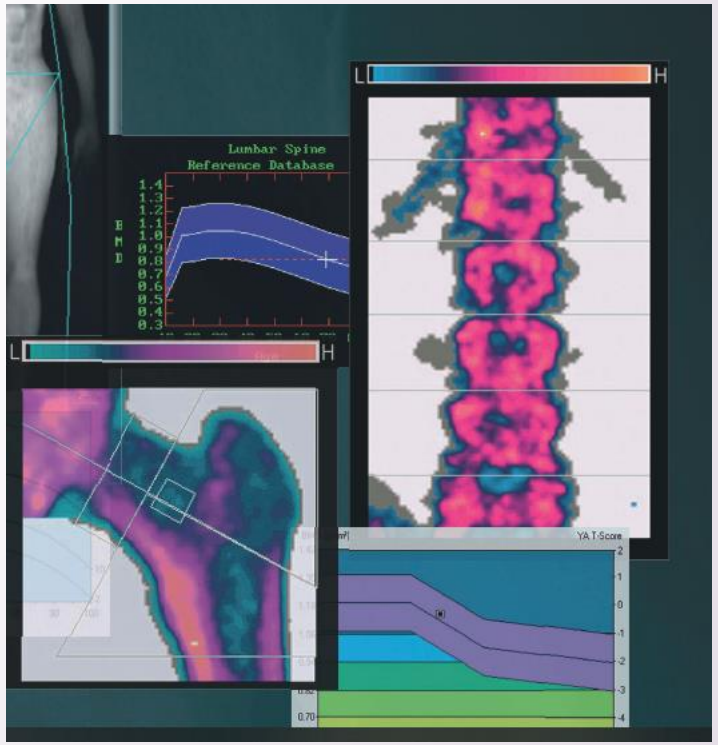
# Management Of Osteoporosis in postmenopausal women

**Prepared by : Dr Yavari**

**2023**

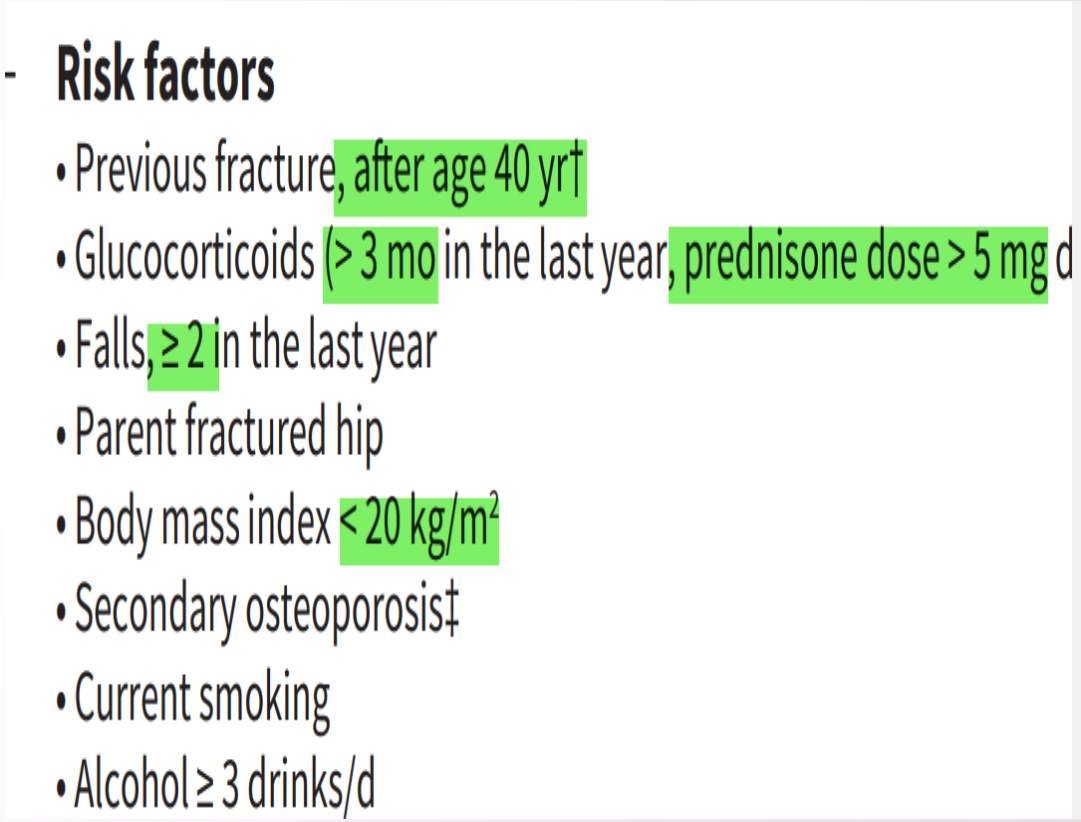


- Clinical practice guideline for management of osteoporosis and fracture prevention in **Canada: 2023** update(CMAJ 2023 October)
- Pharmacologic Treatment of Primary Osteoporosis or Low Bone Mass to Prevent Fractures in Adults: A Living Clinical Guideline From the **American College of Physicians**. Ann Intern Med**. 2023**
- Pharmacological Management of Osteoporosis in Postmenopausal Women: An **Endocrine Society*** Clinical Practice Guideline. J Clin Endocrinol Metab **2019**
- Long-term and **sequential treatment** for osteoporosis.Nature Reviews Endocrinology September **2023**

- Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women- **UpToDate 2023**
- Overview of the management of osteoporosis in postmenopausal women. UpToDate 2023
- Osteoporosis Treatment. A Clinical Overview Elaine Dennison. Springer Nature Switzerland AG 2021

# Screening

- We suggest **BMD testing** in **postmenopausal** females and **males** :
- aged **50–64 yr** with a previous osteoporosis-related **fracture** or **≥ 2 clinical risk** factors
- **aged ≥ 65 yr** with **1 clinical risk** factor for fracture
- aged **≥ 70 yr**
- low-certainty evidence (females), very low-certainty evidence (males)



## TABLE 411-4 Indications for Bone Mineral Density Testing

- Women aged ≥65 and men aged ≥70; regardless of clinical risk factors
- Younger postmenopausal women, women in the menopausal transition, and men aged from 50 to 69 with clinical risk factors for fracture
- Adults who have a fracture at or after age 50
- Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids at a daily dose >5 mg prednisone or equivalent for >3 months associated with low bone mass or bone loss

### Clinical risk factors for fracture independent of bone mineral density

| |
|---|
| Advancing age |
| Previous fracture |
| Glucocorticoid therapy |
| Parental history of hip fracture |
| Low body weight |
| Current cigarette smoking |
| Excessive alcohol consumption |
| Rheumatoid arthritis |
| Secondary osteoporosis (eg, hypogonadism or premature menopause, malabsorption, chronic liver disease, inflammatory bowel disease) |

- The 33% forearm (one-third radius) site is recommended in the following cases:
  - If hip and/or spine cannot be measured or interpreted
  - Hyperparathyroidism
  - Severe obesity (over the weight limit of DXA table)

# Bone turnover markers

- We **do not routinely measure markers** of bone turnover (BTMs) in **postmenopausal** women with osteoporosis.
- While the use of **BTMs in clinical trials** has been **helpful in understanding** the **mechanism of action** of therapeutic agents, their role in the **care of individual patients** is **not well established**.
- Potential roles of BTMs in clinical practice include **prediction of fracture risk**, **monitoring response to therapy**, and **improving compliance with therapy**.
- **Biologic and laboratory variability** in BTM values have **confounded their** widespread use in clinical practice..

# FRAX  Assesment

# Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: Iran  Name/ID:  About the risk factors

## Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age:  Date of Birth: Y: M: D:
2. Sex ○ Male ○ Female
3. Weight (kg)
4. Height (cm)
5. Previous Fracture ◉ No ○ Yes
6. Parent Fractured Hip ◉ No ○ Yes
7. Current Smoking ◉ No ○ Yes
8. Glucocorticoids ◉ No ○ Yes
9. Rheumatoid arthritis ◉ No ○ Yes
10. Secondary osteoporosis ◉ No ○ Yes
11. Alcohol 3 or more units/day ◉ No ○ Yes
12. Femoral neck BMD (g/cm$^2$)

Select BMD

Clear Calculate

### Weight Conversion

Pounds → kg

Convert

### Height Conversion

Inches → cm

Convert

**00224450**
Individuals with fracture risk assessed since 1st June 2011

# What are the limitations of FRAX score

- **The limitations** with **FRAX score** are that it **does not consider independent** risk factors like **number of falls**, **visual impairment**, **neuromuscular** dysfunction, **vitamin D deficiency**, and **physical inactivity**.
- In addition, fracture risk **cannot be assessed** in individuals **aged 90 years**.

- Although **glucocorticoid exposure** (**≥5 mg/day** of prednisolone equivalent for ≥3 months) is considered a risk factor, there is no further subcategorization for doses higher than this. (i.e., a person taking **7.5 mg** or **30 mg** of prednisolone **for >3 months** are presumed to have a **similar** risk of fracture).
- FRAX score is validated only in **drug-naive patients** and **is not useful** for monitoring the **therapeutic response**.

- The emphasis on **absolute fracture** risk **increases the proportion** of older women who are candidates for therapy. As an example, in **a study** using data from the Study of **Osteoporotic Fracture** (SOF), with a prospective **cohort** of community-dwelling **White women ≥65 years** of age, application of the revised 2008 NOF treatment guidelines that **fest** incorporated **FRAX** resulted in **recommendations** for pharmacologic therapy for **72 percent** of women **over 65 years** of age and **93 percent of women over 75 years .**Applying bone density criteria alone (**BMD** lower **than -2.5** at lumbar spine [LS] or femoral neck) resulted in a treatment recommendation for **50 percent of women in both age groups**.

# Trabecular Bone Score

TBS cut-offs proposed for postmenospausal women

| TBS score (no units) | Bone status |
|---|---|
| >1.350 | Normal |
| 1.200 and 1.350 | partially degraded bone |
| ≤1.200 | degraded bone |

BMD= 0.972

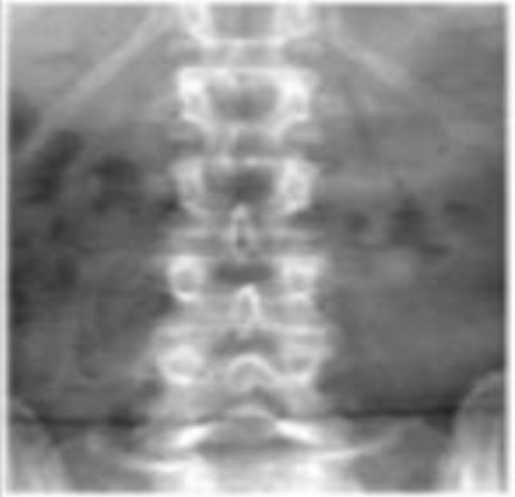
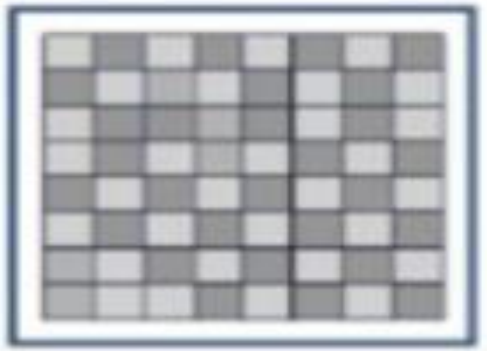
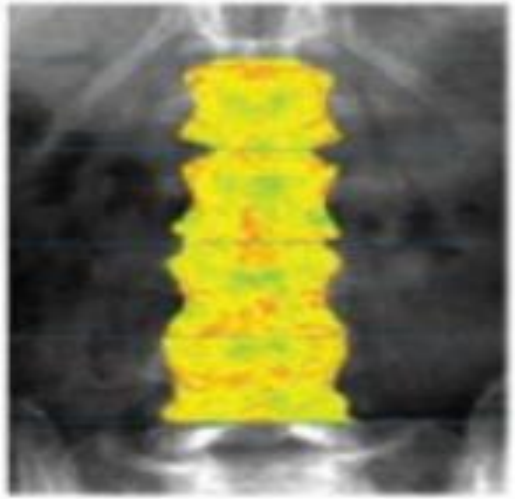


Illustration of Well-structured trabecular bone



TBS= 1.459



Experimental variogram

BMD= 0.969

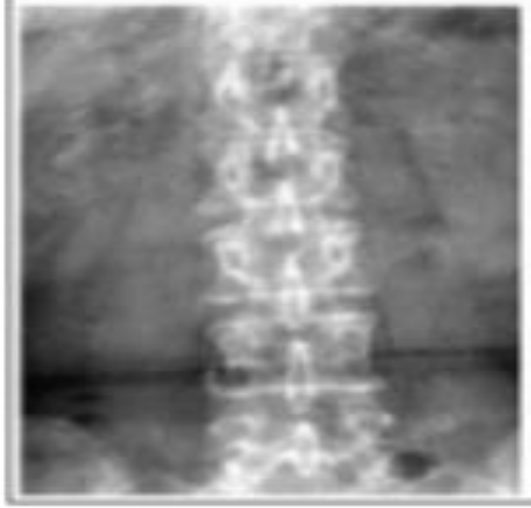
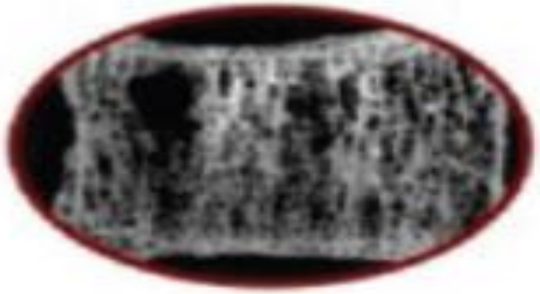
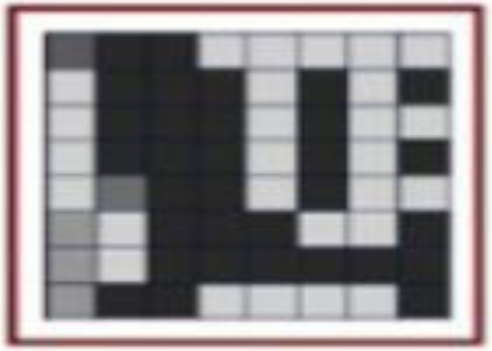
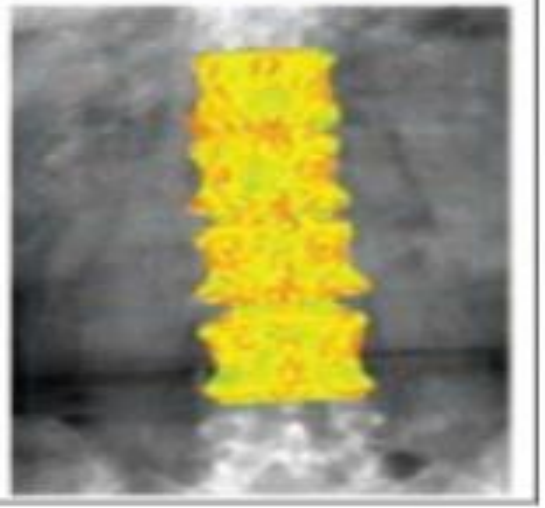


Illustration of Altered trabecular bone





TBS= 1.243



| | aBMD | TBS |
|---|---|---|
| Bone site | Total body | Lumbar spine |
| | Lumbar spine | |
| | Hip | |
| | Forearm | |
| Effective radiation exposure | Adult spine DXA 0.013 mSv | No additional radiation in addition to DXA |
| | Adult hip DXA 0.009 mSv | |
| Scan time | 10-20 mins | Obtained in less than a minute from spine DXA image |
| Advantages | More published literature in different ethnicities and disease cohorts | Indirect measure of bone micro-architecture |
| | | It's a complementary tool to aBMD assessment by DXA |
| | | Can be obtained retrospectively by re-analysis of DXA images |
| Disadvantages | No data on microarchitecture | Not widely available |
| | Cannot separate cortical and trabecular bone | Soft tissue interference, syndesmophytes may falsely increase TBS |
| | Fracture of spine may give falsely high values | Relatively novel tool, hence cannot be used as a stand-alone tool for diagnosing/treating osteoporosis |

# Vertebral Imaging

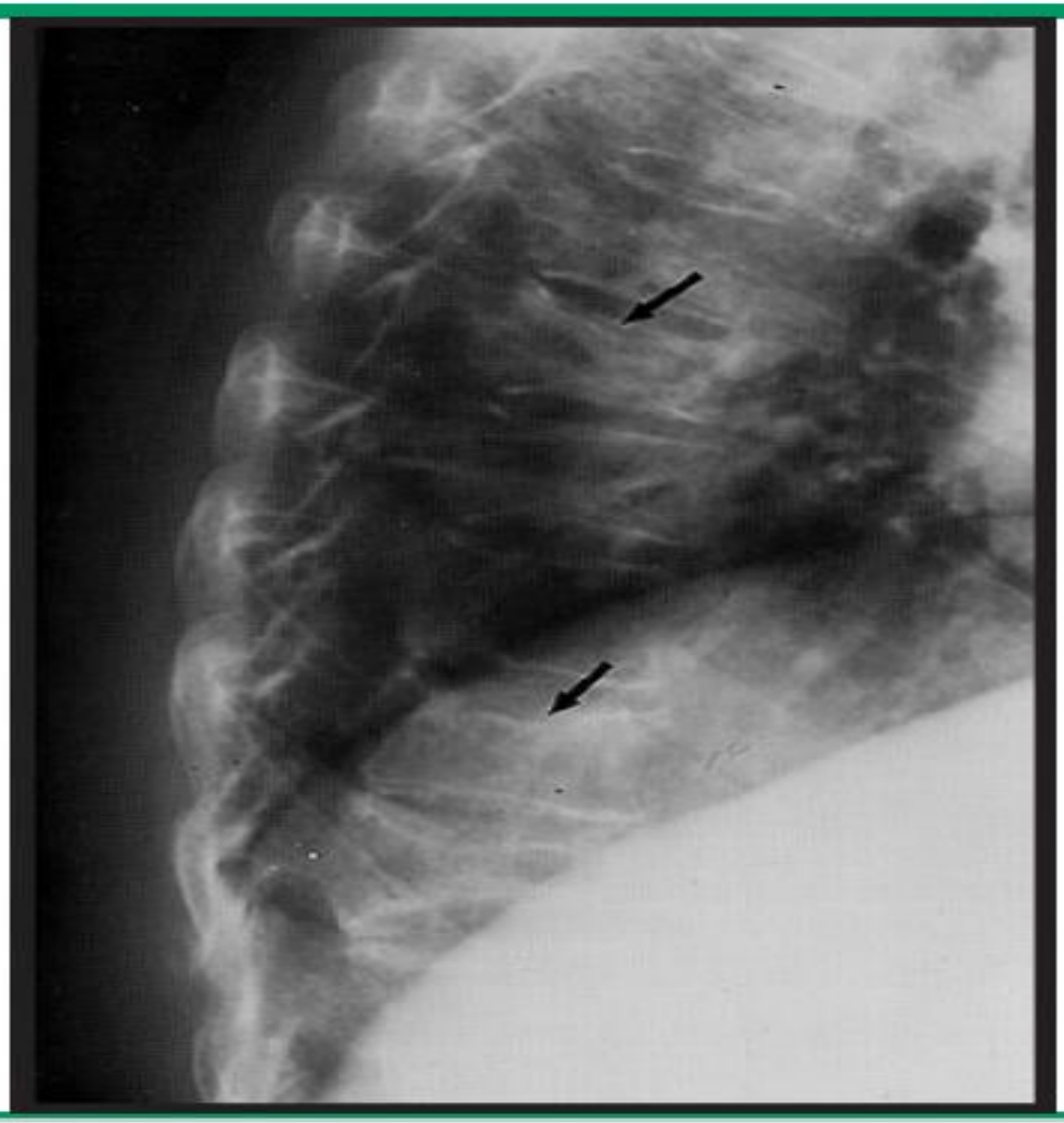
- postmenopausal females and males without known vertebral fractures who
- **aged ≥ 65** yr with a **T-score ≤ –2.5** (femoral neck, total hip or lumbar spine) OR
- have a **10-yr major** osteoporotic fracture risk between **15% and 19.9%.**
- Remark: Lateral spine imaging can also be considered when there are **clinical signs** of undiagnosed vertebral fractures
- The presence of vertebral fractures can guide appropriate **choice and duration** of therapy

**TABLE 411-5 Indications for Vertebral Testing**

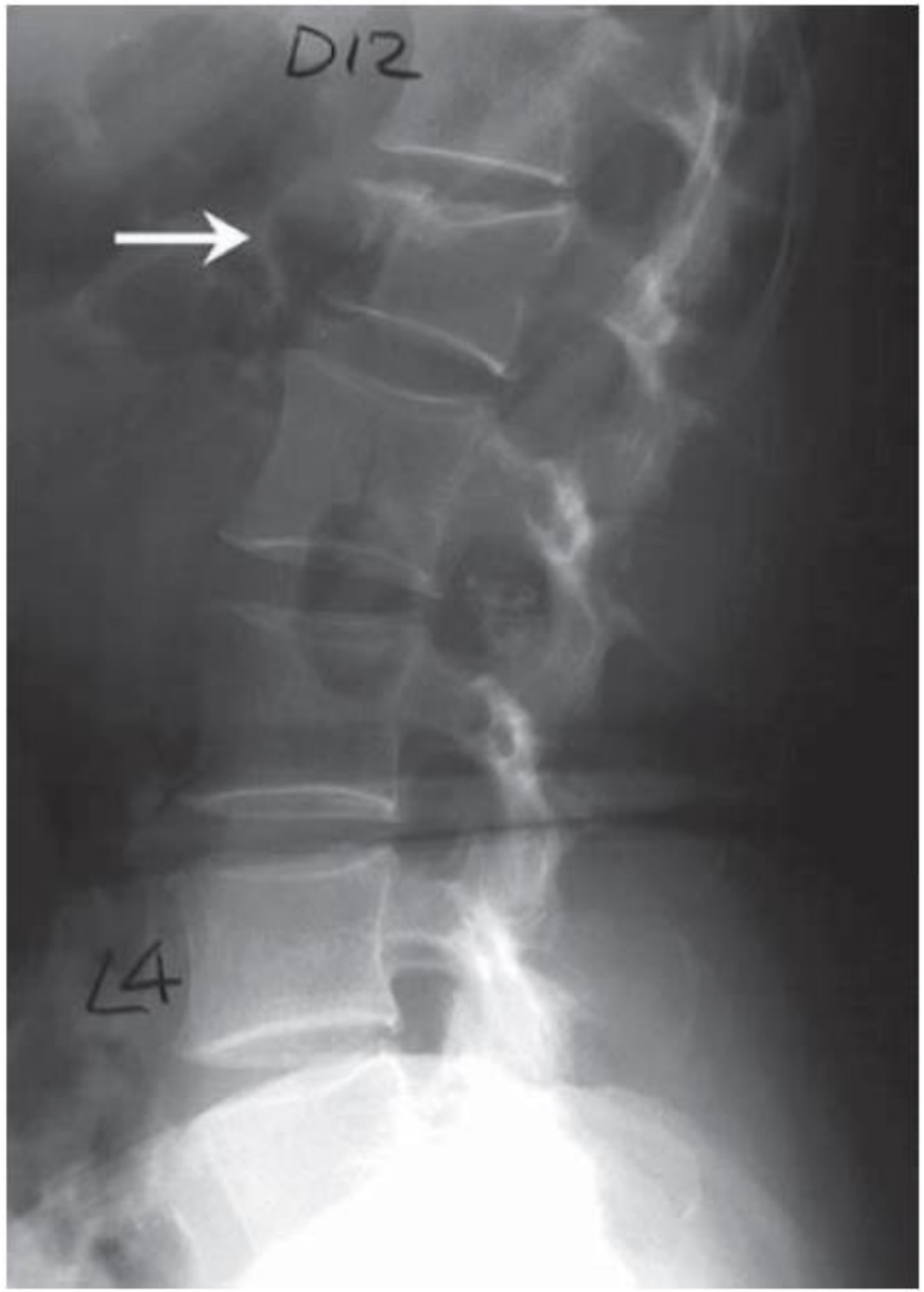
Consider vertebral imaging tests for the following individuals[a]

- All women aged ≥70 and all men aged ≥80 if bone mineral density (BMD) T-score at the spine, total hip, or femoral neck is <1.0
- Women aged from 65 to 69 and men aged from 70 to 79 if BMD T-score at the spine, total hip, or femoral neck is <1.5
- Postmenopausal women and men aged ≥50 with specific risk factors:
  - Low-trauma fracture during adulthood (aged ≥50)
  - Historical height loss of ≥1.5 in. (4 cm)[b]
  - Prospective height loss of ≥0.8 in. (2 cm)[c]
  - Recent or ongoing long-term glucocorticoid treatment

# Thoracolumbar vertebral compression fractures



Radiographic features of spinal osteoporosis include wedging of the vertebra anteriorly with vertebral collapse (arrows), vertebral end-plate irregularity, and general demineralization.


D12
L4

# Exercise/Nutrition/Cessation of smoking

- Women with osteoporosis (or who are seeking to prevent it) should engage in **weightbearing exercise** for at **least 30 minutes** on most days of the week and incorporate **muscle-strengthening** and posture exercises **two to three** days a week.
- Exercises that increase muscular strength and **improve balance** may confer the most benefit for fracture reduction by decreasing risk of falls.
- For patients with fragilty or history of vertebral fracture, **brisk walking** is sufficient and safe waight bearing exercise.

- Postmenopausal women who are getting **adequate calcium from dietary** intake alone (approximately **1200 mg daily**) do not need to take calcium supplements.
- Women with **inadequate dietary intake** should take supplemental elemental calcium (**generally 500 to 1000 mg/day**), in divided doses at mealtime, such that their total calcium intake (diet plus supplements) approximates 1200 mg/day .

- Women should also ingest a total of **800 international units** of vitamin D daily.

  **Higher doses** are required if they have **malabsorption or rapid metabolism** of vitamin D due to concomitant antiseizure medication therapy.

- Most postmenopausal women with osteoporosis require vitamin D supplementation.

## Foods and drinks with calcium

| Food | Calcium in milligrams |
|---|---|
| Milk (skim, 2%, or whole; 8 oz [240 mL]) | 300 |
| Yogurt (6 oz [168 g]) | 250 |
| Orange juice (with calcium; 8 oz [240 mL]) | 300 |
| Tofu with calcium (0.5 cup [113 g]) | 435 |
| Cheese (1 oz [28 g]) | 195 to 335 (hard cheese = higher calcium) |
| Cottage cheese (0.5 cup [113 g]) | 130 |
| Ice cream or frozen yogurt (0.5 cup [113 g]) | 100 |
| Non-dairy milks (soy, oat, almond; 8 oz [240 mL]) | 300 to 450 |
| Beans (0.5 cup cooked [113 g]) | 60 to 80 |
| Dark, leafy green vegetables (0.5 cup cooked [113 g]) | 50 to 135 |
| Almonds (24 whole) | 70 |
| Orange (1 medium) | 60 |

Graphic 67824 Version 7.0

| Characteristics | Calcium carbonate | Calcium citrate |
|---|---|---|
| Elemental calcium | 40% | 20% |
| Absorption | Fair | Good |
| Requirement of acidic pH | Yes, hence given with meals | No, can be given any time |
| GI side effects | Yes | Minimal |
| Milk–alkali syndrome | May occur | Very rare |
| Colloidal liquid form | No | Yes |
| Cost | Inexpensive | Expensive |

# Pharmacological Intervention

# Guidelines for pharmacologic intervention in postmenopausal females and males ≥50 years of age

| |
|---|
| History of fracture of vertebrae (clinical or subclinical), hip, wrist, pelvis, or humerus. |
| T-score ≤–2.5 (DXA) at the lumbar spine, femoral neck, or total hip.* |
| T-score between –1 and –2.5 at the femoral neck or spine, and a 10-year probability of hip fracture ≥3% or a 10-year probability of any major osteoporosis-related fracture ≥20% based upon the United States-adapted WHO algorithm. |

DXA: dual-energy x-ray absorptiometry; WHO: World Health Organization.

* Predictive value of isolated measurement of 1/3 radius varies with clinical context.

- We recommend initiating pharmacotherapy in **postmenopausal** females and males **aged ≥ 50 yr** who :
- a-have had previous hip, **vertebra or ≥ 2 osteoporosis-related fractures**
- b-have a 10-yr major osteoporotic fracture **risk ≥ 20%**
- c-are **aged ≥ 70 yr** and have a **T-score ≤ –2.5** (femoral neck, total hip or lumbar spine).
- **Strong** recommendation; high-certainty evidence (females: a and c), **moderate**-certainty evidence (females: b; males: a, b and c)

Clinical practice guideline for management of osteoporosis and fracture prevention in Canada: 2023 update

- We suggest **initiating pharmacotherapy** in **postmenopausal** females and males **aged ≥ 50** yr who :
- a. have a 10-yr major osteoporotic fracture risk between **15% and 19.9%**
  OR
- b. **aged < 70 yr** and have a **T-score ≤ –2.5** (femoral neck, total hip or lumbar spine).
- Remark: The risk of subsequent **fracture** is greatest **shortly after a fracture**, and greater consideration should be given to a **fracture in the last 2 years**
- Conditional recommendation; **moderate-certainty** evidence (females), **very low-certainty** evidence (males)

# Repeat BMD measurements

- We suggest that for individuals who **do not meet** the threshold for **initiating** pharmacotherapy or choose not to initiate therapy, **BMD testing** can be **repeated** at:
- a. **5–10 yr** if the risk of major osteoporotic fracture **is < 10%**
- b. **5 yr** if the risk of major osteoporotic fracture is **10%–15%**
- c. **3 yr** if the risk of major osteoporotic fracture is **> 15%.**
- Remark: A **shorter retesting** interval may be appropriate for those with **secondary** osteoporosis or **new clinical risk factors**, such as a **fracture.**
- Conditional recommendation; **low-certainty** evidence (females), **very low-certainty** evidence (males)

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- In the presence of **low bone mass** (T-score **-2.00 to -2.49**) at any **site or risk factors** that may cause ongoing bone loss (eg, **glucocorticoid** use, **hyperparathyroidism**), we perform f**ollow-up** measurements approximately **every two years**, as long as risk **factors persis**.
- In the presence of **low bone mass** (T-score **-1.50 to -1.99**) at **any site**, and **with no** risk factors for accelerated bone loss, we will typically perform a follow-up dual-energy x-ray absorptiometry (DXA) in **three** to **five** years.

Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women-UpToDate 2023

- In the presence of **normal or slightly low bone mass** (**T-score -1.01 to -1.49**), with **no risk factors** for accelerated bone loss and with **low absolute fracture** risk, we will typically perform a follow-up DXA in **10 to 15 years**.
- In our practice, we also recommend periodic redetermination of Fracture Risk Assessment Tool (FRAX) 10-year probability of fracture **every five years**. with the further recommendation to perform a **follow-up DXA earlier** if the absolute fracture risk is close to the treatment threshold (ie, **≥3 percent for hip** fracture, **≥20 percent** for major osteoporotic fracture).

# Pharmacologic Intervention

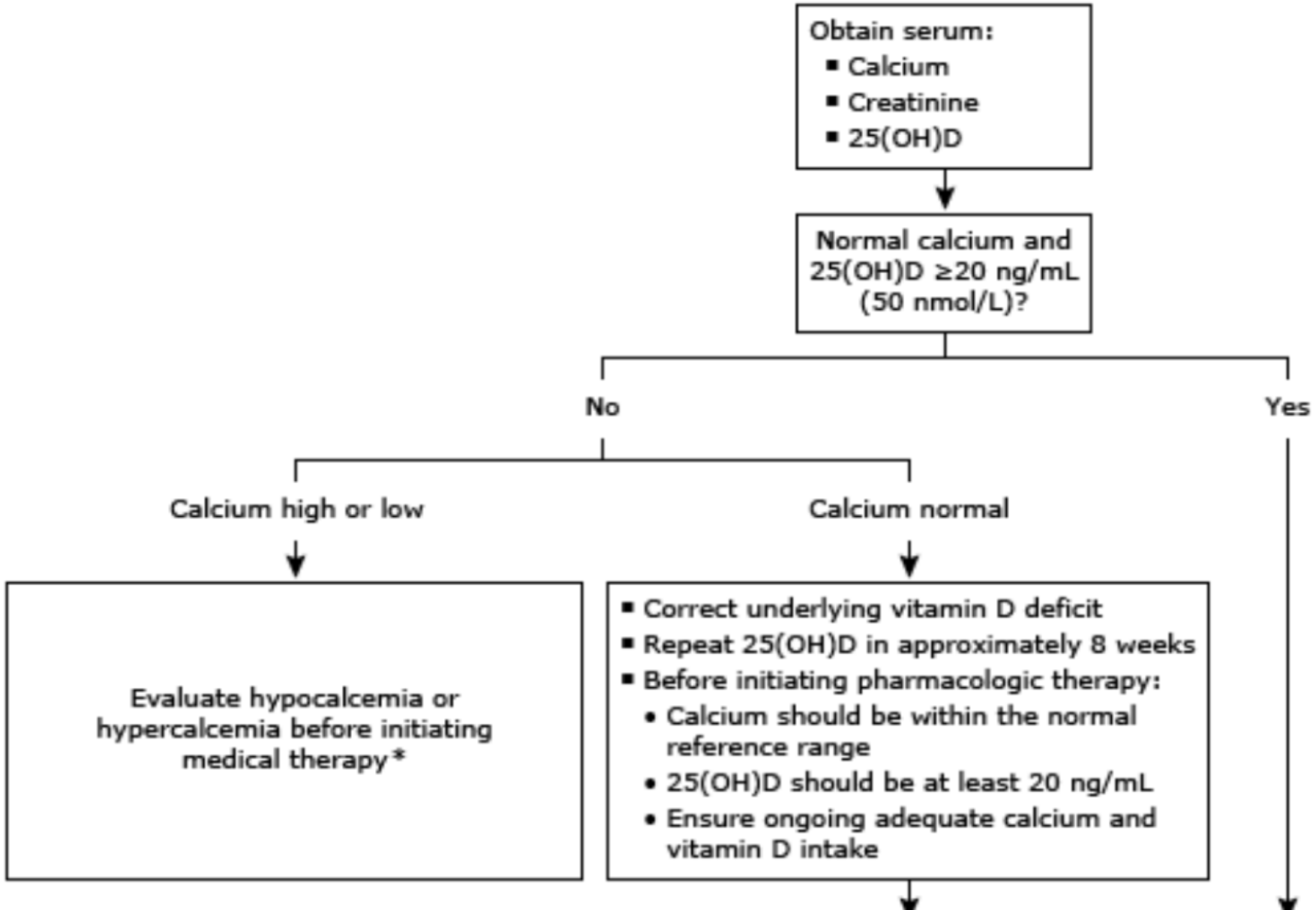
- **Before initiating** pharmacotherapy, good practice includes **assessing for secondary** causes of osteoporosis, and for **potential limitations** when considering specific osteoporosis pharmacotherapy.

## Laboratory evaluation for postmenopausal osteoporosis

| Initial laboratory tests |
| --- |
| Complete chemistry profile (including alkaline phosphatase) |
| Complete blood count |
| Calcium, phosphorus |
| 25-hydroxyvitamin D |

| Additional laboratory tests if indicated |
| --- |
| 24-hour urine for calcium and creatinine |
| 24-hour urine for free cortisol |
| FSH, LH |
| Prolactin |
| Magnesium |
| 1,25-dihydroxyvitamin D |
| Intact PTH |
| TSH |
| Celiac screen |
| Serum protein electrophoresis/urine protein electrophoresis |
| Erythrocyte sedimentation rate |
| Rheumatoid factor |
| Ferritin and carotene levels |
| Iron and total iron binding capacity |
| Serum tryptase and histamine levels |
| Homocysteine |
| Skin biopsy for connective tissue disorders |
| COL1A genetic testing for osteogenesis imperfecta |
| Serum and urine bone turnover markers |

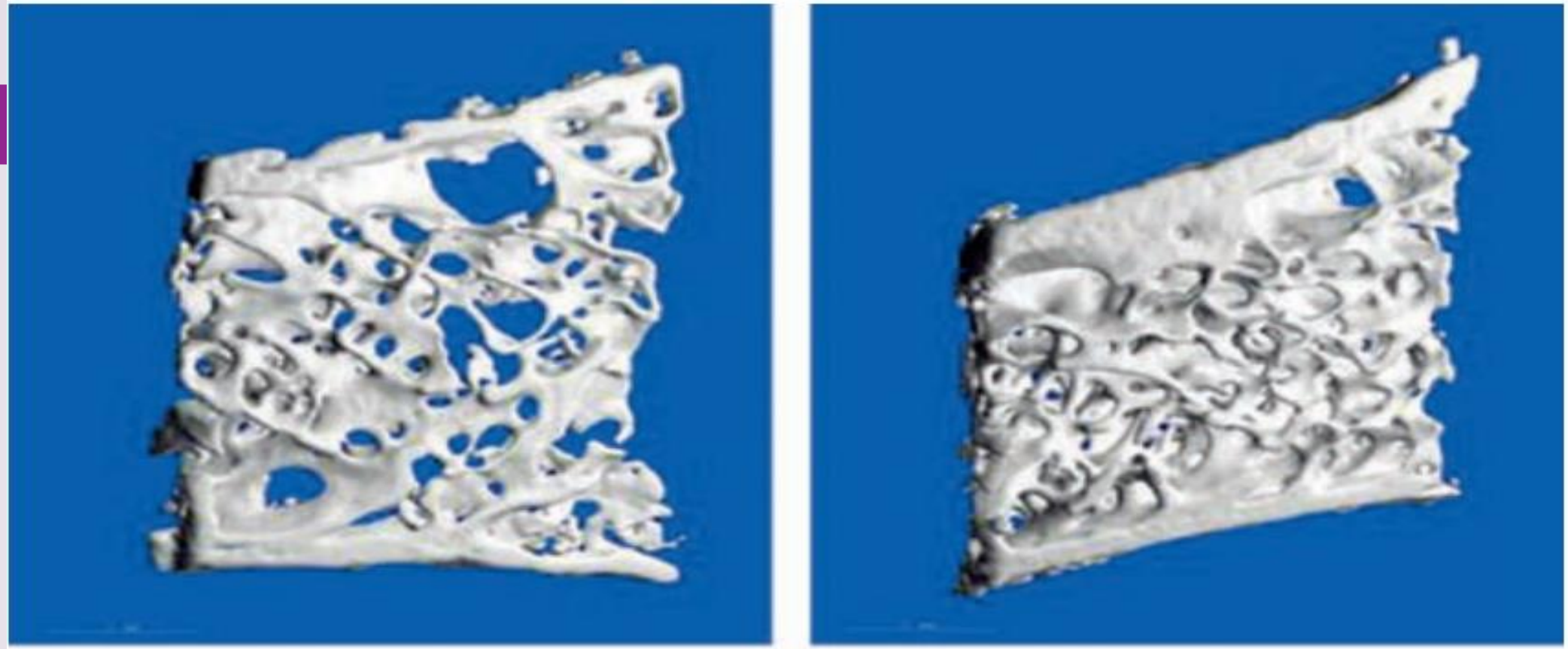
# Medical therapy to prevent fractures in people with low bone density



- For people who meet **criteria for initiation** of pharmacotherapy, we **recommend bisphosphonates** (alendronate, risedronate or zoledronic acid).
- Remark: **Oral bisphosphonates may** be preferred, as drug coverage, **costs** and **access** to **an infusion** centre may be **barriers** to zoledronic acid.
- **Strong recommendation**; high-certainty evidence (females), moderate-certainty evidence (males)

# Anabolic agent

## Initiation of pharmacotherapy?



A B

**FIGURE 411-12 Effect of parathyroid hormone (PTH) treatment on bone microarchitecture.** Paired biopsy specimens from a 64-year-old woman before (***A***) and after (***B***) treatment with PTH. *(Reproduced with permission from DW Dempster et al: Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: A paired biopsy study. J Bone Miner Res 16:1846, 2001.)*

- The aim of **osteoanabolic therapies** is to **increase bone mass** by stimulating **bone formation .**
- The most frequently used osteoanabolic approach is to rely on the activating effects of **intermittent parathyroid hormone** (PTH) administration. PTH **activates bone-lining cells**, leading to an increase in the **number of osteoblasts.**

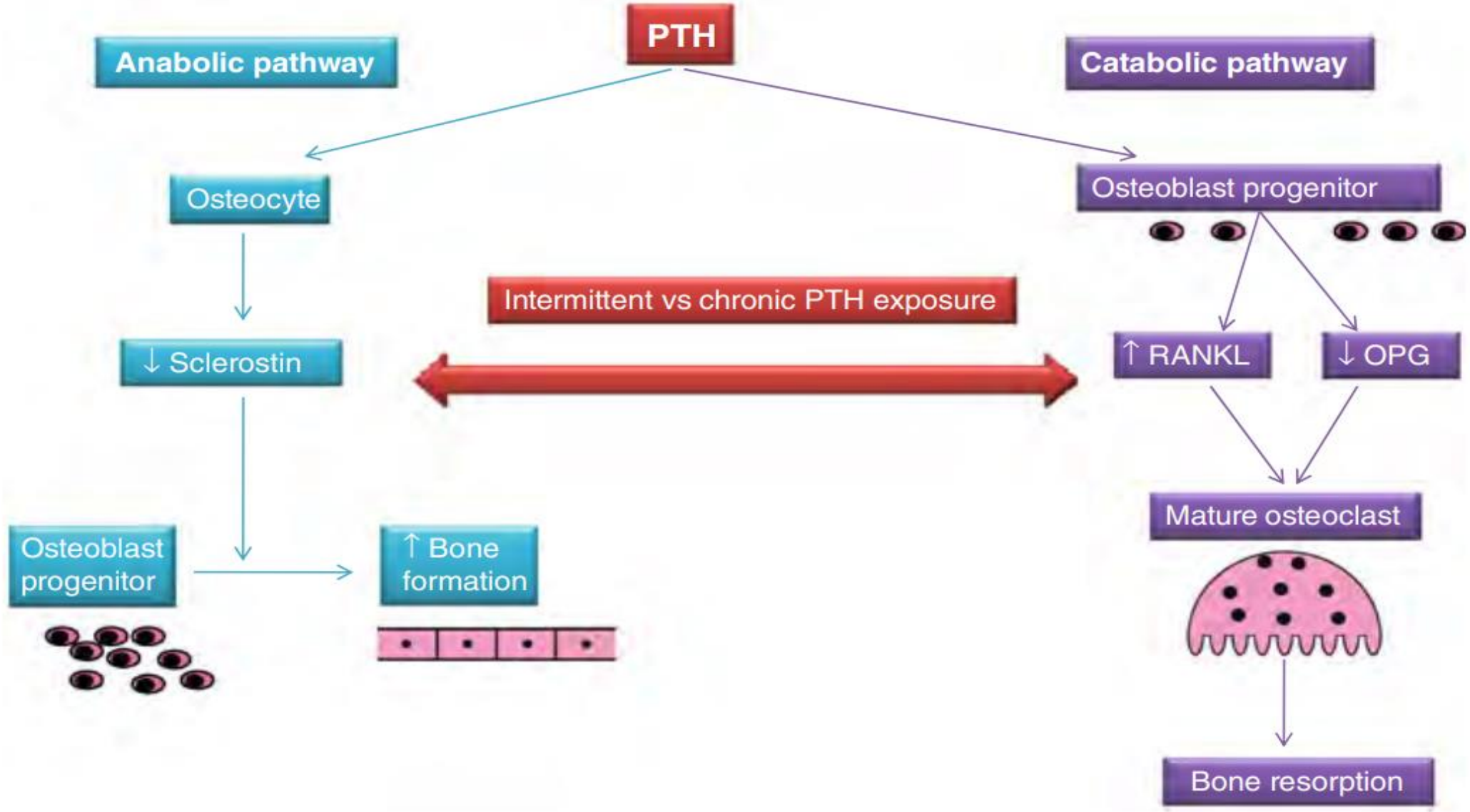



**Fig. 15.3** Differential effects of PTH during continuous versus intermittent exposure

- Teriparatide (**recombinant human PTH(1–34))** is an active fragment of the endogenously produced human PTH.
- Administration of **teriparatide stimulates** the renal production of the **active** form of **vitamin D** (that is, 1,25(OH)2D), which in turn stimulates intestinal **absorption of calcium** and increases the tubular r**e-absorption** of calcium and excretion of phosphate in the kidneys.

- Furthermore**, teriparatide** stimulates **bone formation** directly by its immediate effect on **osteoblasts**.
- Although **osteoclast numbers** are also **increased by teriparatide**, **intermittent** administration in a rat model resulted in a net **increase** in **bone volume**.
- **Abaloparatide** is a **synthetic analogue** of parathyroid hormone-related protein (**PTHrP**), with a mechanism of action that is **similar to** that of teriparatide.

- **Romosozumab** is a **humanized monoclonal antibody** administered subcutaneously that increases **bone formation** by binding to and **inhibiting sclerostin**, a **major inhibitor of bone formation**.
- The inhibition of sclerostin by romosozumab leads to both **decreased bone resorption** and **increased bone formation**, thus this drug is dual-acting.

- For patients **with severe osteoporosis:**
- **T-score of ≤-3.0** even in the absence of fractures
- **T-score of ≤-2.5 plus a fragility fracture**
- **severe or multiple vertebral fractures**
- **some UpToDate experts** prefer initial treatment with an **anabolic agent** (teriparatide, abaloparatide, romosozumab)
- whereas **other UpToDate experts** prefer initial treatment with **bisphosphonates** because of the **cost** of anabolic therapy, **subcutaneous** route of administration, and **long-term safety concerns.**

- For people meeting criteria for **initiation of pharmacotherapy** who have had :
- **recent severe vertebral fracture**, or > **1 vertebral fracture AND** a **T-score ≤ –2.5**
- we suggest seeking advice from a consultant with expertise in osteoporosis about **anabolic therapy** (teriparatide or romosozumab).

- Remark: "**Recent fracture**" is defined as a fracture occurring **within the past 2 yr**, and "**severe** vertebral fracture" as vertebral body **height loss of > 40%.**
- Clinicians may seek **advice from radiologists** to clarify the **degree of severity** of the vertebral fracture. The choice of anabolic therapy may depend on affordability and feasibility of injection schedule.
- Conditional recommendation; high-certainty evidence (females), moderate-certainty evidence (males)

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- In postmenopausal women with osteoporosis at **very high risk** of fracture, such as those with **severe or multiple vertebral fractures**, we recommend **teriparatide or abaloparatide** treatment for **up to 2 years** for the **reduction** of vertebral and nonvertebral **fractures**.(+++-)
- In postmenopausal women with osteoporosis who **have completed a course of teriparatide** or abaloparatide, we recommend treatment with **antiresorptive osteoporosis** therapies to **maintain bone density gains.(++--)**

Pharmacological Management of Osteoporosis in Postmenopausal Women: An **Endocrine Society*** Clinical Practice Guideline. J Clin Endocrinol Metab 2019

- In postmenopausal women with osteoporosis who are at **high risk for osteoporotic fractures**, we recommend using **denosumab** as an alternative initial treatment. (++++)
- The recommended dosage is **60 mg subcutaneously** every 6 months. The effects of denosumab on **bone remodeling**, reflected in **bone turnover** markers, **reverse after 6 months** if the drug is not taken on schedule. Thus, a **drug holiday** or **treatment interruption is not recommended** with this agent.

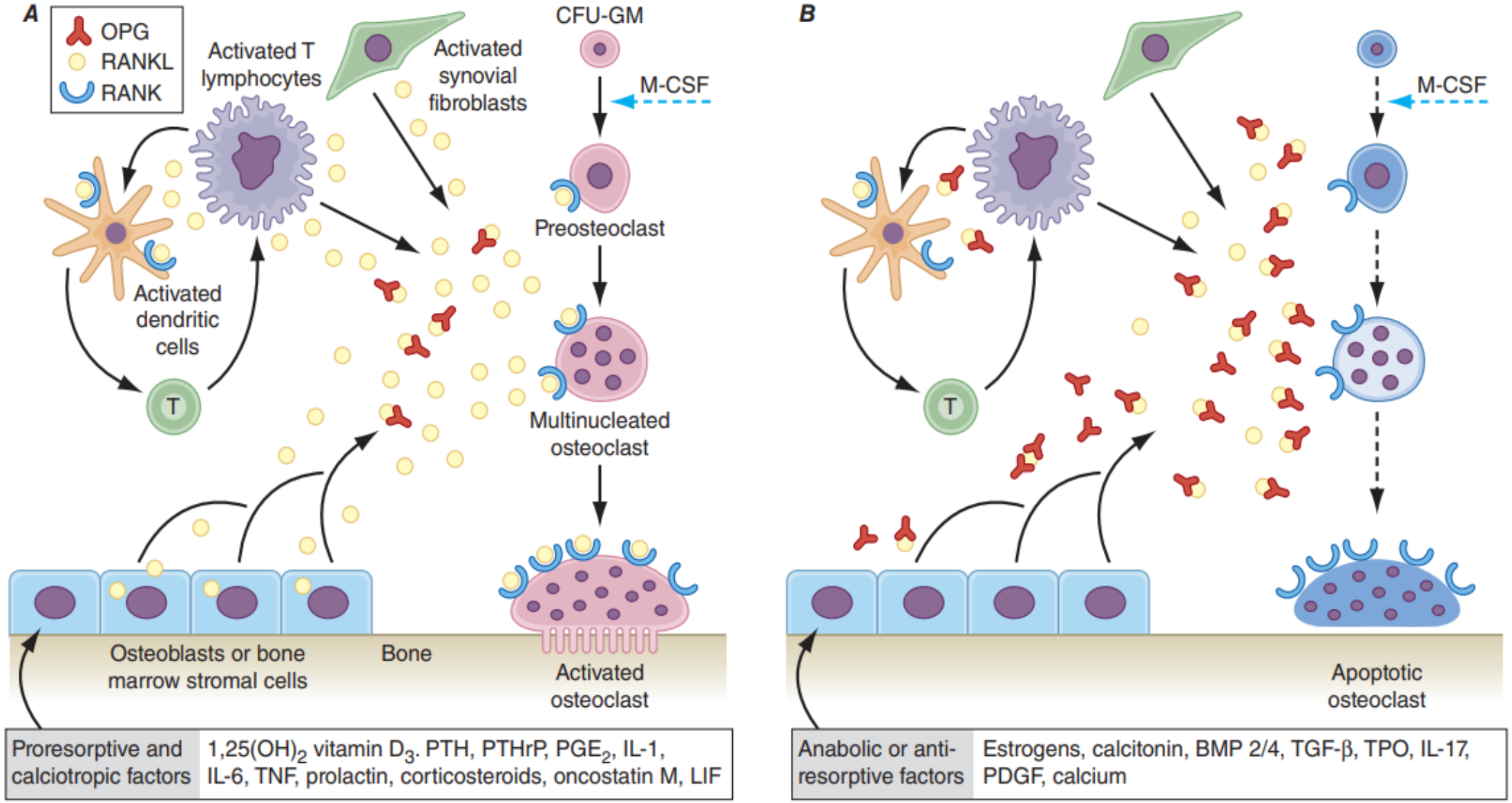
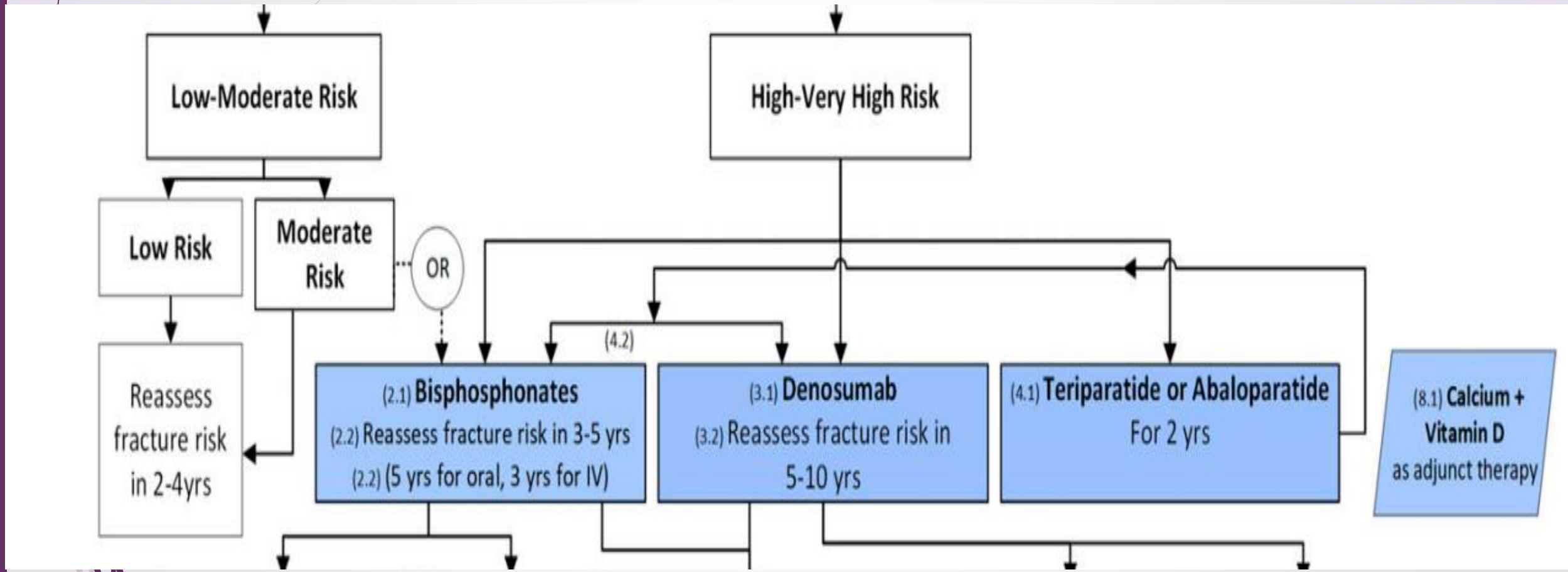
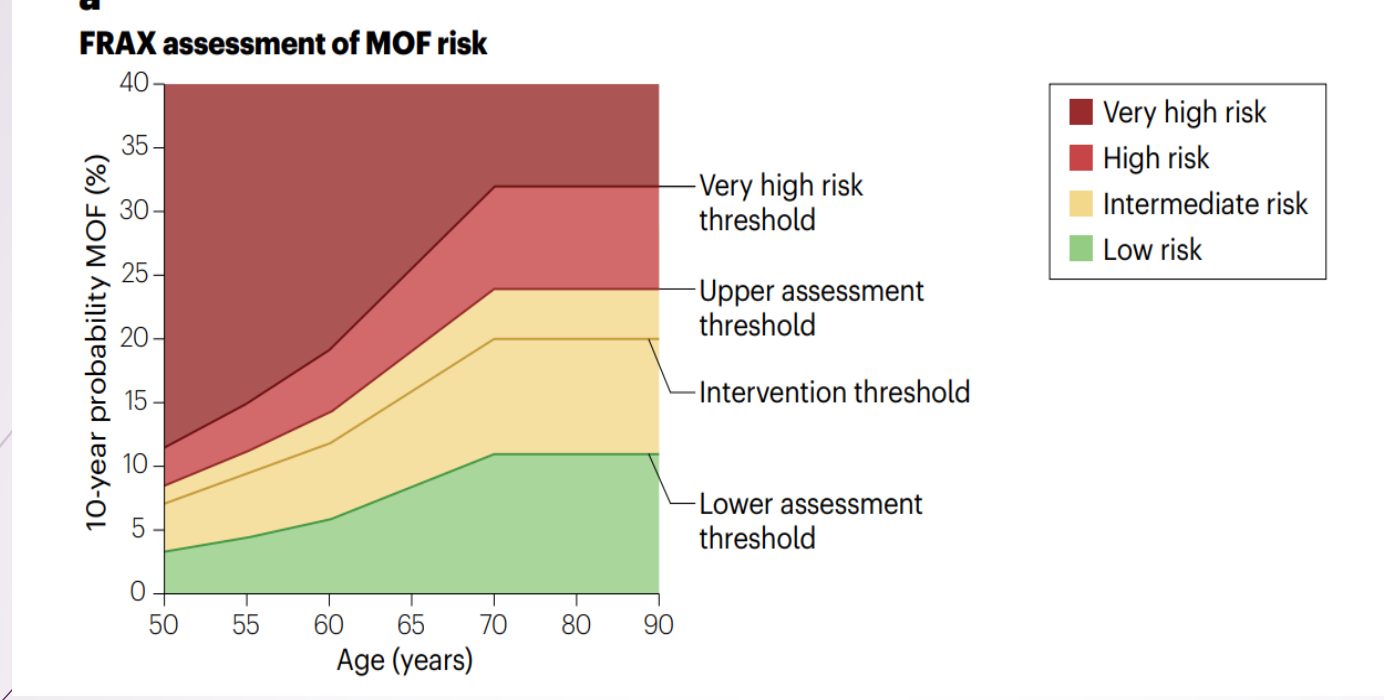



**FIGURE 411-5 Hormonal control of bone resorption.** ***A.*** Proresorptive and calciotropic factors. ***B.*** Anabolic and antiosteoclastic factors. RANKL expression is induced in osteoblasts, activated T cells, synovial fibroblasts, and bone marrow stromal cells. It binds to membrane-bound receptor RANK to promote osteoclast differentiation, activation, and survival. Conversely, osteoprotegerin (OPG) expression is induced by factors that block bone catabolism and promote anabolic effects. OPG binds and neutralizes RANKL, leading to a block in osteoclastogenesis and decreased survival of preexisting osteoclasts. CFU-GM, colony-forming units, granulocyte macrophage;

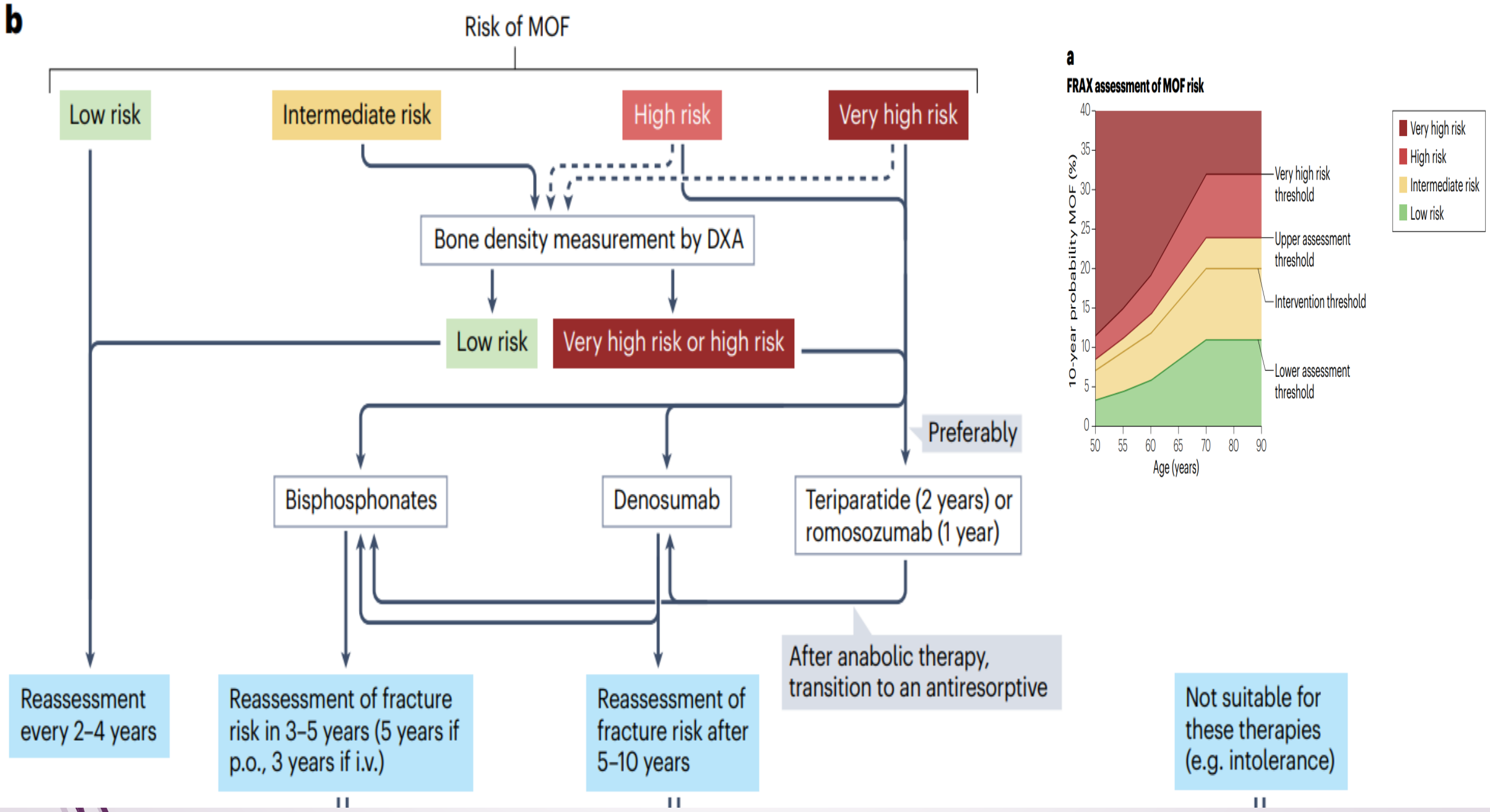
- "**low risk**" includes **no** prior hip or spine **fractures**, a BMD T-score at the hip and spine **both above -1.0** and 10-year hip fracture risk **<3%** and 10-year risk of major osteoporotic fractures **<20%**
- "**moderate risk**" includes **no** prior hip or spine **fractures**, a BMD T-score at the hip and spine both **above -2.5**, or 10-year hip fracture **risk <3%** or risk of major osteoporotic fractures **<20%**

- "**high risk**" includes a prior spine or hip **fracture**, or a BMD T-score at the hip or spine of **-2.5 or below**, **or** 10-year hip fracture risk **>3%**, or risk of major osteoporotic fracture risk **>20%**
- "**very high risk**" includes **multiple spine** fractures **and** a BMD T-score at the hip or spine of **-2.5 or below**


Low-Moderate Risk
High-Very High Risk
Low Risk
Moderate Risk
OR
(4.2)
Reassess fracture risk in 2-4yrs
(2.1) Bisphosphonates
(2.2) Reassess fracture risk in 3-5 yrs
(2.2) (5 yrs for oral, 3 yrs for IV)
(3.1) Denosumab
(3.2) Reassess fracture risk in 5-10 yrs
(4.1) Teriparatide or Abaloparatide
For 2 yrs
(8.1) Calcium + Vitamin D
as adjunct therapy




- women according to fracture risk category. Very high risk is assumed if one or more of the following criteria are met: fracture within the past 12 months ; multiple fractures have previously occurred ; fracture has occurred during osteoporosis therapy; fracture has occurred owing to medication; very low T-score (standard deviation from healthy young adults) (less than −3.0)FRAX risk (calculated 10-year probability of MOF) 10–30% dependent on age, or MOF >4.5% at the hip228–231. Risk assessment should be **done by FRAX score** in the **absence of BMD** measurement. In case of **high or very high risk**, **treatment** should start **immediately** and BMD can be measured as **baseline reference**


b
Risk of MOF
Low risk
Intermediate risk
High risk
Very high risk
Bone density measurement by DXA
Low risk
Very high risk or high risk
Preferably
Bisphosphonates
Denosumab
Teriparatide (2 years) or romosozumab (1 year)
After anabolic therapy, transition to an antiresorptive
Reassessment every 2–4 years
Reassessment of fracture risk in 3–5 years (5 years if p.o., 3 years if i.v.)
Reassessment of fracture risk after 5–10 years
Not suitable for these therapies (e.g. intolerance)
a
FRAX assessment of MOF risk
10-year probability MOF (%)
Age (years)
Very high risk threshold
Upper assessment threshold
Intervention threshold
Lower assessment threshold
Very high risk
High risk
Intermediate risk
Low risk

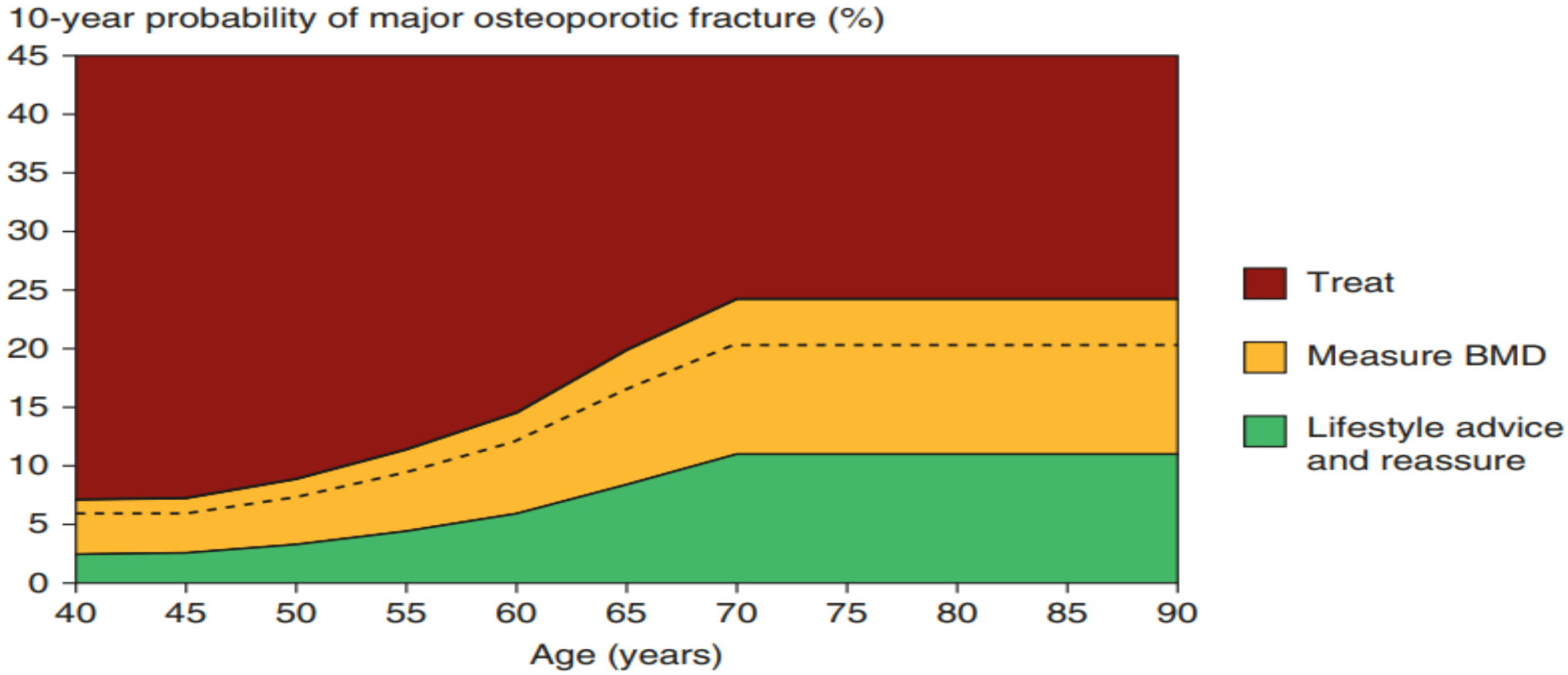



**Fig. 2.2** Normogram demonstrating the age-dependent, 10-year probability of major osteoporotic fracture as used in the NOGG recommendations. Those individuals falling in the red area at to be treated, those in the green to be offered lifestyle advice and reassurance and those in the yellow require further assessment of BMD via DXA in order to inform treatment decisions [14]. Note this figure is taken from an article distributed under the terms of the Creative Commons Attribution 4.0

# Second line Therapy

- For people **meeting criteria for initiation** of pharmacotherapy who have **contraindications**, substantial **intolerance** or **barriers** to bisphosphonates, we suggest **denosumab.**
- Remark: Despite the benefits of denosumab, a **careful assessment** of **indications is required** because of the risk of **rapid bone loss** and **vertebral fractures** with **delayed dosing** or **discontinuation** of denosumab.

- It is important to communicate the need for commitment to long-term therapy and the **need to transition to alternative** antiresorptive therapy if **discontinuing** denosumab.
- **Denosumab** may be preferred when there is a high burden of oral medications, **gastrointestinal intolerance**, contraindication to oral bisphosphonates or barriers **to accessing intravenous zoledronic acid.**
- Conditional recommendation; high-certainty evidence (females), moderate-certainty evidence (males)

- Contraindications/intolerance to any bisphosphonate For postmenopausal women at **very high risk** of fracture (eg, T-score of ≤-3.0 in the absence of fragility fracture, T-score of ≤-2.5 plus a fragility fracture, severe or multiple vertebral fractures), we suggest an **anabolic agentes.**
- Denosumab is an **alternative**. Among the anabolic agents, we prefer **teriparatide** or **abaloparatide** because of efficacy and **longer-term safety** data (particularly for teriparatide).
- Teriparatide and abaloparatide must be injected **subcutaneously daily,** whereas **romosozumab is injected once monthly** by a health care provider.

- For **postmenopausal** females **aged < 60 yr** or within **10 yr** of menopause initiating pharmacotherapy who prioritize alleviation of substantial **menopausal symptoms**, we suggest menopausal **hormone therapy** as an **alternative option** to bisphosphonate therapy.
- Remark: The choice will also depend on **individualized risks** of menopausal hormone therapy, which consists of an estrogen dose equivalent of conjugated equine estrogens of **0.625 mg** daily (plus **progestogen** in those with an **intact uterus**).
- Conditional recommendation; moderate-certainty evidence

- For patients at **high risk for fracture** (eg, **osteoporosis** by BMD in the absence of fragility fracture, **T-score > -2.5 with a fragility fracture**, **single** vertebral fracture), **denosumab** is a reasonable option. As discussed above, because of emerging concerns about an increased risk of vertebral fracture after discontinuation of denosumab, the need for identified administration of denosumab should be **discussed with patients** prior to its initiation.

- For postmenopausal females initiating pharmacotherapy who have **contraindications** or substantial i**ntolerance** to, or who choose not to take other suggested therapies, we suggest **raloxifene rather than no treatment**.
- Remark: Raloxifene should be used only in those who are not at high risk of **venous thromboembolism.**
- Conditional recommendation; moderate-certainty evidence

- In postmenopausal women with osteoporosis who are at **high risk for osteoporotic fractures**, we recommend using **denosumab** as an alternative initial treatment. (++++)
- The recommended dosage is **60 mg subcutaneously** every 6 months. The effects of denosumab on **bone remodeling**, reflected in **bone turnover** markers, **reverse after 6 months** if the drug is not taken on schedule. Thus, a **drug holiday** or **treatment interruption is not recommended** with this agent.

| Drug | Route and dosing | Potential adverse effects | Contraindications | Other considerations | Cost† |
|---|---|---|---|---|---|
| **Antiresorptive agents** | | | | | |
| Bisphosphonates | | | | | |
| Alendronate | Oral: 70 mg weekly *or* 10 mg daily | • Esophageal or GI intolerance<br>• MSK discomfort<br>• Rare: AFF, ONJ | • CrCl < 30–35 mL/min<br>• Esophageal abnormalities<br>• Inability to be upright > 30 min<br>• Hypocalcemia | • Foods, drinks (except plain water), other drugs should be avoided for > 30–60 min<br>• Minerals and dairy impair absorption if taken close together | $ |
| Risedronate | Oral: 35 mg weekly *or* 150 mg monthly *or* 5 mg daily | • Esophageal/GI intolerance<br>• MSK discomfort<br>• Rare: AFF, ONJ | • CrCl < 30–35 mL/min<br>• Esophageal abnormalities<br>• Inability to be upright > 30 min<br>• Hypocalcemia | • Foods, drinks (except plain water), other drugs should be avoided for > 30–60 min<br>• Minerals and dairy impair absorption if taken close together<br>• Delayed-release formulation available (taken with food) | $ |
| Zoledronic acid | Intravenous: 5 mg yearly | • Transient flu-like symptoms<br>• Hypocalcemia<br>• Renal toxicity<br>• Rare: AFF, ONJ | • CrCl < 35 mL/min<br>• Hypocalcemia | • Inadequate vitamin D increases risk for hypocalcemia<br>• Less frequent dosing than yearly may be considered | $$ |

| Drug | Route and dosing | Potential adverse effects | Contraindications | Other considerations | Cost† |
|---|---|---|---|---|---|
| **RANK-ligand inhibitor (monoclonal antibody)** | | | | | |
| Denosumab | Subcutaneous: 60 mg every 6 mo | • Hypocalcemia<br>• Dermatitis, infections<br>• MSK discomfort<br>• Rare: AFF, ONJ | • Hypocalcemia | • Inadequate vitamin D increases risk for hypocalcemia<br>• Caution warranted in severe renal impairment<br>• Rapid bone loss and risk of vertebral fractures if delayed dose or with discontinuation | $$$ |
| **Hormonal therapy** | | | | | |
| Menopausal hormonal therapy | Multiple regimens | • VTE, CVD, stroke<br>• Breast cancer | • VTE, CVD, stroke, estrogen-dependent tumours, abnormal vaginal bleeding, active liver disease | • Only in postmenopausal women | $–$$ |
| Raloxifene (SERM) | Oral: 60 mg daily | • VTE, CVD, stroke<br>• Vasomotor symptoms, leg cramps | • VTE, CVD, stroke, abnormal vaginal bleeding | • Only in postmenopausal women | $ |

| Drug | Route and dosing | Potential adverse effects | Contraindications | Other considerations | Cost† |
|---|---|---|---|---|---|
| **Anabolic agents** | | | | | |
| Parathyroid hormone analog | | | | | |
| Teriparatide | Subcutaneous: 20 µg daily for 24 mo | • Orthostatic hypotension, nausea<br>• Hypercalcemia, hypercalciuria<br>• MSK discomfort | • CrCl < 30 mL/min<br>• Bone malignancy, Paget disease, previous skeletal radiation<br>• Hypercalcemia disorder<br>• Unexplained elevated ALP | • Caution warranted with active or previous kidney stone disease | $$$$$ |
| Sclerostin inhibitor (monoclonal antibody) | | | | | |
| Romosozumab | Subcutaneous: 210 mg monthly for 12 mo | • Myocardial infarction, stroke<br>• Hypocalcemia<br>• MSK discomfort<br>• Rare: AFF, ONJ | • Previous myocardial infarction or stroke<br>• Hypocalcemia | • Inadequate vitamin D increases risk for hypocalcemia<br>• Caution warranted in severe renal impairment | $$$$$ |

Note: AFF = atypical femoral fracture, ALP = alkaline phosphatase, CrCl = creatinine clearance, CVD = cardiovascular disease, GI = gastrointestinal, MSK = musculoskeletal, ONJ = osteonecrosis of the jaw, RANK = receptor activator of nuclear factor κ-β, SERM = selective estrogen receptor modulator, VTE = venous thromboembolism.
*Information in this table is not meant to be exhaustive and should not replace complete details provided by drug monographs (available in the Compendium of Pharmaceuticals and Specialties at myrxtx.ca). Further information on some medications available in selected references.[15,43,46–51]
†Relative cost.

## Table 1 | Pharmacological treatment options in osteoporosis and fracture efficacy, including safety aspects and approvals

| Medication | Dosage | Application | Effect on vertebral fracture | Effect on non-vertebral fracture | Effect on hip fracture | Most relevant safety aspects | Clinical use | Refs. |
|---|---|---|---|---|---|---|---|---|
| Alendronate[a] | 10 mg daily; 70 mg weekly | Oral | + | + | + | Gastric ulcer; creatinine increase; MRONJ; AFF | Women and men; GIOP | 193–196 |
| Risedronate[a] | 5 mg daily; 35 mg weekly | Oral | + | + | + | | Women and men | 197–200 |
| Ibandronate[b] | 3 mg every 3 months intravenously or 150 mg orally once monthly | Intravenous or oral | + | + | – | | Women | 201–204 |
| Zoledronic acid | 5 mg | Intravenous | + | + | + | | Women and men; GIOP; Paget disease | 54,205 |
| Raloxifene | 60 mg | Oral | + | +[c] | – | Hot flushes; deep vein thrombosis; pulmonary embolism; retinal vein thrombosis | Women | 206–208 |
| Bazedoxifene | 20 mg | Oral | + | ±[d] | – | | Women | 32, 209–212 |

**Table 1 | Pharmacological treatment options in osteoporosis and fracture efficacy, including safety aspects and approvals**

| Medication | Dosage | Application | Effect on vertebral fracture | Effect on non-vertebral fracture | Effect on hip fracture | Most relevant safety aspects | Clinical use | Refs. |
|---|---|---|---|---|---|---|---|---|
| Teriparatide | 20 µg daily for maximum 2 years | Subcutaneous | + | + | – | Hypercalcaemia; hypercalciuria; hyperuricaemia; osteosarcoma; orthostatic hypotension | Women and men; GIOP | 37,213 |
| Abaloparatide[e] | 80 µg daily, maximum total duration 18 months | Subcutaneous | + | + | ±[d] | | Not approved in the EU; US approval for women and men | 214–216 |
| Denosumab | 60 mg every 6 months | Subcutaneous | + | + | + | Hypocalcaemia; rebound vertebral fractures; MRONJ; AFF; severe forms of renal impairment; skin infections | Women and men; MHA; GIOP | 217,218 |
| Romosozumab | 210 mg per month for 1 year | Subcutaneous | + | + | + | Cardiovascular (compared with alendronate) | Women | 71,219 |
| MHT or HRT[f] | Depends on the intended therapy goal | Depends on substance used and indication | + | + | + | Venous thromboembolism; pulmonary embolism; breast cancer | NA | 220–227 |

# Osteopenia

- **ACP** suggests that clinicians take an **individualized approach** regarding **whether to start pharmacologic** treatment with a bisphosphonate in **females over the age of 65** with low bone mass (**osteopenia**) to **reduce the risk of fractures**
- (conditional recommendation; **low-certainty** evidence)

### Patient Population

Postmenopausal females diagnosed with low bone mass

### Interventions Compared With Placebo or Each Other

- Bisphosphonates (alendronate, risedronate, zoledronate)
- Denosumab
- Teriparatide
- Abaloparatide
- Romosozumab
- Raloxifene

### Key Outcomes Assessed at 12–36 and ≥36 Months

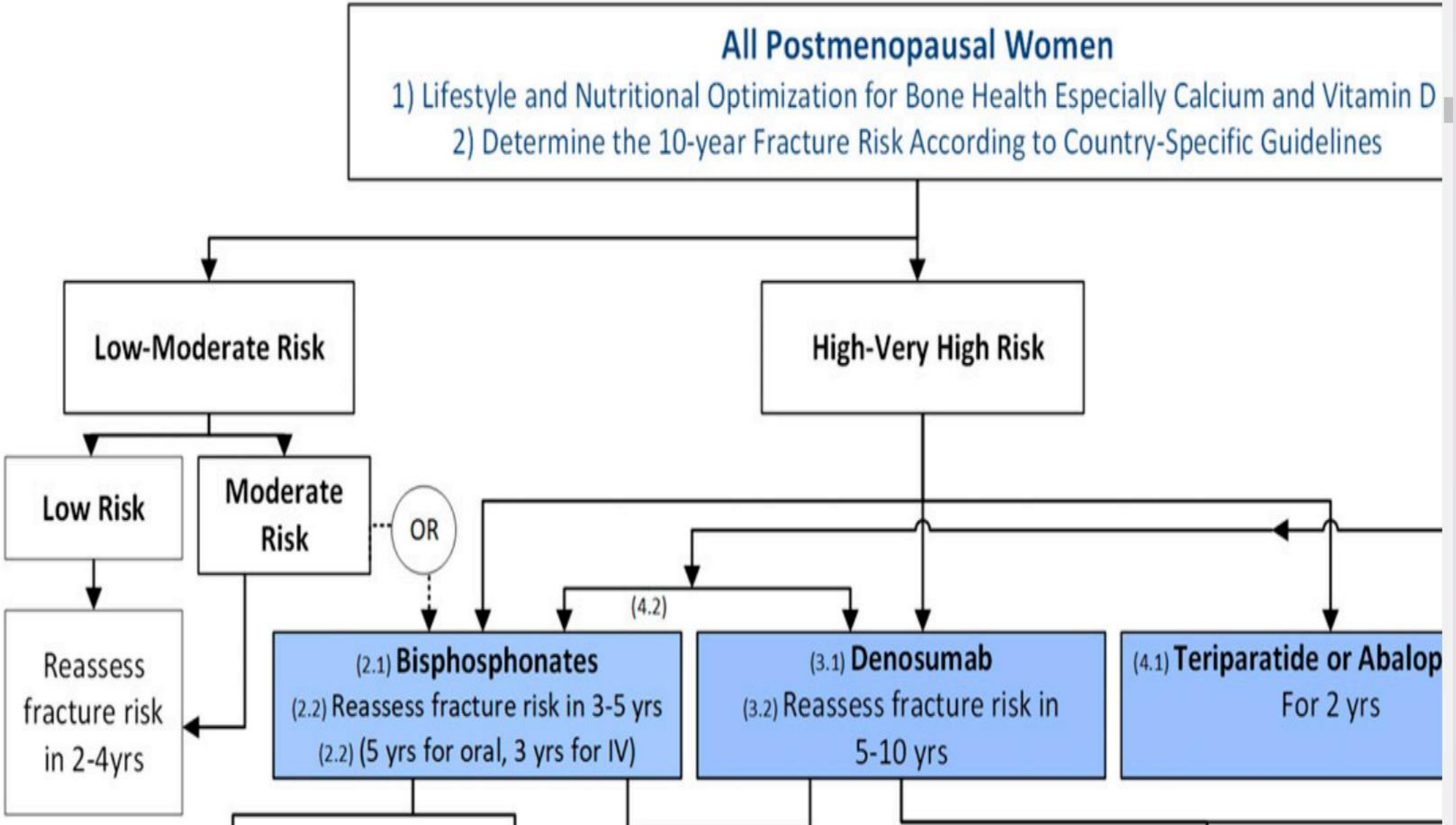
- Hip fracture
- Any clinical and clinical vertebral fractures
- Radiographic vertebral fractures
- Harms (serious adverse effects and treatment withdrawal due to adverse effects)

## Key Outcomes

### Overall, Long-Term

| | *CERTAINTY OF THE EVIDENCE* |
|---|---|
| Zoledronate may have reduced the risk for any clinical or vertebral fractures at 6 years of treatment without higher risk for serious adverse events compared with placebo in a randomized controlled clinical trial. | LOW |
| The evidence is very uncertain about the effect of bisphosphonates (zoledronate) on the risk for hip fractures, withdrawal due to adverse events, and atrial fibrillation at 6 years (insufficient). | INSUFFICIENT |
| Other medications have not been examined yet in females with low bone mass. | |

- "**low risk**" includes **no** prior hip or spine **fractures**, a BMD T-score at the hip and spine **both above -1.0** and 10-year hip fracture risk **<3%** and 10-year risk of major osteoporotic fractures **<20%**
- "**moderate risk**" includes **no** prior hip or spine **fractures**, a BMD T-score at the hip and spine both **above -2.5**, or 10-year hip fracture **risk <3%** or risk of major osteoporotic fractures **<20%**


All Postmenopausal Women
1) Lifestyle and Nutritional Optimization for Bone Health Especially Calcium and Vitamin D
2) Determine the 10-year Fracture Risk According to Country-Specific Guidelines
Low-Moderate Risk
High-Very High Risk
Low Risk
Moderate Risk
OR
Reassess fracture risk in 2-4yrs
(4.2)
(2.1) Bisphosphonates
(2.2) Reassess fracture risk in 3-5 yrs
(2.2) (5 yrs for oral, 3 yrs for IV)
(3.1) Denosumab
(3.2) Reassess fracture risk in 5-10 yrs
(4.1) Teriparatide or Abalop
For 2 yrs

# Guidelines for pharmacologic intervention in postmenopausal females and males ≥50 years of age

| |
|---|
| History of fracture of vertebrae (clinical or subclinical), hip, wrist, pelvis, or humerus. |
| T-score ≤–2.5 (DXA) at the lumbar spine, femoral neck, or total hip.* |
| T-score between –1 and –2.5 at the femoral neck or spine, and a 10-year probability of hip fracture ≥3% or a 10-year probability of any major osteoporosis-related fracture ≥20% based upon the United States-adapted WHO algorithm. |

DXA: dual-energy x-ray absorptiometry; WHO: World Health Organization.

* Predictive value of isolated measurement of 1/3 radius varies with clinical context.

# Fallow up

- **BHOF** – The BHOF recommends repeat BMD assessments (DXA spine or hip) one to two years after initiating therapy and then at individualized intervals thereafter, with more frequent testing in certain clinical situations [28].

- **AACE** – The American Association of Clinical Endocrinologists (AACE) recommends repeat DXA of the LS and total hip every one to two years until stability is achieved, and every two years or at less frequent intervals thereafter [55].

- **NAMS** – The North American Menopause Society (NAMS) recommends repeat DXA one to two years after initiating therapy or when there may be a change in osteoporosis therapy [56].

- **ACP** – The American College of Physicians (ACP) recommends against monitoring during therapy, as many women treated with anti-resorptive therapy have a reduction in fracture even when BMD does not increase [57].

$$\% \text{ Change from Baseline} = [(\text{Follow-up BMD} - \text{Baseline BMD})/\text{Baseline BMD}] \times 100$$

$$\% \text{ Change from Baseline} = [(0.760 \text{ g/cm}^2 - 0.734 \text{ g/cm}^2)/0.734 \text{ g/cm}^2] \times 100$$

$$\% \text{ Change from Baseline} = 3.54\%$$

| Region | BMD[1] (g/cm²) | Young-Adult[2] T-Score | Age-Matched[3] Z-Score |
|---|---|---|---|
| L1 | 0.797 | -2.8 | -2.9 |
| L2 | 0.972 | -1.9 | -2.0 |
| L3 | 1.022 | -1.5 | -1.6 |
| L4 | 0.929 | -2.3 | -2.4 |
| L1-L2 | 0.882 | -2.2 | -2.3 |
| L1-L3 | 0.933 | -2.0 | -2.1 |
| L1-L4 | 0.932 | -2.1 | -2.2 |
| L2-L3 | 0.999 | -1.7 | -1.8 |
| L2-L4 | 0.977 | -1.9 | -2.0 |
| L3-L4 | 0.980 | -1.8 | -2.0 |

| Region | BMD[1] (g/cm²) | Young-Adult[2] T-Score | Age-Matched[3] Z-Score |
|---|---|---|---|
| Neck | 0.967 | -0.1 | -0.4 |
| Wards | 1.069 | 1.2 | 1.6 |
| Troch | 0.943 | 1.4 | 0.8 |
| Shaft | 1.251 | - | - |
| Total | 1.078 | 0.7 | 0.0 |

# Decline in BMD

- When the change in BMD is <5percent and the patient is taking the drug **correctly** and has no discernible contributing factors, we suggest **continuing the same therapy** and **repeating** the BMD **two years later**.

- When the decline in BMD is ≥5 percent, we usually **switch** from an **oral bisphosphonate** to an **IV bisphosphonate**, typically zoledronic acid.
- If the lack of response is related to **poor absorption**, switching to an IV preparation should result in a more favorable response.
- **Other alternatives** include switching to **denosumab**, **teriparatide**, abaloparatide, or romosozumab.

- Remark: **Inadequate response to treatment** should be considered when:
- **> 1 fracture** or substantial **bone density decline** (e.g., **≥ 5%**) occurs despite **adherence to an adequate course** of treatment (**typically > 1 yr**).
- However, fractures or bone density decline during therapy **do not always** indicate inadequate response to treatment (e.g., **secondary** causes of osteoporosis, **falls**, BMD **imprecision errors**)

- When there is **inadequate response** or ongoing substantial concern for **fracture during** bisphosphonate therapy, good practice includes **extending or switching therapy**, reassessing for **secondary causes** and seeking advice from a consultant with expertise in osteoporosis, if needed.

- **Fracture** while taking bisphosphonates – For postmenopausal women with **severe osteoporosis** (**T-score of ≤-2.5** plus a **fragility fracture**) who continue to fracture **after one year of bisphosphonate** therapy, we suggest **discontinuing** the bisphosphonate and **switching to teriparatide**.

# Duration and sequence of therapy

- **Low risk for fracture** – For patients at low risk for fracture in the near future (eg, **stable** bone mineral density [BMD], **no** previous vertebral or hip **fractures**), we suggest **discontinuing the drug** (after three years for zoledronic acid, **five** years for alendronate)

- **High risk for fracture** – For patients at highest risk for fracture (history of osteoporotic **fracture before** or **during** therapy, T-score below **-3.0** in the absence of fractures) who are taking alendronate or risedronate, we suggest continuing therapy **for up to 10 years** as clinical trial data show maintenance of BMD and **fracture benefit** with **no increased risk** of adverse events .
- For similar women treated with **zoledronic acid**, we would continue therapy up to **six years**.

# Length of holiday

- We typically **restart bisphosphonates** within the **five years** of the drug holiday when any of the following occur:
- Reproducible **bone loss** (approximately 5 percent) on at **least two dual-energy** x-ray absorptiometry (DXA) measurements taken **at least two years** apart, using the same make and model DXA scanner.
- Evidence of **bone loss on** one DXA measurement at the **spine and the hip**

# Denosumab

- There are **few data** on the **ideal duration of denosumab** therapy or on **sequential therapy** with other osteoporosis agents.
- The FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) extension trial showed **maintenance of BM**D with continued **use for ten years**.

# Sequential osteoporosis therapy

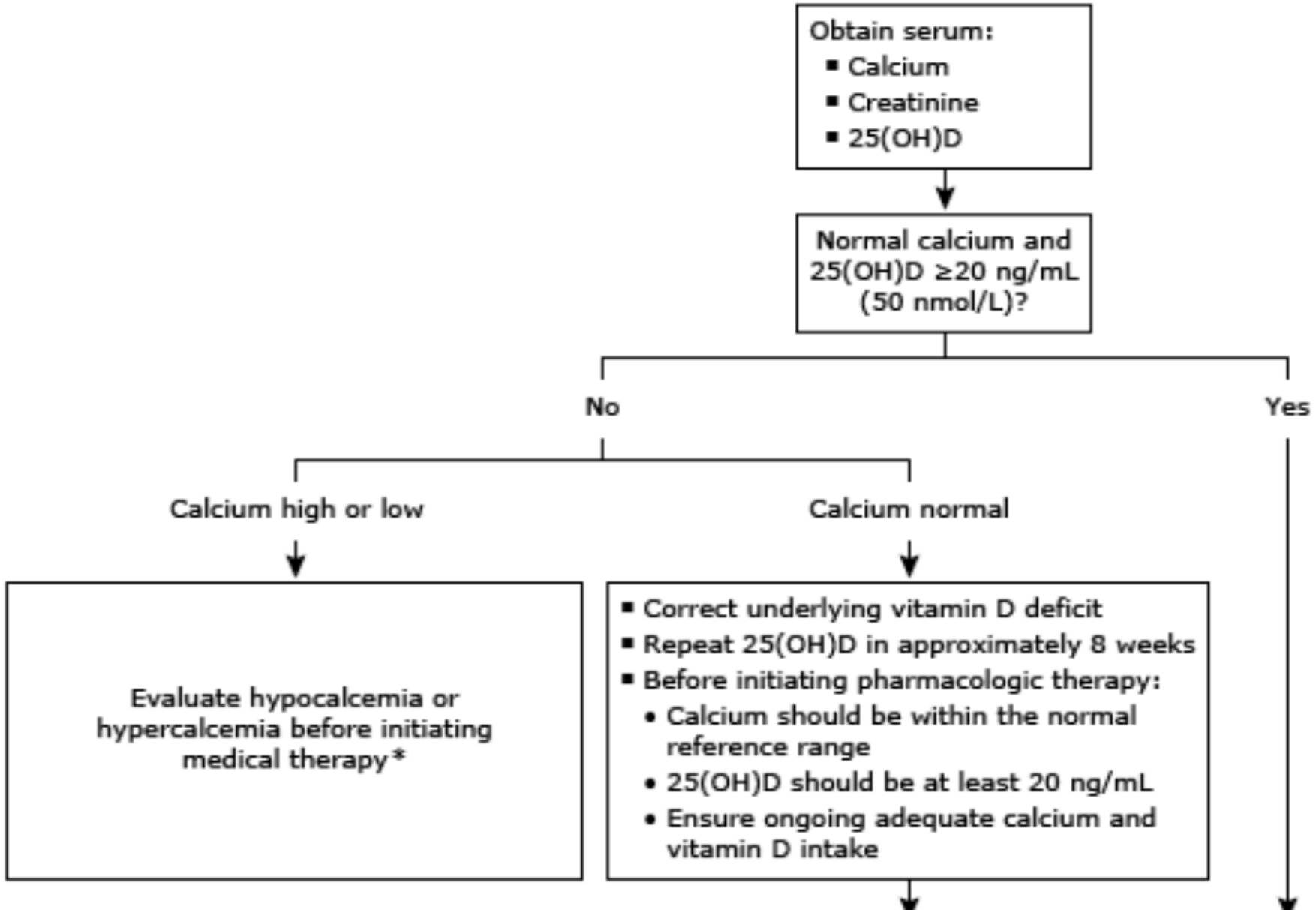
- **Oral alendronate** has been shown to maintain bone density after discontinuation of denosumab .
- It can be initiated **six months after the last denosumab** dose and should be **continued** for **at least one to two years** .

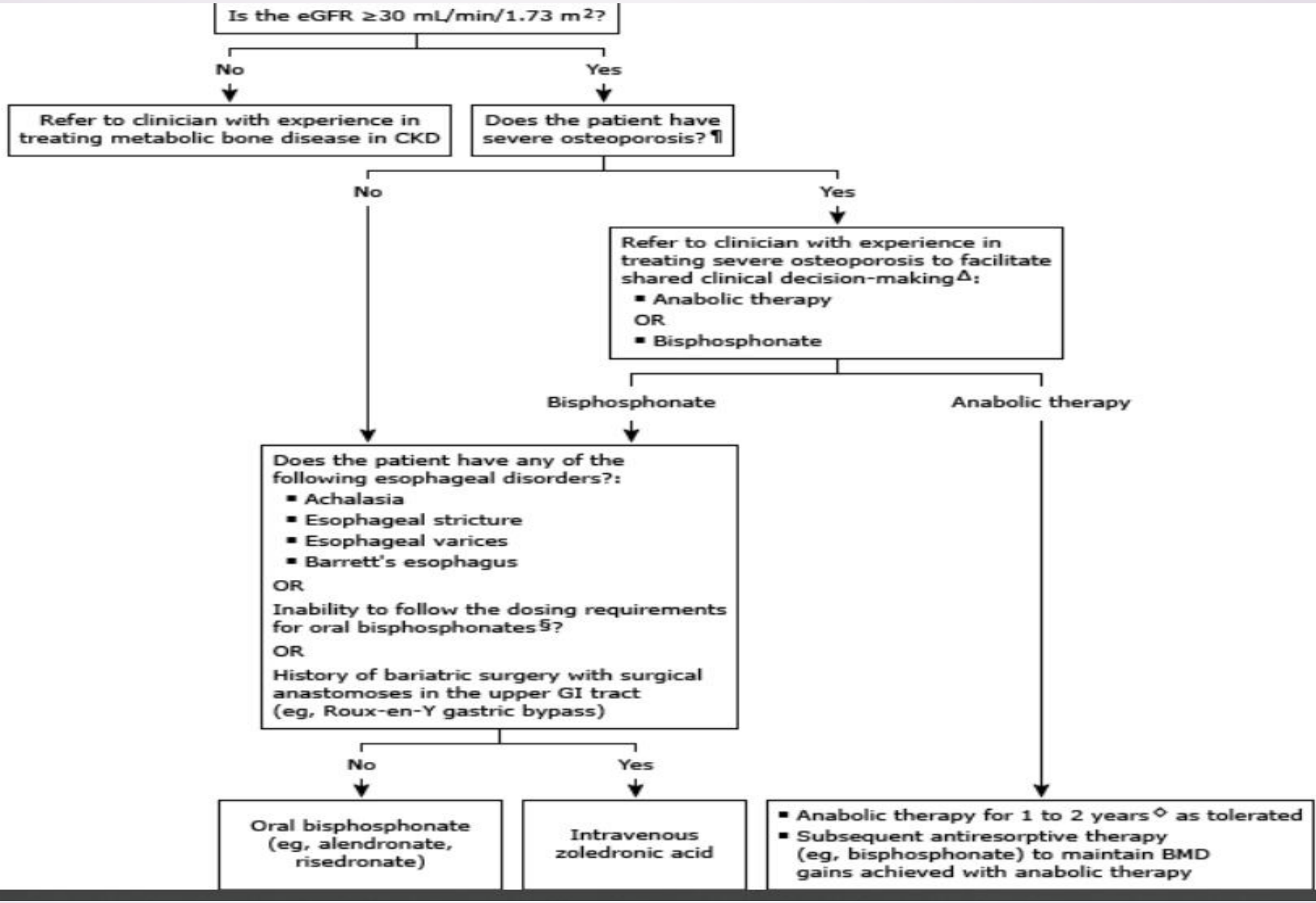
- **Intravenous zoledronic acid** would also likely be e**ffective** and may be more convenient for some patients. However, the **optimal timing** and **frequency** of administration are **still uncertain**.

- If a decision has been made to administer zoledronic acid to prevent bone loss after discontinuation of denosumab, we give the **infusion (5 mg**) **six to seven months after** the last dose of denosumab and measure **a fasting** serum C-telopeptide (**CTX**) **three and six months after the infusion .**
- Some patients may require a **second infusion of zoledronic acid (5 mg**) **three to six months** after the first infusion.(eg, if serum **CTX is >350 pg/mL**)

- We generally **avoid sequential treatment** with **anabolic therapy** (eg, teriparatide, romosozumab) if denosumab was administered first particularly after a long course (eg, **>3 to 4 years**) of denosumab.
- **Anabolic treatment** should precede rather than **follow denosumab** therapy.

# Medical therapy to prevent fractures in people with low bone density



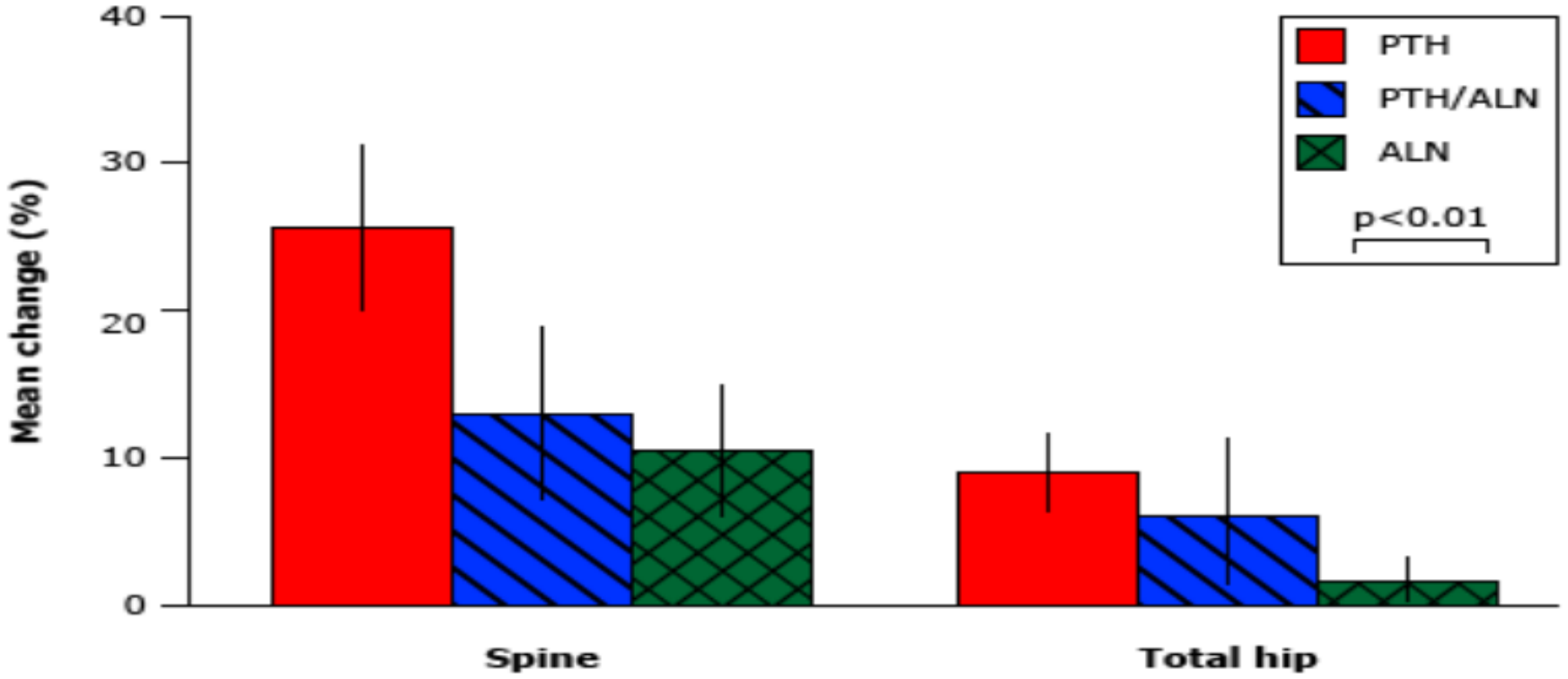

Is the eGFR ≥30 mL/min/1.73 m²?
No
Yes
Refer to clinician with experience in treating metabolic bone disease in CKD
Does the patient have severe osteoporosis? ¶
No
Yes
Refer to clinician with experience in treating severe osteoporosis to facilitate shared clinical decision-making Δ:
Anabolic therapy
OR
Bisphosphonate
Bisphosphonate
Anabolic therapy
Does the patient have any of the following esophageal disorders?:
Achalasia
Esophageal stricture
Esophageal varices
Barrett's esophagus
OR
Inability to follow the dosing requirements for oral bisphosphonates §?
OR
History of bariatric surgery with surgical anastomoses in the upper GI tract (eg, Roux-en-Y gastric bypass)
No
Yes
Oral bisphosphonate (eg, alendronate, risedronate)
Intravenous zoledronic acid
Anabolic therapy for 1 to 2 years ◇ as tolerated
Subsequent antiresorptive therapy (eg, bisphosphonate) to maintain BMD gains achieved with anabolic therapy

# Combination therapy…

- We **suggest not using** PTH/PTHrP analog therapy in combination with other osteoporosis agents. **There are no data** to suggest a benefit.

- Studies investigating the effect of **combining** an **antiresorptive** with an **osteoanabolic** treatment have **led to conflicting results**.
- An early combination of **PTH**(1–84) and **alendronate was not** associated with **higher BMD** increases than either treatment alone in postmenopausal women with osteoporosis.
- **Parallel** alendronate use seemed **to impair** a potential osteoanabolic effect.

# Trabecular volumetric BMD with PTH 1-84, alendronate, or both




Changes in trabecular volumetric BMD in the lumbar spine and total hip by QCT ($g/cm^3$) after 12 months of treatment with PTH 1-84 (100 mcg; red bar), PTH and alendronate (10 mg/day; diagonal-lined blue bar), or alendronate (10 mg/day alone; checkered green bar).

BMD: bone mineral density; PTH: parathyroid hormone; ALN: alendronate; QCT: quantitative computed

- **PTH analog** plus **bisphosphonates** – Several trials have reported that PTH analog therapy plus alendronate (either started concurrently or six months prior to PTH analog) **resulted in no additional benefit.**

- By contrast, the **combination of risedronate** and **teriparatide** **increased BMD** at the **lumbar spine** and the **femoral neck** in **men** with osteoporosis and provided higher BMD increases at the **total hip** than either treatment alone.

- When comparing the effect of **zoledronic acid** once **yearly** and **teriparatide** daily versus either **agent alone** on BMD and BTMs in postmenopausal women with osteoporosis, **teriparatide** increased **spine BMD** more **than zoledronic** acid and zoledronic acid **increased hip** BMD more than teriparatide. A **combination therapy** provided the **largest**, most rapid increments, when **both spine and hip** sites were considered.

- In a **combination** treatment of **teriparatide** and **denosumab** in postmenopausal women with osteoporosis, a **superior increase** in BMD **at the femoral neck**, total **hip** and **spine** was shown compared with either drug alone.

- Of note, **none of these studies** was **powered** to investigate possible effects on **fracture risk**; however, the combination therapy of **teriparatide** with **zoledronic acid** was associated with a **reduction in fractures** compared with **zoledronic acid alone**, but **no difference** was observed for teriparatide with zoledronic acid when compared with **teriparatide alone**.

- **PTH analog** plus **denosumab** – Combination therapy with a PTH analog and denosumab **appears to increase BMD** to a greater extent than either therapy alone, although **fracture data** are **unavailable** and optimal consolidation strategies following treatment have not been determined.

# The Treatment Gap in Osteoporosis Is a Worldwide Problem

- the **GLOW study** demonstrated that **over 80%** of women with a **fragility fracture** did not receive **osteoporosis treatment .**
- In another **international prospective study** of **1795 patients** who sustained a **low trauma hip fractures** in ten countries (Australia, Austria, Estonia, France, Italy, Lithuania, Mexico, Russia, Spain, and the UK), **just 27%** were prescribed **anti-osteoporosis therapy** after the hip fracture.

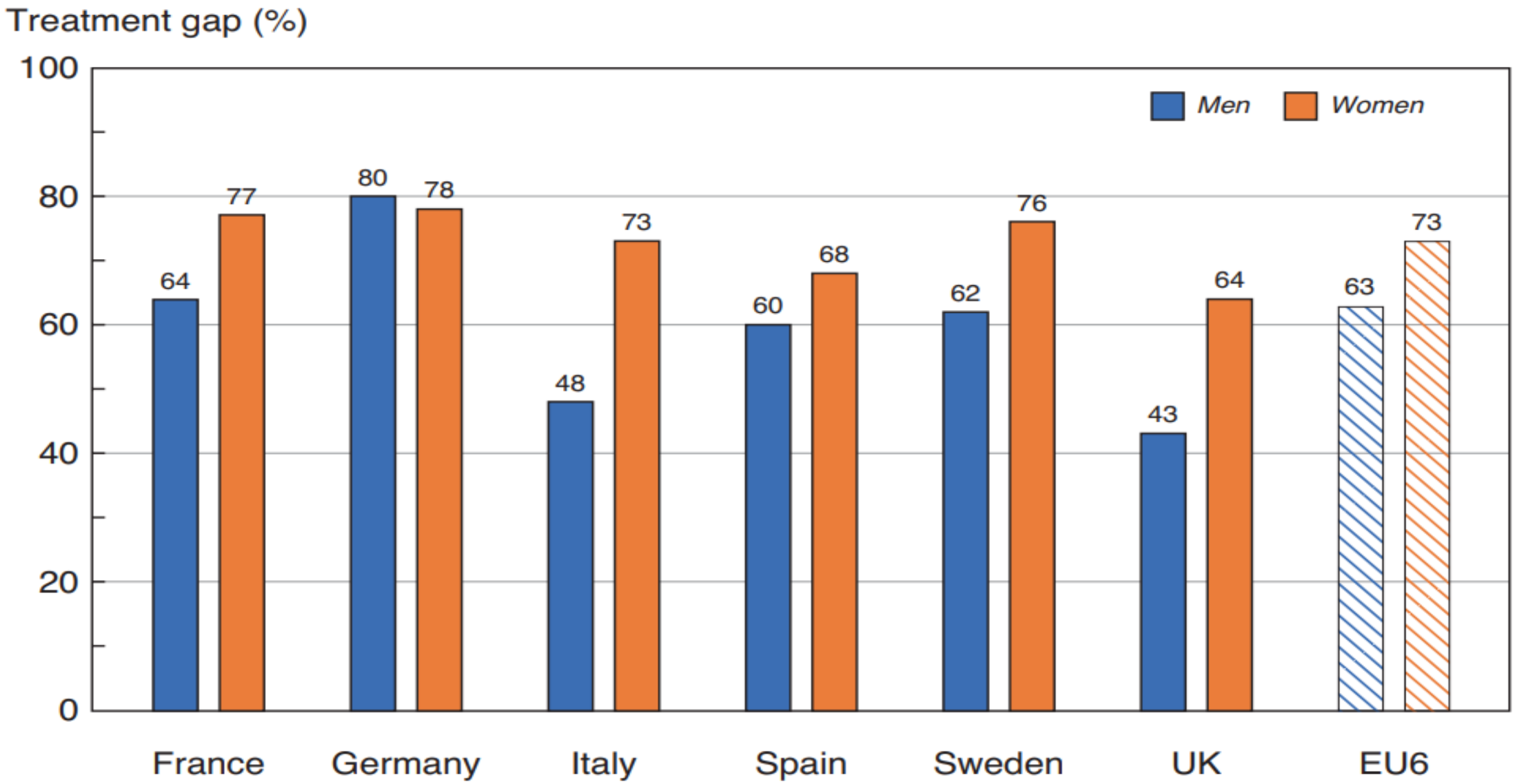



**Fig. 7.2** The treatment gap in six European countries in 2017. The figure shows the percentage of women at high fracture risk who do not receive antiosteoporosis treatment. (Reproduced with permission from [20])


Thank you