WHO Osteoporosis and Fracture Assessment Tool (FRAX): Application and Clinical Decision Making

Steven Ing, MD, MSCE
3/7/2009

Introduction

- Increased demand for osteoporosis management
  - Greater awareness
  - Increasing prevalence (aging population)
  - Efficacious treatment
- BMD by DXA is central in identification of osteoporosis
- Combine DXA with clinical risk factors to target therapy to individuals with higher risk

Case

- 55 year old woman concerned about osteoporosis
- 5 years postmenopausal
- Mother had hip fracture at age 70
- No personal history of fracture
- No medications
- No cigarettes, 1-2 glasses of wine at dinner
- 105 lbs, 5' 2" (BMI 19.2)
- DXA: LS T-score -1.7, femoral neck -1.5

BMD Accuracy

- DXA measures bone mass for prognosis
  - i.e. ability to predict fracture
- Prediction of fracture by BMD
  - Comparable to BP and CVA
    - RR 1.3-2.2 per SD increase in DBP
  - Better than cholesterol and MI
    - RR 1.2-1.5 per SD increase in cholesterol
  - Expressed as "gradient of risk"

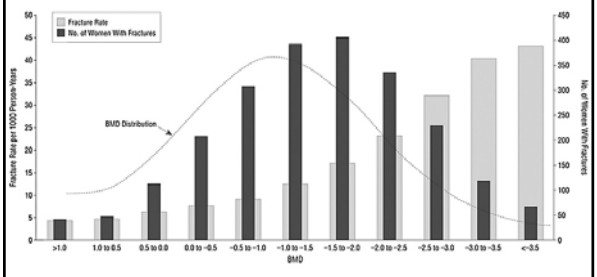
BMD Accuracy: Fracture Prediction by Site

Measured Site	Forearm Fracture	Hip Fracture	Vertebral Fracture	All Fracture
Distal Radius	**1.7** (1.4-2.0)	**1.8** (1.4-2.2)	**1.7** (1.4-2.1)	**1.4** (1.3-1.6)
Femoral Neck	**1.4** (1.4-1.6)	**2.6** (2.0-3.5)	**1.8** (1.1.-2.7)	**1.6** (1.4-1.8)
Lumbar Spine	**1.5** (1.3-1.8)	**1.6** (1.2-2.2)	**2.3** (1.9-2.8)	**1.5** (1.4-1.7)

- Gradient of risk is improved by site-specific measurement

Marshall D, et. al BMJ 1996(312):1254-1259

DXA Limitation: High Specificity/Low Sensitivity



Siris, Arch Intern Med 2004;164(10):1108–1112

DXA Accuracy

- For 65 year old women, assume DXA predicts fracture with risk gradient = 2.0 per 1 SD ↓ BMD
- At this age,10 year probability of osteoporotic fracture = 12.4%
- Wish to target 10% of population at this age with lowest BMD
- Test identifies 23% who will have fracture (sensitivity)
- 76% of women with fractures will have a negative test

Age, BMD, and Fracture

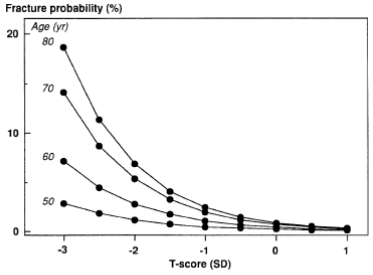


Fig. 1. Ten-year probability (%) of hip fracture in Swedish women according to age and *T*-score for bone mineral density at the femoral neck [9].

Kanis Osteoporos Int 2002;13:527-36

Prior Fracture and Future Fracture

Site of Prior Fracture	Hip Fracture Risk	Spine Fracture Risk	Forearm Fracture Risk
Hip	2.3	2.5	1.4
Spine	2.3	4.4	1.4
Forearm	2.0	1.9	1.8

Klotzbuecher CM, et. al JBMR 2000;15:721-727

1998 NOF Treatment Indications

- Prevalent osteoporotic fracture
- T-score ≤ -2.0 without additional risks
- T-score ≤ -1.5 with additional risks
  - Family history of fragility fracture
  - Personal history of fragility fracture
  - Current cigarette smoker
  - Low body weight (< 127 lbs.)
  - Glucocorticoid therapy

Osteoporos Int 1998;8 S4:S7-80

FRAX: Derive CRFs

9 Prospective Cohorts
- EPOS (Europe):29 centers
- CaMos (Canada): 9 centers
- Rochester (USA)
- Sheffield (England)
- Rotterdam (Netherlands)
- Kuopio (Finland)
- Gothenberg (Sweden)
- Dubbo (Australia)
- Hiroshima (Japan)

→ Estimates for CRFs

N=46,340, 189,852 person-years,
850 hip fractures, 3,318 other osteoporotic fractures

Kanis 2007 Osteopor Int

Choosing Clinical Risk Factor

- Ease in use in primary care setting
- Common enough to be used world-wide
- Does therapeutic intervention lower fractures in subjects with CRF?
  - low BMD
  - prior fracture
  - steroids
  - falls risk

FRAX Clinical Risk Factors

Clinical Risk Factor	RR
Age	
Sex	
BMI (20 vs. 25)	1.42
Personal history of fragility fracture	1.62
Parental history of hip fracture	2.28
Current cigarette smoking	1.60
Ever use of glucocorticoids ≥ 7.5 mg pred x 3 months	2.25
Alcohol (> 2 units daily)	1.70
Rheumatoid arthritis	1.73

Kanis, Osteopor Int 2005;16:581-9

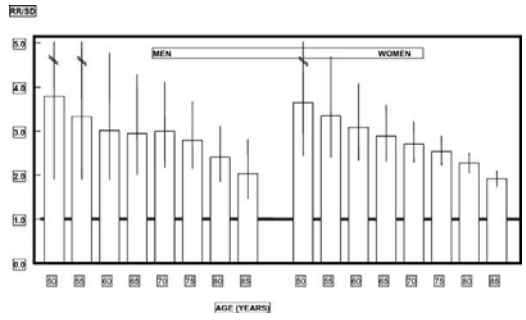
FRAX: Validation

11 Prospective Cohorts
- THIN (UK)
- SOF (USA)
- York (UK)
- Geelong I (Australia)
- Geelong II (Australia)
- OPUS (Europe)
- PERF (Denmark)
- EPIDOS (France)
- Miyama (Japan)
- SEMOF (Switzerland)
- WHI (USA)

→ Validate CRFs
CRF Interactions

N=230,486, 1,208,528 person-years,
3360 hip fractures, 15,183 other osteoporotic fractures Kanis 2007 Osteopor Int

Example of Interaction



Johnell 2005 JBMR 20(7):1185-94

RR/SD (Hip Fracture)

Age	BMD only	CRF only	BMD + CRF
50	3.68	2.05	4.23
60	3.07	1.95	3.51
70	2.78	1.84	2.91
80	2.28	1.75	2.42
90	1.70	1.66	2.02

Kanis Osteopors Int 2007;18:1033-46

FRAX Application

- Apply risk gradients to nation-specific fracture incidence and life expectancy data to derive absolute risk
- Cost-effectiveness analysis
- Offer intervention thresholds
- Combine BMD and CRFs to increase accuracy of fracture prediction, thereby target interventions to those at highest risk

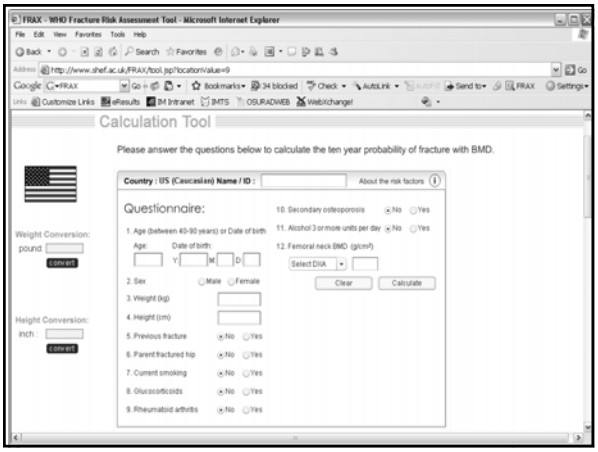
FRAX Application in US

- Use fracture rates in mainly Caucasian population-based data from Olmsted County, MN
- For non-white populations, using ratio of hip fracture incidence:
  - E.g. black women 0.43, black men 0.53
- Assume different populations have same relationships between CRFs and fracture risk

Cost Effectiveness Analysis

- Assumptions:
  - 35% fracture reduction efficacy
  - Drug cost $600/year
  - Prevent 1 hip fracture = $60,000 QALY gained
- Treatment is cost effective if 10 year
  - Hip fracture risk ≥ 3%, or
  - Major osteoporotic fracture risk ≥ 20%

Tosteson, 2008 Osteoporos Int 19:437



Other Secondary Causes of Osteoporosis

- Untreated hypogonadism in men and women
  - Premature menopause, bilateral oophorectomy or orchidectomy, anorexia nervosa, chemotherapy, hypopituitarism
- Inflammatory bowel disease
- Prolonged immobility:
  - Spinal cord injury, Parkinson's disease, stroke, muscular dystrophy
- Organ transplantation
- Type 1 diabetes mellitus
- Thyroid dysfunction:
  - Untreated hyperthyroidism, over treated hypothyroidism
- COPD

Kanis, 2008 WHO Scientific Group

2008 NOF Treatment Intervention

1. Hip fracture, clinical or radiographic spine fracture; OR
2. Osteoporosis by DXA at femoral neck, total hip, or lumbar spine; OR
3. Osteopenia by DXA and any of the following:
   a. secondary causes associated with a high risk of fracture (e.g. glucocorticoid therapy)
   b. other prior fragility fractures
   c. 10 year estimated risk of hip fracture risk ≥ 3%
   d. 10 year major osteoporotic fracture risk ≥ 20%

White women, + Fracture, No BMD, BMI 25

	Age			
Risk	55	65	75	85
None	1.8	3.0	9.9	13
Steroid	3.9	6.3	19	21
RA	3.2	5.3	17	21
Fam Hx	2.4	3.9	30	36
Smoker	2.8	4.5	14	16
Alcohol	2.8	4.6	15	18

Dawson-Hughes 2008 Osteoporos Int

White women, + Fracture, BMI 25, No other CRFs

	Age			
T-score	55	65	75	85
-1.0	0.8	1.0	2.6	3.2
-1.5	1.6	1.6	4.0	4.3
-2.0	2.9	2.7	6.0	5.9
-2.5	5.4	4.7	9.3	8.0

Dawson-Hughes 2008 Osteoporos Int

White women, T= -2.0, + Fracture, BMI 25, 1 other CRF

	Age			
CRF	55	65	75	85
Steroid	5.4	5.0	10	9.5
RA	4.1	3.9	8.4	8.2
Fam Hx	3.1	3.9	23	23
Smoker	5.0	4.6	9.6	8.7
Alcohol	4.4	4.1	9.0	8.8

Dawson-Hughes 2008 Osteoporos Int

White women, No BMD, No Fracture, BMI 25

	Age			
Risk	55	65	75	85
None	0.5	1.2	5.6	8.3
Steroid	1.2	2.6	11	14
RA	1.0	2.1	9.6	14
Fam Hx	0.7	1.6	18	26
Smoker	0.8	1.8	7.9	11
Alcohol	0.8	1.9	8.4	12

Dawson-Hughes 2008 Osteoporos Int

White women, No fracture, BMI 25, no other risks

	Age			
T-score	55	65	75	85
-1.0	0.4	0.6	1.8	2.4
-1.5	0.8	1.0	2.8	3.3
-2.0	1.5	1.6	4.2	4.5
-2.5	2.8	2.8	6.6	6.1

Dawson-Hughes 2008 Osteoporos Int

White women, T= -2.0, No fracture, BMI 25, 1 other CRF

	Age			
CRF	55	65	75	85
Steroid	2.8	3.0	7.4	7.4
RA	2.1	2.3	6.0	6.3
Fam Hx	1.6	1.7	17	18
Smoker	2.6	2.8	6.8	6.7
Alcohol	2.3	2.5	6.4	6.8

Dawson-Hughes 2008 Osteoporos Int

FRAX Implications #1:Cost

- NOF cost-effectiveness analysis assumes
  - Drug cost: $600/year
  - Efficacy: Tx lowers fracture risk by 35% and no side effect
- If cost is $300/year, cost effectiveness if 10 year hip fracture risk >1.4%
- Higher threshold for:
  - More costly drugs
  - Adverse effects
  - ? Reduction of nonvertebral fracture

FRAX Implications #2: Age

- In 55-65 year old woman, T-2.0, fewer would be treated
- In 75+ year old women, more would be treated

FRAX Other Limitations

- Does not take into account dose-response
  - Higher GC dose
  - 1 vs. >1 prior fracture
  - cigarettes, alcohol
- Future FRAX: add spine BMD

Case

- 55 year old woman
- 5 years postmenopausal
- Mother + hip fxr
- No personal history of fxr
- No medications
- No cigarettes, 1-2 glasses of wine at dinner
- 105 lbs, 5' 2" (BMI 19.2)
- DXA: LS -1.7, FN -1.5

- **FRAX: 10 year hip fracture risk: 1.4%**
  13% major osteoporotic fracture