

# **Il Trattamento dell'Osteoporosi. Una Metanalisi**

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# **Osteoporosi: una patologia sottovalutata**

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- ❑ **Scarsa consapevolezza della patologia**
- ❑ **Diagnosi sottostimata**
- ❑ **Scarso supporto terapeutico**

*IOF Survey 2000*

# Evidence-based Review of OP Trials

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- Calcium, Vitamin D
  - HRT
  - SERMs: Raloxifene
  - Bisphosphonates
    - Alendronate, Risedronate, Clodronate,  
Neridronate, Pamidronate, Zoledronate
  - PTH
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# Calcium

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- Meta-analysis including 15 trials (1806 patients) that randomised postmenopausal women to Calcium supplementation or usual Calcium intake in the diet
- Patients treated for > 1 year
- Fracture data reported

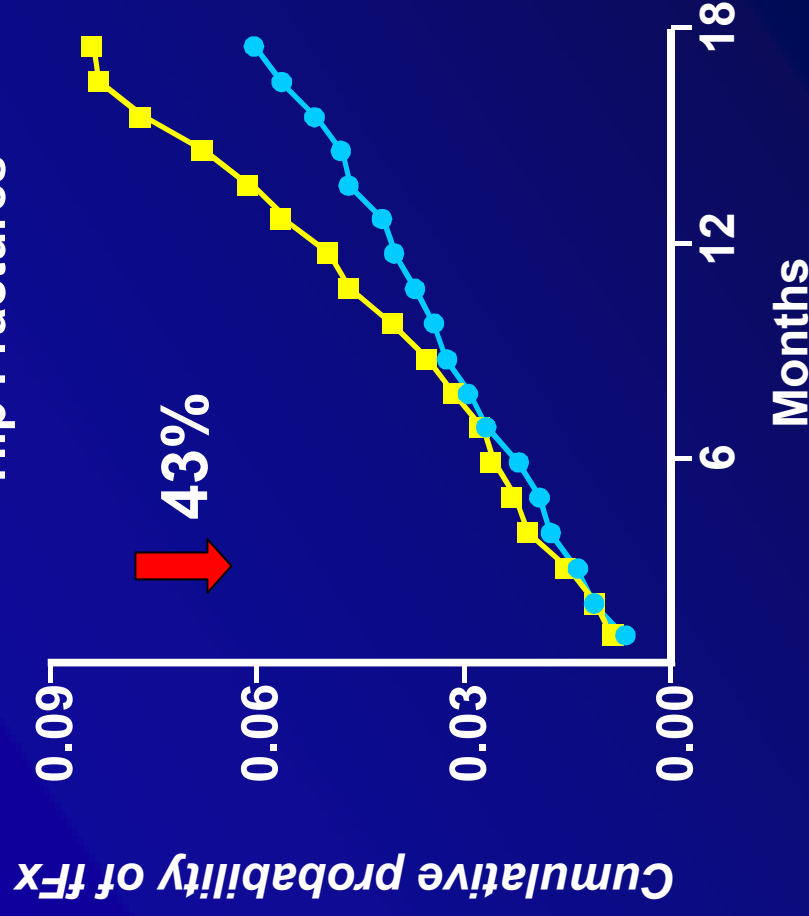
## Summary of results

The RR of vertebral Fx was 0.77 (95% CI 0.54-1.09) and that of non-vertebral Fx 0.86 (95% CI 0.43-1.72)

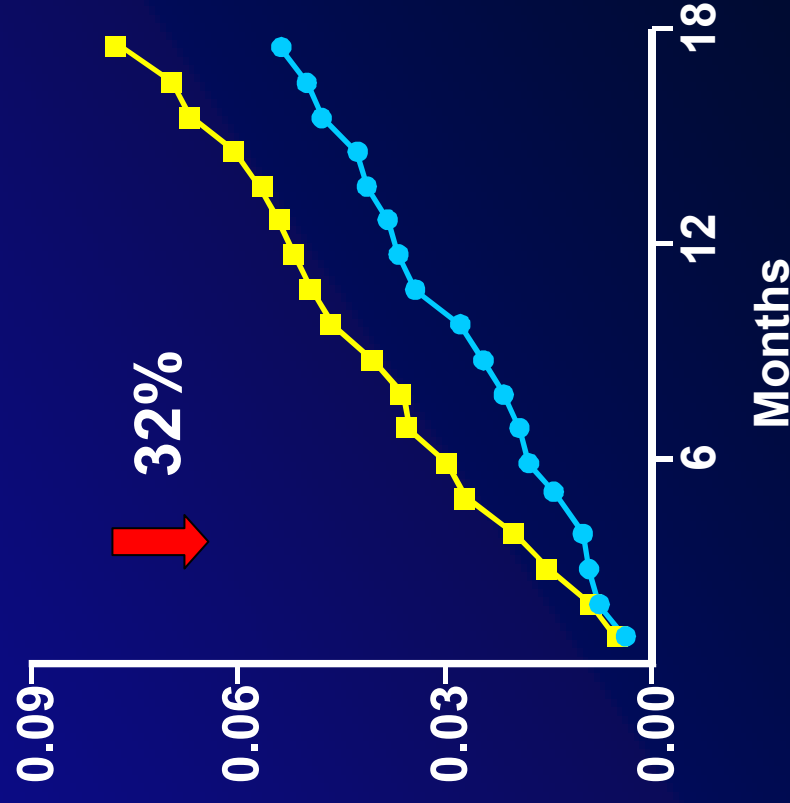
# Probability of Fx among Placebo (n=1636) and Vitamin D/Calcium (n=1634) Treated Institutionalised Women

■ Placebo ● Vit. D 800 IU + Calcium 1.2 g

Hip Fractures

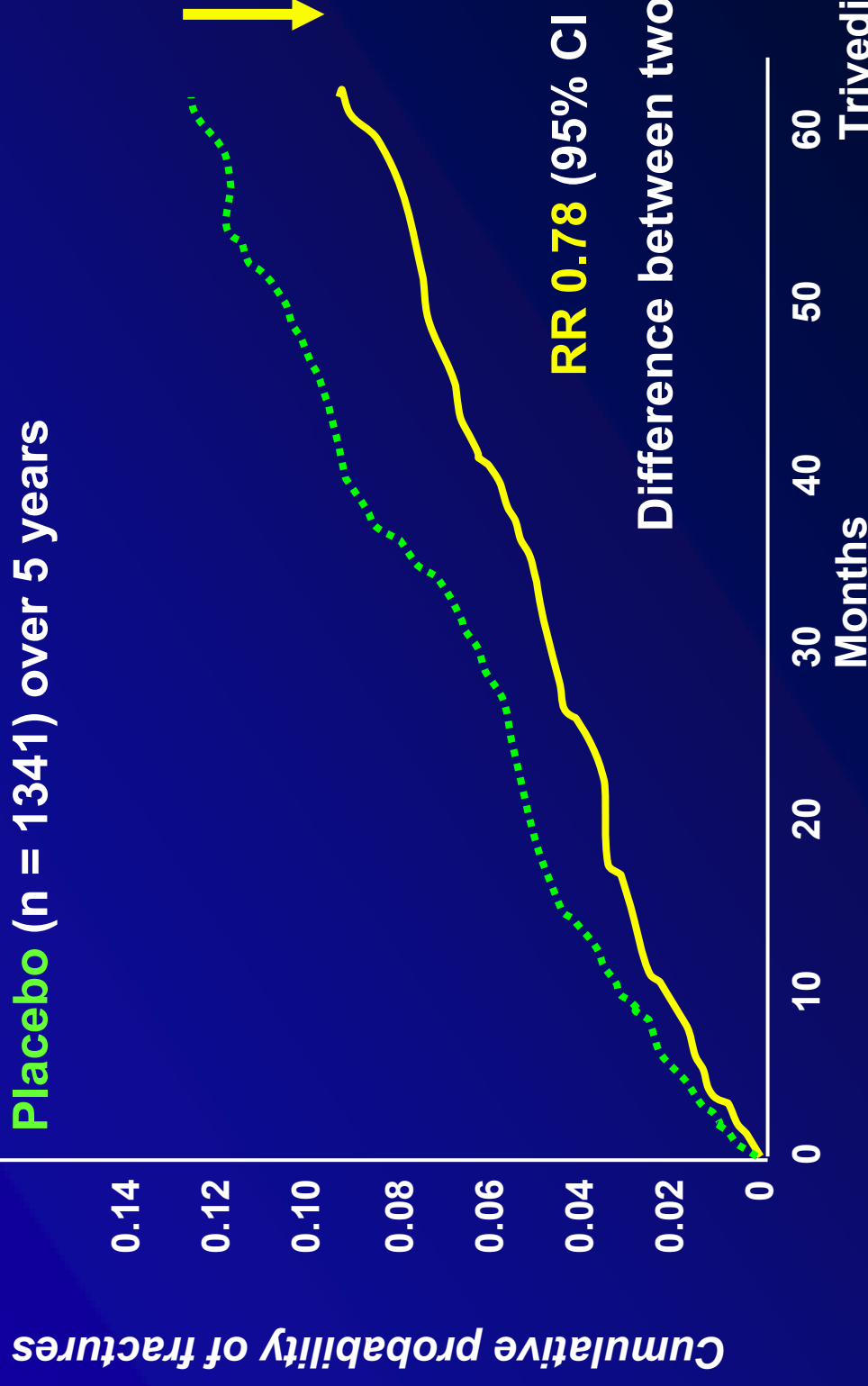


Total Non-vertebral Fractures



# Four Monthly Oral Vitamin D and Fx

Cumulative probability of any first fracture according to treatment with **100.000 IU/4 Months Vitamin D** (n = 1345) or **Placebo** (n = 1341) over 5 years



# Calcium, Vitamin D, Milk Consumption and Hip Fx

- 18-year prospective analysis in 72.337 postmenopausal women to assess relations between hip Fx risk and Calcium, Vitamin D, and milk consumption
- Nutritional data recorded at baseline (1980) and updated several times during follow-up. 603 incident hip Fx identified

## Summary of results

Women consuming  $\geq 12.5$   $\mu\text{g/d}$  vitamin D from food plus supplements had a **37%** lower risk of hip Fx (**RR = 0.63; 95% CI 0.42-0.94**) than did women consuming  $< 3.5$   $\mu\text{g/d}$ .

Total Calcium intake and milk consumption were not associated with a lower risk of hip Fx.

# Examining the Evidence: HRT

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Two meta-analyses of RCTs noted a statistically significant reduction in vertebral and non-vertebral fx

	HRT	Control	RR	95% CI
Vertebral <sup>1</sup>	42/3507	63/3216	<b>0.67</b>	0.45 - 0.98
Non vertebral <sup>2</sup>	258/4929	307/3845	<b>0.73</b>	0.56 - 0.94

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1. Torgerson DJ, BMC Musc Skel Dis 2001

2. Torgerson DJ, JAMA 2001

# Estrogen Plus Progestin in Healthy Postmenopausal Women: the Women's Health Initiative (WHI)

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RCT in 16,608 healthy women (50-79 yrs) with an intact uterus randomised to receive PBO or conjugated estrogen 0.625 mg/d + MPA 2.5 mg/d

**Primary outcome:** coronary heart disease (CHD) (MI and CHD death)

**Primary adverse outcome:** invasive breast cancer

A **Global Index** summarising the balance of risks and benefits included: stroke, pulmonary embolism, endometrial K, colorectal K, hip fracture and death due to other causes plus the two primary outcomes

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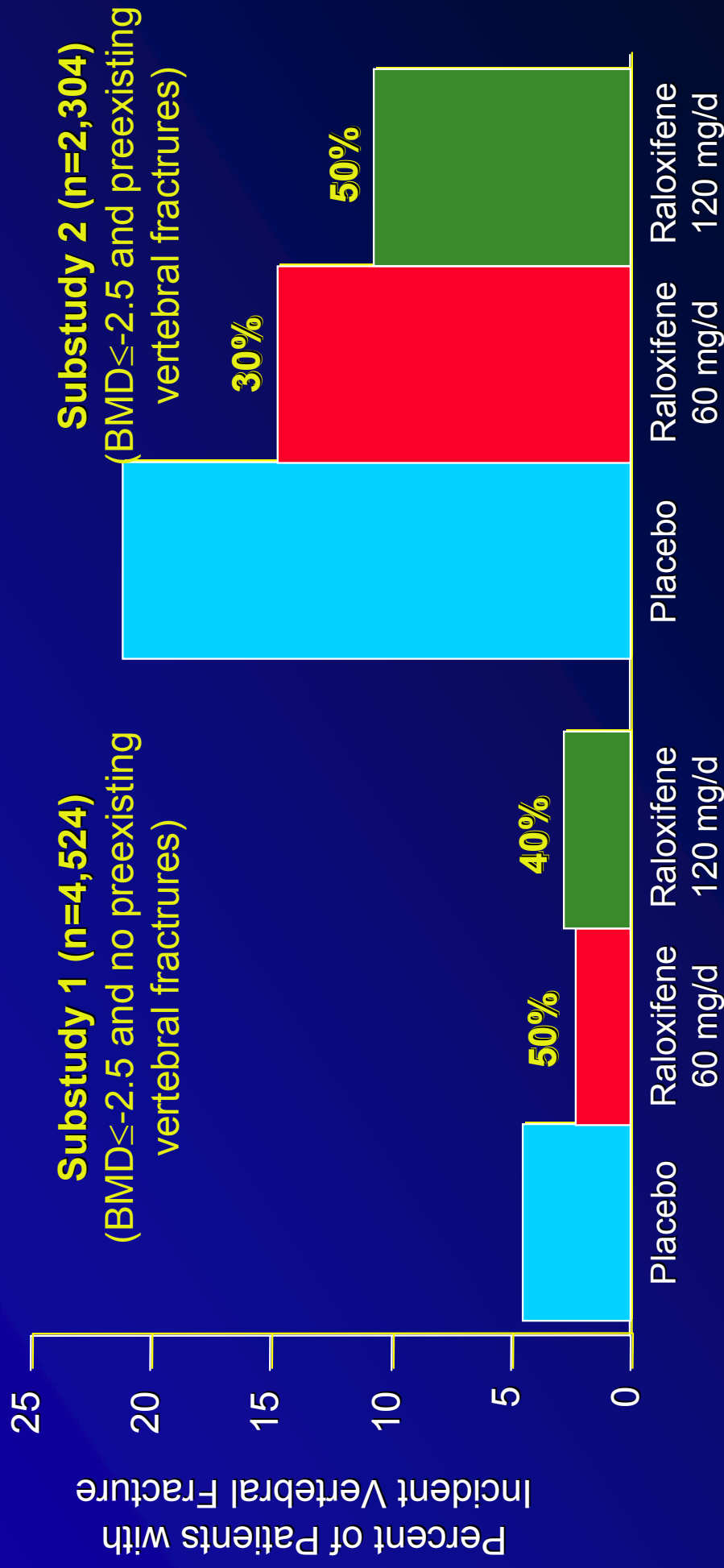
# WHI - Main Clinical and Composite Outcomes: Estimated Hazard Ratios

	HRs	95% CI	HRs	95% CI	
CHD	<b>1.29</b>	1.02 - 1.63	<b>1.22</b>	1.09 - 1.36	
Stroke	<b>1.41</b>	1.07 - 1.85	Total CVD	1.09 - 1.36	
PE	<b>2.13</b>	1.39 - 3.25	Total K	0.90 - 1.17	
Breast K	<b>1.26</b>	1.00 - 1.59	Combined Fx	0.69 - 0.85	
Colon K	<b>0.63</b>	0.43 - 0.92	Total mortality	0.82 - 1.18	
Endom K	0.83	0.47 - 1.47	<i>Global Index</i>	<b>1.15</b>	1.03 - 1.28
Hip Fx	<b>0.66</b>	0.45 - 0.98			
Vert Fx <sup>1</sup>	<b>0.66</b>	0.44 - 0.98			

<sup>1</sup> Clinical

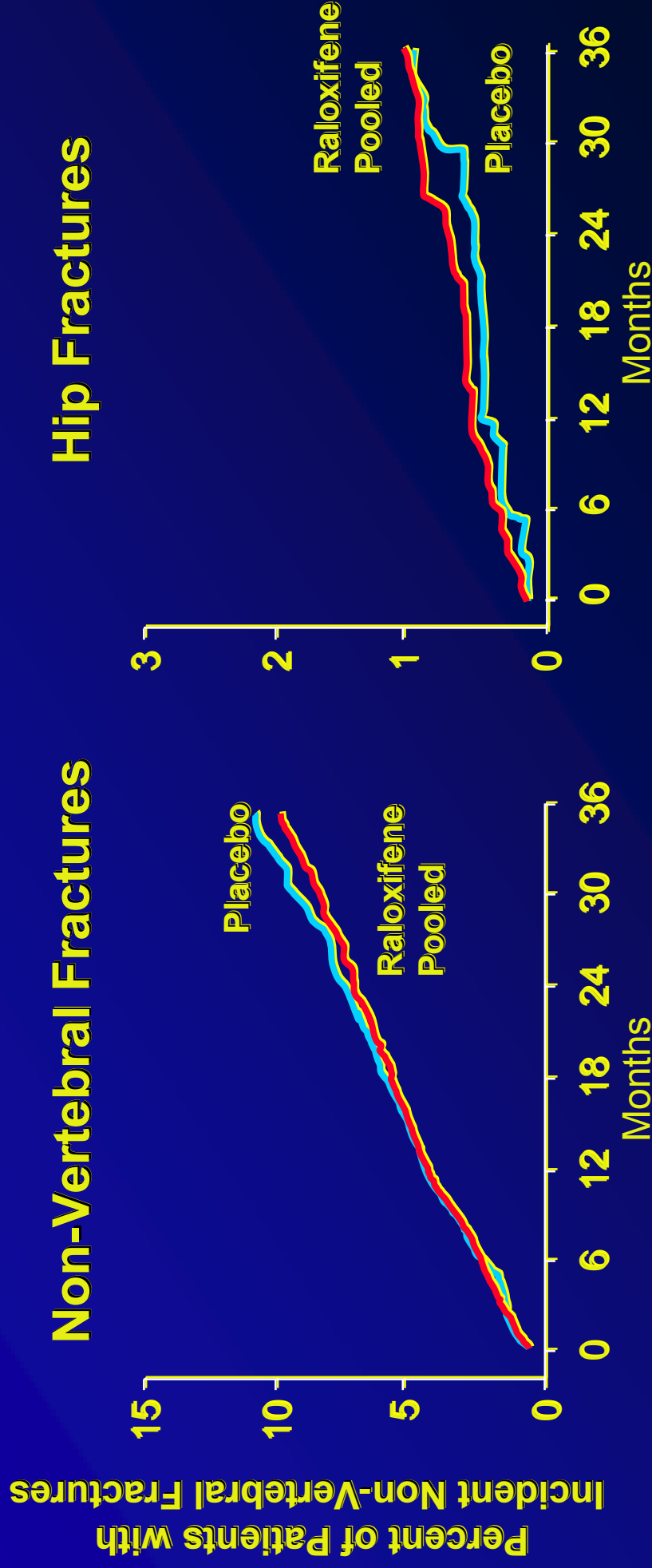
# Effect of Raloxifene on Radiographic Vertebral Fractures (MORE)

## Radiographic Vertebral Fractures

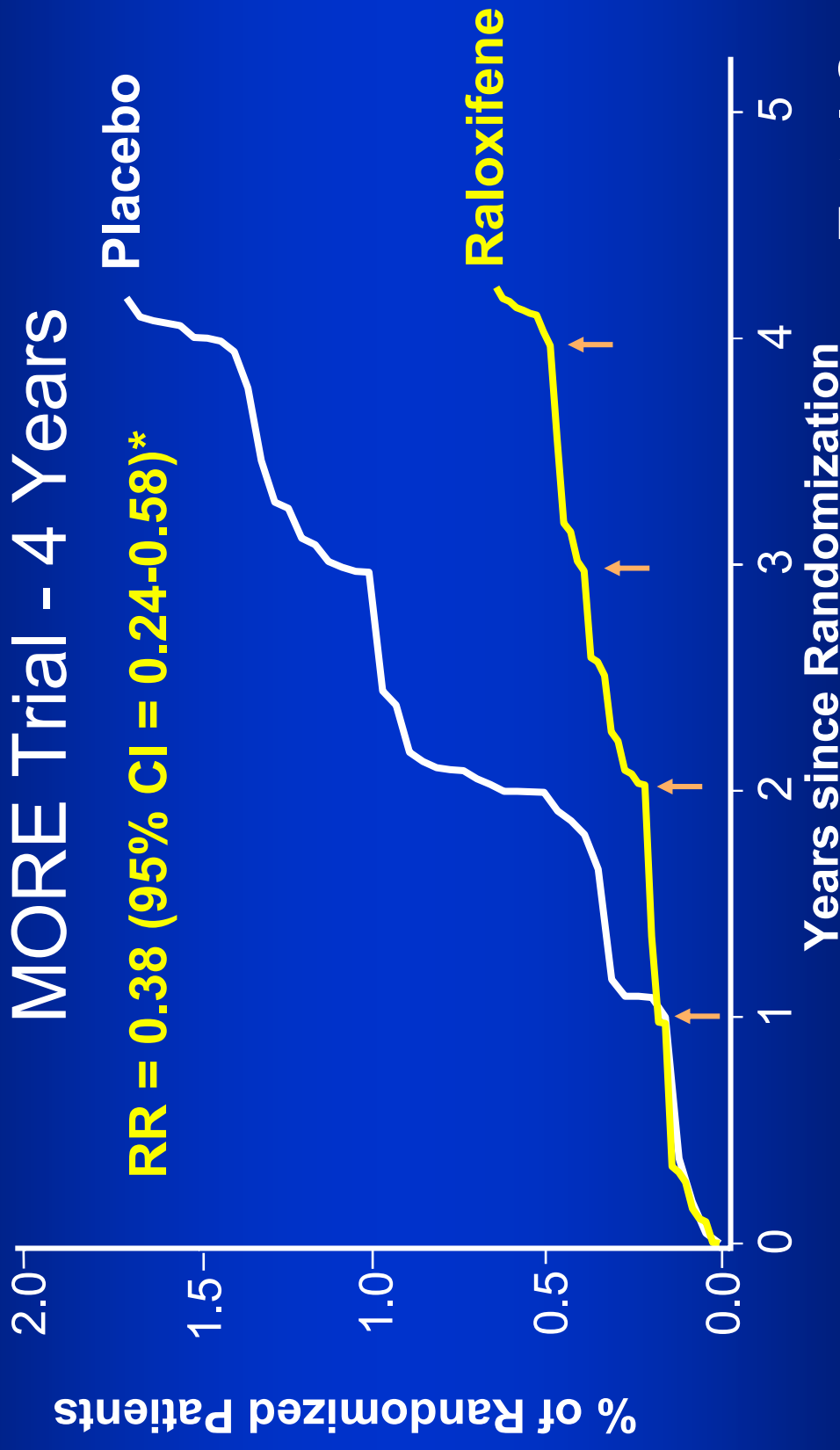


# Raloxifene - Efficacy at the Hip

Effect on Non-Vertebral and Hip Frx  
MORE Pooled Data (60 mg and 120 mg)



# Effect of Raloxifene on Breast Cancer Incidence

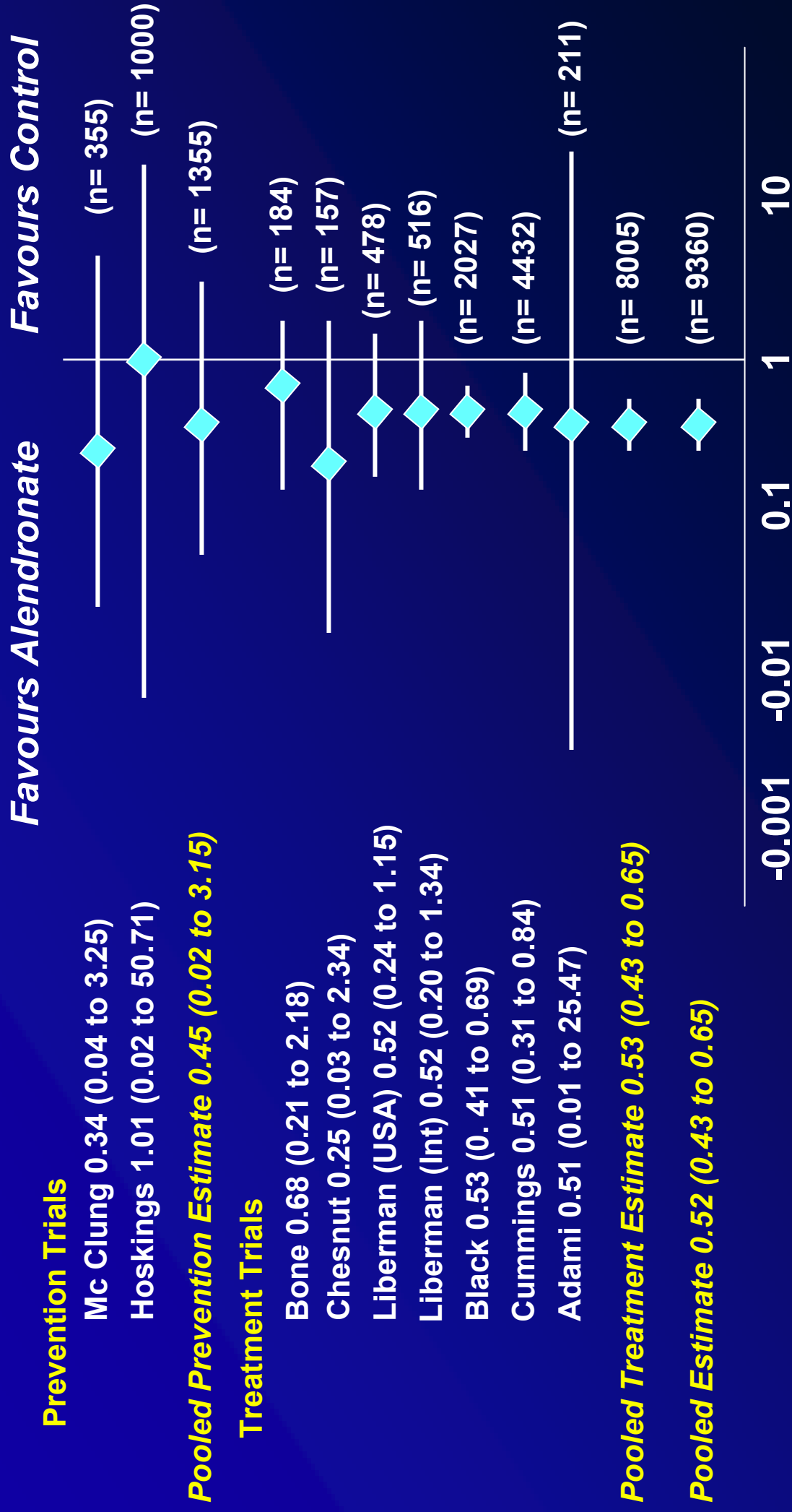


Arrow denotes annual mammogram

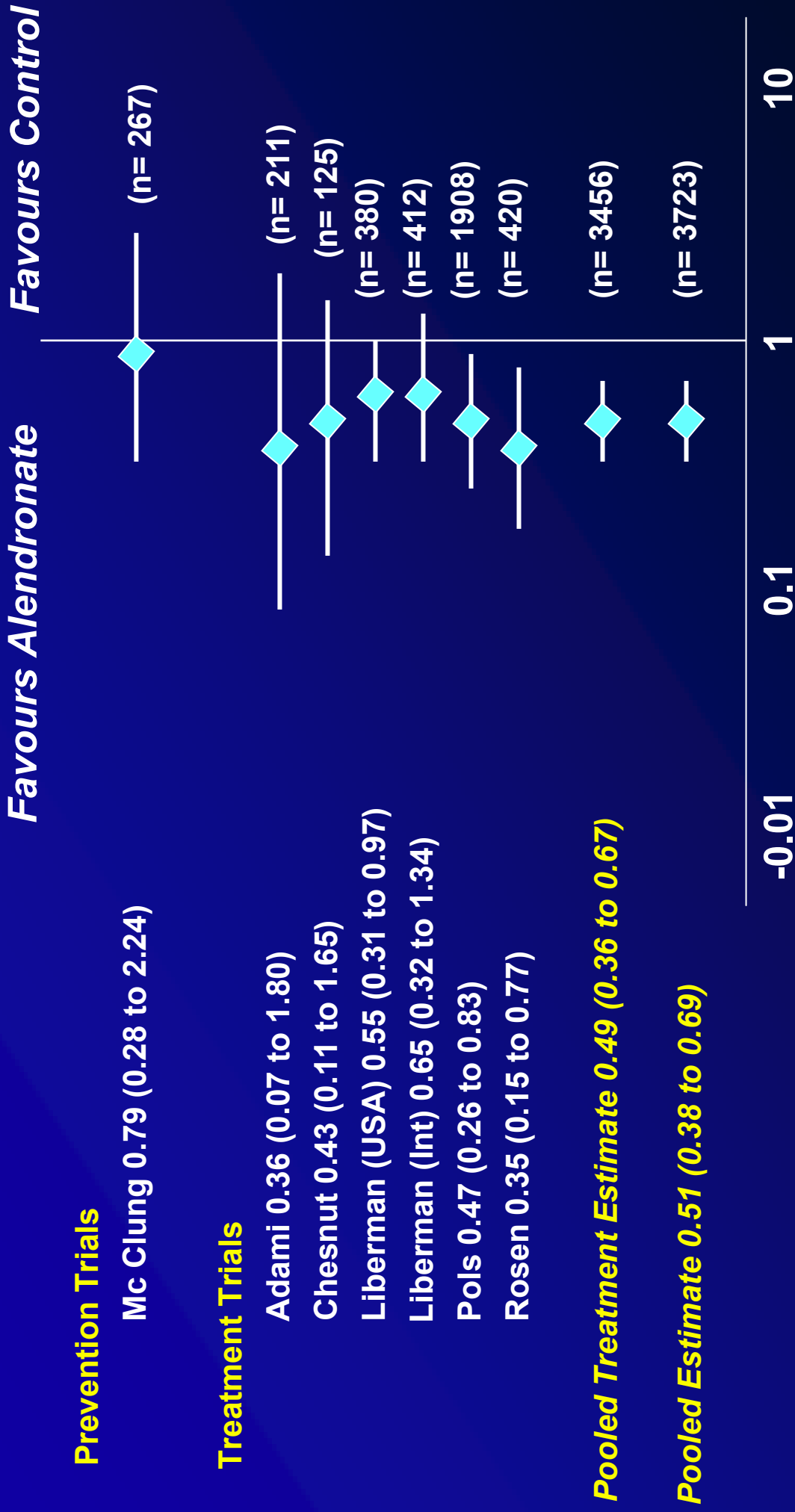
\* $P < .001$

Cauley J, et al. Breast Cancer Res Treatment 2001

# Relative Risk (95% CI) for Vertebral Fx for Doses $\geq$ 5 mg of Alendronate



# Relative Risk (95% CI) for Non-Vertebral Fx for Doses $\geq$ 10 mg of Alendronate

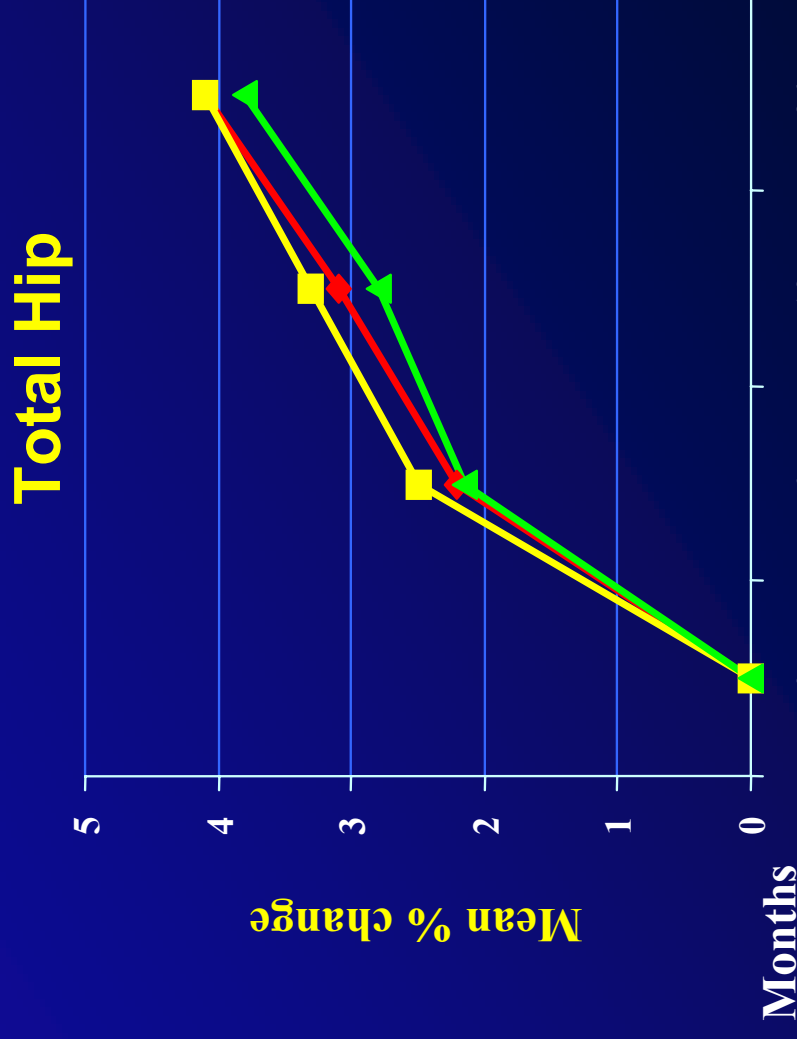
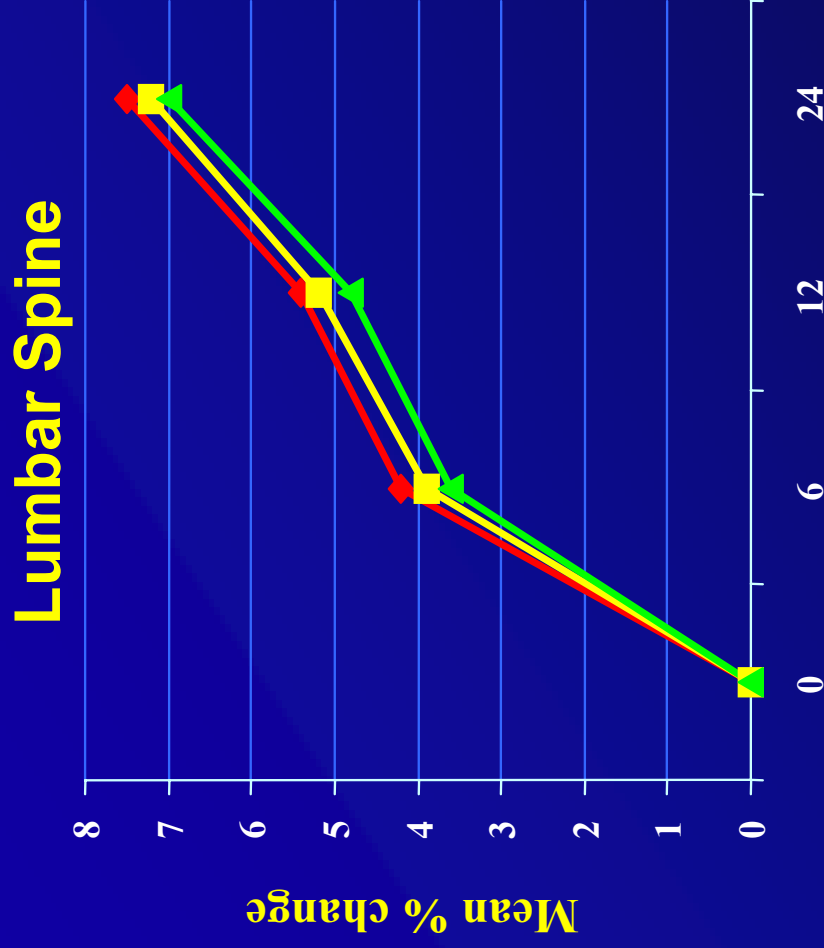


# Alendronate Once-a-Week

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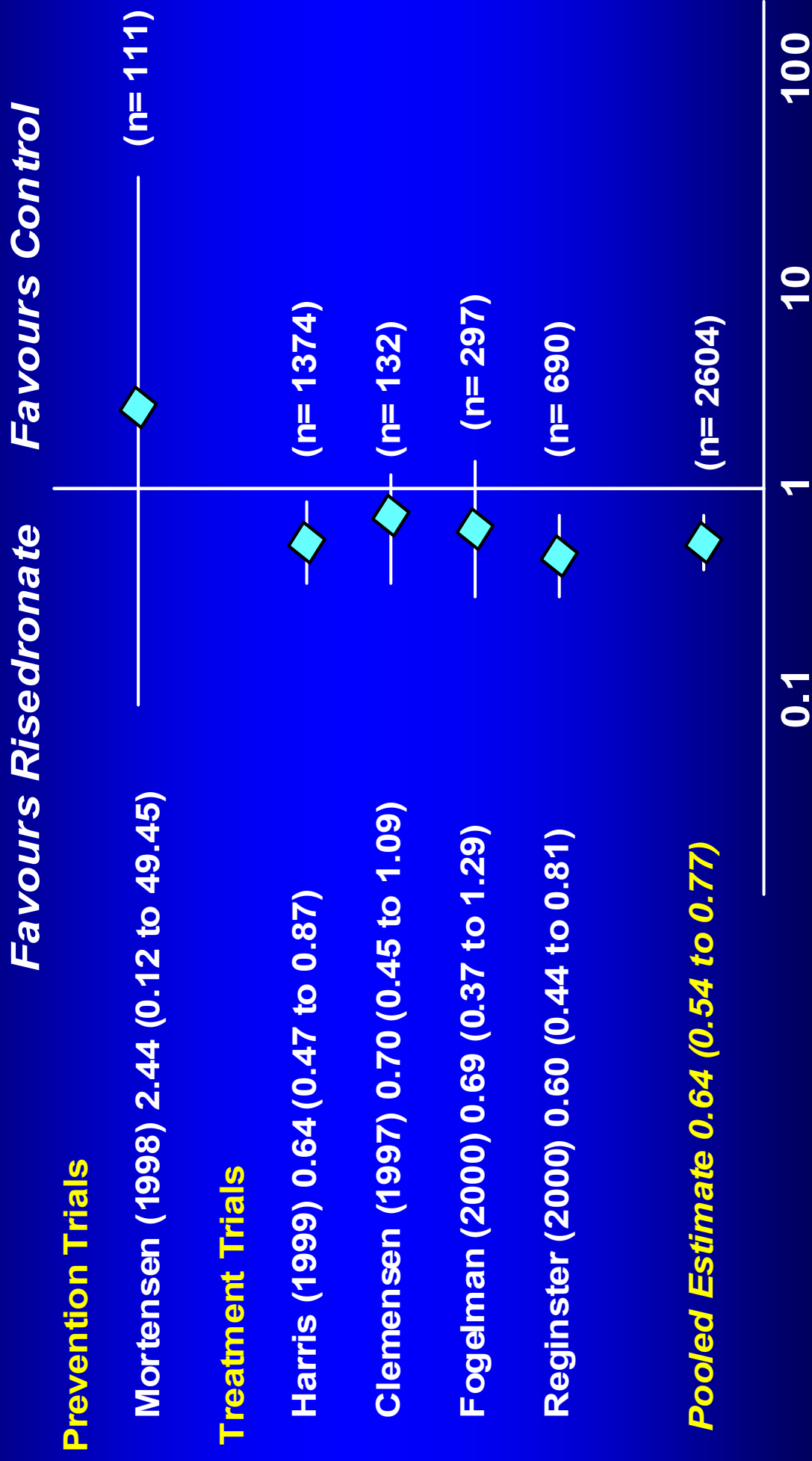
- One-year, double-blind, randomised study
- 1258 Postmenopausal osteoporotic women
- Alendronate regimen:
  - 10 mg daily N = 370
  - 35 mg twice-weekly N = 369
  - 70 mg once-weekly N = 519
- All received 500 mg calcium and 250 IU vitamin D supplementation
- Primary endpoint: BMD changes, according to strictly defined equivalence criteria

# ALN OW - BMD Changes over 2 Years

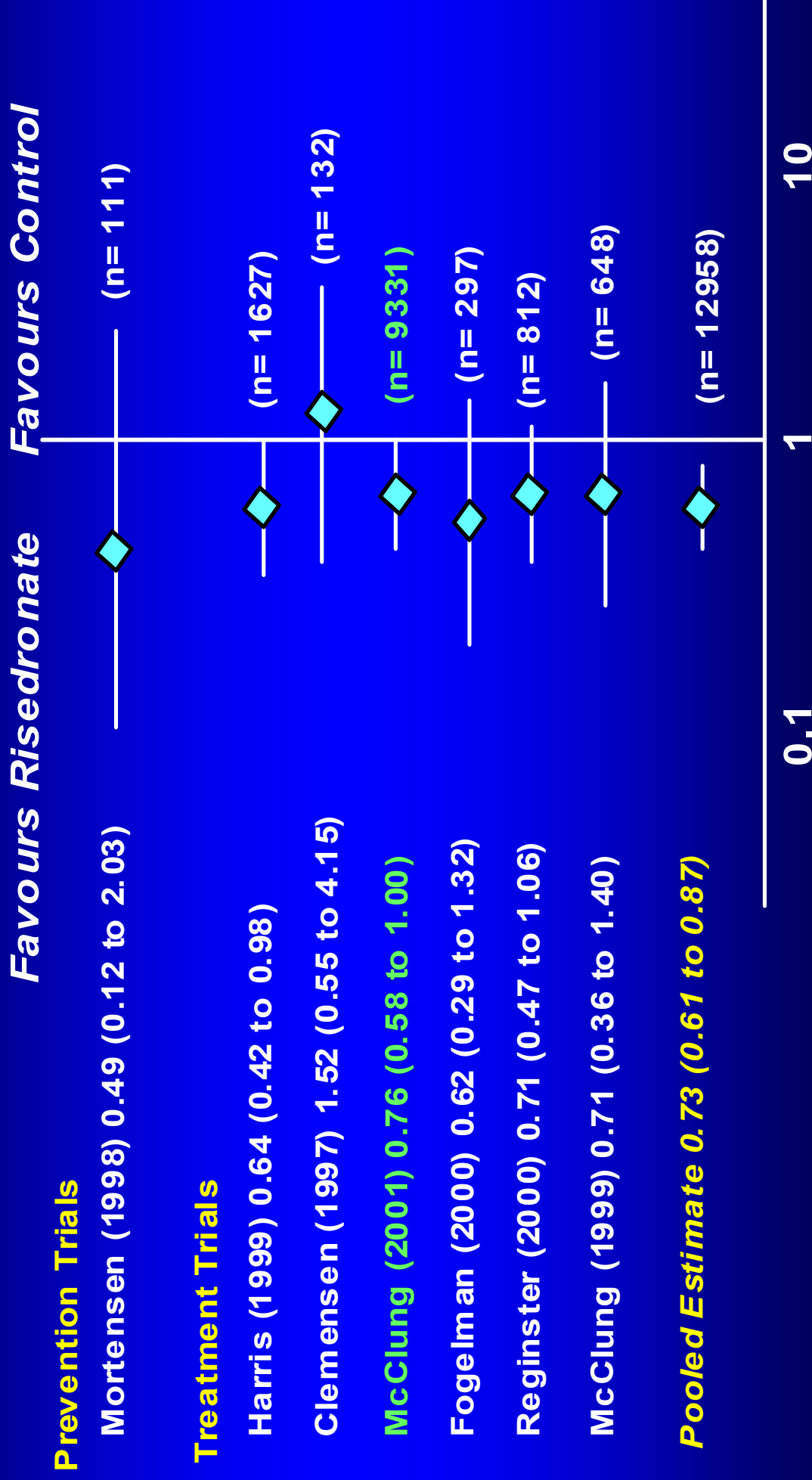


- ALN 10 mg D
- ALN 35 mg TW
- ALN 70 mg OW

# Relative Risk (95% CI) for Vertebral Fracture after Treatment with Risedronate



# Relative Risk (95% CI) for Non-Vertebral Fx after Treatment with Risedronate



# Risedronate Once-a-Week Dosing Study Design

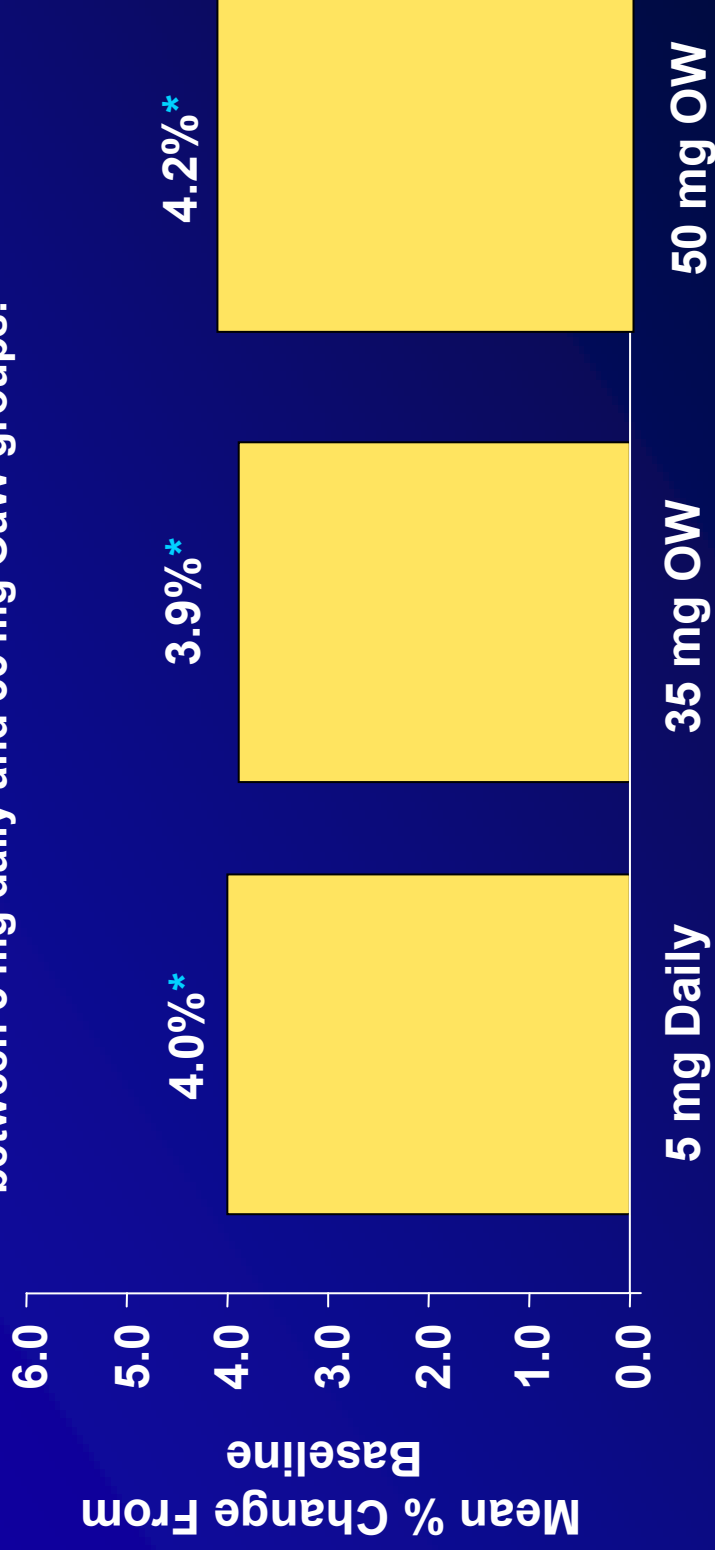
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## Inclusion Criteria

- N = 1456 women
  - Age > 50 years
  - > 5 years postmenopausal
  - T-score < - 2.5, or < - 2 and at least 1 prevalent vertebral fx
  - 1.0 g Calcium supplementation + up to 500 IU Vitamin D if baseline levels were low
  - Primary endpoint: BMD changes, according to strictly defined equivalence criteria
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# Risedronate OW - BMD Changes over 1 Year

\* $p < 0.05$  for comparison with baseline; no significant differences between 5 mg daily and 35 mg OaW groups.



# Oral Clodronate - Incidence of New Vertebral Fx after 1 year

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Clodronate (n = 204)

Placebo (n = 217)

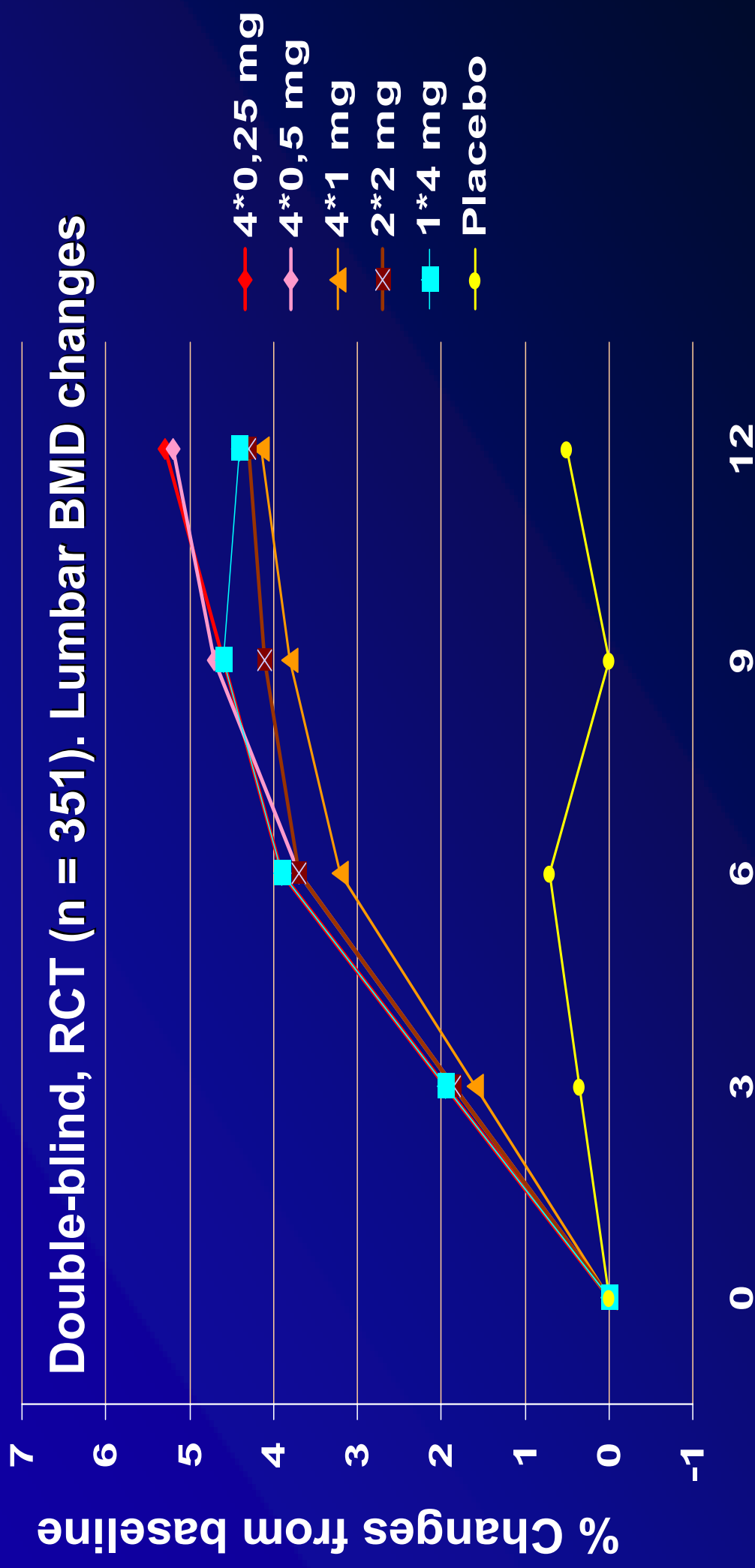
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Pts, No	Incidence, %	Pts, No	Incidence, %
6	3	16	7

**RR (95% CI) 0.40 (0.16-1.00) p value = 0.065**

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# I.V. Zoledronate in Postmenopausal Women

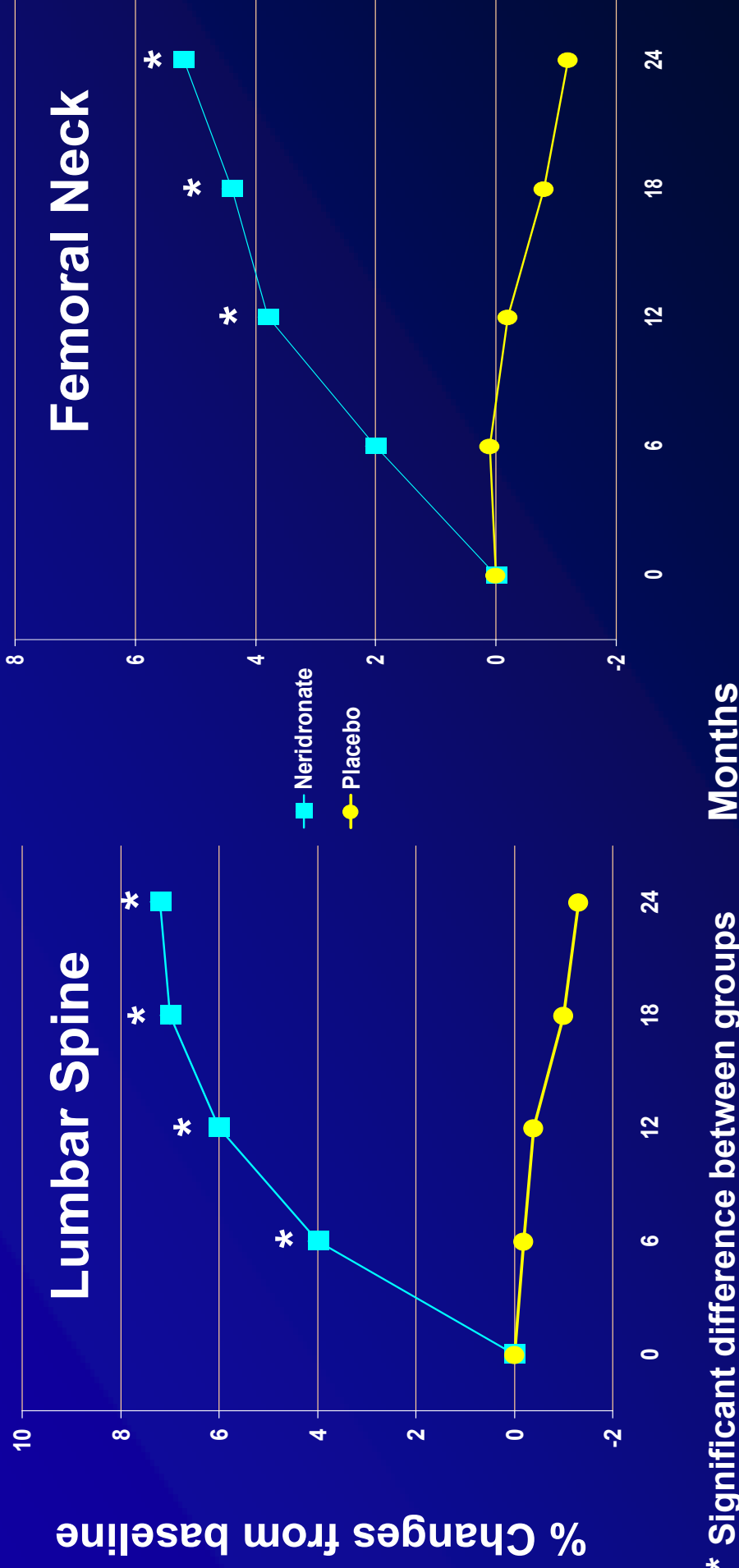


Months

Reid IR, et al. N Engl J Med 2002

# I.V. Neridronate in Postmenopausal OP

Double-blind, RCT. Neridronate 50 mg/2 mo (n=39) or PBO (n=39)



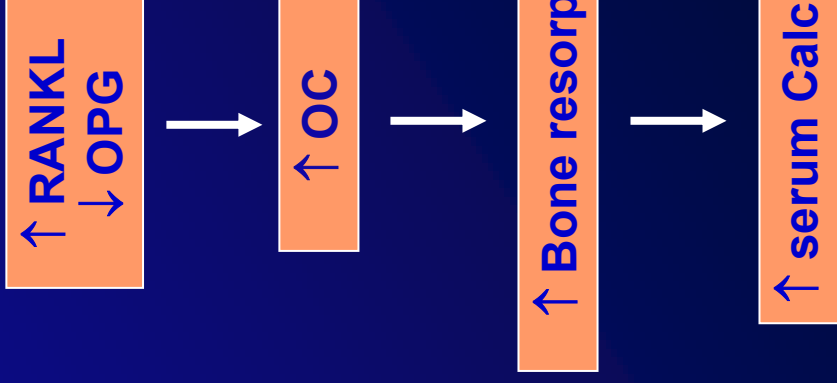
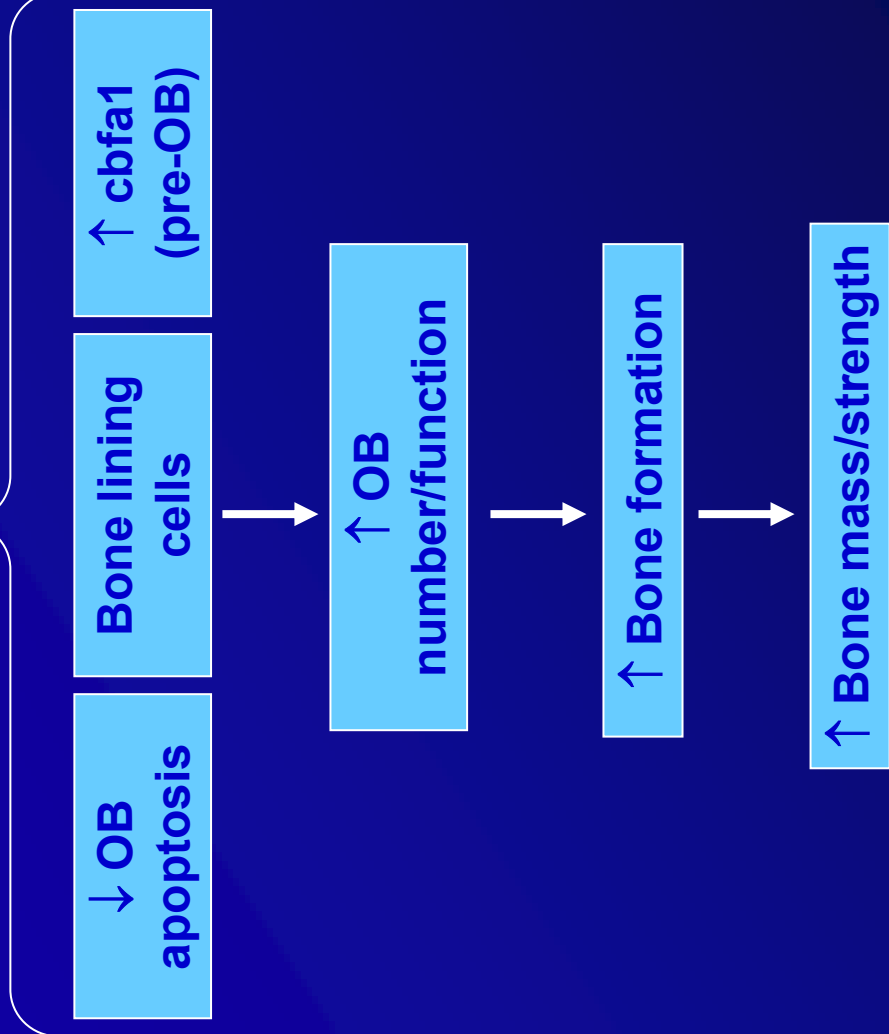
\* Significant difference between groups

Months

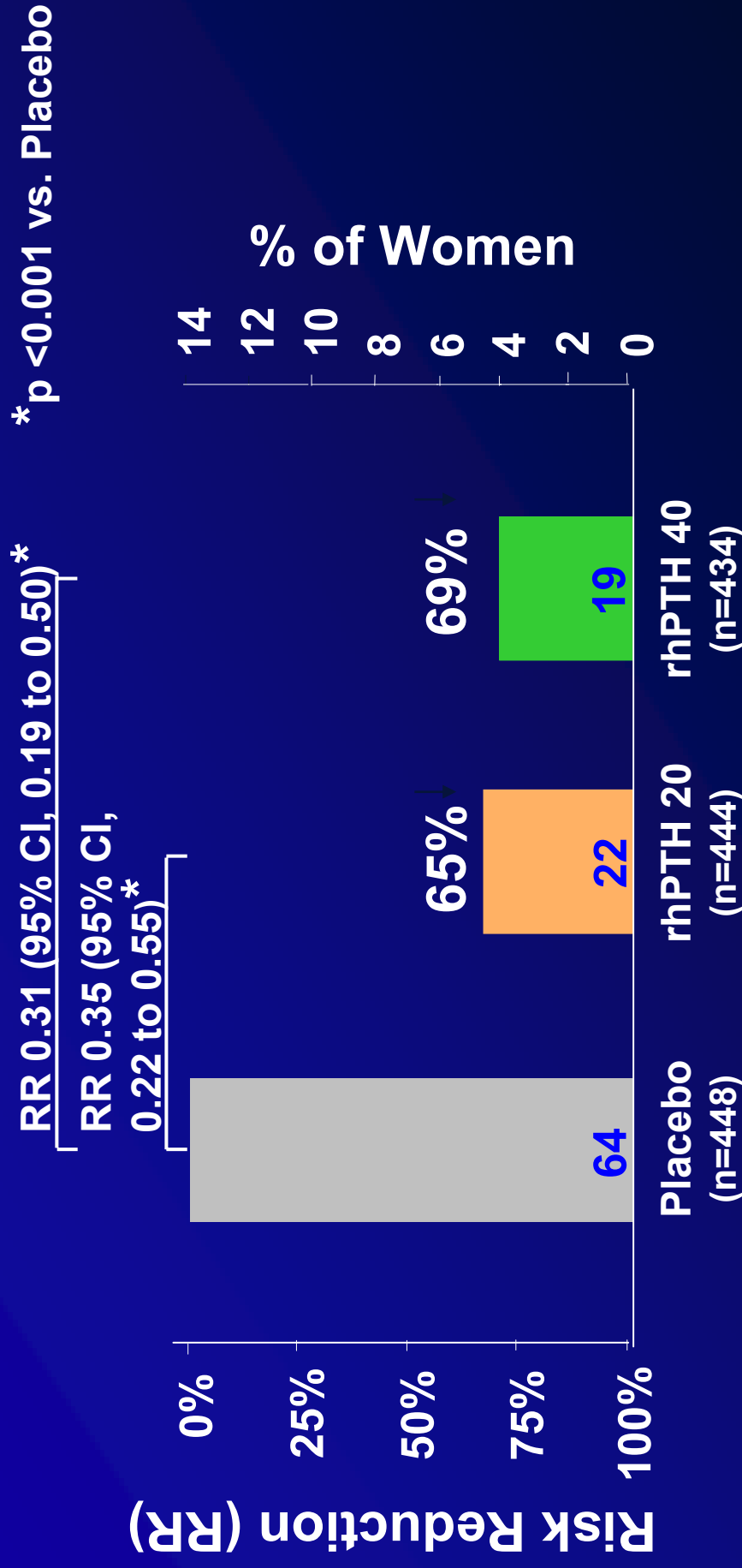
# PTH

Intermittent

Continuous

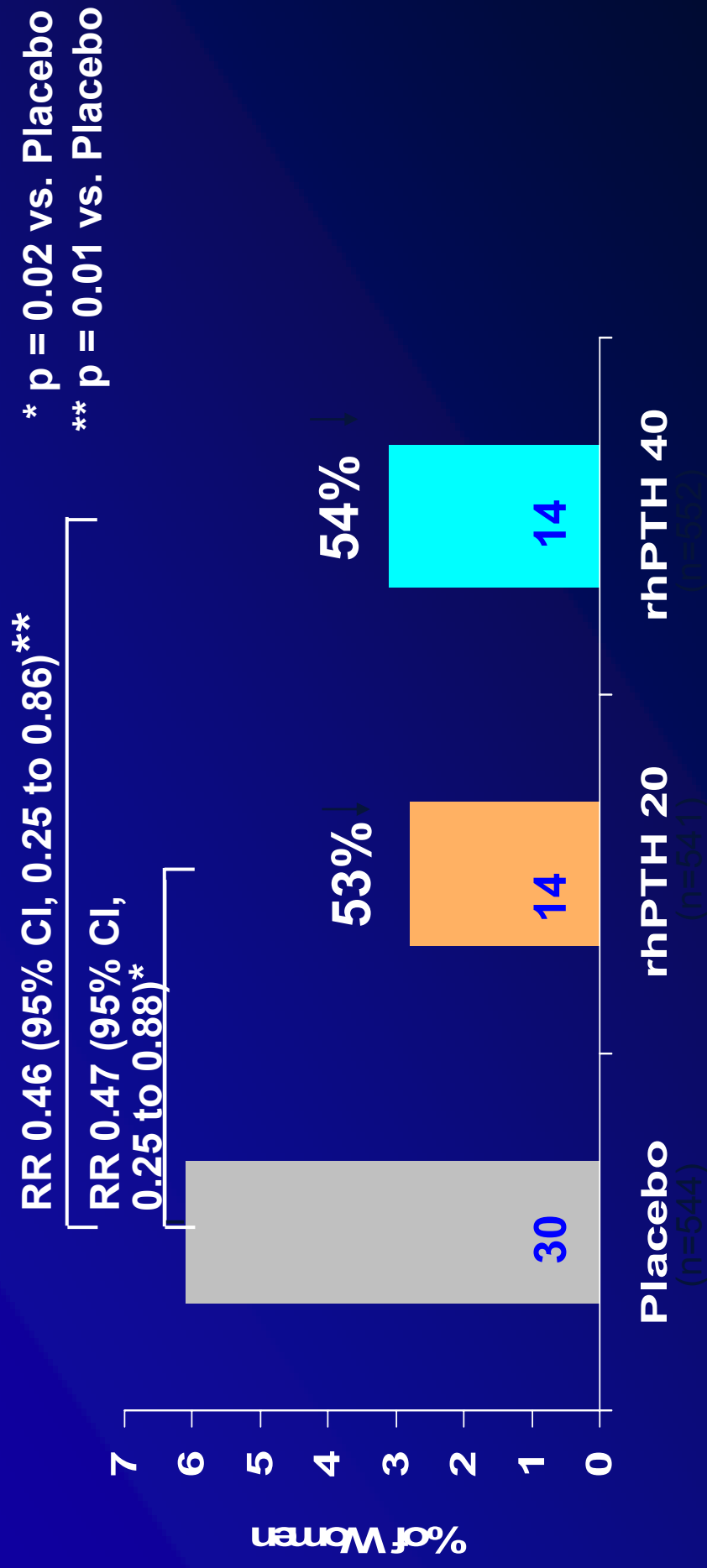


# Effect of PTH(1-34) on the Risk of New Vertebral Fr - 21 Mo Follow-up



No. of women who had  $\geq 1$  fracture

# Effect of PTH(1-34) on the Risk of Non-Vertebral Fragility Fx - 21 Mo Follow-up



No. of women who had  $\geq 1$  fragility fracture

