

Role for Antiresorptive and Anabolic Medications in the Management of Osteoporosis

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Objectives

- Long-term Treatment Strategies
- Brief Overview of Efficacy and Safety of Osteoporosis Medications
 - Antiresorptive Agents
 - Anabolic Agents
- Individualizing Therapy

Long-term Osteoporosis Treatment Strategies

- Osteoporosis is chronic and progressive over a long postmenopausal lifespan
- Need for medication and choice of agent should be individualized
- No one medication should be considered lifelong
- Medications can and should change with age or change in disease severity
 - Risks and benefits of medications differ
 - More intensive therapy might be needed
 - Treatment can be temporarily stopped
 - Treatment can be restarted
- Treatment goals vary at different stages of disease

Pharmacologic Treatment Options

- Antiresorptive Agents: reduce bone remodeling
 - Estrogens, Estrogen/Progestin and Estrogen/Bazedoxifene combinations
 - Raloxifene
 - Bisphosphonates
 - Oral: Alendronate, Risedronate, Ibandronate
 - Intravenous: Zoledronic Acid
 - Denosumab (Antibody to Rank Ligand)
- Anabolic Agents: stimulate bone formation
 - Anabolic Agents that also stimulate bone resorption
 - Teriparatide (PTH1-34)
 - Abaloparatide (PTHrP analogue)
 - Anabolic Agent that inhibits bone resorption
 - Romosozumab (sclerostin antibody)

Antiresorptive Agents

Estrogen/Estrogen Combinations

- Estrogen Alone, Estrogen plus progestins, Estrogen plus bazedoxifene
 - Many types, oral and transdermal, broad range of doses
 - Consistent improvement in spine and hip BMD
 - Magnitude of effect differs based on estrogen type/dose
 - Larger doses needed to maintain BMD in younger women
- Little RCT evidence of antifracture efficacy in women *with* osteoporosis
- WHI demonstrated antifracture efficacy in healthy women (only 5% had osteoporosis)
 - 30% reduction vertebral fracture
 - 30% reduction hip fracture
 - 20% reduction in all nonvertebral fracture
- Estrogens approved for prevention but not treatment of osteoporosis

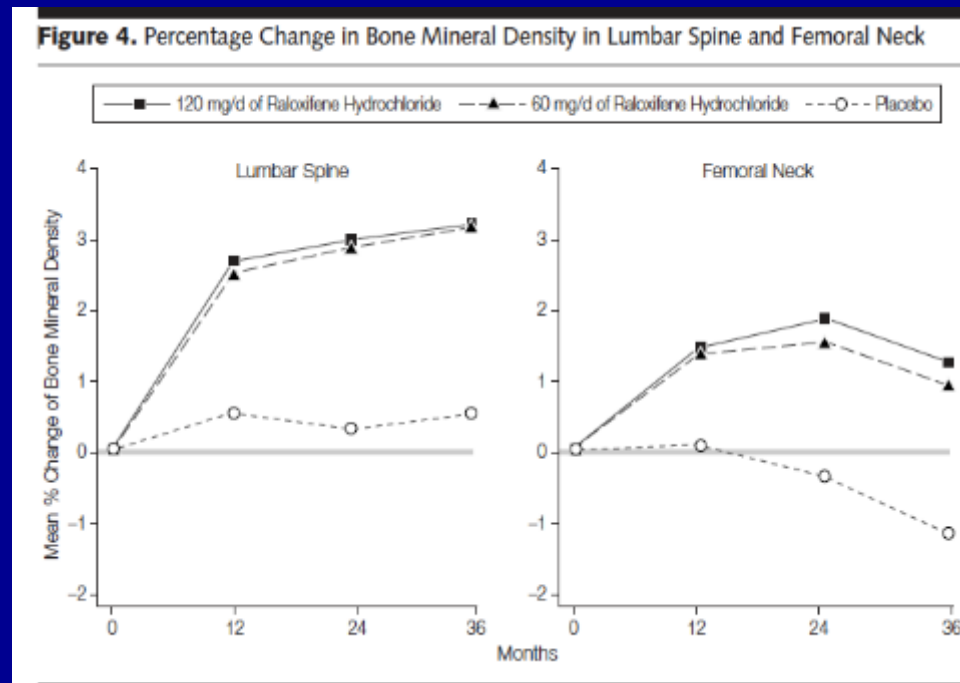
Antiresorptive Agents

Estrogen/Estrogen Combinations

- Safety from WHI for HT (conjugated equine estrogen + medroxyprogesterone acetate)
 - Breast cancer increased 26%
 - Colon cancer reduced 37%
 - Stroke increased 40%
 - Cardiac events increased 30%
 - Venous thrombosis increased 100%
 - Dementia
- Safety Differences from WHI ET alone (conjugated equine estrogen)
 - No increased risk breast cancer
 - No increased risk coronary heart disease
- Younger postmenopausal women much more favorable benefit/risk ratio
- Primary role is for early menopausal women to maintain BMD

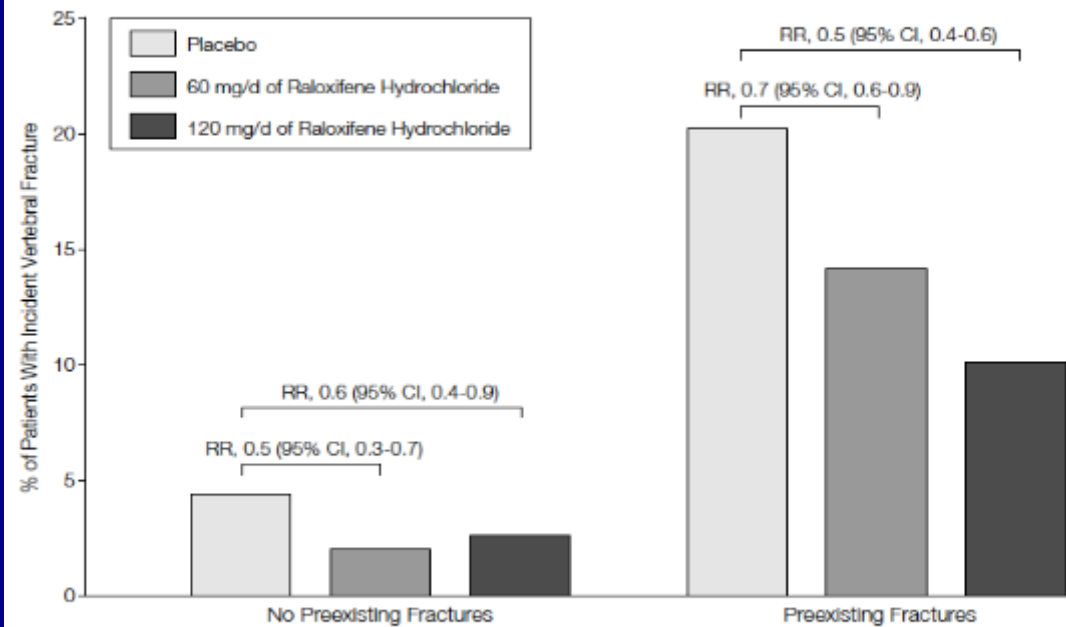
Antiresorptive Agents: Raloxifene

- Raloxifene: an estrogen agonist/antagonist (SERM)
 - estrogenic effect on the skeleton
 - anti-estrogenic effect on the breast
 - neutral uterus effect
- Pivotal trial: MORE randomized 7705 women to placebo, raloxifene 60 mg or raloxifene 120 mg for 3 years
- Approved dose 60 mg daily



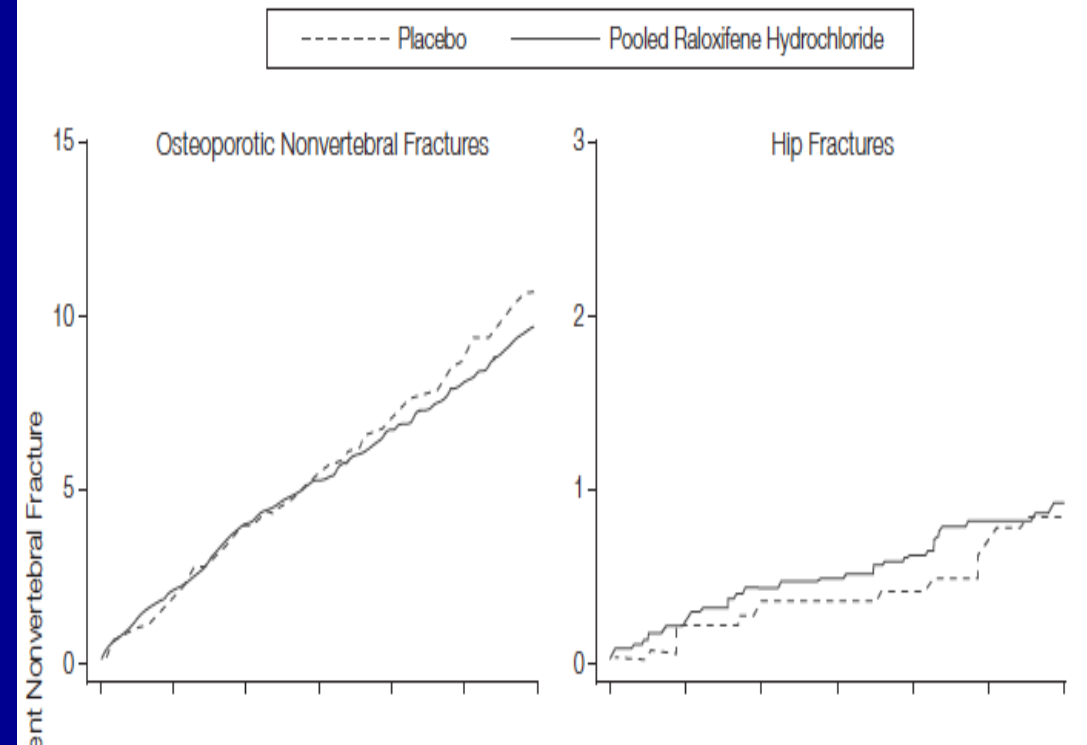
Antiresorptive Agents: Raloxifene MORE Trial

Figure 2. Reduction in New Vertebral Fractures Among 6828 Women Who Completed the Study



Women did or did not have vertebral fracture at the beginning of study. RR indicates relative risk; CI, confidence interval.

Figure 3. Occurrence of First Nonvertebral Fracture Since Start of Study



Antiresorptive Agents: Raloxifene

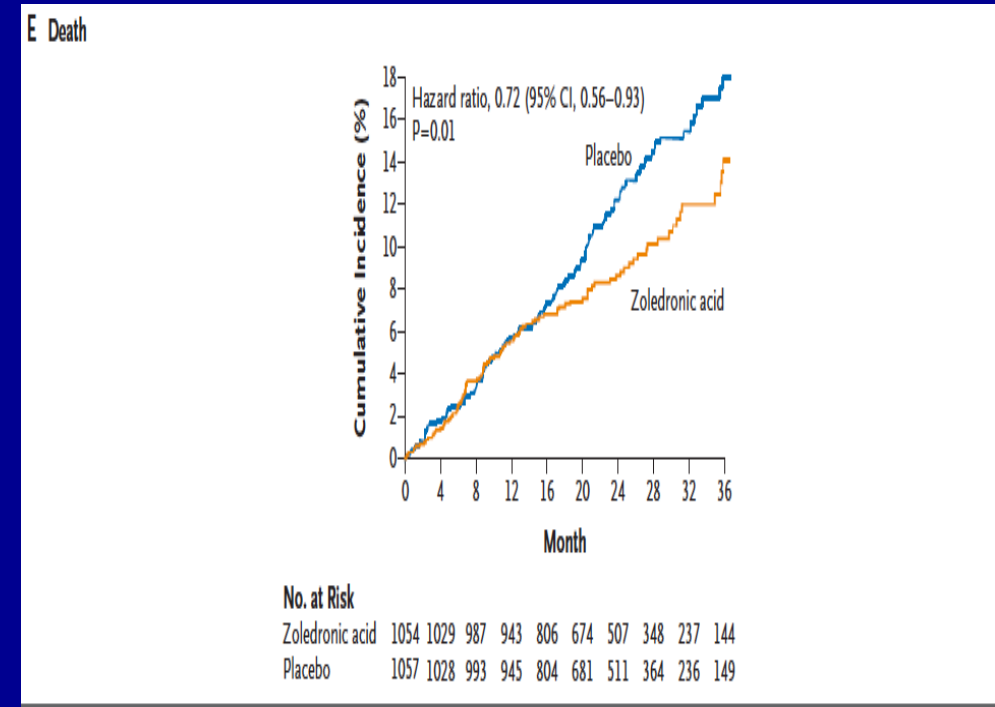
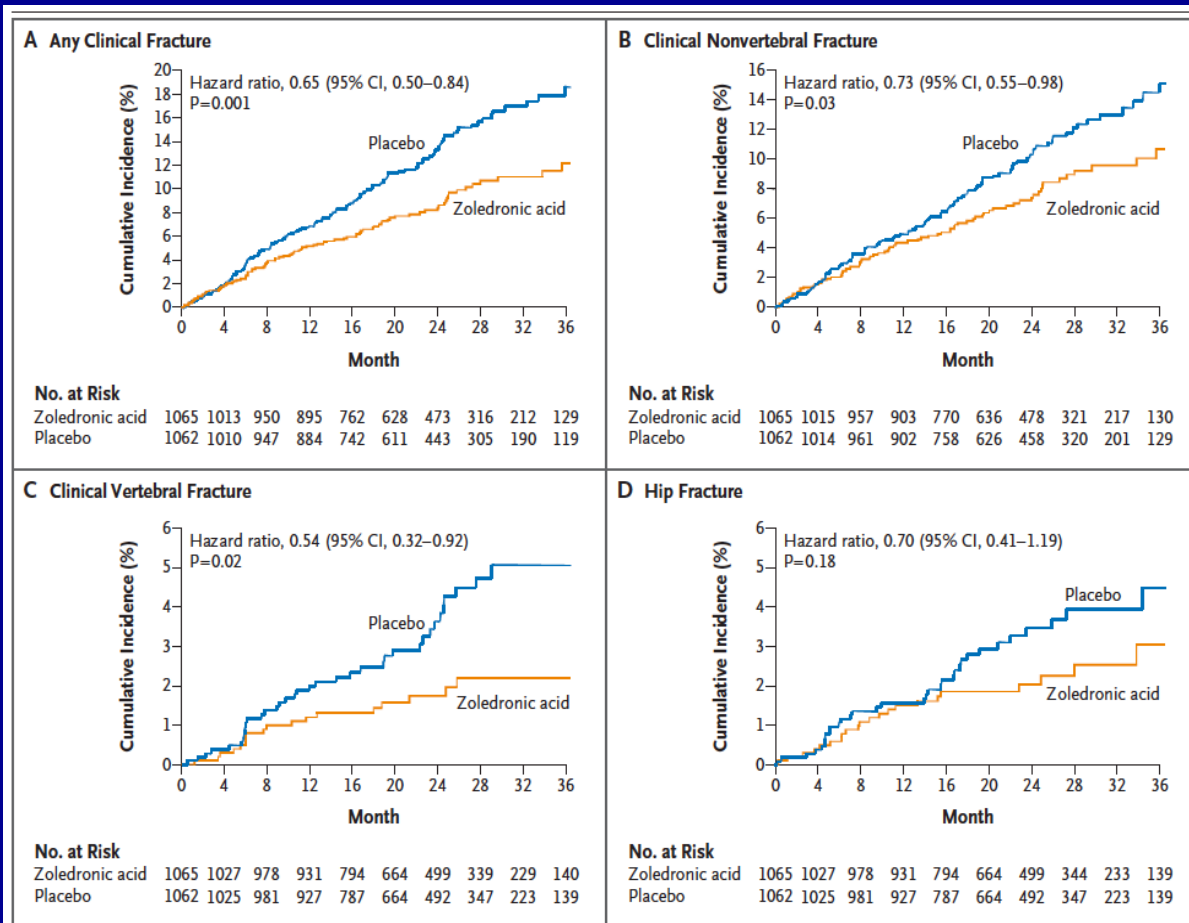
- Safety:
 - 3 fold increased risk of venous thromboembolism (DVT and PE)
 - No increased risk of stroke or coronary events but increased mortality in women with stroke
 - Increased hot flashes and night sweats
- Additional Considerations:
 - MORE study extended to 8 years: still no effect against nonvertebral or hip fx
 - 50-75% reduced risk of estrogen receptor positive breast cancer
 - No increased risk uterine cancer
- Primary Role: very good choice for younger women (50s and 60s) without major menopausal symptoms, without known VT risk, especially if at increased risk for breast cancer

Antiresorptive Agents: Bisphosphonates

- Bisphosphonates bind to hydroxyapatite in bone, particularly at sites of active bone remodeling
 - When osteoclasts uptake bisphosphonate, bone resorption is inhibited
- Four bisphosphonates are available
 - 3 oral (alendronate, ibandronate, risedronate)
 - 1 intravenous (zoledronic acid)
- Pivotal trials for alendronate, risedronate and zoledronic acid
 - Reduced risk of vertebral fracture 40-70%,
 - Reduced risk of nonvertebral fracture 20-35%
 - Reduced risk of hip fracture 30-50%
- Pivotal Ibandronate trial- reduced risk of vertebral fracture only
- Zoledronic acid tested in patients with acute hip fracture

Recurrent Fracture Trial: Zoledronic Acid in Hip Fracture Patients

N=2127 patients within 3 months of acute hip fracture



Antiresorptive Agents: Bisphosphonates

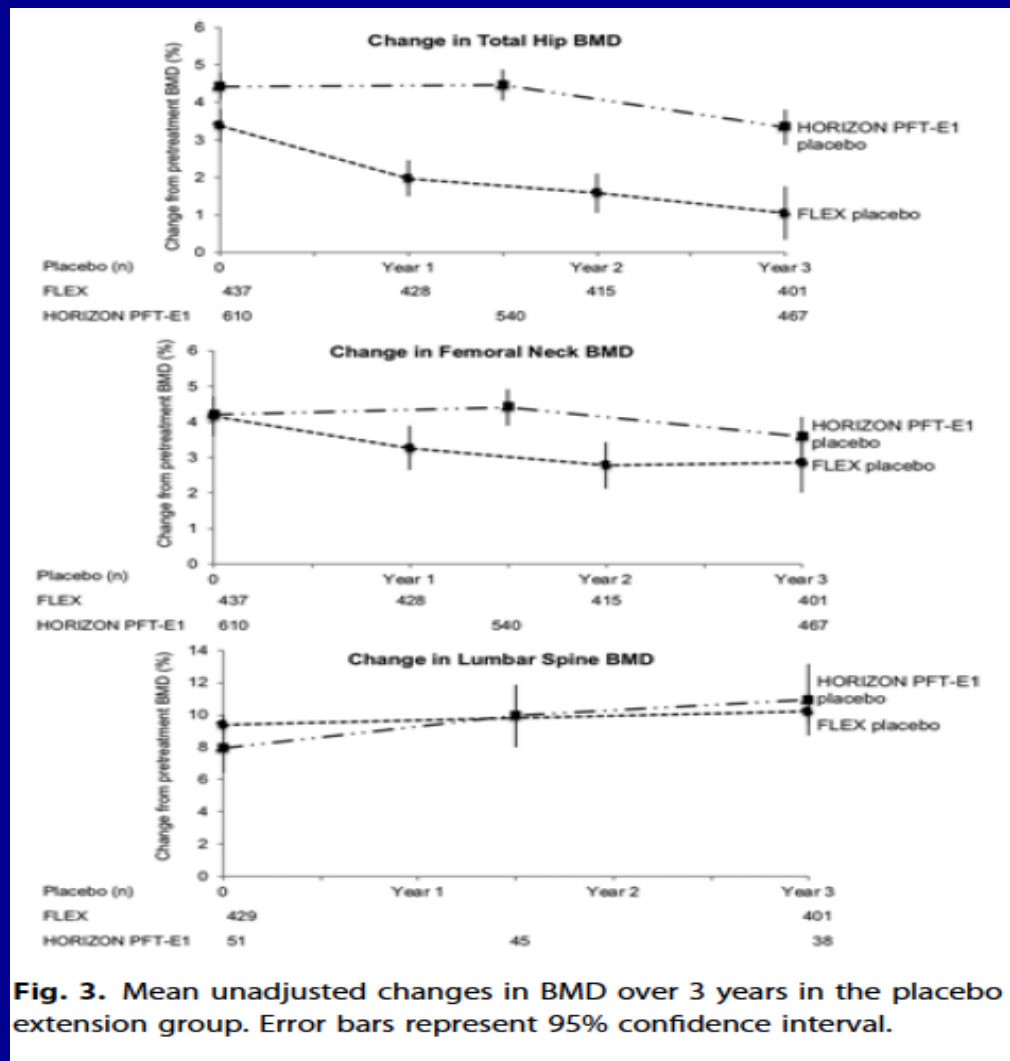
- Contraindications to oral IV bisphosphonate therapy
 - hypocalcemia
 - reduced kidney function (GFR <30-35 ml/min)
- Other contraindications to oral bisphosphonates include
 - inability to follow the regimen (fasting AM with water only; wait 30-60 minutes upright before eating)
 - One formulation of risedronate can be taken with food
 - esophageal abnormalities that inhibit transit of the tablet
 - GI malabsorption
- Acute phase reactions in up to 30% with first IV (or less frequently oral) BPs
- Rare safety concerns
 - Atypical femur fracture- duration dependent
 - Osteonecrosis of the jaw

Antiresorptive Agents: Bisphosphonates

- BMD increments seen for up to 3 years
 - No further gains thereafter
- No further reduction in fracture risk beyond 3-5 years
 - Consider alternative therapy beyond that time if necessary
- Bisphosphonates are retained in the skeleton with a long half life
 - Residual effects persist after discontinuation
 - Effects eventually wane, but slowly
 - Duration of residual effect varies with type of bisphosphonate
 - Zoledronic Acid- longest
 - Risedronate- shortest

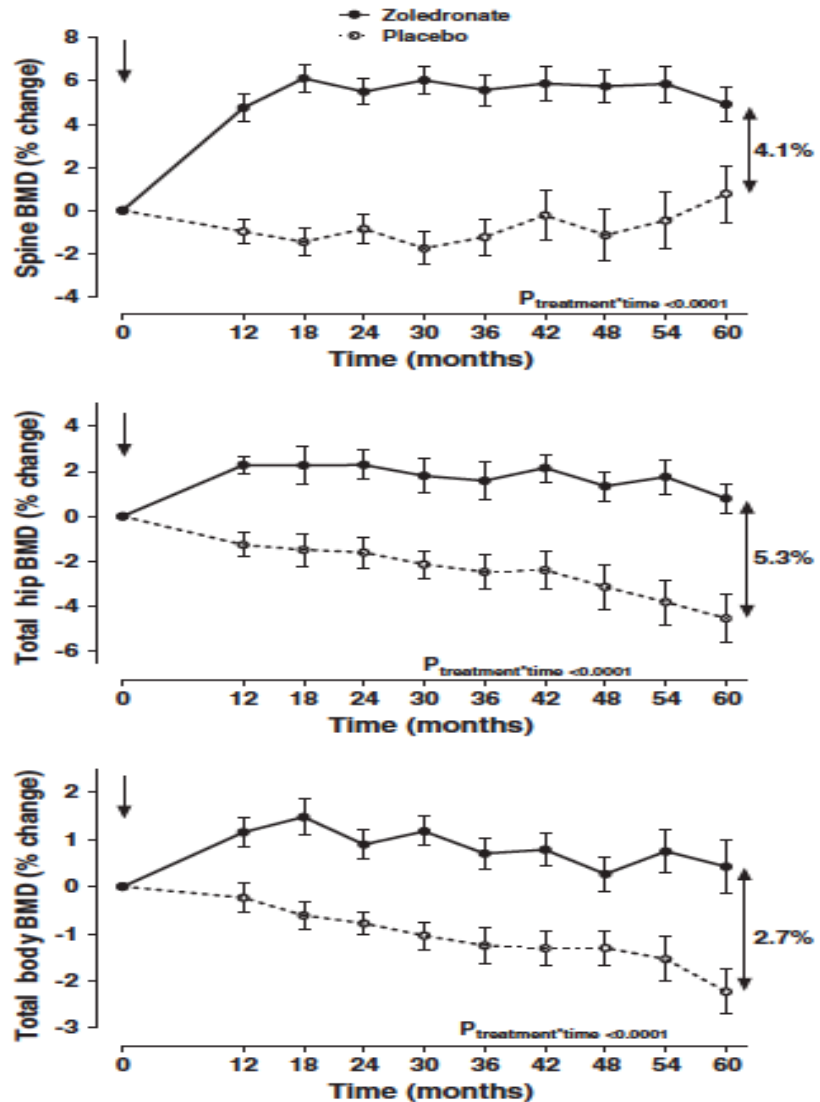
Changes in BMD After Discontinuation of Alendronate or Zoledronic Acid

Patients randomized to placebo after in FLEX after 5 years alendronate and HORIZON after 3 years of zoledronic acid



Total Hip Bone Loss >LSC seen in 25% prior alendronate patients and 18% prior zoledronic acid patients
Minimal changes in proportion of patients with T-Scores ≤ -2.5

Antiresorptive Agents: Bisphosphonates



Maintenance of BMD for 5 years after 1 infusion of zoledronic Acid

Antiresorptive Agents: Bisphosphonates

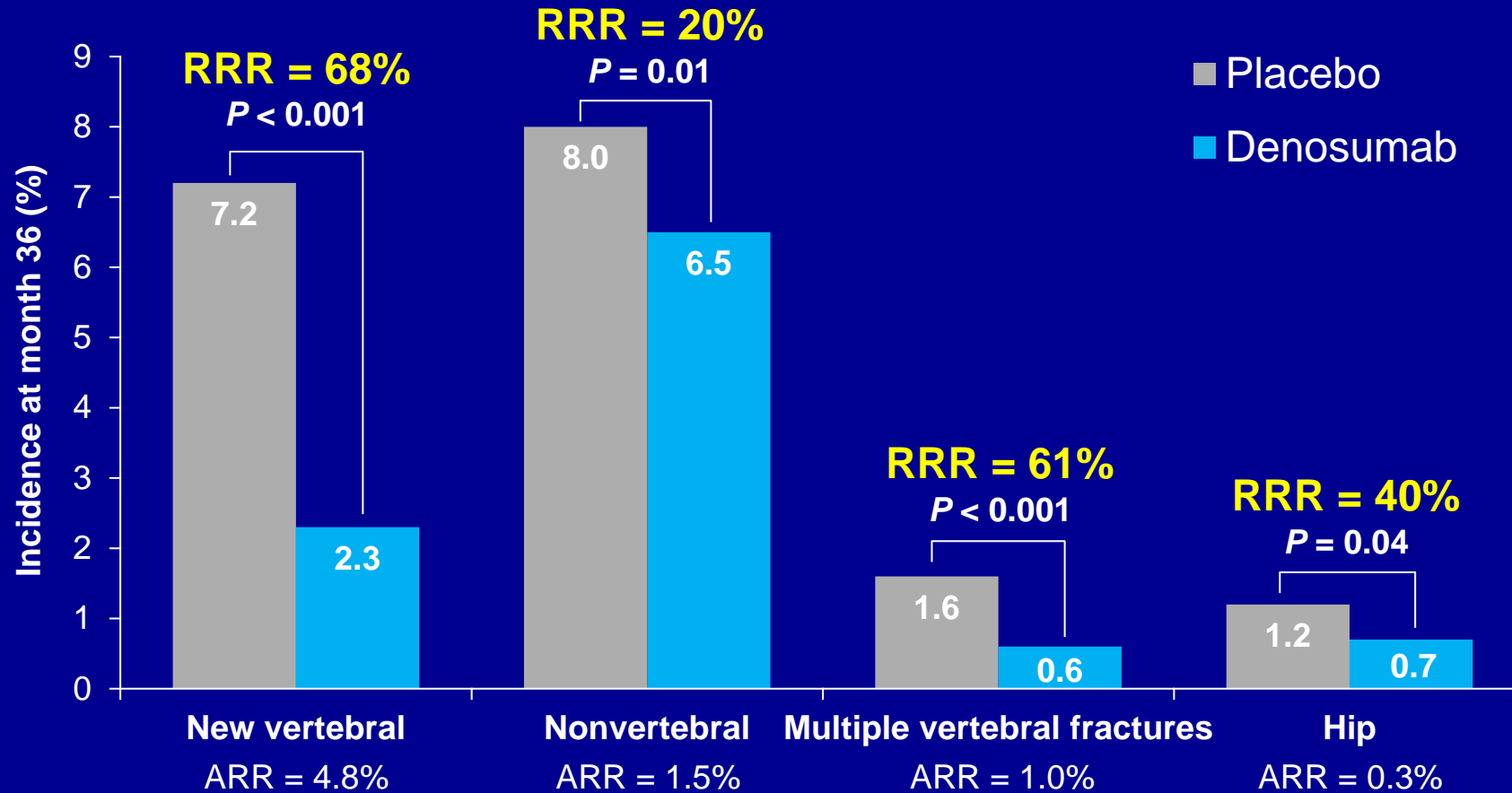
- Additional Considerations:
 - Drug holidays after bisphosphonates are possible
 - Fracture risk starts to increase about 2 years after stopping BP
 - Risk of AFF resolves quickly (1 year)
 - Longterm maintenance with intermittent bisphosphonate treatment is possible
- Role for Bisphosphonates:
 - Initial treatment for moderate osteoporosis by BMD criteria
 - Last treatment of an anabolic treatment sequence to maintain the benefits
 - Treatment after denosumab withdrawal
 - Long-term maintenance of BMD

Antiresorptive Agents: Denosumab

- Denosumab is a monoclonal antibody to RANK-Ligand
 - prevents RANK-Ligand from binding to its receptor (RANK) on osteoclast precursors and mature osteoclasts
 - inhibits differentiation of osteoclast precursors into mature osteoclasts
 - decreases the function and survival of activated osteoclasts.
- Approved Dose: 60 mg by subcutaneous injection every 6 months
- Pivotal Trial: FREEDOM
 - 3-year, placebo-controlled clinical trial of 7,808 women with osteoporosis

Denosumab vs Placebo at 3 Years in the FREEDOM Trial

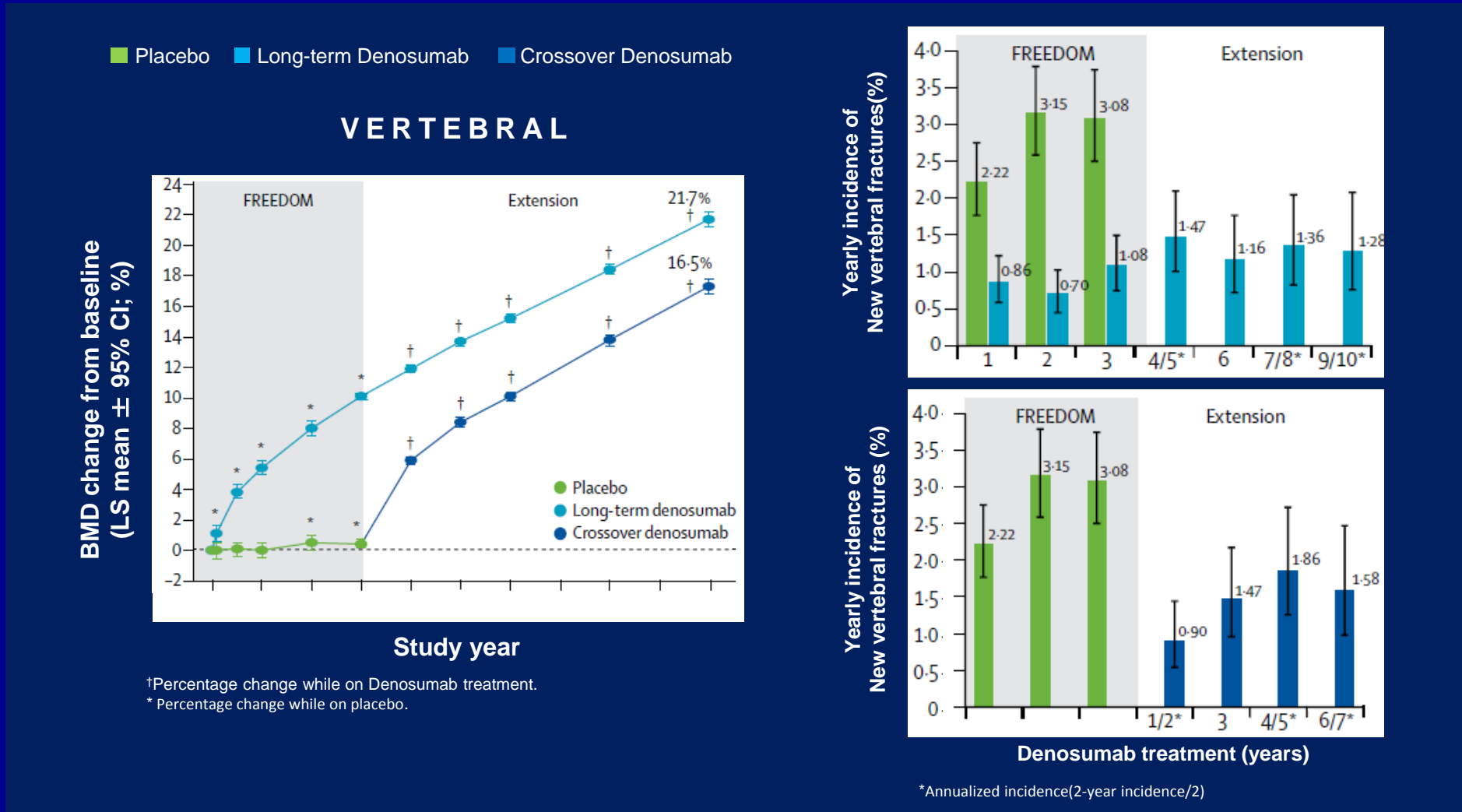
The Pivotal Phase 3 FREEDOM Trial¹



ARR, absolute risk reduction; RRR, relative risk reduction.

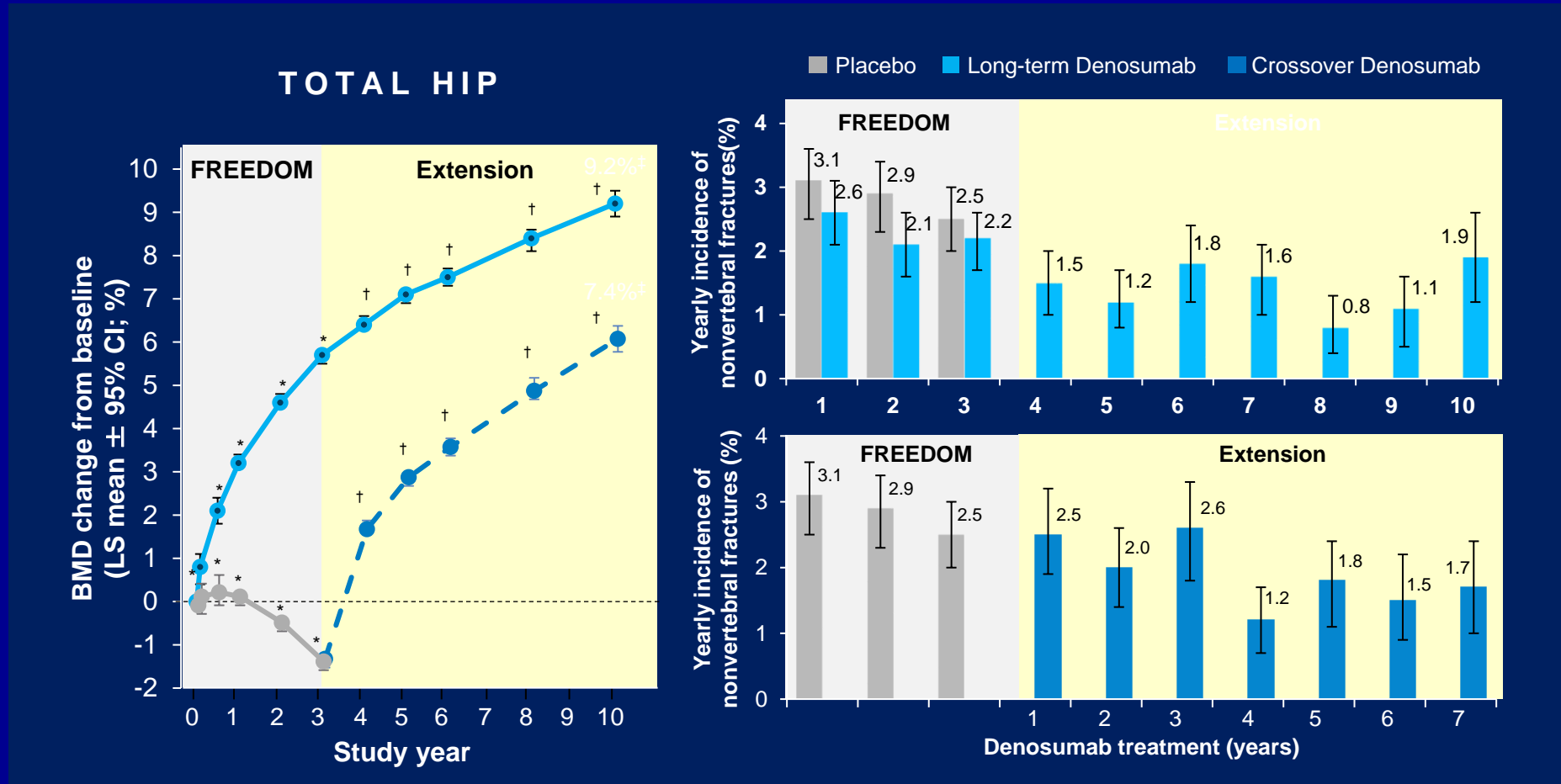
Continued BMD Gains and Sustained Low Fracture Rates Through 10 Years of Denosumab Treatment

Phase 3 FREEDOM Trial and Open-Label Extension



Continued BMD Gains and Sustained Low Fracture Rates Through 10 Years of Denosumab Treatment

Phase 3 FREEDOM Trial and Open-Label Extension



Percentages for nonvertebral fractures are Kaplan–Meier estimates.

* $P < 0.05$ versus FREEDOM baseline. † $P < 0.05$ versus FREEDOM baseline and extension baseline.

‡Percentage change while on Denosumab treatment.

Antiresorptive Agents: Denosumab Safety

- Hypocalcemia
- No concerns about infections over long-term treatment or fracture healing
- Rare ONJ: 5/10,000 per patient years treatment
- Very Rare AFF: <1/10,000 per patient years treatment
- No Drug holiday
 - Stopping treatment leads to rapid and prominent bone loss
 - Multiple vertebral fractures risk increased
- Stopping Denosumab may be advantageous in some individuals but requires careful planning
 - Zoledronic Acid
 - Might be more difficult after longer term denosumab treatment

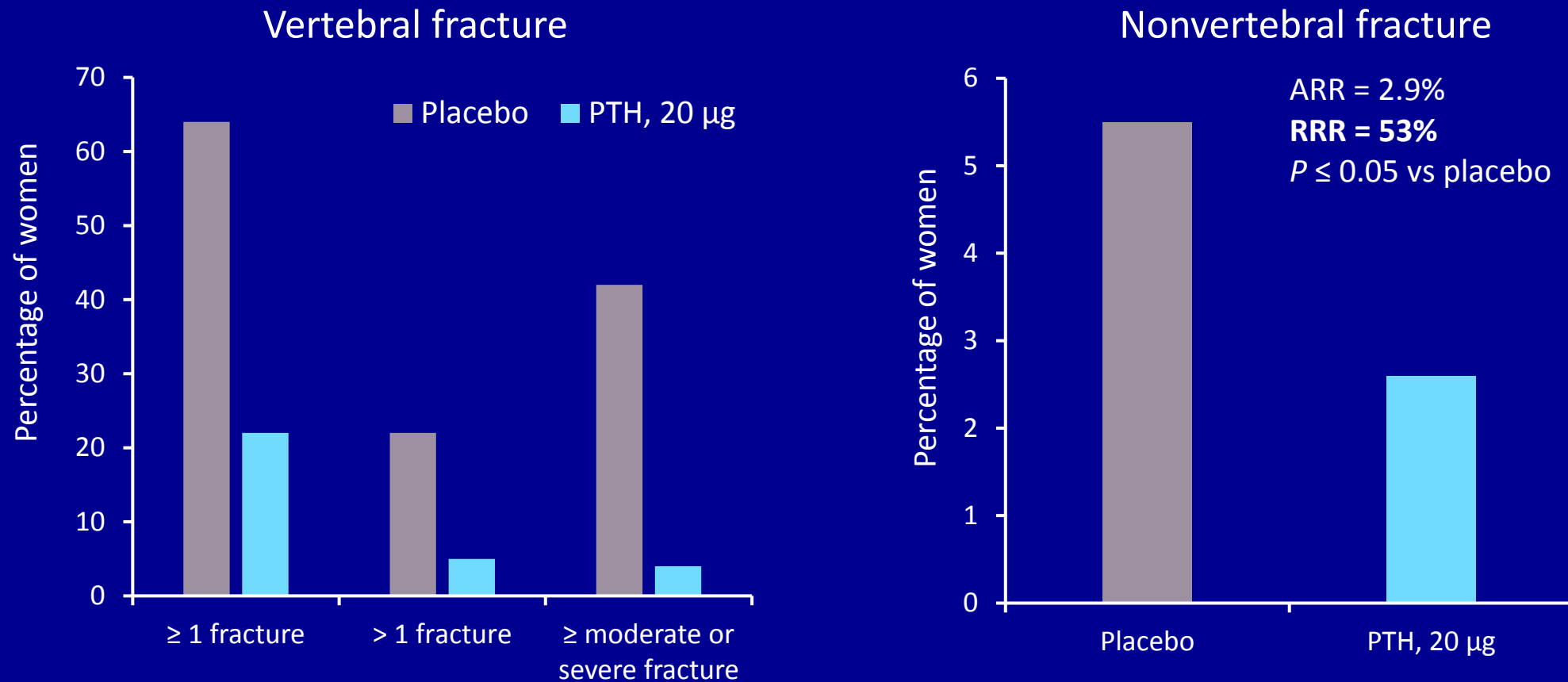
Antiresorptive Agents: Denosumab

- Primary Role:
 - High Risk Patients
 - BMD gains exceed those seen with bisphosphonates
 - Fracture risk further reduced with longer-term therapy
 - In sequence after anabolic therapy in very High Risk Patients

Anabolic Agents: Teriparatide

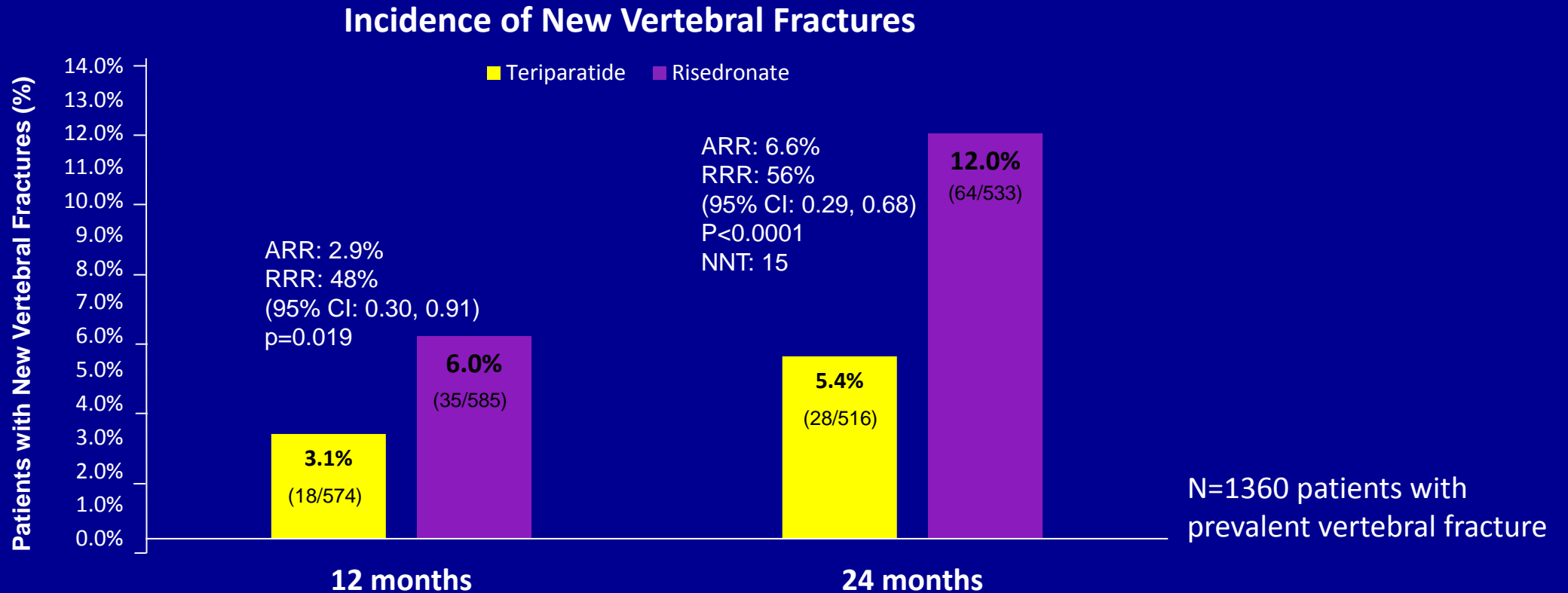
- Teriparatide binds to PTH Receptor 1 on Osteocytes and Osteoblasts
 - Reduces Sclerostin expression
 - Activates Wnt Signaling pathway
 - Increased bone formation (increased osteoblast formation, lifespan and activity)
 - Increases RANK Ligand and decreases osteoprotegerin
 - Increases bone remodeling
- Pivotal trial: 1637 women with prevalent vertebral fracture randomized to one of two different doses of teriparatide or placebo
- Approved dose teriparatide: 20 mcg daily by subcutaneous injection

Effects of Teriparatide on Vertebral and Nonvertebral Fractures over 19 Months



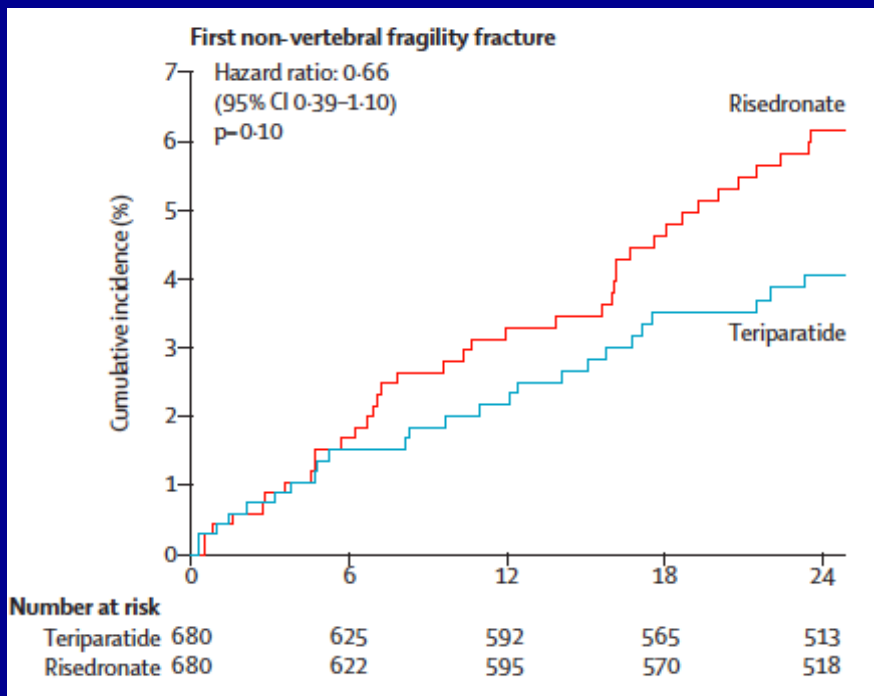
ARR, absolute risk reduction; RRR, relative risk reduction

VERO: Teriparatide vs Risedronate in Patients with Prevalent Fracture



Analysis at 12 months was a pre-specified exploratory endpoint. ARR, absolute risk reduction; RRR, relative risk reduction; CI, confidence interval; NNT, number needed to treat

VERO: Teriparatide vs Risedronate: Incidence and Number of Nonvertebral Fractures



Subject incidence fragility NVF TPTD vs RIS:
HR 0.66 (0.39-1.1), p=0.10

	Teriparatide (N =680)	Risedronate (N =680)
Patients with ≥ 1 NVF n (%)	25 (3.7)	38 (5.6)
n (%) with 1 NVF	23 (3.4)	28 (4.1)
n (%) with 2 NVF	2 (0.3)	10 (1.5)
Total number of NVF	27	48

Adjusted rate ratio for absolute number of NVF TPTD vs RIS:
0.56 (0.35; 0.90); $P = 0.017^*$

Fractures of the clavicle, scapula, ribs, sternum, sacrum, coccyx, humerus, radius, ulna, carpus, pelvis, hip, femur, patella, tibia, fibula, ankle, calcaneus, tarsus, or metatarsus (excluding pathologic fractures and fractures of skull, face, fingers, metacarpals, and toes).

Anabolic Agents: Abaloparatide

- Abaloparatide: synthetic analogue of PTH-related peptide^{1,2}
 - PTHrP has role in bone remodeling regulation and fracture repair¹
 - 75% homology with PTHrP
 - 40% homology with PTH(1-34)
- Acts through PTH1 receptor
 - much greater binding affinity for RG compared with R⁰ conformation²
 - Stimulation of Bone formation > Bone resorption vs teriparatide
- Pivotal trial: ACTIVE enrolled 2463 women with osteoporosis defined by BMD and/or fracture criteria
 - Randomized to abaloparatide, teriparatide or placebo for 18 months
 - Abaloparatide and placebo transitioned to alendronate for 2 years in the extension study

1. Martin TJ *Physiol Rev* 2016

2. Hattersley G et al. *Endocrinology* 2016;157:141-9

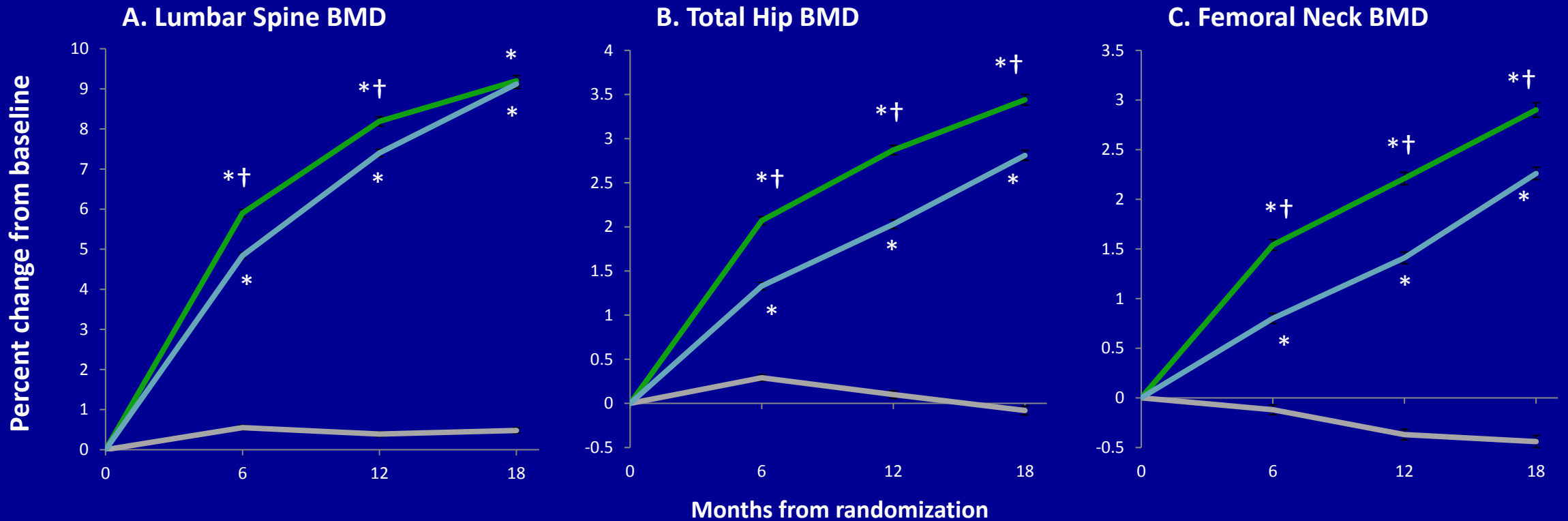
ACTIVE: BMD Changes at Spine and Hip

ITT Population N=2463

■ Abaloparatide-SC

▲ Teriparatide

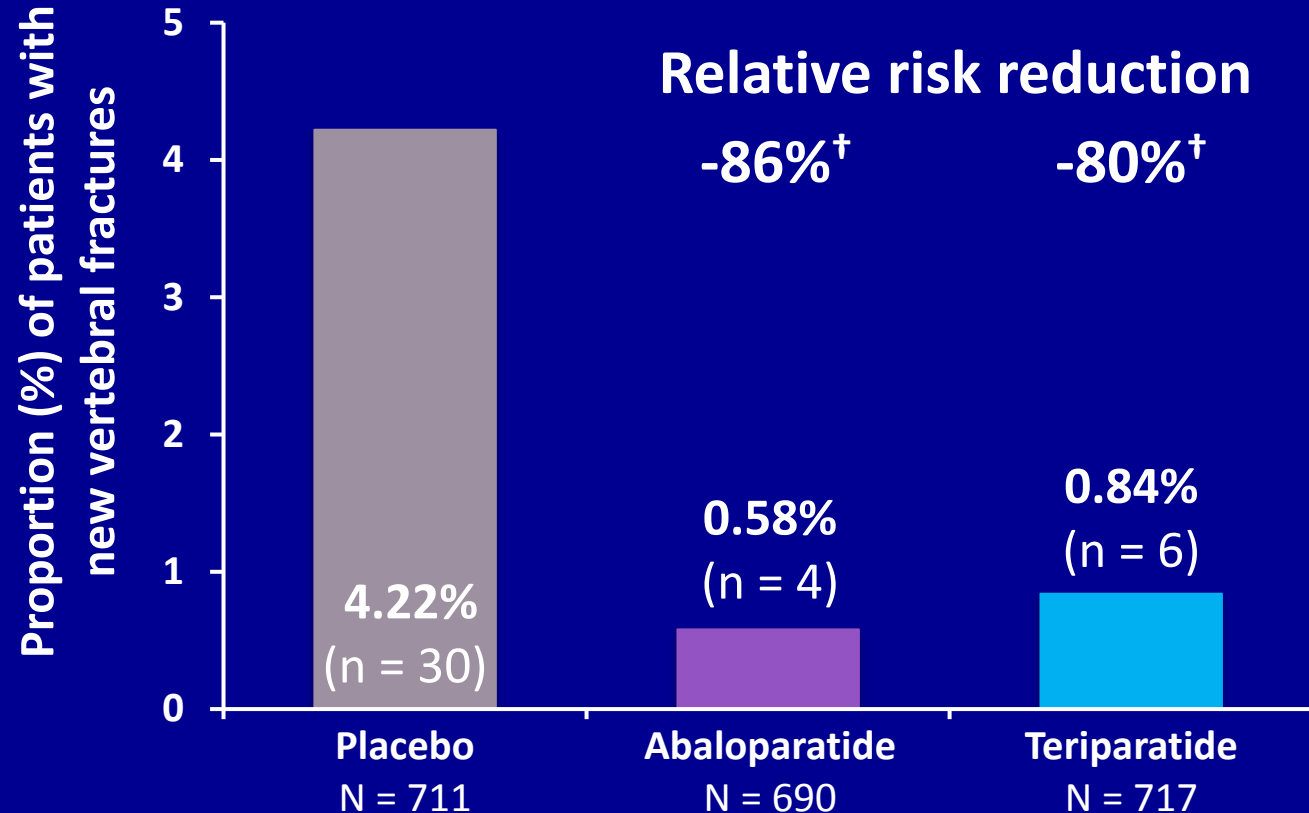
◆ Placebo



* $P < .001$ compared with placebo; † $P < .01$ compared with teriparatide. Missing BMD was imputed using last observation carried forward.

ACTIVE: New Vertebral Fractures over 18 Months

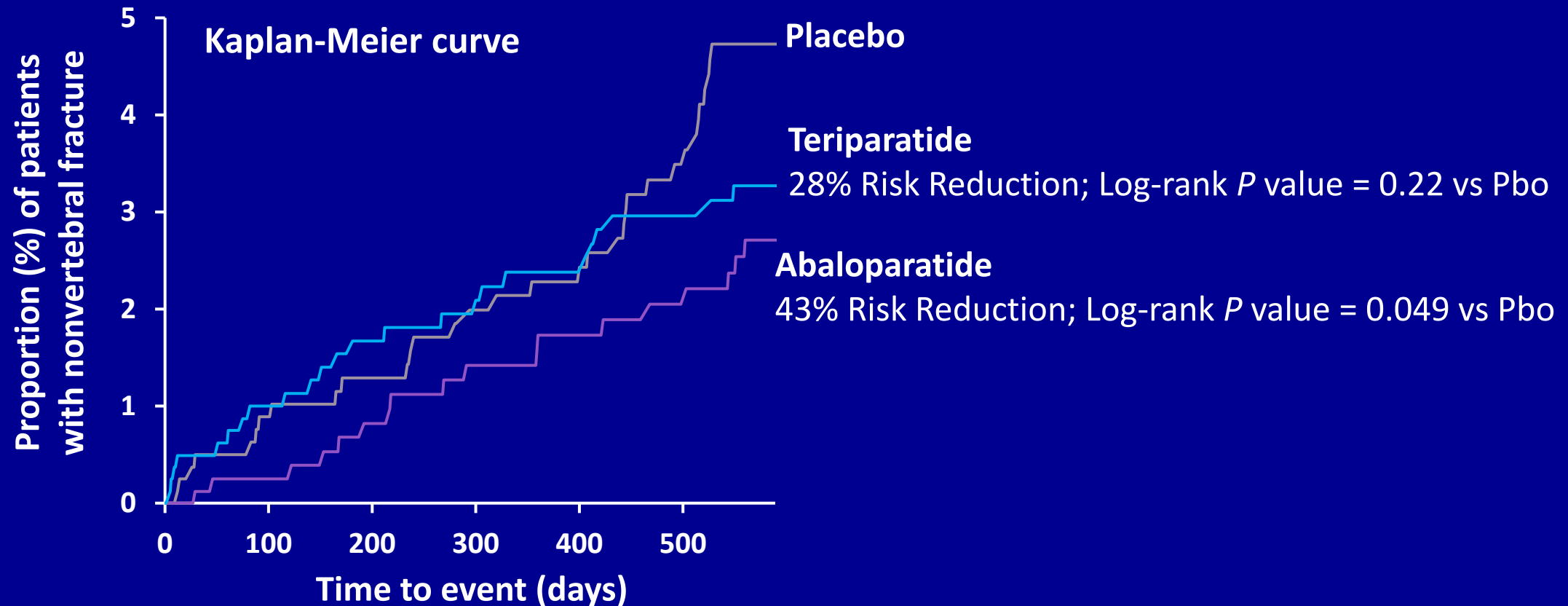
Modified ITT population* N = 2118



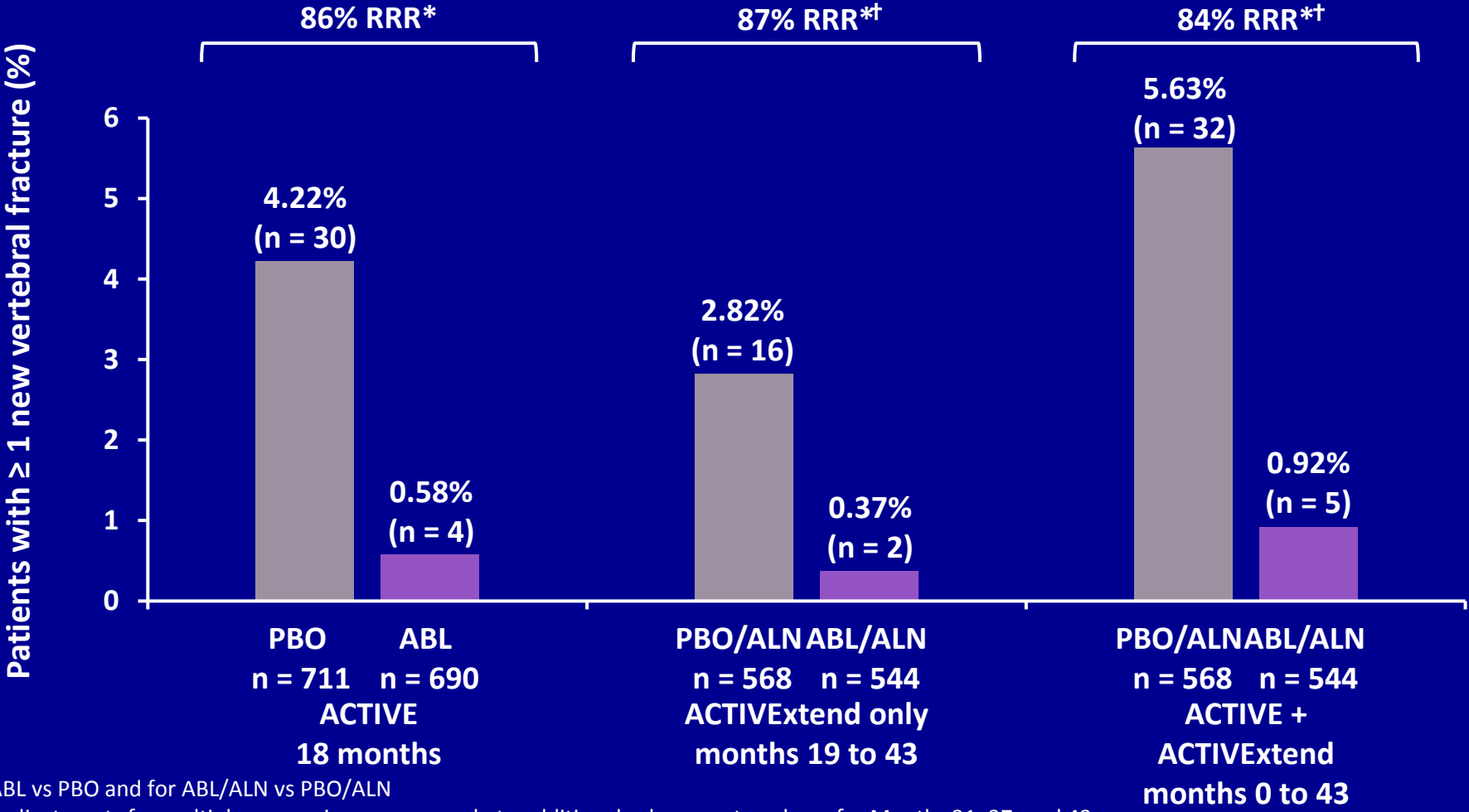
*Includes all ITT patients who had pre-treatment and post-baseline evaluable radiologic assessments; [†]P < 0.001 vs placebo.

ACTIVE: Time to First Nonvertebral Fracture

ITT Population N = 2463



ACTIVE/ACTIVEExtend: New Vertebral Fractures

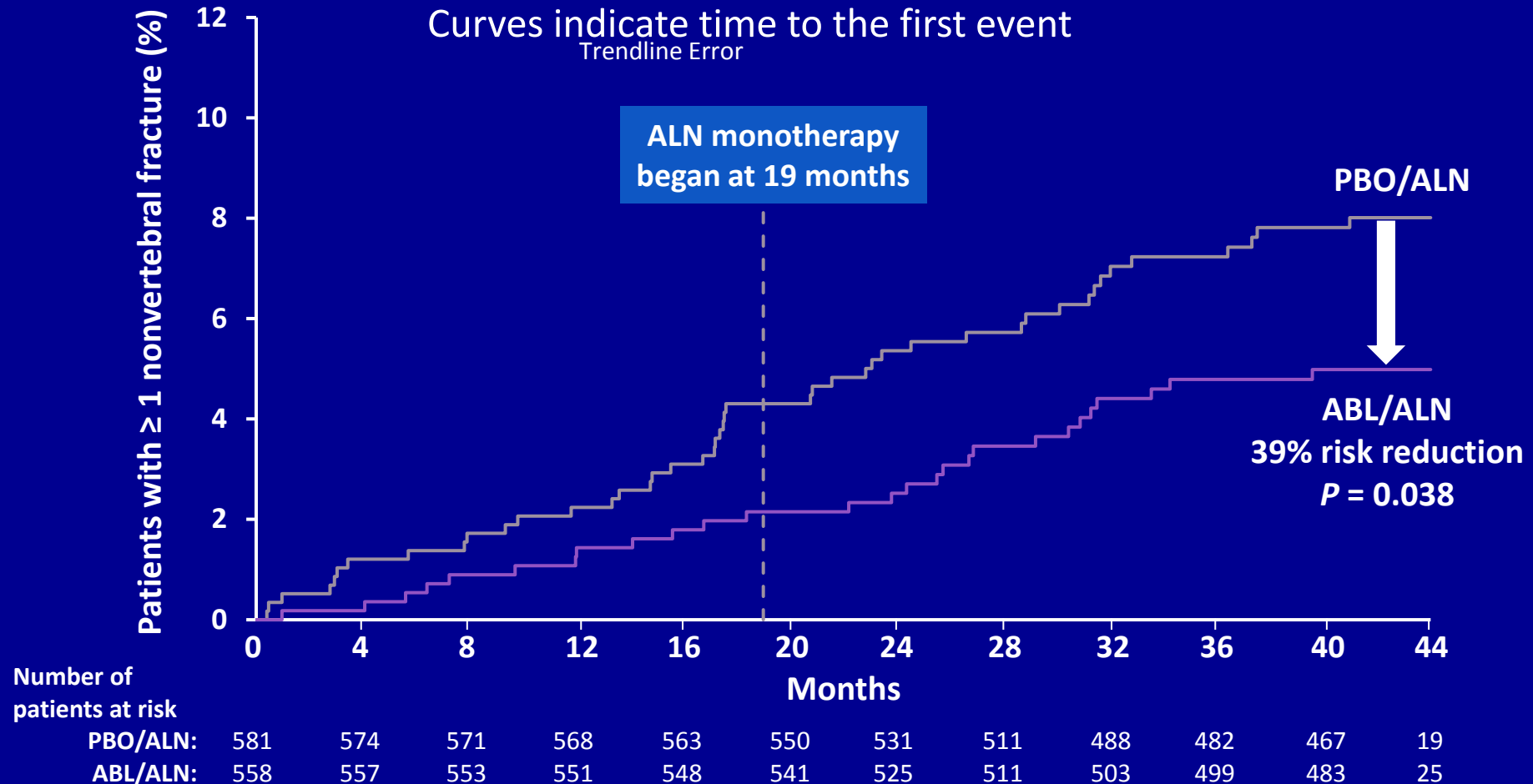


* $P \leq 0.001$ for ABL vs PBO and for ABL/ALN vs PBO/ALN

† No statistical adjustments for multiple comparisons were made to additional subsequent analyses for Months 31, 37, and 43

ABL, abaloparatide; ALN, alendronate; PBO, placebo; RRR, relative risk reduction

ACTIVE/ACTIVEExtend: Time to First Nonvertebral Fx



Kaplan-Meier estimates were calculated at 43 months. No statistical adjustments for multiple comparisons were made to additional subsequent analyses for Months 31, 37 and 43.
ABL, abaloparatide; ALN, alendronate; PBO, placebo.

Anabolic Agents: Teriparatide/Abaloparatide

- Primary Role: Initial Therapy in Very High Risk Patients
 - Abaloparatide produces earlier effect vs teriparatide against nonvertebral fracture and more rapid gain in BMD
- Safety Issues:
 - Rodent osteosarcoma- not likely human issue
 - Hypercalcemia and hypercalciuria
 - Orthostatic hypotension- dizziness, tachycardia, nausea
 - Erythema at injection site
 - Leg cramps/musculoskeletal pains/fatigue

Anabolic Agents: Romosozumab

- Sclerostin- osteocyte protein that binds to LRP5/6 receptor on osteoblasts and osteoblast precursors
 - inhibits Wnt Signaling
 - Reduces formation, function and survival of osteoblasts leading to *decreased* bone formation
 - Stimulates production of rank ligand by osteocytes through an autocrine function leading to *increased* bone resorption
- Romosozumab - monoclonal antibody that binds and *inhibits sclerostin*
 - stimulates bone formation and reduces bone resorption

Anabolic Agents: Romosozumab

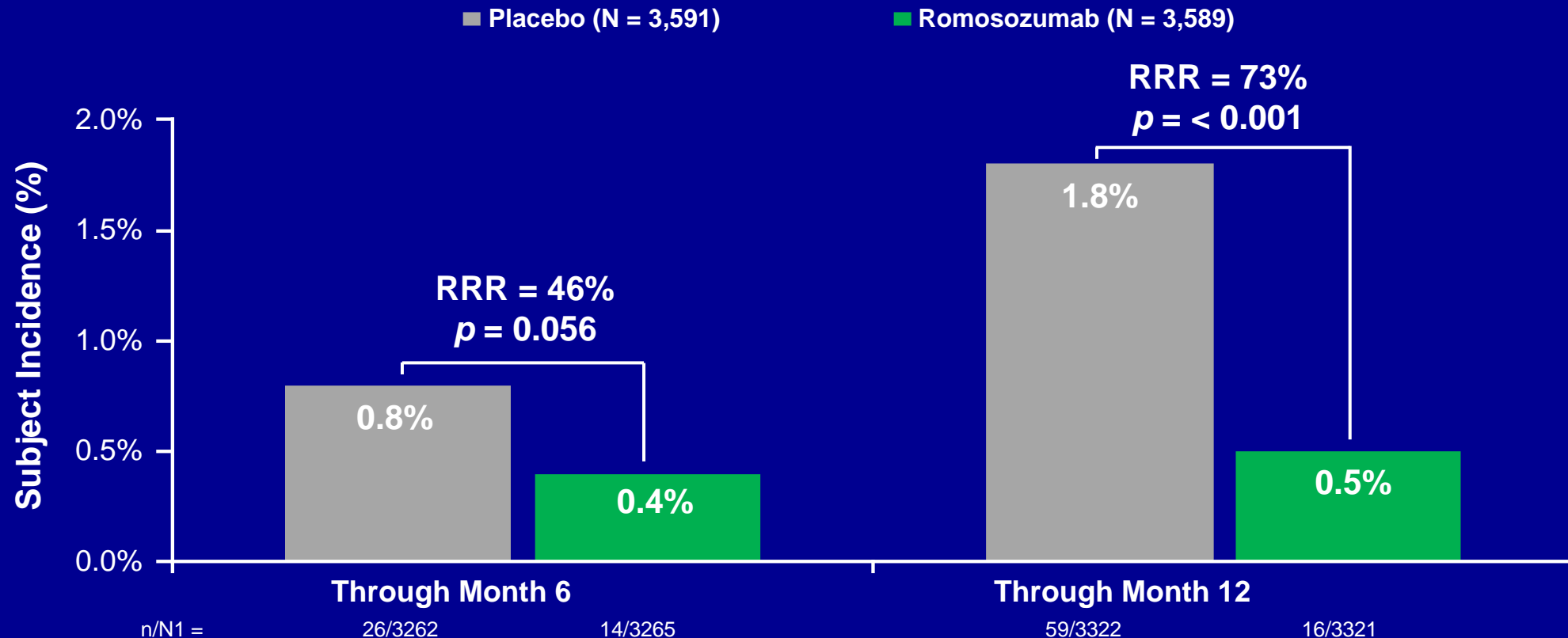
- Pivotal Fracture Trials:
 - FRAME: 7180 women with osteoporosis randomized to romosozumab vs placebo for 1 year followed by denosumab for 1 year in both groups
 - Extension: 1 additional year in extension study
 - ARCH: 4093 women with prevalent fracture randomized to romosozumab or alendronate for 1 year followed by alendronate in all women
 - Event driven trial- median treatment period just under 3 years

Cosman F et al. *N Engl J Med* 2016;375:1532–43.

Lewiecki EM, et al. *J Bone Miner Res* 2019;34:419-428.

Saag K et al. *N Engl J Med* 2017;377:1417-27

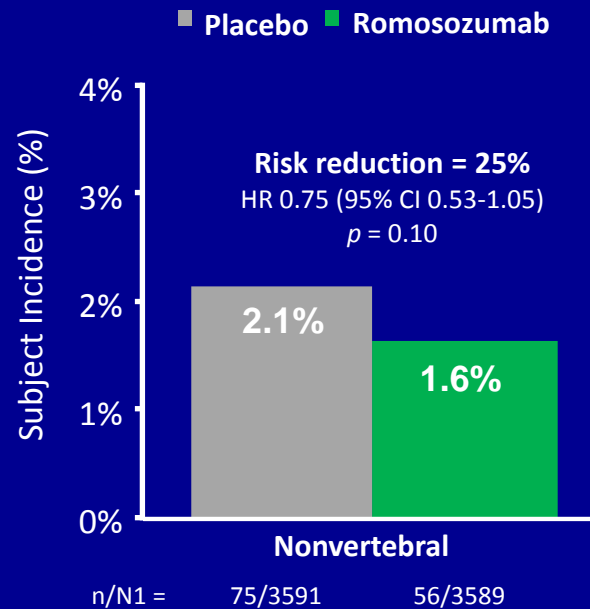
FRAME: New Vertebral Fracture Incidence Through Month 12 (Coprimary Endpoint)



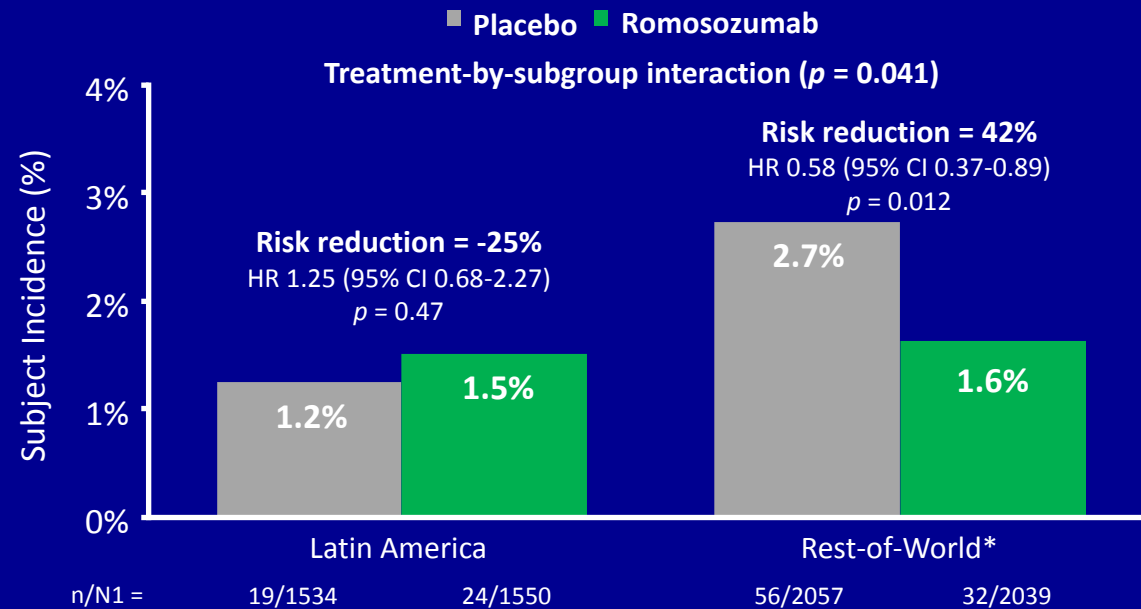
n/N1 = number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures
 p -value based on logistic regression model adjusted for age (< 75 , ≥ 75) and prevalent vertebral fracture

FRAME: Nonvertebral Fracture Outcomes Through Month 12

Overall FRAME population

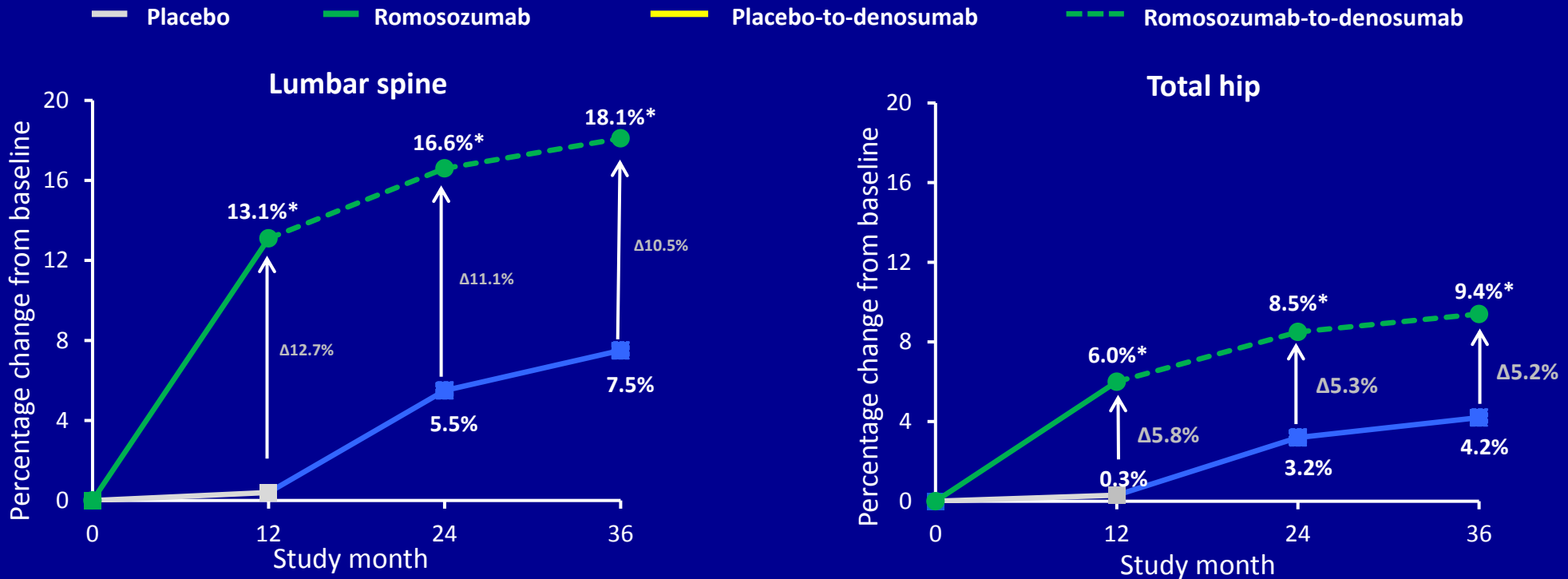


Nonvertebral fracture incidence through month 12 in Latin America (43% of FRAME population) vs Rest-of-World*



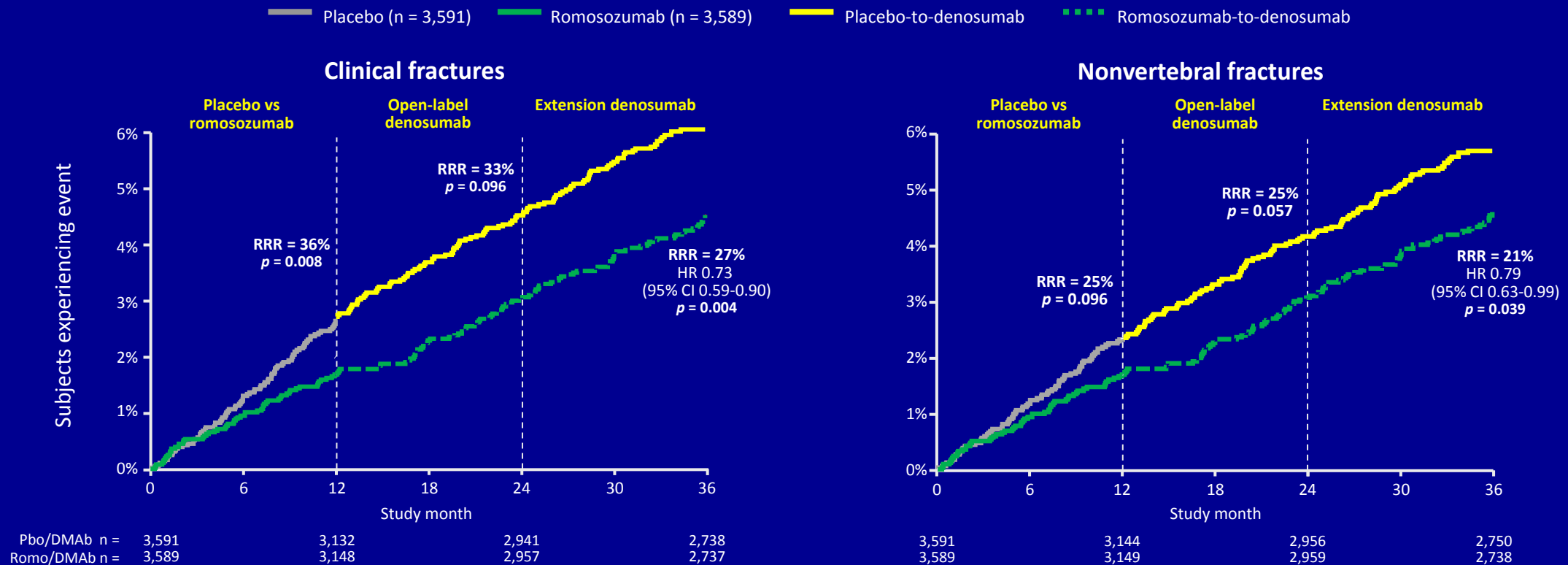
*Regions excluding Latin America grouped post hoc. n/N1 = number of subjects with fractures/number of subjects in the full analysis set. Nonvertebral fractures exclude fractures of the skull, face, metacarpals, fingers, and toes, pathologic fractures and those due to high trauma. CI, confidence interval; HR, hazard ratio.

FRAME Extension: Spine and hip BMD Through Month 36



*Nominal $p < 0.001$. Data are least-square mean (95% CI) based on ANCOVA model adjusting for treatment, age, and prevalent vertebral fracture stratification variables, baseline value, machine type, and baseline value-by-machine type interaction. For subjects with a baseline and at least one post baseline DXA, $n = 3,176$ for placebo and $n = 3,169$ for romosozumab at the lumbar spine, and $n = 3,256$ for placebo and $n = 3,237$ for romosozumab at the total hip. ANCOVA, analysis of covariance; BMD, bone mineral density; CI, confidence interval.

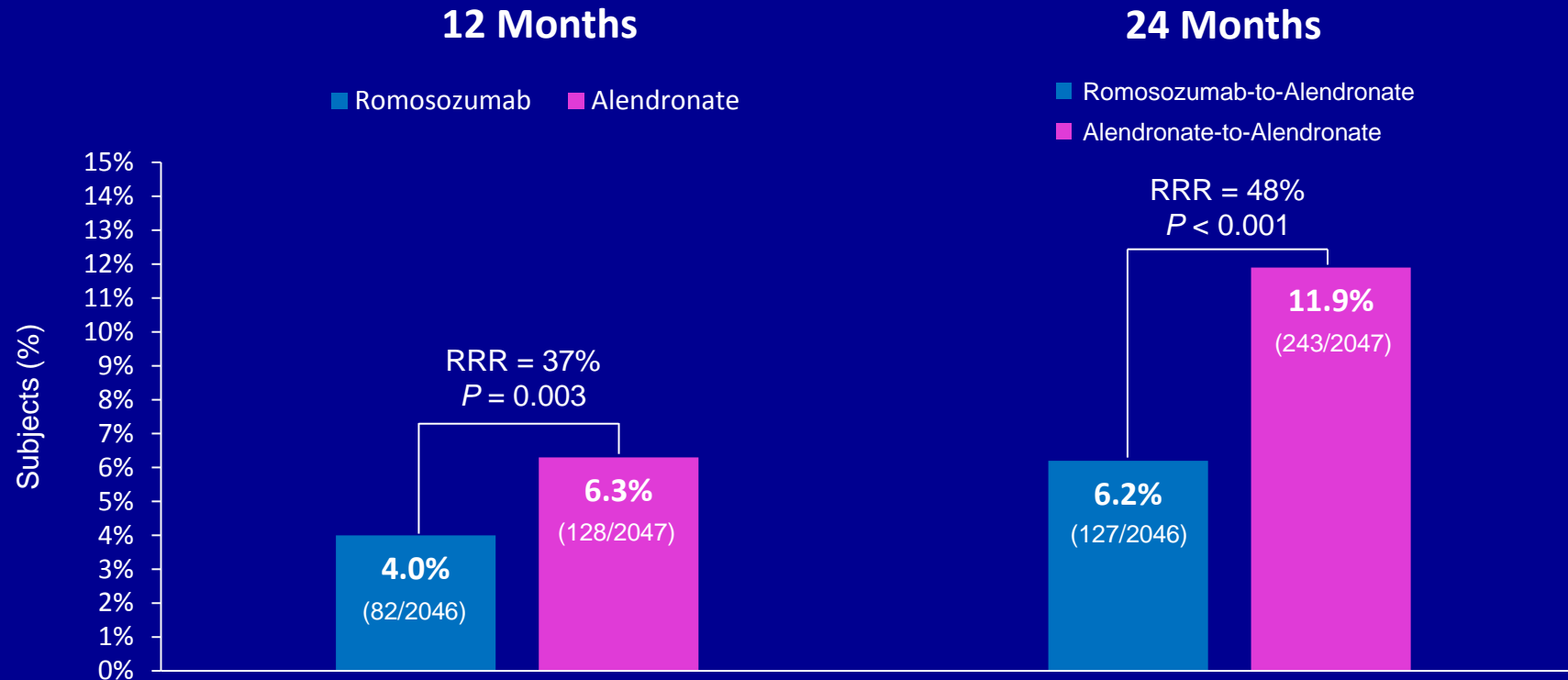
FRAME Extension: Time to first clinical and nonvertebral fracture through month 36



Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures. n = number of subjects at risk for event at time point of interest. Relative risk reduction and p-values for 12-month and 24-month periods are adjusted values based on a sequential testing procedure as reported for the primary analysis. P-values for month 36 are nominal.

CI, confidence interval; DMAb, denosumab; HR, hazard ratio; Pbo, placebo; Romo, romoosozumab; RRR, relative risk reduction.

ARCH: Incidence of New Vertebral Fracture Through Month 24 (Coprimary Endpoint)



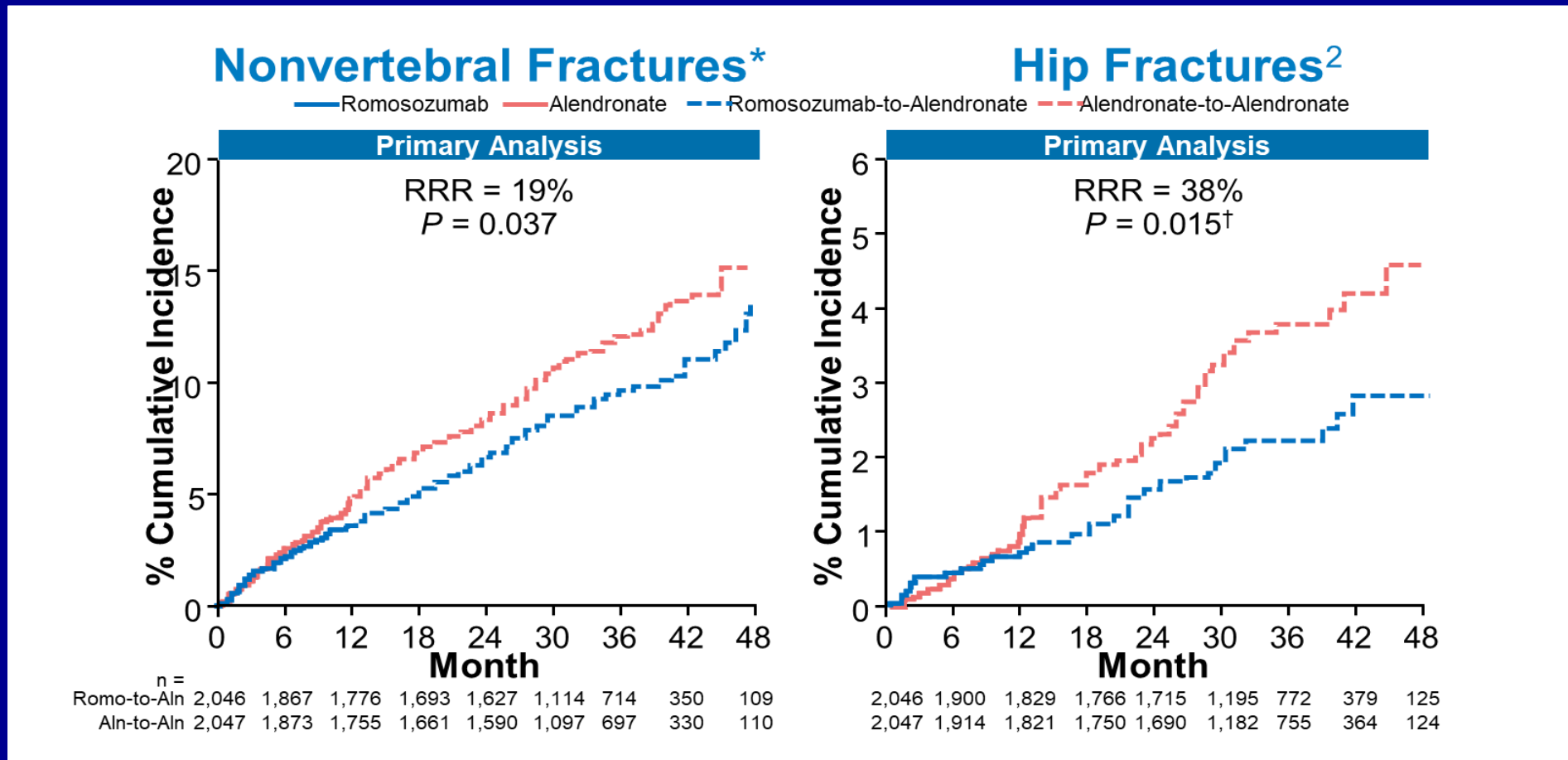
n/N1 = number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures.

*Missing fracture status was imputed by multiple imputation for patients without an observed fracture at an earlier time point. n and % are based on the average across 5 imputed data sets.

†RRR at 12 months by LOCF: 36% (nominal P = 0.008): romosozumab 3.2% (55/1696) vs alendronate 5.0% (85/1703).

‡RRR at 24 months by LOCF: 50% (nominal P < 0.001): romo-to-ALN 4.1% (74/1825) vs ANL-to-ALN 8.0% (147/1843).

ARCH: Incidence of Nonvertebral and Hip Fracture at Primary Analysis



*Secondary endpoint. †Not adjusted for multiplicity. N = number of subjects at risk for event at time point of interest.

Romosozumab

- Primary Role: Initial therapy in Very High Risk Patients
- Safety:
 - Injection site reactions
 - Hypersensitivity
 - Hypocalcemia
 - Immunogenicity
 - MACE (Major Adverse Cardiac Events of MI, Stroke, Cardiovascular Death)
 - Imbalance in ARCH compared to alendronate (2% with romosozumab vs 1.1% with alendronate)
 - No imbalance in FRAME where romosozumab was compared to placebo

Risk Stratification

Low Risk	Moderate Risk	High Risk	Very High Risk
<p>No Prior fracture, T-Score ≥ -1, and FRAX probabilities $<20\%$ MOF, $<3\%$ Hip</p>	<p>No prior fracture, and T-Score between -1 and -2.5 and FRAX probabilities $<20\%$ MOF, $<3\%$ Hip</p>	<p>Older single Prior fracture (> 2 years earlier), or T-Score ≤ -2.5, or T-Score -1 to -2.5 with FRAX probabilities $\geq 20\%$ MOF or $\geq 3\%$ Hip</p>	<p>High Imminent Risk: Recent Fracture Multiple Fractures T-Score -3, especially if additional factors</p>
<p>No pharmacologic treatment needed</p>	<p>Goal: Maintain BMD Some may benefit from sequential antiresorptive monotherapy especially those with BMD close to -2.5</p> <ul style="list-style-type: none"> • Estrogens in early menopausal • Raloxifene 50s to late 60s • Bisphosphonates mid/late 60s 	<p>Goal: Improve BMD to T-Score > -2.5 and Reduce Fracture Risk</p> <ul style="list-style-type: none"> • Younger women may benefit from estrogens/raloxifene especially if spine T-Score low and hip > -2.5 • Usually bisphosphonates or denosumab • Anabolic agents appropriate for some 	<p>Goal: Reduce fractures rapidly Improve BMD rapidly to target at least above -2.5</p> <ul style="list-style-type: none"> • Anabolics optimal as initial therapy • Follow with potent Antiresorptives

Modified from:

Camacho PM et al. Endocrine Practice 2020. AACE/ACE Clinical Practice Guidelines

Shoback D et al, JCEM 2020 Endocrine Society Guidelines.

Ferrari S et al. 2020 recommendations Swiss Association against Osteoporosis. Swiss Med Wkly 2020;150:w20352

Individualizing Osteoporosis Therapy Based on Risk and Age: Moderate Risk Risk Patients

- 52 year old healthy recently menopausal woman with hot flashes, no history of fracture
 - Spine T-Score -2.3, Hip T-Score -2.0
 - Best initial treatment some form of estrogen therapy
- 58 year old postmenopausal woman with *no* hot flashes, no history of fracture
 - Same BMD (Spine T-Score -2.3, Hip -2.0)
 - Maternal history of breast cancer or high breast density
 - Best initial treatment probably raloxifene
- 65 year old woman with no fracture and no clinical risk factors for fracture
 - Same BMD (Spine T-Score -2.3, Hip -2.0)
 - Best initial treatment probably a bisphosphonate- short-term (< 3 years)

Individualizing Osteoporosis Therapy Based on Risk and Age: High Risk Patients

- For patients in the High Risk category *based on Spine BMD only*, treatment is probably the same as for the moderate risk woman at different ages:
 - 52 year old woman with hot flashes, no fracture, T-Score in spine -2.6, hip -2.0
 - Estrogen therapy
 - 58 year old postmenopausal woman, no fracture, same BMD
 - Raloxifene
 - 65 year old woman with no fracture, same BMD
 - Bisphosphonate- short-term (< 3 years)

Individualizing Osteoporosis Therapy: High Risk Patients

- 68 year old woman, no fracture with T-Score Spine -2.6, and Hip -2.5
 - Best initial treatment probably a bisphosphonate
 - High probability of attaining BMD above osteoporosis range both sites
- 68 year old woman, with risk factors (family history, underlying comorbidities/meds), and *same BMD*
 - Best initial treatment might be denosumab
 - Goal to attain higher T-Scores than bisphosphonates usually provide
- 68 year old woman, no fracture, lower BMD (Spine -2.8, Hip T-Score -2.7)
 - Best initial treatment probably denosumab
 - Goal to attain Hip and Spine T-Scores above -2.5
- 68 year old woman with history of vertebral fracture 5 years earlier
 - **Anabolic therapy optimal**

AACE Guidelines: Very High Risk Patients Definition and Management

- **R23.** Consider patients with a **recent fracture** (e.g., within the past 12 months), fractures while on approved osteoporosis therapy, **multiple fractures**, fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids), **very low T-score** (e.g., less than **-3.0**), high risk for falls or history of injurious falls, and very high fracture probability by FRAX[®] (fracture risk assessment tool) (e.g., major osteoporosis fracture >30%, hip fracture >4.5%) or other validated fracture risk algorithm to be at very high fracture risk.
- **R25.** **Abaloparatide**, denosumab, **romosozumab**, **teriparatide**, and zoledronate should be considered for patients unable to use oral therapy and as **initial therapy** for patients at very high fracture risk, as defined in R23.

Summary

- Osteoporosis treatment should be individualized and tailored to age and risk
- Some moderate risk patients should receive sequential therapy with AR agents most appropriate for age (estrogens, raloxifene, bisphosphonates)
- High risk patients- very broad category
 - Some should receive sequential antiresorptive therapy with estrogens, raloxifene, bisphosphonates
 - Some should receive denosumab
 - Some should receive anabolic agents
- Very high risk includes high imminent fracture risk over next 2 years
 - Optimally should receive anabolic treatment first
 - reduces fracture risk rapidly and potently
 - produces sustained fracture risk reduction during antiresorptive treatment
 - produces greatest improvement in hip BMD