My goals:

1. The key messages are:
   - No falling!
   - Vitamin D is sometimes needed
   - Practice, practice, practice (i.e. exercise)

2. Use of bisphosphonates for 5 years and then reassess
   - Know when to use
   - Know what to look out for

3. Consider options beyond bisphosphonates
   - Combination therapy
   - Biologics
USPSTF Guidelines for screening

Screening women for osteoporosis, 2 year interval (Grade B, 100% covered by ALL plans)

Women ≥ 65 years
Women ≤ 60 years whose 10 year fracture risk ≥ 65 year old white women without RF

Screening men for osteoporosis, 2 year interval (Grade Indeterminate, NOT covered)

Men whose 10 year fracture risk is ≥ 65 year old white women without RF
Bone Densitometry: DXA (Quantitative Digital Radiography)

“z” Score: S.D. difference vs. age and sex matched individuals

“t” Score: S.D. difference vs. early life
- Vertebral fracture risk increases 2 - 2.4 times for each S.D. of bone loss
- Non-vertebral fracture risk increases 1.7 times for each S.D. of bone loss
WHO categories of osteoporosis

Osteopenia: BMD -1 to -2.5 S.D. below healthy mean (30-40 yr)

Osteoporosis: BMD < -2.5 S.D. below healthy mean

Severe osteoporosis: Osteoporosis with a non-violent fracture
Falls cause fractures
Hospitalizations for osteoporosis fracture exceed MI, CVA and breast CA.

Hospitalizations 2000-2011, women ≥ 55 yrs

- Brst CA
- CVA
- MI
- OF

Risk factors add up!

Calcaneal Bone Density

Rate of hip fracture (per 1000 women-years)

Lowest Third: 2.6, Middle Third: 1.1, Highest Third: 1.1

Framingham cohort pre bisphosphonones (1987-99), mean age 74.8 years, what about lifetime risks:

12 year hip fracture prevalence

T > -1.0
T -1.01 to -2.49
T < -2.5

Over 50 % hip fracture risk / 12 yrs

JAMA 2013; 310:1256-1262
NORA data: BMD and fracture risk (White women; age 64.5)

Fracture rate per 1000 person-years

- Fracture Rate
- No. of women with fractures

BMD distribution

No. of women with fractures

Fracture Rate and BMD distribution relationship.
Falls predict risk for subsequent falls

Women

No falls

One fall

Men

Fracture free over 5 yrs

20%

50%

Any fall increases the risk of a second fall to over 60%

5 years of follow-up

JAMA 2007;297:390
Medications associated with fall risk

Odds Rates (95% C.I.)

Sedative/hypnotics \(1.31\ (1.14-1.50)\)
Neuroleptics/antipsychotics \(1.71\ (1.44-2.04)\)
Antidepressants \(1.72\ (1.40-2.11)\)
Antihypertensives \(1.26\ (1.08-1.46)\)

Arch Intern Med 2009;169:1957
Trust your clinical judgment: “Timed Up and Go” (TUG) over 10 seconds predicts hip fracture risk

Timed Up and Go (TUG): Time taken to get out of a chair, walk 10 feet (3 M) and return to the chair; normal ≤10 seconds

Australian cohort of 1126 women, followed for 10 years

Ten year risk for fracture 54% higher in highest risk group, low BMD and prolonged TUG
10 year hip fracture risk for frail patients with osteopenia is 12%

Good BMD and TUD

Low BMD and TUG

2.6% Fx Risk

11.8% Fx risk

Arch Intern Med 2011; 171:1665-1661
<table>
<thead>
<tr>
<th>Contributors to Osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
</tr>
<tr>
<td>Vitamin D</td>
</tr>
<tr>
<td>Estrogens</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Exercise</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Exogenous steroids</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Growth hormone</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Anticoagulants</td>
</tr>
<tr>
<td>Excessive Vitamin A</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Homocysteine elevation</td>
</tr>
<tr>
<td>Androgen deficiency</td>
</tr>
<tr>
<td>Breast cancer survivors</td>
</tr>
<tr>
<td>Pelvic irradiation</td>
</tr>
<tr>
<td>PPI usage</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
</tr>
</tbody>
</table>
Subclinical hypothyroidism and hip fracture risk

Meta-analysis, N = 70 298, 13 RCTs

TSH levels

0.45-4.49
0.10-0.44
< 0.10

JAMA 2015; 313:2055-2065
Laboratory tests:

All patients:
- CBC & ESR
- Ca++
- PO$_4$=
- TSH
- Vitamin D (25 OH)
- Bone densitometry
- ? PTH (for vitamin D deficiency and hyperparathyroidism)
When to order bone densitometry:

- Diagnosis and screening
- Screening for high risk:
  - history of steroid use
  - history of calcium loss (multipregnancy)
  - low Vitamin D level
  - unexpected non traumatic fracture
  - family history
  - estrogen deficiency (anorexia, anovulatory cycling, etc.)
- Monitoring therapy: every 2-3 years
- Assisted decision-making
Severe osteopenia (T -2.00 to -2.49) 1.1 yrs

Mild osteopenia 11.5 yrs

Normal: 16.8 yrs

Good early BMD predicts lower future risk for progression to osteoporosis

(9704 North Carolina white women followed 15 yrs)
# Osteoporosis screening for men: Routine >80, high risk over 65 years

<table>
<thead>
<tr>
<th>Age</th>
<th>No fracture ($ per QALY)</th>
<th>Previous clinical Fracture ($ per QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 65</td>
<td>129,665</td>
<td>47,537</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>92,769</td>
<td>35,037</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>66,071</td>
<td>23,260</td>
</tr>
<tr>
<td>&gt; 80</td>
<td>45,587</td>
<td>15,477</td>
</tr>
</tbody>
</table>

JAMA 2007;298:629-637
Markers of bone turnover of little clinical value:

- Do not predict BMD
- Increased in women with high turnover postmenopausal osteoporosis
- Useful for monitoring response to therapy
What about online tools?

- FRAX has become the standard but... only 70% accurate
- No measure of frailty
- Based on country-specific date
- Little added value beyond the BMD and age
FRAX risk factors

Age
BMI
Sex
Personal fracture history
Steroid use
RA
Presence of DM, osteogenesis imperfecta, untreated hyperthyroidism, early menopause, malnutrition, liver disease
Parental hip fracture
Current smoking
Alcohol (≥ 3/d)

Osteoporosis Int 2007;19:285-397
FRAX with BMD no different then BMD alone in predicting hip fractures in women

Arch Intern Med 2009;169:2091
Let’s talk about interventions

- “Non pharmacologic”
  - Exercise
  - Calcium
  - Vitamin D
- Antiresorptive
  - Estrogens
  - Bisphosphonates
- Anabolic
  - Teriparatide
  - Denosumab
What is the value of exercise and balance training?

Physical activity encourages bone growth along lines of stress.

• The bone density in the dominant arm of a tennis player is 35% higher.

Balance training reduces fall risk.
Balance training reduces fall risk in patients with Parkinson’s Disease

<table>
<thead>
<tr>
<th></th>
<th>Tai Chi (N=65)</th>
<th>Resistance (N=65)</th>
<th>Stretching (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total falls</td>
<td>62</td>
<td>133</td>
<td>186</td>
</tr>
<tr>
<td>Falls/group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>19</td>
<td>31</td>
<td>26</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>≥3</td>
<td>12</td>
<td>16</td>
<td>20</td>
</tr>
</tbody>
</table>

Six month exercise intervention reduced fractures over the next 7 years

<table>
<thead>
<tr>
<th>Fractures</th>
<th>Exercise</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Knee/tibia/fibula</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Femur</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>17</strong></td>
<td><strong>23</strong></td>
</tr>
</tbody>
</table>

Arch Intern Med 2010;170:1548-1556
What are benefits of an ambitious exercise intervention?

Finnish RCT, 2010-2013
N = 409, women age 70-80
Home dwelling
Four groups:
1. Exercise and placebo
2. Exercise and vitamin D
3. No exercise and vitamin D
4. No exercise and placebos

JAMA Intern Med Mar 23, 2015
Finnish exercise intervention

No exercise = Maintain pre-study levels
Exercise = Twice a week for 12 weeks
  - Once a week thereafter for 2 years
  - PT directed classes
  - Balance, weight bearing, strength, agility, function
  - Machines, free weights
  - Home training all other days
## Finnish exercise participants

<table>
<thead>
<tr>
<th></th>
<th>Placebo and no exercise</th>
<th>Vitamin D and no exercise</th>
<th>Placebo and exercise</th>
<th>Vitamin D and exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>73.8</td>
<td>74.1</td>
<td>74.8</td>
<td>74.1</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>72</td>
<td>73</td>
<td>71</td>
<td>73</td>
</tr>
<tr>
<td><strong>Vitamin D</strong></td>
<td>27.1</td>
<td>26.4</td>
<td>27.8</td>
<td>26.2</td>
</tr>
<tr>
<td><strong>HTN</strong></td>
<td>42</td>
<td>52</td>
<td>36</td>
<td>53</td>
</tr>
<tr>
<td><strong>DM, %</strong></td>
<td>9</td>
<td>12</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td><strong>No meds</strong></td>
<td>2.5</td>
<td>2.6</td>
<td>2.3</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>Sys BP</strong></td>
<td>146</td>
<td>148</td>
<td>148</td>
<td>148</td>
</tr>
</tbody>
</table>
Two years of an aggressive exercise program reduced injurious falls but not overall fall rates.
Calcium homeostasis

GUT

0.5 - 1.5 gm

ECF
1-2 gm

KIDNEY

0.35 - 0.6 gm

Bone
1500 gm

0.15 - 0.4 gm
Meta-analysis (17 RCTs) show calcium reduces fracture risk

<table>
<thead>
<tr>
<th></th>
<th>Risk Reduction (95% C.I.)</th>
<th>NNT (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium+/-Vitamin D</td>
<td>12% (5-17)</td>
<td>63 (37-192)</td>
</tr>
</tbody>
</table>

Lancet 2007;370:657-666
WHI: Calcium reduces fracture rate (N=36282, 62 yrs of age, 7 yrs follow-up)

<table>
<thead>
<tr>
<th></th>
<th>Calcium + D+</th>
<th>Placebo</th>
<th>Hazard Ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip fracture rate/year (%)</td>
<td>0.14</td>
<td>0.16</td>
<td>0.88 (0.72-1.08)</td>
</tr>
<tr>
<td>Intention to treat</td>
<td>0.10</td>
<td>0.14</td>
<td>0.71 (0.52-0.97)</td>
</tr>
<tr>
<td>Adherent patients ++</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+ Calcium 1000 mg/d + Vitamin D 400 I.U./d
++ Took 80% or more of medication
# Calcium Content

<table>
<thead>
<tr>
<th>Food</th>
<th>Calcium (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Mills Total (3/4 cup)</td>
<td>1,000*</td>
</tr>
<tr>
<td>Lactaid Calcium Enriched Milk (1 cup)</td>
<td>500*</td>
</tr>
<tr>
<td>Silk Almondmilk or soymilk (1 cup)</td>
<td>450*</td>
</tr>
<tr>
<td>Orange juice, with calcium (1 cup)</td>
<td>350*</td>
</tr>
<tr>
<td>Yogurt, plain, nonfat (6 oz.)</td>
<td>340</td>
</tr>
<tr>
<td>Milk (1 cup)</td>
<td>300</td>
</tr>
<tr>
<td>Yogurt, fruited, nonfat (6 oz.)</td>
<td>260</td>
</tr>
<tr>
<td>Sardines, canned (3 oz.)</td>
<td>250</td>
</tr>
<tr>
<td>Salmon, canned, with bones (3 oz.)</td>
<td>240</td>
</tr>
<tr>
<td>Mozzarella, Part skim (1 oz.)</td>
<td>220</td>
</tr>
<tr>
<td>Swiss cheese (1 oz.)</td>
<td>220</td>
</tr>
<tr>
<td>Frozen yogurt, premium (1/2 cup)</td>
<td>200</td>
</tr>
</tbody>
</table>

* Contains added calcium
## Calcium Content (cont’d)

<table>
<thead>
<tr>
<th>Food</th>
<th>Calcium (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheddar cheese (1 oz.)</td>
<td>190</td>
</tr>
<tr>
<td>Greek yogurt, plain, nonfat (6 oz.)</td>
<td>190</td>
</tr>
<tr>
<td>Cottage cheese, 2% (1/2 cup)</td>
<td>130</td>
</tr>
<tr>
<td>Spinach (1/2 cup cooked)</td>
<td>120</td>
</tr>
<tr>
<td>Frozen yogurt, regular (1/2 cup)</td>
<td>100</td>
</tr>
<tr>
<td>Almonds (23 nuts, 1 oz.)</td>
<td>80</td>
</tr>
<tr>
<td>Bok choy (1/2 cup cooked)</td>
<td>80</td>
</tr>
<tr>
<td>Kale (1/2 cup cooked)</td>
<td>60</td>
</tr>
<tr>
<td>Edamame, shelled (1/2 cup cooked)</td>
<td>50</td>
</tr>
<tr>
<td>Cream cheese, tub (2 Tbs.)</td>
<td>40</td>
</tr>
<tr>
<td>Broccoli, shopped (1/2 cup cooked)</td>
<td>30</td>
</tr>
</tbody>
</table>

* Contains added calcium
Calcium (1000 mg/day) and Vitamin D reduce steroid effect on bone density.
Calcium and risk for MI

Study design:
190 studies in the published literature, 1966-2010 but 162 excluded (111 too small, 30 too short, 21 poor design).

15 studies included
- 5 with “patient level” CV outcome data
- 6 with partial CV outcome data
- 4 with no CV outcome data

Patient level data available on 63% (8151/11921)
Calcium and risk for MI

Patient outcomes

The CI for MI is very wide and barely significant
NS for CVA and mortality
How much Vitamin D should you recommend?

Vitamin D is a hormone (i.e. a mediator)!!
Calcium absorption
Immune response
Inflammatory response
Soft tissue

Do you need to “treat to a level?”
2011 IOM target 50 nmol/L for “efficacy”
Vitamin D deficiency is common

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Location</th>
<th>Mean Age</th>
<th>Vitamin D deficiency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis center</td>
<td>Italy</td>
<td>68</td>
<td>76</td>
</tr>
<tr>
<td>Chronic shoulder pain</td>
<td>MN</td>
<td>10-65</td>
<td>93</td>
</tr>
<tr>
<td>Women with hip fx</td>
<td>UK</td>
<td>81</td>
<td>70</td>
</tr>
<tr>
<td>Women with OA</td>
<td>Boston</td>
<td>66</td>
<td>22</td>
</tr>
<tr>
<td>Osteoporosis patients</td>
<td>Spain</td>
<td>69</td>
<td>67</td>
</tr>
<tr>
<td>Osteoporosis patients</td>
<td>N. Am</td>
<td>71</td>
<td>52</td>
</tr>
<tr>
<td>on active therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis patients</td>
<td>S. Calif.</td>
<td>--</td>
<td>53</td>
</tr>
<tr>
<td>Hospital fx patients</td>
<td>MN</td>
<td>&gt; 50</td>
<td>97</td>
</tr>
</tbody>
</table>

Is it time to stop worrying about vitamin D? USPSTF says yes!

<table>
<thead>
<tr>
<th></th>
<th>Risk Ratio (95% C. I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality overall</td>
<td>0.83 (0.70-0.99)</td>
</tr>
<tr>
<td>Mortality, institutional</td>
<td>0.72 (0.56-0.94)</td>
</tr>
<tr>
<td>Mortality, non institutional</td>
<td>0.93 (0.73-1.18) NS</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.96 (0.72-1.29) NS</td>
</tr>
<tr>
<td>Any fracture</td>
<td>0.98 (0.82-1.16) NS</td>
</tr>
<tr>
<td>Any fall</td>
<td>0.84 (0.69-1.02) NS</td>
</tr>
</tbody>
</table>

Ann Inter Med 2015; 162:109-122, 133-140
# Current “target” levels for Vitamin D

<table>
<thead>
<tr>
<th>Category</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency</td>
<td>&lt;20 ng/mL</td>
</tr>
<tr>
<td>Probably normal</td>
<td>20-30 ng/mL</td>
</tr>
<tr>
<td>Optimal</td>
<td>30-50 ng/mL</td>
</tr>
<tr>
<td>Possibly toxic</td>
<td>&gt; 50 ng/mL</td>
</tr>
<tr>
<td>Clearly toxic</td>
<td>&gt;499 ng/mL</td>
</tr>
</tbody>
</table>

*Ann Inter Med 2015; 162:109-122*
Vitamin D supplement of 6-800 units/d is adequate to maintain levels.

Vitamin D supplement levels

Annals Intern Med 2012; 156:425-437
Vitamin D treatment strategies

Recommended daily
- Age 19-50 years: 600 units/d
- Age > 50 years: 600-800 units/d

Deficiency treatment
- 50,000 units/week for 8 weeks
- or
- 6000 units/d
- Then...
- 1500-2000 units/d for maintenance

J Clin Endocrine Metab 2011;97:1-20
Bisphosphonates

Inhibits bone resorption
Renal clearance (avoid when GFR under 30-35)
Long “terminal” half life for alendronate (i.e. is stored in the bone and recycled for 10-20 years)
Work in all age groups
Bisphosphonates are your preferred treatment

- Bisphosphonates
- Estrogens
- SERM
US: Alendronate reduces fracture rate in severe osteoporosis
(T< -2.1 and fracture history, 1996)

Placebo

Alendronate

Proportion of women with fracture

Hip Fracture

2.2% / 3 years

51% lower hip fx

1.1% / 3 years

Lancet 1996;348:1538
1998 US study: Alendronate **DID NOT** reduce fracture rate in patients with osteopenia (T<-1.6)

<table>
<thead>
<tr>
<th>Type of FX</th>
<th>Placebo (N=2218)</th>
<th>Alendronate (N=2214)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>1.1%</td>
<td>0.9%</td>
<td>0.79 (0.43-1.44)</td>
</tr>
<tr>
<td>Wrist</td>
<td>3.2%</td>
<td>3.7%</td>
<td>1.19 (0.87-1.64)</td>
</tr>
</tbody>
</table>
Annual Zoledronate infusions reduce hip fracture rates

Hazard ratio, 0.59 (95% CI, 0.42–0.83)
P=0.002

Cumulative Incidence [%]

Month

No. at Risk
Zoledronic acid
Placebo

3875  3807  3674  3553  3494  3387  3161
3861  3806  3694  3577  3499  3397  3144

41% lower hip fracture rate
Hip BMD declines slightly after 5 years among patients on alendronate but fracture rate did not.

NS change in fx rate
Alendronate continued
Alendronate stopped

JAMA 2006;296:2932
Alendronate and ERT substantially improve BMD at three years.
Alendronate stabilizes BMD after discontinuation of ERT

Mean % change from baseline (95% CI)

Femoral Neck

P < 0.01

P < 0.05

Arch Intern Med 2003;163:789-794
Alendronate at HALF DOSE reduces steroid effect on bone density

Lumbar Spine

Mean (± SE) percent change in bone mineral density

0 12 24 36 48

Week

10 mg of alendronate
5 mg of alendronate
Placebo

Bisphosphonates now challenged

September 2011. FDA report on bisphosphonates:

“The safety of long-term bisphosphonate therapy continues to be unclear as study results are conflicting as to whether or not ONJ, atypical femoral fractures or esophageal cancer are associated with use of bisphosphonates for the prevention and treatment of osteoporosis… findings with increased duration of exposure to oral bisphosphonates, with the highest prevalence observed at 4 or more years of use.”
Bisphosphonates: The dark side

- Jaw osteonecrosis
- Myopathy
- “Chalk stick” fractures
- Acute MI
- AF
Black box warning: Jaw osteonecrosis

2004 report of unexpected cluster in patients with malignancies on iv bisphosphonates. Also seen in patients with osteoporosis on oral agents (7/63).
Jaw osteonecrosis
Bisphosphonates and jaw osteonecrosis (N=368, 2006 literature review)

Diagnoses

- Multiple myeloma 46.5%
- Metastatic breast CA 38.8%
- Metastatic prostate CA 6.2%

Therapies

- Zoledronate/Pamidronate 94%
- Oral Alendronate 4.2%
Myopathy

In 2008 the FDA issued a warning about the “possibility” of “severe and sometimes incapacitating bone, joint, and/or muscle pain in patients taking bisphosphonates.”
Femoral shaft fractures

In 2008, Neviaser et al reported a case series of 20 patients with low energy transverse or shot oblique femoral fractures, 19 taking alendronate. RR calculated at 139 (95% C.I. 19-939)
Femoral shaft fractures
**Meta-analysis of bisphosphonate trials:**

**Risk for fracture by type for 3 years of treatment**

<table>
<thead>
<tr>
<th>Type of fracture</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip prevented:</td>
<td>90</td>
</tr>
<tr>
<td>Subtrochanteric induced:</td>
<td></td>
</tr>
<tr>
<td>High risk from bisphosphonate</td>
<td>725</td>
</tr>
<tr>
<td>Low risk from bisphosphonate</td>
<td>2899</td>
</tr>
</tbody>
</table>

* Hypothetical risk limits, literature suggests average risk is 2.3.

Subtrochantic fracture risk highest after five years of bisphosphonate use

<table>
<thead>
<tr>
<th>Transient</th>
<th>&lt; 3 years</th>
<th>3-5 years</th>
<th>≥ 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio</td>
<td>1.0</td>
<td>0.9 (NS)</td>
<td>1.59 (NS)</td>
</tr>
</tbody>
</table>

JAMA: 2011;305:783-789
Bisphosphonate use increased risk for subtrochanteric fractures but risk disappeared within 2 years of stopping

<table>
<thead>
<tr>
<th>Bisphosphonate use</th>
<th>Adjusted Relative Risk</th>
<th>Adjusted Absolute Risk Per Patient Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever</td>
<td>47.3</td>
<td>1/2000</td>
</tr>
<tr>
<td>&lt; 1 yr off</td>
<td>42.9</td>
<td>1/2000</td>
</tr>
<tr>
<td>1-2 yrs off</td>
<td>3.5</td>
<td>&lt; 1/10,000</td>
</tr>
<tr>
<td>&gt; 2 yrs off</td>
<td>3.2</td>
<td>&lt; 1/10,000</td>
</tr>
</tbody>
</table>

Acute myocardial infarction (2014)

In the VAMC cohort of 14,256 followed after femoral or vertebral fractures, 1998, bisphosphonate use was associated with increased risk for an acute MI.
Bisphosphonate use and increased risk for AMI

Acute MI RR = 1.38

% no AMI
Atrial fibrillation (2014)

A meta-analysis of RCT and cohort data from 135,347 patients showed an increased risk for AF

Am J of Cardiology 2014:133: 1815 - 1821
Bisphosphonate use and increased risk for atrial fibrillation

Pooled po and iv bisphosphonate
AF RR= 1.28
<table>
<thead>
<tr>
<th>Bisphosphonates side by side</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td>Alendronate</td>
</tr>
<tr>
<td>Risedronate</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Zolendronate</td>
</tr>
</tbody>
</table>
Do not treat osteopenia with bisphosphonates

<table>
<thead>
<tr>
<th>Age</th>
<th>Femoral neck T-score</th>
<th>2005: Cost benefit analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-1.5</td>
<td>-2.0</td>
</tr>
<tr>
<td>Age 55</td>
<td>$255,823</td>
<td>$94,386</td>
</tr>
<tr>
<td>Age 65</td>
<td>$283,933</td>
<td>$92,409</td>
</tr>
<tr>
<td>Age 75</td>
<td>$322,250</td>
<td>$108,714</td>
</tr>
</tbody>
</table>
Patients who take their bisphosphonates do better!
(N=35,537, national cohort)

<table>
<thead>
<tr>
<th>Persistent (%)</th>
<th>Non-persistent (%)</th>
<th>RR (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphos use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥80%</td>
<td>&lt;80%</td>
<td></td>
</tr>
<tr>
<td>Vertebral fracture</td>
<td>1.7</td>
<td>2.6</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>1.3</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Mayo Clin Prac 2006;81:1013-1022
When should your patients take a bisphosphonate holiday?

- 5 years for alendronate
- Follow BMD and resume if decline
- Follow BMD and switch to alternative if decline
There MAY be patients who should continue on bisphosphonates, those with persistent severe osteoporosis.

FLEX Extension (beyond 5 yrs of alendronate)

Vert fx rate

<table>
<thead>
<tr>
<th>BMD, start of extension</th>
<th>Placebo</th>
<th>Alend</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>T &lt; -2.5</td>
<td>9.3%</td>
<td>4.5%</td>
<td>21</td>
</tr>
<tr>
<td>T -2.5 to -2.0</td>
<td>5.8%</td>
<td>2.8%</td>
<td>33</td>
</tr>
<tr>
<td>T &gt; -2.0</td>
<td>2.3%</td>
<td>1.2%</td>
<td>81</td>
</tr>
</tbody>
</table>

Bisphosphonates should be used with circumspection

- When are bisphosphonates appropriate?
  - T ≤ -2.5 at the hip
  - “Advancing” osteopenia
- How long should they be used?
  - Five years
- What do you need to know about the side effects?
  - More than you thought
TIME

Estrogen

EVERY WOMAN'S DILEMMA
Mechanism:

Estrogens inhibit osteoclastic activity. The response is based on the dose, higher doses increase bone density more. Estrogens can improve bone density at any age after menopause. The improvement of bone density is lost within 1-2 years after cessation.
WHI: Combination ERT vs. placebo, hip fracture risk

34% lower hip fracture rate

JAMA 2002;288:328
PEPI: Bone density change and ERT usage

Continuous HRT

HRT started after PEPI-RCT

HRT stopped during PEPI-RCT

HRT stopped after PEPI-RCT

No HRT

Arch Intern Med 2002;162:669
WHI: Patient outcomes
Combination estrogen/progestin vs. placebo

Absolute excess events per 10,000 patient years

CAD events 7
CVAs 8
PEs 8
Invasive breast cancer 8

Total 31+

*Approximate three events for 200 women treated for five years
What about raloxifene?

- Not equal to estrogen
- Data is not substantial
Raloxifene does not reduce hip fractures (N=10,101; 5.6 year follow up; age 67.5)

(Hazard ratio, 95% C.I.)

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary events</td>
<td>NS</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>0.56 (0.38-0.83)</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>1.49 (1.0-2.24)</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>1.44 (1.06-1.95)</td>
</tr>
<tr>
<td>Vertebral fracture</td>
<td>0.65 (0.47-0.89)</td>
</tr>
<tr>
<td>Non vertebral fracture</td>
<td>NS</td>
</tr>
</tbody>
</table>
Raloxifene increases vascular event rates (N=10,101; 5.6 year follow up; Age 67.5)

Reduction of invasive breast cancer 1.2/1000 patient yrs
Reduction in vertebral fractures 1.2/1000 patient yrs
Increase in fatal stroke 0.7/1000 patient yrs
Increase in venous thromboembolic events 1.2/1000 patient yrs
Raloxifene does not match estrogens (RCT, N=619 women with TAHs)

Estrogen

Raloxifene, 60 mg or 150 mg/d

Placebo

Mean Change From Baseline, %

Months Receiving Study Drug

Arch Intern Med 2004; 164:875
What are the options for your patients who need more...enter the anabolics

- **Hormonal**
  - Teriparatide

- **Biologics**
  - Denosumab
  - Romosozumab

- **Combination therapies**
  - Estrogens and bisphosphonates
  - Teriparatide and denosumab
Teriparatide mechanism:
Intermittent PTH fraction administration has an \textit{anabolic} effect. Trabecular bone density and strength increase. Cortical bone strength increases by improving the bone thickness with little change in bone density. \textit{NOT} used with bisphosphonates.

**Dosage:**
20-40 mg subcutaneously

**Side effects:**
Myalgia
PTH thickens internal bone trabeculation and cortex with less impact on BMD.
PTH alone improves bone density more than combination or Alendronate alone.

N Engl J Med 2003;349:1221
Teriparatide works, especially at LS spine

2013 Meta-analysis:
8 RCTs, 2388 patients with osteoporosis

<table>
<thead>
<tr>
<th></th>
<th>Spine</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD increase</td>
<td>8.14%</td>
<td>2.48%</td>
</tr>
<tr>
<td>Fracture reduction</td>
<td>70.0 %</td>
<td>38.0%</td>
</tr>
</tbody>
</table>

Denosumab mechanism:
Monoclonal antibody directed against the receptor ligand (RANKL). Binding the ligand reduces osteoclastic activity. This is a “biologic” that interacts with other receptors, hence the dermatologic SE

Dosage:
60 mg subcutaneously every 6 months

Side effects:
Eczema, cellulites
Denosumab reduces hip fractures

20% lower hip fracture rate

No. at Risk
Placebo       3906  3799  3672  3538  3430  3311  3221
Denosumab     3902  3796  3676  3566  3477  3397  3311

Month 3 years
More biologic anabolics are coming
Romosozumab mechanism:
Monoclonal antibody that binds sclerostin, an osteocyte-derived inhibitor of osteoblast activity, and increases bone formation.

Dosage:
Subcutaneously monthly (at a dose of 70 mg, 140 mg, or 210 mg) or every 3 months (140 mg or 210 mg)

Side effects:
Mild local reactions
Romosozumab outperforms other anabolic agents... in osteopenia.

3.7% increase in BMD at 12 months with Romosozumab.

< 1% increase in BMD with both alendronate and teriparatide.

Placebo
Teriparatide and denosumab combination therapy

RCT, 1 year, 94 women with osteoporosis
Outcome: % BMD increase

- Fem Neck: 9.1%
- LS Spine: 4.2%

Lancet Online, May 15, 2013
## Costs of teriparatide and denosumab

<table>
<thead>
<tr>
<th>Dose</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teriparatide 20 mcg/d SC</td>
<td>$8000/yr</td>
</tr>
<tr>
<td>Denosumab 60 mg/6 mo SC</td>
<td>$2000/yr</td>
</tr>
</tbody>
</table>
Is there an optimal pharmacologic approach?

- Choose therapies that have been shown to work
  - Estrogens
  - Bisphosphonates
- Innovative therapies are in development
  - Use cautiously
  - Severe osteoporosis
Comparative benefits: NNT to prevent one fracture over 3 years

**Bisphosphonates**
- **Alendronate**: Vertebral 60-89, Hip 50-60
- **Zolendronic Acid**: Vertebral 30

Ann Intern Med 2014;161:711-756
In summary: Fracture prevention 101

- Assess risk
  - Level of frailty
  - Medications (are you contributing to risk?)
  - Hazards at home
- Emphasize the basics, intervene when needed
  - Exercise/balance (be creative!)
  - Calcium (500 - 1000 mg/day)
  - Vitamin D (800-1000 U/day)
Patient messages:

It is not thin bones that break, it is people who fall and break thin bones!

You walk to exercise because you need to be able to walk, practice, practice, practice.

Beware of the hazards at home.

Use all the options available, especially the “stick”.
Thank you

• Questions?
Recommendations
Major risk factors for osteoporosis:

- Parental history of hip fracture
- Current or past cigarette smoking
- Current or past alcoholism
- Body weight (BMI<23)
- Steroid use
- Hyperthyroid
- Early menopause, anovulatory cycles
Major risk factors for osteoporosis:

Always look at the medications
Benzodiazepines
Sedatives (Including OTCs like Tylenol PM)
Antihypertensives
Medications for neuropathies
Tricyclics
Your clinical assessment:

“Timed Up and Go (TUG)” = Chair-to 10 foot walk-to chair in ≤ 10 sec.
Balance/proprioception
Judgment/decision-making
Focus/attention/affect
Strength

“Social history”
Life style risks, e.g. alcohol
Risk taking activities
Recommendations:

• *Bone density*

Diagnosis
Patient education and motivation
To assess high risk situations
To monitor therapy every 2-3 years
Men over 80 (or over 65 if fracture history or risk factors).
Recommendations (cont):

- **FRAX** online assessment may be useful for determining whether to initiate therapy for men and women with osteopenia. The model may significantly overestimate risk.

- **Markers of bone turnover**
  
  To follow patients for response
Recommendations (cont’d)

- **Calcium**
  - 1000 - 1500 mg/day

- **Vitamin D**
  - 800 - 1000 IU/day, treat to level of over 25 ng/mL
Recommendations (cont’d)

• *Estrogens*
  Conjugated estrogen 0.3 - 0.625 mg/day
  Progestin if uterus intact but with high breast cancer risk
  Mammograms and clinical breast exams annually
  Can combine with bisphosphonates
Recommendations (cont’d)

• *Bisphosphonates*

  - Alendronate or residronate
    - 70 mg./wk. for alendronate
    - 35 mg./wk. for residronate
    - severe osteoporosis
    - osteoporosis
    - men and women on short-term corticosteroids, half dose
    - “advancing” osteopenia
Recommendations (cont’d):

-Zoledronate

- infusion therapy, every 12 months
- men on leuprolide
- alternative to alendronate and residronate
Recommendations (cont’d)

- **Tamoxifen/Raloxifene**
  - limited value, vascular risk
- **Teriparatide**
  - expensive, two years followed by bisphosphonate
- **Calcitonin**
  - ? painful stress fractures
Recommendations (cont’d)

• **Denosumab**
  - 60 mg subcutaneously every 6 months

• **Combination therapy**
  - estrogens and bisphosphonates
  - teriparatide and denosumab