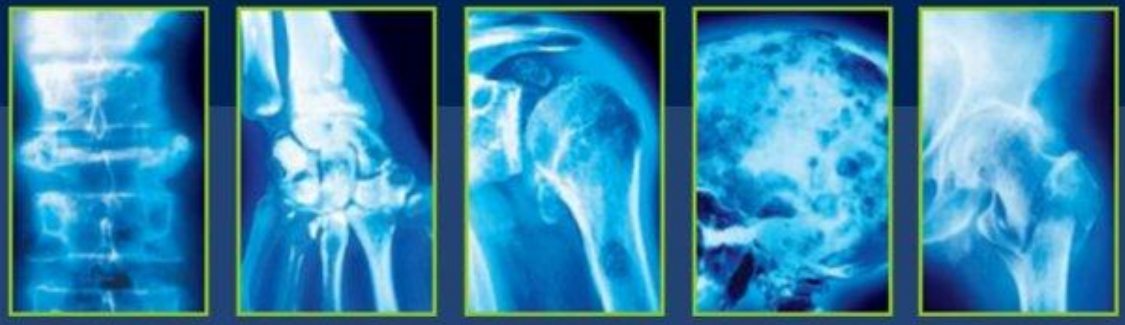


The Prevention and Treatment of Cancer Therapy Induced Bone Loss and Osteoporosis

Robert J Wilson MD , FRCP©

October 13 , 2017

Disclosures

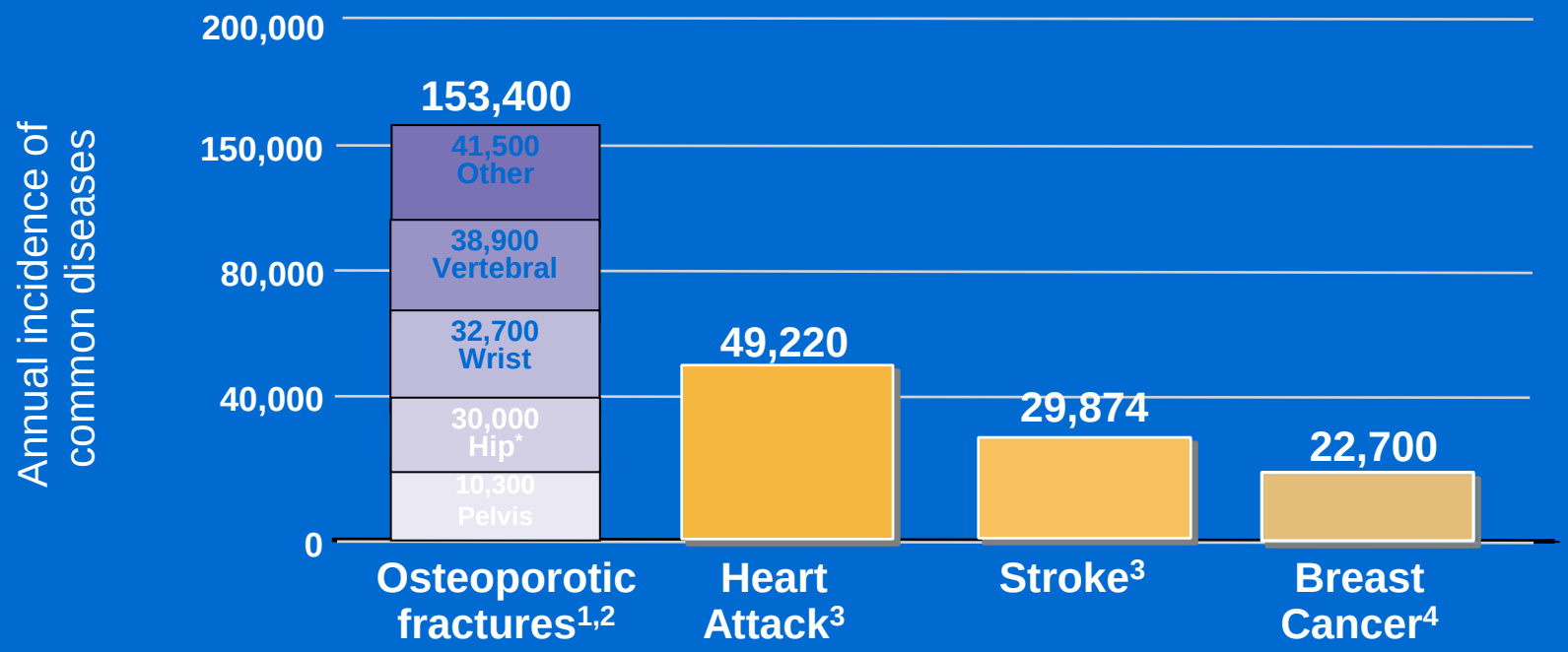
- I have received honorariums from Amgen for presentations on Osteoporosis and treatment using Denusomab (Prolia)
- Many of the slides that you will see during this presentation were generously provided without bias by Amgen Pharmaceuticals
- I will not be discussing any off label use of drug therapies used in the prevention and treatment of cancer therapy induced bone loss

Learning Objectives

- To understand the prevalence of osteoporotic fractures
- To learn how to assess fracture risk
- To understand the role of RANKL in the pathogenesis of bone loss and fracture occurrence
- To understand the consequences of aromatase inhibitor agents and androgen deprivation therapies on bone loss and fracture risk
- To become familiar with the recommended lifestyle and drug therapy interventions that can be employed to prevent and treat cancer therapy induced bone loss

Fractures from Osteoporosis are more Prevalent than Heart Attack, Stroke and Breast Cancer Combined[1]

Prevalence in Canadian Women



*Canadian hip fractures from (1); Non-hip fracture data extrapolated from (2).
†Other represents non-osteoporotic fractures sites (humerus, clavicle, hands/fingers, patella, tibia, fibula).[2]

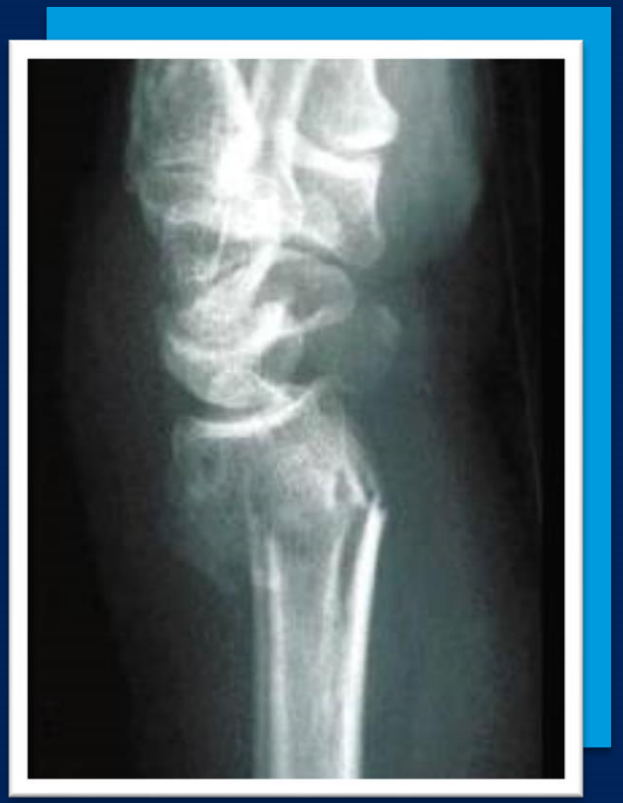
1. Leslie WD, et al. *Osteoporos Int .* 2010; 21:1317-1322; 2. Burge J, et al. *J Bone Miner Res.* 2007;22:465-475;
3. Canadian Institute for Health Information (2009) Health Indicators. ; 4. Canadian Cancer Society. 2009.

What is a Fragility Fracture?

Definition of a fragility fracture*:

A fracture that occurs *spontaneously* or following a *minor trauma* such as:

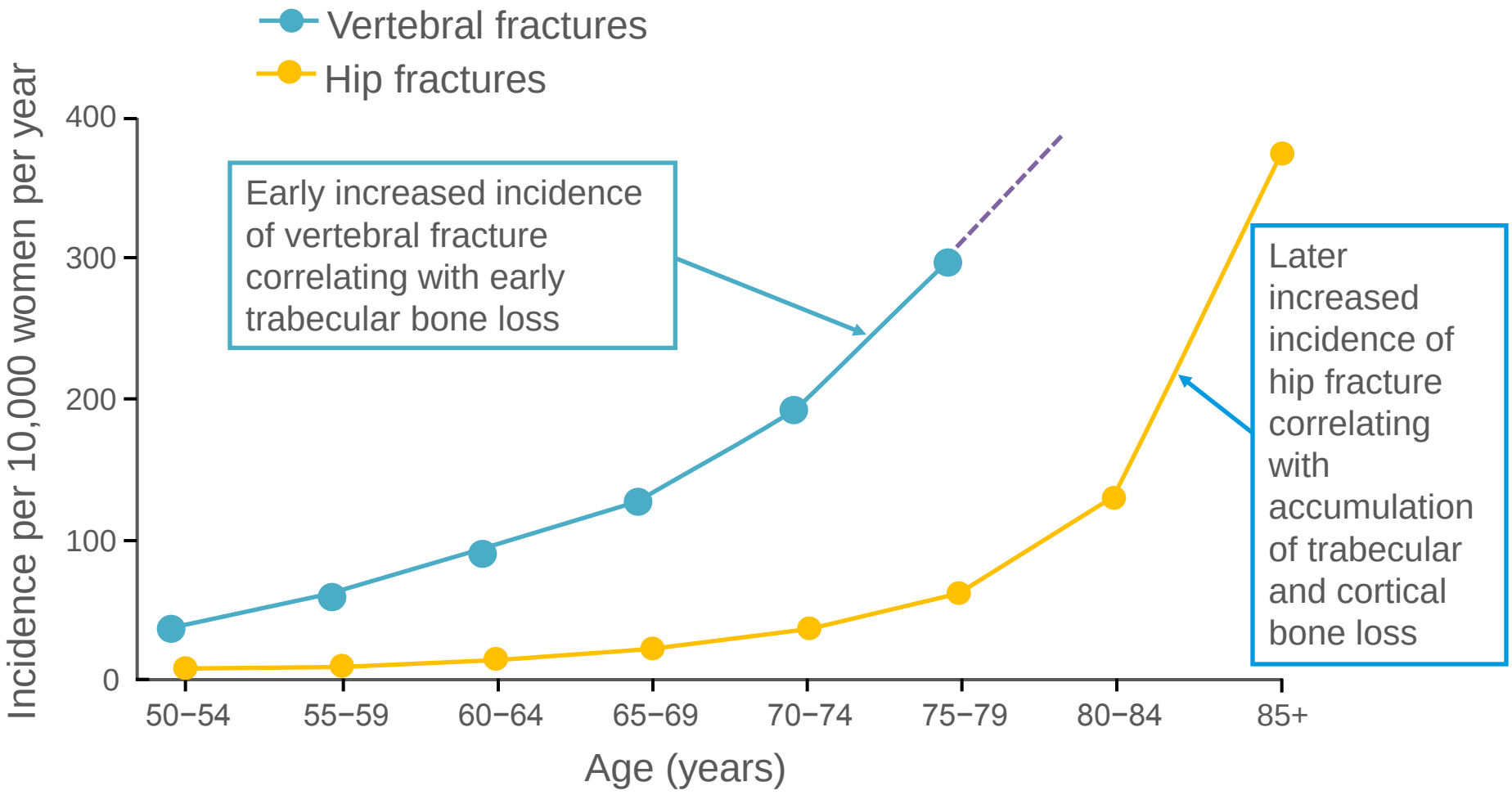
- Fall from a standing height (i.e. on the ice)
- Fall from a sitting position
- Fall from a supine position (bed or reclining deck chair < 1 metre high)
- Fall after having missed 1 to 3 steps in a staircase
- After a movement outside of the typical plane of motion or coughing



*Fragility fracture includes all bones, except skull and face, patella, hands and feet, cervical spine

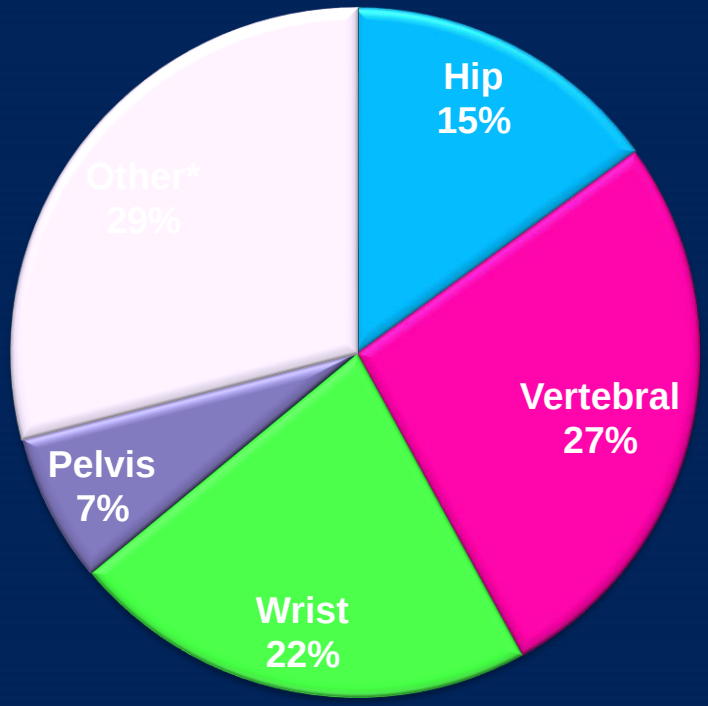
1. Bessette L, et al. Contemp Clin Trials. 2008; 29:194-210.
2. Brown JP, et al. J Bone Miner Res. 2007;23(Suppl 1):M350.

As Trabecular and Cortical Bone Loss Progresses, Vertebral and Hip Fracture Rates Increase Exponentially



Adapted from: Sambrook P & Cooper C. *Lancet* 2006;367:2010–2018.

Osteoporotic Fracture Incidence in Women over 50 Years of Age

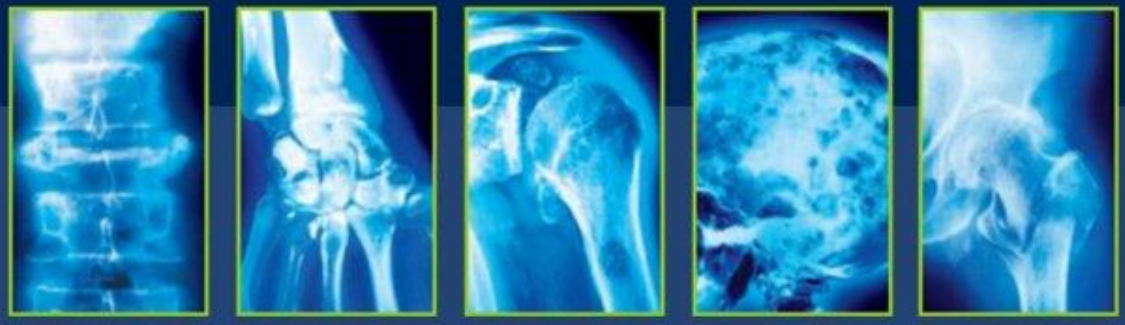


≥ 50% of fractures occur at the spine, wrist, or hip and are associated with significant morbidity[2,3, 4]

*Includes clavicle, humerus, femur, tibia/fibia, and hands/fingers.

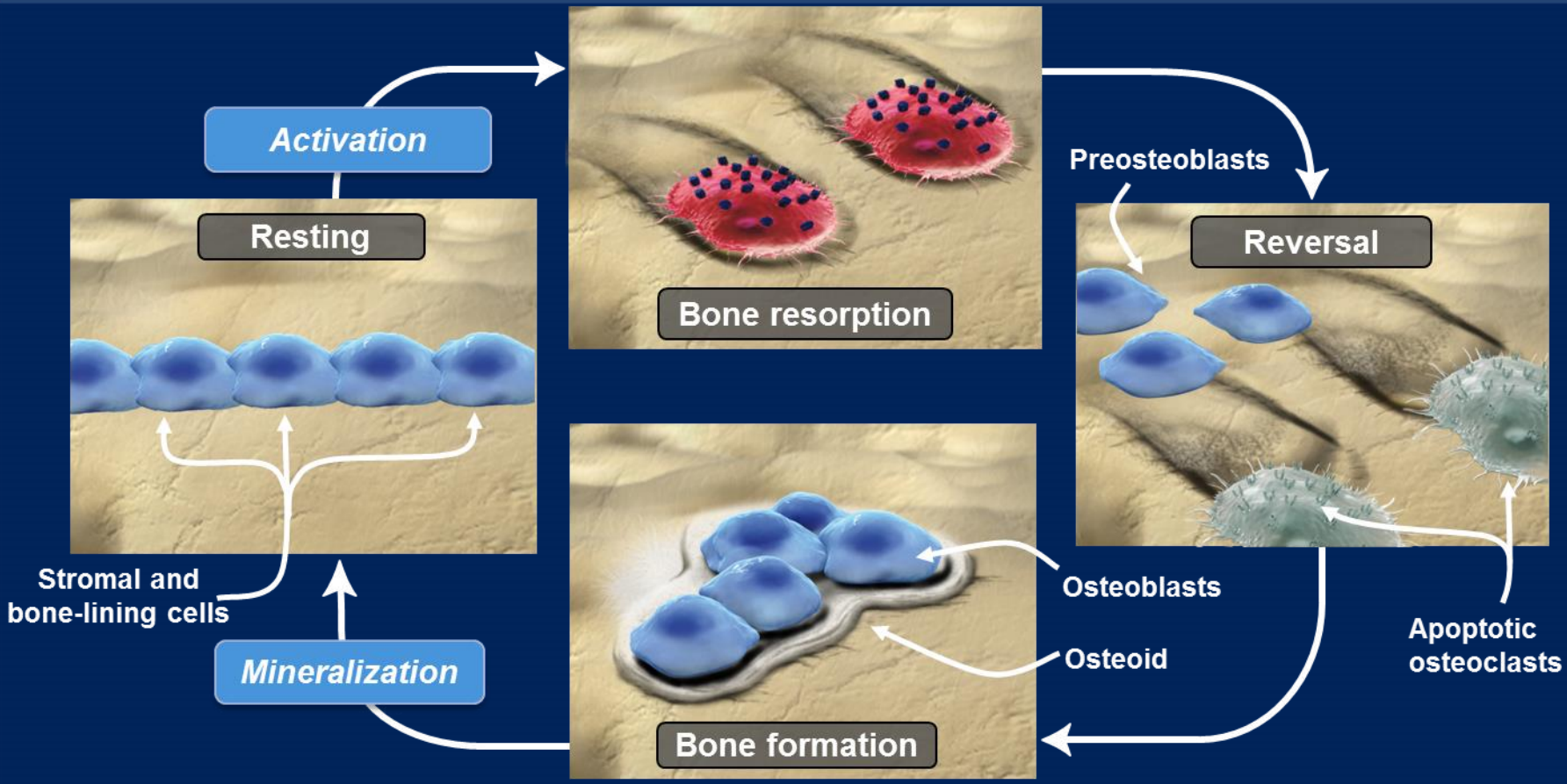
Adapted from: Burge R, et al. *J Bone Miner Res*. 2007;22:465-475.

1. Watts NB, et al. *Endocr Pract*. 2010;16:1-37. 2. Hajcsar EE, et al. CMAJ 2000, 163:819-822.; 3. Cooper C. Am J Med. 1997:103:12S-19S; 4. Jean et al . JBMR 2013; 28:360-71.



The Role of RANK Ligand in Bone Remodeling

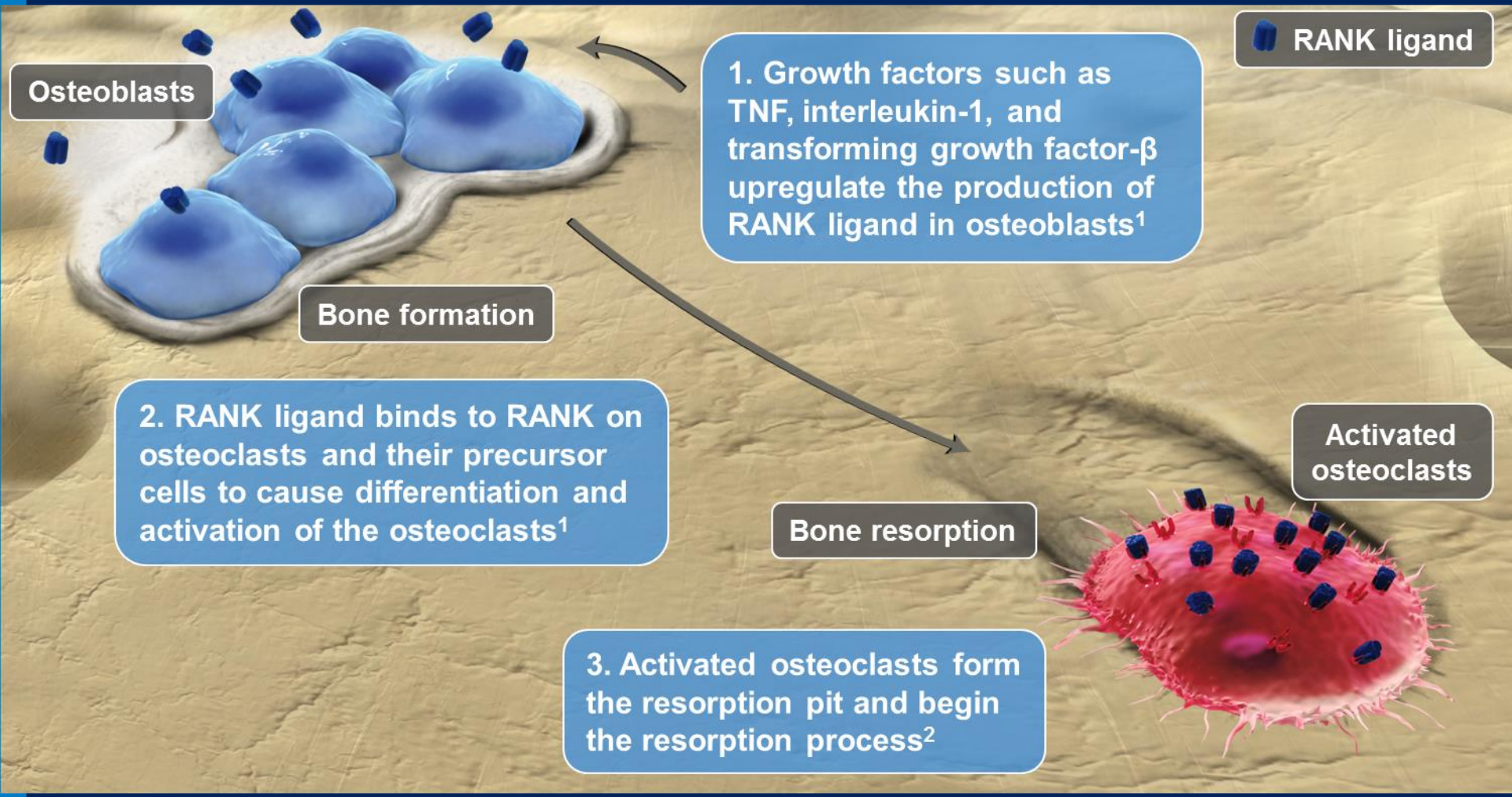
Normal Physiology Requires a Balance Between Bone Resorption and Formation in the Mature Adult



When bone turnover is increased, bone loss dominates

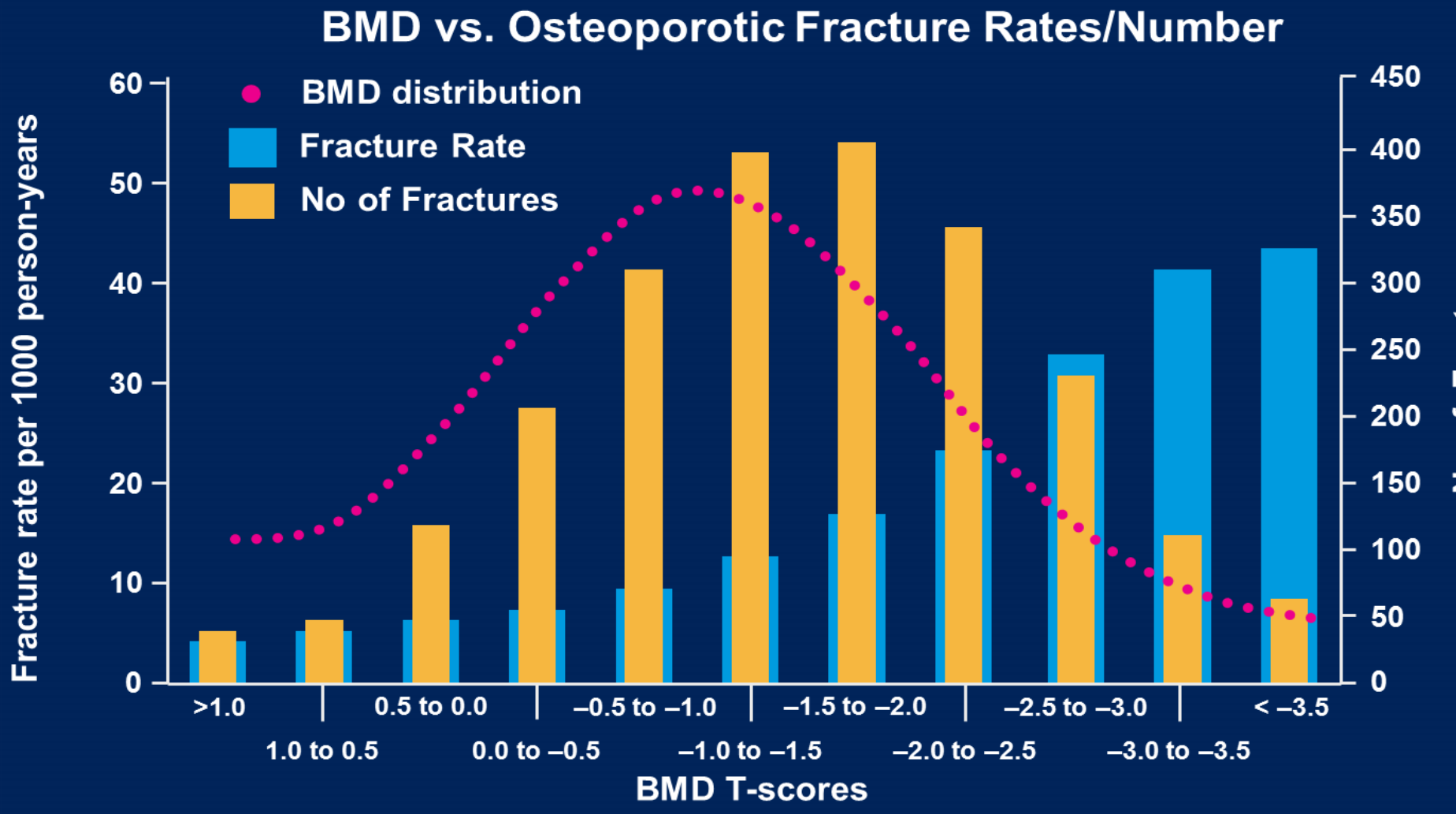
Adapted from: Baron R. In: Favus MJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*; 2003:1-8. Raisz LG. *J Clin Invest*. 2005;115:3318-3325.

RANK Ligand Is an Essential Mediator of Osteoclast Formation, Function, and Survival



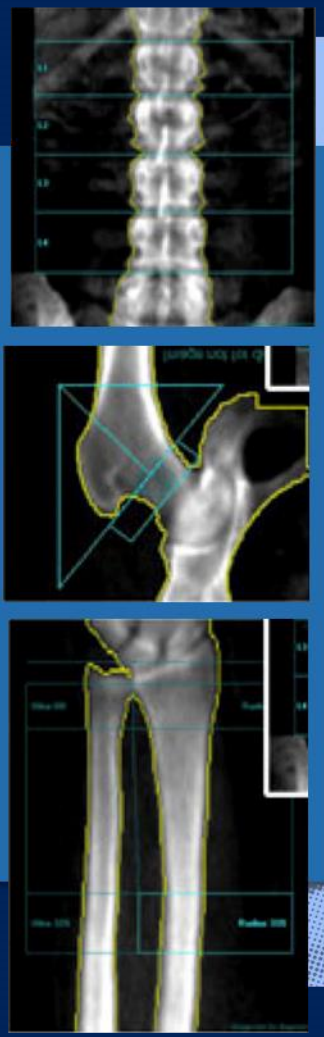
1. Adapted from: Boyle WJ, et al. *Nature.* 2003;423:337-342.
2. Roodman GD. *N Engl J Med.* 2004;350:1655-1664.

BMD and Fracture: More to the Story



Adapted from Siris ES, et al. *JAMA*. 2001;286:2815-22.

BMD is Not the Sole Predictor of Fracture Risk



60%

of women with fractures have *non-osteoporotic* bone mineral density (T-score >-2.5)

Adapted from Siris ES, et al. JAMA. 2001; 286:2815-22.

How do I determine my patient's fracture risk?

When to do a BMD:
2010 Osteoporosis Canada Clinical Practice Guidelines[1]

Aged ≥ 65 years	Aged 50-64 years	Aged < 50 years
Everyone	One or more risk factors for fracture: • Fragility fracture after age 40 • Parental hip fracture • Vertebral fracture or osteopenia identified on radiography • Medication with high risk of bone loss (i.e. steroids) • Smoking, alcohol (≥ 3/d) • Disorders associated with osteoporosis (i.e. RA) • Low weight or major weight loss	2°causes of osteoporosis (ie, malabsorption) Prior fragility fracture Medication with high risk of bone loss

1. Papaioannou A, et al CMAJ 2010;182:1864-1873.

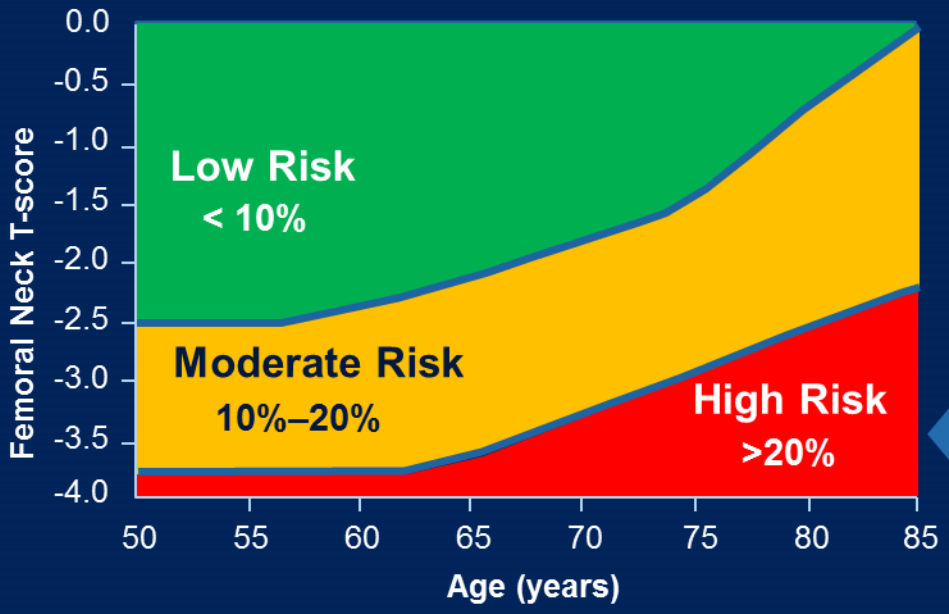
Calculating 10-Year Absolute Fracture Risk for Postmenopausal Women: CAROC

10-year absolute fracture risk in treatment naïve women combining femoral neck T-score and age[1]

Increases to the next risk category

Prior fragility fracture after age 40

Prolonged corticosteroid therapy*



Prior hip or vertebral fracture, or >1 non-vertebral fragility fracture

Lumbar spine or total hip T-score ≤ -2.5: consider the individual to be at least at moderate risk

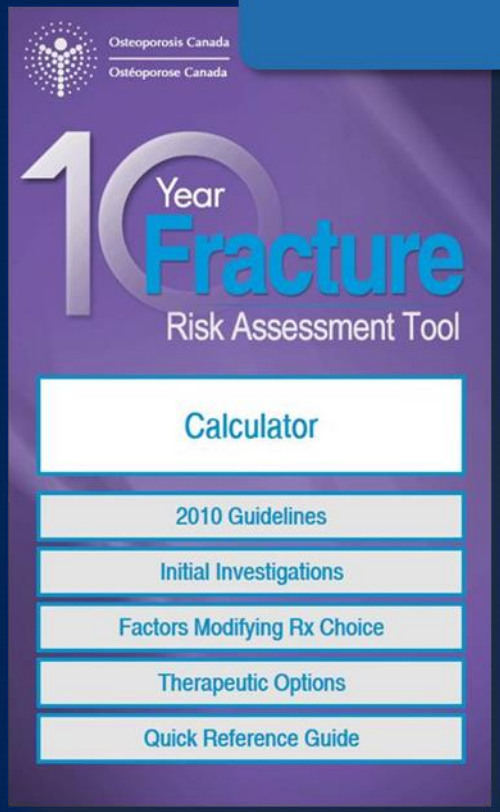
Calibrated using Canadian fracture data and have been directly validated in Canadians[2]

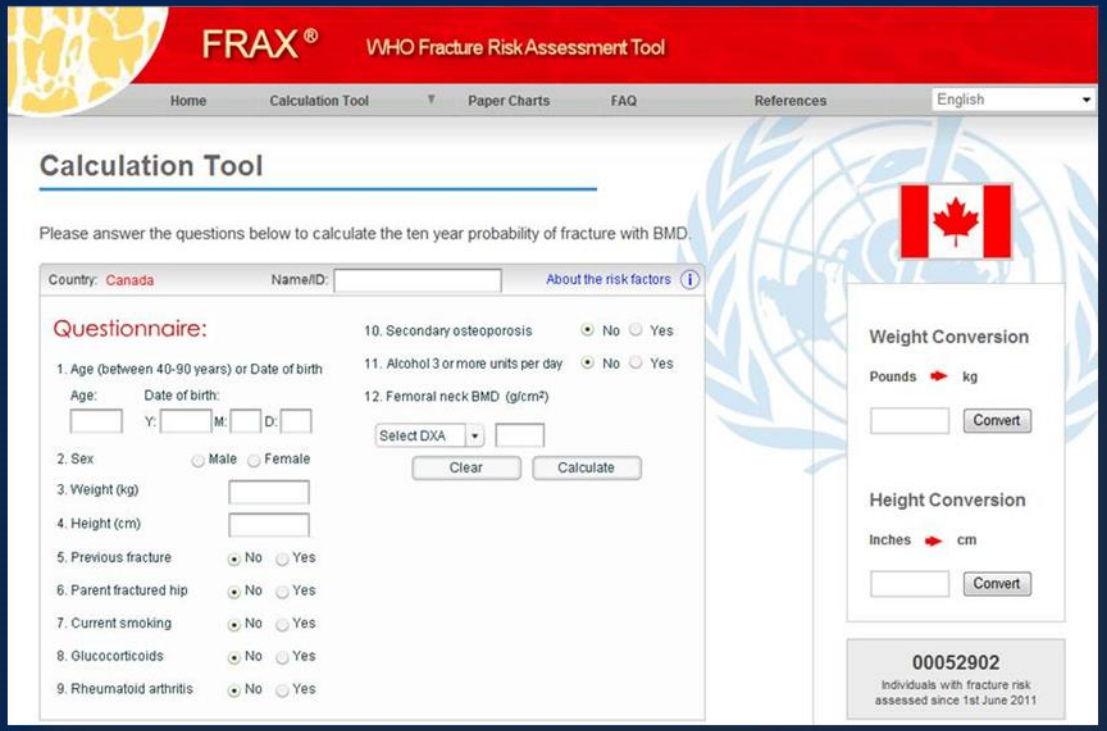
*At least three months cumulative use during the preceding year at a prednisone-equivalent dose ≥ 7.5 mg daily.

1. Papaioannou A, et al. *CMAJ*. 2010;182:1864-1873. 2. Leslie WD, et al. *J Bone Miner Res*. 2009;24:353-360.

There are Two Tools Available for Fracture Risk Assessment

These tools incorporate other clinical risk factors for fracture in addition to BMD





FRAX can be used without a BMD

1. OC Guidelines tool available at: http://www.osteoporosis.ca/multimedia/FractureRiskTool/index.html#/Home.
2 FRAX® tool available at: http://www.shef.ac.uk/FRAX/tool.jsp 3. National Osteoporosis Foundation guidelines: www.nof.org/professionals/NOF_Clinicians_Guide.pdf

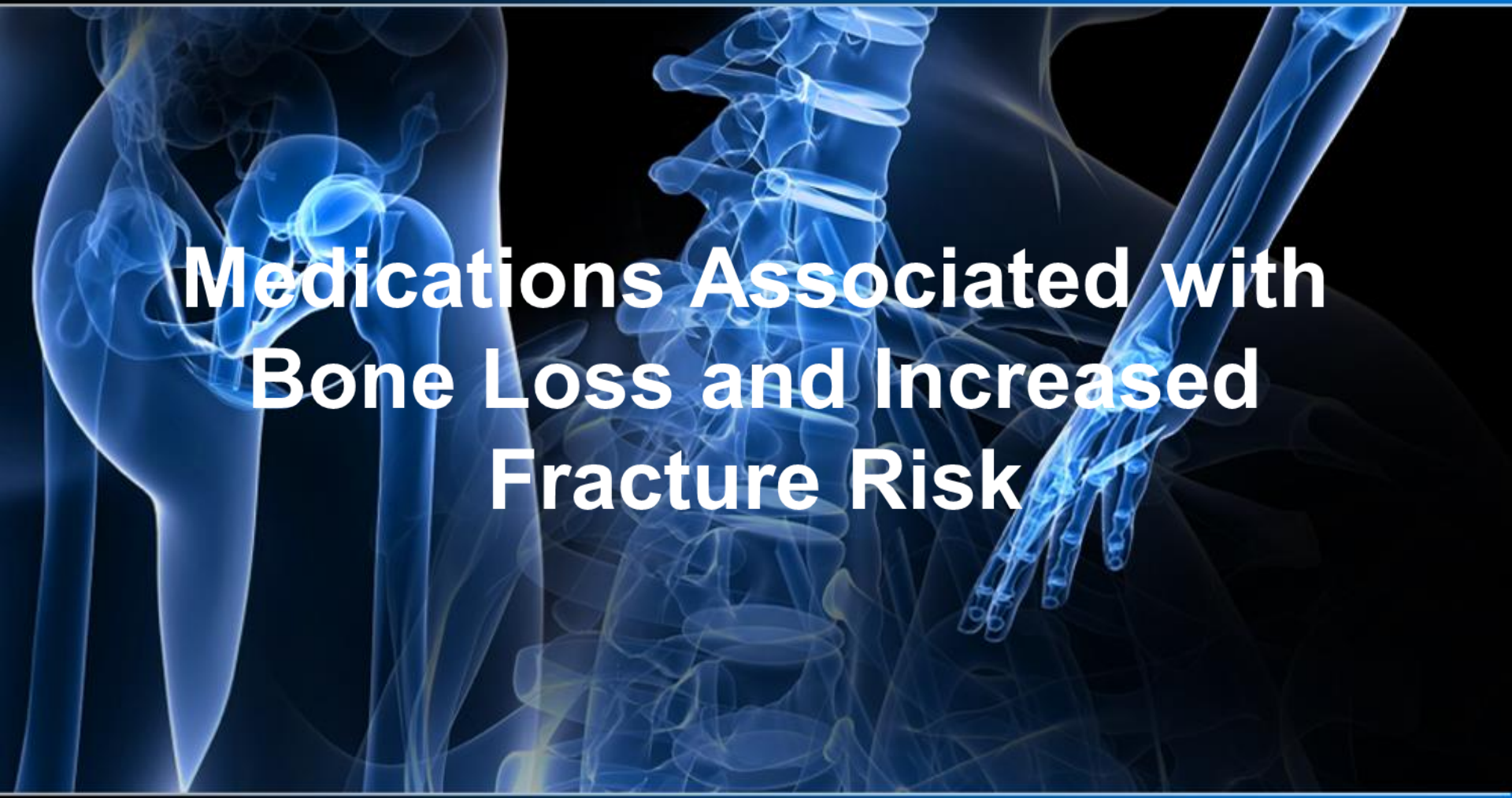
Risk Factors for Fracture Risk Assessment

CAROC*	FRAX®‡
Risk Factors: • Sex • Age • BMD • Fragility fracture after 40 • Systemic glucocorticoid use (≥ 3 months)†	**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

- *Both tools are recognized by Osteoporosis Canada as validated methods for the prediction of fracture risk, with 90% concordance between results*
- **CAROC may add simplicity, requiring only 5 parameters*
- *FRAX® can be used in the absence of BMD*
- *‡FRAX® has country-specific tools; ensure the Canadian version is used*

*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.

Papaioannou A, et al. *CMAJ*. 2010;182:1864-1873.



Medications Associated with Bone Loss and Increased Fracture Risk

RML Class D CA-162SA-103355

Glucocorticoid-induced Osteoporosis (GIOP)

- Glucocorticoids (GCs) are widely used to suppress inflammation and to treat various immune-mediated diseases[1]
- Glucocorticoid use is associated with deleterious effects on bone, leading to GIOP[1]

Immune-mediated Diseases Treated With Glucocorticoids[1]	
• Rheumatoid Arthritis	• Lung Diseases (eg, COPD, Emphysema, Asthma)
• Polymyalgia Rheumatica	• Inflammatory Bowel Diseases
• Systemic Lupus Erythematosus	• Chronic Liver Disease
• Vasculitis	• Skin Diseases
• Organ Transplantation	

1. Rizzoli, R et al. *Calcif Tissue Int.* 2012;91:225-243

Calculating 10-Year Absolute Fracture Risk for Postmenopausal Women: CAROC

10-year absolute fracture risk in treatment naïve women combining femoral neck T-score and age[1]

Increases to the next risk category

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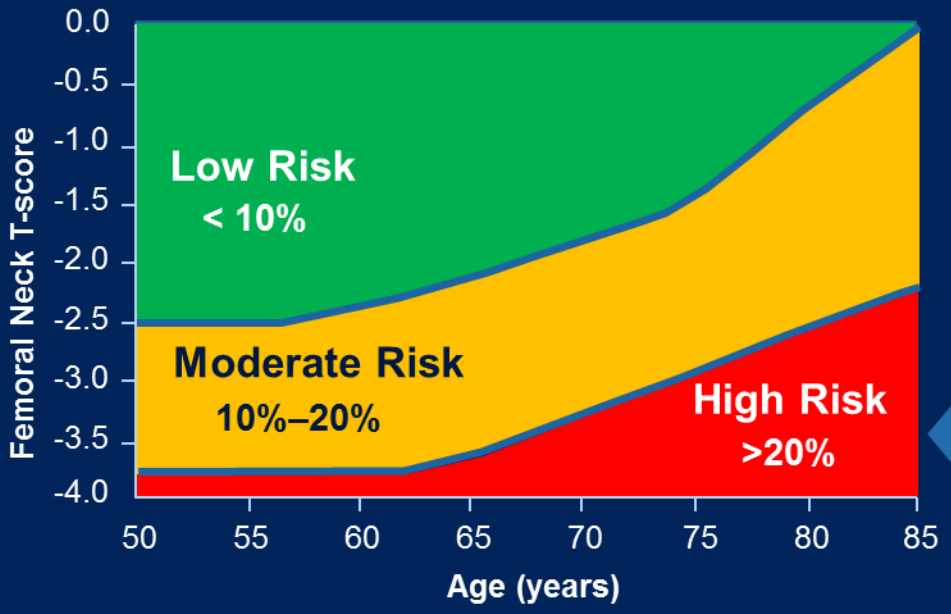

Prior hip or vertebral fracture, or >1 non-vertebral fragility fracture

Lumbar spine or total hip T-score ≤ -2.5: consider the individual to be at least at moderate risk

Calibrated using Canadian fracture data and have been directly validated in Canadians[2]

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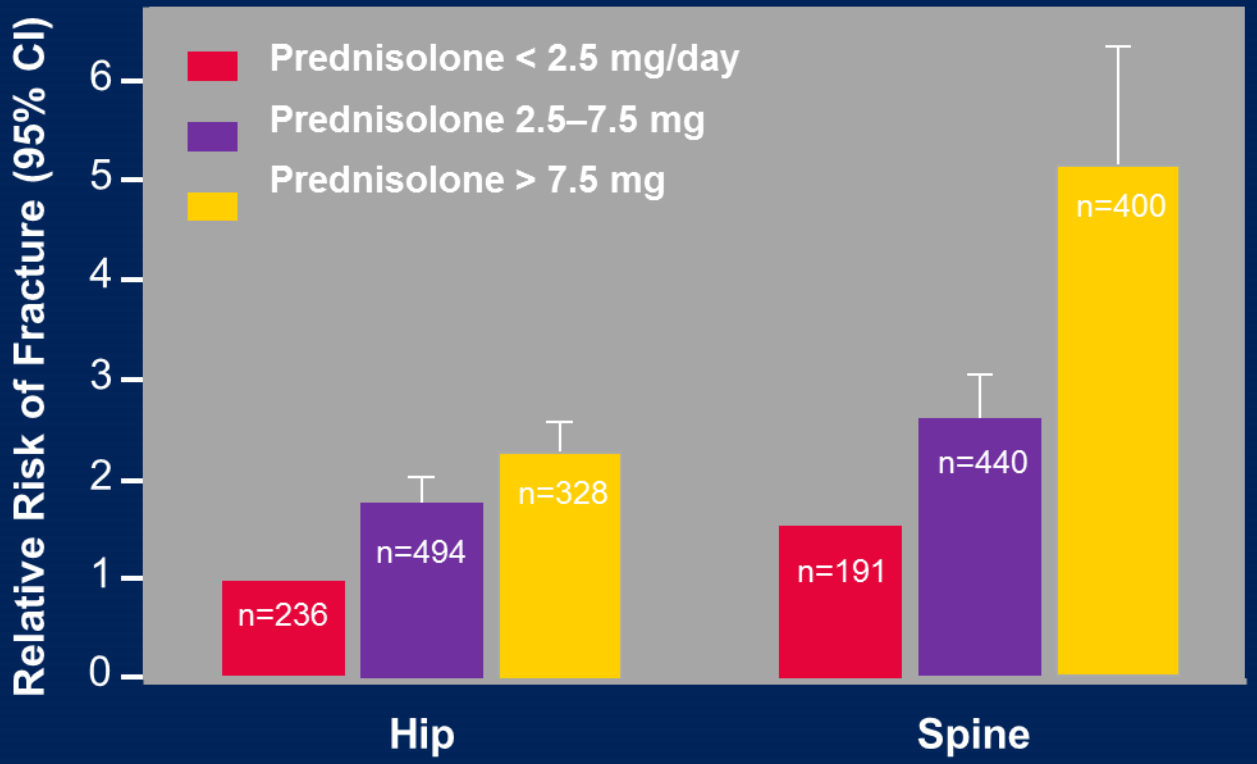
1. Papaioannou A, et al. *CMAJ*. 2010;182:1864-1873. 2. Leslie WD, et al. *J Bone Miner Res*. 2009;24:353-360.

Fracture Risk Increases With Increasing Daily Dose of Glucocorticoids



Adapted from van Staa TP et al. $P<0.05$ for all.

In patients taking ≥7.5 mg/day prednisolone or its equivalent, greatest increase in risk is seen for vertebral fracture (RR 2.92, 95% CI, 2.0 to 4.3)[1,2]

1. van Staa TP, et al. *J Bone Miner Res* 2000;15:933–1000
2. Lekamwasam S, et al. *Osteoporos Int*. 2012;23:2257-2276

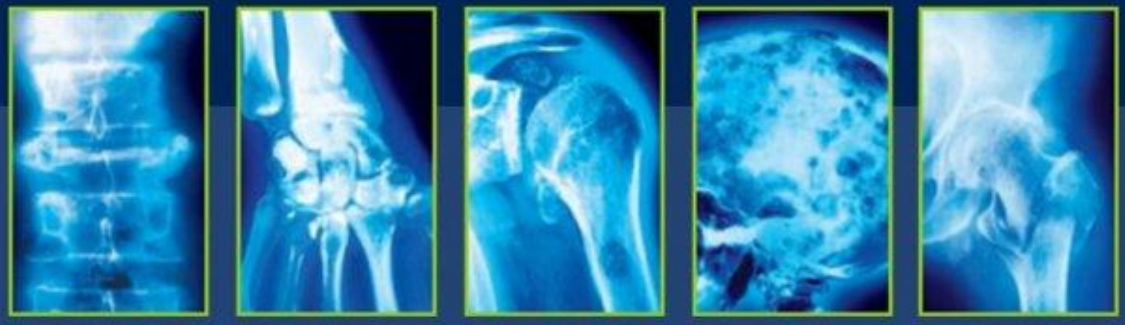
Summary: GIOP

- GIOP is the most common form of secondary osteoporosis[1]
- Up to 4.6% of postmenopausal women world-wide currently take oral glucocorticoids[2]
- GIOP is characterized by reduced bone formation and increased bone resorption, driven by increased apoptosis of osteocytes and osteoblasts and decreased apoptosis of osteoclasts[2]
- Fracture risk increases with increasing daily dose of steroids[3]
- GC use is associated with increased fracture risk independent of BMD and prior fracture[4]

1. Lekamwasam S et al. *Osteoporos Int*. 2012;23(9):2257-76. 2. Rizzoli, R. et al. *Calcif Tissue Int.* 2012;91:225-243. 3. van Staa TP et al. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res* 2000;15:933–1000 . 4. Kanis JA et al. *J Bone Miner Res*. 2004;19:893–899.

Prevention of GIOP

- Activity and fall prevention
- Ensure total calcium intake of 1500mg and at least 1000 unit Vitamin D3 daily’
- The bisphosphonates alendronate and risedronate have been approved for prevention of bone loss and fractures in patients being treated with long term glucocorticoid therapy (> 3 months per year at a equivalent dose of greater than Prednisone 7.5mg per day)



Cancer Treatment-Induced Bone Loss Due to Adjuvant Aromatase Inhibitor Therapy in Nonmetastatic Breast Cancer

Aromatase Inhibitors (AIs)

Aromatase Inhibitors (AIs)

- AIs are anti-estrogen agents used for the treatment of estrogen receptor positive breast cancer in postmenopausal women
- AIs inhibit the cytochrome P450 CYP-19 enzyme necessary to convert androgens to estrogens
- Because AIs result in rapid depletion of estrogen they are associated with significant bone loss and increased fracture risk

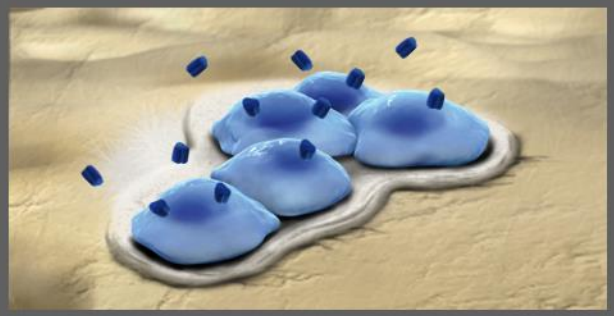
Rinaldi RZ. *Curr Osteoporos Rep*. 2013;11:61–64

Pathophysiology of AI Therapy-Induced Bone Loss

AI

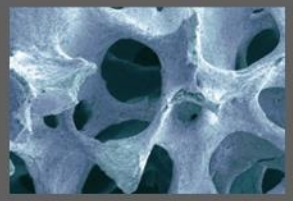
Androgen → ↓ Estrogen

↓ Estrogen → ↑ RANK Ligand



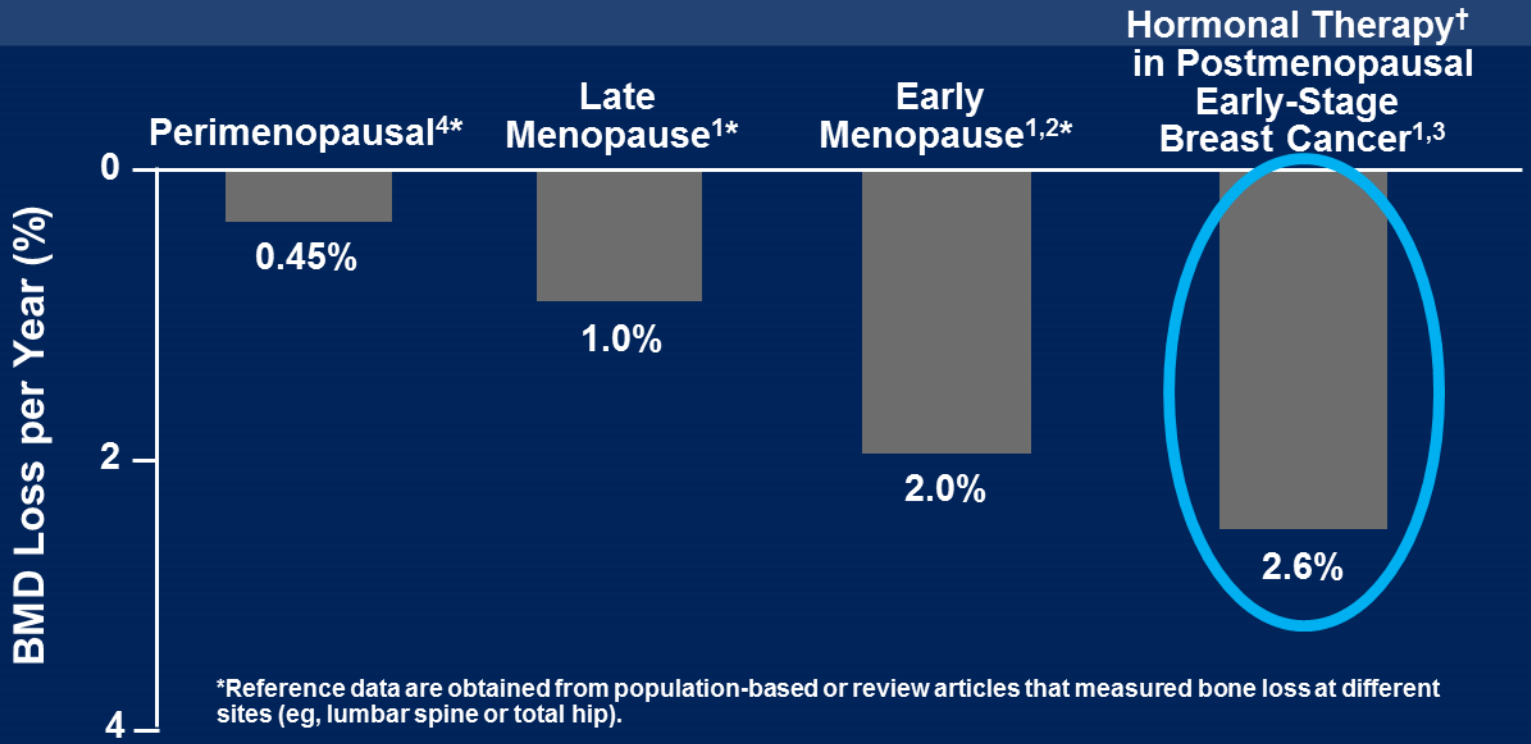
↑ RANK Ligand → ↑ Osteoclast # and Activity

↑ Osteoclast # and activity → ↑ Bone Resorption → ↓ Bone Strength



Michaud LB, Goodin S. *Am J Health Syst Pharm.* 2006;63:419-430.
Brufsky AM. *Oncologist.* 2008;13:187-195.
Shevde NK, et al. *Proc Natl Acad Sci U S A.* 2000;97:7829-7834.
Raisz LG. *J Clin Invest.* 2005;115:3318-3325.

Bone Loss Is Seen in Different Populations Due to Natural and Iatrogenic Causes



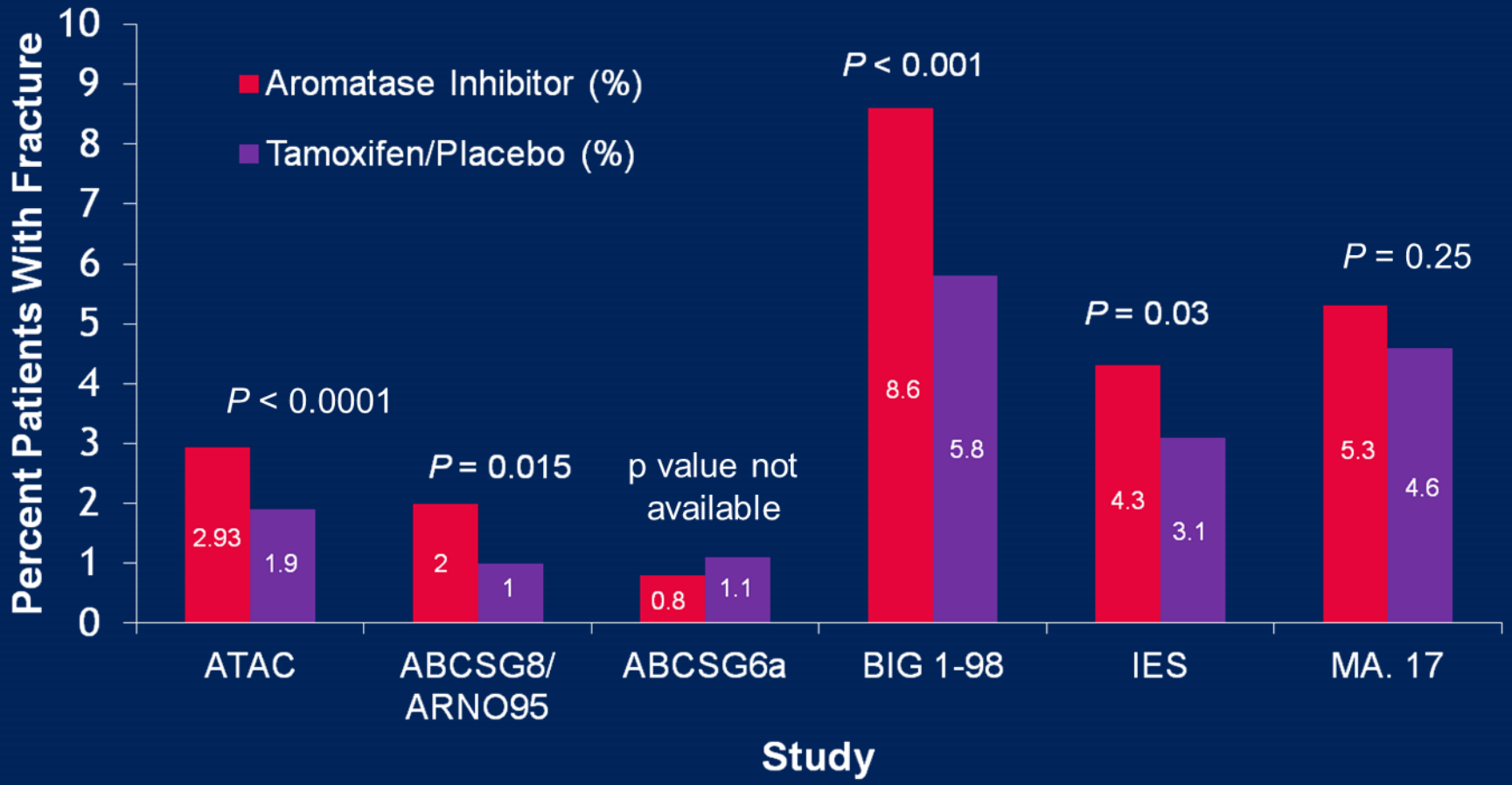
*Reference data are obtained from population-based or review articles that measured bone loss at different sites (eg, lumbar spine or total hip).

- Hormone-ablation therapies for breast cancer can potentially lead to significant bone loss

† Hormone therapy consisted of the AI anastrozole.

1. Higano CS. *Nat Clin Pract Urol.* 2008;5:24-34.
2. Kanis JA. *Osteoporosis*; 1997:22-55.
3. Eastell R, et al. *J Bone Miner Res.* 2006;21:1215-1223.
4. Recker R, et al. *J Bone Miner Res.* 2000;15:1965-1973.

Several Studies Demonstrate an Increased Incidence of Fracture Among AI Users Treated for Breast Cancer



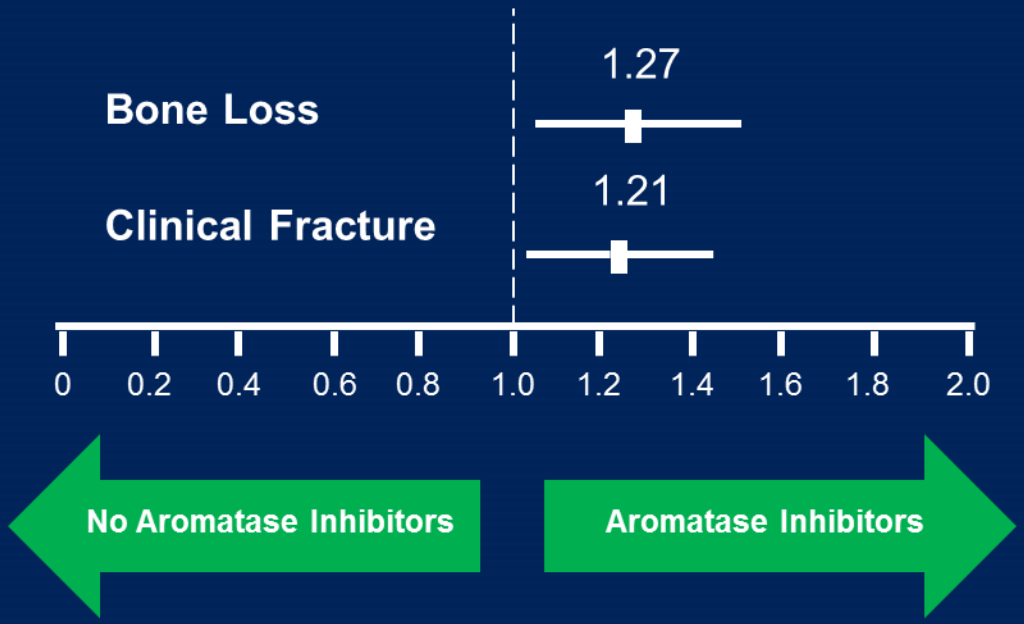
ATAC=Arimidex, Tamoxifen, Alone or in Combination; ABCSG=Austrian Breast and Colorectal Cancer Study Group; ARNO=Arimidex-Nolvadex; BIG=Breast International Groups; IES=International Exemestane Study; MA=Massachusetts

Adapted from Gaillard and Stearns. *Breast Cancer Research.* 2011;13:205-216

AIs Use is Associated with Bone Loss and Increased Fracture Risk

Retrospective Analysis of a Patient-Claims Database

27% increased risk of bone loss
21% increased risk of clinical fracture



Adapted from Brufsky et al. *The Oncologist.* 2008;13:187-195.

International Osteoporosis Foundation Guidelines regarding Cancer Therapy Induced Bone Loss April 26 , 2017

- Clinical trials have shown an approximate 10% increase in ABSOLUTE fracture risk for women on AI therapy
- Other real world studies suggest the risk may be significantly higher than 10%
- Breast cancer patients hospitalized for a fracture have higher risk of death compared to breast cancer patients without fracture
- Compelling reasons for all women on AI therapy to receive early assessment and treatment
- In ALL patients initiating AI treatment , fracture risk should be assessed and recommendations given in regards to exercise , and calcium/Vitamin D supplementation

IOF Guidelines – CTIBL (cont'd)

- Bone directed therapy should be recommended for the DURATION of AI therapy in ALL patients with :

  T-score < 2.0 SD

  T-score < 1.5 with 1 additional risk factor
  OR
  2 or more risk factors

  (age > 65 , BMI < 20kg/m , personal history of fragility fracture after age 50 , family history of hip fractures , oral corticosteroid therapy > 6 months , cigarette smoking) **without** BMD measurement

IOF Guidelines – CTIBL (cont'd)

- Those with T-score > -1.5 SD and no risk factors should be managed based on bone loss the 1st year
- Efficacy of therapy and compliance should be assessed by BMD after 12-24 months on therapy

Calcium and Vitamin D dosing

- Calcium – 500 to 1200mg/day (based on estimated dietary intake with goal to reach total daily intake of 1200-1500 mg per day

- Vitamin D – deficiency increases the risk of cancer mortality and secondary hyperparathyroidism related to low Vitamin D reduces the anti-resorptive effect of bisphosphonates.

  In conjunction with calcium , Vitamin D at doses of 700-800u/day results in a 20% reduction in non-vertebral fractures and 18% reduction in hip fractures in women without cancer (no data for those with cancer)

Canada 2010 Guidelines for First-line Therapies in Post-menopausal Women with Osteoporosis

Based on GRADE A Evidence

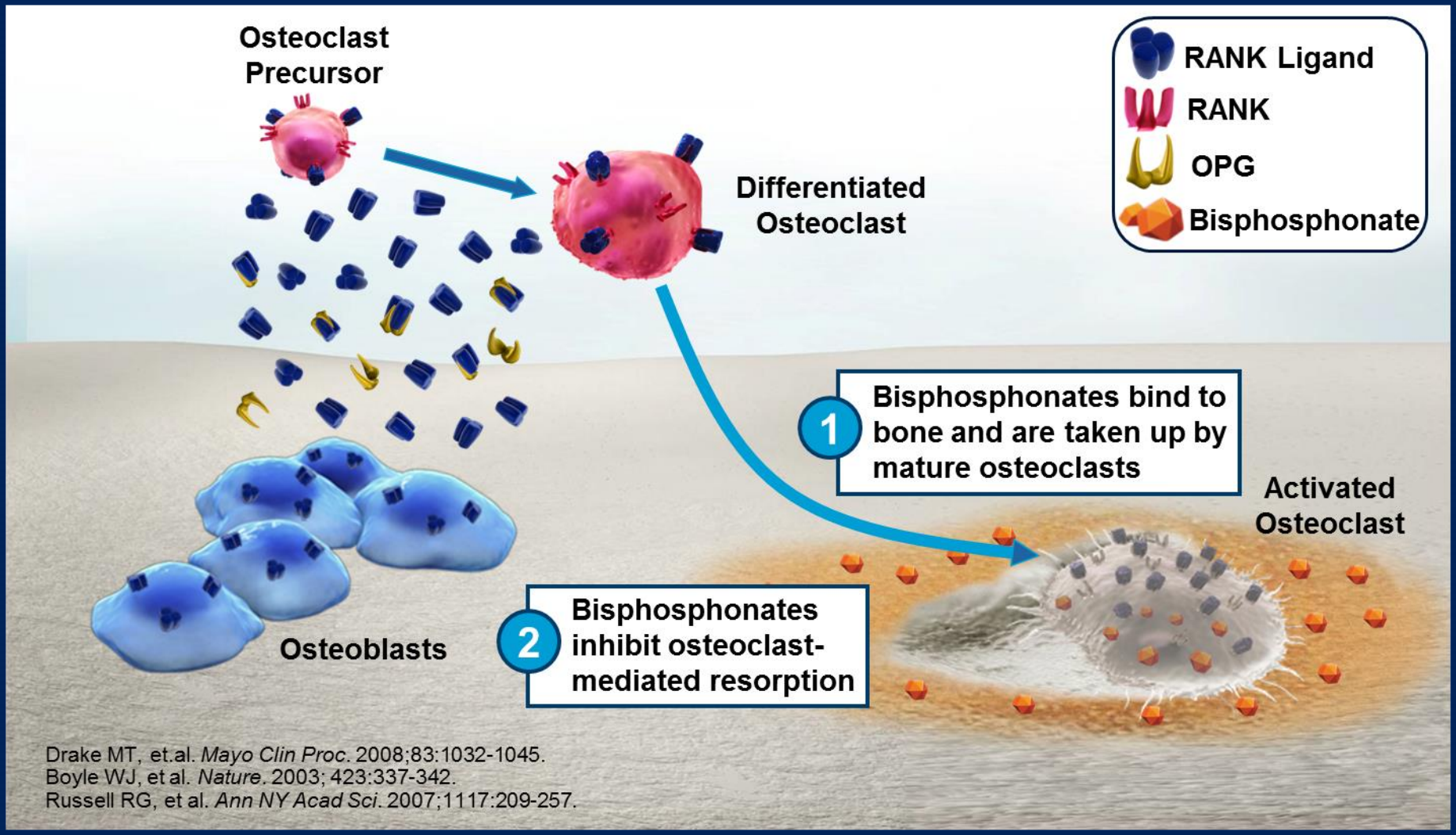
Type of Fracture	Antiresorptive Therapy						Bone Formation Therapy
	Bisphosphonates						
	Alendronate	Risedronate	Zoledronic Acid	Denosumab	Raloxifene	Estrogen* (Hormone Therapy)	Teriparatide
Vertebral	✓	✓	✓	✓	✓	✓	✓
Hip	✓	✓	✓	✓	-	✓	-
Non-vertebral†	✓	✓	✓	✓	-	✓	✓

*Can be used as first-line therapy in women with menopausal symptoms.

† Non-vertebral fractures are a composite endpoint including hip, femur, pelvis, tibia, humerus, radius, and clavicle.

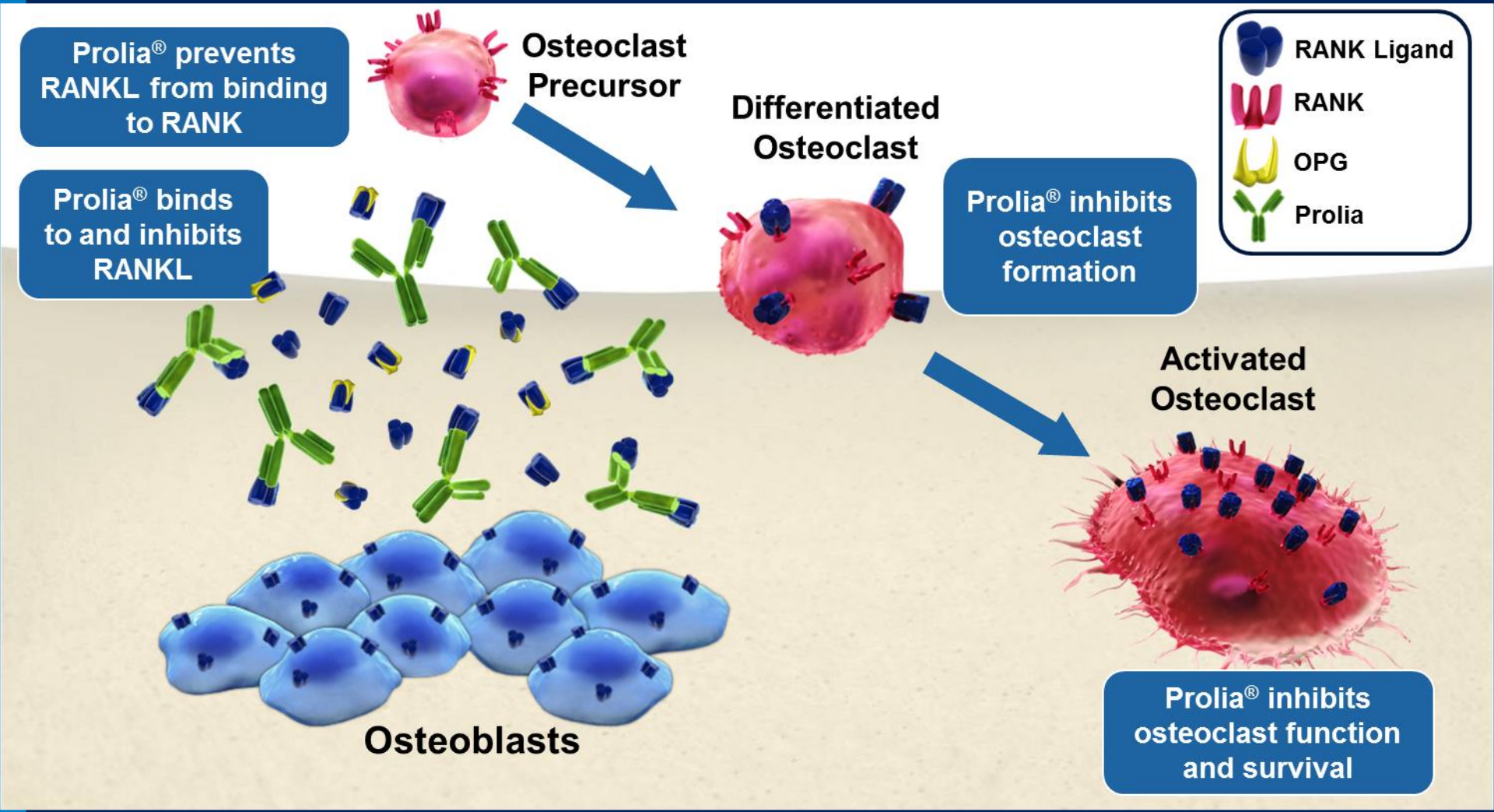
Adapted from Papaioannou A, et al. *CMAJ*. 2010.

Bisphosphonates Bind to Bone and Inhibit Osteoclasts at the Bone Surface



Drake MT, et.al. *Mayo Clin Proc*. 2008;83:1032-1045.
Boyle WJ, et al. *Nature*. 2003; 423:337-342.
Russell RG, et al. *Ann NY Acad Sci*. 2007;1117:209-257.

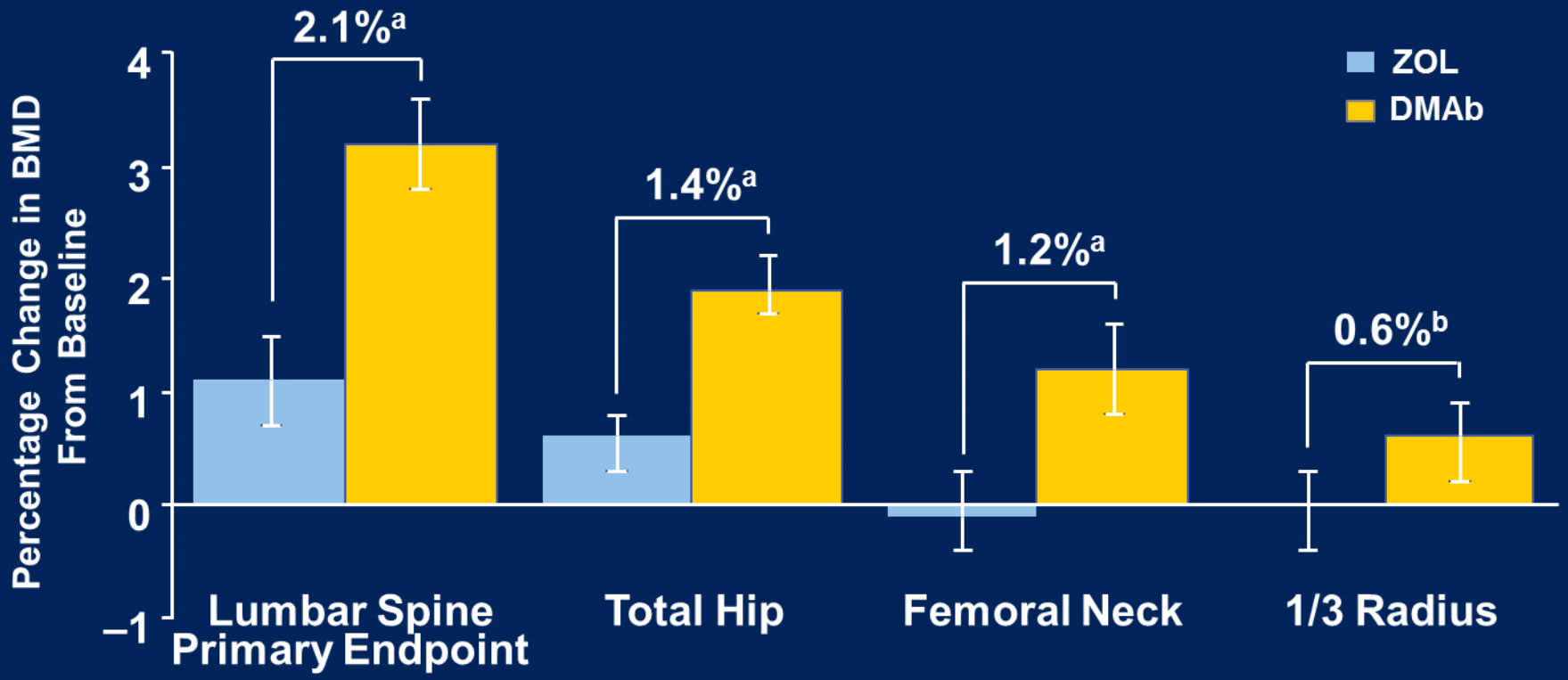
Prolia® (denosumab) Inhibits Osteoclast Formation, Function and Survival



Prolia® (denosumab) product monograph, Amgen.

Denosumab vs Zoledronic Acid in PMO, Previously Treated With Oral Bisphophonates: Study Results

Percentage Change From Baseline in BMD at Month 12



[a]$p < 0.0001$ for superiority; [b]$p = 0.0184$ for superiority.
Data displayed are least-squares means and 95% CIs based on an ANCOVA model adjusting for treatment, serum CTX stratification variable (< 300 pg/mL vs 300–500 pg/mL), baseline BMD, DXA machine type, and baseline value-by-DXA machine type interaction.
BMD = bone mineral density; DMAb = denosumab; ZO = zoledronic acid.

Miller PD, et al. *J Clin Endocrinol Metab*. 2016;101(8):3163-3170.

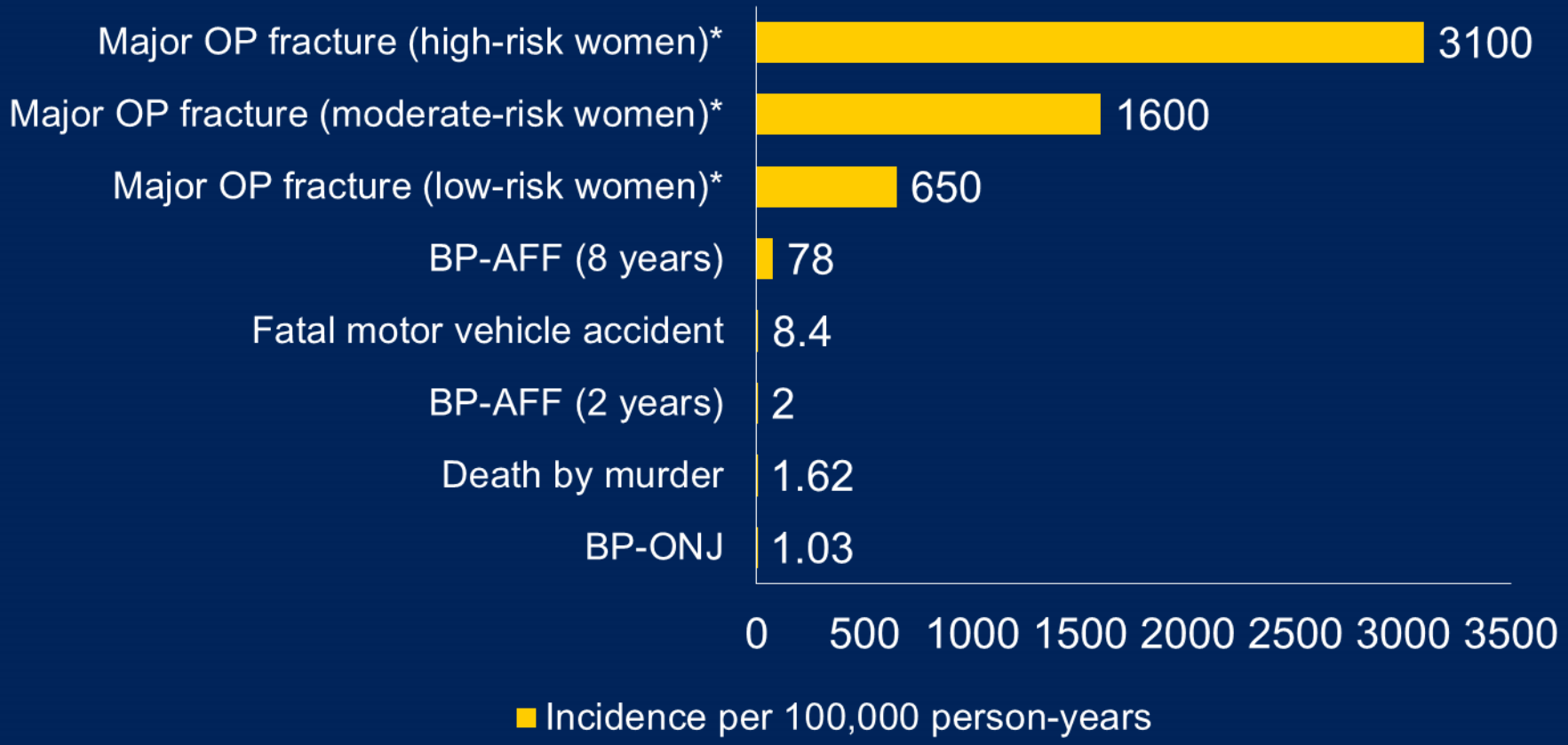
IOF CTIBL Guidelines (April 26 , 2017) - Drug Therapy

- Recommendations based on current evidence !

  6 monthly denusomab (Prolia) OR yearly zolendronate for the duration of AI therapy to prevent AI induced bone loss in postmenopausal women on adjuvant AI therapy

- Zolendronate recommended when effects on disease recurrence is the priority (because of the decreased incidence of bone recurrence and breast cancer specific mortality)
- Denusomab recommended when fracture is the dominant concern

What is the "Real-World" Risk of ONJ and Atypical Fractures?



OP = osteoporotic; BP-AFF = bisphosphonate-associated atypical subtrochanteric and diaphyseal femur fracture; BP-ONJ = bisphosphonate-associated osteonecrosis of the jaw.
*10-year risk of major osteoporotic fracture by Canadian FRAX.

Adapted from: Brown JP, et al. *Can Fam Physician*. 2014;60:325-333.

Summary: AIs

- AIs are anti-estrogen agents used in the treatment of estrogen receptor positive breast cancer in postmenopausal women[1]
- AIs decrease aromatase activity and inhibit the conversion of adrenal androgens to estrogen, which reduces circulating and tissue levels of estrogen[2]
- Lack of estrogen leads to increased RANK ligand activity and an overall increase of mature osteoclasts, which results in increased bone resorption[2]
- AI users are at an increased risk for fracture and bone loss[3,4]

1. Rinaldi RZ. *Curr Osteoporos Rep*. 2013;11:61–64. 2. Michaud LB, Goodin S. *Am J Health Syst Pharm*. 2006;63:419-430. 3. Gaillard and Stearns. *Breast Cancer Research* 2011;13:205-216. 4. Brufsky et al. *The Oncologist* .2008;13:187-195.

Bone Loss in Pre-menopausal Women with Breast Cancer

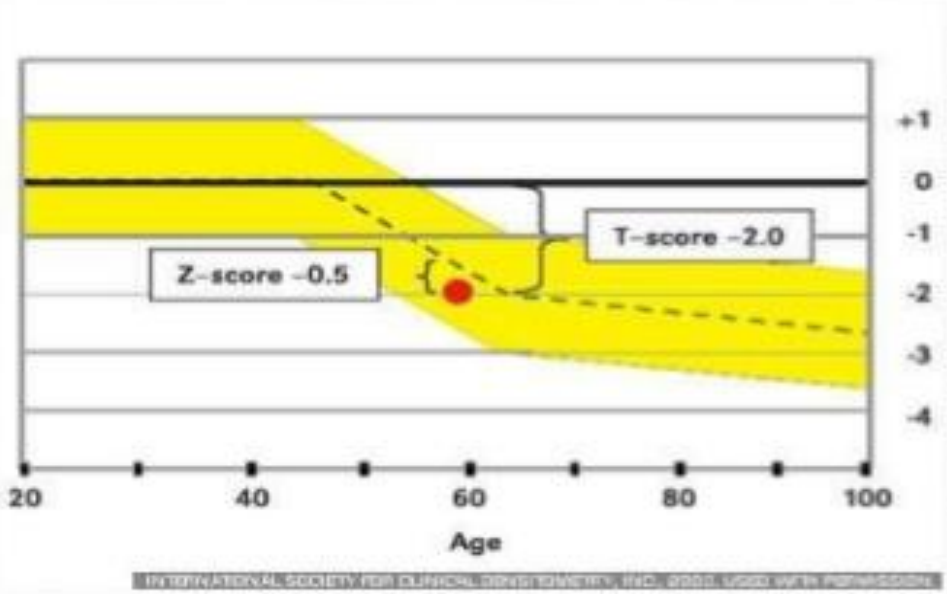
- Potential for bone loss during treatment is a significant unmet need requiring more study
- Available evidence suggests premenopausal women experience significant bone loss regardless of the anticancer regimen AND that rates of bone loss are further increased in many women experiencing temporary or permanent amenorrhea
- Baseline BMD not usually obtained and the CAROC and FRAX tools are designed to assess fracture in older healthy women.
- ISCD recommends use of Z score – represents the SD in BMD relative to the expected BMD for women of similar age

Bone Loss in Pre-menopausal Women with Breast Cancer

- Expert group recommendation – premenopausal women with Z-score < -2.0 or Z-score < -1.0 and an annual decrease of BMD of 5-10% should receive bisphosphonate therapy plus calcium and Vitamin D
- Most experience with IV zoledronic acid in doses of anywhere from 4mg IV every 6 months to 4 mg IV every 3 months. Studies report BMD remaining stable during treatment and improving after treatment done while women not treated had BMD loss at 1 year of 5.5% and 6.3% at 2 years

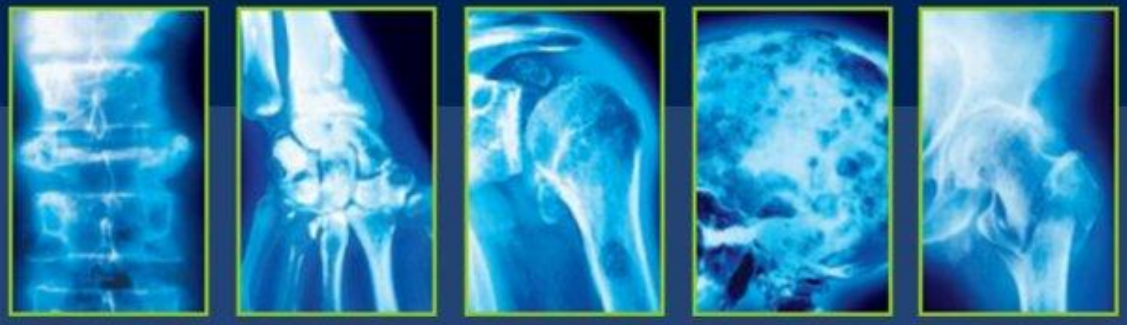
Another Report Card

- For example, if the T-score is -2.0, the BMD is lower than average by two standard deviations. If the Z-score is -0.5, your bone density is less than the norm for people your age by one-half of a standard deviation



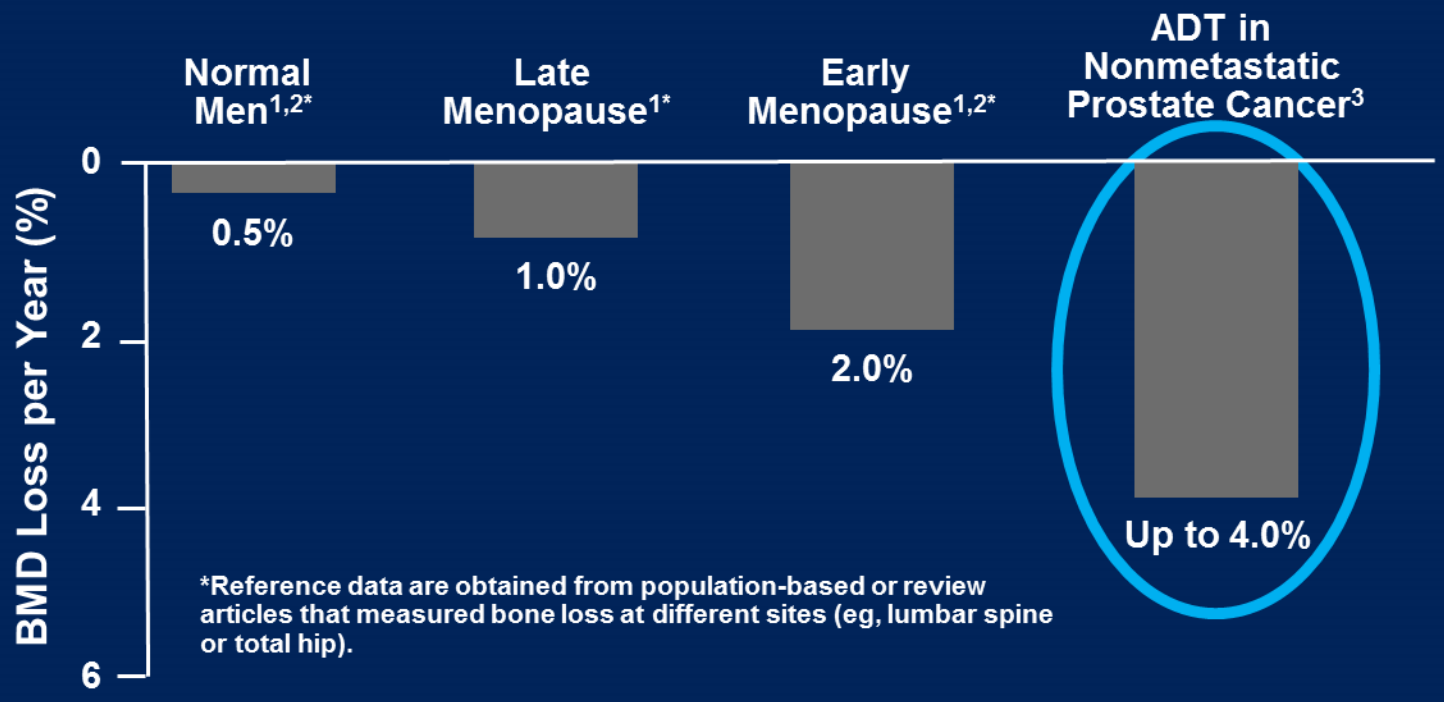
Bone Loss in Pre-menopausal Women with Breast Cancer

- ABCSG-12 study –in addition to sustained bone health in substudy results of overall study showed that compared to endocrine therapy alone adding zoledronic acid led to-
  Significant improved disease free survival (HR .64 , P=.01). Benefit maintained at median follow up of 64 months (HR 0.68 , P<.05) AND overall survival significantly increased (HR 0.66 , P<.05)
- Denosumab has not been evaluated in premenopausal women with breast cancer



Cancer Treatment-Induced Bone Loss due to Androgen-Deprivation Therapy in Nonmetastatic Prostate Cancer

Bone Loss Is Seen in Different Populations Due to Natural and Iatrogenic Causes



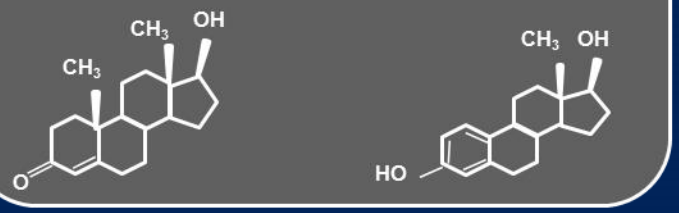
- Men receiving ADT lose up to 4.0% of bone mass in year 1[1,3]

1. Higano CS. *Nat Clin Pract Urol*. 2008;5:24-34.
2. Kanis JA. *Osteoporosis*; 1997:22-55
3. Greenspan SL, et al. *J Clin Endocrinol Metab*. 2005;90:6410-6417.

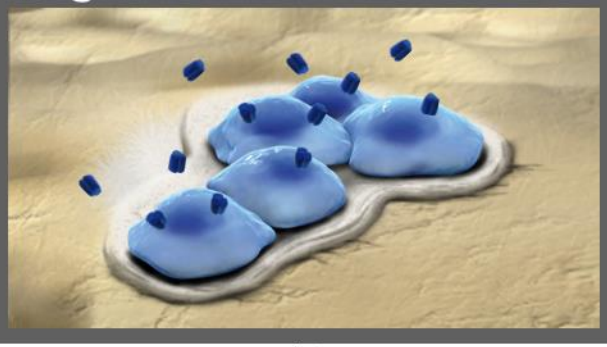
Pathophysiology of ADT-Induced Bone Loss

ADT

↓ Androgen → ↓ Estrogen



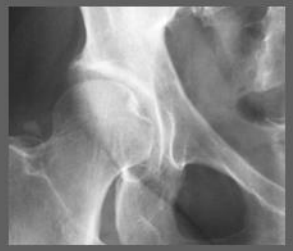
↓ Estrogen → ↑ RANK Ligand



↑ RANK Ligand → ↑ Osteoclast # and activity

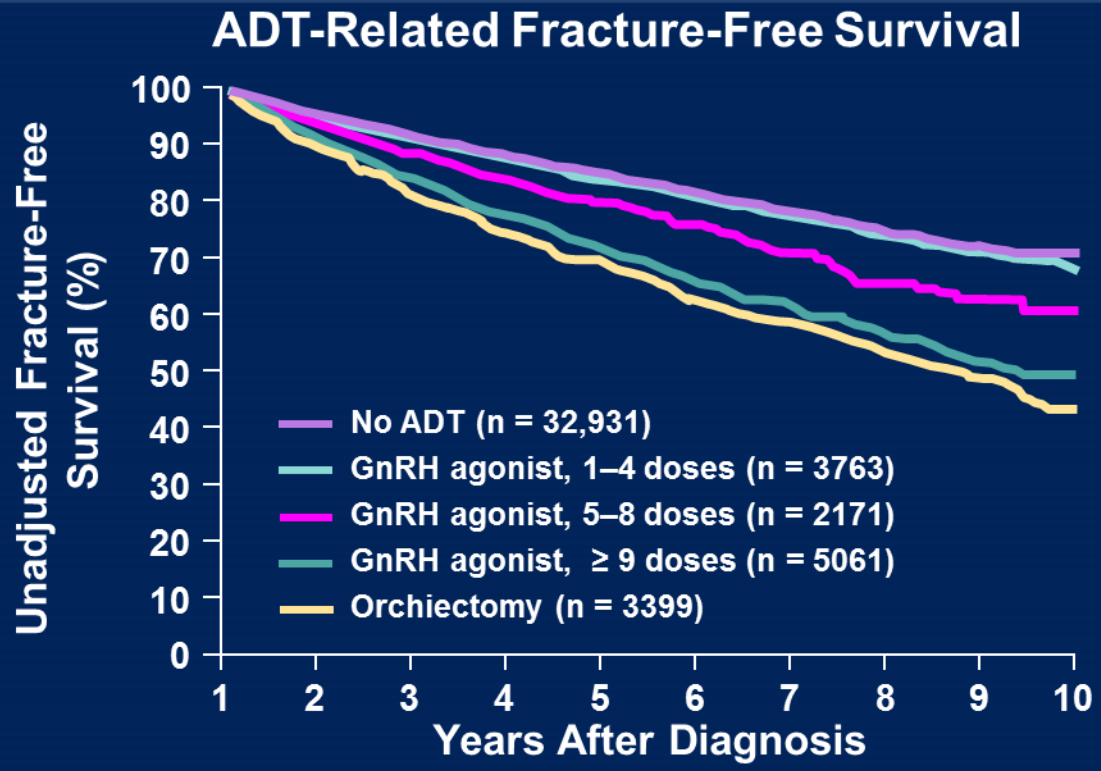
↑ Osteoclast # and activity → ↑ Bone Resorption

↑ Fractures



Michaud LB, Goodin S. *Am J Health Syst Pharm.* 2006;63:419-430.
Brufsky AM. *Oncologist.* 2008;13:187-195.
Shevde NK, et al. *Proc Natl Acad Sci USA.* 2000;97:7829-7834.
Raisz LG. *J Clin Invest.* 2005;115:3318-3325.

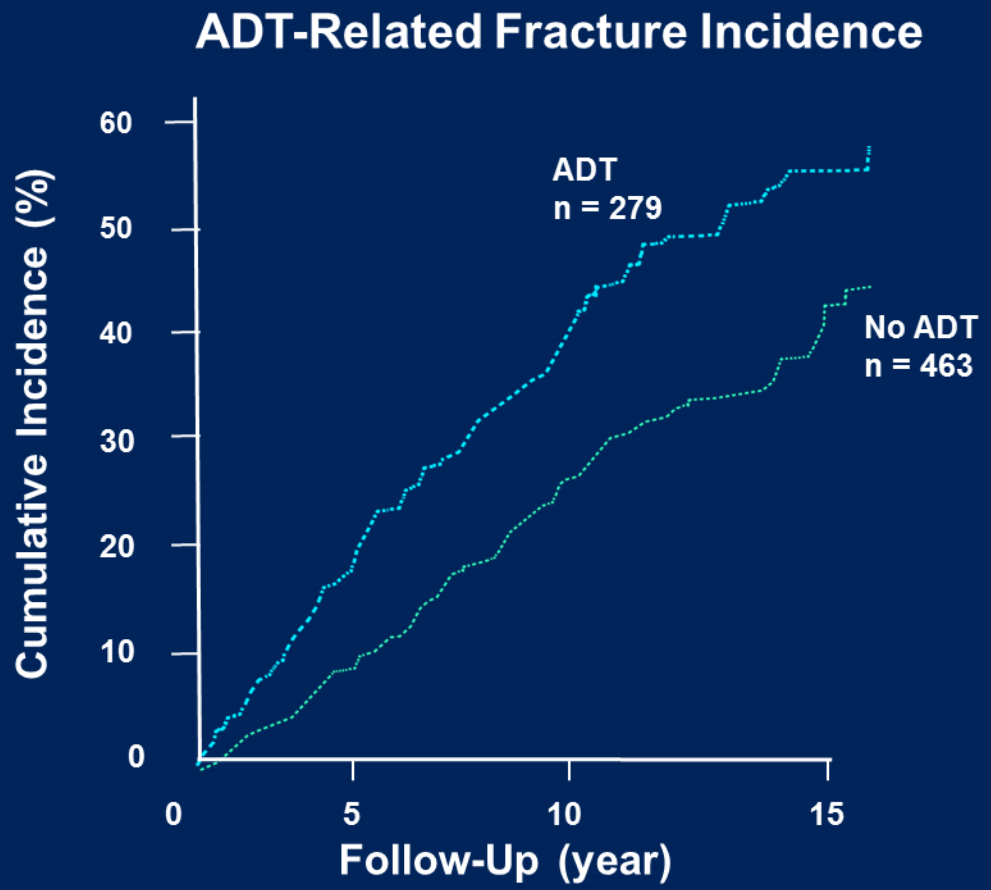
ADT Is Associated With Fractures



- **In men surviving at least 5 years after diagnosis:**
  - Of those receiving ADT, 19.4% experienced a fracture
  - Of those **NOT** receiving ADT, 12.6% experienced a fracture
  - ADT resulted in an excess risk of fracture of 45%

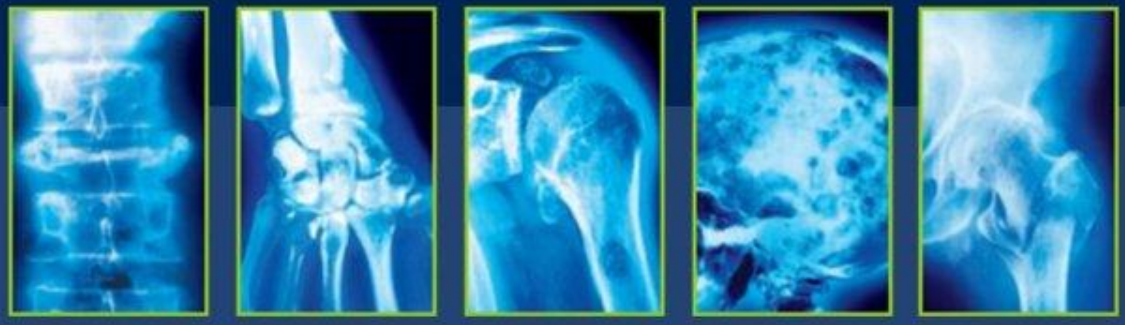
GnRH = gonadotropin-releasing hormone
Adapted from: Shahinian VB, et al. *N Engl J Med.* 2005;352:154-164.

ADT Increased the Risk of Fractures



- In men receiving ADT, there was a 70% increased risk of an osteoporotic fracture (HR = 1.7; 95% CI; 1.1–2.6)

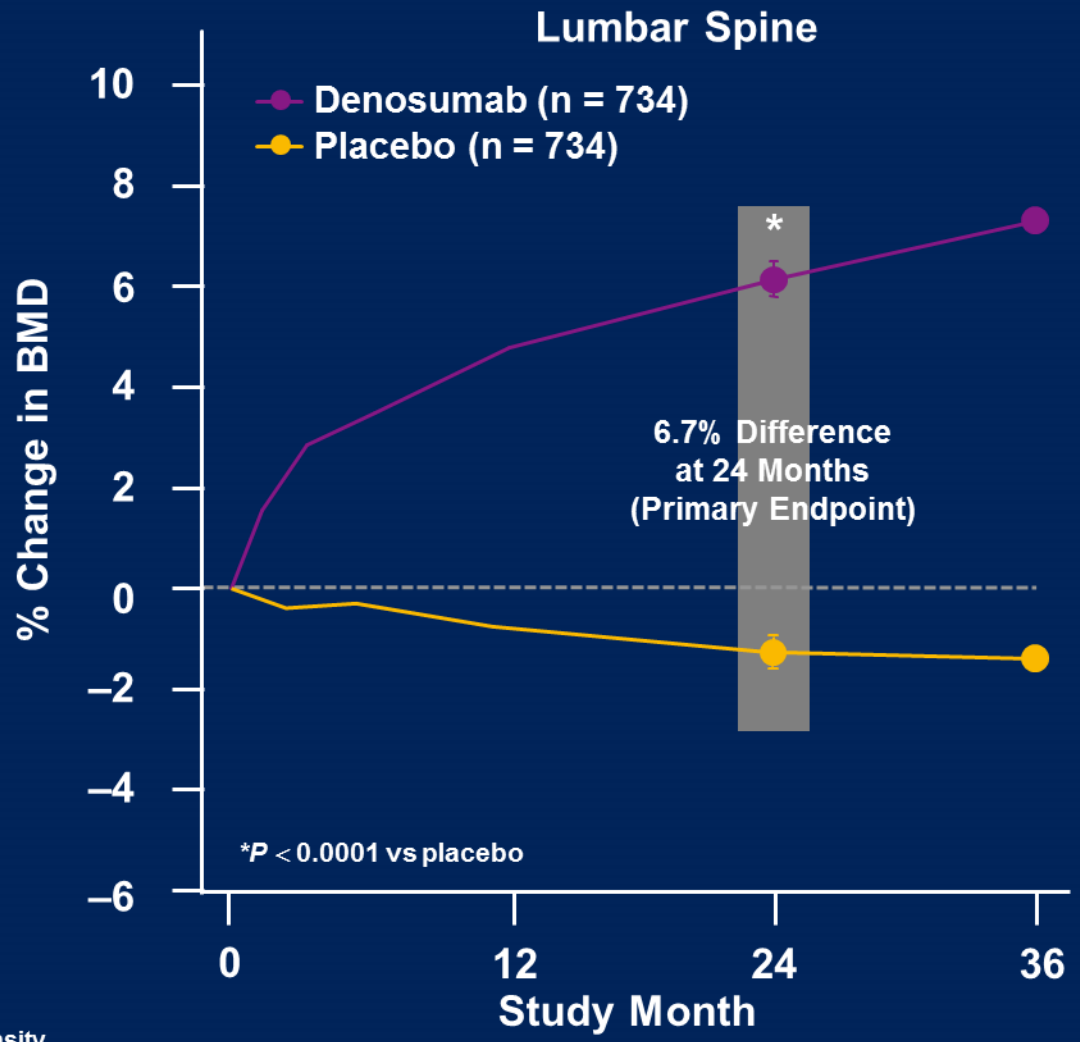
Adapted from: Melton LJ 3rd, et al. *J Bone Miner Res.* 2011;26:1808-1815.



Denosumab in Men Receiving Androgen-Deprivation Therapy for Prostate Cancer

Smith MR, et al. *N Engl J Med*. 2009;361:745-755.

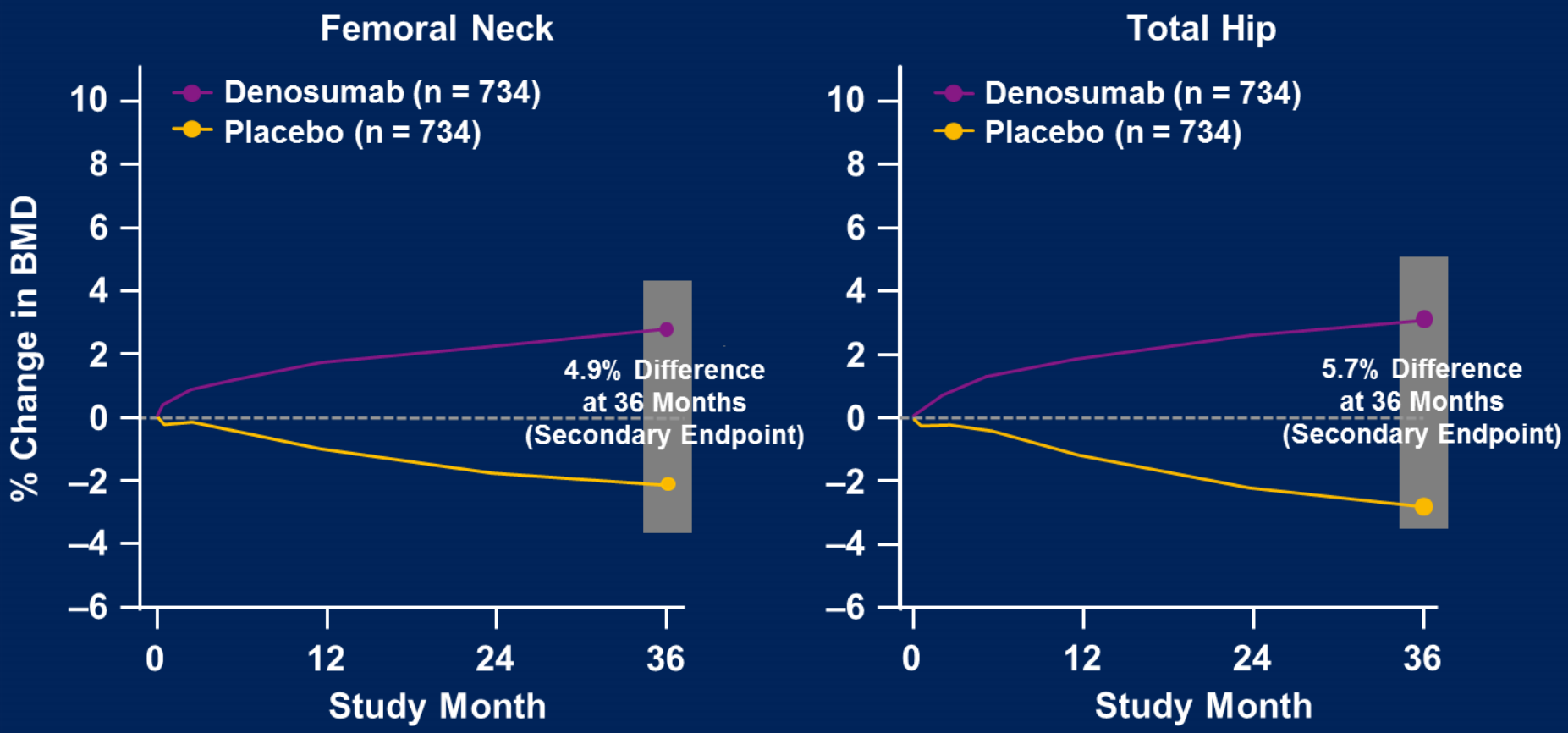
Changes in Lumbar Spine BMD Over 36 Months



BMD = Bone Mineral Density

Adapted from : Smith MR, et al. *N Engl J Med.* 2009;361:745-755.

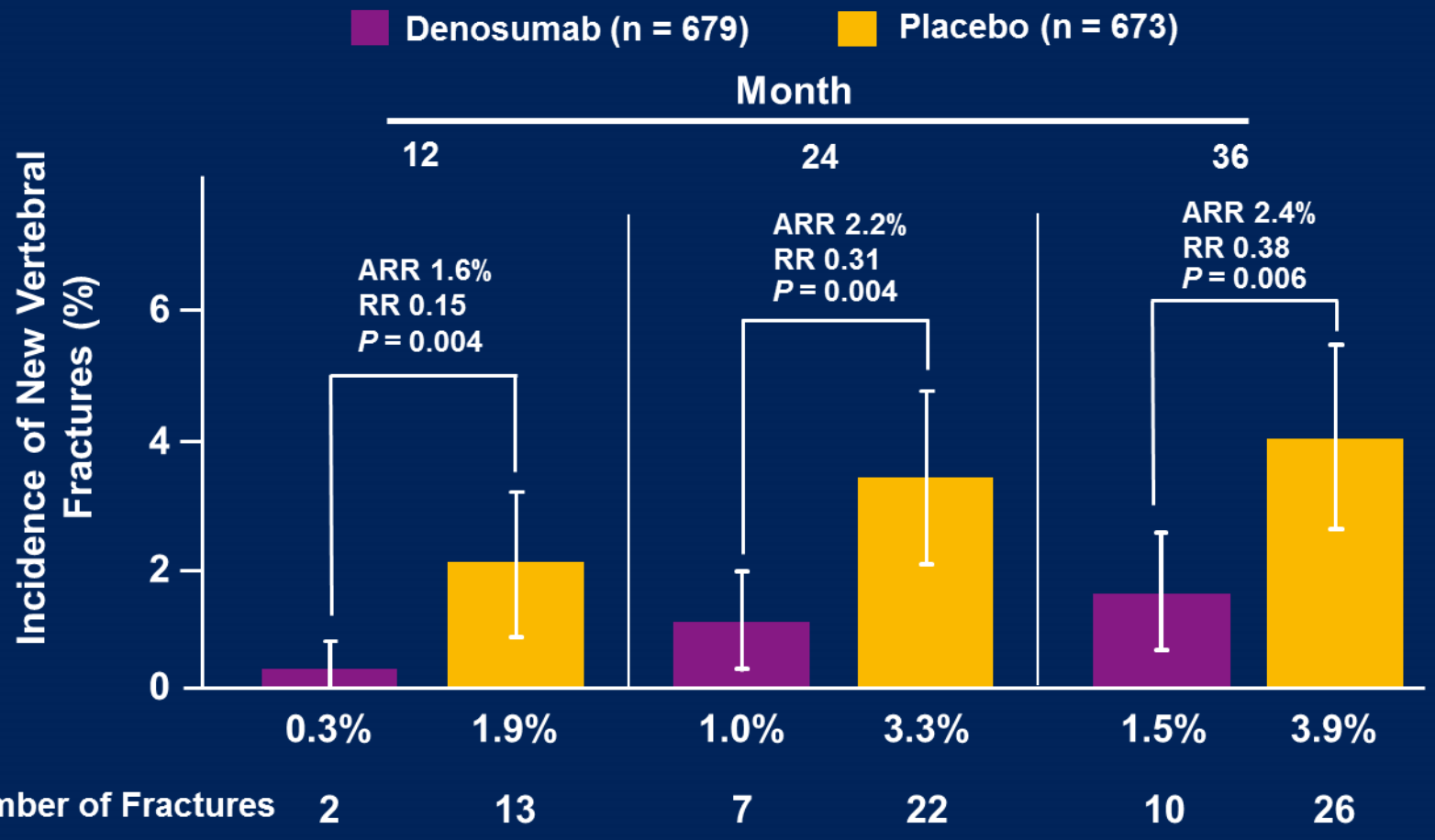
Changes in Femoral Neck and Total Hip BMD Over 36 Months



BMD = Bone Mineral Density

Adapted from: Smith MR, et al. *N Engl J Med.* 2009;361:745-755.

Cumulative Incidence of New Vertebral Fractures at 12, 24, and 36 Months

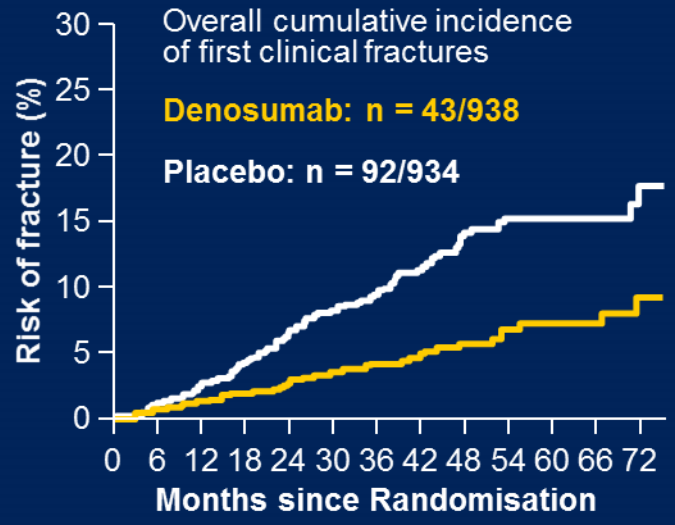


ARR = absolute risk reduction.
BMD = Bone Mineral Density
RR = relative risk.
Adapted from: Smith MR, et al. *N Engl J Med.* 2009;361:745-755.

ABCSG-18 Trial: Denosumab Significantly Reduced the Incidence of Clinical Fractures vs Placebo Regardless of Baseline BMD

Normal BMD (Baseline T-score ≥ –1.0)

HR = 0.44 (95% CI: 0.31–0.64)
P < 0.0001

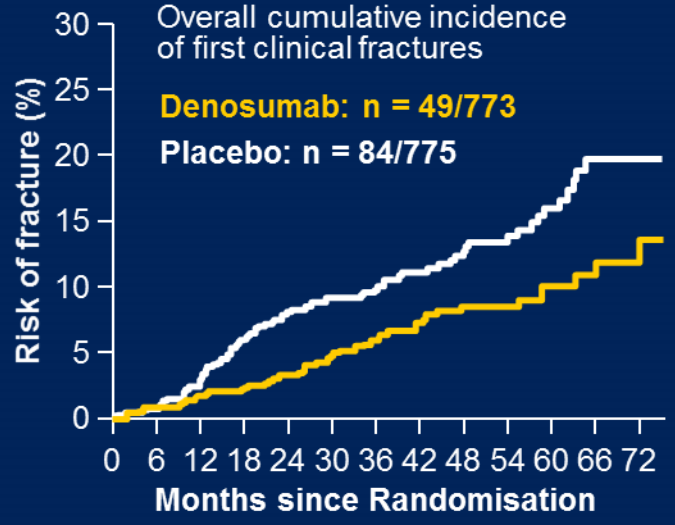


Number at risk

Placebo	934	906	806	702	588	498	416	337	268	197	141	97	62
Denosumab	938	915	828	717	624	532	453	381	301	234	168	126	66

Low BMD (Baseline T-score < –1.0)

HR = 0.57 (95% CI: 0.40–0.82)
P = 0.002

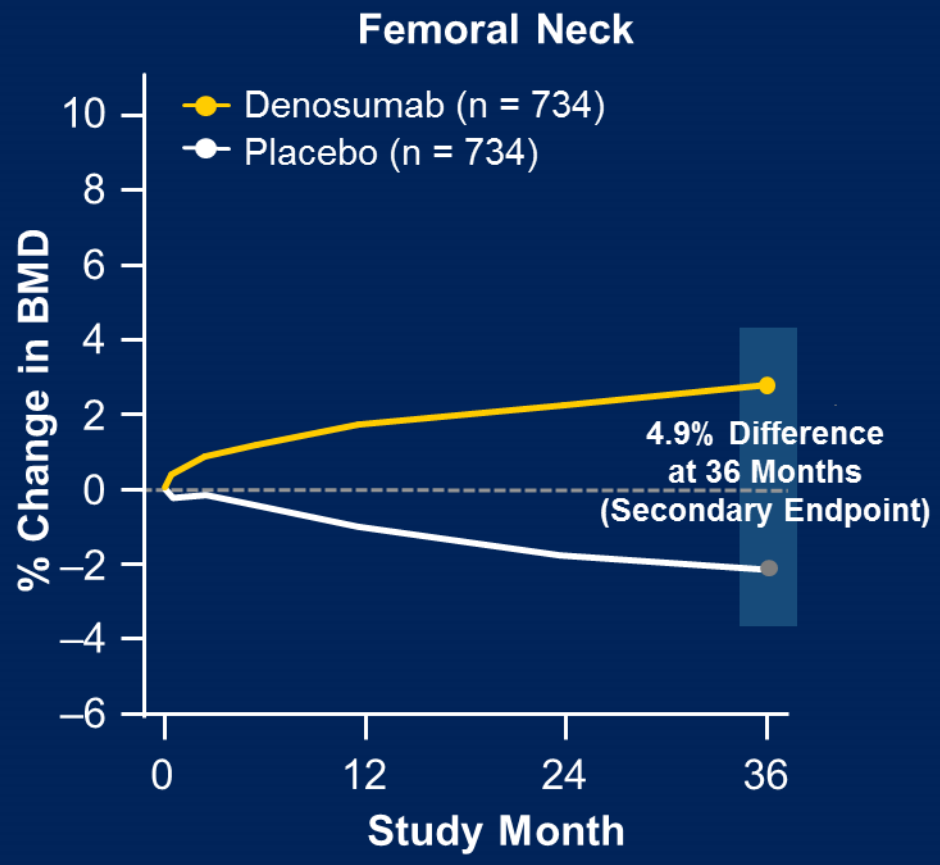


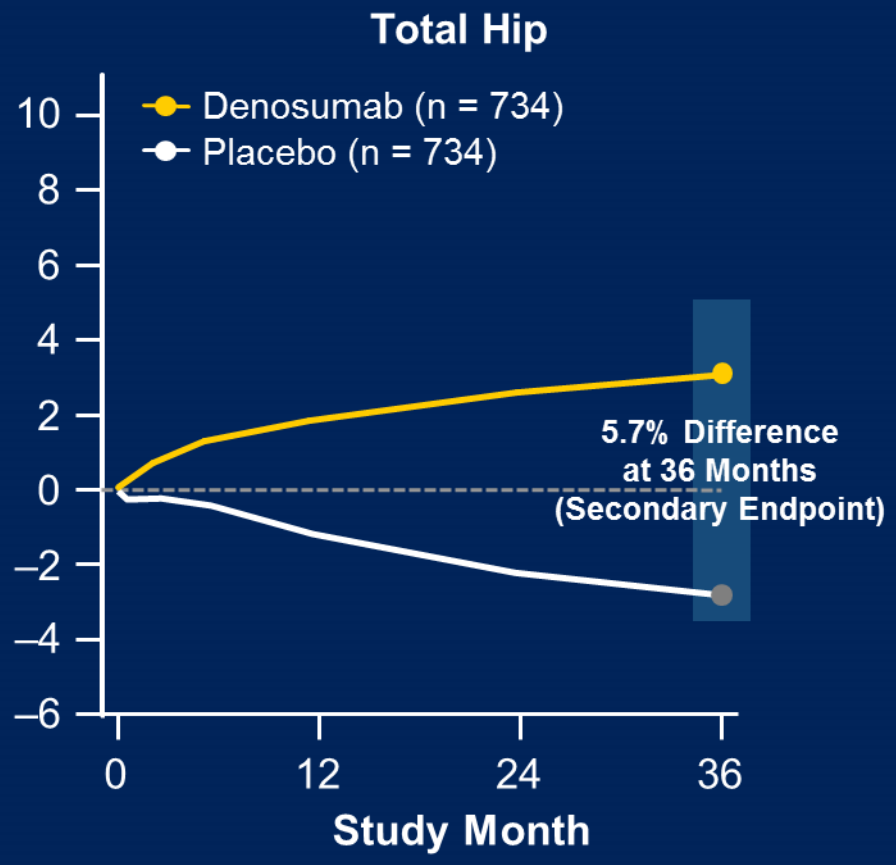
Number at risk

Placebo	775	754	664	563	481	423	369	300	245	187	134	88	50
Denosumab	773	750	660	580	494	433	370	307	248	198	137	95	50

Gnant M, et al. *Lancet* .2015.386:433–43 (and supplementary appendix).

Denosumab in Men Receiving Androgen-Deprivation Therapy for Prostate Cancer: Changes in Femoral Neck and Total Hip BMD Over 36 Months





BMD = Bone Mineral Density

Adapted from: Smith MR, et al. *N Engl J Med.* 2009;361:745-755.

Summary

- In men receiving androgen deprivation therapy for prostate cancer, twice-yearly denosumab given over 36 months was associated with increases in bone mineral density at all skeletal sites and a reduction in new vertebral fractures.

Smith MR, et al. *N Engl J Med.* 2009;361:745-755.

Prolia® (denosumab) Indications and Clinical Use

Treatment to Increase Bone Mass in Men with Osteoporosis at High Risk for Fracture

Treatment to increase bone mass in men with osteoporosis at high risk for fracture, High fracture risk defined as:

- History of osteoporotic fracture, or
- Multiple risk factors for fracture

OR

- Patients who have failed or are intolerant to other available osteoporosis therapy

Prolia® (denosumab) Product Monograph, Amgen

Overall Summary

- RANK ligand is an essential mediator for osteoclast formation, function, and survival[1,2]
- Cancer treatment-induced bone loss (CTIBL) can be caused by AI treatment for breast cancer or ADT for prostate cancer[3,4]
  - Both inhibit androgen production, resulting in ↑ bone resorption and bone loss[5]
- New indications of denosumab include[6]:
  - Treatment to ↑ bone mass in men receiving ADT for prostate cancer
  - Treatment to ↑ bone mass in women receiving adjuvant AI therapy for nonmetastatic breast cancer

1. Roodman GD. *N Engl J Med.* 2004;350:1655-1664.
2. Boyle WJ, et al. *Nature.* 2003;423:337-342.
3. Greenspan SL, et al. *J Clin Endocrinol Metab.* 2005;90:6410-6417.
4. Rinaldi RZ. *Curr Osteoporos Rep.* 2013;11:61–64.
5. Brufsky AM. *Oncologist.* 2008;13:187-195.
6. Prolia® (denosumab) Product Monograph, Amgen Canada Inc. March 13, 2014.