New Revisions of U.S. FRAX risk estimates

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D. Black: Disclosures

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- Consulting: Nycomed, Zosano
Outline of Presentation

• Background
  – BMD and risk factors
  – Use of FRAX

• Problems with FRAX risk estimates for U.S.

• Recent revision (7/09) of FRAX/U.S.
Risk of hip fracture, by quartile of DXA BMD: Study of Osteoporotic Fractures (SOF)

Hip (FN) BMD

Quartile of BMD

1 2 3 4

RR/SD = 2.7

Spine BMD

Quartile of BMD

1 2 3 4

RR/SD = 1.5

Incidence per 1000 person-years

*Study of Osteoporotic Fractures, Black, et. al.*
BMD T-score and Fracture Risk (Sweden)

BMD T-score and Fracture Risk (Sweden)
BMD T-score and Fracture Risk in Sweden

Slide courtesy Mike McClung
Combining BMD with Clinical Risk Factors

Cummings et al., NEJM 332(12):767-773, 1995
WHO Risk Model: Overview

- Begun in about 1999
- Headed by John Kanis and Olof Johnell
- Base system on 10 year risk of fracture
- Combine a set of observational studies from around the world to define a set of robust risk factors
- Build models with and without BMD
- Make country-specific risk-based diagnostic and treatment thresholds based on local cost effectiveness models
WHO Risk Model

- 10 year risk of 2 categories of fracture:
  - A. Hip
  - B. Major osteoporotic
    - Hip
    - Wrist
    - Proximal humerus
    - Clinical vertebral
Choosing Who to Treat - Now

T-score threshold for treatment

Slide courtesy Mike McClung MD
Choosing Who to Treat - Future

Risk threshold for treatment
Risk Factors in Final WHO model

1. Age
2. Sex
3. Femoral neck BMD
4. Prior fragility fracture after age 50
5. Body mass index
6. Ever use of corticosteroids
7. Secondary osteoporosis (e.g., rheumatoid arthritis)
8. Parental history of hip fracture
9. Current cigarette smoking
10. Alcohol intake ≥ 3 units/day

1hip, spine, distal forearm, proximal humerus, pelvis, ribs, proximal tibia in women
Use of WHO online risk calculator
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

FRAX in 7/09
(Version 2)

Links:
International Osteoporosis Foundation: http://www.iotbonehealth.org/
National Osteoporosis Foundation: http://www.nof.org/
Japan Osteoporosis Foundation: http://www.jopo.or.jp/
Fracture Risk Charts on FRAX website

- Country-specific
  - Ethnic specific in U.S.
- Gender and age specific
- With and without BMD
- Count the number of risk factors
Use of risk charts: Count number of clinical risk factors (CRF’s)

France, Women, BMD known, hip fracture risk

<table>
<thead>
<tr>
<th>Number of CRFs</th>
<th>BMD T-score (femoral neck)</th>
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<tbody>
<tr>
<td></td>
<td>-4.0</td>
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<td>0</td>
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**Risk**

**Range**

Risk is the estimated risk

Range is the range of risks—not a confidence interval.

- Higher for more potent risk factors (e.g. history of fracture)
- Lower for less potent risk factors (e.g. smoking)
How to move from general risk calculations to country-specific risks

• Required parameters—specific to each country
  – Absolute levels of fracture risk (annual)
  – Hip
  – Major osteoporotic (any of 4)
  – Mortality rates

• Initial versions implemented in US based on fracture risk in Olmsted Cty, MN (Mayo) in 1989-91

• Version 2 of US FRAX put online in about 3/08
U.S. NOF Treatment Guidelines—Revised March 2008:

- T-score $\leq -2.5$ at any site (hip, femoral neck, spine) OR
- Hip or vert fx including morphometric OR
- Low BMD (aka osteopenia)† at any site +
  - 10 year prob of hip fx $\geq 3\%$ϒ or prob of major osteo fx $\geq 20\%$

New (!) and improved?

†Low BMD = T-score between -1.0 and -2.5. At FN hip, total hip or spine
Comparison of 10 year risk (%) of major osteoporotic fractures in U.S. vs. Sweden/UK (FRAX version 2)

<table>
<thead>
<tr>
<th></th>
<th>Men aged 65</th>
<th>Women aged 65</th>
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<tbody>
<tr>
<td></td>
<td>No CRFs</td>
<td>Prior fracture</td>
</tr>
<tr>
<td><strong>Major fracture</strong></td>
<td></td>
<td></td>
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<tr>
<td>U. S. v2</td>
<td>7.5</td>
<td>14</td>
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<tr>
<td>Sweden</td>
<td>6.1</td>
<td>12</td>
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<tr>
<td>UK</td>
<td>4.9</td>
<td>9.5</td>
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<td>10</td>
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<td></td>
<td>8.4</td>
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U.S. risks of fractures were very high compared to other countries and risks from U.S. cohort studies

Major areas of problems:
- Major osteoporotic fractures all ages
- Hip Fractures, ages 50-70

Results: Using U.S. NOF guidelines, a lot...A LOT...of women (and men would be treated)
How many women would be treated under new NOF guidelines?

• Use Study of Osteoporotic Fractures using FRAX version 2*

Results
  – Age > 65 years: Treat 72%
  – Age > 75 years: Treat 93%

• Many fewer among women under 65

Why were FRAX risks in U.S. so high?

- U.S. implementation of FRAX based on rates of fractures from Rochester County, MN, epidemiology study (Mayo clinic) 1989-91
  - Small population
  - May be higher risk than general U.S. population

- Risk of clinical vertebral fracture (one of “major osteo”) from Mayo are 3 to 4 times higher than any other U.S. and European study
  - Based on hospital visits (no way to adjust for multiple visit for same event for same person)
Facts: To fix FRAX…

- Flaks (B & D) try to get facts to fix FRAX

- Need age specific annual rates of:
  - Hip fractures
  - Major osteoporotic fractures (hip, wrist, humerus or clinical vertebral fractures)

*Ettinger, Black, et. al Osteo. International, 2009*
Facts: To fix FRAX…
(Hip Fracture solution)

- Update U.S. hip fracture incidence from National Inpatient Survey (NIS)
  - Sample of US hospital admissions in 27 states (used 2005)
  - Many 1000’s of hip fractures (vs. low numbers in Rochester, MN sample)
  - Rates in those 50 to 70 years about 50% of Mayo rates

Fixing FRAX: Major Osteoporotic Fracture

- Finding population-based estimates of “any of the 4” was very challenging:
  - Hip
  - Wrist
  - Proximal humerus
  - Clinical vertebral

- Need to find rates of each and then adjust for overlap (people with more than 1)

*Ettinger, Black, et. al Osteo. International, 2009*
Updating risks for Major Osteoporotic Fracture

- **Solutions (long story short...)**
  - Hip (NIS, 2005)
  - Wrist (retained 1989 Mayo rates)
  - Proximal humerus (1989 Mayo rates)
  - Clinical vertebral (based on rates in European studies)

*Ettinger, Black, et. al Osteo. International, 2009*
FRAX update to U.S. rates

- In Version 3.0 of FRAX
- Live in September, 2009
FRAX Release Notes

07.09.2009 Release (FRAX v3.0)

Update of fracture incidence and mortality rates for the US calculation tools based on data provided by NOF (this will tend to result in lower 10-year probabilities, particularly at younger ages)

Inclusion of new country models for Argentina, Belgium, Finland, Hong Kong, Lebanon and New Zealand

Inclusion of NOF statement about intervention thresholds (this is specifically provided for the US calculation tools but due to some current limitations of the website may also be visible on other calculators (this will be fixed in the next version of FRAX).
## FRAX Version 3 update to U.S. rates

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* Kanis, et al O.I, 2009
Impact of FRAX update: Ratio of new FRAX incidence (Version 3) to old FRAX (ver. 2)

Major impacts:

1. Major fracture risk reduced by 20-30%

2. Hip fracture risk reduced greatly in ages < 70 (50% lower)

* Kanis, et al O.I, 2009
Impact of revisions to U.S. FRAX

• Impacts
  – Use new version of FRAX (3.0)
  – Fewer people meet guidelines from treatment
  – Perhaps 20% fewer to be treated (not certain)

• Lessons
  – Estimating FRAX risk hard even in U.S. (where data are pretty good)—much for difficult in some areas
    • Especially for major osteoporotic fractures
  – In many other countries, rates are only good guesses
NOGG in UK use of FRAX: Risk threshold varies with age

10 Year Risk Intervention Threshold

Major Fracture – 10 year fracture probability

Hip - 10 year hip fracture probability