Executive Summary- Lebanese FRAX-Based Osteoporosis Guidelines 2013

Marlene Chakhtoura, MD, Rafic Baddoura, MD, MPH and Ghada El-Hajj Fuleihan, MD, MPH.

On behalf of

National Task Force for Osteoporosis and Metabolic Bone Disorders Members
Ghada El-Hajj Fuleihan, MD, MPH, Rafic Baddoura, MD, MPH ,Asma Arabi, MD, MSc ,George Halaby, MD, Imad Uthman, MD, Jad Okais, MD, Ibrahim Salti, MD, PhD, Muheiddine Seoud, MD, Asaad Taha, MD, Naji Attallah, MD.

MOH Representatives to National Task Force
Abdel Rahman El Hout, MD, and Assaad Khoury, MD.

WHO Representative to National Task Force
Alissar Rady, MD, MPH.

International Expert Advisory Panel
John A Kanis, MD, FRCP
Professor Emeritus
WHO Collaborating center for Metabolic Bone disorders
University of Sheffield, United Kingdom.

Michael McClung, MD, FACE, FACP
Associate Professor of Medicine
Founding Director
Oregon Osteoporosis Center, Portland

William Leslie, MD, FRCPC, MSc
Professor of Medicine and Radiology
University of Manitoba, Canada

Angela Cheung, MD, PhD, FRCP(C), CCD
Associate Professor in the Departments of Medicine, Health Policy Management and Evaluation, Public Health Sciences
Founding Director Centre of Excellence in Skeletal Health Assessment
University Health Network, Toronto

Address queries and correspondence to:
Ghada El-Hajj Fuleihan, MD, MPH
Professor of Medicine
Director Calcium Metabolism and Osteoporosis Program
WHO Collaborating Center for Metabolic Bone Disorders
American University of Beirut Medical Center
Beirut, Lebanon
Email: gf01@aub.edu.lb

WHO To TEST:

Definite indications in both men and women:

- ≥65 years: age as a risk factor (1/5 women >65 have vertebral fracture, 13% of men)
- Presence of vertebral deformity or fragility fracture
- Radiologic evidence of demineralization
- Chronic corticosteroid therapy (>3-6 months)
- Aromatase inhibitors or androgen deprivation therapy

All other indications in postmenopausal women and older men

Use FRAX Risk Factors to decide on BMD.

If FRAX risk estimate based on risk factors is close to 10%, measure BMD to further refine risk assessment**.**

WHO To TREAT:

Definite indications: regardless of FRAX and BMD

- Postmenopausal women and men (≥50 years) with history of fragility fracture: Spine or Hip or with two or more (≥ 2) other fragility fractures.

All Other conditions LISTED BELOW: use FRAX and treat at age-specific cut-offs

- Postmenopausal women and men ≥ 65 years
- Women and men -2.5 ≤ T ≤ - 1.5 with/without risk factors including GIOP
- Women and men with T ≤ -2.5
- To reassure younger women and men about low risk despite low BMD (and/or with history of fractures)

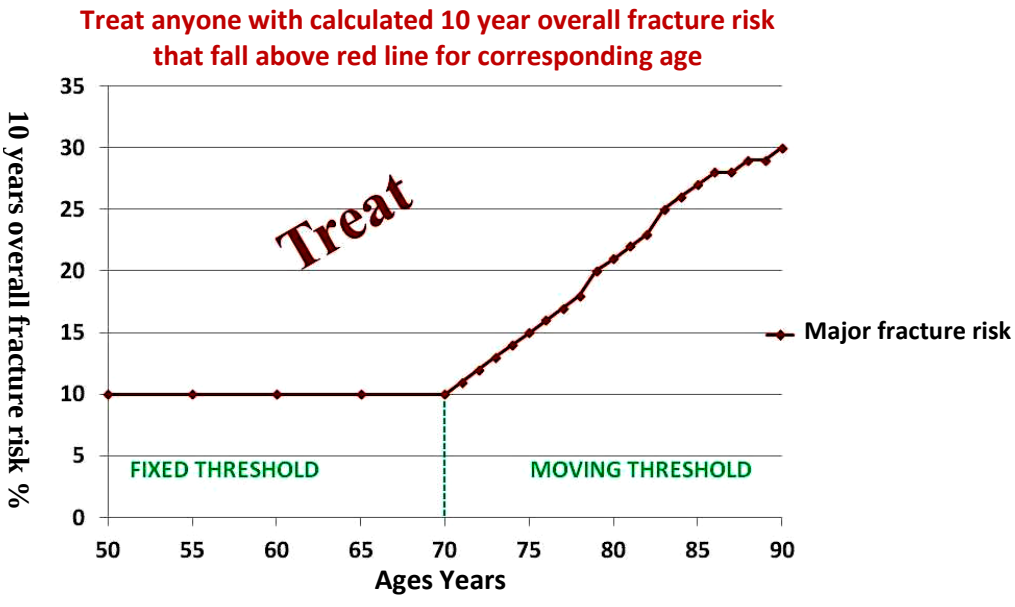
Risk Stratification: FRAX overall fracture risk

Cut-offs for treatment

Below age 70 years: Intervention threshold 10%.

Age ≥ 70 years moving threshold as per Table:

Age (years)	Intervention threshold (10%)
70	10
75	15
80	21
85	27
90	30



WHAT to TREAT WITH?

I-Prevention treatment:

-General measures to all as originally recommended in the 2002 (1) and 2007 (2) endorsed Lebanese guidelines and reemphasized in the upcoming 2013 vitamin D guidelines: (http://www.aub.edu.lb/FM/CMOP/Pages/LebaneseGuidelines.aspx)

-Regular weight-bearing exercise.
-Fall prevention.
-Avoid tobacco use and excess alcohol intake.
-Elemental calcium (including dietary intake) at 1200 mg/day.
-Vitamin D supplementation:
    -Desirable range 30-60 ng/ml.
    -The recommended vitamin D intake, as a maintenance regimen, is:
        -Children-adolescents: 15–25 µg (600–1000 IU) daily.
        -Adults under 50 years of age: 15–25 µg (600–1000 IU) daily.
        -High-risk* and older adults: 20–50 µg (1000–2000 IU) daily.

*High risk individuals are those with osteoporosis on pharmacologic therapy, with fractures, or conditions known to affect vitamin D metabolism or action: steroids, anticonvulsants, malabsorption, bypass surgery, cirrhosis and patients with secondary hyperparathyroidism.

A recent meta-analysis showed that calcium and vitamin D supplementation (in combination) reduce hip fractures by 19% (3).

II-Pharmacologic therapy targeted to high risk individuals:

According to the 2013 Lebanese FRAX-based osteoporosis guidelines high risk individuals are:
-Postmenopausal women and men ≥ 50 years with history of fragility fracture: Spine or Hip or ≥2 other fragility fractures.
-Individuals defined by the Lebanese guidelines based on age specific FRAX threshold. (http://www.aub.edu.lb/FM/CMOP/Pages/LebaneseGuidelines.aspx)

The below recommendations for pharmacologic interventions are based on the original 2002 Lebanese guidelines (1), incorporating additional information based on the following references (4-7).

-Postmenopausal osteoporosis (PMO):

- For menopausal women requiring treatment of osteoporosis, alendronate, risedronate, zoledronic acid and denosumab can be used as first-line therapies for prevention of hip, nonvertebral and vertebral fractures.
- For women 65 years or older with severe osteoporosis defined as a low BMD (T-score ≤–2.5) and a prevalent vertebral fracture, teriparatide can be used as a first-line therapy to reduce vertebral fracture risk.
- Other potential candidates for teriparatide include :

  - Postmenopausal women with very low BMD (T-score ≤ –3.5).
  - Postmenopausal women who sustain > 2 fragility fractures despite an adequate trial of bisphosphonates (1-year period).
- For early postmenopausal women (< 65 years of age) requiring treatment of osteoporosis, raloxifene can be used as a first-line therapy for prevention of vertebral fractures.
- For early postmenopausal women (< 60 years of age) requiring treatment of osteoporosis in combination with treatment for vasomotor symptoms, hormone therapy can be used as a first-line therapy for prevention of hip, nonvertebral and vertebral fractures.

-Osteoporosis in men:

- For men requiring treatment of osteoporosis, alendronate, risedronate and zoledronic acid and Denosumab can be used as first-line therapies for prevention of fractures.
- Teriparatide should be considered as a second-line therapy for men 65 years or older who have severe osteoporosis and prevalent fragility fractures.
- Testosterone is only indicated in men with a definite diagnosis of hypogonadism and under close expert medical supervision due to various complications.

-Glucocorticoid induced osteoporosis (GIOP):

- Recommendations are based on the American College of Rheumatology (ACR) 2010 guidelines (4) and Osteoporosis Canada guidelines (5) and summarized as below :

	Daily Dose[1]	Treat [2,3]
Postmenopausal women and men ≥ 50 yrs	≥7.5 mg for > 3 months →	Regardless of FRAX and fracture history[4,5,6]
	<7.5 mg for > 3 months	Treat if [5,6]
	or →	♦ Previous hip, spine or two or more other fragility fractures
	Any dose for less than 3 months	♦ 10-year risk for MOF, **adjusted for steroid dose**[7], is above the age dependent FRAX Lebanon treatment thresholds [8].
Premenopausal women and men < 50 yrs	♦ **If no previous fragility fracture, no recommendation was made by ACR.** ♦ **If history of FRAGILITY fracture AND [5]:**	
A- Men and non-childbearing women	> 3 months regardless of dose → > 5 mg for 1-3 months →	Treat [8] Treat [8]
B- Childbearing women	≥ 7.5 mg for > 3 months → < 3 months or <7.5 mg →	Treat [8] No consensus

MOF: Major Osteoporotic Fracture.

[1] Prednisone or prednisolone.

[2] FDA approved therapies for GIOP: alendronate, risedronate, zoledronic acid and teriparatide.

[3] Teriparatide is indicated in high risk individuals. High risk individuals are defined as postmenopausal women and men ≥ 50 years with high FRAX estimate as defined by FRAX Lebanon treatment thresholds, or premenopausal women and men < 50 years who have a history of fragility fracture and on a prednisone dose ≥7.5 mg daily for more than 3 months.

[4] Osteoporosis Canada guidelines 2010.

[5] ACR 2010 guidelines.

[6] IOF-ECTS 2012 guidelines .

[7] 10-year risk for MOF adjustment: dose <2.5 mg/day, decrease FRAX by 20% ; dose 2.5-7.5 mg/day: no adjustment; Dose ≥ 7.5 mg/day: increase FRAX by 15%.

[8] Treat for the duration of steroid therapy.

-Aromatase inhibitors and androgen deprivation therapy patients:

For women who are taking aromatase inhibitors and men who are undergoing androgen deprivation therapy, bisphosphonates (alendronate, risedronate, ibandronate , zoledronic acid) or Denosumab should be considered.

Table: Efficacy of Osteoporosis Approved Medications in North America and Europe by Approval Indication and by Skeletal Site for Fracture Reduction (Updated December 2014, http://www.aub.edu.lb/fm/cmop/downloads/e-summary.pdf)

	Postmenopausal Osteoporosis		Men	GIO [a]	Fracture Risk Reduction		
	Prevention	Treatment			Vertebral fracture	Hip fracture	Non Vertebral fracture
ANTI-REMODELING AGENTS							
Alendronate	✓	✓	✓	✓	**PMW**	**PMW**	**PMW**
Ibandronate	✓	✓	-	-	**PMW**	-	**PMW** [b]
Risedronate	✓	✓	✓	✓	**PMW**	**PMW**	**PMW**
Zoledronic acid	✓	✓	✓	✓	**PMW and M** [c]	**PMW and M** [c]	**PMW and M** [c]
Bazedoxifene [d]	✓[e]	✓	-	-	**PMW**	-	**PMW** [f]
Lasofoxifene [d]	✓[e]	✓	-	-	**PMW**	-	**PMW**
Raloxifene	✓	✓	-	-	**PMW**	-	-
Denosumab	-	✓	✓	-	**PMW and M** [g]	**PMW**	**PMW**
Estrogen [h]	✓	-	-	-	**PMW**	**PMW**	**PMW**
Conjugated estrogen/ Bazedoxifene [i]	✓	-	-	-	-	-	-
Calcitonin [j]	-	✓	-	-	**PMW**	-	-
Tibolone [d]	✓	-	-	-	**PMW**	-	**PMW**
ANABOLIC AGENTS							
Teriparatide	-	✓	✓	✓	**PMW and M** [k]	-	**PMW**
OTHERS							
Strontium ranelate [d, l]	✓	✓	✓	-	**PMW**	**PMW** [m]	**PMW**

FRAX-Leb-OP-Guidelines-2013

PMW=Post-menopausal women; M=Men

a GIOP fracture data: One Alendronate and one Residronate trial each showed a significantly reduction in vertebral fractures compared to placebo; one trial showed that Teriparatide significantly reduced vertebral fractures compared to Alendronate One trial compared Zoledronic acid to Risedronate and showed no significant difference in vertebral fracture reduction; There are no studies comparing Zoledronic acid or Teriparatide to Placebo.

b Post hoc analysis, in women with FN BMD T-score <-3.

c Same study included men and women and there was no treatment by gender interaction; there was a lack of a statistically significant fracture reduction in men sub-population, as the gender-based subset analysis was powered

d Only approved in Europe.

e European Medicines Agency : drug "is used for the treatment of osteoporosis (a disease that makes bones fragile) in women who have been through the menopause. It is used in women who are at risk of fracture (broken bones)".

f Post hoc analysis.

g Trial in men with prostate cancer on androgen deprivation therapy (ADT).

h In 2003, the MHRA stated that "The risk: benefit of HRT is unfavorable for the prevention of osteoporosis as first-line use. HRT remains an option for those who are intolerant of other osteoporosis prevention therapies, for whom these are contraindicated, or for whom there is evidence of a lack of response to other therapies. In such cases the individual risk :benefit balance should be carefully assessed.

i Approval indication: FDA approval for osteoporosis prevention and European Medicines Agency approval for estrogen deficiency symptoms.

for a BMD endpoint and not for anti-fracture efficacy. Vertebral fracture reduction has been demonstrated also in another trial conducted exclusively in men.

j European approval withdrawn in 2013.

k In all the study group there was a significant reduction in moderate to severe fractures in the combined group (Teriparatide 20 mcg and 40 mcg). In the subgroup of men who had prevalent fracture at baseline, there was a significant reduction in all vertebral fractures in the combined group (Teriparatide 20 mcg and 40 mcg) and a significant reduction in moderate to severe vertebral fractures in each group separately.

l Approved by EMEA with restrictions: "Strontium ranelate is now restricted to the treatment of severe osteoporosis in postmenopausal women and adult men at high risk of fracture who cannot use other osteoporosis treatments due to, for example, contraindications or intolerance. The risk of developing cardiovascular disease should be assessed before starting treatment. Treatment should not be started in people who have or have had: ischemic heart disease or peripheral arterial disease or cerebrovascular disease or uncontrolled hypertension. Cardiovascular risk should be monitored every 6–12 months. Treatment should be stopped if the individual develops ischemic heart disease, peripheral arterial disease, or cerebrovascular disease, or if hypertension is uncontrolled".

m Subgroup of high risk post-menopausal women, age ≥74 years and femoral neck bone mineral density T score ≤−3, corresponding to −2.4 according to NHANES reference.

The potential benefits and risks of the prescribed agents should be discussed before therapy is initiated, to support informed decision-making.

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