Bones of Contention 2020
Osteoporosis Controversies and Conundrums

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  - NIAMS: AHRQ, NCATs, NCMRR
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- Immediate Past President, Board of Trustee, National Osteoporosis Foundation
- Secretary, American College of Rheumatology
- Consultant: Abbvie, Amgen, Radius, Roche

Osteoporosis 2020

Challenges, Controversies, Possibilities…

- Growing osteoporosis burden
- What's new/controversial with…
  - Calcium and vitamin D?
  - Bisphosphonates?
  - Denosumab?
  - Anabolics?
  - Vertebral Augmentation?

The New York Times

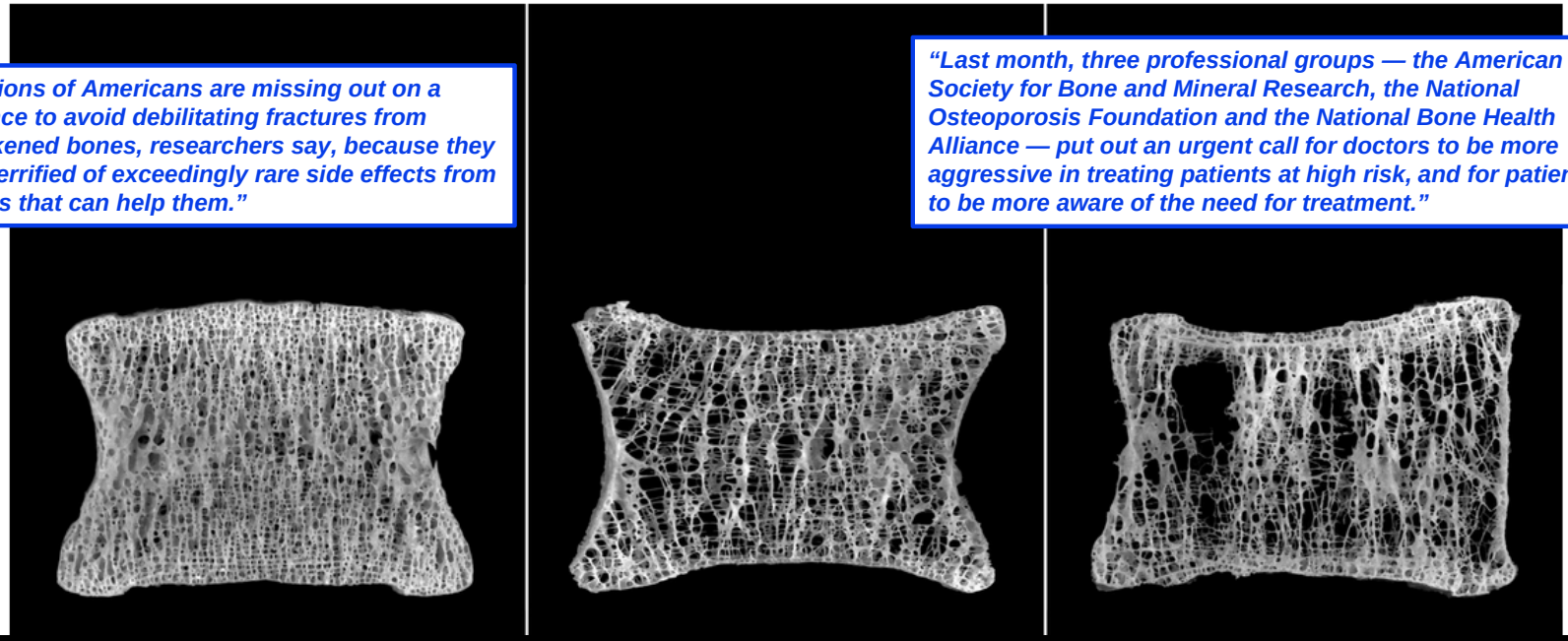
HEALTH

Fearing Drugs' Rare Side Effects, Millions Take Their Chances With Osteoporosis

By GINA KOLATA JUNE 1, 2016

"Millions of Americans are missing out on a chance to avoid debilitating fractures from weakened bones, researchers say, because they are terrified of exceedingly rare side effects from drugs that can help them."

"Last month, three professional groups — the American Society for Bone and Mineral Research, the National Osteoporosis Foundation and the National Bone Health Alliance — put out an urgent call for doctors to be more aggressive in treating patients at high risk, and for patients to be more aware of the need for treatment."



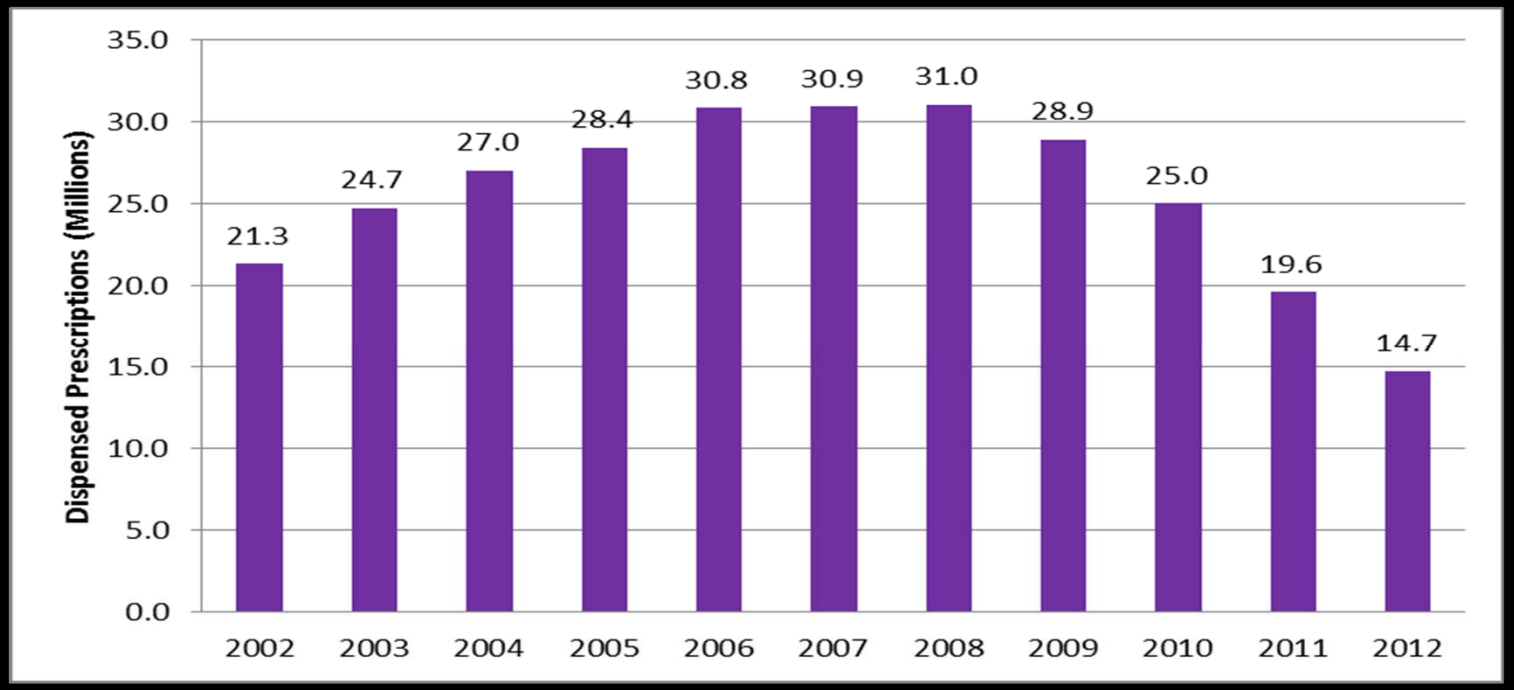
EDITORIAL

JBMR®

A Crisis in the Treatment of Osteoporosis

Khosla and Shane, 2016

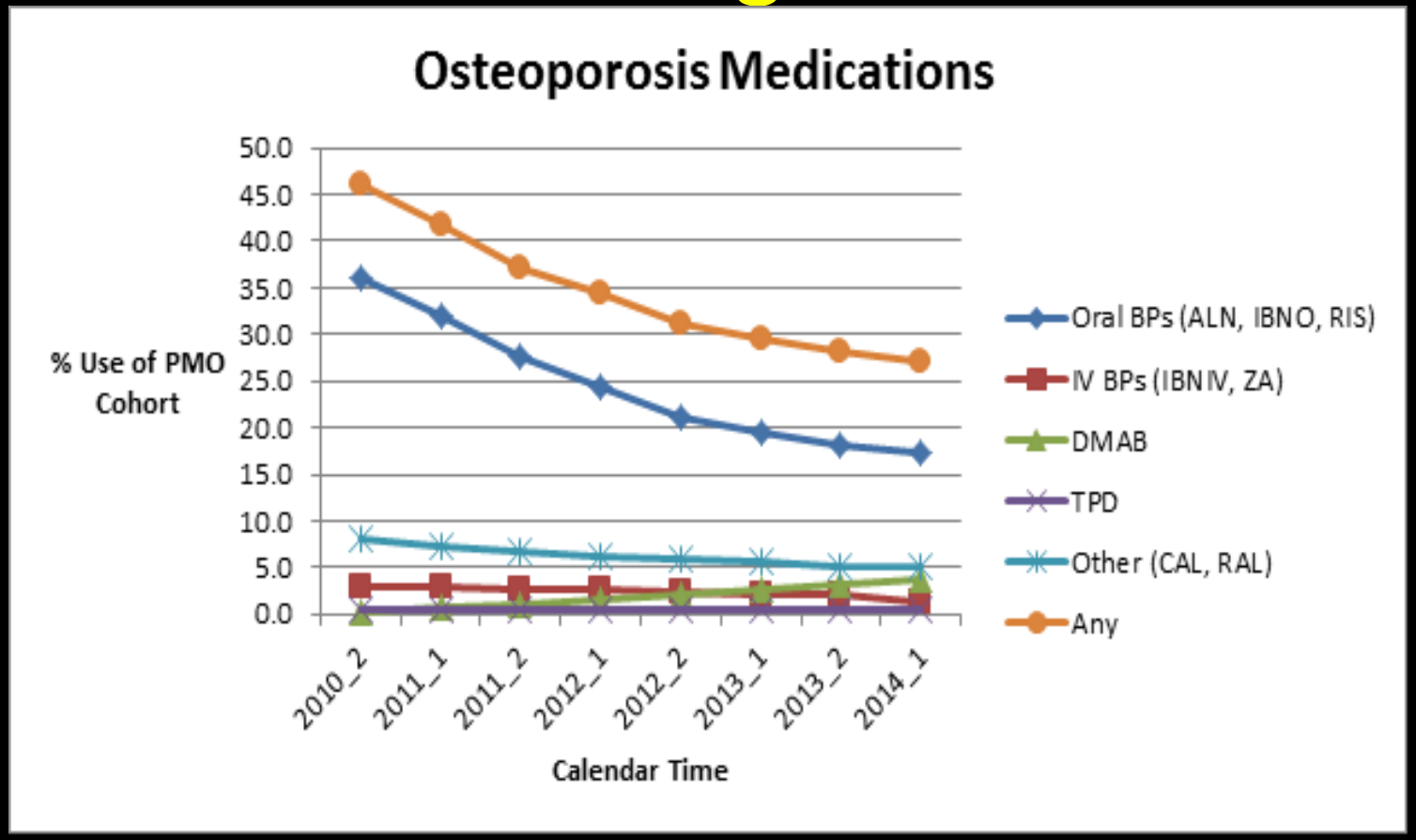
Oral Bisphosphonates Use is Declining (alendronate, risedronate, and ibandronate) Use in USA, 2002-2012



Source: IMS Vector One: National, Years 2002-2012 Data Extracted February 2013

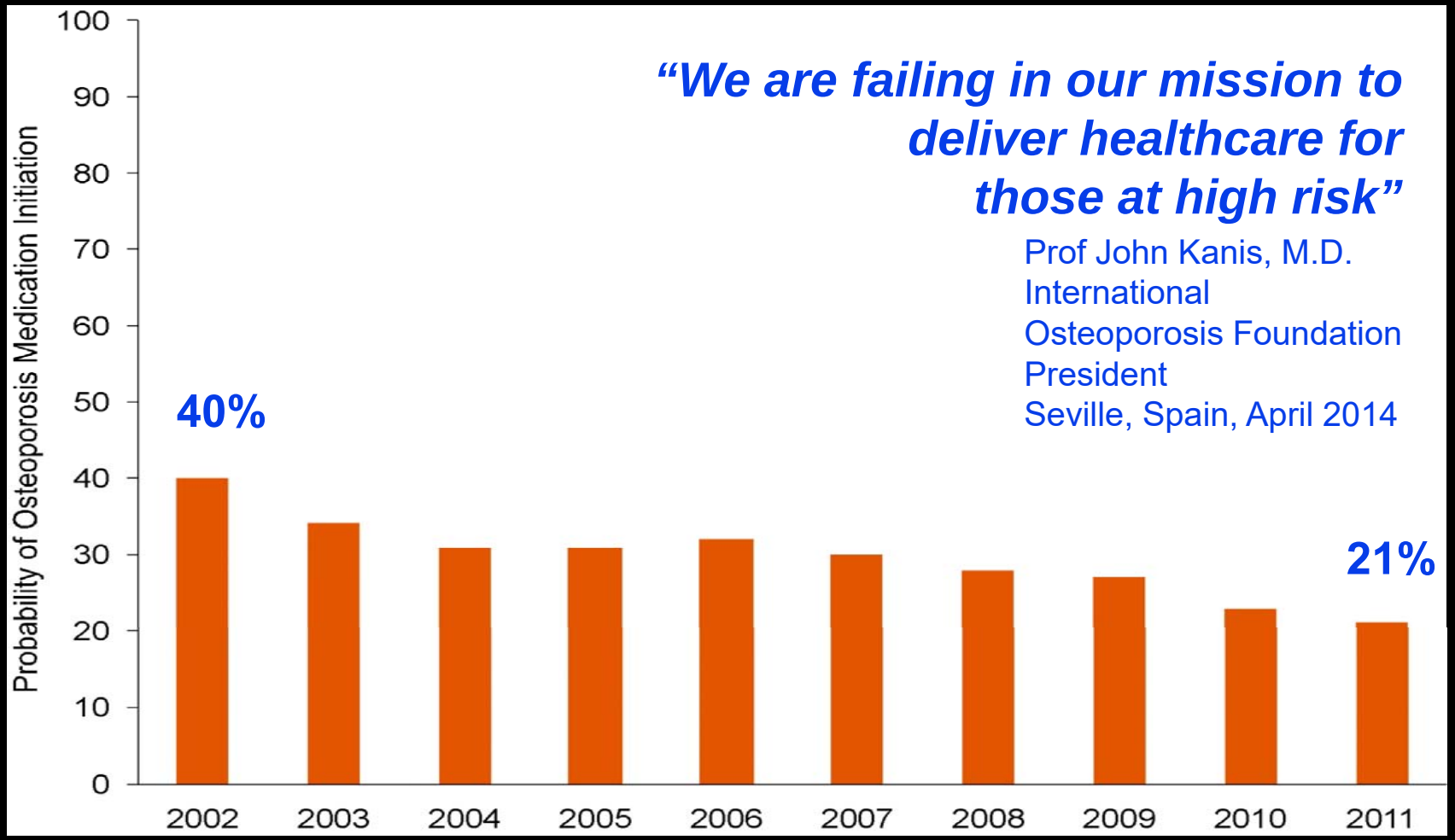
Wysowski D. *Bone* 2012;57: 423

Updated Medicare Data on Drug Rx



Curtis J. et al, personal communication

Treatment Post-fracture is Declining

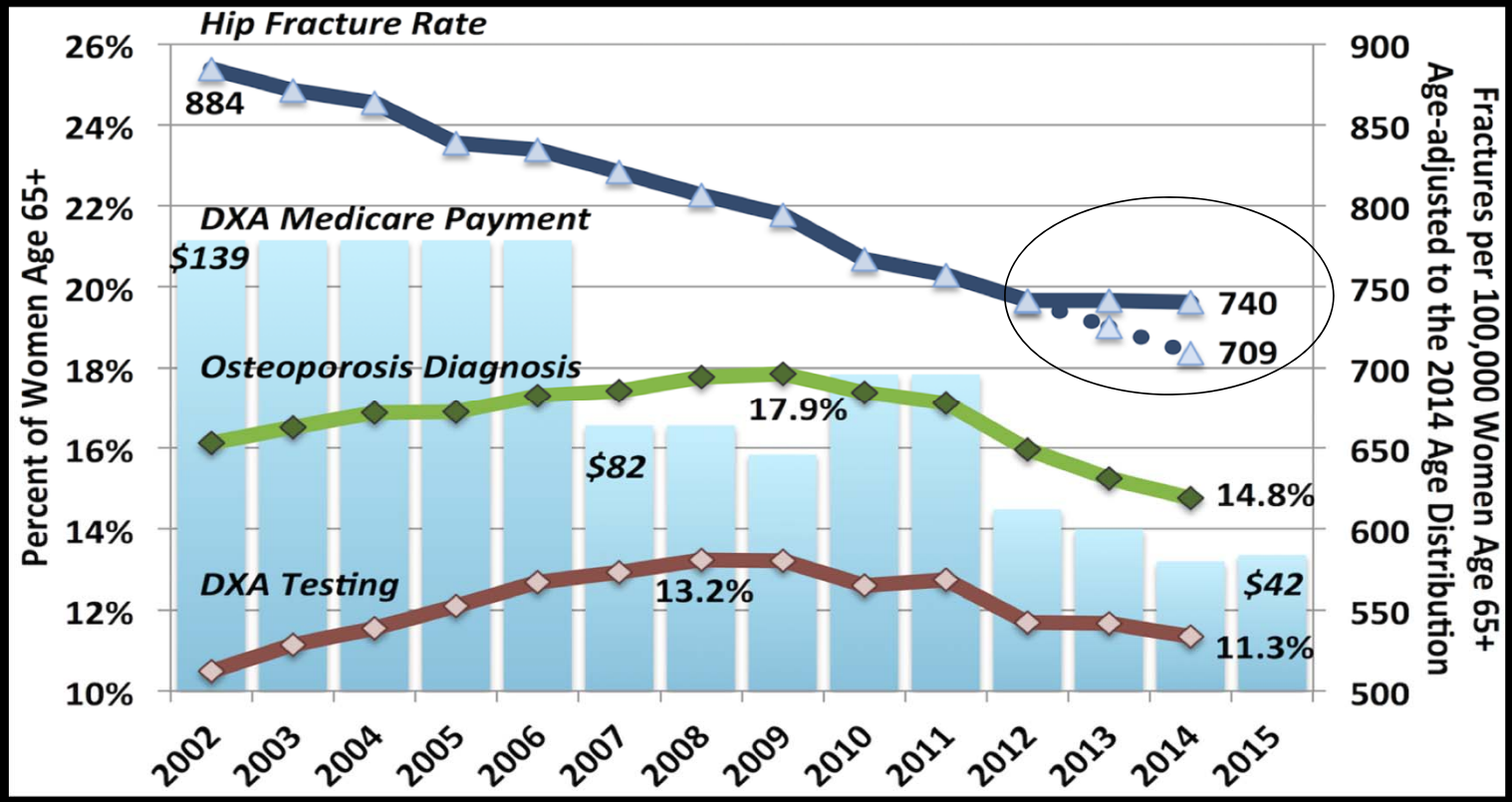


"We are failing in our mission to deliver healthcare for those at high risk"

Prof John Kanis, M.D.
International
Osteoporosis Foundation
President
Seville, Spain, April 2014

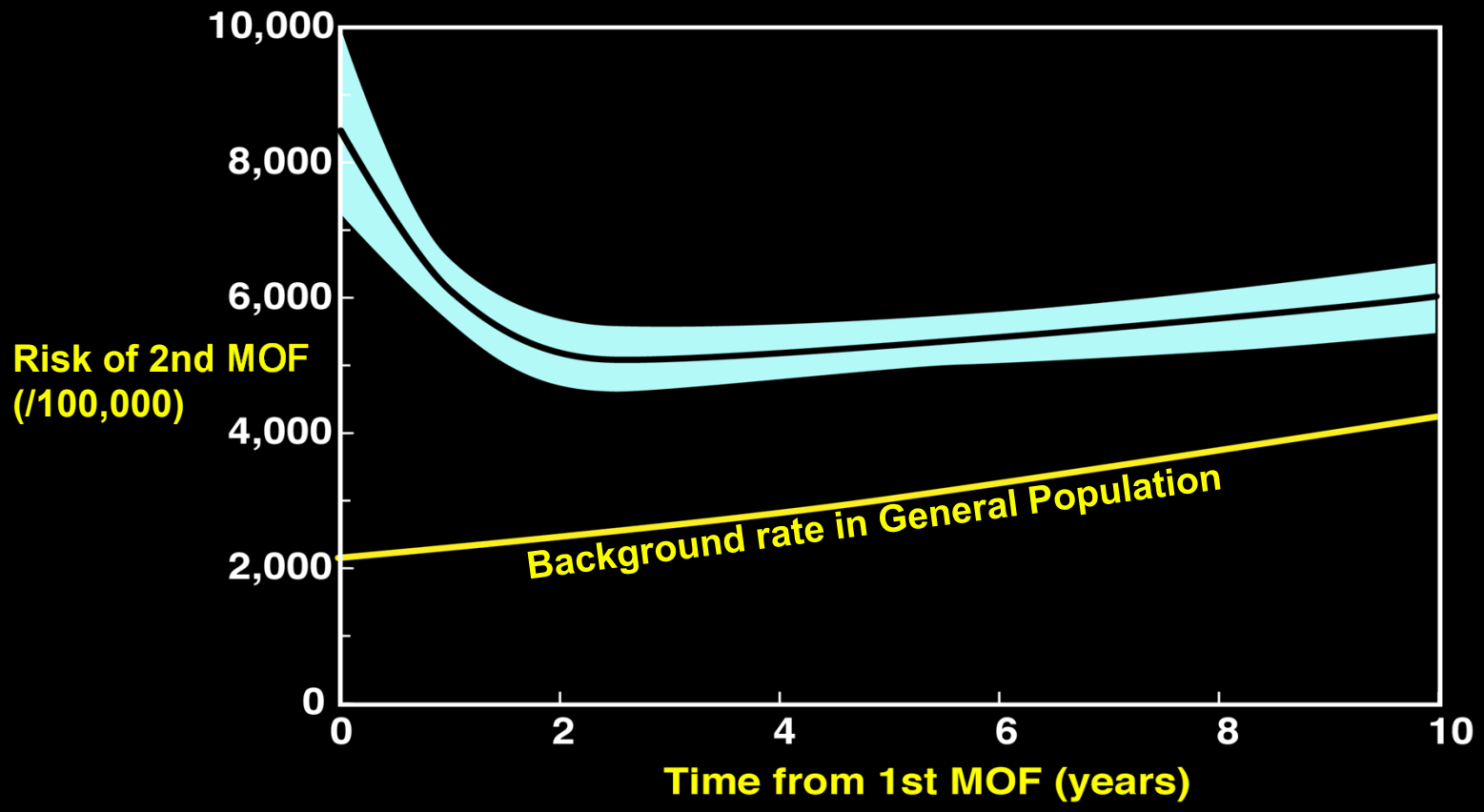
Solomon D. *J Bone Min Res* 2014;29:1929

Most Recent Changing Testing and Fracture Rates in US



Lewicki M. *Osteop Int*, 2018;29:717

Major Osteoporosis Fracture (MOF)-after-Fracture Icelandic Registry (n = 19K)



Johanason H. *Osteoporos Int* 2017;28:775

What is New/Controversial with Calcium and Vitamin D?

Calcium Controversies

- How much is needed?
- Does it cause heart disease?
- Does it reduce fractures?
- From diet vs. supplements?
- If supplements, what types?

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Calcium and Vitamin D Recommended Daily Allowances

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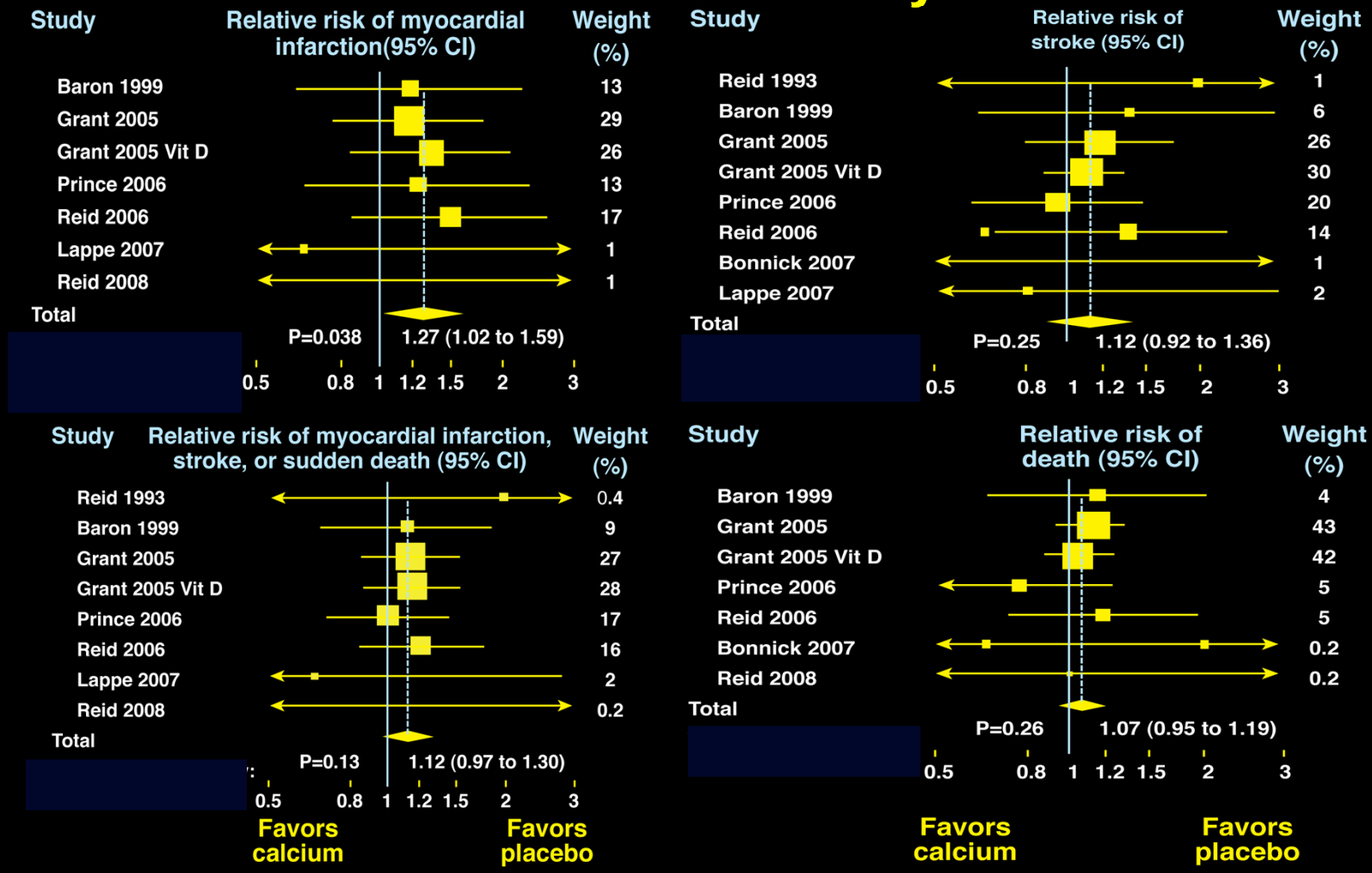
Age Range (yrs)	Calcium (mg/day)	Vitamin D (IU/day)
9-18	1300	600
19-50 51-70 (men)	1000	600
51-70 (women)	1200	600
> 70	1200	800

Calcium Meta-analysis

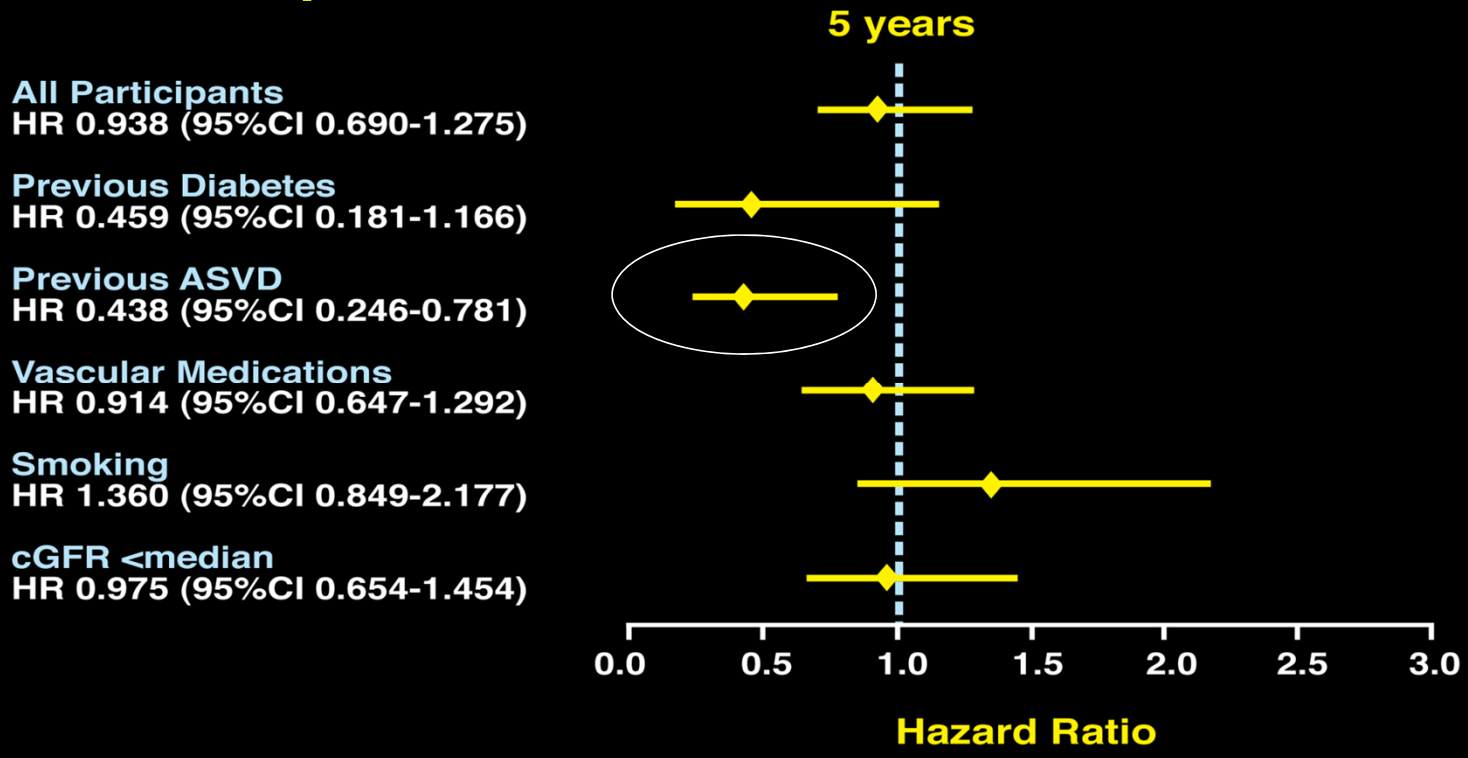


Bolland MJ. *BMJ* 2010; 341: c3691

Calcium Meta-analysis Limitations

- No trial had primary cardiovascular outcome
- Endpoint adjudication - only 2 trials by blinded investigators
- Renal function not known
- Calcium may be safer when given with magnesium salts and/or vitamin D
- Need sensitivity analysis with different study selection criteria

Calcium Treatment Compared to Placebo on Atherosclerotic Vascular Disease, Hospitalizations, and Death Outcomes



Analyses used groups with named baseline risk factor.
Adjusted for age, calcium intake, compliance, cardiovascular disease, eGFR, diabetes, previous/current smoking, & baseline cardiovascular medications unless covariate subject of analysis.

eGFR = estimated glomerular function rate; ASVD = atherosclerotic vascular disease

Lewis JR. *JBMR* 2011; 26:35

Heart. 2012 Jun;98(12):920-5. doi: 10.1136/heartjnl-2011-301345.

Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg).

Li K[1], Kaaks R, Linseisen J, Rohrmann S.

Calcium supplements 'double risk of heart attack', study finds

Doctors dispute results but advise people not to take supplements unless required for medical condition

▲ The new study challenges traditional wisdom on the benefits of calcium supplements. Photograph: Anthony Devlin/PA

Annals of Internal Medicine

CLINICAL GUIDELINE

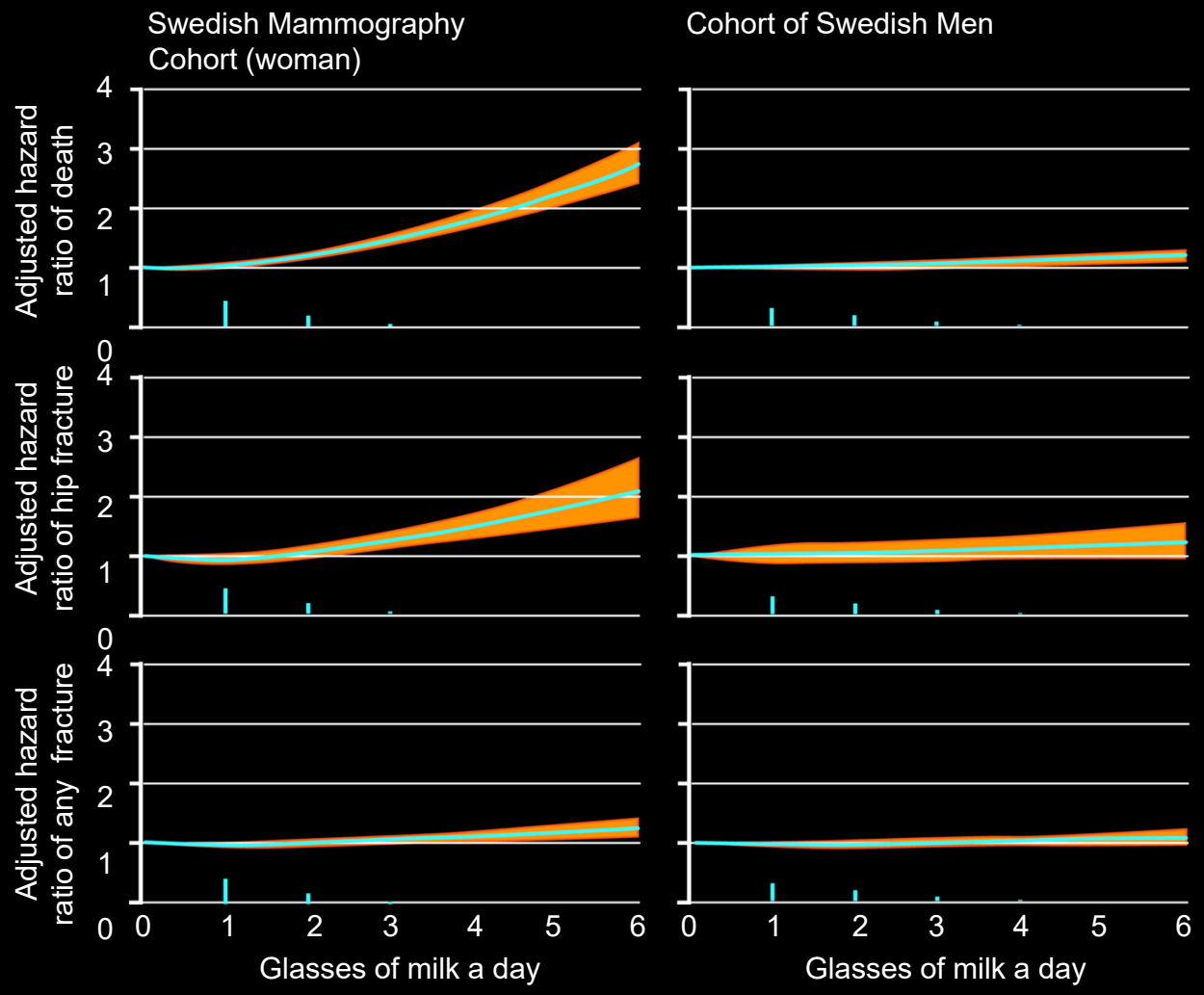
Lack of Evidence Linking Calcium With or Without Vitamin D Supplementation to Cardiovascular Disease in Generally Healthy Adults: A Clinical Guideline From the National Osteoporosis Foundation and the American Society for Preventive Cardiology

Stephen L. Kopecky, MD; Douglas C. Bauer, MD; Martha Gulati, MD; Jeri W. Nieves, PhD; Andrea J. Singer, MD; Peter P. Toth, MD, PhD; James A. Underberg, MD; Taylor C. Wallace, PhD; and Connie M. Weaver, PhD

"Calcium with or without vitamin D intake from food or supplements that does not exceed the tolerable upper level of intake (defined by the National Academy of Medicine as 2000 to 2500 mg/d) has no relationship (beneficial or harmful) to the risk for cardiovascular and cerebrovascular disease, mortality, or all-cause mortality in generally healthy adults at this time."

Kopecky SL. *Ann Intern Med*. 2016;165:867

Milk and Mortality



Michaellsson K
BMJ 2014;
349:g6015

“Milk & Mortality/ Encounters with Vampires”

Annals of Internal Medicine

ORIGINAL RESEARCH

Association Among Dietary Supplement Use, Nutrient Intake, and Mortality Among U.S. Adults

A Cohort Study

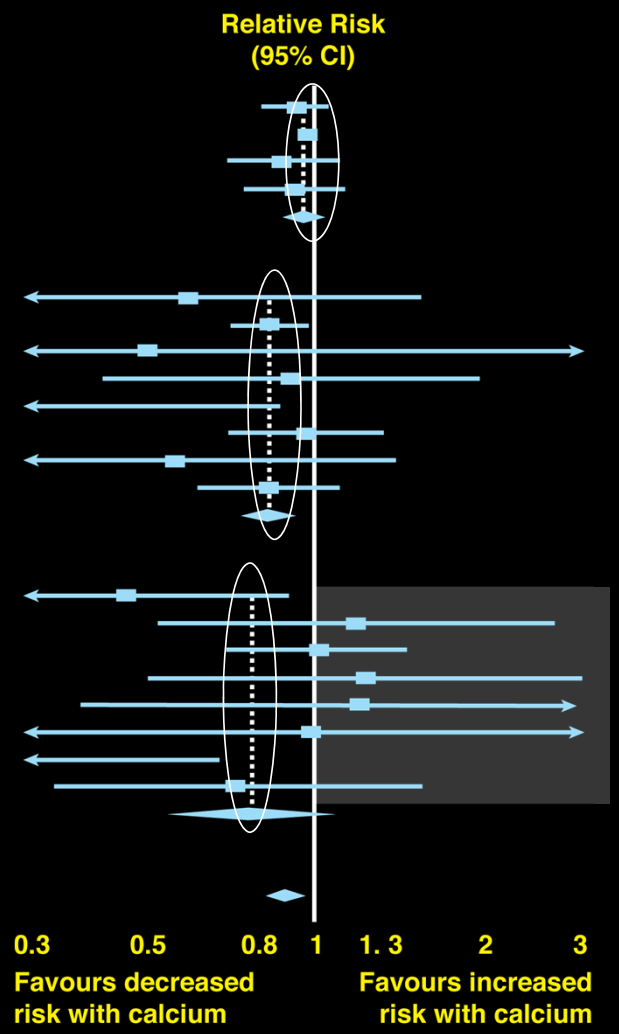
Fan Chen, MS, MPH; Mengxi Du, MS, MPH; Jeffrey B. Blumberg, PhD; Kenneth Kwan Ho Chui, PhD, MPH; Mengyuan Ruan, MS; Gail Rogers, MA; Zhilei Shan, MD, PhD; Luxian Zeng, MD, MPH; and Fang Fang Zhang, MD, PhD

- **NIH funded study of NHANES data in 30,899 adults**
- **"Excess intake of calcium was associated with increased risk for cancer death"**
- **"the association seemed related to calcium intake from supplements (≥ 1000 mg/d vs. no use)" – 1.5 extra deaths per 1000 patient-treatment-years**

Chen F. *Ann Intern Med* 2019;170:604.

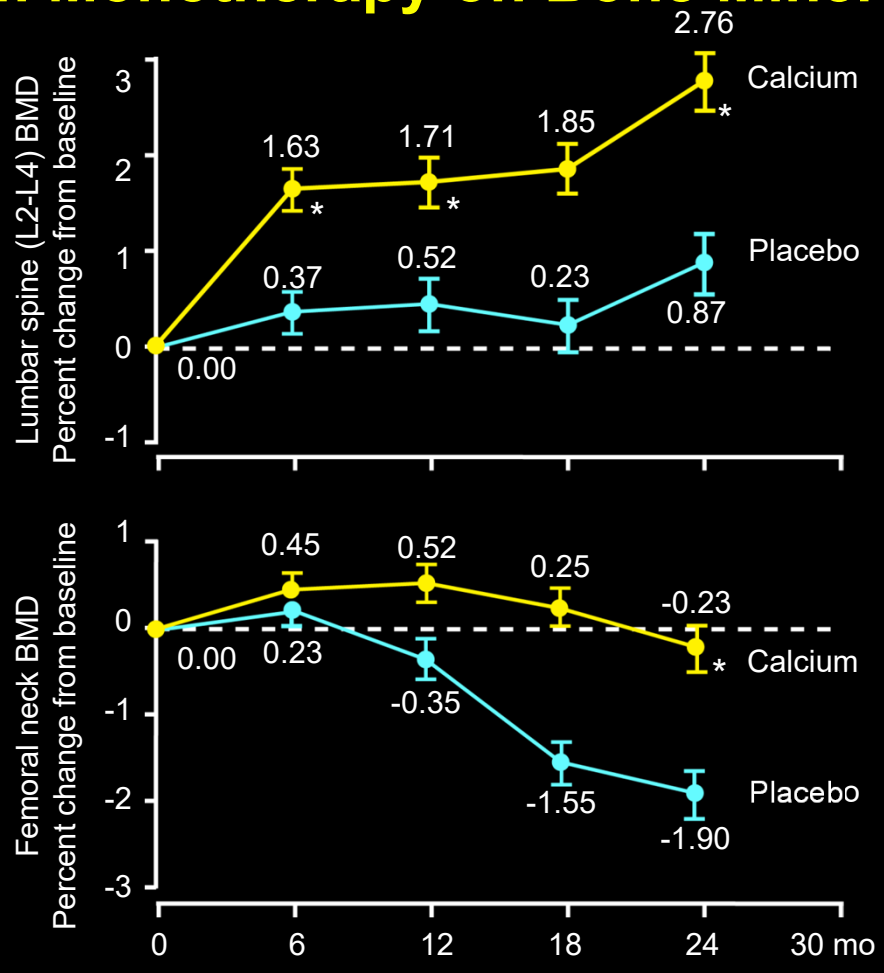
Calcium Supplements and Fractures

Study	No. of events/Total Calcium	Control	Weigh (%)	Relative risk (95% CI)
Low risk of bias				
Grant 2005	364/2617	400/2675	14	0.93 (0.82 to 1.06)
Jackson 2006	2102/18,176	2158/18,106	76	0.97 (0.92 to 1.03)
Prince 2006	110/730	126/730	4	0.87 (0.69 to 1.10)
Reid 2006	134/732	147/739	5	0.92 (0.75 to 1.14)
Total (95% CI)	2710/22,255	2831/22,250	100	0.96 (0.91 to 1.01)
Test for heterogeneity: P=0.77, I^2=0%				
Moderate risk of bias				
Reid 1993	6/68	10/67	2	0.59 (0.23 to 1.54)
Chapuy 1994	240/1537	290/1539	61	0.83 (0.71 to 0.97)
Chevalley 1994	2/62	2/31	0	0.50 (0.72 to 3.38)
Riggs 1998	11/119	12/117	2	0.90 (0.41 to 1.96)
Baron1999	4/464	14/466	1	0.29 (0.10 to 0.87)
Porthouse 2005	58/1321	91/1993	14	0.96 (0.70 to 1.33)
Reid 2008	9/216	8/107	2	0.56 (0.22 to 1.40)
Salovaara 2010	78/1718	94/1714	17	0.83 (0.62 to 1.11)
Total (95% CI)	408/5505	521/6034	100	0.83 (0.73 to 0.93)
Test for heterogeneity: P=0.56, I^2=0%				
High risk of bias				
Dawson-Hughes 1997	11/187	26/202	15	0.46 (0.23 to 0.90)
Peacock 2000	11/126	10/135	12	1.18 (0.52 to 2.68)
Chapuy 2002	69/389	34/194	24	1.01 (0.70 to 1.47)
Avenell 2004	9/64	8/70	11	1.23 (0.51 to 3.00)
Harwood 2004	6/75	5/75	8	1.20 (0.38 to 3.76)
Bolton-Smith 2007	2/62	2/61	3	0.98 (0.14 to 6.76)
Bonnick 2007	9/282	28/281	12	0.32 (0.34 to 1.54)
Sambrook 2012	11/170	14/156	13	0.77 (0.53 to 1.11)
Total (95% CI)	128/1355	127/1174	100	0.89 (0.81 to 0.96)
Test for heterogeneity: P=0.08, I^2=44%				
Test for heterogeneity between subgroups: p=0.05				
All studies	3246/29,115	3479/29,458		
Overall: P=0.004				
Test for heterogeneity: P=0.17. I^2=27%				



Bolland M. *BMJ* 2015; 351:h4580

Calcium Monotherapy on Bone Mineral Density



Rajatanavin R. *Osteoporos Int* 2013;24:2871

Vitamin D Controversies

- If supplements, How much? Vitamin D2 vs. D3?
- When should we measure it, is it accurate?
- What is optimal target level?
- Does Vitamin D reduce fractures? Increase fx rate? Other Health Benefits?
- Are kidney stones a worry?

Armas. *JCEM*, 2004;89:5387-91
Jackson R.D. *NEJM*, 2006;254:669
Hanson K. *JBMR,* 2008;23:1052
Holick, M. *JCEM*, 2008;93:677-81
Ensrud K. *JCEM*, 2009;94:2773
Rosen CJ. *NEJM*, 2011;364:248

Calcium and Vitamin D Recommended Daily Allowances

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Age Range (yrs)	Calcium (mg/day)	Vitamin D (IU/day)
9-18	1300	600
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PERSPECTIVE

JBMR

Why the IOM Recommendations for Vitamin D Are Deficient

Robert P Heaney[1] and Michael F Holick[2]

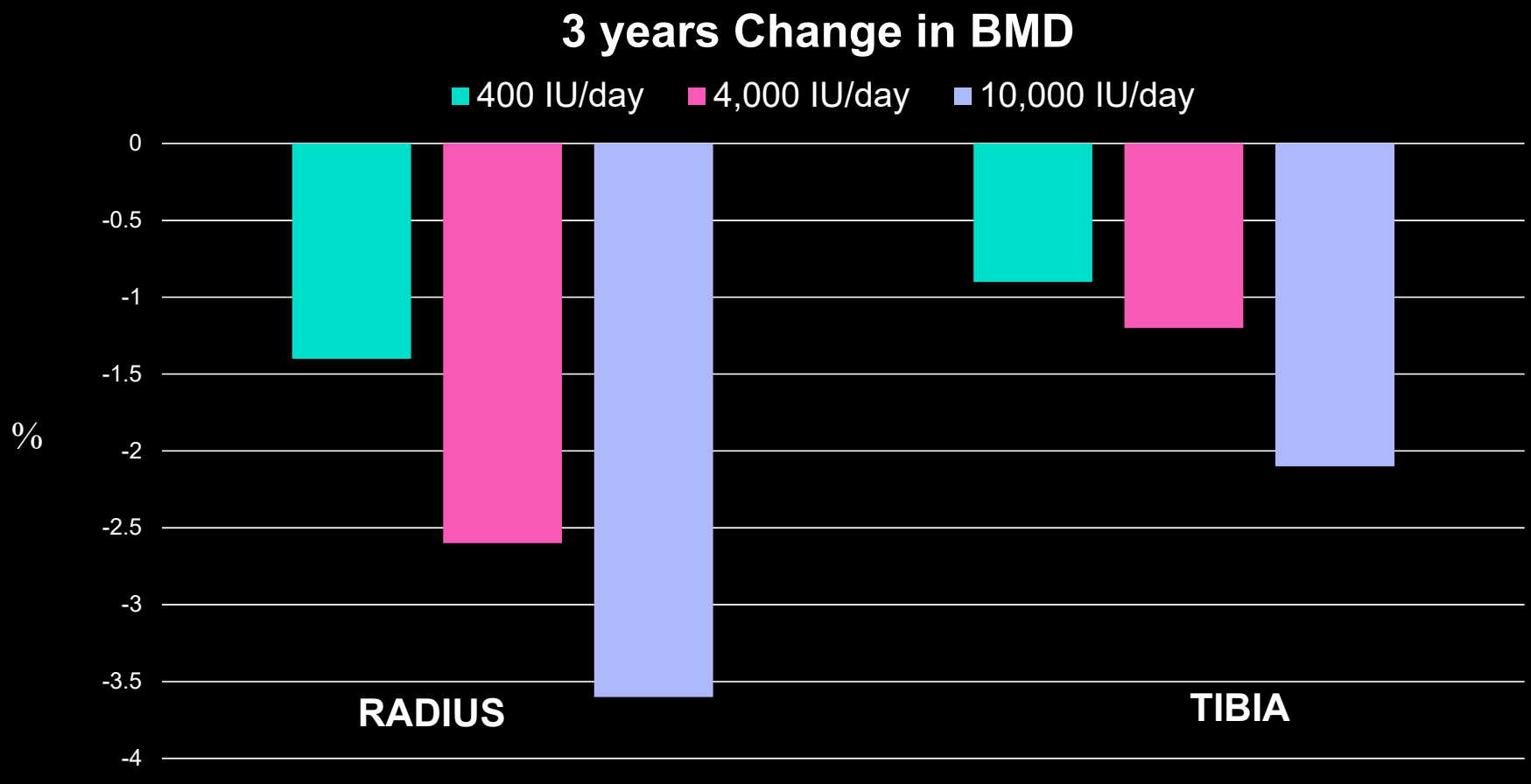
- **"In this perspective, we have deliberately avoided a mind-numbing laundry list of the vast number of factual inaccuracies and misinterpretations in this report."**
- **"Our recommendation to the public is that the IOM report should be taken with a grain of salt (another nutrient the IOM finds risky)"**

Updated US Preventive Services Task Force Recommendations on Calcium and Vitamin D

- Evidence insufficient to assess balance of benefits and harms of calcium and vitamin D supplements to prevent fractures for primary prevention in community dwelling
  - Premenopausal women and men (any dose)
  - Postmenopausal women (at sl higher dose)
- No benefit of lower doses of calcium and vitamin D in postmenopausal women
- Vitamin D USEFUL to prevent falls in older adults at fall risk
- Recommendations Do NOT apply to women at high risk for fractures, osteoporosis or known to be vitamin D deficient

USPSTF, *JAMA*, online 2018

Calgary Vitamin D Study



Boyd SK, *ASBMR 2018*, Presentation 1062
Burt LA. *JAMA*. 2019;322:736

VITAL Study

Design

- 25,871 patients - follow-up 6 years

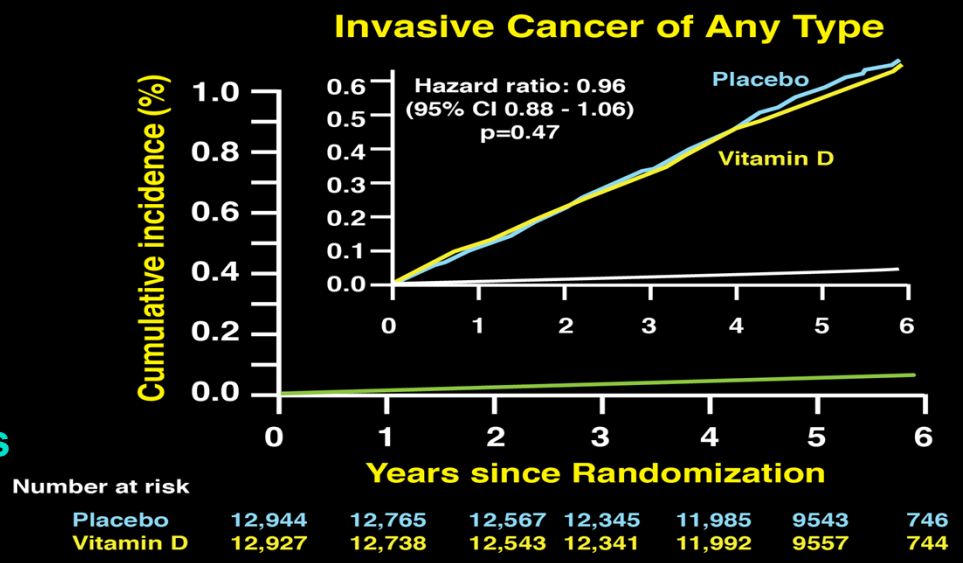
Main Results

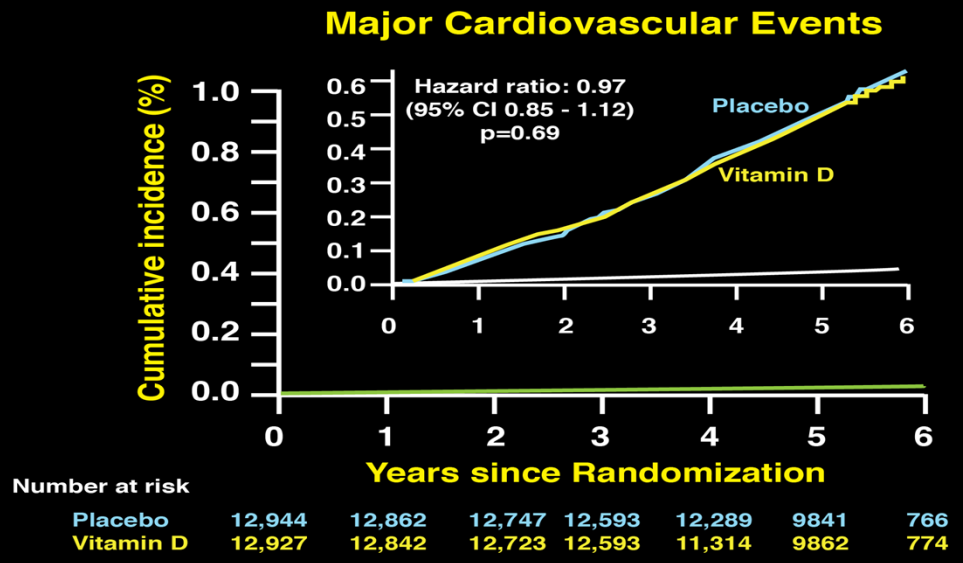
- Baseline 25(OH)D - 31 ng/ml
- No differences in invasive cancer or CV events
- No differences based on baseline 25(OH)D (threshold 20 ng/ml)

Limitations

- Effect of very low 25(OH)D not investigated
- Allowed out-of-trial supplementations

Manson J. *N Eng J Med* 2019;380:33





Calcium and Vitamin D Controversies

Summary Points

- Adequate calcium & vitamin D essential for bone health, vitamin D may have other health benefits

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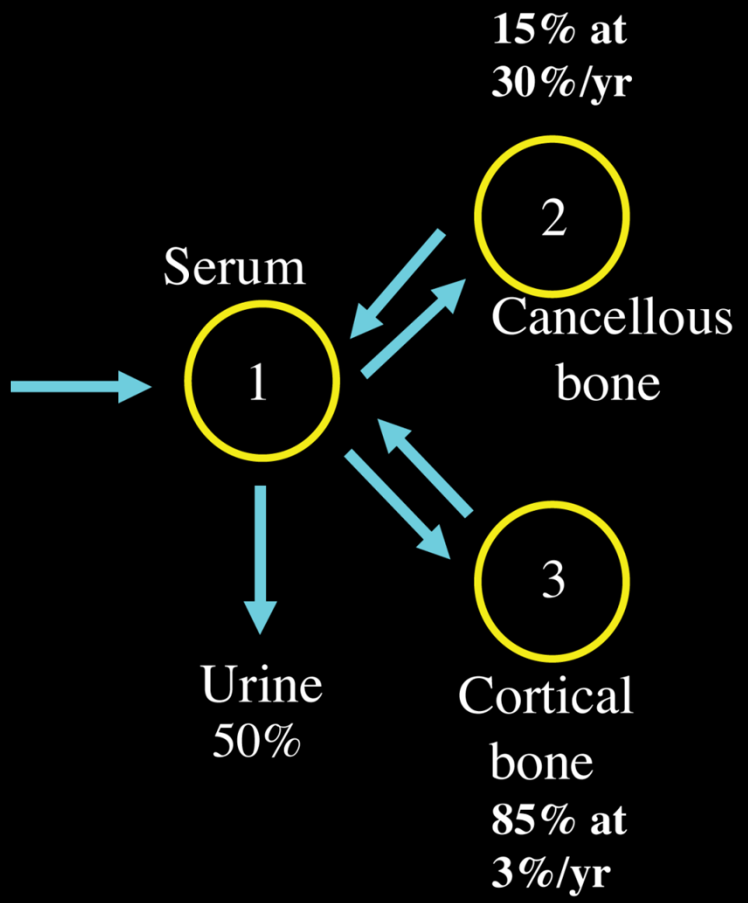
Summary Points

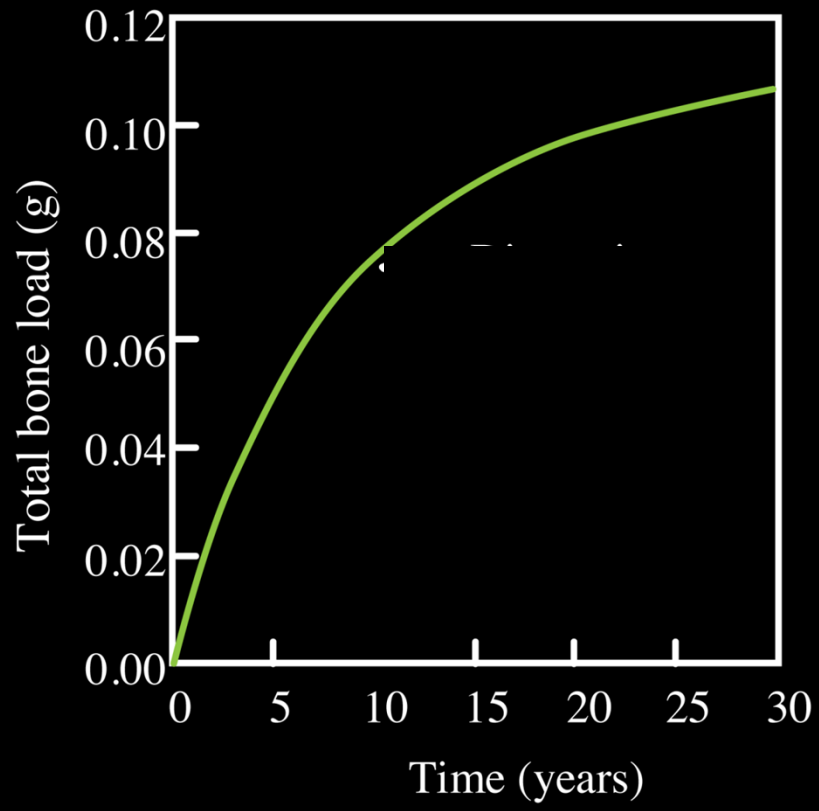
- Adequate calcium & vitamin D essential for bone health, vitamin D may (or may not?) have other health benefits
- Supplements won't help If your not deficient or dose inadequate
- Overzealous use of calcium and vitamin D supplements may be deleterious
- Calcium:
  - Best sourced from diet, citrate for older adults
  - 1200 mg/d is adequate for most adults
- Vitamin D:
  - Avoid dose that will not be adequate or is too high
  - 800 IU/D reasonable supplement for those at risk for fractures
  - 25 OH Vitamin D level:
    - Maintained at ~20 ng/ml
    - Target 30 to 50 ng/ml for those at high fracture risk

What's New/Controversial with Bisphosphonates?

Bisphosphonates

"The Gift that Never Stops Giving"

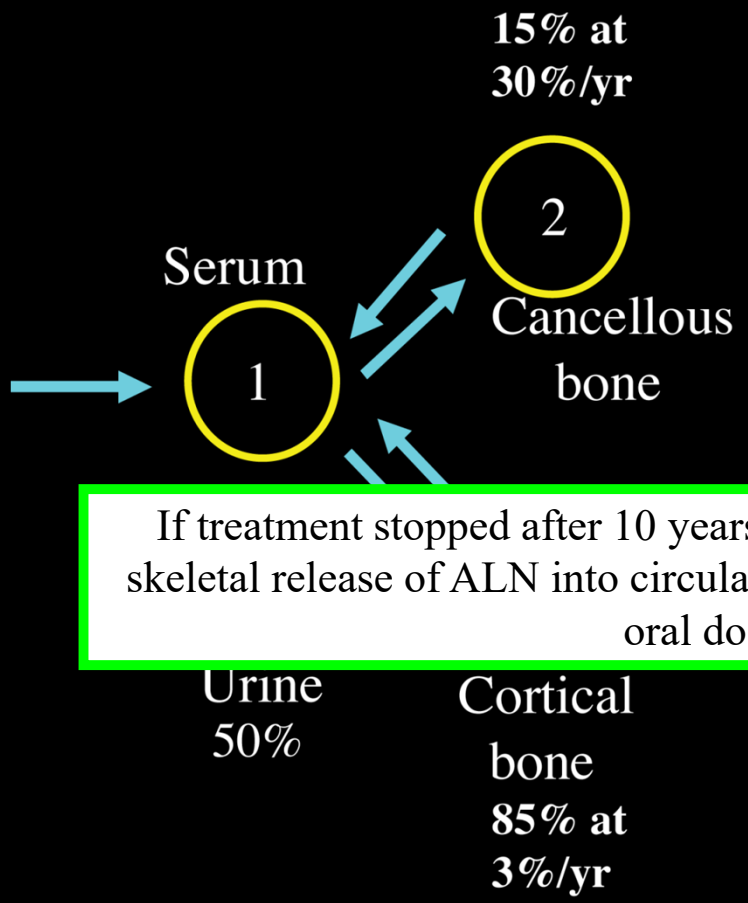


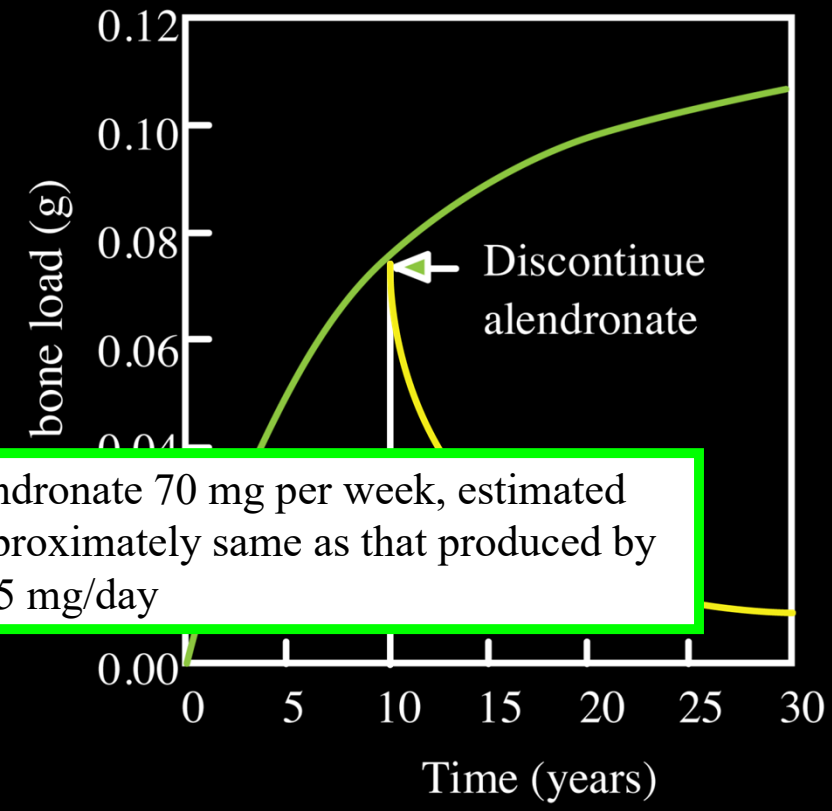


Rodan G. *Curr Med Res*, 2004;20:1291

Bisphosphonates

"The Gift that Never Stops Giving"





If treatment stopped after 10 years of alendronate 70 mg per week, estimated skeletal release of ALN into circulation approximately same as that produced by oral dose of 2.5 mg/day

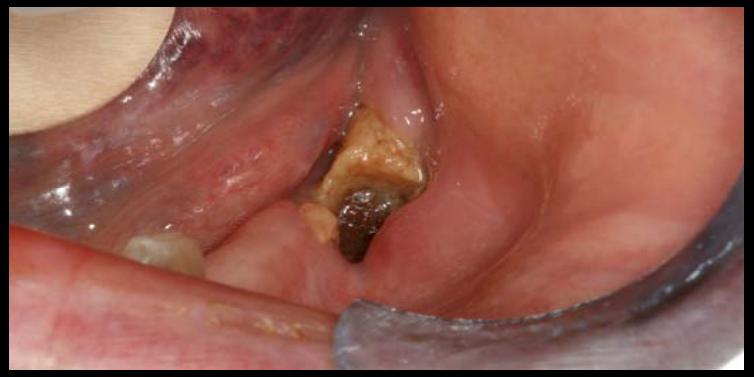
Rodan G. *Curr Med Res*, 2004;20:1291

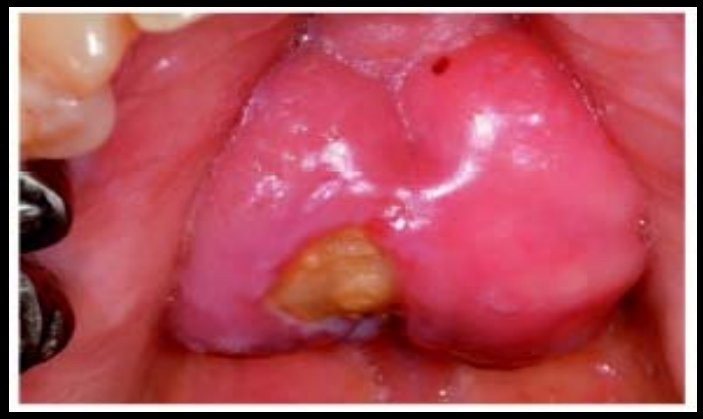
Bisphosphonate Potential Safety Issues

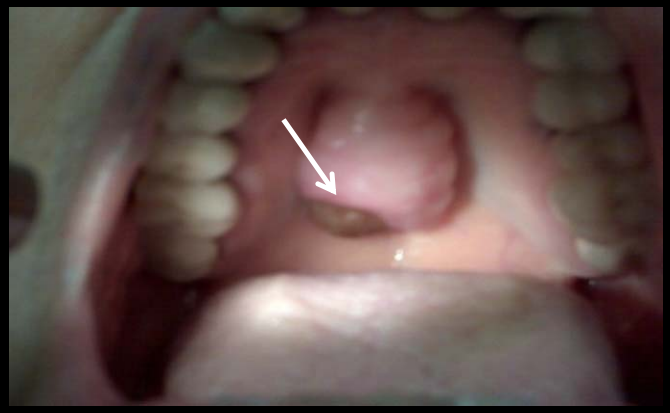
- Osteonecrosis of the Jaw (ONJ)
- Atypical Fractures
- Acute phase reactions
- Esophageal Cancer
- Atrial Fibrillation
- Fracture Non-union
- Uveitis

Osteonecrosis of the jaw

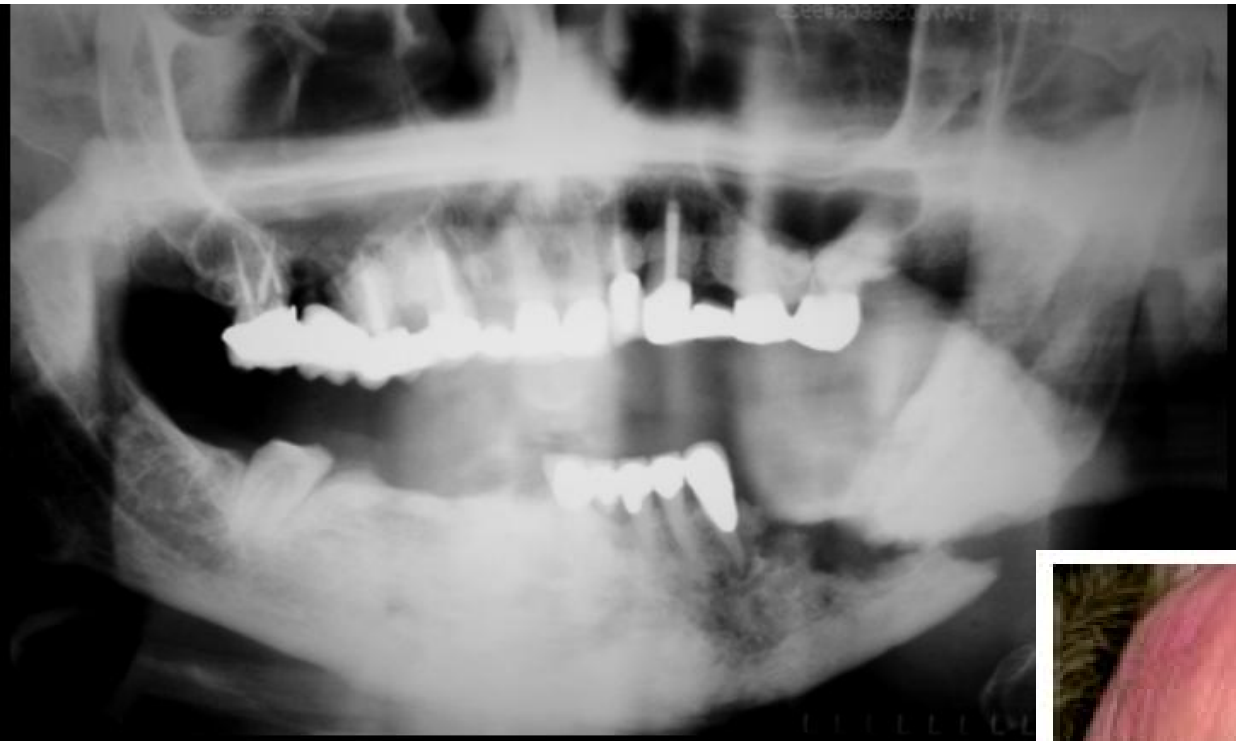
- Area of exposed and necrotic bone in maxillofacial region that does not heal within 8 weeks of identification
- No history of radiation therapy to craniofacial region
- Estimated incidence in patients receiving bisphosphonates for osteoporosis: 1/1000 to 1/10K

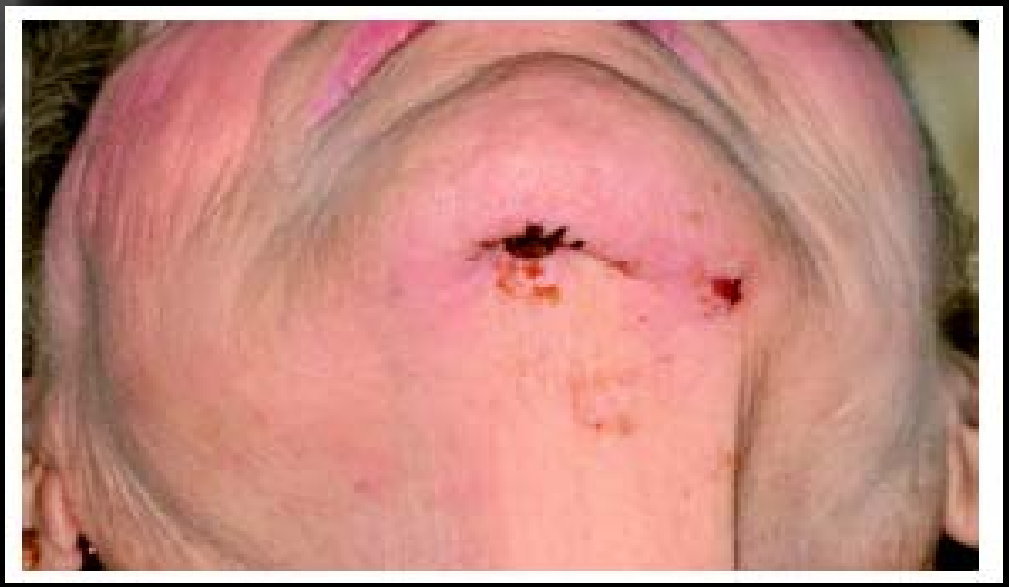


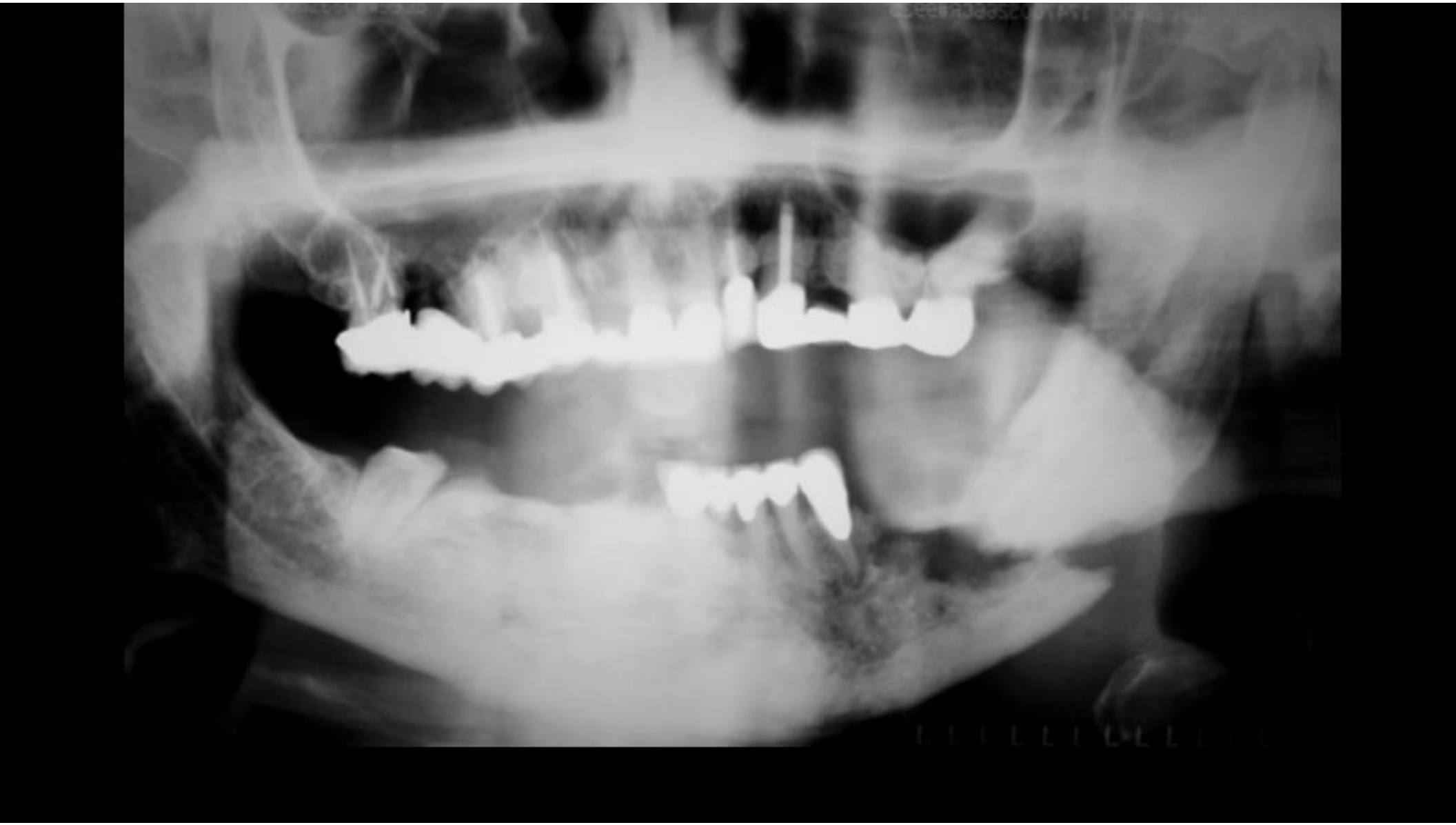




Woo S. *Annals Int Med* 2006;144:753







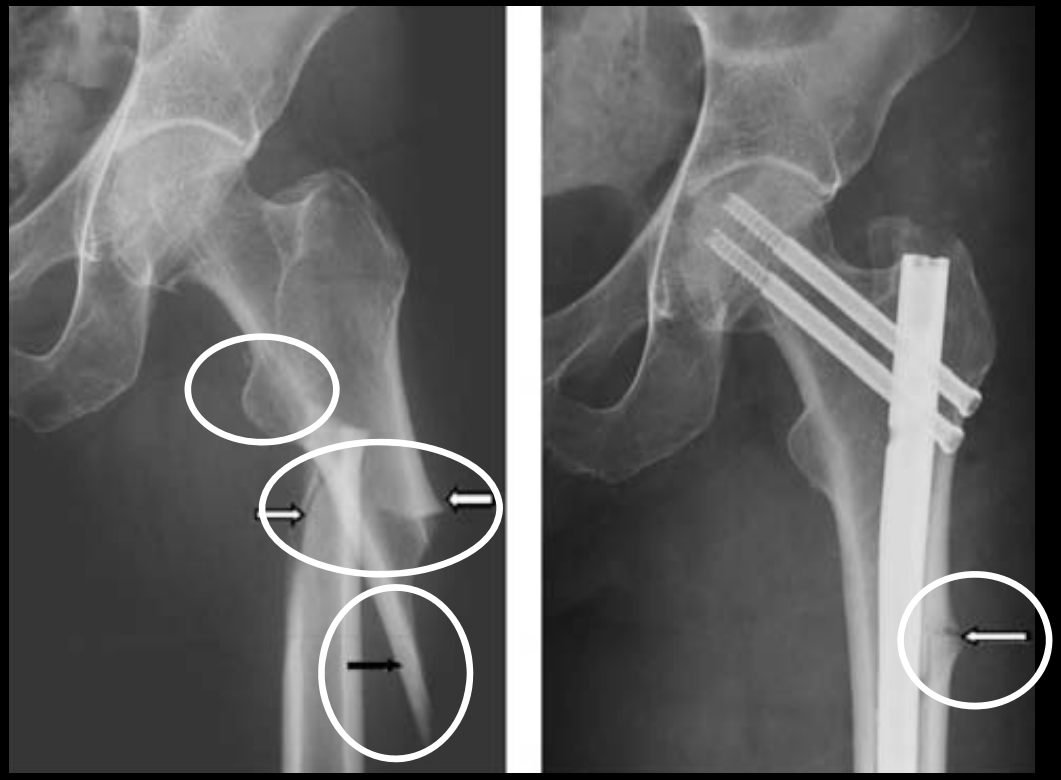
Prevention of ONJ

- **Prior to Anti-resorptive Treatment**
  - Remove oral infection, pathology and use antibiotics
  - Extract partially embedded or very poor teeth
  - Periodontal stabilization for teeth with excessive mobility in patients with good dental hygiene
  - Anti-resorptives deferred until surgical sites mucosalized (2–3 weeks)
  - Inadequate dentures modified, rebased, or replaced, especially along lingual flange region or at mandibular tori
- **Prior to invasive dental treatments**
  - Bone turnover markers (CTX/NTX) generally <u>not</u> helpful
  - Debate over bisphosphonate discontinuation- consider 2 month break

Marx RE. *J Oral Maxillofac Surg* 2005;63:1567
Hellstein JW. *J Am Dent Assoc* 2011;142:1243
Vandone AM. *Ann Oncol* 2012;23:193
Ruggiero SL. *J Oral Maxillofac Surg* 2014;72:1938

Atypical Femur Fractures

Fracture Along Femoral Diaphysis from Lesser Trochanter to Supracondylar Flare



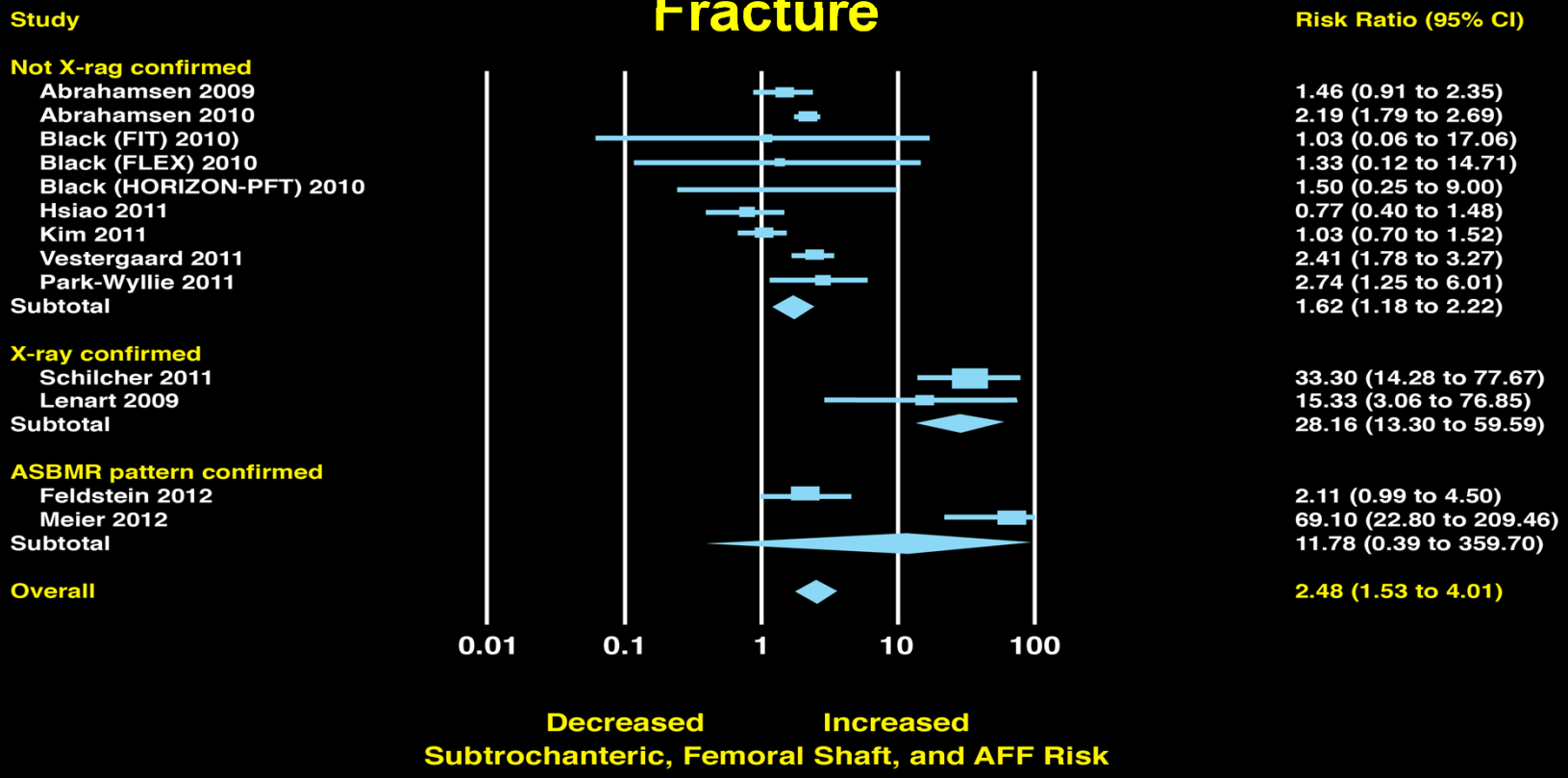
Major Criteria

1. Non-comminuted
2. No trauma
3. Transverse short oblique
4. Both cortices, medial spike

5. Periosteal reaction lateral cortex

Shane E. JBMR 2014;29:1

Association Between Bisphosphonate use and Subtrochanteric or Femoral Shaft Atypical Femur Fracture



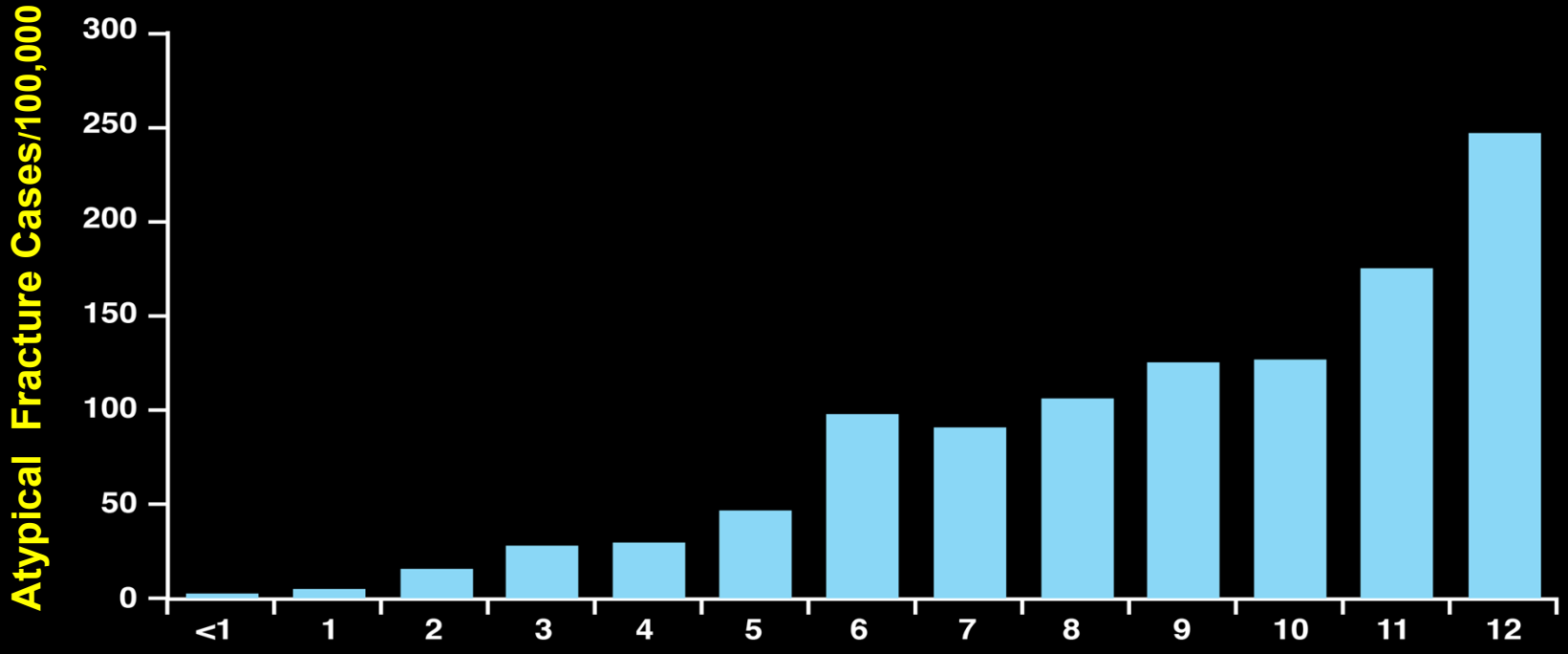
Gedmintas L. *J Bone Miner Res* 2013;28:1729

Balancing Benefits and Risks

- Assume risk of atypical (stress) fracture 8/10,000 (per Schilcher study)
- Number Needed to Treat (NNT) with 3 years of bisphosphonate to prevent:
  - Hip fracture = 91
  - Radiographic vertebral fracture = 14
- Number needed to Harm (NNH) with an atypical fracture = 417 for 3 years
- For each stress (atypical) fracture caused, at least 30 vertebral and 5 hip fractures prevented

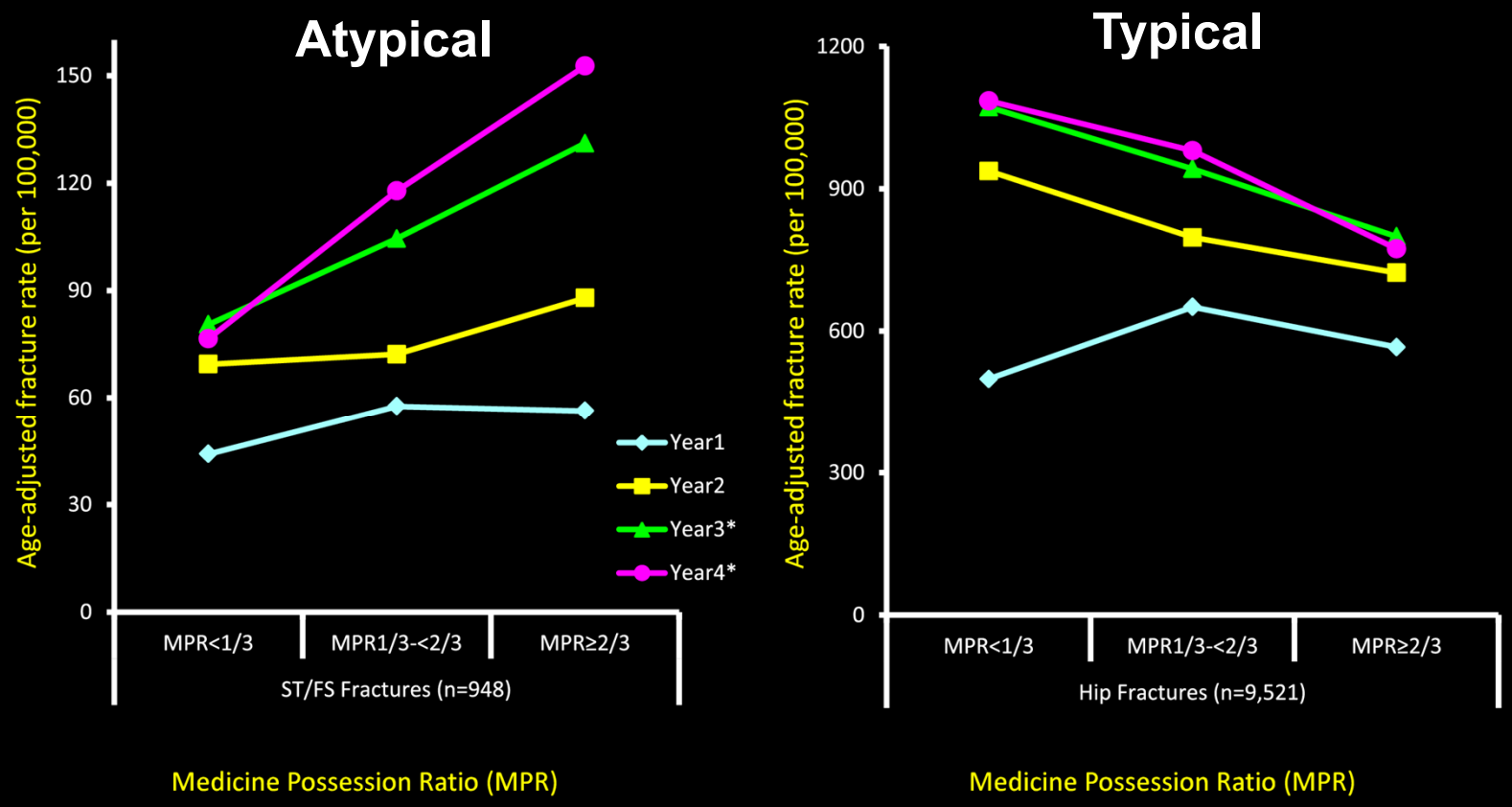
Schilcher, J. Letter to editor reply, *NEJM,* 2011

Atypical Femoral Fractures (AFF) Increase with Longer Bisphosphonate Exposure



Dell R. *J Bone Min Res* 2012;27:2544

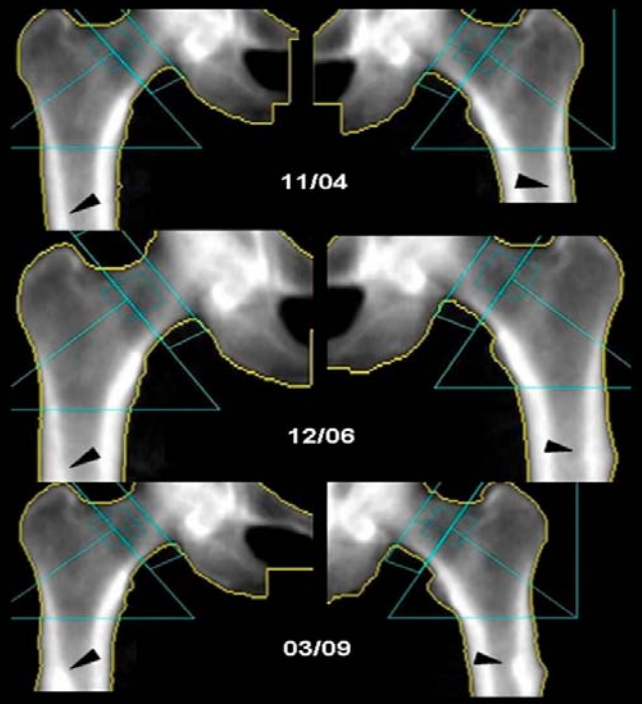
Reciprocal Relationship of Atypical and Typical Hip Fracture with BP Adherence



Wang Z. Osteoporosis Int 2014;25:109

Surveillance for Atypical Femoral Fractures

- History
  - New hip or thigh pain
- Physical Examination
  - Painful ROM or tenderness to palpation over hip/proximal thigh
- Laboratory Tests and Imaging
  - Plain radiographs
  - NM imaging or MRI
  - DXA



McKiernan F. *J Clin Densitometry* 2010;13:102

Medical and Surgical Management of AFFs

Thigh pain with stress reaction or incomplete AFF
Consider prophylactic rodding
1) Stop anti-resorptive immediately 2) Limit weight-bearing 3) Workup for other causes (i.e. osteomalacia) 4) Warn patient of progression risk 5) Consider an osteoanabolic (limited data) 6) If pain not decreasing within 2 to 3 months or dreaded black line, consider rodding

Dell R. *Osteoporos Int* 2018;29:1277

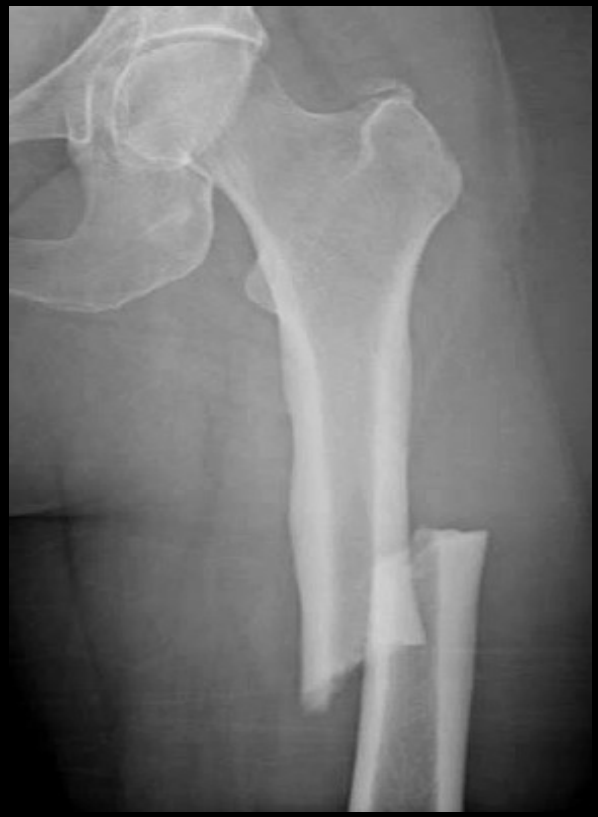
Medical and Surgical Management of AFFs

Thigh pain with stress reaction or incomplete AFF	Complete AFF
Consider prophylactic rodding	Surgery (see below)
1) Stop anti-resorptive immediately 2) Limit weight-bearing 3) Workup for other causes (i.e. osteomalacia) 4) Warn patient of progression risk 5) Consider an osteoanabolic (limited data) 6) If pain not decreasing within 2 to 3 months or dreaded black line, consider rodding	1) Avoid platting and short rods 2) Over-ream canal 3) Check for contra-lateral stress reaction 4) Watch for delayed healing 5) Consider excision of dreaded black line

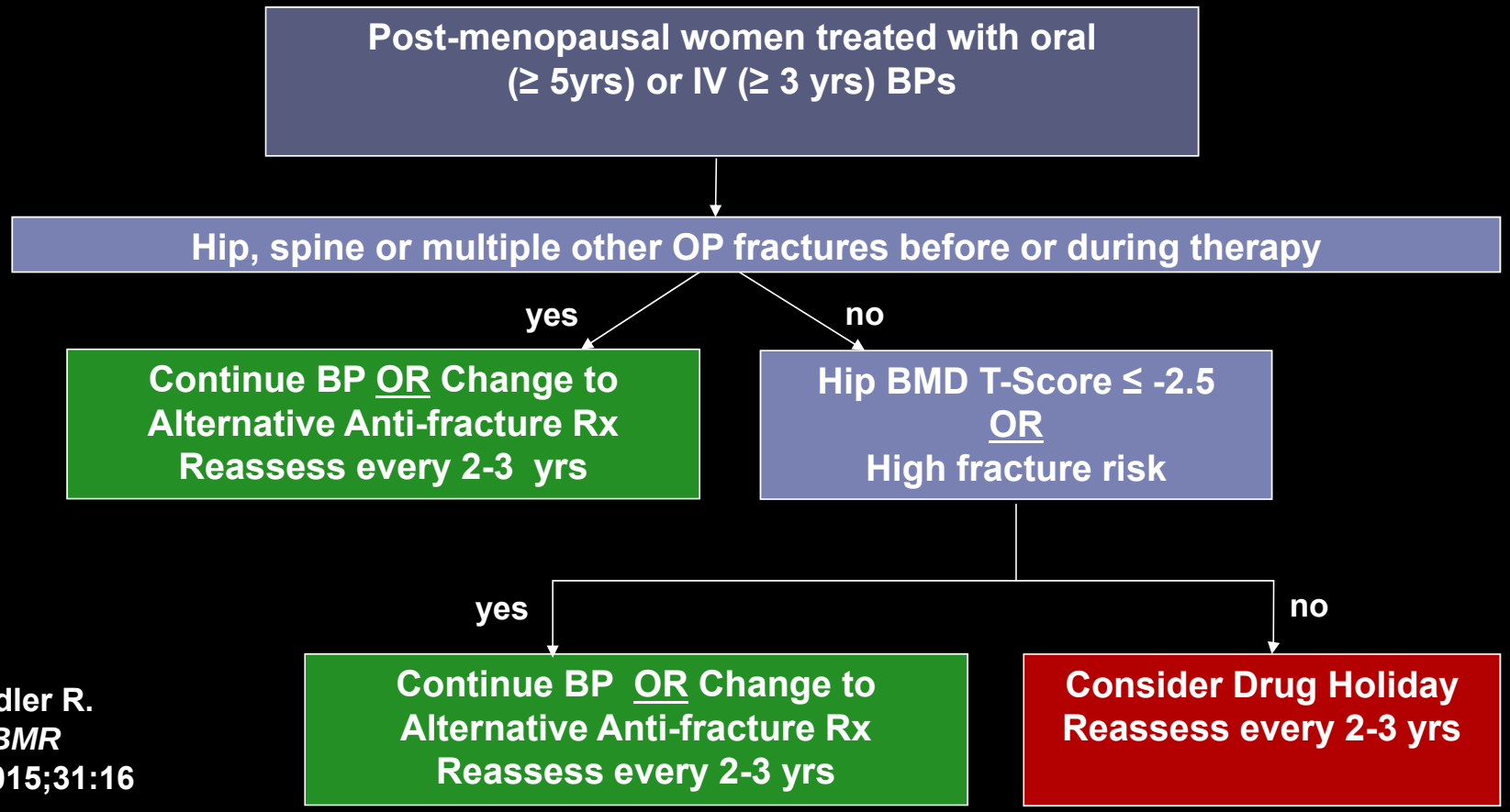
Dell R. *Osteoporos Int* 2018;29:1277

Bisphosphonate Associated Atypical Femoral Fractures (AFFs)- Summary

- Incidence likely increases with duration of therapy and declines with discontinuation
- Higher incidence
  - Asian ancestory
  - Glucocorticoid use
  - Low bone turnover
  - Hypophosphatasia (?)
- Monitor and intervene as early as possible due to high morbidity



ASBMR Algorithm for Management of Postmenopausal Women on Long Term Bisphosphonate (BP) Therapy



Adler R.
JBMR
2015;31:16

While We Await Evidence, Who Should Get a Drug "Sabbatical*" Rather than Bisphosphonate Drug "Holiday" ?

- Fracture while on therapy
- Femoral neck T-score still ≤ -2.5
- FRAX above intervention threshold
- Significant loss of BMD while on therapy
- Persistent high bone turnover by biochemical marker (?)

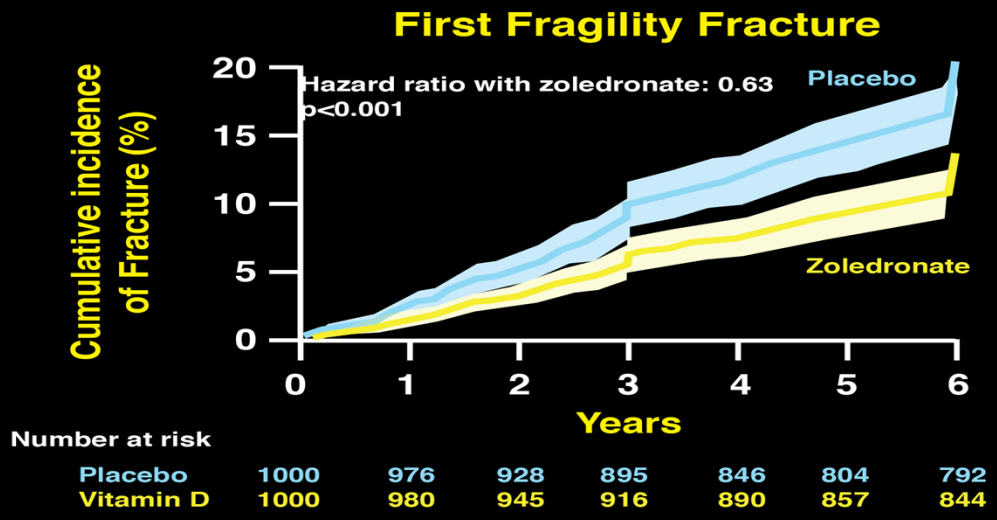
**Sabbatical = an extended leave or rest, to "re-energize"*

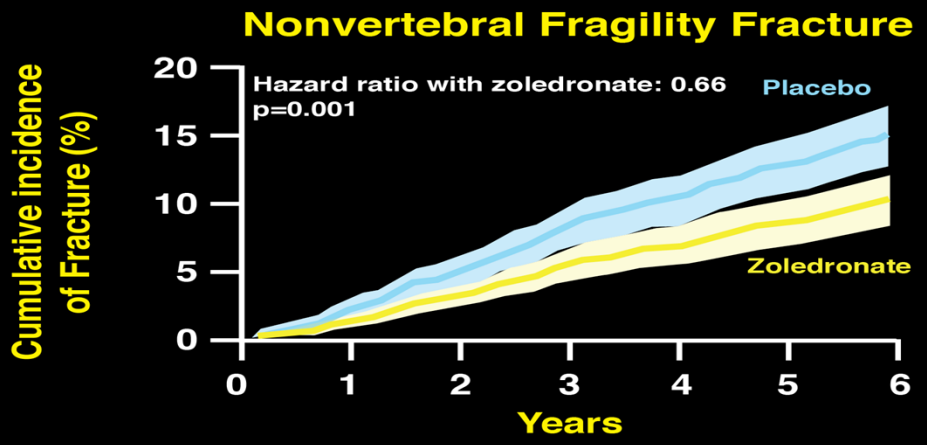
What Happens After a Drug Holiday of > 2 yrs ?
US Medicare Data Summary (n = 74K)

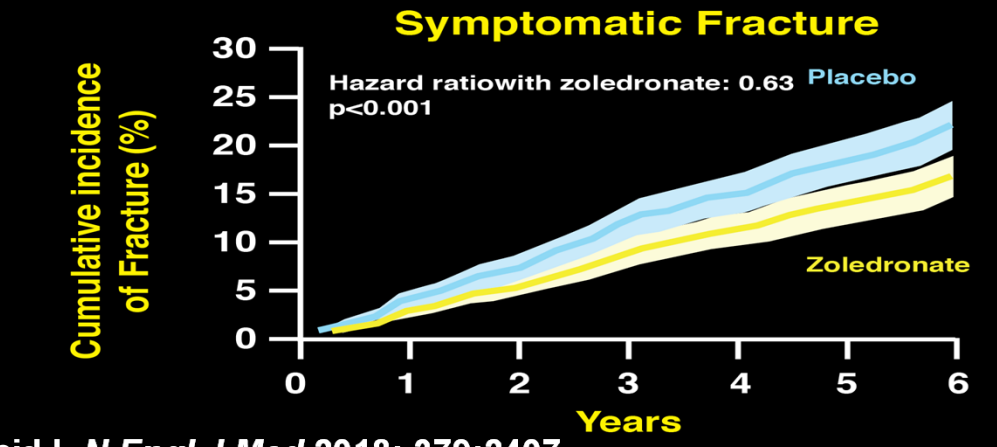
- Hip fracture (fx)
  - ALN- 30% ↑
  - RIS- 50% ↑
  - ZA- 30% ↑
- Vertebral fractures
  - ALN- 20% ↑
  - RIS- 60% ↑
  - ZA - 40% ↑
- Other fracture types
  - 0-40% ↑ depending on fx site

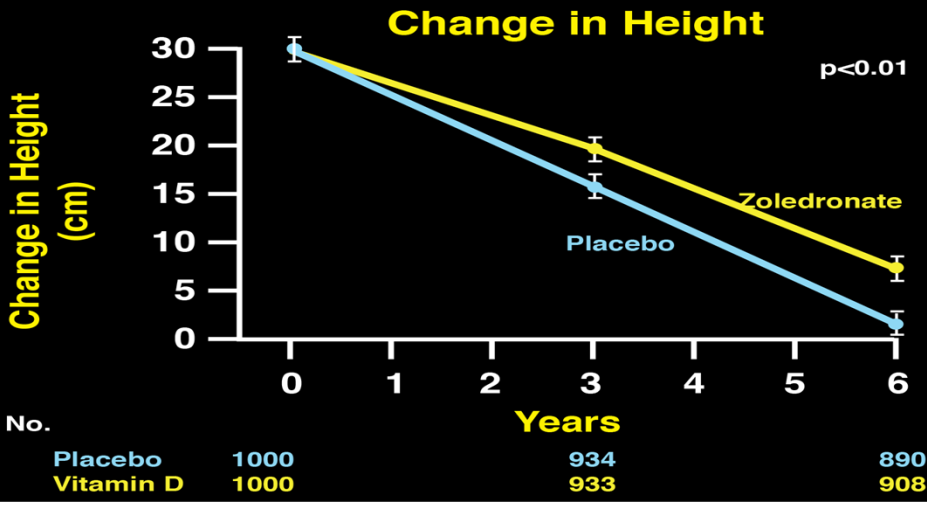
Curtis J. *Medical Care*, 2020, in press
Black DM. *J Clin Endocrinol Metab* 2000;85:4118

Zoledronic Acid in Osteopenia





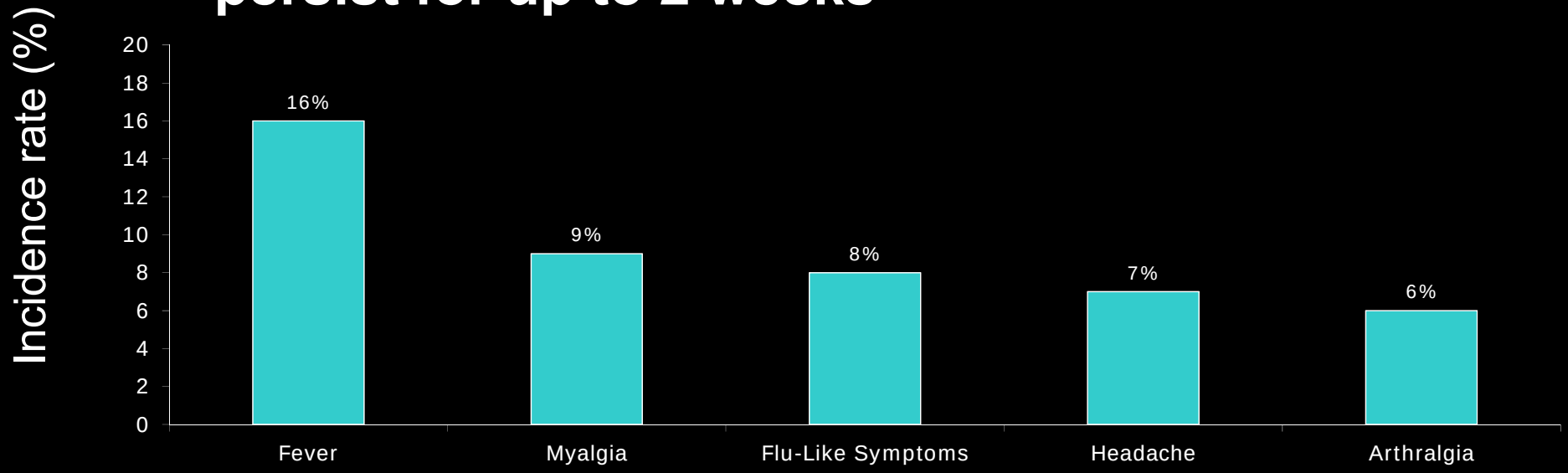




Reid I. *N Engl J Med* 2018; 379:2407

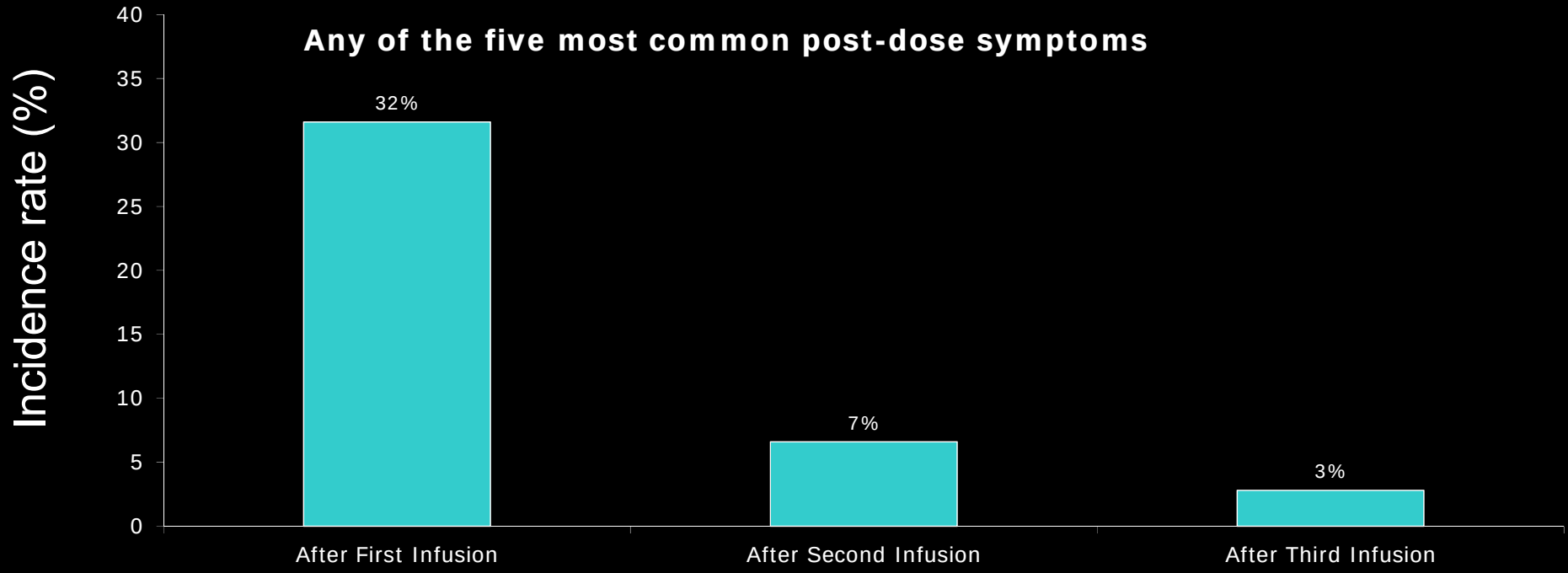
Zoledronic Acid Acute Phase Reactions
RCT data

- Majority occur within 3 days after dosing
- Usually resolves within several days, but may persist for up to 2 weeks



Black DM. *N Engl J Med* 2007;356:1809

Zoledronic Acid Acute Phase Reactions
RCT data



Black DM. *N Engl J Med* 2007;356:1809

Zoledronic Acid Acute Phase Reactions
"Real World" Data

Reference	Previous BP	% Acute Phase Response
Bertoldo F. JBMR 2010	None	67.7%
Tompson K. Bone 2011	None	61.7%
Karga H. Endocr J 2011	None	66%
Makras P. Calcif Tissue Int 2011	None	71.4%
Silverman SL. Osteoporos Int 2011	None	60.7%
Rossini M. JBMR 2011	None	42.5%
Anastasilakis AD. Bone 2012	37.2%	54.9%

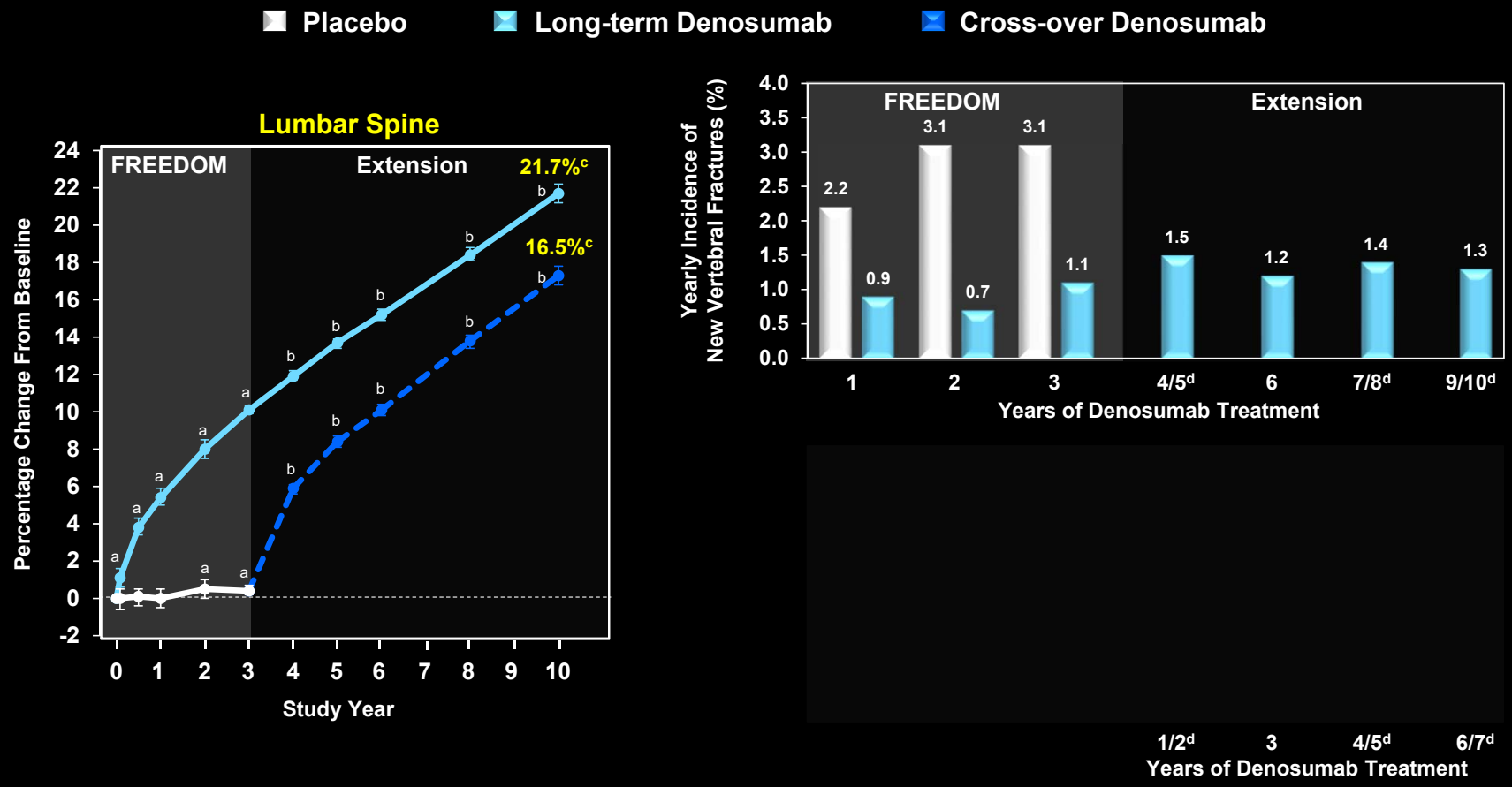
Potential Risk Factors for Acute Phase Reactions (APRs)

- Positive risk factor
  - Lower age (children up to 85%)
  - Circulating γδ T cells (78% of patients with γδ values > 3%)
  - NSAID use (OR 1.35)
  - Low vitamin D status (more severe APR)
- Protective factors
  - Prior BPs treatment
  - Current smoker (OR 0.73)
  - Diabetes (OR 0.73)
  - Prior calcitonin use (OR 0.66)

Popp AW. *Osteoporos Int* 2017;28:1995
Rossini M. *J Bone Min Res* 2012;27:227
Reid IR. *J Clin Endocrinol Metab* 2010;95:4380

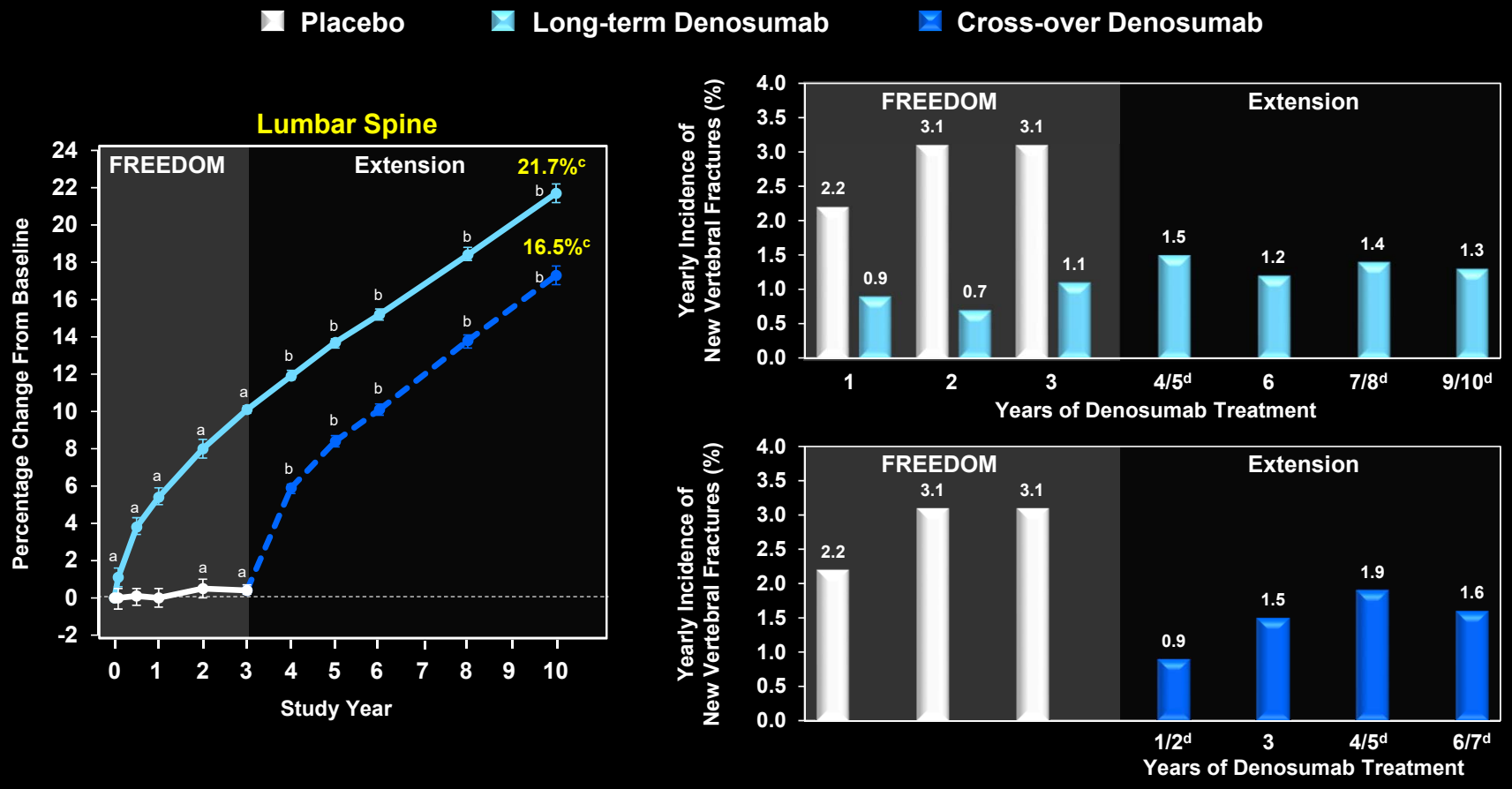
What's New/Controversial with Denosumab?

Effects of Denosumab Treatment on Lumbar Spine BMD and New Vertebral Fractures Through 10 Years



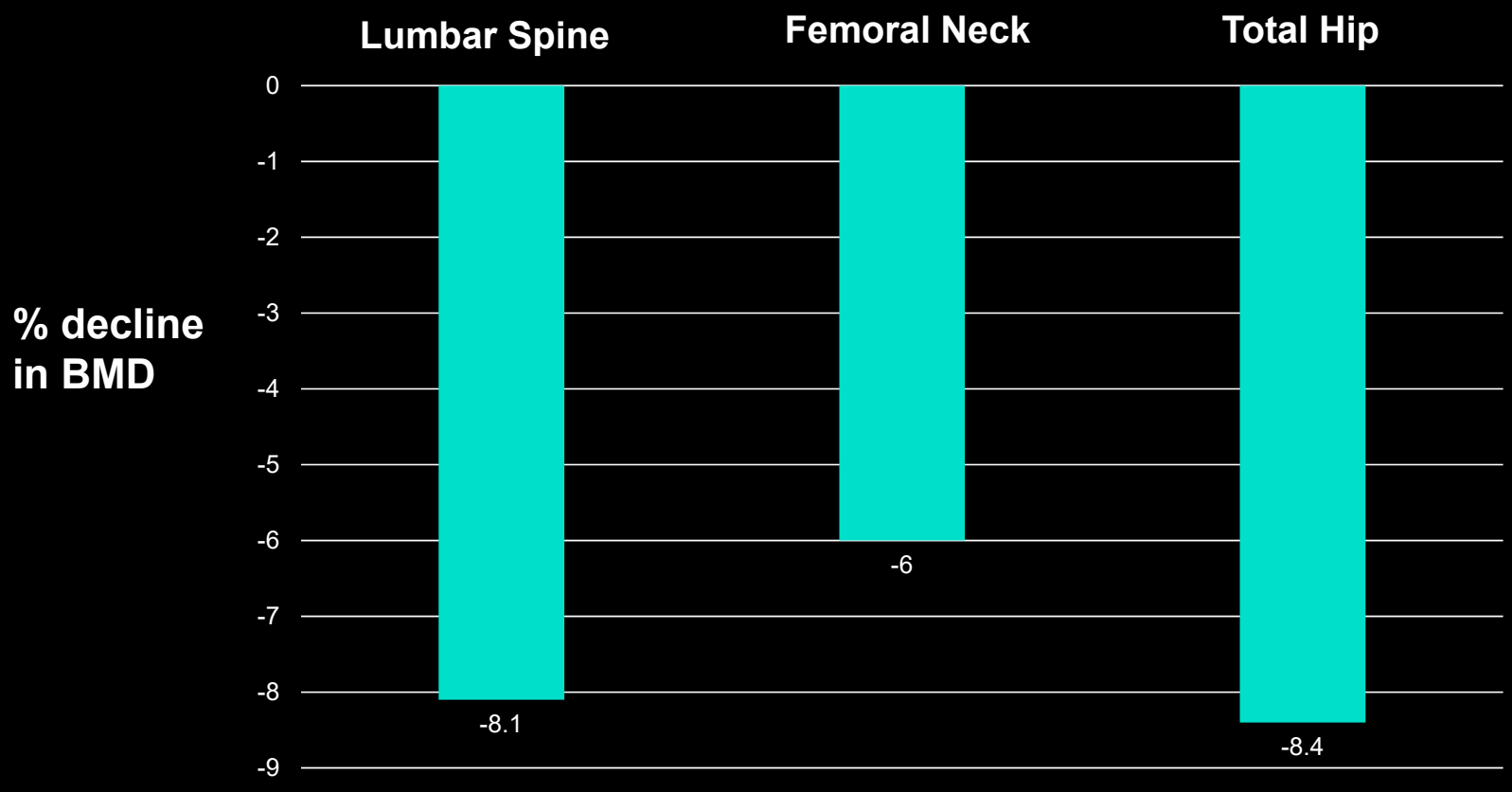
Bone HG. *Lancet Diab Endo* 2017;5:513

Effects of Denosumab Treatment on Lumbar Spine BMD and New Vertebral Fractures Through 10 Years



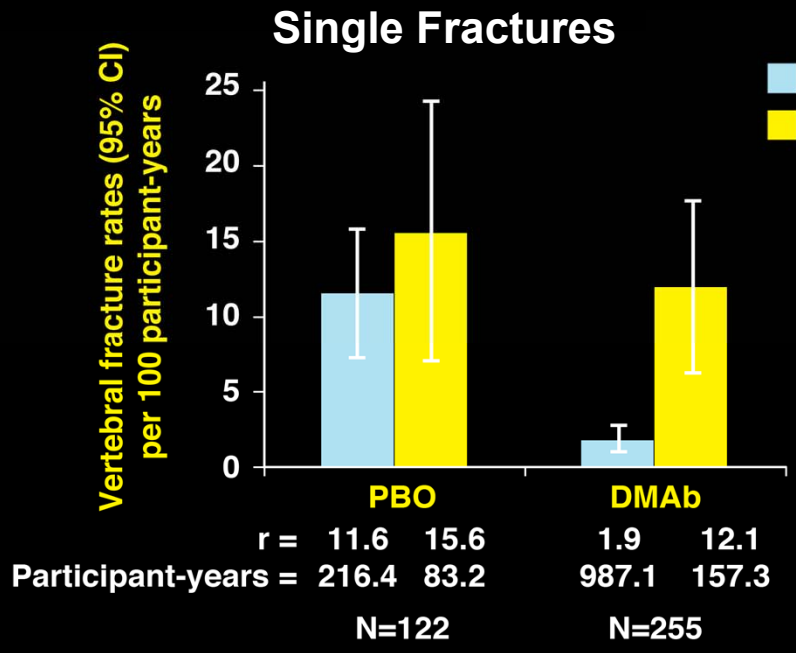
Bone HG. *Lancet Diab Endo* 2017;5:513

Bone Loss after Denosumab Stop



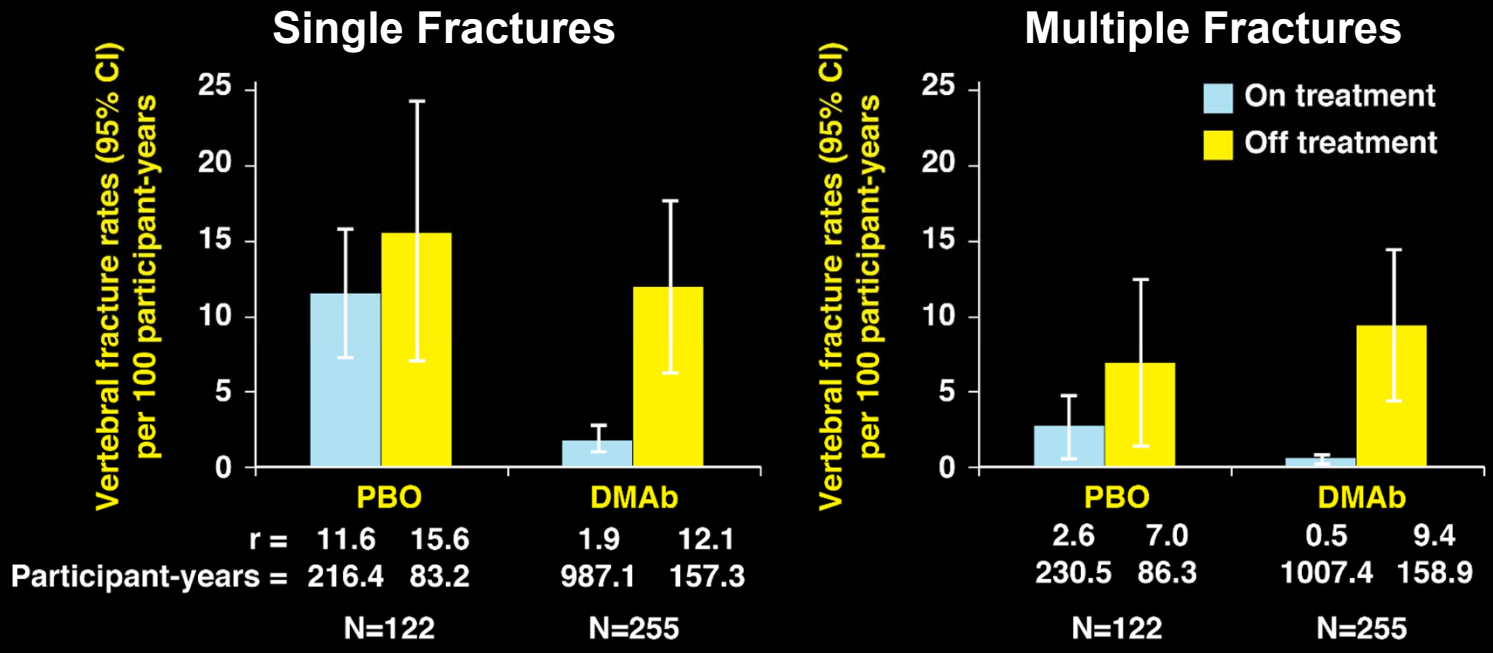
Zanchetta MB. *Osteoporos Int* 2018;29:41

Fractures After Stopping Denosumab (DMAb)



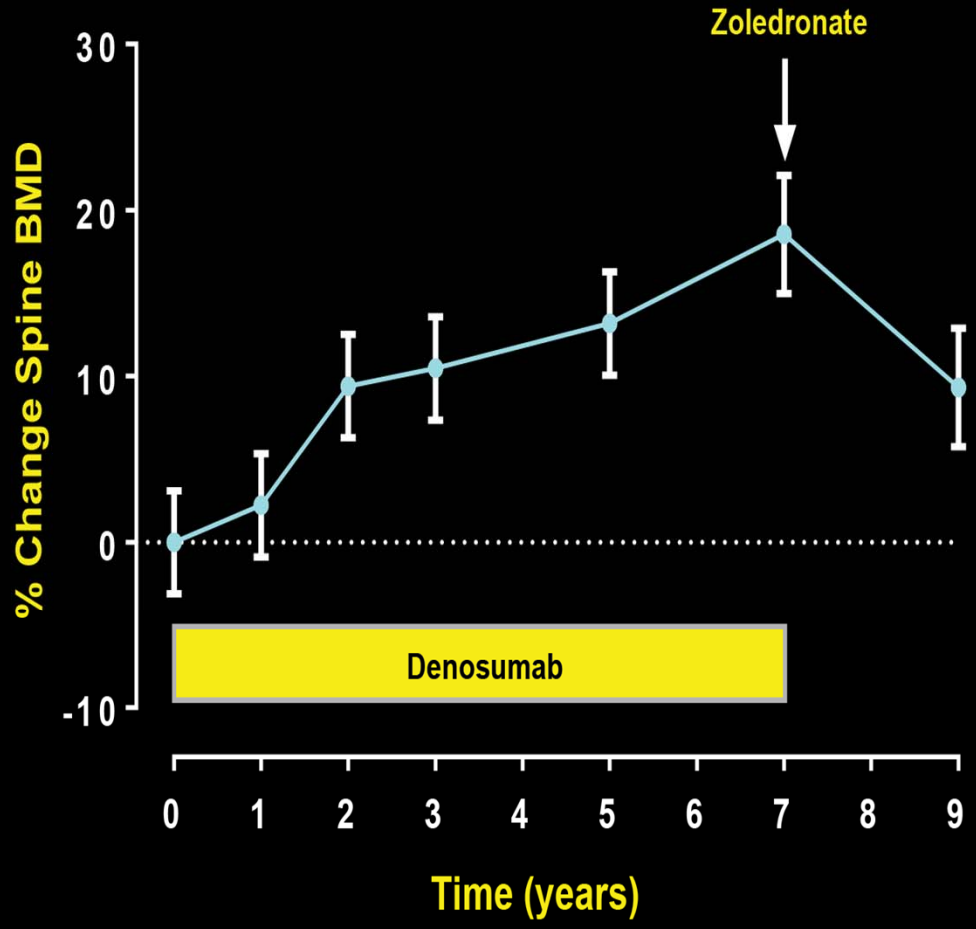
Cummings S. *JBMR* 2018;33:190

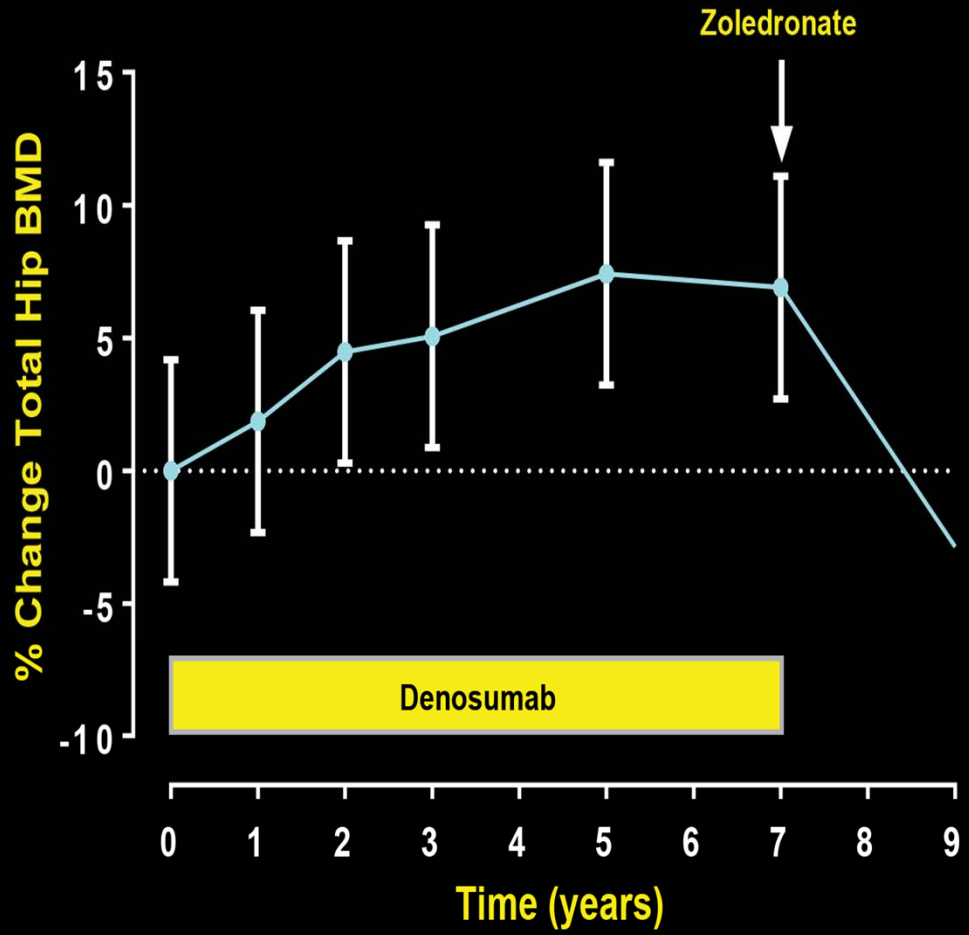
Fractures After Stopping Denosumab (DMAb)



Cummings S. *JBMR* 2018;33:190

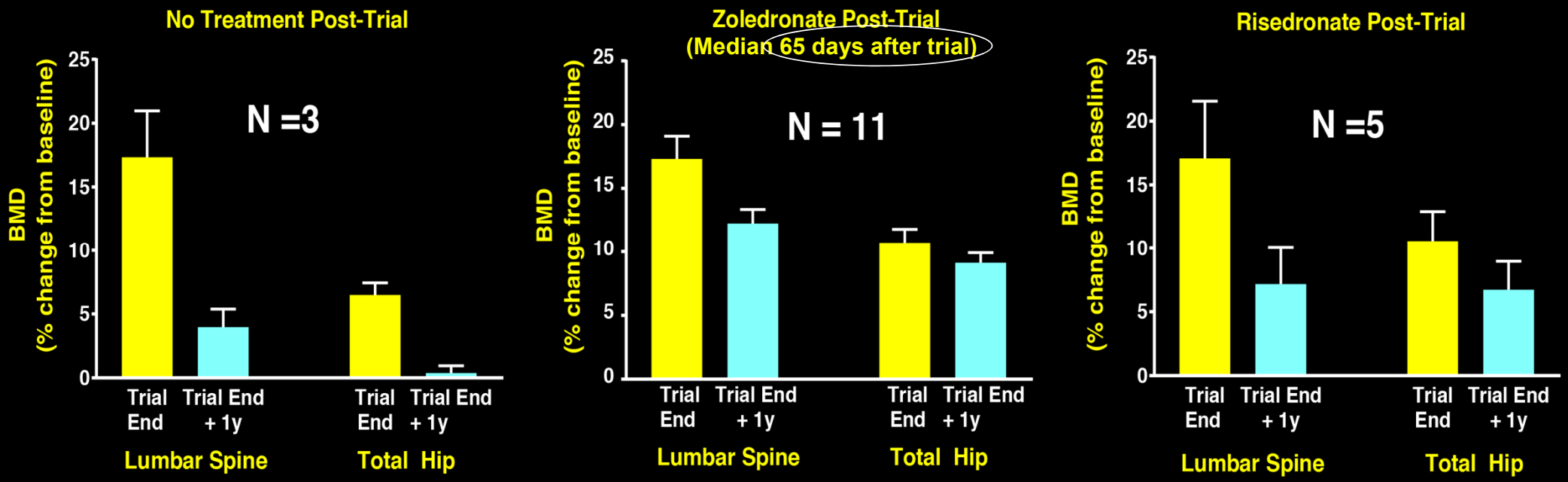
Immediate Zoledronic Acid May not Attenuate BMD Loss with Denosumab





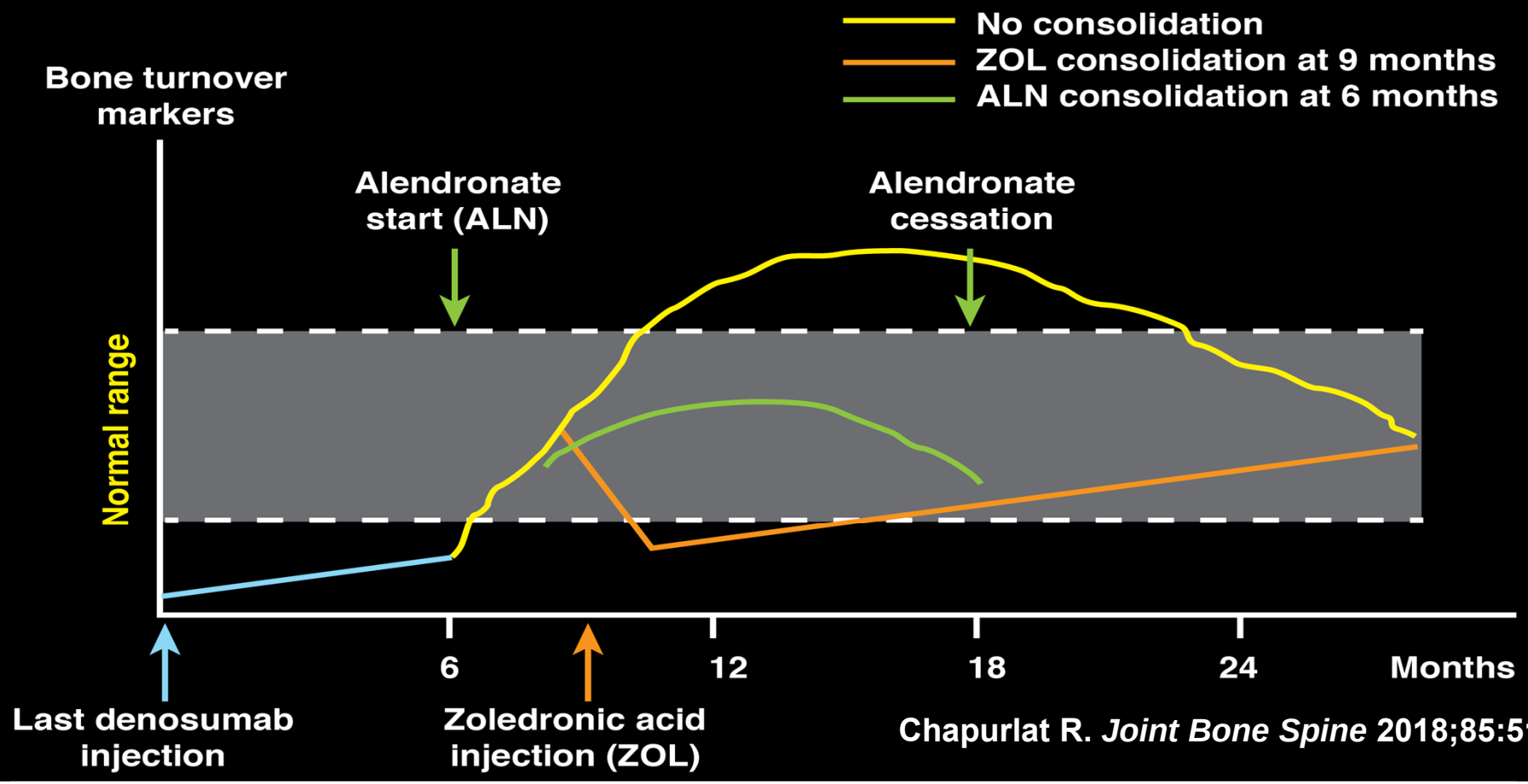
Reid I. *Calcif Tissue Int*, online first

Delayed Zoledronic Acid Attenuates Bone Loss After Dmab More Than Risedronate



Horne A. *Calcif Tissue Int*, online first

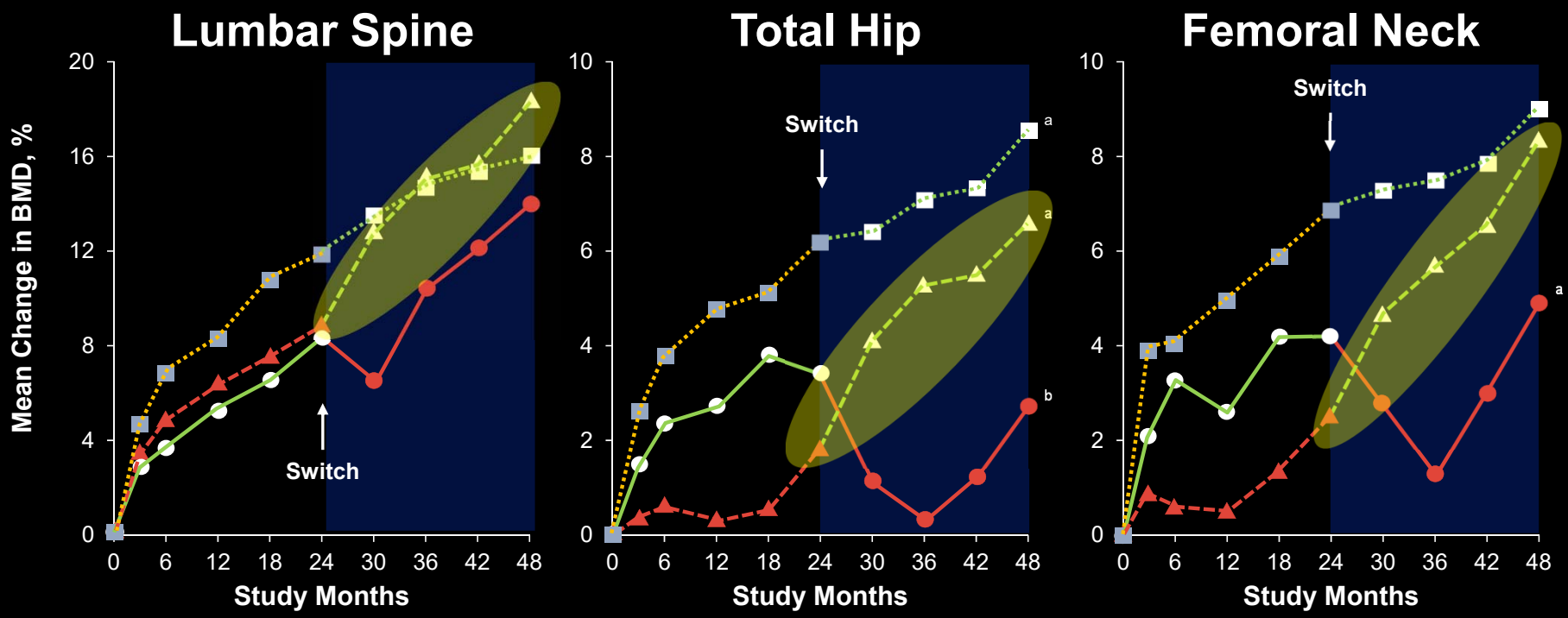
If you Stop Denosumab When Should you Start a Bisphosphonate?



Chapurlat R. *Joint Bone Spine* 2018;85:515

BMD Drops When Switching DMAb to TPTD

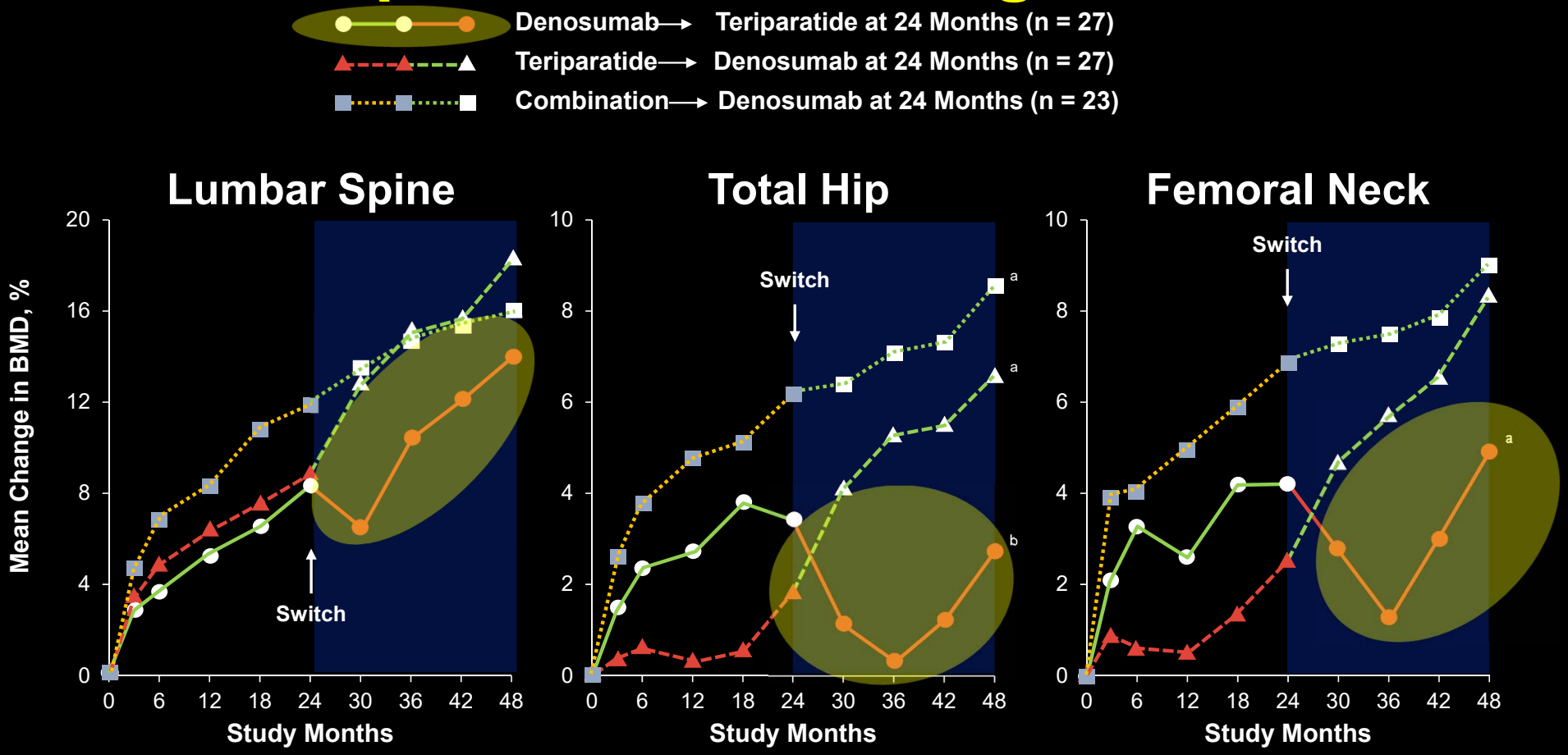
Denosumab → Teriparatide at 24 Months (n = 27)
Teriparatide → Denosumab at 24 Months (n = 27)
Combination → Denosumab at 24 Months (n = 23)



[a]$p < 0.05$ vs both other groups.
[b]$p < 0.0005$ vs both other groups.

Leder B. *Lancet* 2015;386:1147

BMD Drops When Switching DMAb to TPTD



[a]$p < 0.05$ vs both other groups.
[b]$p < 0.0005$ vs both other groups.

Leder B. *Lancet* 2015;386:1147

ONJ/AFFs Associated with Denosumab for Osteoporosis

FREEDOM Trial and Extension

- No events of either type in first 3 years
- AFFs
  - 2 after 3 and 7 years in extension study
- ONJ
  - 7 during first 5 yrs of extension and 6 during years 8–10

Bone HG. *Lancet Diab Endo* 2017;5:513

Denosumab and ONJ

- 13 cases in FREEDOM Extension study (5.2/10,000 subject-years)
- 45% of responders to questionnaire during Extension reported at least one invasive oral procedures or event
- ONJ incidence higher in those reporting an oral procedure or event (0.68%) than not (0.05%)
- 212 patients had dental implants – no ONJ
- 6 of the 13 patients with ONJ had ill-fitting dentures
- Most cases resolved with conservative therapy or surgery while denosumab therapy continued
- No literature of denosumab administration after ONJ has healed

Bone HG *Lancet Diabetes Endocrinol* 2017;5:513
Watts NB. *J Clin Endocrinol Metab* 2019 Feb 13. doi: 10.1210/jc.2018-01965

Denosumab and Immune Dysfunction

- RANK ligand is expressed in some lymphocytes
- What roles RANKL play in the immune system is unknown
- Adults with genetic syndromes of RANKL deficiency do not have immune dysfunction

Watts NB. *Osteoporos Int* 2012;23:327

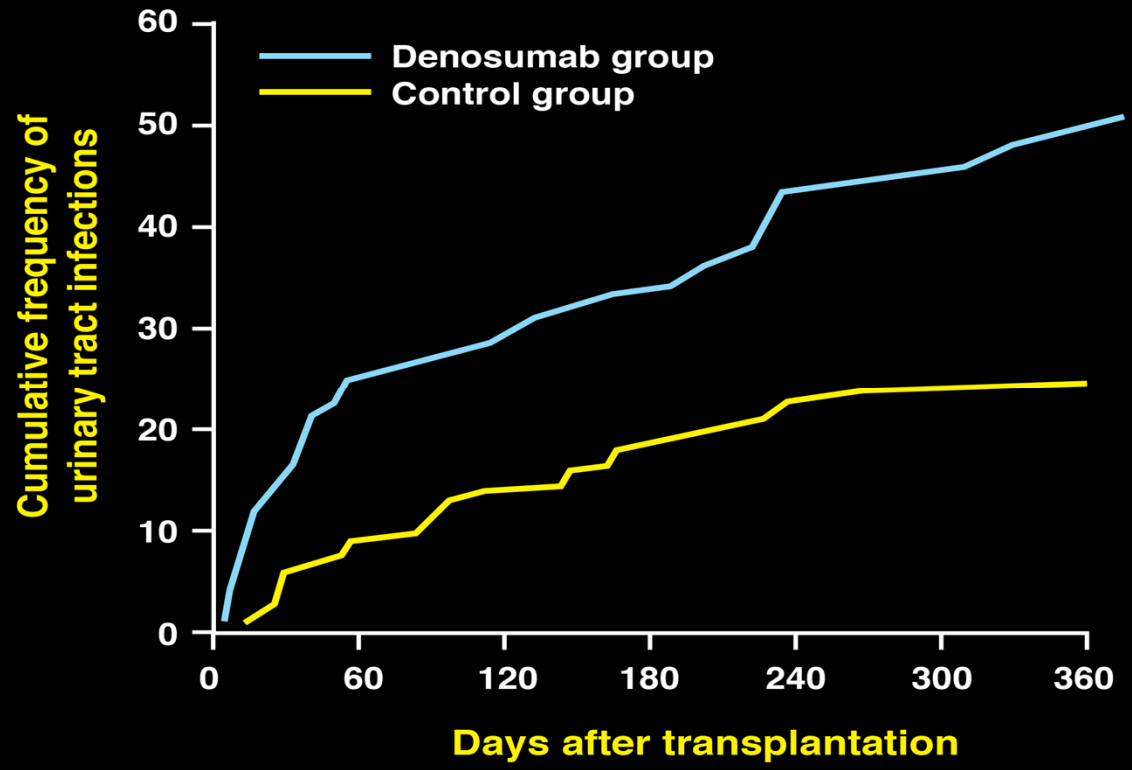
Serious Infectious Adverse Events in Dmab Osteoporosis RCTs

		Dmab (%)	PBO or ALN (%)
DEFEND[1]	(n ≈ 320)	4.9	0.06
DECIDE[2]	(n ≈ 1200)	1.5	1.0
STAND[3]	(n ≈ 500)	0.4	1.2
FREEDOM[4]	(n ≈ 7900)	4.1	3.4

1. Bone HG. *J Clin Endocrinol Metab* 2008;93:2149
2. Brown JP. *J Bone Miner Res* 2009;24:153
3. Kendler DL. *ASBMR*. 2008 Poster M395
4. Cummings SR. N Engl J Med,2009;361:756

Infections on Denosumab in Transplant Patients

- Urinary tract infections (p = 0.008) more frequent with denosumab than in controls
- Overall infections greater than control group (p=0.044)
- Transplant-related AEs occurred with similar frequency in both groups



Bonani M. *Transplantation* 2017;101:2139

Denosumab and Infection in RA Patients on Biologics

- Rate of hospitalized infection
  - Mean age 72 yrs
  - On biologic agents for RA
  - Denosumab user (n=1340) compared to matched patients receiving zoledronic acid (ZA; n=4460)
- *After adjustment, Hazard ration (HR) of hospitalized infection for denosumab users non-inferior to ZA users (HR 0.89 [95% CI 0.69-1.15])*

Curtis JR. *Arthritis Rheum* 2015;67:1456

Lack of Tetracycline Label in Bone of Denosumab Treated Patients

	Trabecular		Cortical	
	Control*	Denosumab	Control*	Denosumab
FREEDOM				
Evaluable biopsies	62	53	62	53
Double label	58 (94)	10 (19)	61 (98)	16 (30)
Single label only	3 (5)	8 (15)	1 (2)	14 (26)
No label	1 (2)	35 (66)	0	23 (43)
STAND				
Evaluable biopsies	21	15	21	15
Double label	19 (90)	3 (20)	21 (100)	8 (53)
Single label only	2 (10)	6 (40)	0	3 (20)
No label	0	6 (40)	0	4 (27)

*Control group = placebo in FREEDOM study and alendronate in STAND study. Data are n (%)

Reid I. *J Bone Miner Res* 2010;25:2556

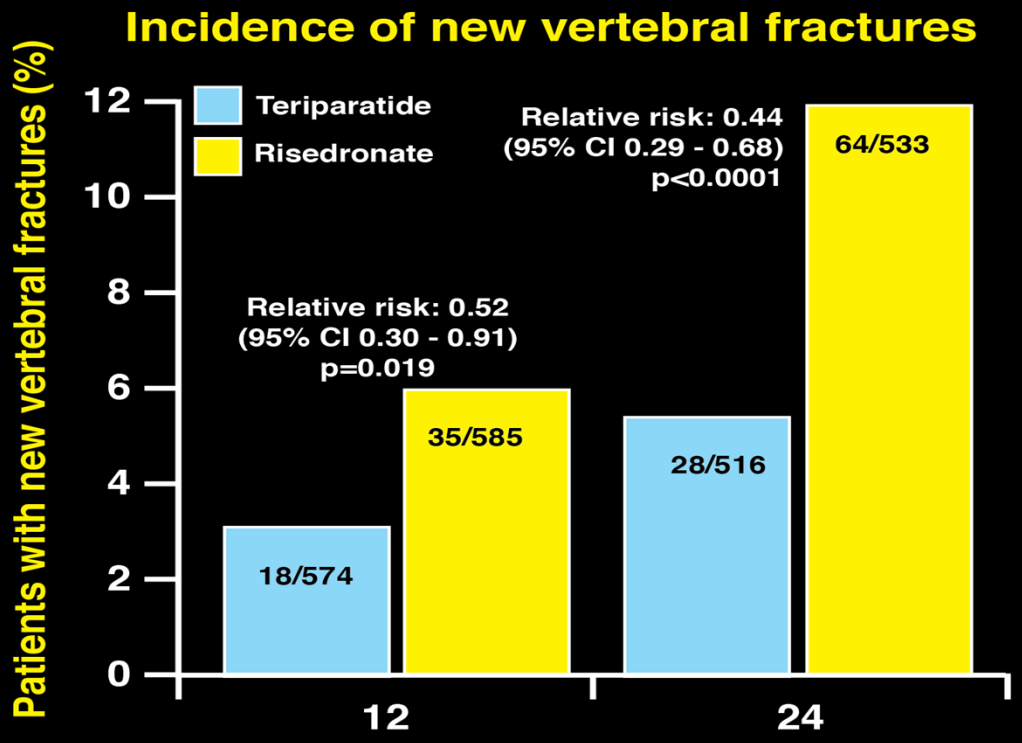
Remodeling Status in Postmenopausal Women Who Discontinue Denosumab

- Bone biopsies at ≥ 12 and < 36 months after completion of original trial
- All biopsies showed normal histology without evidence of pathology
- Double TC labels present in all biopsies, suggesting active remodeling

Dempster D. *J Clin Endo & Metab* 2018;103:2498

What's New/Controversial with Anabolic Approaches?

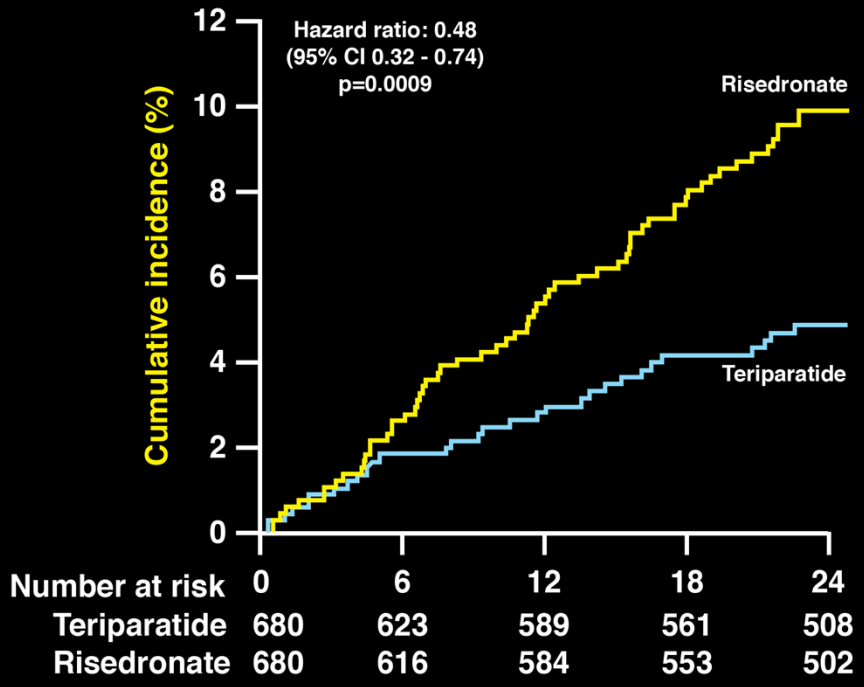
Teriparatide vs. Risedronate VERtebral Fracture Comparisons in severe Osteoporosis (VERO) Trial



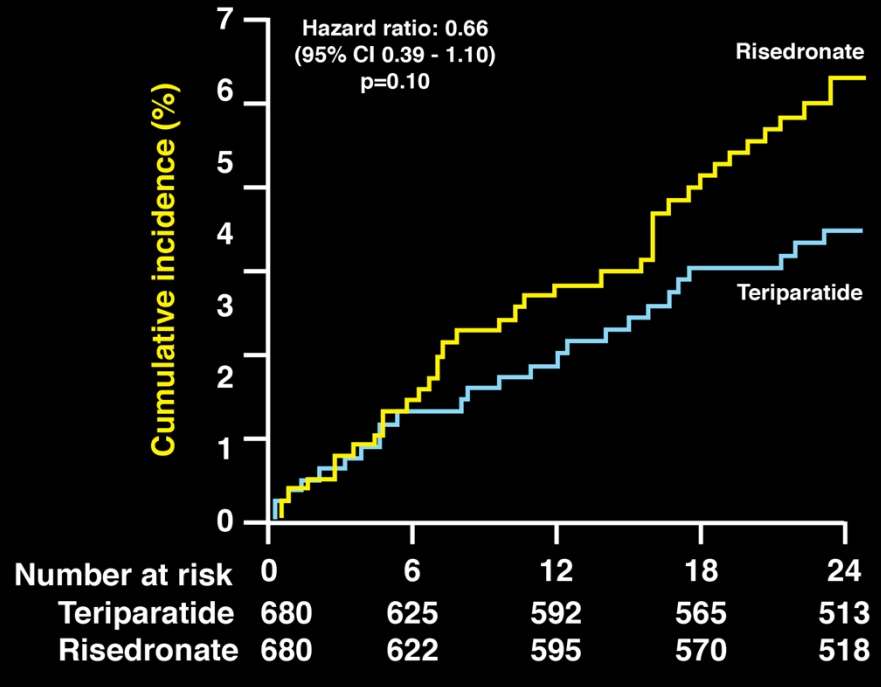
Kendler DM. *Lancet* 2018;391:230

Teriparatide vs. Risedronate VERtebral Fracture comparisons in severe Osteoporosis (VERO) Trial

First clinical fracture



First non-vertebral fragility fracture



Kendler DM. *Lancet* 2018;391:230

VERO Study Conclusions

- Teriparatide significantly more efficacious than an oral bisphosphonate at preventing Vertebral fxs and clinical fxs, but not non-vertebral fractures in patients at high risk for fracture
- Results contradict new American College of Physician (ACP) Osteoporosis Guidelines that do not include anabolics

American College of Physicians (ACP) Osteoporosis Guidelines

- What they do well…
  - Give broad and somewhat reasonable guidance to generalists
  - Heighten awareness of osteoporosis
  - Introduce the idea of Drug Holiday

Qaseem A. *Ann Intern Med.* 2017;166:818
Caplan L. *Arthritis Rheum* 2017;69:20197

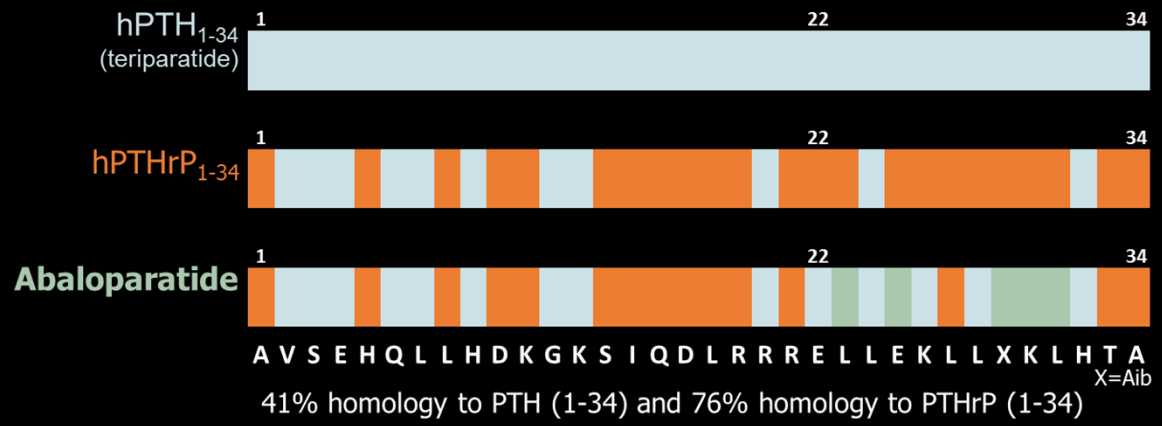
American College of Physicians (ACP) Osteoporosis Guidelines

- What they do well…
  - Give broad and somewhat reasonable guidance to generalists
  - Heighten awareness of osteoporosis
  - Introduce the idea of Drug Holiday
- What they do <u>less</u> well…
  - Deal with nuanced patients seen by specialists
  - Apply levels of evidence equally (why a universal holiday rec and no anabolic recs?)
  - Recognize risks of drug holidays, in some circumstances

Qaseem A. *Ann Intern Med.* 2017;166:818
Caplan L. *Arthritis Rheum* 2017;69:20197

Abaloparatide Background

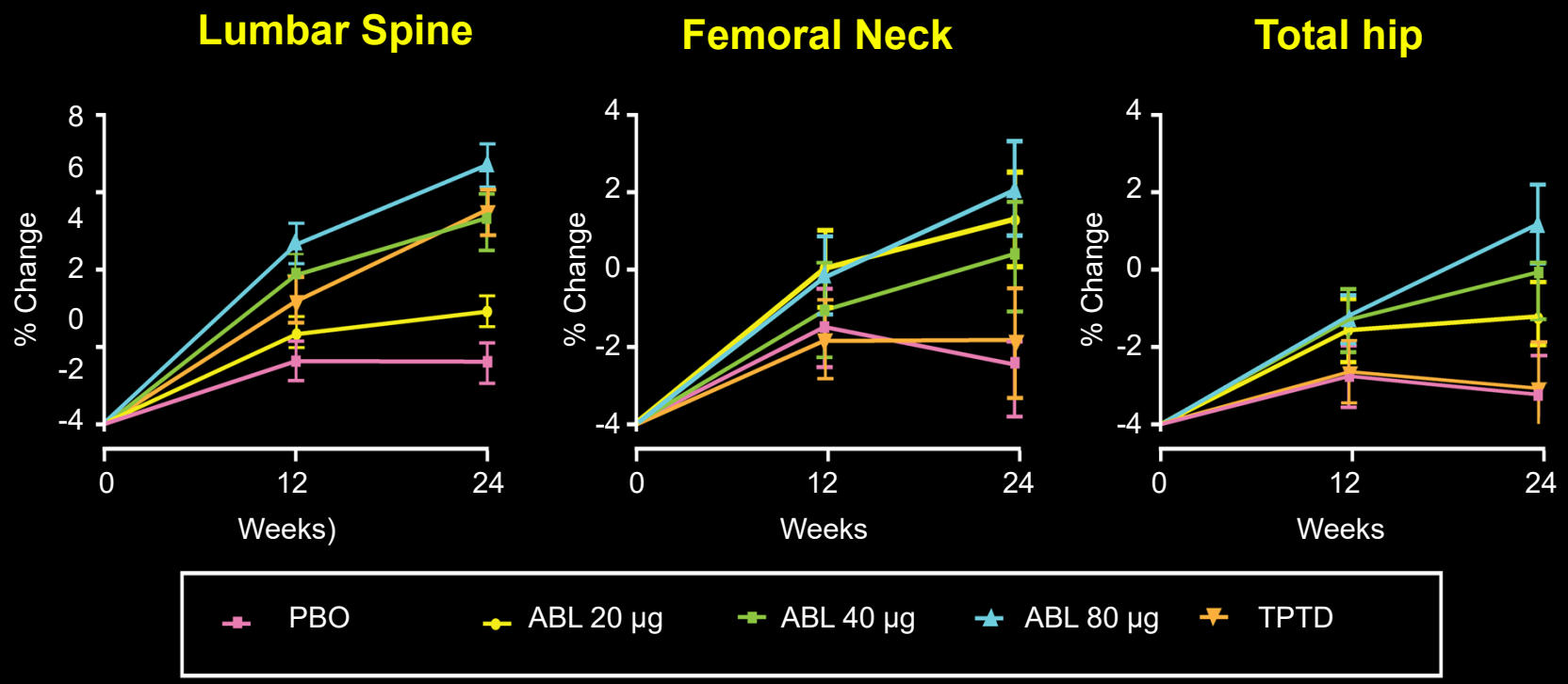
- Abaloparatide - novel synthetic 34-amino acid peptide created to produce anabolic effect with less stimulation of bone resorption than other PTHR agonists



- Preclinical models and Phase 2 study findings suggested that abaloparatide
  - Produced rapid BMD increases at both vertebral and nonvertebral sites
  - Produced less calcium mobilization than PTH

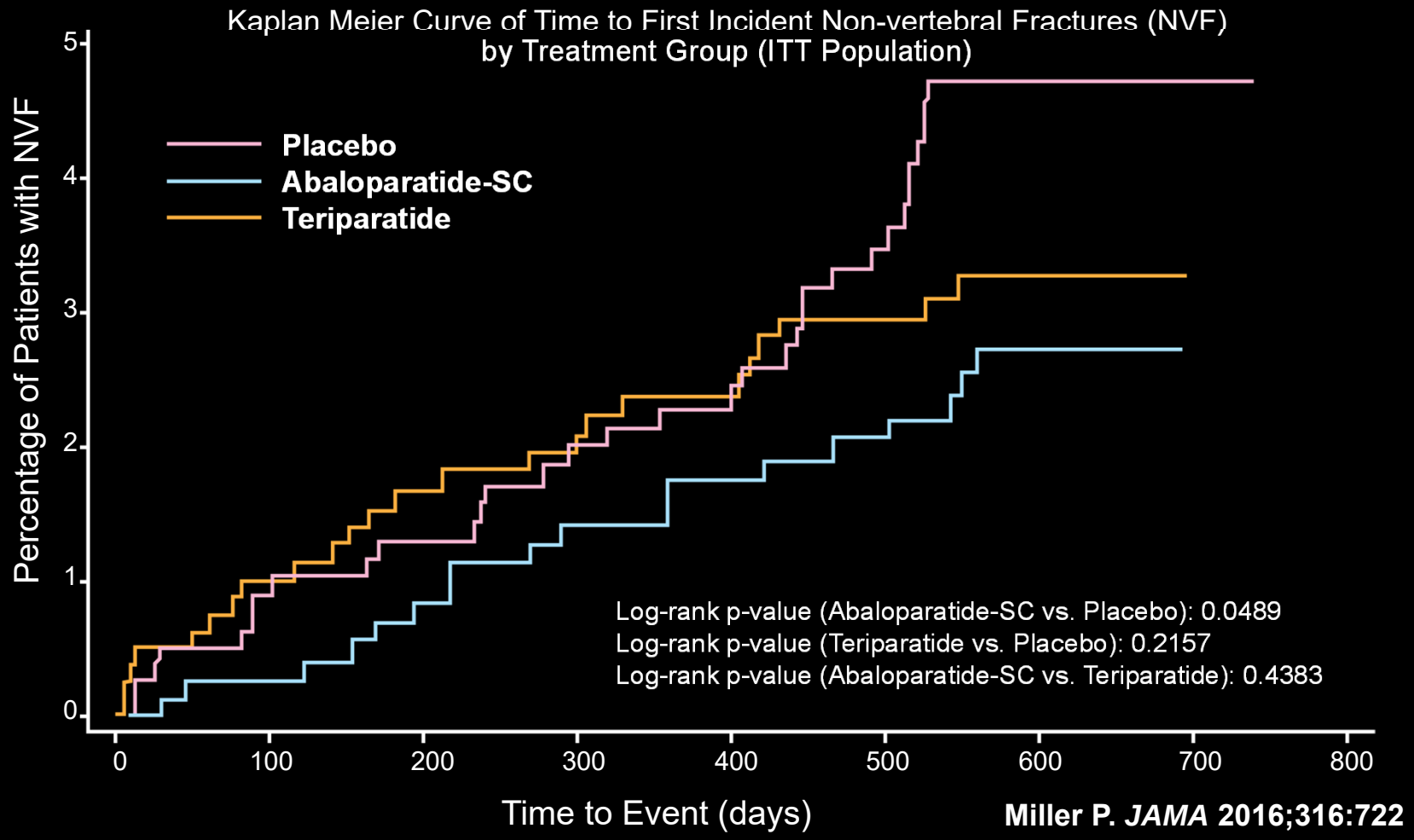
Hattersley G. *Endocrinology*. 2016;157:141

Abaloparatide PTH-rp Analog Effects on BMD



Leder B. *J Clin Endo Metab* 2015;100:697

Abaloparatide Compared to Teriparatide and PBO
ACTIVE Trial Non-vertebral Fractures



Miller P. *JAMA* 2016;316:722

Teriparatide and Abaloparatide Adverse Effects Summary

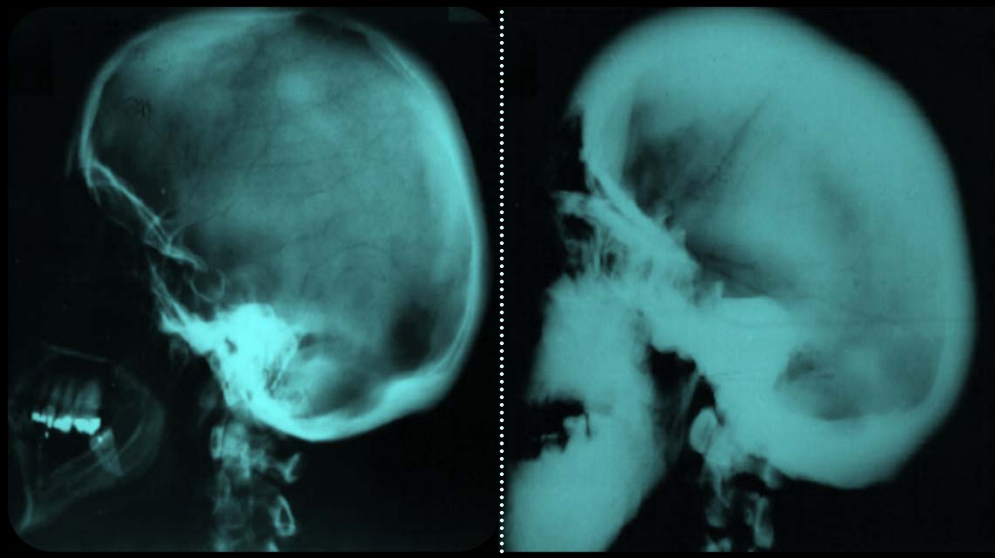
- Osteosarcomas increased in rats but, so far, not in humans
  - Contraindications: XRT, open epiphyses, Paget's
- Symptomatically generally well tolerated with vasodilation greater with abaloparatide and calcium rise greater with teriparatide
- Limited treatment duration due to safety concerns and short anabolic window

Sclerosteosis Highlighted Potential Role for Sclerostin Inhibition in Treatment of Osteoporosis[1]

Sclerostin is an osteocyte-derived inhibitor of bone formation[2]

Sclerosteosis is a rare genetic disorder resulting in a sclerostin deficiency and increased modeling-based bone formation[3]

Sclerosteosis patients are typically fracture resistant[3]



HETEROZYGOUS CARRIER[4] SCLEROSTEOSIS[4]

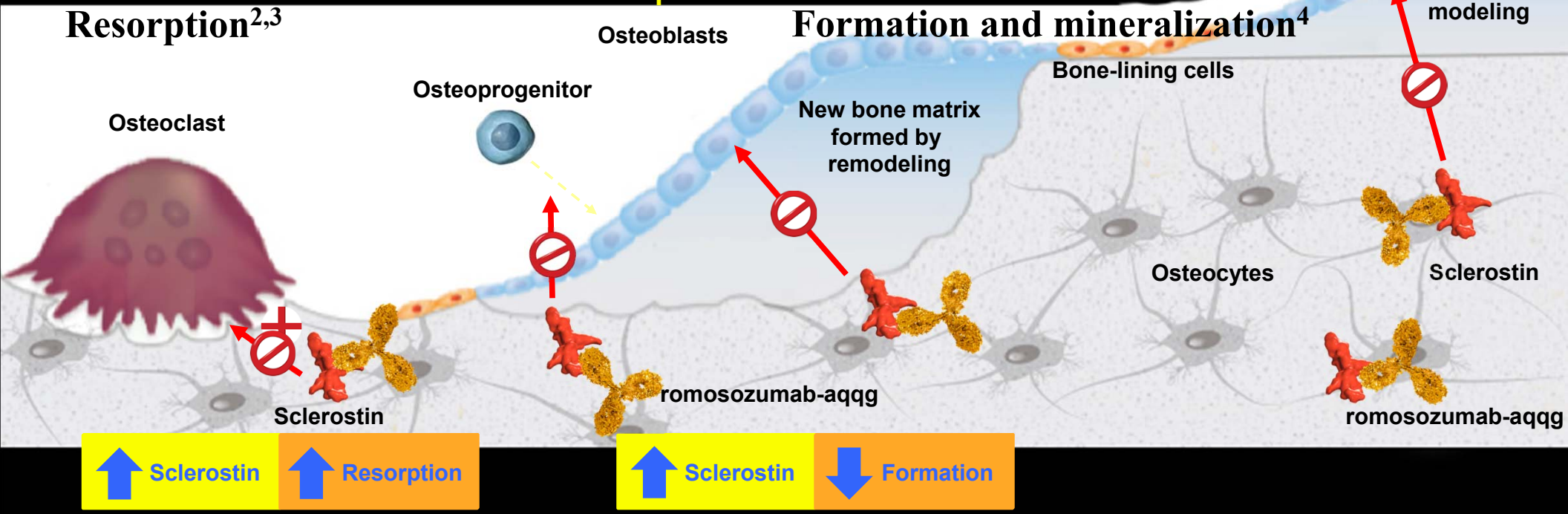
Image adapted from Gardner JC, et al. *J Clin Endocrinol Metab*. 2005;90:6392-6395.

1. Brunkow ME, et al. *Am J Hum Genet*. 2001;68(3):577-589. 2. Robling AG, et al. *J Musculoskelet Neuronal Interact*. 2006;6:354. 3. Hamersma H, et al. *Clin Genet*. 2003;63:192-197. 4. Gardner JC, et al. *J Clin Endocrinol Metab*. 2005;90:6392-6395.

Romosozumab Dual Effect through Multiple Molecular Processes[1-4]

Sclerostin regulates bone formation and resorption through multiple molecular processes[1-4]

Romosozumab increases bone formation and, to lesser extent, decreases bone resorption[1]



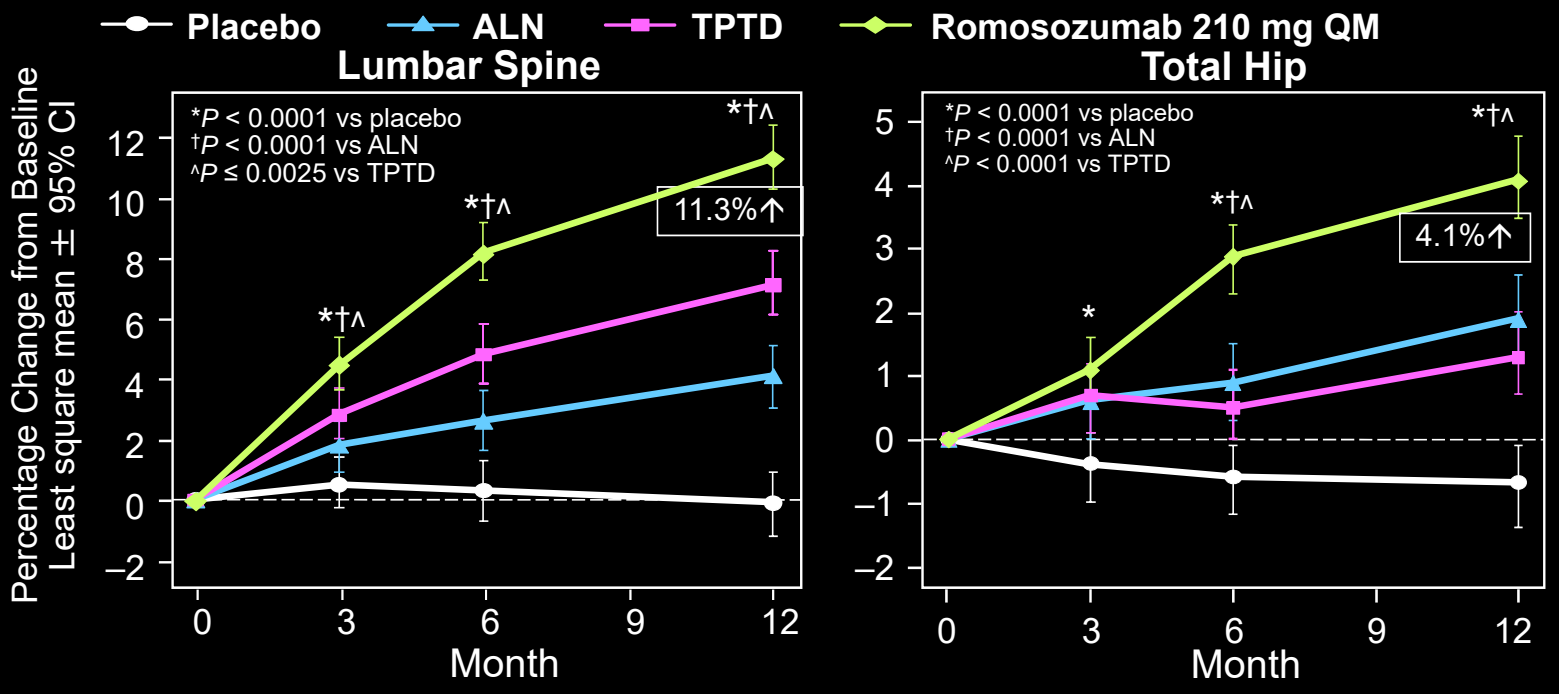
…through changes in cytokines[5]

…through effects on osteoblast differentiation and activity[1,6]

1. EVENITY™ prescribing information. 2. Dempster DW. *Clin Ther*. 2012;34:521. 3. Ominsky M. *Bone*. 2017;96:63. 4.Crockett JC. *J Cell Sci.* 2011;124:991. 5. Chan BY. *Osteoarthritis Cartilage*. 2011;19:874.. 6. Winkler DG. *EMBO J*. 2003;22:6267.

Anti-Sclerostin Antibody

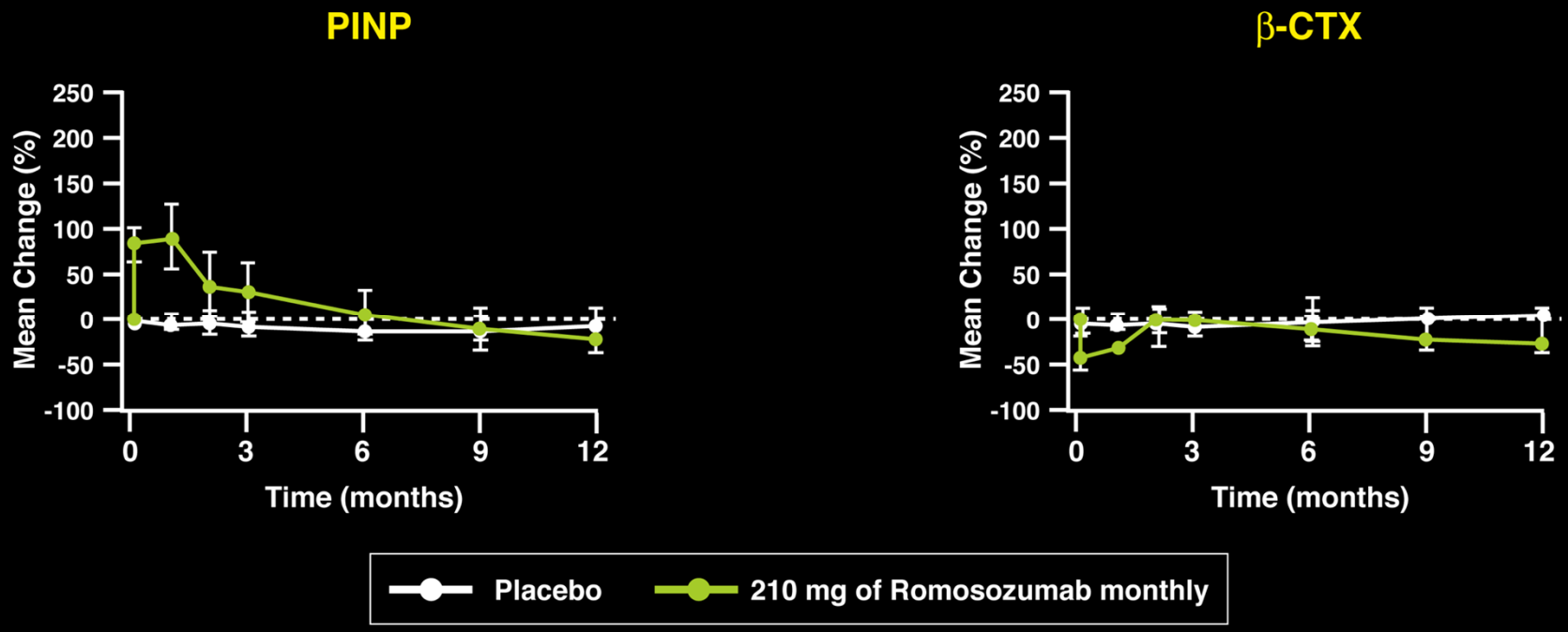
Romosuzumab Phase 2, BMD



McClung MR et al, *N Engl J Med* 2014

Anti-Sclerostin Antibody

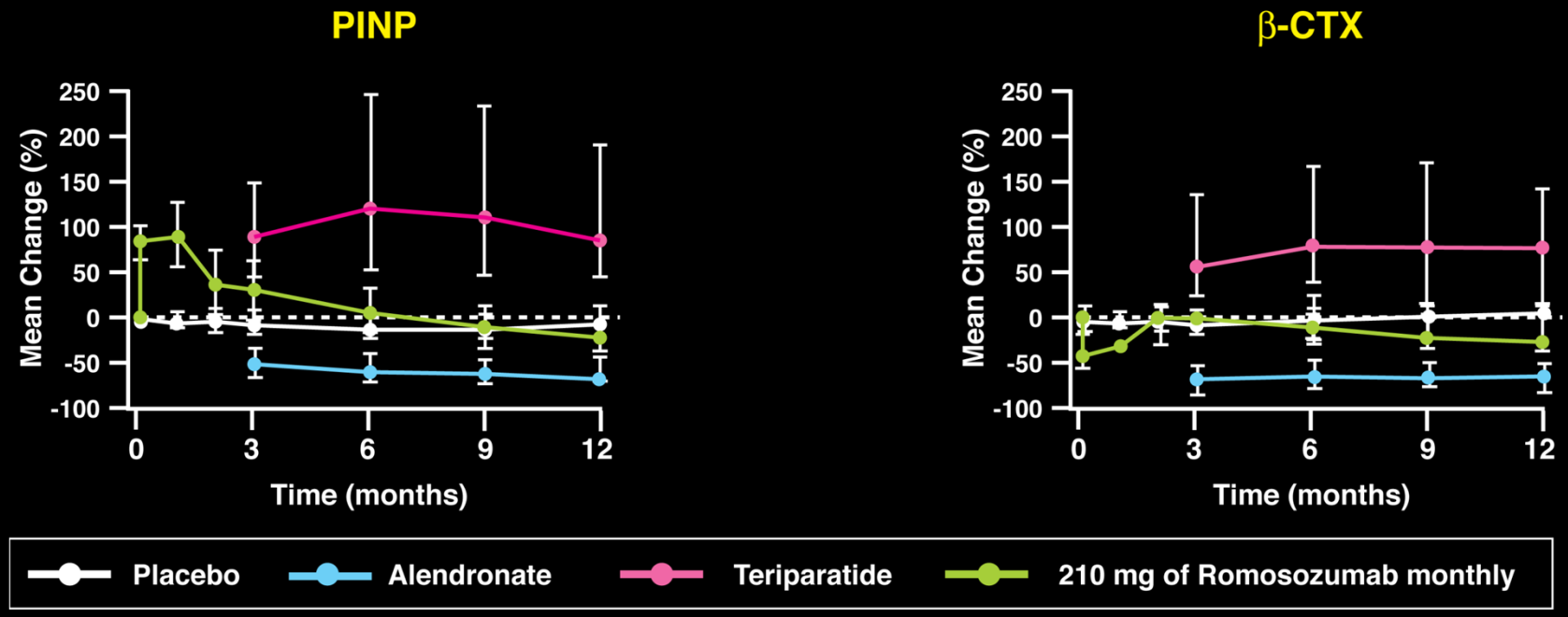
Romosozumab Phase 2, Bone Turnover Markers



McClung M. *N Engl J Med* 2014;370:412

Anti-Sclerostin Antibody

Romosozumab Phase 2, Bone Turnover Markers



McClung M. *N Engl J Med* 2014;370:412

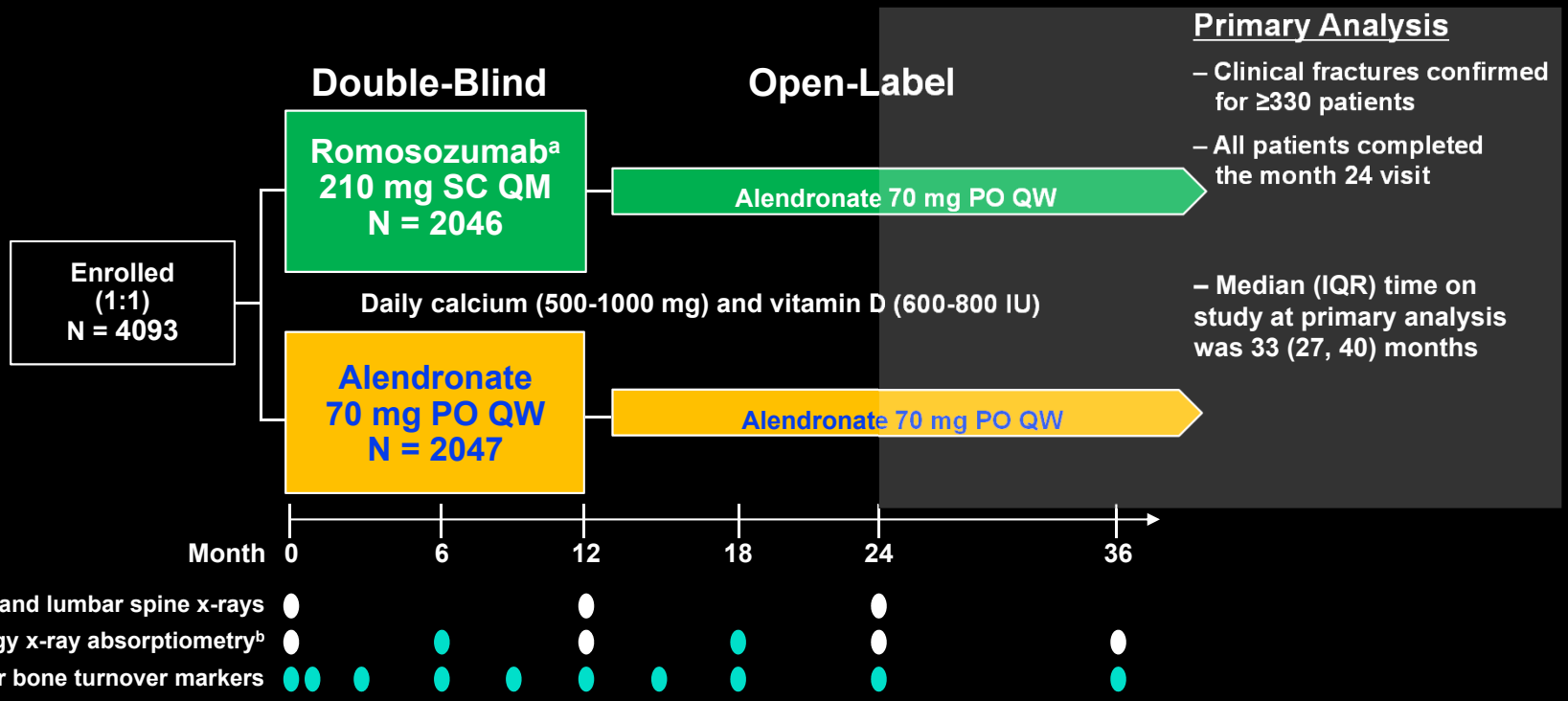
Anti-Sclerostin Antibody Fracture Data

FRActure study in postmenopausal woMen with ostEoporosis (FRAME)

- Reduced new vertebral fracture through months 12 (RRR 73) and 24 (RRR 75)
- Reduced clinical fractures (composite of vertebral and non-vertebral fractures) at 12 months (RRR 36)
- Did not meet secondary endpoint of reducing non-vertebral fractures at 24 months
- 5% injection site reactions, 2 ONJs and 1 AFF

Cosman F. *NEJM* 2016; 375:1532

Romosozumab ARCH Study Design

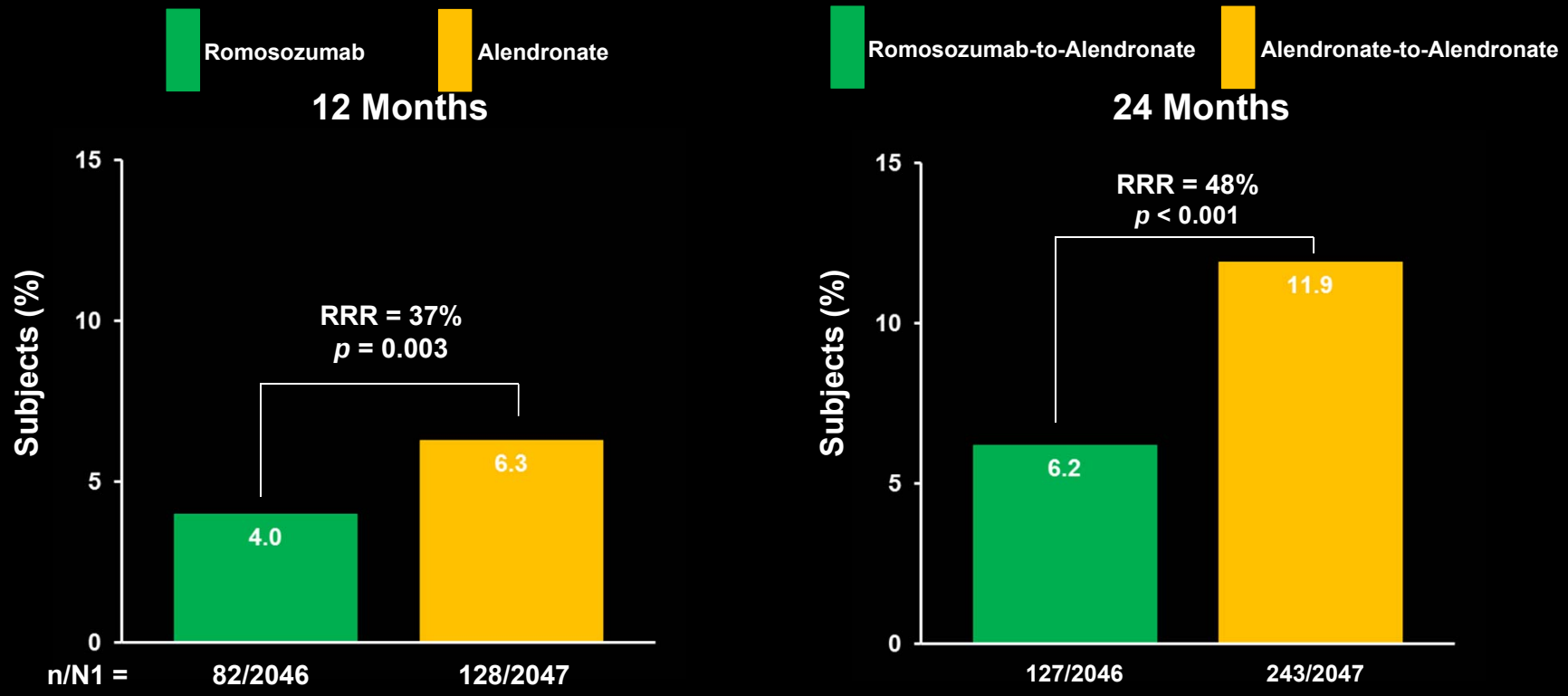


[a]Loading dose of 50,000–60,000 IU vitamin D ; [b]BMD assessed at months 6 and 18 in a subset of patients in substudy; n=167. Yellow ovals indicate timepoints for substudy.

Saag K. *NEJM* 2017; 377:1417

Romosozumab ARCH Study

Primary Endpoint: New Vertebral Fracture Through 24 mos

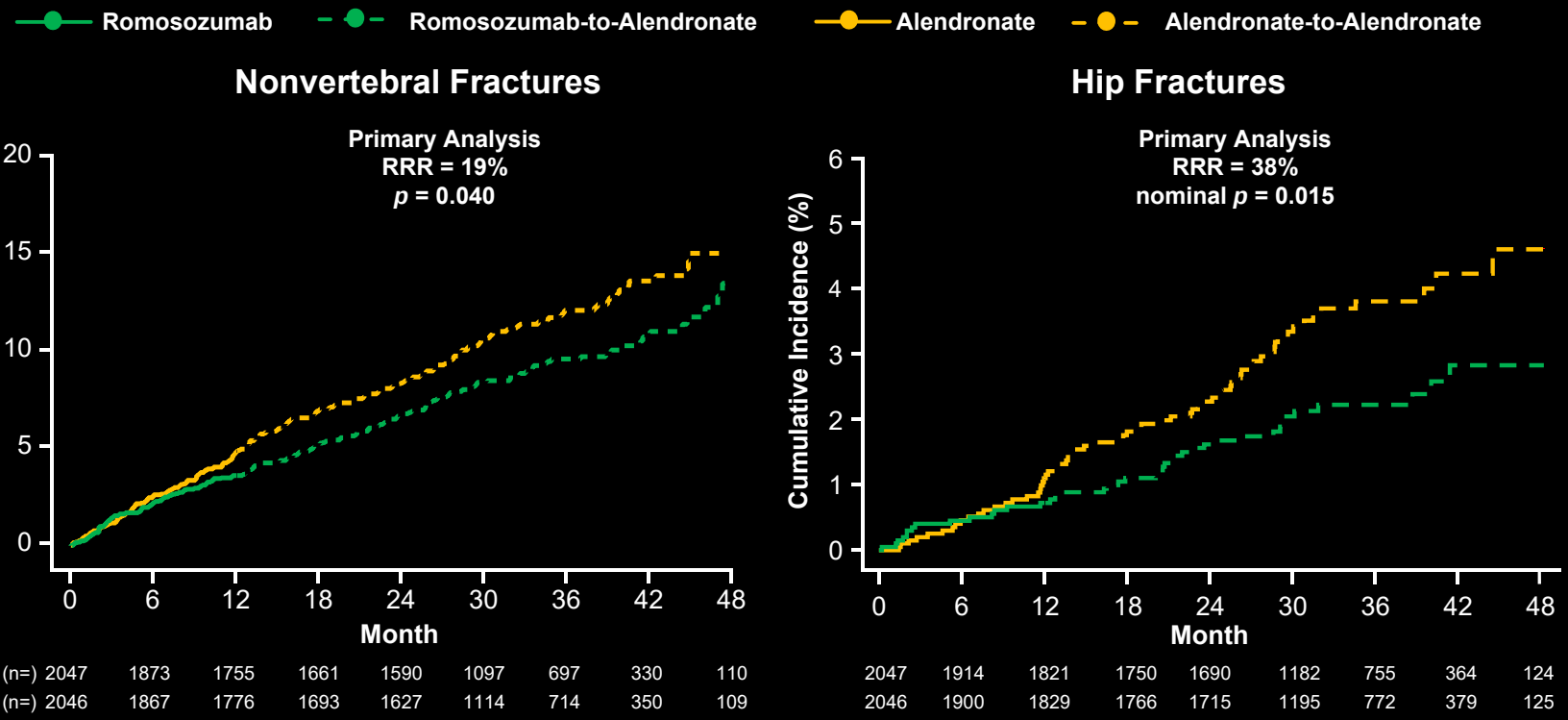


n/N1 = Number of subjects with fractures/Number of subjects in the primary analysis set for vertebral fractures. Missing fracture status was imputed by multiple imputation for patients without observed fracture at an earlier timepoint. n and % are based on the average across 5 imputed datasets. RRR = relative risk reduction.

Saag K. *NEJM* 2017; 377:1417

Romosozumab ARCH Study

Secondary Endpoints: Nonvertebral Fracture and Hip Fracture



n = number of subjects at risk for event at time point of interest. Aln = alendronate; Romo = romosozumab.

Saag K. *NEJM* 2017; 377:1417

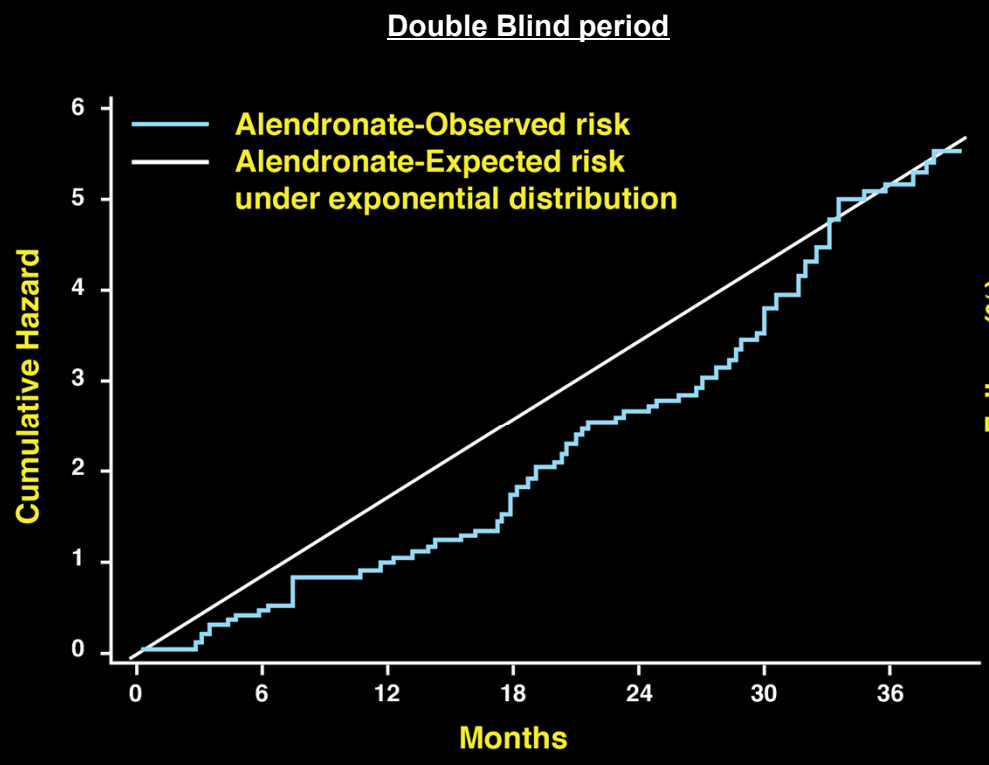
Serious Adverse Events in ARCH

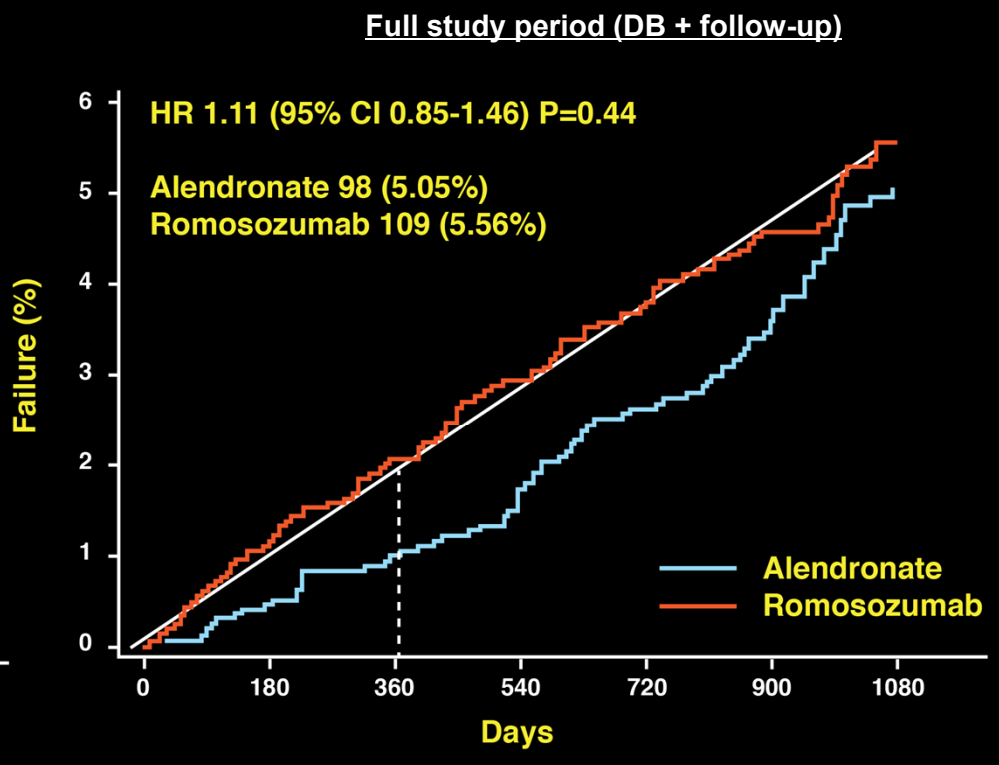
	Month 12 Double-Blind Period	
	Romosozumab N = 2040	Alendronate N = 2014
All adverse events	1544 (75.7)	1584 (78.6)
Serious adverse events	262 (12.8)	278 (13.8)
Adjudicated serious cardiovascular event[a]	50 (2.5)	38 (1.9)
Cardiac ischemic event	16 (0.8)	6 (0.3)
Cerebrovascular event	16 (0.8)	7 (0.3)
Heart failure	4 (0.2)	8 (0.4)
Cardiovascular death	17 (0.8)	12 (0.6)
Non-coronary revascularization	3 (0.1)	5 (0.2)
Peripheral vascular ischemic event not requiring revascularization	0 (0.0)	2 (< 0.1)
Death	30 (1.5)	21 (1.0)

Data are n (%). N = number of subjects who received ≥ 1 dose of investigational product. [a]Adverse events adjudicated positive by an independent adjudication committee. Cardiovascular deaths includes fatal events adjudicated as cardiovascular-related or undetermined (presumed cardiac-related). [b]Incidence rates through primary analysis were cumulative and included all events in the double-blind and open-label period in subjects who received ≥ 1 dose of investigational product.

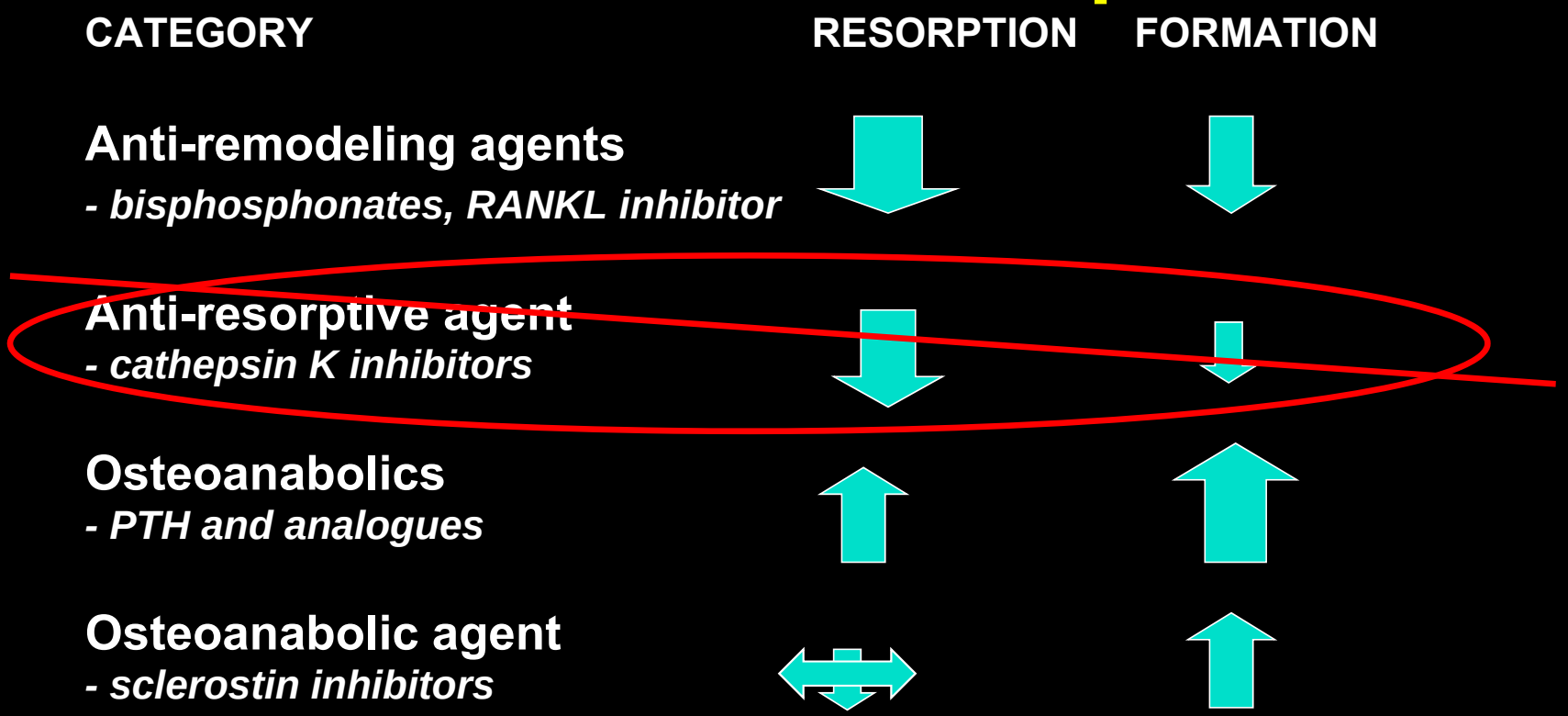
Saag K. *NEJM* 2017; 377:1417

TIMI assessment of MACE-1 in ARCH: "Misbehavior" of Alendronate Treatment Group

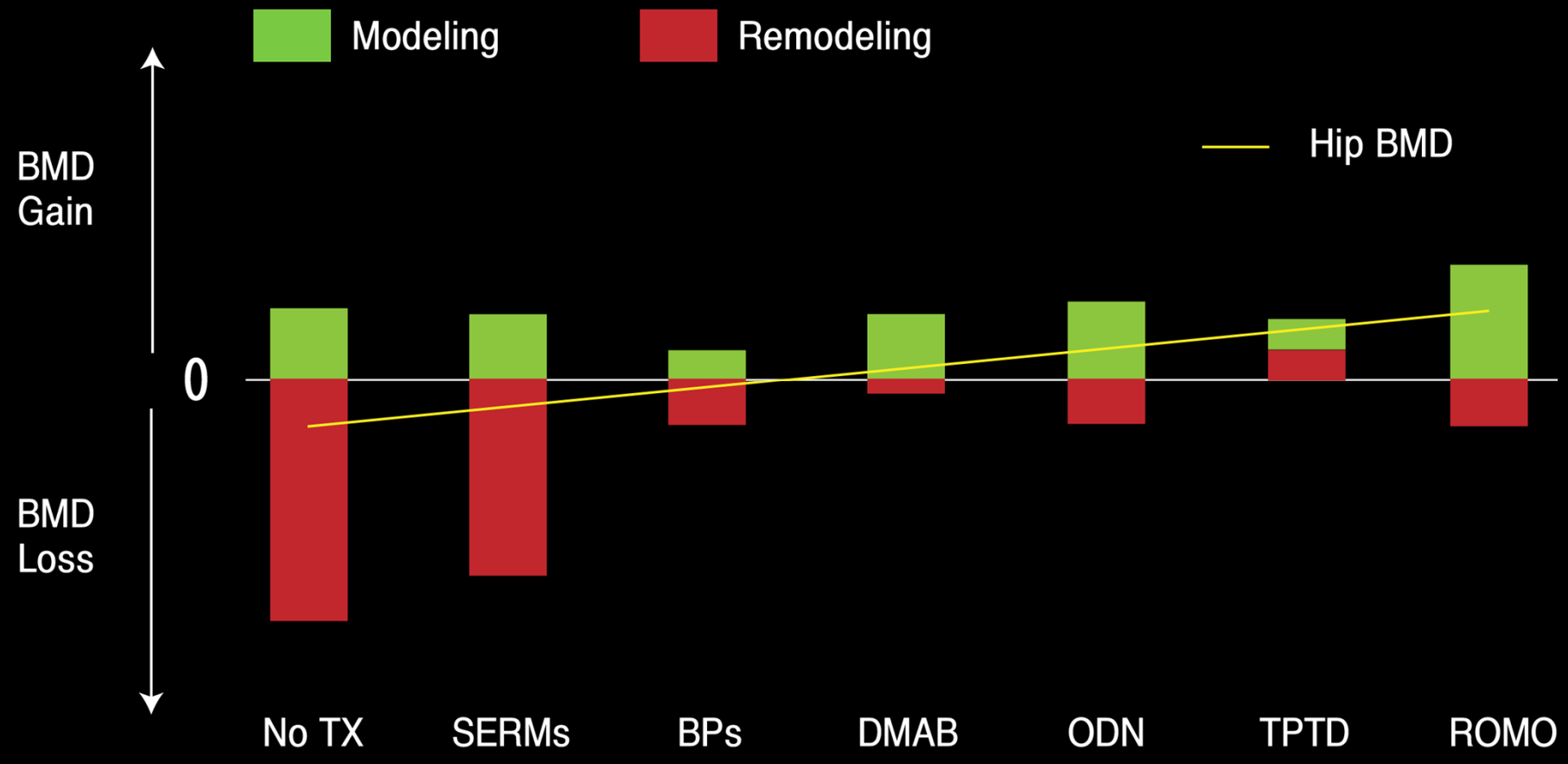




Osteoporosis Current and Possible Future Treatment Options



Theoretical Contribution of Bone Remodeling and Modeling to Change in Hip Bone Mineral Density (BMD)

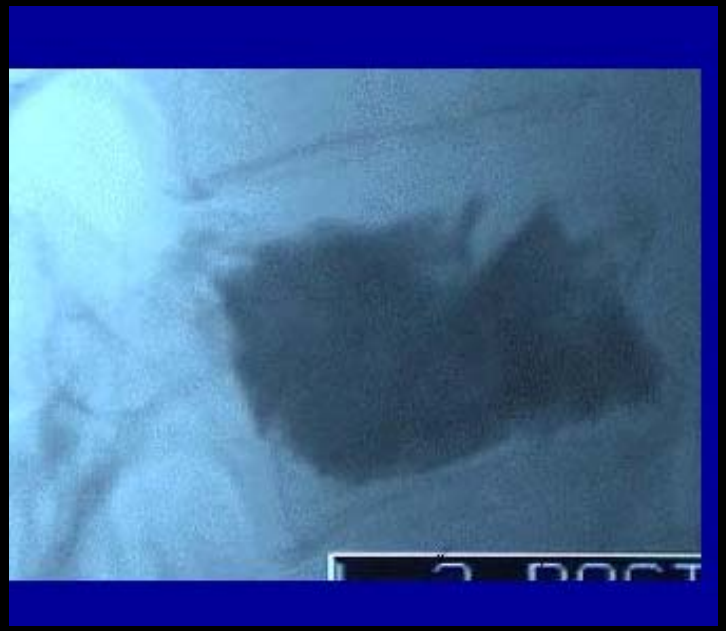


Langdahl B. *Ther Adv Musculoskel Disease* 2016, 8; 225.

What is New/Controversial on Vertebral Augmentation?

New ASBMR Task Force Report On Vertebral Augmention

- Percutaneous vertebroplasty → no clinically significant benefit over placebo or sham procedure (High to Moderate QoE)
- Balloon kyphoplasty → small clinical benefit over nonsurgical management, percutaneous vertebroplasty, vertebral body stenting, or KIVA. (Low QoE)
- Uncertain whether percutaneous vertebroplasty increases risk of incident or radiographic vertebral fractures (Moderate QoE)



Ebeling PR. *J Bone Miner Res* 2019;34:3-21

NIH P2P and ASBMR Secondary Prevention

Annals of Internal Medicine

POSITION PAPER

National Institutes of Health Pathways to Prevention Workshop: Research Gaps for Long-Term Drug Therapies for Osteoporotic Fracture Prevention

Albert Siu, MD, MSPH; Heather Allore, PhD, MS, MA; Darryl Brown, PhD, MPA; Susan T. Charles, PhD; and Matthew Lohman, PhD, MHS

TASK FORCE REPORT

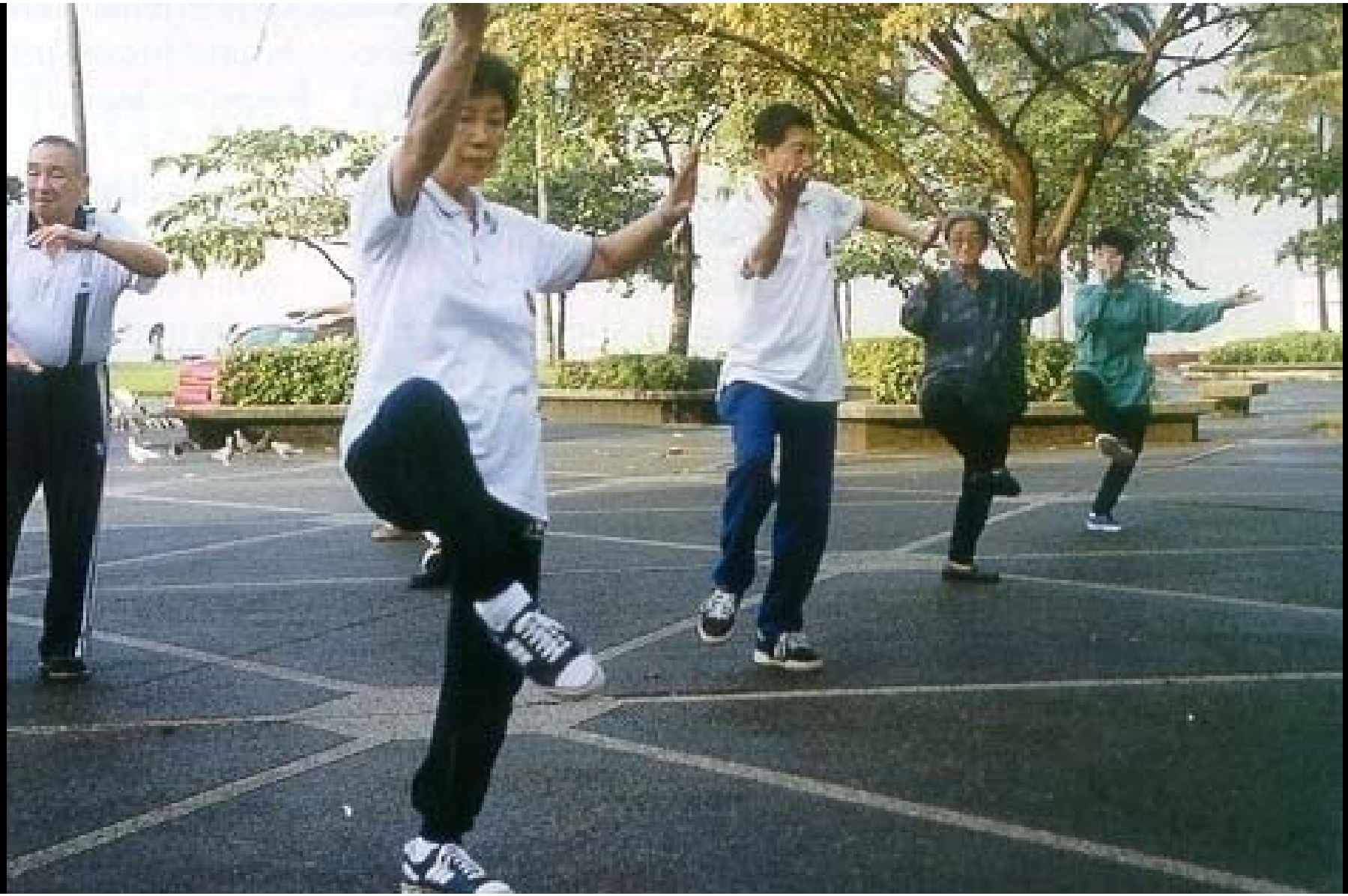
JBMR®

Secondary Fracture Prevention: Consensus Clinical Recommendations from a Multistakeholder Coalition

Robert B Conley,[1] Gemma Adib,[2] Robert A Adler,[3] Kristina E Åkesson,[4] Ivy M Alexander,[5] Kelly C Amenta,[6] Robert D Blank,[7,8] William Timothy Brox,[9] Emily E Carmody,[10] Karen Chapman-Novakofski,[11] Bart L Clarke,[12] Kathleen M Cody,[13] Cyrus Cooper,[14] Carolyn J Crandall,[15] Douglas R Dirschl,[16] Thomas J Eagen,[17] Ann L Elderkin,[18] Masaki Fujita,[19] Susan L Greenspan,[20] Philippe Halbout,[21] Marc C Hochberg,[22] Muhammad Javaid,[23] Kyle J Jeray,[24] Ann E Kearns,[12] Toby King,[25] Thomas F Koinis,[26] Jennifer Scott Koontz,[27,28] Martin Kužma,[29] Carleen Lindsey,[30] Mattias Lorentzon,[31,32,33] George P Lyritis,[34] Laura Boehnke Michaud,[35] Armando Miciano,[36] Suzanne N Morin,[37] Nadia Mujahid,[38] Nicola Napoli,[39,40] Thomas P Olenginski,[41] J Edward Puzas,[10] Stavroula Rizou,[34] Clifford J Rosen,[42,43] Kenneth Saag,[44] Elizabeth Thompson,[45] Laura L Tosi,[46] Howard Tracer,[47] Sundeep Khosla,[12] and Douglas P Kiel[48]

Conclusions

- Calcium and vitamin D are necessary for bone health but too much may not be optimal
- Bisphosphonates- consider holidays/sabbaticals for some patients, balancing long-term benefits and risks is key
- Alternative therapies such as anabolics and shorter lasting anti-resorptives may be useful for patients at high risk, during a bisphosphonate break
- Newer treatment approaches focus on potent stimulation of bone formation; safety questions exist for Romosozumab



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