What’s new in Osteoporosis

Jesse A Pewarchuk, MD FRCPC
Table of Contents

Section 1: Osteoporosis in 2012
Section 2: Diagnosis of Osteoporosis – FRAX & CAROC
Section 3: Treatment of Osteoporosis
Section 4: Drug Costs
Section 5: Drug Holidays
Section 6: Glucocorticoids
Section 7: Men
Section 8: Osteonecrosis
Section 9: Atypical Fractures
What is osteoporosis in ‘13

• Defined based on fracture risk not bone density (major change from 2002)!
• Osteoporosis: High risk of fragility fracture
  – HIGH RISK: Risk of fracture > 20% over next 10 years
  – MODERATE: Fracture Risk 10-20% over next 10 years
  – LOW RISK: Risk of fracture < 10% over next 10 years
Who to screen??
Who would the experts screen?

<table>
<thead>
<tr>
<th>Adults aged 50 to 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragility Fracture</td>
</tr>
<tr>
<td>Prolonged Glucocorticoid use</td>
</tr>
<tr>
<td>Use of other high risk medications</td>
</tr>
<tr>
<td>Premature gonadal failure (before 45) Hypogonadism</td>
</tr>
<tr>
<td>Malabsorption syndrome</td>
</tr>
<tr>
<td>Primary</td>
</tr>
<tr>
<td>Parental Hip Fracture</td>
</tr>
<tr>
<td>Vertebral Fracture or Osteopenia on X-ray</td>
</tr>
<tr>
<td>Active smoking</td>
</tr>
<tr>
<td>&gt; 3 alcoholic beverages per day</td>
</tr>
<tr>
<td>Body weight below 60 kg</td>
</tr>
<tr>
<td>Weight loss of &gt; 10% from age 25</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adults under age 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism</td>
</tr>
</tbody>
</table>

Return to menu
Great, but where’s your calculator?

- Two options endorsed by Osteoporosis Canada
  - WHO’s FRAX risk calculation tool
  - CAROC’s Risk index

- Both are only valid if aged 50 or over, no valid tool exists for people under 50.

- Outstanding concordance between the two!
FRAX!

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: Canada

Name/ID: A. Woman

About the risk factors

**Questionnaire:**

1. Age (between 40-90 years) or Date of birth
   - Age: 67
   - Date of birth: MM DD

2. Sex
   - Male
   - Female

3. Weight (kg)
   - 60

4. Height (cm)
   - 170

5. Previous fracture
   - No
   - Yes

6. Parent fractured hip
   - No
   - Yes

7. Current smoking
   - No
   - Yes

8. Glucocorticoids
   - No
   - Yes

9. Rheumatoid arthritis
   - No
   - Yes

10. Secondary osteoporosis
    - No
    - Yes

11. Alcohol 3 or more units per day
    - No
    - Yes

12. Femoral neck BMD (g/cm²)
    - Select DXA
    - [ ]

[ ] Clear [ ] Calculate

---

**BMI 17.3**

The ten year probability of fracture (%) without BMD

- [ ] Major osteoporotic 20
- [ ] Hip fracture 8.0

---

http://www.sheffield.ac.uk/FRAX/tool.jsp?country=19

[Return to menu]
FRAX

• Developed by the WHO
• Each country has individualized formulae taking into account local risk patterns
• Very simple to use and gives a very accurate, well validated risk score
FRAX Variables

- Age
- Gender
- Rheumatoid arthritis
- Secondary osteoporosis (disorder strongly associated with OP)
- A prior osteoporotic fracture (including vertebral fracture)
- Parental history of hip fracture
- Femoral neck BMD
- Current smoking
- Low body mass index (kg/m²)
- Alcohol intake (3 or more drinks/d)
- Oral glucocorticoids ≥5 mg/d of prednisone for ≥3 m (ever)
FRAX

• Not included in FRAX currently but also an independent predictor of fragility fracture is a history of Diabetes.
FRAX Advantages

• Web-based format that is easily accessed and can be bookmarked
• Very user friendly
• Includes wide variety of important risk factors
• DOES NOT REQUIRE BONE MINERAL DENSITY
• BMD helps refine the score but is not essential
FRAX Disadvantages

• Must use the WHO sponsored website
• No downloadable program for PC, need to have web access to use
• Only iPhone/iPad app is $5.99 at App Store
• May underestimate effect of high dose prolonged steroids
• No access to base formulae, just the output
• Takes 30 seconds to input the variables
### Clinical Information provided by the referring physician

No clinical information provided.

A detailed patient interview was conducted during the bone densitometry appointment. Additional clinically relevant information obtained during that interview is documented in this report and has been included in the fracture risk assessment and in the interpretation of the bone densitometry results.

### Diagnostic Category

Osteoporosis

Seminiski et al, Can Assoc Radiol J 2005; 56:178-188

### Ten Year Fracture Risk (in untreated individuals)

High fracture risk (> 20%)

Fracture risk applies for a finite period and may change depending on clinical circumstances. Fracture risk is reduced by effective therapy.

Seminiski et al, Can Assoc Radiol J 2005; 56:178-188

### Interpretation
CAROC

• Simple system developed in Edmonton and used by radiologists across the nation
• Base Risk is derived from a nomogram of bone mineral densities
• The patient is pushed into the next risk category by having a fragility fracture OR greater than 3 months of glucocorticoids
• If both risk factors, automatically High Risk
CAROC: Advantages

• Very simple to use, it’s laid out for you on paper in an unambiguous manner
CAROC disadvantages

• Does not take into account most of the contributing risk factors
• For example, does not take into account important items such as family history that are heavily weighted in FRAX
Prevention: Exercise

• Exercise involving RESISTANCE TRAINING or weight bearing aerobic exercise
• Exercises focusing on BALANCE (tai chi, etc) should be considered in those at fall risk
• In nursing home patients, HIP PROTECTORS should be used in those deemed high risk for falling
PREVENTION: Vitamins/Minerals

• These numbers apply to people aged 50+
  – Calcium (all risk groups): Total Daily Dose (diet plus supplement): 1200 mg
  – Vitamin D (low risk): 400-1000 iu daily
  – Vitamin D (mod risk): 800-1000 iu daily
  – Vitamin D (high risk): up to 2000 iu daily plus measurement of body Vitamin D levels after 4 months of supplementation
PREVENTION: LIFESTYLE

• Smoking Cessation
• Elimination of excess alcohol consumption
Treatment

• Tailored based on risk category

• Nonpharmacologic
  – Diet
  – Lifestyle
  – Vitamins and minerals

• Pharmacologic
Oral Bisphosphonates

• Examples:
  – Alendronate, Risedronate

• Mechanism:
  – Incorporated into bone, prevents osteoclast action

• Adverse Effects:
  – Peptic Ulcer Disease, Esophagitis, Dyspepsia
  – Rare: Osteonecrosis of jaw, atypical femur fracture

• Important that these be taken on empty stomach or poor absorption
Oral Bisphosphonate Benefits

- Risedronate reduces vertebral fractures by 41-49% and non-vertebral fractures by 36% over three years
- Hip fractures reduced by 26%
- Similar numbers for alendronate
- NOTE: Etidronate (Didrocal) is the only bisphosphonate with no proven reduction in hip fracture

IV Bisphosphonate

• Examples:
  – Zoledronic Acid/Aclasta

• Side effects:
  – IV route eliminates very common GI side effects and assures compliance
  – Flu like symptoms following administration are common (10%) but diminish on subsequent doses
  – Risk of osteonecrosis reported less than 1/10,000
  – Rare atypical femur fractures

IV Bisphosphonate

• Zoledronic Acid is much better:
  – Vertebral Fracture 68% relative risk reduction
  – Hip fracture 40% relative risk reduction
  – Nonvertebral 20% relative risk reduction

• But Zoledronic acid goes further than simply fracture prevention. It has been shown to reduce mortality by 28% vs placebo when given to patients with recent hip fracture.
  NNT = 29

SERM Agents

• Raloxifene
• Side Effects:
  – Hot flushes (less than 10%)
  – Leg cramps (uncommon)
  – Increased risk of VTE (OR = 2.08)
• Mechanism:
  – Stimulates estrogen receptors on bone
• Increases bone density and shown to reduce vertebral fractures (no effect shown on other sites); RR = 0.60; NNT = 99 to 2381 over 2 years

Calcitonin

• Calcitonin Nasal Spray
• Inhibits osteoclast function
• Side Effects:
  – Rhinitis > 10%
• Modest effect makes this second line agent
• Decreased vertebral fracture rate - but barely RR = 0.79 (CI 0.62 – 1.00)
• Can also be used as an adjuvant analgesic in acute vertebral fractures

Calcitonin

- In 2012, the European Medicines Agency determined that long term Calcitonin use increases Cancer risk by 2.4%.
- Osteoporosis Canada now advises not to use this medication as the minimal benefit does not justify this risk.
- This does NOT apply to short term use for vertebral compression fracture pain.
PTH analogues

• Synthetic recombinant peptide
• Teriparatide/Forteo (injected SQ daily)
• Side Effects:
  – Injection site pain; nausea, leg cramps, mild hypercalcemia, long term use concern of cancer
• Reduced vertebral fractures (RR 0.35, 95% CI 0.22–0.55; NNT = 11 for 21 months of treatment)
• Nonvertebral fractures (RR 0.65, 95% CI 0.43–0.98; number needed to treat = 29)

RANKL Antibodies

• Denosumab/Prolia
• An injected treatment that interferes with RANK-Ligand signaling pathways that cause bone breakdown
• Main side effect is increased eczema, cellulitis
• Reduction in fractures of all types at 3 years:
  – Vertebral 68%
  – Nonvertebral 20%
  – Hip 40%

# CO$T$ 

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>COST ($CDN) per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate 70 mg PO weekly (generic)</td>
<td>$390.00</td>
</tr>
<tr>
<td>Risedronate 35 mg PO weekly (generic)</td>
<td>$370.50</td>
</tr>
<tr>
<td>Zoledronic Acid/Aclasta 5 mg IV over 15 min ONCE</td>
<td>$735.00</td>
</tr>
<tr>
<td><strong>YEARLY</strong></td>
<td></td>
</tr>
<tr>
<td>Raloxifene 60 mg PO daily</td>
<td>$941.20</td>
</tr>
<tr>
<td>Teriparatide 20 mcg SQ daily (not available)</td>
<td>$12,000</td>
</tr>
<tr>
<td>Calcitonin 200 iu intranasally daily</td>
<td>$819.00</td>
</tr>
<tr>
<td>Vitamin D 1000 iu PO daily</td>
<td>$32.85</td>
</tr>
<tr>
<td>Calcium 500 mg PO BID (generic Calcium Carbonate)</td>
<td>$20.50</td>
</tr>
<tr>
<td>Denosumab/Prolia</td>
<td>$734.00</td>
</tr>
<tr>
<td>Didrocal Pack (generic)</td>
<td>$134.00</td>
</tr>
</tbody>
</table>

Quotes from LONDON DRUGS, Colwood Corners, Victoria BC.  
**Priced as of February 13, 2011.**

[Return to menu]
What is best? Menopausal Women

• First-line treatments recommended for prevention of hip, vertebral and nonvertebral fractures:
  – alendronate,
  – risedronate,
  – zoledronic acid
  – Denosumab
Guidelines for Menopausal Women

- Second-line for prevention of vertebral fractures (not other types)
  - Raloxifene
- If other indication for hormone replacement, this can function as first line therapy to prevent hip, vertebral and non vertebral fractures
- If intolerant of ALL FIRST LINE or SECOND LINE AGENTS, calcitonin and etidronate (didrocal) are recommended
Drug Holidays

• “Individuals at high risk for fracture should continue osteoporosis therapy without a drug holiday” – 2010 Canadian Osteoporosis Guidelines

• FLEX trial: 50% more fractures in those stopping Fosamax after 5 years of therapy over subsequent 5 years compared to those who continue

• HORIZON 6 year data showed similar divergence
Who do I offer Holidays to?

• Patients that were started purely based on BMD and are actually at low or medium risk when FRAX calculation is applied
• Medium risk FRAX/CAROC score
Who do I offer Holidays to?

• Brief holiday for dental surgery (3 months on each side of procedure)
  – Done more to satisfy Dentist demands
  – An ongoing Cochrane Review is looking into this question specifically with dental surgery

• 2008 BONJ Guidelines from Journal of Rheumatology suggest this, however concede there is no evidence to support the practice
Who should not be offered a Holiday?

• Anyone at high risk should be only given “drug holidays” for brief time periods to overcome dentist apprehension
• Note that BONJ risk is correlated with dosage, and risk factors such as poor oral hygiene, smoking, periodontal disease.
• These are all modifiable risk factors!
Osteoporosis in men: therapy

• Amino-bisphosphonates are standard approach
  – effective in men with low sex steroids
  – Men with hip fractures, suggest IV zoledronic acid
• Teriparatide good for severe osteoporosis, especially if corticosteroid induced
  – low BMD and multiple fractures, especially spinal
• Testosterone not a good therapy for osteoporotic men
  – No fracture reduction data
  – No data on combinations with testosterone
• Canadian Guidelines only support Bisphosphonates for male osteoporosis. Prolia approved for men by FDA, not yet by Health Canada. Data supports its use.
Glucocorticoid-Induced Osteoporosis

• Glucocorticoids alter BMD/fracture relationship
  – Bone weaker than BMD suggests
  – Rapid losses in bone strength
• Weakens muscle and increases falls risk
• FRAX likely
  – underestimates for doses >7.5 mg/d
  – overestimates for doses <2.5 mg/d
  – High dose intermittent and inhaled steroids may also not be adequately considered
• Adjustment for FRAX coming soon
Treatment of Glucocorticoid-Induced Osteoporosis

- ALL PATIENTS should receive prophylactic Vitamin D and Calcium. (Cochrane Review supports)
- Bisphosphonate efficacy similar for glucocorticoid-induced and postmenopausal osteoporosis
- Zoledronic acid vs risedronate
  - superiority for zoledronic acid
- Teriparatide vs alendronate
  - teriparatide significantly less new vertebral fractures than alendronate
- Teriparatide vs risedronate
  - At 18 months teriparatide had greater BMD and bone strength than risedronate
Glucocorticoid-Induced Osteoporosis recommendations

• Low risk – Vitamin D and Calcium
• Medium risk – any non-etidronate bisphosphonate
• High risk – any non-etidronate bisphosphonate or teriparatide
• Data-free zone
  – Indications: Premenopausal women?
  – Surveillance: frequency of DXA, use BTMs?
  – Duration of Therapy: What after teriparatide?
  – Use of therapy after glucocorticoid discontinuation
  – Drug holidays?

Grossman et al. 2010, Arth Care Res; Harrison et al. 2011, JBMR
What’s my practice?

- There is a lot of steroid use at doses above 7.5 mg Prednisone for over 3 months in GIM
- Do a FRAX score at the outset of therapy (usually no BMD available)
- Assume glucocorticoid use in FRAX
- ALL patients get full dose Vitamin D and Cal
- Medium and high risk patients are offered bisphosphonates
When to stop?

- At the conclusion of glucocorticoid therapy, check a BMD
- If high risk, continue agent
- If not high risk, stop, but re-check BMD in 3 years.
Osteonecrosis of the Jaw

- A condition of exposed jaw bone for > 8 weeks
- Incidence unknown but estimated to be under 1/10,000 for osteoporosis patients – a large German registry study put the rate at <1/100,000 for osteoporosis dosage
- Much more common in patients receiving high dose therapy for cancer – the rate may be as high as 0.1% in this unique population

BRONJ

• Recent evidence from the dental literature suggests BRONJ is the result of actinomyces infection
• This is not a “spontaneous problem” and has clear risk factors
• Can and does occur without any osteoporosis medication

BRONJ

• Patients should be told that this condition can occur and is very rare but can be persistent
• Good oral hygiene must be stressed
• A pre-bisphosphonate dental exam is not recommended for osteoporosis patients (it is for cancer patients, however)
• Patients should stop smoking and drink minimal alcohol

Atypical Fractures

• So-called “Chalk-stick fractures”
• Often spontaneous fractures in areas that are not typical for osteoporosis such as the femoral shaft and subtrochanteric femur
Atypical Fractures

• Very large case-control study between comparing postmenopausal women age 68 or older taking > 5 years of bisphosphonates with matched controls taking < 5 years
• Huge population of 52,595 studied


Return to menu
Atypical Femoral Fractures

• 71 extra patients had an atypical femoral fracture at year 6 on bisphosphonates compared to those who stopped

• 46 more patients had a fracture of this sort by 7 years on bisphosphonates

• BUT, incremental reduction in typical osteoporotic fractures continued beyond 5 years if medication was continued (OR, 0.76; 95% confidence interval, 0.63-0.93)
Atypicals

• Essentially, so long as only high risk patients are treated, the risk/benefit analysis favors treatment
RebalanceMD Osteoporosis Clinic

- Physicians desiring assistance with the management of Osteoporosis cases can consult the Osteoporosis Clinic
- Common referral form available upon request from RebalanceMD
- Currently clinic consists of consultation services, however, plans are in place to provide allied health care services in future
Summary

• Osteoporosis has changed a great deal in the last 5 years
• Risk stratification is key to determining who to treat
• Many treatment options are available
• Side effects are rare and so long as high risk people are selected for treatment, the risk/benefit calculus clearly favors treatment
Thank you

For more information:
OSTEOPOROSIS CANADA
www.osteoporosis.ca
REBALANCE^MD
www.rebalancemd.com