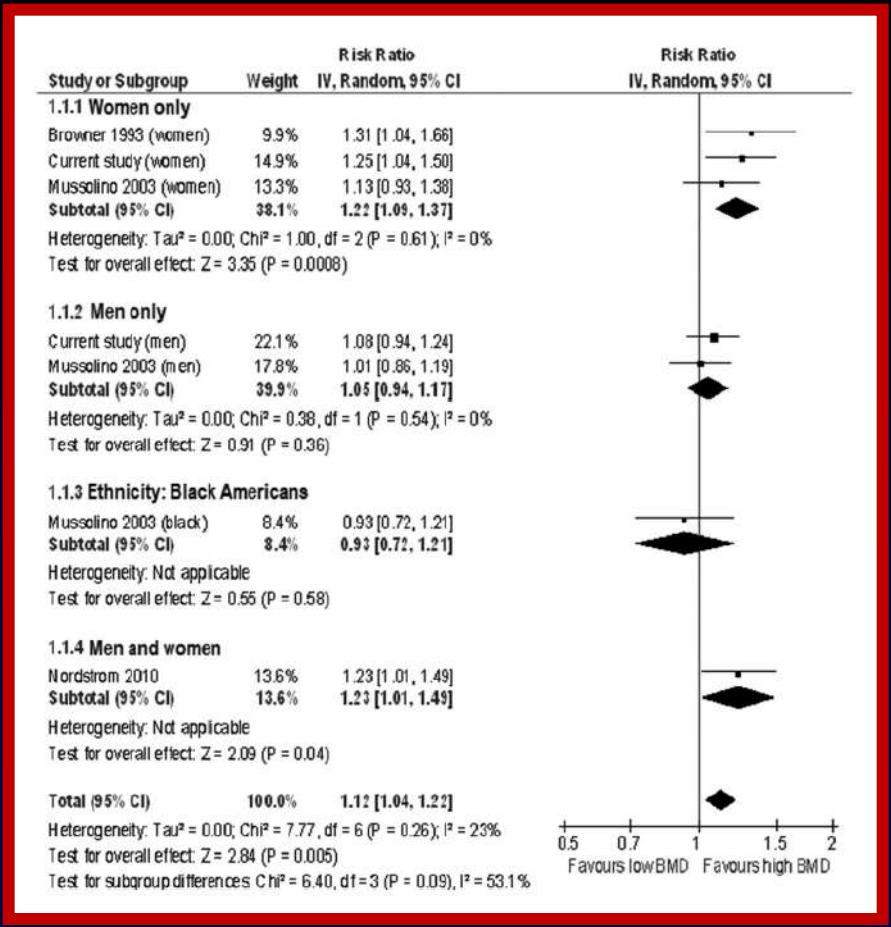


Otto E et al. Int J Mol Sci, 2020



Laroche M et al, Joint Bone Spine, 2017

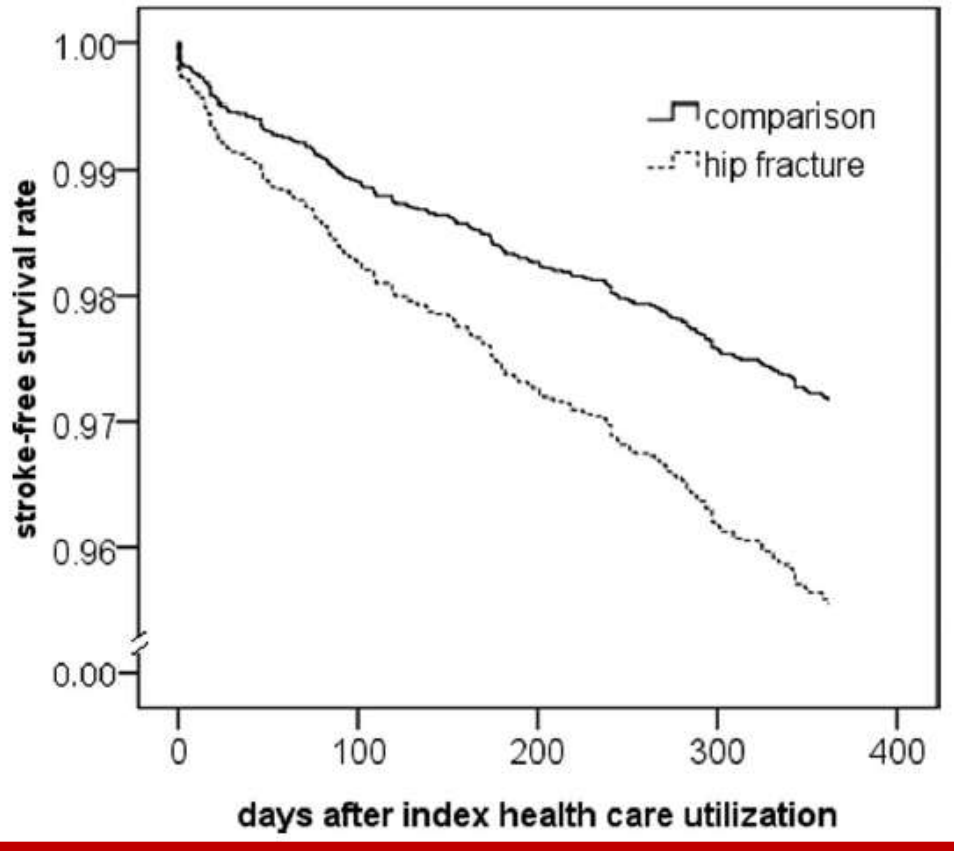
Meta-analysis risk of incident stroke with decreasing bone mineral density in different patient group



1 SD decrease in BUA/VOS
17% increase in RR of stroke

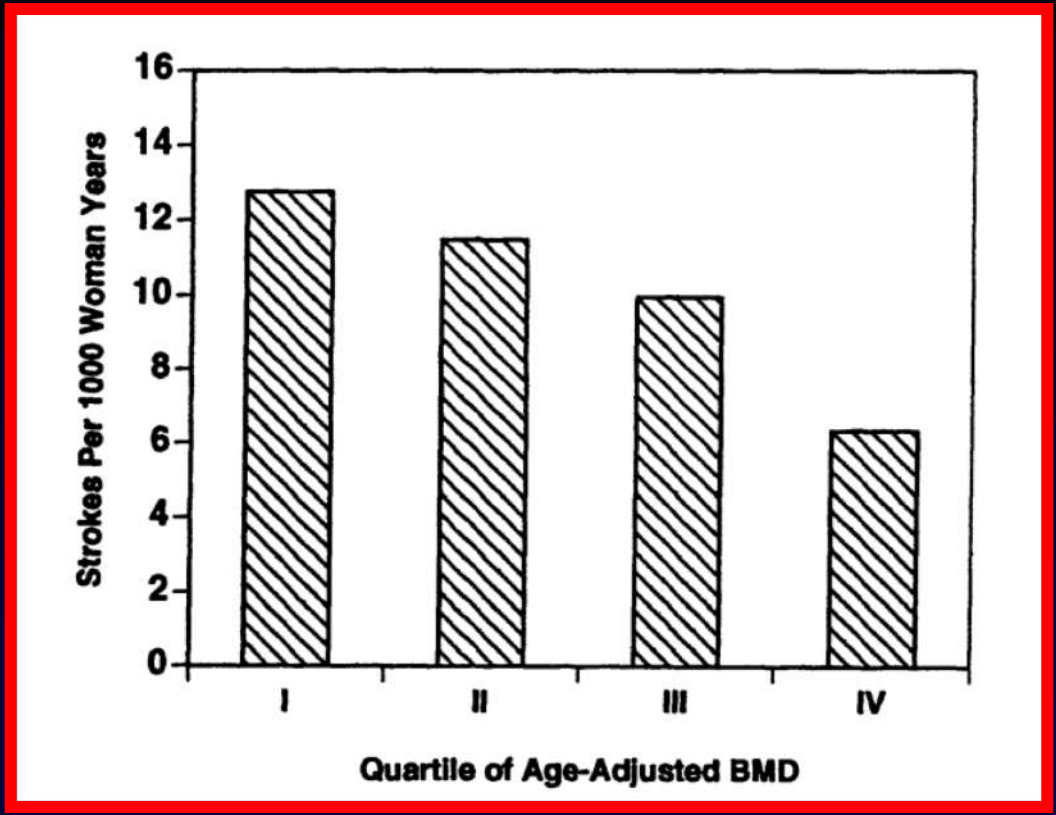
Myint PK et al, Stroke 2014

Increased risk of stroke in the year after a hip fracture



Kang JH et al, Stroke 2011

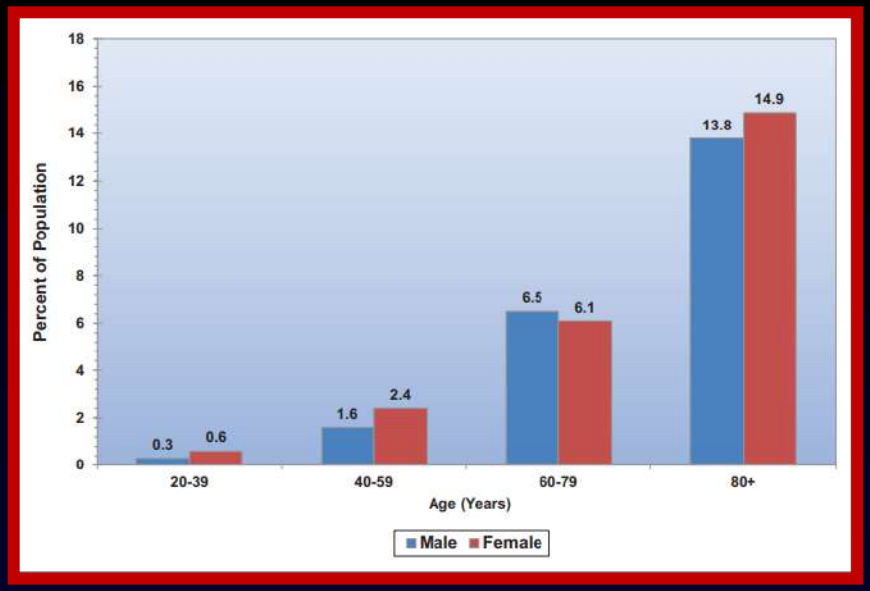
Common risk factor for Atherosclerotic Stroke and Osteoporosis



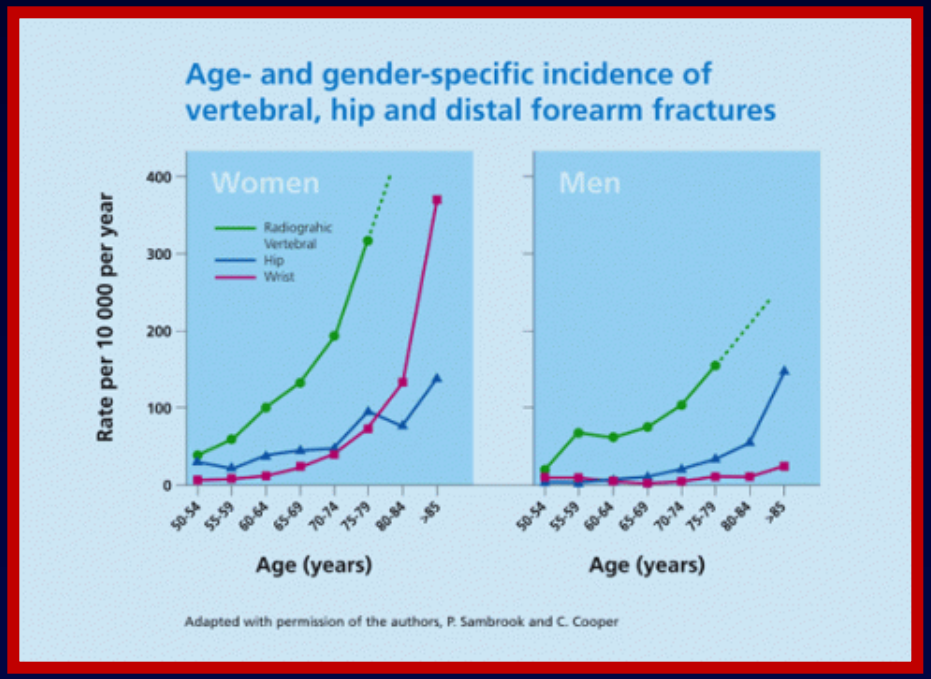
Age
Hypertension
Alcohol intake
Smoking
Diabetes
Cardiovascular disease

Browner WS et al. Stroke, 1993

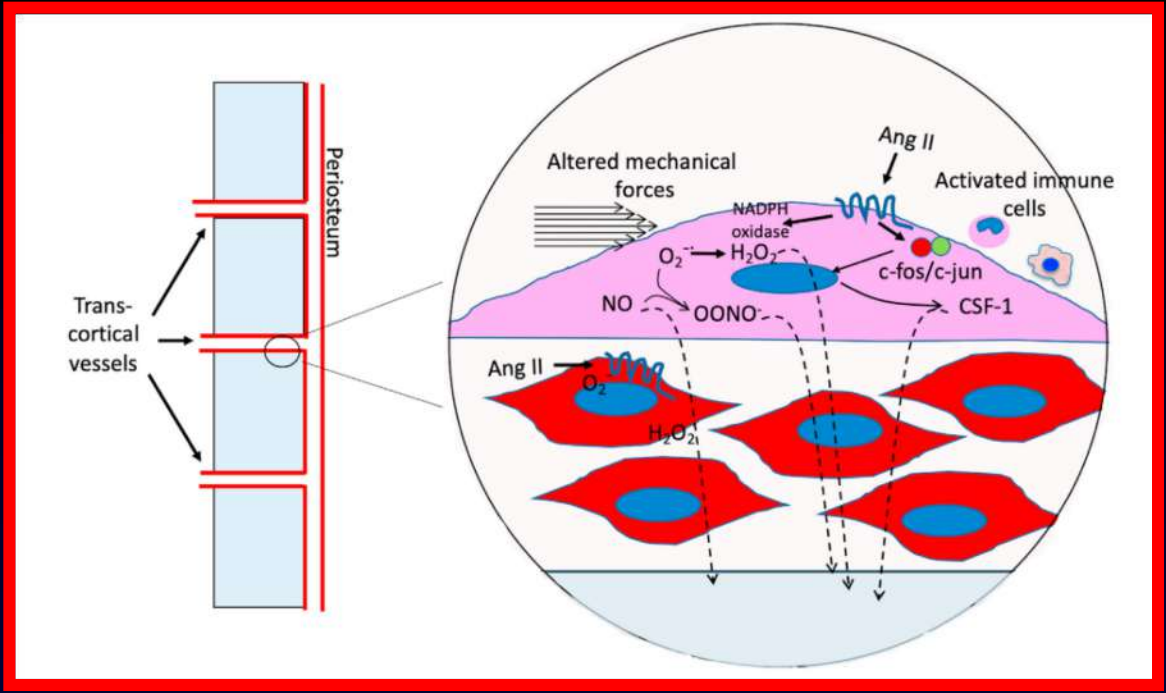
Tasso annuo di primo stroke per età e sesso



Heart Disease and Stroke Statistics—2018 Update



Factors linking Hypertension and Osteoporosis



Sympathetic tone
Vascular perturbations
Cytokines
Renin/angiotensin/aldosterone
Vitamin D

Do Carmo L and Harrison DG.
Med Novel Technology Device, 2020

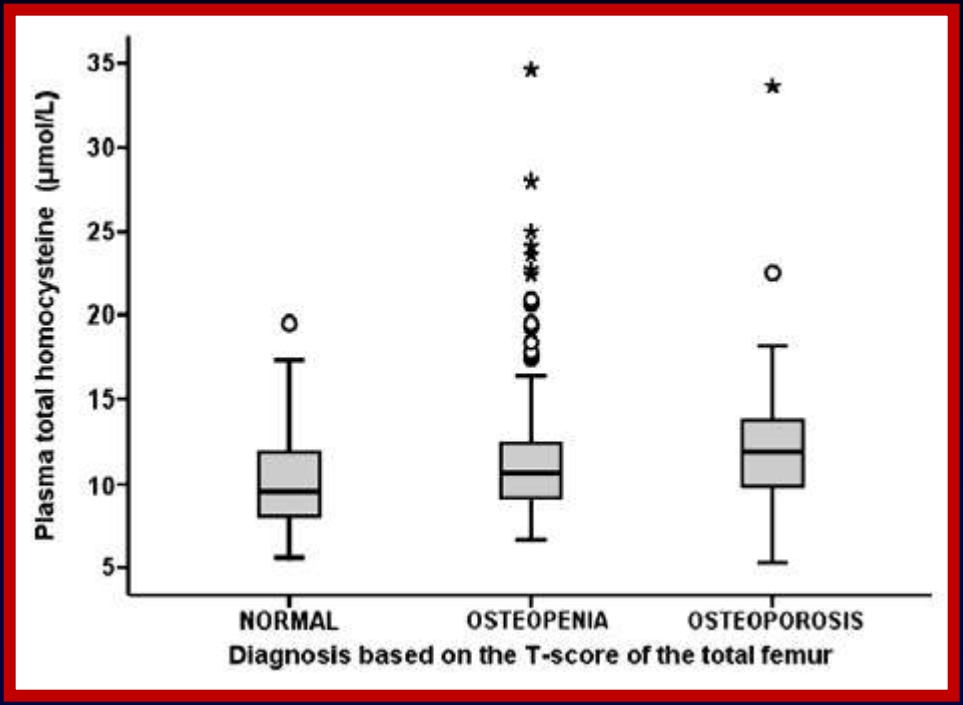
Increased Urinary Calcium Excretion

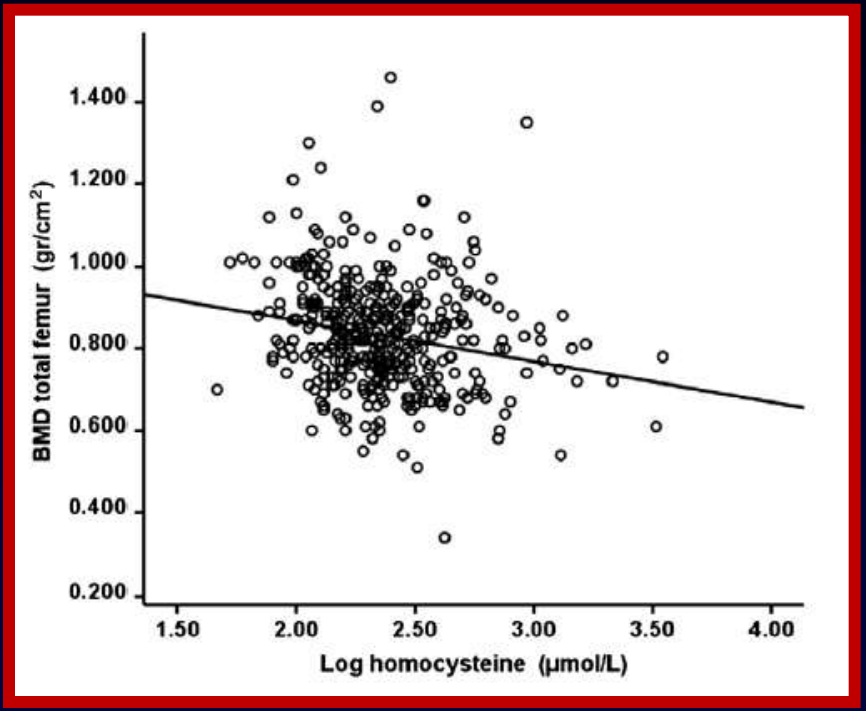
Caudarella R et al. J Clin Invest, 2009

The Role of Low Dairy Intake

Varenna M et al. Calcif Tissue Int, 2013

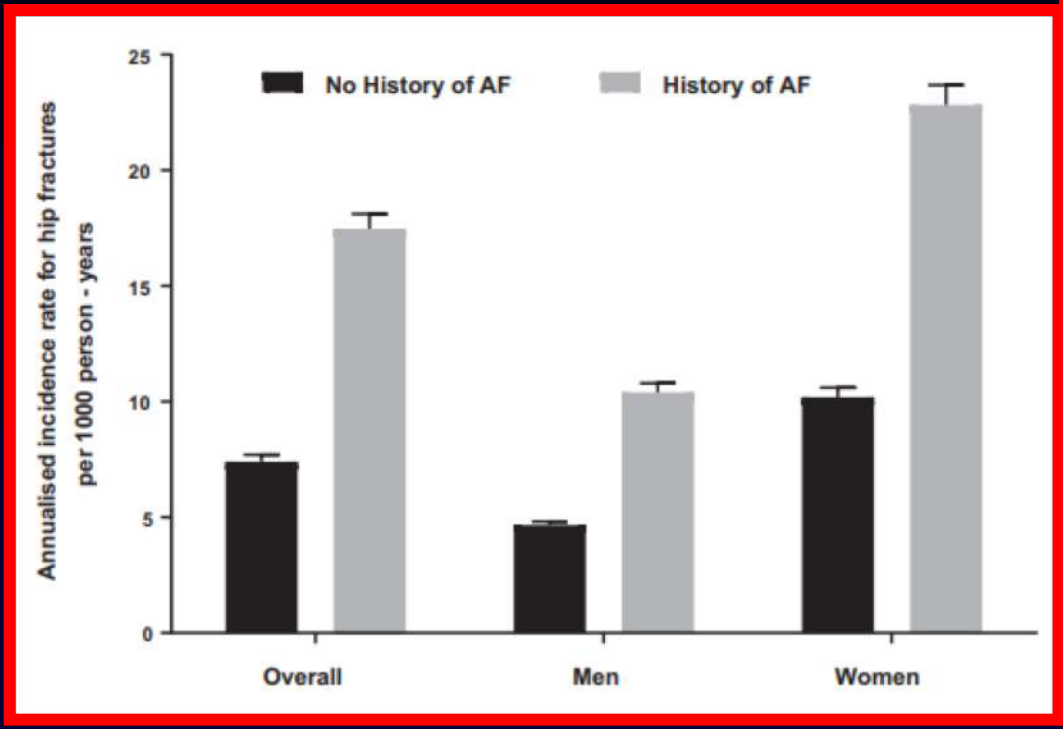
The relationship between plasma homocysteine levels and bone mineral density in post-menopausal women

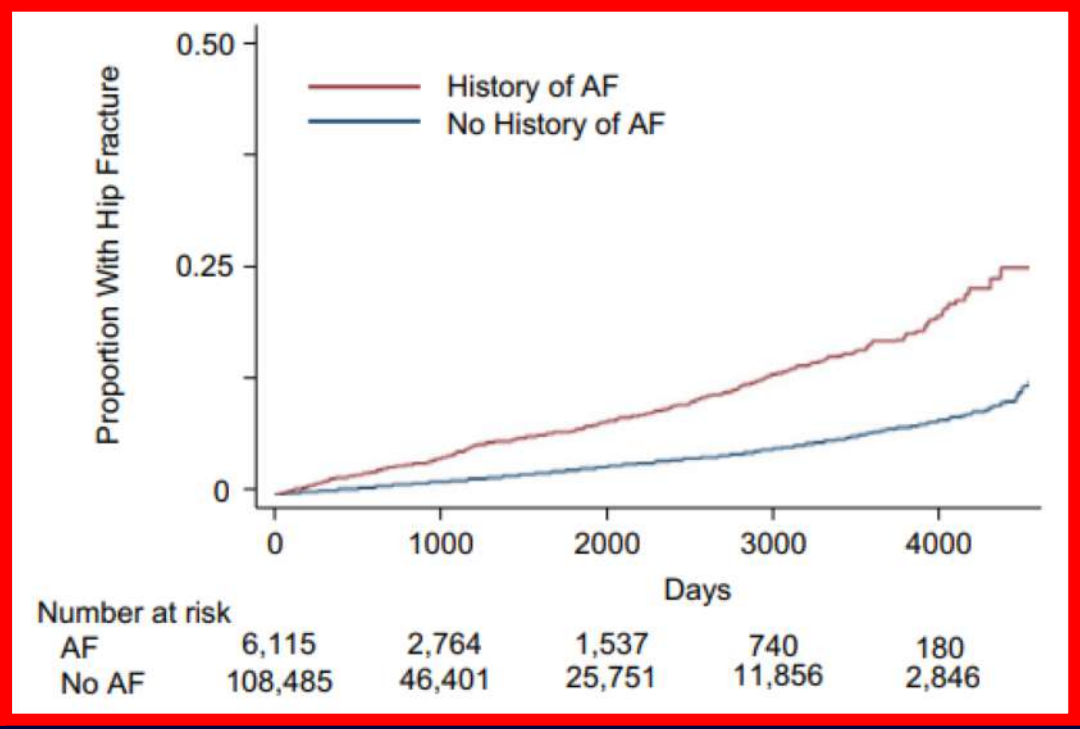




Bucciarelli P et al, Eur J Int Med, 2010

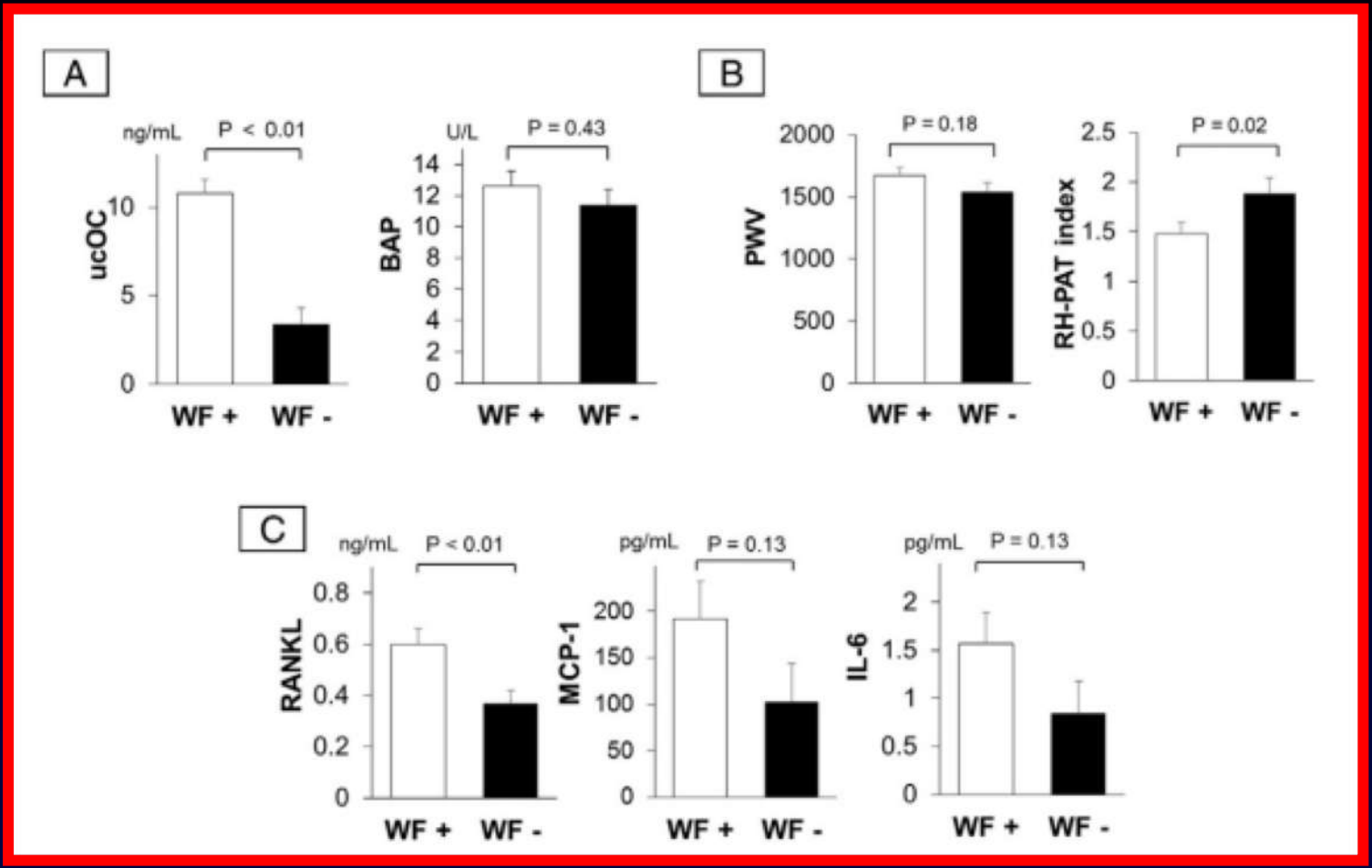
Atrial fibrillation and risk of hip fracture: A population-based analysis of 113,600 individuals





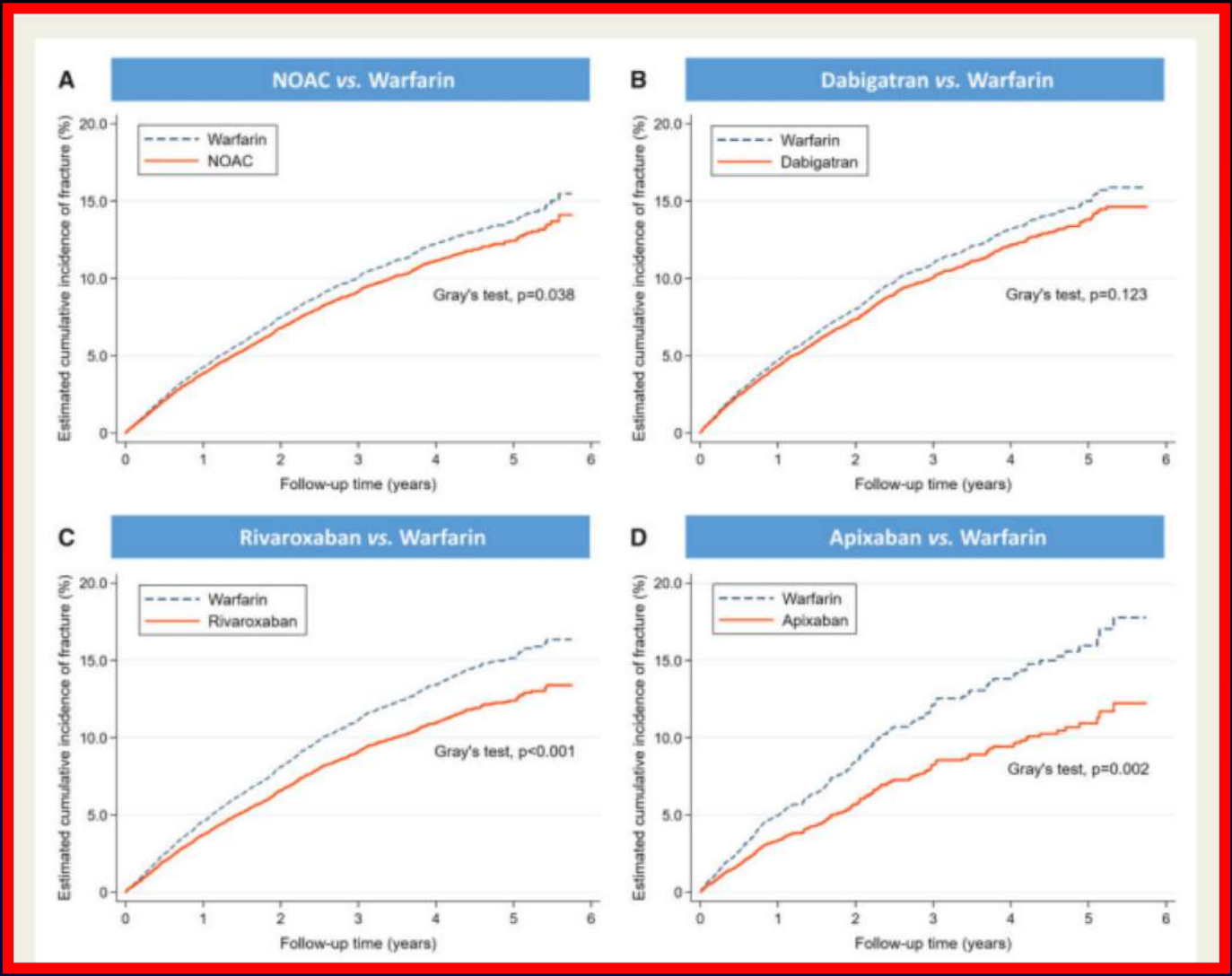
Wong CX et al. Int J Cardiol, 2017

Long-term Warfarin therapy and biomarkers for osteoporosis and atherosclerosis



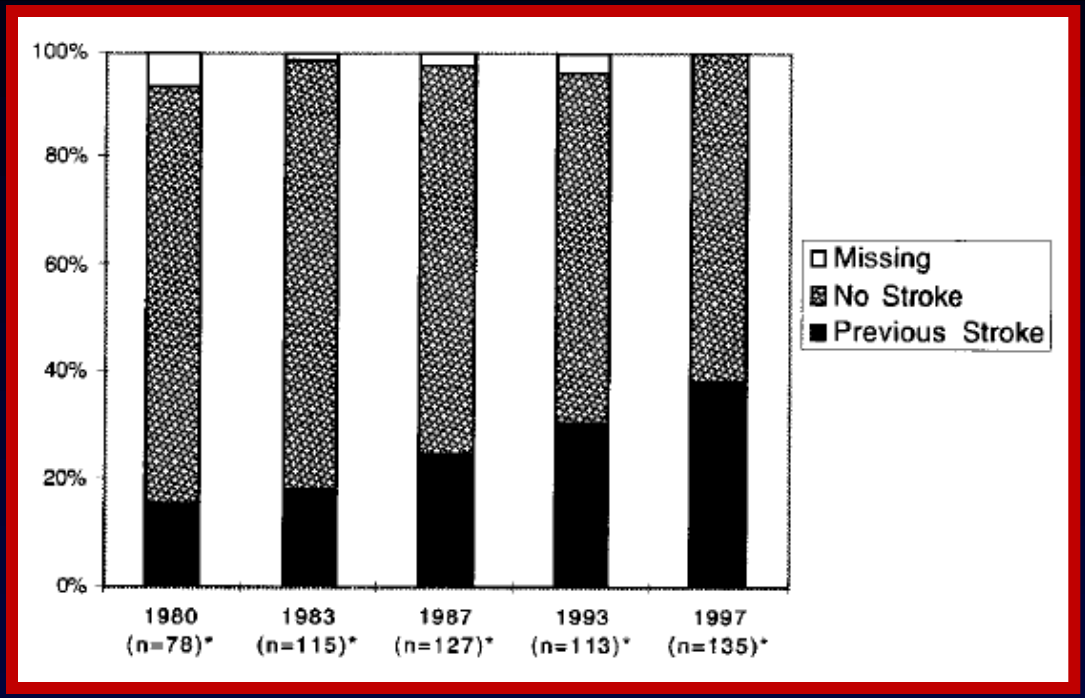
Namba S et al. BBA Clinical 4, 2015

Fracture risk among patients with atrial fibrillation receiving different oral anticoagulants: a real-world nationwide cohort study

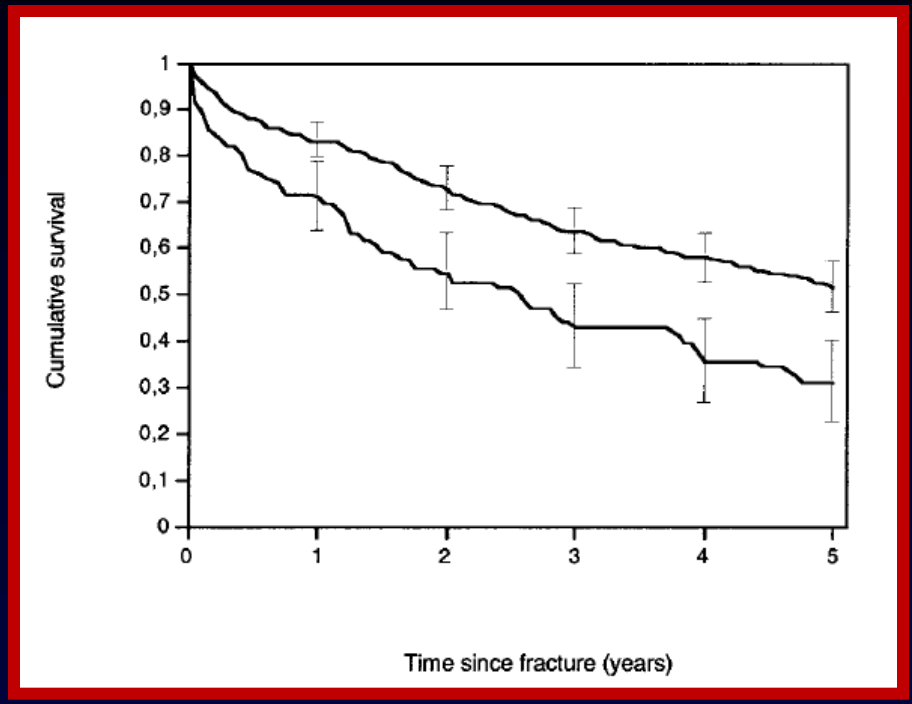


Huang HK et al. Eur Heart, 2020

Stroke, a mayor and increasing risk factor for femoral neck fracture



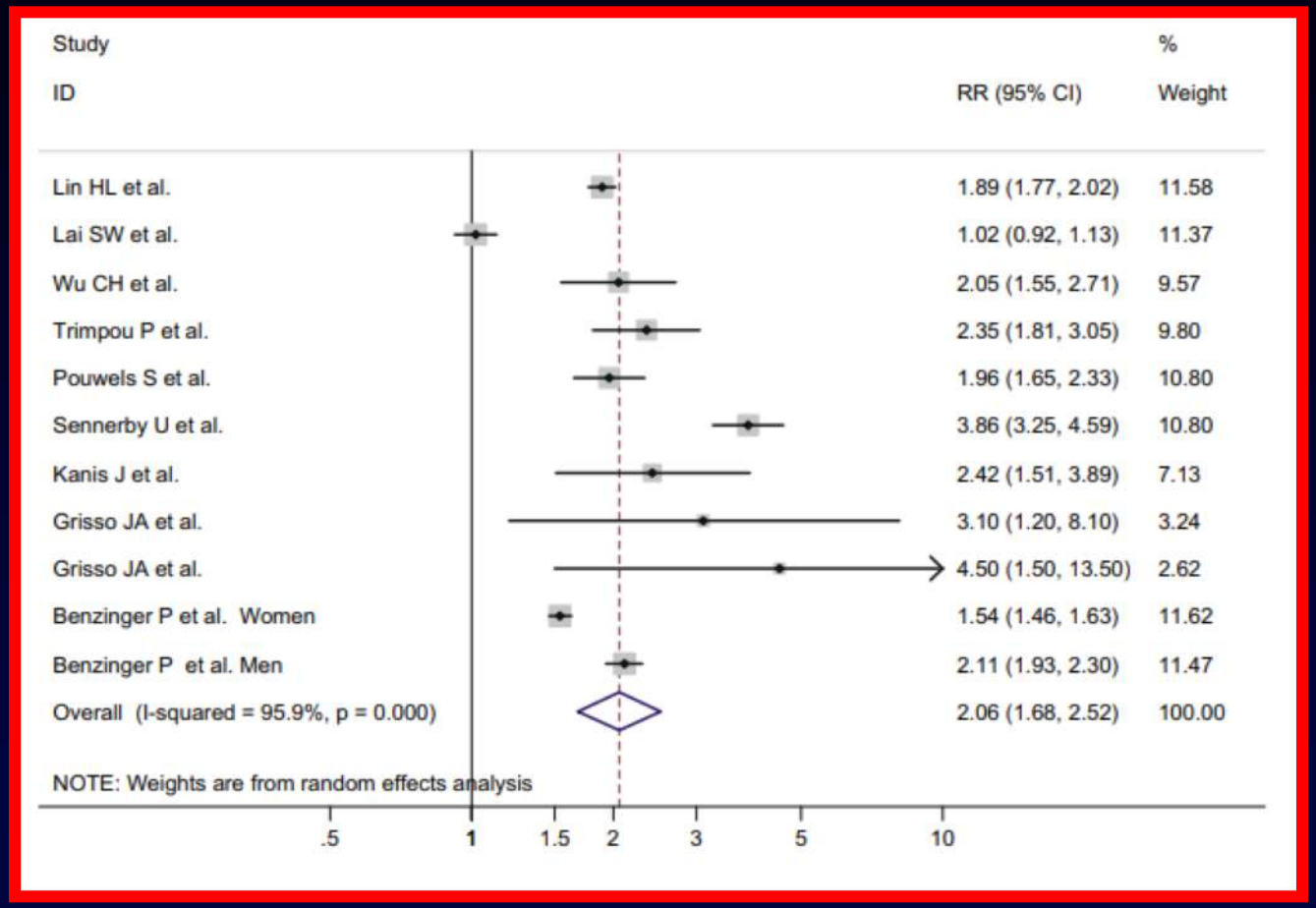
Proportion of previous stroke among patients with femoral neck fracture



Survival after femoral neck fracture in patients with and without previous stroke

Ramnemark et al, Stroke, 2000

Stroke increases the risk of hip fracture: a systematic review and meta-analysis



Luan L et al. Osteopor Int, 2016

Association between post-stroke disability and 5-year hip fracture risk: The Women's Health Initiative

Cumulative risk of hip fracture

	30 days	1 year	5 years
All Stroke	0.07%	0.99%	3.97%
Ischemic Stroke	0.07%	1.01%	3.99%
Other Stroke	0.00%	0.82%	4.00%
Good Recovery	0.00%	0.50%	3.28%
Moderate Disability	0.07%	0.78%	3.58%
Severe Disability	0.16%	2.05%	5.72%*
<65 years	0.00%	0.43%	1.16%
≥65 years	0.07%	1.06%	4.44%*

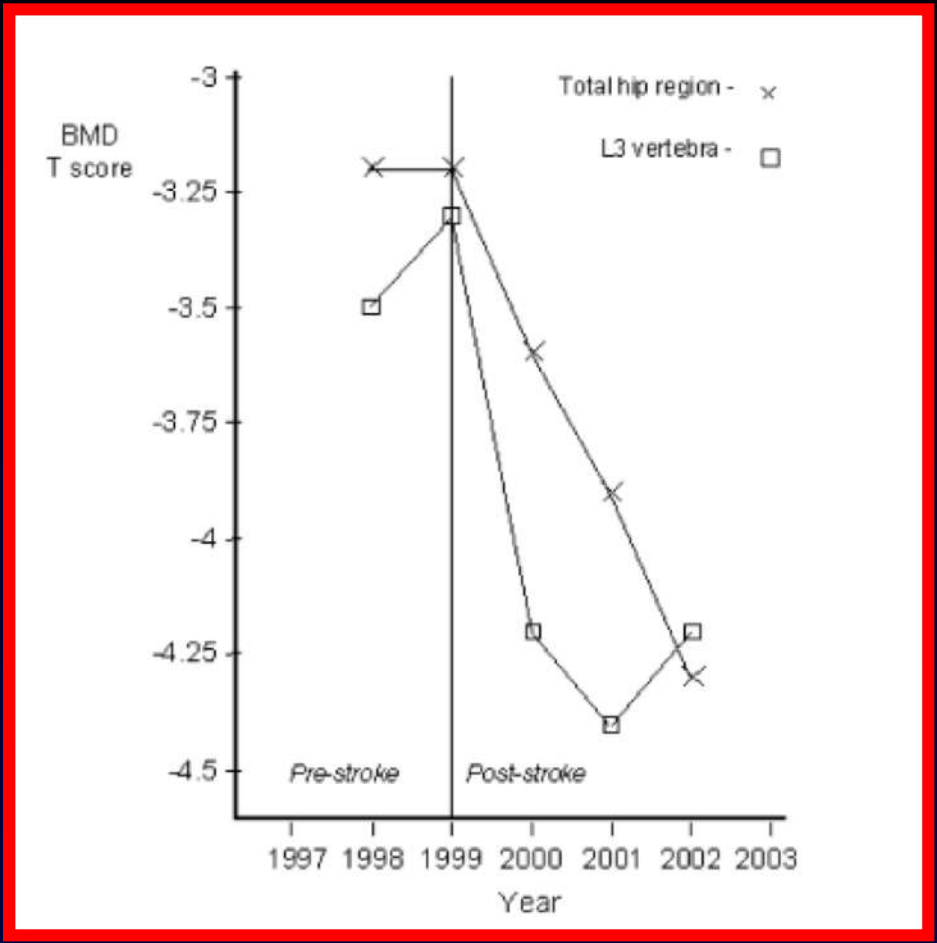
* logrank: $p<0.05$

Northuis CA et al. J Stroke Cerebrovasc Dis, 2020

Fractures after stroke

- Pre-existing osteoporosis
- Hemi-osteoporosis
- Propensity to fall
- Vitamin D deficiency
- Bone remodelling

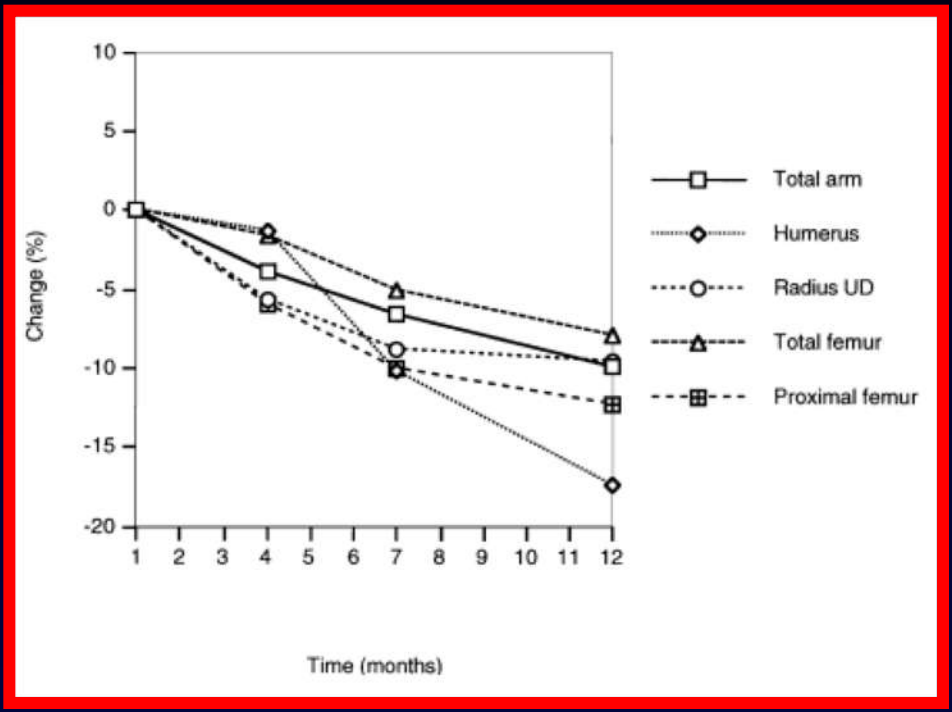
Low Bone Mass and Stroke



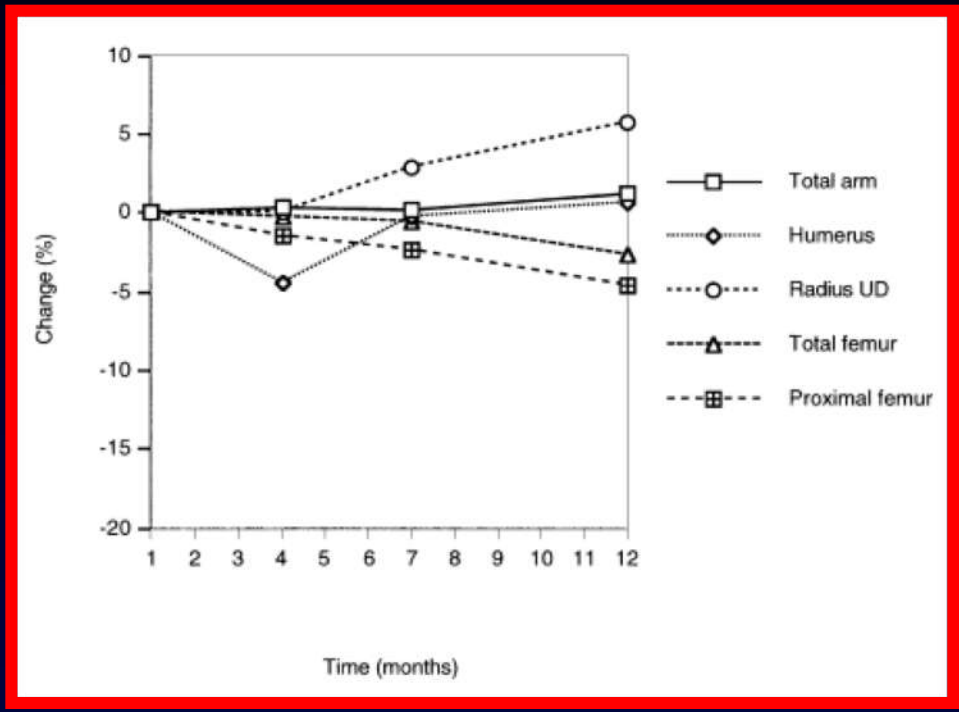
Poole KES et al. Osteoporos Int, 2005

Change in BMD % in the first year after stroke

Paretic side



Nonparetic side



Ramnemark A et al. Osteopor Int, 1999

Exercise protects bone after stroke

Table 3: Principles of exercise to maximise bone adaptation.

Exercise principle	More effective	Less effective
Weight bearing	(i) High impact (jogging, jumping) (ii) Bursts of activity (iii) Rapid movement	(i) Low impact (walking) (ii) Sustained activity (iii) Slow movement (iv) Non-weight-bearing aerobic (swimming or cycling) does not enhance bone density
Resistance training	(i) Heavy weight (ii) Rapid lifting (power training)	(i) Light weight (ii) Slow lift (traditional resistance training)
Muscle groups	(i) Target muscle connected to bones at risk of osteoporotic fracture (hip, wrist, spine)	(i) Non-specific-muscle groups
Length of training	(i) Short bouts interspersed with rest breaks	(i) Continuous movement
Direction of force	(i) Novel force patterns (change in direction or height of jumps)	(i) Repetitive force patterns (jogging in one direction, consistent height jumps)

Adapted from http://www.osteoporosis.org.au/images/stories/documents/internal/oa_exercise_gphp.pdf.

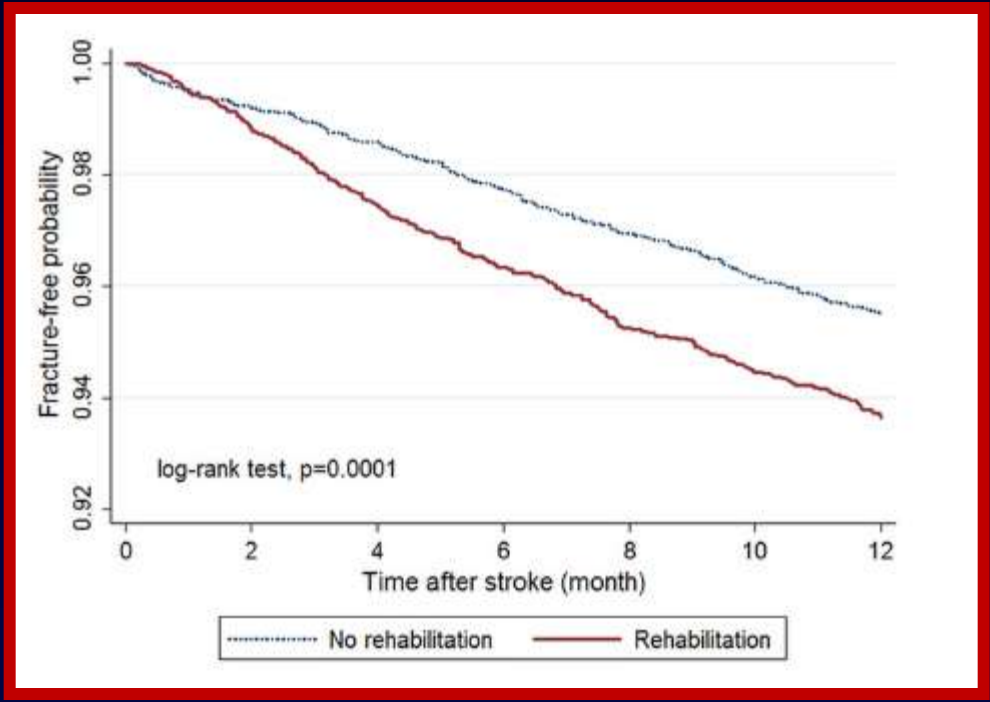
Borschman K, Stroke Research and Treatment, 2012

Anatomic site		Ambulatory level at baseline	n	BMD at baseline mean (SD)	Change at 7 months mean (95% CI)	% change at 7 months	p value	Change at 1 year mean (95% CI)	% change at 1 year	p value
Femoral neck	Paretic leg	FAC 1	17	0.84 (0.15)	−0.07 (−0.11; −0.03)	−8	0.003	−0.08 (−0.11; −0.05)	−10	<0.001
		FAC 2–6	23	0.80 (0.16)	−0.03 (−0.04; ÷0.01)	−4	0.006	−0.02 (−0.04; −0.01)	−3	0.01
	Nonparetic leg	FAC 1	17	0.84 (0.11)	−0.02 (−0.04; −0.01)	−2	0.007	−0.04 (−0.07; −0.01)	−5	0.009
		FAC 2–6	23	0.80 (0.18)	−0.01 (−0.04; 0.02)	−1	0.5	−0.01 (−0.04; 0.01)	−1	0.3
Trochanter	Paretic leg	FAC 1	17	0.83 (0.14)	−0.06 (÷0.09; −0.03)	−7	<0.001	−0.08 (−0.11; −0.04)	−10	<0.001
		FAC 2–6	23	0.79 (0.18)	−0.03 (−0.05; −0.01)	−4	0.004	−0.02 (−0.04; 0.01)	−3	0.1
	Nonparetic leg	FAC 1	17	0.82 (0.14)	−0.03 (−0.06; 0.00)	−4	0.04	−0.04 (−0.08; 0.00)	−5	0.04
		FAC 2–6	23	0.78 (0.20)	0.00 (−0.02; 0.02)	0	0.9	0.00 (−0.03; 0.02)	0	0.9

Jorgensen L et al, Osteoporos Int, 2000

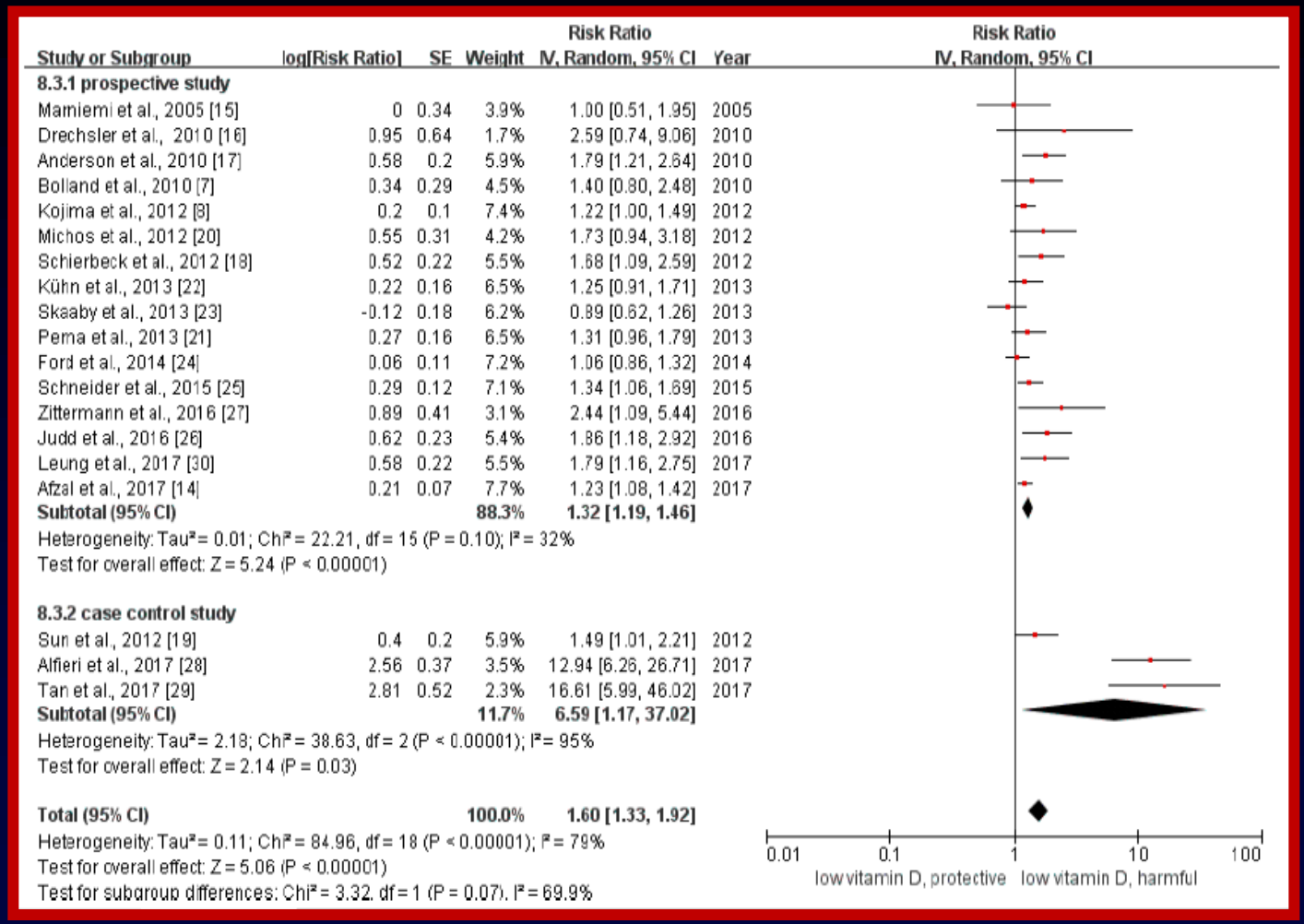
Stroke rehabilitation is associated with a higher risk of fractures in older women

	Rehabilitation (n = 4192)	Non-rehabilitation (n = 4192)	p value
Demographic factors			
Age (y), mean ± SD	68.0 ± 12.4	67.9 ± 12.4	0.774
Male, n (%)	2,533 (60.4%)	2,521 (60.1%)	0.789
Comorbidities			
Charlson Comorbidity Index	12.7 ± 1.85	2.72 ± 1.82	0.938
Hypertension	3,311 (79.0%)	3,310 (79.0%)	0.979
Diabetes mellitus	1,768 (42.2%)	1,744 (41.6%)	0.595
Osteoporosis	169 (4.0%)	171 (4.1%)	0.912
COPD	772 (18.4%)	736 (17.6%)	0.306
Congestive heart failure	386 (9.2%)	379 (9.0%)	0.791
Chronic kidney disease	371 (8.9%)	361 (8.6%)	0.699
Malignancy	256 (6.1%)	245 (5.8%)	0.612
Parkinsonism	128 (3.1%)	123 (2.9%)	0.749
Epilepsy	60 (1.4%)	64 (1.5%)	0.717
Dementia	208 (5.0%)	204 (4.9%)	0.840
Depression	179 (4.3%)	174 (4.2%)	0.786



Huang KU et al, Plos One, 2017

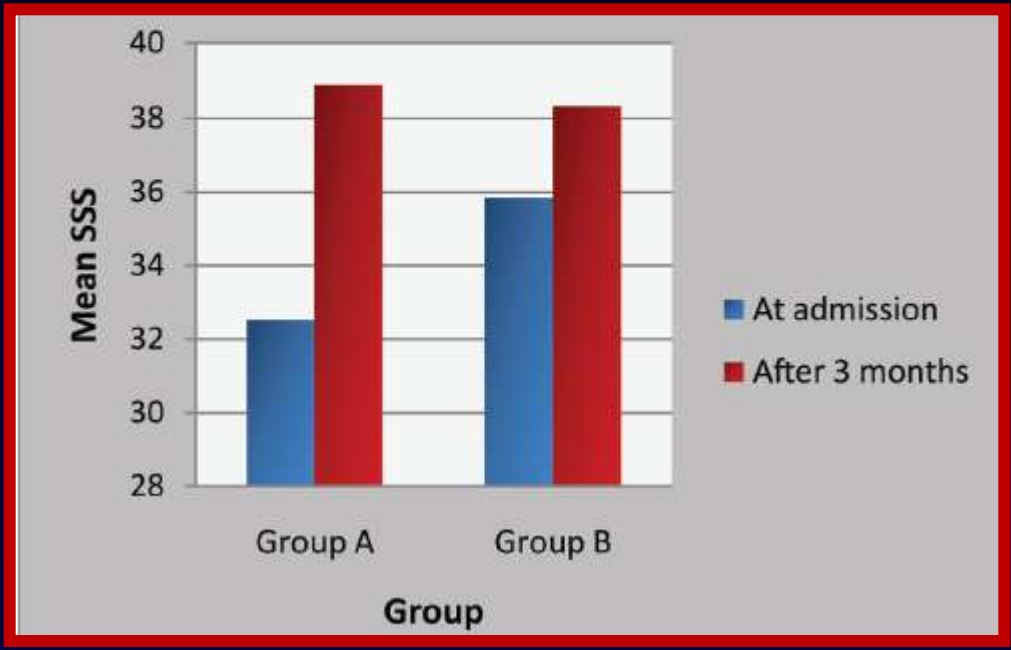
Lower vitamin D status is associated with an increased risk of ischemic stroke



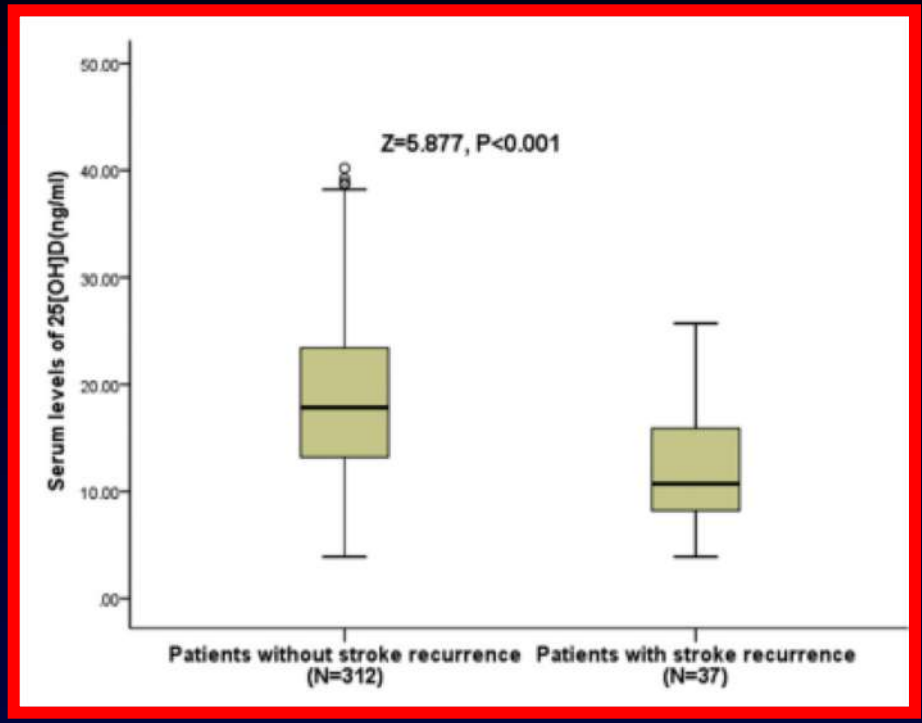
Zhou R et al., Nutrients, 2018

Role of vitamin D in the outcome of ischemic stroke

Group	Mean±SD of vitamin D (ng/ml) in vitamin D deficiency patients	Mean±SD of vitamin D (ng/ml) in vitamin D insufficiency patients
A	15.59±1.48	23.04±1.36
B	14.92±1.38	24.13±1.11

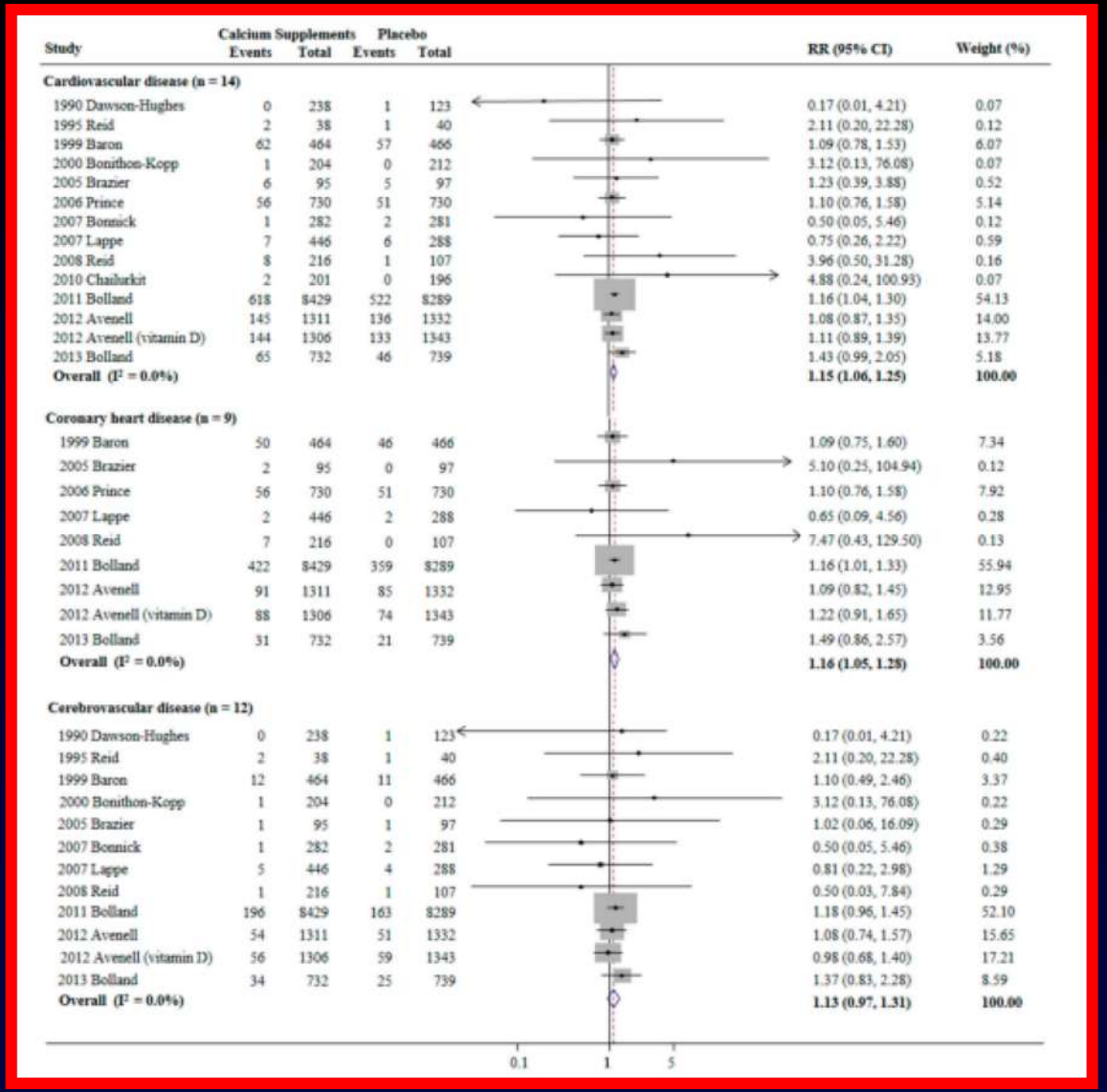


Narashiman S et al., J Clin Diag Res, 2017



Huang H et al. 2016

Calcium intake and cardiovascular risk



Study	Calcium Supplements Events	Total	Placebo Events	Total	RR (95% CI)	Weight (%)
Cardiovascular disease (n = 14)						
1990 Dawson-Hughes	0	238	1	123	0.17 (0.01, 4.21)	0.07
1995 Reid	2	38	1	40	2.11 (0.20, 22.28)	0.12
1999 Baron	62	464	57	466	1.09 (0.78, 1.53)	6.07
2000 Bonithon-Kopp	1	204	0	212	3.12 (0.13, 76.08)	0.07
2005 Brazier	6	95	5	97	1.23 (0.39, 3.88)	0.52
2006 Prince	56	730	51	730	1.10 (0.76, 1.58)	5.14
2007 Bonnick	1	282	2	281	0.50 (0.05, 5.46)	0.12
2007 Lappe	7	446	6	288	0.75 (0.26, 2.22)	0.59
2008 Reid	8	216	1	107	3.96 (0.50, 31.28)	0.16
2010 Chaiharkit	2	201	0	196	4.88 (0.24, 100.93)	0.07
2011 Bolland	618	8429	522	8289	1.16 (1.04, 1.30)	54.13
2012 Avenell	145	1311	136	1332	1.08 (0.87, 1.35)	14.00
2012 Avenell (vitamin D)	144	1306	133	1343	1.11 (0.89, 1.39)	13.77
2013 Bolland	65	732	46	739	1.43 (0.99, 2.05)	5.18
Overall (I^2 = 0.0%)					**1.15 (1.06, 1.25)**	**100.00**
Coronary heart disease (n = 9)						
1999 Baron	50	464	46	466	1.09 (0.75, 1.60)	7.34
2005 Brazier	2	95	0	97	5.10 (0.25, 104.94)	0.12
2006 Prince	56	730	51	730	1.10 (0.76, 1.58)	7.92
2007 Lappe	2	446	2	288	0.65 (0.09, 4.56)	0.28
2008 Reid	7	216	0	107	7.47 (0.43, 129.50)	0.13
2011 Bolland	422	8429	359	8289	1.16 (1.01, 1.33)	55.94
2012 Avenell	91	1311	85	1332	1.09 (0.82, 1.45)	12.95
2012 Avenell (vitamin D)	88	1306	74	1343	1.22 (0.91, 1.65)	11.77
2013 Bolland	31	732	21	739	1.49 (0.86, 2.57)	3.56
Overall (I^2 = 0.0%)					**1.16 (1.05, 1.28)**	**100.00**
Cerebrovascular disease (n = 12)						
1990 Dawson-Hughes	0	238	1	123	0.17 (0.01, 4.21)	0.22
1995 Reid	2	38	1	40	2.11 (0.20, 22.28)	0.40
1999 Baron	12	464	11	466	1.10 (0.49, 2.46)	3.37
2000 Bonithon-Kopp	1	204	0	212	3.12 (0.13, 76.08)	0.22
2005 Brazier	1	95	1	97	1.02 (0.06, 16.09)	0.29
2007 Bonnick	1	282	2	281	0.50 (0.05, 5.46)	0.38
2007 Lappe	5	446	4	288	0.81 (0.22, 2.98)	1.29
2008 Reid	1	216	1	107	0.50 (0.03, 7.84)	0.29
2011 Bolland	196	8429	163	8289	1.18 (0.96, 1.45)	52.10
2012 Avenell	54	1311	51	1332	1.08 (0.74, 1.57)	15.65
2012 Avenell (vitamin D)	56	1306	59	1343	0.98 (0.68, 1.40)	17.21
2013 Bolland	34	732	25	739	1.37 (0.83, 2.28)	8.59
Overall (I^2 = 0.0%)					**1.13 (0.97, 1.31)**	**100.00**

0.1 1 5

Myung SK et al. Nutrients, 2021

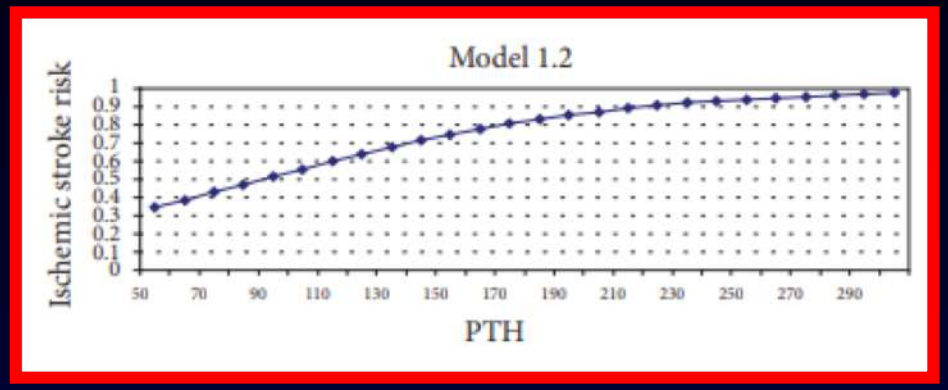
Parathyroid hormone levels in the prediction of ischemic stroke

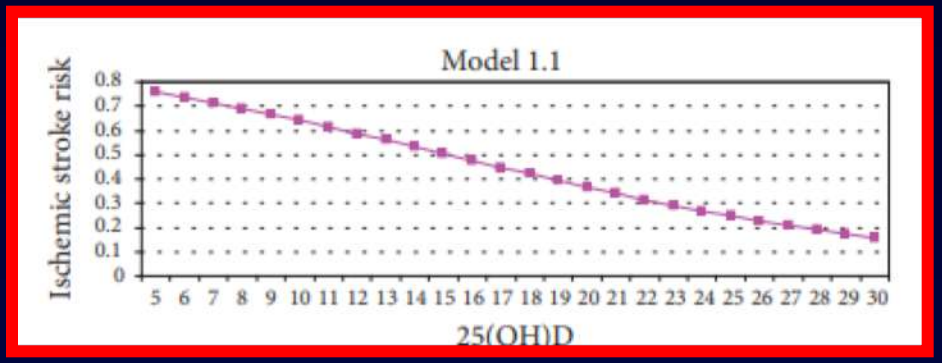
Acta med. scand. Vol. 192, pp. 299–308, 1972

STROKE IN HYPERPARATHYROIDISM

Harry Boström and Alv Alveryd

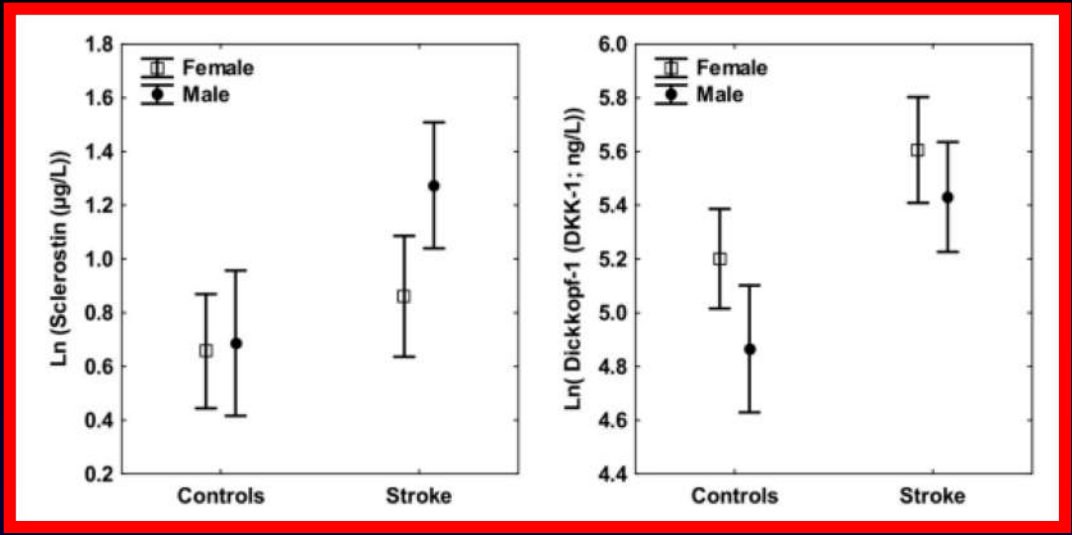
From Medical Department III, St. Erik's Hospital, and the Department of Surgery, Karolinska Institutet at Serafimerlasarettet, Stockholm, Sweden

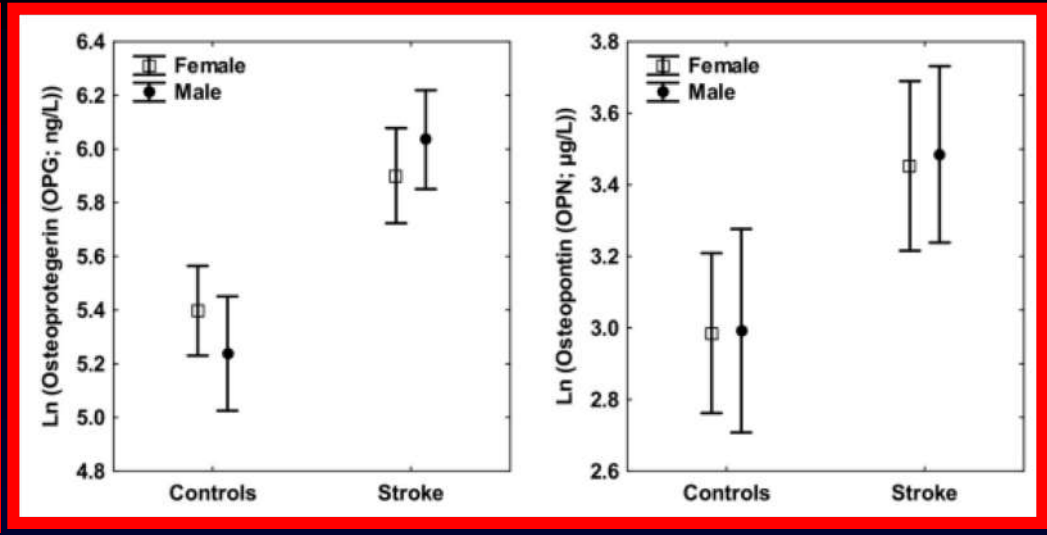


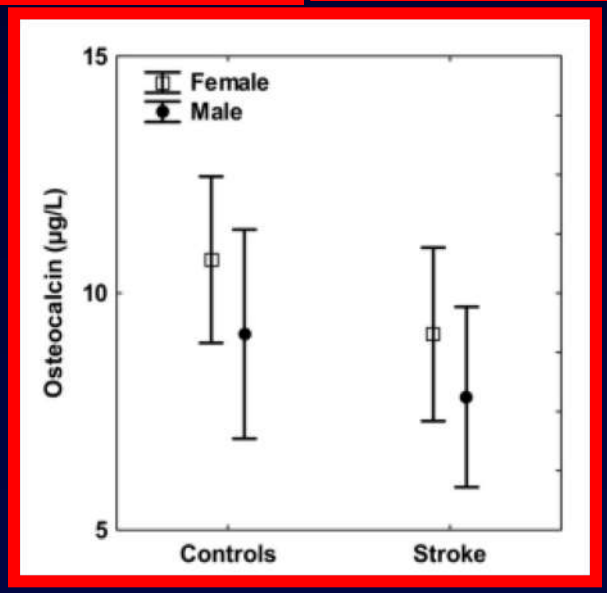


Celik G et al. Disease Markers,2017

Alterations in bone turnover markers in patients with noncardio-embolic ischemic stroke

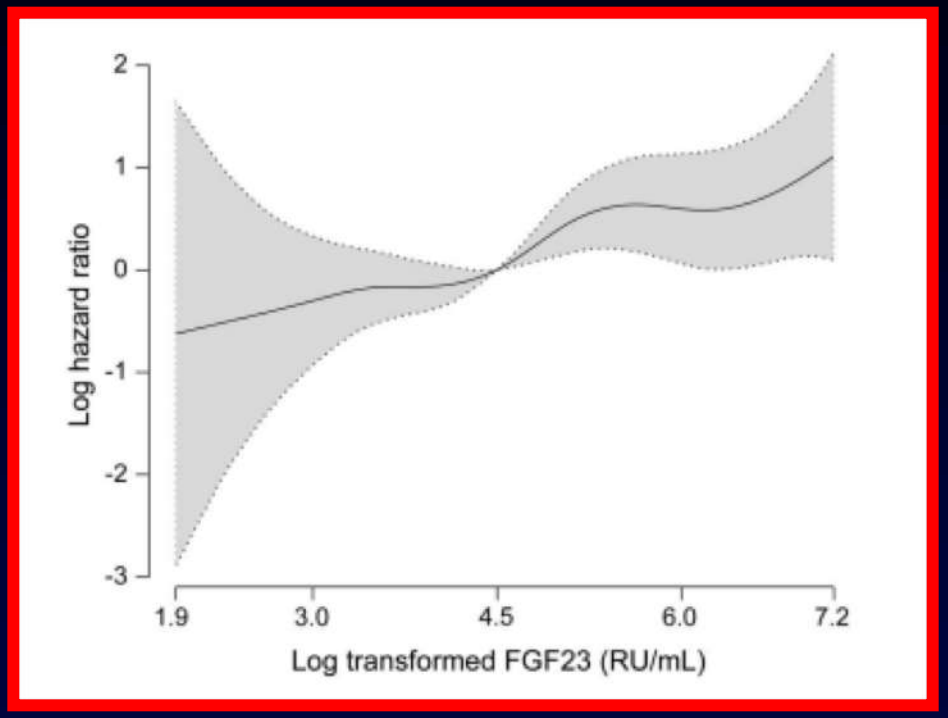


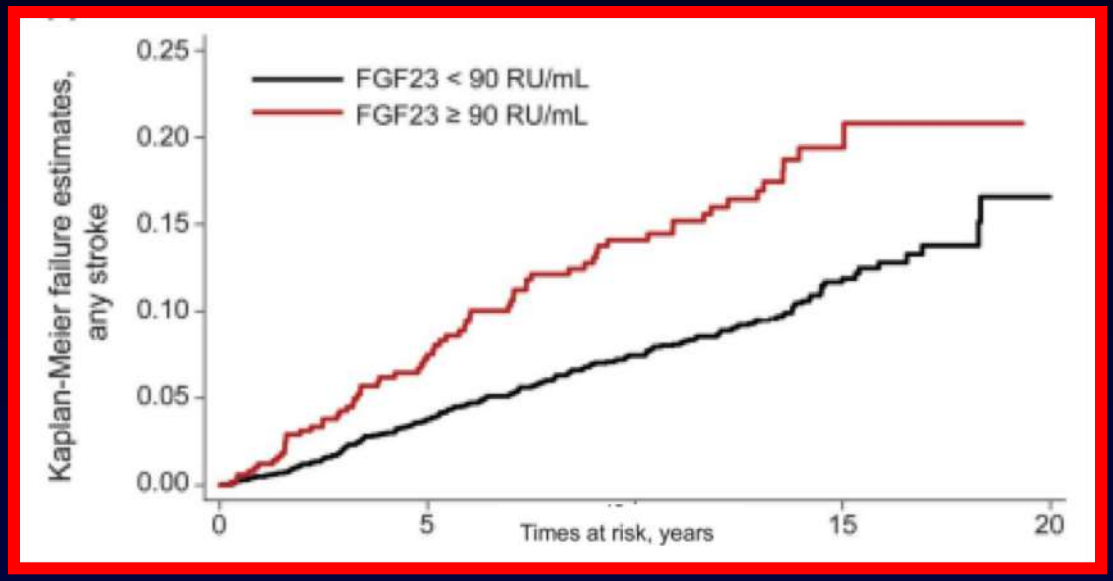




Mathold K te al. Plos One, 2018

Plasma FGF23 and the risk of stroke





Wright CB et al. Neurology, 2014

197 ictus ischemici

40 ictus emorragici

474 controlli

Lo scopo del nostro studio è stato quello di valutare le concentrazioni plasmatiche dei metaboliti ossei principali (25-OH vitamina D, PTH, FGF-23, sclerostina) in pazienti ospedalizzati per stroke e indagare le loro implicazioni nella severità della patologia.

Table 1. Baseline Characteristics of Cases and Controls

	Ischemic Stroke	Hemorragic Stroke	Controls
Age *(yrs)*	69.9±15	68.5±13	67.9±18
Sex *(M/F)*	110/87	26/14	270/204
NHISS	9.2±8	8.9±10	-
Rankin	0.41±0.9	0.25±0.6	-
25-OHD *(ng/ml)*	19.2±9	19.1±10	22.1±12
PTH *(pg/ml)*	64.1±46	56.7±28	35.7±27*
Int-FGF23 *(RU/ml)*	36.0±12	37.9±13	28.5±12*
Sclerostin *(pmol/l)*	47.6±25	54.8±44	39.5±16*

** p<0.01 vs. ischemic and hemorragic stroke*

Figure 1. Correlation between s-PTH and NIHSS at hospital admission (A) and discharge (B)

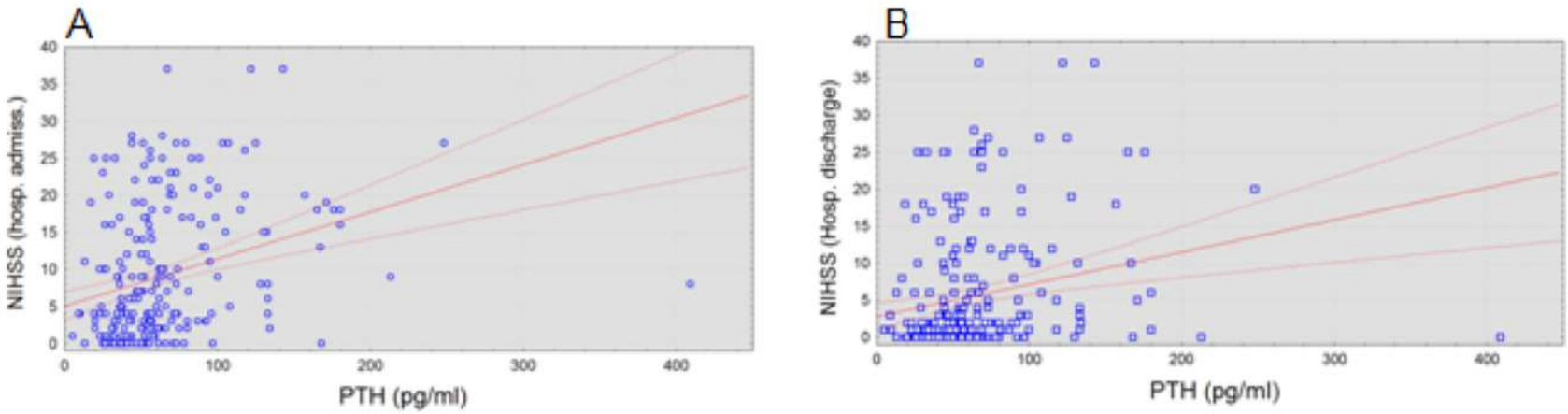
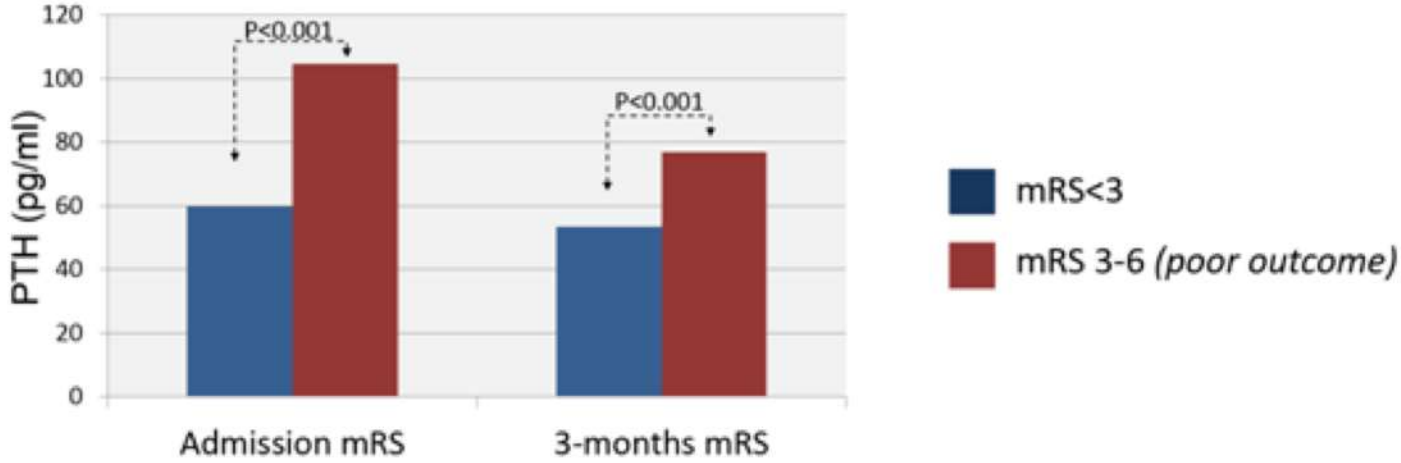
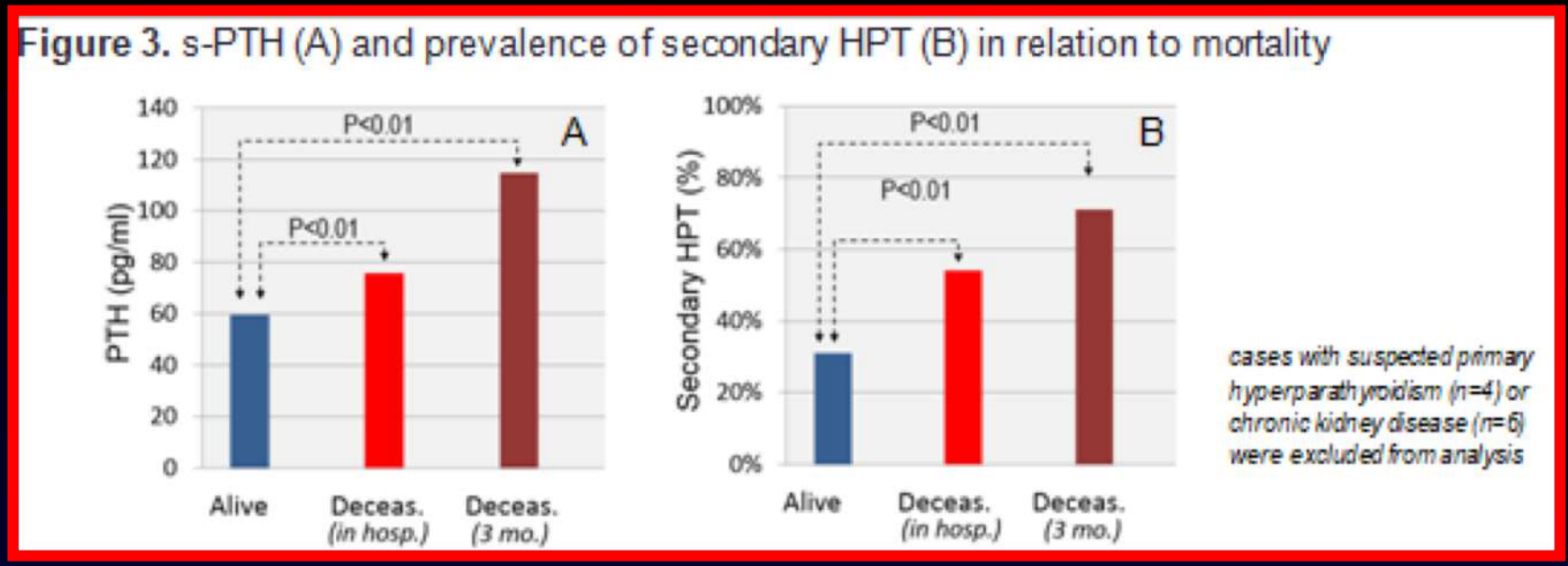


Figure 2. s-PTH in relation to mRS score at hospital admission and after 3 months





I nostri dati suggeriscono una possibile implicazione tra i livelli sierici di PTH e l'iperparatiroidismo secondario nella patogenesi, nel grado di disabilità e nella mortalità dell'ictus cerebri.

Al contrario FGF-23 e sclerostina non sembrano correlare significativamente nè con la severità nè con la prognosi dell'evento cerebrovascolare.

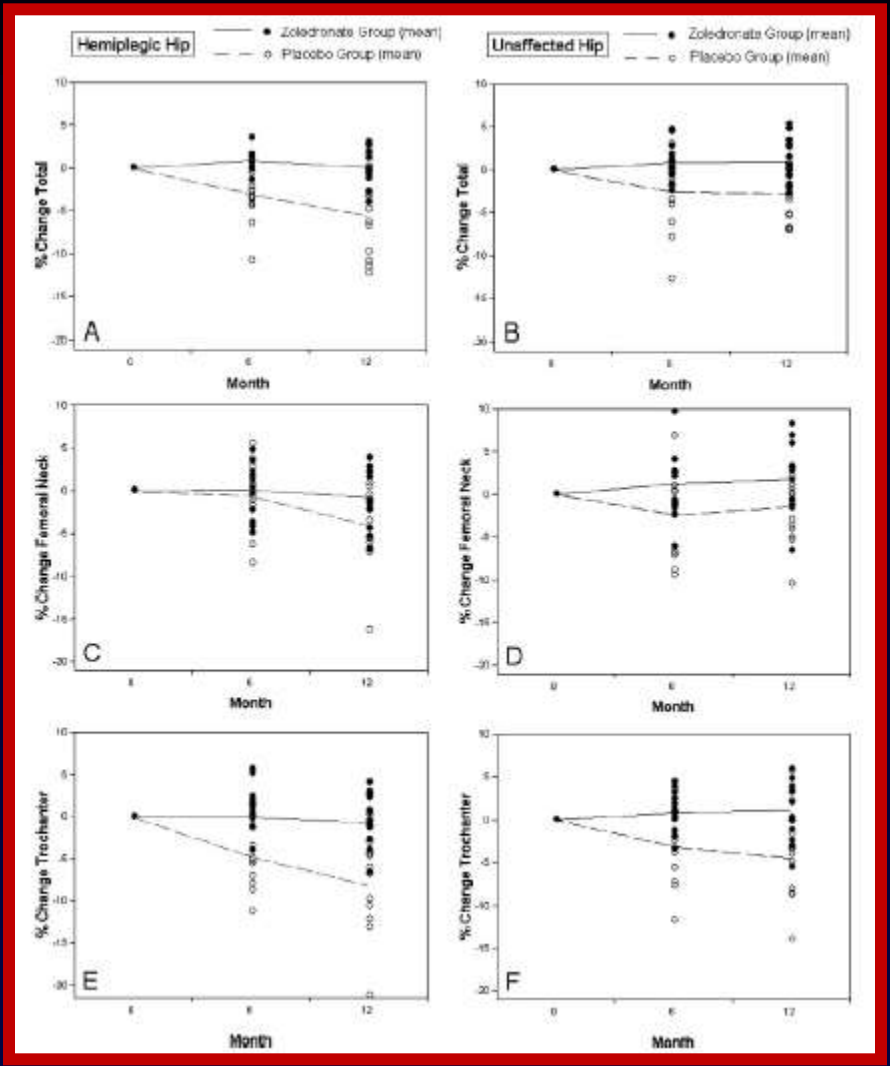
Trattamento della Osteoporosi dopo un Ictus

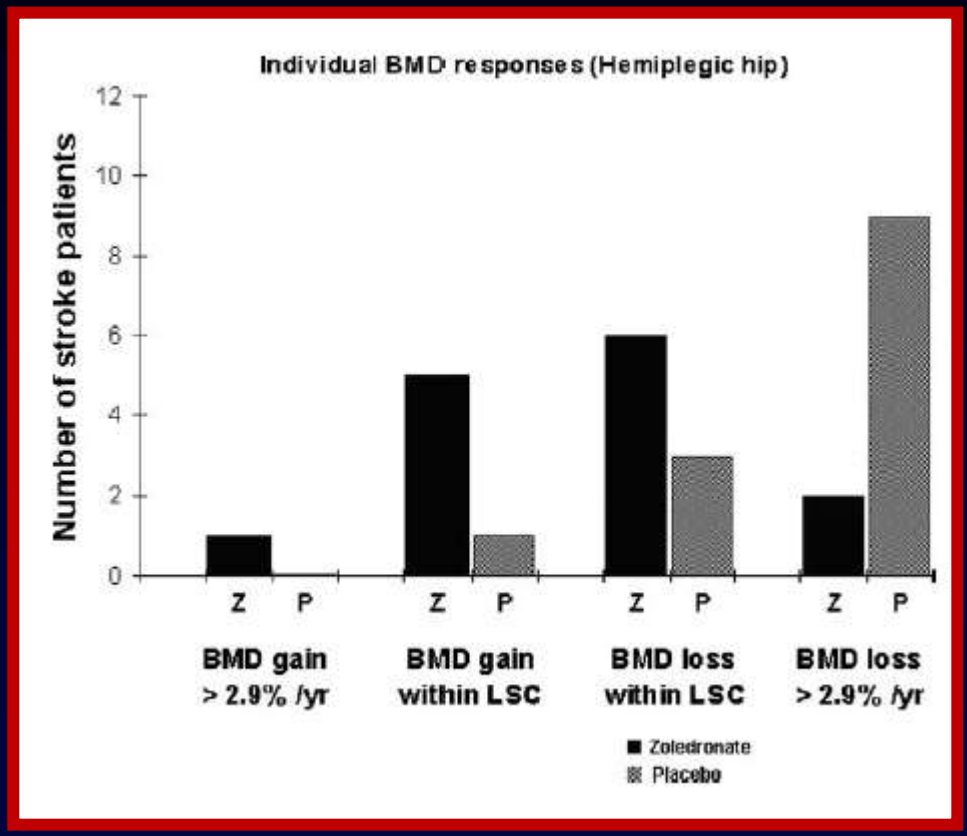
- L'ictus è un fattore di rischio per l'osteoporosi, le cadute e le fratture
- I pazienti con ictus sono raramente valutati e trattati per la osteoporosi

Ontario Stroke Registry

- 16581 stroke patients
- 5.1% overall and 2.9% of those without prior testing underwent screening
- 15.5% overall and 3.2% of those not previously on treatment were treated

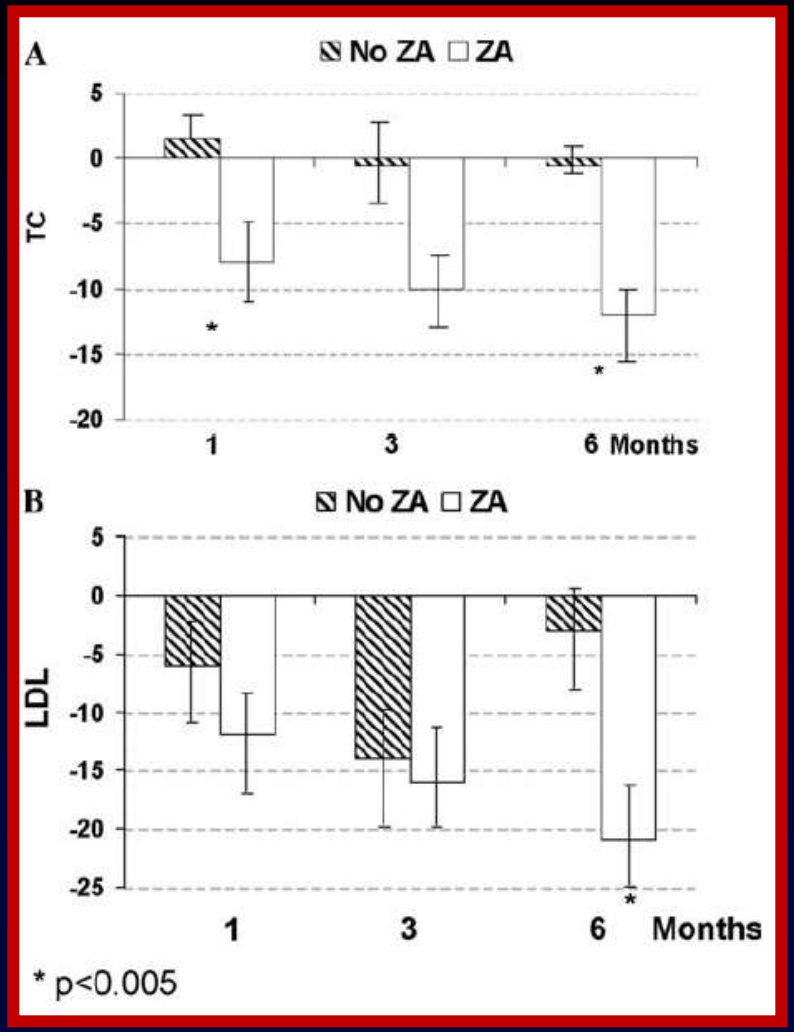
A Single Infusion of Zoledronate Prevents Bone Loss After Stroke





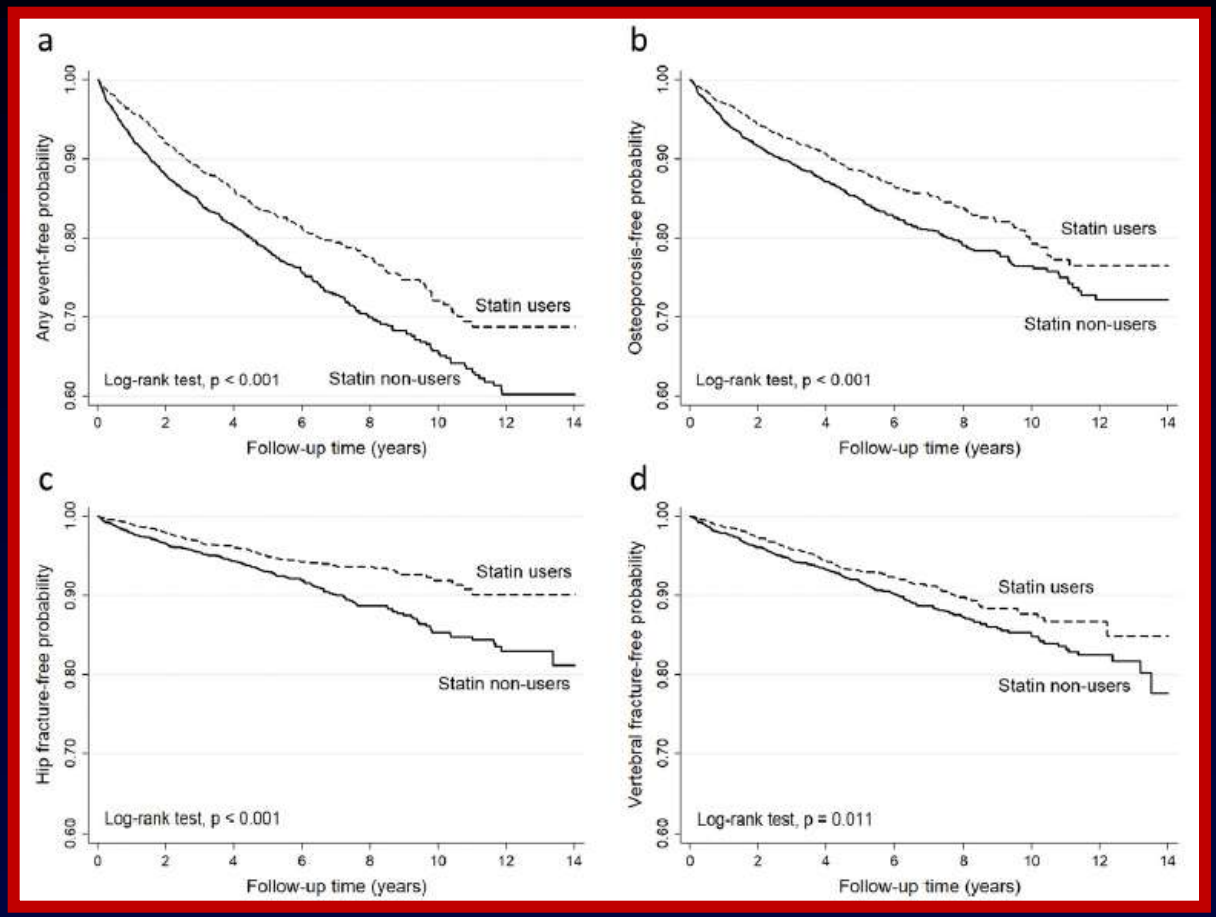
Poole K et al., Stroke, 2007

The effects of Zoledronic Acid on Serum Lipids



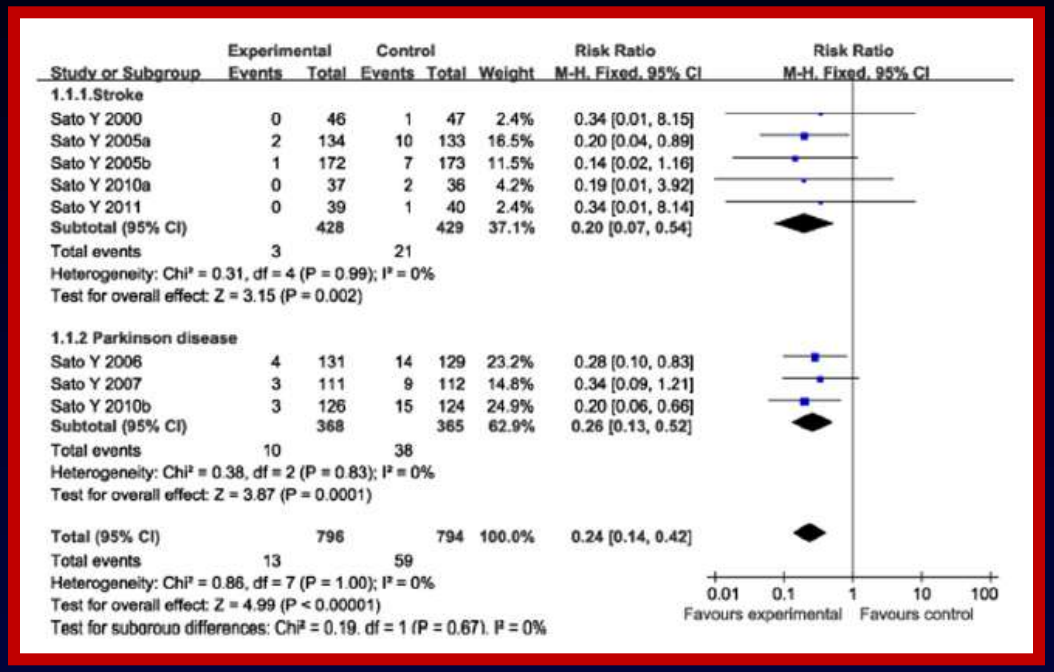
Gozzetti A, Martini G, Calc Tissue Int, 2008

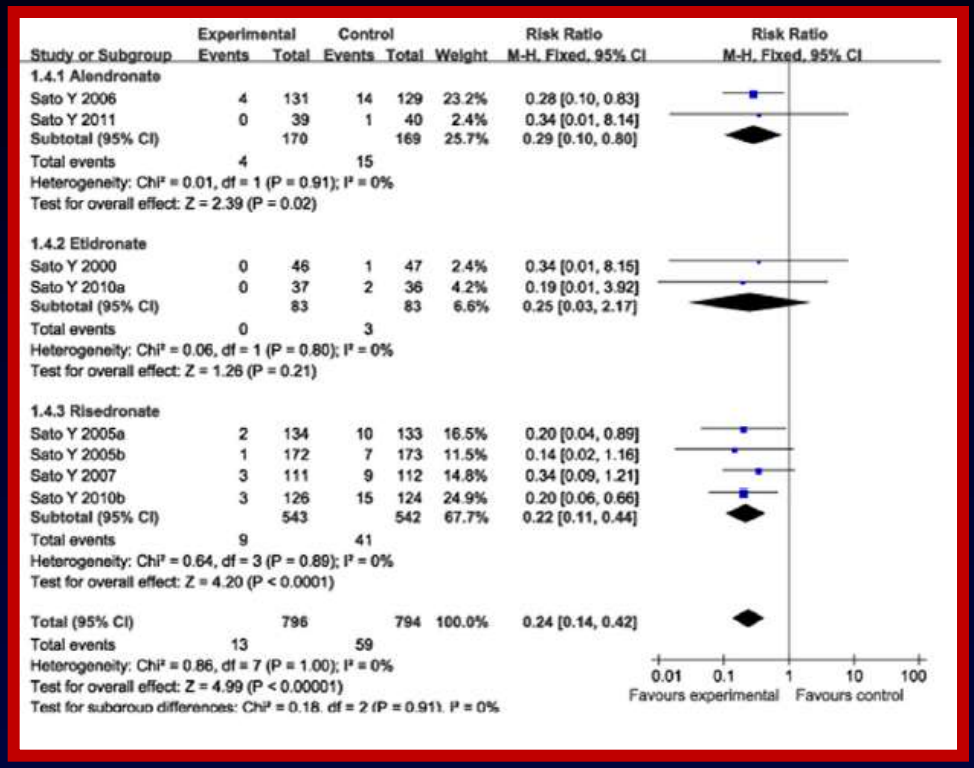
Statin use is associated with decreased osteoporosis and fracture risk in stroke patient



Lin SM, JCEM, 2018

Efficacy of bisphosphonates against hip fracture in elderly patients with Stroke e Parkinson Disease





Zhang W et al, J Stroke Cerebrovasc Dis, 2014

Terapia della osteoporosi nelle malattie neurologiche

- Terapia della malattia di base
- Programmi di riabilitazione (riduzione delle cadute)
- Supplementazione di calcio e vitamina D
- Farmacoterapia: bisfosfonati

Risedronate and ergocalciferol prevent hip fracture in elderly men with Parkinson disease

Yoshihiro Sato, MD; Yoshiaki Honda, MD; and Jun Iwamoto, MD

Journal of Stroke and Cerebrovascular Diseases
Volume 19, Issue 3, May 2010, Pages 198-203

Original Article

Beneficial Effect of Etidronate Therapy in Chronically Hospitalized, Disabled Patients with Stroke

Yoshihiro Sato MD *, Jun Iwamoto MD †, Yoshiaki Honda MD *

Original Investigation

August 8, 2005

Risedronate Sodium Therapy for Prevention o… Years or Olde…

Yoshihiro Sato, MD; Jun Iwamot…
Author Affiliations | Article…

Arch Intern Med. 2005;165(15):1…

…ention of …e in …

Kei Satoh, MD

RETRACTED

Movement Disorders
Vol. 21, No. 7, 2006, pp. 924–929

Alendronate and Vitamin D2 for Prevention of Hip Fracture in Parkinson's Disease: A Randomized Controlled Trial

Yoshihiro Sato, MD,[1]* Jun Iwamoto, MD,[2] Tomohiro Kanoko, BSc,[3] and Kei Satoh, MD[4]

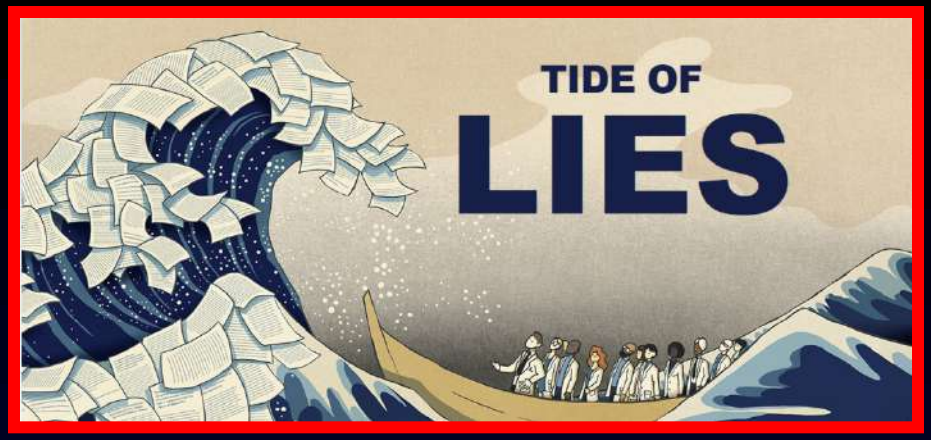
Original Article

An Open-Label Trial Comparing Alendronate and Alphacalcidol in Reducing Falls and Hip Fractures in Disabled Stroke Patients

Yoshihiro Sato MD *, Jun Iwamoto MD †, Yoshiaki Honda MD *

Once-weekly risedronate for prevention of hip fracture in women with Parkinson's disease: a randomised controlled trial

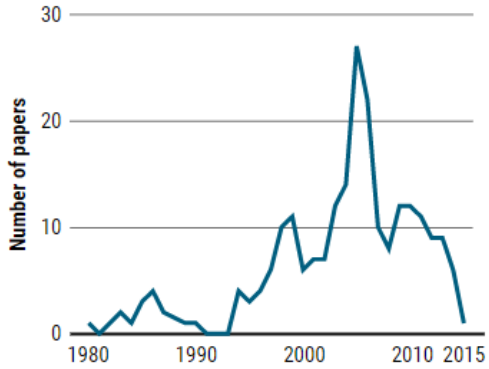
Yoshihiro Sato,[1] Jun Iwamoto,[2] Yoshiaki Honda[1]



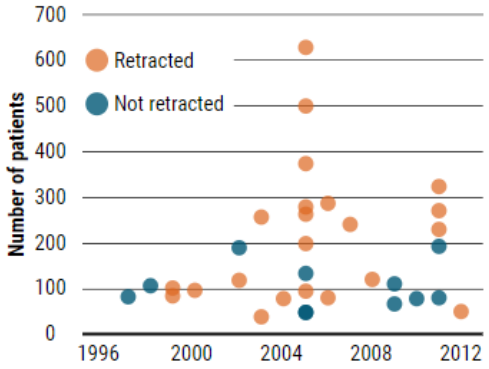
A far-reaching fraud

A team of four researchers has worked since 2012 to expose scientific misconduct by Japanese bone researcher Yoshihiro Sato, who published more than 200 papers before he died in 2016. The team has focused on Sato's 33 clinical trials, together involving 5894 patients.

Total scientific output



Clinical trials



LETTER

The American Journal of Medicine, Vol 131, No 3, March 2018

THE AMERICAN JOURNAL of MEDICINE®

Andrew Grey, MBChB MD[a]
Alison Avenell, MBBS MD[b]
Greg Gamble, MSc[a]
Mark Bolland, MBChB PhD[a]
[a]Department of Medicine
University of Auckland, New Zealand
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University of Aberdeen, Scotland

Concerns About the Integrity of Sato et al. *Am J Med.* 2005;118: 1250-1255

To the Editor:

Recently we highlighted wide-ranging concerns about the integrity of 33 randomized trials reported by a research group in Japan.[1] Data fabrication, text duplication, and authorship misconduct are publicly acknowledged among the 17 publications retracted to date.[2,3] We have concerns about a publication by these investigators in **The American Journal of Medicine**.[4]

of participants represented all women in Iizuka province with PD, it exceeds that expected from other published surveys.

No funding statement is provided. The study was approved by the Human Investigation Committee of Futase Hospital. It seems unlikely that such a small hospital would have an ethics committee. We cannot find any studies by investigators other than Dr Sato and colleagues that were approved by that committee.

There are inconsistencies in the reported data. In Table 1 the mean ages of participants by quartiles of plasma homocysteine are 69.0, 70.6, 71.9, and 72.6 years. The correspondin mean years since menopause are 13.7, 14.6, 15.2, and 16. years, meaning that the average age of menopause is 55-5 years, implausibly older than the expected value of 50 year

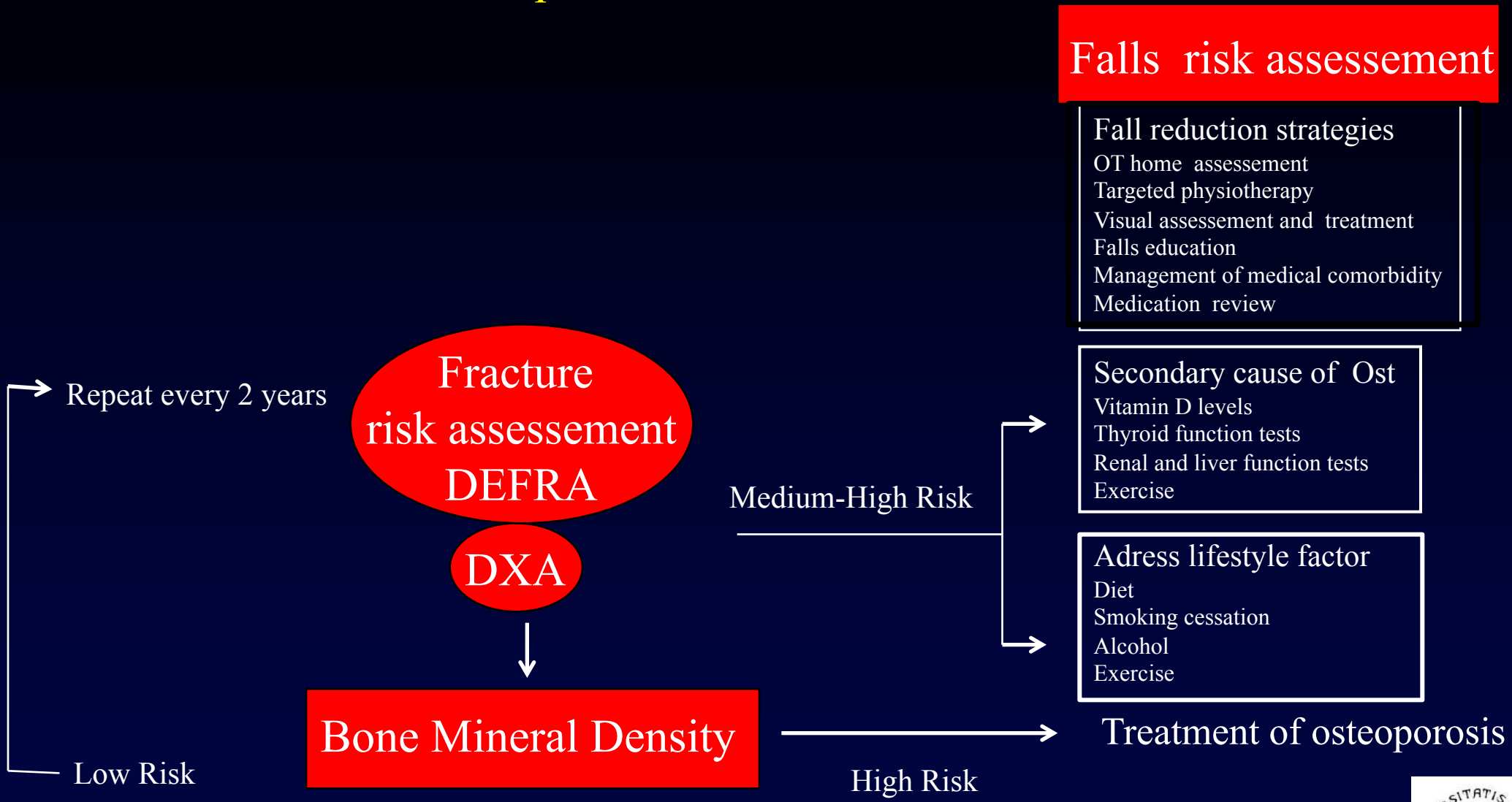
Terapia della osteoporosi nelle malattie neurologiche

Prevenzione secondaria o pazienti con Stroke acuto e Rankin scale > 3

- Terapia della malattia di base
- Programmi di riabilitazione (riduzione delle cadute)
- Supplementazione di calcio e vitamina D
- Farmacoterapia: 1° Bisfosfonati preferibilmente per via ev (Zoledronato)
  2° Teriparatide
  3° Denosumab

Terapia della osteoporosi nelle malattie neurologiche

Prevenzione primaria e stroke acuto con Rankin < 3



Nuova nota AIFA 79 (30.03.2017)

Prevenzione secondaria in soggetti con pregresse fratture oteoporotiche

- vertebrali o di femore
- non vertebrali e non femorali

Prevenzione primaria in donne in melopausa o uomini di età >= 50 aa a rischio elevato di frattura a causa di almeno una delle cause sottoelencate:

- trattamento in atto o previsto per >3 mesi con prednisone >5 mg/die
- trattamento in corso di blocco ormonale in carcinoma mammario o carcinoma prostatico

T-score colonna e femore <= -4

T-score colonna o femore >= -3 + almeno una delle seguenti condizioni:

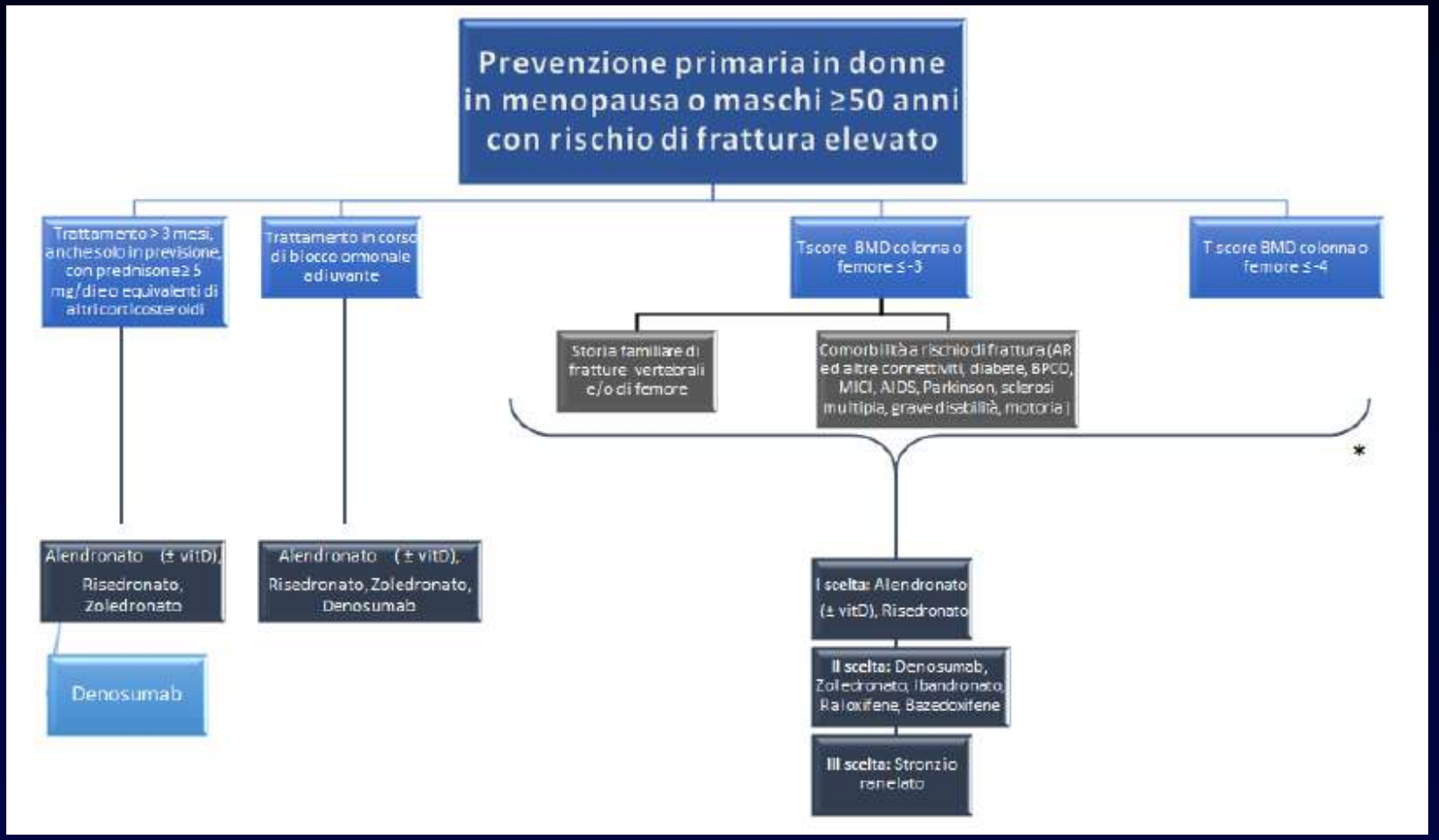
- familiarità per fratture di vertebre o femore
- comorbilità: artrite reumatoide e altre connettiviti, diabete, BPCO, BID, AIDS, **Parkinson, Sclerosi multipla, grave disabilità motoria**

Agenzia Italiana del Farmaco

AIFA

DETERMINAZIONE

Modifiche alla Nota 79 di cui alla Determinazione del 7 giugno 2011



Clinical guidelines for the prevention and treatment of osteoporosis: summary statements and recommendations from the Italian Society for Orthopaedics and Traumatology

Umberto Tarantino[1] · Giovanni Iolascon[2] · Luisella Cianferotti[3] · Laura Masi[3] · Gemma Marcucci[3] · Francesca Giusti[3] · Francesca Marini[3] · Simone Parri[3] · Maurizio Feola[1] · Cecilia Rao[1] · Eleonora Piccirilli[1] · Emanuela Basilici Zanetti[4] · Noemi Cittadini[4] · Rosaria Alvaro[4] · Antimo Moretti[2] · Dario Calafiore[2] · Giuseppe Toro[2] · Francesca Gimigliano[2] · Giuseppina Resmini[5] · Maria Luisa Brandi[3]

Table 4 Risk factors for low BMD and fragility/low-energy fractures: levels of evidence are also shown (level 1: evidence from RCTs or metanalyses of RCTs; level 2: evidence from prospective cohort studies or poor-quality RCTs; level 3: evidence from case–control studies or retrospective cohort studies). Reproduced (with permission) from Table 1 of *Guidance for the diagnosis, prevention and therapy of osteoporosis in Italy* (Cianferotti and Brandi [73])

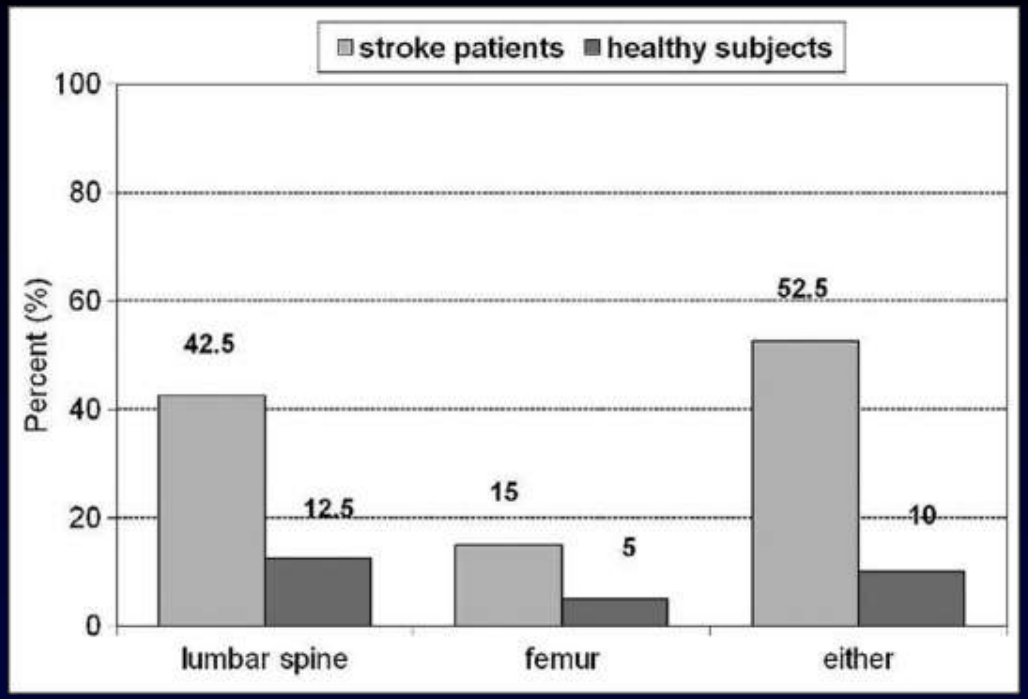
Risk factor	For BMD	For fracture
BMD	1	1
Age	1	1
Fragility fractures after 40 years of age	2	1
Family history of fragility fractures	2	2
Chronic corticosteroid therapy	1	1
Premature menopause (< 45 years)	1	2
Weight	1	2
Reduced calcium intake	1	1
Reduced physical activity	2	2
Smoking	2	1
Alcohol	2	3
Risk factors for falls	–	1

usually associated with an increased fracture risk are rheumatoid arthritis, untreated hypogonadism in men and women (e.g., premature menopause, bilateral oophorectomy or orchidectomy, anorexia nervosa, chemotherapy for breast cancer, hypopituitarism, androgen deprivation therapy in men with prostate cancer), inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis), prolonged immobility (e.g., spinal cord injury, Parkinson's disease, stroke, muscular dystrophy, ankylosing spondylitis), organ transplantation, type 1 and type 2 diabetes, thyroid disorders (e.g., untreated hyperthyroidism, thyroid hormone suppressive therapy), and chronic obstructive pulmonary disease.

Medical treatments

Several drugs have been associated with an increased risk of fragility fracture. Among these, glucocorticoid therapy is the most common cause of secondary osteoporosis, mostly due to factors independent of BMD. Fragility fracture occurs in 30–50% of patients receiving long-term glucocorticoid therapy [77]. Other drugs, such as adjuvant hormone block-

J Orthop Traumatol 2017

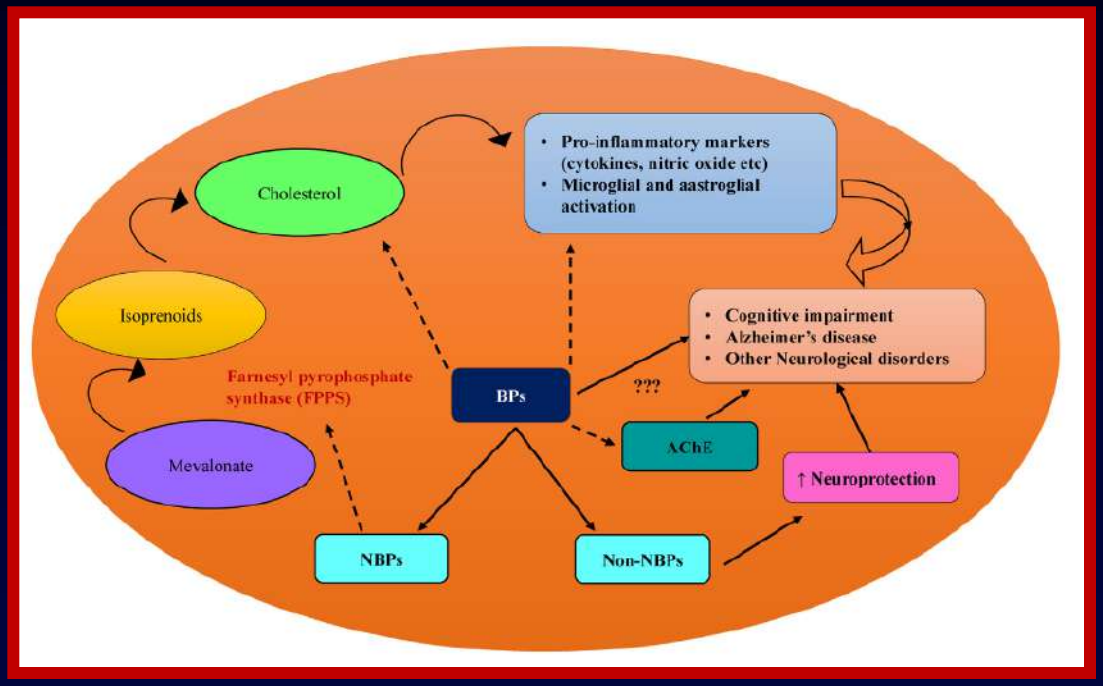


Hemiparetic side	Femur total		Femur neck	
	T-score	BMD	*T*-score	BMD
Right side (*N*=26)	−1.7±0.82	0.802±0.122	−2.7±0.63	0.738±0.316
Left side (*N*= 14)	−1.3±1.07	0.860±0.230	−1.6±1.07	0.804±0.161
P	0.034	0.193	0.001*	0.195

*$P < 0.05$ significant

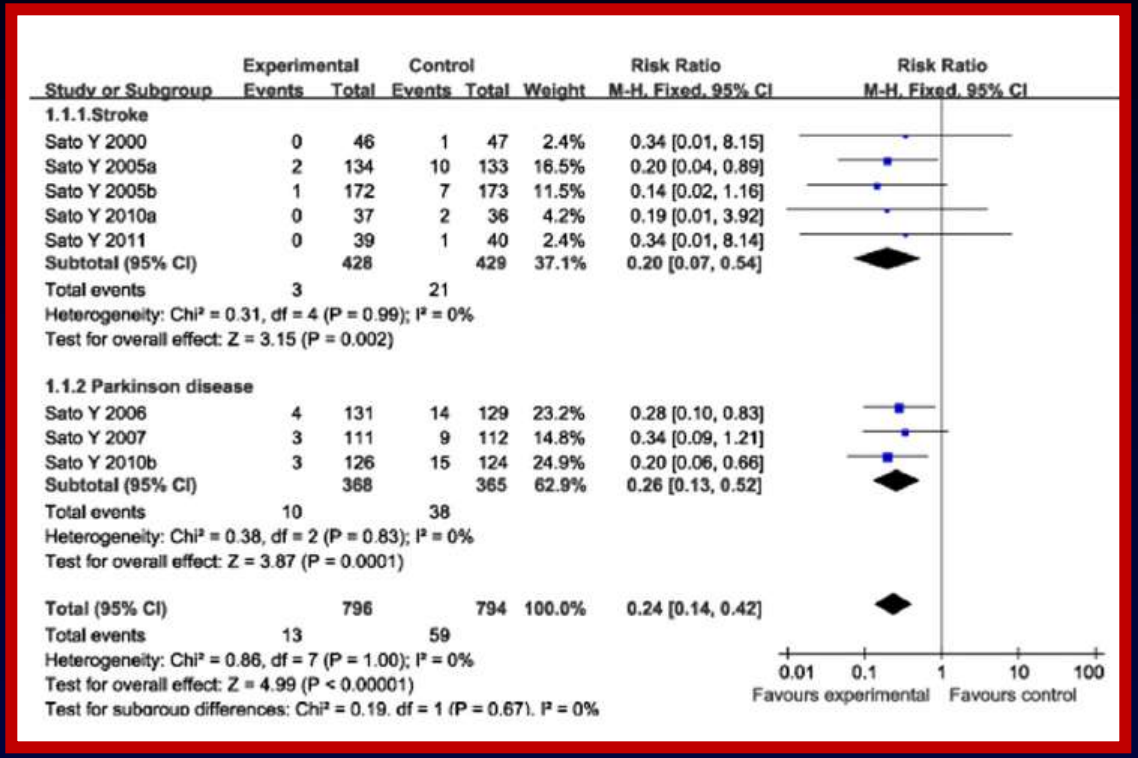
Tomasevic-Todorovic S et al. Ann Ind Acad Neurol, 2016

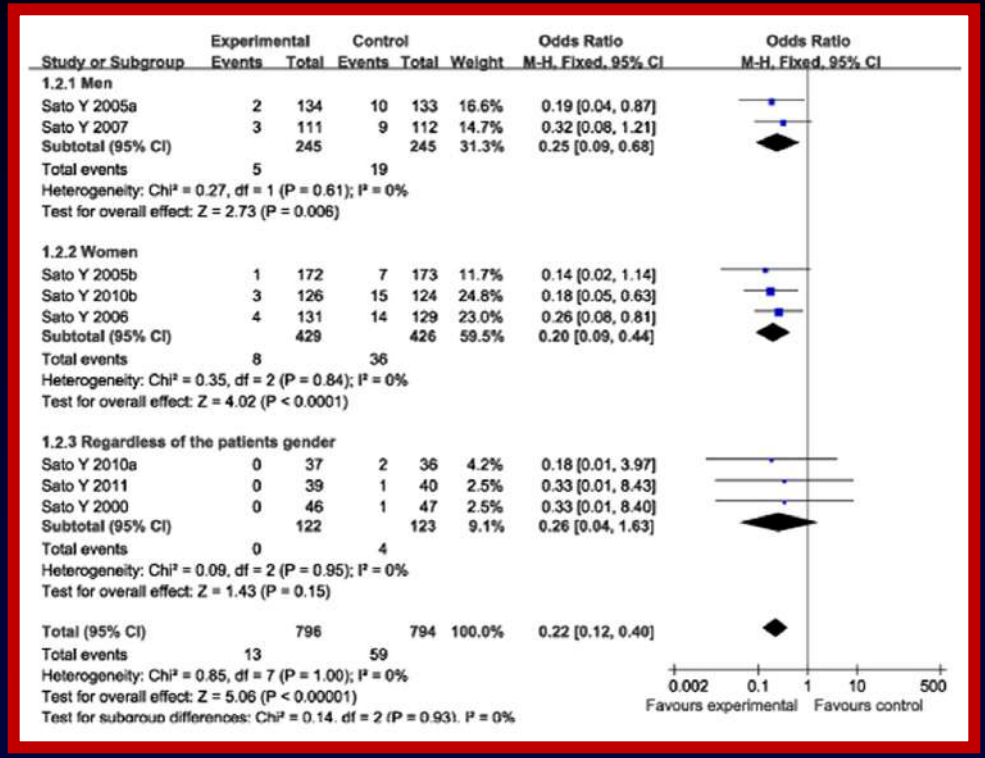
Role of BPs in modulation of factors which in turn affect neurological diseases including pro-infiammatory cytokines, glial functions and neuroprotection



Zameer S et al, Pharmacological Reports, 2018

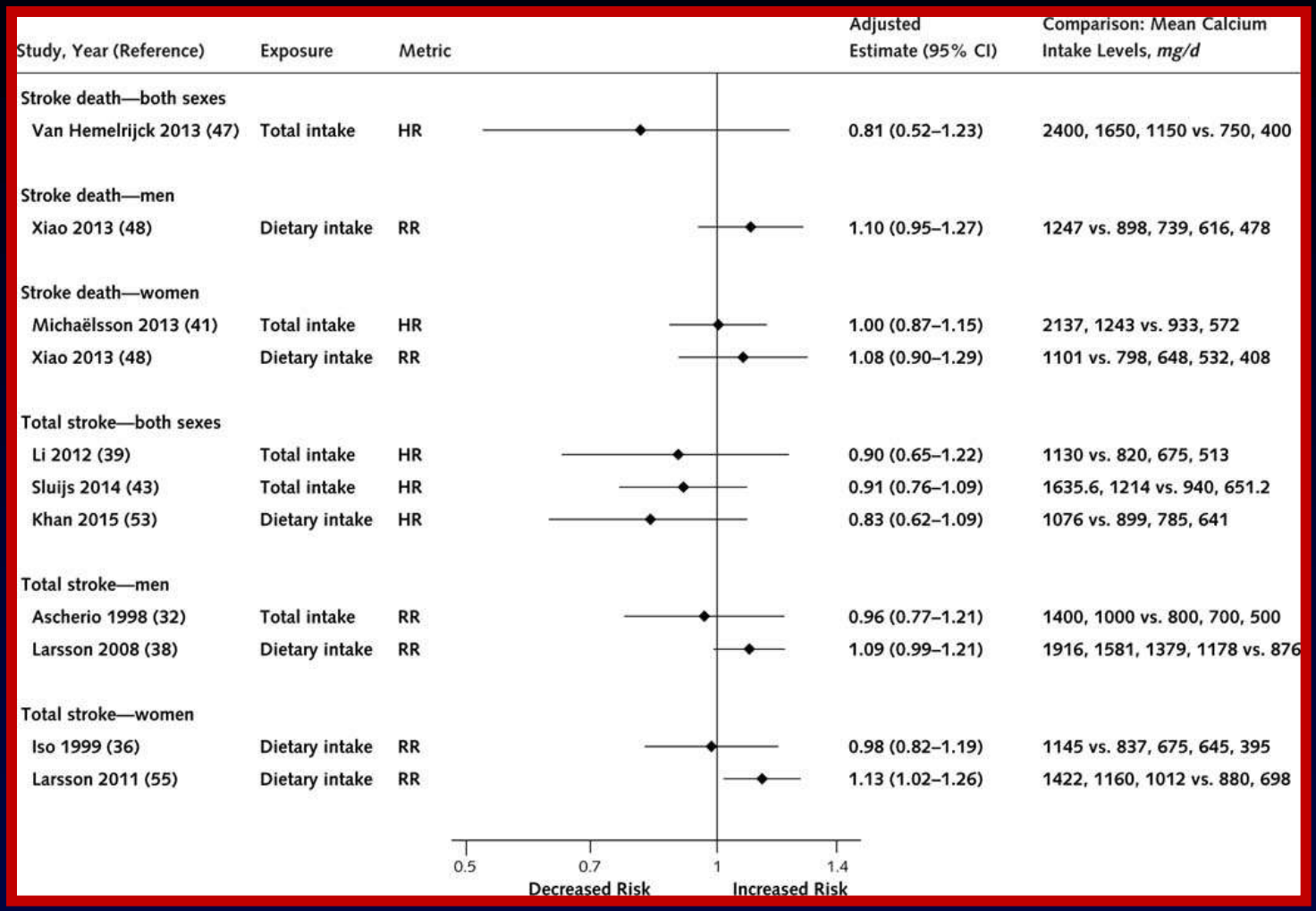
Efficacy of bisphosphonates against hip fracture in elderly patients with Stroke e Parkinson Disease





Zhang W et al, J Stroke Cerebrovasc Dis, 2014

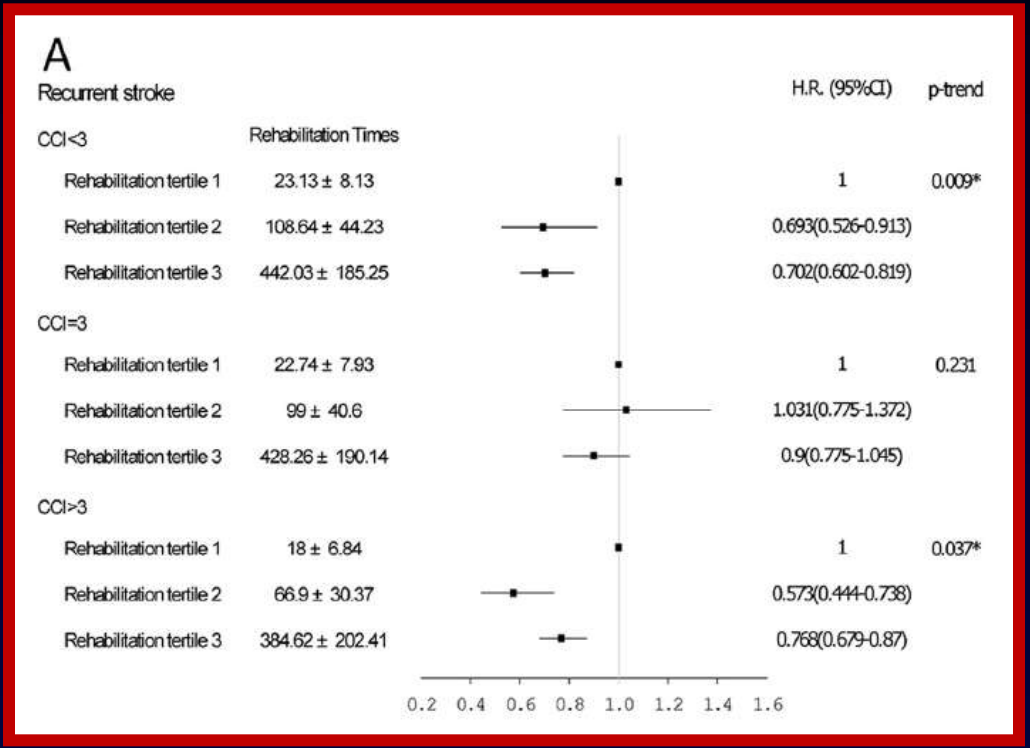
Calcium intake and cardiovascular risk

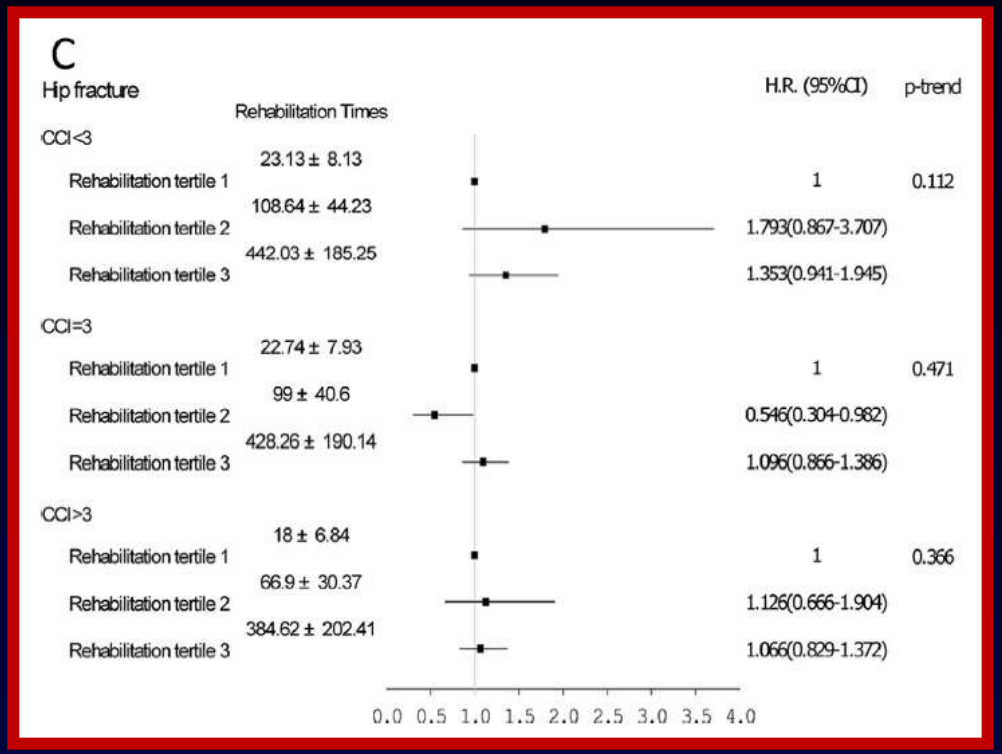


Study, Year (Reference)	Exposure	Metric	Adjusted Estimate (95% CI)	Comparison: Mean Calcium Intake Levels, *mg/d*
Stroke death—both sexes				
Van Hemelrijck 2013 (47)	Total intake	HR	0.81 (0.52–1.23)	2400, 1650, 1150 vs. 750, 400
Stroke death—men				
Xiao 2013 (48)	Dietary intake	RR	1.10 (0.95–1.27)	1247 vs. 898, 739, 616, 478
Stroke death—women				
Michaëlsson 2013 (41)	Total intake	HR	1.00 (0.87–1.15)	2137, 1243 vs. 933, 572
Xiao 2013 (48)	Dietary intake	RR	1.08 (0.90–1.29)	1101 vs. 798, 648, 532, 408
Total stroke—both sexes				
Li 2012 (39)	Total intake	HR	0.90 (0.65–1.22)	1130 vs. 820, 675, 513
Sluijs 2014 (43)	Total intake	HR	0.91 (0.76–1.09)	1635.6, 1214 vs. 940, 651.2
Khan 2015 (53)	Dietary intake	HR	0.83 (0.62–1.09)	1076 vs. 899, 785, 641
Total stroke—men				
Ascherio 1998 (32)	Total intake	RR	0.96 (0.77–1.21)	1400, 1000 vs. 800, 700, 500
Larsson 2008 (38)	Dietary intake	RR	1.09 (0.99–1.21)	1916, 1581, 1379, 1178 vs. 876
Total stroke—women				
Iso 1999 (36)	Dietary intake	RR	0.98 (0.82–1.19)	1145 vs. 837, 675, 645, 395
Larsson 2011 (55)	Dietary intake	RR	1.13 (1.02–1.26)	1422, 1160, 1012 vs. 880, 698

Chung M et al. Ann Int Med, 2017

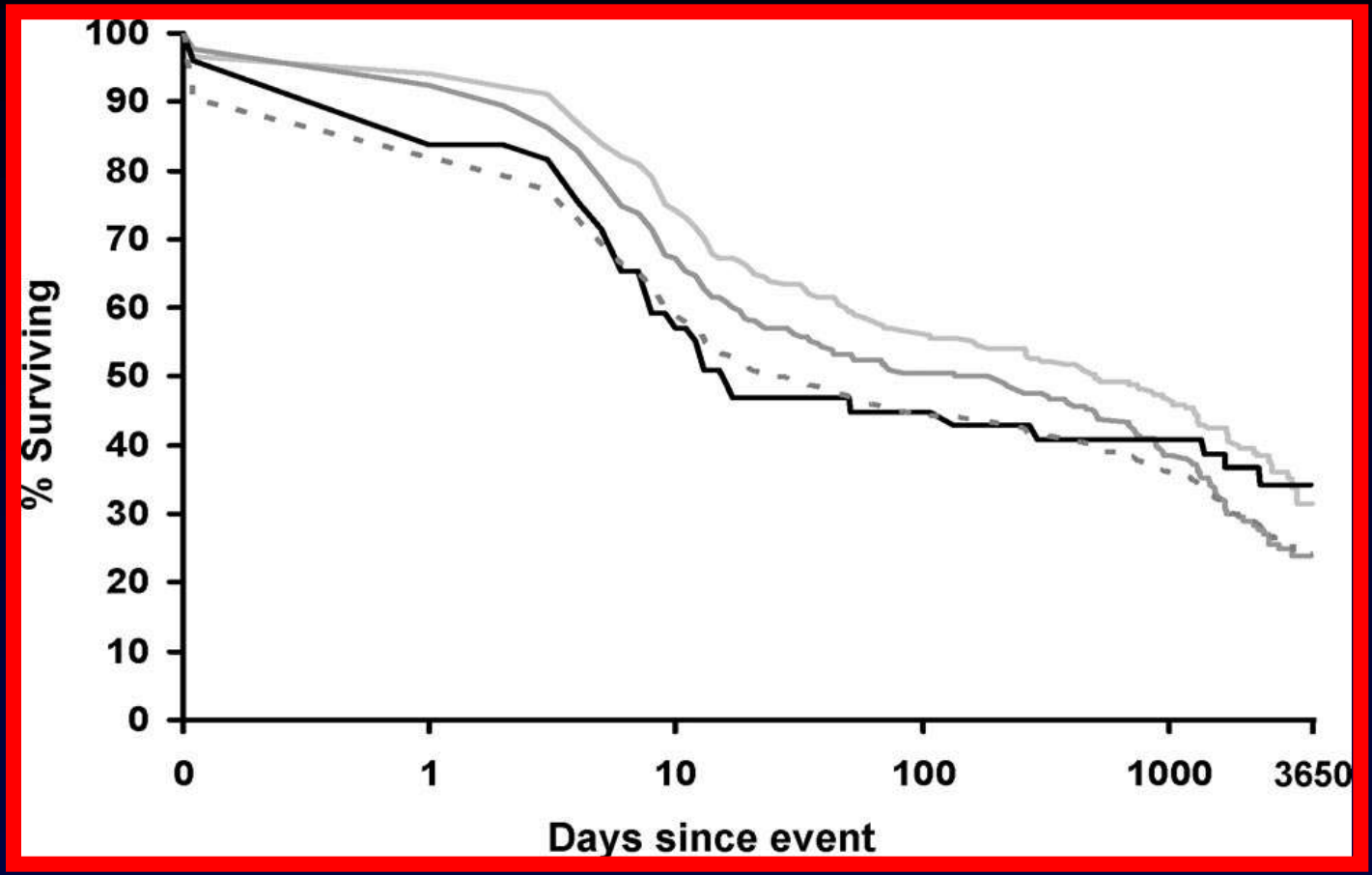
The impact of rehabilitation frequencies in the first year after stroke





Cheng Y-Y, J Stroke Cerebrovasc Dis, 2017

Incidence and 10-year survival of intracerebral hemorrhage in a population-based registry



Case fatality rate

7-days	34.6%
30-days	50.3%
1-year	59.0%

Survival rate

10-year	24.1%

Sacco S et al, Stroke, 2009

Terapia osteoporosi e malattie neurologiche

Ictus

Morbo di parkinson

Sclerosi multipla

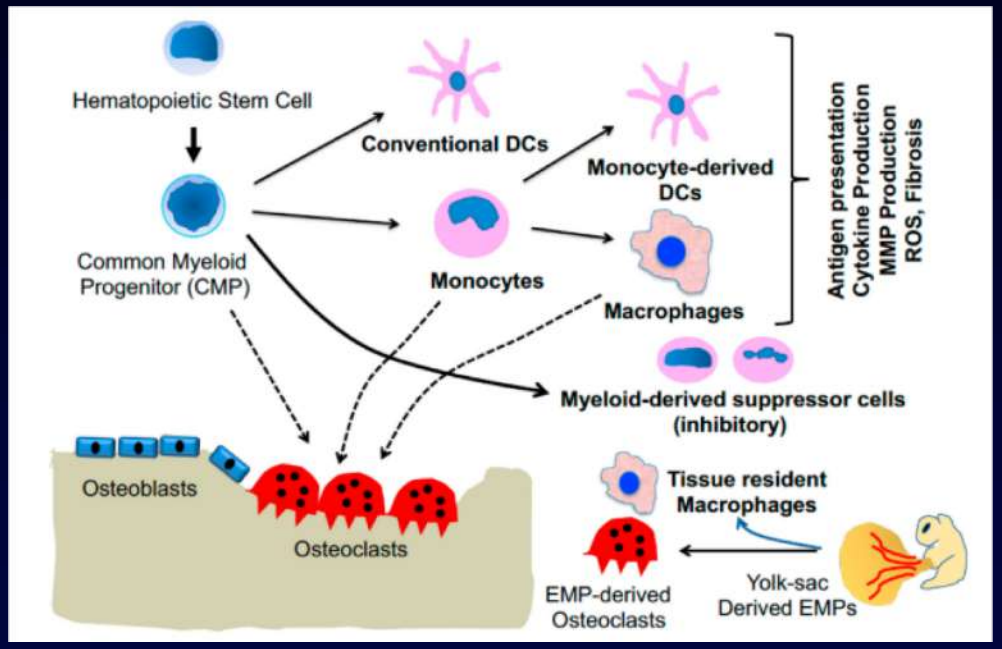
Disability Post Stroke in People >65 Years at 6 Months

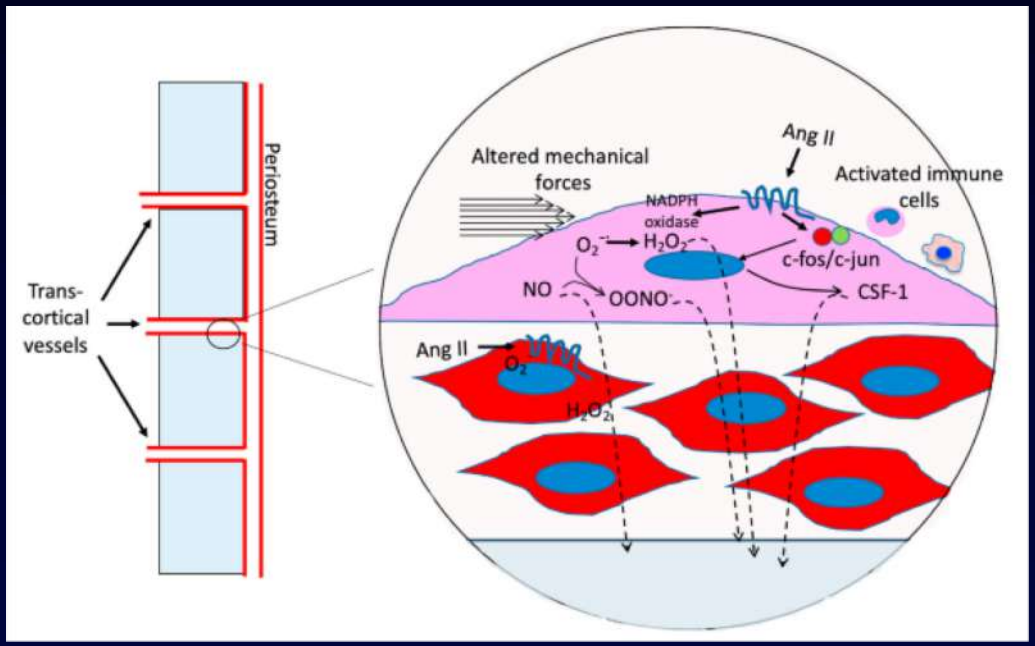
- 50% had some hemiparesis
- 30% were unable to walk without assistance
- 26% were dependent in the activity of daily living
- 19% had aphasia
- 35% had depressive symptoms
- 26% were institutionalized in a nursing home

Heart Disease and Stroke Statistics. Circulation 2018

Common Risk Factors for Stroke and Osteoporosis

Age – Hypertension – Smoking – Alcohol Intake – Diabetes

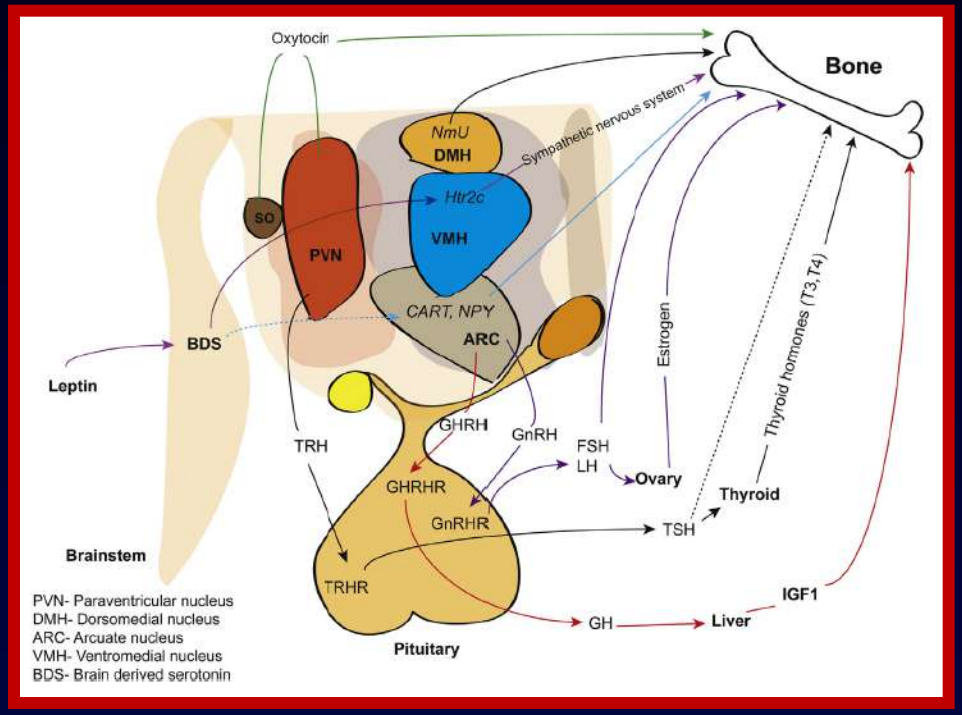




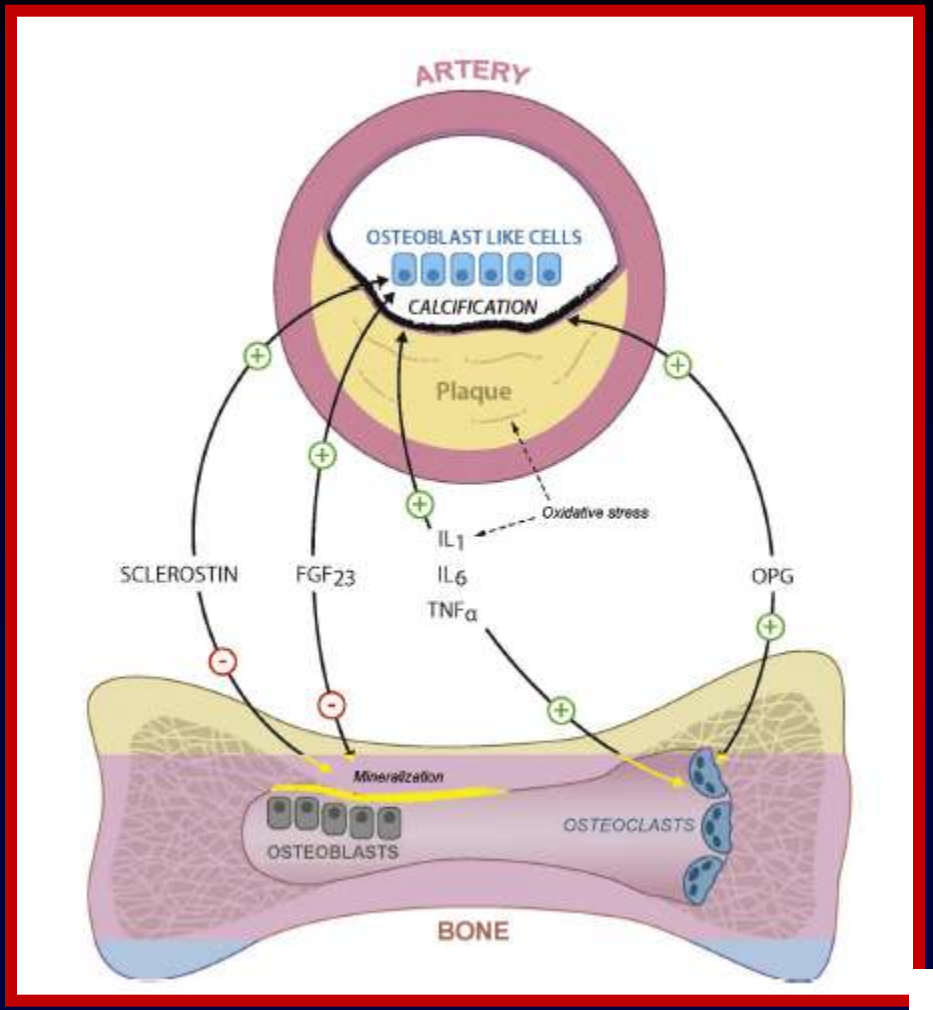
Moayyeri A et al, Arch Bioch Biophys, 2010

Cytokine and growth factor involved in bone turnover and in calcified vascular plaque formation

Hypothalamic control of bone metabolism

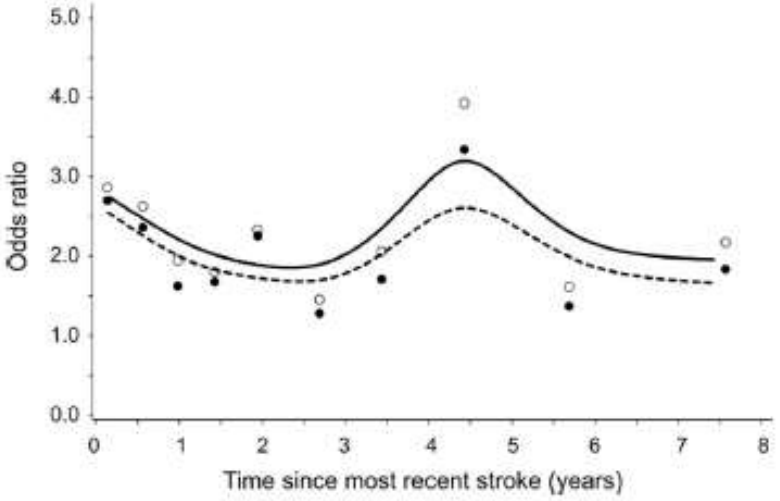


Sharan K et al. 2014



Laroche M et al, Joint Bone Spine, 2017

Risk of hip/femur fracture and type of stroke



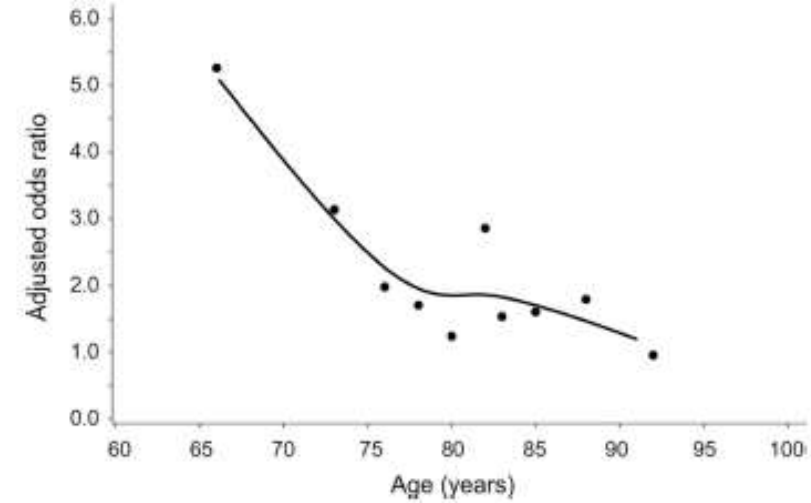
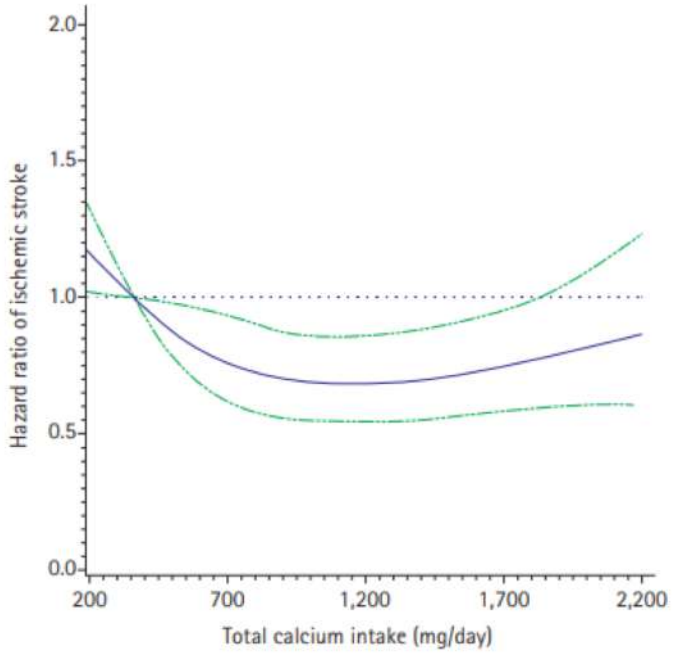


Table 2. Risk of Hip/Femur Fracture and Type of Stroke

	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)

Pouwels S et al, Stroke, 2009

Calcium intake and serum calcium level on the risk of ischemic stroke: findings from REGARDS study



Serum Ca, range (μg/g)	67.6–92.5	92.6–95.9	96.0–98.80	98.9–102.3	102.4–150.5	
No. of cases	161	160	151	129	129	
Person-years	4,345.59	4,232.65	4,389.08	4,461.59	4,463.73	
Model 1	1.00	0.97 (0.72–1.30)	0.92 (0.69–1.24)	0.80 (0.59–1.08)	0.77 (0.57–1.05)	0.046
Model 2	1.00	0.99 (0.74–1.34)	0.95 (0.71–1.27)	0.78 (0.57–1.06)	0.74 (0.54–1.00)	0.017
Model 3	1.00	1.01 (0.75–1.37)	0.97 (0.71–1.30)	0.79 (0.57–1.09)	0.74 (0.54–1.02)	0.026
Model 4	1.00	1.01 (0.76–1.35)	0.95 (0.71–1.26)	0.79 (0.58–1.07)	0.73 (0.53–0.99)	0.013

Weighted Cox proportional hazard regression with robust sandwich estimate for the variance was used to fit the models. Model 1 was adjusted for age, sex, race, and the interaction of age and race; Model 2 was adjusted for covariates in Model 1, education, income, smoking, and alcohol; Model 3 was adjusted for variables in Model 2, regular aspirin use, and dietary Ca intake; Model 4 was adjusted for variables in Model 3, low density lipoprotein, triglyceride, and serum magnesium.
HR, hazard ratio; CI, confidence interval; Ca, calcium.
*P for linear trend was calculated by modeling the median of serum Ca for each quintile as a continuous variable.

Dibaba DT et al. JOS, 2019

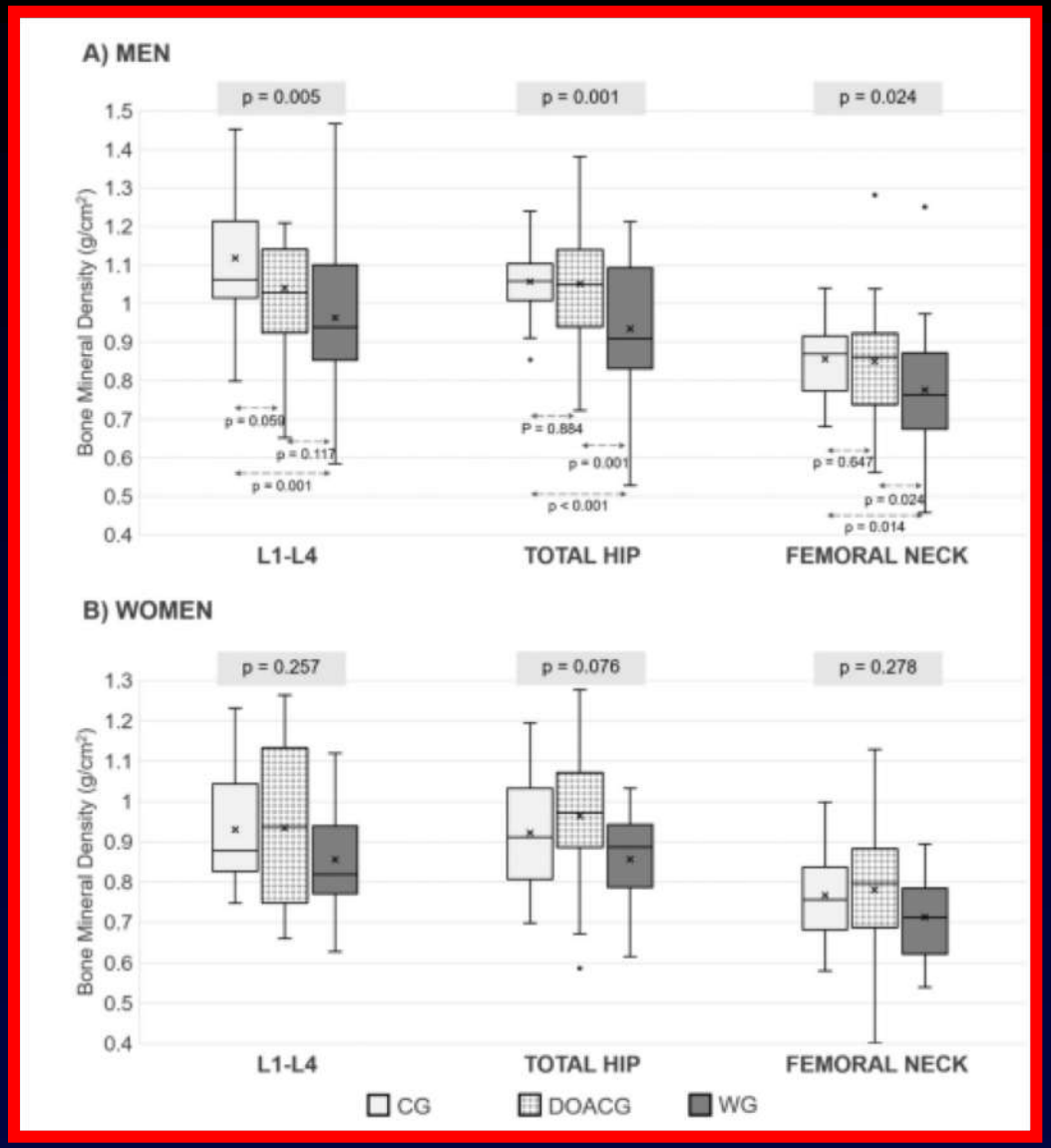
Low Bone Mass and Stroke

Table 2. Estimated risks of fractures at various ages.

	Current age (years)	Any fractures	Radius/ulna	Femur/hip	Vertebral
Life-time risk:					
Women	50	53.2%	16.6%	11.4%	3.1%
	60	45.5%	14.0%	11.6%	2.9%
	70	36.9%	10.4%	12.1%	2.6%
	80	28.6%	6.9%	12.3%	1.9%
Men	50	20.7%	2.9%	3.1%	1.2%
	60	14.7%	2.0%	3.1%	1.1%
	70	11.4%	1.4%	3.3%	1.0%
	80	9.6%	1.1%	3.7%	0.8%
10-year risk:					
Women	50	9.8%	3.2%	0.3%	0.3%
	60	13.3%	4.9%	1.1%	0.6%
	70	17.0%	5.6%	3.4%	1.3%
	80	21.7%	5.5%	8.7%	1.6%
Men	50	7.1%	1.1%	0.2%	0.3%
	60	5.7%	0.9%	0.4%	0.3%
	70	6.2%	0.9%	1.4%	0.5%
	80	8.0%	0.9%	2.9%	0.7%

Reproduced from Van Staa et al (2001, *Bone* **29:** 517–522) with permission.

Bone density in patients treated with DOA versus Warfarin



Nalevaiko JZ et al. Bone, 2021

Calcium supplementation and risk of dementia in women with cerebrovascular disease

	Any dementia		Vascular or mixed dementia		Alzheimer disease	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Calcium use at baseline	2.1 (1.01–4.37)	0.046	4.4 (1.54–12.61)	0.006	0.66 (0.19–2.25)	0.503

	No history of stroke (n = 592)	
	OR (95% CI)[a]	p Value
Calcium use at baseline[b] (dementia/total); no (n = 33/n = 509); yes (n = 18/n = 83)	1.49 (0.61–3.63)	0.381
	History of stroke up to 2005 (n = 108)	
	OR (95% CI)[a]	p Value
Calcium use at baseline[c] (dementia/total); no (n = 12/93); yes (n = 6/15)	6.77 (1.36–33.75)	0.020

Kern J et al, Neurology, 2016

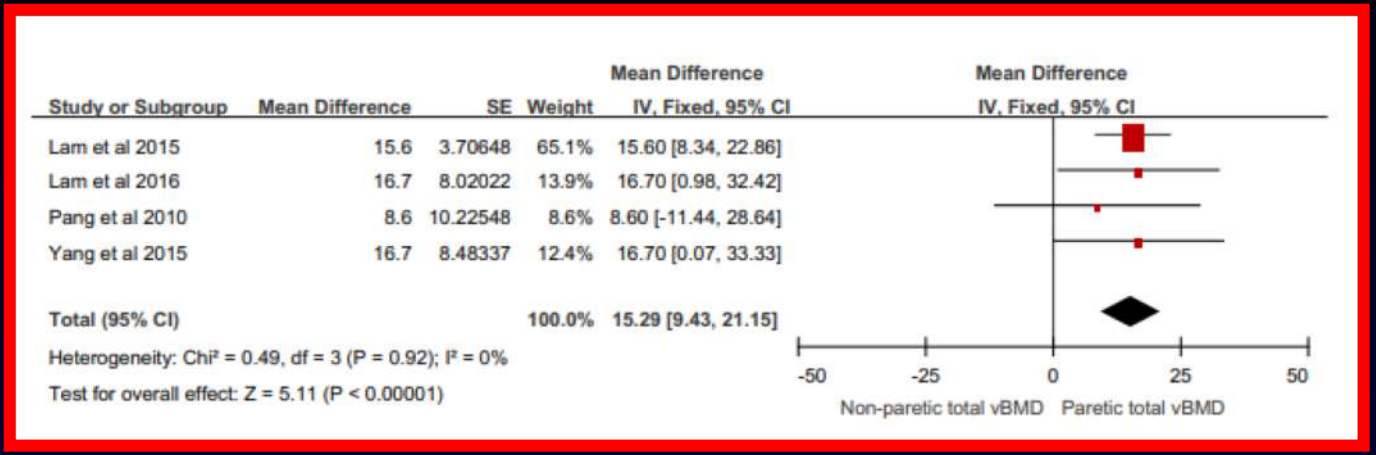
RISULTATI

- All'ingresso in ospedale, i pazienti con ictus mostravano una maggiore prevalenza di ipovitaminosi D rispetto ai controlli, ed il 34,5% di loro aveva associato un iperparatiroidismo secondario.

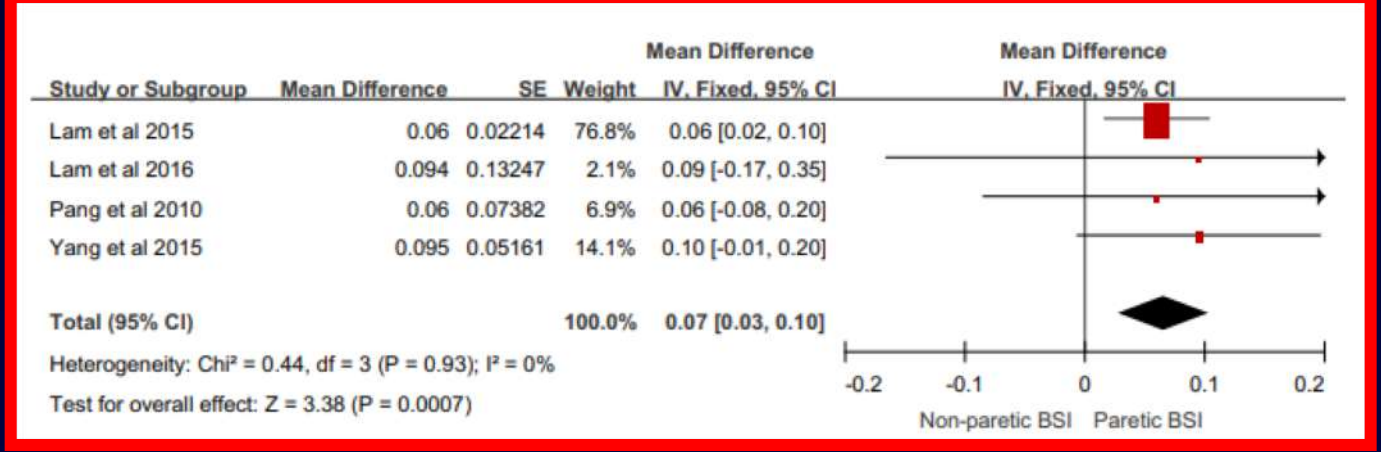
- PTH, FGF-23 e sclerostina risultavano più elevati nei pazienti con ictus rispetto ai controlli.

The impact of stroke on bone properties

Total volumetric bone mineral density (vBMD) (mh/cm3)

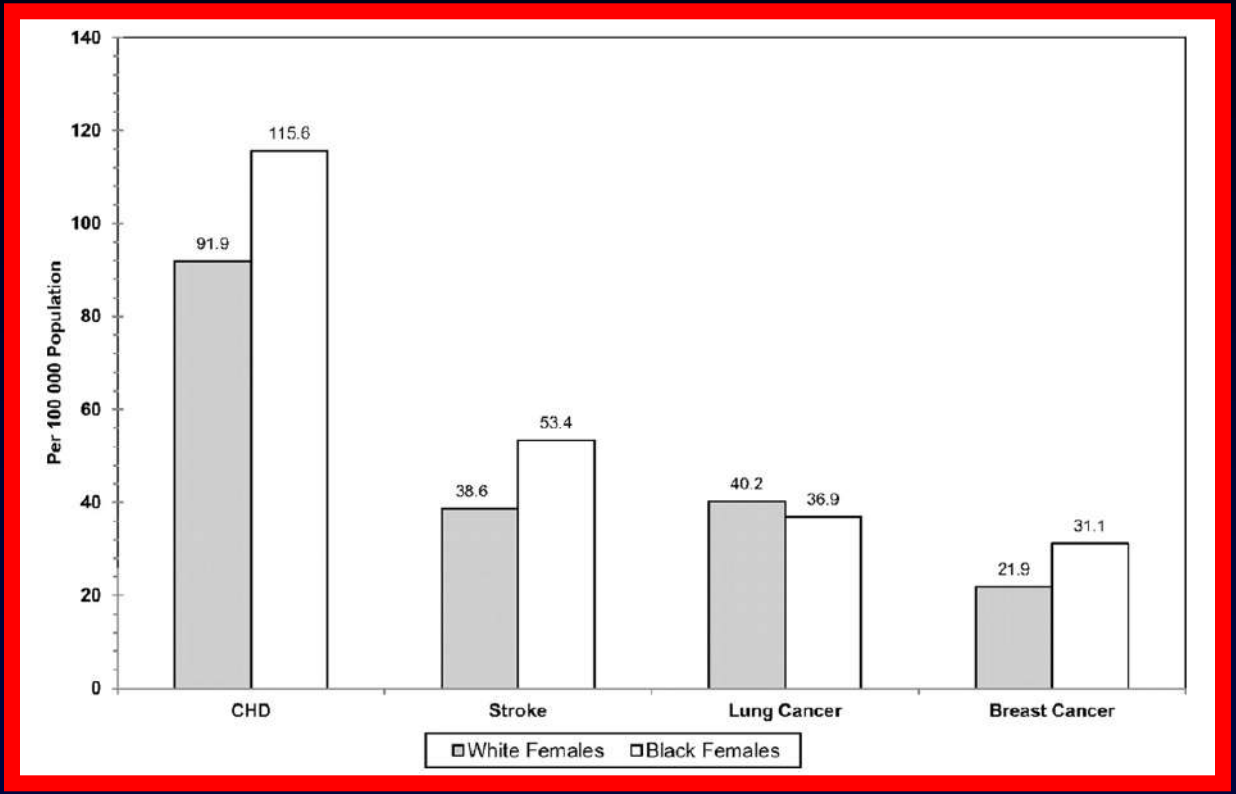


Bone strenght index (BSI, g2/cm4)



Yang FZ et al, Osteopor Int, 2020

Age-Adjusted deaths rates for Coronary Heart Disease, Stroke, Lung and Breast Cancer (United States: 2012)



In Italia

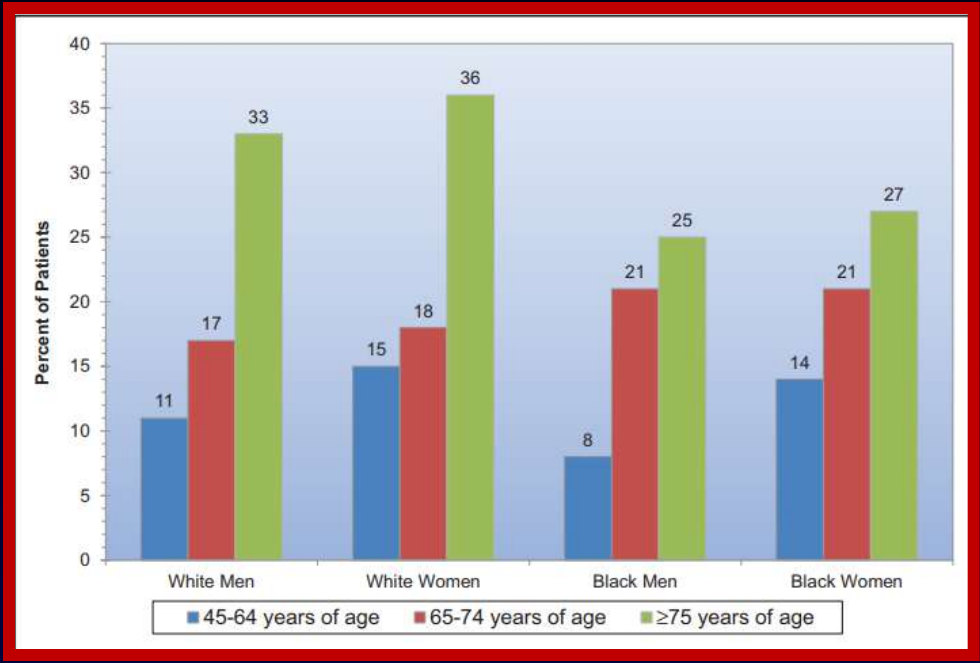
E' frequente: 170.000 pts/y

E' grave: prima causa di disabilità
quarta causa di morte
seconda causa di demenza

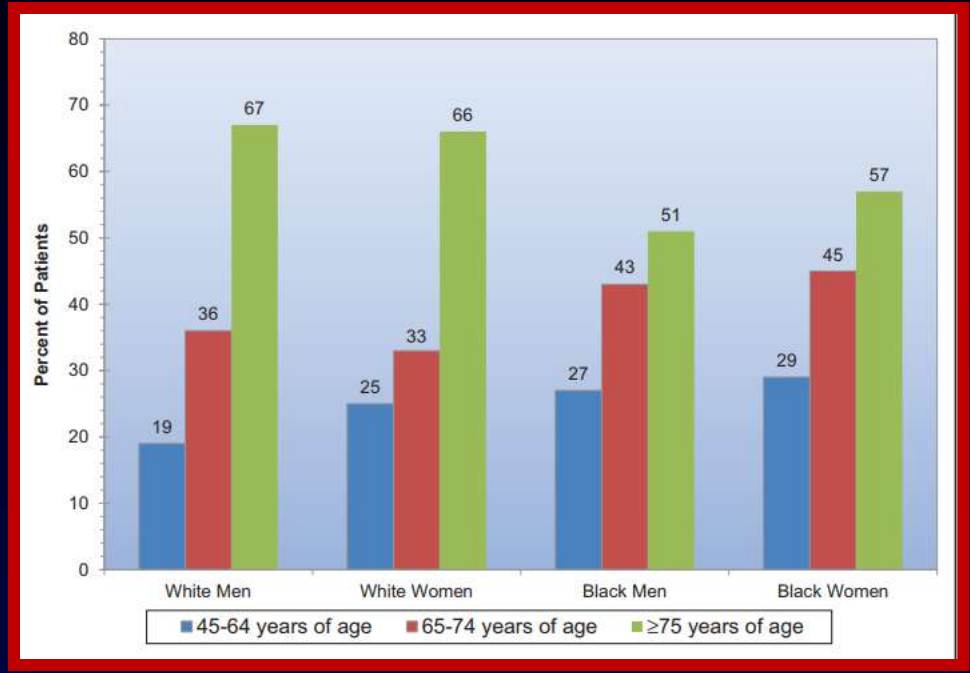
E' costoso: 4 miliardi di euro/y
4% della spesa sanitaria

Heart Disease and Stroke Statistics. Circulation 2018

Proportion of patients dead after first stroke



within 1 years



within 5 years

Heart Disease and Stroke Statistics. Circulation 2018