Fracture Prevention at Different Stages of Life

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Consulting fees and honorarium for speaking: from Amgen
Osteoporosis

• Several osteoporosis drugs effectively and quickly reduce fracture risk in women with postmenopausal osteoporosis

• Drugs work by modulating bone metabolism
  
  • Anti-remodeling (anti-resorptive) drugs: inhibit bone resorption and bone formation; improve bone strength but do not restore trabecular architecture

  • Osteoanabolic agents: activate bone formation; increase or decrease bone resorption; improve bone strength and restore trabecular architecture


Images Courtesy of Drs. David Dempster, Roger Zebazi and Sergio Ragl
Therapy to Prevent Fractures

- Fractures are common across the lifespan
- Fracture rates are highest in older adults

- Risk factors for fracture are numerous including
  - advanced age
  - low bone mineral density
  - frequent falls
  - many diseases and medications

Amin S. Epidemiology of Fractures in Osteoporosis in Men, Ed 2, pages 351-360. Academic Press 2010
Almost all of the evidence we have about fracture prevention comes from industry-sponsored registration studies in postmenopausal women with osteoporosis.

Exceptions include small, usually small, demonstrating reduced fracture risk in:
- postmenopausal women without osteoporosis
- men with osteoporosis
- Idiopathic forms of osteoporosis
- men and women receiving medicines harmful to the skeleton
- children with osteogenesis imperfecta
Anti-remodeling (anti-resorptive) agents (*inhibit resorption more than formation*)
- Estrogen agonists
  - estrogen and, in some countries, tibolone
  - estrogen agonists/antagonists (SERMs): raloxifene
- Bisphosphonates; alendronate, ibandronate, risedronate, zoledronate
- RANK ligand inhibitor; denosumab
- Calcitonin salmon in USA
- **Osteoanabolic agents** (*activate bone formation*)
  - Remodeling stimulators (*increase formation and resorption*)
    - Parathyroid hormone receptor activators
      - teriparatide and abaloparatide
  - Modeling stimulator (*increase formation, decrease resorption*)
    - Sclerostin inhibitor
      - romosozumab
Fracture Prevention in Postmenopausal Osteoporosis

- Randomized trials enroll otherwise healthy women with postmenopausal osteoporosis, average age 68-74 years, at various levels of fracture risk
- Compared to placebo, osteoporosis drugs reduce risks of
  - vertebral fracture by 30-86%
  - multiple vertebral fractures by 75-85%
  - hip fracture by up to 50%
  - non-vertebral fracture by 20-53%

- Fracture risk
  - occurs as early as 6 months after beginning therapy
  - persists as long as therapy is given
  - decreases upon stopping therapy
  - is similar or greater relative risk reduction in patients with high FRAX probability
# Osteoporosis Management of Osteoporosis

*According to Current Fracture Risk*

## RISK CATEGORIES

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
<th>Very High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal</td>
<td>Postmenopausal women with low BMD but few or no other risk factors, especially if they are recently estrogen deficient, are candidates for <em>prevention therapy</em></td>
<td>Younger postmenopausal women with lumbar spine BMD consistent with osteoporosis without prior fracture; low risk for hip fracture</td>
<td>Osteoporosis in spine or hip; low bone mass with remote history of non-spine, non-hip fracture or multiple other risk factors</td>
<td>Recent (within 1-2 years) fracture; very low BMD (&lt;-3.0) or very high fracture probability by FRAX (&gt;30% MOF or 4.5% hip fracture) hip region</td>
</tr>
</tbody>
</table>

## RECOMMENDED DRUGS

- **Hormone therapy**
  - Raloxifene
  - Bisphosphonates
  - Teriparatide
  - Abaloparatide
  - Romosozumab

- **Low-dose bisphosphonates**
  - Denosumab

* to be followed by an anti-remodeling drug

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Camacho PM et al.. *Endocr Pract* 2020;26(Suppl 1):1-46
Kanis JA et al. *Osteoporos Int* 2020;31:1-12
Preventing Fractures in Postmenopausal Osteoporosis

- Randomized trials enroll otherwise healthy women with postmenopausal osteoporosis, average age 68-74 years, at various levels of fracture risk
- Compared to placebo, osteoporosis drugs reduce risks of
  - vertebral fracture by 30-86%
  - multiple vertebral fractures by 75-85%
  - hip fracture by up to 50%
  - non-vertebral fracture by 20-53%

- Fracture risk reduction
  - occurs as early as 6 months after beginning therapy
  - persists as long as therapy is given
  - decreases at variable rates upon stopping therapy
In post hoc analyses, fracture risk reduction is similar to or, more often, greater in patients with high vs low FRAX probability of major osteoporotic fracture (MOF).

**Left:** Relative fracture risk was lower in patients treated with denosumab with FRAX estimates of MOF above 15% and hip fracture risk above 4%.

**Right:** Hazard ratios of Clinical fractures and Major osteoporotic fracture in patients treated with romosozumab as a function of FRAX Probability of MOF.
Subgroup analyses of registration trials with alendronate, risedronate, zoledronate, denosumab and abaloparatide have evaluated effects of therapies on fracture risk in elderly subgroups.

In general, fracture risk reductions are similar in those 75 years and older compared to the younger subset or overall study population.

Reductions in fracture risk in elderly subgroups are not always statistically significant due to small numbers of events and limited statistical power.

### Drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Zoledronate Risk reduction (95% CI) (2)</th>
<th>Denosumab Risk reduction (95% CI) (3,4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral fracture</td>
<td>35% (22%, 46%)</td>
<td>64% (47%, 75%)</td>
</tr>
<tr>
<td>Non-vertebral fracture</td>
<td>27% (10%, 40%)</td>
<td>16% (-12%, 37%)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>18% (-20%, 44%)</td>
<td>62% (22%, 82%)</td>
</tr>
</tbody>
</table>

Fracture prevention in postmenopausal women aged 75 years and older over 3 years

1. Boonen S et al. JAGS 2004;52:1832–9
Most of the drugs approved for treating postmenopausal osteoporosis (PMO) are also approved for men with osteoporosis. Approval was achieved with BMD studies showing similar results in women with PMO. BMD responses were similar in men with normal or low serum testosterone. Studies with alendronate and teriparatide have demonstrated reduction in vertebral fracture in men with osteoporosis (1,2). Zoledronate reduced hip fracture risk in men and women after hip fracture. The effect in men specifically has not been reported (3).

Most fractures occur after a fall
Multifactorial fall prevention programs are routinely advised for older adults (1)
While many such programs have been shown to reduce the risk and frequency of falls, none has been large or long enough to reduced fracture risk (2)

Exercise to improve strength and balance
Correct severe vitamin D deficiency
  - reduces falls and hip fracture
Better nutrition including adequate protein intake
Correct visual impairment
Correct polypharmacy


Bischoff-Ferrari H et al. JAMA 2005;293:2257-64
Very few studies have evaluated fracture prevention in men or postmenopausal women without osteoporosis.

Fracture rates are lower in patients with higher T-scores, requiring much larger sample size to observe a treatment effect.

Data adapted from Cummings et al. JAMA1998;280:2077-82

ARR = relative risk reduction; CI = confidence interval; RRR = relative risk reduction
Preventing Fractures in Adults Without Osteoporosis

- Even in “osteoporosis studies”, therapies have not been shown to reduce fracture risk in subgroups with T-scores \( > -2.5 \)
  
  - Alendronate reduced clinical and hip fracture risk only in postmenopausal women with femoral neck T-score of \( -2.5 \) or lower (1)
  
  - Risedronate did not reduce hip fracture risk in women aged 80 and older when femoral neck T-scores were \( > -2.5 \) (2)
  
  - Denosumab did not reduce nonvertebral fractures in the subgroup with femoral neck T-score \( > -2.5 \) (3)
  
  _BUT – none of these studies were designed to ask that question_

In the Women's Health Initiative, 16,608 postmenopausal women were enrolled and followed for an average of 5.6 years.

- At baseline: mean age 63 years; 44% were older than 65 years
- Average T-scores in the BMD subgroup (N = 1024) were -1.28 at lumbar spine and -0.92 at total hip

<table>
<thead>
<tr>
<th>Fracture category</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fractures</td>
<td>0.76</td>
<td>0.69-0.83</td>
<td>24%</td>
</tr>
<tr>
<td>Vertebral (clinical)</td>
<td>0.65</td>
<td>0.46-0.92</td>
<td>35%</td>
</tr>
<tr>
<td>Wrist/lower arm</td>
<td>0.71</td>
<td>0.59-0.85</td>
<td>29%</td>
</tr>
<tr>
<td>Hip</td>
<td>0.67</td>
<td>0.47-0.96</td>
<td>33%</td>
</tr>
</tbody>
</table>

CI = confidence interval; RRR = relative risk reduction

Cauley J et al. JAMA 2003;290:1729-38
Denosumab reduced vertebral fracture risk in men and women receiving hormone ablative therapy for non-metastatic prostate or breast cancer, including those with T-scores > -1.0.

Fractures in Infants and Children

- Fractures in children are common
- About 1/3 of children will experience a fracture by age 16
- Before the age of 2 years, fracture incidence is equal in boys and girls and occurs at a rate of approximately 80/10,000 person years
- After age 2, fractures are more common in boys
- Most are related to mild trauma
- Other causes include
  - metabolic bone disease of prematurity
  - rickets
  - child abuse
  - genetic disorders – most common is osteogenesis imperfecta
Diagnosing Osteoporosis in Children

- Pediatric osteoporosis cannot be diagnosed solely by BMD criteria.
- Diagnosis is made with:
  - Presence of one or more vertebral fractures (VFs) in the absence of local disease or high-energy trauma.
  - History of 2 or more clinically significant fractures of long bones by age 10 or 3 or more long bone fractures at any age up to 19.
    - *plus a*
  - Z-score of BMD or BMC ≤ −2 (age- and gender-matched and adjusted for size in case of impaired growth).
Preventing Fractures in Children

*Osteogenesis Imperfecta*

- Bisphosphonates
  - IV and oral bisphosphonates improve BMD
  - Effects on fractures are inconsistent
    - one randomized trial with risedronate showed significant reduction (30.8% vs 48.9%; p = 0.0446)
    - a Cochrane review and a meta-analysis of randomized trials have both concluded that the effects of bisphosphonates on fracture rate are uncertain
- Denosumab increases BMD – no fracture data

Nijhuis W et al. Children 2022;9:268
Preventing Fractures in Children

Osteogenesis Imperfecta

- PTH analogues have not been evaluated in children
- Anti-sclerostin therapy, mesenchymal stem cell treatment and gene therapy are being evaluated
- Orthopedic management:
  - Alignment surgery with intramedullary rodding to increase bone strength should be considered to decrease the fracture risk in children with moderate to severe OI
Preventing Fractures in Children
*Idiopathic Juvenile Osteoporosis*

- Idiopathic juvenile osteoporosis is a rare, usually self-limiting disorder of bone pain and fractures, usually vertebral
- Incidence is ~1 in 100,000
- Onset is typically between ages 8 and 14 years coinciding with 2–3 years prior to puberty
- Fractures tend to abate upon conclusion of puberty
  - Deformities lessen over time
- Bisphosphonates appear to reduce vertebral fracture rates and to hasten the recovery phase

Krassas GE. Ann N Y Acad Sci 2000;900:409-12
Baroncelli GI et al. J Bone Miner Metab 2013;31:533-43
• Bisphosphonates have also been used to treat children with other genetic and secondary forms of osteoporosis including
  • Hajdu-Cheney syndrome
  • Osteoporosis-pseudoglioma syndrome
  • Cystic fibrosis
  • Post liver and kidney transplants

• Expert panel consensus recommendations for diagnosis and treatment of secondary osteoporosis in children have been published (1)

• However, unlike children with primary osteoporosis such as osteogenesis imperfecta, where the potential for recovery from osteoporosis without medical therapy is limited, many children with secondary osteoporosis can undergo complete recovery in the absence of bisphosphonate intervention. (2)

Preventing Fractures in Premenopausal Women

Pregnancy- and Lactation-associated Osteoporosis (PLO)

- Pregnancy- and lactation-associated osteoporosis with predominantly subsequent vertebral fracture is a rare but severe disease with an estimated incidence of 0.4 in 100,000 pregnancies (1-3)
- Risk factors include older age and obesity; more common with first pregnancy
- Women with PLO have low bone remodeling rates at the tissue level (4)
- Mutations in LRP5, COL1A1, and COL1A2 have been reported in PLO patients (5)
- During a median of 6 years of follow-up, 26 (24.3%) of patients who had a fracture at baseline reported a subsequent fracture (6)
  - 20% of 30 women with PLO reported a fracture during a subsequent pregnancy
- After weaning, BMD often improves spontaneously and fracture risk diminishes (1)

2. Qian et al. BMC Musculoskelet Disord 2021;22:926
3. Hardcastle S. Calcif Tissue Int. 2022;110:531-45
Preventing Fractures in Premenopausal Women

Pregnancy- and Lactation-associated Osteoporosis (PLO)

• Bisphosphonates:
  • In women with post-partum PLO and multiple vertebral fractures, bisphosphonates increase BMD and appear to reduce fracture rates
  • Concern exists about their use in women who might subsequently become pregnant

• Denosumab:
  • Case reports of PLO treated with denosumab demonstrated increased BMD without subsequent fractures (1)
  • a case of PLO was treated with denosumab for 18 months (2)
    • BMD of the lumbar spine and total hip increased by 32.2% and 11.5%, respectively with no further subsequent fractures
    • denosumab was discontinued and a second pregnancy was carried to term, at the end of which BMD values in LS and TH were 8.8% and 7.0% lower than values at end of denosumab therapy

1. O’Sullivan SM et al. Osteoporos Int. 2006;17:1008-12

Preventing Fractures in Premenopausal Women
_Pregnancy- and Lactation-associated Osteoporosis (PLO)_

- **Teriparatide:**
  - Several studies have suggested benefit of treating PLO with teriparatide
    - teriparatide for 18 months with or without follow-on anti-remodeling therapy (1)
    - teriparatide for 6 months followed by denosumab (2)
  - 47 patients with PLO with a mean of 4 existing fractures were treated with teriparatide for 24 months (3)
    - 4 patients (7.8%) sustained a subsequent fracture, two after 3 - 5 months of treatment and two at > 6 months of treatment

Preventing Fractures in Young Women and Men

Premenopausal Osteoporosis and Idiopathic Osteoporosis in Men

• Premenopausal osteoporosis includes women who present with fractures before menopause and have Z-scores <-2.0 in whom osteomalacia and other secondary causes have been ruled out
• Men aged 50 or younger with fractures and/or low Z-scores without known cause are said to have idiopathic osteoporosis
• Some have various genetic abnormalities (LRP5, etc.)
• These patients have abnormalities in trabecular and cortical microarchitecture, lower estimates of bone strength and lower TBS values than age-adjusted controls
• Bone resorption markers are generally normal while formation markers are lower than average for than age-matched controls
• Women with fractures before menopause are at 35-74% higher risk for postmenopausal fractures

Herath M et al. JBMR Plus 2022;6:e10594
Cohen A et al. J Clin Endocrinol Metab. 2009; 94:4351–60
Cohen A et al. J Clin Endocrinol Metab. 2011; 96:3095
Preventing Fractures in Young Women and Men

Premenopausal Osteoporosis and Idiopathic Osteoporosis in Men

- Bisphosphonates and denosumab would be expected to have limited efficacy on increasing BMD in these patients with normal to low bone turnover in these estrogen-replete women.

- Teriparatide increases BMD significantly and improves measures of trabecular microarchitecture. Do they need anti-remodeling drug after 18-24 months?
  - In 15 women whose BMD had increased 11.1 ± 7.2% at the lumbar spine and 6.1 ± 6.5% at the total hip were followed for 2 years without anti-remodeling therapy. During the two years post-treatment LS BMD decreased by 4.8 ± 4.3% (P = .0007) while values in the proximal femur remained stable.

- None of these small treatment studies in these patients have evaluated the effectiveness to prevent fractures in these patients.

Cohen A et al. J Clin Endocrinol Metab 2015;100:4208-14
Preventing Fractures in Premenopausal Women

**Premature Ovarian Insufficiency (POI)**

- Women with spontaneous or iatrogenic menopause before age 40 years are at increased for osteoporosis
- There are limited data about fracture risk
- TBS values are lower compared to age-matched controls
- Estrogen therapy preserves or improves BMD and TBS
- No studies have adequately assessed the effects of estrogen or other treatments on fracture risk in these patients


Navira Samad N et al. Front Endocrinol (Lausanne) 2022;13:860853
Preventing Fractures in Early Menopausal Women

- A phase or relatively rapid bone loss occurs for 5-7 years over the menopausal transition – average 9% at the femoral neck and 10-12% in the lumbar spine
  

- That rapid bone loss results in destruction of trabecular bone microarchitecture

- In the 5 years before through the 5 years after the final menstrual period, the average decline in spine TBS was 6.3% (P < 0.0001)


Baseline

Placebo
Deterioration in bone architecture

Dufresne et al. Calcif Tiss Int 2003;73:423-32

1 year

Risedronate
Preservation of architecture
Preventing Fractures in Early Menopausal Women

- Could slowing the rise in bone resorption and decline in BMD be associated with less trabecular damage?

- In a group of women followed across the menopausal transition (MT), both the rate of increase in bone resorption, as measured by u-NTX, and peak u-NTX level were significantly associated with fracture risk over average observation period of 8.5 years since last menstrual period.

<table>
<thead>
<tr>
<th>Category</th>
<th>Relative Fracture Hazard (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast MT increase and low early postmenopausal peak</td>
<td>1.54 (0.68-3.47)</td>
<td>0.2</td>
</tr>
<tr>
<td>Slow MT increase and high early postmenopausal peak</td>
<td>1.04 (0.43-2.50)</td>
<td>0.8</td>
</tr>
<tr>
<td>Fast MT increase and high early postmenopausal peak</td>
<td>1.80 (1.00-3.22)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

The hazard ratio per SD increment in peak u-NTX in early postmenopause was 1.27 with 95% confidence interval 1.04-1.54; p-value 0.01

Preventing Fractures in Early Menopausal Women

- Improved BMD with estrogen therapy persist as long as treatment is given but is quickly lost upon discontinuation.
- Transition to alendronate prevents the bone loss associated with stopping estrogen.

![Graph showing BMD changes over time](chart.png)

Young postmenopausal women randomly assigned to estrogen/progestin or placebo. Study drug discontinued after 4 years in all groups.

Postmenopausal women who discontinued estrogen therapy were randomly assigned to alendronate or placebo for 12 months.

**References:***
Preventing Fractures in Early Menopausal Women

- The increase in urinary NTX (u-NTX) and decline in BMD were much slower upon stopping alendronate after 4 years compared to estrogen.

Young postmenopausal women randomly assigned to estrogen/progestin or placebo. Study drug discontinued after 4 years in all groups.

Postmenopausal women who discontinued estrogen therapy were randomly assigned to alendronate or placebo for 12 months.


Preventing Fractures in Early Menopausal Women

- Estrogen with or without progestins, conjugated estrogen with bazedoxifene, raloxifene and each of the 4 bisphosphonates has government approval for osteoporosis prevention.
- All were approved with 2-year BMD studies.
- BMD increased over 6 years with alendronate therapy.
- None of the studies were large or long enough to demonstrate fracture risk reduction.

### Drug Dose

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>35 mg po weekly *</td>
</tr>
<tr>
<td>Risedronate</td>
<td>35 mg po weekly</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>150 mg po monthly</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>5 mg IV Q 2 years *</td>
</tr>
</tbody>
</table>

* NOTE: Dose smaller than the osteoporosis treatment dose

A successful BMD prevention study with denosumab was completed but government approval was not granted.
Preventing Fractures in Early Menopausal Women

- The Danish Osteoporosis Prevention Study followed more than 1000 women ages 48-55 (average 50.8 +/- 2.8 years) for 5 years on estrogen +/- progestin or placebo.

- Adherence to estrogen therapy was 65%

<table>
<thead>
<tr>
<th>Analysis</th>
<th>All fractures Relative Fracture Hazard (95% CI)</th>
<th>Wrist fractures Relative Fracture Hazard (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention to Treat analysis</td>
<td>0.73 (0.50, 1.05)</td>
<td>0.45 (0.22, 0.90)</td>
</tr>
<tr>
<td>Per protocol analysis (adherence to initial treatment allocation)</td>
<td>0.61 (0.39, 0.97)</td>
<td>0.24 (0.09, 0.69)</td>
</tr>
</tbody>
</table>

Mosekilde L et al. Maturitas 2000;36:181-93
Preventing Fractures in Early Menopausal Women

• In WHI, average age was 63.3 years and average T-scores in lumbar spine and total hip were -1.28 and -0.92, respectively.

• Total, vertebral and hip fractures were reduced by 24%, 35% and 33%, respectively.

• The relative risk reductions of total and hip fractures were not influenced by categories of age from 50 to 80 years (vertebral fracture subgroups not reported), by history of falls nor by baseline fracture risk as assessed by FRAX.

Cauley J et al. JAMA 2003;290:1729-38
Preventing Fractures in Early Menopausal Women

- In WHI, average age was 63.3 years and average T-scores in lumbar spine and total hip were -1.28 and -0.92, respectively.
- Total, vertebral and hip fractures were reduced by 24%, 35% and 33%, respectively.
- These data suggest that estrogen therapy to prevent bone loss at menopause would be effective in reducing fracture risk.

Cauley J et al. *JAMA* 2003;290:1729-38
Fracture Prevention at Different Stages of Life

Summary

- Fractures occur over the entire lifespan
- Maintaining or improving bone strength and reducing the frequency of falls and injuries are mainstays of fracture prevention management
- Perhaps the best way to prevent fractures would be to prevent bone loss and the development of osteoporosis at and after menopause in women and loss of muscle mass with aging
- Almost all of the data about fracture prevention comes from registration drug trials in women with postmenopausal osteoporosis
- With recent decision by FDA to accept changes in hip BMD as a surrogate for fracture, we may have less direct information about fracture risk reduction with the next new drugs
Thank you

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Request updated slides from
mmcclung.ooc@gmail.com
The relative risk reduction of fractures with estrogen therapy was similar across the spectrum of baseline risk as assessed by FRAX.
Preventing Fractures in Adults Without Osteoporosis

- Vitamin D 2000 IU daily is not effective
- In 25,871 participants (50.6% women and 20.2% Black), followed for an average of 5.3 years randomly assigned to vitamin D 2000 IU daily vs placebo, no effect on fracture risk was observed

<table>
<thead>
<tr>
<th>Fracture category</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fractures</td>
<td>0.98</td>
<td>0.89 to 1.08</td>
</tr>
<tr>
<td>Nonvertebral fractures</td>
<td>0.97</td>
<td>0.87 to 1.07</td>
</tr>
<tr>
<td>Hip fractures</td>
<td>1.01</td>
<td>0.70 to 1.47</td>
</tr>
</tbody>
</table>

CI = confidence interval