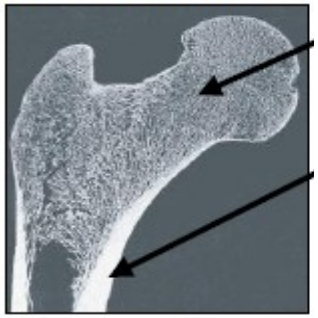


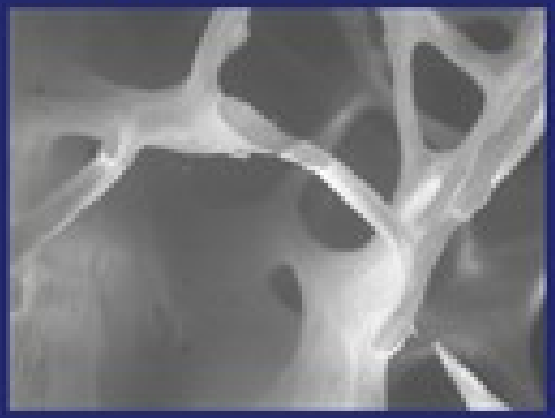
Σπογγώδες και φλοιώδες οστό:
η διαφοροποίηση του ιστού προαναγγέλλει και τη δράση της διαφοροποίησης των αντιοστεοπορωτικών φαρμάκων;

Γεώργιος Παν. Καμπάκης
Ρευματολόγος

Components of Bone Quality

Mineralization

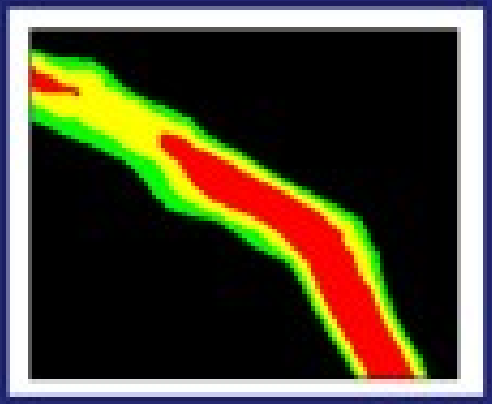
Microarchitecture



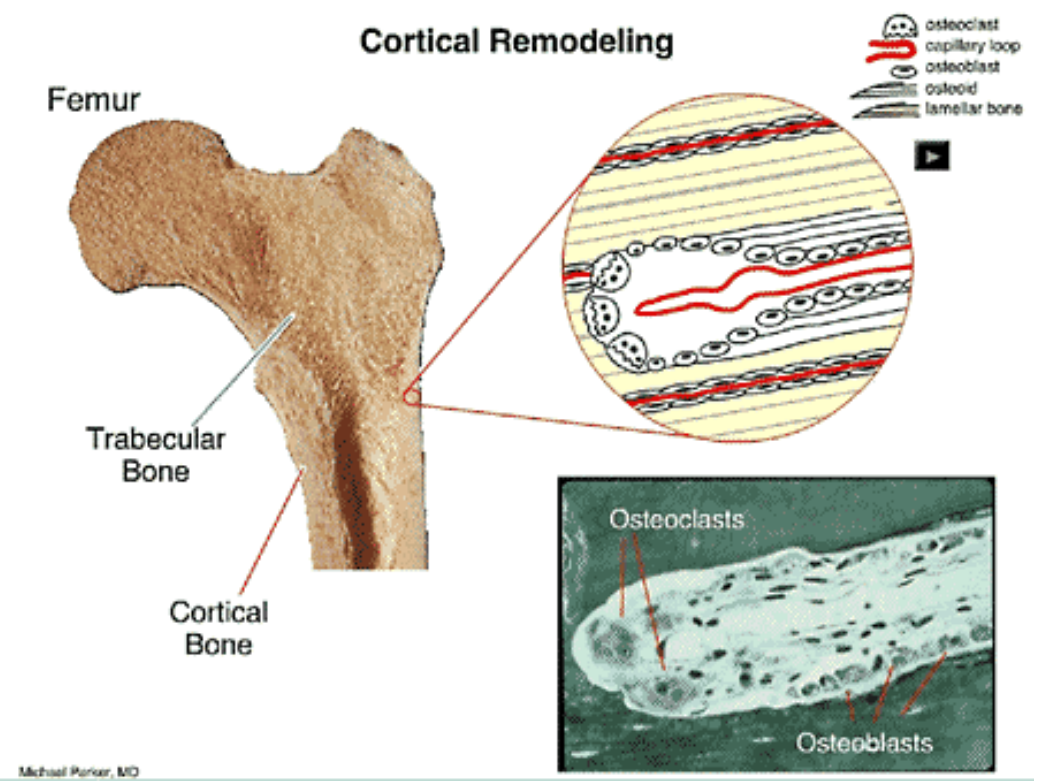
Microfracture

Microcracks

Matrix Composition

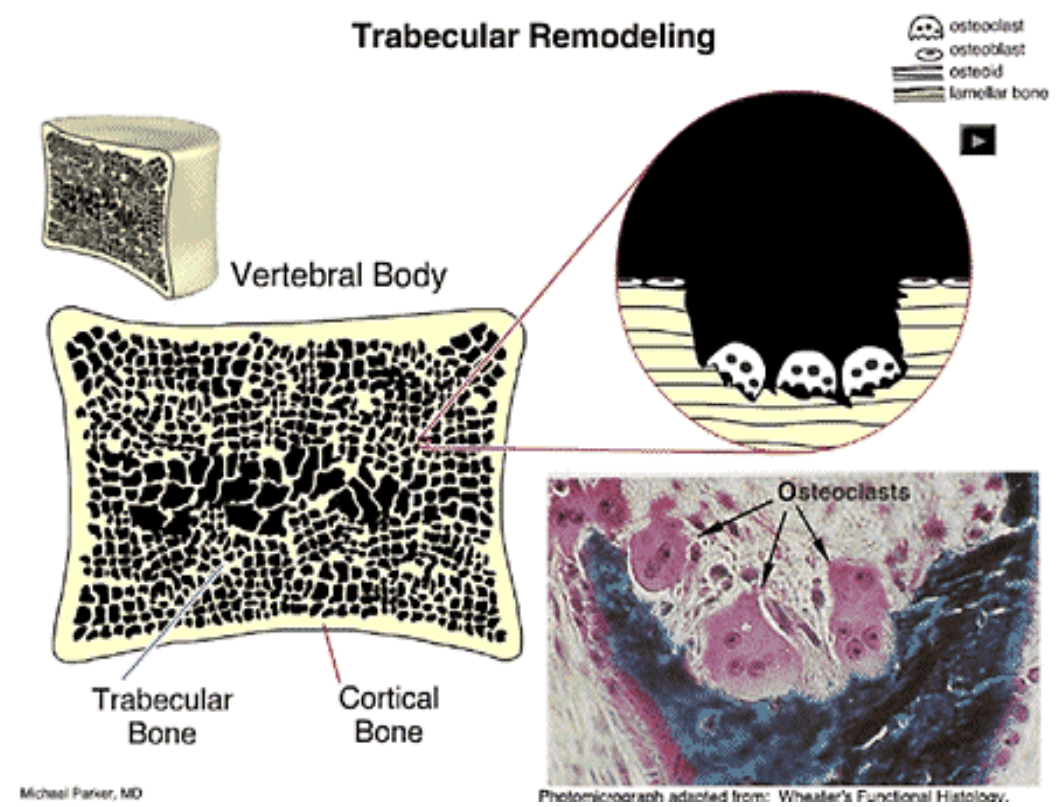


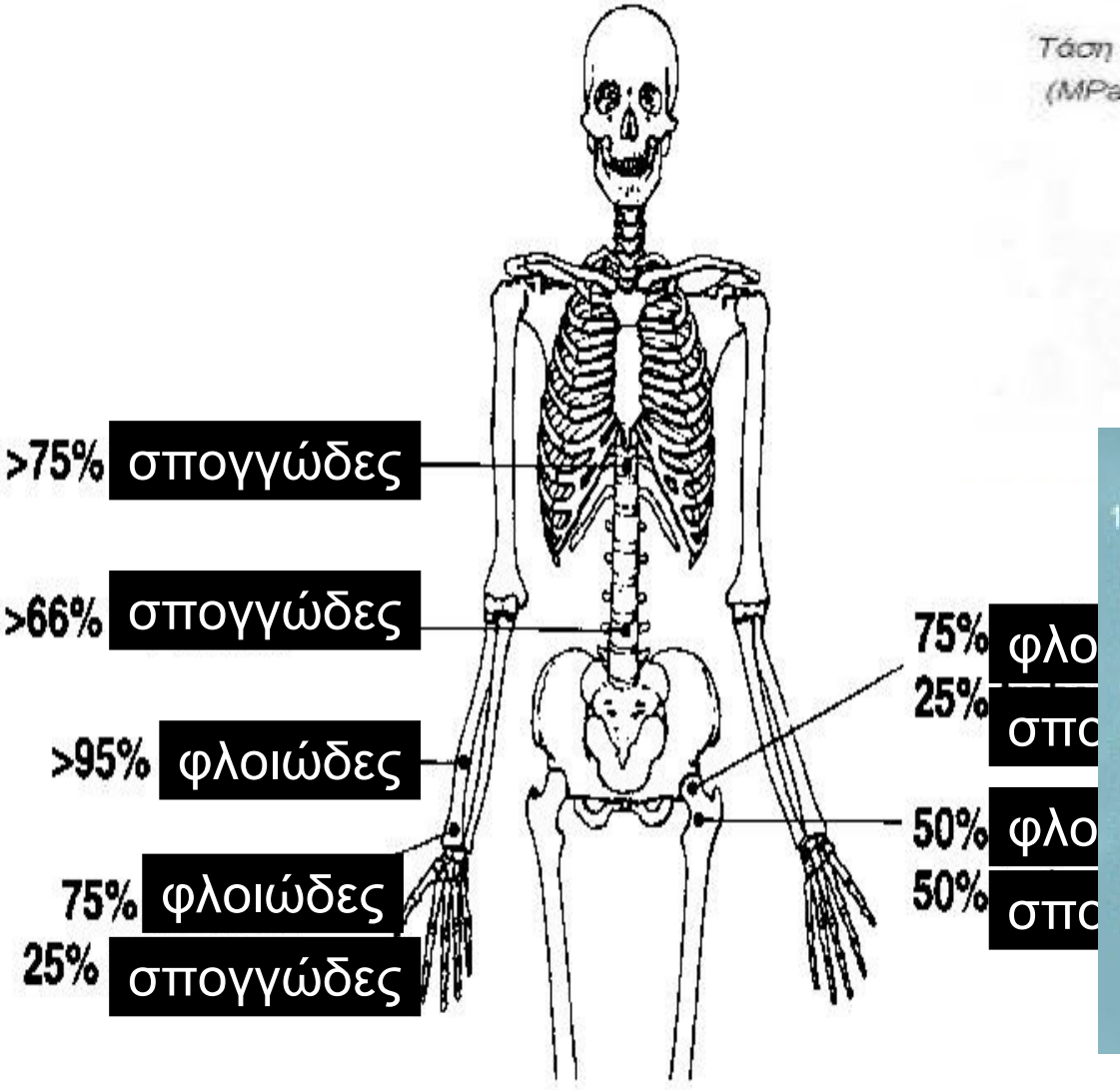
Mineral Composition

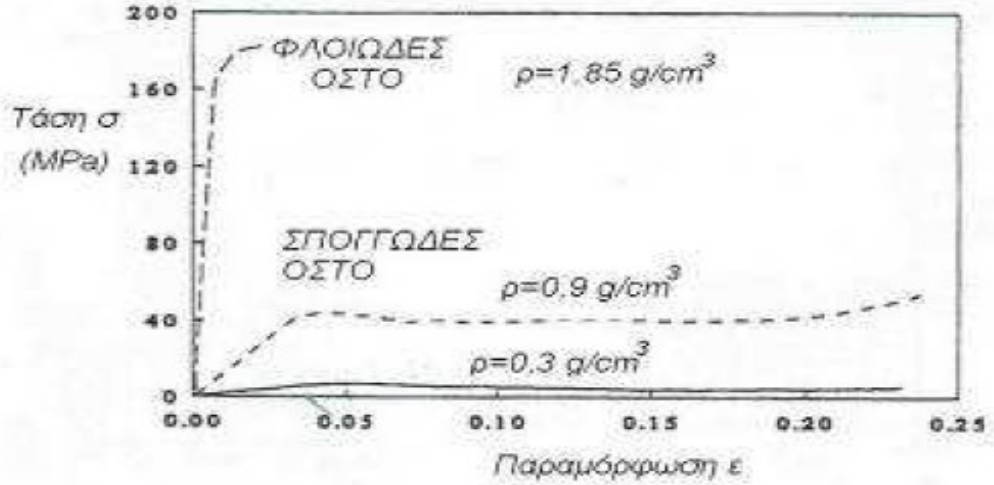


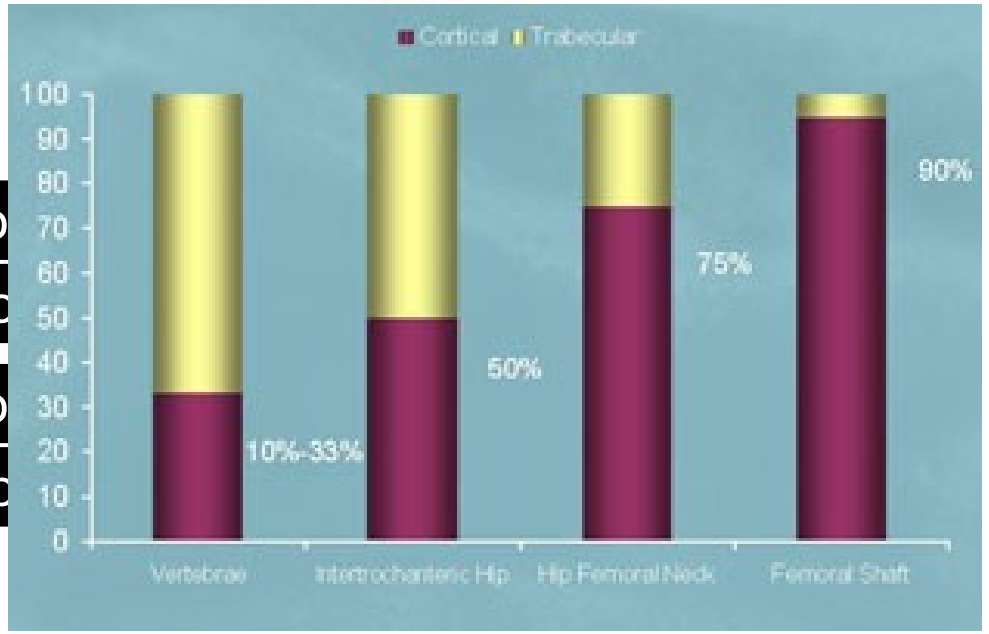
- **Φλοιώδες Οστούν**
  - 80% του σκελετού
  - 20% ενεργό σε κύκλο αναδιαμόρφωσης
  - Σχέση επιφάνειας/ όγκο ↓ Οστεοκύτταρα σπάνια
  - Διάρκεια κύκλου 7μήνες
  - Porosity 10%
  - Αντιστέκεται σε στρέψη και καμπύλ

- **Σπογγώδες Οστούν**
  - 20% του σκελετού
  - 80% ενεργό σε κύκλο αναδιαμόρφωση
  - Σχέση επιφάνειας/ όγκο ↑
  - Διάρκεια κύκλου 3-4μήνες
  - Porosity 50-90%
  - Δυνάμεις συμπίεσης







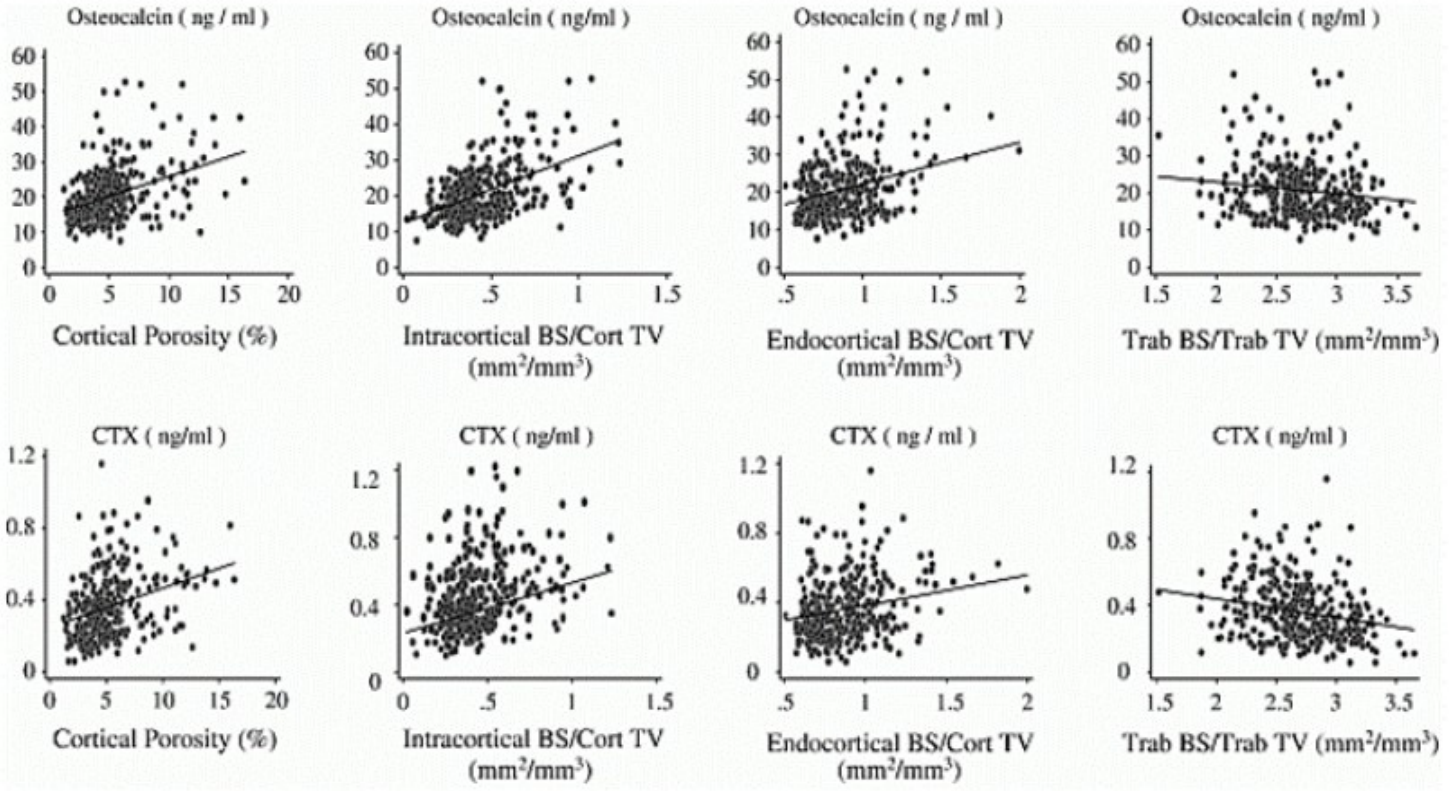


Δομικό Χαρακτηριστικό	Φλοιώδες Οστό	Σπογγώδες Οστό
Volume fraction (mm^3/mm^3)	0.90 (0.85 - 0.95)	0.20 (0.05 - 0.60)
Επιφάνεια / Όγκος οστού (mm^2/mm^3)	2.5	20
Συνολικός Όγκος Ιστού (mm^3)	1.4×10^6	0.35×10^6
Συνολική Εσωτερική Επιφάνεια (mm^2)	3.5×10^6	7.0×10^6

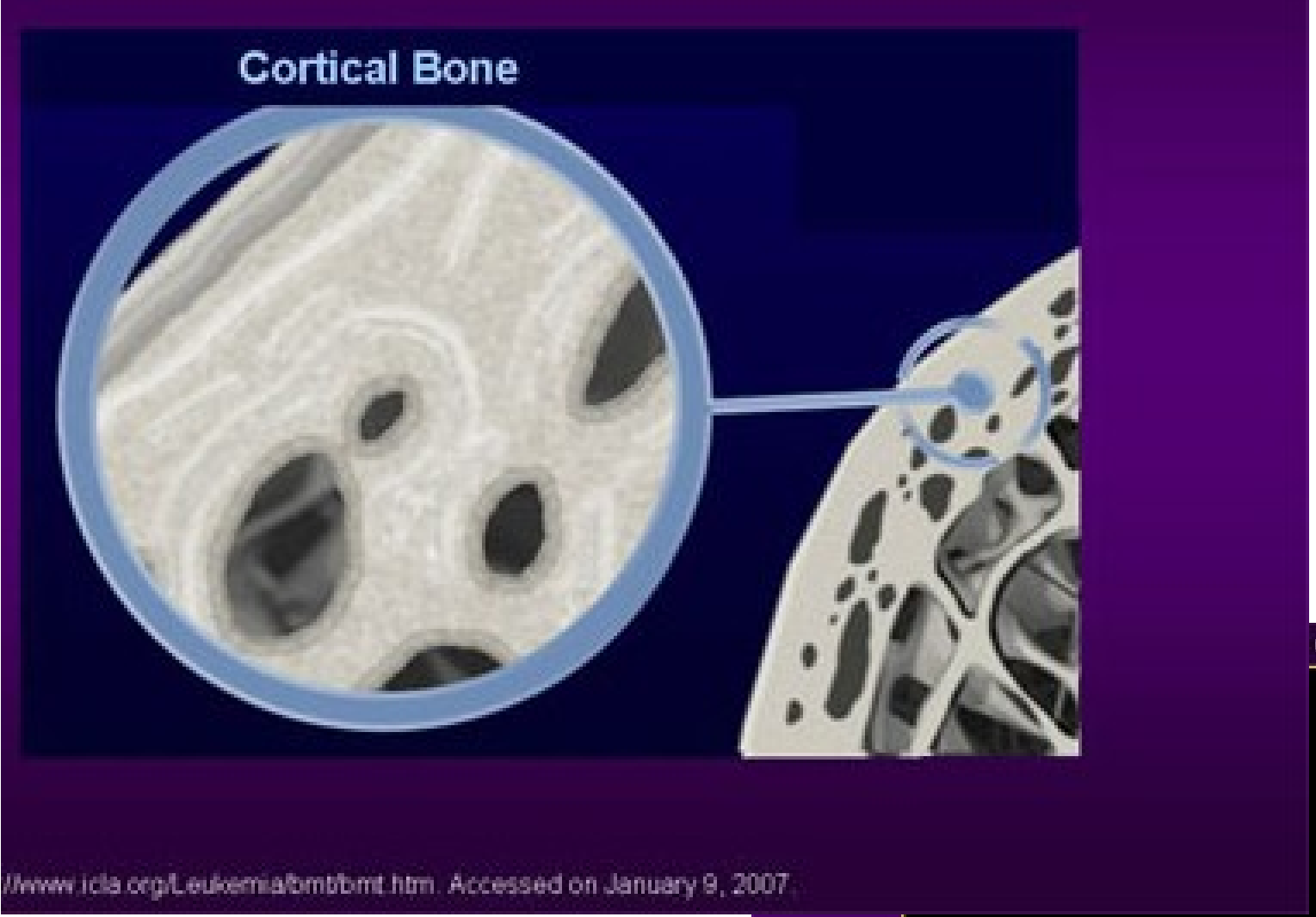
Remodeling markers are associated with larger intracortical surface area but smaller trabecular surface area: A twin study

Åshild Bjørnerem, Ali Ghasem-Zadeh, Minh Bui, Xiaofang Wang, Christian Rantzau, Tuan V. Nguyen, John L. Hopper, Roger Zebaze, Ego Seeman

Bone
Volume 49, Issue 6 , Pages 1125-1130, December 2011



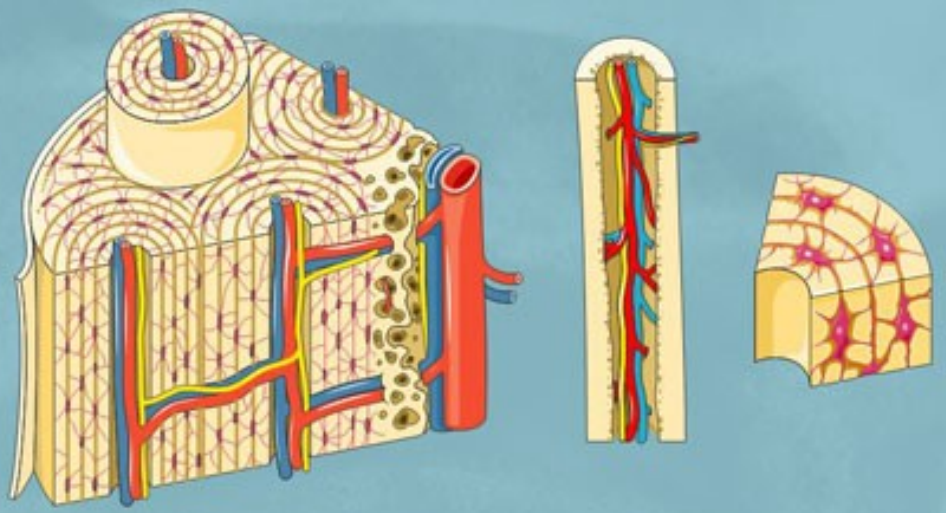
intracortical remodeling may be **self perpetuating**
by creating intracortical porosity and so more bone surface for remodeling to occur upon, while
remodeling upon the **trabecular bone surface is self limiting**
because it removes trabeculae with their surface



//www.icla.org/Leukemiabmtbmt.htm. Accessed on January 9, 2007.

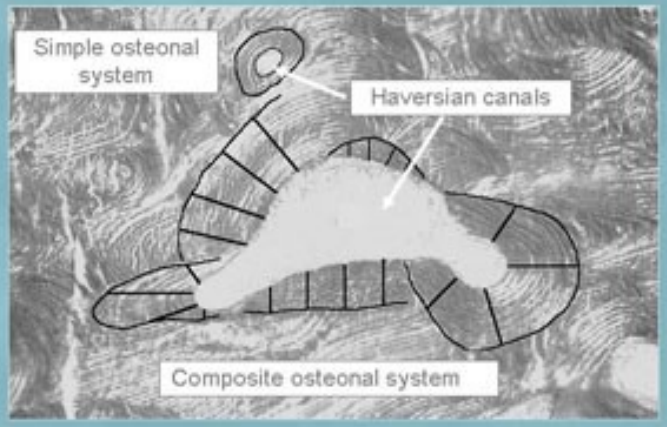
http://www.icla.org/Leukemiabmtbmt.htm. Accessed on

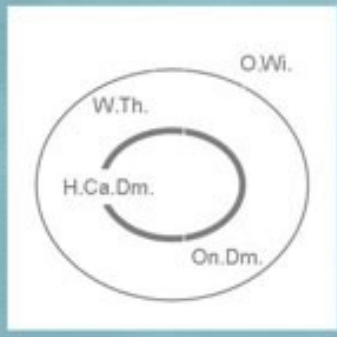
Osteon



Mechanism for Increased Cortical Porosity

Generation of composite osteonal systems with giant Haversian canals



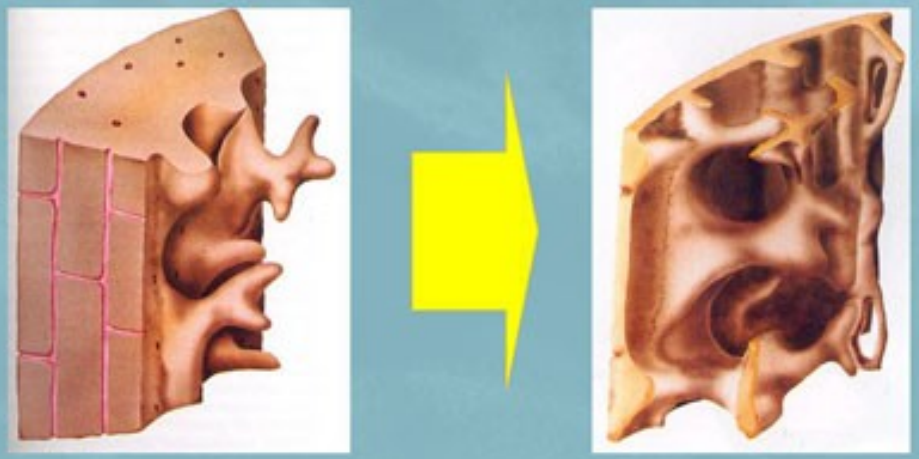


Minimum Dimensions Measured Within Osteons

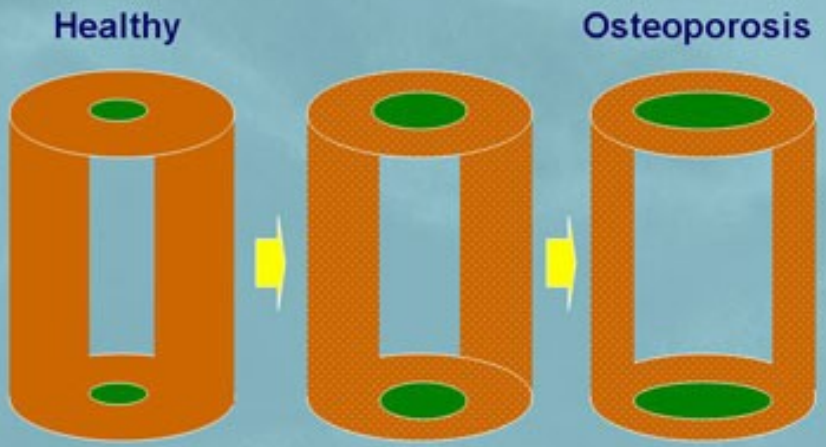
On.Dm, osteon diameter; H.Ca.Dm, Haversian canal diameter; W.Th, wall thickness; O.Wi, osteoid width

Bell KL, Loveridge N, Jordan GR, Power J, Constant CR, Reeve J. *Bone* 2000;27:297-304.

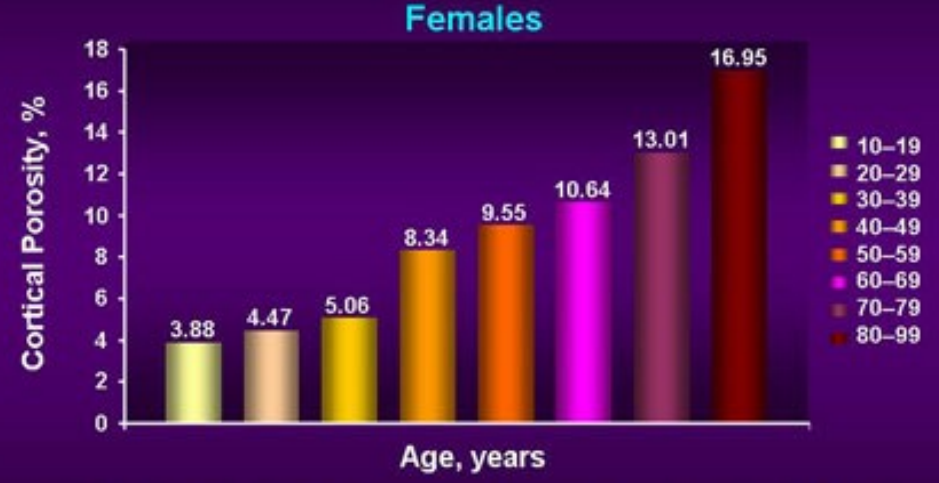
"Trabeculization" of the Cortex due to Progressive Increases on Cortical Porosity



Progressive Impairment of Cortical Bone Structure in Postmenopausal Osteoporosis



Cortical Porosity Increases Significantly with Age



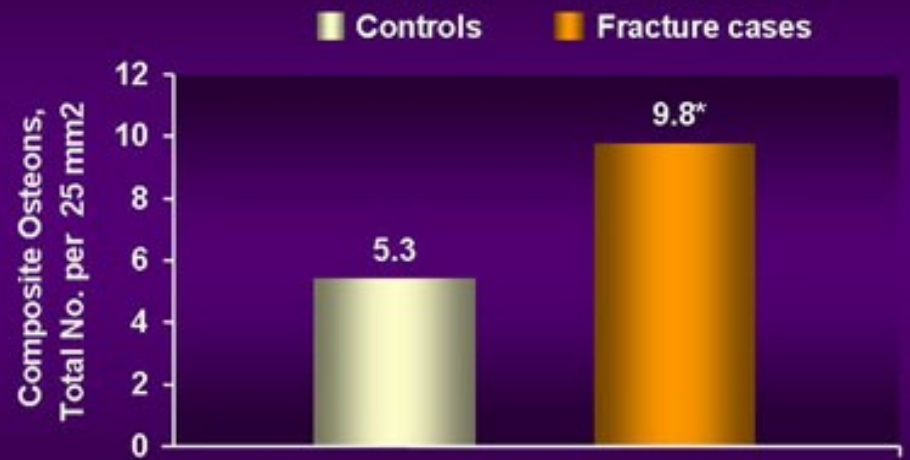
Relationship between age and increasing porosity, $P<0.001$

Roux JP, Wegrzyn J, Arlot ME, et al. Radiology. 2010;256:879–888.

Cortical Thickness Decreases Significantly in Women Older Than 50 Years

Relationship between age and decreasing thickness, $P<0.001$

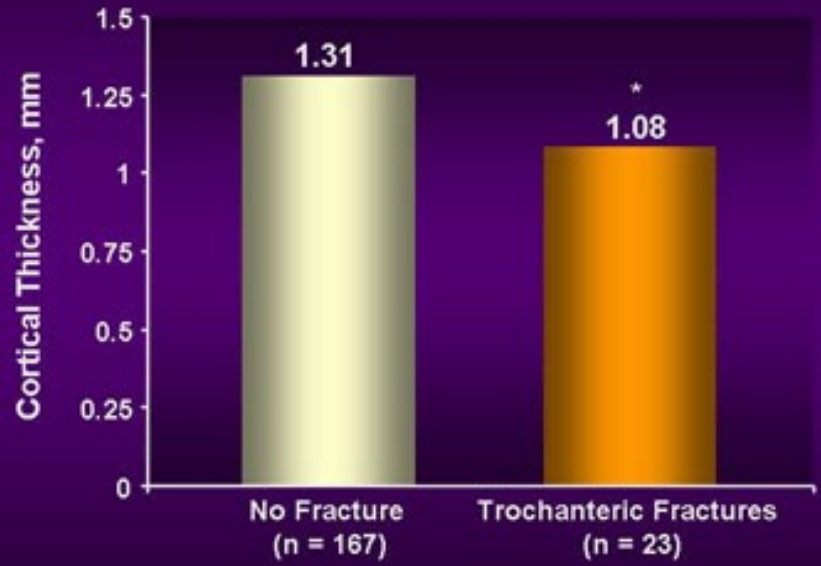
Increased Cortical Porosity is Associated With Hip Fracture



*$P<0.0001$ vs control women

Adapted from Bell KL, Loveridge N, Jordan GR, Power J, Constant CR, Reeve J. *Bone*. 2000;27:297–304.

Decreased Cortical Thickness is Associated With Hip Fracture



*$P<0.0001$ vs the nonfracture women

Adapted from Szulc P, Duboeuf F, Schott AM, Dargent-Molina P, Meunier PJ, Delmas PD. *Osteoporos Int*. 2006;17:231–236.

Αντικαταγματική δράση

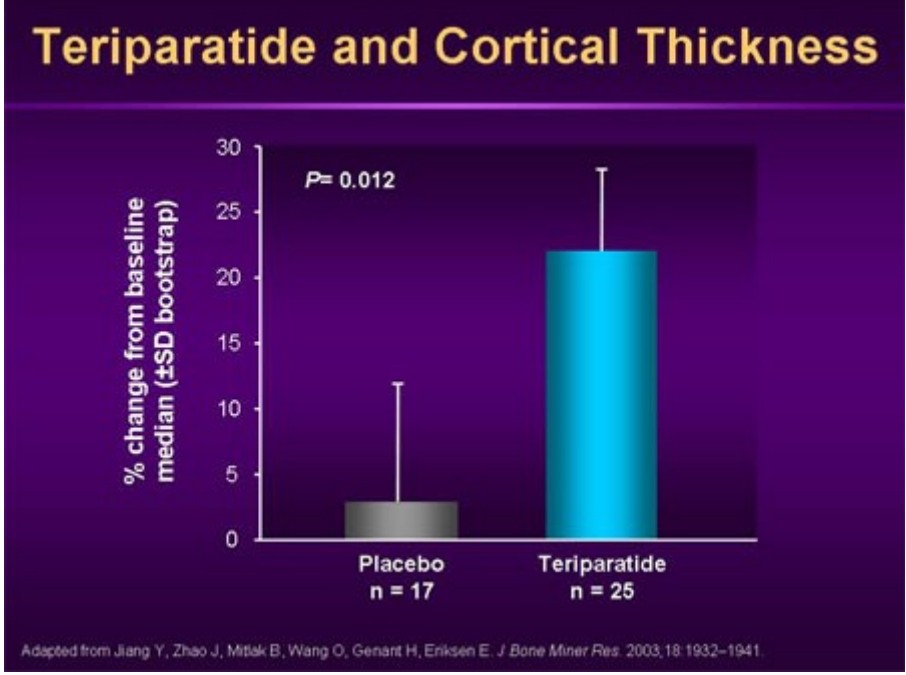
	Σπονδυλικά	ΜηΣπονδυλικά	Ισχίου
Οιστρογόνα	+	+	+
Καλσιτονίνη	+		
Ραλοξιφαίνη	+	(+)	
Αλενδρονάτη	+	+	+
Ρισεδρονάτη	+	+	+
Ζολεδρονικό	+	+	+
Ιμπανδρονάτη	+		
Τεριπαρατίδη	+	+	
Ρανελικό Στρόντιο	+	+	(+)
Denosumab	+	+	+

Τεριπαρατιδη

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 18, Number 3, 2003

Effects of Teriparatide [Recombinant Human Parathyroid Hormone (1-34)] on Cortical Bone in Postmenopausal Women With Osteoporosis

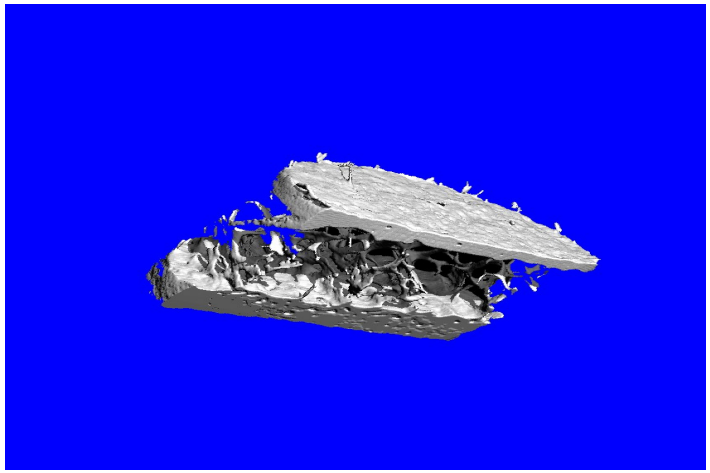
JR ZANCHETTA,[1] CE BOGADO,[1] JL FERRETTI,[1] O WANG,[2] MG WILSON,[3] M SATO,[2] GA GAICH,[2] GP DALSKY,[2] and SL MYERS[2]

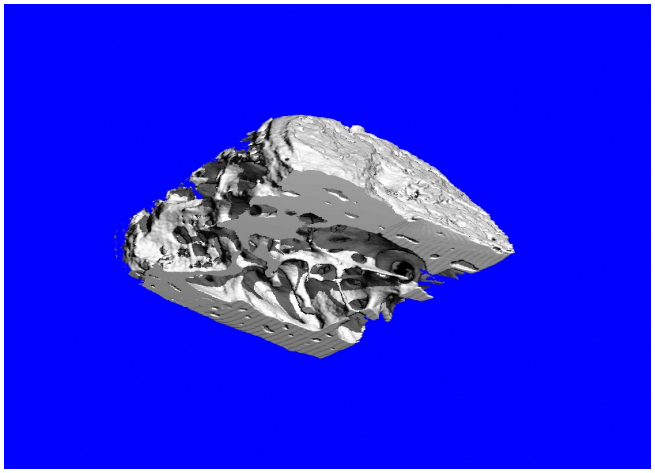


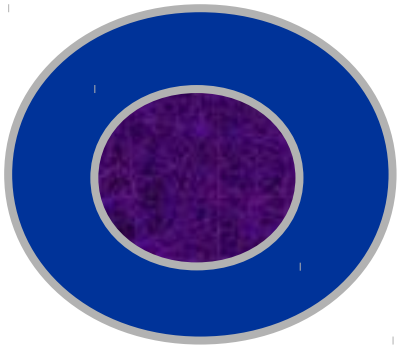
JOURNAL OF BONE AND MINERAL RESEARCH
Volume 18, Number 11, 2003

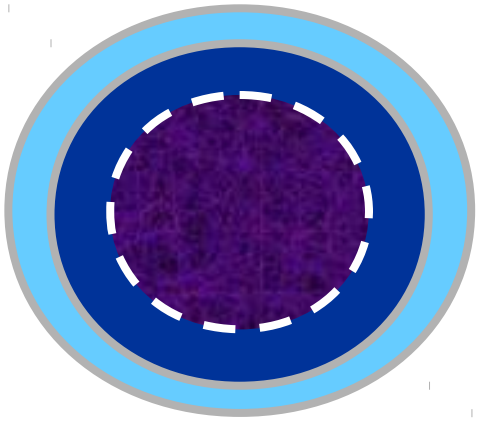
Recombinant Human Parathyroid Hormone (1-34) [Teriparatide] Improves Both Cortical and Cancellous Bone Structure

YEBIN JIANG,[1] JENNY J ZHAO,[1] BRUCE H MITLAK,[2] OUHONG WANG,[2] HARRY K GENANT,[1] and ERIK F ERIKSEN[2]



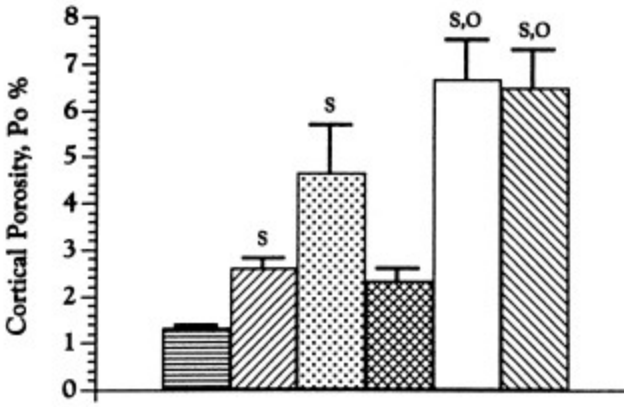






JOURNAL OF BONE AND MINERAL RESEARCH
Volume 16, Number 1, 2001

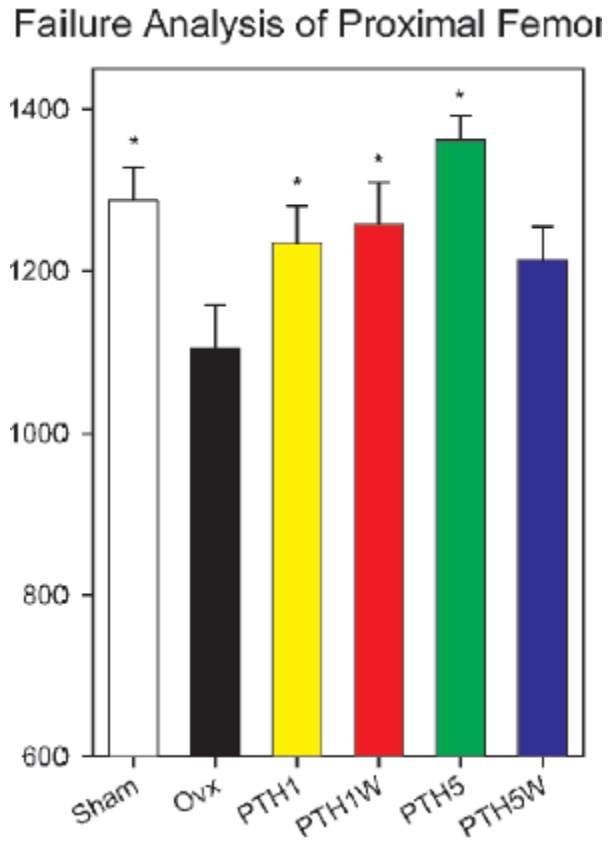
Intermittently Administered Human Parathyroid Hormone(1-34) Treatment Increases Intracortical Bone Turnover and Porosity Without Reducing Bone Strength in the Humerus of Ovariectomized Cynomolgus Monkeys



JOURNAL OF BONE AND MINERAL RESEARCH
Volume 19, Number 4, 2004
Published online on January 12, 2004; doi: 10.1359/JBMR.040112

Teriparatide [PTH(1-34)] Strengthens the Proximal Femur of Ovariectomized Nonhuman Primates Despite Increasing Porosity

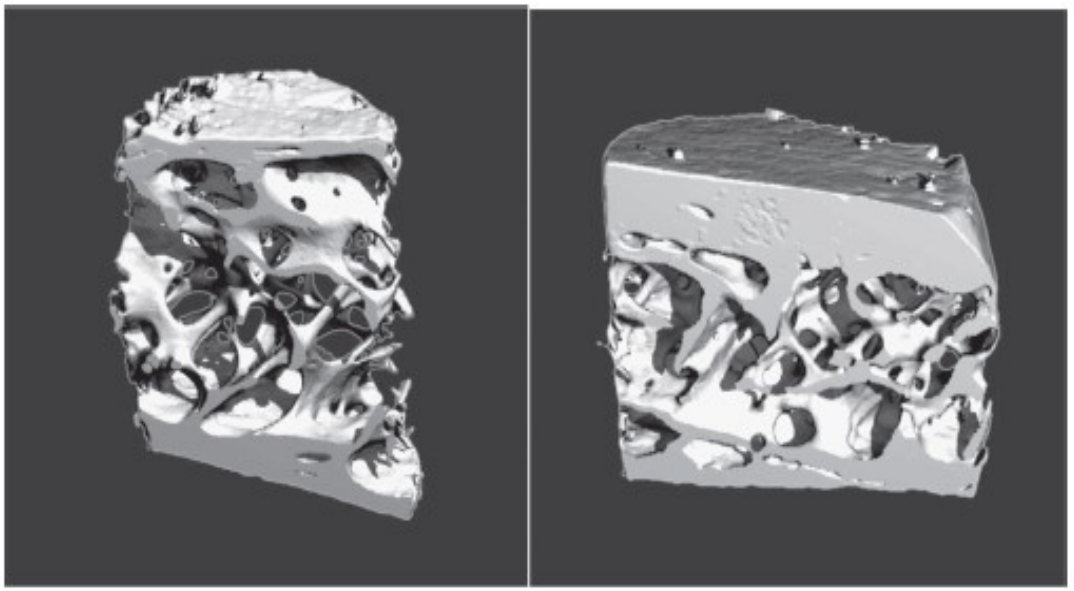
Masahiko Sato,[1] Michael Westmore,[1] Yanfei L Ma,[1] Allen Schmidt,[1] Qing Q Zeng,[1] Emmett V Glass,[2] John Vahle,[1] Robert Brommage,[3] Christopher P Jerome,[4] and Charles H Turner[5]



JOURNAL OF BONE AND MINERAL RESEARCH
Volume 23, Number 2, 2008
Published online on October 8, 2007; doi: 10.1359/JBMR.071012

Histomorphometric and μCT Analysis of Bone Biopsies From Postmenopausal Osteoporotic Women Treated With Strontium Ranelate

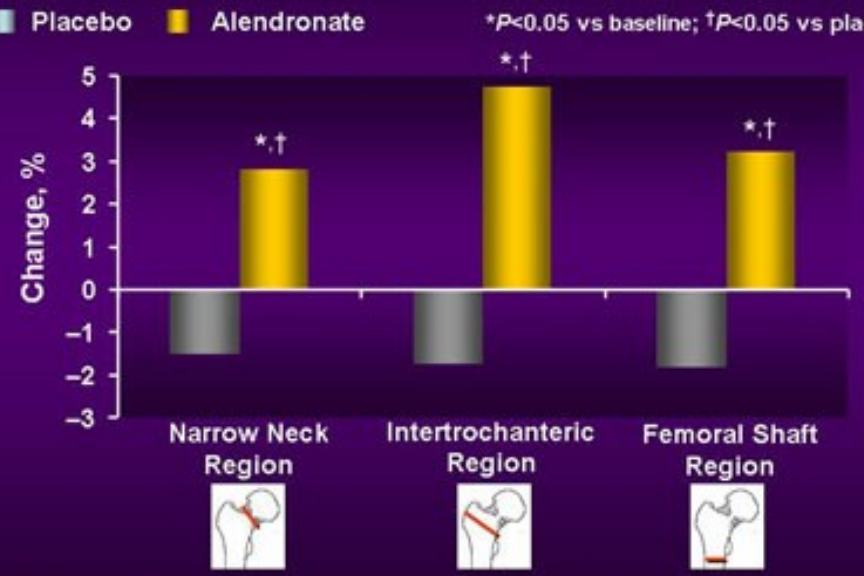
Monique E Arlot,[1] Yebin Jiang,[2,3] Harry K Genant,[2,4] Jenny Zhao,[2,3] Brigitte Burt-Pichat,[1] Jean-Paul Roux,[1] Pierre D Delmas,[1] and Pierre J Meunier[1]



PLACEBO STRONTIUM RANELATE

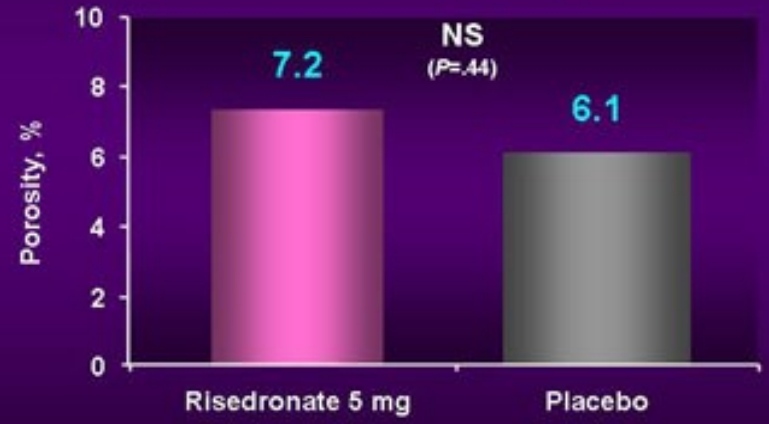
Διφωσφονικά

Alendronate and Cortical Thickness



Risedronate and Cortical Porosity

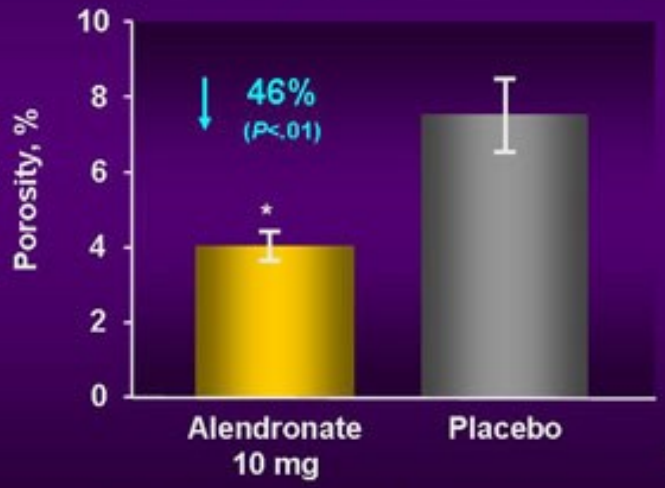
Trans-iliac biopsies after 5 years' treatment with risedronate 5 mg, daily or placebo



Adapted from Ste-Marie LG, Sod E, Johnson T, Chines A. *Calcif Tissue Int*. 2004;75:469-476.

Alendronate and Cortical Porosity

Trans-iliac biopsies after 2 or 3 years' treatment with alendronate 10 mg, daily or placebo



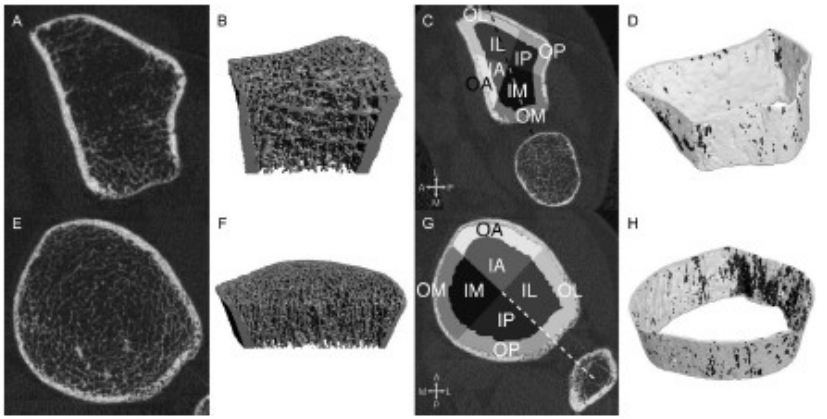
*P<.01 vs placebo

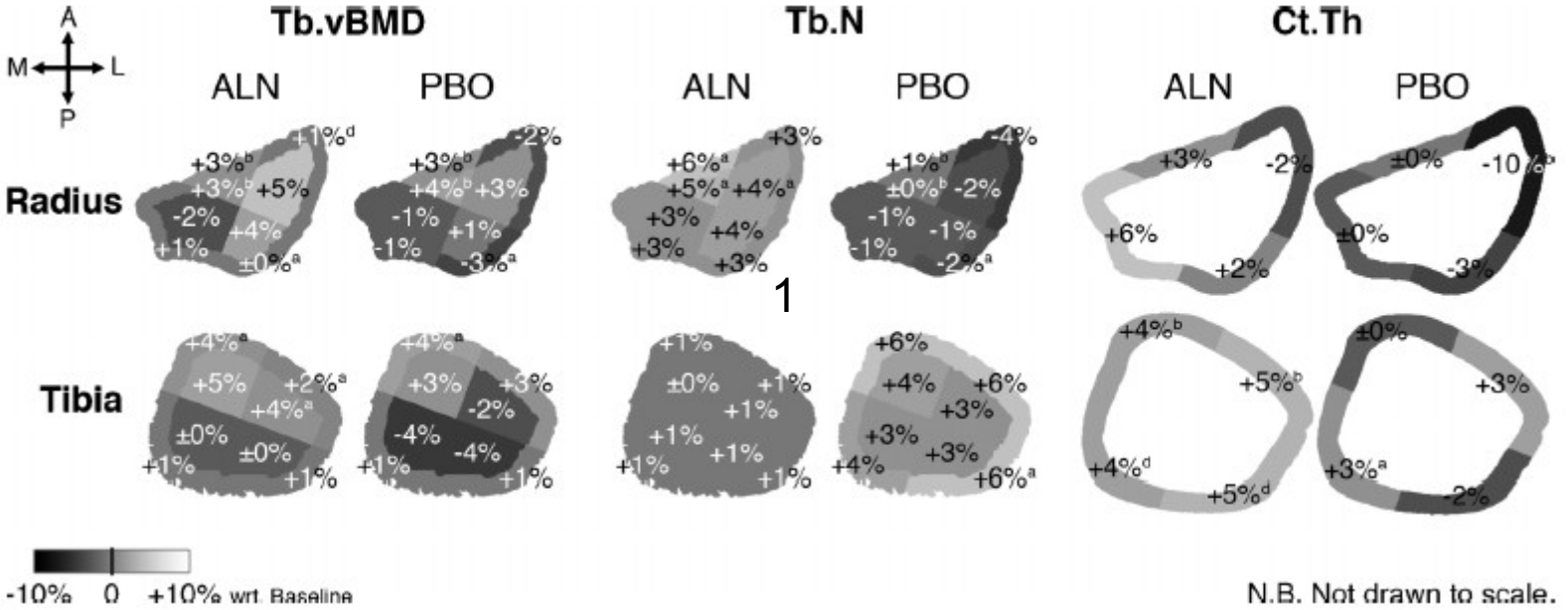
ORIGINAL ARTICLE

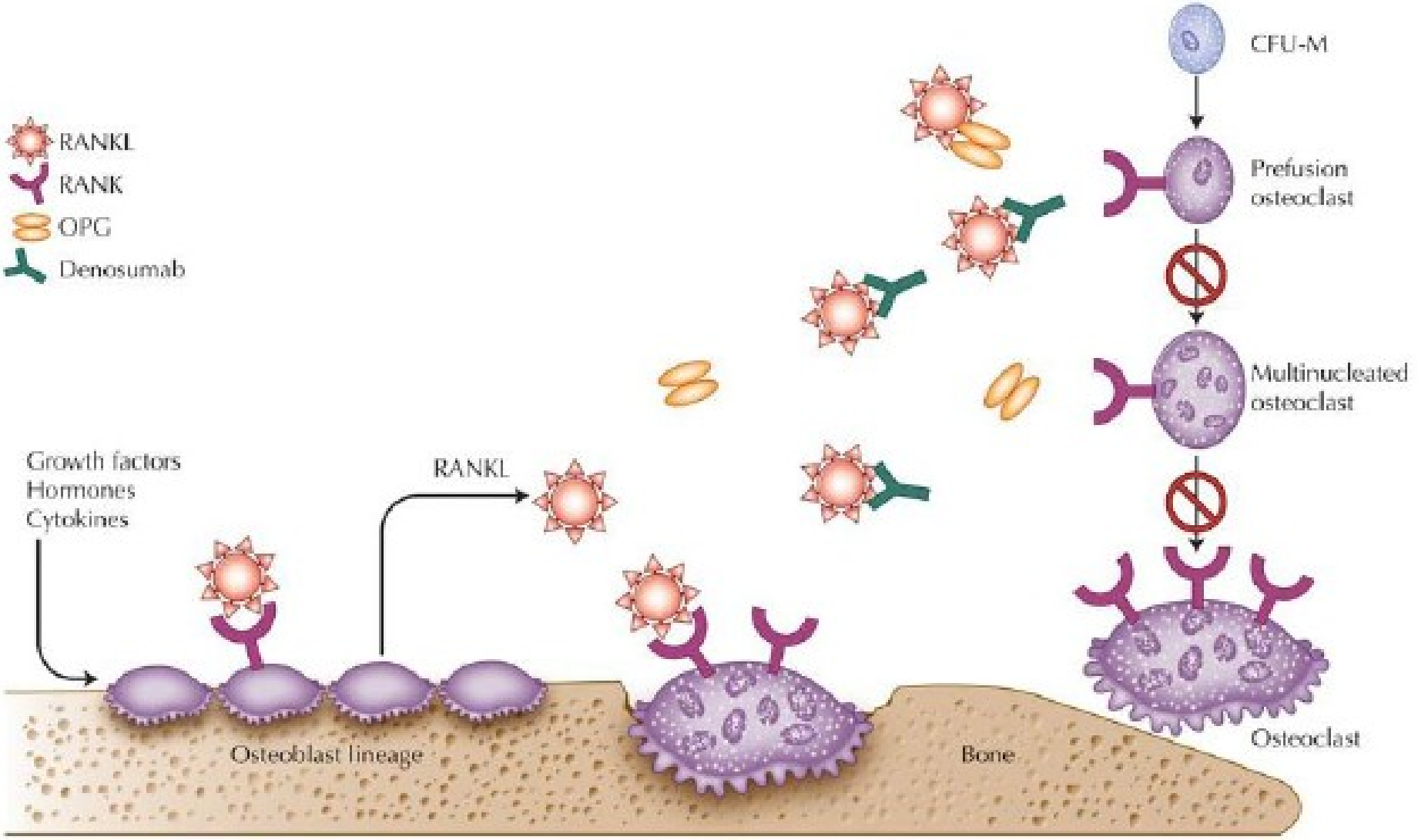
JBMR

A Longitudinal HR-pQCT Study of Alendronate Treatment in Postmenopausal Women With Low Bone Density: Relations Among Density, Cortical and Trabecular Microarchitecture, Biomechanics, and Bone Turnover

Andrew J Burghardt,[1] Galateia J Kazakia,[1] Miki Sode,[1,2] Anne E de Papp,[3] Thomas M Link,[1] and Sharmila Majumdar[1,2]

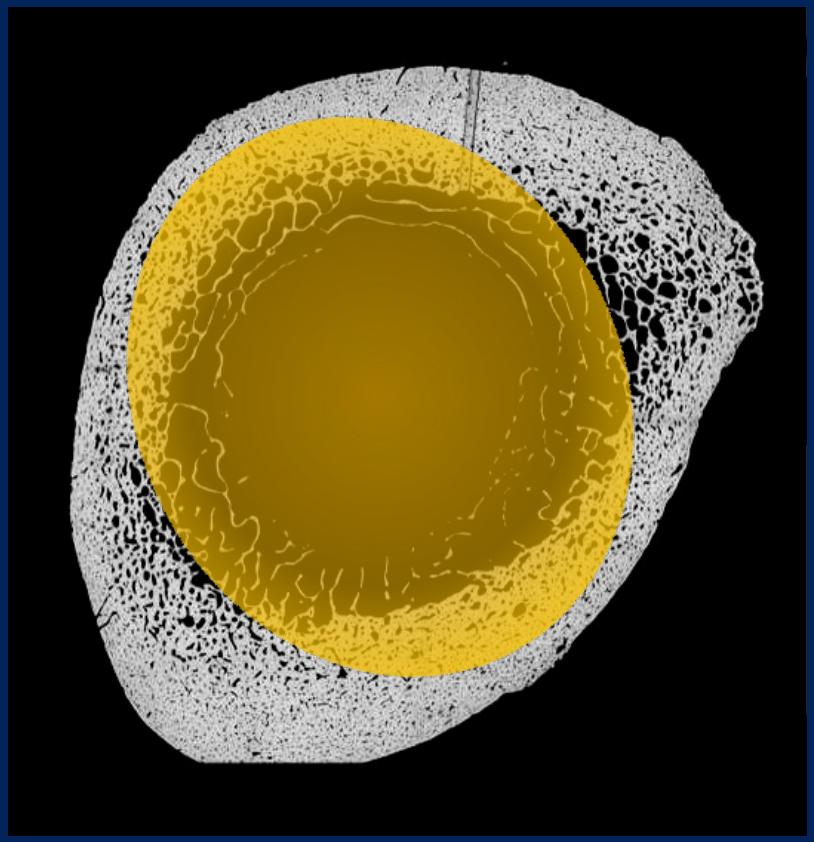





RANKL
RANK
OPG
Denosumab
CFU-M
Prefusion osteoclast
Multinucleated osteoclast
Osteoclast
Growth factors
Hormones
Cytokines
RANKL
Osteoblast lineage
Bone

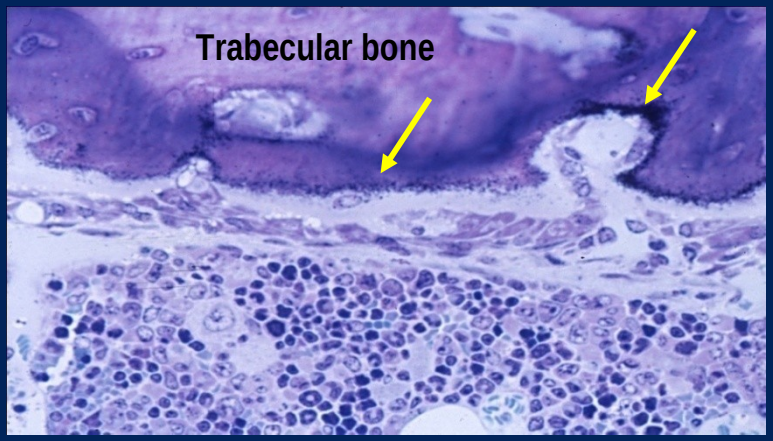
Schematic representation of the skeletal distribution of bisphosphonates

Bisphosphonates are rapidly absorbed to bone surfaces at sites of bone turnover[1,2]



Alendronate (ALN) on bone surface in rodent[3]

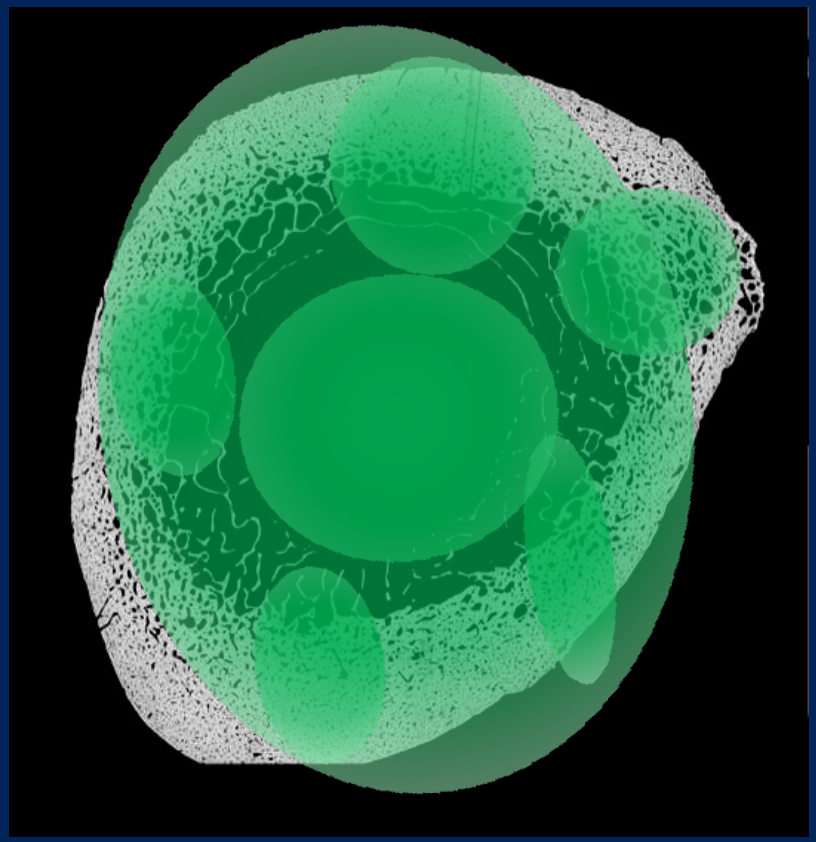
ALN on bone surfaces at 24 hrs



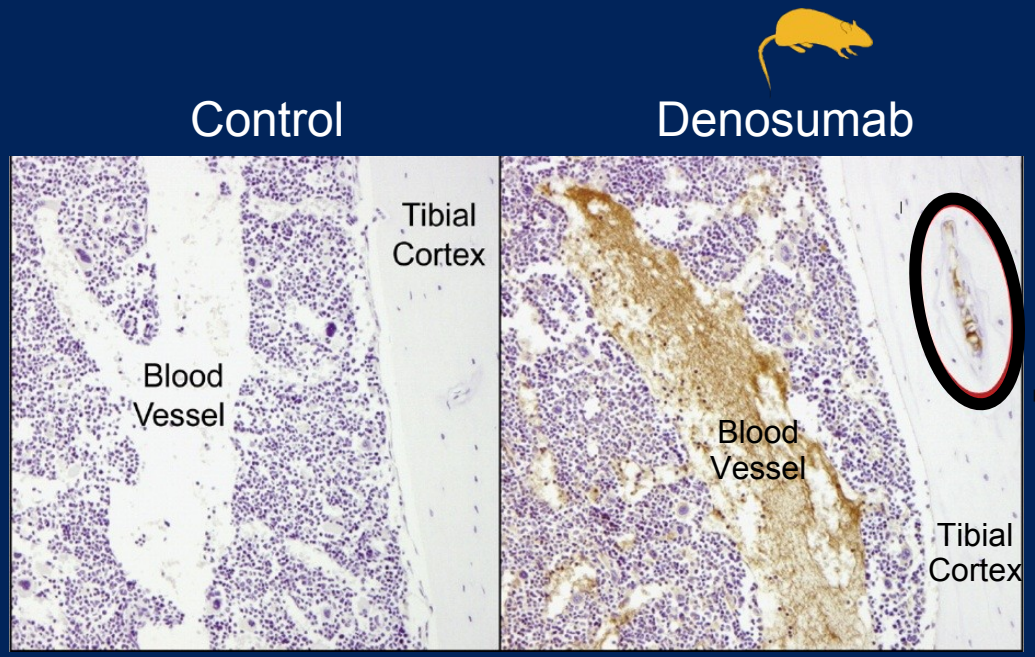
1. Baron R et al, *Bone* 2011;48 (4): 677-692. 2. Kimmel DB *J Dent Res* 86(11):1022-1033, 2007
3.Masarachia P, et al. Bone 1996;19:281-90.

Schematic representation of the skeletal distribution of denosumab

Denosumab continuously circulates in blood and extracellular fluid[1]



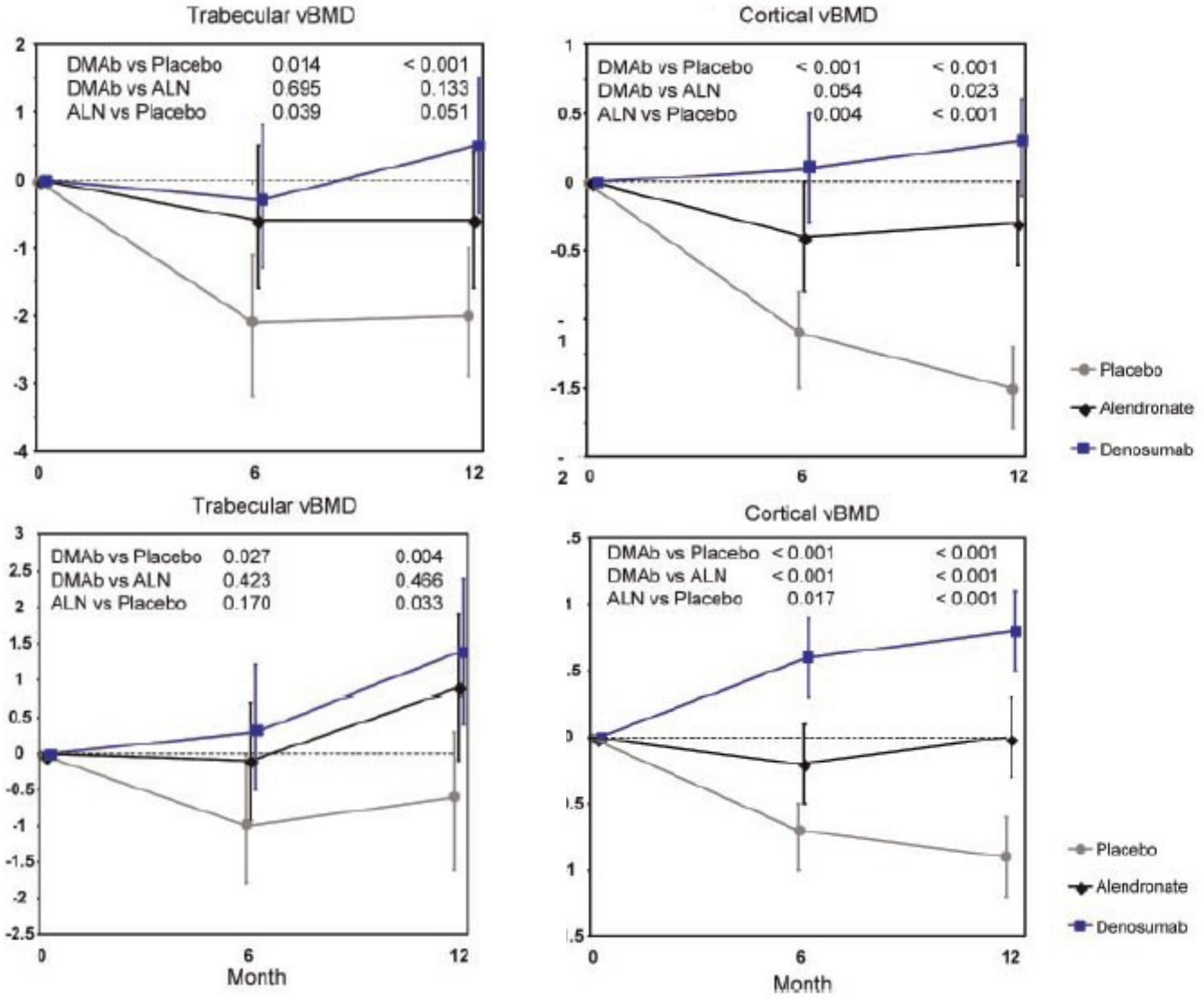
Denosumab in blood vessels within bone tissue in rodent[2]

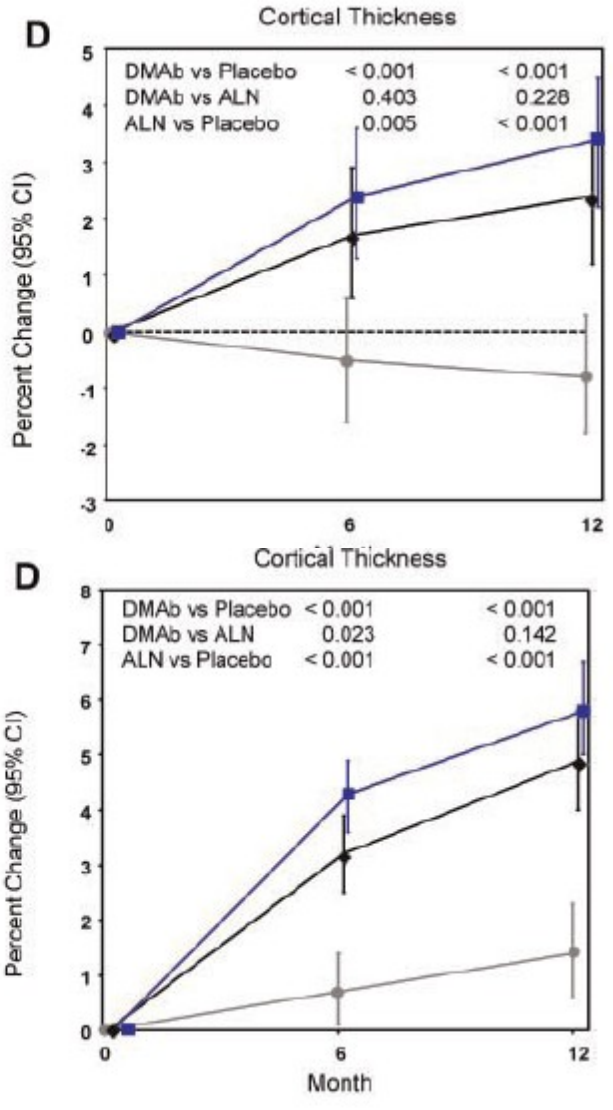


1. Baron R et al, *Bone* 2011;48 (4): 677-692.
2. Kostenuik PJ, et al. *J Bone Miner Res* 2009;24:182-95

JBMR

Microarchitectural Deterioration of Cortical and Trabecular Bone: Differing Effects of Denosumab and Alendronate

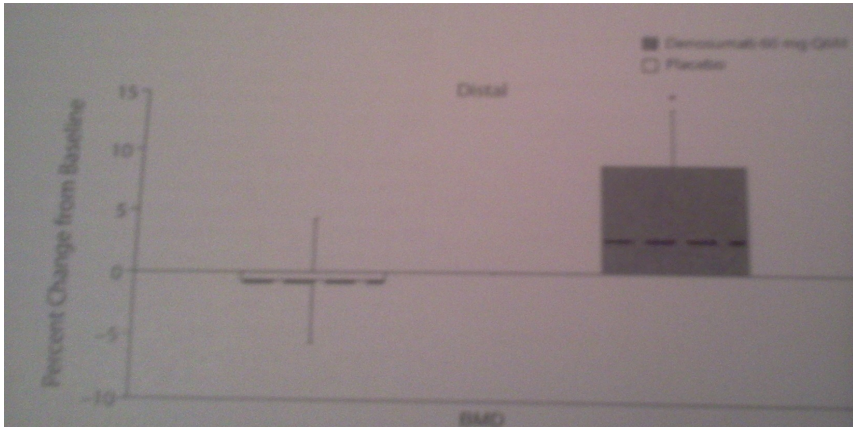


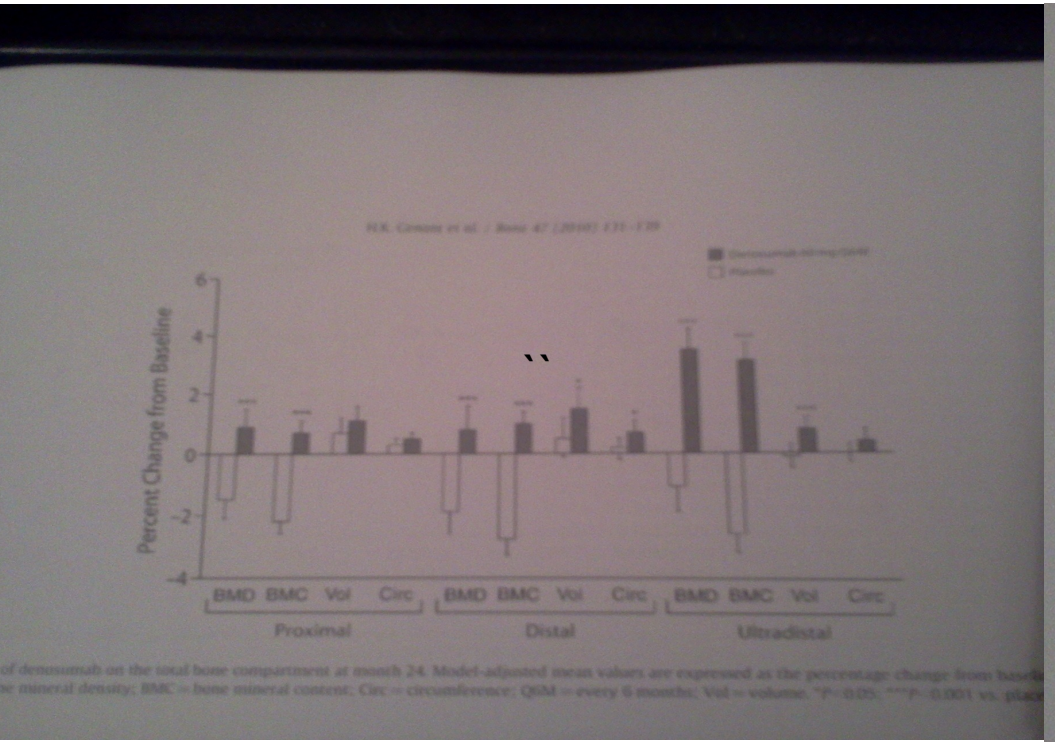


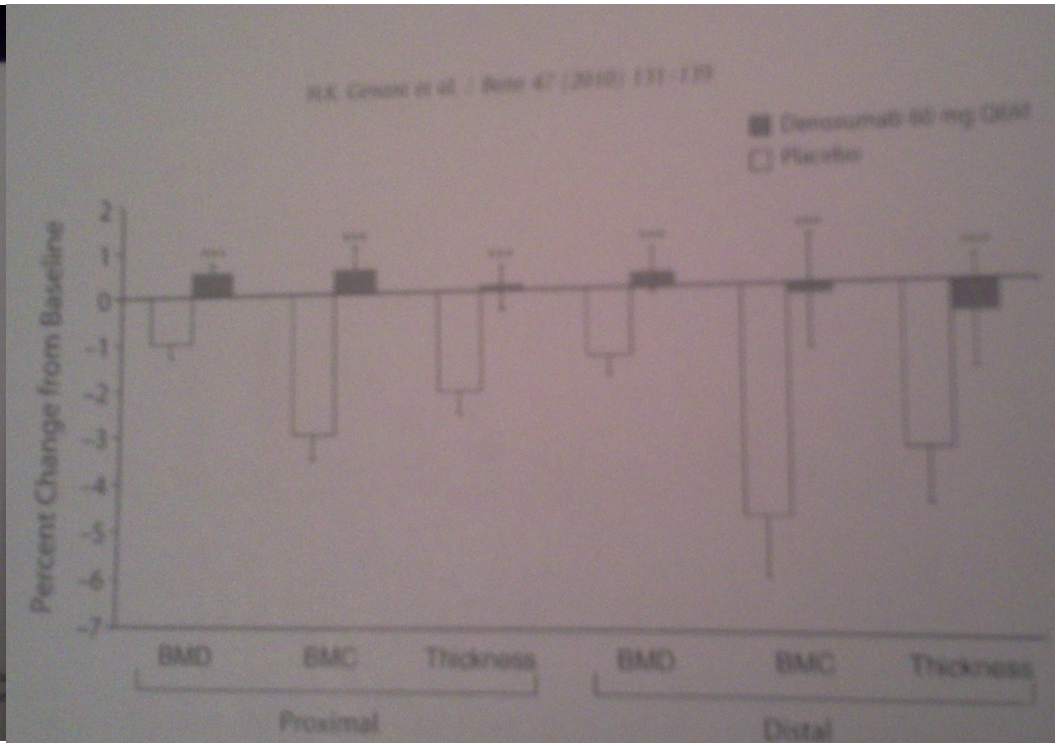
Denosumab improves density and strength parameters as measured by QCT of the radius in postmenopausal women with low bone mineral density☆

H.K. Genant✉, K. Engelke, D.A. Hanley, J.P. Brown, M. Omizo, H.G. Bone, A.J. Kivitz, T. Fuerst, H. Wang, M. Austin, C. Libanati

Bone
Volume 47, Issue 1 , Pages 131-139, July 2010



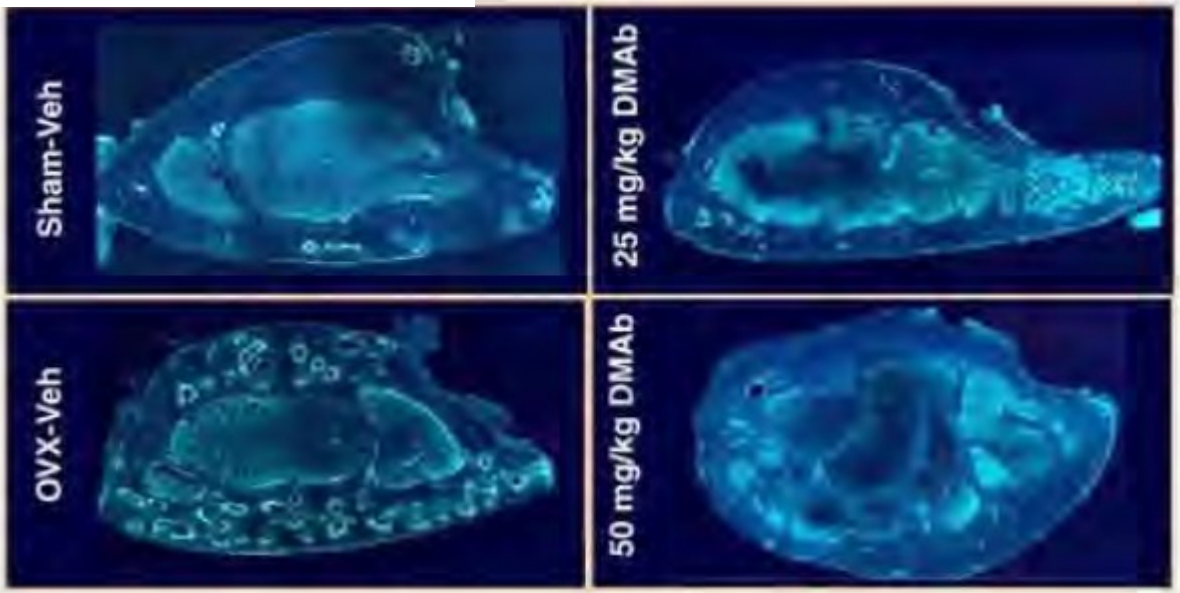


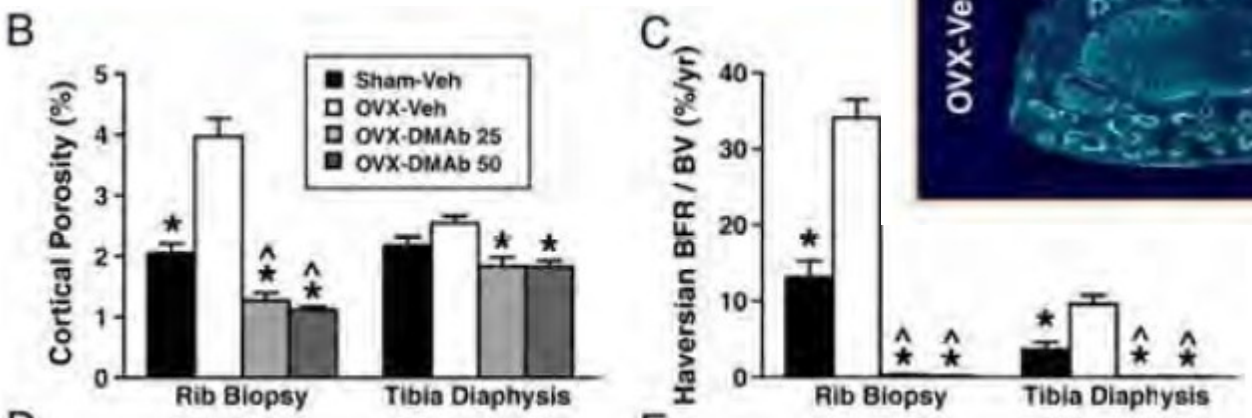


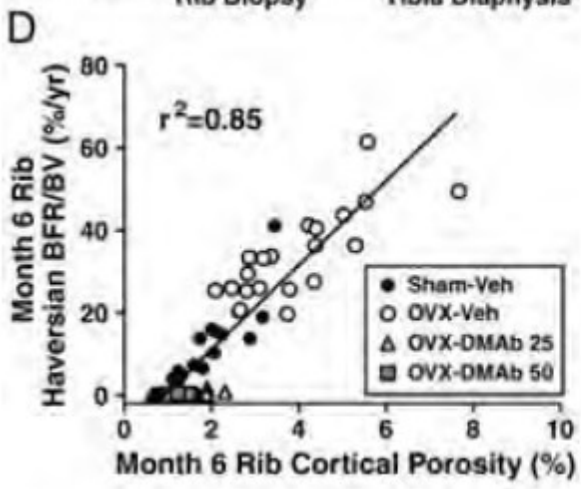
Decreased bone remodeling and porosity are associated with improved bone strength in ovariectomized cynomolgus monkeys treated with denosumab, a fully human RANKL antibody☆

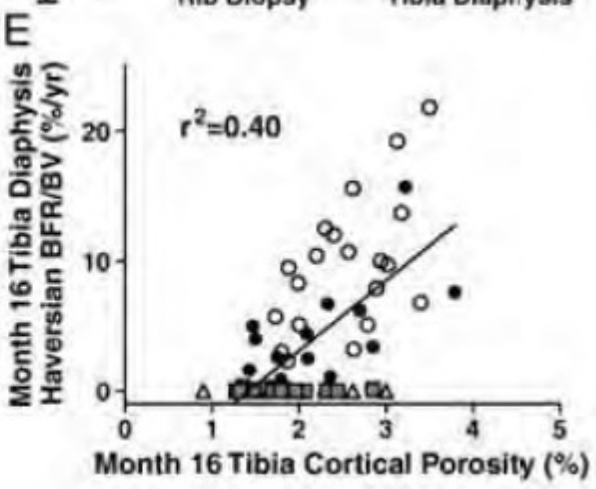
Paul J. Kostenuik, Susan Y. Smith, Jacquelin Jolette, Joseph Schroeder, Ian Pyrah, Michael S. Ominsky

Bone
Volume 49, Issue 2 , Pages 151-161, August 2011









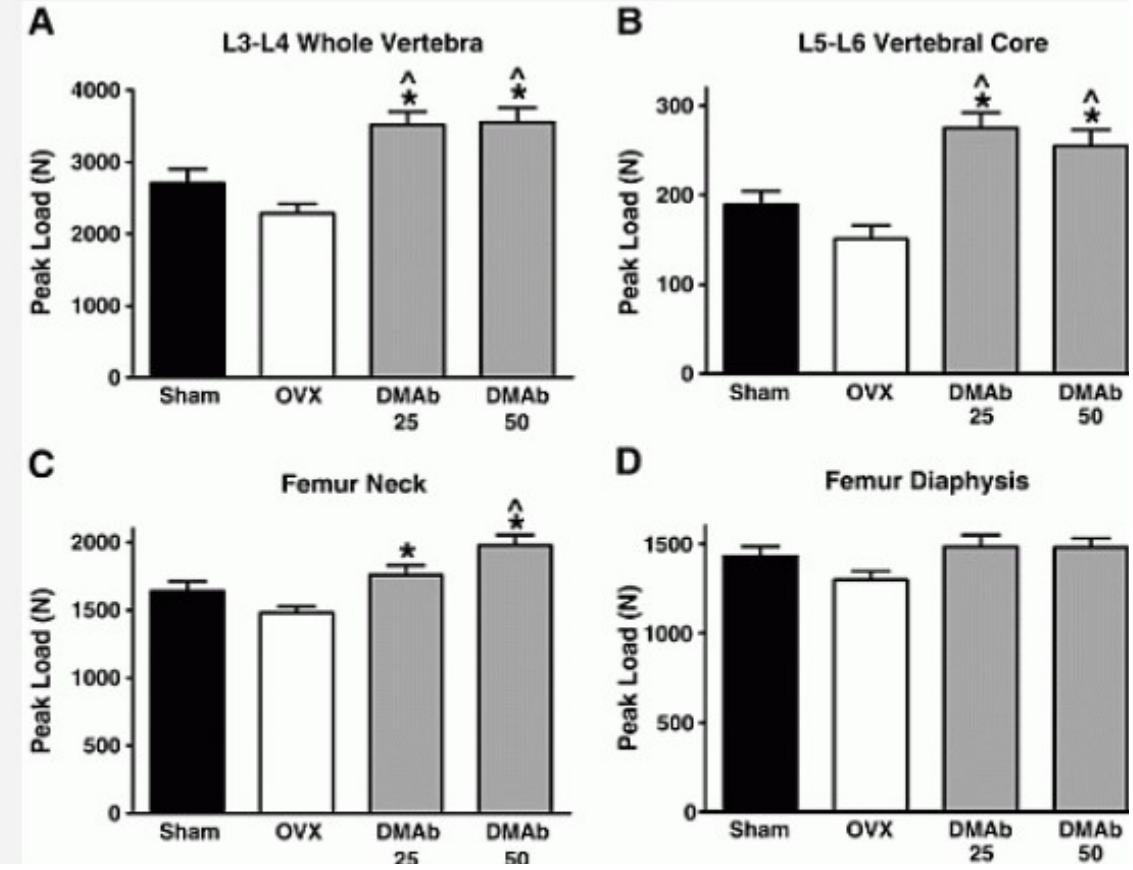
Cortical Porosity

28-72% ↓

Denosumab, a fully human RANKL antibody, reduced bone turnover markers and increased trabecular and cortical bone mass, density, and strength in ovariectomized cynomolgus monkeys☆☆☆

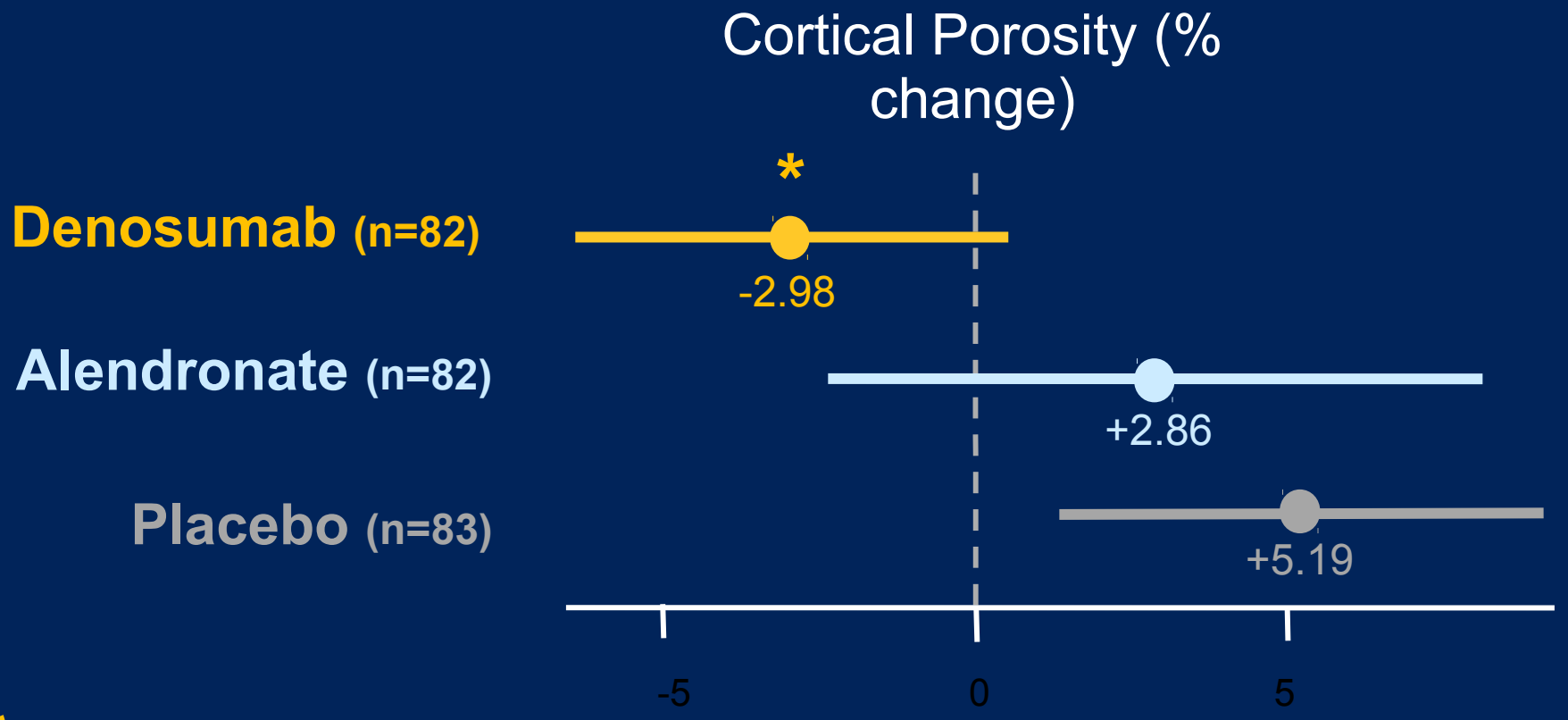
Michael S. Ominsky, Brian Stouch, Joseph Schroeder, Ian Pyrah, Marina Stolina, Susan Y. Smith, Paul J. Kostenuik

Bone
Volume 49, Issue 2 , Pages 162-173, August 2011



Dmab prevents increases in distal radius cortical porosity (HRpQCT)

Bone architecture pilot study

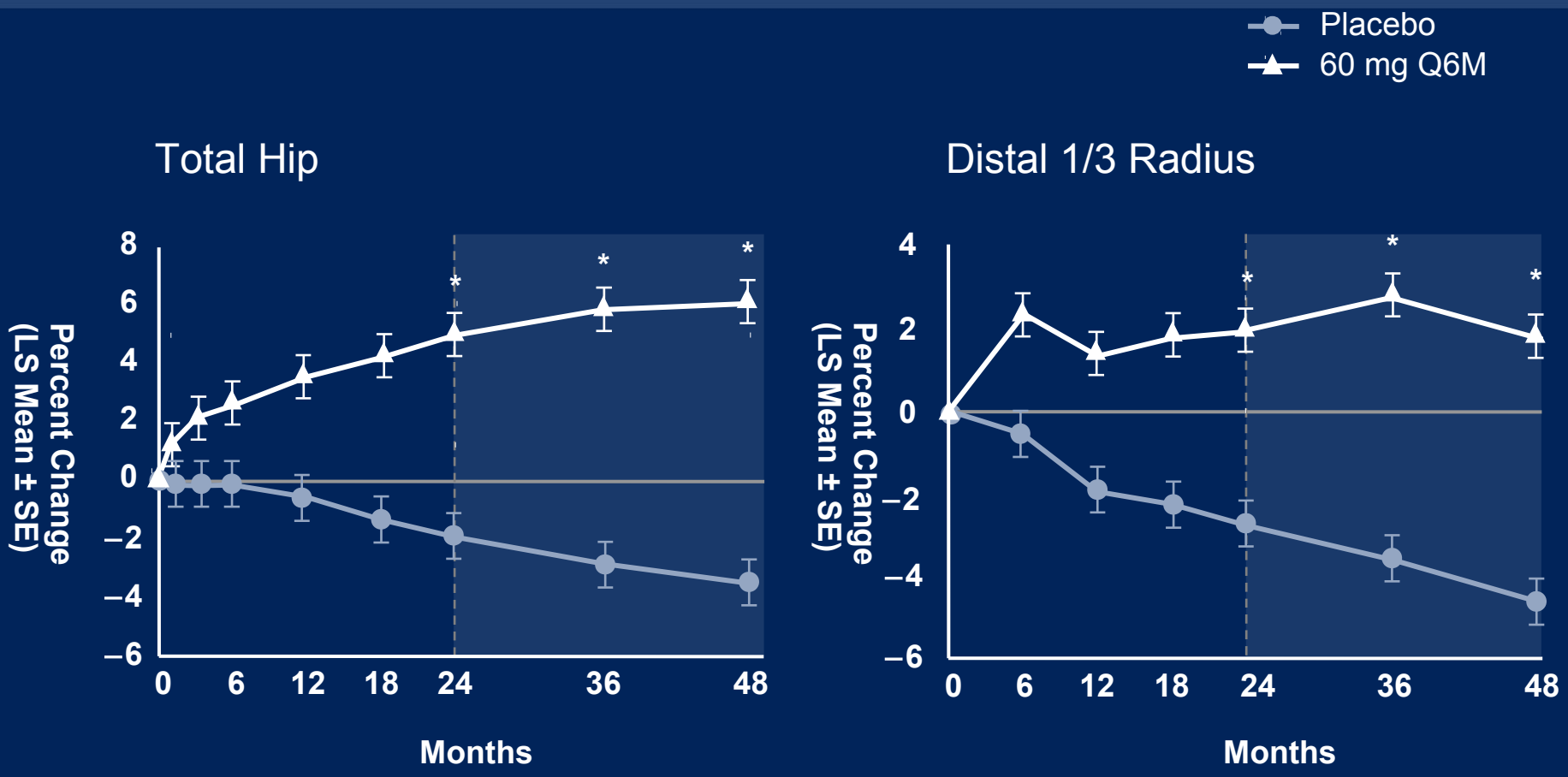


* p=0.02 vs placebo

Boyd et al. ECTS congress 2011, abstract and poster PP264

Effect of 4 Years of Denosumab Treatment on Total Hip and Distal 1/3 Radius BMD

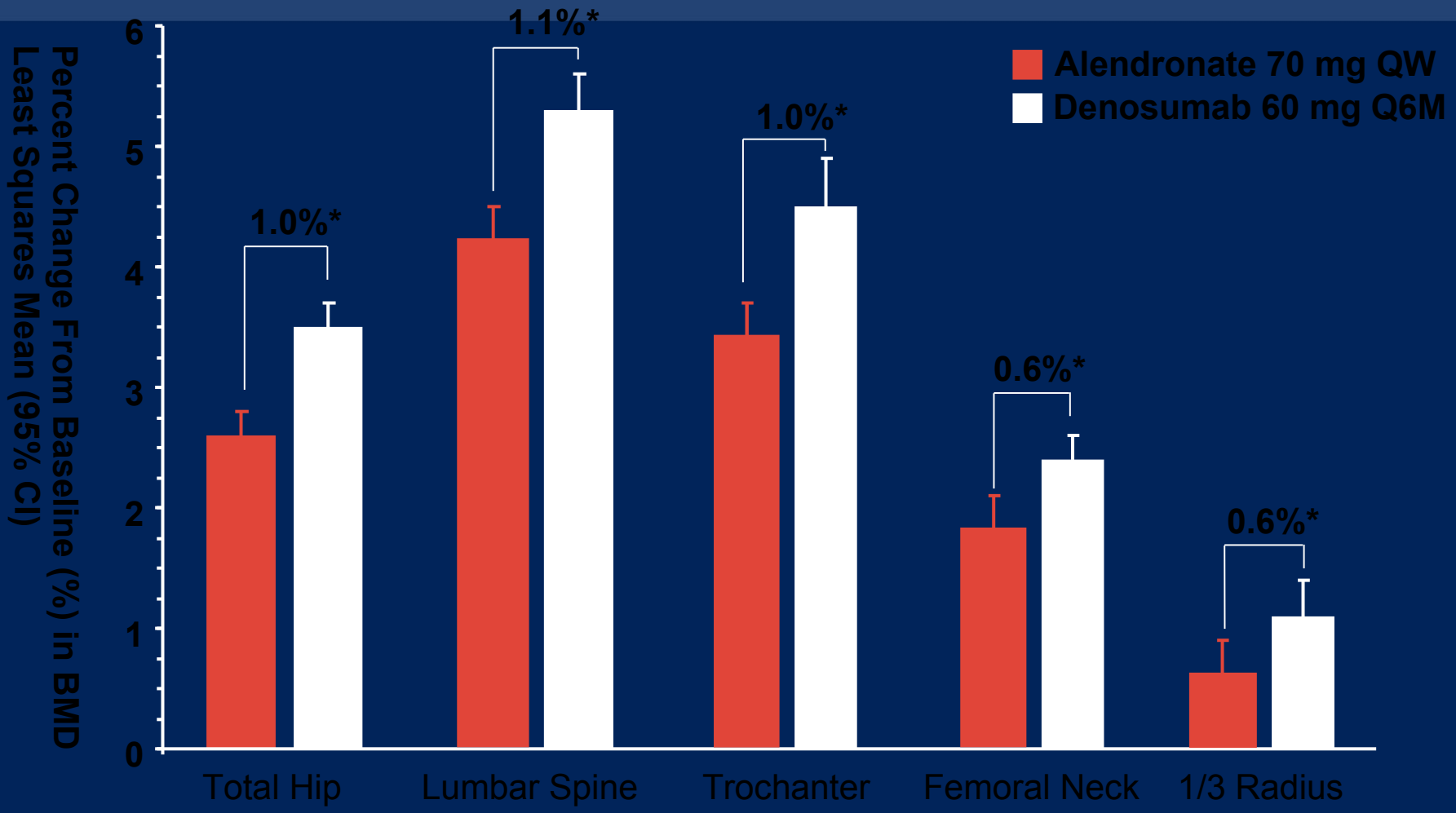
Phase 2 Study in Women With Low BMD



*P < 0.001 for 60-mg Q6M group vs placebo.
Note: Graph depicts only the 60-mg Q6M group from baseline through 48 months.
Adapted from Miller PD, et al. *Bone*. 2008;43:222-229.

BMD at Month 12 for All Measured Skeletal Sites

Phase 3: The DECIDE Trial

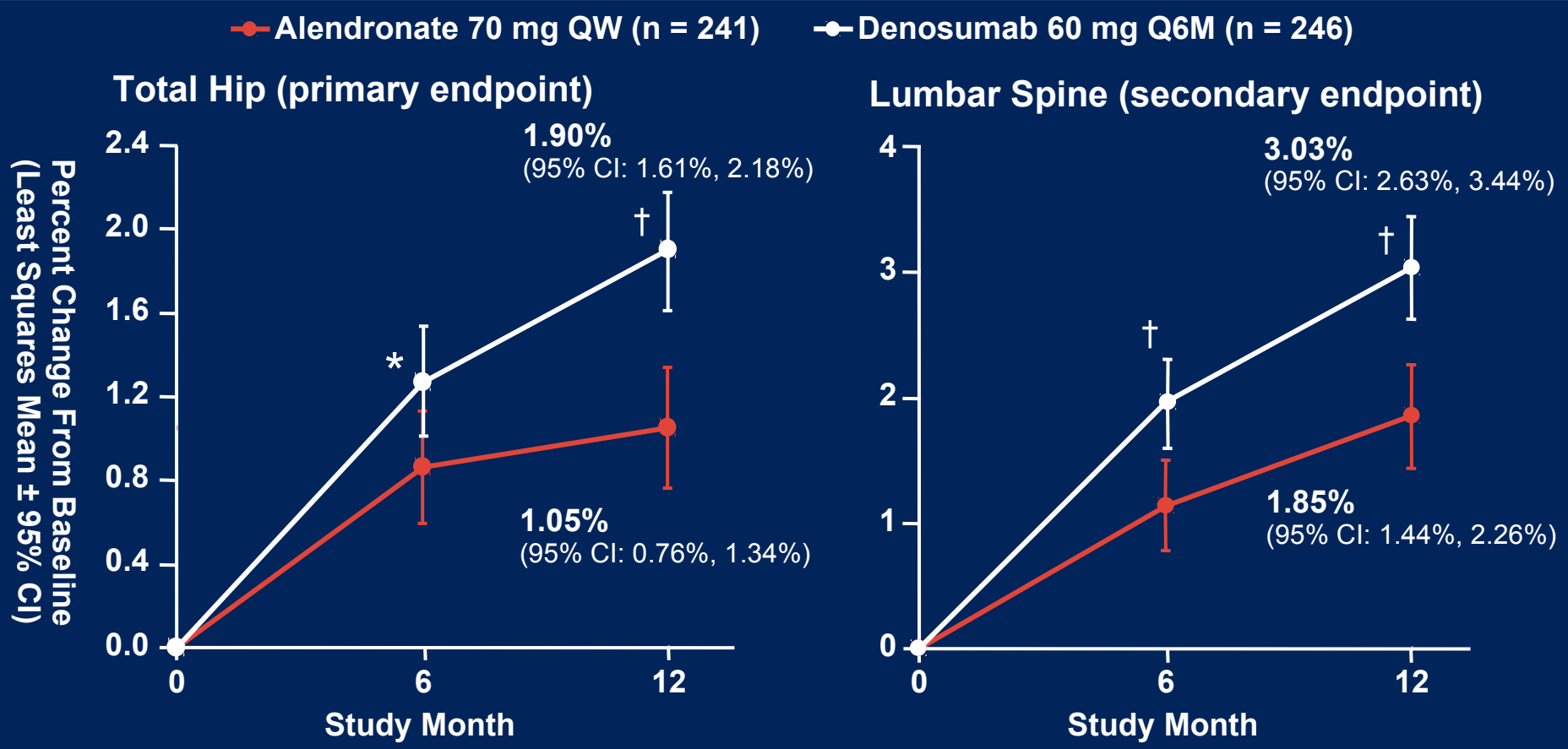


*$P \leq 0.0001$.

Brown JP, et al. *J Bone Miner Res.* 2009;24:153-161.

Brown JP, et al. Presented at: 35th Annual European Symposium on Calcified Tissues; May 24-28, 2008; Barcelona, Spain. Late breaking abstract LB2.

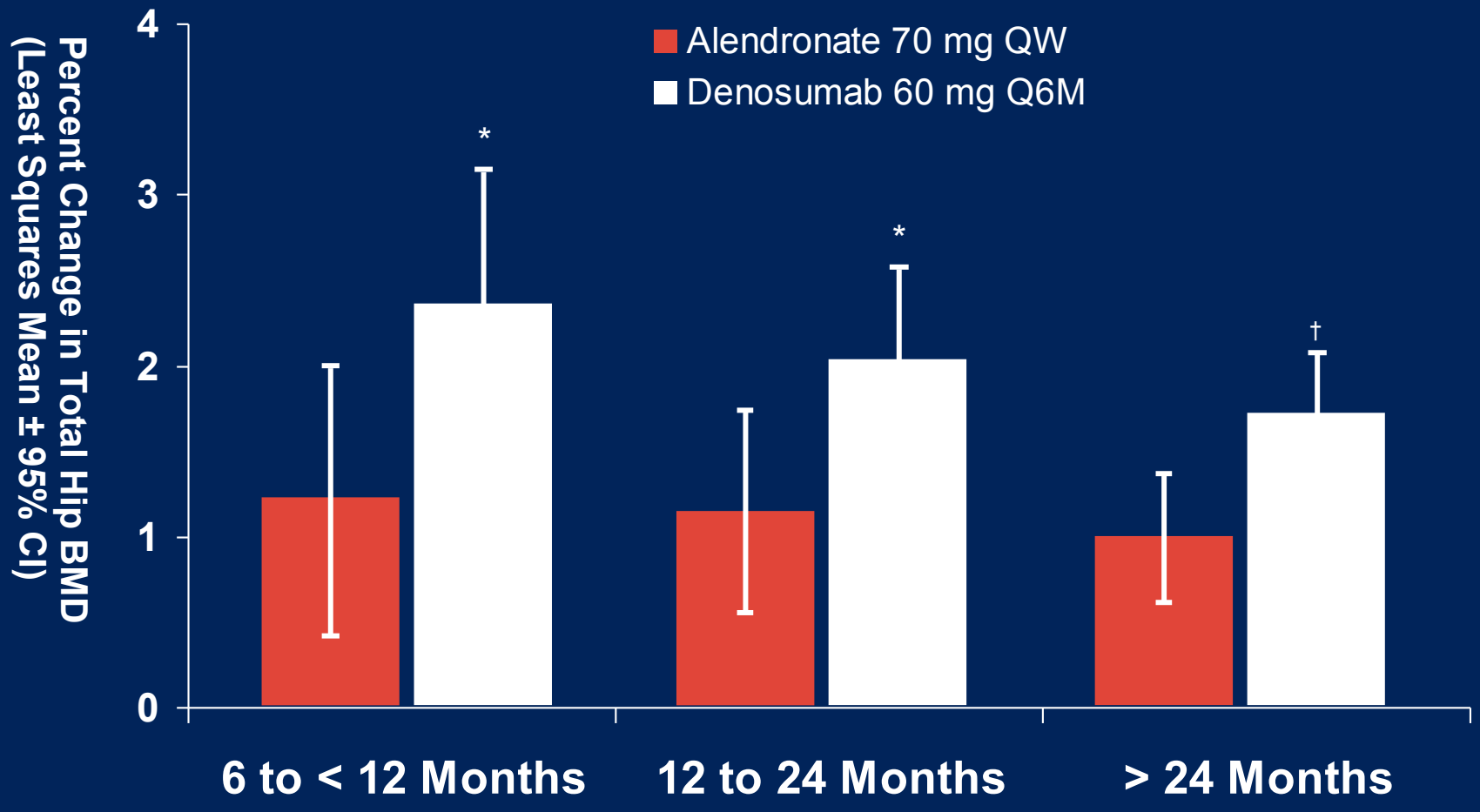
Effects of Treatment on BMD Over 12 Months
Phase 3: The STAND Trial



n = number of patients who have a baseline and ≥ 1 postbaseline evaluation.
*$P < 0.05$; †$P < 0.01$.
CI = confidence interval
Adapted from: Kendler DL, et al. *J Bone Miner Res*. 2010;25:72-81

Effect of Time-on-Prior Alendronate on Total Hip BMD Changes

Phase 3: The STAND Trial



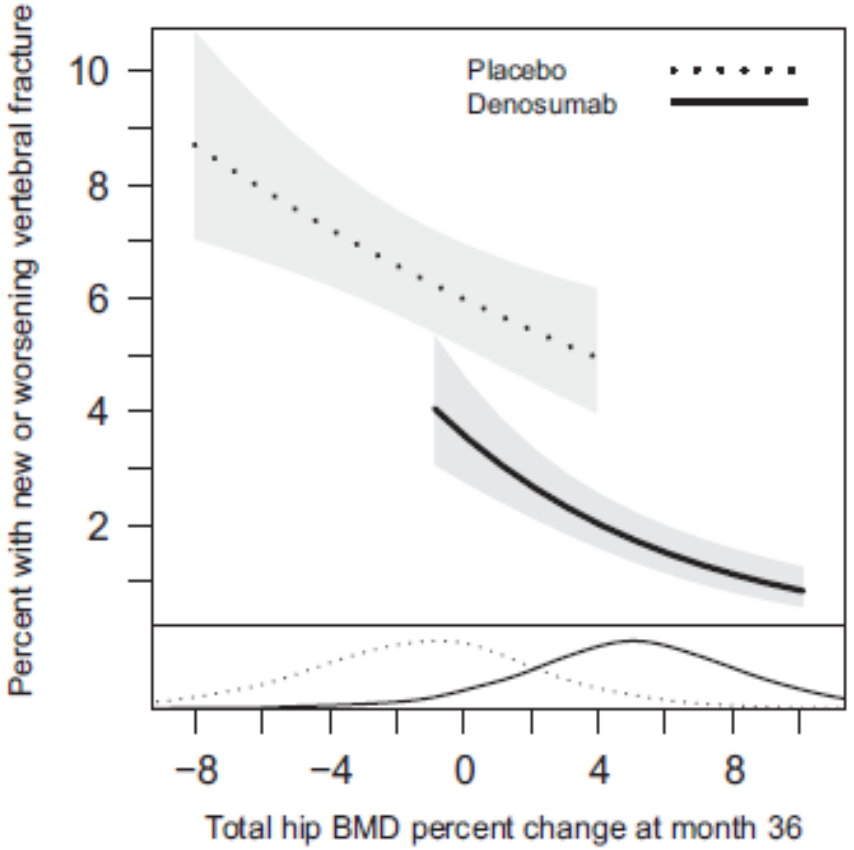
*$P < 0.05$
†$P < 0.01$

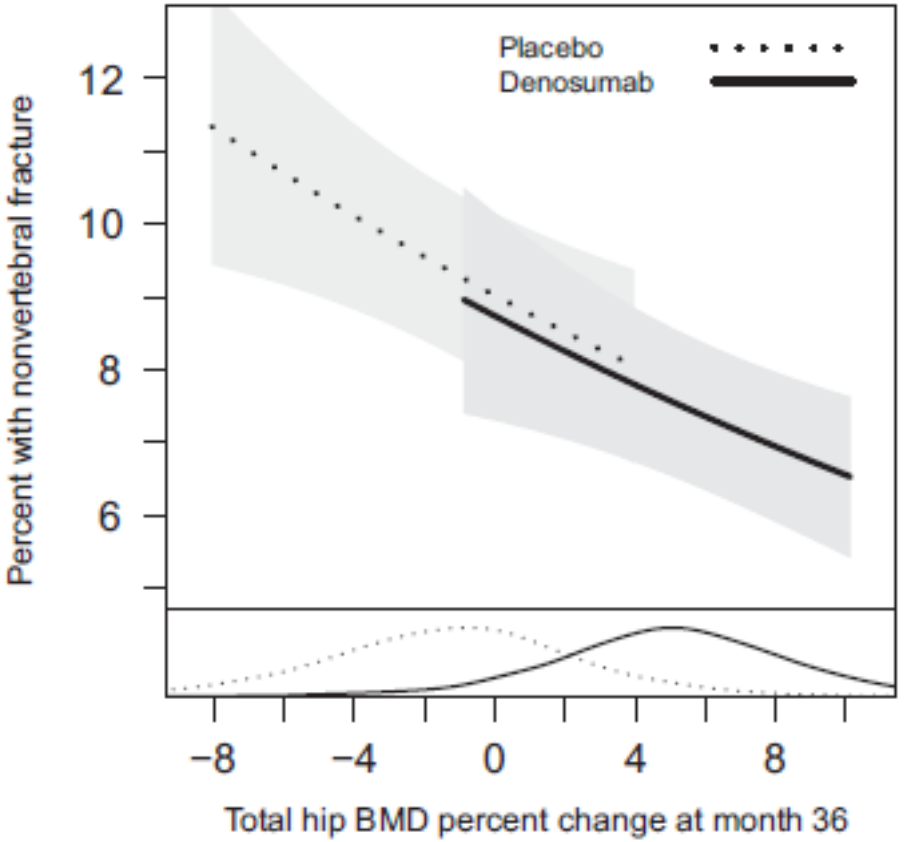
Adapted from: Kendler DL, et al. *J Bone Miner Res*. 2010;25:72-81

JBMR

Relationship Between Bone Mineral Density Changes With Denosumab Treatment and Risk Reduction for Vertebral and Nonvertebral Fractures

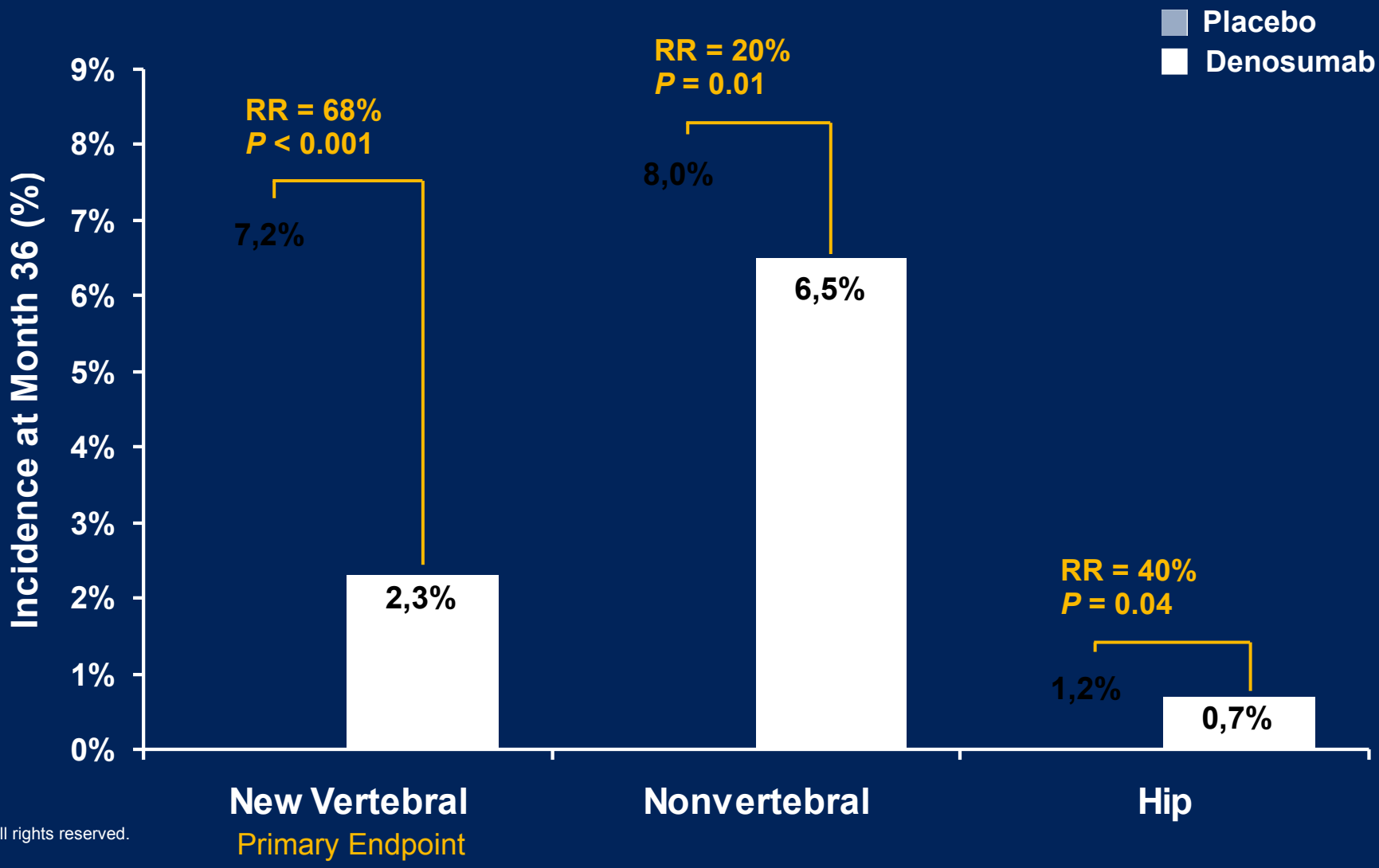
Matthew Austin,[1] Yu-Ching Yang,[1] Eric Vittinghoff,[2] Silvano Adami,[3] Steven Boonen,[4] Douglas C Bauer,[2] Gerolamo Bianchi,[5] Michael A Bolognese,[6] Claus Christiansen,[7] Richard Eastell,[8] Andreas Grauer,[1] Federico Hawkins,[9] David L Kendler,[10] Beatriz Oliveri,[11] Michael R McClung,[12] Ian R Reid,[13] Ethel S Siris,[14] Jose Zanchetta,[15] Cristiano AF Zerbini,[16] Cesar Libanati,[1] and Steven R Cummings[17] for the FREEDOM Trial





The Effect of Denosumab on Fracture Risks at 36 Months

Phase 3: The FREEDOM Trial

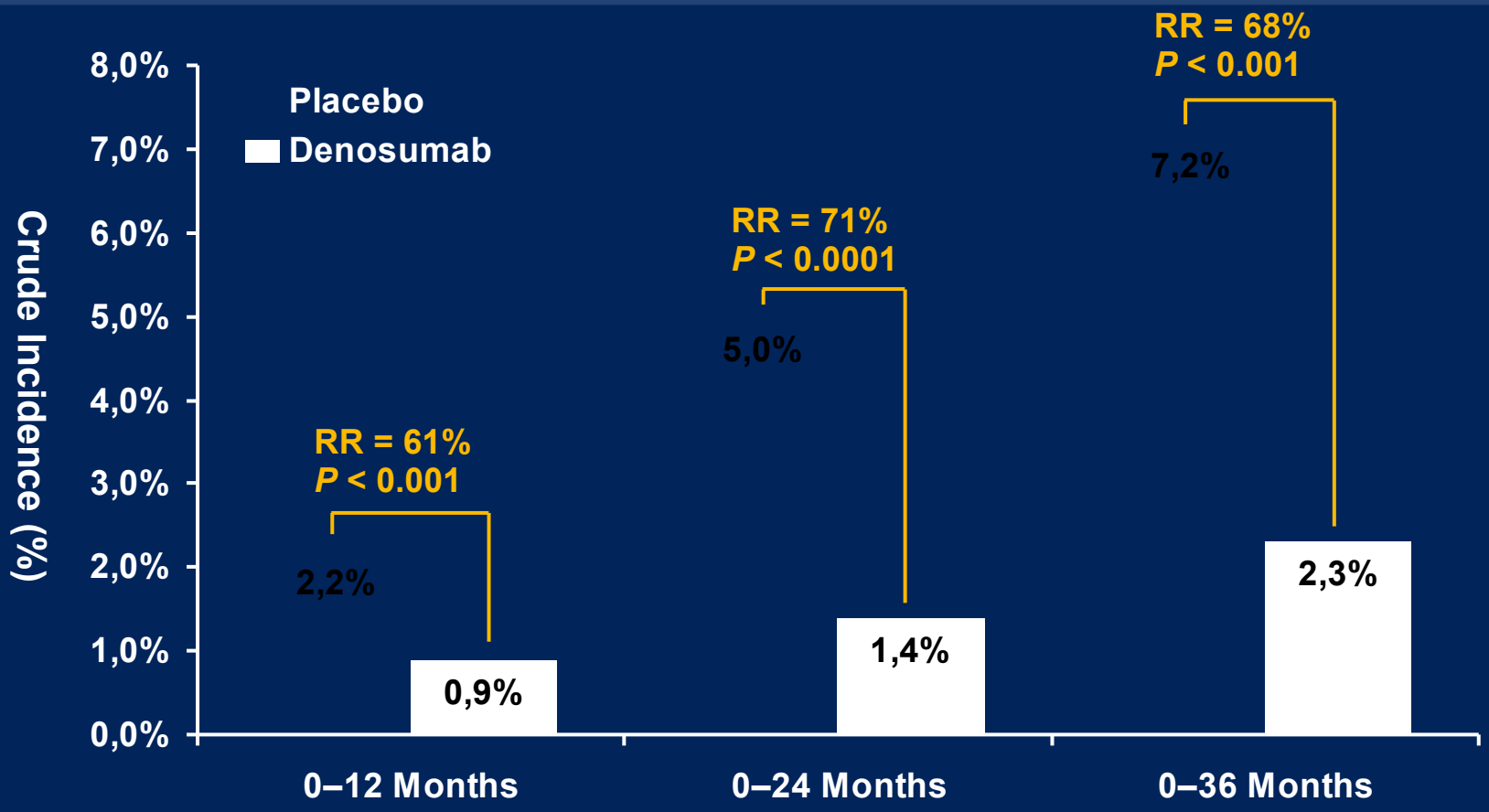


RR = risk reduction

Cummings SR, et al. *N Engl J Med*. 2009;361:756-765.

The Effect of Denosumab on New Vertebral Fractures At Month 12, 24, and 36

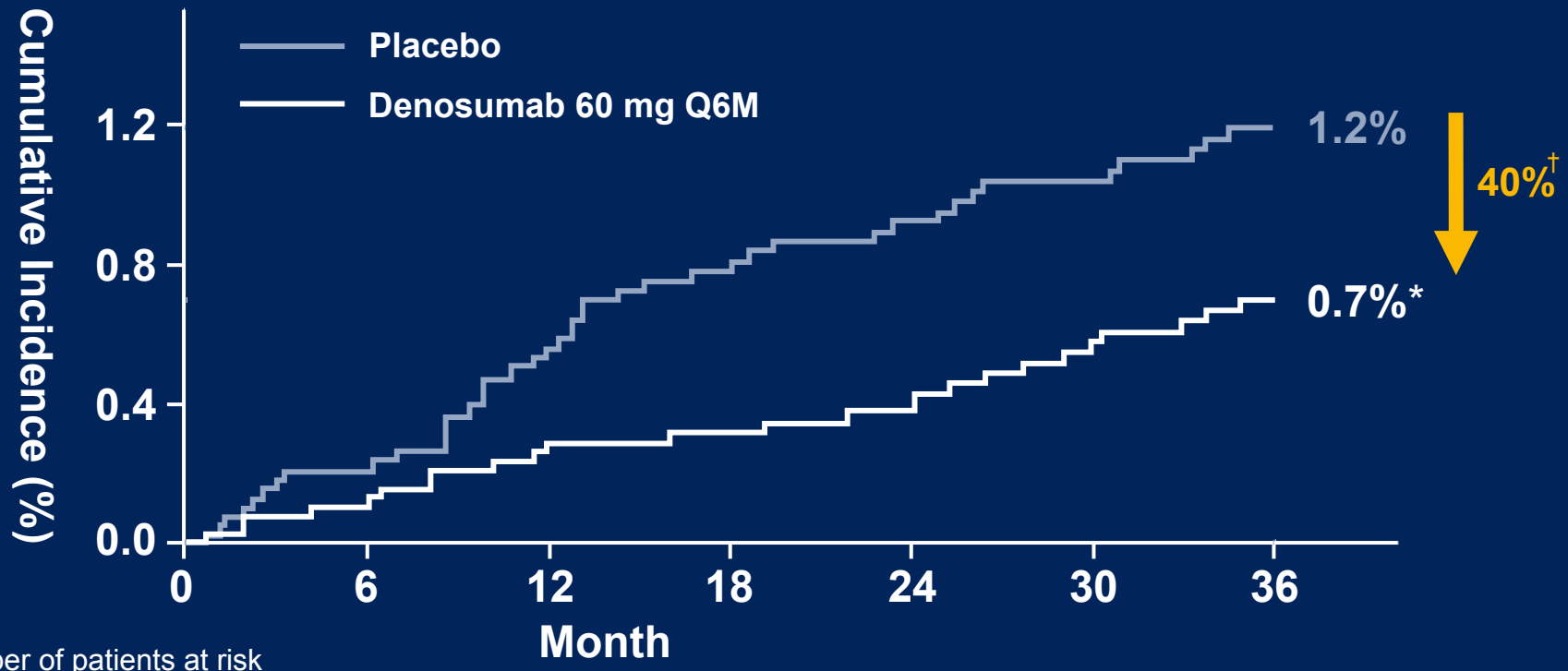
Phase 3: The FREEDOM Trial



Intent-to-treat, last observation carried forward analysis
Data on file, Amgen.

The Effect of Denosumab on Time to First Hip Fracture Through 36 Months

Phase 3: The FREEDOM Trial



Number of patients at risk

Placebo, n	3,906	3,799	3,672	3,538	3,430	3,311	3,221
Denosumab, n	3,902	3,796	3,676	3,566	3,477	3,397	3,311

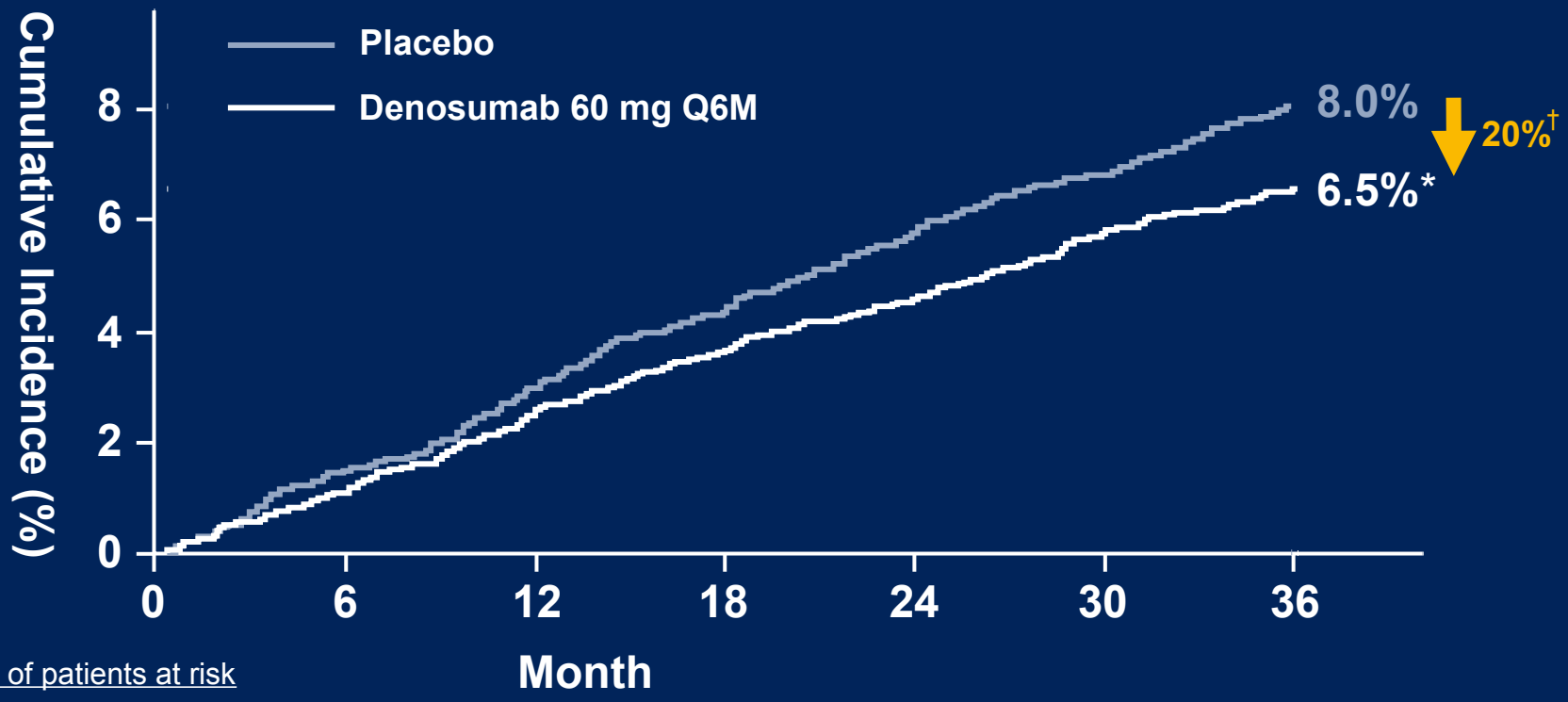
† Hip fractures were reduced by 40% (95% CI: 0.37, 0.97)

**P* = 0.04

Cummings SR, et al. *N Engl J Med*. 2009;361:756-765. Copyright © *2009 Massachusetts Medical Society. All rights reserved.*

The Effect of Denosumab on Time to First Nonvertebral Fracture Through 36 Months

Phase 3: The FREEDOM Trial



Number of patients at risk

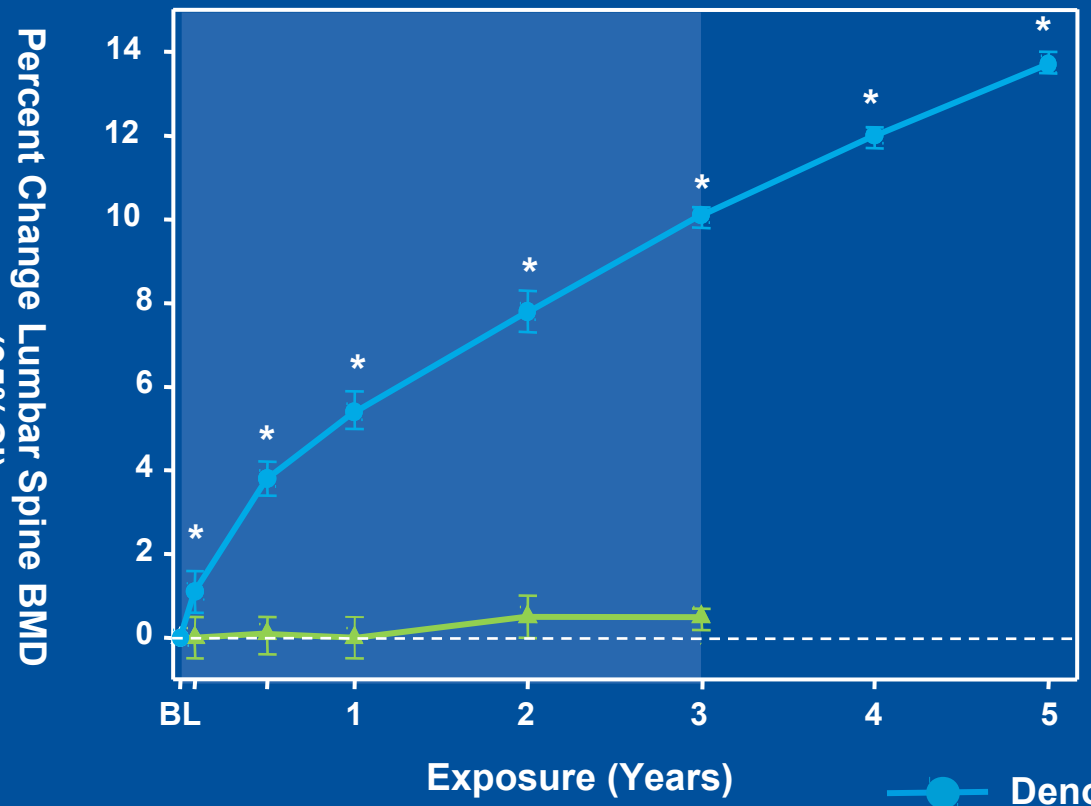
Placebo, n	3,906	3,750	3,578	3,410	3,264	3,121	3,009
Denosumab, n	3,902	3,759	3,594	3,453	3,337	3,228	3,130

† Nonvertebral fractures were reduced by 20% (95% CI: 0.67, 0.95)

*P = 0.01

Cummings SR, et al. *N Engl J Med*. 2009;361:756-765. Copyright © *2009 Massachusetts Medical Society. All rights reserved.*

Percent Change in Lumbar Spine BMD

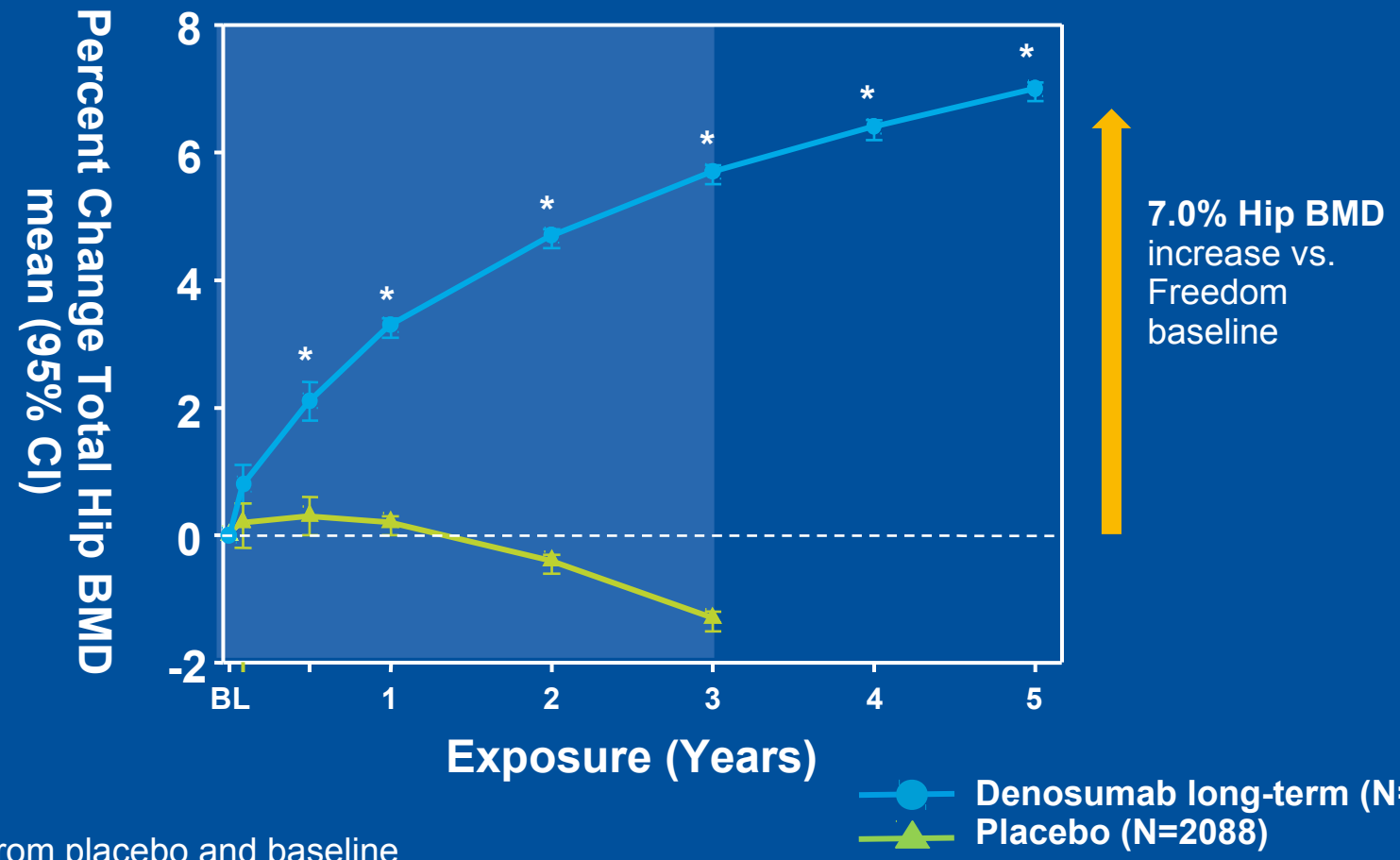


*p < 0.002 from placebo and baseline

BMD continued to significantly increase in years 4 and 5 with long-term denosumab treatment

Papapoulos S, et al. *Osteoporos Intl* *2011*(suppl 1) OC25

Percent Change in Total Hip BMD

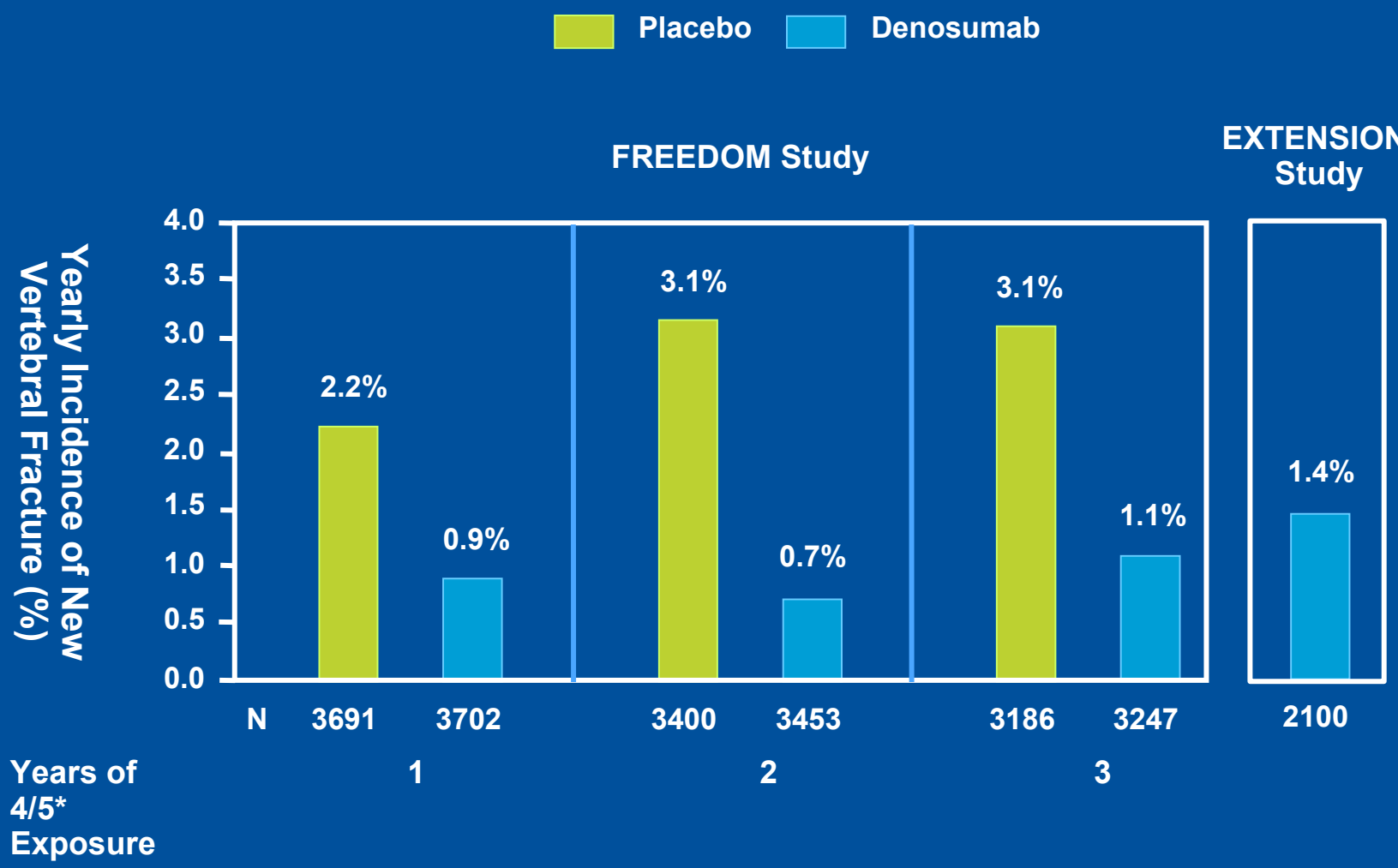


*p < 0.002 from placebo and baseline

BMD continued to significantly increase in years 4 and 5 with long-term denosumab treatment

Papapoulos S, et al. *Osteoporos Intl* *2011*(suppl 1) OC25

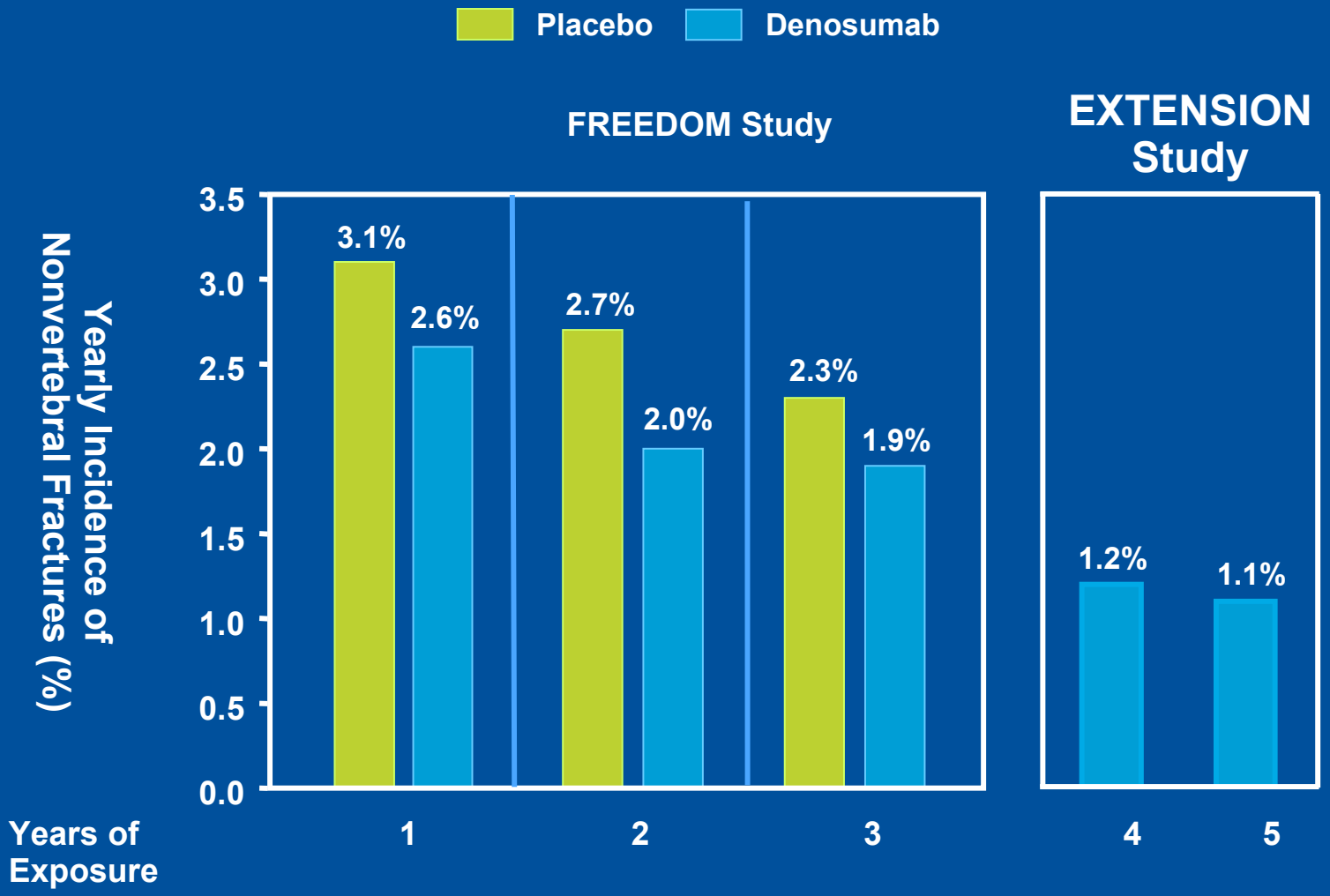
Yearly Incidence of New Vertebral Fractures



*Annualized rate

Papapoulos S, et al. *Osteoporos Intl 2011*(suppl 1) OC25

Yearly Incidence of Nonvertebral Fractures



Papapoulos S, et al. *Osteoporos Intl 2011*(suppl 1) OC25

Hopkins et al. BMC Musculoskeletal Disorders 2011, 12:209
http://www.biomedcentral.com/1471-2474/12/209

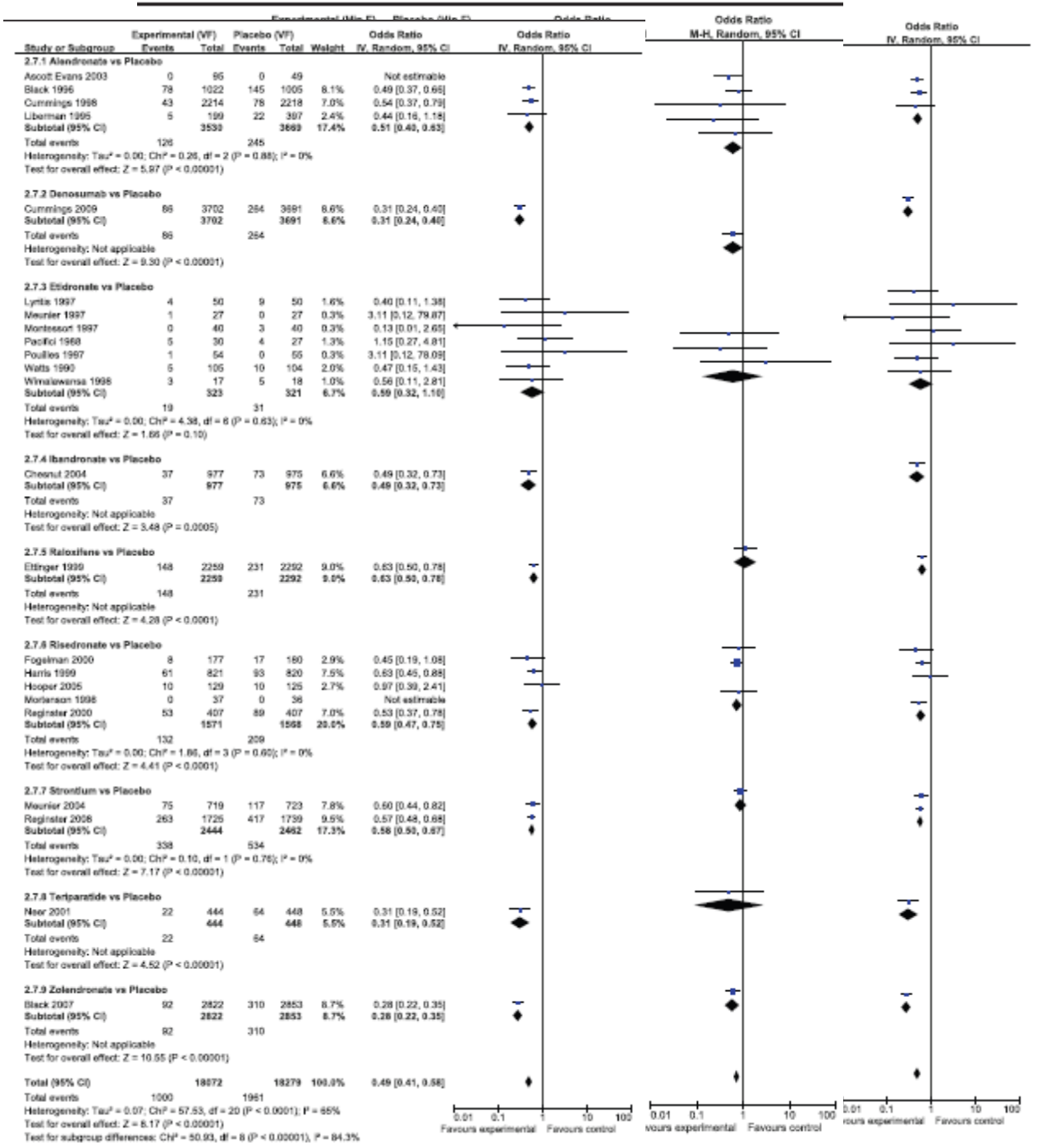
BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

The relative efficacy of nine osteoporosis medications for reducing the rate of fractures in post-menopausal women

Robert B Hopkins[1,2*], Ron Goeree[1,2,3], Eleanor Pullenayegum[1,3,4], Jonathan D Adachi[5], Alexandra Papaioannou[5], Feng Xie[1,2,3] and Lehana Thabane[1,3,4]

Teriparatide, zoledronic acid and denosumab have the highest probabilities of being most efficacious for non-vertebral and vertebral fractures, and having the greatest effect sizes. The estimates from indirect comparisons were robust to differences in methodology



Αντικαταγματική δράση

	Σπονδυλικά	ΜηΣπονδυλικά	Ισχίου
Οιστρογόνα	+	+	+
Καλσιτονίνη	+		
Ραλοξιφαίνη	+	(+)	
Αλενδρονάτη	+	+	+
Ρισεδρονάτη	+	+	+
Ζολεδρονικό	+	+	+
Ιμπανδρονάτη	+		
Τεριπαρατίδη	+	+	
Ρανελικό Στρόντιο	+	+	(+)
Denosumab	+	+	+