Oral Anti-osteoporotic Drugs

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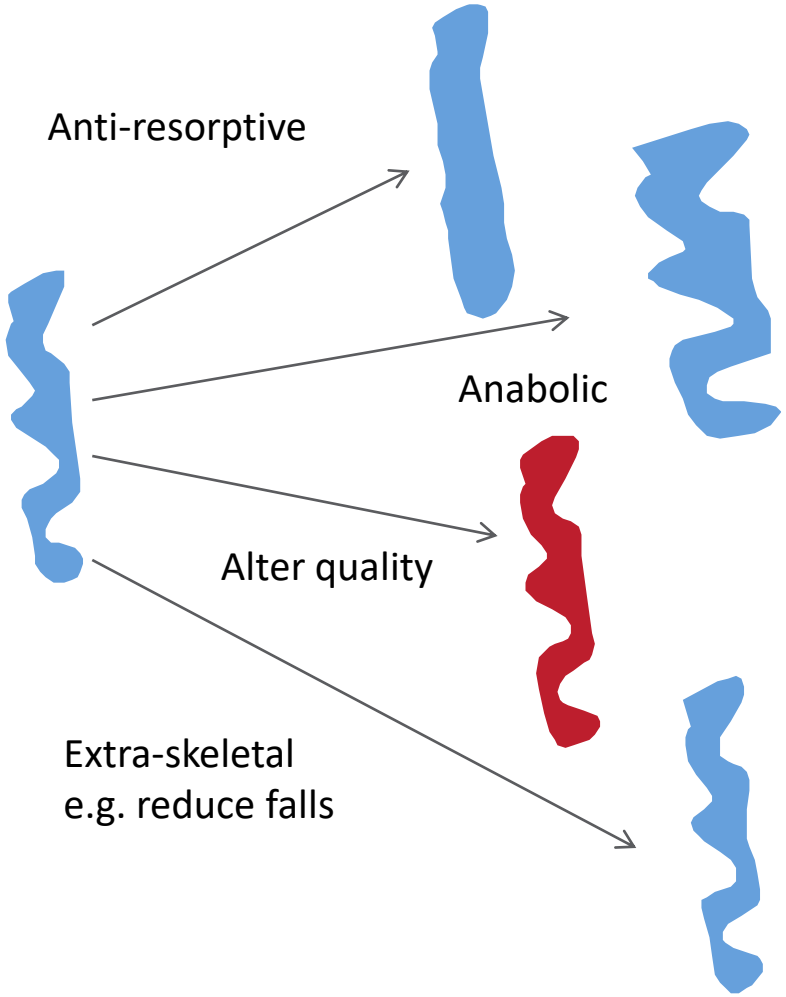
Osteoporosis - Treatment

- Ideal treatment:
  - Increase bone mass
  - Improve bone architecture and strength
  - Reduce the risk of fracture

How Do Osteoporosis Medications Work?



The Result of These Changes is That Fracture Risk is Reduced

Bisphosphonates: Alendronate, Risedronate, Ibandronate, Zoledronic Acid

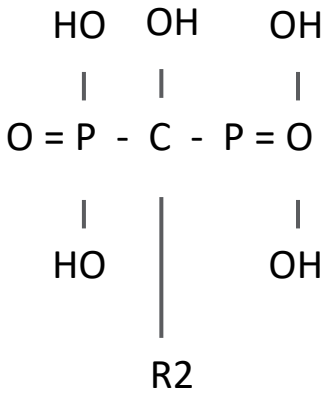
- Class: antiresorptive
- BMD: increases BMD at various skeletal sites
- Bone turnover markers: decreased
- Fractures: reduces risk of fractures

Russell RG. Bone 2011; 49, 2-19

Bisphosphonates Structure and Function

OH enhances binding to OH-Apatite

P-C-P = bone hook



P-C-P essential for action

R2 side chain determines potency

R2 = $-CH_3$: Etidronate
R2 = $-CH_2CH_2CH_2NH_2$: Alendronate
R2 = $-CH_2CH_2NH_2$: Pamidronate
……
……

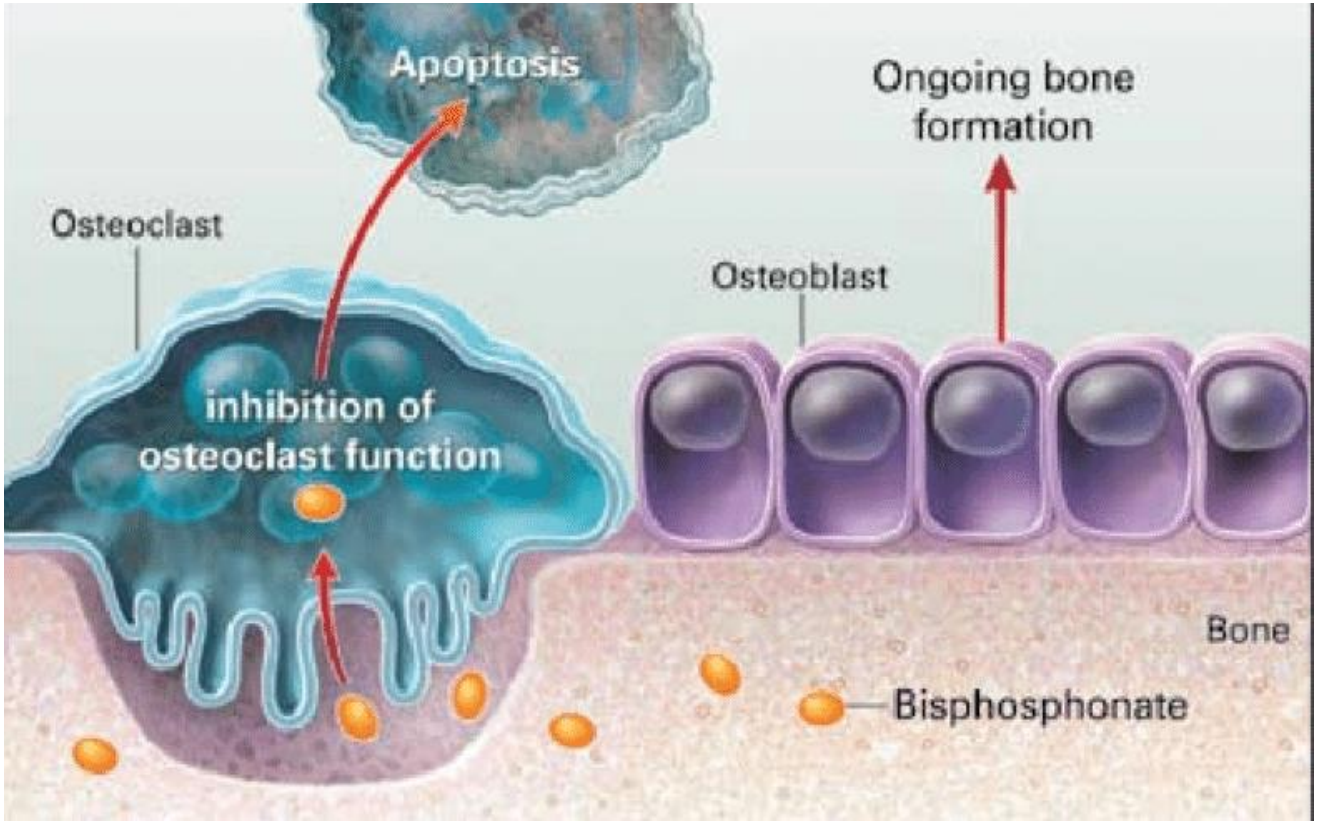
Bisphosphonates

- Pharmacological properties
  - Intestinal absorption = poor (~1%)
  - Plasma half-life = short
  - Administered dose
    - ~ 50% in bone
    - ~ 50% excreted unaltered in urine
- Stored in bone
  - Duration of retention uncertain

➔ Bisphosphonate effect can be long lasting after discontinuation: Unique to bisphosphonates

Russell RG. Bone 2011; 49, 2-19

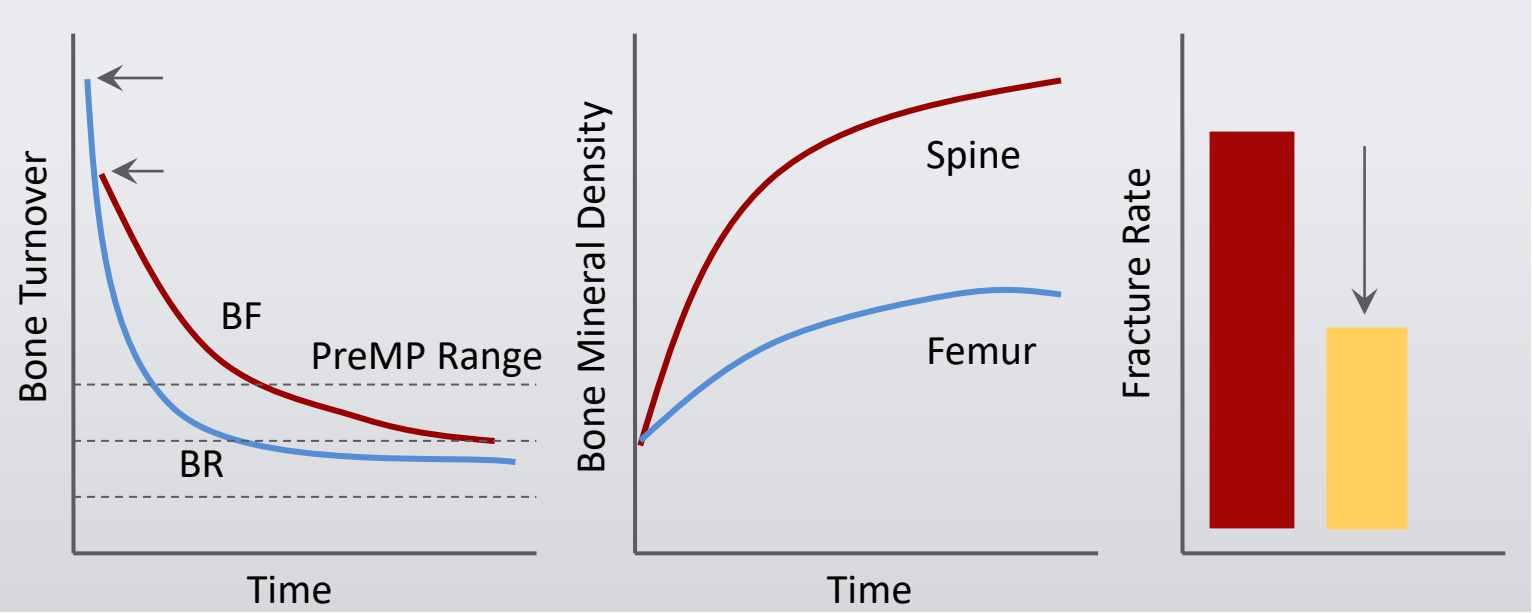
Bisphosphonates: Mechanism of Antifracture Efficacy



During bone resorption the bisphosphonate is ingested by osteoclasts. Once inside the cell, most bisphosphonates inhibit the enzyme, farnesyl pyrophosphate synthase, a critical step in the mevalonate pathway which leads to the synthesis of cholesterol. Disruption of this pathway adversely affects the osteoclast cytoskeleton, thus inhibiting bone resorption and, when present in high concentrations, resulting in osteoclast apoptosis.

B.L.Riggs and M.Parfitt J Bone Miner Res. 2005;20:177

Bisphosphonate are Antiresorbers, Increase BMD and Reduce Fracture Risk

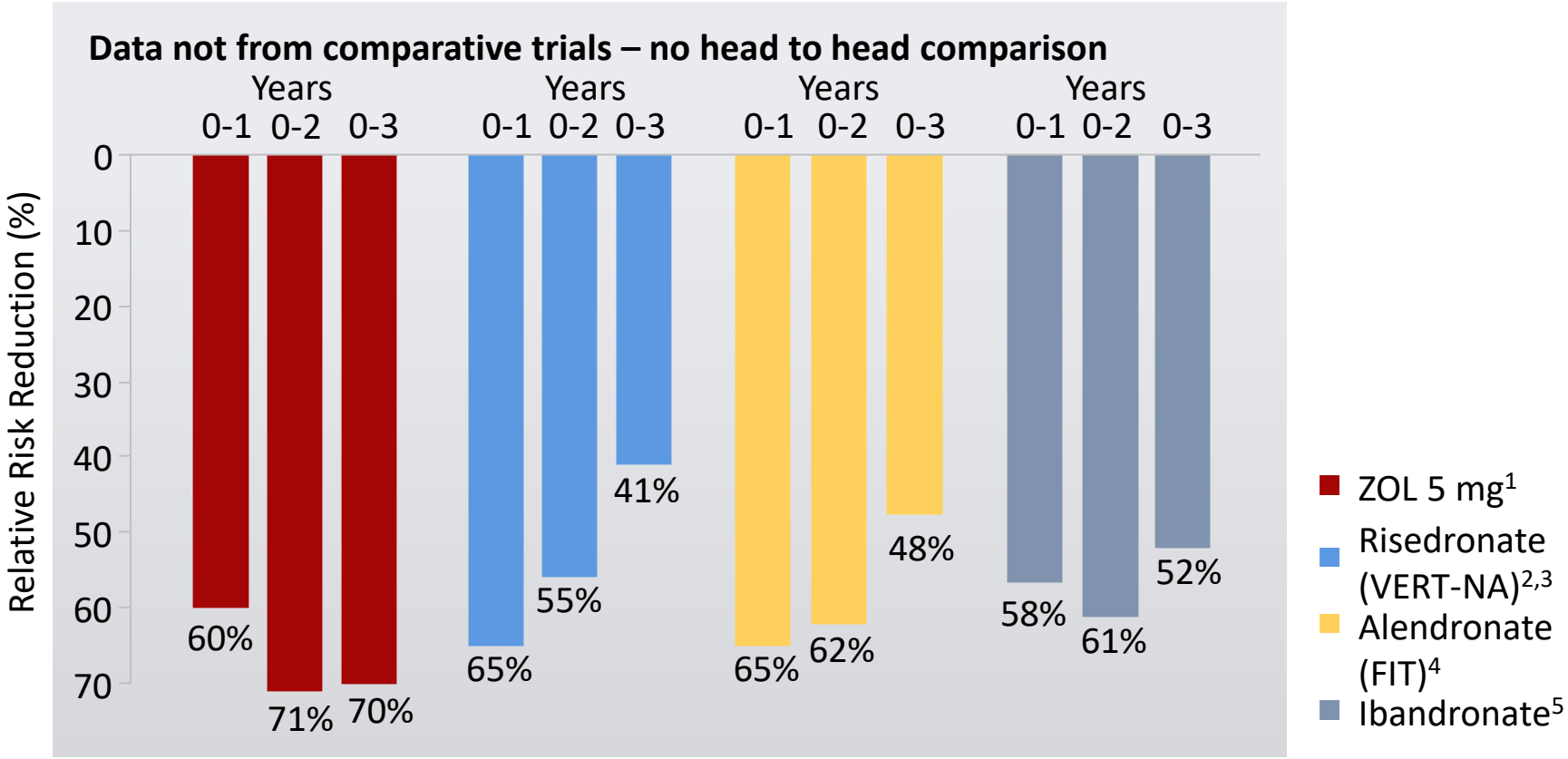


Rapid decrease in bone resorption (BR), followed by a decrease in bone formation (BF)

Refill remodeling space + secondary mineralisation ↑
→ Increase in BMD spine > hip

Reduction in fracture risk

Reduction of Vertebral Fracture Risk



[1]Black DM, et al. N Engl J Med. 2007;356:1809-1822.
[2]Harris ST, et al. JAMA. 1999;282:1344.
[3]Actonel Prescribing Information.
[4]Black D, et al. J Clin Endocrinol Metab. 2000;85:4118-4124.
[5]Chesnut CH, et al. J Bone Miner Res. 2004;19:1241.

Risedronate Treatment Reduces Hip Fracture Risk with in those with Osteoporosis…

	Incidence (%)		RR	p
	Risedronate	Placebo		
Overall	2.8	3.9	0.7 (0.6-0.9)	0.02
Age 70-79 yrs				
with OP	1.9	3.2	0.6 (0.4-0.9)	0.009
with vert. Fx	2.3	5.7	0.4 (0.2-0.8)	0.003
no vert. Fx	1.0	1.6	0.6 (0.3-1.2)	ns
Age > 80 yrs				
with > 1 clinical risk factor	4.2	5.1	0.8 (0.6-1.2)	ns

McClung M et al. NEJM 2001;344:333

BMD Response

Medication	Spine	Hip
Estrogen	↑↑	↑
Alendronate	↑↑↑	↑↑
Risedronate	↑↑↑	↑↑
Ibandronate	↑↑↑	↑↑
Zoledronic acid	↑↑↑	↑↑
Calcitonin	~	~
Raloxifene	↑	(↑)
Bazedoxifene	↑	(↑)
Denosumab	↑↑↑	↑↑
Teriparatide	↑↑↑↑	↑
PTH 1-84	↑↑↑↑	↑

Statistically Significant Relative Risk Reductions in Fractures

Drug	Spine Fractures	Non-vertebral Fxs	Hip Fractures
Alendronate	0.55	0.84	0.61
Risedronate	0.63	0.80	0.74
Zoledronic Acid	0.30	0.75	0.59
Ibandronate	0.48	N/S	N/S
Raloxifene	0.70	N/S	N/S
Denosumab	0.32	0.80	0.60
Teriparatide	0.35	0.62	N/S

Eiken al., Osteoporos Int 2016; 27(1): 1-12

Bisphosphonates:

- FDA-approved indications for bisphosphonates:
  - Osteoporosis in postmenopausal women
  - Osteoporosis in men
  - Glucocorticoid-induced osteoporosis
- Contraindications to oral or IV bisphosphonate:
  - Drug hypersensitivity
  - Hypocalcemia.
  - GFR <30 mL/min for risedronate and ibandronate or <35 mL/min for alendronate and zoledronic acid)

Camacho, et. al., Endocrine Practice, 2016; *22*(suppl *4*), 1111-8
Uptodate, accessed 2019

Bisphosphonates Approved by the US Food and Drug Administration for Prevention and Treatment of Osteoporosis

Drug	Prevention	Treatment
Alendronate (Fosamax)	5 mg PO daily 35 mg PO weekly	10 mg PO daily 70 mg PO weekly[b] 70 mg + D[c]
Ibandronate (Boniva, generic form)	2.5 mg PO daily 150 mg PO monthly	2.5 mg PO daily 150 mg PO monthly 3 mg IV every 3 mo
Risedronate (Actonel, Atelvia, generic form)[a]	5 mg PO daily 35 mg PO weekly 150 mg PO monthly	5 mg PO daily 35 mg PO weekly 150 mg PO monthly

Camacho, et. al., Endocrine Practice, 2016; *22*(suppl *4*), 1111-8

Bisphosphonates:

- Orally administered bisphosphonates:
  - Taken after a prolonged fast (usually fasting overnight and taken in the morning soon after arising)
  - Swallowed with a full glass of water (with at least a 30-minute wait after ingestion before other medications, food, or beverages other than water).
  - Remain upright for 30-60 minutes
- IV bisphosphonate for patients who:
  - Cannot tolerate oral bisphosphonates
  - Have difficulty with dosing requirements or to swallow a pill.
  - Have active gastroesophageal disease.
  - Have documented or potential GI malabsorption e.g., gastric bypass procedures, celiac disease, Crohn's disease, infiltrative disorders, etc.

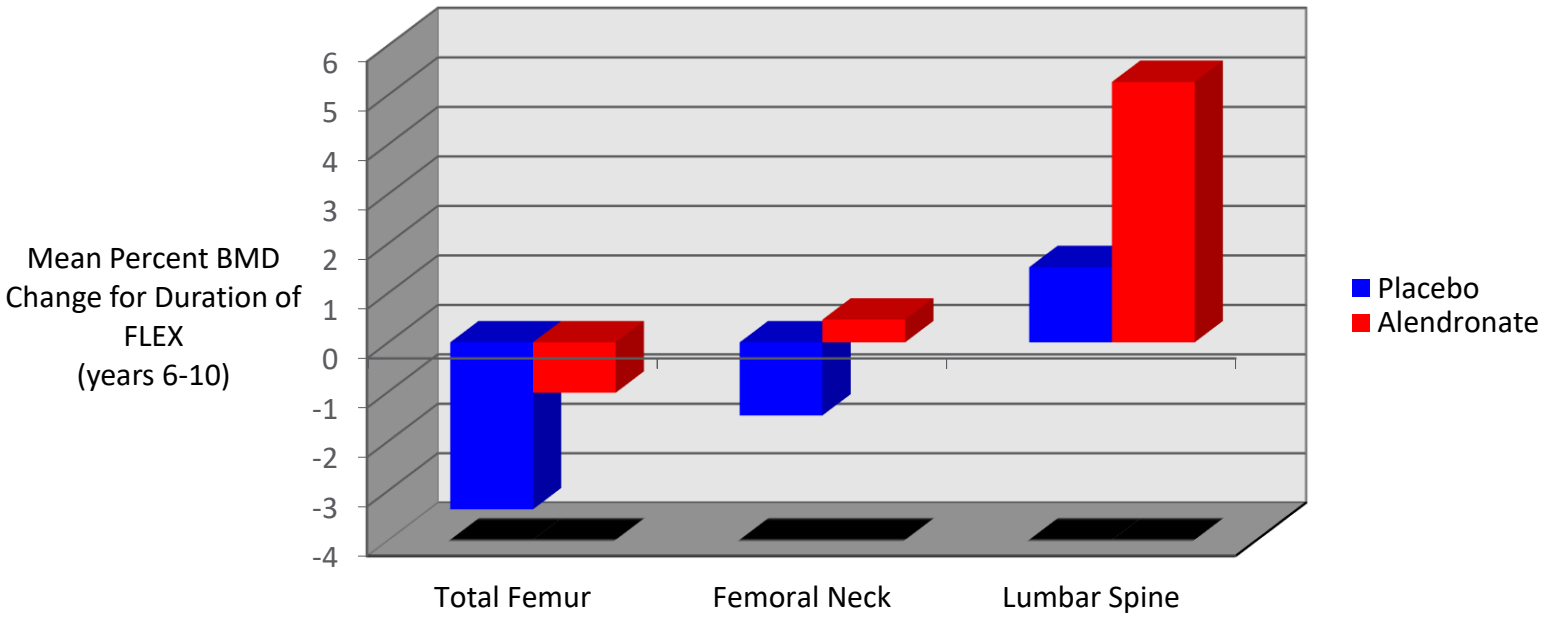
Camacho, et. al., Endocrine Practice, 2016; *22*(suppl *4*), 1111-8
Uptodate, accessed 2019

How Long to Treat?

- Information needed:
  - Duration / persistence of effect with continued use
  - What happens when treatment is discontinued
  - Safety of long term use

Continued ALN Treatment for 10 years is Associated with Further Gains in Spine BMD and Prevention of Loss at the Hip

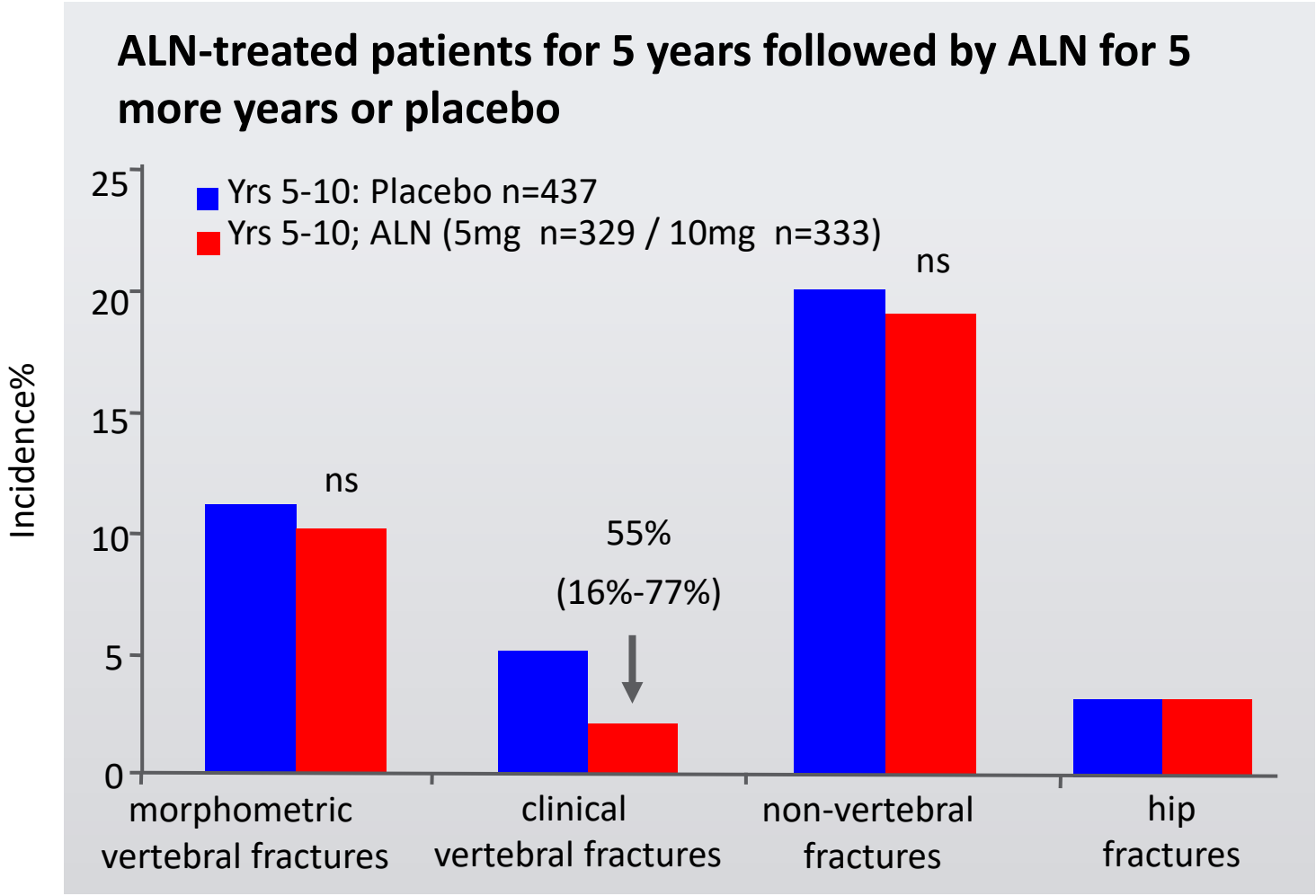
ALN treated patients for 5 years followed by ALN for 5 more years or placebo



Postmenopausal women, n=1099
FLEX baseline age, 73 yrs
FLEX baseline BMD T-score FN, -2.2
Prevalent VFx 34%, prevalent clinical Fx 60%

Black et al, JAMA 2006, 296: 2927

FLEX Trial: Fracture Assessment



Adapted from Black et al, JAMA 2006, 296: 2927

Bisphosphonate holiday

- For oral bisphosphonates, consider a bisphosphonate holiday after 5 years of treatment if fracture risk is no longer high (such as when the T score>-2.5, or the patient has remained fracture free), but continue treatment up to an additional 5 years if fracture risk remains high (Grade B; BEL 2).
- For oral bisphosphonates, consider a bisphosphonate holiday after 6 to 10 years of stability in patients with very high fracture risk (Grade B; BEL 2).
- The ending of a bisphosphonate holiday should be based on individual patient circumstances such as an increase in fracture risk, a decrease in bone mineral density beyond the LSC of DXA machine, or an increase in bone turnover markers (Grade A; BEL 1)

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Camacho, et. al., Endocrine Practice, 2020

Bisphosphonate holiday

Restart bisphosphonates within the first five years of the drug holiday when any of the following occur:

- Reproducible bone loss (approximately 5 percent) on at least two DXA measurements taken at least two years apart
- Evidence of bone loss on one DXA measurement at the spine **and** the hip.
- Evidence of bone loss on one DXA measurement at either site **and** a fasting CTX >600 pg/mL (ie, above the upper limit of the premenopausal reference range).
- New fracture

Alternative: bisphosphonates can be restarted after a three- to five-year holiday in women who showed improvement during their initial course of bisphosphonates and did not have a previous fracture.

Bisphosphonates – Possible Side Effects

- GI-Intolerance (oral)
- Hypocalcemia
- Renal toxicity

} **Check calcium and creatinine prior to treating**

- Ocular effects (conjunctivitis, uveitis, episcleritis, scleritis, and keratitis)
- Acute phase reaction and Flu-like symptoms (myalgia, arthralgia, fever): Common In 12-48 hours after IV dosing, Lasts usually for 1-2 days, sometimes 1 week
- Musculoskeletal pain
- Atrial fibrillation ?
- Esophageal cancer ?
- Osteonecrosis of the jaw (ONJ)
- Atypical femoral fractures (AFF)

Renal Failure and BPs?

- Bisphosphonates are cleared, unaltered, by the kidney
- Initial experience with zoledronic acid (ZA) in oncology patients documented a risk of acute renal failure with rapid infusion
  - Infusion time of at least 15 minutes
- September 2011: after additional case reports of acute renal failure, FDA mandated a change in ZA product labeling: "….contraindicated in patients with creatinine clearance < 35 ml/min and in those with evidence of acute renal impairment"

However, "The mechanism(s) by which bisphosphonates are associated with nephrotoxicity are not well understood."

Perazella and Markowitz, Kidney Int, 74:1385-93, 2008

Prospective Studies Find Little or No Increased Renal Risk

- Increase in creatinine > 0.5 mg/dl
  - ZA: 1.2%
  - PBO: 0.4% ($p < 0.001$)

"These changes were transient… At 3 years, there was no significant difference in either serum creatinine levels or creatinine clearance between the groups."[1]

- Increase in creatinine > 0.5 mg/dl
  - ZA: 6.2%
  - PBO: 5.6% (ns)

"We did not find an increased incidence of renal adverse events, despite high baseline rates of mild-to-moderate chronic kidney disease."[2]

[1]Black, et. al., NEJM, 356:1809-1822, 2007
[2]Lyles, et. al., NEJM, 357:1799-1809, 2007

Do Bisphosphonates Cause Muscle and Joint Pain?

- No evidence in clinical trial data for oral meds
- 2005: Case reports from post-marketing data suggests diffuse musculoskelatal pain can occur with bisphosphonates, but it is rare[1]
- 2008 FDA alert (reissued, but not based on new data):
  - "There is a possibility of severe and sometimes incapacitating bone, joint, and/or muscle (musculoskeletal) pain in patients taking bisphosphonates"[2]

[1]Wysowski DK Arch Intern Med 165(3):346-7, 2005
[2]http://www.fda.gov/cder/drug/infopage/bisphosphonates/default.htm

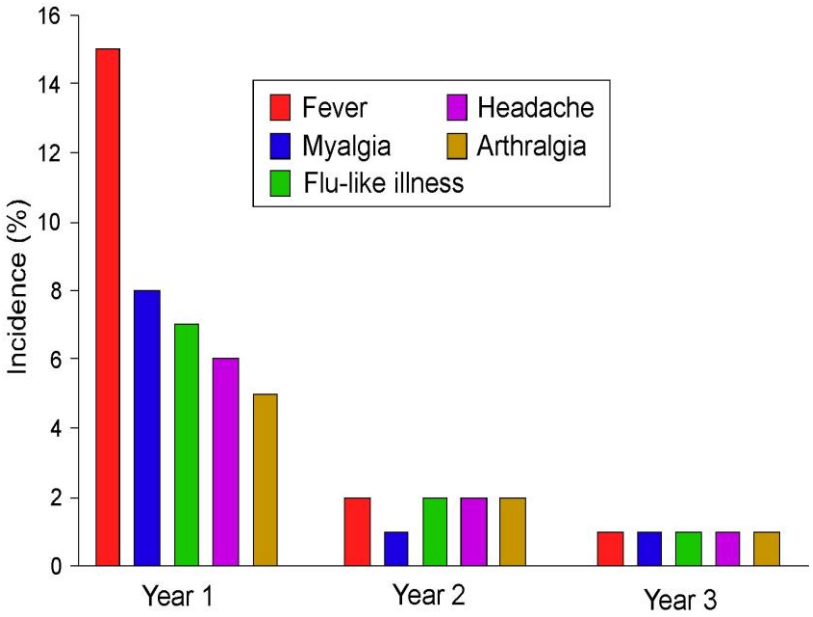
Retrospective Cohort Study: No Evidence Oral Bisphosphonates Cause Musculoskeletal Pain (MSKP)

- Retrospective cohort study: All US veterans 65+ with spine/hip fracture treated with bisphosphonates for at least 1 year n = 26,545
- Primary outcome was time until an ICD-9 diagnosis consistent with diffuse musculoskeletal pain
- Conclusion:

"Bisphosphonate use was not associated with a statistically higher rate of MSKP in this cohort. Individual patients may rarely report MSKP while taking bisphosphonates…"

Caplan, et. al., Mayo Clin Proc, 85:341-348, 2010

An Acute Phase Reaction is Seen With IV Bisphosphonates



- Overall, 42% had acute phase reaction symptoms with first infusion[1]
- Peak onset within one day
- The risk at the time of subsequent infusions is markedly reduced

Due to release of inflammatory cytokines from peripheral blood T-cells[2,3]

[1]Adapted from Reid et. al., JCEM, 95:4380-7, 2010
[2]Hewitt, et. al., Clin Exper Immunol, 139:101-111, 2005
[3]Roelofs et al., Br J Haematol, 144:245-250, 2009

Atrial Fibrillation & Bisphosphonates

- AF as a serious adverse event (SAE) more common in those receiving zoledronic acid (1.3%) than placebo (0.5%) over 36 months in the pivotal fracture study[1]
  - Overall incidence of AF did not differ between groups
- Observational alendronate studies suggested bisphosphonate use more common in patients with atrial fibrillation[2]
- Other clinical trials showed no association including:
  - Other zoledronic acid trials
    - HORIZON – Recurrent fracture trial (N = 2127)
      - No difference atrial fibrilllation or stroke
      - 28% ↓ mortality (9.6% vs 13.3%)[3]
    - Male osteoporosis (N = 302)[4]
  - Alendronate, risedronate and ibandronate trials

[1]Black, et. al, N Engl J Med 2007;356:1809-22. [3]Lyles KW et al NEJM 357:1799-1809, 2007
[2]Heckbert Arch Int Med 4/08, Sorensen BMJ 4/08 [4]Orwoll ES J Bone Miner Res 25(10):2239-50, 2010

FDA Found No Association of BP Use With Atrial Fibrillation

- Reviewed clinical trial and post-marketing data
- Did not identify an association between bisphosphonates and atrial fibrillation
- Did not believe healthcare providers or patients should change their use of bisphosphonates

htpp://www.fda.gov/cder/drug/early_comm/bisphosphonates_update_200811.htm

Bisphosphonate Use & Esophageal Cancer

- Concern raised by a report of 23 patients on alendronate diagnosed with esophageal cancer over ~12.7 years[1]
- A 2012 study found no increased risk of esophageal cancer
  - Registry-based cohort study in Denmark of 30,606 ALN users and 122,424 controls[2]
  - Note that prior reports did not address endoscopy rates which could potentially be higher in ALN users and thus lead to more cancers being diagnosed earlier
  - "ALN users more likely to have upper endoscopy (4.1 vs. 1.7%). ALN users had a lower risk of gastric cancer and no increased risk of esophageal cancer."

[1]Wysowski, New Engl J Med, 360:89-90, 2009
[2]Abrahamsen, et. al., J Bone Miner Res, 27:679-686, 2012

Osteonecrosis of the Jaw (ONJ)

- Exposed bone in maxillofacial area for 8 weeks or more in absence of radiation therapy to area
- May be associated with pain, swelling and infection
- Most cases in patients with cancer on high dose IV bisphosphonates often in combination with glucocorticoids or chemotherapy

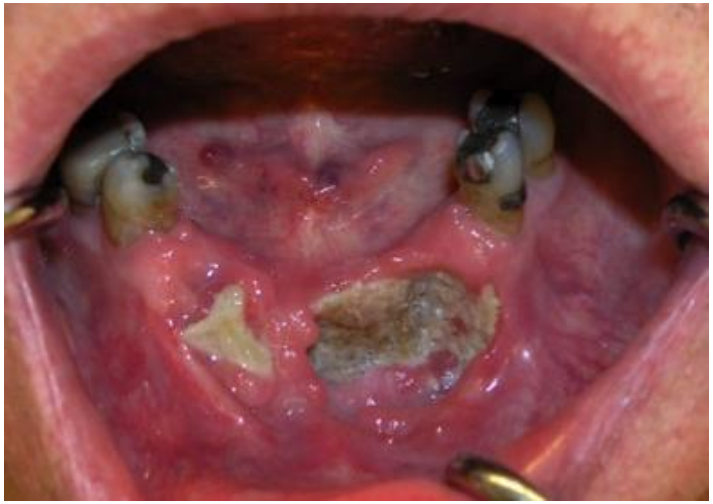


Photo Courtesy of M Kraenzlin

- Risk in oral BP users of 1:10,000 to 1:100,000 patient years
- Unclear if stopping therapy prior to invasive dental procedures is helpful, but reasonable if elective procedure and appropriate to wait

Khosla S et al. ASBMR Task Force Report J Bone Miner Res. 2007;22:1479

Osteonecrosis of the Jaw
Prevention and Treatment

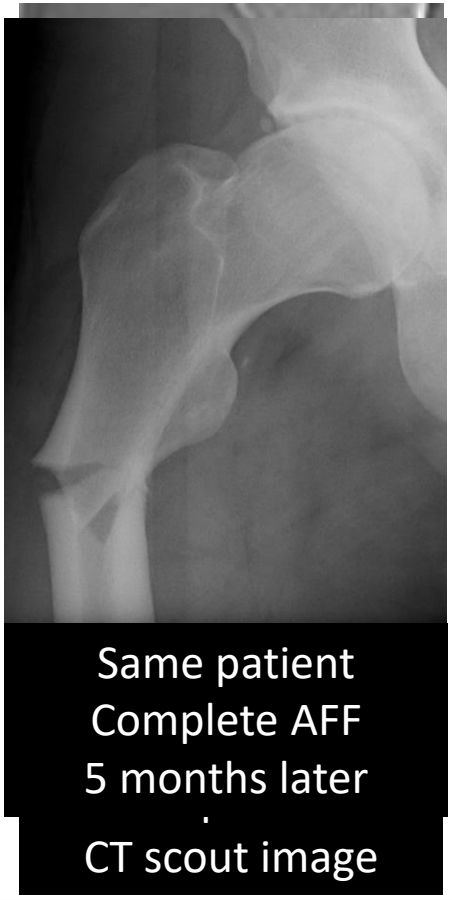
- Cancer patients
  - Regular oral hygiene and dental care (every 6-12 months)
  - Before bisphosphonate use, repeat dental exam recommended
- Patients with osteoporosis
  - Information to patient that risk is present but extremely rare
  - No specific interventions prior to starting bisphosphonate therapy required, except to ensure routine dental care
  - Before dental intervention or surgery in maxillofacial region
    - Discussion with dentist often helpful
    - Avoid infections
    - In presence of risk factors such as diabetes or corticosteroid use
      - » Close follow-up
      - » Consider prophylactic antibiotics and mouth rinses

R.Rizzoli et al. Bone 2008, 42; 841-847

Atypical Femur Fractures (AFF)
Must be Located in the Femoral Diaphysis

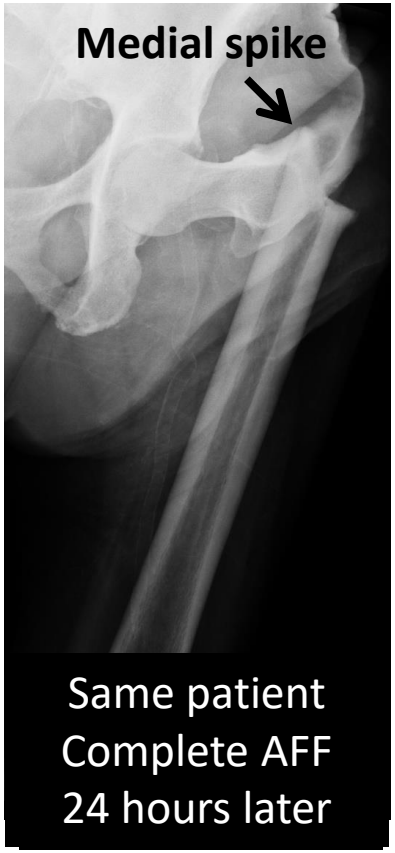
Diagnosis Requires 4 of the Following 5 **Major Features**

1. Localized periosteal or endosteal thickening of the lateral cortex at the fracture site ("beaking")
2. Incomplete fractures involve only the lateral cortex; complete fractures extend through both cortices, often with a medial spike
3. Fracture line originates at the lateral cortex, is substantially transverse, may become oblique
4. Non-comminuted or minimally comminuted
5. Associated with minimal or no trauma



Same patient
Complete AFF
5 months later

CT scout image



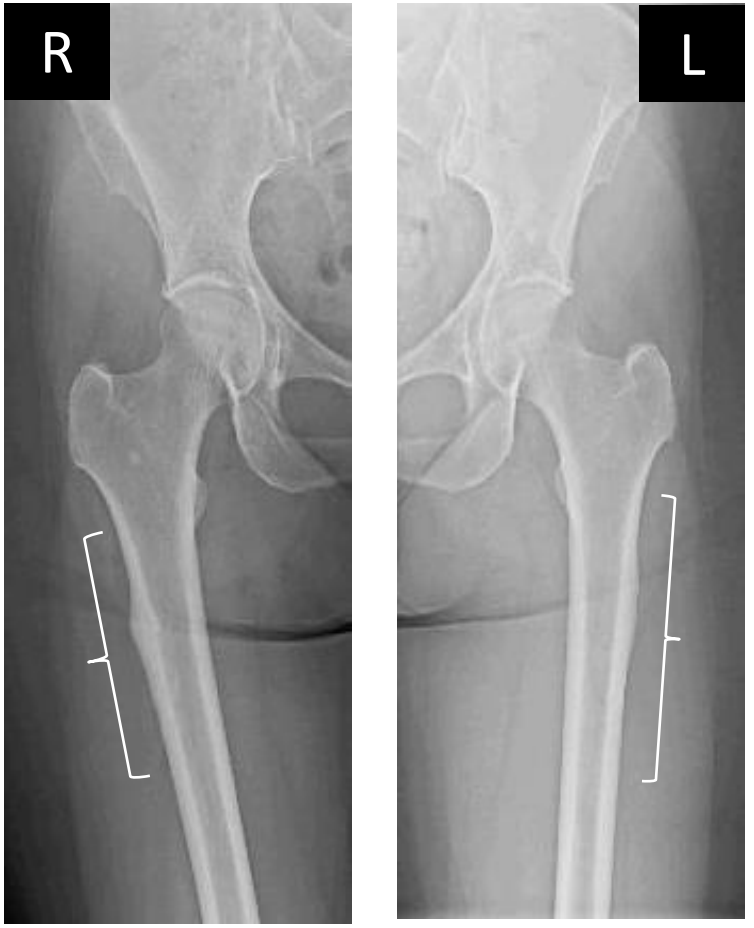
Same patient
Complete AFF
24 hours later

Shane E, JBMR 2014, 29; 1-23

AFF **Minor** Features

Associated but not Required for Diagnosis

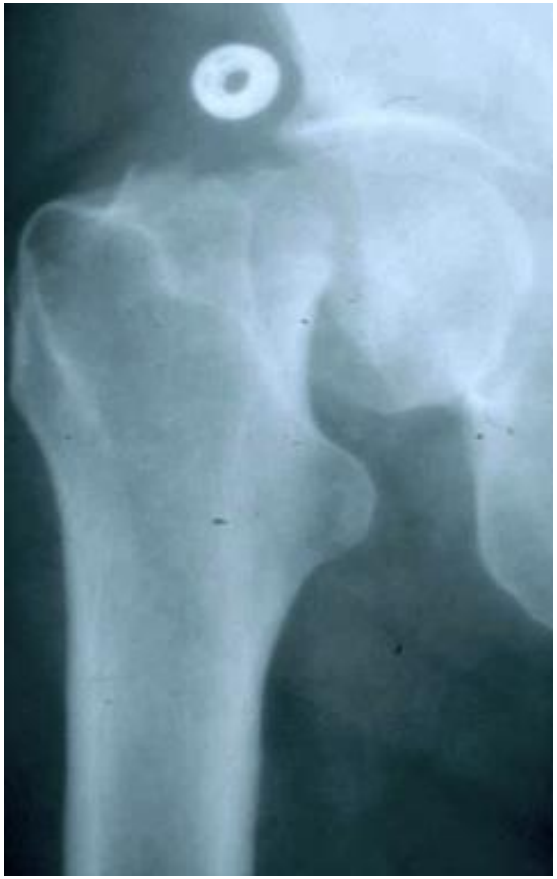
- Generalized increase in cortical thickness of femoral diaphysis
- Bilateral incomplete or complete femoral diaphysis fractures
- Unilateral or bilateral prodromal symptoms
  - Dull or aching pain in the groin or thigh
- Delayed fracture healing



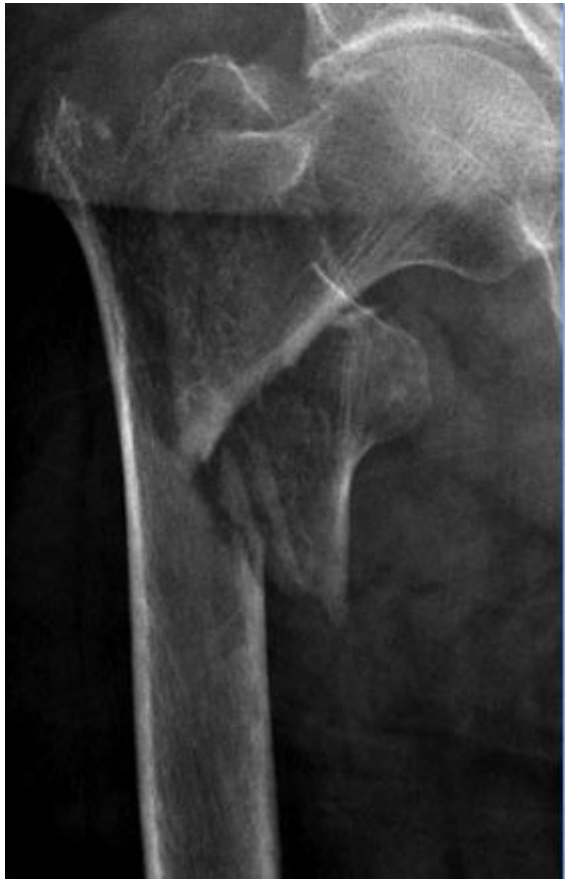
Shane E, JBMR 2014, 29; 1-23

Typical Hip Fractures

Femoral Neck Fracture



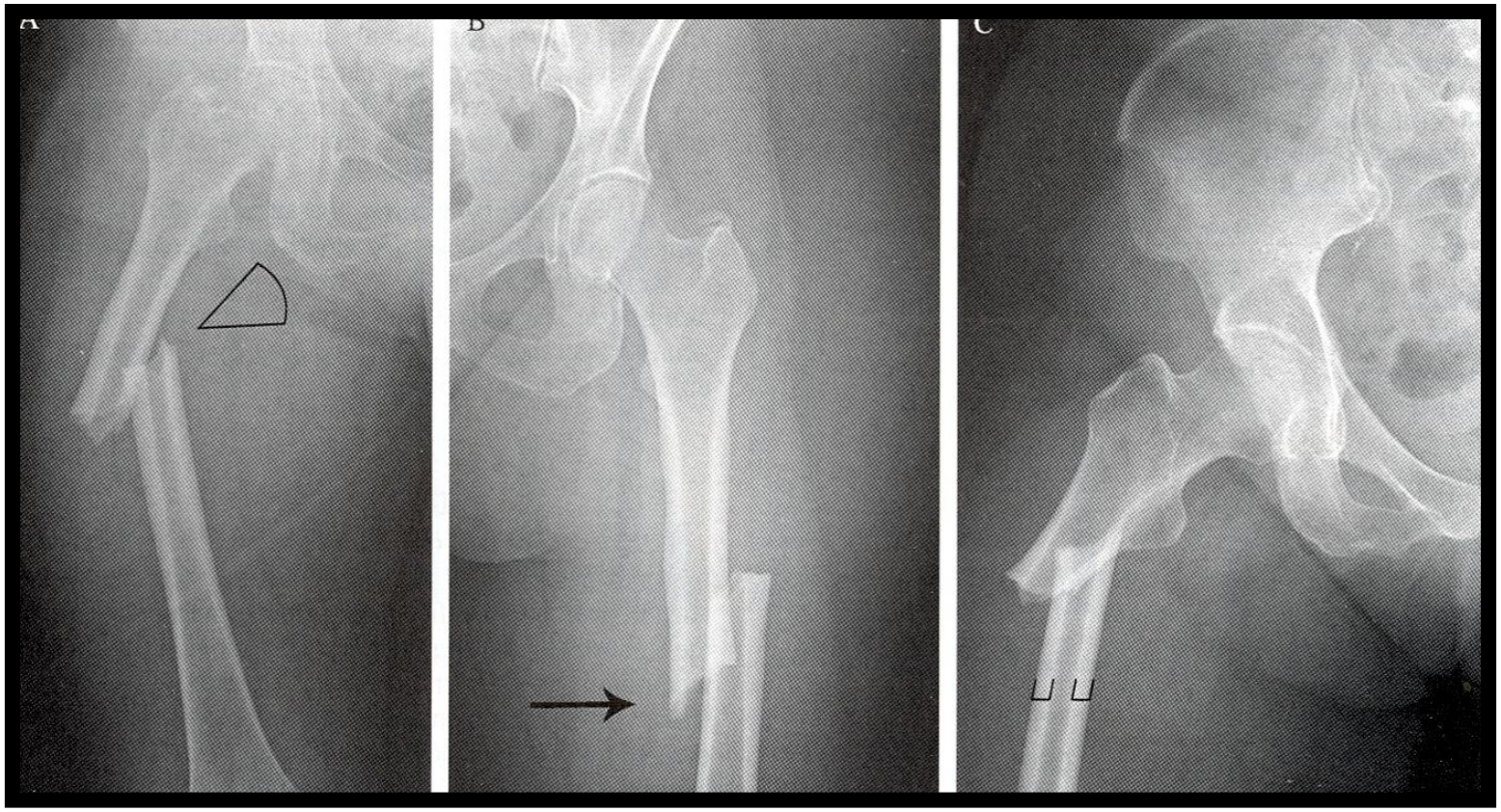
Intertrochanteric Fracture



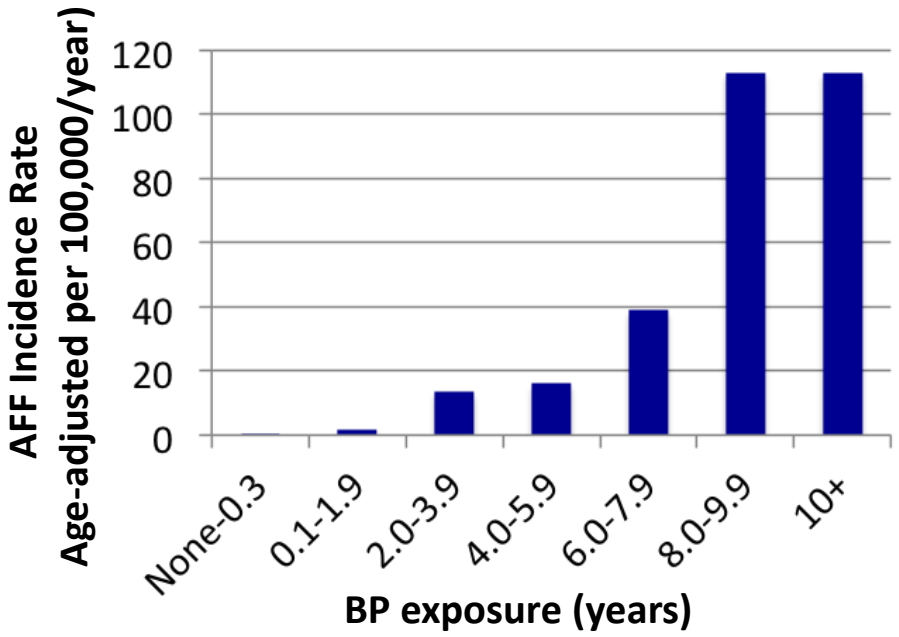
Atypical Femur Fractures

Femoral Shaft or Diaphyseal Locations

Subtrochanteric Location



Atypical Femoral Fracture Incidence Increases With Duration of Bisphosphonate Exposure



Adapted from Dell RM, J Bone Miner Res, 2012;27:2544-50

Incidence of AFF in Bisphosphonate Users

- Highest report estimates (case-series)
  - 1-3% after 3-5 years in highly compliant , tertiary referral populations [1, 2]
- Best population-based estimates[3,4]
  - 0.01% after 3 years,
  - 0.1% after 10 years
- Assuming all AFF are caused by BPs (<u>they are not!</u>)
  - 15-100 typical osteoporotic hip fractures might be prevented for every AFF caused by BPs [3, 4]
  - "Patients at risk for osteoporotic fractures should not be discouraged from initiating BPs"… but "the risk of AFF should be taken into consideration when continuing BPs beyond 5 years" [5]

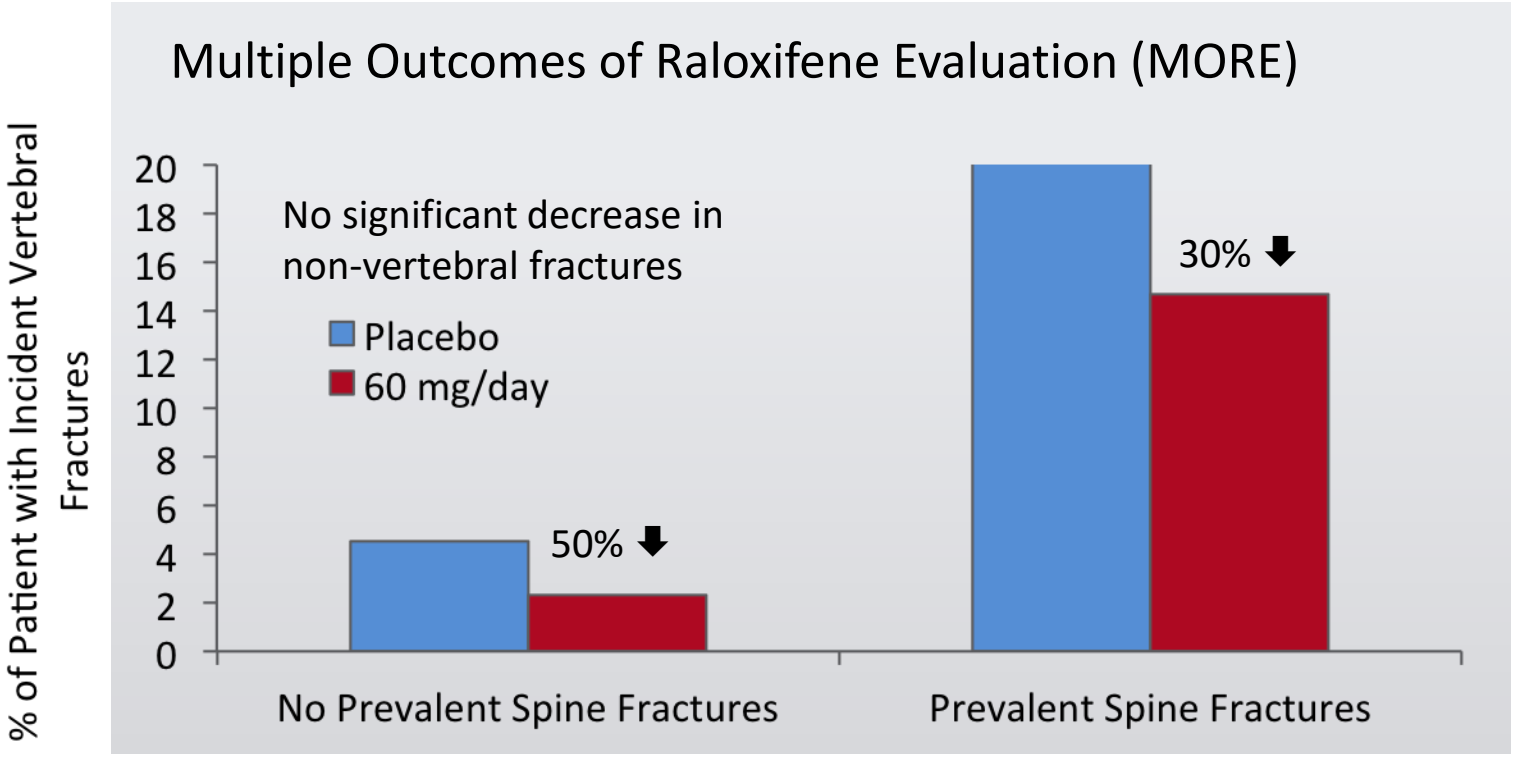
[1]Allison MB, Bone 2013;55:113-8
[2]McKenna M, J Clin Densitom, 2013;doi: 10.1016/j.jocd.2013.06.004. [Epub ahead of print]
[3]Rizzoli R, Osteoporos Int 2011;22:373-90
[4]Wang, J Bone Miner Res, 2011;26:553-60
[5]Dell RM, J Bone Miner Res, 2012;27:2544-50

Raloxifene

- Class: antiresorptive, selective estrogen receptor modulator
- BMD: increases at spine and hip
- Bone turnover markers: decreased
- Fractures: reduces risk of vertebral fractures, no proven benefit for hip or nonvertebral fractures

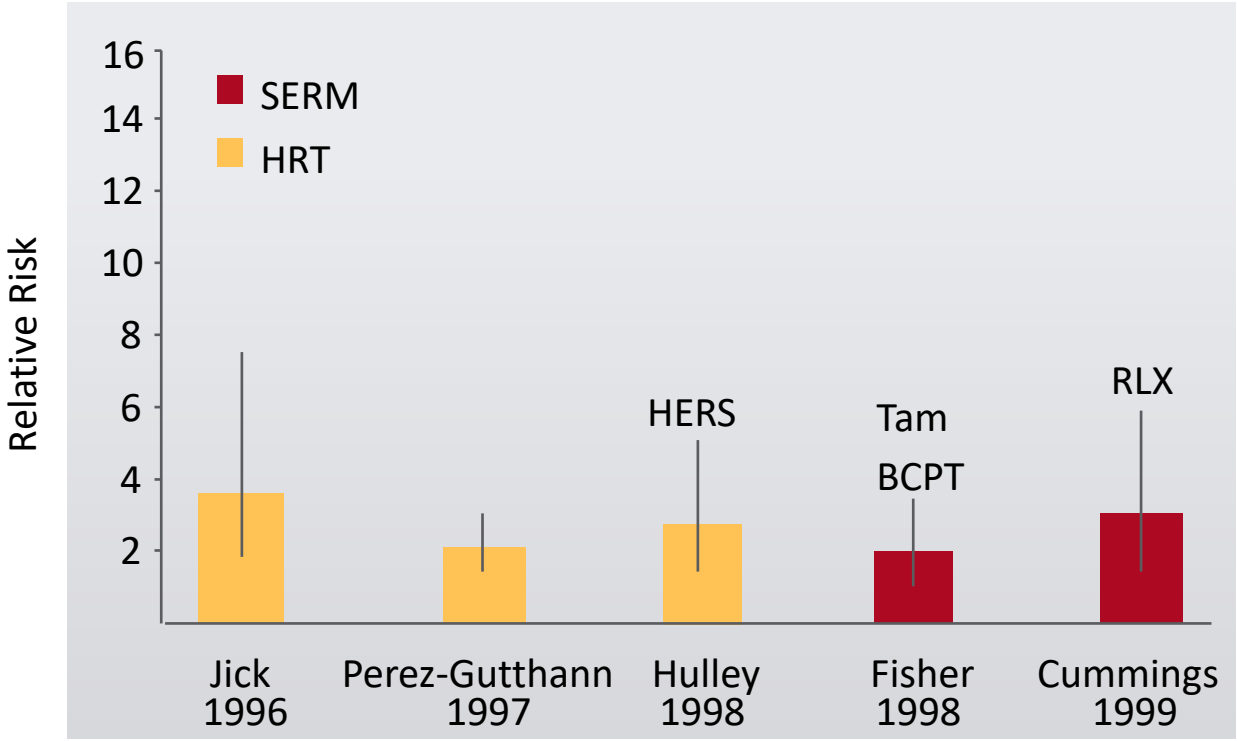
Raloxifene Reduces Spine Fractures

3-year RCT of 7705 women with postmenopausal osteoporosis, age 31-80



Adapted from Ettinger B, et al. JAMA. 1999;282:637.

Venous Thromboembolism Risk with Raloxifene is Similar to Estrogen and Tamoxifen



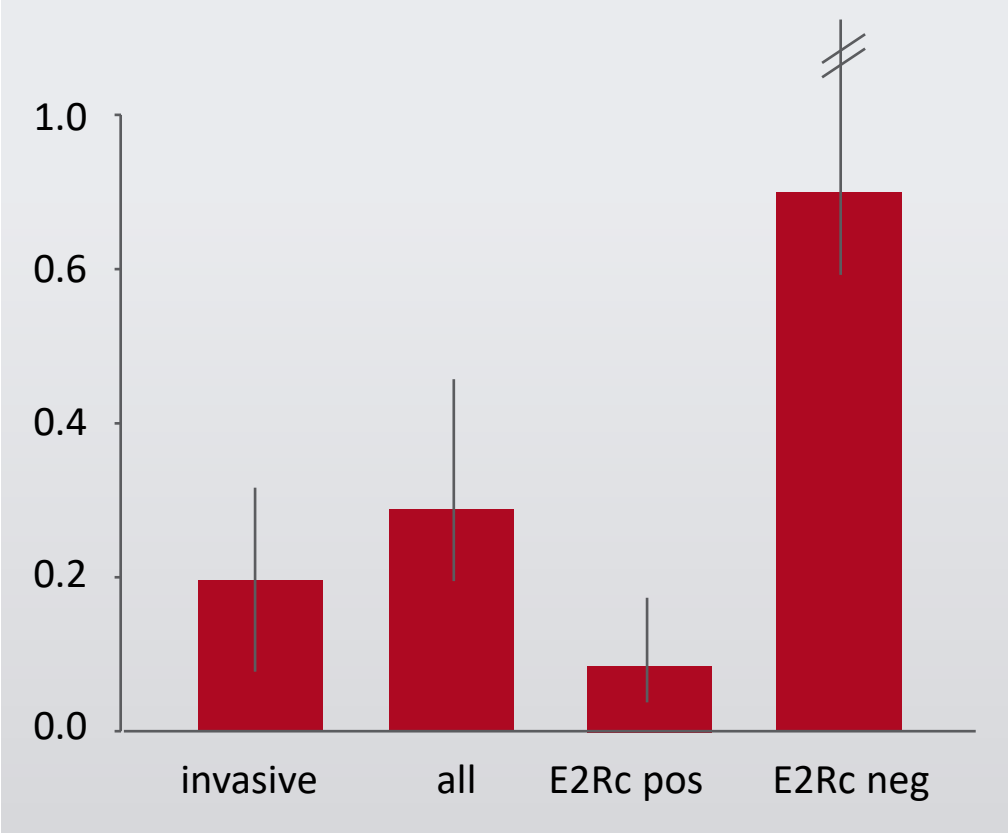
Case Age Range (years)	(50-74)	(50-79)	(44-79)	³50	(35-80)
DVT/PE Incidence Rate / 1000 pt.-years			4.1	2.5	3.1

Raloxifene and Vascular Events

The Heart (RUTH) Trial (10,000+ patients with 5+ year follow up): RLX had no significant effect on the risk of coronary events (HR 0.95). There were no differences in overall stroke risk, but raloxifene was associated with an increased risk of fatal stroke (HR 1.49; absolute risk increase 0.7 per 1000), and venous thromboembolism (HR 1.44; absolute risk increase 1.3 per 1000)

Barrett-Connor, et al. NEJM. 2006, 355; 125-137.

Raloxifene Reduces Relative Risk of Breast Cancer (MORE trial)



Cummings S. et al, JAMA. 1999; 281: 2189-2197: MORE STUDY

Raloxifene – Summary of Effects

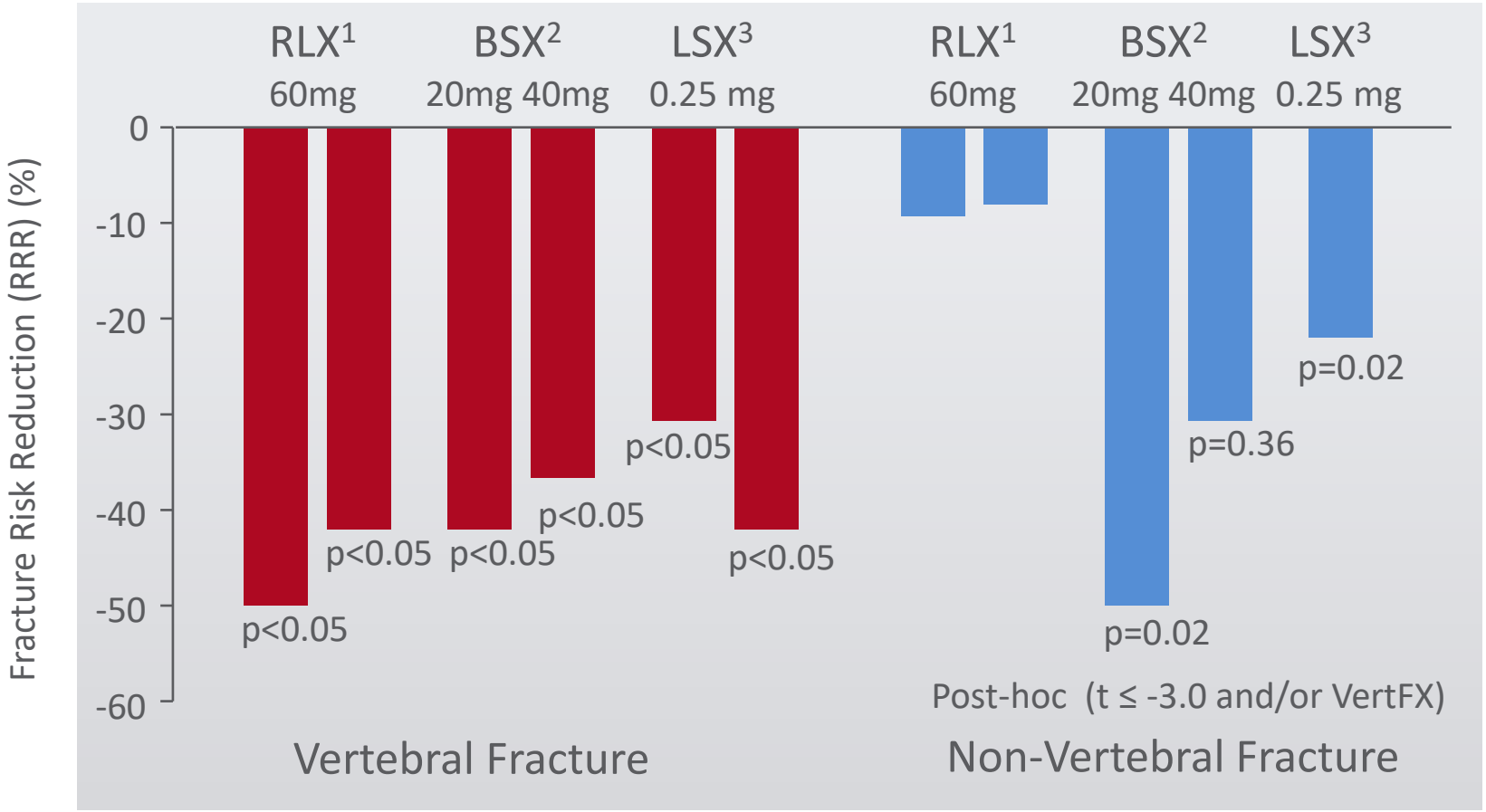
- Dose: 60 mg PO daily
- Increases bone mass
- Reduces the incidence of vertebral fractures

AND

- Has a favorable effect on lipid profile
- Reduces the relative risk of breast cancers
- Does not stimulate the endometrium
- Does not reduce hot flashes
- DVT risk similar to that for estrogen
- Has no effect on risk for coronary events
- Has no effect on overall stroke risk, but is associated with an increased risk of fatal stroke

Other SERMS for the Prevention of Osteoporosis

SERM Treatment and Fracture Risk Reduction



[1] *B.Ettinger et al. JAMA 1999;282:637*
[2] *S.Silvermann et al. J Bone Miner Res. 2008;23:1923*
[3] *S.Cummings et al. ASBMR2008 Montreal*

basedoxifene (BSX)
lasofoxifene (LSX)

Global Consensus Statement on Menopausal Hormone Therapy

- *"MHT is effective and appropriate for the prevention of osteoporosis-related fractures in at-risk women before age 60 years or within 10 years after menopause.*
- *Randomized clinical trials and observational data as well as meta-analyses provide evidence that standard-dose estrogen-alone MHT may decrease coronary heart disease and all cause mortality in women younger than 60 years and within 10 years of menopause."*

Note: Estrogen use for osteoporosis treatment would be off label

De Villiers, et. al., Climacteric, 2013; 16: 203-204

Summary of Evidence for Reduction of Fracture Risk with Pharmacologic Agents			
	Reduction of Fracture Risk		
Drug	**Vertebral**	**Nonvertebral**	**Hip**
Abaloparatide (Tymlos) (273, 282)	Yes	Yes	No effect demonstrated[a]
Alendronate (Fosamax) (223)	Yes	Yes	Yes
Calcitonin (Miacalcin, Fortical) (191)	Yes	No effect demonstrated[a]	No effect demonstrated[a]
Denosumab (Prolia) (193, 242)	Yes	Yes	Yes
Ibandronate (Boniva) (187, 227)	Yes	No effect demonstrated[a]	No effect demonstrated[a]
Raloxifene (Evista) (192)	Yes	No effect demonstrated[a]	No effect demonstrated[a]
Risedronate (Actonel, Atelvia) (188, 189)	Yes	Yes	Yes
Romosozumab (Evenity) (213, 283)	Yes	[b]	[b]
Teriparatide (Forteo) (194, 306)	Yes	Yes	No effect demonstrated[a]
Zoledronate (Reclast) (202)	Yes	Yes	Yes

[a]The lack of demonstrable effect at these sites should be considered in the context that the studies may not have been adequately powered.
[b]Clinical fracture reduction was shown in both trials. Nonvertebral and hip fracture reductions were shown at month 24 for patients receiving 12 months of romosozumab followed by 12 months of alendronate compared with patients receiving 24 months of alendronate (213).

FDA-Approved Medications

Drug	PMO		GIO		Men
	Prevention	Treatment	Prevention	Treatment	
Estrogen	✓				
Alendronate	✓	✓		✓	✓
Risedronate	✓	✓	✓	✓	✓
Ibandronate	✓	✓			
Raloxifene	✓	✓			

AACE/ACE 2020 POSTMENOPAUSAL OSTEOPOROSIS TREATMENT ALGORITHM

Lumbar spine or femoral neck or total hip T-score of ≤ -2.5, a history of fragility fracture, or high FRAX® fracture probability*

Evaluate for causes of secondary osteoporosis

Correct calcium/vitamin D deficiency and address causes of secondary osteoporosis

- Recommend pharmacologic therapy
- Education on lifestyle measures, fall prevention, benefits and risks of medications

High risk/no prior fractures**

- Alendronate, denosumab, risedronate, zoledronate***
- **Alternate therapy:** Ibandronate, raloxifene

Reassess yearly for response to therapy and fracture risk

Increasing or stable BMD and no fractures

Consider a drug holiday after 5 years of oral and 3 years of IV bisphosphonate therapy

Resume therapy when a fracture occurs, BMD declines beyond LSC, BTM's rise to pretreatment values or patient meets initial treatment criteria

Progression of bone loss or recurrent fractures

- Assess compliance
- Re-evaluate for causes of secondary osteoporosis and factors leading to suboptimal response to therapy

- Switch to injectable antiresorptive if on oral agent
- Switch to abaloparatide, romosozumab, or teriparatide if on injectable antiresorptive or at very high risk of fracture
- Factors leading to suboptimal response

ABBREVIATIONS GUIDE

BMD – bone mineral density
LSC – least significant change
BTM – bone turnover marker

Very high risk/prior fractures**

- Abaloparatide, denosumab, romosozumab, teriparatide, zoledronate***
- Alternate therapy: Alendronate, risedronate

Reassess yearly for response to therapy and fracture risk

Denosumab	Romosozumab for 1 year	Abaloparatide or teriparatide for up to 2 years	Zoledronate
Continue therapy until the patient is no longer high risk and ensure transition with another antiresorptive agent.	Sequential therapy with oral or injectable antiresorptive agent	Sequential therapy with oral or injectable antiresorptive agent	• If stable, continue therapy for 6 years**** • If progression of bone loss or recurrent fractures, consider switching to abaloparatide, teriparatide or romosozumab

* 10 year major osteoporotic fracture risk ≥ 20% or hip fracture risk ≥ 3%. Non-US countries/regions may have different thresholds.

** Indicators of very high fracture risk in patients with low bone density would include advanced age, frailty, glucocorticoids, very low T scores, or increased fall risk.

*** Medications are listed alphabetically.

**** Consider a drug holiday after 6 years of IV zoledronate. During the holiday, an anabolic agent or a weaker antiresorptive such as raloxifene could be used.

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Very high fracture risk:

- A recent fracture (e.g., within the past 12 months)
- Fractures while on approved osteoporosis therapy
- Multiple fractures
- Fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids)
- Very low T-score (e.g., less than −3.0)
- High risk for falls or history of injurious falls
- Very high fracture probability by FRAX® (e.g., major osteoporosis fracture >30%, hip fracture >4.5%).

Thank you