

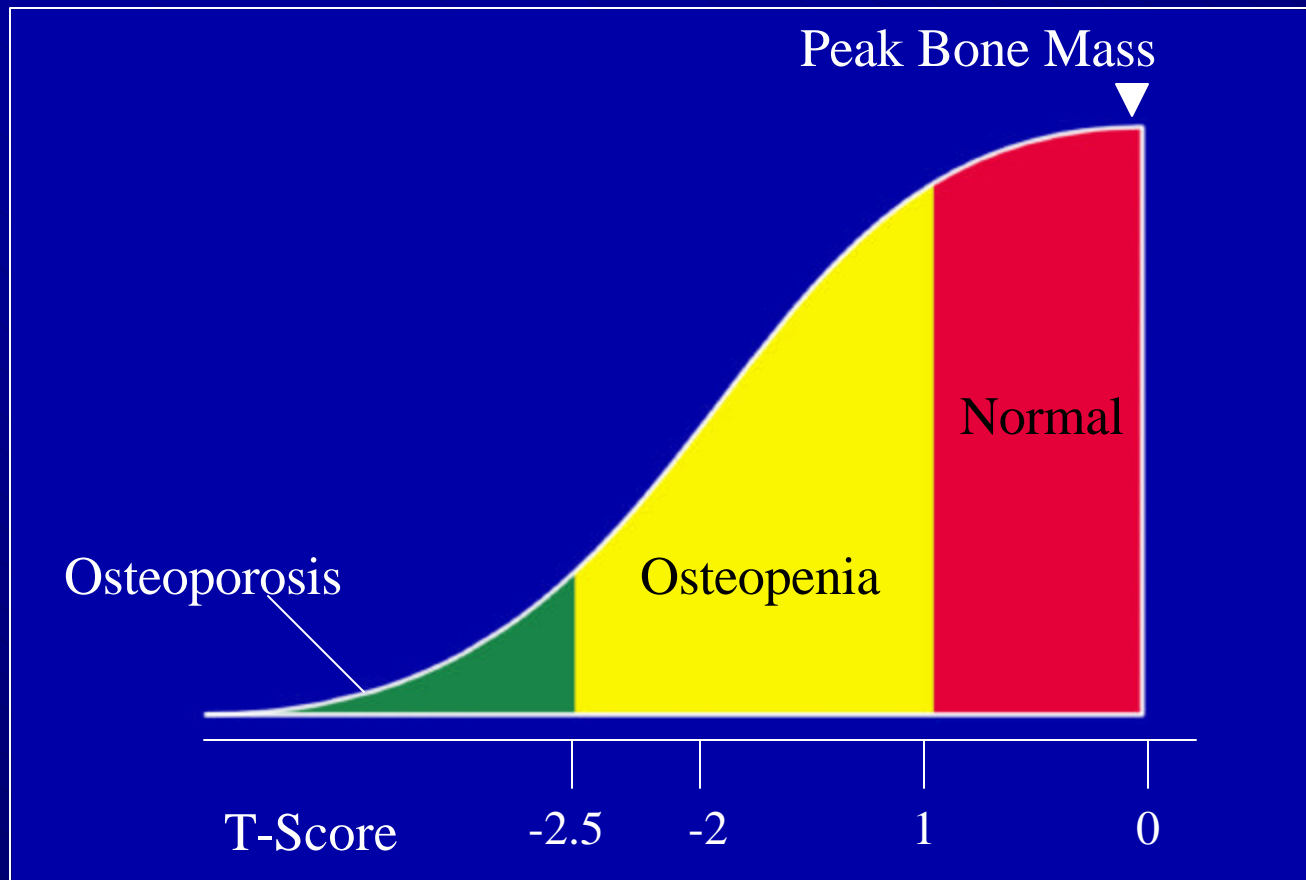
Osteoporosis:

The era of the bisphosphonates

Part 2

PowerPoint Slides

World Health Organization (WHO) guidelines for osteoporosis



Current treatment options for osteoporosis

Treatment	Dosage Form
Calcium and vitamin D Hormone replacement therapy (HRT) Calcitonin Selective estrogen receptor modulators (SERMs) Bisphosphonate: alendronate Bisphosphonate: risedronate Parathyroid hormone (PTH) (teriparatide)	Oral (daily) Oral, transdermal Nasal spray (daily) Oral (daily) Oral (daily or weekly) Oral (daily or weekly) Daily subcutaneous

Calcium and Vitamin D

- Used as adjunctive therapies to the more potent antiresorptives
- Benefits of calcium are modest:
 - Meta-analysis shows small positive effect on BMD
 - Trend towards vertebral fracture reduction
 - No conclusions about nonvertebral fractures
- Chapuy et al:
 - Hip fractures reduced by 43% ($p= 0.043$)
 - Nonvertebral fractures reduced by 32% ($p= 0.015$)

Hormone Replacement Therapy (HRT)

- WHI study halted when risk of HRT exceeded benefits
 - Hip and vertebral fractures reduced by 34%
 - All osteoporotic fractures reduced by 24%
 - Slight increases in risk of heart attacks, strokes, and blood clots
 - Risk of invasive breast cancer increased by 25%
 - No increase in all-cause mortality

Selective estrogen receptor modulators (SERMs)

- Raloxifene is the first SERM approved for osteoporosis
 - Produces estrogen-agonist effects on bone and estrogen-antagonist effects on endometrial and breast tissue
 - Minimizes undesirable effects of estrogen
- Meta-analysis shows positive effects on bone density; these increased over time and were independent of dose
- Significant increases in BMD for total body, lumbar spine, combined forearm, and combined hip BMDs ($p < 0.01$)

Calcitonin

- A polypeptide hormone that inhibits bone resorption by osteoclasts
- Recommended as an alternative to HRT or alendronate
- Results of meta-analysis of randomized studies:
 - 54% reduction in vertebral fractures
 - No effect on nonvertebral fractures
 - Results of largest study in meta-analysis (PROOF) compromised by large dropout rate

FIT: Risk reduction of alendronate vs. placebo (n= 3658)

Fracture class	Risk reduction	p-value
Radiologic vertebral	48%	< 0.001
Multiple vertebral (radiologic)	87%	< 0.001
Clinical vertebral	45%	0.003
Any clinical	30%	< 0.001
Nonvertebral	27%	< 0.001
Nonvertebral (osteoporotic)	36%	0.002
Hip	53%	0.005
Wrist	30%	0.038

FIT: Number of patients needed to treat with alendronate for five years to prevent selected types of fractures

Fracture class	Women with existing vertebral fractures	Women without vertebral fractures and T-score <-2.5
Any radiologic fracture	8	29
Any clinical	13	11
Any Nonvertebral	21	12
Hip	46	66

Results of meta-analysis of risedronate trials

- Vertebral fractures reduced by 35%
- Nonvertebral fractures reduced by 27%
- Pooled estimate of difference in percent change in BMD (risedronate vs. placebo)
 - 4.54% for the lumbar spine
 - 2.75% for the femoral neck

Results of VERT trial (risedronate 5 mg/day)

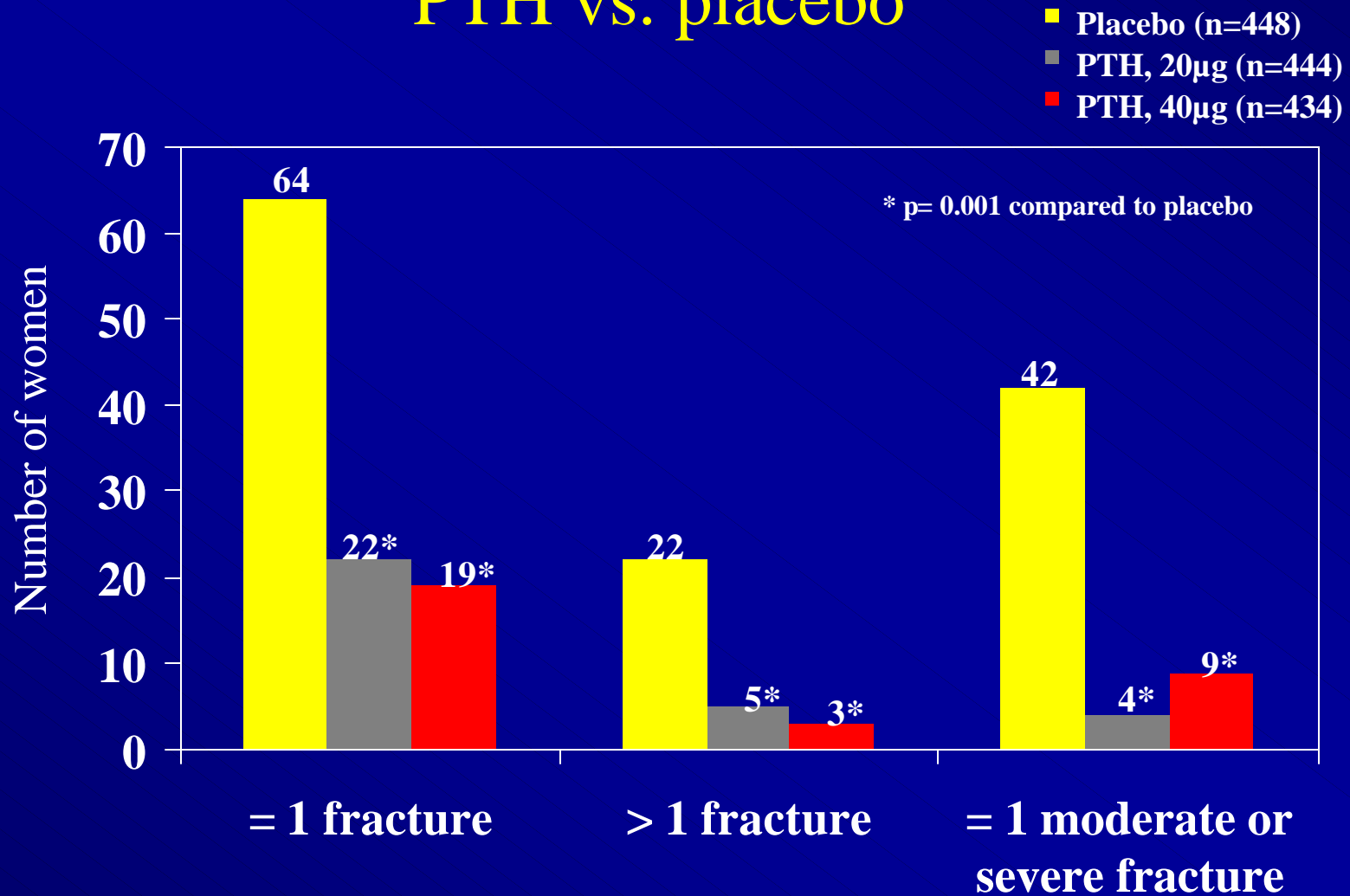
- New vertebral fractures reduced by 41% (p= 0.003)
- Nonvertebral fractures reduced by 39% (p= 0.02)
- BMD increased significantly
- Results compromised by high dropout rate

Effect of risedronate on hip fracture

- Overall reduction in hip fracture: 30% ($p=0.02$)
- Reduction in hip fracture among women aged 70-79 with osteoporosis: 40% ($p=0.009$)
- No reduction seen in women over age 80 with nonskeletal risk factors
- Results compromised by lack of follow-up in 36% of patients

Radiographic evidence of new vertebral fractures:

PTH vs. placebo



Estimate of relative risk reduction of available osteoporosis agents

Intervention	Risk reduction (95% CI)	p-value	Risk reduction	p-value
Calcium	33%	0.14	14%	0.66
Vitamin D	37%	<0.01	23%	0.09
HRT*	34%	0.12	13%	0.10
Raloxifene	40%	0.01	9%	0.24
Calcitonin [†]	21%	0.05	20%	0.16
Alendronate	48%	< 0.01	49% * *	< 0.01
Risedronate	46%	0.01	27%	< 0.01

* Does not include WHI results

* * Alendronate doses of 10 -40 mg

[†] Estimate obtained from the PROOF trial