Advances in non-hormonal drug therapy for fracture prevention

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- Review of medication available
  - Bisphosphonates (ibandronate, zoledronate)
  - Strontium
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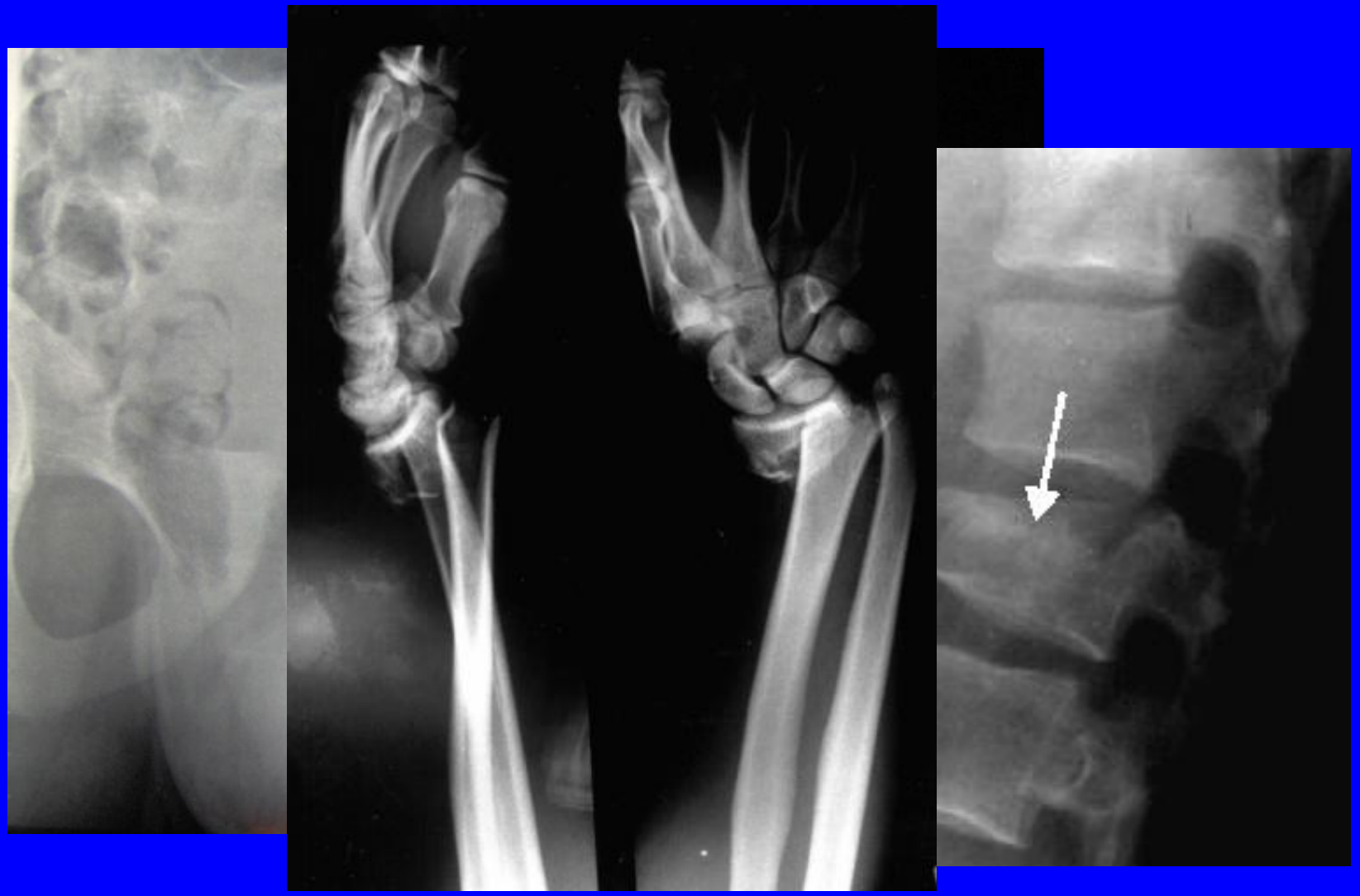
- NICE
- FRAX^{tm}
- NOGG

Potential conflict of interest/ support

EMD has received honoraria from the following companies:

- Novartis
- Servier
- Eli Lilly

Why does it matter?



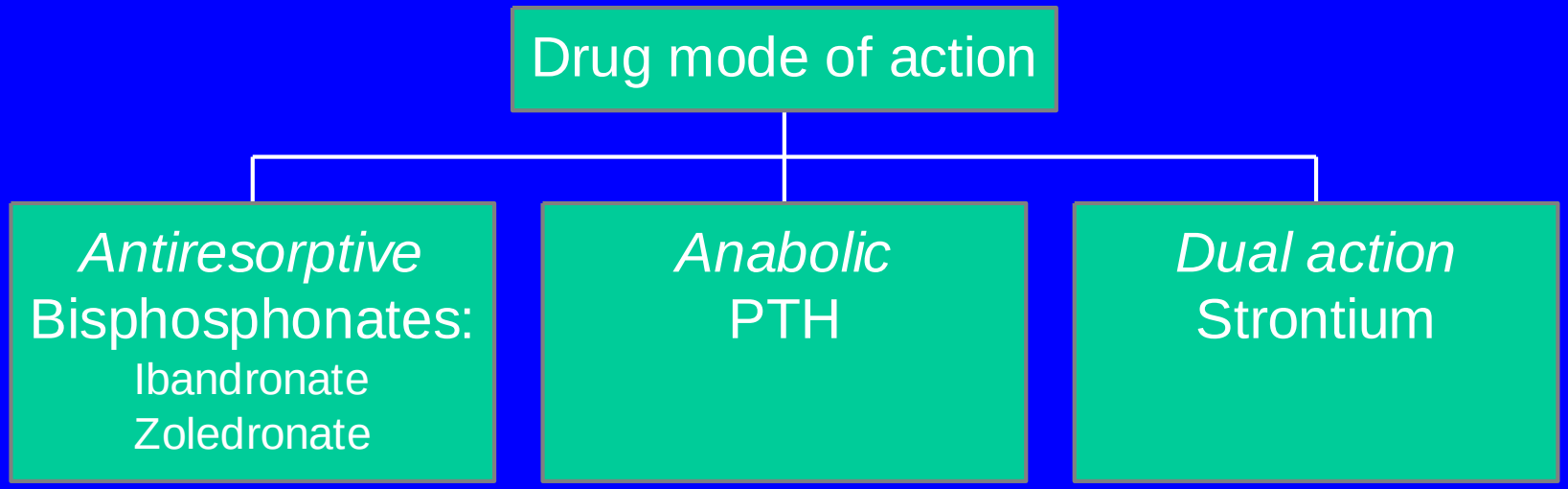
The scale of the problem

	Hip	Spine	Wrist
Lifetime risk (%)			
Women	14	11	13
Men	3	2	2
Cases/yr	400,000	270,000	330,000
Hospitalization (%)	100	2–10	22
Relative survival	0.83	0.82	1.00

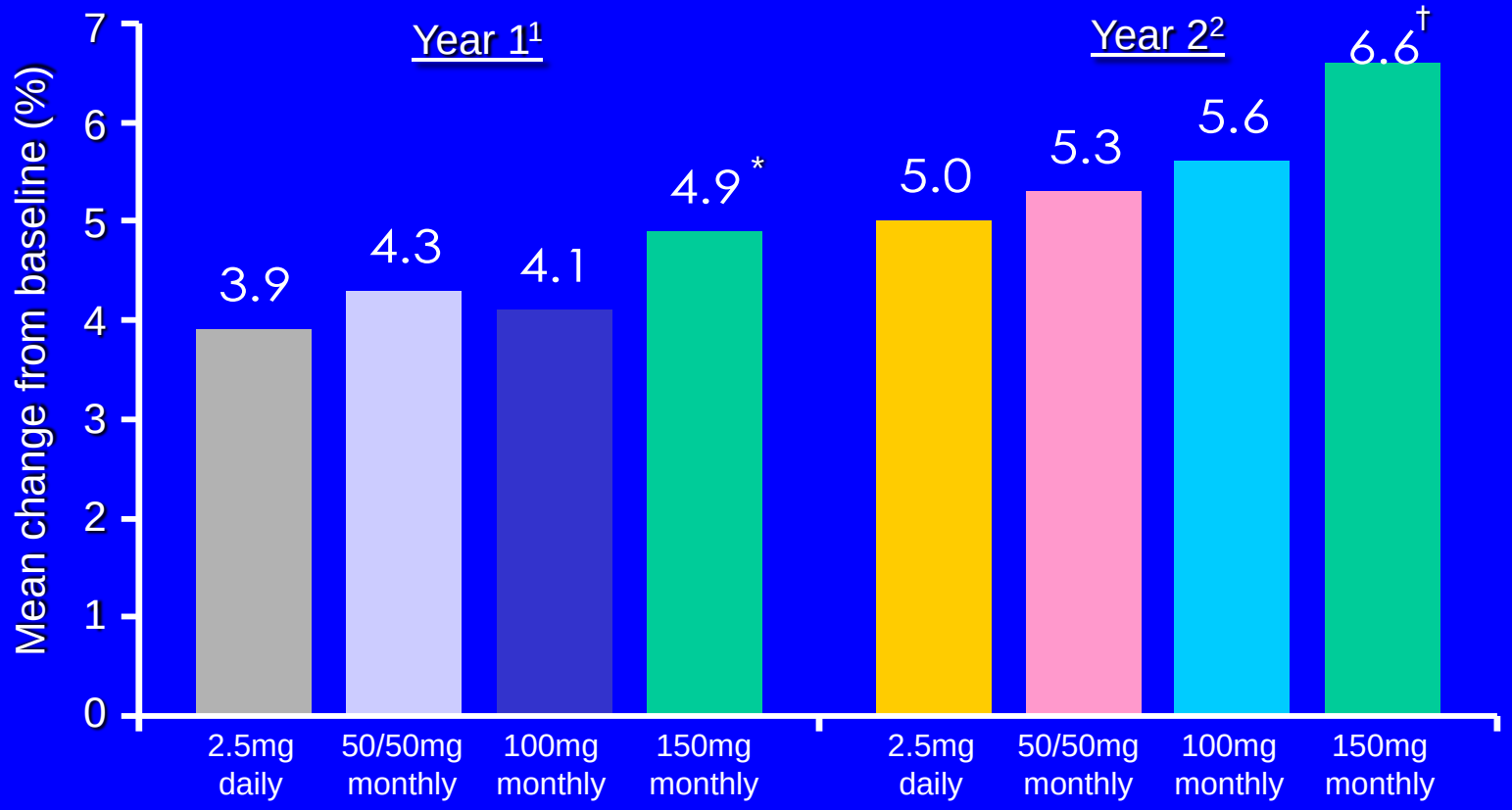
Costs: All sites combined ~ €13 billion

IOF (2002); Cooper C. *Osteoporos Int.* 1999;9 Suppl 2:S2–8.

Drugs for osteoporosis

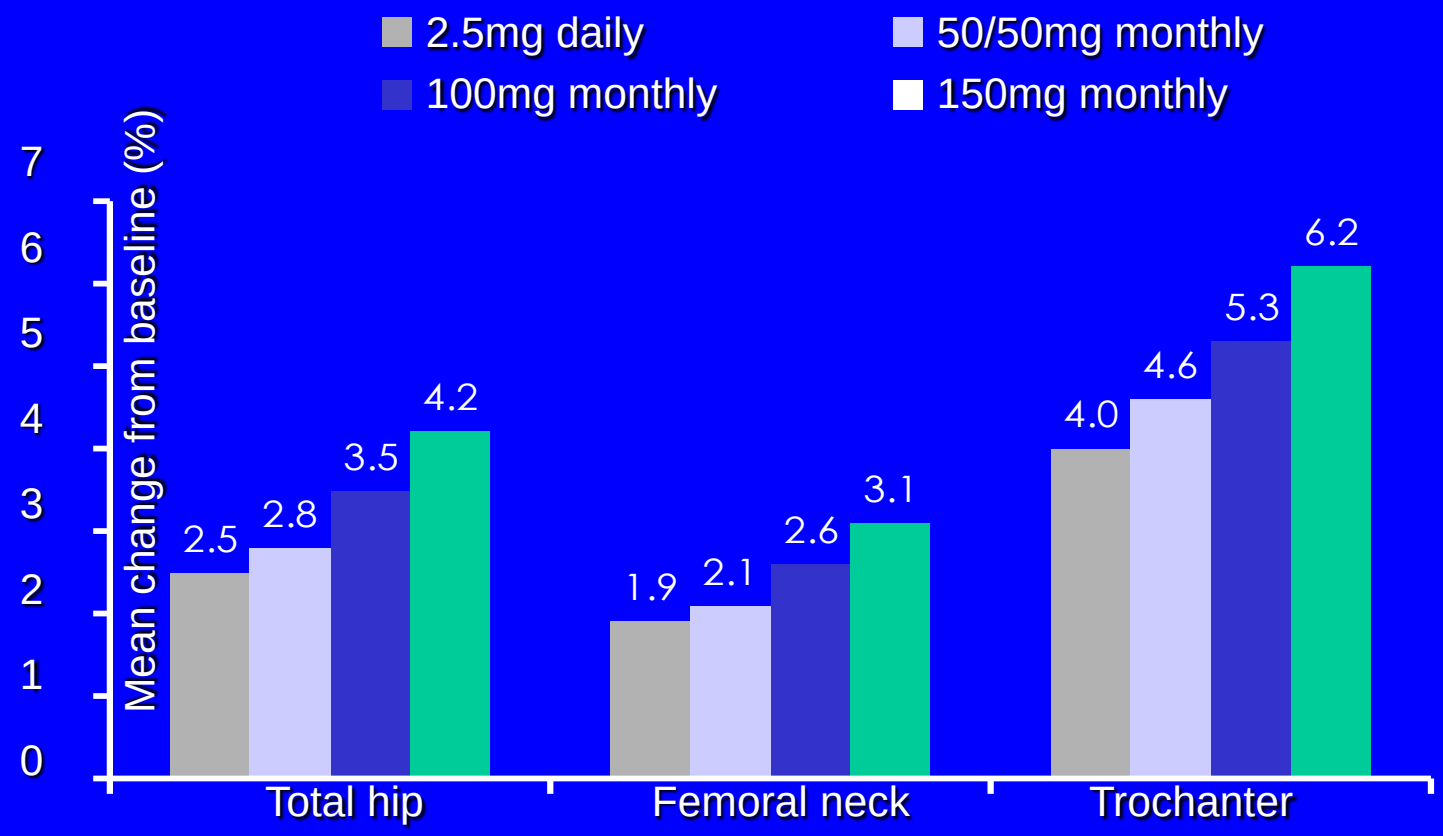


MOBILE study: Change in lumbar spine BMD

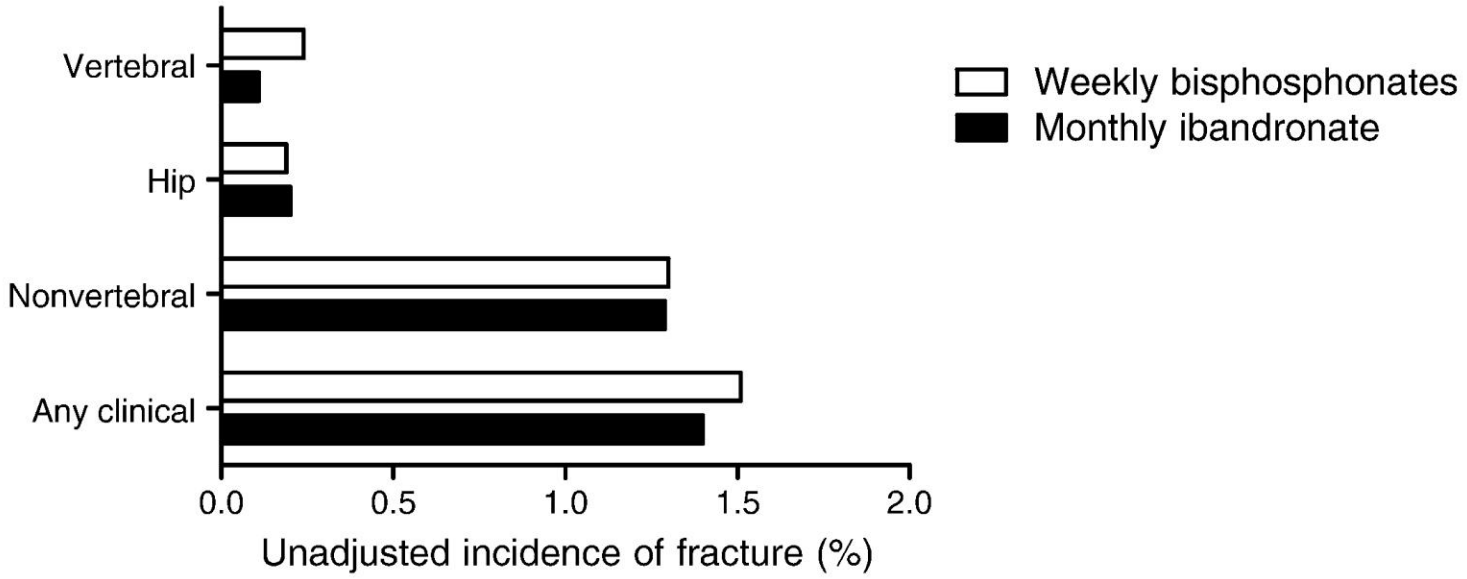


***p=0.002 vs daily ibandronate (2.5mg) †p<0.001 vs daily ibandronate (2.5mg)**

MOBILE study: Change in proximal femur BMD



VIBE

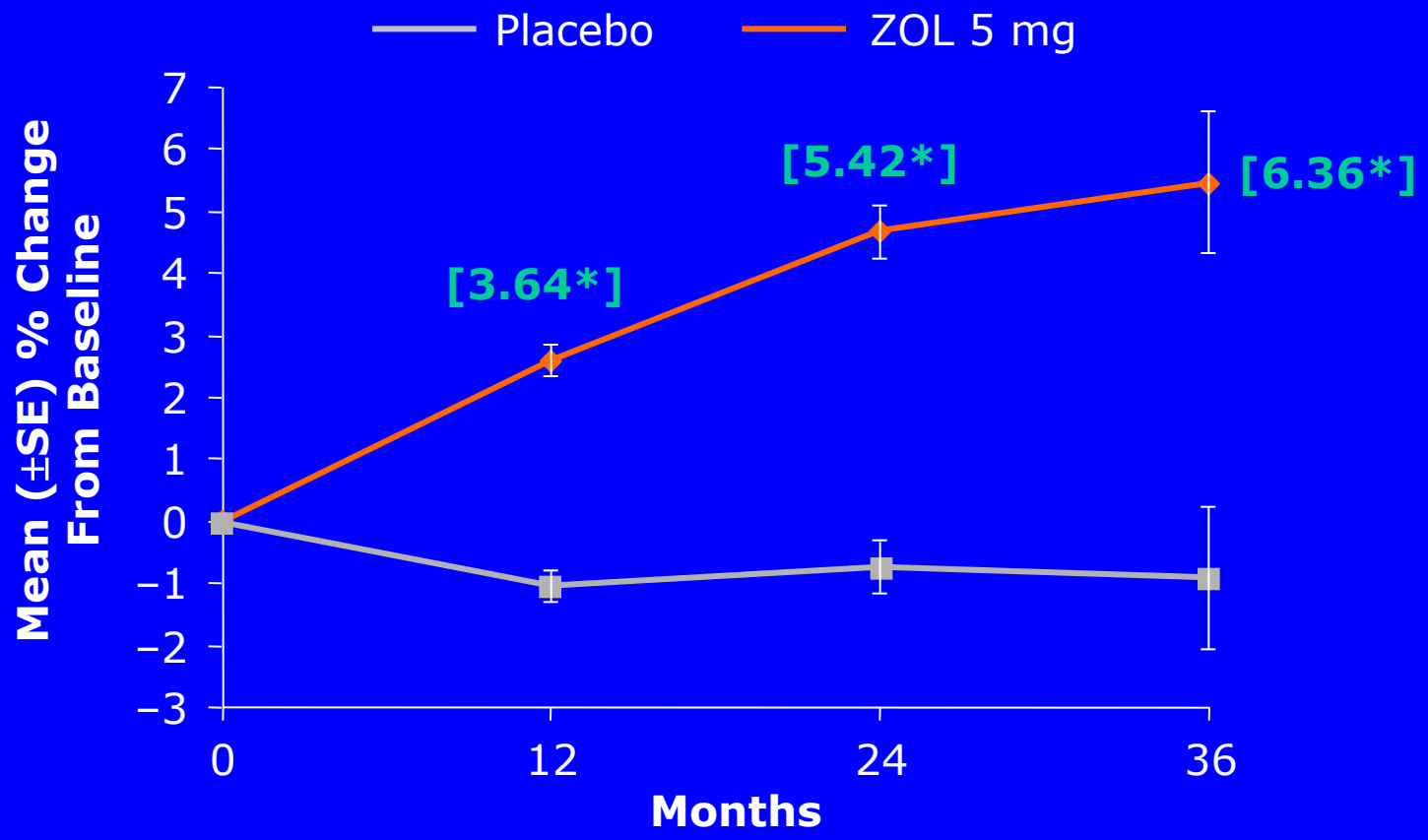


Fracture type	Unadjusted relative risk[a]	Adjusted relative risk (95% CI)[b]	*p*
Vertebral	0.44	0.36 (0.18–0.75)	0.006
Hip	1.07	1.06 (0.61–1.83)	0.840
Nonvertebral	0.97	0.88 (0.71–1.09)	0.255
Any clinical	0.90	0.82 (0.66–1.00)	0.052

Ibandronate: summary

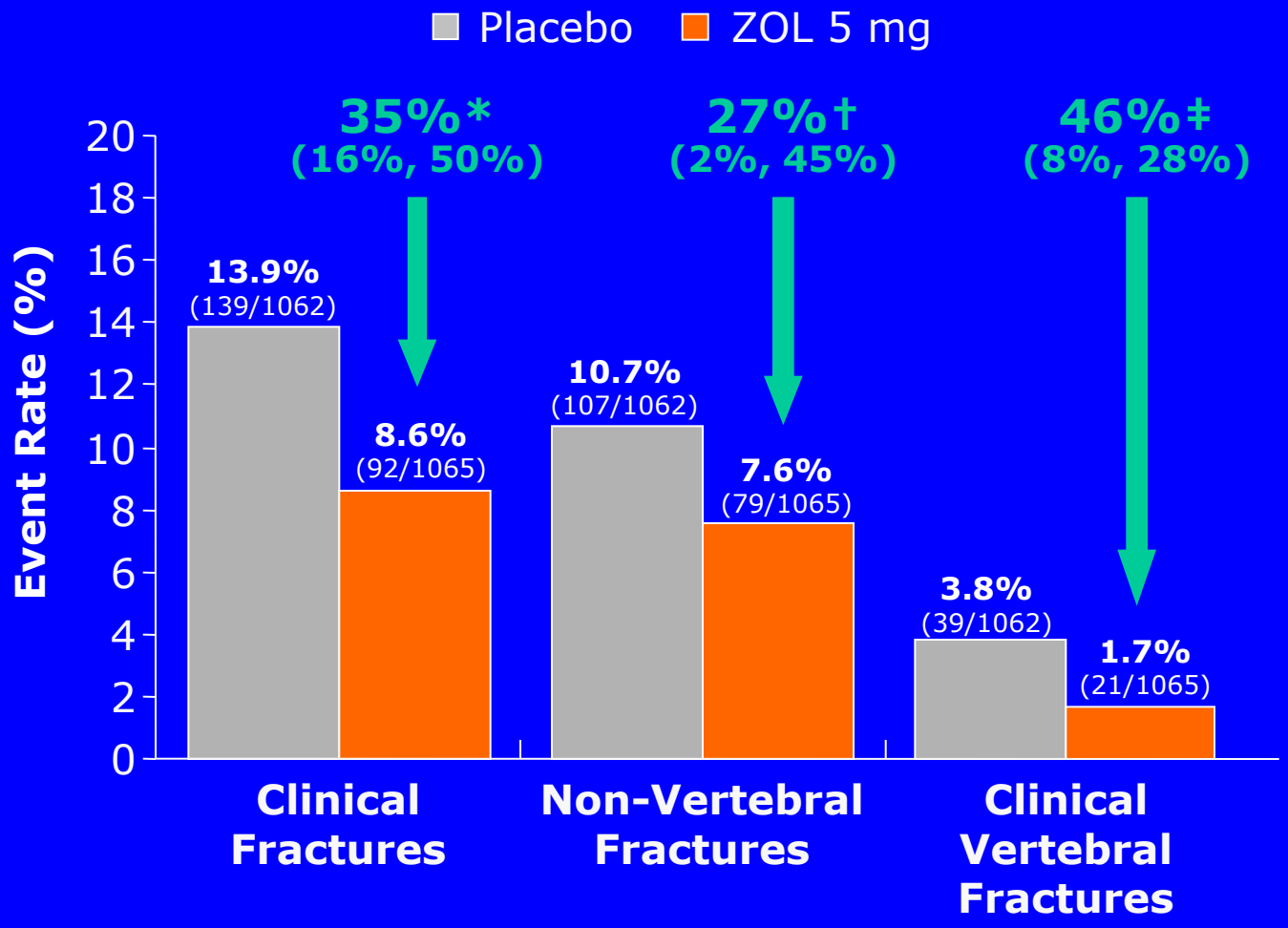
- Improves BMD at all sites
- Shown to reduce vertebral, but not hip fractures
- Available as oral monthly dose, or 3 monthly iv dose

Change in Total Hip BMD Over 3 Years with Zoledronate

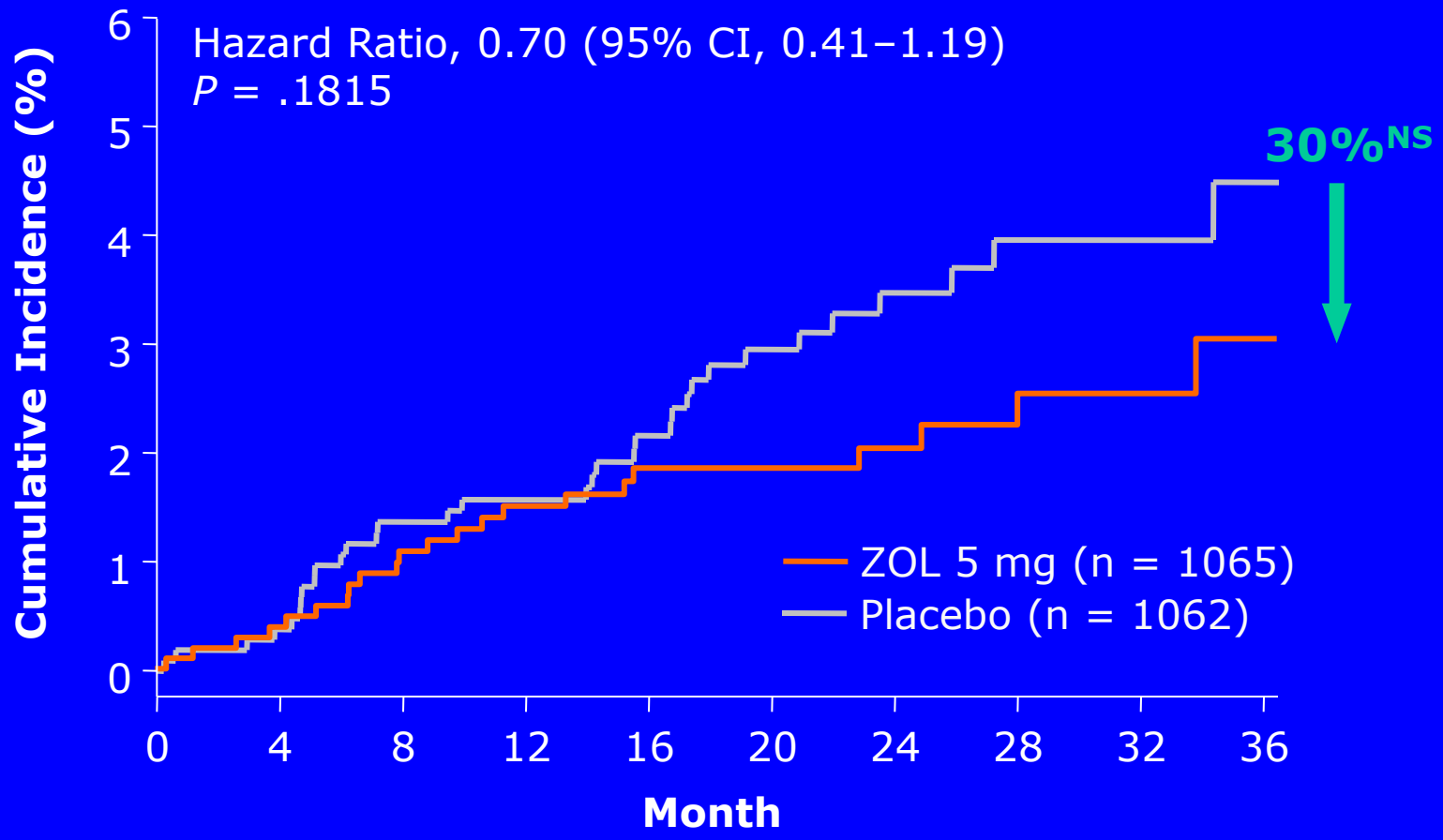


ZOL 5 mg	n=	681	405	128
Placebo	n=	683	400	124

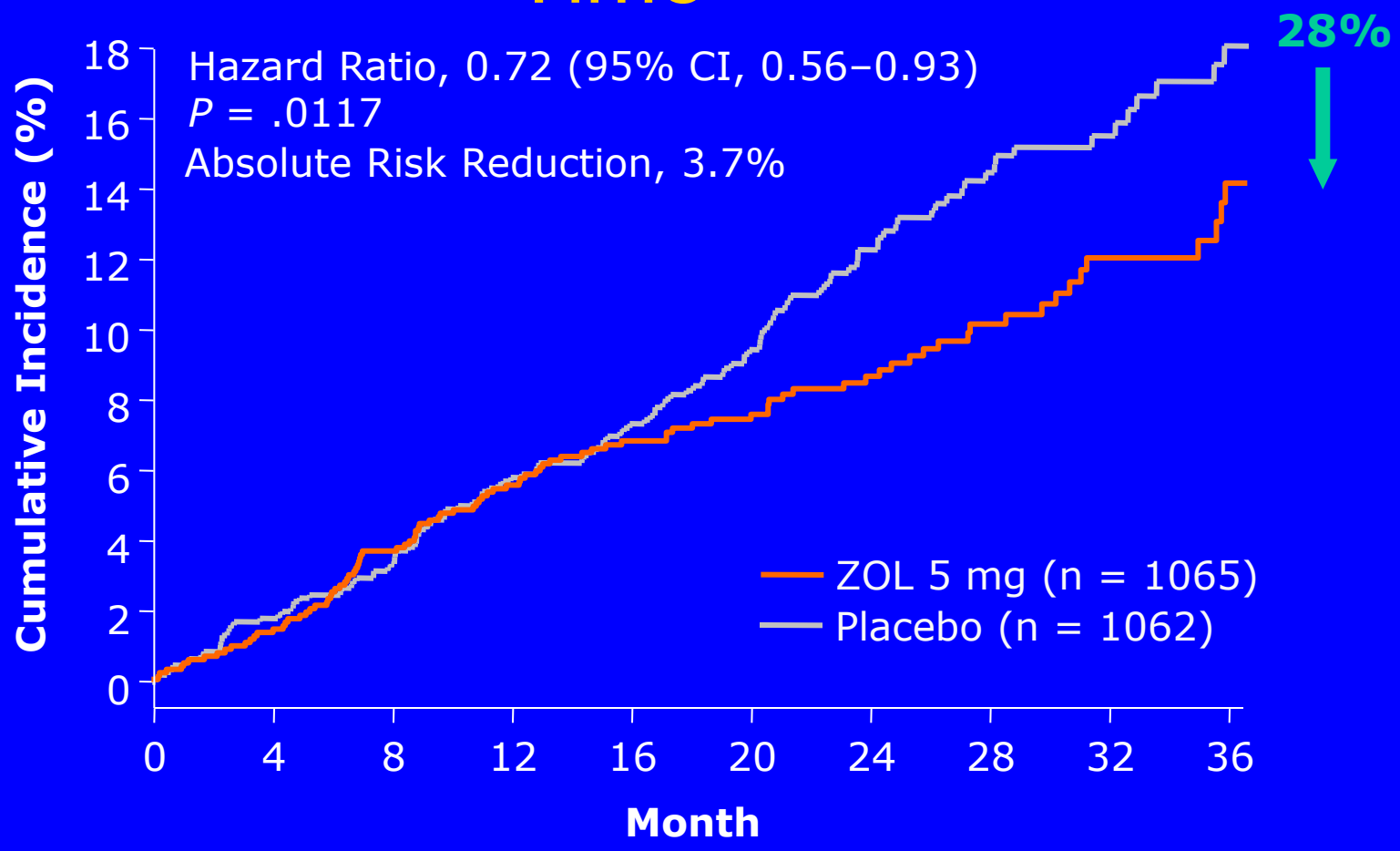
Fracture reduction with zoledronate



Effect on Hip Fractures Over Time



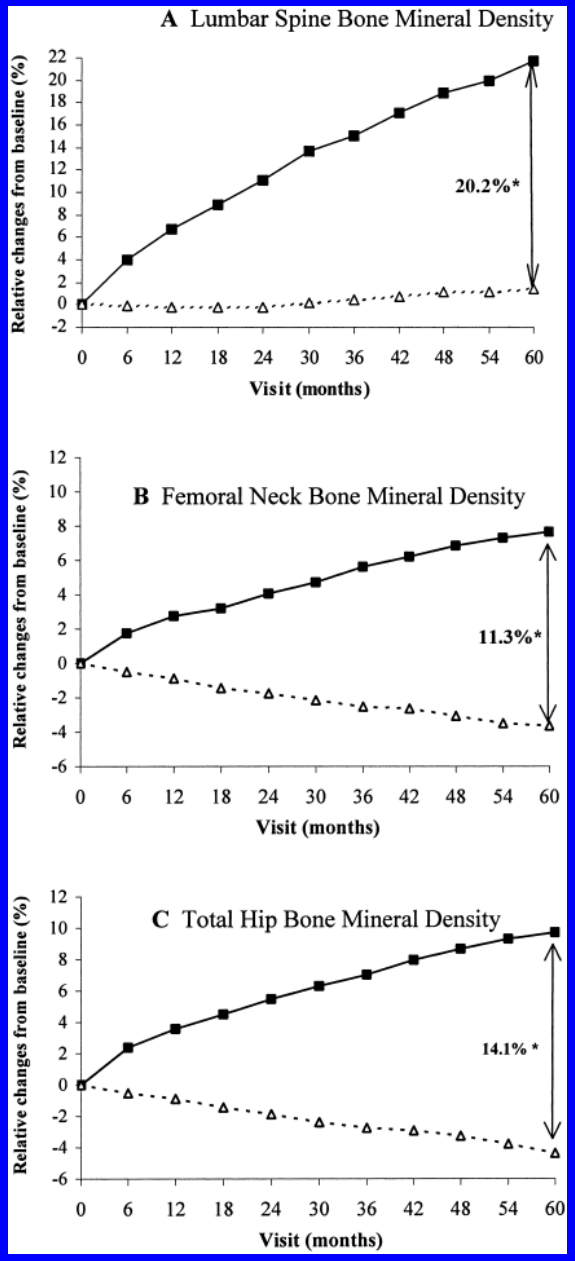
Risk of All-Cause Mortality Over Time

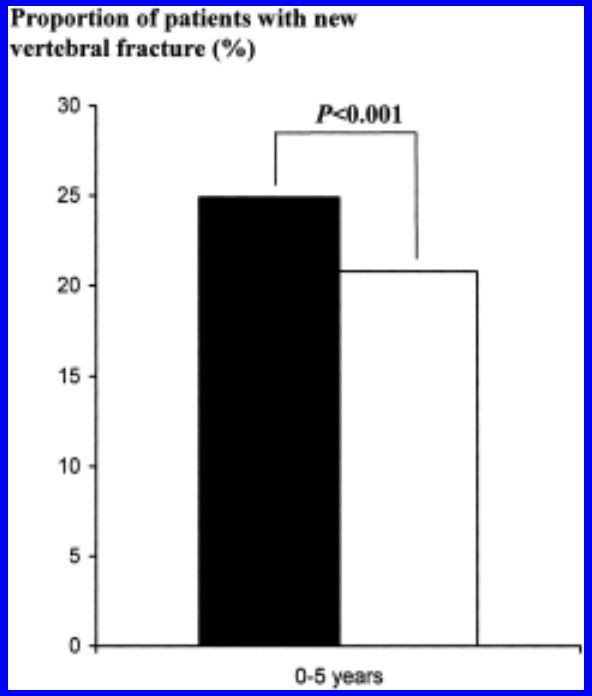


Zoledronate: summary

- Anti-fracture efficacy at all sites
- Reduced mortality in treated group in HORIZON recurrent fracture study ? cause
- Increased risk AF in treated group in HORIZON – Pivotal fracture trial

Strontium


A Lumbar Spine Bone Mineral Density
Relative changes from baseline (%)
22
20
18
16
14
12
10
8
6
4
2
0
-2
20.2%*
0 6 12 18 24 30 36 42 48 54 60
Visit (months)
B Femoral Neck Bone Mineral Density
Relative changes from baseline (%)
12
10
8
6
4
2
0
-2
-4
-6
11.3%*
0 6 12 18 24 30 36 42 48 54 60
Visit (months)
C Total Hip Bone Mineral Density
Relative changes from baseline (%)
12
10
8
6
4
2
0
-2
-4
-6
14.1% *
0 6 12 18 24 30 36 42 48 54 60
Visit (months)

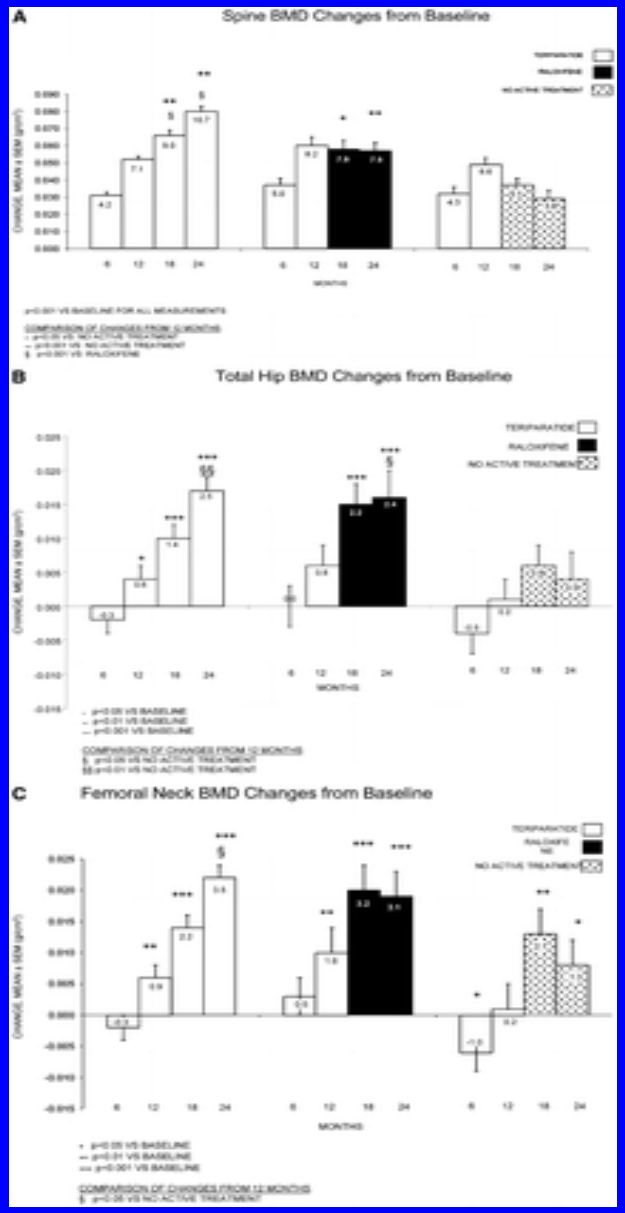

Proportion of patients with new vertebral fracture (%)
30
25
20
15
10
5
0
P<0.001
0-5 years

Strontium – to monitor or not?

- Strontium has a higher atomic number than calcium, leading to overestimation of BMD when assessed by DXA
- Many correction algorithms proposed but none validated
- BMD overestimation may be 50% due to properties of strontium
- What to do on drug discontinuation?
- A role for markers of bone turnover?

PTH

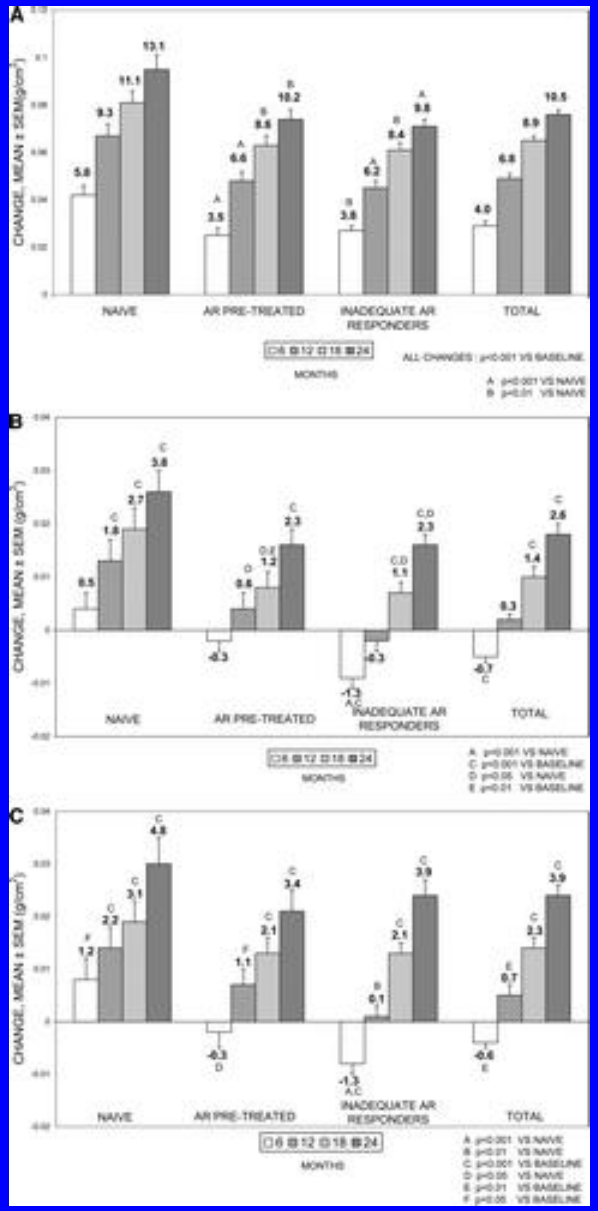
- Available as
  - (i) recombinant human PTH [1-34]
  - (ii) full length recombinant molecule (hPTH 1-84)
- Reduces vertebral fractures by 65% and non-vertebral fractures by 53%
- Studies not powered for hip fracture
- 24 month course recently approved in UK



Sequential treatment after Teriparatide

- Antiresorptive therapy is necessary after PTH course
- Hierarchy of therapeutic effect

JBMR 2009; 24: 726-736



Effect of treatment prior to Teriparatide

- Effect seen greatest in treatment naïve group
- Significant increases seen in all 3 groups

JBMR 2008; 23: 1591-1600

Antifracture efficacy of pharmacological interventions for osteoporosis

Intervention	Vertebral	Non-vertebral	Hip
Alendronate	+	+	+
Risedronate	+	+	+
Zoledronic acid	+	+	+
Etidronate	+	-	-
Ibandronate	+	+*	-
Raloxifene	+	-	-
PTH (1-84)	+	-	-
Teriparatide	+	+	-
Strontium ranelate	=	=	=*

* post-hoc analysis in high risk group

Denosumab

- RANKL pathway involved in bone breakdown
- OPG inhibits RANK-RANKL
- OPG not available clinically
- Denosumab = human monoclonal Ab to block RANKL
- SC injection every 6/12
- 5% increase in spine BMD at 1 year
- 80% decrease in CTX

NICE – areas of controversy

- Threshold for treatment is different for alendronate than other therapies
- Clinical risk assessment complicated
- No mention of FRAX^{tm}

Primary prevention: first treatment option

- Initial treatment offered: alendronate

Postmenopausal women aged	Independent clinical risk factor for fracture	Indicator of low BMD	Osteoporosis confirmed
younger than 65 years	1 or more **and**	at least one additional indicator	Required
65–69 years	1 or more	n/a	Required
70 years and older	1 or more **or**	Yes	Required In women ≥ 75 years: not required if two or more clinical risk factors or indicators of low BMD

Primary prevention: alternative treatment option (1)

- Alternative treatment – risedronate or etidronate when women:
  - are unable to comply with administration of, or have a contraindication to or are intolerant of alendronate **and**
  - have a combination of T-score, age and number of clinical risk factors as outlined in the table.

	Number of independent clinical risk factors for fracture		
Age (years)	**0**	**1**	**2**
65–69	[a]	−3.5	−3.0
70–74	−3.5	−3.0	−2.5
75 or older	−3.0	−3.0	−2.5

[a] Treatment with risedronate or etidronate is not recommended.

Primary prevention: alternative treatment option (2)

- Alternative treatment – strontium ranelate when women:
  - are unable to comply with administration of, or have a contraindication to or are intolerant of alendronate and either risedronate or etidronate **and**
  - have a combination of T-score, age and number of clinical risk factors as outlined in the table.

	Number of independent clinical risk factors for fracture		
Age (years)	**0**	**1**	**2**
65–69	[a]	−4.5	−4.0
70–74	−4.5	−4.0	−3.5
75 or older	−4.0	−4.0	−3.0

[a] Treatment with strontium ranelate is not recommended.

Secondary prevention: first treatment option

- Initial treatment offered: alendronate
  - Postmenopausal women with confirmed osteoporosis
  - A DXA scan may not be required in women aged 75 or over

Secondary prevention: alternative treatment option (1)

- Alternative treatment – risedronate or etidronate when women:
  - are unable to comply with administration of, or have a contraindication to or are intolerant of alendronate **and**
  - have a combination of T-score, age and number of clinical risk factors as outlined in the table.

	Number of independent clinical risk factors for fracture		
Age (years)	**0**	**1**	**2**
50–54	[a]	−3.0	−2.5
55–59	−3.0	−3.0	−2.5
60–64	−3.0	−3.0	−2.5
65–69	−3.0	−2.5	−2.5
70 or older	−2.5	−2.5	−2.5

[a] Treatment with risedronate or etidronate is not recommended.

Secondary prevention: alternative treatment option (2)

- Alternative treatment – strontium ranelate or raloxifene when women:
  - are unable to comply with administration of, or have a contraindication to or are intolerant of alendronate and either risedronate or etidronate **and**
  - have a combination of T-score, age and number of clinical risk factors as outlined in the table.

	Number of independent clinical risk factors for fracture		
Age (years)	**0**	**1**	**2**
50–54	[a]	−3.5	−3.5
55–59	−4.0	−3.5	−3.5
60–64	−4.0	−3.5	−3.5
65–69	−4.0	−3.5	−3.0
70–74	−3.0	−3.0	−2.5
75 or older	−3.0	−2.5	−2.5

[a] Treatment with raloxifene or strontium ranelate is not recommended.

Secondary prevention: alternative treatment option (3)

- Alternative treatment – teriparatide when women:
  - are unable to take, have a contraindication to or are intolerant of alendronate and either risedronate or etidronate, **or**
  - have a contraindication to, or are intolerant of strontium ranelate **or**
  - have had an unsatisfactory response to treatment with alendronate, risedronate or etidronate **and**
  - have a combination of T-score, age and number of fractures as outlined in the table.

Age (years)	T-score	Fractures
> 65 years	−4.0 SD or below	–
> 65 years	−3.5 SD or below	More than two
55–64 years	−4 SD or below	More than two

FRAX®.....

integrates clinical risk factors, with or without femoral neck BMD, to calculate the 10-year probability of a major osteoporotic fracture and hip fracture for several countries, including the UK

(www.shef.ac.uk/FRAX)

FRAX WHO Fracture Risk Assessment Tool

HOME | CALCULATION TOOL | FAQ | REFERENCE

Your Country : UK Name / ID : Patient About the risk factors

Weight Conversion:

pound: [ ] convert

1 pound = 0.453592 kg

Height Conversion:

inch : [ ] convert

1 inch = 2.54 cm

Questionnaire:

1. Age (between 40-90 years) or Date of birth
   Age: 65 Date of birth: Y: M: D:
2. Sex: ○ Male ● Female
3. Weight (kg): 65
4. Height (cm): 165
5. Previous fracture: ○ No ● Yes
6. Parent fractured hip: ● No ○ Yes
7. Current smoking: ● No ○ Yes
8. Glucocorticoids: ● No ○ Yes
9. Rheumatoid arthritis: ● No ○ Yes
10. Secondary osteoporosis: ● No ○ Yes
11. Alcohol 3 more units per day: ● No ○ Yes
12. Femoral neck BMD: T-score -2.5

Clear Calculate

BMI: 24

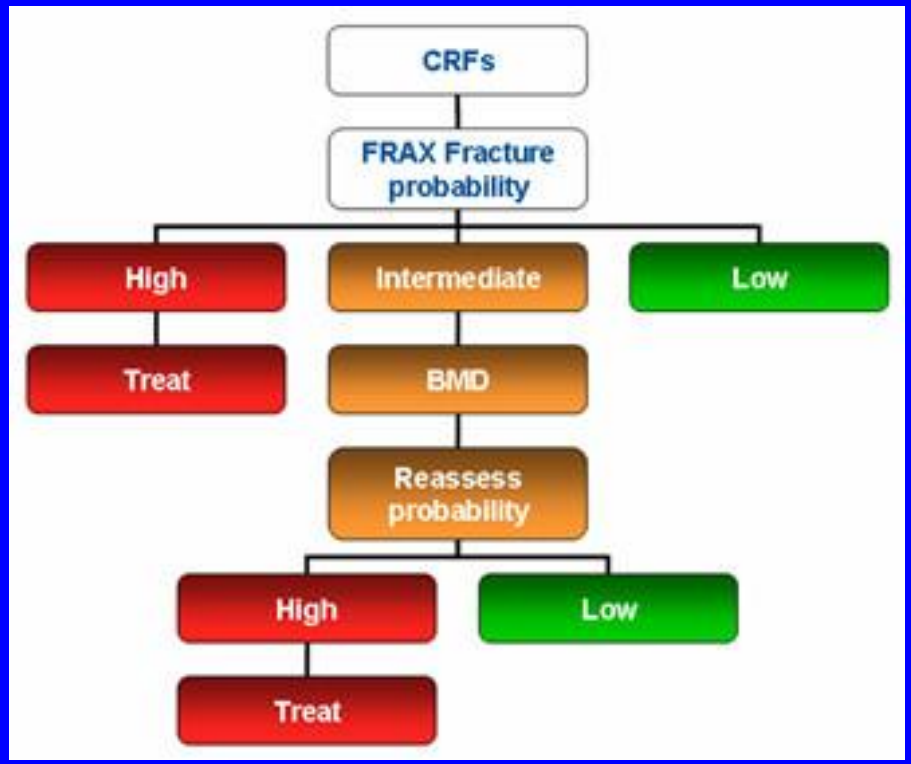
The ten year probability of fracture (%) with BMD

Major osteoporotic fracture	23.9
Hip fracture:	8.0

The National Osteoporosis Guideline Group* (NOGG)……

- Was established to provide a clinical guideline for the management of men and women at high fracture risk, particularly to integrate the output from FRAX® with current clinical management of osteoporosis
- Provide assessment thresholds for the use of BMD i.e. the fracture probabilities at which a BMD test might or might not be recommended
- Revise intervention thresholds, based on the existing RCP case-finding strategy, to provide the fracture probability at which intervention is recommended

Management algorithm for the assessment of patients at risk of fracture



http://www.shef.ac.uk/NOGG

Questions?