

Osteoporosis: Who to Treat and For How Long?

Endocrinology Topics for Clinicians
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Disclosure and Conflict of Interest

I receive research grants and consulting fees from the following companies:

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Outline

- Choosing who to treat
- Effectiveness of current therapies
- How long to use bisphosphonates

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Introduction

- We have very effective treatments to reduce fracture risk in patients with or at risk of osteoporosis ¹
- The clinical challenges are
 - to identify the appropriate patients to treat
 - to select among the treatment options
 - to use the drugs in the most effective way

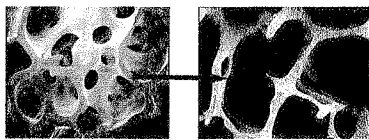
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¹Delmas PD, *Lancet* 2000;359:2018

Osteoporosis: The Definition



- impaired bone strength
 - low BMD
 - poor bone quality
- increased fracture risk



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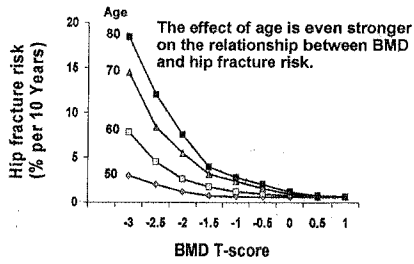
Images Courtesy of Dr. David Dempster

Osteoporosis Diagnosis and Treatment

- The diagnosis of osteoporosis is based on BMD (T-score -2.5)
- Most patients with fracture do not have osteoporosis by BMD criteria
- BMD is but one of several important risk factors for fracture
- We must distinguish between making diagnosis of osteoporosis (a risk factor) and assessing risk of fracture

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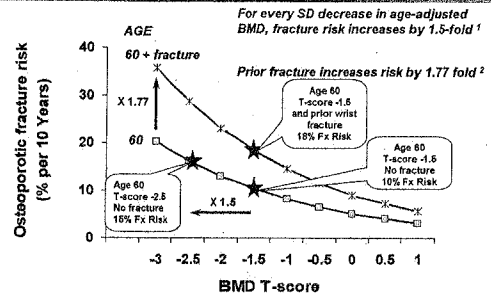
BMD and Hip Fracture Risk



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Kanis et al, *Osteopor Int* 2001

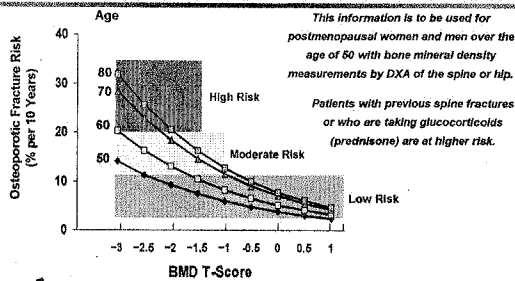
Estimating Fracture Risk



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¹Core data from Kanis et al, *Osteopor Int* 2001;12:889-896
²Kanis JA, et al. *Bone*. 2005;38:375-382

Bone Density and Fracture Risk



ORFONK OSTEOPOROSIS CENTER

Core data from Kanis JA, et al. *Osteopor Int*. 2001;12:889-896.
McClung MR. *Current Osteoporosis Reports* 2005;3:67-69.

WHO Scientific Group on Fracture Risk Reporting

OBJECTIVES:

- to base treatment decision on absolute risk
- to optimise sensitivity for fracture risk prediction
- case finding strategy
- with or without BMD
- men and women
- applicable to primary care setting
- cost-effective setting
- scientific rigour and international validity

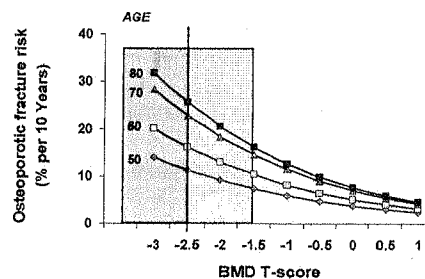
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WHO Absolute Risk Prediction Model

- Input of up to 7 clinical risk factors
- Output will be 10-year probability of experiencing a fracture of the hip, spine, humerus or wrist fracture
- Will be based, where possible, on country- or ethnic-specific fracture incidence rates
- Intervention threshold will be determined by the health care resources and priorities of different countries
- Recommendations for treatment will be based on absolute fracture risk – not simply on T-scores

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Estimating Fracture Risk



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Kanis JA, et al. *Osteoporos Int*. 2001;12:889-896.
McClung MR. *Current Osteoporosis Reports* 2005;3:67-69.

Osteoporosis Treatment 2007

- Bisphosphonates:
 - oral therapy almost always an option in absence of contraindication (swallowing difficulty)
 - IV therapy when po not an option
- Raloxifene: when concern is risk of spine fracture but not hip fracture
- Calcitonin: rarely a first choice
- Estrogen: approved for prevention but not treatment
 - Not recommended for long-term use in women without symptoms
- Teriparatide: for "high risk" patients

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Bisphosphonates and Osteoporosis

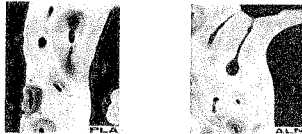
- Inhibit osteoclast proliferation, activity and lifespan
- Reduce indices of bone turnover and increase bone density at important skeletal sites
- In women with osteoporosis, reduce incidence of
 - vertebral fracture 40-70%
 - multiple vertebral fractures 77-96%
 - hip fracture 40-60%
 - non-vertebral fracture 25-40%
- Mainstay of osteoporosis therapy since 1995

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Bisphosphonates: Reasons to Stop Therapy - Concern About Long-term Safety

- Accumulate in the skeleton; theoretical concern about long-term therapy
 - Accumulation of "micro-cracks"
 - Increase in tissue mineralization Boivin 2000

MICORADIOGRAPHS OF CORTICAL BONE



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Bisphosphonates: Reasons to Stop Therapy - Concern About Long-term Safety

- Accumulate in the skeleton; theoretical concern about long-term therapy
 - Accumulation of "micro-cracks"
 - Increase in tissue mineralization
- Anecdotal concerns about long-term safety in patients
 - Non-healing unusual fractures Odvina 2005
 - Sub-trochanteric fractures (5/9 were on alendronate) Goh 2007

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Bisphosphonates and Non-healing Fractures - "Frozen Bone"

- 9 patients reported slow healing nonvertebral insufficiency fractures
 - Alendronate therapy for 3-8 years in standard doses
 - Fractures of sacrum, rib, pelvis, femoral shaft
 - Re-fracture of femur in patents on GC
 - 3 took ERT
 - 2 took glucocorticoids
 - Bone biopsy: low osteoclastic activity and absent osteoblastic activity
 - NTX-u: 8-54 units (reference 5-65)

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Odvina C et al. *J Clin Endo Metab.* 2005;90:1294-1301

Bisphosphonates: Reasons to Stop Therapy - Persistent Benefit After Stopping

- BMD remains stable or decreases slowly when therapy is stopped
- Markers remain suppressed when alendronate is stopped

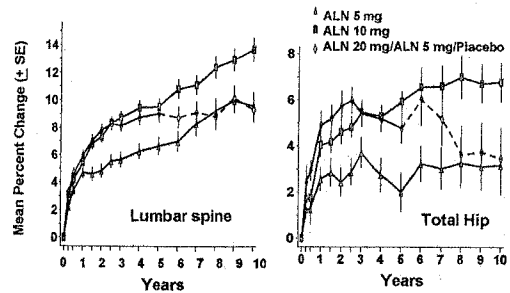
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Bisphosphonates: Long-term Therapy

- Persistent but not progressive inhibition of bone turnover (markers and bone biopsy)
- BMD increase is maintained (hip) or progressive (spine)
- No evidence of waning of effects
- Fracture risk reduction seems to persist
- No new side effects with long-term therapy
- No suggestion of adverse skeletal effect

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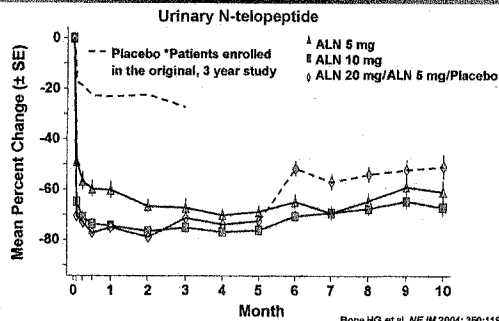
Stopping Alendronate Therapy



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Bone HG et al. *NEJM* 2004; 350:1189-1199.

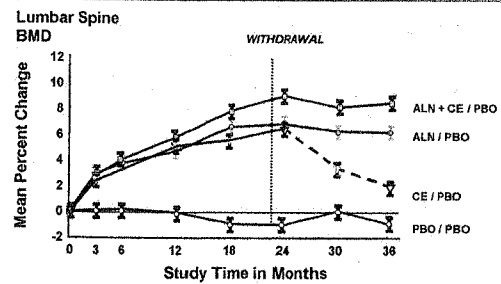
Stopping Alendronate Therapy



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Bone HG et al. *NEJM* 2004; 350:1189

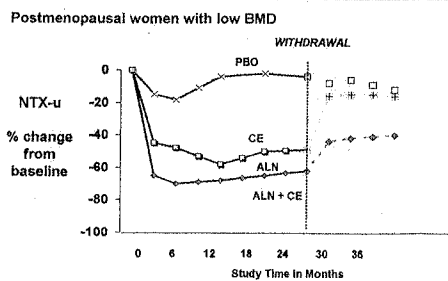
Long-term Alendronate and Estrogen Therapy



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Bone HG et al. *J Clin Endocrinol Metab* 2000;85:720-726
 Greenspan SL et al. *Annals Intern Med* 2002;137:875-883

NTX-u: Stopping Alendronate Therapy

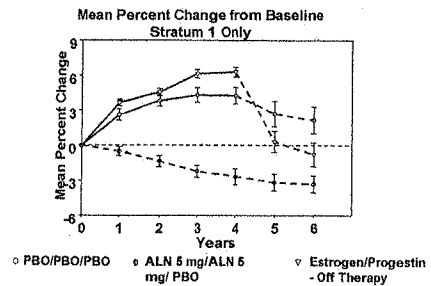


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Greenspan SL et al. *Ann Intern Med* 2002;137:875-83

Effect of Withdrawing Alendronate or E/P: Lumbar Spine BMD: Mean Percent Change (± SE)

Women between ages 45-59

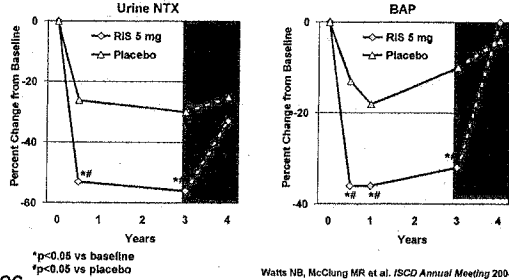


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Wasnich, McClung et al. *Menopause* 2004;1:822-830

Long-term Experience with Risedronate

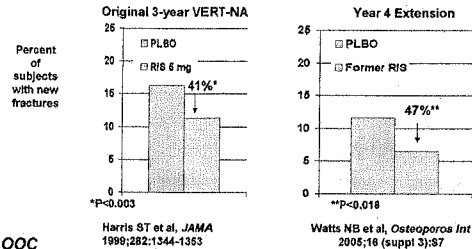
VERT-NA Extension



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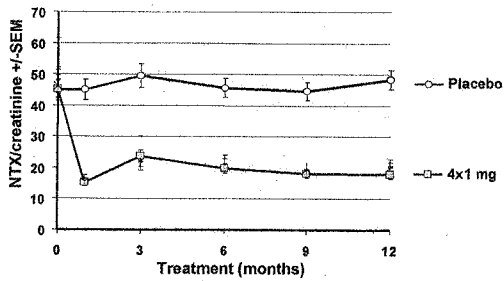
Vertebral Fractures with Risedronate

EFFECT ON NEW RADIOGRAPHIC VERTEBRAL FRACTURES



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Zoledronic Acid: Single Dose Persists for At Least 1 year



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Case 1

- 73 year-old woman diagnosed with osteoporosis and 1 vertebral fracture in 1998.
- Alendronate therapy was begun which has taken without difficulty.
- She has had no new fractures

	1998	2001	2004	2007
BMD T-score: LSpine	-3.1	-2.5	-2.3	-2.3
THip	-2.5	-2.4	-2.4	-2.4

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Case 1: Options

- Continue alendronate 70 mg Q week
- Switch to
 - Another bisphosphonate
 - SERM (raloxifene)
 - Calcitonin
 - Teriparatide
- Discontinue treatment (drug holiday)
- Reduce dose of alendronate

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Case 2

- 53 year-old woman, 2 years postmenopausal, diagnosed with low BMD. No other risk factors.
- Calcium and vitamin D intake are adequate.
- Alendronate therapy was begun which has taken without difficulty.
- She has had no fractures

	2004	2007
BMD T-score: LSpine	-2.1	-1.5
THip	-1.7	-1.5

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COMMENTARIES

Bisphosphonate Therapy: To Stop or Not to Stop?

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Commentary on: Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, Satterfield S, Wallace RB, Bauer DC, Palermo L, Wehren LE, Lombardi A, Santora AC, Cummings SR; FLEX Research Group. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA*. 2006 Dec 27;296(24):2927-38.

Bisphosphonate therapy is now the mainstay of treatment for patients with primary and secondary forms of osteoporosis. This class of drugs has earned this role because of multiple studies documenting the reduction in the incidence of vertebral and other fragility fractures in older women with osteoporosis at moderate to high fracture risk and the prevention of bone loss in many other medical conditions with bisphosphonate therapy (1). After beginning therapy, clinicians then confront the question of how long therapy should be continued. Unless there are obvious safety issues, long-term therapy is generally planned for chronic degenerative disorders such as osteoporosis. Such therapy with bisphosphonates poses unique challenges. The drugs accumulate in the skeleton, theoretical concerns about the safety of long-term treatment with potent inhibitors of bone remodeling exist, and there are suggestions that significant clinical benefit persists well beyond the treatment interval (2-4). Needed is a study in which important clinical outcomes are assessed in patients who have been on bisphosphonate therapy for several years and who then either continue or discontinue treatment. The recent FLEX study by Black and colleagues provides much of that information and is the most comprehensive set of data we have to determine whether there is value or harm in continuing alendronate therapy beyond 3-6 years (5). Even with these

results, there will be debate about the need for and safety of long-term bisphosphonate treatment.

There are several components to the question of whether therapy should be continued or stopped after a finite interval:

1. *Do the effects of treatment persist with continued use or do patients ultimately escape the effects of treatment?*

There is strong and consistent evidence that the anti-remodeling effects of bisphosphonate therapy, assessed by biochemical indices of bone turnover or by histomorphometry, persist for at least seven years with risedronate and ten years with alendronate, and no evidence suggests that patients become refractory to treatment (4;6). However, the objective of osteoporosis treatment is to protect patients from the occurrence of fragility fractures. Direct evidence for the reduction in fracture risk has been demonstrated for only 3 years with ibandronate, 4 years with alendronate and 5 years with risedronate, while less direct evidence suggests that the effectiveness of risedronate persists for up to 7 years (6-8).

2. *Are there safety concerns with long-term use?*

In clinical trials, the bisphosphonates are consistently well tolerated, and no non-skeletal adverse events have been reported in long-term studies that were not recognized in the early short-term trials. Theoretical concern about possible over-

The important comparison of the fracture incidence in patients withdrawn from therapy with that in women who continued to receive either dose of alendronate was an exploratory post-hoc analysis. Three sets of fracture data are provided: clinical and morphometric vertebral fracture and nonvertebral fracture. As often occurs when more than one outcome is evaluated, the results of the three sets of data are not clearly consistent. The incidence of clinical vertebral fractures was higher in those who stopped therapy, arguing strongly that continuing treatment is better than stopping. However, the nonvertebral fracture rate was identical in the two groups, suggesting just as strongly that there was no benefit in continuing treatment compared to stopping.

Which of these results is more convincing? With the exception of vertebral fracture, non-skeletal risk factors such as falls and frailty are important determinants of fracture risk. If the non-skeletal risk factors are not affected by antiresorptive therapy, the ability to detect an effect of bone-strengthening treatment in fracture risk is blunted. Protection from nonvertebral or hip fracture has been documented with bisphosphonate therapy only in postmenopausal women with clear evidence of osteoporosis, diagnosed either by pre-existing vertebral fracture or BMD values that meet the criteria for diagnosis (8;20;21). Many women in FLEX did not have osteoporosis by those criteria, perhaps limiting the ability to evaluate the effectiveness of treatment on nonvertebral fracture risk.

The clinical vertebral fracture outcome may be the least robust of the three fracture endpoints. The ascertainment of clinical vertebral fracture involves significant variables and uncertainties, especially when this outcome is not a predefined endpoint with a clear and consistent definition. Whether a patient experienced a "clinical" vertebral fracture depends upon the sensitivity of the patient to her symptoms and of the clinical investigator to the patient's complaints.

Morphometric vertebral fractures are the most appealing outcome and could serve as

the "tie-breaker" set of data. This has been the primary endpoint in almost all of the major fracture prevention studies. Vertebral fracture is the quintessential fragility fracture and is less influenced by frailty and trauma than are hip and wrist fractures. All patients had similar predefined evaluations with paired spinal X-rays at the beginning and end of the FLEX study. Unfortunately, these results are indeterminate. A modest but statistically insignificant reduction in risk was observed in those who remained on therapy. It is unlikely that the results would have been clearer had all patients received 10 mg daily, for no difference in morphometric vertebral fracture incidence was observed in women receiving either 5 mg or 10 mg daily for 3 years (22).

The FLEX results leave us with substantial uncertainties regarding our clinical question. We can conclude that stopping alendronate therapy after 3-6 years is justified in patients at low or moderate risk of fracture. We can also conclude, with equal conviction, that patients at high risk are better served by remaining on therapy. The most important conclusion from FLEX is that there was no suggestion of skeletal harm with continued treatment. No signal of increased fracture rates with continued therapy was observed, and no new safety concerns with long-term treatment were noted, consistent with data from other long-term treatment studies.

Even these limited results cannot be extrapolated to other bisphosphonates, alternate dosing regimens including intravenous dosing, or other clinical conditions such as osteoporosis associated with glucocorticoid therapy. Despite these limitations, the FLEX study is the best prospective data we will have regarding the long-term safety of oral bisphosphonates.

As much as we wish for firm evidence upon which to base our clinical decisions, we are left with the need to make many decisions with clinical judgment. We must tailor therapy to the needs of our individual patients, being both thoughtful and flexible in our approaches to patient care.

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