Osteoporosis Update: Top 5 things to know in 2019

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2019 SHS/UHN Toronto Geriatrics Update Course

October 31, 2019

Learning Objectives

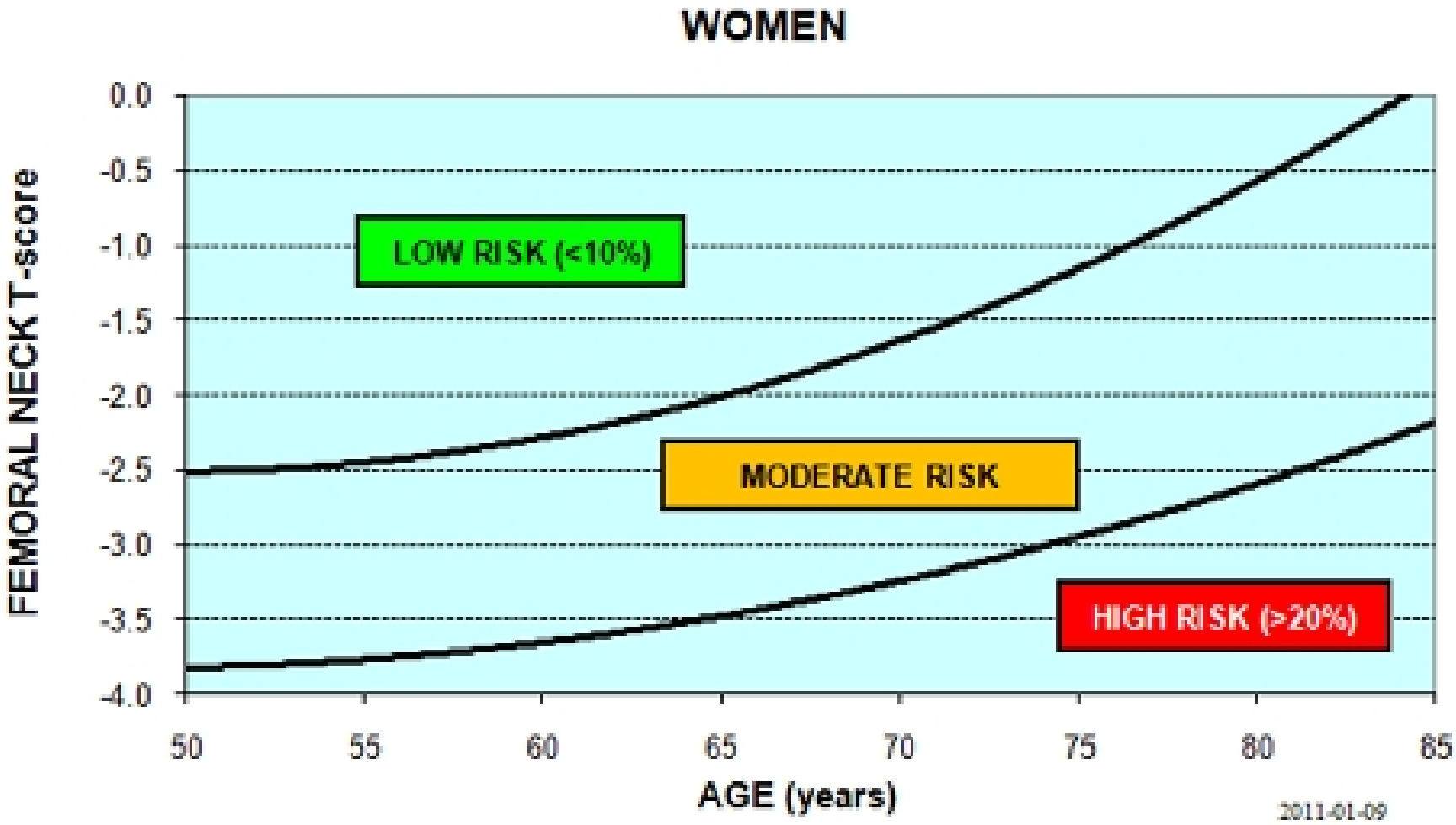
At the end of the session, the participant will be able to:

1) Determine fracture risk – FRS tool
2) Discuss current data regarding vitamin D
3) Choose the right therapy for the right patient based on current evidence (bone formation vs antiresorptive therapies)
4) Determine whether your patient should have a drug holiday and for how long

Fracture Risk Assessment

5: FRACTURE RISK SCALE

Assessment of Basal 10-year Fracture Risk: CAROC System



Sinai Health System | University of Toronto | UHN Toronto General Toronto Western Princess Margaret Toronto Rehab — COURAGE LIVES HERE

FRAX® Fracture Risk Assessment Tool

Home | Calculation Tool | Paper Charts | FAQ | References | English

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: Canada Name/ID: About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: 75 Date of Birth: Y: M: D:
2. Sex — Male / Female
3. Weight (kg): 54.4
4. Height (cm): 160
5. Previous Fracture — No / Yes
6. Parent Fractured Hip — No / Yes
7. Current Smoking — No / Yes
8. Glucocorticoids — No / Yes
9. Rheumatoid arthritis — No / Yes
10. Secondary osteoporosis — No / Yes
11. Alcohol 3 or more units/day — No / Yes
12. Femoral neck BMD (g/cm^2): Hologic 0.600 T-score: -2.2

Clear | Calculate

BMI: 21.2
The ten year probability of fracture (%)
with BMD

Major osteoporotic	12
Hip Fracture	3.4

If you have a TBS value, click here: Adjust with TBS

Weight Conversion

Pounds → kg Convert

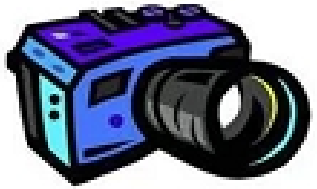
Height Conversion

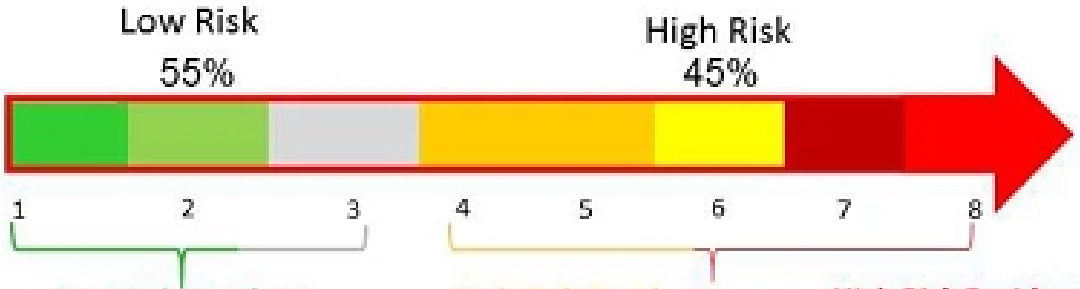
Inches → cm 63 Convert

00563859
Individuals with fracture risk assessed since 1st June 2011

Fracture Risk Scale

FRS – Risk Prediction: Snapshots of Residents at High and Low Risk





Low Risk Resident
Walks in corridor and
BMI > 30
or
Unable to walk in corridor
and
no fall past 30 days

High Risk Resident
Walks in corridor and
BMI 18-30
& one of the following:
- Prior fall
- Prior fracture
- Cognitive impairment
- Tendency to wander
- Age >85

or

High Risk Resident
Unable to walk in corridor
and has a fall past 30 days

High Risk Resident
Walks in corridor and
BMI <18
with or without a fall

Ioannidis G, et al. BMJ Open, 2017;7.

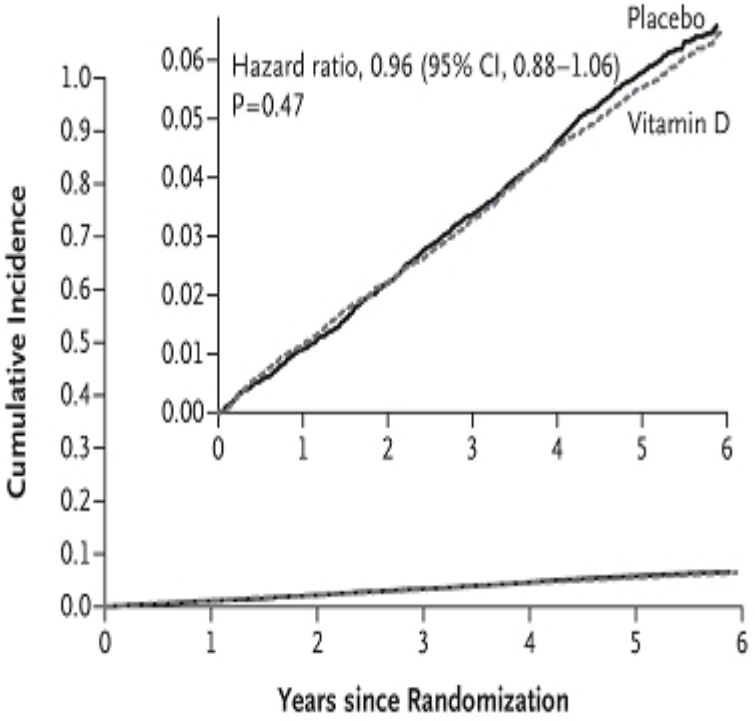
New Data on Supplements and Nutrition

4: VITAMIN D

VITAL Study – NEJM Nov 10, 2018

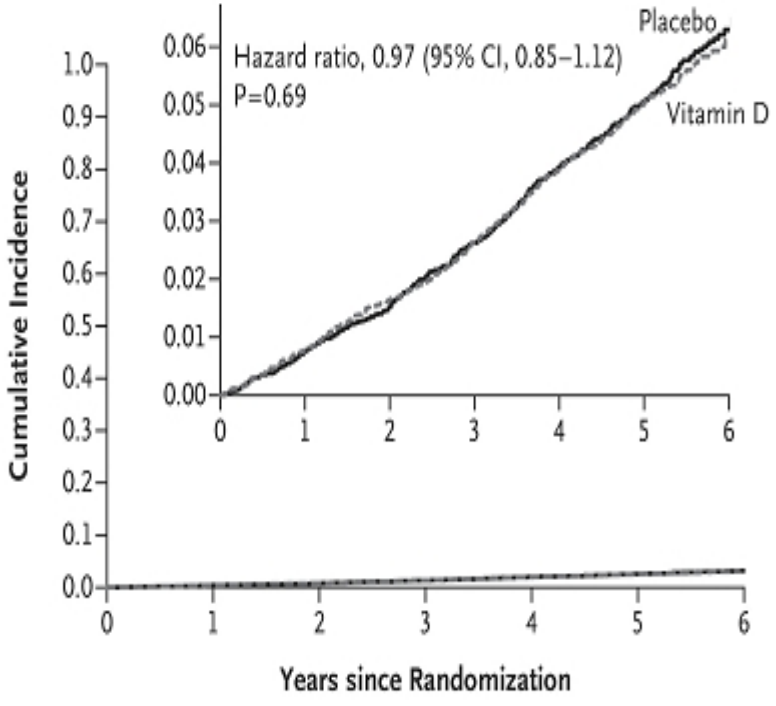
Multicenter randomized 2x2 factorial design study
N=25,871 men ≥50y and women ≥55y

A Invasive Cancer of Any Type



No. at Risk							
Placebo	12,944	12,765	12,567	12,345	11,985	9543	746
Vitamin D	12,927	12,738	12,543	12,341	11,992	9557	744

B Major Cardiovascular Events



No. at Risk							
Placebo	12,944	12,862	12,747	12,593	12,289	9841	766
Vitamin D	12,927	12,842	12,723	12,593	12,314	9862	774

The Calgary Vitamin D Study

JAMA (JAMA 2019)

In this double-blind, randomized controlled trial, healthy adults (n=373) aged 55 to 70 years with baseline 25-hydroxyvitamin D (25OHD) 30 to 125 nmol/L were randomized 1:1:1 to the following interventions for three years:

- Vitamin D3 400 IU/d
- Vitamin D3 4000 IU/d
- Vitamin D3 10,000 IU/d

} If dietary calcium intake was <1200 mg/day, a supplement of 300 or 600 mg elemental calcium (as citrate) was provided as needed, to reach a maximum intake of 1200 mg

Participants were evaluated at baseline 3, 6, 12, 18, 24, 30 and 36 months. The following safety measures were assessed:

- **Biochemical Safety Parameters:** 25OHD, serum calcium, serum creatinine, hepatocellular liver enzymes (ALT and AST), 24 hour urine calcium
- **Clinical Safety Parameters:** serious adverse events, falls, low-trauma fractures, nephrolithiasis, cancer, infections, upper respiratory tract infections

The Calgary Vitamin D Study
(2018 ASBMR abstract)

No Benefit from high dose vitamin D on bone outcomes!

- Primary outcome –
  - dose dependent ***detrimental effect*** on total volumetric BMD,
  - no difference (trend of detrimental effect) in FEA at radius or tibia
- Secondary outcomes –
  - no difference in total hip BMD,
  - dose dependent ***detrimental effect*** on trabecular compartment (trabecular BMD, trabecular number)

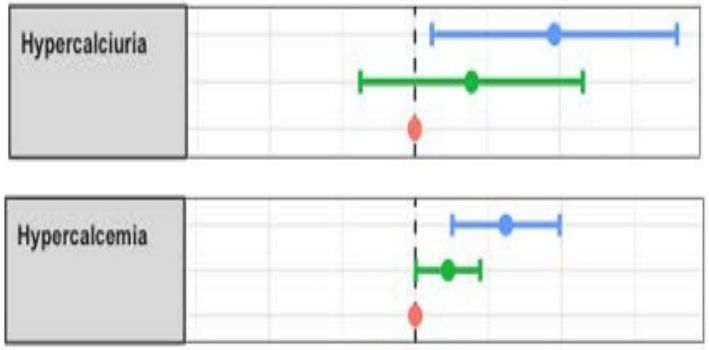
Serum 25(OH)D [nmol/L]

	3 Mo	36 Mo
400 IU	76.7	77.3
4000 IU	115.0	132.2
10 000 IU	188.3	144.4

The Calgary Vitamin D Study
(2018 ASBMR abstract)

No Benefit from high dose vitamin D on bone outcomes!

- Calcium issues –
  - Dose-dependent hypercalcuria (occurs in 23%)
  - Dose-dependent hypercalcemia (mild) (occurs in 4%)
  - No difference in Cr, eGFR, kidney stones



- Falls and fractures – no difference between groups
- Aortic calcification – no difference between groups

Vitamin D

- Vitamin D 1000-2000iu a day
- serum 25-hydroxyvitamin D level ≥75nmol/L
- Not to exceed serum 25 OH-D ≤ 150nmol/L

Osteoporosis.ca
Osteoconnections.com

Calcium

- Calcium (Dietary and supplement)

  = 1000-1200mg a day → 500-600mg

Osteoporosis.ca

Osteoconnections.com

Nutrition

- Under-nutrition is common
  - Inadequate protein intake reduces muscle synthesis
  - ~40% of older adults not meeting current RDA of 0.8 g/kg daily
  - Protein intake of 1.2-1.5 g/kg daily is likely optimal

Hanger, et. al. N Z Med J. 1999 26;112:88-90
Morley, J Nutr, Health, Aging, 12;452-456, 2008
Mithal, et. al., Ost Int, 2013; doi 10.1007/s00198-012-2236y

New Data on Drug Therapies

CURRENT EVIDENCE ON DRUG THERAPIES

Therapies with Proven Fracture Prevention

Osteoporosis Canada 2010 Clinical Practice Guidelines

Based on GRADE A evidence							
Type of Fracture	**Antiresorptive Therapy**						**Bone Formation Therapy**
	Bisphosphonates			Denosumab	Raloxifene	Estrogen * (Hormone Therapy)	Teriparatide
	Alendronate	Risedronate	Zoledronic Acid				
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.

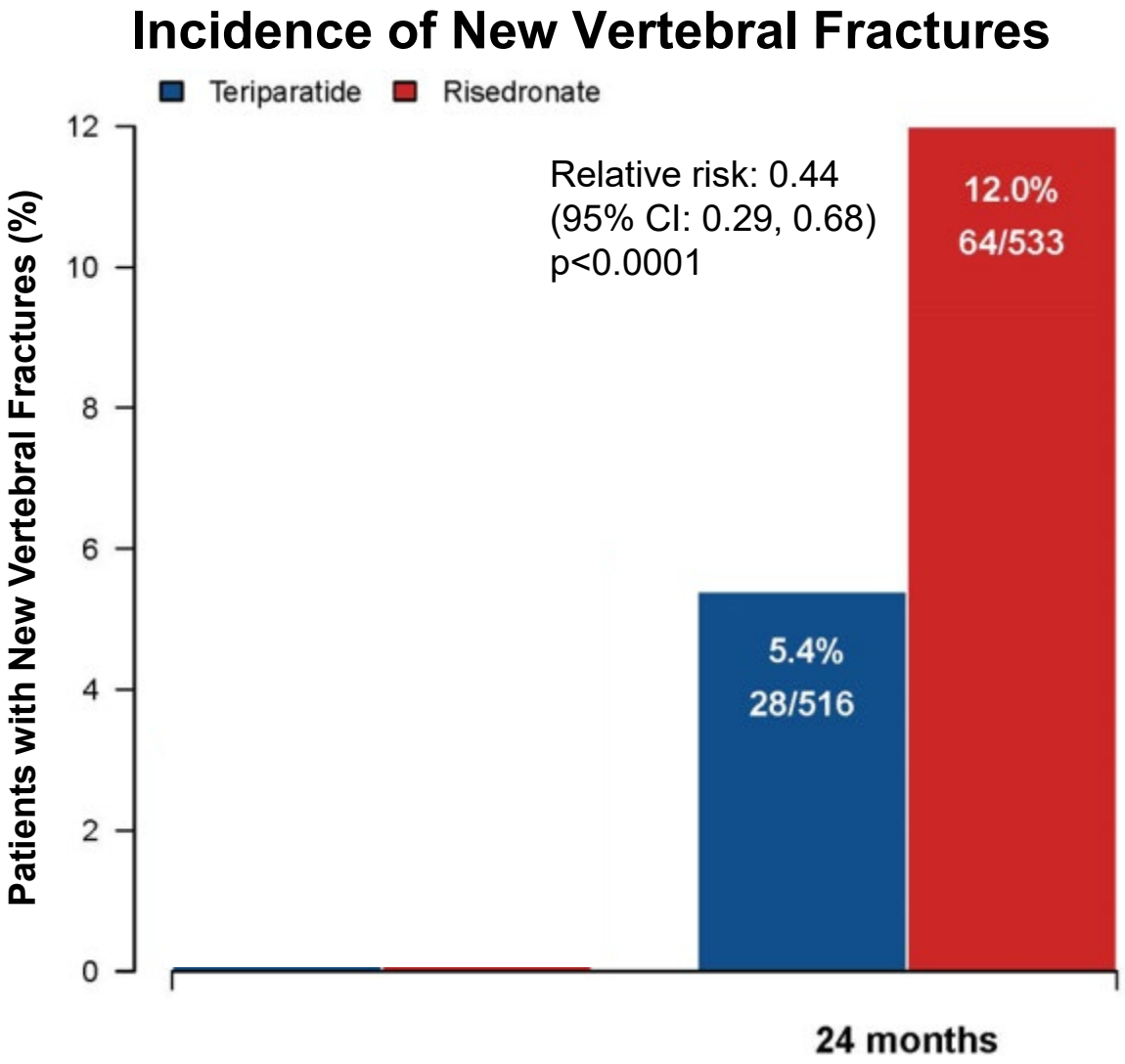
Papaioannou A, *et al. CMAJ*. 2010;182:1864-1873.

Papaioannou A, et al *CMAJ* 2010.

Current Evidence on Drug Therapies

3. TERIPARATIDE

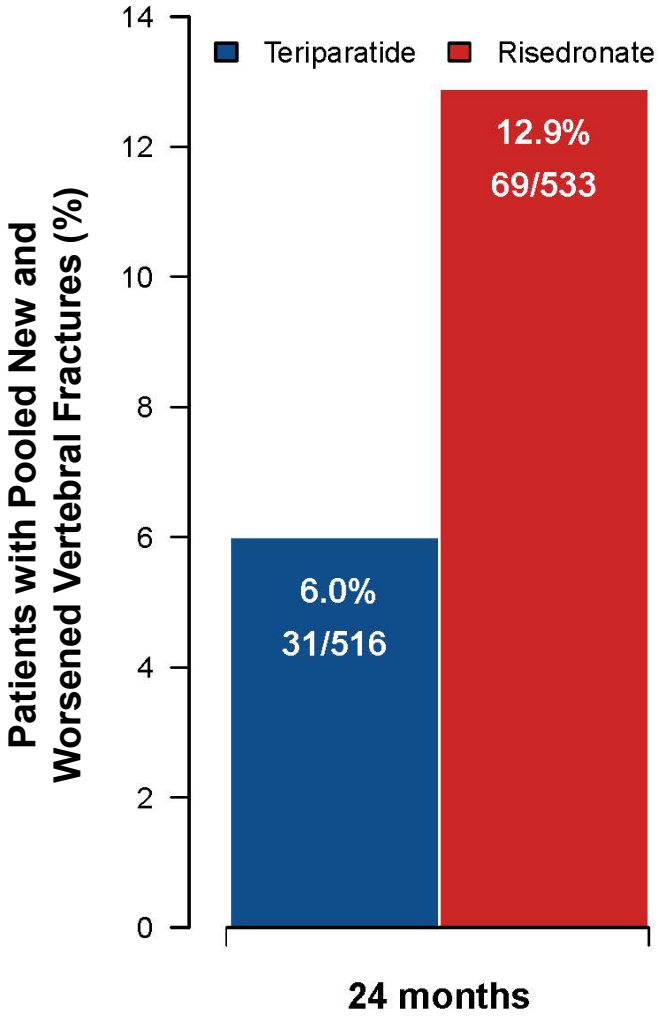
VERO Trial: Primary Endpoint



Kendler DL et al. *The Lancet* (2018):391: 230–40

VERO Trial: Secondary Endpoint

Incidence of Pooled New and Worsened Vertebral Fractures



Relative risk: 0.46
(95% CI: 0.31, 0.68)
p<0.001

Kendler DL et al. *The Lancet* (2018):391: 230–40

Teriparatide versus Risedronate: VERO fracture endpoint RCT

Postmenopausal women with one severe or two moderate vertebral fractures
Randomized to weekly risedronate or daily teriparatide for two years

	TPTD	RIS	RRR
n	680	680	
Vertebral fracture	5.4%	12%	56%
Nonvertebral fracture	3.9%	6.2%	19% (p =0.1)
Clinical fracture	4%	10%	52%

Kendler DL et al. Osteoporos Int (2017): Suppl 1: 63-64

Results: Safety – Adverse Events

	Teriparatide (N=680)	Risedronate (N=680)	P-value[a]
Patients with ≥1 TEAE, number of patients (%)	495 (72.8)	500 (73.5)	0.760
Serious TEAE	137 (20.1)	115 (16.9)	0.125
Related to study drug	87 (12.8)	66 (9.7)	0.072
Related to study procedure	4 (0.6)	4 (0.6)	1.000
Leading to treatment discontinuation	67 (9.9)	48 (7.1)	0.064
Leading to death	15 (2.2)	7 (1.0)	0.131
TEAEs (preferred term) with statistically significant difference, number of patients (%)			
Pain in extremity	37 (5.4)	18 (2.6)	0.013
Dizziness	30 (4.4)	12 (1.8)	0.007
Hypercalcaemia	15 (2.2)	1 (0.1)	<0.001
Pain	10 (1.5)	2 (0.3)	0.038
Vitamin D decreased	9 (1.3)	1 (0.1)	0.021
Dental caries	6 (0.9)	0	0.031
Bone contusion	0	6 (0.9)	0.031

[a] p-value from Fisher's exact or chi-squared test. In case of fewer than 10 patients with outcome data in one of the treatment groups, Fisher's exact test was used

N = total number of patients; TEAE: = treatment-emergent adverse event.

Kendler DL et al. *The Lancet* (2018):391: 230–40

Results: Key Laboratory Safety Findings

	Teriparatide (N=680)	Risedronate (N=680)	P-value[a]
Key laboratory events, n/N (%)[b]			
Hypercalcemia	61/630 (9.7)	3/637 (0.5)	<0.001
>10.6 and <11.0 mg/dL	39/630 (6.2)	3/637 (0.5)	<0.001
>11 and ≤12.5 mg/dL	18/630 (2.9)	0	<0.001
>12.5 mg/dL	4/630 (0.6)	0	0.061
Hyperuricemia			
Month 6	63/594 (10.6)	13/605 (2.1)	<0.001
Month 24	65/500 (13.0)	17/511 (3.3)	<0.001
Hypermagnesemia			
Month 6	31/594 (5.2)	4/604 (0.7)	<0.001
Month 24	24/500 (4.8)	4/511 (0.8)	<0.001

[a] P-value from Chi-squared test or Fisher's exact test (if <10 evaluable patients in either treatment groups).
[b] Based on central laboratory data and not on reports of clinical adverse events. Hypercalcemia was predefined as albumin-corrected serum calcium of ≥10.6 mg/dL at any time point, hyperuricemia as serum urate level of ≥7.5 mg/dL at any time point, and hypomagnesemia as a serum magnesium <1.5 mg/dL at any time point. To convert the laboratory values to mmol/L multiply by 0.25 for calcium.
N = total number of patients; n = number of patients in the specified category

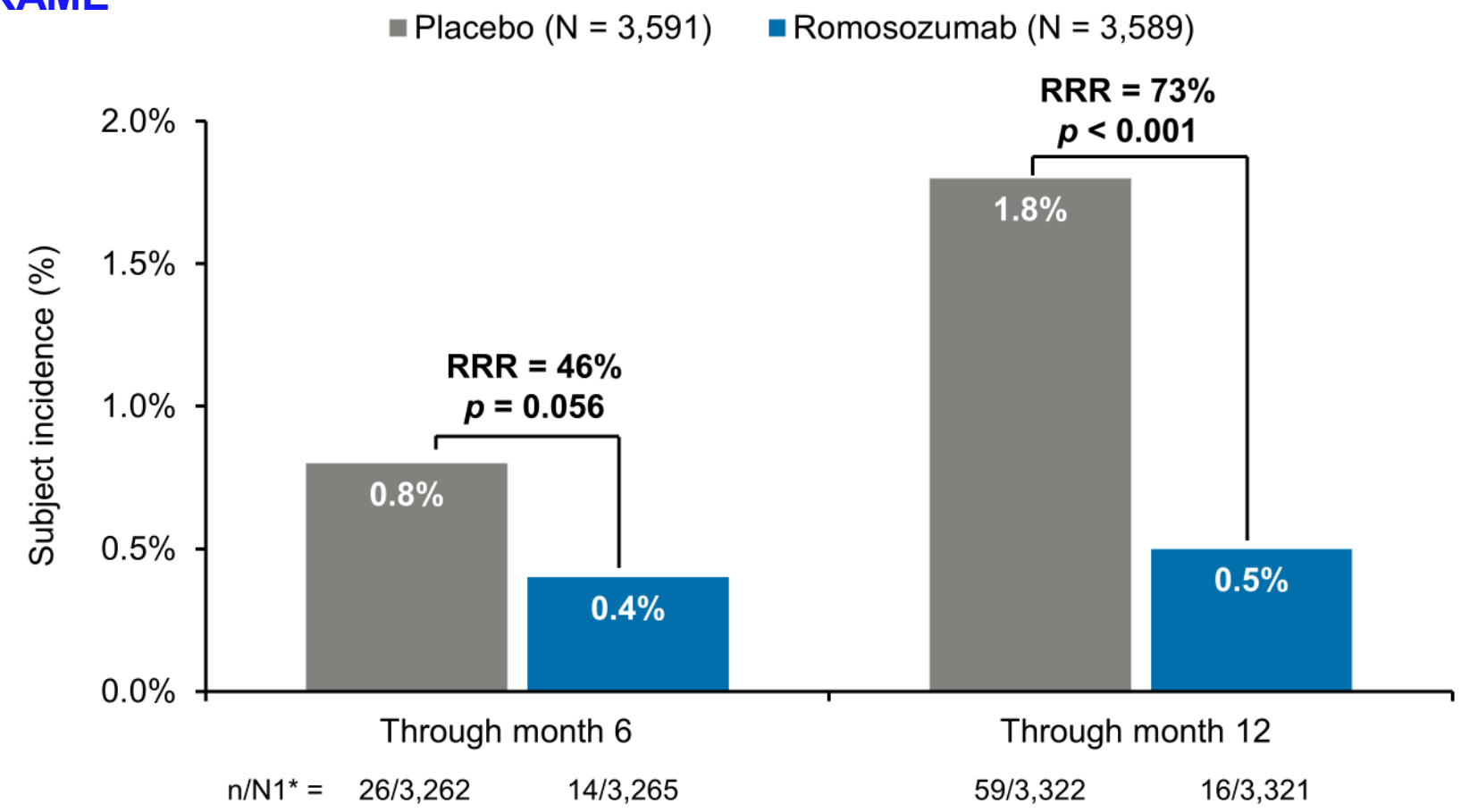
Kendler DL et al. *The Lancet* (2018):391: 230–40

Current Evidence on Drug Therapies

2. ROMOSOZUMAB

Incidence of new vertebral fracture through month 12

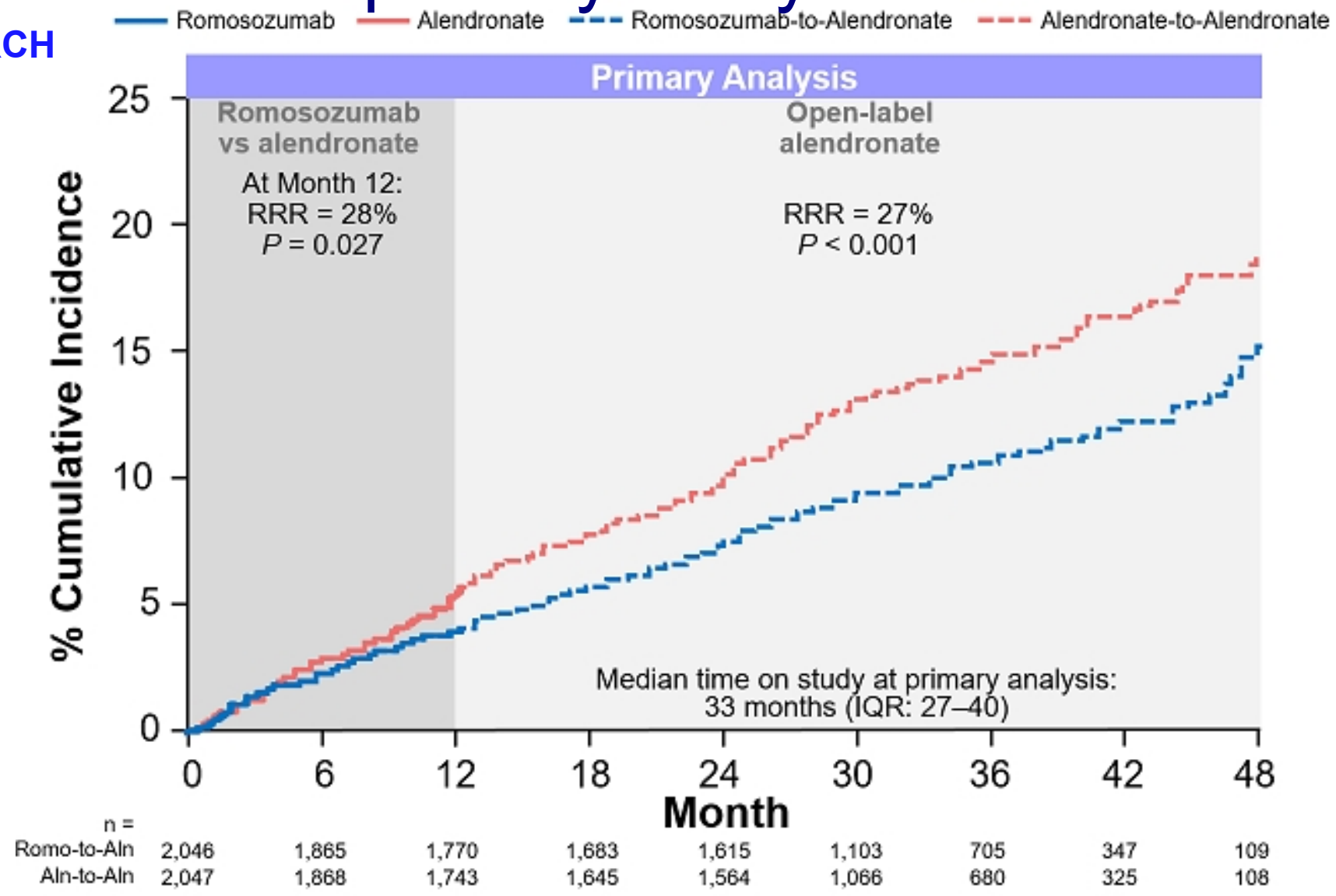
FRAME



p-value based on logistic regression model adjusted for age (<75, ≥75) and prevalent vertebral fracture.
n/N1 = number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures; RRR = relative risk reduction.
1. Adapted from: Cosman F, et al. *N Engl J Med*. 2016;375:1532–1543; 2. Data on file, Amgen.

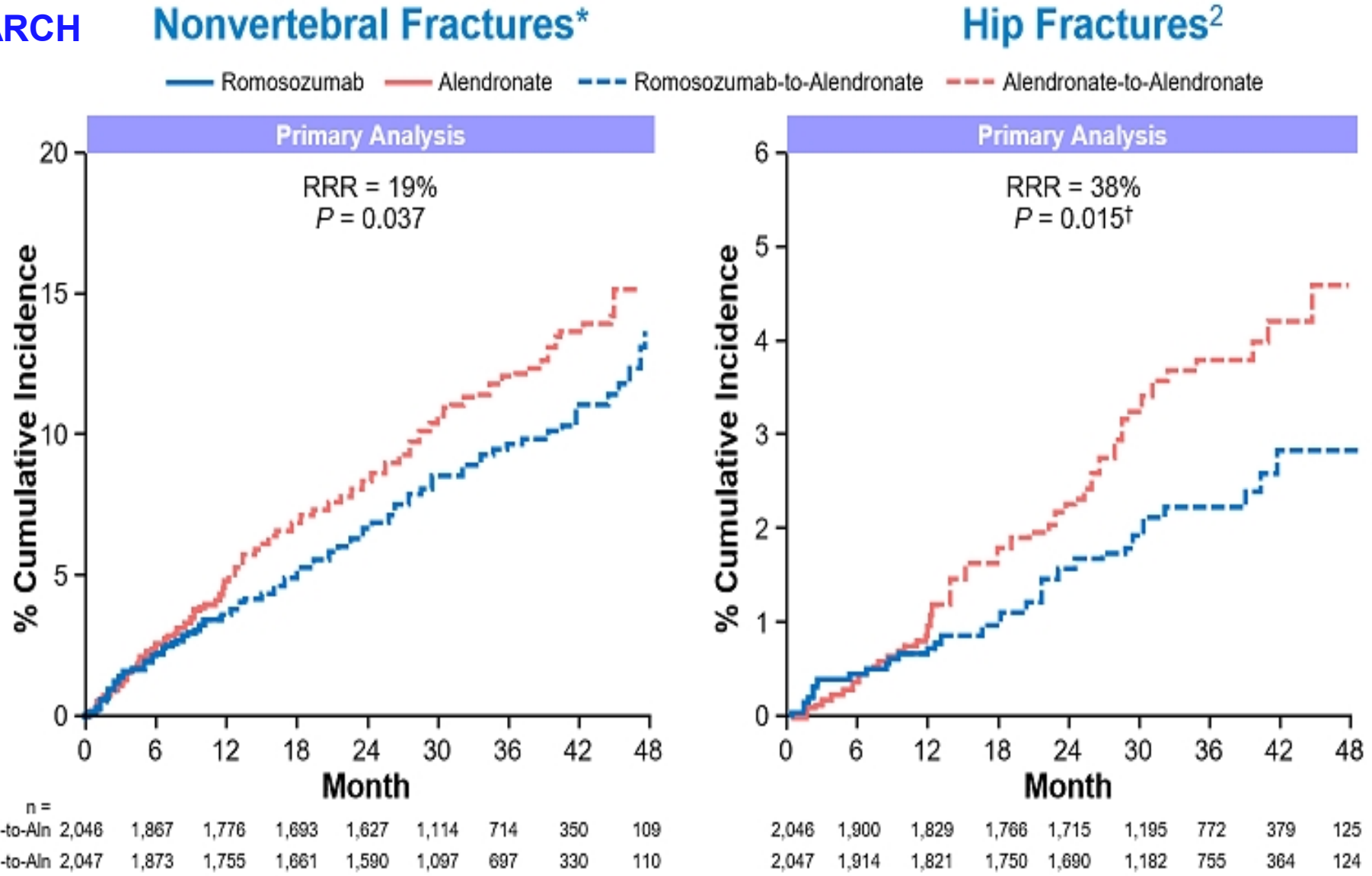
Incidence of clinical fracture at primary analysis

ARCH



Nonvertebral and Hip Fractures

ARCH



Romosozumab vs alendronate: Subject incidence of adverse events

Event	Month 12: double-blind period		Primary analysis: double-blind and open-label period*	
	Romosozumab (N = 2,040)	Alendronate (N = 2,014)	Romosozumab to alendronate (N = 2,040)	Alendronate to alendronate (N = 2,014)
Adverse event during treatment	1,544 (75.7%)	1,584 (78.6%)	1,766 (86.6%)	1,784 (88.6%)
Back pain†	186 (9.1%)	228 (11.3%)	329 (16.1%)	393 (19.5%)
Nasopharyngitis†	213 (10.4%)	218 (10.8%)	363 (17.8%)	373 (18.5%)
Event leading to discontinuation of trial regimen	70 (3.4%)	64 (3.2%)	133 (6.5%)	146 (7.2%)
Event leading to discontinuation of trial participation	30 (1.5%)	27 (1.3%)	47 (2.3%)	43 (2.1%)
Event of interest‡				
Osteoarthritis§	138 (6.8%)	146 (7.2%)	247 (12.1%)	268 (13.3%)
Hypersensitivity	122 (6.0%)	118 (5.9%)	205 (10.0%)	185 (9.2%)
Injection-site reaction**	90 (4.4%)	53 (2.6%)	90 (4.4%)	53 (2.6%)
Cancer	31 (1.5%)	28 (1.4%)	84 (4.1%)	85 (4.2%)
Hyperostosis††	2 (<0.1%)	12 (0.6%)	23 (1.1%)	27 (1.3%)
Hypocalcemia	1 (<0.1%)	1 (<0.1%)	4 (0.2%)	1 (<0.1%)
Atypical femoral fracture‡‡	0	0	2 (<0.1%)	4 (0.2%)
Osteonecrosis of the jaw‡‡	0	0	1 (<0.1%)	1 (<0.1%)

*Incidence rates at the time of the primary analysis were cumulative and included all events in the double-blind and open-label period (to February 27, 2017) in patients who received at least one dose of open-label alendronate.
†Shown are events that occurred in 10% or more of the patients in either group during the double-blind period.
‡Events of interest were those that were identified by prespecified Medical Dictionary for Regulatory Activities search strategies.
§Prespecified events were osteoarthritis, spinal osteoarthritis, exostosis, arthritis, polyarthritis, arthropathy, monoarthritis, and interspinous osteoarthritis. **The most frequent adverse events of injection-site reactions (occurring in > 0.1% of the patients) in the romosozumab group during the double-blind period included injection-site pain (1.6% of patients), erythema (1.3%), pruritus (0.8%), hemorrhage (0.5%), rash (0.4%), and swelling (0.3%).
††Prespecified events were exostosis (mostly reported as heel spurs), lumbar spinal stenosis, spinal column stenosis, cervical spinal stenosis, enostosis, extraskeletal ossification, and vertebral foraminal stenosis.
‡‡Potential cases of osteonecrosis of the jaw and atypical femoral fracture were adjudicated by independent committees.
Adapted from: Saag KG, et al. *N Engl J Med*. 2017;377:1417–1427.

ARCH and FRAME: Subject incidence of positively-adjudicated CV SAEs in the overall study period*

Category Subcategory	Subject incidence during overall study period*			
	FRAME		ARCH	
	Placebo N = 3,576 n (%)	Romosozumab N = 3,581 n (%)	Alendronate N = 2,014 n (%)	Romosozumab N = 2,040 n (%)
Positively-adjudicated CV SAE	**124 (3.5)**	**128 (3.6)**	**137 (6.8)**	**144 (7.1)**
Cardiac ischemic event	38 (1.1)	36 (1.0)	25 (1.2)	32 (1.6)
Myocardial infarction	19 (0.5)	23 (0.6)	21 (1.0)	23 (1.1)
Cerebrovascular event	36 (1.0)	43 (1.2)	27 (1.3)	47 (2.3)
Stroke	31 (0.9)	37 (1.0)	24 (1.2)	42 (2.1)
Cardiovascular death†	50 (1.4)	43 (1.2)	68 (3.4)	67 (3.3)
Heart failure	15 (0.4)	12 (0.3)	25 (1.2)	14 (0.7)
Noncoronary revascularization	4 (0.1)	2 (<0.1)	10 (0.5)	7 (0.3)
Peripheral vascular ischemic event not requiring revascularization	3 (<0.1)	8 (0.2)	5 (0.2)	2 (<0.1)
MACE‡	**86 (2.4)**	**95 (2.7)**	**102 (5.1)**	**117 (5.7)**
Myocardial infarction	19 (0.5)	23 (0.6)	21 (1.0)	23 (1.1)
Stroke	31 (0.9)	37 (1.0)	24 (1.2)	42 (2.1)
Cardiovascular death†	50 (1.4)	43 (1.2)	68 (3.4)	67 (3.3)

A subject may be counted in more than one category.
*Overall study period for FRAME: 36 months, and for ARCH: median 36 months (Q1, Q3: 30, 43). †Includes fatal events adjudicated as CV-related or undetermined. ‡A post-hoc analysis was performed using the composite endpoint of positively-adjudicated MI, stroke, and CV death (MACE).
CV = cardiovascular; MACE = major adverse cardiovascular event; MI = myocardial infarction; SAE = serious adverse event.
Amgen Briefing Information for the January 16, 2019 Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee. Available at: https://www.fda.gov/media/121255/download. Accessed March 4, 2019.

ARCH and FRAME: Major adverse cardiovascular events (MACE) summary[1]

	At month 12 (double-blind period)			
	FRAME*#†1 (N = 7,180)		ARCH*&†1 (N = 4,093)	
	Romosozumab (N = 3,589)	Placebo (N = 3,591)	Romosozumab (N = 2,046)	Alendronate (N = 2,047)
Myocardial infarction	**9** (0.3%)	**8** (0.2%)	**16** (0.8%)	**5** (0.2%)
Stroke	**8** (0.2%)	**10** (0.3%)	**13** (0.6%)	**7** (0.3%)
CV death	**17** (0.5%)	**15** (0.4%)	**17** (0.8%)	**12** (0.6%)
MACE	**30** (0.8%)	**29** (0.8%)	**41** (2%)	**22** (1.1%)

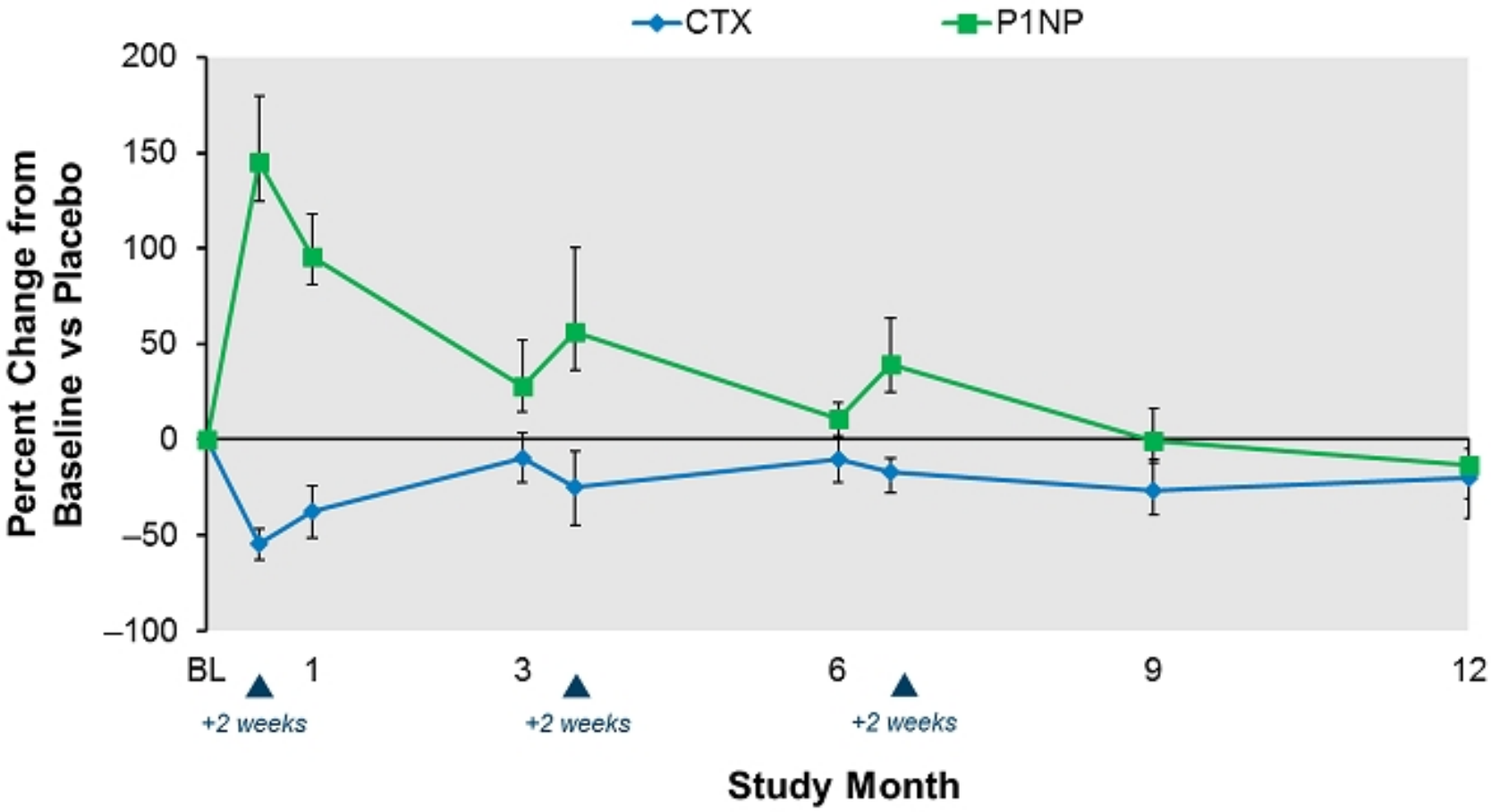
*A post-hoc analysis was performed using the composite endpoint of positively-adjudicated non-fatal MI, non-fatal stroke, and CV death (MACE).
#Subjects were randomized to receive 12 months of romosozumab or placebo; subjects then received denosumab for an additional 12 months.
&Subjects were randomized to receive 12 months of romosozumab or alendronate; subjects then received alendronate until primary analysis.
†The MACE events were reported in patients with or without a history of MI or stroke.
CV = cardiovascular; MACE = major adverse cardiovascular event; MI = myocardial infarction.
1. EVENITY™ (romosozumab) product monograph, Amgen, September 2019.

ARCH and FRAME trial populations

Baseline Characteristic	ARCH[1]		FRAME[2]	
	Romosozumab (N = 2,046)*	Alendronate (N = 2,047)*	Romosozumab (N = 3,589)	Placebo (N = 3,591)
Age, years	74.4 ± 7.5	74.2 ± 7.5	70.9 (7.0)	70.8 (6.9)
Bone mineral density T-score				
Femoral neck	–2.89 ± 0.49	–2.90 ± 0.50	–2.76 (0.28)	–2.74 (0.29)
Lumbar spine	–2.94 ± 1.25	–2.99 ± 1.24	–2.72 (1.04)	–2.17 (1.04)
Total hip	–2.78 ± 0.68	–2.81 ± 0.67	–2.48 (0.47)	–2.46 (0.47)
Prevalent vertebral fracture	96.2%	95.9%	18.7%	18.0%
Previous nonvertebral fracture	37.5%	37.6%	21.7%	21.8%
FRAX score	20.2 ± 10.2	20.0 ± 10.1	13.4 ± 8.8	13.4 ± 8.5

1. Saag KG, et al. *N Engl J Med*. 2017;377:1417-1427. 2. Cosman F, et al. *N Engl J Med*. 2016;375:1532-1543.

Change in BTMs with Romosozumab

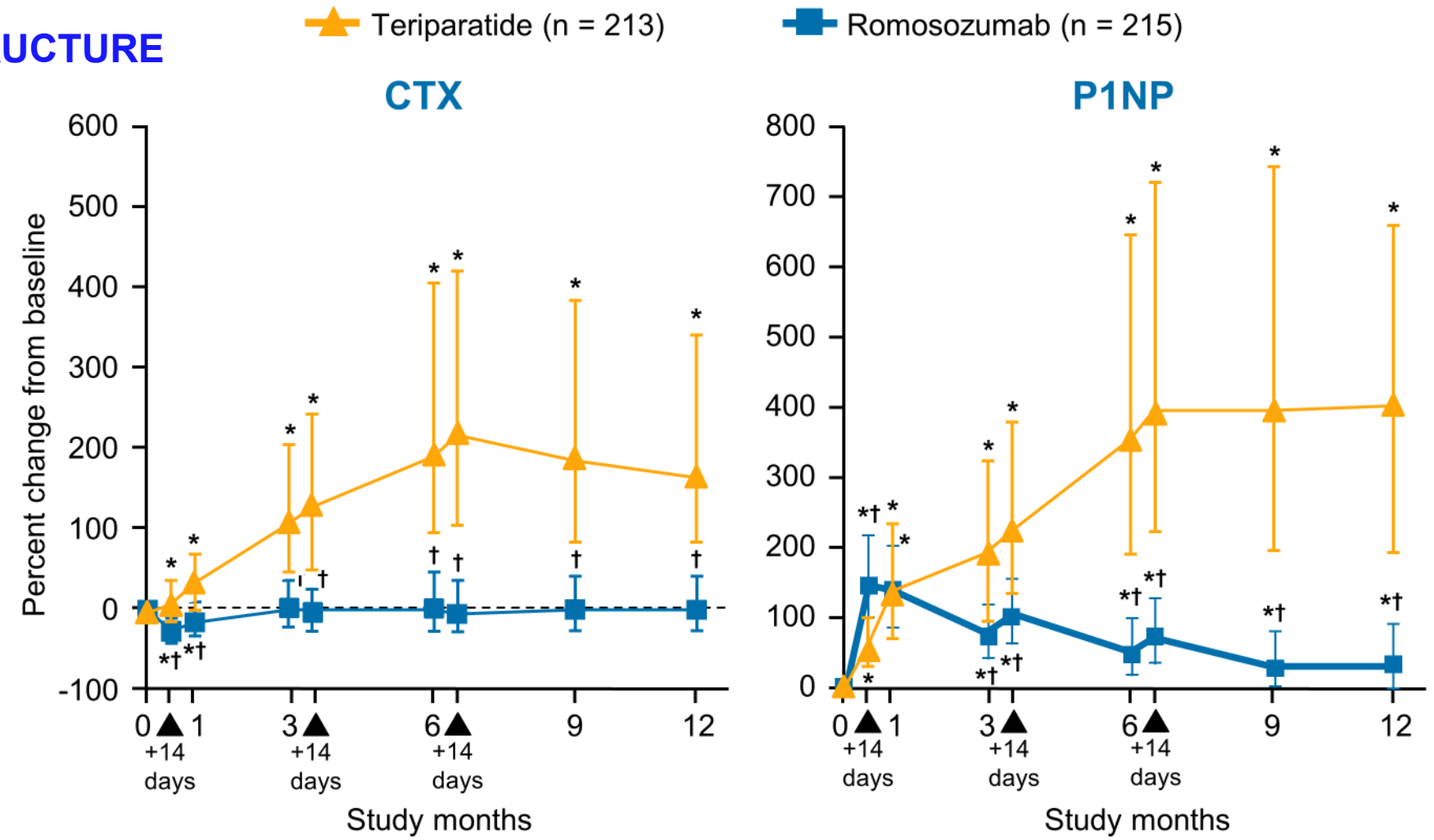


P1NP, romosozumab n=62, placebo n=62; CTX, romosozumab n=61, placebo n=62. Data presented as bootstrapped median treatment difference and 95% CI.

Cosman F, et al; [published online ahead of print Sep 18, 2016]. *N Engl J Med*. doi: 10.1056/NEJMoa1607948

Median percent change from baseline in serum P1NP and CTX over 12 months

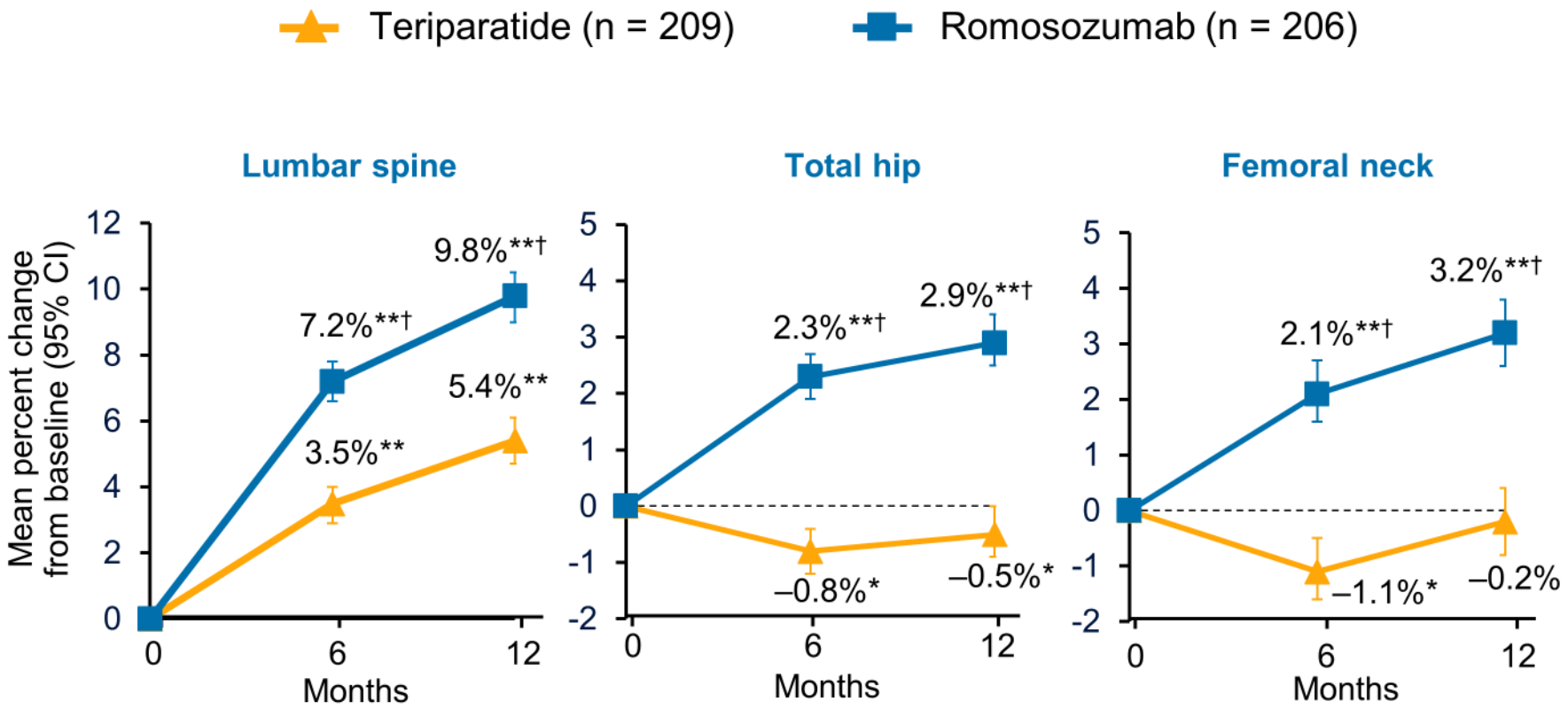
STRUCTURE



Data are median (IQR). *p < 0.0001 versus baseline. †p < 0.0001 versus teriparatide.
CTX = serum C-telopeptide of type 1 collagen; IQR = interquartile range; P1NP = serum procollagen type 1 N-terminal propeptide.
Adapted from: Langdahl BL, et al. *Lancet*. 2017; 390:1585–1594.

Percent change in lumbar spine, total hip and femoral neck aBMD by DXA at months 6 and 12

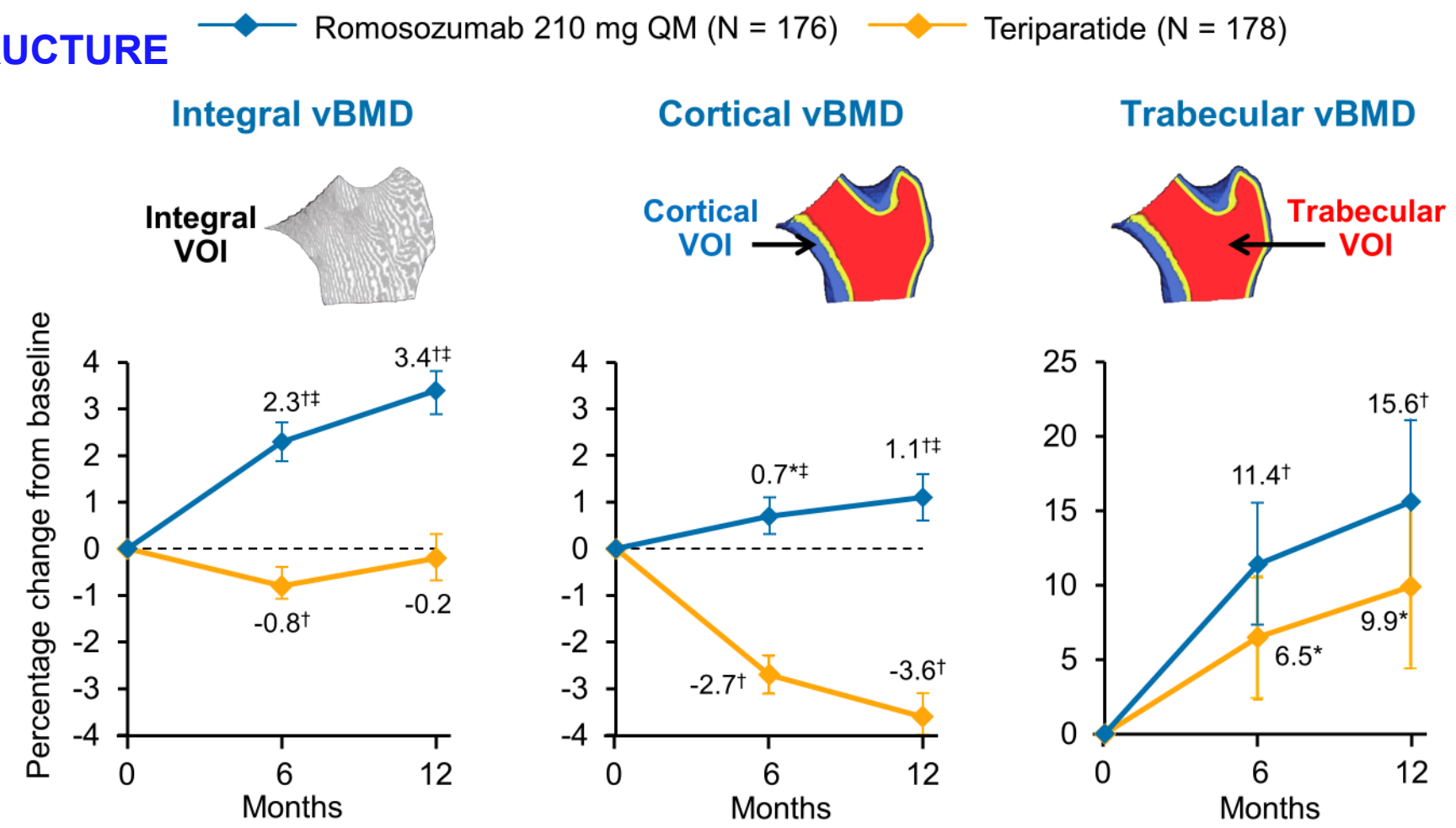
STRUCTURE



Data are least-square means and 95% CI. *$p < 0.05$; **$p < 0.0001$ versus baseline. †$p < 0.0001$ versus teriparatide.
aBMD = areal bone mineral density; CI = confidence interval; DXA = dual-energy x-ray absorptiometry.
Adapted from: Langdahl BL, et al. *Lancet.* 2017; 390:1585–94.

Hip vBMD in response to romosozumab vs teriparatide[1–3]

STRUCTURE



Data are LS means and 95% CI. *$p < 0.05$ compared with baseline †$p \leq 0.0001$ compared with baseline. ‡$p < 0.0001$ compared with teriparatide
BMD = bone mineral density; CI = confidence interval; Integral = cortical + trabecular; LS = least squares; QM = once monthly; vBMD = volumetric bone mineral density; VOI = volume of interest; N = number of subjects in the primary efficacy set.

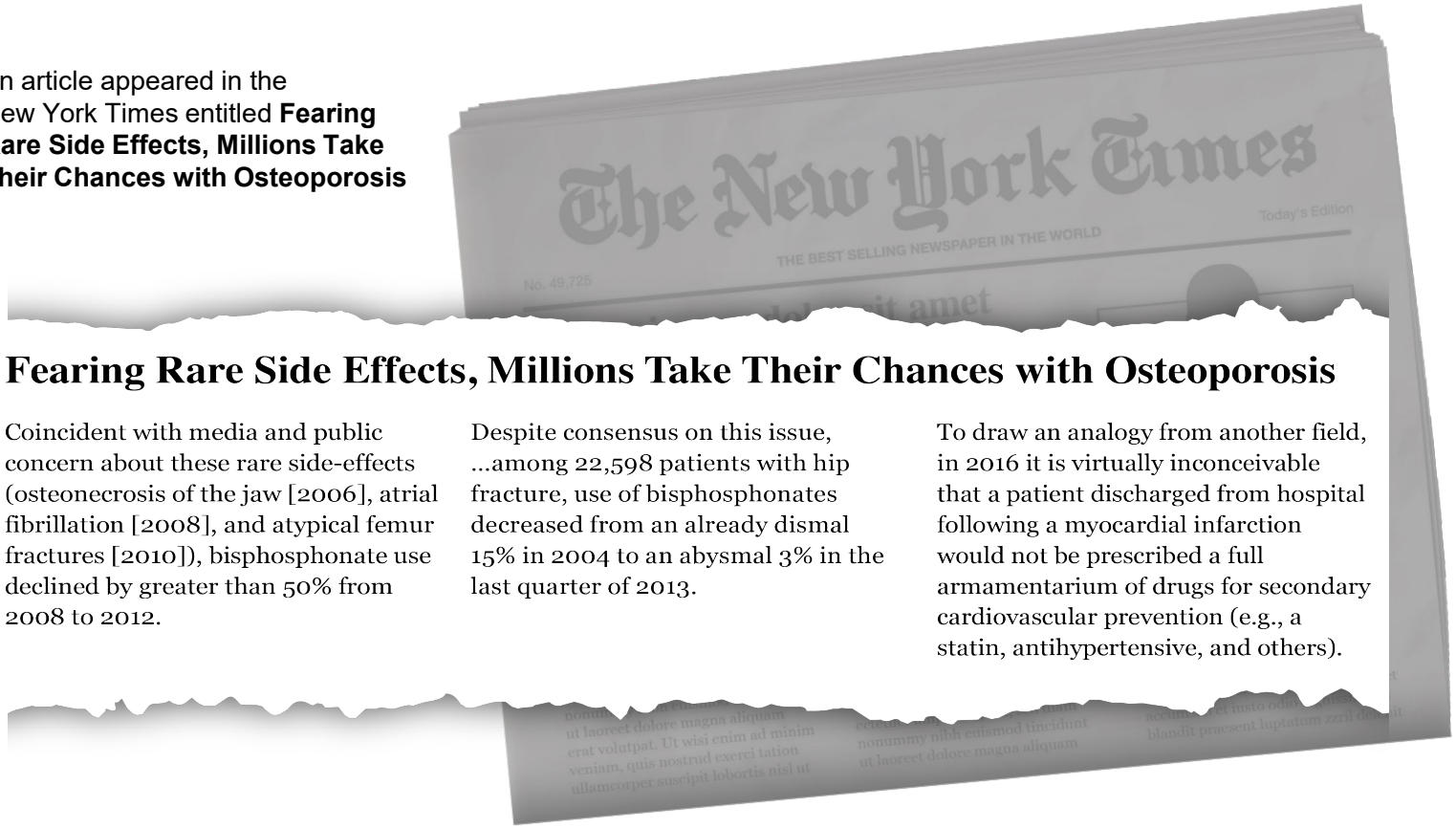
1. Langdahl BL, et al. *Lancet*. 2017;390(Suppl):1585–1594; 2. Langdahl B, et al. Presented at: ECTS Annual Meeting. May 13–16, 2017; Salzburg, Austria. Oral OC1.5; 3. Images adapted with permission granted from Genant HK, et al. *Bone*. 2013;56:482–488. © Elsevier, Inc.

Potential Adverse Effects of Drug Therapies

1: DRUG HOLIDAYS

Drug Therapy and the Media:
A Crisis in the Treatment of Osteoporosis

An article appeared in the New York Times entitled **Fearing Rare Side Effects, Millions Take Their Chances with Osteoporosis**



The New York Times

THE BEST SELLING NEWSPAPER IN THE WORLD

Today's Edition

Fearing Rare Side Effects, Millions Take Their Chances with Osteoporosis

Coincident with media and public concern about these rare side-effects (osteonecrosis of the jaw [2006], atrial fibrillation [2008], and atypical femur fractures [2010]), bisphosphonate use declined by greater than 50% from 2008 to 2012.

Despite consensus on this issue, ...among 22,598 patients with hip fracture, use of bisphosphonates decreased from an already dismal 15% in 2004 to an abysmal 3% in the last quarter of 2013.

To draw an analogy from another field, in 2016 it is virtually inconceivable that a patient discharged from hospital following a myocardial infarction would not be prescribed a full armamentarium of drugs for secondary cardiovascular prevention (e.g., a statin, antihypertensive, and others).

Sundeep Khosla, M.D and Elizabeth Shane MD. A Crisis in the Treatment of Osteoporosis
Journal of Bone and Mineral Research DOI 10.1002/jbmr.2888

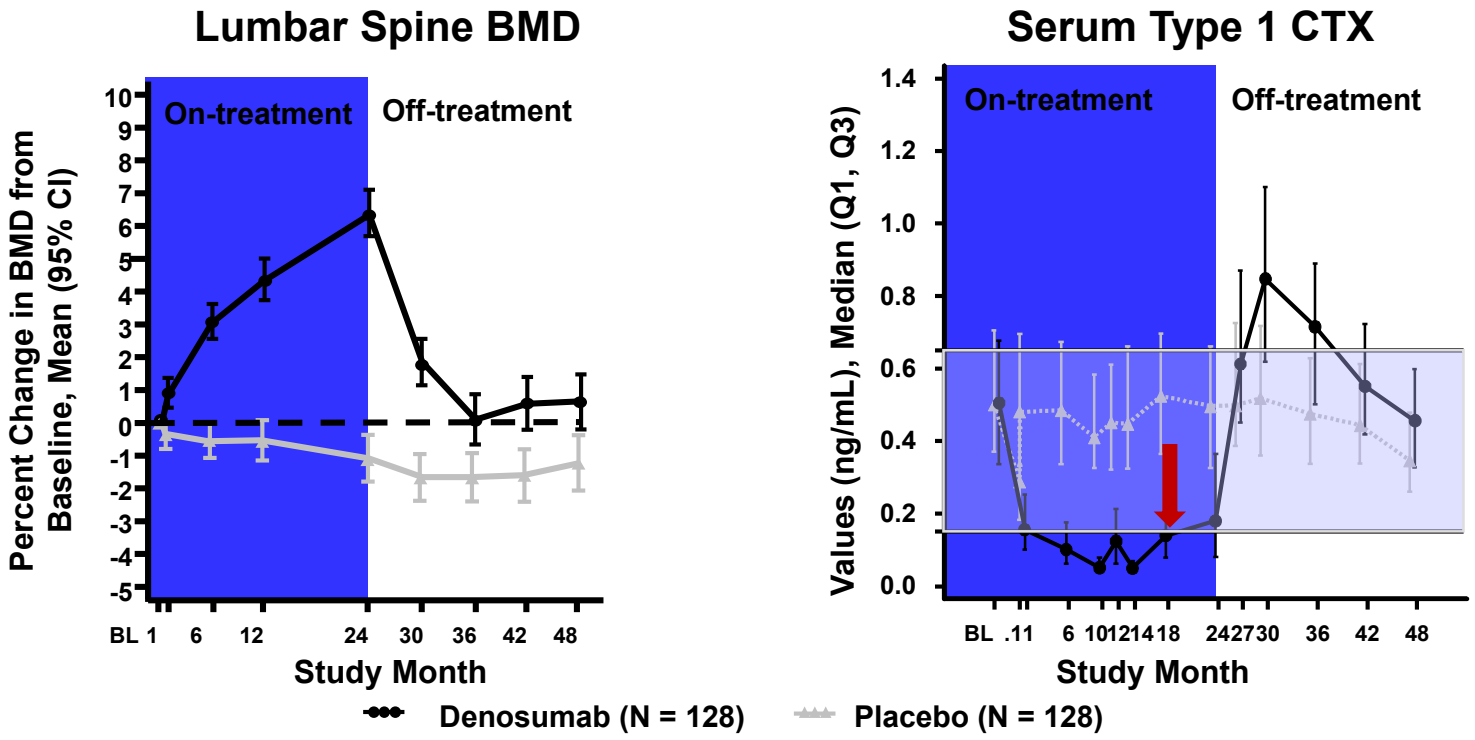
Vertebral Fractures after Denosumab Discontinuation

(2018 ASBMR Abstract – Elena Gonzalez-Rodriguez)

- single centre observational study
- 35 patients with 172 spontaneous vert fxs
- 1/3 had prior vertebral fractures

Vertebral Fractures after Discontinuation of Denosumab

Reversibility of Denosumab Action on Bone Turnover & BMD



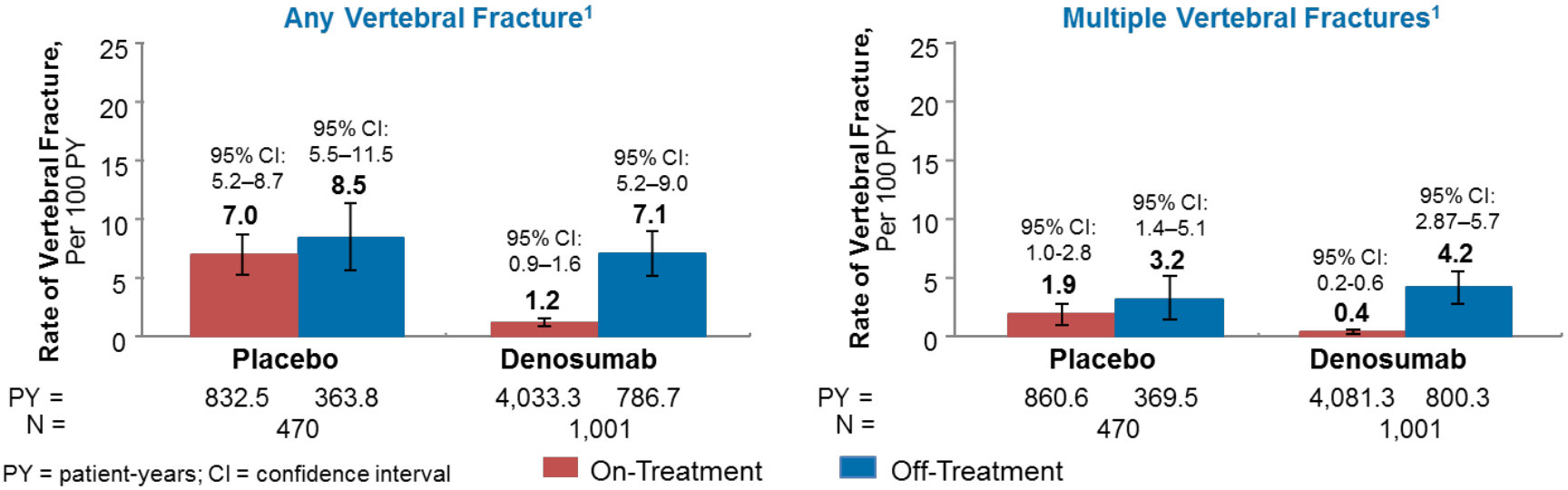
[1]Bone HG, et al. *J Clin Endocrinol Metab* 2011. Includes subjects who enrolled in the off-treatment phase

CTX: carboxy-terminal collagen crosslinks; Q1, Q3: first, third quartile; BMD: bone mineral density; CI: confidence interval

On- vs Off-Treatment Vertebral Fracture Rate: All Patients

Pivotal Phase 3 Trial and Extension Study – Analysis of MVF

- During treatment, the rate of new vertebral fractures was lower in patients receiving denosumab compared to placebo (1.2 versus 7.0 per 100 patient-years)
- After discontinuation of denosumab, the rate of vertebral fractures increased relative to the on-treatment period and became similar to that of patients discontinuing placebo (7.1 versus 8.5 per 100 patient-years)
- The rate of multiple vertebral fracture was slightly higher in patients discontinuing denosumab compared to discontinuing placebo (4.2 versus 3.2 per 100 patient-years)



PY = patient-years; CI = confidence interval

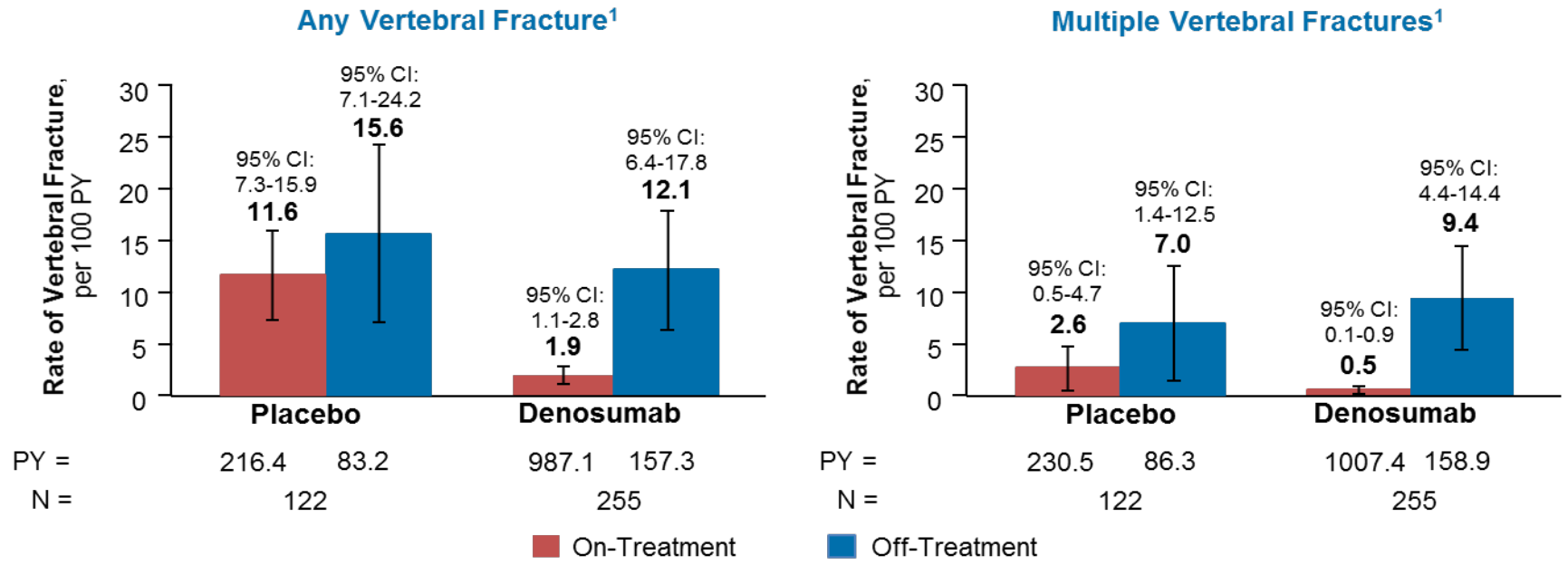
Adapted from: Cummings SR, et al. *J Bone Miner Res.* 2017; [Published only ahead of print November 4, 2017]. 10.1002/jbmr.3337.

1. Data on File, Amgen Canada

On- vs Off-Treatment Vertebral Fracture Rate: Patients With Prior Vertebral Fracture at IP Baseline

Pivotal Phase 3 Trial and Extension Study – Analysis of MVF

- Vertebral fracture rates were higher both during treatment and off treatment in patients with prevalent vertebral fracture that occurred before treatment compared to overall patients studied
- Similarly to the all-patient analysis, vertebral fracture rates were higher off-treatment than during treatment



PY = patient-years; CI = confidence interval

Adapted from: Cummings SR, et al. *J Bone Miner Res.* 2017; [Published only ahead of print November 4, 2017]. 10.1002/jbmr.3337.
1. Data on File, Amgen.

Significant Predictors of Off-Treatment MVF

- Prior vertebral fracture is the strongest predictor of off-treatment vertebral fractures
- Other predictors of MVF were time off-treatment and rate of off-treatment total hip BMD loss

Significant Covariates	772 Patients Included† OR (95% CI)	1,471 Patients Included* OR (95% CI)
Prior VFx‡ (yes vs no)	3.6 (1.8–7.1)	3.9 (2.1–7.2)
Off-treatment duration (per year)	1.4 (1.1–1.7)	1.6 (1.3–1.9)
Annualized off-treatment total hip BMD loss§ (per 1%)	1.2 (1.1–1.3)	NA

*1,471 patients included 470 patients who discontinued placebo and 1,001 patients who discontinued denosumab; †772 patients included 307 patients who discontinued placebo and 465 patients who discontinued denosumab, and had available off-treatment annualized total hip BMD change assessments; ‡"Prior VFx" includes any VFx sustained before or during treatment; §"Off-treatment annualized total hip BMD loss" was defined as annualized percent change in total hip BMD after treatment discontinuation, ie, between the last on- and off-treatment BMD assessments.
BMD = bone mineral density; CI = confidence interval; NA = not applicable; OR = odds ratio; VFx = vertebral fracture

Adapted from: Cummings SR, et al. *J Bone Miner Res.* 2017; [Published only ahead of print November 4, 2017]. 10.1002/jbmr.3337.

Contents lists available at ScienceDirect

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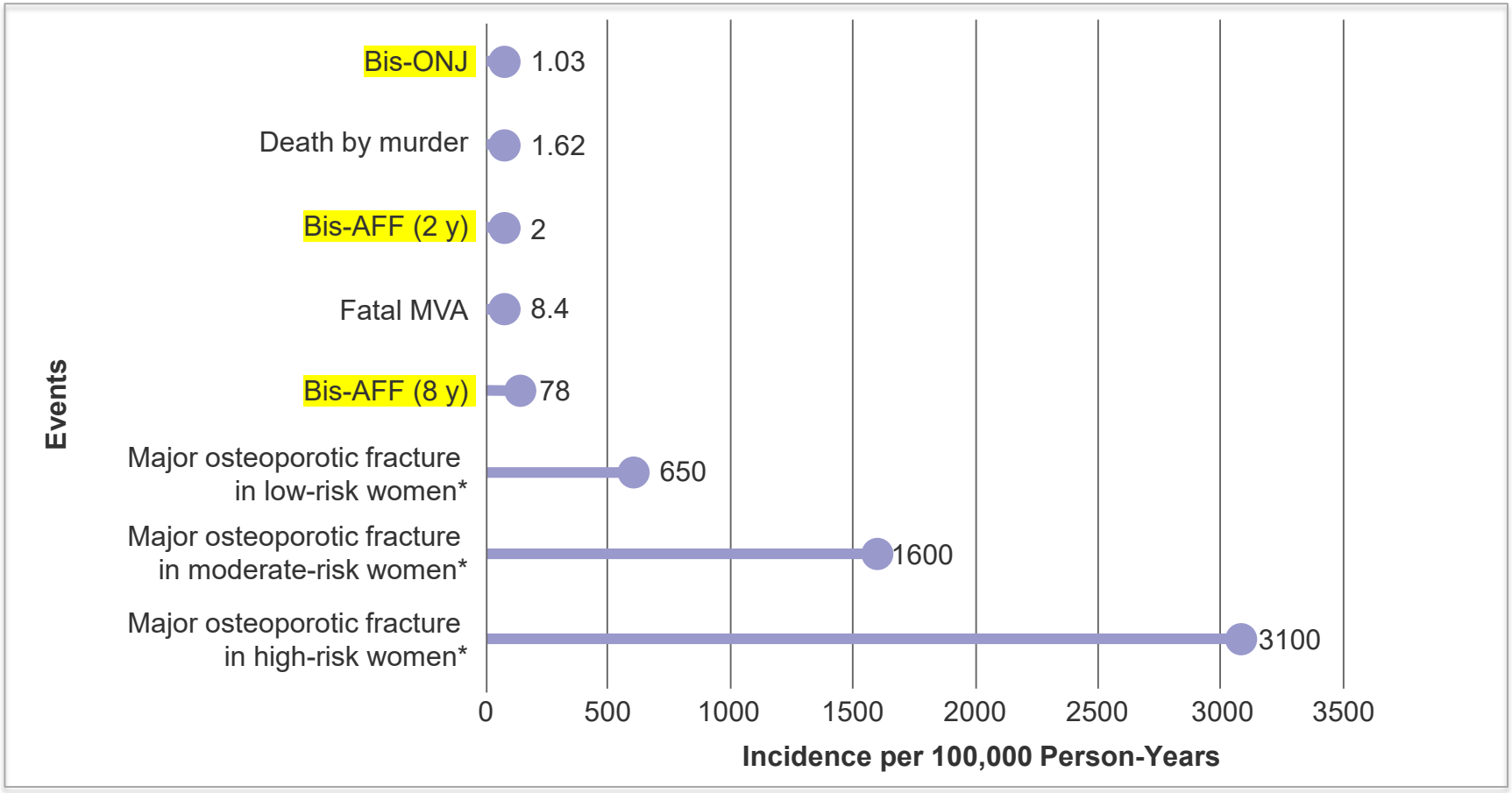
Review Article

Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS

Elena Tsourdi [a,b], Bente Langdahl [c], Martine Cohen-Solal [d], Bérengere Aubry-Rozier [e], Erik Fink Eriksen [f], Nuria Guañabens [g], Barbara Obermayer-Pietsch [h,i], Stuart H. Ralston [j], Richard Eastell [k], M. Carola Zillikens [l,*]

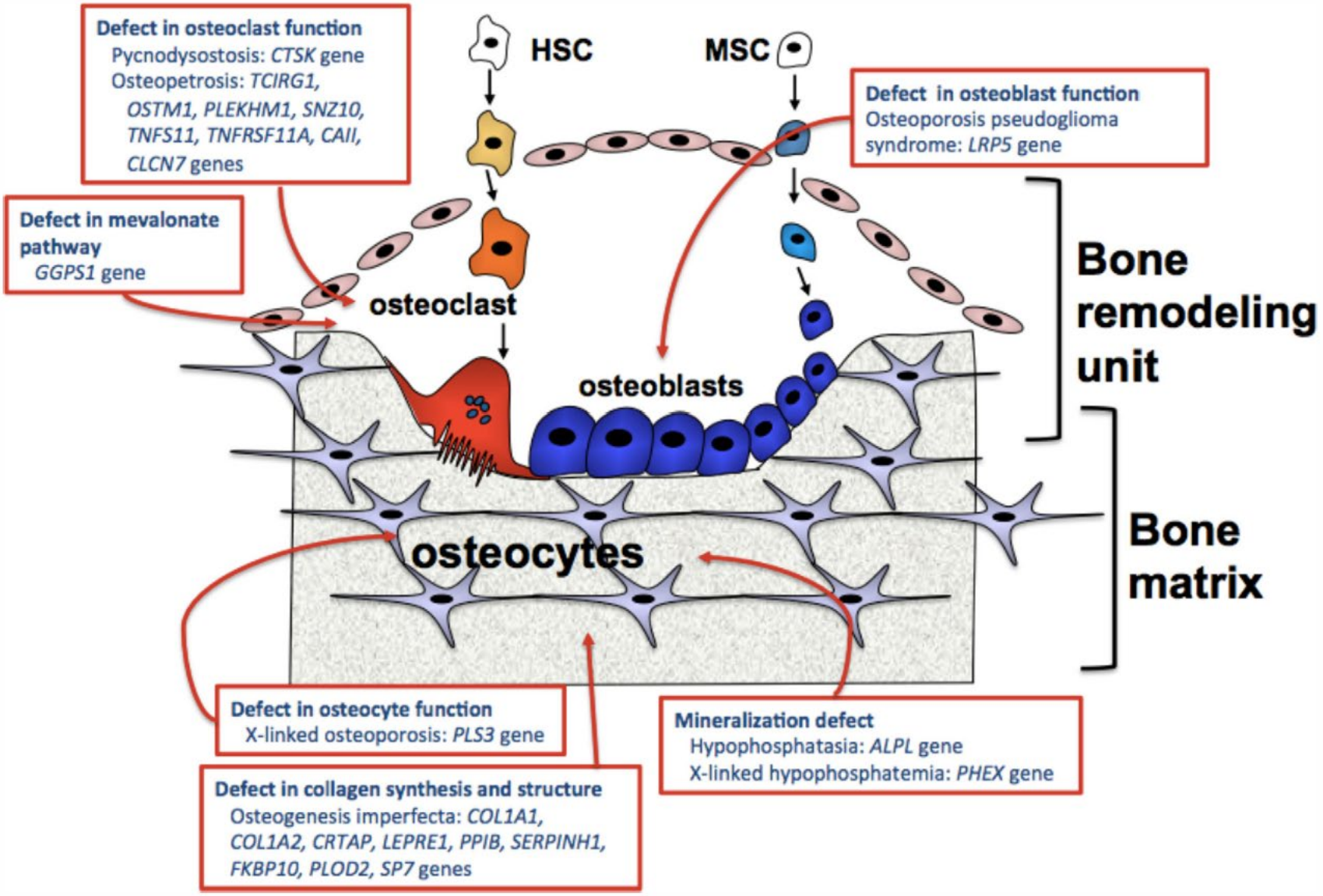
Introduction: The optimal duration of osteoporosis treatment is controversial. As opposed to bisphosphonates, denosumab does not incorporate into bone matrix and bone turnover is not suppressed after its cessation. Recent reports imply that denosumab discontinuation may lead to an increased risk of multiple vertebral fractures.
Methods: The European Calcified Tissue Society (ECTS) formed a working group to perform a systematic review of existing literature on the effects of stopping denosumab and provide advice on management.
Results: Data from phase 2 and 3 clinical trials underscore a rapid decrease of bone mineral density (BMD) and a steep increase in bone turnover markers (BTMs) after discontinuation of denosumab. Clinical case series report multiple vertebral fractures after discontinuation of denosumab and a renewed analysis of FREEDOM and FREEDOM Extension Trial suggests, albeit does not prove, that the risk of multiple vertebral fractures may be increased when denosumab is stopped due to a rebound increase in bone resorption.
Conclusion: There appears to be an increased risk of multiple vertebral fractures after discontinuation of denosumab although strong evidence for such an effect and for measures to prevent the occurring bone loss is lacking. Clinicians and patients should be aware of this potential risk. Based on available data, a re-evaluation should be performed after 5 years of denosumab treatment. Patients considered at high fracture risk should either continue denosumab therapy for up to 10 years or be switched to an alternative treatment. For patients at low risk, a decision to discontinue denosumab could be made after 5 years, but bisphosphonate therapy should be considered to reduce or prevent the rebound increase in bone turnover. However, since the optimal bisphosphonate regimen post-denosumab is currently unknown continuation of denosumab can also be considered until results from ongoing trials become available. Based on current data, denosumab should not be stopped without considering alternative treatment in order to prevent rapid BMD loss and a potential rebound in vertebral fracture risk.

Risk of ONJ and Atypical Fractures



Bis-AFF: Bisphosphonate-associated atypical subtrochanteric and diaphyseal femur fracture
Bis-ONJ: Bisphosphonate-associated osteonecrosis of the jaw
BMD=bone mineral density. FN=femoral neck. FRAX=fracture Risk Assessment Tool. MVA=motor vehicle accident
*10-year risk of major osteoporotic fracture by Canadian FRAX

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



Nguyen et al, JBMR Plus 1, 2017

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- **Clinical and Genetic Risk Factors for Atypical Femur Fractures (AFF):**
- *Personalizing Osteoporosis Care*

Principal Investigators: Angela Cheung, Shinya Ito

Co-Investigators: *R Bleakney; B Carleton; R Rottapel; L Strug; G Tomlinson*

Collaborators: *JD Adachi; A Khan; Algis Jovasis; D Kendler; D Kiel; L Michou; C Thorne*

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HOW YOU CAN HELP: TELL YOUR PATIENTS

We are actively **recruiting 760 control subjects** for this study.

RECRUITMENT: To be included, participants must:

1. Females over the age of 18
2. Currently on bone medications such as

- bisphosphonates such as Alendronate (Fosamax, Fosavance), Etidronate (Didrocal, Didronel), risedronate (Actonel), zoledronic acid (Aclasta, Zometa), pamidronate (Aredia) or
- denosumab (Prolia, Xgeva),
- or others for a minimum of 5 years (no maximum).

WHAT'S INVOLVED IN STUDY PARTICIPATION:

1 study visit only where participants will provide:

- Medical/family health history, bone health, types of bone medications use/length.
- BMD hip/spine (if not done within the last 12 months, or access to recent scan for study purposes).
- Bilateral SE femur scan or bilateral femur x-ray to rule out AFF.
- Blood sample collection (preferably fasting) for standard bone panel, genetics and serum banking
- Finger nail clipping to be analyzed for keratin structure

No cost to participation and no remuneration.

My thoughts on duration of therapy…

Moderate 10yr Fx Risk

after 3-5yrs of antiresorptive therapy

1) Consider BP drug holiday of 1-5 yrs,
2) If on Dmab, may want to follow with 6 months of ALN or RIS
3) Reassess 1-2 yrs after stopping

High 10yr Fx Risk

1) Continue on antiresorptive therapy
2) Consider switching to bone formation therapies

after 5-10 yrs of antiresorptive therapy

1) Consider switching to bone formation therapies
2) Consider drug holiday of 1-5 yrs
3) If on Dmab, may want to follow with 1 year of ALN or RIS
4) Reassess 1-2 yrs after stopping

HOW THIS APPLIES TO YOUR PATIENTS

POINTS to consider:

- Fractures are common
- Fracture risk scale is a tool for LTC residents
- Bisphosphonates, denosumab, teriparatide, romosozumab are all effective therapies
- Use a sequential combination of anabolic and antiresorptive therapy

POINTS to consider:

- Adverse effects (such as MVFx, AFF, ONJ) are rare
- STOP potent antiresorptive therapies after AFF and ONJ
- Duration of therapy: reassess after 3-5 yrs
- If wish to discontinue denosumab → follow with short course of antiresorptive therapy

Summary

1) Apply FRS for fracture risk assessment in LTC residents
2) Discuss current data regarding vitamin D, calcium and nutrition
3) Choose the right therapy for the right patient based on current evidence
4) Determine whether your patient should have a drug holiday and for how long

Questions and Discussion

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Angela M. Cheung

Thank You