Preventing Osteoporotic Fractures: Who, When and How?

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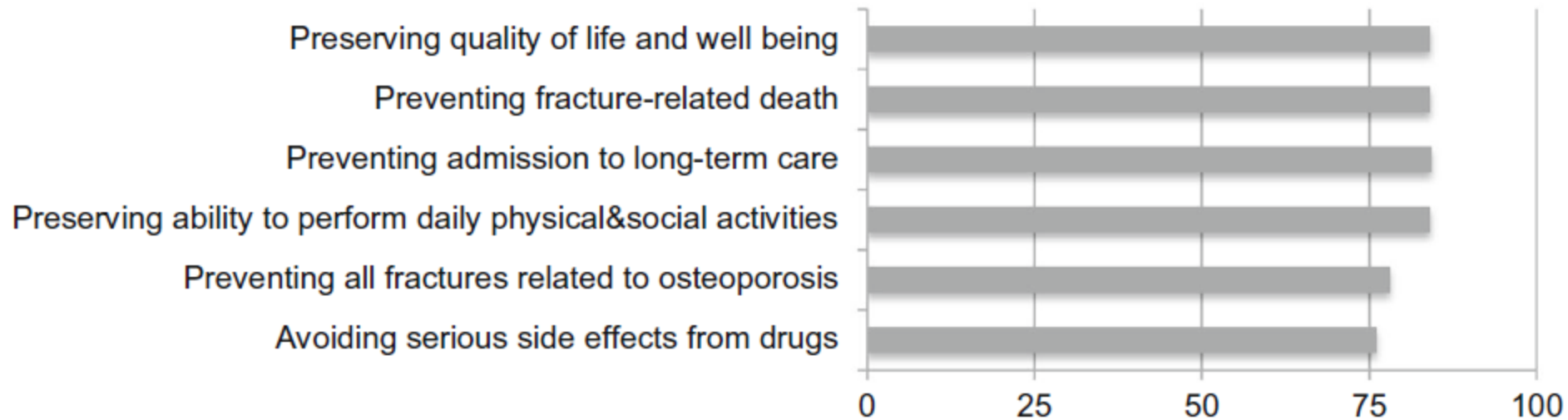
Conflict of Interest

- Past Chair of Osteoporosis Canada Scientific Advisory Council
- Member of the International Osteoporosis Foundation Council of Scientific Advisors
- Member of the Advisory Board of CIHR Institute of Musculoskeletal Health and Arthritis
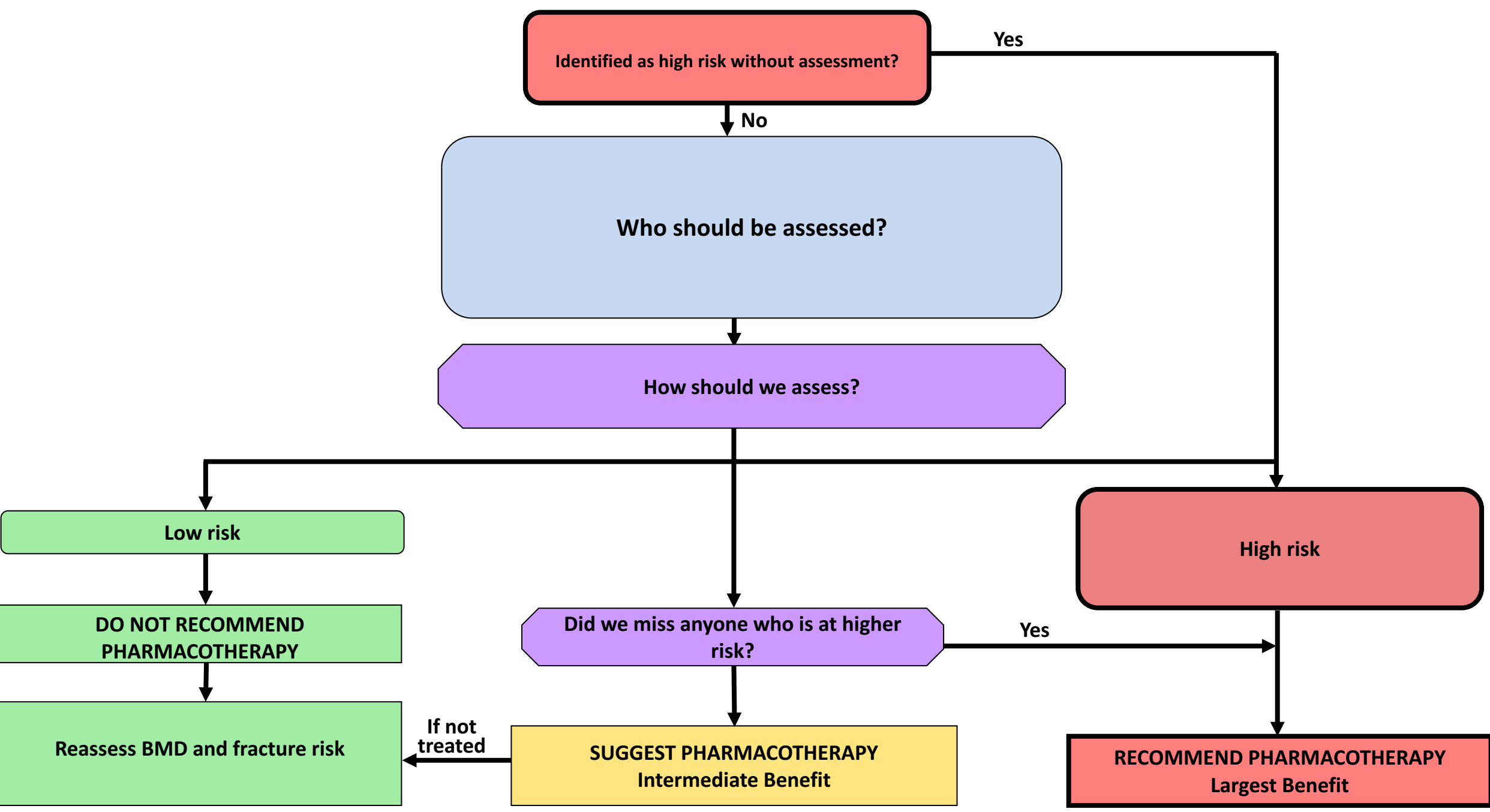- No Industry COI

Learning Objectives

- Identify individuals at high risk for fractures for whom pharmacotherapy is recommended

- Propose evidence-based treatment initiation, interruption and monitoring plans for fracture prevention

- Explore fracture risk assessment and fracture prevention in special populations

What is important to patients in Osteoporosis management?

b) Outcomes critical to consider in osteoporosis management guideline development

Morin SN, Djekic-Ivankovic M, Funnell L, et al. Patient engagement in clinical guidelines development: input from > 1000 members of the Canadian Osteoporosis Patient Network Osteo Int. 2019

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                    ┌─────────────────────────────────┐
                    │ Identified as high risk without  │──── Yes ────┐
                    │         assessment?              │             │
                    └─────────────────────────────────┘             │
                                   │ No                             │
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                    │                                 │             │
                    │    Who should be assessed?       │             │
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                    └─────────────────────────────────┘             │
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                    │     How should we assess?        │             │
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┌───────────────┐                  │                  └────│    High risk      │
│   Low risk    │                  │                       └───────────────────┘
└───────────────┘                  │                               │
        │                          │                               │
┌───────────────┐      ┌─────────────────────────────┐  Yes        │
│ DO NOT RECOMMEND│     │ Did we miss anyone who is at │────────────┤
│ PHARMACOTHERAPY │     │        higher risk?          │            │
└───────────────┘      └─────────────────────────────┘            │
        │                          │                               │
┌───────────────┐  If not  ┌──────────────────────┐   ┌───────────────────────┐
│ Reassess BMD  │◄─treated─│ SUGGEST PHARMACOTHERAPY│   │ RECOMMEND PHARMACOTHERAPY│
│ and fracture  │          │  Intermediate Benefit │   │     Largest Benefit   │
│     risk      │          └──────────────────────┘   └───────────────────────┘
└───────────────┘
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Lowest risk ────────────────────────────────► Highest risk

Who should we assess for skeletal fragility?

- 57 y old man, Nurse
- HBP, Left hip OA with recent THR, Degenerative changes lumbar spine with chronic pain, overweight (BMI 28.5)
- Severe back pain while pushing a heavy object last month
- Rx: irbersartan, ibuprofen
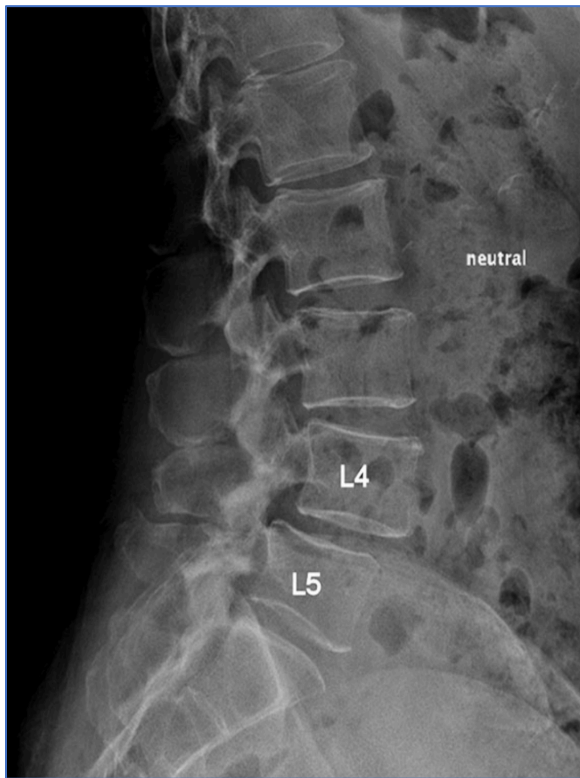- No previous fractures
- No ETOH; smoker 1 ppd

- 68 y old woman, High school Math teacher
- Chronic lumbar pain, overweight (BMI 28)
- Rx: Vitamin D, calcium, acetaminophen prn
- No previous fractures
- Family history Hip Fx
- No ETOH, non smoker

How do we assess ?

58 y old man

68 y old woman

WORK UP (Osteoporosis Canada Guidelines-2010)

❖ CBC, TSH, renal function, serum calcium and phosphorus, alkaline phosphatase

❖ Serum protein electrophoresis in those with vertebral fractures

❖ 25 (OH) vitamin D in selected cases
  o Malabsorption
  o Obesity
  o Chronic kidney disease
  o Chronic liver disease

❖ Bone mineral density
  o In everyone >65 years
  o In people >50 with risk factors

❖ Lateral X-ray thoracolumbar spine

Osteoporosis Canada Guidelines 2010, CMAJ

Who do we assess skeletal fragility?

2010 OC Guidelines

Clinical risk factors:
• Previous fracture
• Parental hip fracture
• Current smoking
• Prolonged use of glucocorticoids or other high risk medications
• Rheumatoid arthritis
• Spine fracture or osteopenia on x-ray
• High alcohol intake
• Low body weight, major weight loss
• Other disorders strongly associated with Osteoporosis (secondary osteoporosis)

Falls
Diabetes

High Risk Fracture:
• Prior hip or spine fracture
• More than one fracture event

Yes

No

All men and women age ≥ 65
Additional clinical risk factors 50-64
Medical conditions < 50

Obtain BMD and
Calculate 10-year fracture risk with BMD

- **Evidence for population-based screening strategy** (with goal to prevent fractures)

- Systematic review & Meta-analysis (Merlijn T et al 2020)

- 42,000 women, 3 RCTs

- Major osteoporotic Fractures:
  - HR 0.91; 95% CI 0.84-0.98
  - 7 fewer fractures over 4.6 years per 1000 women 65 y and older

- Hip Fractures:
  - HR 0.80; 95% CI 0.71- 0.91
  - 5 few hip fractures over 4.6 years per 1000 women 65 y and older

1. Merlijn, T., Swart, K. M. A., van der Horst, H. E., Netelenbos, J. C., Elders, P. J. M.. Fracture prevention by screening for high fracture risk: a systematic review and meta-analysis. Osteoporosis Int; 2020.

How do we assess fracture risk?

Who do we treat?

High Risk Fracture:
- **Prior hip or spine fracture**
- **More than one fracture event**

Yes →

No ↓

Clinical risk factors:
- Previous fracture
- Parental hip fracture
- Current smoking
- Prolonged use of glucocorticoids or other high risk medications
- Rheumatoid arthritis
- Spine fracture or osteopenia on x-ray
- High alcohol intake
- Low body weight, major weight loss
- Other disorders strongly associated with Osteoporosis (secondary osteoporosis)

+ Falls and Diabetes

All men and women age ≥ 65
Additional clinical risk factors 50-64
Medical conditions < 50

Obtain BMD and Calculate 10-year fracture risk with BMD

All others

10-year fracture risk 10-19% OR T-score ≤-2.5

- **10-year fracture risk ≥ 20%**
- **Prior hip or spine fracture**
- **More than one fracture event**

DO NOT RECOMMEND PHARMACOTHERAPY Low Risk

Lateral spine imaging — **Vertebral fracture** →

No vertebral fracture ↓

If not treated ←

Factors warranting consideration... Moderate Risk

Repeat BMD in 1–3 yr and reassess risk

RECOMMEND PHARMACOTHERAPY High Risk
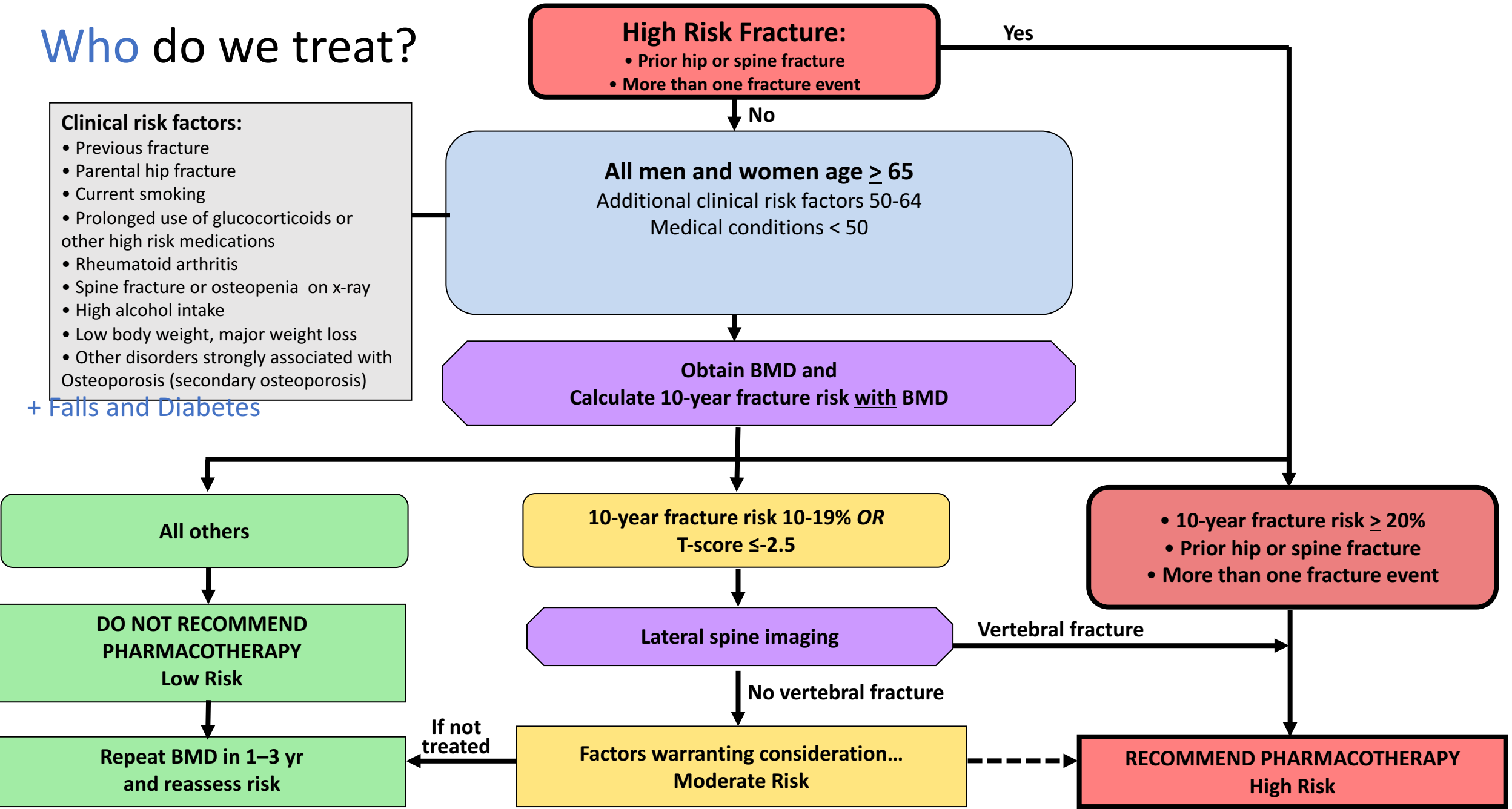
Bone remodeling, bone loss and therapeutic approaches

Compston J, McCLung and Leslie *Lancet* 2019
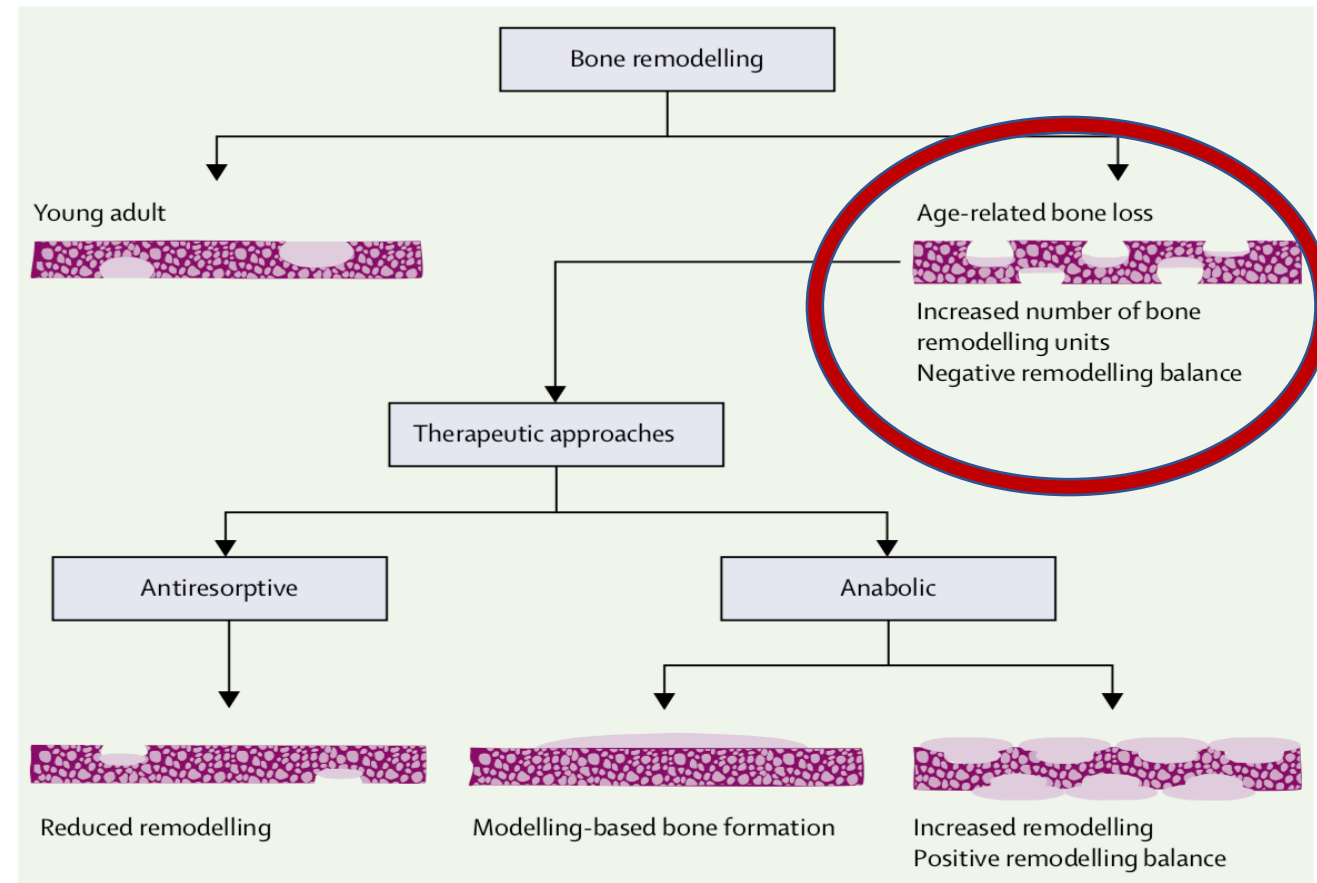
How do we treat those at risk of fractures:
Antiresorptive Agents

Drug	Effect of remodeling	Effect on Fracture	Offset	Adverse events
Bisphosphonate ALN, RIS, ZOL	↓ to ↓↓	↓↓ to ↓↓↓	slow	GI, acute phase reaction, AFF, ONJ
RANKL inhibitor DMAB	↓↓↓	↓↓↓	rapid	Hypocalcemia, AFF, ONJ
SERMs Raloxifene	↓	↓	rapid	Thromboembolic ds

	Contraindications
Bisphosphonates Denosumab (MS 153) Raloxifene	Upper GI, eGFR < 35 ml/min Hypocalcemia, eGFR <15 ml/min Thromboembolic disease

Compston J, McCLung and Leslie *Lancet* 2019

How do we treat those at risk of fractures: Anabolic Agents

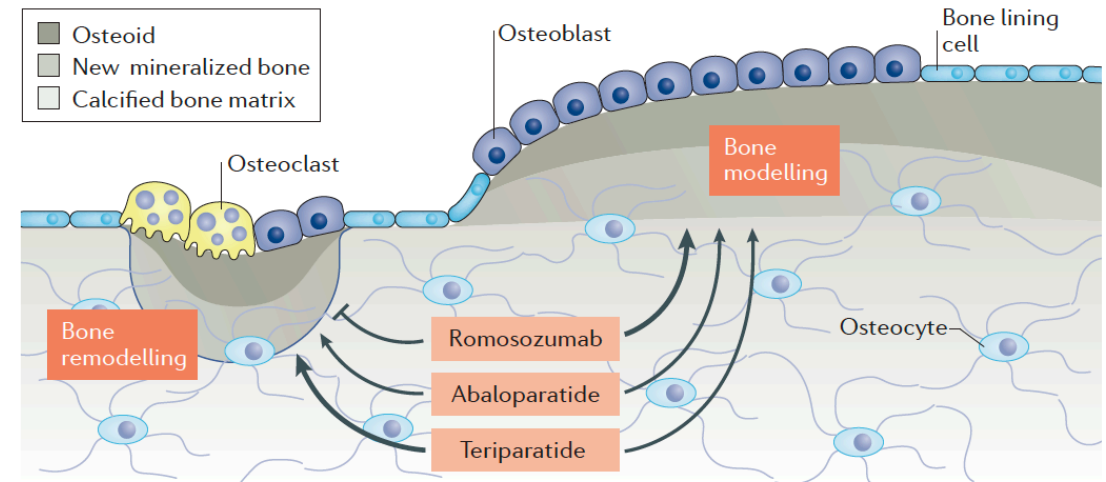| Drug	Effect on bone formation	Effect on fractures	offset	Adverse events
PTH receptor agonist Teriparatide	Increased -remodeling-	↓↓ to ↓↓↓	Rapid	*osteosarcoma
Anti Sclerostin antibody Romozumab	Increased transiently -Modeling-	↓↓ to ↓↓↓	Rapid	*cardiovascular

Fig. 1 | **Differential effects of bone-forming agents on bone surfaces.** Teriparatide and abalopa-ratide act primarily by activating bone formation coupled to bone resorption at remodelling surfaces, and to a lesser extent by activating quiescent bone-forming cells at modelling surfaces. Romosozumab acts primarily by activating modelling-based bone formation while inhibiting bone resorption at remodelling surfaces.

Compston J, McCLung and Leslie *Lancet* 2019

Monitoring: BMD

- **BMD**: It is suggested to monitor BMD 2- 3 years after starting or changing antiresorptive pharmacotherapy to prevent fractures

Table 5. Estimated Fracture Risk Reduction Associated With BMD Improvement

	Vertebral fracture	Hip fracture	Nonvertebral fracture
Δ Total hip BMD			
2%	28%	16%	10%
4%	51%	29%	16%
6%	66%	40%	21%
Δ Femoral neck BMD			
2%	28%	15%	11%
4%	55%	32%	19%
6%	72%	46%	27%
Δ Lumbar spine BMD			
2%	28%	22%	11%
8%	62%	38%	21%
14%	79%	51%	30%

BMD = bone mineral density.

Figure 1. Cumulative fracture risk, by change in total hip BMD.
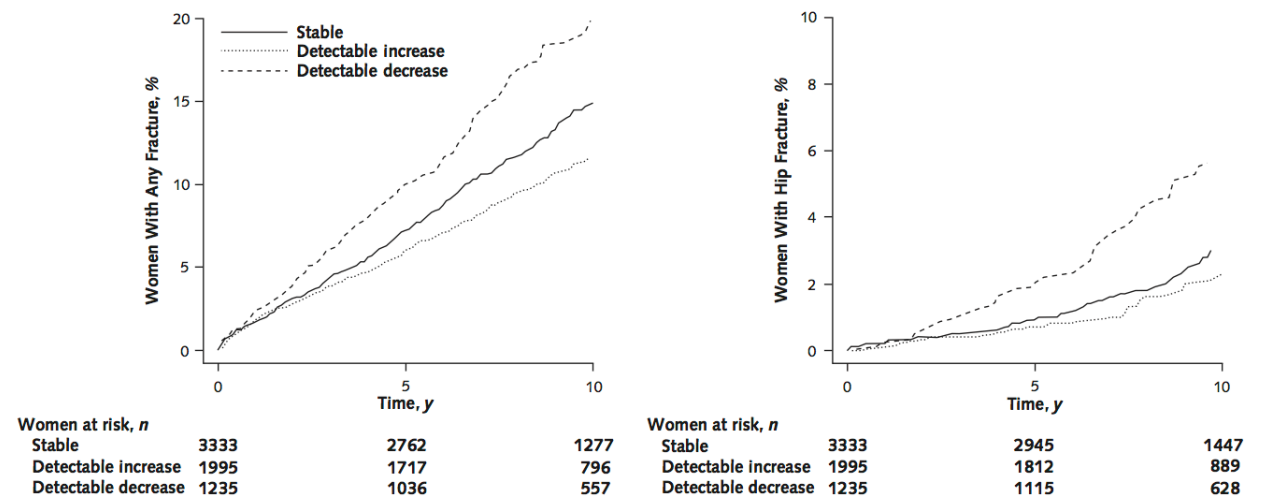
Cumulative incidence functions are directly adjusted for baseline fracture probability. BMD = bone mineral density. **Left.** For any fractures, the detectable decrease vs. stable BMD (*P* < 0.001) and detectable increase vs. stable BMD (*P* = 0.004) are depicted. **Right.** For hip fractures only, the detectable decrease vs. stable BMD (*P* < 0.001) and detectable increase vs. stable BMD (*P* = 0.167) are depicted.

Monitoring: Fractures
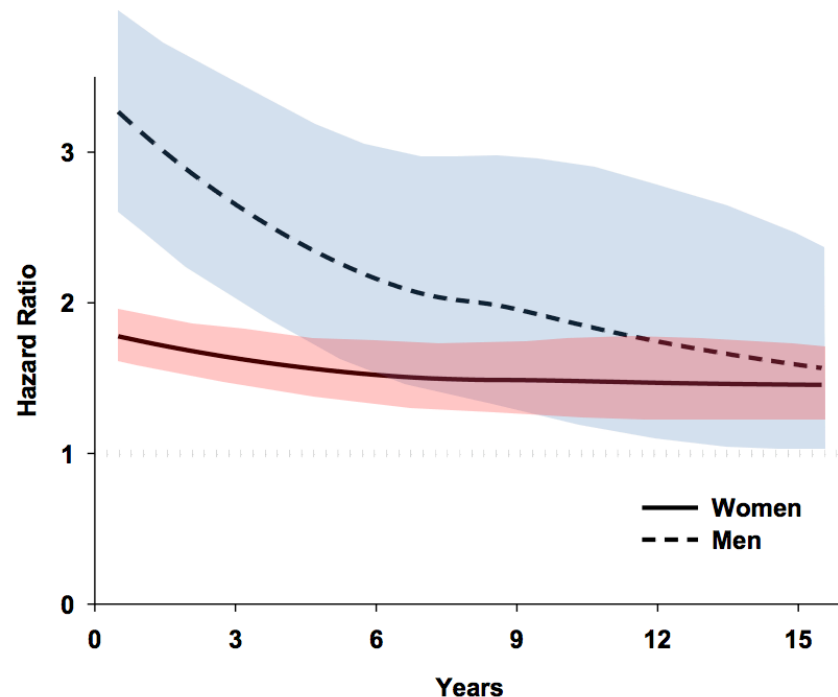
Long term risk of Subsequent fractures in men and women following a first fracture

- Time interval since the initial fracture has been documented to impact the risk of subsequent fracture conveying a higher immediate risk in those who have sustained a more recent fracture
- Recently published guidelines recommend use of anabolic therapy as first line in those with a recent severe vertebral fracture or hip fracture

Morin SNM et al; Osteoporosis int 2021

How long do we treat for?

- OP is a chronic disease

- Management should be long-term: fall prevention, exercise, nutrition

- We use pharmacotherapy sequentially more frequently

- Concept of Drug Holiday applies to Bisphosphonates
  - Mechanism of action- skeletal retention- slow offset
  - Evidence: 3 to 6 years of therapy in patients not at very high risk for fracture
  - Drug holiday 2 to 3 years and then resume (sequential) treatment if required

Harms	RCTs	Cohort studies
Osteonecrosis Jaw	rare	1 per 100,000 p-years of Tx
Atypical Femur Fx	rare	110 per 100,000 p- years of Tx

- Teriparatide and Romozosumab can only be used for short term and should be followed by antiresorptive therapy

- Denosumab should not be stopped, as increased risk for rapid bone loss and fractures ensues

Denosumab: Increased Risk of Vertebral Fractures after Stopping Therapy

Lumbar Spine BMD
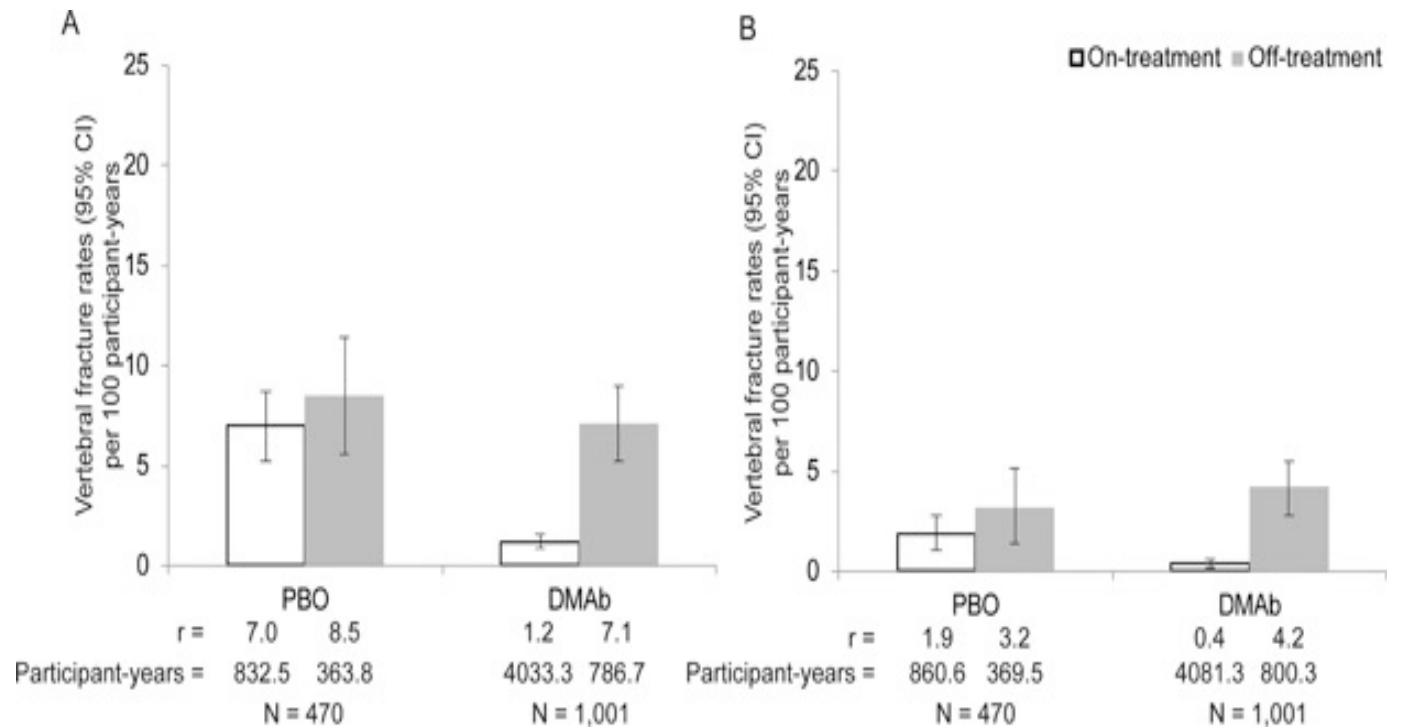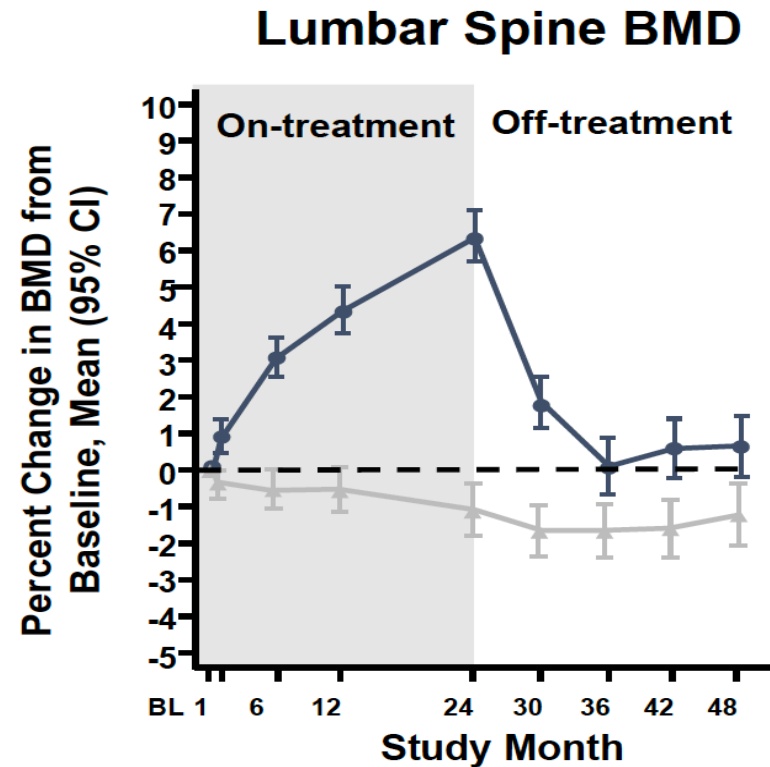
When prescribing denosumab, clinicians should counsel patients against discontinuation without medical consultation.
Patient should be transitioned on a bisphosphonate (iv) if treatment is to be interrupted

In Whom should we <u>not</u> consider a drug holiday ?

- Very low Femoral Neck BMD

- Recent fracture < 2 years (hip, spine, humerus and wrist)

- FRAX probability for MOF of >25%

- High frailty score, falls++

- Consider continuing bisphosphonate for longer (up to 7 years) or switching to another molecule (denosumab, teriparatide or romozosumab)

What to monitor when patient is on a drug holiday?

- Fractures

- New or worsening risk factors (weight loss, medical conditions, medications- PPI, AI, glucocorticoids)

- BMD within 2- 3 years

- Bone Turnover Markers not recommended

- If there is worsening in parameters, treatment can be resumed (same or different, depending on the situation)

What to do if inadequate response to therapy?

- Fracture while on therapy (x 12 months)

- BMD loss:
  - T- Score lower that the initial T-score at the time of treatment initiation
  - Significant BMD decrease (>5%) while on therapy

- Ensure adherence

- Repeat biochemistry work up

- Consider treatment change
  - Parenteral agents
  - Anabolic agents

Special populations: Older patients with comorbidities

High risk conditions are common

Diagnosis	Number of patients in the US / yr.	Increased risk (RR) hip fracture
Dementia	5,400,000	2.6
Heart Failure	5,100,000	3.5
Parkinson's	1,000,000	2.4
Stroke (recent)	800,000	2.4
ESRD (≥ stage 3)	600,000	4.8
Type 1 diabetes (>age 50)	~100,000	4.9
Total with a high risk diagnosis	~13,000,000	>= 2-fold

- High hip fracture risk despite accounting for competing mortality risk
- Absolute benefit of treatment is probably greatest among those with more comorbidities
- Treatment is effective in those with BMD T-score below or above -2.5; but more effective in those with osteoporosis
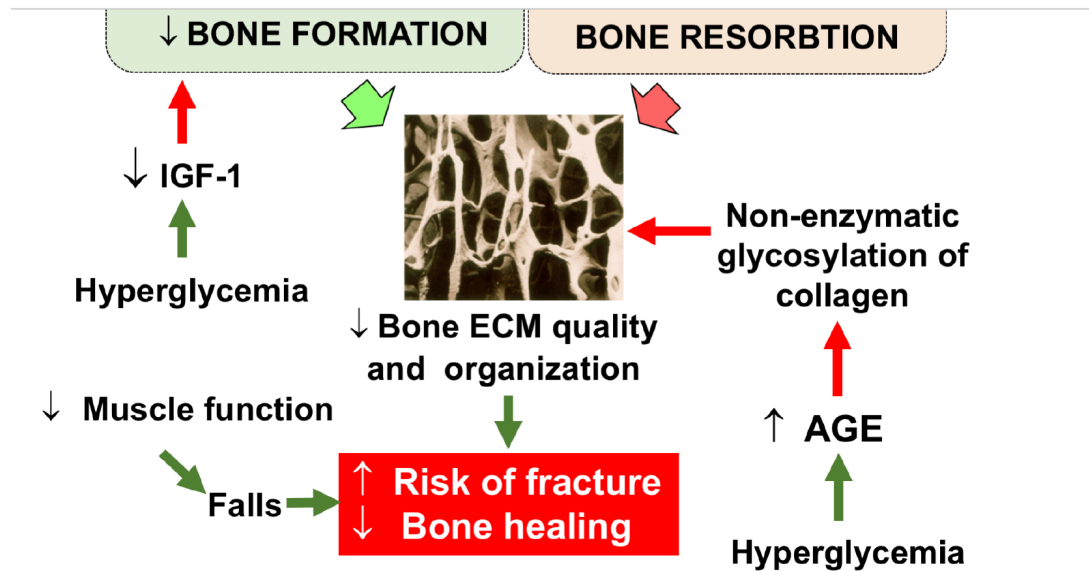
Special Population: Diabetes

TABLE 1: Bone health in adults with Type 1 and Type 2 diabetes - a survey

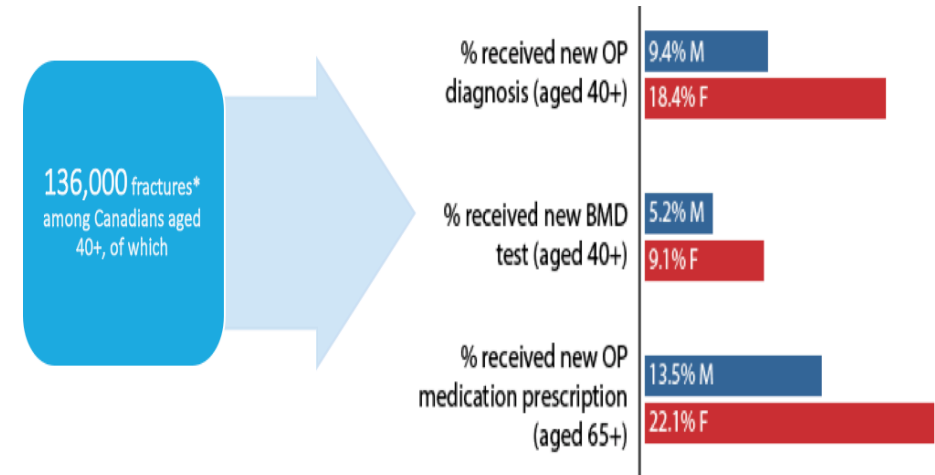| Participants	T1D N=171	T2D N=261
Age, years, mean (SD)	61 (8)	67 (9)
Women, N, %	100 (58)	183 (70)
Duration of diabetes, years, mean (SD)	33 (17)	14 (11)
Fragility fracture after the age of 40, N (%)	31 (18)	33 (13)
Fall in the past 6 months, N (%)	36 (21)	80 (31)
Believe that diabetes increases one's fracture risk, N (%)	25 (15)	58 (22)
Believe that diabetes increases one's fall risk, N (%)	48 (28)	86 (33)
Informed by physician of diabetes-related fracture risk, N (%)	17 (10)	21 (8)

Unpublish data (S. Morin)

In the computation of fracture risk assessment diabetes can be entered in the FRAX tool as "rheumatoid arthritis"
To provide a better estimate of the fracture risk.

Objective 1 Identify individuals at high risk for fractures for whom pharmacotherapy is recommended
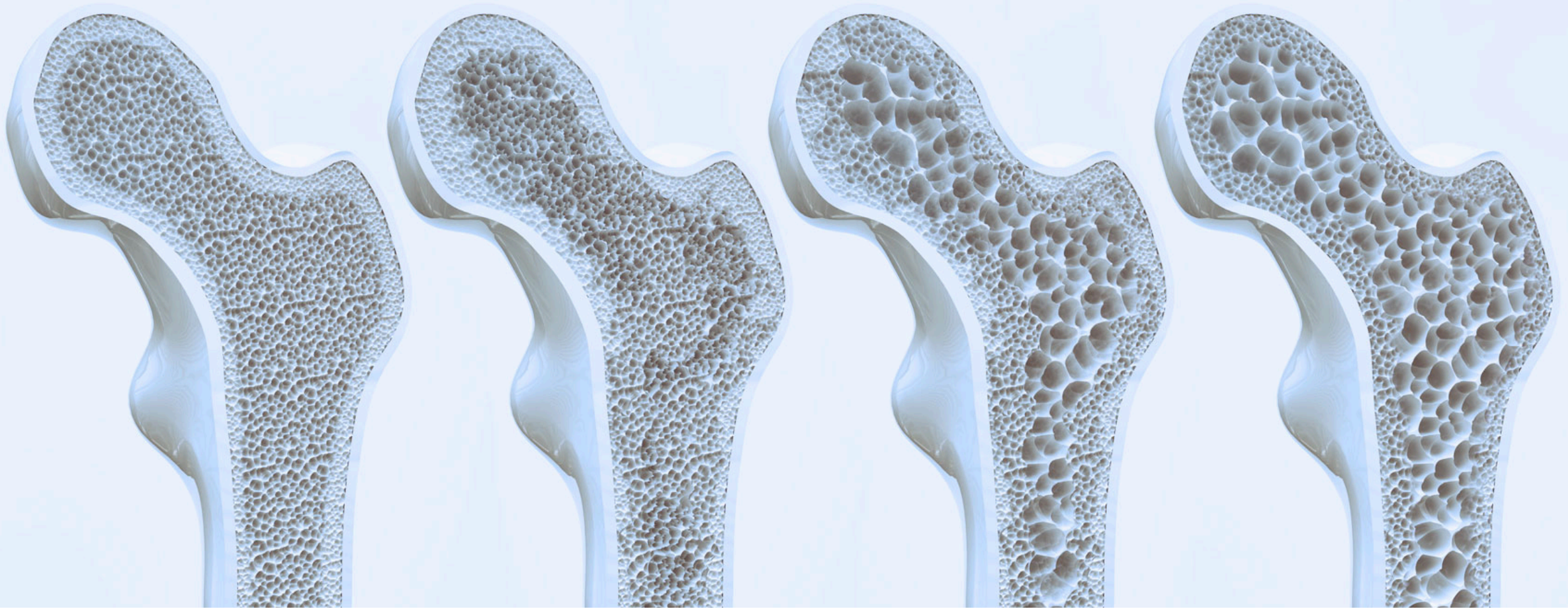
- ## Assessment:
  - The assessment of osteoporosis should be guided by a targeted approach
  - The work up should include basic biochemistry, BMD and spine X-Rays
  - Decision to treat should be guided by the patient's 10-year absolute fracture risk using a validated fracture risk assessment tool

136,000 fractures* among Canadians aged 40+, of which

% received new OP diagnosis (aged 40+)
9.4% M
18.4% F

% received new BMD test (aged 40+)
5.2% M
9.1% F

% received new OP medication prescription (aged 65+)
13.5% M
22.1% F

Objective 2 Propose evidence-based treatment initiation, interruption and monitoring plans for fracture prevention

Agent	Time to change in bone remodelling (Bone turn over markers)	BMD improvement at the lumbar spine (12 months)	Other Comments
Alendronate	3-6 months	4.5%	Weekly; do not use if UGI disease Drug holiday after 3-6 years
Risedronate	3-6 months	4%	Weekly; do not use if UGI disease Drug holiday after 3-6 years
Zoledronate MS153- women Patient d'exception -men	< 1 month	3.9%	Yearly; monitor renal function Ensure vitamin D status OK Drug holiday after 3 infusions
Denosumab MS153-women Patient d'exception -men	< 1 month	7.4%	Twice per year; monitor renal function Ensure vitamin D status OK No Drug holiday
Teriparatide Patient d'exception	< 1 month	6.5%	Daily, s.c injection 18 à 24 months- should be followed by antiresorptive
Romosozumab Patient d'exception	< 1 month	14%	Monthly, s.c. injection should be followed by antiresorptive

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