Osteoporosis Updates

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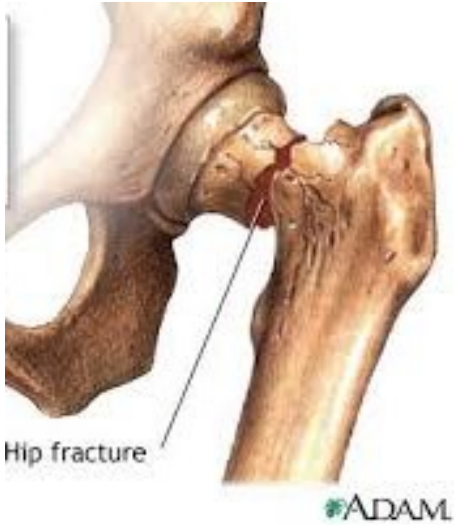
DISCLOSURE

Dr. Zhang has no relevant conflicts of interest with this activity.

LEARNING OBJECTIVES

1. Raise the awareness of importance of osteoporosis management
2. Identify the risk factors of osteoporosis
3. Discuss the diagnosis and treatment options of osteoporosis

Osteoporosis



- Systemic skeletal disorder of compromised bone strength increased risk of fracture
- Among the 50+ adults in US
  - Low bone mass 43.4 million
  - Osteoporosis 10.2 million
- 1 in 2 women and 1 in 4 men >age 50 will have an osteoporosis-related fracture in their lifetime

Nicole C Wright, et al. Journal of Bone and Mineral Research, Vol. 29, No. 11, November 2014, pp 2520-2526

Fracture Facts!

- 2 million bone breaks a year ("2 million 2 many")[1]
- Fractures may have serious consequences[2]
  - Hip fracture
    - 10%-20% additional mortality per year
    - 20% of hip fracture patients require long-term nursing home care
    - Only 40% fully regain their pre-fracture level of independence[1]

1. National Bone Health Alliance. *2 Million 2 Many*. Available at: http://www.2million2many.org/. Accessed September 13, 2013.
2. 2. US Department of Health and Human Services. *Bone Health and Osteoporosis: A Report of the Surgeon General*. Rockville, MD: US Department of Health and Human Services, Office of the Surgeon General; 2004.

Underdiagnosed and Undertreated

- Underdiagnosed: National Osteoporosis Risk Assessment (NORA) study (200,160 postmenopausal women)[1]
  - 39.6% low bone mass
  - 7.2% osteoporosis
  - 11% already had ≥1 fracture after age 45
- Undertreated: women meeting criteria for treatment[2]
  - 15.7% not taking calcium
  - 18.6% not taking vitamin D
  - 52.7% not exercising >2 hrs per week
  - 35.3% not receiving therapy

1. Siris ES, et al. *JAMA.* 2001;286:2815-2822.
2. Schnatz PF, et al. *Menopause.* 2011;18:1072-1078.

The Clinical Challenges

- Often asymptomatic[1]
  - Until fracture occurs[1]
  - Even after some fractures (eg, 2/3 of vertebral fractures are asymptomatic)[2]
- The challenge to clinicians[1]:
  - Identify patients at high risk for fracture
  - Prevent first fracture

1. South-Paul JE. *Am Fam Physician*. 2001;63:1121-1128.
2. Lenchnik L, et al. *AJR*. 2004;183:949-958.

Recommendations for DEXA Test

USPSTF 2011 recommendations:

--women 65+ years old

--younger women whose fracture risk is equal to or greater than that of a 65-year-old white woman who has no additional risk factors,

--No recommendation of screening for osteoporosis in men)

ACPM 2009 recommendations:

--all women 65+

--all men 70+

--postmenopausal women <65 and men 50-69 yo if > 1 major or >2 minor risk factors for osteoporosis

Risk Factors for Osteoporosis

Major risk factors	Minor risk factors
• Age > 65 years • Vertebral compression fracture • Fragility fracture after age 40 • Family history of osteoporosis fracture (especially maternal hip fracture) • Systemic glucocorticoid therapy of > 3 months' duration • Malabsorption syndrome • Primary hyperparathyroidism • Propensity to fall • Osteopenia apparent on x-ray film • Hypogonadism • Early menopause (before age 45)	• Rheumatoid arthritis • Past history of clinical hyperthyroidism • Long-term anticonvulsant therapy • Low dietary calcium intake • Smoker • Excessive alcohol intake • Excessive caffeine intake • Weight < 57 kg • Weight loss > 10% of weight at age 25 • Chronic heparin therapy

Adapted from *CMAJ* 2002;167(Suppl 10):1-34.[3]

Conditions and Medications Associated with Increased Risk of Osteoporosis

- AIDS/HIV
- AS, RA and SLE
- Cushing syndrome
- Cystic fibrosis
- Diabetes mellitus
- Eating disorders
- Gastrectomy or gastric bypass
- Malabsorption syndromes (celiac disease)
- IBD (Crohn's or UC)
- Hyperparathyroidism
- Hyperthyroidism
- Hypogonadism, Amenorrhea
- Vitamin D deficiency
- Severe liver and kidney disease
- Severe liver disease
- And More

- Aluminum
- Anticoagulants (warfarin, Heparin)
- Anticonvulsants (phenobarbital, phenytoin)
- Aromatase inhibitors (Letrozole)
- Cancer chemotherapeutic drugs
- Glucocorticoids and ACTH
- Gonadotropin-releasing hormone agonists (leuprolide and goserelin)
- Immunosuppressants
- Lithium
- Proton pump inhibitors (PPIs)
- SSRIs (Citalopram, Fluoxetine, Paroxetine, Sertraline)
- Thiazolidinediones (Rosiglitazone, Pioglitazone, Troglitazone)

Diagnosis of Osteoporosis

- DEXA
  - Normal: T scores ≥ -1.0
  - Low bone mass: -1> T scores > -2.5
  - Osteoporosis: T scores ≤ -2.5
  - Severe osteoporosis: T scores ≤ -2.5 & >1 fragility fracture
- Fragility fractures
  - Even if T scores > -2.5
- FRAX
  - Treat as osteoporosis if
    - 10 year probability of major osteoporotic fracture risk ≥ 20%
    - 10 year probability of hip fracture risk ≥ 3%

Osteoporosis Management

Lifestyle modifications

- Calcium and vitamin D
- Exercise
- Smoking cessation, avoidance of excessive alcohol
- Fall prevention
- Avoid drugs that cause bone loss, eg. glucocorticoids

Pharmacologic interventions

- Antiresorptives- bisphosphonates, denosumab, romosozumab
- Anabolics- PTH analogs, romosozumab

Calcium

- Daily calcium requirement: 1000-1200 mg
- Who should take calcium supplements
  - vegan diet
  - lactose intolerance and limit dairy products
  - consume large amounts of protein or sodium, which increase secretion of calcium
  - long-term treatment with corticosteroids
  - malabsorption of calcium, eg IBD or celiac disease
- Types of calcium supplements
  - Calcium carbonate (40% elemental calcium)
  - Calcium citrate (21% elemental calcium)
  - Calcium gluconate (9% elemental calcium)
  - Calcium lactate (13% elemental calcium)
- Absorbability
  - ≤ 500 mg each time at mealtime
  - Calcium citrate absorb better, esp if on acid blockers

Vitamin D

- Recommended daily intake of Vit D 600-800 IU
- Check baseline Vit D to determine the individual needs
- Monitor Vit D level if taking high dose of Vit D
- Possible interactions with other meds:
  - Aluminum, anticonvulsant, Atorvastatin (Lipitor), Calcipotriene (Dovonex, Sorilux), Cholestyramine (Prevalite), Cytochrome P-450 3A4 (CYP3A4) substrates, Digoxin (Lanoxin), Diltiazem (Cardizem, Tiazac, others), Orlistat (Xenical, Alli), Thiazide diuretics, Steroids, Stimulant laxatives, Verapamil

Benefits of Exercise

What type?

- Weight-bearing
- Muscle-strengthening
- Balance exercises
- Flexibility exercises

Expected benefits?

- Small (1% to 2%) effect on adult BMD
- Reduces the loss of muscle mass
- May reduce risk of falls by improving strength and balance
- Regular walking decreases risk of hip fractures

Centers for Disease Control and Prevention. Injury Center. www.cdc.gov/injury.

Whom to Treat (NOF Guidelines 2010)

After exclusion of secondary causes, treat postmenopausal women and men >50 yo who have…

Osteoporosis

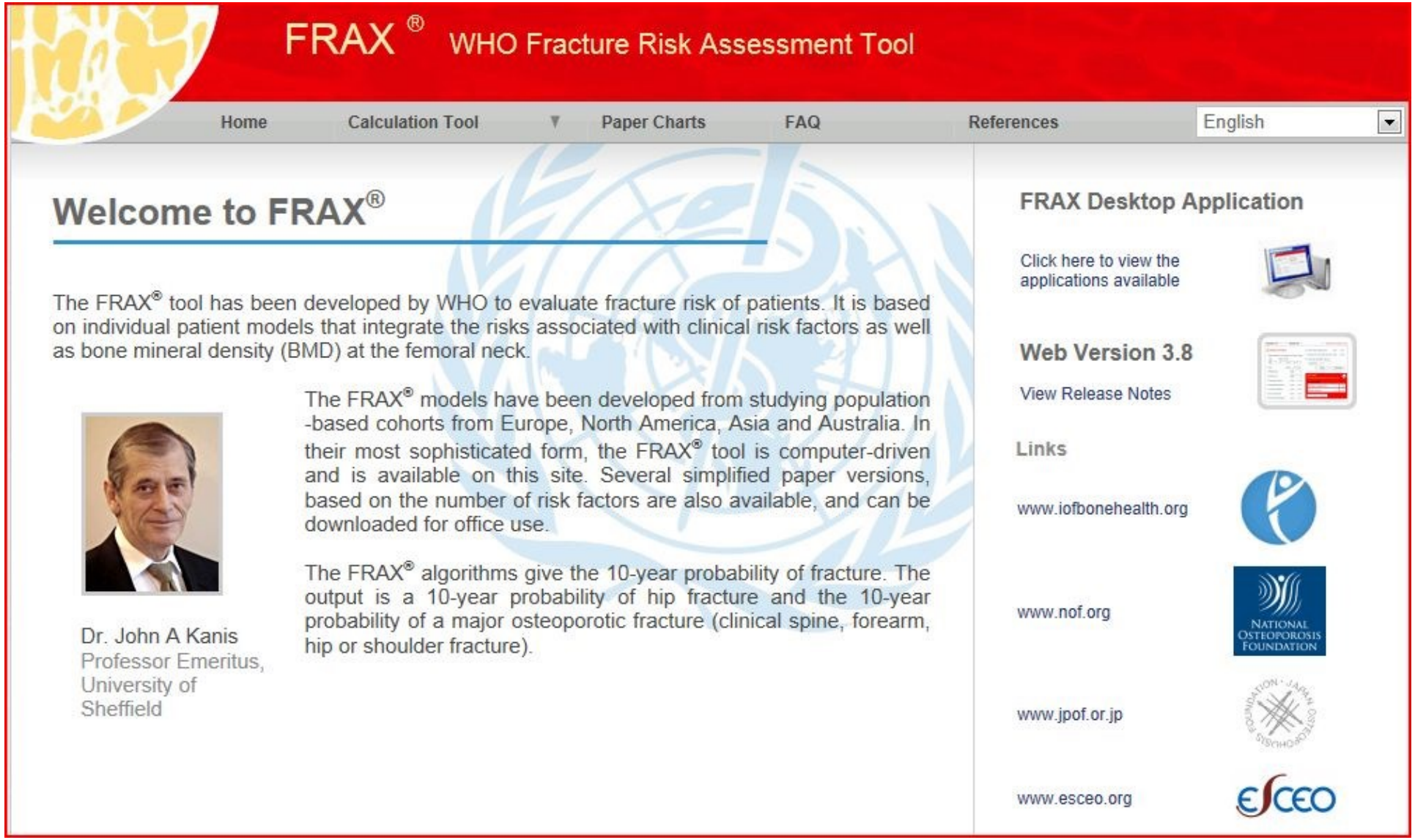
Clinical diagnosis:
Hip or spine fracture

DXA diagnosis:
T-score -2.5 or below in the spine or hip

T-scores between -1.0 and -2.5 and

10-year risk of fractures:

≥3% for hip fracture
or
≥20% for a major osteoporotic fracture


FRAX ® WHO Fracture Risk Assessment Tool
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Paper Charts
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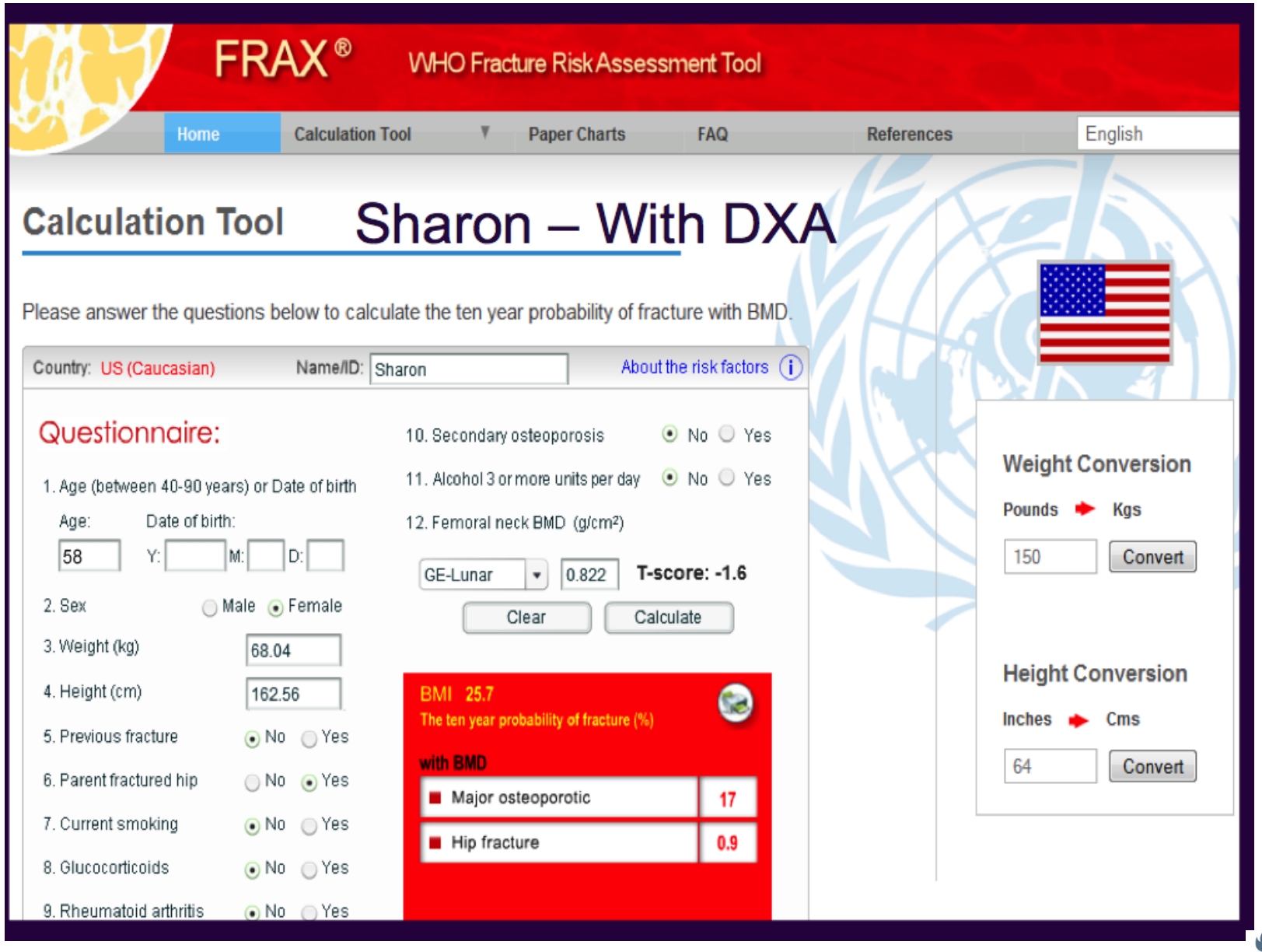
Welcome to FRAX®
The FRAX® tool has been developed by WHO to evaluate fracture risk of patients. It is based on individual patient models that integrate the risks associated with clinical risk factors as well as bone mineral density (BMD) at the femoral neck.
Dr. John A Kanis
Professor Emeritus, University of Sheffield
The FRAX® models have been developed from studying population -based cohorts from Europe, North America, Asia and Australia. In their most sophisticated form, the FRAX® tool is computer-driven and is available on this site. Several simplified paper versions, based on the number of risk factors are also available, and can be downloaded for office use.
The FRAX® algorithms give the 10-year probability of fracture. The output is a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture).
FRAX Desktop Application
Click here to view the applications available
Web Version 3.8
View Release Notes
Links
www.iofbonehealth.org
www.nof.org
NATIONAL OSTEOPOROSIS FOUNDATION
www.jpof.or.jp
www.esceo.org
ESCEO


FRAX®
WHO Fracture Risk Assessment Tool
Home
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Calculation Tool
Sharon – With DXA
Please answer the questions below to calculate the ten year probability of fracture with BMD.
Country: US (Caucasian)
Name/ID: Sharon
About the risk factors
Questionnaire:
1. Age (between 40-90 years) or Date of birth
Age: 58
Date of birth: Y: M: D:
2. Sex Male Female
3. Weight (kg) 68.04
4. Height (cm) 162.56
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)
GE-Lunar 0.822 T-score: -1.6
Clear Calculate
BMI 25.7
The ten year probability of fracture (%)
with BMD
Major osteoporotic 17
Hip fracture 0.9
Weight Conversion
Pounds Kgs
150 Convert
Height Conversion
Inches Cms
64 Convert

Antiresorptive and Anabolic Therapies

- Antiresorptive
  - Decrease bone resorption
  - Examples: Bisphosphonates, SERMs, calcitonin, estrogen, denosumab
- Anabolic
  - Stimulate bone formation
  - Examples: Teriparatide, Abaloparatide
- Dual benefit --increase bone formation and decrease bone resorption
  - Romosozumab

Bisphosphonates

- Alendronate: 70 mg/wk or 35 mg/wk
- Ibandronate: 150 mg/M (po) or 3 mg IV Q3M

Risedronate: 35 mg/wk or 150 mg/M

Zoledronic acid: 5 mg IV QY or Q2Y for prevention

Skeleton Effects:

- Increased BMD in the spine by 5-8% and at the hip by 3-6% after 3 years
- Reduced incidence of vertebral fractures by 40-70%
- Alendronate, risedronate and zoledronic acid reduced non-vertebral fractures (25-40%), including hip fractures (40-60%), in women
- Ibandronate: non-vertebral fracture reduction was seen in a high-risk subgroup with a baseline femoral neck T-score less than -3.0

Bisphosphonates

Contraindications/Warnings/Precautions

- Hypocalcemia
- ClCr <30 cc/min (<35 cc/min for zoledronic acid)
- For oral dosing: Esophageal stricture or impaired esophageal motility; inability to stand or sit for > 30 min (alendronate/risedronate) or >60 min (ibandronate)
- certain types of bariatric surgery, eg, Roux-en-Y gastric bypass

Oral dosing requirements

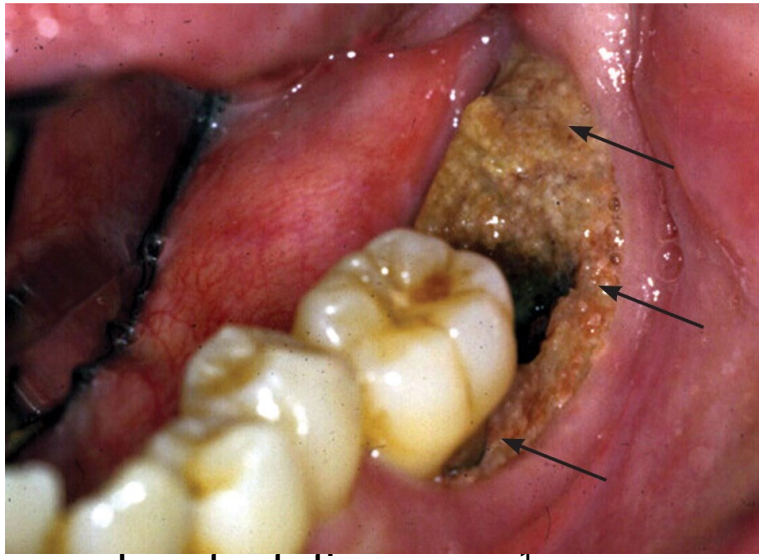
- Tablets taken on an empty stomach with 6-8 oz of water in an upright position
- Not to eat or lie down for > 30 min (alendronate and risedronate) or >60 min (ibandronate)
- Calcium and Vit D supplements, if needed, should be taken at a different time of day

National Osteoporosis Foundation. *Med Lett.* 2011;53(1360):24.

Bisphosphonates: Side Effects

- “Class warning” regarding UGI symptoms
- Influenza-like symptoms may occur after first monthly oral dose or IV bisphosphonate
- “Class warning” regarding infrequent bone, joint, and/or muscle pain
- “Class warning” regarding jaw osteonecrosis
- “Class warning” about atypical fractures following long-term therapy

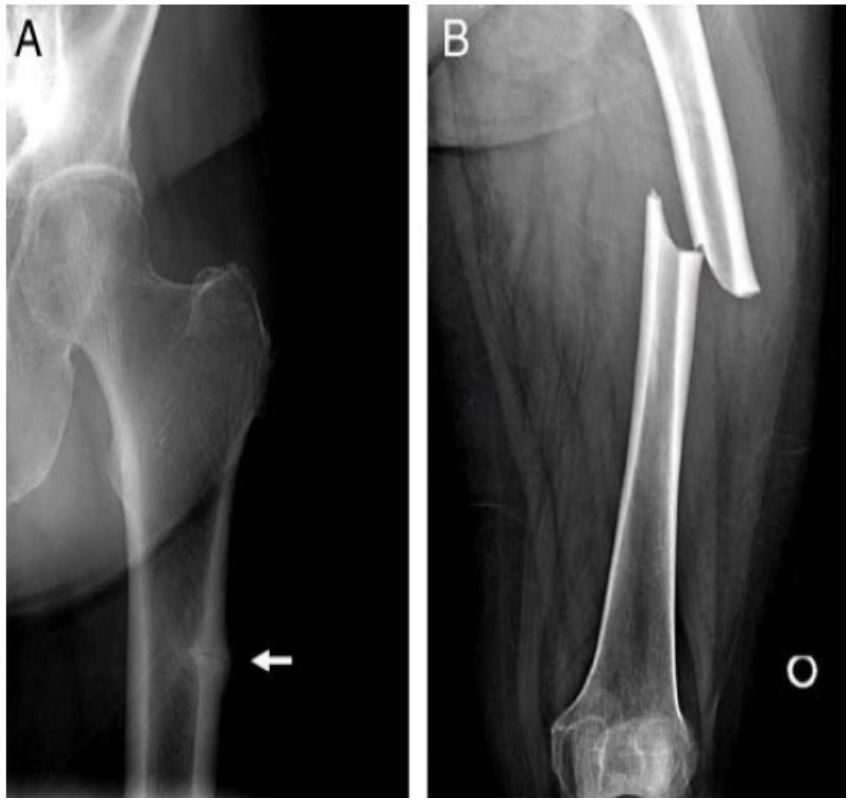
Osteonecrosis of the Jaw



- An area of exposed alveolar or palatal bone with poor healing over several months
  - 95% of cases with high-dose, chronic IV bisphosphonate for myeloma and metastatic cancer[1]
  - 5/10,000/yr in first 5 yrs of bisphosphonates, increase with duration of treatment
  - Can occur with denosumab as well[2]
  - Pain in 2/3 cases: infection may or may not be present
  - Risk factors: invasive dental procedures, oral trauma, periodontitis, poor oral hygiene, radiotherapy to the jaw, chemotherapy, corticosteroids, infection

1. Woo SB, et al. *Ann Intern Med.* 2006;144:753-761. 2. Sutton EE, Riche DM. *Ann Pharmacother*. 2012;46:1000-1009.
3. Khosla S, et al. *J Bone Miner Res.* 2007;22:1479-1491.

Atypical Fractures of Femur in Patients Taking Anti-Resorptive Agents Long Term



- May begin with stress reaction or stress fracture of lateral femoral cortex (A)
- Transverse fractures of femoral diaphysis or in subtrochanteric region (B)
- Often bilateral
- Prodromal pain in thigh or groin in 70%
- Occurs in untreated patients, but increased incidence with long-term antiresorptive therapy, particularly bisphosphonates and denosumab

Park-Wyllie LY, et al. *JAMA*. 2011;305:783-789. Shane E, et al. *J Bone Miner Res*. 2013 May 28. [Epub ahead of print]. Watts NB, Diab DL. *J Clin Endocrinol Metab.* 2010;95:1555-1565. Meier RP. *Arch Intern Med*. 2012;172:930-936.

Bisphosphonate Holidays

- In patients at high risk for fractures, continued treatment seems reasonable. Consider a drug holiday of 1- 2 years after 10 years of treatment
- For lower risk patients, consider a “drug holiday” after 4- 5 years of stability
- Follow BMD and bone turnover markers during a drug holiday period, and reinitiate therapy if bone density declines or markers increase

Watts NB et al; AACE Osteoporosis Task Force. *Endocr Pract.* 2010;16(Suppl 3):1-37.
Whitaker M, et al. *N Engl J Med*. 2012;366(22):2048-2051.

Denosumab

- Monoclonal antibody to RANKL
- 60 mg subcutaneous injection every 6 months
- 9% increase in spinal BMD after 3 years in the pivotal FREEDOM trial; 4-5% increase in hip BMD
- Reduction in fracture risk after 3 years:
  - 68% decrease in new vertebral fractures, 40% decrease in hip fractures
  - 20% decrease in nonvertebral fractures
- 8-year data: continued increase BMD, reduced bone turnover, good safety

Cummings SR, et al. *N Engl J Med*. 2009;368:756-765
Prolia (prescribing information). Thousand Oaks, CA: Amgen; June 2012.
McClung MR, et al. *Osteoporos Int*. 2013;24(1):227-235.

Denosumab: Adverse Events

- Serious infections leading to hospitalization
- Dermatitis, eczema, rashes
- Back pain, pain in the extremity, musculoskeletal pain, hypercholesterolemia, cystitis
- Pancreatitis
- Osteonecrosis of the jaw
- Significant suppression of bone remodeling

Prolia (prescribing information). Thousand Oaks, CA: Amgen; June 2012.

Estrogen Treatment (ET)

- Several approved oral and transdermal preparations
- Treats symptoms of estrogen deficiency
- Skeletal effects:
  - Decrease in biochemical markers of 50% to 60%
  - 2-year BMD increase of 4% to 6% at hip and spine
  - Decreased incidence of vertebral and hip fractures (34%) after 5 years in the Women's Health Initiative (WHI)
  - No longer first line of osteoporosis treatment
- Concern about adverse effects
- Long-term use not recommended

Rossouw JE, et al. Writing Group for the Women's Health Initiative Investigators. *JAMA.* 2002;288:321-333.

Selective Estrogen Receptor Modulator

Raloxifene (60 mg daily)

- Skeletal effects:
  - Decrease in biochemical markers of 30%
  - 3-year BMD increases of 2- 3% at hip and spine
  - Decreased vertebral fractures (30-50%) in women with pre-existing vertebral fractures or low BMD. No effect on nonvertebral or hip fractures
- Extra-skeletal effects: reduction in invasive breast cancer
- Adverse effects
  - Hot flashes
  - 2-3-fold increased risk of venous thromboembolic events
  - No increased risk of stroke, but *BBW* for increased risk of death following stroke
  - Leg cramps

PTH Analogs (Teriparatide and Abaloparatide)

- Anabolic agents—stimulates bone formation
- Teriparatide 20 µg/d SC/day; Abaloparatide 80 µg/d SC; max 2 years
- Indication: treatment of men (teriparatide) and postmenopausal women (both) with osteoporosis who are at high risk for fracture
- Skeletal Effects:
  - Increased BMD in spine by 9% and hip by 3% over 18 months
  - Reduced incidence of vertebral fractures (65%) and nonvertebral fragility fractures (53%) in women with pre-existing vertebral fractures
- Adverse reactions: arthralgia, myalgia, nausea, hypercalcemia
- BBW about osteosarcoma risk in rats

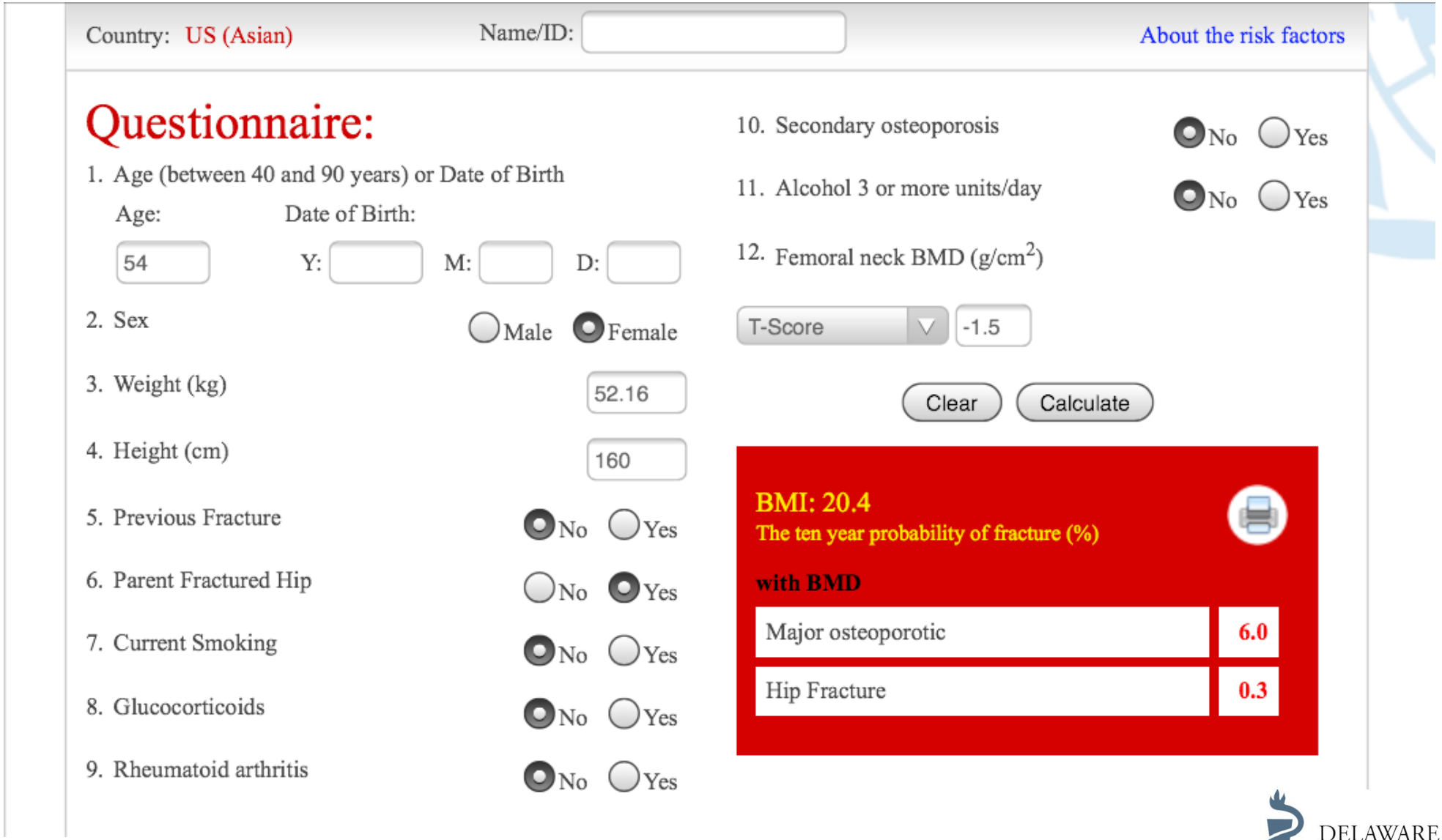
Neer RM, et al. *N Engl J Med.* 2001;344:1434-1441.
Forteo (prescribing information). Indianapolis, IN: Eli Lilly and Company; March 21, 2012.

Sclerostin Inhibitor: Romosozumab

- Dural effects: increase bone formation and decrease bone resorption
- Indications: postmenopausal women, w/ osteoporotic fractures, failed or intolerant other osteoporosis tx
- Contraindications: hypocalcemia, MI/stroke within 12mo
- Cautions: cardiac dz risk, eGFR <30, invasive dental procedure, infection, anemia, coagulation dz, corticosteroid use, malignancy, recent chemoTx or XRT
- No renal or hepatic adjustment
- BBW: risk of MI, Stroke and Cardiovascular death

Case 1: 56 yo F with FMH of Hip Fracture

- Age: 56 years
- Height: 5´3˝ (5´3˝ at age 30)
- Weight 115 lbs (baseline 105 lbs)
- Race: Asian American
- Natural menopause age 52
- No HT/ET
- DEXA T score L spine -1.2, hips -1.5
- Parental hip fracture (at age 70)
- Does not drink alcohol
- Does not smoke
- Daily MVI, calcium and Vit D
- Active lifestyle, tennis/golf


Country: US (Asian)
Name/ID:
About the risk factors
Questionnaire:
1. Age (between 40 and 90 years) or Date of Birth
Age:
Date of Birth:
54
Y:
M:
D:
2. Sex
Male
Female
3. Weight (kg)
52.16
4. Height (cm)
160
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/day
No
Yes
12. Femoral neck BMD (g/cm2)
T-Score
-1.5
Clear
Calculate
BMI: 20.4
The ten year probability of fracture (%)
with BMD
Major osteoporotic
6.0
Hip Fracture
0.3

- **Assessment:**
  - Low risk of osteoporotic fracture
  - No obvious risk factors of bone loss
- **Plans:**
  - Regular weight-bearing exercises
  - Calcium 1200 mg from all sources
  - Vitamin D 800-1000 IU from all sources
  - Notify her clinician if any changes in health or medication

Case 2: 68-yo WF, on alendronate X 10 yrs for bone loss, would like to stop it if possible

- HT: 5´3˝ (5´3.5˝ at age 58)
- WT: 140 lbs (135 lbs at age 58)
- Menopause at age 55, no HT
- No FMHx of osteoporosis or hip fracture
- < 5 alcoholic beverages/week
- Non-smoker
- Calcium-rich diet and Calcium 500mg daily
- Vit D 400 IU daily
- Rarely exercises, but active lifestyle
- HTN on ACEI
- Alendronate 70 mg/wk X 10 yrs
- No history of falls
- No history of fracture as adult
- Baseline BMD: Hip T-score -2.5; L spine T-score: -2.1
- Current BMD: Hip T-score -2.3; L spine T-score -1.9

- **Assessment:**
  - Osteopenia, was osteoporosis
  - Benefited from alendronate with stable BMD, no height loss, no fractures
  - Moderate risk of osteoporotic fractures
    - FRAX only to evaluate the fracture risk in the untreated patients
  - No additional risk factors of bone loss, except age, race, postmenopause
- **Plans:**
  - 2 yrs drug holiday, with monitor, bone-healthy lifestyle, dietary practices and increase physical activity

Case 3: 80-YO man on oral Risedronate recovering from hip fracture

- Race: Asian American
- HT: 5´ 4˝ (5´ 8˝ at age 50)
- WT: 140 lbs (155 lbs at age 50)
- Risedronate 5 mg daily X 3 yrs
- Assisted living apartment
- Fractures in wrist and hip
- GERD on PPI
- Non-smoker
- Average 5/wk alcoholic beverages
- Little sun exposure
- Sedentary lifestyle
- History of kidney stones
- No dietary supplements
- Balanced diet, lactose intolerant
- BMD 3 yrs ago: T scores Hip -2.6; L spine -2.8
- Current BMD: T scores Hip -3.4; L spine -3.1

- **Assessment:**
  - Treatment failure of oral Risedronate with HT loss, fractures, decreased BMD
    - Secondary osteoporosis? Non-effective? Non-compliance?
  - High risk for osteoporotic fractures
    - Very low BMD and Fractures
  - Additional risk factors of bone loss:
    - Age, race, diet, activity, possible Vit D def, PPI use
- **Plans:**
  - Correct risk factors if possible
  - Other treatment options:
    - Zoledronic acid – fastest, potent, secondary fracture prevention, convenient and less GI side effect
    - Denosumab, potent, expensive
    - Teriparatide, daily injections


Thank You
Mahalo
Kiitos
Tack
Toda
Grazie
Obrigado
Thanks
Takk
Merci
Gracias