Other Treatments of Osteoporosis-
Who Should Get Bisphosphonates

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Drugs Approved for Prevention and Treatment of Postmenopausal Osteoporosis

- Estrogen: Prevention
- Raloxifene: Prevention and Treatment
- Calcitonin: Treatment
- Bisphosphonates: Prevention and Treatment
  - Alendronate
  - Ibandronate
  - Risedronate
  - Zoledronic Acid
- Denosumab: Treatment
- Teriparatide: Treatment
What is the evidence that bisphosphonates are helpful in treating postmenopausal osteoporosis

Alendronate for the Treatment of Postmenopausal Osteoporosis

(Liberman et al. NEJM 1995;333:1437)

- 994 women
- Mean age 64 (45-80)
- Spine T-score <2.5
- ALN 5 mg, 10 mg, or 20 mg 2 years/5 mg one year/day or placebo for 3 years
- New vertebral fractures 48% reduction (3.2 vs. 6.2%) P=0.03
- Decreased progression of vertebral deformities (33 vs. 41%) P=0.028
Risedronate Reduces Risk of First Vertebral Fracture in 1 Year

Risedronate and Hip Fracture in Postmenopausal Osteoporosis

- 5445 women 70-79 yr
  FN T-score <-4.0 or < -3.0 and non-skeletal risk factor for hip fx.
- 3886 women >80 yr
  one non-skeletal risk factor for hip fracture or low FN BMD -4.0 and other criteria
Ibandronate: Vertebral and Nonvertebral Fractures (BONE)

Patients with Prior Vertebral Fractures

Relative Risk = 52%

Placebo (n = 975)
Ibandronate* (n = 977)

Rate of Fractures, %

- New Vertebral Fracture
- New Nonvertebral Fracture

* Ibandronate 2.5 mg daily.

Oral monthly Ibandronate (MOBILE Study) in postmenopausal osteoporosis

(Reginster et al Ann Rheum Dis 2006;65:654)

- MOBILE study (Monthly Oral iBandronate In LadiEs)
- 2 year study
- 1609 women randomised
- T-score <-2.5
- Non-inferiority study
Zoledronic Acid for Postmenopausal Women with Low Bone Density
(Reid et al. NEJM 2002;346:653)

- 354 postmenopausal women age 45-80
- LS T-score lower than -2.0
- Mean age 64
- 1 year study
- zoledronic acid or placebo

Yearly Zoledronic Acid for Postmenopausal Osteoporosis
(HORIZON Pivotal Fracture Trial)
Black et al. NEJM 2007;356:1809
Prolonged response to one zoledronic acid infusion

Grey et al. JBMR 2010;25:2251

- 50 healthy women more than 5 years postmenopausal
- T-score between -1.0 and -2.0
- One infusion 5 mg
- After 3 years BMD higher in ZA group and BTM 40-44% lower

Most Common Adverse Events Within 3 Days After Infusion in HORIZON PFT and RFT

*Patients received acetaminophen up to 72 hours prn after infusion.*
Are bisphosphonates efficacious after 5 years and what happens when they are discontinued.

The Fracture Intervention Trial (FIT): Design

Study Population:
Postmenopausal women with low bone mass

VFx at baseline?

YES
FIT VFA¹
2,027 randomized
55 to 81 years
T-score ≤−1.6*
1° end point: radiographic VFx
2° end point: clinical (symptomatic) fractures
Study duration: 3 years

NO
FIT CFA²
4,432 randomized
54 to 81 years
T-score ≤−1.6*
1° end point: clinical (symptomatic) fractures
2° end point: radiographic VFx
Study duration: 4.25 years

¹After National Health and Nutrition Examination Survey (NHANES) adjustment at baseline.
²VFA = Vertebral Fracture Arm; CFA = Clinical Fracture Arm; VFx = vertebral fracture.
Reduction in VFx at Year 3

<table>
<thead>
<tr>
<th>Radiographic</th>
<th>Clinical</th>
<th>Multiple Radiographic</th>
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<tbody>
<tr>
<td>Patients With Fracture, %</td>
<td></td>
<td></td>
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<tr>
<td>PBO 966</td>
<td>ALN 984</td>
<td>PBO 966</td>
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<tr>
<td>16</td>
<td>12.0%</td>
<td>47% Reduction P&lt;0.001</td>
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PBO = placebo; ALN = alendronate; ARR = absolute risk reduction; VFx = vertebral fracture.


Effect of Alendronate on the Incidence of Hip Fracture: FIT

Patients With History of VFx  Patients Without History of VFx

| FIT VFA¹ T-score ≤–1.6* | | FIT CFA² T-score ≤–2.5* |
|-------------------------|--------------------------|
| Patients With Fracture, % | | |
| PBO n = 1,005 | ALN n = 1,022 | PBO n = 812 | ALN n = 819 |
| 2.2% | 51% Reduction at Year 3 P = 0.047 ARR 1.1% | 2.2% | 56% Reduction at Year 4 P = 0.044 ARR 1.2% |

VFx = vertebral fracture.

¹ After National Health and Nutrition Examination Survey (NHANES) adjustment.
**FLEX: Study Timeline**

FIT: 3 to 4.5 years

FLEX: 5 years

Time Between FIT and FLEX
1 to 2 years

Year

Total Hip BMD Change in FLEX Population:
From Beginning of FIT to Completion of FLEX

Mean Percent Change From FIT Baseline,

F = FIT; FL = FLEX.


Femoral Neck BMD Change in FLEX Population: From Beginning of FIT to Completion of FLEX

- FIT: 3 to 4.5 years
- Time Between FIT and FLEX: 1 to 2 years
- FLEX: 5 years

Mean Percent Change from FIT Baseline, %

- F0: ALN/placebo (n = 437)
- FL: ALN/ALN (pooled 5-mg and 10-mg groups: n = 662)

- 1.9% (p < 0.001)

F = FIT, FL = FLEX

Lumbar Spine BMD Change in FLEX Population: From Beginning of FIT to Completion of FLEX

- FIT: 3 to 4.5 years
- Time Between FIT and FLEX: 1 to 2 years
- FLEX: 5 years

Mean Percent Change from FIT Baseline, %

- F0: ALN/placebo (n = 437)
- FL: ALN/ALN (pooled 5-mg and 10-mg groups: n = 662)

- 3.7% (p < 0.001)

F = FIT, FL = FLEX
**Serum CTx: Mean Absolute Value Change From FIT and FLEX Baselines**

![Graph showing mean absolute value of Serum CTx change from FIT and FLEX baselines across different years.](image)

- FIT: 3 to 4.5 years
- Time Between FIT and FLEX: 1 to 2 years
- FLEX: 5 years

- ALN/placebo (n = 97)
- ALN/ALN (pooled 5-mg and 10-mg groups: n = 139)

*F = FIT; FL = FLEX; CTx = C-telopeptide of type 1 collagen.*


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**FLEX: Incidence of Fractures by Treatment Group**

![Graph showing fracture incidence by treatment group.](image)

- ARR = absolute risk reduction; RR = relative risk; CI = confidence interval.

FLEX: Bone Biopsies

- 31 transilial biopsies performed at conclusion of FLEX, after dual fluorochrome labeling
- Findings
  - No quantitative differences between groups
  - Double fluorochrome label seen in all specimens


FLEX: Summary

- In FLEX, continued alendronate treatment over 5 years resulted in:
  - Maintenance of BMD increases (vs discontinuation)
  - Maintenance of reductions in bone turnover
  - No reduced risk of nonvertebral, radiographically detected vertebral, or hip fractures
  - Reduced relative risk of clinical vertebral fracture
  - No evidence of compromised bone quality
**FLEX: Summary**

- Discontinuation of alendronate treatment in FLEX resulted in:
  - Modest decrease in BMD relative to continuation
  - Gradual rise in biochemical markers of bone turnover
  - More clinical vertebral fractures

**Bone Morphometry Safety Issues**

- In HORIZON PFT,
  - Histomorphometry evaluable in 152 bone biopsies
  - Label seen in all but 1 specimen, indicating ongoing bone remodeling
  - Fracture healing
    - Non-union: 2 in ZOL 5 mg, 1 in placebo
    - Avascular necrosis (hip or knee)
    - 4 in ZOL, 3 in placebo

HORIZON-PFT Extension
(Black et al. JBMR 2012;27:243)
Discontinuing Risedronate
(Eastell et al JCEM 2011;96:3367)

• Postmenopausal osteoporotic women (VERT-MN)
• 8 year study; year 8 off drug
• After 1 yr. discontinuation NTX/Cr increased towards baseline
• TH and trochanter BMD decreased; FN and LS BMD maintained or slightly increased.
Discontinuing Risedronate
(Eastell et al. JCEM 2011;96:3367)

Bisphosphonates: How Long To Treat
Bisphosphonates: How long to treat?

- FDA performed a systematic review of long-term bisphosphonate efficacy
- Focused on studies of at least 3 years with fracture data. Three extension studies.
- FDA looked at composite end-point of all fractures, vertebral and non-vertebral.
- Unlike initial trials, extension primary end-point BMD and not fractures.

Bisphosphonate Extension Studies

(Whitaker et al. NEJM 366:2048)

- Fosamax Fracture Intervention Trial Long-Term Extension (FLEX)
- Reclast Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly-Pivotal Fracture Trial (HORIZON-PFT) Extension
- Actonel Vertebral Efficacy with Risedronate Therapy-Multinational Trial (VERT-MN) Extension
Bisphosphonate Extension Studies

(Whitaker et al. NEJM 366:2048)

Continuation of treatment beyond 5 years: BMD maintained in FN and further increase in LS
Switch to placebo: BMD in FN decreased modestly during 1-2 years then stabilized; LS continued to increase
Initial trials 3000-5000; extension 164-1233 patients.
Fracture protection inconsistent. FLEX clinical vertebral fx; HORIZON PFT morphometric fx.
Bisphosphonate Extension Studies
(Whitaker et al. NEJM 366:2048)

Labeling contains:”Important Limitation of Use Statement” from FDA.

• “The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis”

Bisphosphonate Therapy: For whom and how long?
(Black et al NEJM 2012;366:2051)

Current evidence supports the following:

• Patients with low BMD at FN (<-2.5) after 3-5 years treatment are at highest risk for vertebral fracture and appear to benefit most from continuing treatment

• Patients with existing vertebral fracture who have somewhat higher (not higher than -2.0) BMD may benefit from continuing therapy
**Bisphosphonate Therapy: For whom and how long?**

(Black et al. NEJM 2012;366:2051)

- Patients with FN T-score above -2.0 have low risk of vertebral fracture and unlikely to benefit from continued treatment
- Not all bisphosphonates are alike so recommendations are drug-specific.
- When to reinstitute treatment is unclear and awaits further study.

**Antiresorptive Agent-induced Osteonecrosis of the Jaw**

(ARONJ)
Osteonecrosis of the Jaw


Definition of ARONJ

• Dorland’s Medical Dictionary: necrosis of bone due to obstruction of its blood supply.

• AAOMS: exposed bone in the maxillofacial region persisting for more than eight weeks in a patient who is taking, or has taken, a bisphosphonate and has not had radiation therapy to the head and neck.
**Definition of ARONJ**

• ASBMR: area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to a bisphosphonate and had not had radiation therapy to the craniofacial region.

**Osteonecrosis of the Jaw: Clinical Observations**

• Estimated incidence of 1-10% in patients receiving monthly IV bisphosphonates therapy for metastatic bone disease
• Estimated incidence 1:5,000 to 1:100,000 patient years of bisphosphonates for osteoporosis
• Most cases occur after invasive dental procedures
• Recently reported in cancer patients treated with denosumab.
Potential risk factors for ARONJ
(J Am. Dent Assoc 2011;142:1243)

- Prolonged bisphosphonate use (>2 yrs)
- Older age (>65 yrs)
- Diabetes Mellitus
- Clinically and radiographically apparent periodontitis
- Tooth extractions
- Denture wearing
- Smoking
- Corticosteroids (not consistently found)

Clinical signs and symptoms ARONJ

- Pain
- Soft-tissue swelling and infection
- Loosening of teeth
- Halitosis
- Drainage
- Exposed bone
• “With the possible exception of orthognatic surgery, even dento-alveolar procedures involving periosteal penetration or intramedullary bone exposure (e.g., extractions, implant) … seem to carry a minimal risk for ARONJ”

• “At present, there is insufficient evidence to recommend serum tests, such as sCTX as a predictor of ARONJ risk. In addition, there is insufficient evidence to recommend an antiresorptive “drug holiday” or waiting periods for prevention of ARONJ”
Osteonecrosis of the Jaw and Bisphosphonate Treatment in Osteoporosis
(Proposed Mechanisms)

- Low bone turnover, decreased blood flow, bone cell necrosis and apoptosis (inside-out process).
- Mucosal damage precedes infection and bone necrosis (“outside-in process).
- Inflammation and infection important; angiogenesis inhibition possible
- Osteoclast inhibition causing a refractory osteomyelitis
- Trauma to oral cavity (tooth extraction, implants, ill-fitting dentures), use of immunosuppressive drugs and comorbid conditions are important.

Management:
- Insufficient data on risk factors to allow construction of evidence-based guidelines
- Normal oral health should be suggested
- Treatment of ONJ is empirical (conservative).
- No data to suggest stopping therapy will influence the course of the lesion and improve dental outcomes
- No evidence to delay onset of treatment if undergoing major dental surgery (but best to hold)
Microdamage: Bisphosphonates

Atypical Femur Fractures
Hip Fractures

Atypical Femur Fractures

- Cohort study: national healthcare data
- 39,567 ALN users
- 158,268 untreated controls
- Subtrochanteric and diaphyseal fracture rates: 13/10,000 patient-years untreated women; 31/10,000 ALN users
- Risks of subtrochanteric/diaphyseal fracture similar in pts. who received 9 years or 3 months of ALN
Atypical Fractures
(Odvina et al JCEM 2005, 90: 1294)

- 9 patients who sustained atypical spontaneous fractures after receiving alendronate for 1-8 years
- 4 patients fractures not healed 8-12 mo.
- Histomorphometry: low bone turnover with absence of double label tetracycline

Atypical Fractures
(Odvina et al JCEM 2005:90:1294)
Atypical Subtrochanteric and Femur Fractures

**Atypical Femur Fractures: Major Features**

- Located anywhere along the femur from just distal to lesser trochanter to just proximal to supracondylar flare
- Associated with no or minimal trauma, as in a fall from standing height or less
- Transverse or short oblique configuration
- Non-comminuted
- Complete fractures extend through both cortices and may be associated with medial spike; incomplete involve only lateral cortex

Shane et al JBMR 2010;25:2267
Atypical Femur Fractures: Minor Features

- Localized periosteal reaction lateral cortex (beaking or flaring)
- Generalized increase in cortical thickness
- Prodromal symptoms e.g. dull or aching pain in groin
- Bilateral fractures and symptoms
- Delayed healing
- Comorbid conditions (vitamin D deficiency, RA)
- Use of pharmaceutical agents (e.g., BPs, GCs, PPIs)

Shane et al. JBMR 2010;25:2267

Atypical femoral shaft fracture (pre- and post-operative)

- Oblique and transverse components (white)
- Medial spike (black)
- Lateral transverse lucent line
- Focal thickening with “beaked” appearance

Shane et al. JBMR 2010;25:2267
Microdamage: Bisphosphonates

Excessive bone suppression causing accumulation of micro-fractures and increased skeletal fragility.

Atypical Femoral Shaft Fractures: Proposed Mechanism

Komatsubara et al JBMR 2004; 19:999
Other Issues with Bisphosphonates

Atrial Fibrillation and Bisphosphonates

- HORIZON PFT Study:
  Serious AF with ZA 1.3%; placebo 0.5%
- No AF in HORIZON RFT, oncology trials
- Retrospective analysis of FIT NS trend
- VERT no association at all
- Other case-control studies mixed results
- Summary: No convincing evidence to support causal relationship. FDA no change in prescribing patterns and continue to monitor
Renal Safety

- Generally no problem if CCr above 30-35 ml/min
- However, not recommended in patients with lower CCr,
- After IV zoledronic acid, transient reduction in renal function which returns to baseline.
- Make sure patients are well hydrated and the infusion rate can be prolonged.

Is there an association between bisphosphonates and esophageal cancer?

(JAMA 2010;304:657)
Oral Bisphosphonates and Risk of Esophageal Cancer

A: Cardwell et al JAMA 2010;304:657
B: Green et al BMJ 2010;341:c4444
Oral Bisphosphonates and Risk of Esophageal Cancer

Cardwell et al. JAMA 2010;304:657

Oral Bisphosphonates and Risk of Esophageal Cancer

Green et al. BMJ 2010;341:c4444
Denosumab

RANK Ligand Is an Essential Mediator of Osteoclast Activity

1. Osteoblasts express RANKL
2. RANKL binds to RANK
3. Differentiated osteoclasts are formed
4. RANKL mediates osteoclast formation, function, and survival

In premenopausal women, estrogen regulates RANKL expression.

OPG blocks binding of RANKL to RANK


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Denosumab in the treatment of postmenopausal osteoporosis

• Human monoclonal antibody that targets the receptor activator of nuclear factor-kappa B ligand (RANKL)
• RANKL is a cytokine member of the tumor necrosis family (TNF) that is the final principal mediator of osteoclastic bone resorption
• Denosumab prevents RANKL from binding to its receptor on the surface of osteoclasts and their precursors, thus inhibiting osteoclast formation, function and survival

Denosumab

• Denosumab does not become incorporated into bone and bone resorption markers return to baseline 6 months after the last injection.
• Unaffected by renal impairment
Denosumab (FREEDOM Trial) in the treatment of postmenopausal osteoporosis (Cummings et al NEJM 2009;361:756)

- 7686 women age 60-90 yr
- BMD T-score of less than -2.5 but not less than -4.0 at LS or TH
- Randomly assigned to either 60 mg denosumab or placebo SC q 6 mo x 36 mo.
- Primary end point: new vertebral fracture
- Secondary end point: nonvertebral and hip fracture
Denosumab (FREEDOM Trial) in the treatment of postmenopausal osteoporosis
(Cummings et al. NEJM 2009;361:756)

Denosumab (FREEDOM Extension) in the treatment of postmenopausal osteoporosis
(Papapoulos et al. JBMR 2012;27:694)
Denosumab (FREEDOM Extension) in the treatment of postmenopausal osteoporosis
(Papapoulos et al. JBMR 2012;27:694)
Denosumab: Adverse Events

- Serious skin infections (cellulitis, eczema), as well as infections of the abdomen, urinary tract and ear were more frequent in denosumab group
- Eczema (118 vs. 65); cellulitis (12 vs 1)
- Overall incidence of infections similar
- Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk
- ONJ has been reported in cancer trials

Denosumab: When to use it

- Stay tuned: “New kid on the block”
- Currently second line therapy in patient who cannot take oral or IV bisphosphonate
- First line potential in specific patient populations or after long-term safety data
- Do not need to monitor renal function
What about hormone therapy?

WHI Estrogen+Progestin Trial Study Results - Fractures

34% Reduced Risk* 34% Reduced Risk**

*Hip Fractures: HR 0.66; Nominal 95% CI (0.45-0.98), Adjusted 95% CI (0.33-1.33)
**Vertebral Fractures: HR 0.66; Nominal 95% CI (0.44-0.98), Adjusted 95% CI (0.32-1.34)

OSTEOPOROSIS

- RCT evidence that standard-dose HT reduces PMO fractures including hip, spine, non-spine fractures, even in women without osteoporosis
- Low doses are effective in maintaining or improving BMD
- No HT product is currently approved for treatment of osteoporosis
- Many are approved for prevention of PMO

If alternate therapies are not appropriate or cause adverse effects, extended use of HT is an option for women at high risk for fracture.

- No evidence HT stops working with long-term treatment but dissipates rapidly if stopped.
- Unless contraindication, women with early menopause who require prevention of bone loss are probably best served by HT or OC, rather than bone-specific treatment until normal age of menopause and then treatment reassessed.
CONCLUSIONS/RECOMMENDATIONS

- Individualization is of key importance and incorporates woman’s health and QOL priorities and personal risk factors (e.g. venous thrombosis, CHD, stroke, breast cancer)
- Recommendation for duration of therapy differs for EPT and ET.
- For EPT, duration limited by increased risk of breast cancer associated with 3-5 yrs use
- For ET, more favorable benefit-risk profile during a mean of 7 yrs with 4 yrs follow-up, allowing more flexibility in duration of use.

ET is the most effective treatment of symptoms of vulvar and vaginal atrophy; low dose, local vaginal ET advised for vaginal sx.

- Women with premature or early menopause who are otherwise candidates for HT can use HT at least until medial age of natural menopause (age 51). Longer duration possible if symptomatic
- Both transdermal and low-dose oral E associated with lower risks of VTE and stroke than standard doses of oral E, but RCT evidence not available.
Should we consider SERM’s?

Concept of a SERM (estrogen agonist/antagonist)

- **S**elective
- **E**strogen
- **R**eceptor
- **M**odulator

- Not an estrogen, progestin or other hormone
- Binds to estrogen receptors
- Has estrogen-like effects in some tissues
- Blocks estrogen effects in some tissues
Raloxifene reduced the incidence of vertebral fractures in postmenopausal women with osteoporosis

MORE (Group 1)\(^1\)
With Prior VFx=11%
Hip or Spine T-score ≤-2.5
Age Range=31 to 80

MORE (Group 2)\(^1\)
With Prior VFx=89%
Hip or Spine T-score ≤-2.5
Age Range=31 to 80

- 50% decrease at Year 3, p<0.005
- 30% decrease at Year 3, p<0.005

RUTH Trial (Raloxifene Use and the Heart)

- Large scale placebo-controlled trial with more than 10,000 women from 26 countries.
- Raloxifene did not increase or decrease the combined endpoint of non-fatal heart attack, fatal heart attack or hospitalized acute coronary syndrome compared to placebo.
- Raloxifene treatment decreased invasive breast cancer compared to placebo.

Who Should We Treat?

Who should be considered for treatment (NOF Clinician’s Guide 2010)

- Postmenopausal women and men age 50 and older presenting with the following:
- Hip or vertebral (clinical or morphometric) fracture
- T-score -2.5 or lower at the FN or spine after evaluation to exclude secondary causes
Who should be considered for treatment (NOF Clinician’s Guide 2010)

• Low bone mass (T-score between -1.0 and -2.5 at the FN or spine) and 10 year probability of a hip fracture 3% or more or major osteoporosis fracture of 20% or more based on US-adapted WHO algorithm
• Clinician’s judgment and/or patient preference