Managing Medication Issues

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Disclosure and Conflicts of Interest
Steven T Harris MD 2020-2021

- **Speakers Bureaus and Consulting**
  - **Amgen**
  - **Radius Health**

Bisphosphonates and Denosumab
Duration of Therapy

- Optimal duration of therapy
  - "Drug holiday" is a notion that applies only to the bisphosphonates
  - The benefits and risks of both continuation and discontinuation must be considered
    - One might consider a "drug holiday" if continued therapy is not associated with any greater benefit
    - One might also consider a "drug holiday" if continued therapy is associated with an increased risk of adverse events

Two Common Management Problems

Problem #1

- Is it necessary to stop bisphosphonate therapy after a certain number of years?
  - If so, how might patients be monitored to decide whether to restart therapy?
    - BMD changes? Biochemical markers? Clinical progress? All of the above?

Two Common Management Problems

Problem #2

- Is it necessary to stop denosumab therapy after a certain number of years?
  - No. At least based on the 10-year FREEDOM extension trial
  - Stopping denosumab is associated with relatively rapid bone loss and a risk of multiple vertebral fractures (“MVF”)

Challenges of Osteoporosis Treatment

- Success has been defined as the absence of fracture—which from a patient perspective is not very “exciting”
- Economic cost of treatment
- Other costs of treatment: nuisance value of taking another medication, reminder of illness, worry about consequences of therapy
- Side effects of treatment

“Relative Risk” vs “Absolute Risk”

- The media will almost always cover medical issues—both risks and benefits--with numbers related to “relative risk”
  - If you do “this,” you will double your risk of “that” (something undesirable)
  - Alternatively, if you do “this other thing,” you will reduce your risk of “that” in half (“by 50%”)

The next question must be:

“What is the risk to begin with?”

“Relative Risk” vs “Absolute Risk”

- For example, imagine that the risk of “badness” is 1% (1 out of 100)
  - If you do something that doubles your risk, the risk is now 2% (2 out of 100)
    - The harm (absolute risk) is 1% (1 out of 100)
  - On the other hand, if you do something that will reduce your risk in half (“by 50%”), then the risk is now 0.5% (1 out of 200)
    - The benefit (absolute benefit) is 0.5% (1 out of 200)

“Relative Risk” vs “Absolute Risk”

- For example, imagine that the risk of “badness” is 20% (20 out of 100)
  - If you do something that doubles your risk, the risk is now 40% (40 out of 100)
    - The harm (absolute risk) is 20% (20 out of 100)
  - On the other hand, if you do something that will reduce your risk in half (“by 50%”), then the risk is now 10% (10 out of 100)
    - The benefit (absolute benefit) is 10% (10 of out 100)

Bisphosphonates: Current Uses and Challenges

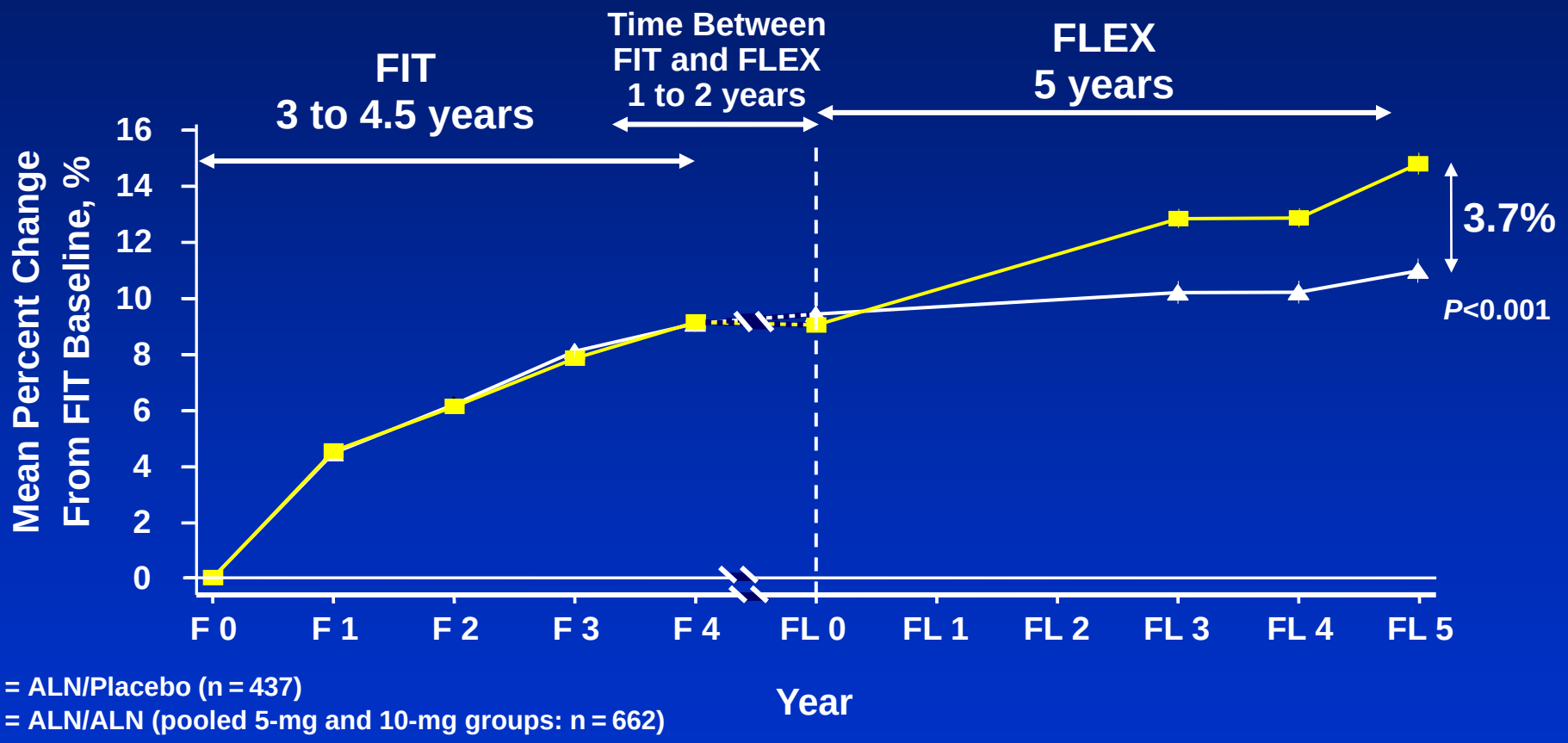
- Efficacy
  - "Short-term" efficacy usually established on the basis of fracture risk reduction over 3 years
  - "Long-term" efficacy (Is treatment "forever?")
- Safety
  - "Short-term" concerns
  - "Long-term" concerns that have been raised
    - Osteonecrosis of the jaw (ONJ)
    - Atrial fibrillation
    - Abnormal bone quality/atypical fractures
    - Esophageal cancer

FIT Long-Term Extension (FLEX)

- Women previously on alendronate for 3-6 years were randomly assigned to 5 years of alendronate (5 or 10 mg daily) or placebo
- Alendronate vs placebo
  - Clinical spine fracture: RR=0.45 (0.23, 0.84)
  - Morphometric spine fracture: RR=0.87 (0.61, 1.25)
  - Nonspine fracture: RR=1.00 (0.76, 1.32)

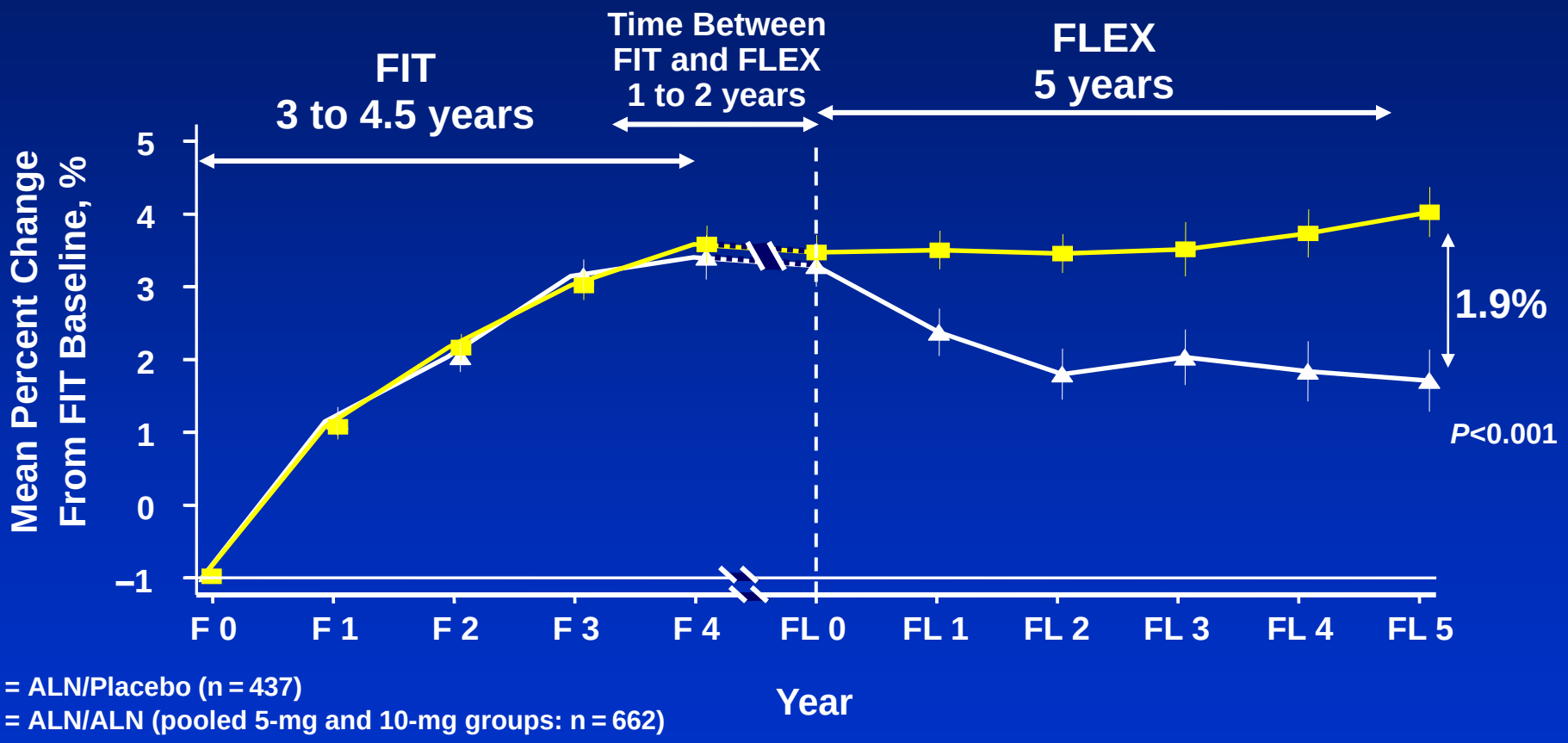
Black DM, et al. *JAMA* 2006;296:2927-2938

FLEX: % Change in Spine BMD



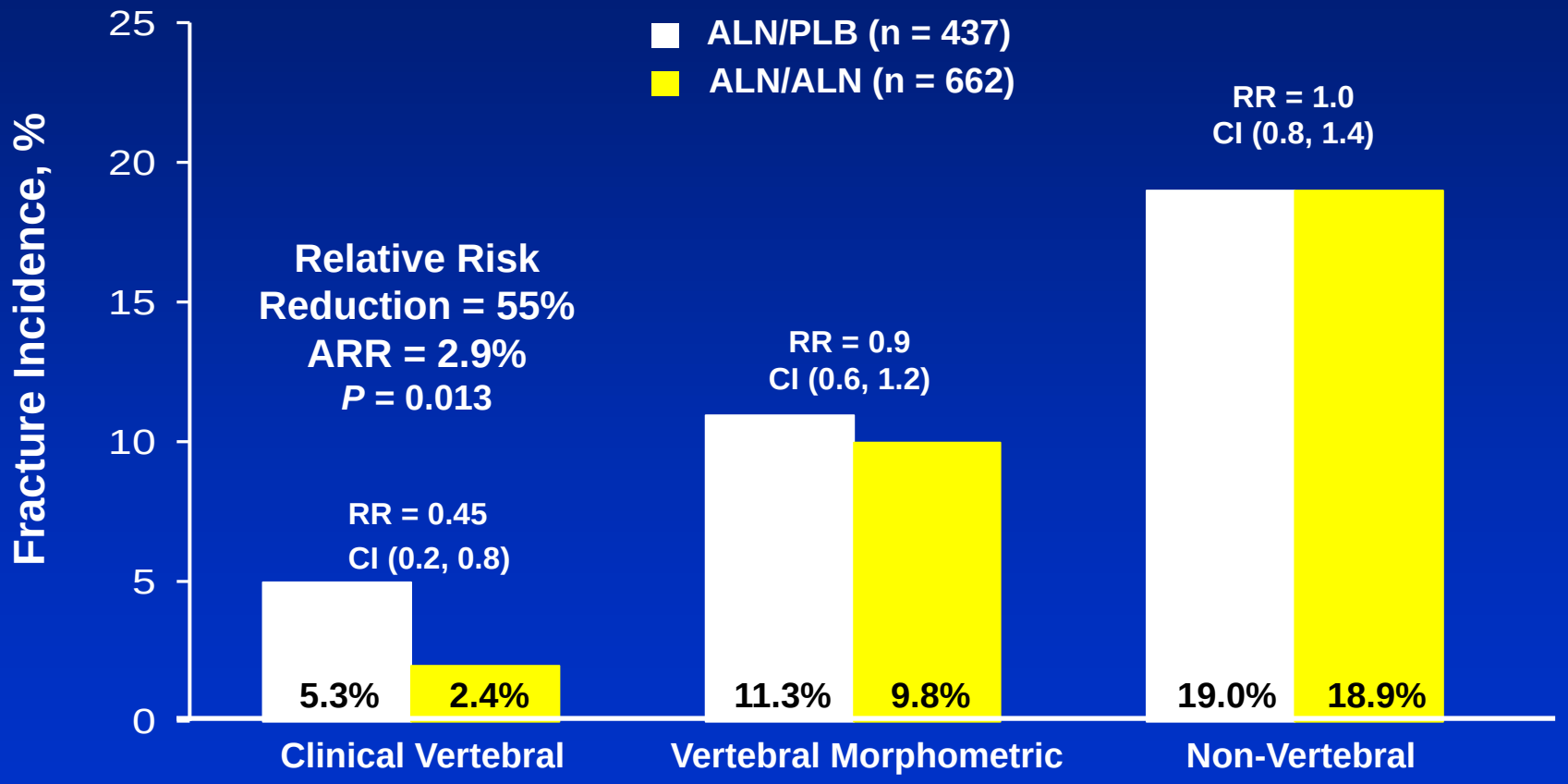
Black DM, et al. *JAMA* 2006;296:2927-2938

FLEX: % Change in Femoral Neck BMD



Black DM, et al. *JAMA* 2006;296:2927-2938

FLEX: Incidence of Fractures



Black DM, et al. *JAMA* 2006;296:2927-2938

FLEX Summary and Conclusions

- Over 10 years (FIT and FLEX), continuous alendronate treatment:
  - Prevented bone loss at the total hip and increased BMD at the femoral neck and lumbar spine
  - Maintained biochemical markers of bone turnover at levels similar to FLEX baseline
  - Reduced the relative risk of clinical vertebral fracture by 55% (ARR 2.9%)
  - Resulted in normal bone histology
- Discontinuation of alendronate treatment in FLEX:
  - Resulted in a loss of total hip and femoral neck BMD
  - Led to a rise in biochemical markers of bone turnover
  - Resulted in more clinical vertebral fractures—but had no effect on morphometric vertebral fractures or non-vertebral fractures in the entire study group

Black DM, et al. *JAMA* 2006;296:2927-2938

FLEX: NVF Risk with Extended Alendronate Therapy
Stratified by Baseline Femoral Neck BMD

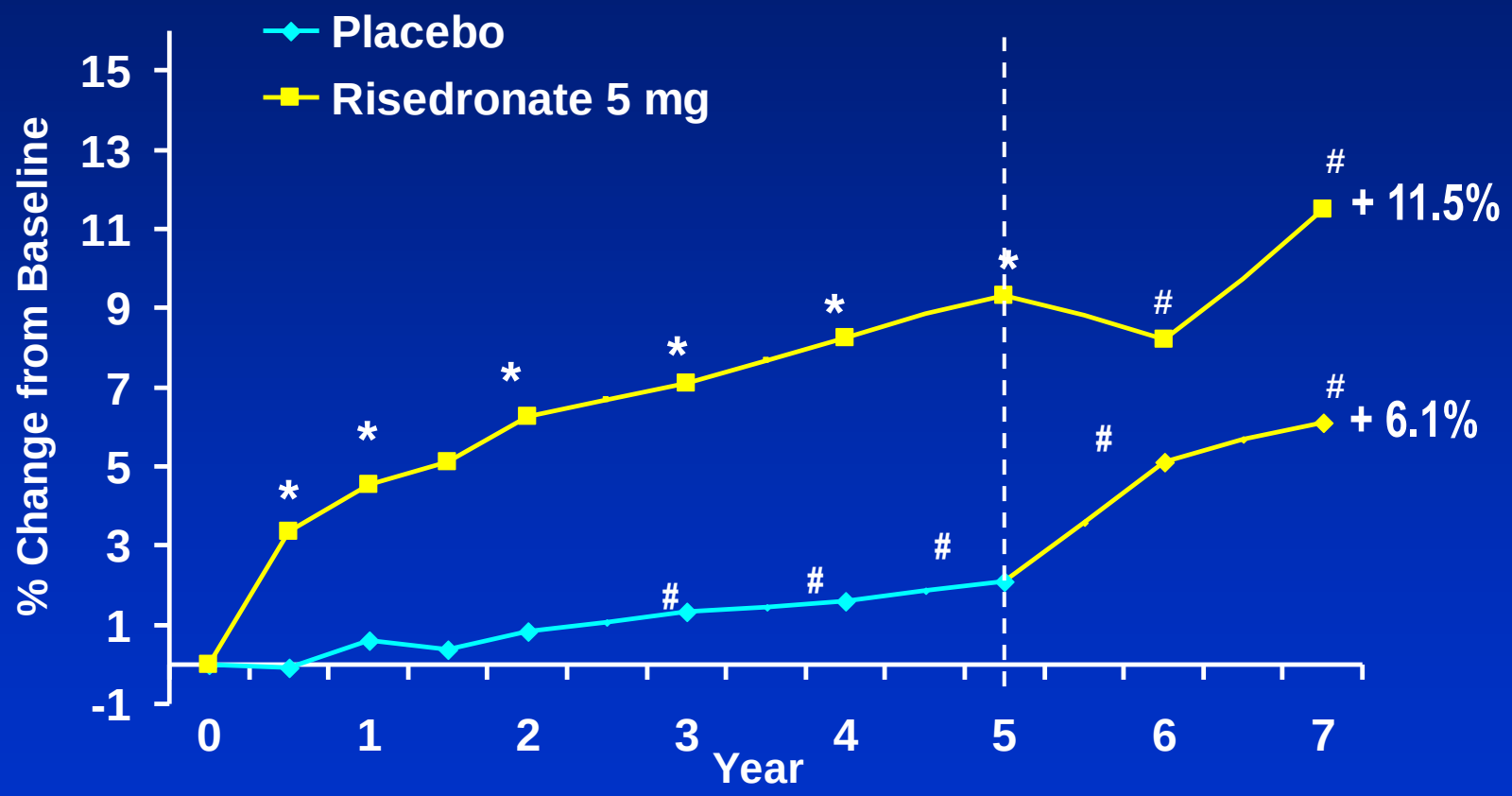
- 1099 patients enrolled in FLEX
- 723 with no vertebral fracture at FLEX baseline

Baseline FN BMD	Risk Difference	Relative Risk
T-score > -2	4.01%	1.41 (0.75, 2.66)
T-score ≤ -2.5	-13.32%	0.50 (0.26, 0.96)

Schwartz AV, et al. Efficacy of continued alendronate for fractures in women without prevalent vertebral fracture: The FLEX Trial. ASMBR 29th Annual Meeting, Presentation 1057

Risedronate 7-year Experience

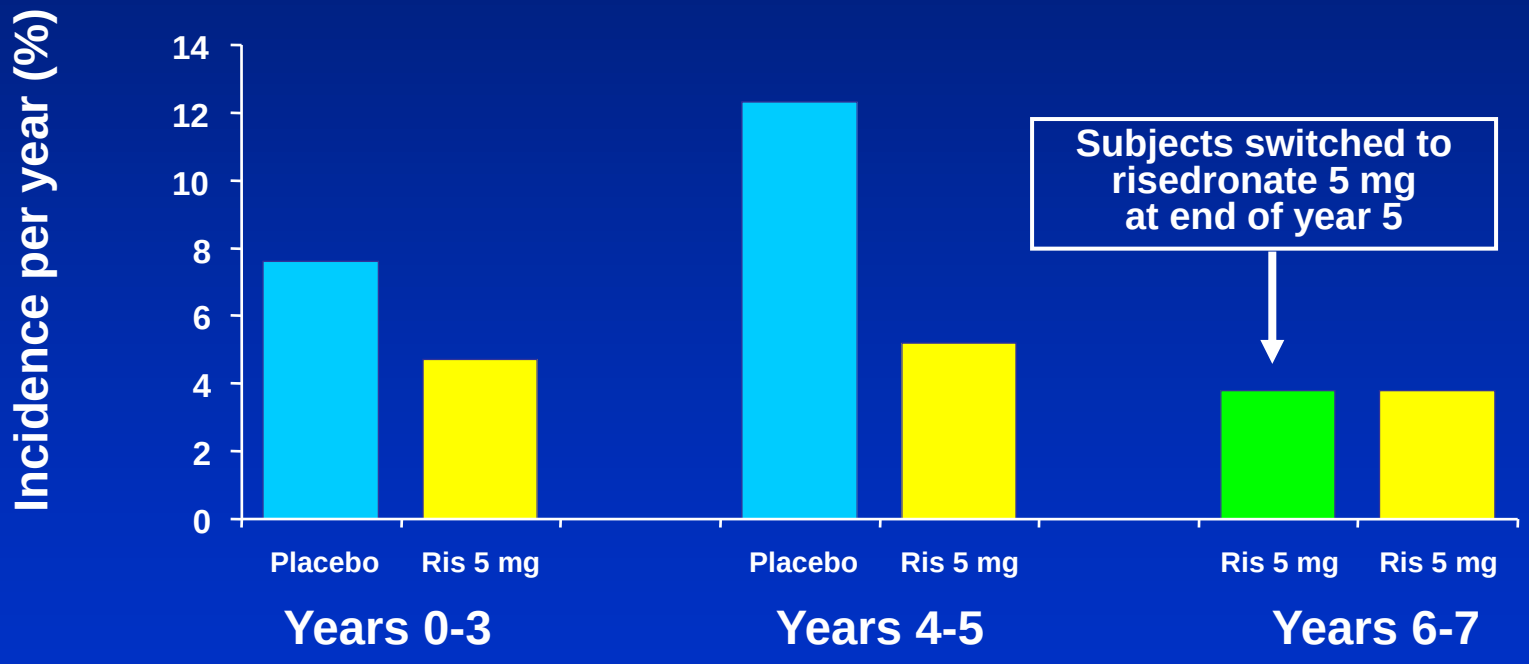
Lumbar Spine BMD



Abstract: European Calcified Tissue Society meeting, May 2003

Vertebral Fractures Over 7 Years of Risedronate Therapy

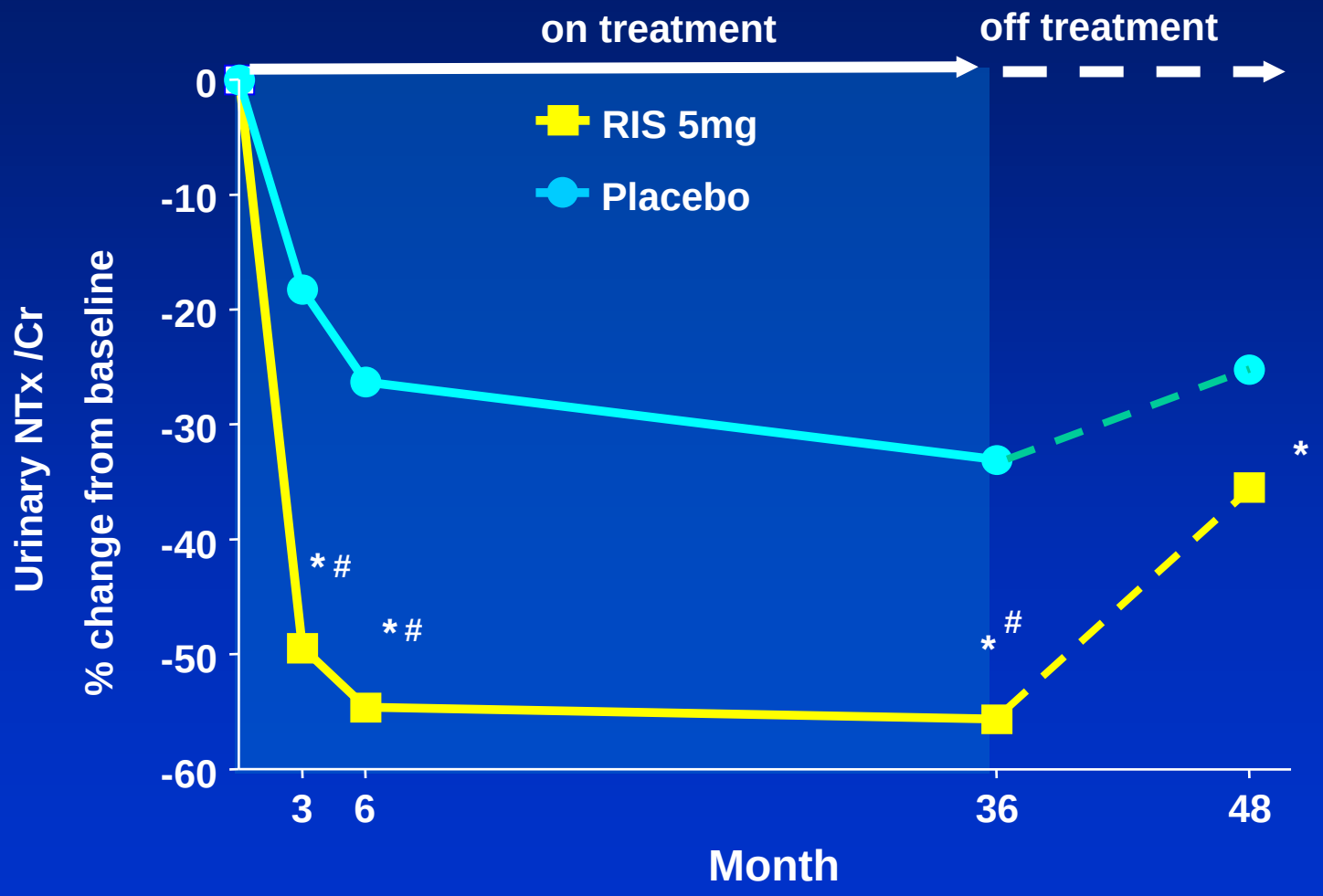
VERT-MN: Radiographic Vertebral Fracture*



*Annualized fracture incidence represents the percentage of patients experiencing any new vertebral fracture divided by the number of years in the observed interval.

NTx Change After Risedronate Treatment

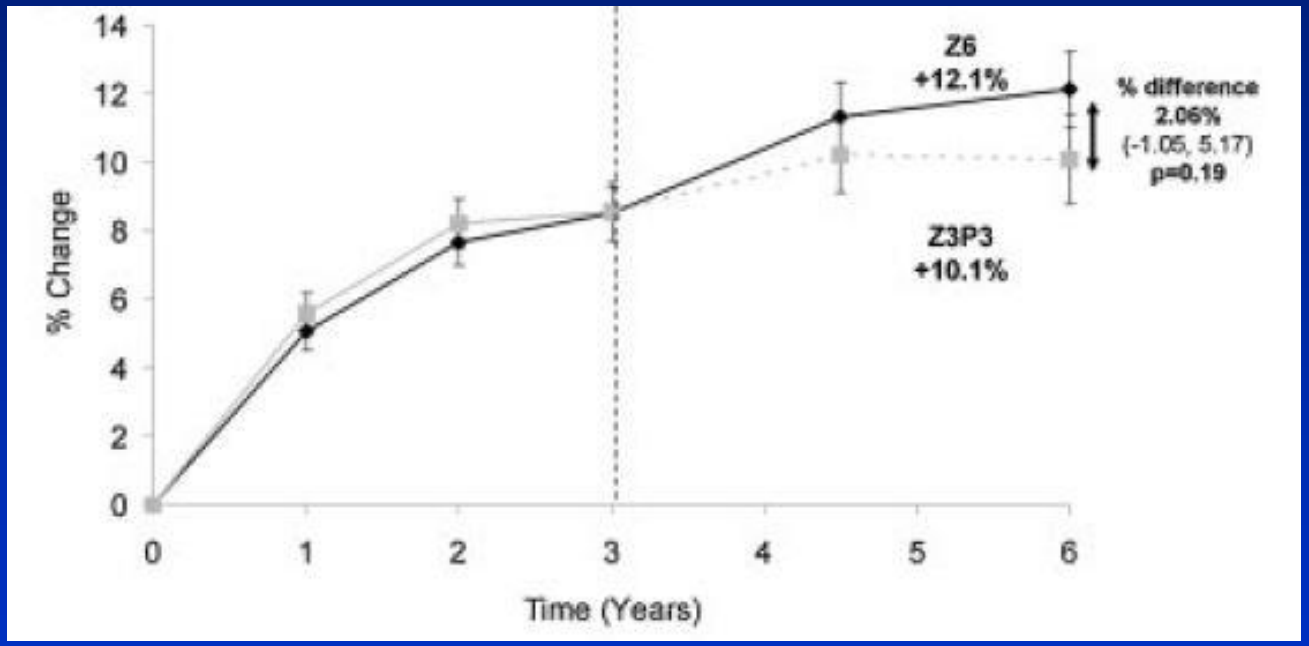
VERT-NA Extension Cohort



Watts NB, et al. ISCD 2004

Zoledronic Acid: Long-Term Therapy

Change in Lumbar Spine BMD over 6 years
6 years of therapy vs 3 years of therapy

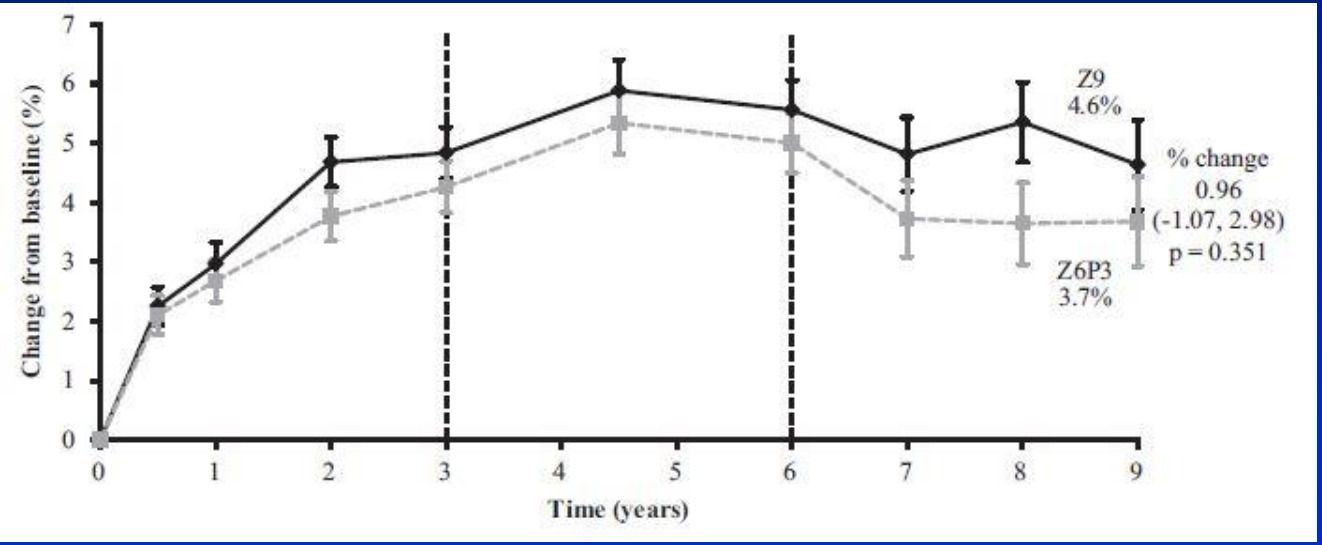


Continuing treatment for 6 years reduced morphometric vertebral fractures, without an effect on clinical vertebral fractures or non-vertebral fractures

Black DM, et al. *J Bone Miner Res* 2012: 27(2):243-254

Zoledronic Acid: Long-Term Therapy

Change in Total Hip BMD over 9 years
9 years of therapy vs 6 years of therapy



Continuing treatment for 9 years had no significant effect on fracture rates--but the statistical power was limited

Black DM, et al. *J Bone Miner Res* 2015:30(5):934-944

Long-term Treatment and Discontinuation

- **FLEX Trial**
  - **Compared the effects of discontinuing alendronate treatment after 5 years vs. continuing for 10 years**
  - **Switching to placebo for 5 years resulted in declines in BMD and increases in biochemical markers of bone turnover, but not to pretreatment levels**
  - **Incidence of all clinical fractures and nonvertebral fractures similar in both groups, but lower risk of clinical vertebral fractures in those who continued therapy**
  - **Post hoc analyses suggested that continuation was associated with lower risk of nonvertebral fractures in women with femoral neck T-score ≤ -2.5**
- **VERT-NA Extension Study**
  - **After treatment with risedronate for 3 years and discontinuation for 1 year:**
    - **Spine and hip BMDs decreased significantly and biochemical markers of bone turnover increased to placebo levels**
    - **The risk of new vertebral fractures was reduced by 46% in the former risedronate users compared with the former placebo patients in the year off of treatment**

1. Black, DM et al. *JAMA.* 2006;296:2927-38. 2. Watts NB, et al. *Osteoporos Int.* 2008;19:365-72.
3. Recker, RR et al. *J Bone Miner Res.* 2004;19(suppl 1)1173.

Long-term Treatment and Discontinuation

- **HORIZON Pivotal Fracture Trial Extension Study**
  - **Compared the effects of discontinuing zoledronic acid treatment after 3 years vs. continuing for an additional 3 years**
  - **Femoral neck BMD remained constant in the continuation group and showed a small decrease in the discontinuation group**
  - **Significantly fewer morphometric vertebral fractures occurred in the continuation group than in the discontinuation group; no difference in nonvertebral, clinical vertebral, or hip fractures**

Black, DM et al. *J Bone Miner Res.* 2012;27(2):243-54

Long-term Treatment and Discontinuation

Based on these findings, continued BP therapy beyond 3 years with ZOL and beyond 5 years with ALN may be an option in high-risk individuals, based on evidence for reductions in the risk of vertebral fractures only. In lower-risk patients and in light of lack of evidence for fracture reduction with long-term therapy, discontinuation of treatment beyond 3 to 5 years, with monitoring, may be considered with periodic reassessment of fracture risk.

Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research

Adler RA et al. *J Bone Miner Res* 2016:31(1)16-35

Bisphosphonate Drug Holidays

- Optimal duration of therapy
  - "Drug holiday" is a notion that applies only to the bisphosphonates
  - The benefits and risks of both continuation and discontinuation must be considered
    - One might consider a "drug holiday" if continued therapy is not associated with any greater benefit
    - One might also consider a "drug holiday" if continued therapy is associated with an increased risk of adverse events

High-Profile Adverse Events

- Osteonecrosis of the jaw (ONJ)
  - Risk factors:
    - Cancer and anti-cancer therapy
    - Poor oral hygiene
  - Prevalence of 1/10,000 to ≤1/100,000 patient-years in patients treated for osteoporosis
- Atypical femur fractures
  - Associated with bisphosphonates - low absolute risk
  - Causality not established
  - Pathophysiology unknown - low bone turnover leading to impaired remodeling and accumulation of microdamage?

Khosla S, et al. *J Bone Miner Res*. 2007;22(10):1479-1489

Rizzoli R, et al. *European Society for Clinical and Economic Aspects of Osteoporosis. Impact of ONJ Executive Summary*. Watts NB, Diab DL. *J Clin Endocrinol Metab.*, April 2010, 95(4): 1555-1565

Bisphosphonate-Related ONJ: Incidence

The Background Incidence in the General Population is Not Known

	Underlying Malignancy	Osteoporosis Paget's Disease
IV	1% to 10%	Rate not published
PO	Rate not published	1/10,000 to <1/100,000 patient-treatment-years

Khosla S, et al. *J Bone Miner Res* 2007;22;1479-1491

ASBMR Report on Atypical Femoral Fractures

Journal of Bone and Mineral Research

JBMR

Perspective

Atypical subtrochanteric and diaphyseal femoral fractures: Report of a task force of the american society for bone and mineral Research†

Elizabeth Shane*‡, David Burr*‡, Peter R Ebeling, Bo Abrahamsen, Robert A Adler, Thomas D Brown, Angela M Cheung, Felicia Cosman, Jeffrey R Curtis, Richard Dell, David Dempster, Thomas A Einhorn, Harry K Genant, Piet Geusens, Klaus Klaushofer, Kenneth Koval, Joseph M Lane, Fergus McKiernan, Ross McKinney, Alvin Ng, Jeri Nieves, Regis O'Keefe, Socrates Papapoulos, Howe Tet Sen, Marjolein CH van der Meulen, Robert S Weinstein, Michael Whyte

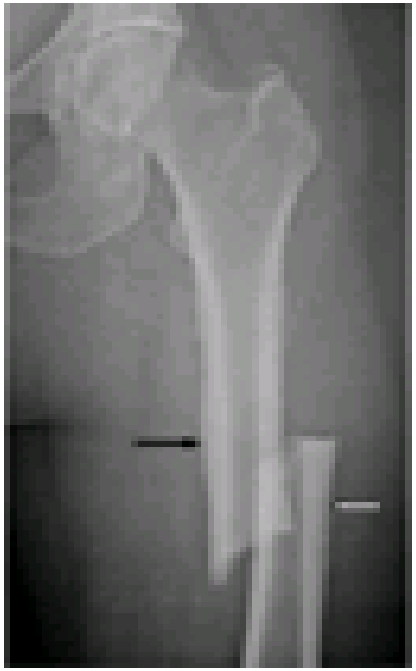
Article first published online: 25 OCT 2010

DOI: 10.1002/jbmr.253

Issue

Journal of Bone and Mineral Research

Volume 25, Issue 11, pages 2267–2294, November 2010



- 310 reported cases
- Age range 36-92
- Mostly women
- Duration of bisphosphonate treatment 1.3-17 years, median duration 7 years

Shane E, et al. *J Bone Miner Res* 2010;25:2267-94

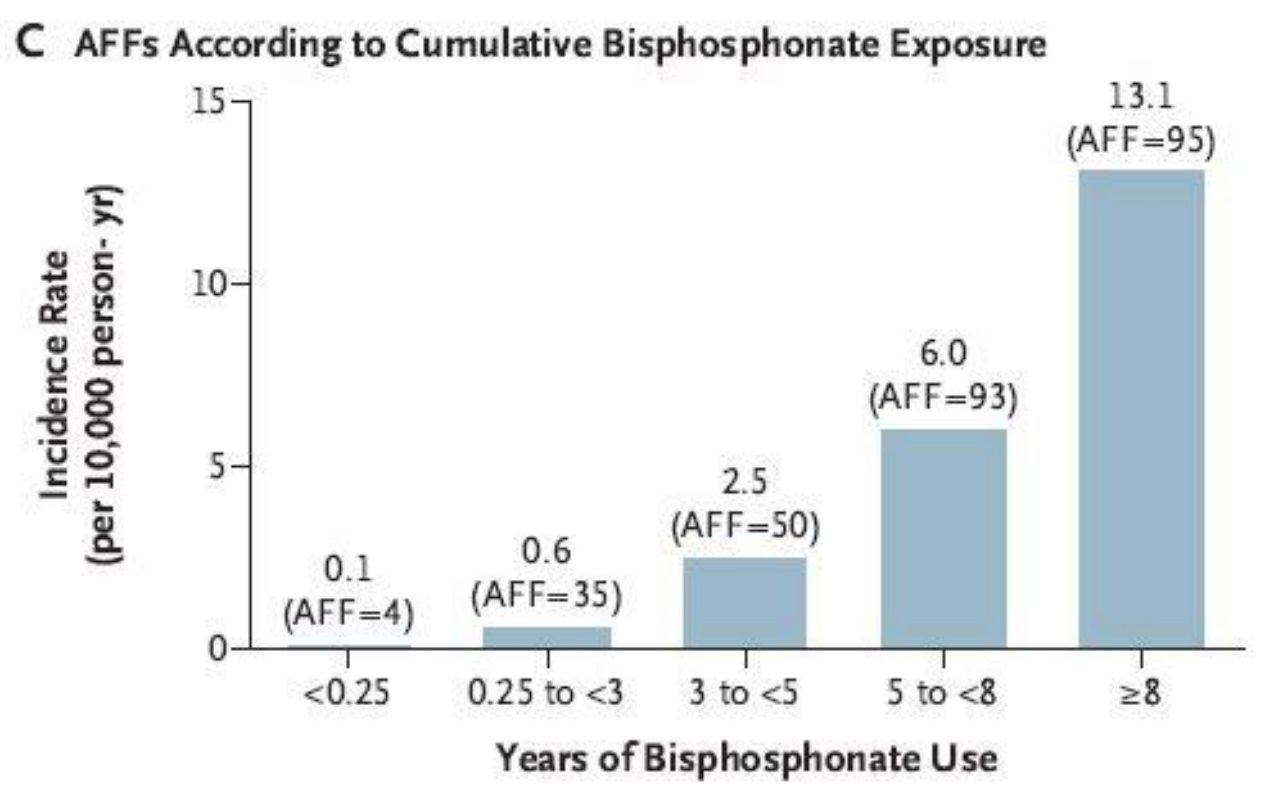
Benefit/Risk Estimates

- If you treat 1000 women with bisphosphonates for 5 years
  - Fracture risk similar to Fracture Intervention Trial (FIT), the pivotal clinical trial of alendronate
  - Femoral neck T-score ≤ -1.5, with or without prevalent vertebral fractures
- You would prevent 35-50 non-vertebral fractures
- You would prevent 50-115 vertebral fractures
- You might cause as many as 5 atypical femur fractures (AFF)
- The risk of an AFF is low compared to the risk of common osteoporotic fractures

Shane E, et al. *J Bone Miner Res* 2010;25:2267-94

Atypical Femoral Fracture

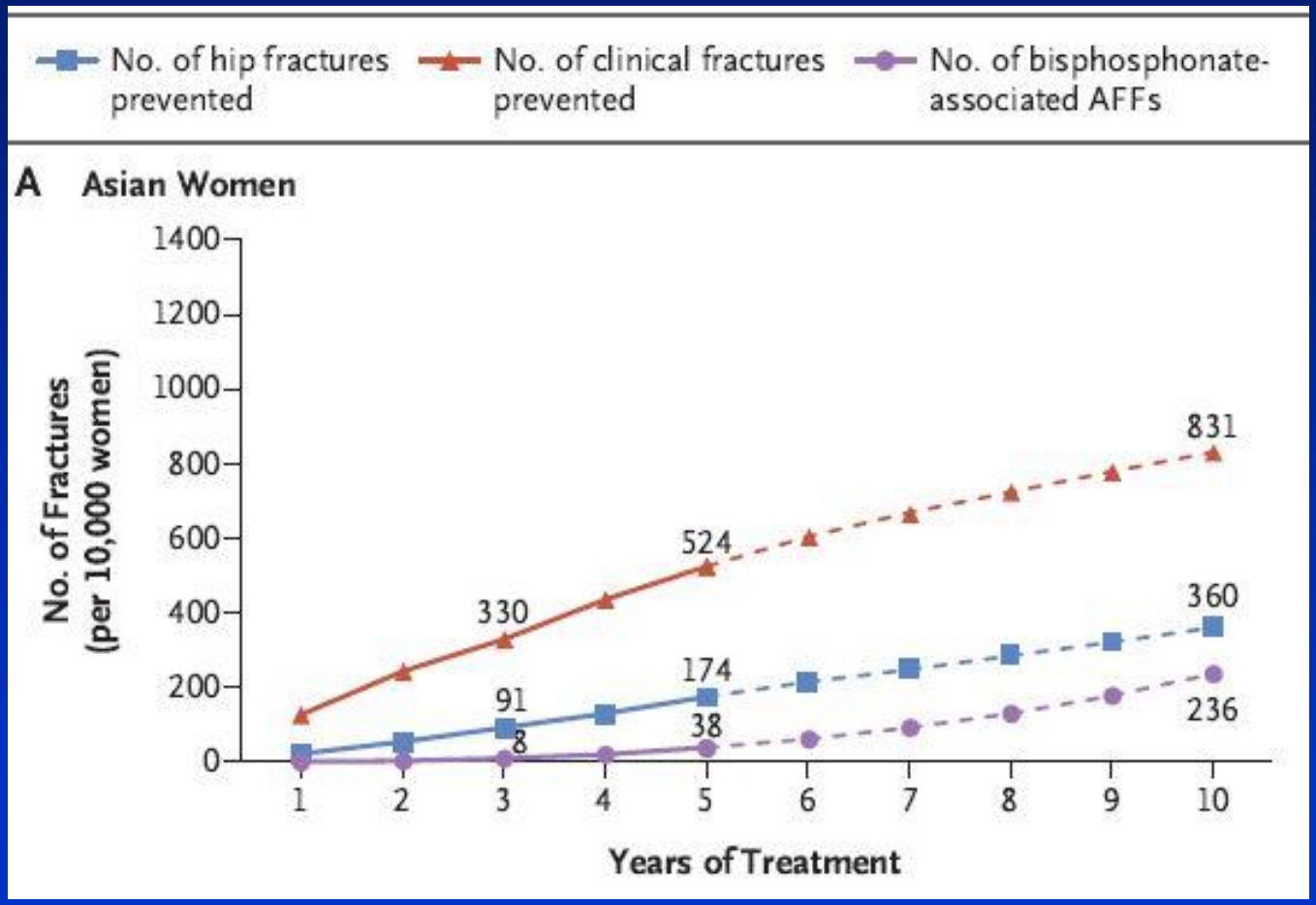
Observational Data in Kaiser Southern California



Black DM, et al. *N Engl J Med* 2020;383:743-753

Atypical Femoral Fracture

Observational Data in Kaiser Southern California



Black DM, et al. *N Engl J Med* 2020;383:743-753

Bisphosphonate Drug Holidays

- 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 is greater than -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)
- For oral bisphosphonates, consider a bisphosphonate holiday after 6 to 10 years of stability in patients with very high fracture risk (Grade B)

Camacho PM et al; AACE Clinical Practice Guidelines; *Endocr Pract* 2020;26(Suppl 1):1-46

Bisphosphonate Drug Holidays

- For zoledronate, consider a bisphosphonate holiday after 3 years in high-risk patients or until fracture risk is no longer high, and continue for up to 6 years in very-high-risk patients (Grade A)
- 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 least significant change (LSC) of the dual-energy X-ray absorptiometry (DXA) machine, or an increase in bone turnover markers (Grade A)

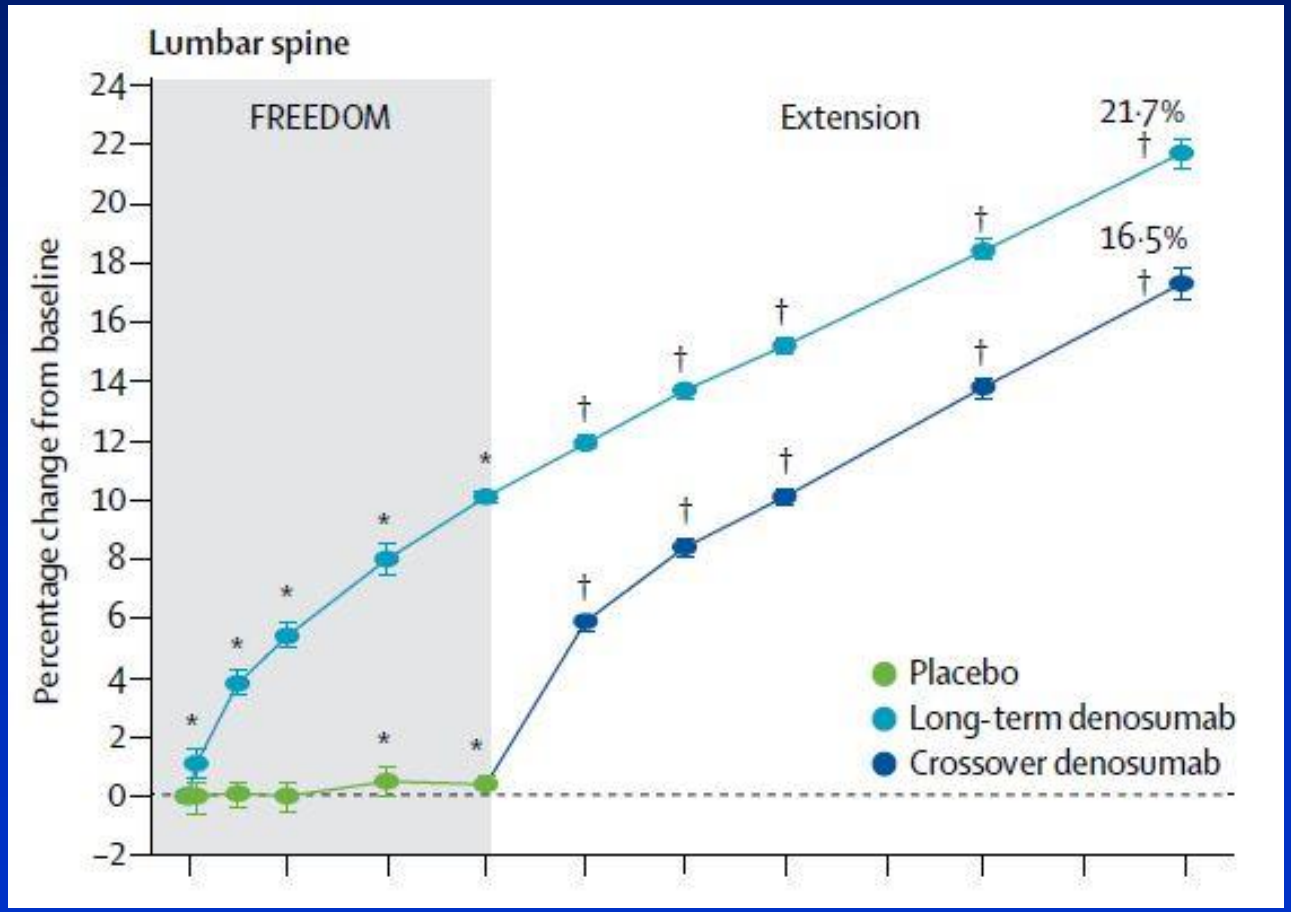
Camacho PM et al; AACE Clinical Practice Guidelines; *Endocr Pract* 2020;26(Suppl 1):1-46

Denosumab

- Monoclonal antibody to RANKL
- 60 mg subcutaneous injection every 6 months
- 9% increase in spinal BMD after 3 years in the pivotal FREEDOM trial; 4%-5% increase in hip BMD
- Reduction in fracture risk after 3 years:
  - 68% decrease in new vertebral fractures
  - 40% decrease in hip fractures
  - 20% decrease in nonvertebral fractures
- 10-year data: continued increase BMD, reduced bone turnover

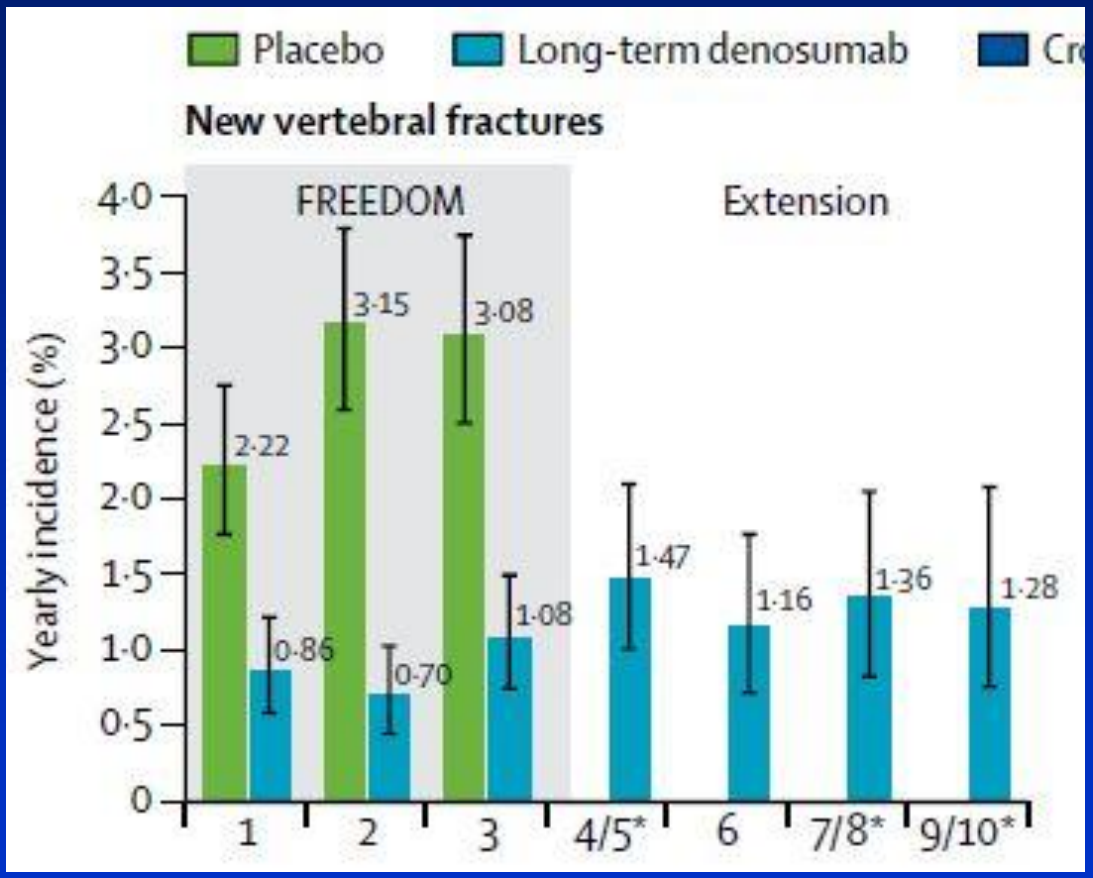
Cummings SR et al. *N Engl J Med*. 2009;368:756-765

Denosumab: Long-Term Extension



Bone HG et al. *Lancet Diabetes Endocrinol* 2017;513-23

Denosumab: Long-Term Extension



Bone HG et al. *Lancet Diabetes Endocrinol* 2017;513-23

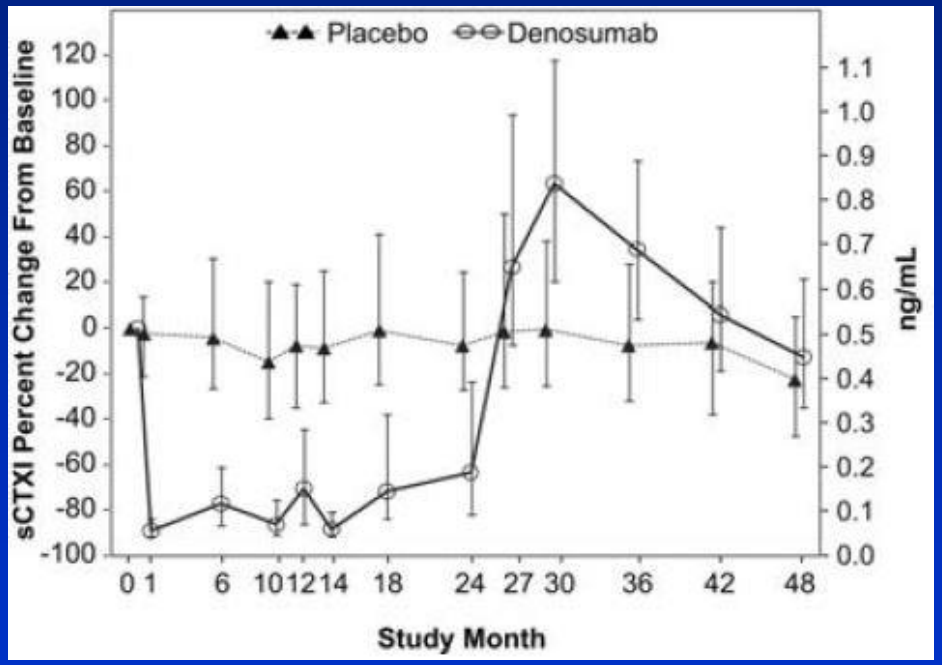
Denosumab Long-Term Extension Adverse Events

- Osteonecrosis of the jaw occurred in 5.8 cases per 10,000 patient years
- Atypical femoral fracture occurred in 0.8 case per 10,000 patient years

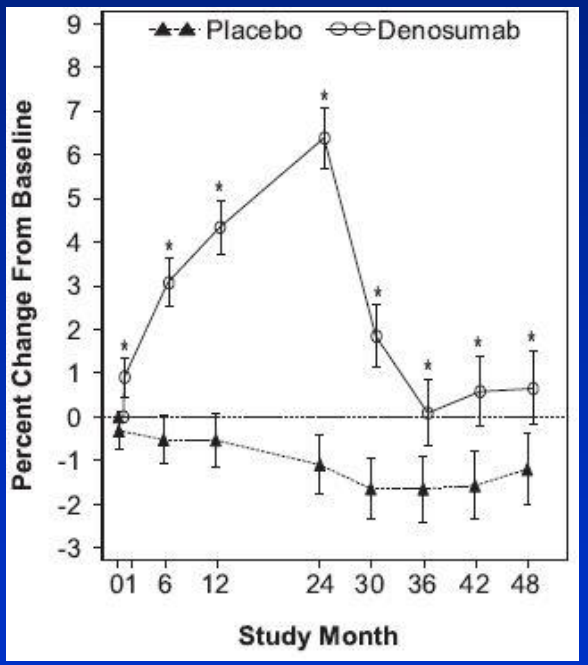
Bone HG et al. *Lancet Diabetes Endocrinol* 2017;513-23

Change after Stopping Denosumab

Serum CTx (C-telopeptide)



Spine BMD

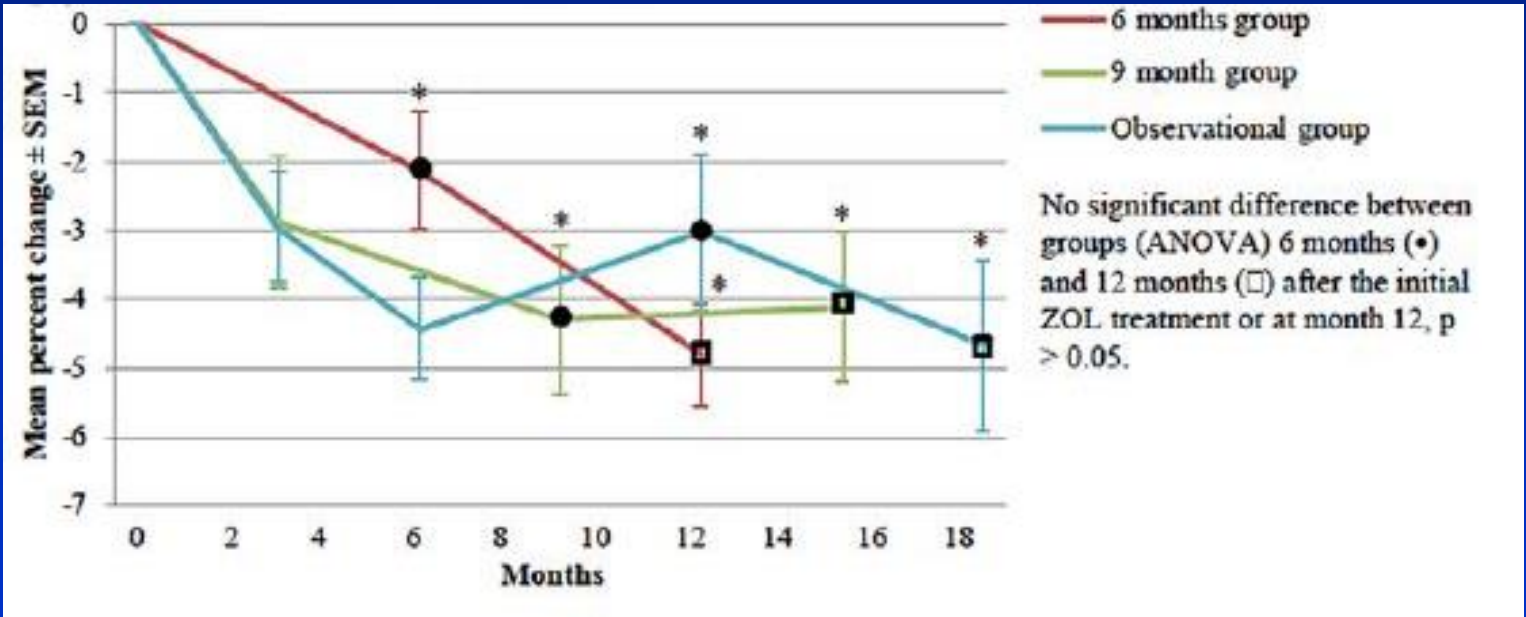


Bone HG et al. *J Clin Endocrinol Metab* 2011;96(4):972-980

Zoledronic Acid after Denosumab

Zoledronic acid administered at the time of the next scheduled denosumab injection—or 3 months later

Spine BMD



Solling AG et al. *J Bone Miner Res* 2020;35(10):1858-1870

Change after Stopping Denosumab

- Stopping denosumab is associated with a brisk increase in bone resorption and a corresponding decrease in BMD
- That increase in bone remodeling after stopping has been associated with an increased risk of multiple vertebral fractures ("MVF")
- Switching to another antiresorptive agent does not fully protect against that increased bone resorption
  - That is true even if zoledronic acid is administered when the next denosumab injection is due—or after a delay of 3 months

Two Common Management Problems

Problem #1

- Is it necessary to stop bisphosphonate therapy after a certain number of years?
- The risk of ONJ is not clearly time-related, but the risk of AFF does appear to increase over time--and the absolute risks remain relatively small
- Because the bisphosphonates “stick” to bone, there is continued fracture reduction even after treatment is discontinued. As such, it is probably appropriate to consider a drug holiday after years of bisphosphonate therapy

ST Harris, personal opinion

Two Common Management Problems

Problem #2

- Is it necessary to stop denosumab therapy after a certain number of years?
- Probably not. Extended therapy is associated with persistently-low fracture rates, even after a decade
- Treatment is associated with AFF and ONJ, but the absolute risks again appear to be relatively small
- If treatment is to be discontinued, it appears to be best to transition to another antiresorptive therapy—but the optimal way to do so is a matter of active ongoing clinical investigation

ST Harris, personal opinion