

Bisphosphonate Drug Holiday: Who, When and How Long?

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Disclosures

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Learning Objectives

- Discuss fracture risk assessment and treatment options for patients at high risk for fractures
- Describe adverse clinical events that have been associated with long term use of bisphosphonates
- Review the evidence to support a strategy towards optimal duration of therapy and drug holiday for patients on bisphosphonates

Bisphosphonates for treatment of osteoporosis

Expected benefits, potential harms, and drug holidays

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FP's role

- As Family Physician: important role to play for identification, investigation and treatment initiation in patients who would benefit from anti-osteoporosis treatment
- Ensure adherence and compliance in our patients
- Evaluate, monitor and stop treatment if indicated

FP's role

- Treatment indication changes: primary prevention in the 1990... guidelines of 2002 and 2010... fracture risk... drug holiday in 2014...
- Keep it simple!
- No absolute truth or recommendation about drug holiday but ...
- Prevent fracture but cause no harm

Mrs. Roy

- 66 y.o., has been on risedronate 35 mg once a week and vitamin D 1000 IU daily for the last **7 years** after **wrist fracture** at age 59
- Initial BMD
 - Lumbar spine T score -2.8
 - Femoral Neck T score -2.5
 - CAROC 10 year absolute risk at the time was high
- High BP for which she takes HCTZ, no smoking, no alcohol, no family history of fractures

Mrs. Roy

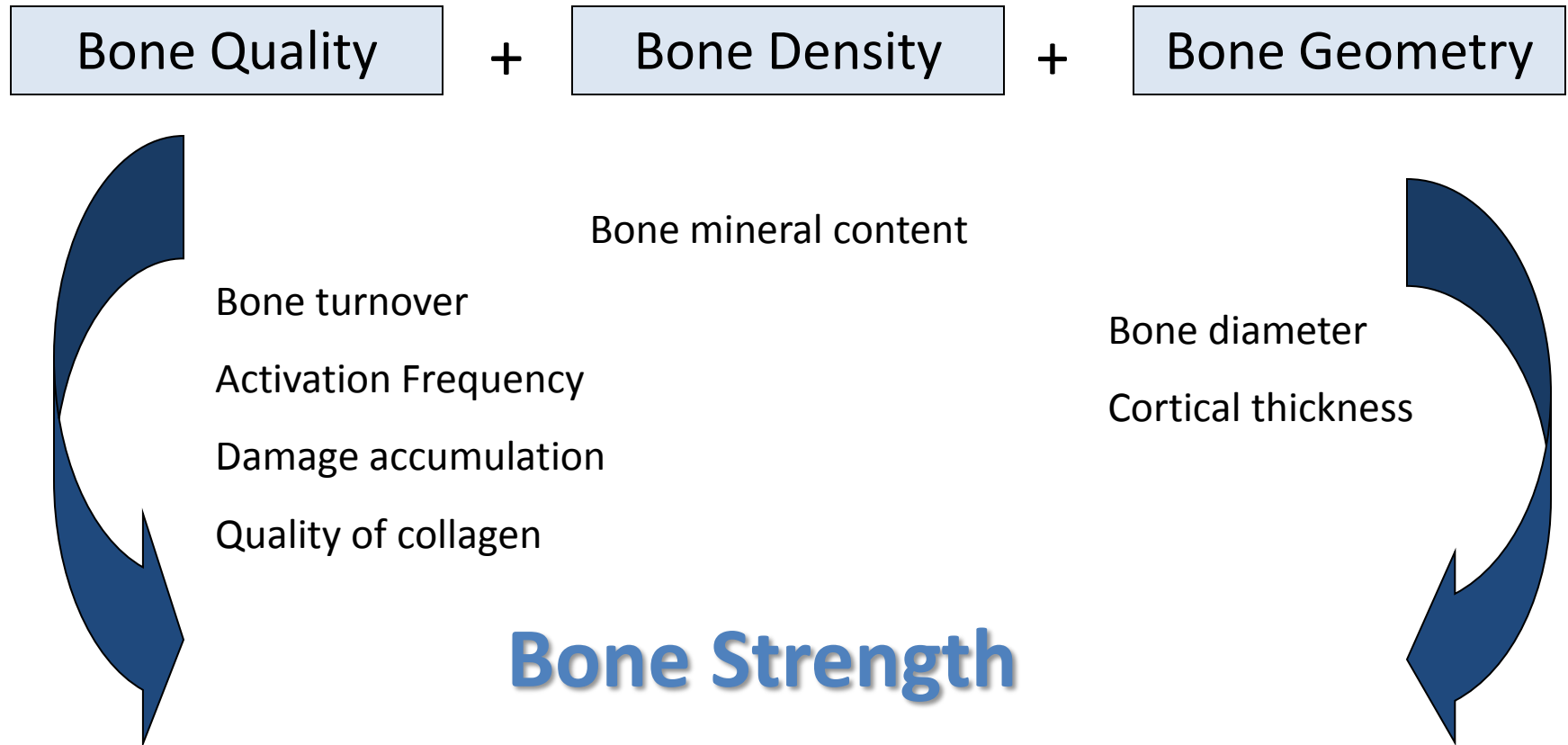
- Tolerates treatment well
- Has not sustained any new fracture
- Walks three times a week, good calcium intake with diet
- Repeat BMD is stable
- No glucocorticoids, no kidney disease
- However...

Concerns with long-term use of bisphosphonates

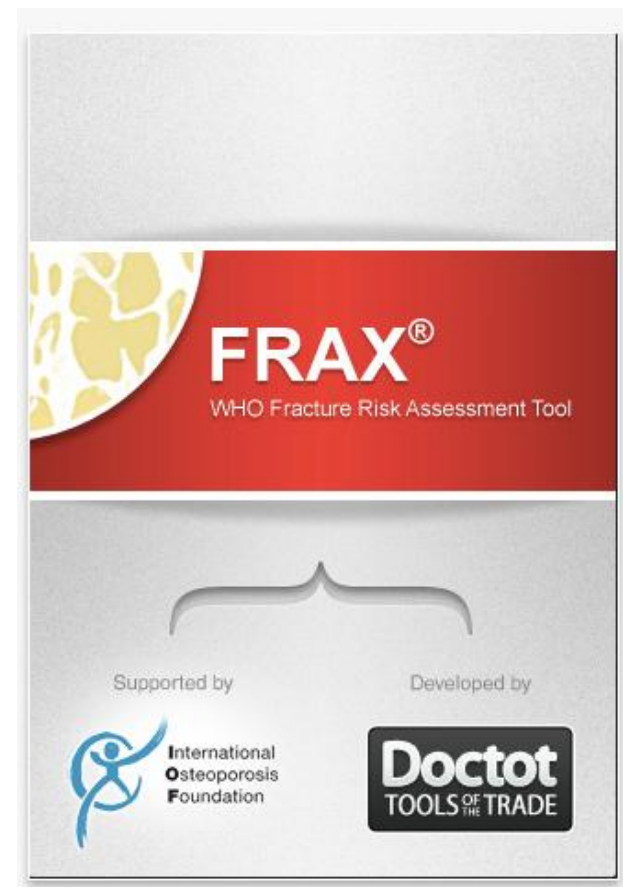
- Osteonecrosis of the Jaw
- Atypical femur fractures
- Acute kidney injury
- Atrial fibrillation
- Esophageal cancer

Bone Strength

Biomechanical, biological and genetic factors



Fracture Risk Assessment: Importance of Using Tools



Fracture Risk Assessment tools

CAROC*

Risk Factors:

- Sex
- Age
- BMD
- Fragility fracture after 40
- Systemic glucocorticoid use (≥ 3 months)[†]

FRAX^{®‡}

Additional Risk Factors:

- Low BMI
- Parental history of fracture (especially hip)
- Current smoking
- Alcohol intake ≥ 3 units/day
- Rheumatoid arthritis, or other secondary causes of osteoporosis

Calibrated with Canadian data and validated in Canadians

*Canadian Association of Radiologists and Osteoporosis Canada, 2010

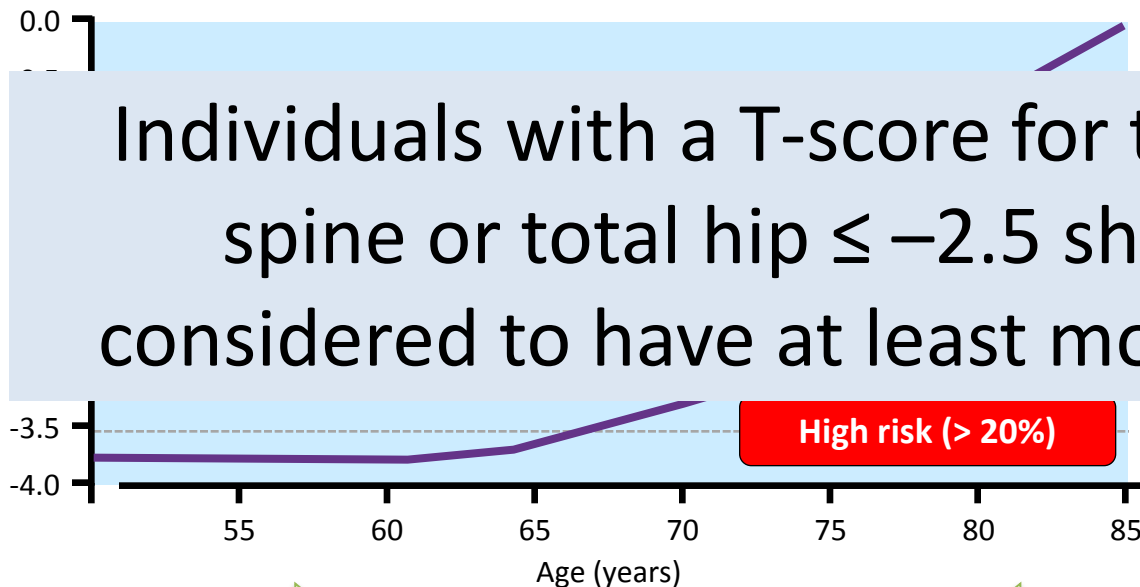
[†] ≥ 3 months in the prior year of a prednisone equivalent dose ≥ 7.5 mg daily

[‡] Fracture Risk Assessment Tool of the World Health Organization

Fracture Risk Assessment

CAROC Assessment Tool Stratification

Women (treatment naive)



Increases to the next
risk category

Fragility
fracture

Individuals with a T-score for the lumbar spine or total hip ≤ -2.5 should be considered to have at least moderate risk

Hip / vertebral fracture

High risk
(> 20%)

> 1 non-vertebral
fragility fracture

* At least three months cumulative use during the preceding year at a prednisone-equivalent dose ≥ 7.5 mg daily

How do we Choose

- Patient Preference
- Safety Profile
- Compliance- Adherence to therapy
- Provincial Reimbursement Plan

First Line Therapy		Grade*					
Type of Fracture							Prevention of Fracture
							Therapy
							Therapy
	Alendronate	Risedronate	Zoledronic acid	Teriparatide	Teriparatide	Teriparatide	Teriparatide
Vertebral	✓	✓	✓	✓	✓	✓	✓
Hip	✓	✓	✓	✓	----	✓	---
Non-Vertebral ⁺	✓	✓	✓	✓	----	✓	✓

+ In clinical trials, non-vertebral fractures are a composite endpoint including hip, femur, pelvis, tibia, humerus, radius, and clavicle.

* For postmenopausal women, ✓ indicates first line therapies and **Grade A** recommendation. For men requiring treatment, alendronate, risedronate, and zoledronic acid can be used as first line therapies for prevention of fractures [Grade D].

** Estrogen or hormone therapy can be used as first line therapy in women with menopausal symptoms.

Bisphosphonates

- Anti-Fracture efficacy, effectiveness and cost-effectiveness documented¹⁻³
- 1st line agents for treatment of patients at high risk for fragility fracture
 - Generally well tolerated
 - Low cost (generic formulation)

¹ McClung M et al. *Am J Med* 2013 126: 13-20

² Whitaker M et al. *New Engl J Med* 2012; 366: 2048-51

³ Langsetmo LA et al. *Osteoporos Int* 2009; 283-290

Bisphosphonates

- Inhibit osteoclastic activity and reduce bone remodeling -> increase BMD, lower fracture risk
- Prolonged residence in the skeleton
- Concerns have been raised:
 - Over-suppression of bone turnover
 - Microdamage accumulation and microcrack progression
 - Over-mineralization and greater homogeneity of crystalline maturity
 - Advanced glycation end-products loaded collagen

Bisphosphonates: good and bad ?

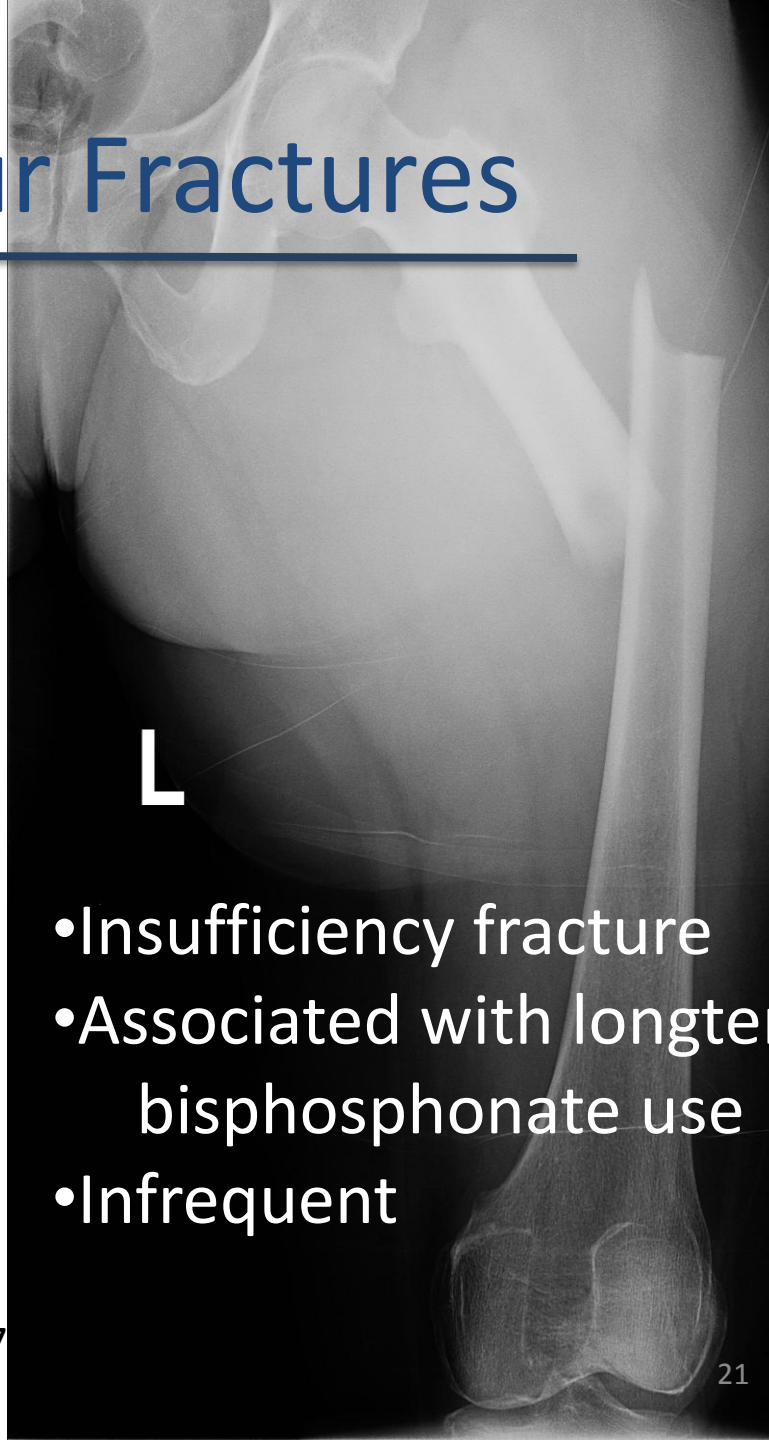
- Osteonecrosis of the jaw
- Atypical femur fractures
- Atrial fibrillation
- Acute kidney injury
- Oesophageal cancer

Osteonecrosis of the Jaw

- Presence of exposed bone in the maxillofacial region that does not heal within 8 weeks
- In the absence of radiation therapy
- Incidence between 1 in 10,000 to 1 in 100,000 patient-treatment-years.
- Higher in oncology population
- Recommendations for elective or urgent dental procedures:
 - Withhold bisphosphonates for up to 3 months prior and until complete healing
 - www.osteoporosis.ca (healthcare professionals)

Atypical Femur Fractures

- Case reports
- Case series
- RCT re-analyses
- Cohort studies
- Case-control studies
- Meta-Analysis

- 
- Insufficiency fracture
 - Associated with longterm bisphosphonate use
 - Infrequent

Feldstein A et al. *J Bone Miner Res.* 2012; 27: 977-86
Gedmintas L et al. *J Bone Miner Res.* 2013 28:1729-37
Shane E et al *J Bone Miner Res.* Epub 2013 May 28

Incidence of AFF

- Incidence estimated to be¹
 - 1.78/100,000 p-years with exposure of < 2 years
 - 113/ 100,000 p-years with exposure 8 to 10 years
- Meta-analysis shows increased risk of subtrochanteric, diaphyseal and atypical fractures with bisphosphonate use²

¹Dell RM et al. *J Bone Miner Res* 2012; 27: 2544-50

²Gedmintas L et al. *J Bone Miner Res.* 2013 28:1729-37

Atypical Femur Fractures

ASBMR Task Force 2013 Revised Case Definition of AFFs

- Associated with **minimal or no trauma**
- **Transverse** and originates at the **lateral cortex** (may become oblique as progresses across femur)
- **Complete fractures** extend through both cortices and may be associated with a **medial spike**; **Incomplete fractures** involve only the lateral cortex
- **Noncomminuted or minimally comminuted**
- Localized **periosteal reaction** of the lateral cortex present at fracture site ("beaking" or "flaring")

(Shane et al. J Bone Miner Res. 2014;29:1-24)

Additional features which may be present but are not required:
Generalized increase in cortical thickness • Unilateral or bilateral prodromal pain in the groin or thigh • Bilateral incomplete or complete femoral diaphysis fractures • Delayed healing

Specifically excluded are:
Fractures of the femoral neck • Intertrochanteric fractures with spiral subtrochanteric extension • Periprosthetic fractures • Pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (eg, Paget's disease, fibrous dysplasia).



Long-term Adverse Events associated with Bisphosphophate Use

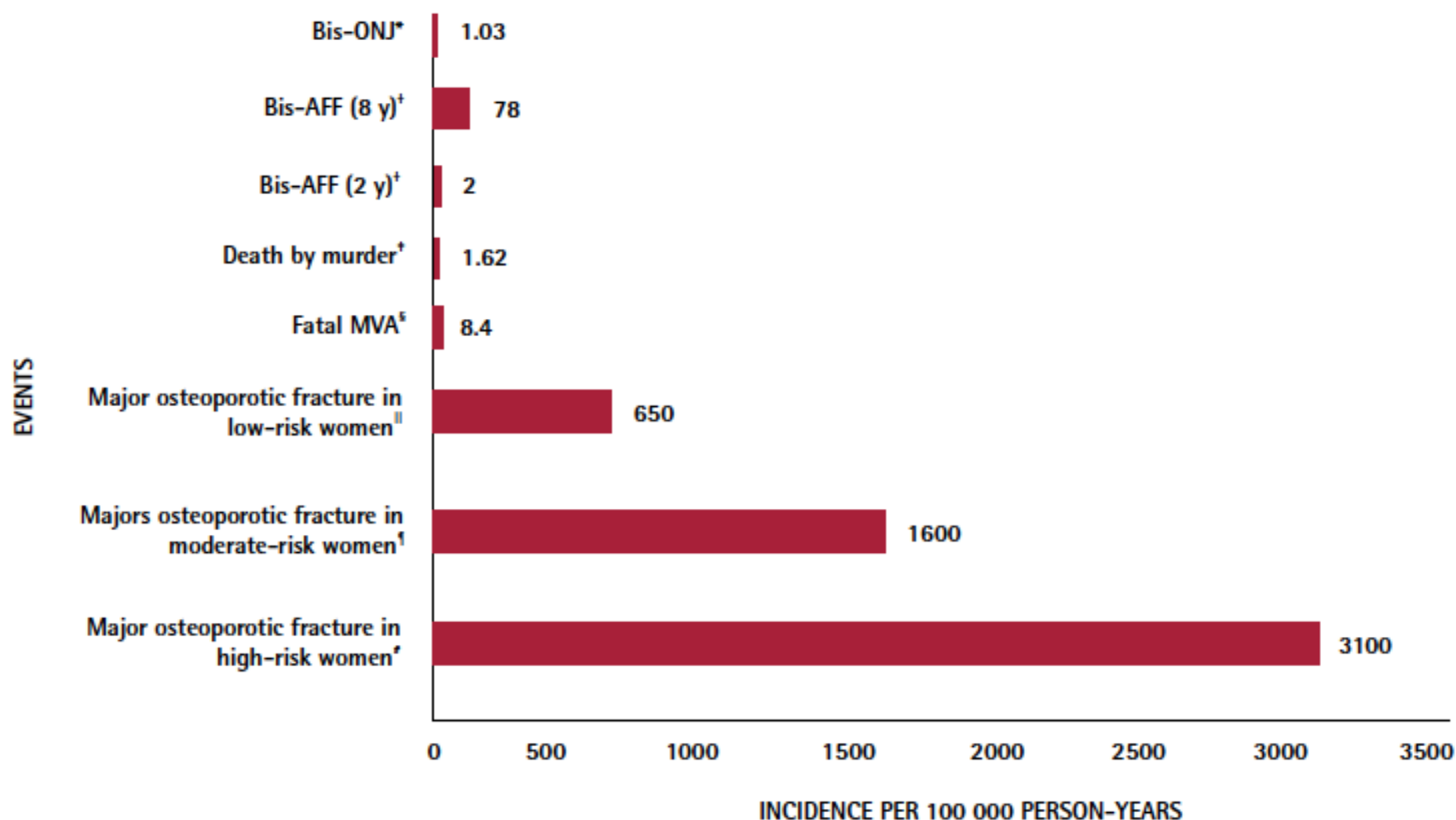
Adverse event	Incidence	Risk Factors	Recommendation
Osteonecrosis of the Jaw	<1/ 100,000 person-years	Poor oral hygiene, diabetes, glucocorticoid use and chemotherapy	Hold bisphosphonates 3 months prior to intervention and resume once healing is documented by dentist
Atypical Femur Fractures	2 à 110 / 100,000 person-years	Cumulative duration of bisphosphonates use (> 5years), use of glucocorticoids, proton pump inhibitors	Use bisphosphonates ONLY in patients at moderate or high risk of fractures Consider drug holiday Inquire about pain in groin or thigh
Esophageal cancer	Lack of data to establish link	Barrett' s esophagus, severe GERD	Avoid oral bisphosphonates in patients with risk factors
Atrial fibrillation	After revision from FDA, there is not enough evidence to support association	-	No need to consider this potential adverse event when prescribing anti-osteoporosis medication

Papaioannou A et al *Canadian Medical Association Journal* 2010;182(17):1864-1873.

Shane E et al *J Bone Miner Res.* May 28 2013.

Koshla S et al . *J.Bone Miner.Res.* 2007;22:1479-1491.

Figure 1. Risks of major osteoporotic fracture and other rare events



How long should we keep patients on therapy?

- Question applies to bisphosphonate therapy
 - Because:
 - Rising incidence of rare, but serious adverse events associated with prolonged use
 - NOT because the medications stop working
- Patient's risk for fracture
- Affinity of bisphosphonate for bone

Concept of Drug Holiday

- Alendronate data
- Risedronate data
- Zoledronic Acid data
- NO data on drug holiday with raloxifene or denosumab but, we know that if you stop these medications, there is no residual effect of therapy on bone remodeling and bone loss resumes rapidly

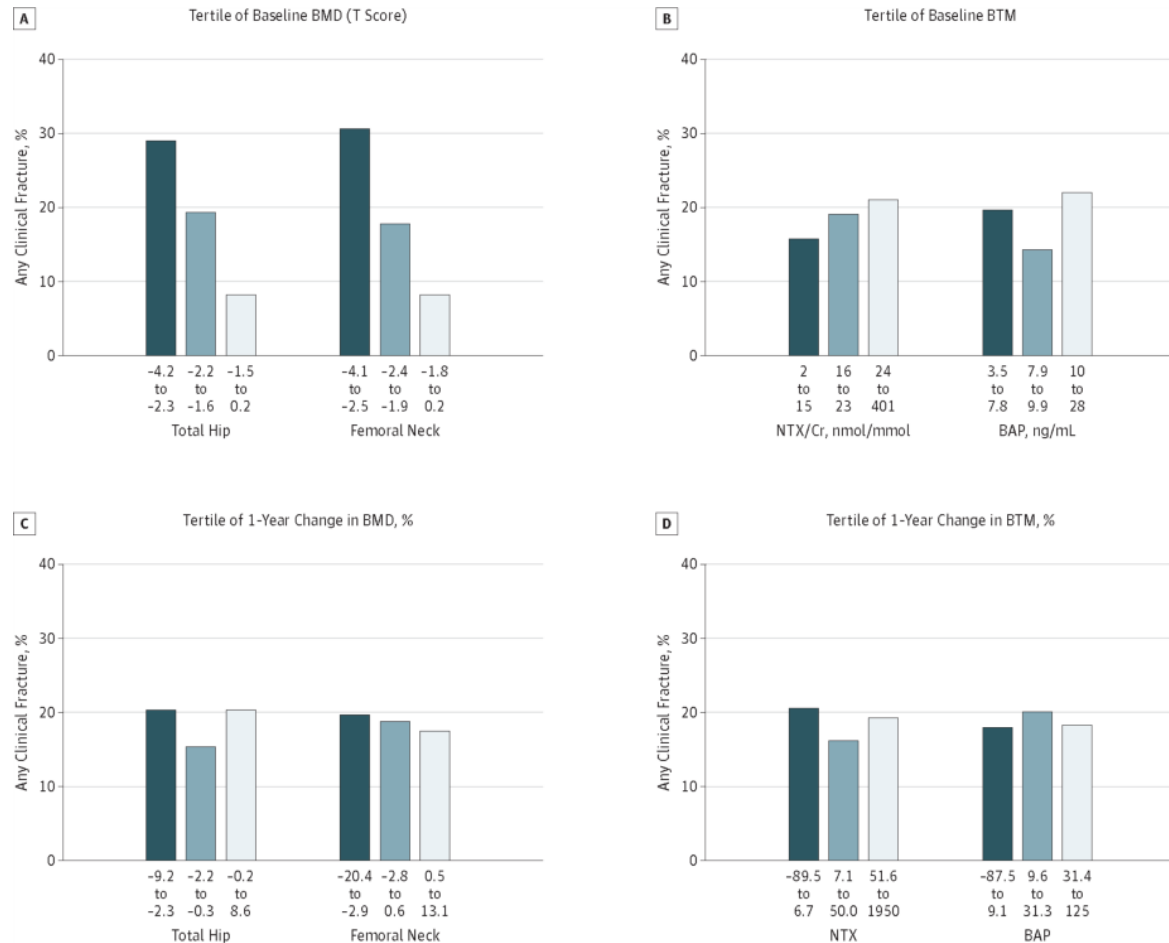
Duration of Bisphosphonate Therapy

Fracture Risk	Duration of Therapy	Duration of Drug Holiday
Low (<10%)	NO indication for bisphosphonates	-
Moderate (10 to 20%) Without recent Fxs	Between 5 and 7 years	1 to 3 years depending on bisphosphonate used Risedronate< Alendronate< Zoledronic Acid
High (>20%) Recent Fxs, Hip or Vertebral Fxs	Do not stop therapy or switch to another class of agents	Monitor for adverse events

What should we Monitor during a Drug Holiday?

- Fractures and Falls
- Bone Turnover Markers
- BMD
- 10 year Fracture Risk (FRAX)

Should we monitor BMD or BTMs?



¹McNabb et al. *J Clin Endocrinol Metab* 2014 Epub Aug 15

²Bauer DC et al *JAMA Intern Med* 2014; 174: 1126-34

What are the Therapeutic Options After a Drug Holiday

Remember to assess the risk for fractures
with CAROC or FRAX

Always consider patient's preference

- Resume bisphosphonate
- Change class: Denosumab
- Consider to change over to anabolic agent (teriparatide) but, restriction of reimbursement by Provincial Drug Plan

Mrs. Roy

- Could consider stopping bisphosphonate for 2-3 years, but should re-evaluate and perform fracture risk assessment every year
- If new fracture: resume treatment
- If no fracture: observation or change treatment, mode of administration ?

Mrs. Roy. What if...

- Vertebral or hip fracture?
- 2 Fragility fractures at other sites?
- Positive family history of hip fracture ?
- Breast cancer at 52 yo and early menopause ?
- Asthmatic with regular use of inhaled steroids and intermittent use of oral glucocorticoids ?
- History of malabsorption ?

Key Messages

- Use fracture assessment tools
- Avoid basing treatment decisions on BMD alone
- Use anti-osteoporosis medications only in patients at moderate and high risk for fractures
- Monitor adherence, tolerability, falls and fractures, BMD and ?bone turnover markers
- Consider a drug holiday in patients at low and moderate risk after 5 to 7 years of treatment with bisphosphonates

Questions ?



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