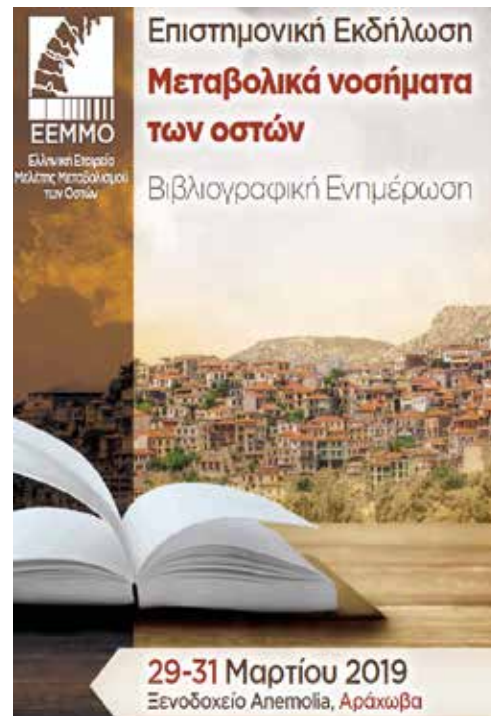


# Αντικαταβολική αγωγή οστεοπόρωσης



**Αθανάσιος Αναστασιλάκης**  
**Ενδοκρινολογικό Τμήμα 424 ΓΣΝΕ**

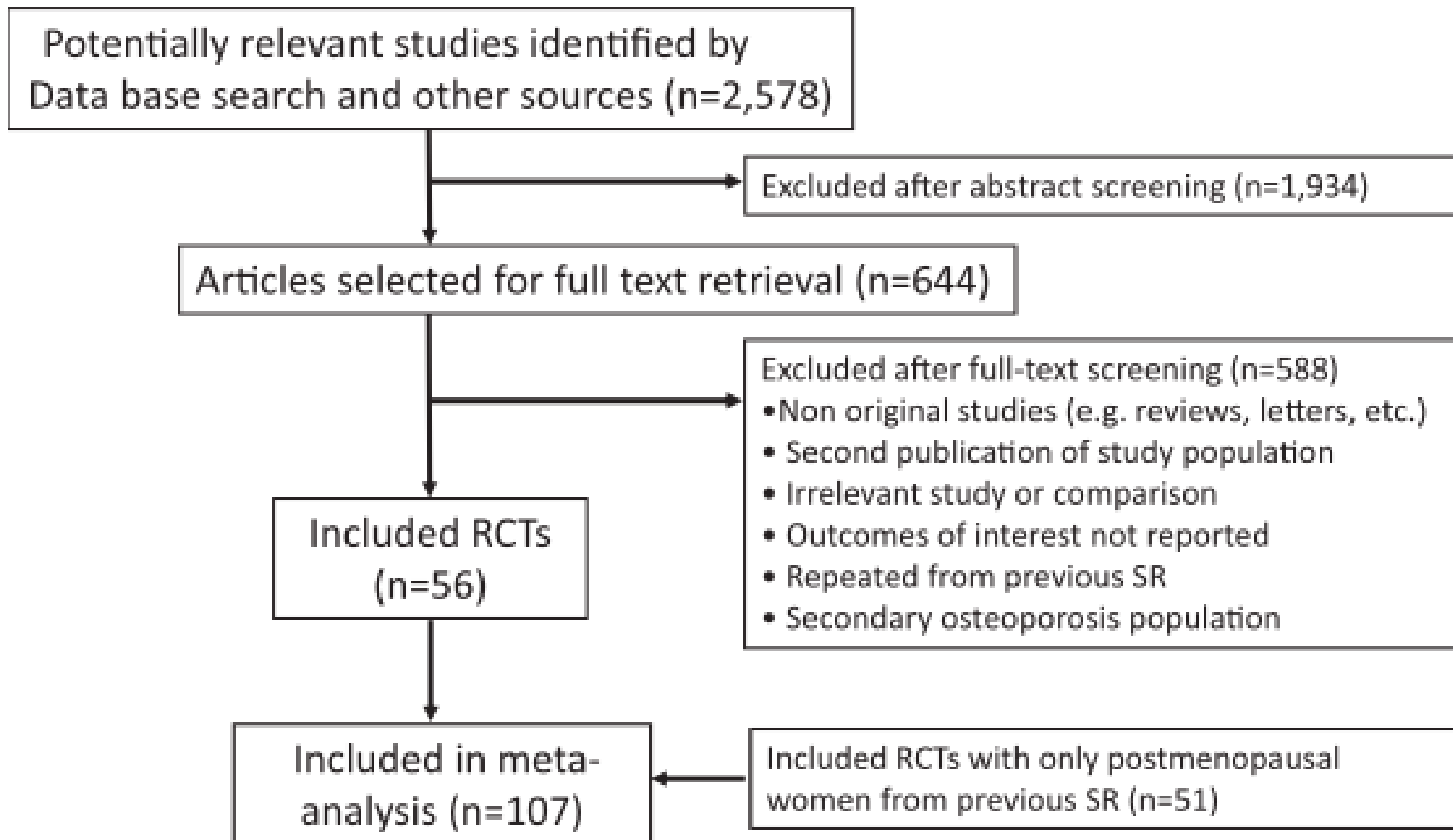
# Δήλωση συμφερόντων

- *Lecture fees:* Amgen, Lilly, ITF Hellas, ΕΛΠΕΝ, ΒΙΑΝΕΞ

## **Efficacy of Pharmacological Therapies for the Prevention of Fractures in Postmenopausal Women: A Network Meta-Analysis**

Patricia Barrionuevo,<sup>1,2</sup> Ekta Kapoor,<sup>1,3</sup> Noor Asi,<sup>1</sup> Fares Alahdab,<sup>1</sup> Khaled Mohammed,<sup>1</sup> Khalid Benkhadra,<sup>4</sup> Jehad Almasri,<sup>1</sup> Wigdan Farah,<sup>1</sup> Maria Sarigianni,<sup>1</sup> Kalpana Muthusamy,<sup>1</sup> Alaa Al Nofal,<sup>5</sup> Qusay Haydour,<sup>1</sup> Zhen Wang,<sup>1</sup> and Mohammad Hassan Murad<sup>1</sup>

- ✓ 107 μελέτες – 193987 ασθενείς
  - § Μέση ηλικία 66 έτη – μέση παρακολούθηση 28 μήνες
- ✓ Αμπαλοπαράτιδη, τεριπαράτιδη, PTH 1-84, romosozumab, denosumab, αλενδρονάτη, ρισενδρονάτη, ιμπανδρονάτη, ζολενδρονάτη, στρόντιο, λασοξιφένη, βαζεδοξιφένη, ραλοξιφένη, τιμπολόνη, HRT, καλσιτονίνη, βιτ. D, βιτ. D+Ca, Ca



# Συμπεράσματα – σπονδυλικά # vs placebo

- ✓ Αμπαλοπαρατίδη RR 0,14
- ✓ Τεριπαρατίδη RR 0,27
- ✓ Denosumab RR 0,32
- ✓ Romosozumab RR 0,33
- ✓ Ζολενδρονάτη RR 0,38
- ✓ PTH 1-84 RR 0,41
- ✓ Τιμπολόνη RR 0,56
- ✓ Αλενδρονάτη RR 0,57
- ✓ Ραλοξιφένη RR 0,59
- ✓ Στρόντιο RR 0,60
- ✓ Ρισενδρονάτη RR 0,61
- ✓ Βαζεδοξιφένη RR 0,61
- ✓ HRT RR 0,65
- ✓ Καλσιτονίνη RR 0,65
- ✓ Ιμπανδρονάτη RR 0,67
- ✓ Λασοξιφένη RR 0,67

# Συμπεράσματα – μη-σπονδυλικά # vs placebo

- ✓ Βιτ. D RR 0,44
- ✓ Αμπαλοπαρατίδη RR 0,51
- ✓ Τεριπαρατίδη RR 0,62
- ✓ Romosozumab RR 0,67
- ✓ Τιμπολόνη RR 0,73
- ✓ HRT RR 0,78
- ✓ Ρισενδρονάτη RR 0,78
- ✓ Ζολενδρονάτη RR 0,79
- ✓ Denosumab RR 0,80
- ✓ Ca + D RR 0,81
- ✓ Αλενδρονάτη RR 0,84
- ✓ Λασοξιφένη RR 0,84

# Συμπεράσματα - # ισχίου vs placebo

- ✓ Romosozumab RR 0,44
- ✓ Denosumab RR 0,56
- ✓ Ζολενδρονάτη RR 0,60
- ✓ Αλενδρονάτη RR 0,61
- ✓ HRT RR 0,72
- ✓ Ρισενδρονάτη RR 0,73
- ✓ Ca + D RR 0,81

# Συμπεράσματα

- ✓ Αμπαλοπαρατίδη, τεριπαρατίδη, romosozumab, denosumab το υψηλότερο RRR
- ✓ Ιμπανδρονάτη, SERMS το χαμηλότερο RRR
- ✓ Περιορισμένα τα δεδομένα ως προς την επίδραση βιτ. D-Ca στα # παρά τις πολλές μεγάλες υπάρχουσες μελέτες

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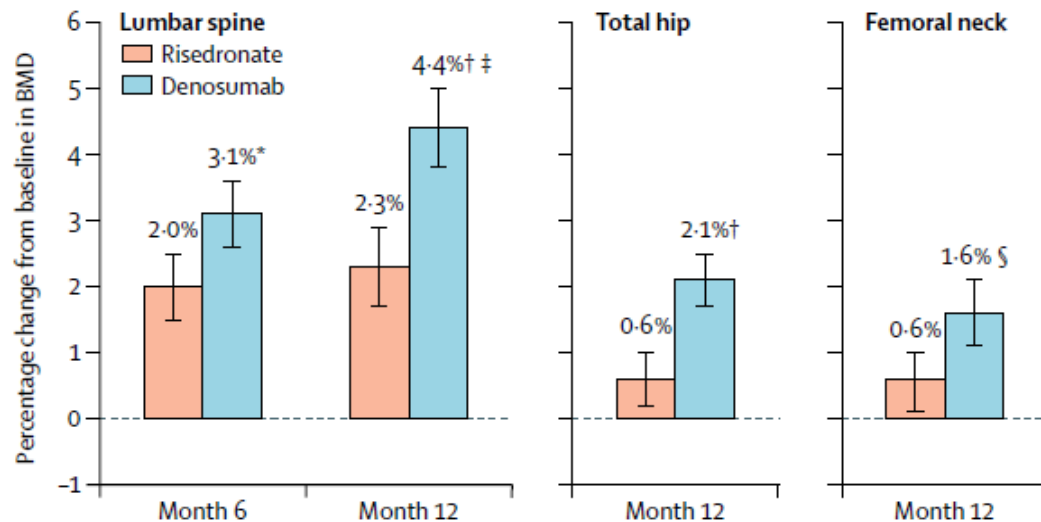
# Denosumab versus risedronate in glucocorticoid-induced osteoporosis: a multicentre, randomised, double-blind, active-controlled, double-dummy, non-inferiority study

*Kenneth G Saag, Rachel B Wagman, Piet Geusens, Jonathan D Adachi, Osvaldo D Messina, Ronald Emkey, Roland Chapurlat, Andrea Wang, Nicola Pannacciulli, Willem F Lems*

# Χαρακτηριστικά μελέτης

- ✓ 795 ασθενείς > 18 ετών με λήψη κορτικοειδών  $\geq 7,5$  mg πρεδνιζόνης
  - § <50 ετών με ΟΠ κάταγμα
  - § > 50 ετών T-score σε ΟΜΣΣ αυχένα ή ολικό ισχίο  $\leq -2,0$  ή  $\leq -1,0$  + ΟΠ κάταγμα
  - ∅ 290 υπό κορτικοειδή < 3 μήνες (glucocorticoid initiating)
  - ∅ 505 υπό κορτικοειδή > 3 μήνες (glucocorticoid continuing)
- ✓ Τυχαιοποίηση 1:1 σε Dmab ή ρισεδρονάτη (RIS) 5mg/ημ
- ✓ *Διάρκεια*: 12 μήνες
- ✓ *Κύριο καταληκτικό σημείο*: μη κατωτερότητα σε BMD ΟΜΣΣ

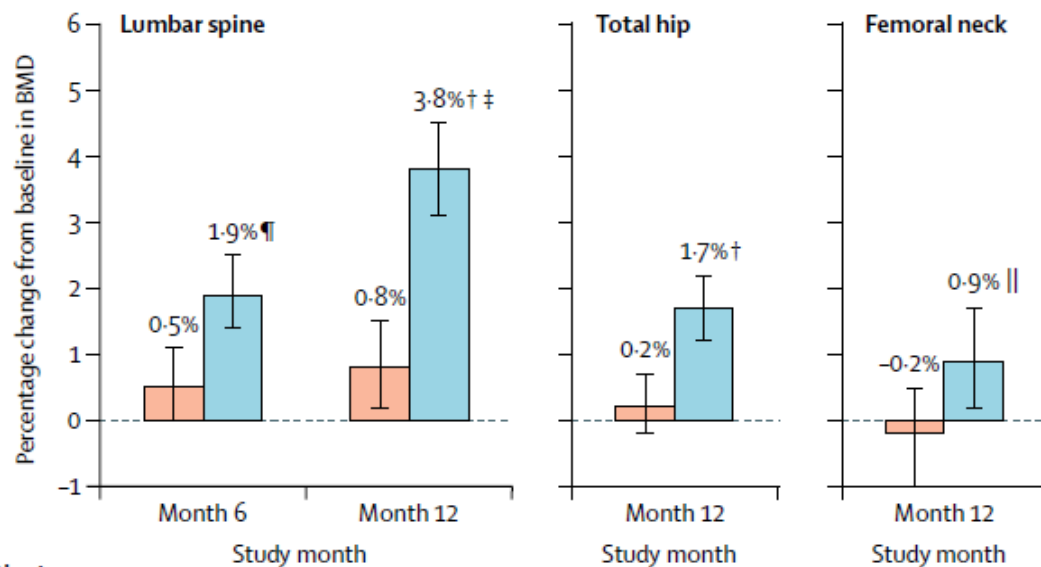
### A Glucocorticoid continuing



#### Number of patients

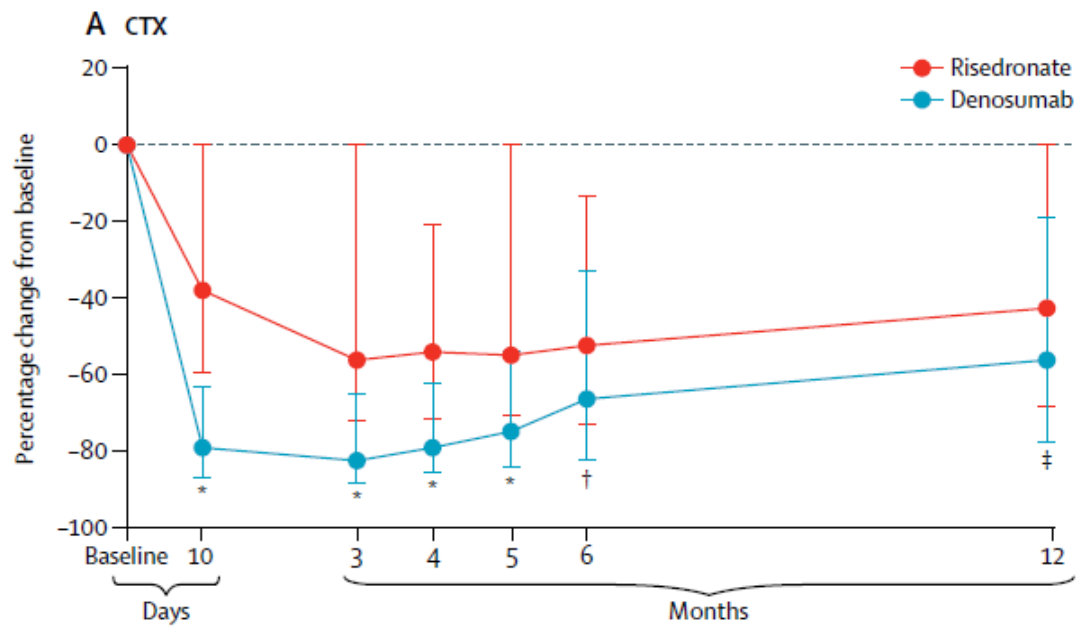
Risedronate	227	211
Denosumab	224	209

### B Glucocorticoid initiating



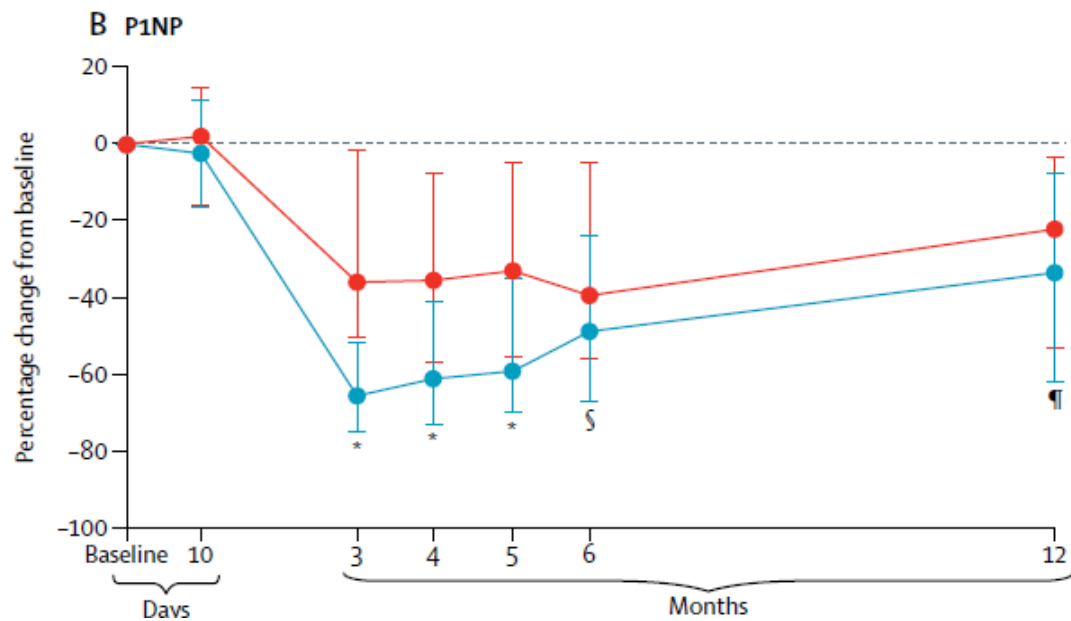
#### Number of patients

Risedronate	128	126
Denosumab	127	119



**Number of patients**

Risedronate	119	106	108	103	101	99	86
Denosumab	126	111	108	110	110	106	98



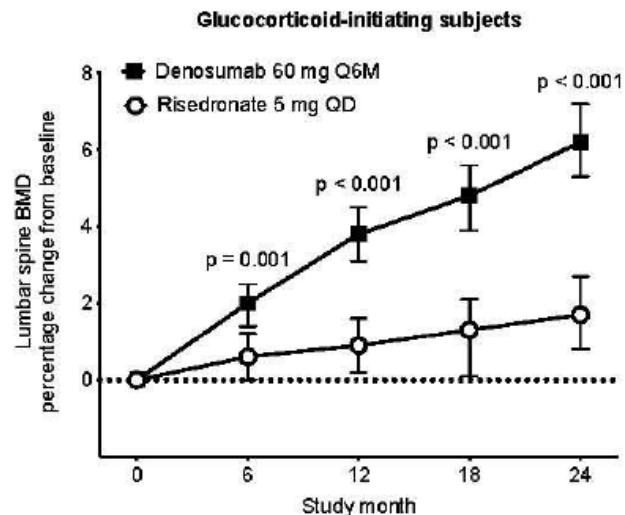
# Συμπεράσματα μελέτης

- ∨ Dmab αυξάνει BMD περισσότερο από RIS σε ασθενείς που αρχίζουν κορτικοειδή ή είναι υπό θεραπεία με κορτικοειδή

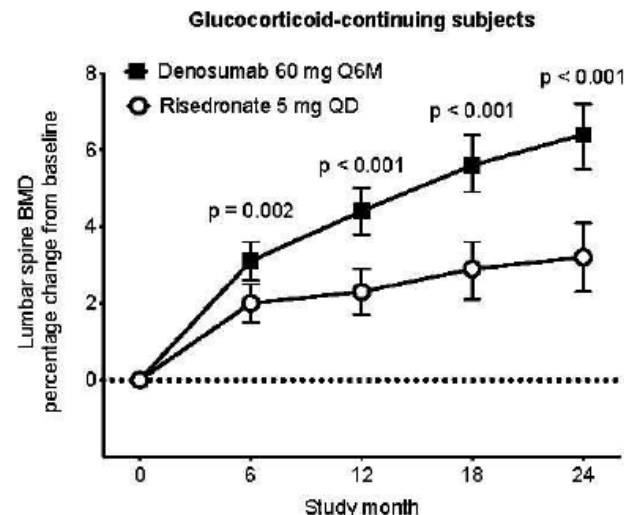
**Denosumab vs risedronate in glucocorticoid-induced osteoporosis: final results of a 24-month randomized, double-blind, double-dummy trial**

Kenneth G. Saag, MD, MSc,<sup>1</sup> Nicola Pannacciulli, MD, PhD,<sup>2</sup> Piet Geusens, MD, PhD,<sup>3</sup> Jonathan D. Adachi, BSc, MD,<sup>4</sup> Osvaldo D. Messina, MD,<sup>5</sup> Jorge Morales-Torres, MD,<sup>6</sup> Ronald Emkey, MD,<sup>7</sup> Peter W. Butler, MD,<sup>2</sup> Xiang Yin, PhD,<sup>2</sup> Willem F. Lems MD, PhD<sup>8</sup>

A

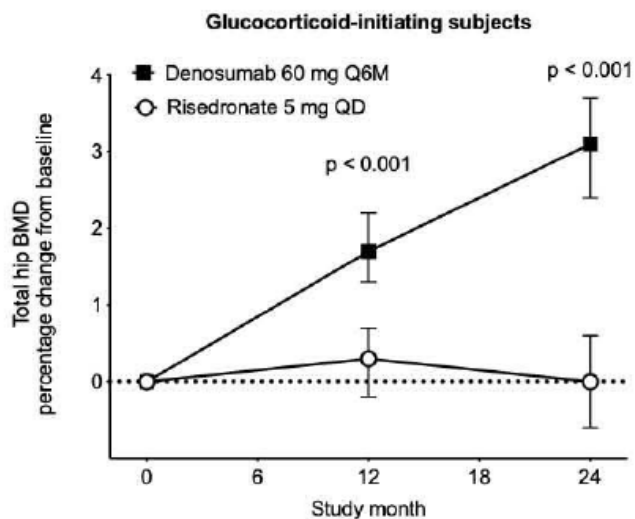


Denosumab (n=)	128	127	119	109	107
Risedronate (n=)	133	128	128	114	113

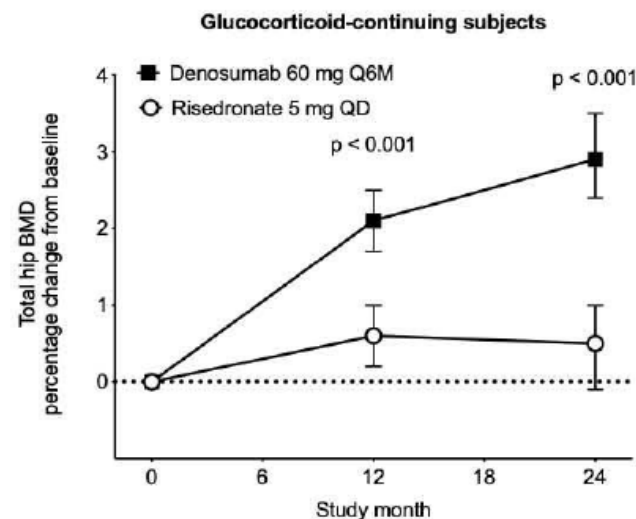


Denosumab (n=)	228	224	209	190	183
Risedronate (n=)	230	227	211	187	174

B

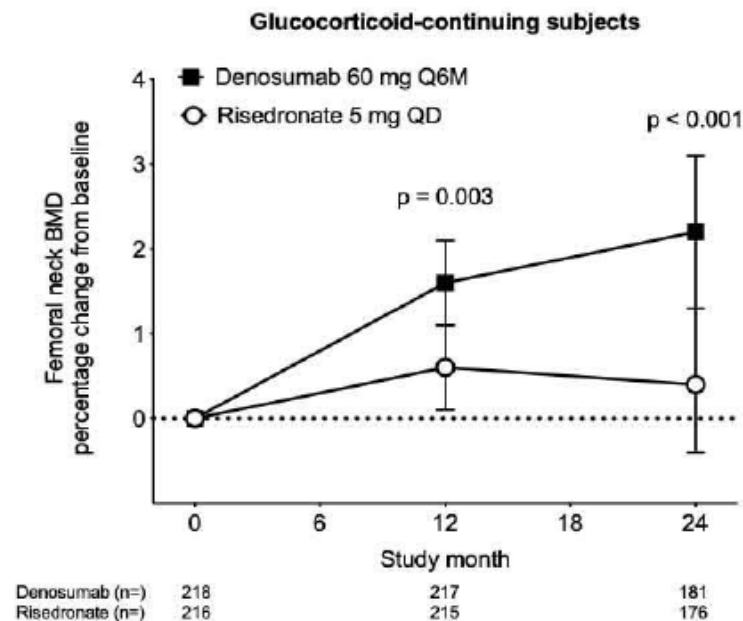
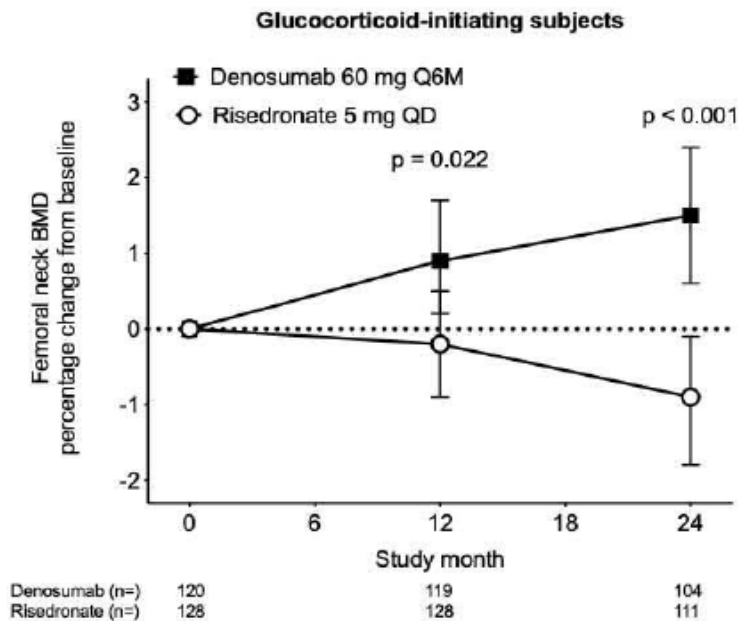


Denosumab (n=)	120	119	104
Risedronate (n=)	128	128	111

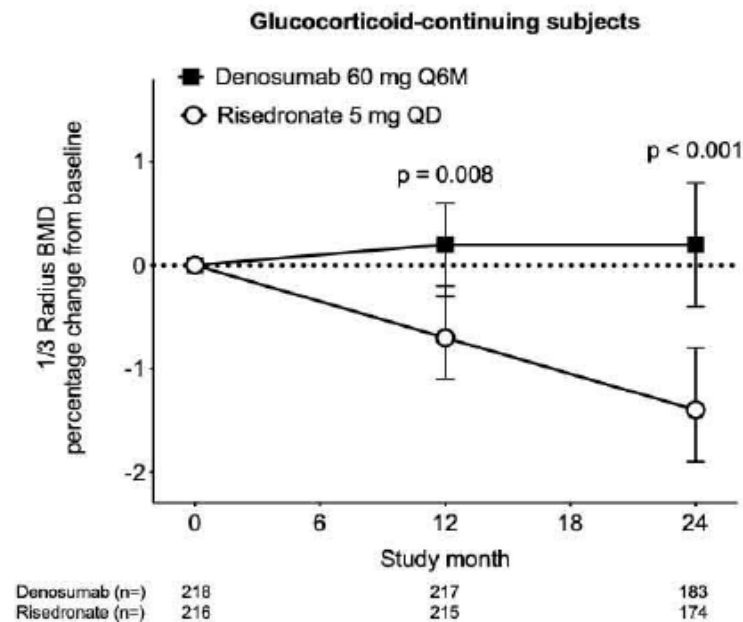
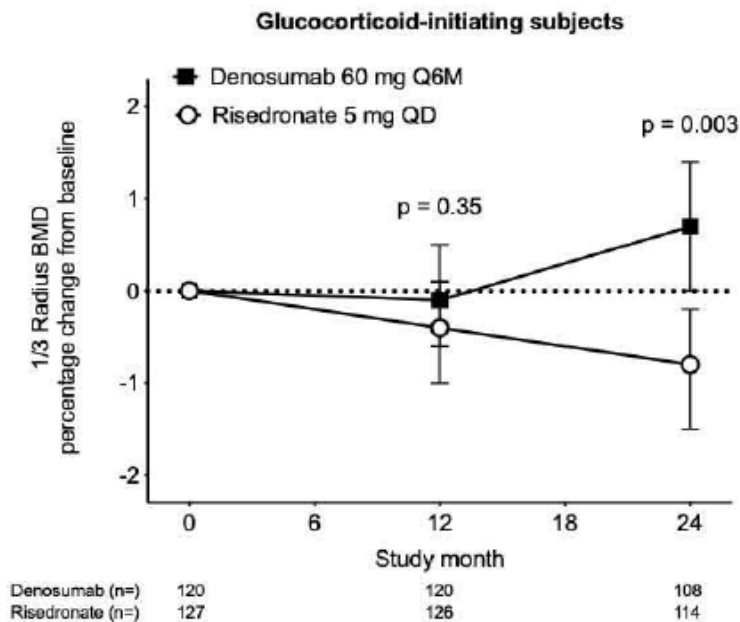


Denosumab (n=)	218	217	181
Risedronate (n=)	216	215	176

C



D



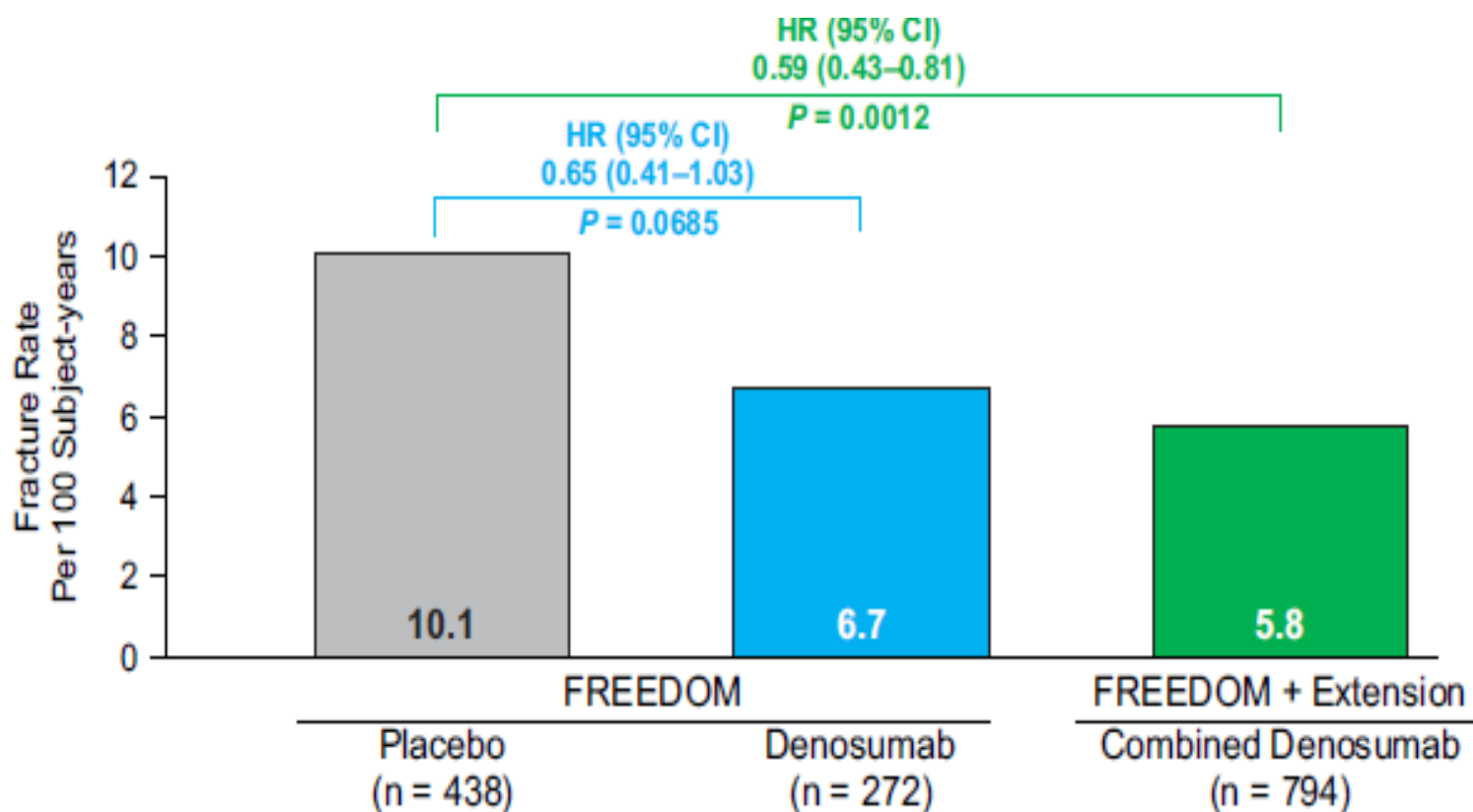
**Table 3.** Subject incidence of fractures through month 24

	Risedronate	Denosumab
Any osteoporosis-related fracture, n/N (%) <sup>*</sup>	36/397 (9.1)	35/398 (8.8)
New and worsening vertebral fracture, n/N1 (%) <sup>†</sup>	24/346 (6.9)	15/338 (4.4)
Men	5/101 (5.0)	1/100 (1.0)
Women	19/245 (7.8)	14/238 (5.9)
Premenopause	2/29 (6.9)	2/33 (6.1)
Postmenopause	16/211 (7.6)	12/202 (5.9)
Unknown	1/5 (20.0)	0/3 (0.0)
Nonvertebral fracture (low trauma), n/N (%)	15/397 (3.8)	21/398 (5.3)



## The risk of subsequent osteoporotic fractures is decreased in subjects experiencing fracture while on denosumab: results from the FREEDOM and FREEDOM Extension studies

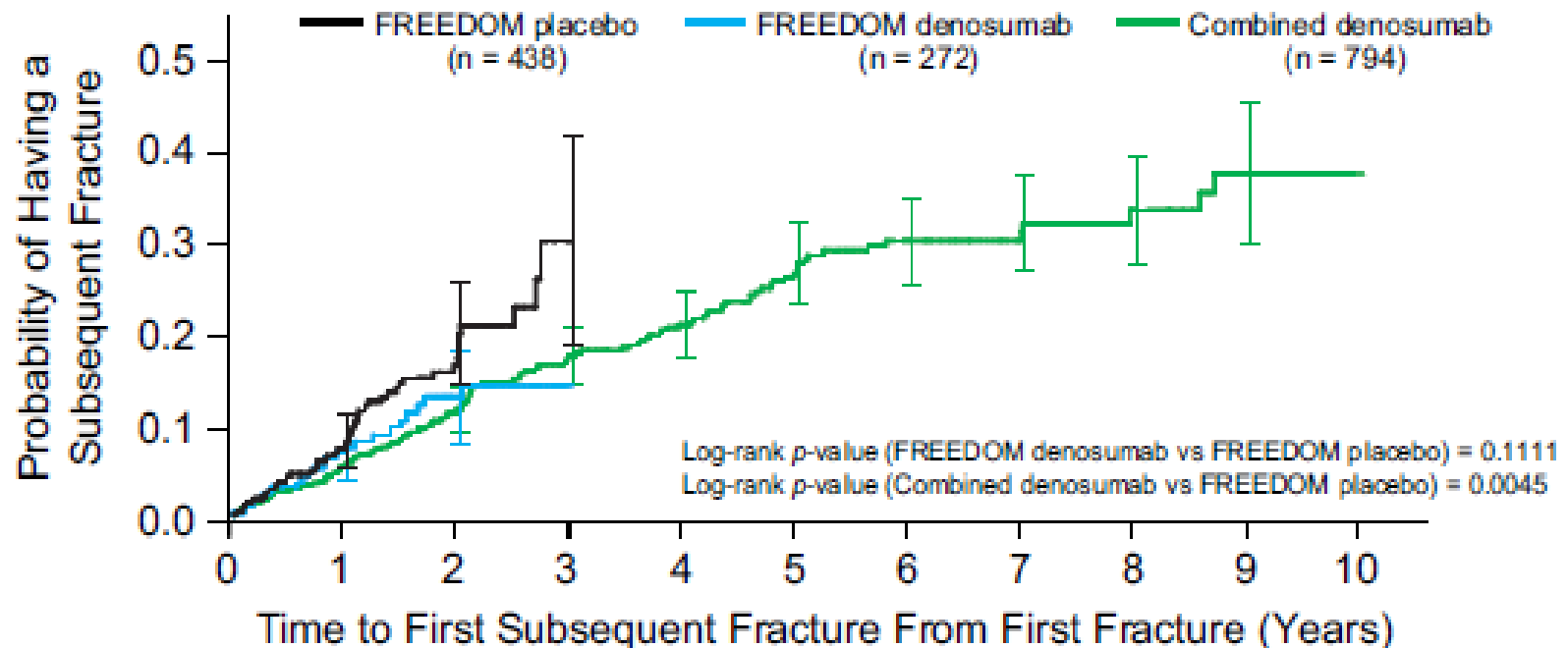
D. L. Kendler<sup>1</sup> · A. Chines<sup>2</sup> · M. L. Brandi<sup>3</sup> · S. Papapoulos<sup>4</sup> · E. M. Lewiecki<sup>5</sup> · J-Y. Reginster<sup>6</sup> · M. Muñoz Torres<sup>7</sup> · A. Wang<sup>2</sup> · H. G. Bone<sup>8</sup>



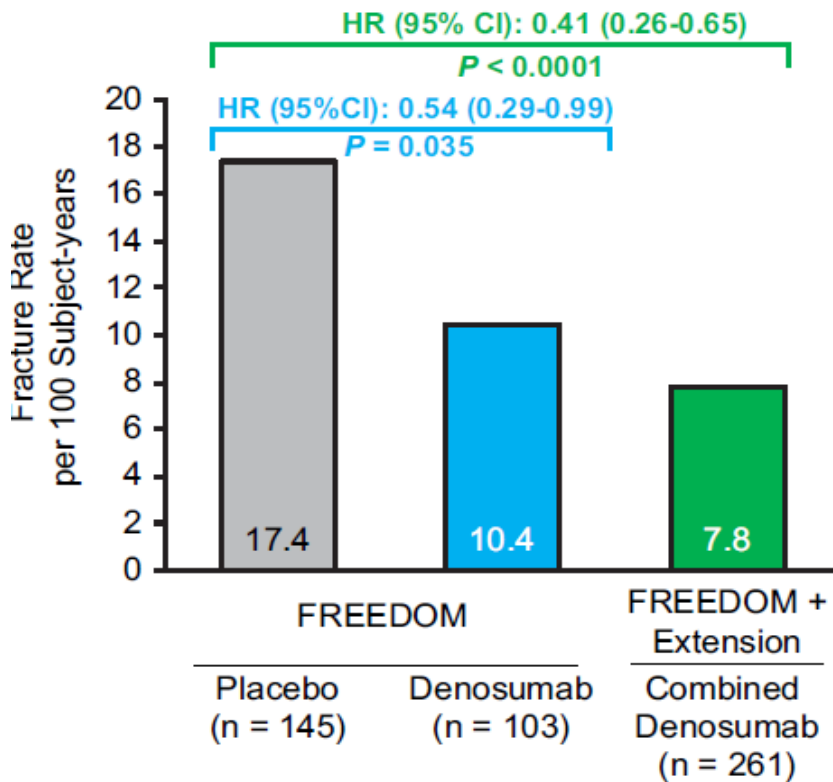


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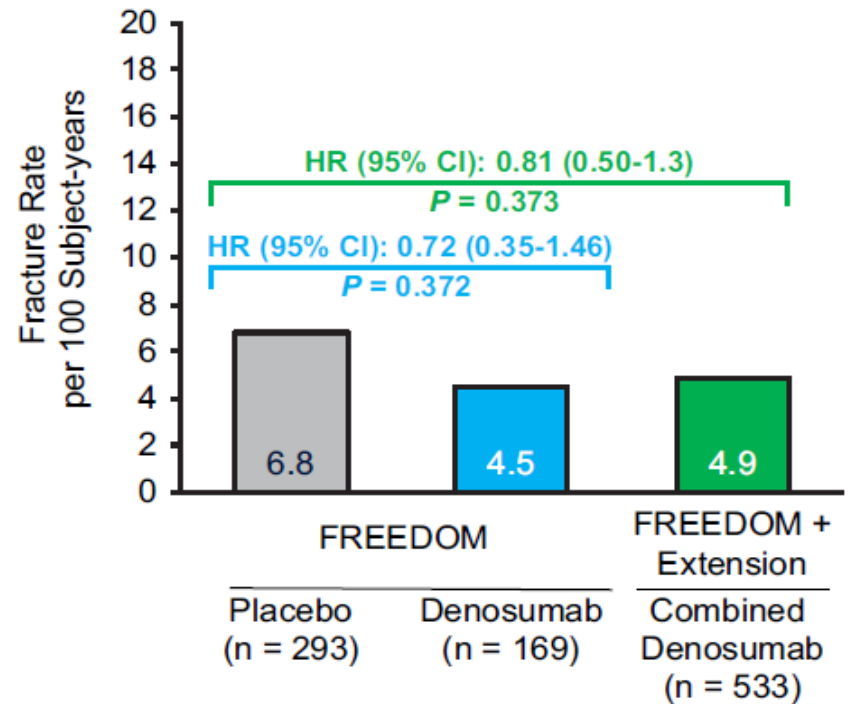
D. L. Kendler<sup>1</sup> • A. Chines<sup>2</sup> • M. L. Brandi<sup>3</sup> • S. Papapoulos<sup>4</sup> • E. M. Lewiecki<sup>5</sup> • J-Y. Reginster<sup>6</sup> • M. Muñoz Torres<sup>7</sup> • A. Wang<sup>2</sup> • H. G. Bone<sup>8</sup>



### Subjects With Baseline Vertebral Fracture



### Subjects Without Baseline Vertebral Fracture



# Invasive Oral Procedures and Events in Women With Postmenopausal Osteoporosis Treated With Denosumab for up to 10 Years.

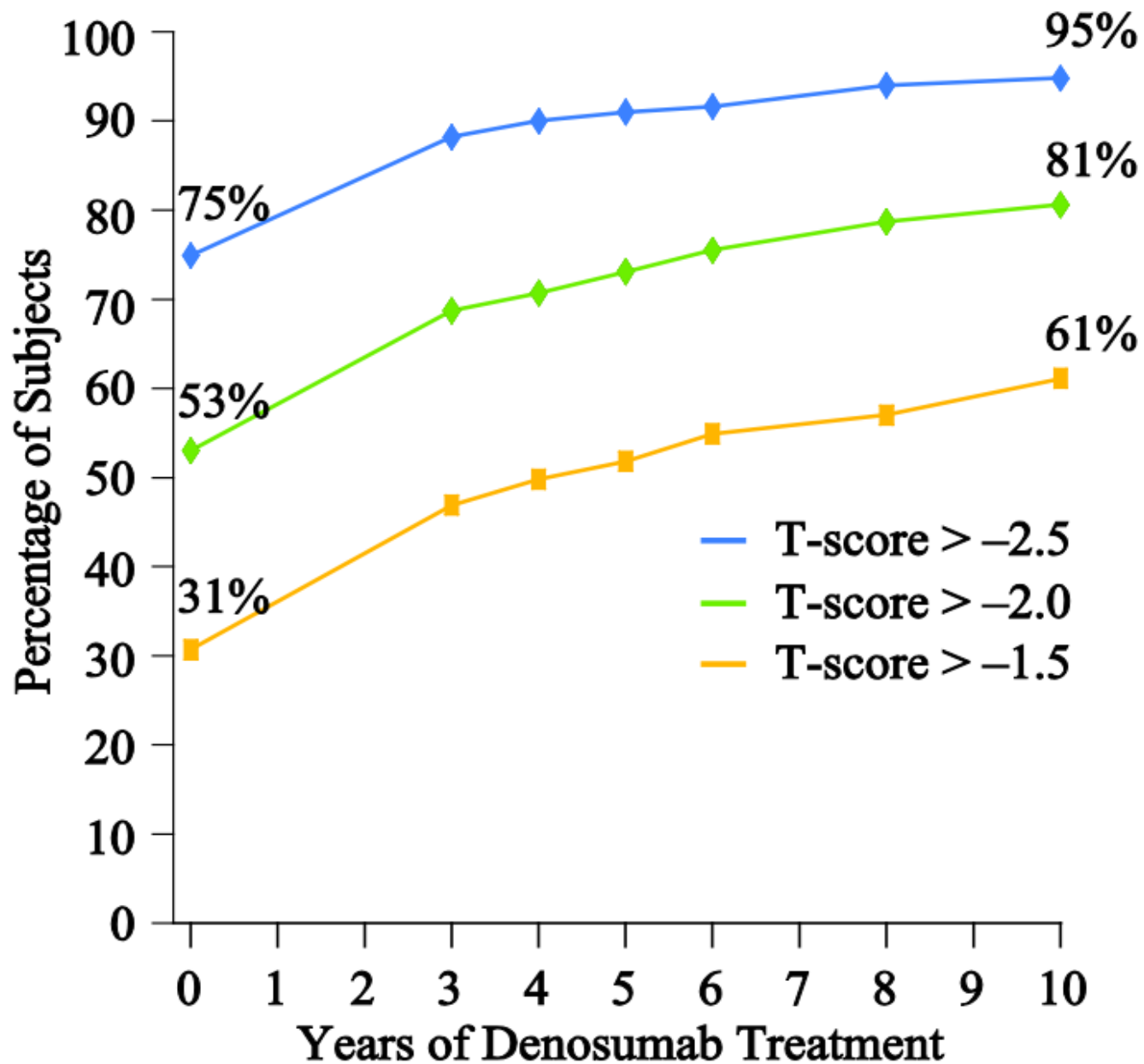
Watts NB, Grbic JT, Binkley N, Papapoulos S, Butler PW, Yin X, Tierney A, Wagman RB, McClung M

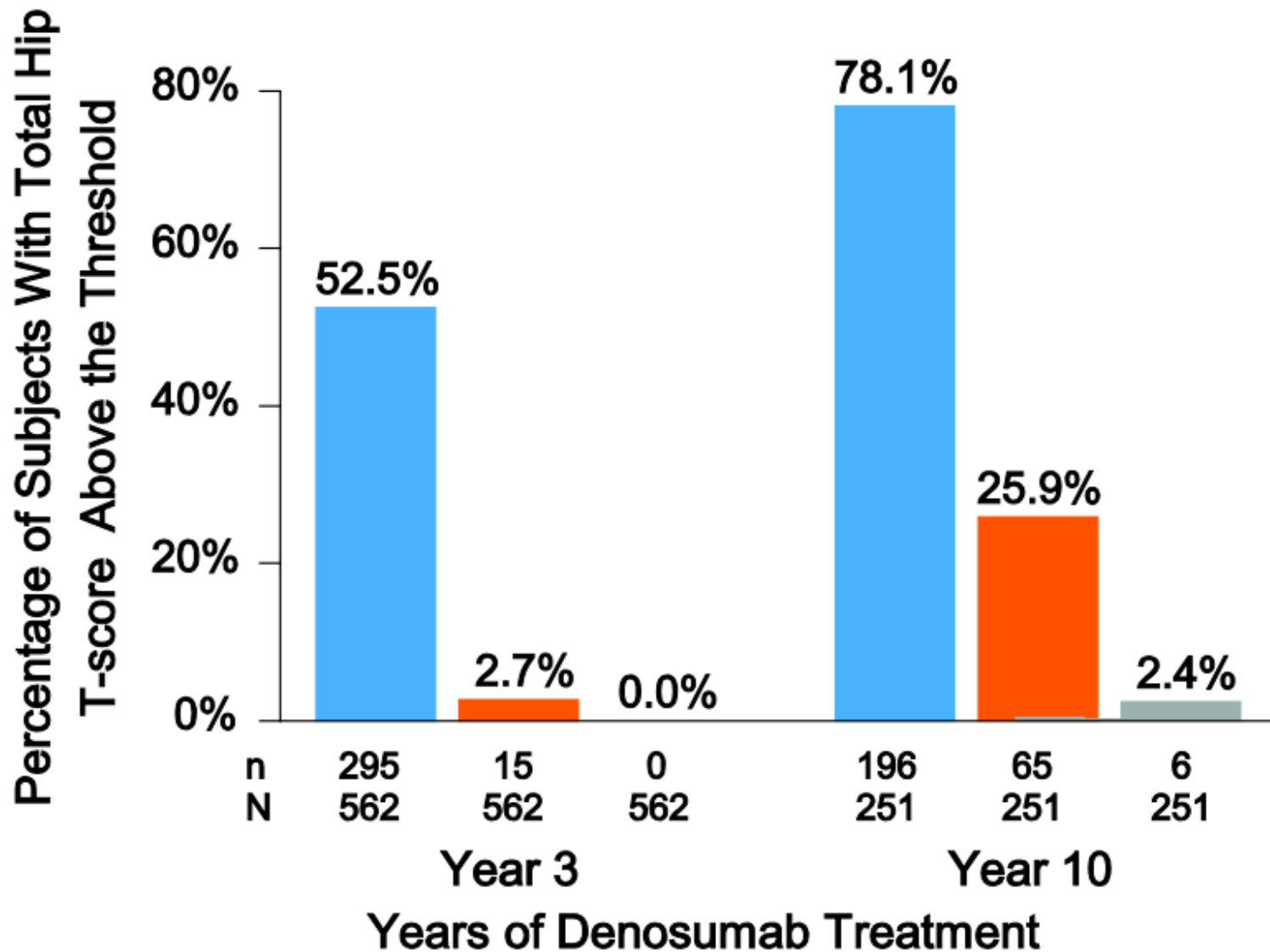
- ασθενείς μελέτης FREEDOM υπό Dmab επί 10 έτη
- η διενέργεια οδοντιατρικών εργασιών συχνή (45%)
- Dmab σχετίστηκε με ήπιπωση ONJ
  - ο απόλυτος κίνδυνος ήταν μικρός
  - όλα τα περιστατικά ONJ αποκαταστάθηκαν με την κατάλληλη θεραπεία

# **Relationship Between Bone Mineral Density T-score and Nonvertebral Fracture Risk Over 10 Years of Denosumab Treatment**

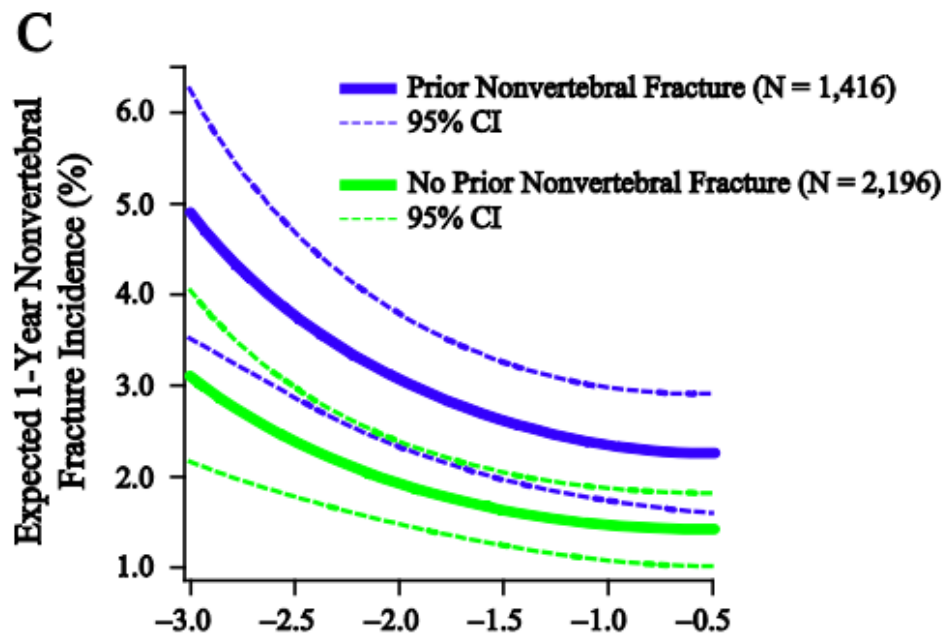
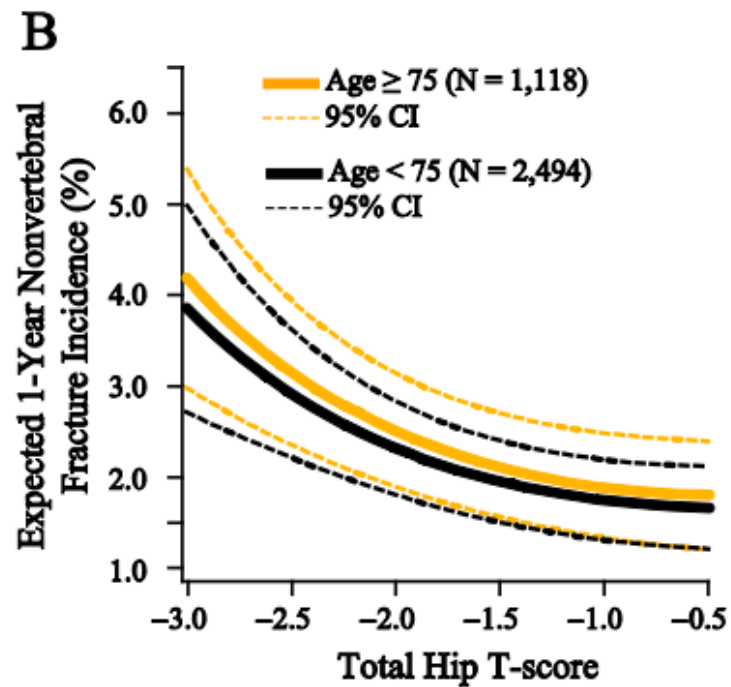
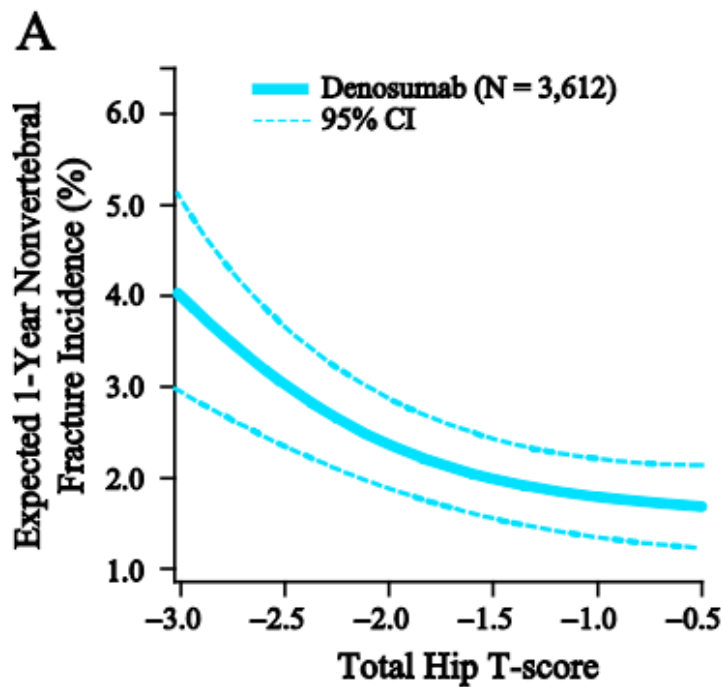
Ferrari S,<sup>1</sup> Libanati C,<sup>2</sup> Lin CJF,<sup>2</sup> Brown JP,<sup>3</sup> Cosman F,<sup>4</sup> Czerwiński E,<sup>5</sup> de Gregório LH,<sup>6</sup> Malouf-Sierra J,<sup>7</sup> Reginster J-Y,<sup>8</sup> Wang A,<sup>2</sup> Wagman RB,<sup>2</sup> Lewiecki EM<sup>9</sup>

- ασθενείς μελέτης FREEDOM που συμπλήρωσαν Dmab επί 10 έτη
- Βελτίωση BMD 21.7% σε ΟΜΣΣ, 9,2% σε ολικό ισχίο & 9% σε αυχένα
- Η αύξηση της BMD ολικού ισχίου εξηγούσε μεγάλο μέρος της μείωσης του καταγματικού κινδύνου
- 10,3% μη-σπονδυλικά # υπό Dmab (1,2% ισχίου, 4,3% αντιβραχίου)





**Fig. 3.** Percentage of subjects with a total hip T-score  $\leq -2.5$  at FREEDOM baseline attaining T-scores of  $> -2.5$ ,  $> -2.0$ , and  $> -1.5$  after 3 and 10 years of denosumab



<b>Initial Total Hip T-score<sup>a</sup></b>	<b>Total Hip T-score + 1<sup>a</sup></b>	<b>Nonvertebral Fracture Risk Reduction</b>	<b>P-value</b>
-2.5	-1.5	-1.01%	0.011
-2.4	-1.4	-0.91%	0.016
-2.3	-1.3	-0.83%	0.023
-2.2	-1.2	-0.75%	0.034
-2.1	-1.1	-0.67%	0.049
-2.0	-1.0	-0.60%	0.071
-1.9	-0.9	-0.54%	0.101
-1.8	-0.8	-0.48%	0.140
-1.7	-0.7	-0.42%	0.190
-1.6	-0.6	-0.37%	0.251
-1.5	-0.5	-0.32%	0.322

# Συμπεράσματα

- Επίπτωση μη-σπονδυλικών # χαμηλότερη όσο υψηλότερο το T-score ολικού ισχίου
- Η σχέση αυτή επιπεδώνεται (plateau) σε T-score ολικού ισχίου μεταξύ -2 κι -1,5
  - ανεξάρτητα από ηλικία & προϋπάρχον #
- Treat to target

ORIGINAL ARTICLE

# Fracture Prevention with Zoledronate in Older Women with Osteopenia

Ian R. Reid, M.D., Anne M. Horne, M.B., Ch.B., Borislav Mihov, B.Phty.,  
Angela Stewart, R.N., Elizabeth Garratt, B.Nurs., Sumwai Wong, B.Sc.,  
Katy R. Wiessing, B.Sc., Mark J. Bolland, Ph.D., Sonja Bastin, M.B., Ch.B.,  
and Gregory D. Gamble, M.Sc.

This article was published on October 1,  
2018, at NEJM.org.

DOI: 10.1056/NEJMoa1808082

# Χαρακτηριστικά μελέτης

- ✓ 2000 μετεμμηνοπαυσιακές γυναίκες > 65 ετών
- ✓ T-score αυχένα ή ολικού ισχίου μεταξύ -1 και -2,5 τουλάχιστον σε 1 ισχίο (όχι > -2,5 σε κανένα ισχίο)
- ✓ T-score ΟΜΣΣ < -3,0
- ✓ Όχι αντιοστεοπορωτική αγωγή ή κορτιζόνη το προηγούμενο έτος
- ✓ Τυχαιοποίηση σε ζολεδρονικό ή εικονικό φάρμακο
- ✓ Δεν συγχορηγήθηκαν σκευάσματα Ca (σύσταση για διαιτητική πρόσληψη)
- ✓ Διάρκεια: 6 έτη = 4 εγχύσεις (ανά 18μηνο)
- ✓ Κύριο καταληκτικό σημείο: χρόνος ως το 1<sup>ο</sup> κάταγμα (σπονδυλικό ή μη)

**Table 1. Characteristics of the Trial Participants at Baseline.\***

Characteristic	Placebo (N = 1000)	Zoledronate (N = 1000)
Age — yr	71±5.1	71±5.0
Ethnic group — no. (%)†		
European	940 (94.0)	954 (95.0)
Maori	14 (1.4)	17 (1.7)
Pacific Islander	15 (1.5)	7 (0.7)
East Asian	24 (2.4)	15 (1.5)
Indian	5 (0.5)	5 (0.5)
Other	2 (0.2)	2 (0.2)
Height — cm	160.4±5.8	160.7±5.8
Weight — kg	69.2±12.2	69.1±12.5
Body-mass index‡	26.9±4.7	26.8±4.6
Dietary calcium intake — mg per day	882±388	871±360
History of nonvertebral fracture after 45 yr of age — no. (%)§	238 (23.8)	237 (23.7)
Prevalent vertebral fracture — no. (%)¶	126 (12.6)	137 (13.7)
Median 10-year risk of osteoporotic fracture (IQR) — %	12 (9–15)	12 (9–16)
Median 10-year risk of hip fracture (IQR) — %	2.3 (1.5–3.8)	2.4 (1.5–3.9)
Bone mineral density — g/cm <sup>2</sup>		
Lumbar spine	1.08±0.14	1.07±0.13
Total hip	0.85±0.08	0.85±0.08
Femoral neck	0.81±0.07	0.81±0.07
Total body	1.06±0.07	1.06±0.07
Bone density T score		
Lumbar spine	-0.87±1.16	-0.91±1.12
Total hip	-1.24±0.60	-1.27±0.59
Femoral neck	-1.63±0.47	-1.64±0.47
Total body	-0.80±0.90	-0.81±0.86
Current smoker — no. (%)	33 (3.3)	23 (2.3)

\* Plus-minus values are means ±SD. There were no significant differences between the trial groups in any of the characteristics evaluated at baseline. Percentages may not sum to 100 because of rounding. IQR denotes interquartile range.

† Ethnic group was reported by the participant.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Nonvertebral fracture excludes fractures of the skull, face, mandible, hands, and feet.

¶ The fracture was assessed by radiography as grade 2 or 3 on the Genant grading scale (grades range from 0 to 3, with higher grades indicating greater severity).

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Lumbar spine	1.08±0.14	1.07±0.13
Total hip	0.85±0.08	0.85±0.08

## Bone density T score

Lumbar spine	-0.87±1.16	-0.91±1.12
Total hip	-1.24±0.60	-1.27±0.59
Femoral neck	-1.63±0.47	-1.64±0.47
Total body	-0.80±0.90	-0.81±0.86

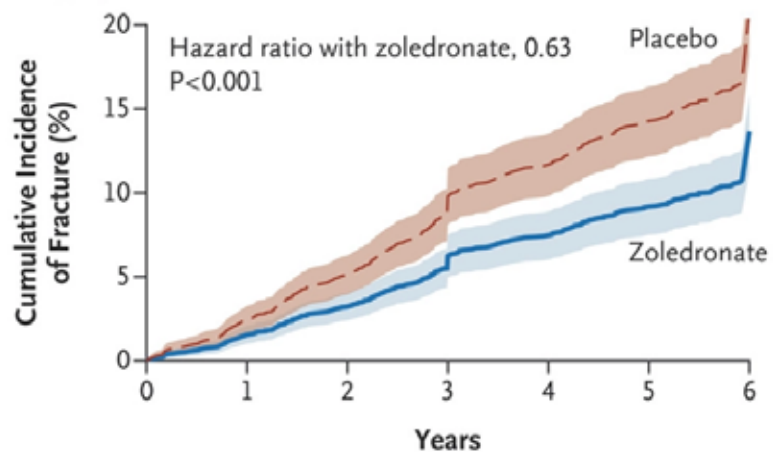
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Median 10-year risk of osteoporotic fracture (IQR) — %	12 (9–15)	12 (9–16)
Median 10-year risk of hip fracture (IQR) — %	2.3 (1.5–3.8)	2.4 (1.5–3.9)
Bone mineral density — g/cm <sup>2</sup>		
Lumbar spine	1.08±0.14	1.07±0.13
Total hip	0.85±0.08	0.85±0.08
Femoral neck	0.81±0.07	0.81±0.07
Total body	1.06±0.07	1.06±0.07
Bone density T score		
Lumbar spine	-0.87±1.16	-0.91±1.12
Total hip	-1.24±0.60	-1.27±0.59
Femoral neck	-1.63±0.47	-1.64±0.47
Total body	-0.80±0.90	-0.81±0.86
Current smoker — no. (%)	33 (3.3)	23 (2.3)

**Table 1. Characteristics of the Trial Participants at Baseline.\***

Characteristic	Placebo (N=1000)	Zoledronate (N=1000)
Age — yr	71±5.1	71±5.0
Ethnic group — no. (%)†		
European	940 (94.0)	954 (95.0)
Maori	14 (1.4)	17 (1.7)
Pacific Islander	15 (1.5)	7 (0.7)
East Asian	24 (2.4)	15 (1.5)
Indian	5 (0.5)	5 (0.5)
Other	2 (0.2)	2 (0.2)
Height — cm	160.4±5.8	160.7±5.8
Weight — kg	69.2±12.2	69.1±12.5
History of nonvertebral fracture after 45 yr of age — no. (%)§	238 (23.8)	237 (23.7)
Prevalent vertebral fracture — no. (%)¶	126 (12.6)	137 (13.7)
Median 10-year risk of osteoporotic fracture (IQR) — %	12 (9–15)	12 (9–16)
Median 10-year risk of hip fracture (IQR) — %	2.3 (1.5–3.8)	2.4 (1.5–3.9)
Bone mineral density — g/cm <sup>2</sup>		
Lumbar spine	1.08±0.14	1.07±0.13
Total hip	0.85±0.08	0.85±0.08
Femoral neck	0.81±0.07	0.81±0.07
Total body	1.06±0.07	1.06±0.07
Bone density T score		
Lumbar spine	-0.87±1.16	-0.91±1.12
Total hip	-1.24±0.60	-1.27±0.59
Femoral neck	-1.63±0.47	-1.64±0.47
Total body	-0.80±0.90	-0.81±0.86
Current smoker — no. (%)	33 (3.3)	23 (2.3)

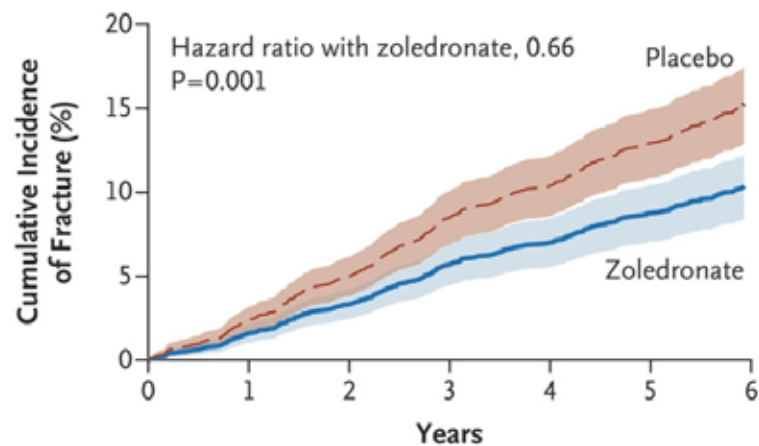
### A First Fragility Fracture



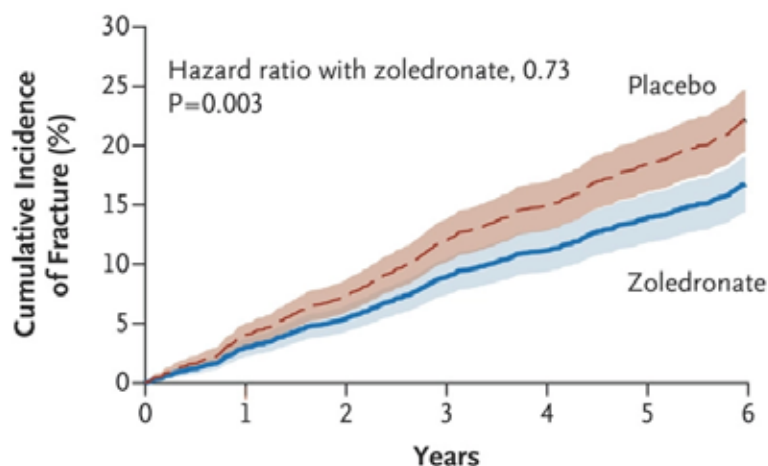
#### No. at Risk

Placebo	1000	976	928	895	846	804	792
Zoledronate	1000	980	945	916	890	857	844

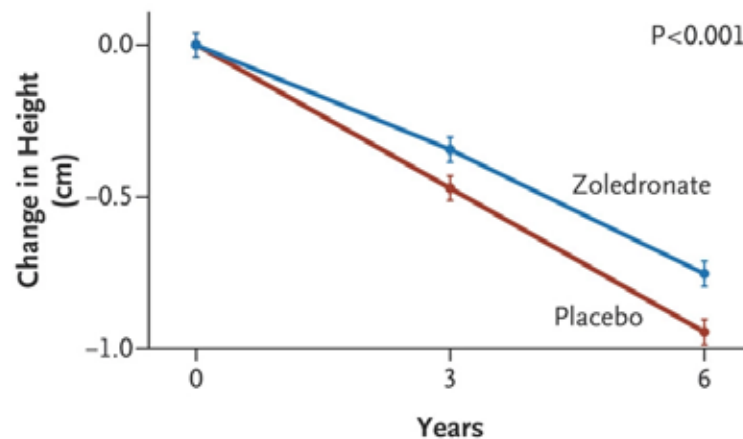
### B Nonvertebral Fragility Fracture



### C Symptomatic Fracture



### D Change in Height

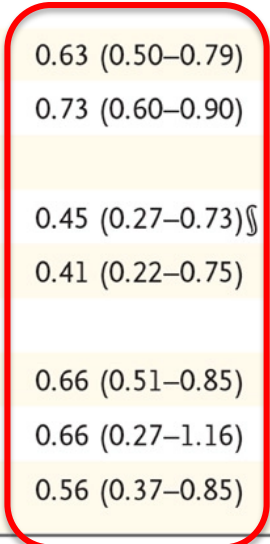


#### No.

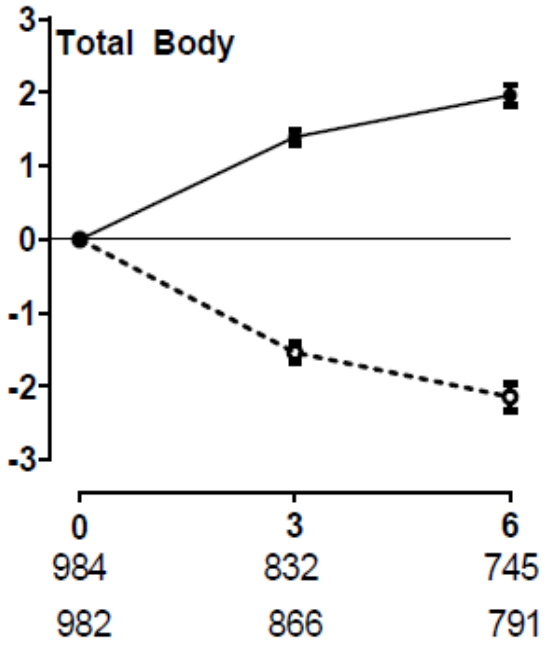
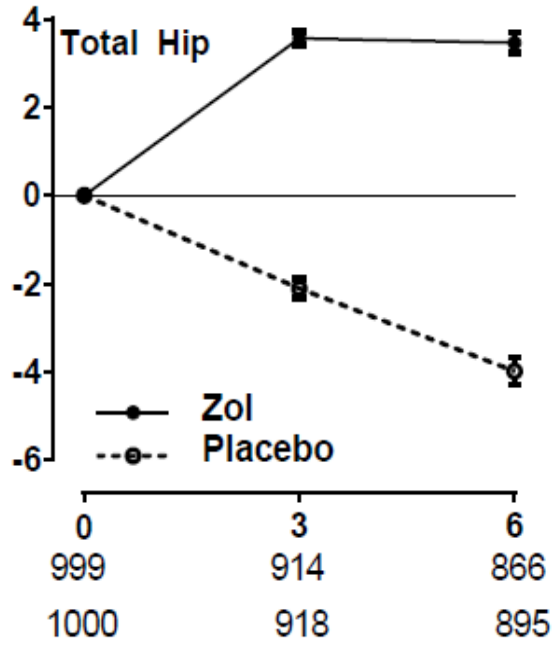
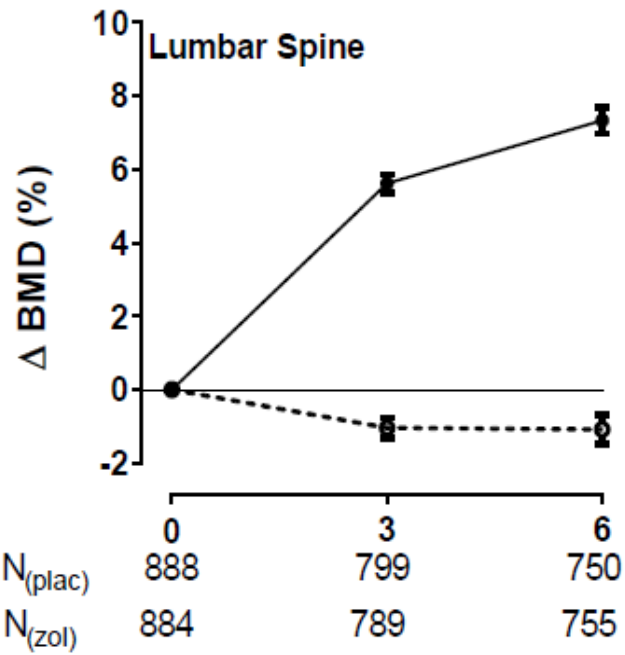
Placebo	1000	934	890
Zoledronate	1000	933	908

**Table 2. Overview of Fracture Data at 6 Years.**

Fracture Category	Placebo (N = 1000)			Zoledronate (N = 1000)			Hazard Ratio with Zoledronate (95% CI)
	Fractures	Fractures per 1000 Woman-Yr (95% CI)	Women with Fracture	Fractures	Fractures per 1000 Woman-Yr (95% CI)	Women with Fracture	
Fragility*	227	38.5 (33.8–43.8)	190	131	22.1 (18.5–26.1)	122	0.63 (0.50–0.79)
Symptomatic†	276	46.9 (41.6–52.6)	214	185	31.2 (26.9–35.9)	163	0.73 (0.60–0.90)
Vertebral							
Total	64	10.9 (8.4–13.8)	49	25	4.2 (2.8–6.1)	23	0.45 (0.27–0.73)§
Symptomatic	39	6.6 (4.8–9.0)	34	14	2.4 (1.3–3.9)	14	0.41 (0.22–0.75)
Nonvertebral							
Fragility‡	178	30.2 (26.0–34.9)	148	108	18.2 (15.0–21.9)	101	0.66 (0.51–0.85)
Hip	12	2.0 (1.1–3.5)	12	8	1.3 (0.6–2.6)	8	0.66 (0.27–1.16)
Forearm or wrist	68	11.6 (9.0–14.6)	63	38	6.4 (4.6–8.7)	36	0.56 (0.37–0.85)



\* This category included nonvertebral fragility fractures (excluding fractures of the toes, metatarsal bones, fingers, metacarpal bones, skull, facial bones, and mandible) and morphometric vertebral fractures.  
† This category included symptomatic vertebral fractures and all nonvertebral fractures.  
‡ This category excluded fractures of the toes, metatarsal bones, fingers, metacarpal bones, skull, facial bones, and mandible.  
§ These data are the odds ratio and 95% CI.



Time (y)

**Table 3.** Prespecified Adverse Events of Interest.

Adverse Event	Placebo (N=1000)			Zoledronate (N=1000)			Odds Ratio with Zoledronate (95% CI)
	Events	Events per 1000 Woman-Yr (95% CI)	Women with at Least One Event	Events	Events per 1000 Woman-Yr (95% CI)	Women with at Least One Event	
	<i>no.</i>		<i>no.</i>	<i>no.</i>		<i>no.</i>	
Death	41	7.0 (5.4–9.4)	41	27	4.5 (3.0–6.6)	27	0.65 (0.40–1.05)
Sudden death	1	0.2 (0.002–0.9)	1	3	0.5 (0.1–14.8)	3	3.01 (0.3–28.9)
Myocardial infarction	43	7.3 (5.3–9.8)	39	25	4.2 (2.7–6.2)	24	0.61 (0.36–1.02)
Coronary-artery revascularization	32	5.4 (3.7–7.7)	30	23	3.9 (2.5–5.8)	21	0.72 (0.41–1.27)
Stroke	22	3.7 (2.3–5.7)	20	20	3.4 (2.1–5.2)	17	0.85 (0.44–1.63)
Composite of vascular events*	98	16.6 (13.5–20.3)	69	71	12.0 (9.3–15.1)	53	0.76 (0.52–1.09)
Transient ischemic attack	15	2.5 (1.4–4.2)	14	24	4.0 (2.6–6.0)	23	1.66 (0.85–3.24)
Cancer†	127	21.5 (18.0–18.1)	121	87	14.7 (11.7–18.1)	84	0.67 (0.50–0.89)
Osteonecrosis of the jaw	0	0	0	0	0	0	Not applicable
Atrial fibrillation	92	15.6 (12.6–19.1)	55	88	14.8 (11.9–18.3)	54	0.98 (0.67–1.44)

\* This category included any of the following events: sudden death, myocardial infarction, coronary-artery revascularization, or stroke.

† This category excluded nonmelanoma skin cancers.

# Συμπεράσματα μελέτης

- ✓ ΖΟΛ σε γυναίκες > 65 με οστεοπενία ισχίου:
  - μείωση σπονδυλικών και μη-σπονδυλικών #
  - μείωση μη-σπονδυλικών # παραπλήσια με οστεοπόρωση
  - χορήγηση ανά 18μηνο αποτελεσματική (vs ετήσια)
  - αποτελεσματικό χωρίς συγχορήγηση Ca
  - μείωση καρδιαγγειακών – κακοηθειών?

Ευχαριστώ πολύ