Fracture Risk Assessment (FRAX™)

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Bone Density and Fracture Risk

- Bone mineral density is important determinant of bone strength
- Bone strength is important predictor of fracture risk

→ Bone density is important predictor of fracture risk

but there is more
Risk of Fracture

- Bone Changes not reflected by BMD
  - aging → trabecular connectivity ↓
  - → trabecular spacing ↑
  - → trabecular thickness ↓↓

NORMAL BONE  OSTEOPOROTIC BONE
The Problem with FX Assessment

There are no satisfactory clinical tools available to assess bone quality independently of bone density in routine clinical practice.

Since BMD forms but one component of fracture risk, accurate assessment of fracture risk should ideally take into account other readily measured indices of fracture risk that add information to that provided by BMD.
Bone Density and Fracture Risk

- Low BMD is associated with higher fracture risk
- Relationship between BMD and fracture risk is a continuous gradient
Basics - Characterising Fracture Risk

- **Relative risk**
  - ratio of absolute risks for two groups
  - e.g. if absolute risk of fracture in women who smoke is 6% and in women who do not smoke is 2%. Relative risk of fracture for smokers is $\frac{6}{2} = 3$

- **Absolute risk**
  - e.g. if 6 of 100 women who smoke have a fracture. absolute risk is $\frac{6}{100} = 6\%$

Absolute Risk = \text{Number of people who develop the disease} \div \text{Number of people at risk}
Standardizing Gradients of Risk

To compare risk ratios of different methods, the concept of *standardized risk ratios* (sRR) is introduced:

\[
sRR = \frac{\text{Change in relative risk}}{1 \text{ SD population variance}}
\]
Basics-Bone Density and Fracture Risk

Gradient of risk is characterized by:
- change in risk (e.g. 2-fold) per change in BMD (e.g. 0.1 g/cm²)

Gradient is exponential, e.g.:
- 2 fold / 0.1 g/cm²
- 4 fold / 0.2 g/cm²
- 8 fold / 0.3 g/cm²
Basics - Gradients of Risk

Relative risk

Quartile

- BMD ↓ & hip fracture
- Blood pressure ↑ & stroke
- Cholesterol ↑ & MI
Enhancing predictive power by combining bone densitometry with other predictors:

- Sporadic Factors
- Heredity
- Local Factors
- Menopause
- Aging

- Low Peak Bone Mass
- Increased Bone Loss

- Low Bone Density
- Other Risk Factors
- Fractures
- Trauma
• **Age:**
The same T-score with the same technique at any site has a different significance at different ages, because age contributes to risk independently of BMD.

• **Other Clinical Risk Factors:**
Interest lies in those factors that contribute significantly to fracture risk over and above that provided by BMD or age.
### Meta-Analysis on Predictive Power in Women

(11 cohort studies, 90,000 person/years, > 2000 fractures)

<table>
<thead>
<tr>
<th>Site</th>
<th>Hip Fracture</th>
<th>Vertebral Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal radius</td>
<td>1.8</td>
<td>1.7</td>
</tr>
<tr>
<td>Proximal radius</td>
<td>2.1</td>
<td>2.2</td>
</tr>
<tr>
<td>Calcaneus</td>
<td>2.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Spine</td>
<td>1.6</td>
<td>2.3</td>
</tr>
<tr>
<td>Femoral neck</td>
<td><strong>2.6</strong></td>
<td>1.8</td>
</tr>
</tbody>
</table>

→ Measurement at fracture site is advantageous

50% of Fractures under Tscore -2.5

% vertebral fractures vs. T-score, cumulated

T-score femoral neck

% patients

0 10 20 30 40 50 60 70 80 90 100
0,9 0,5 0,2 0,1 0,3 0,5 0,7 0,9 1,1 1,3 1,5 1,7 1,9 2,1 2,3 2,5
Hip Fracture Prediction with Femoral Neck BMD in Men and Women by Age

Gradient of risk is decreasing with increasing age

O. Johnell et al. J Bone Miner Res 2005;1185
10-Year Fracture Probability (Femur, Vertebra, Radius, prox.Humerus)
Absolute Hip Fracture Risk
… based on hip BMD at a given age

J. Kanis et al., Osteoporos Int 2001;12:417
Clinical Risk Factors

Clinical dichotomized Risk Factors [BMI = 25]

- Age
- Prevalent Fragility Fractures
- Family History Hip-Fracture
- Glucocorticoids
- Rheumatoid Arthritis
- Secondary Osteoporosis
- Daily C2 Consumption ≥ 3 Units/d
  $(1 \text{ U} \sim 8-10\text{g})$

Fig. 2 Effect of combinations of clinical risk factors on the 10-year probability of a major osteoporotic fracture in women aged 65 years and a BMI of 25 kg/m². [05Ca201]
Previous Fracture and Fracture Risk

Kanis et al Bone 2004;35:375
Parental History of Hip Fracture and Fracture Risk

Kanis et al 2004
Current Smoking and Risk of Hip Fracture (Male and Female)

Kanis et al 2004
Corticosteroid Use and Fracture Risk

Meta-analysis of 59,000 men and women from 9 cohorts

RR adjusted for BMD

Hip fracture

Any fracture

Age (years)

J. Kanis et al. J Bone Miner Res. 2004;19:893
BMI and Fracture Risk

![Graph showing the risk ratio (RR) for osteoporotic fracture and hip fracture with and without BMD (Bone Mineral Density). The graph compares BMI at 20 kg/m² and 25 kg/m².](image-url)
Bone Mineral Density, Bone Turnover and Fracture Risk

OFELY Study

<table>
<thead>
<tr>
<th>Condition</th>
<th>RR of Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low hip BMD</td>
<td>2.0</td>
</tr>
<tr>
<td>prev. FX</td>
<td>2.5</td>
</tr>
<tr>
<td>CTX high</td>
<td>3.0</td>
</tr>
<tr>
<td>BMD low prev. FX</td>
<td>3.5</td>
</tr>
<tr>
<td>BMD low CTX high</td>
<td>4.0</td>
</tr>
<tr>
<td>prev. FX CTX high</td>
<td>4.5</td>
</tr>
<tr>
<td>BMD low prev. FX CTX high</td>
<td>6.0</td>
</tr>
</tbody>
</table>

10-Year Fracture Probability at Age 65

Effect of Clinical Risk Factors in a 55 Year-old Postmenopausal Female

- Age and sex
- +BMD
- +smoking
- +RA
- +FH Hip Fx

10 Year Fracture Risk (%)

- Major fractures
- Hip fracture

- 7,4
- 9,9
- 10
- 13
- 23
- 0,5
- 1,5
- 2,5
- 3,5
- 3,7

0
10
20
30
Which Woman is at Higher Fracture Risk?

54-year-old lady, smoker and a T-score of -2.0

10 year risk of hip fracture = 2.5%; major osteoporotic fracture = 10%

or

81-year-old lady, no prior fracture and a T-score of -1.4

10 year risk of hip fracture = 3.2%; major osteoporotic fracture = 26%
Welcome

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.

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).

This is a beta version

Dr. John A Kanis
Professor Emeritus, University of Sheffield

Links:
International Osteoporosis Foundation: http://www.osteofound.org/
National Osteoporosis Foundation: http://www.noif.org/
Japan Osteoporosis Foundation: http://www.jpof.or.jp/

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Implications of the FRAX-Model

- Diagnostic classification of osteoporosis will not change
- Distinguishes between diagnostic threshold and intervention threshold
- Fewer younger patients at low risk will be treated; more older patients at higher risk will be treated
FRAX™: Methodology

• Construction from baseline and follow up data from more than 10 prospective population based cohorts

• Calculation of the 10 year probability of a major osteoporotic/hip fracture

• Multivariate models using Poisson regression and the weighted $\beta$ coefficient of the clinical risk factors with and without BMD, for fracture and for death were used
• Fracture data over a time interval over 10 years

• Population number over the 10 years period in 5 years steps

• Deaths over the same 10 years period in 5 years steps

• Why 10 years?

• The 10 years period covers the likely duration of treatments and the benefits that may continue once treatment is stopped
Hip Fractures in Austria

Quelle: Statistik Austria; ICD-9, ICD-10
Korrekturfaktor Mehrfachregistrierung: ~0.97
Dimai HP et al, 2009 unpublished data
FRAX Example I – change of risk

FRAX Example II- change of risk

# 10-Years Fracture-Probability (Vertebral, prox. Femur, Radius, Humerus)

## no prevalent Fracture or additional Risk Factor

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Bone Mineral Density: t-score proximal Femur</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-4.0</td>
</tr>
<tr>
<td>50</td>
<td>17</td>
</tr>
<tr>
<td>55</td>
<td>20</td>
</tr>
<tr>
<td>60</td>
<td>23</td>
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<tr>
<td>65</td>
<td>27</td>
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<td>70</td>
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<td>80</td>
<td>33</td>
</tr>
<tr>
<td>85</td>
<td>34</td>
</tr>
<tr>
<td>90</td>
<td>29</td>
</tr>
</tbody>
</table>

**Risk**
- **low ≤10%**
- **intermediate 10-20%**
- **high ≥20%**

J.Kanis et al. Osteoporos Int. 2008; epub [www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX)
10-Year Fracture-Probability (Vertebral, prox. Femur, Radius, Humerus)

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**Risk Factors besides BMD and Age:**
- Prior fracture after age 50 years
- Parental history of hip fracture
- Smoking
- Alcohol >2 units daily
- Glucocorticoid treatment
- Rheumatoid arthritis
- High bone turnover

J.Kanis et al. Osteoporos Int. 2008; epub
www.shef.ac.uk/FRAX
Current Treatment Threshold

- BMD Threshold T-score ≤-2.5 SD

- Age: 80, 70, 60, 50

- 10-Year Fracture Probability
Future Treatment Threshold

Graph showing the relationship between 10-Year Fracture Probability, Age, and BMD T-Score. The graph indicates high risk (≥20%) and intermediate risk (≥10%) thresholds for treatment based on these parameters.
Future Treatment Threshold

Risk Factors besides BMD and Age:

- Prior fracture after age 50 years
- Parental history of hip fracture
- Smoking
- Alcohol >2 units daily
- Glucocorticoid treatment
- Rheumatoid arthritis
- High bone turnover
Intervention Treshold

- Fracture probability
  - Age and BMD
  - Presence of clinical risk factors
- Efficiency of treatment
- Costs / willingness to pay
- Side effects
Summary

• The gradient of risk, i.e. increase in fracture risk for specific change in BMD depends on the technique used and the site measured

• The relative risk increases by about 1.5-3.0 per SD decrease in BMD

• T-score has a different prognostic significance at different ages

• The combination of BMD with other risk factors improves the risk assessment

• Intervention tresholds should be based on fracture probability rather than on any particular level of BMD
2nd Summit Conference on Osteoporosis - Central Eastern Europe
2nd Summit Conference on Osteoporosis
CEE
Warsaw, Poland  21-22 November 2008
Present status and future perspectives for implementation of FRAX into local diagnostic algorithms

- 1. FRAX™ has been developed as a 10 years fracture risk calculation based on femoral neck densitometry together with *independent fracture risk factors*.
- 2. FRAX™ BMI can be a helpful screening tool to identify the group of patients with high fracture risk *independently of access to densitometry*.
- 3. To improve the fracture probability major fractures instead of only hip fracture should be utilized during diagnostic evaluations. A possibility to incorporate *BMD T-scores of spinal instead femoral neck into FRAX™ is still missing*. However, it is not clear whether validated, reliable spinal fracture data from population studies are available presently.