FRAX Adjustments

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Disclosure

- Institutional research support - Amgen, Radius
- Consultant and speaker - Amgen

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More Disclosure

- I am not a biostatistician
- I am not an epidemiologist
- I am not a public health physician
- I am a clinician and clinical researcher
- I will focus on practical applications of FRAX adjustments

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Objectives

- Describe the origins of FRAX
- Characterize the benefits and limitations of FRAX
- Discuss the role of FRAX adjustments in making clinical decisions

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Brussels, Belgium, 2004.

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FRAX

Fracture Risk Algorithm developed at University of Sheffield, launched in 2008

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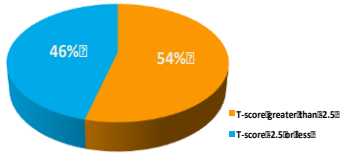
Why FRAX?

Most Women with Hip Fracture have T-score > -2.5



Wainwright SA et al. J Clin Endocrinol Metab. 2005;90:2787-2793.

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FRAX to Diagnose Osteoporosis

- BMD testing (WHO, ISCD)
  - T-score ≤ -2.5 at LS, TH, FN, or 33%R
- Fragility fracture (NBHA)
  - Low trauma hip fracture regardless of BMD
  - Low trauma vertebral, proximal humerus, pelvis or some distal forearm fractures with T-score between -1.0 and -2.5
- FRAX (NBHA, USA only)
  - MOF risk ≥ 20% or HF risk ≥ 3%

WHO Technical Report.1994; ISCD Official Positions. 2015.
Siris ES et al. Osteoporos Int. 2014;25:1439-1443.

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FRAX in Treatment Guidelines

Consider pharmacological therapy for postmenopausal women and men age 50 and older who have:

Osteoporosis by T-score

- T-score -2.5 or less at FN, TH, LS, or 33%R, or . . .

Osteoporosis by fracture

- Hip or vertebra (clinical or morphometric) regardless of BMD , or . . .
- Proximal humerus, pelvis, or distal forearm regardless of BMD in some clinical circumstances

Osteoporosis by combination of factors

- T-score between -1.0 and -2.5 at the FN or TH and . . .
  - Fracture of proximal humerus, pelvis, or distal forearm, or . . .
  - FRAX 10-year probability of hip fracture ≥ 3% or major osteoporotic fracture ≥ 20%

BHOF. Clinician's Guide to Prevention and Treatment of Osteoporosis. 2022. In press.

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FRAX for Selection of Initial Therapy

Level of Risk	Examples	Treatment
Low (ES, AACE)	T-score > -1.0, and no hip or vertebral fracture, and FRAX MOF/HF < 20%/3%	Non-pharmacological
Moderate (ES)	T-score > -2.5, and no hip or vertebral fracture, and FRAX MOF/HF < 20%/3%	Non-pharmacological or bisphosphonate
High (ES, AACE)	T-score ≤ -2.5, or prior hip or vertebral fracture, or FRAX MOF/HF ≥ 20%/3%	Bisphosphonate Denosumab SERM
Very High (ES)	T-score ≤ -2.5 and fractures, or multiple vertebral fractures, or severe vertebral fracture (> 40% vertebral height loss)	Anabolic Bisphosphonate Denosumab
Very High (AACE)	T-score < -3.0, fracture in last 12 months, fracture on treatment, fracture on harmful drugs, multiple fractures, high fall risk, FRAX MOF/HF > 30%/4.5%	Anabolic Bisphosphonate Denosumab

Endocrine Society Guideline Update. J Clin Endocrinol Metab. 2020;105:1-8.
AACE Guideline Update. Endocrine Pract. 2020;26:1-46.

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FRAX Clinical Risk Factors

FRAX input

- Age
- Sex
- Height and weight - BMI
- Prior fracture - any adult fracture
- Parental hip fracture - not other types
- Current smoking - not previous
- Systemic glucocorticoids - ≥5 mg/day, ≥3 mo
- Excess alcohol - ≥3 units/day *
- Rheumatoid arthritis - not OA or others
- Other secondary osteoporosis (if no BMD)
- FN BMD (if available) – T-score not so good
- TBS (if available)

* 3 units = 10 oz. beer, 4 oz. wine, 1 oz. spirits

Why these risk factors?

- Easily obtainable and quantifiable
- Independent of BMD
- Validated in large cohorts of men and women age 40-90 worldwide
- Although inclusion of additional risk factors generally contributes little to fracture risk estimation, there is continuing interest in improving FRAX by adding or modifying risk factors included in the algorithm

FRAX models are available for 23 countries or territories in 35 languages for more than 80% of the world population, with more than 3 million hits per year.

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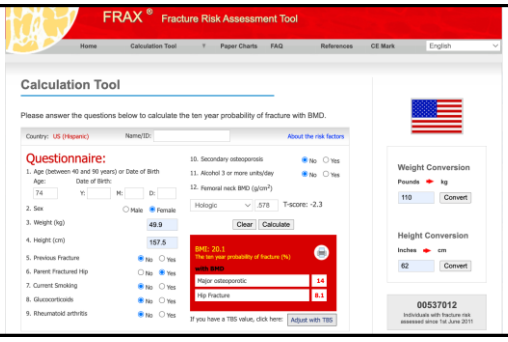

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Benefits of FRAX

- BMD + CRFs predict fracture risk better than BMD or CRFs alone
- Robust supporting data
- Can be used without BMD when DXA is not available
- Quantitative assessment of fracture probability is more clinically useful than relative risk
- Can be used with cost-utility analysis to develop treatment guidelines
- Diagnostic classification (USA)

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Limitations of FRAX (1)

- BMD input is for FN only
- "Dose effect" not considered with dichotomized input for risk factors (smoking, glucocorticoids, alcohol, RA)
- Many risk factors not included: falling, rate of bone loss, bone turnover, diabetes, family history of fractures other than parental hip, etc
- Limited to Caucasian, Black, Hispanic, and Asian in USA

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Limitations of FRAX (2)

- Secondary osteoporosis is a "dummy" risk factor that does nothing if BMD is provided
- Validated only in untreated patients age 40-90
- Invalid T-score is often entered in the calculator
- May underestimate or overestimate actual risk
- Range of uncertainty with fracture risk not clear

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When FRAX Might Be Wrong

Overestimation of Fx Risk

- Lower than average dose or exposure to CRF with variable risk

Uncertainty of Fx Risk

- Poor quality data on country-specific fracture prevalence and mortality
- Not all CRFs are known

Underestimation of Fx risk

- Higher than average dose or duration of exposure to CRF with variable risk
- LS spine BMD much lower than FN BMD
- Not all CRFs are entered
- Other CRFs not considered
  - High fall risk
  - High bone turnover
  - Rapid bone loss
  - Diabetes

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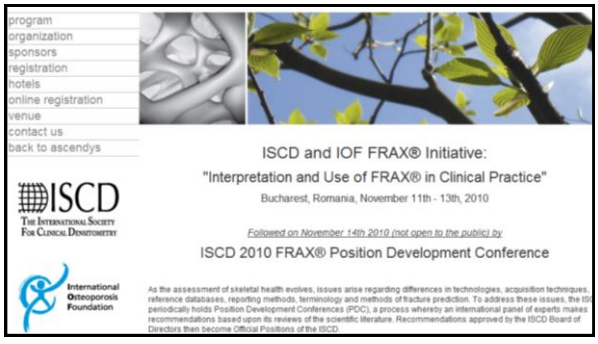

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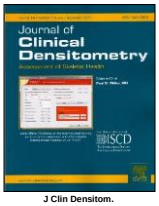
ISCD-IOF Official Positions on FRAX

www.iscd.org
www.iofbonehealth.org



J Clin Densitom.
2011;14(3):171-262

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FRAX Official Positions

- General: FRAX may underestimate or overestimate fracture risk depending on many variables
- Specific: For Native Americans in the USA, enter Caucasian in the FRAX calculator
- Lack of data: "Although the list of proposed enhancements to FRAX is large, in many instances these cannot presently be implemented due to insufficient data."

J Clin Densitom. 2011;14(3):171-262.

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FRAX Adjustments

- Validated (included in FRAX)
  - Trabecular bone score
- Exploratory (not currently included in FRAX)
  - Hip-spine discordance
  - Glucocorticoid dose
  - Type 2 diabetes
  - Age of parental hip fracture
  - Multiple sclerosis
  - Hip axis length
  - Falls
  - Immigration status
  - Recency of fracture

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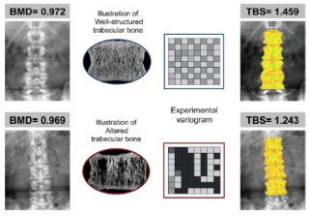
Trabecular Bone Score (TBS)

Gray-level textural measure derived from LS image by DXA



Silva BC et al. J Bone Miner Res. 2014;29:518-530.

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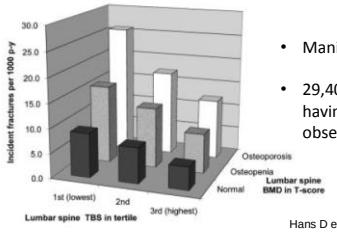
TBS Predicts Fractures Independently of BMD



- Manitoba Bone Density Program
- 29,407 women age ≥ 50 years having 1668 fractures over mean observation period of 4.7 years

Hans D et al. J Bone Miner Res. 2011;26:2762-2769.

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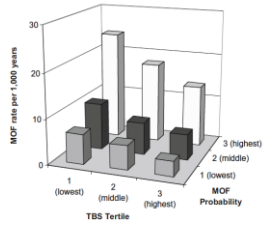
TBS Predicts MOF Independently of FRAX CRFs



- Manitoba Bone Density Program
- 33,352 women age 40-100 years (mean age 63 years) with 1872 having 1 or more MOF over mean observation period of 4.7 years
- Supports inclusion of TBS as an additional FRAX CRF

Leslie WD et al. Osteoporos Int. 2014;25:2271-2277.

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FRAX Adjustments that Include TBS

- **TBS**: included in FRAX algorithm
  - Leslie WD et al. J Clin Endocrinol Metab. 2013;98:602-609.
- **T2D**: RA, FN T-score -0.5, or TBS
  - Schacter GI, Leslie WD. Calcif Tissue Int. 2017;100:150-164.
- **Spine-Hip BMD Discordance**: Increase MOF risk by 15% for every T-score unit LS is less than FN, or TBS
  - Leslie WD et al. Osteoporos Int. 2011;22:839-847.
- **High Dose Glucocorticoids**: Increase MOF risk by 15% and HF risk by 20% for prednisone > 7.5 mg/day, or TBS
  - Kanis JA et al. Osteoporos Int. 2011;22:809-816.

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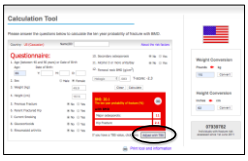
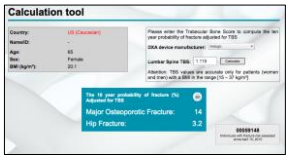
Example of TBS Adjusting FRAX Upwards

65 year-old Caucasian woman with osteopenia by DXA
and no clinical risk factors



65 y/o Caucasian woman
FN T-score = -2.3
FRAX below treatment threshold:
MOF 11%, HF 2.1%



TBS = 1.118 (degraded)
Adjusted FRAX above treatment threshold:
MOF 14%, HF 3.2%

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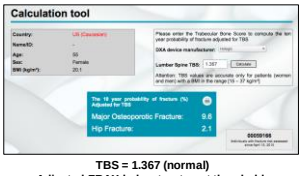
Example of TBS Adjusting FRAX Downwards

65 year-old Caucasian woman with osteoporosis by DXA
and no clinical risk factors

65 y/o Caucasian woman
FN T-score = - 3.0
FRAX above treatment threshold:
MOF 11%, HF 3.2%



TBS = 1.367 (normal)
Adjusted FRAX below treatment threshold:
MOF 9.6%, HF 2.1%

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Examples of TBS Helping with Clinical Decisions

- FRAX adjustments may be helpful when treatment decisions are borderline
- Disorders where fracture risk is out of proportion to BMD: type 2 diabetes mellitus, anti-estrogen treatment for breast cancer, chronic kidney disease, chronic glucocorticoid therapy, possibly primary hyperparathyroidism
- "Soft bones" at time of surgery, not explained by BMD
- Low trauma fracture with normal or slightly low BMD

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Adjustment for Hip-Spine Discordance

- 65-year-old Caucasian woman with L1-L4 T-score = -3.5 and right FN T-score = -1.5
- FRAX-related CRFs include mother with hip fracture at age 78, current smoking, and alcohol 3 units per day
- FRAX: MOF 18%, HF 2.4%
- To treat or not to treat?
- **For every rounded T-score difference of 1 unit, adjust FRAX risk of MOF up or down by 10%** [Manitoba database]
- For this patient, L1-L4 T-score is 2 T-score units lower than than FN
- Increasing MOF by 20% ➡ adjusted MOF risk = 1.2 x 18% = 21.6%

Leslie WD et al. Osteoporos Int. 2011;22:839-847.

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Adjustment for High Dose Glucocorticoids

- 77-year-old Black man with COPD on long-term prednisone 10 mg per day
- No known fracture or other risk FRAX-related risk factors
- DXA: L1-L4 T-score = -1.7 and left FN T-score = -2.3
- FRAX: MOF 5.2%, HF 2.5%
- **For prednisone > 7.5 mg per day, adjust FRAX risk upwards by 15% for MOF and 20% for hip fracture** [General Practice Research Database]
- Applying this formula, adjusted MOF = 1.15 x 5.2% = 6% and adjusted HF + 1.2 x 2.5% = 3%
- Pharmacological therapy may now be considered according to BHOF guide

Kanis JA et al. Osteoporos Int. 2011;22:809-816.

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BMD and Fx Risk with T1D and T2D

Meta-analysis of 80 Epidemiological Studies

- T1D: Increase hip fracture risk (RR = 6.94) and low BMD
- T2D: Increase hip fracture risk (RR = 1.38) and high BMD
- BMI was major determinant of BMD
- Patients with complications of DM had lower BMD and higher fracture risk

Vestergaard P. Osteoporos Int. 2007;18:427-444.

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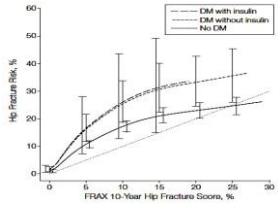
FRAX Underestimates Fx Risk with DM



- Hip fracture risk is higher than predicted by FRAX
- Hip fracture risk in women shown here
- Conclusion: Refinements are needed in current diagnostic and treatment algorithms for use in older patients with T2D

Schwartz AV et al. JAMA. 2011;305:2184-2192.

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FRAX Adjustments for Diabetics

- T1D
  - Not a primary input variable
  - Can be entered as cause of secondary osteoporosis when BMD not included
  - No studies have directly evaluated FRAX performance for T1D
- T2D
  - Enter rheumatoid arthritis as proxy for T2D
  - Reduce femoral neck T-score by 0.5 units
  - VFA
  - TBS

Schacter GI, Leslie WD. Calcif Tissue Int. 2017;100:150-164.

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Adjustments for Type 2 Diabetes

65 y/o obese woman with BMI = 30.5, T2D, prior fracture, FN T-score = -2.0, TBS = 1.160 (degraded, 10th percentile)

	FRAX MOF	FRAX HF
Basal FRAX	17%	2.6%
RA input	22%	3.6%
FN T-score decreased by 0.5	21%	4.4%
TBS input	20%	3.4%

Schacter GI, Leslie WD. Calcif Tissue Int. 2017;100:150-164.

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Parental HF and Fx Risk in Offspring

- Parental HF is considered a risk factor for fractures in offspring and included as input for FRAX
- Studies prior to this one relied on self-reported information
- This study tested the association of objectively verified parental HF with offspring fractures in 478,792 parents and 261,705 offspring in Manitoba, Canada, with 2.9 million person-years of offspring follow-up

Yang S et al. J Bone Miner Res. 2016;31:1753-1759.

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Adjustment for Age of Parental HF

- Strong correlation between HF in either parent and offspring risk of MOF and HF
- The younger the parental HF the greater the fracture risk in offspring
- The risk in offspring was no longer significant when parental HF was at age ≥ 80
- These findings suggest we consider NOT including parental HF occurring at ≥ 80 in FRAX calculations

Yang S et al. J Bone Miner Res. 2016;31:1753-1759.

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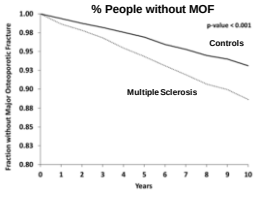
Multiple Sclerosis is a Risk Factor for Fracture



- FRAX is reported to underestimate fracture risk in people with MS
- Study of population-based database in Manitoba, Canada
- 5810 people with MS were identified, with 744 having DXA with data for FRAX compared with 3721 controls
- Follow-up time about 8.5 years
- Findings: FRAX with and without BMD underestimated the risk of MOF by 3% to 5%

Bisson EJ et al. J Bone Miner Res. 2019;34:1095-1100.

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Adjustments for Multiple Sclerosis

- When BMD is included in FRAX, RA input was the best surrogate for the increase of MOF associated with MS
- When BMD is not available, secondary osteoporosis is a good surrogate for the increase of MOF associated with MS

Bisson EJ et al. J Bone Miner Res. 2019;34:1095-1100.

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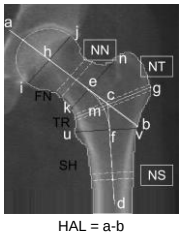
Hip Axis Length



HAL = a-b

- Analysis of Manitoba DXA database of 55,158 women and men with HAL and FRAX followed for 6.2 years
- HAL was risk factor for hip fracture independent of BMD and FRAX
- For every 1 mm increase of HAL, hip fracture increased by 4.8% in women and 3.4% in men
- HAL is a potential FRAX adjustment

Yang L et al. J Bone Miner Res. 2009;24:33-42. Leslie WD et al. J Clin Densitom. 2016;19:326-331.

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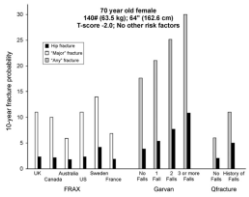
Falls



10-Year Fracture Risk with Three Fracture Risk Calculators

- FRAX underestimates fracture risk in patients with frequent falls
- Falls should should be evaluated in patients with osteoporosis and interventions to reduce risk of falls initiated
- Quantification of falls risk for FRAX input is not yet possible
- FRAX: https://www.sheffield.ac.uk/FRAX/
- Garvan: https://www.garvan.org.au/bone-fracture-risk/
- Qfracture: https://qfracture.org/

Masud T et al. J Clin Densitom. 2011;14:194-204.

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Immigration and FRAX

- Age-specific fracture and mortality rates vary markedly in different countries
- FRAX is calibrated according to country-specific data
- For immigrants, is it better to use FRAX of the destination country or the country of origin?
- Study of HF incidence in men and women age ≥ 50 years in Sweden between 1987 and 2002
- 2.8 million Swedish-born and 270,000 foreign-born individuals
- HF incidence 2x higher in Swedish-born vs. immigrants
- HF incidence slowly increased in immigrants but still remained lower than Swedish-born 40 years after immigration
- Conclusion: using destination-country FRAX (Sweden) overestimated fracture risk in immigrants from countries with lower risk

Johansson H et al. Osteoporos Int. 2015;26:2617-2622.

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FRAX Adjustment for Fracture Recency

- Background: fracture risk is higher in the first 2 years after an initial fracture (imminent fracture risk) than in subsequent years; recent fracture multipliers for FRAX have been proposed but not fully validated
- Study: Manitoba database of 67,671 women was analyzed to compare FRAX MOF and HF with observed fractures over 2 years and over 10 years since baseline, stratified by prior fracture status at baseline (none, ≥2 years ago, <2 years ago)
- Findings: recent fracture was associated with increased fracture risk in the following 2 years; however, this effect was attenuated over 10 years of observation, although FRAX continued to underestimate fracture risk in women < age 65 with recent VF or humerus fracture
- Conclusion: effect of fracture recency was not consistent across fracture sites and varied according to age; further quantification of effect size and specificity is needed in order to develop and refine multipliers for inclusion in FRAX

Leslie WD et al. J Bone Miner Res. 2022;Epub.

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T-score vs. FRAX Conundrum for Treatment Decisions

- USA guidelines recommend drug treatment when T-score is ≤ -2.5 and when T-score is between -1.0 and -2.5 with high fracture risk by FRAX
- However, what if T-score is ≤ -2.5 and fracture risk is low by FRAX?

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T-score vs. FRAX Conundrum for Treatment Decisions

- USA guidelines bypass this issue by telling us not to consider FRAX when T-score is ≤ -2.5
- European guidelines bypass this issue by basing treatment decisions on age-adjusted risk, using BMD as a tiebreaker when risk is between high and low and the decision to treat is indeterminant
- However, doing FRAX when T-score is ≤ -2.5 may be helpful

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Early Postmenopausal Woman with Osteoporosis

- Healthy 53-year-old Hispanic woman with LMP age 51
- No risk factors except mother with kyphosis and VFs
- DXA shows T-score -2.6 at L1-L4 and -2.2 at left FN
- FRAX: MOF 3.5%, HF 0.5%
- To treat or not to treat?
- Consider FRAX as an educational tool with shared decision making
- For patient reluctant to take drugs, low FRAX supports non-pharmacologic therapy and appropriate monitoring
- For patient who worries about becoming like her mother, low T-score supports drug therapy, perhaps with ET, RLX, or ZOL with long dosing interval

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Other Potential Uses of FRAX

- Retroactive FRAX to decide if treatment should have been started in the first place
- FRAX in patients on bisphosphonate drug holiday to determine when to restart treatment
- FRAX in treated patients to determine whether to continue treatment

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FRAX in Treated Patients

- Study of 35,764 women age ≥ 50 in Manitoba database with baseline DXA 1996-2007 and FRAX calculations followed up to 10 years
- Treatment categories: untreated, current high adherence, current low adherence, past users of BP, RLX, calcitonin, estrogen
- Findings: good agreement between FRAX and observed fractures in untreated and each treated group (except for subgroup of highest risk tertile of highly adherent women with ≥ 5 years of BP)
- Conclusion: FRAX may be useful in predicting fracture risk in women currently or previously treated for osteoporosis to guide the need for ongoing treatment, but is not useful for estimating the reduction of fracture risk in treated patients

Leslie WD et al. J Bone Miner Res. 2012;27:1243-1251.

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Summary

- Wise use of FRAX can help with treatment decisions
- FRAX predicts fracture risk in populations but cannot predict which individual will fracture
- FRAX is only one of many data points to consider when treating patients
- FRAX adjustments generally have a small effect but may move the risk estimation above or below treatment thresholds in some patients
- Using a different fracture risk calculator, such as Garvan, may provide much greater change in risk estimation than using FRAX with adjustments

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