

Osteoporosis Treatment in 2026: Window of Opportunity

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Disclosures

- Clinical Trials
 - Prometheus
 - Genentech
 - Mitsubishi
- Advisory Board
 - Boehringer Ingelheim
 - Johnson & Johnson
- Honoraria
 - The Merck Manual
 - American Board of Internal Medicine
 - Medscape

Educational Objectives

- Recognize the role for anabolic therapy
 - Age-related osteoporosis
 - Glucocorticoid-induced osteoporosis (GIOP)
- Describe the anabolic window
- Discuss the timing of anabolic and antiresorptive medications



Tuscany, 2022

Case 1

- 58 yo woman with psoriatic arthritis who is taking adalimumab.
 - Has been doing well and presents for routine follow-up
 - No prior DXA scan

- DXA scan is performed

	<u>T-score</u>
• Total lumbar	-3.5
• Total hip	-2.7
• Femoral neck	-2.8

- Discussion of treatment options



Treatment Options

- Weight bearing exercise
- Fall prevention
- Calcium + Vitamin D

Daily

- Estrogen
 - Raloxifene
 - Teriparatide
 - Abaloparatide
- **Weekly**
 - Alendronate
 - Risedronate

- **Monthly**

- Risedronate
- Ibandronate
- Romosozumab

- **Quarterly**

- Ibandronate IV

- **Twice yearly**

- Denosumab

- **Yearly**

- Zoledronic acid

Alendronate

Denosumab

Abaloparatide

Estrogen

Ibandronate

Romsozumab

Zoledronic acid

Raloxifene

Risedronate

Teriparatide

Antiresorptive

Anabolic

Estrogen
Raloxifene

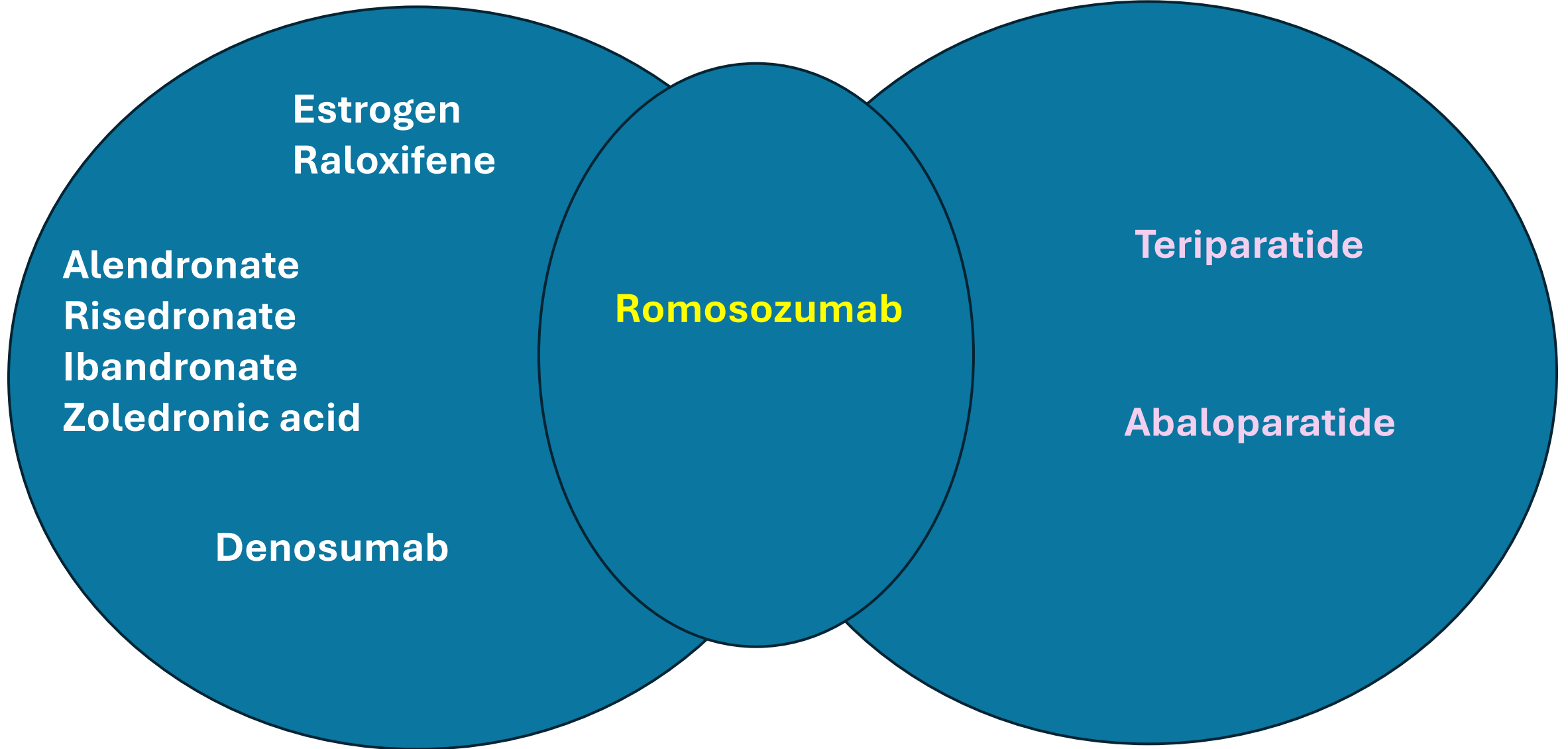
Alendronate
Risedronate
Ibandronate
Zoledronic acid

Denosumab

Romsozumab

Teriparatide

Abaloparatide



Case 1

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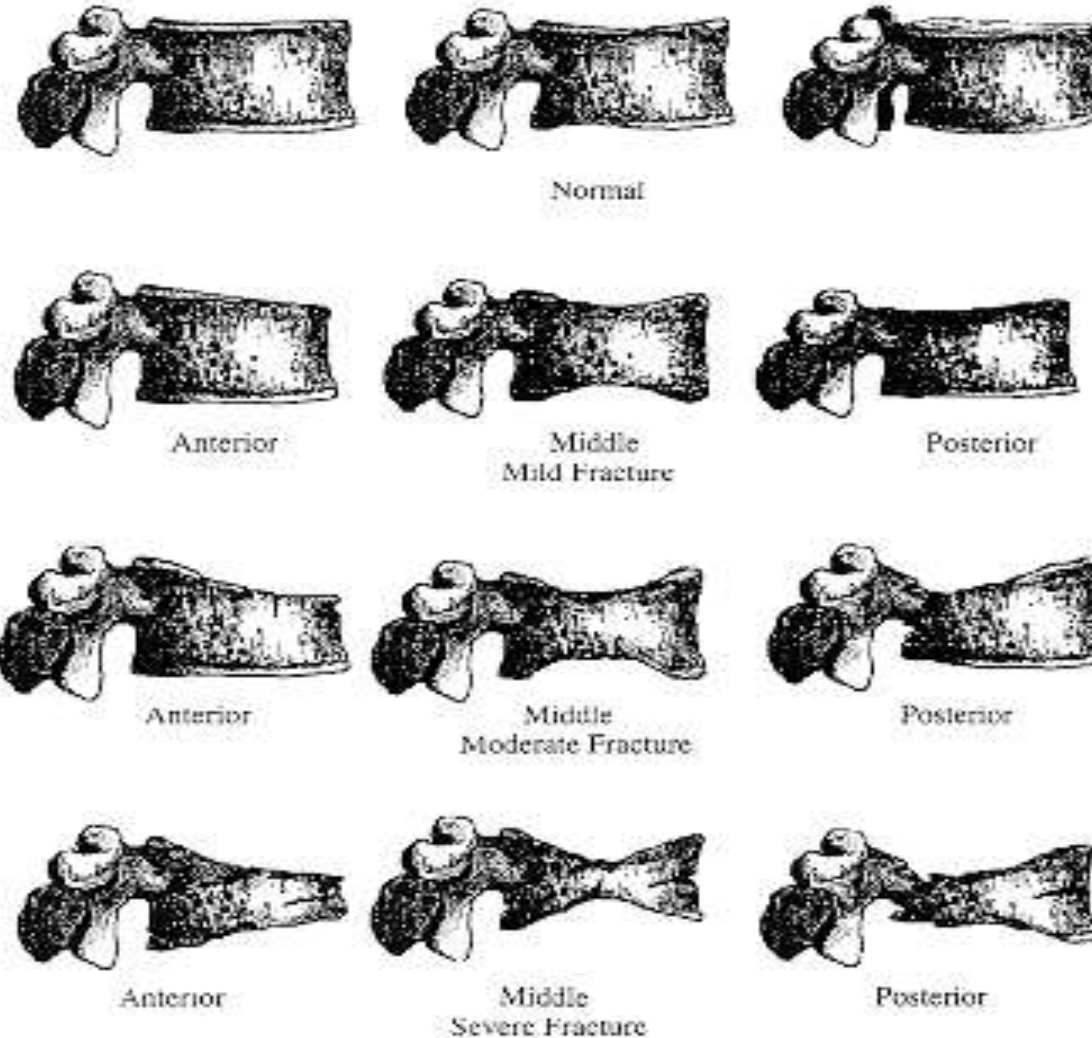
Consider the role of
anabolic therapy

PTH Analogs

- Teriparatide and abaloparatide should be considered in those at very high risk of fracture.
 - Studies with 18-24 months of treatment
 - Teriparatide
 - Spine efficacy
 - Abaloparatide
 - Spine and non-vertebral efficacy
 - Greater effect at total hip and femoral neck

Vertebral Insufficiency Fractures

Clinical
Or
Morphometric



Grade
0- Normal

1- Mild
(20-25%)

2- Moderate
(26-40%)

3- Severe
(>40%)

- 1637 postmenopausal women
- 2 doses TPTD vs. Placebo for 24 months
- >1 moderate OR >2 mild vertebral fractures
- Vertebral radiographs at baseline and at end of study

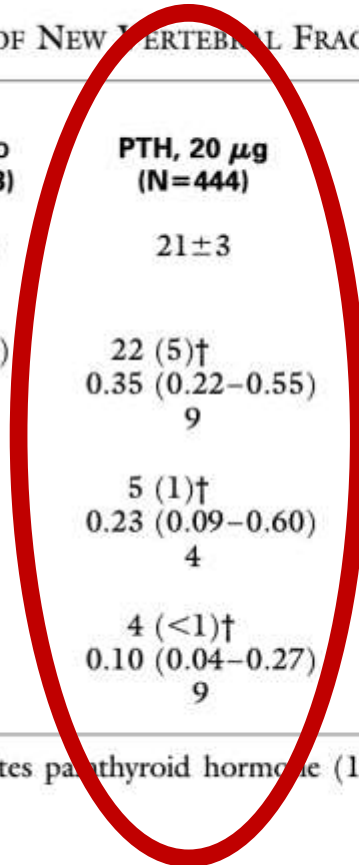


TABLE 2. RADIOGRAPHIC EVIDENCE OF NEW VERTEBRAL FRACTURES.*

VARIABLE	PLACEBO (N=448)	PTH, 20 μ g (N=444)	PTH, 40 μ g (N=434)
No. of months at risk (randomization to final radiograph)	21 \pm 3	21 \pm 3	20 \pm 4
\geq 1 Fracture			
No. of women (%)	64 (14)	22 (5) [†]	19 (4) [†]
Relative risk (95% CI) vs. placebo	—	0.35 (0.22–0.55)	0.31 (0.19–0.50)
Percent reduction in absolute risk	—	9	10
>1 Fracture			
No. of women (%)	22 (5)	5 (1) [†]	3 (<1) [†]
Relative risk (95% CI) vs. placebo	—	0.23 (0.09–0.60)	0.14 (0.04–0.47)
Percent reduction in absolute risk	—	4	4
\geq 1 Moderate or severe fracture			
No. of women (%)	42 (9)	4 (<1) [†]	9 (2) [†]
Relative risk (95% CI) vs. placebo	—	0.10 (0.04–0.27)	0.22 (0.11–0.45)
Percent reduction in absolute risk	—	9	7

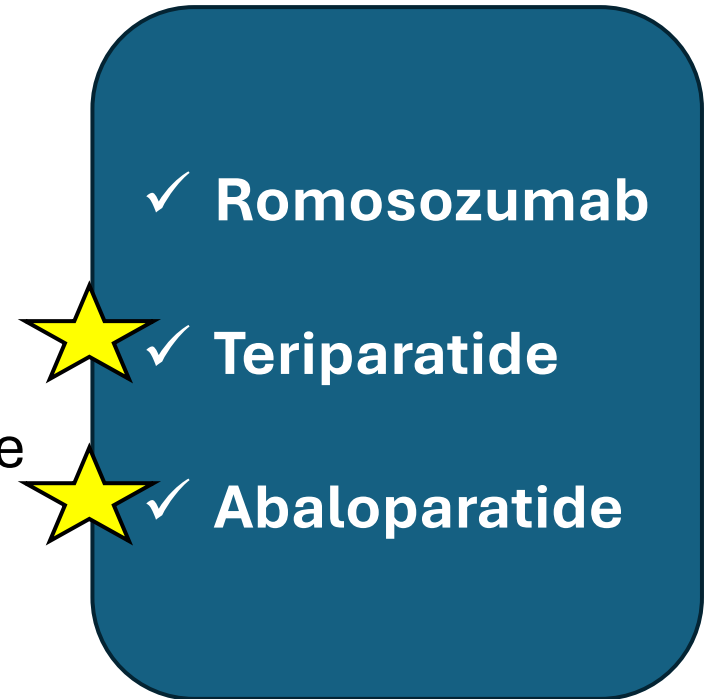
*Plus-minus values are means \pm SD. PTH denotes parathyroid hormone (1-34), and CI confidence interval.

[†]P \leq 0.001 for the comparison with placebo.



Case 1: Thoughts about Anabolic Therapy

- No history of
 - Bone malignancy
 - Radiation therapy (XRT)
 - Paget disease of bone
 - Unexplained elevation of PTH or alkaline phosphatase



- ✓ **Romosozumab**
- ★ ✓ **Teriparatide**
- ★ ✓ **Abaloparatide**

PTH Analogs

Black box warning – **REMOVED**

Treatment course 18-24 months


Avoid prescribing for those with increased risk for osteosarcoma

Anabolic agent followed by antiresorptive agent

May give for longer than 2 years in a lifetime

Case 2

- 58 yo woman with psoriatic arthritis who is taking adalimumab
 - Has been doing well and presents for routine follow-up
 - History of breast cancer treated with lumpectomy, XRT
 - No prior DXA scan
- DXA scan is performed



	T-score
• Total lumbar	-3.5
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- Discussion of treatment options

Consider the role of
anabolic therapy

Antiresorptive

Anabolic

Estrogen
Raloxifene

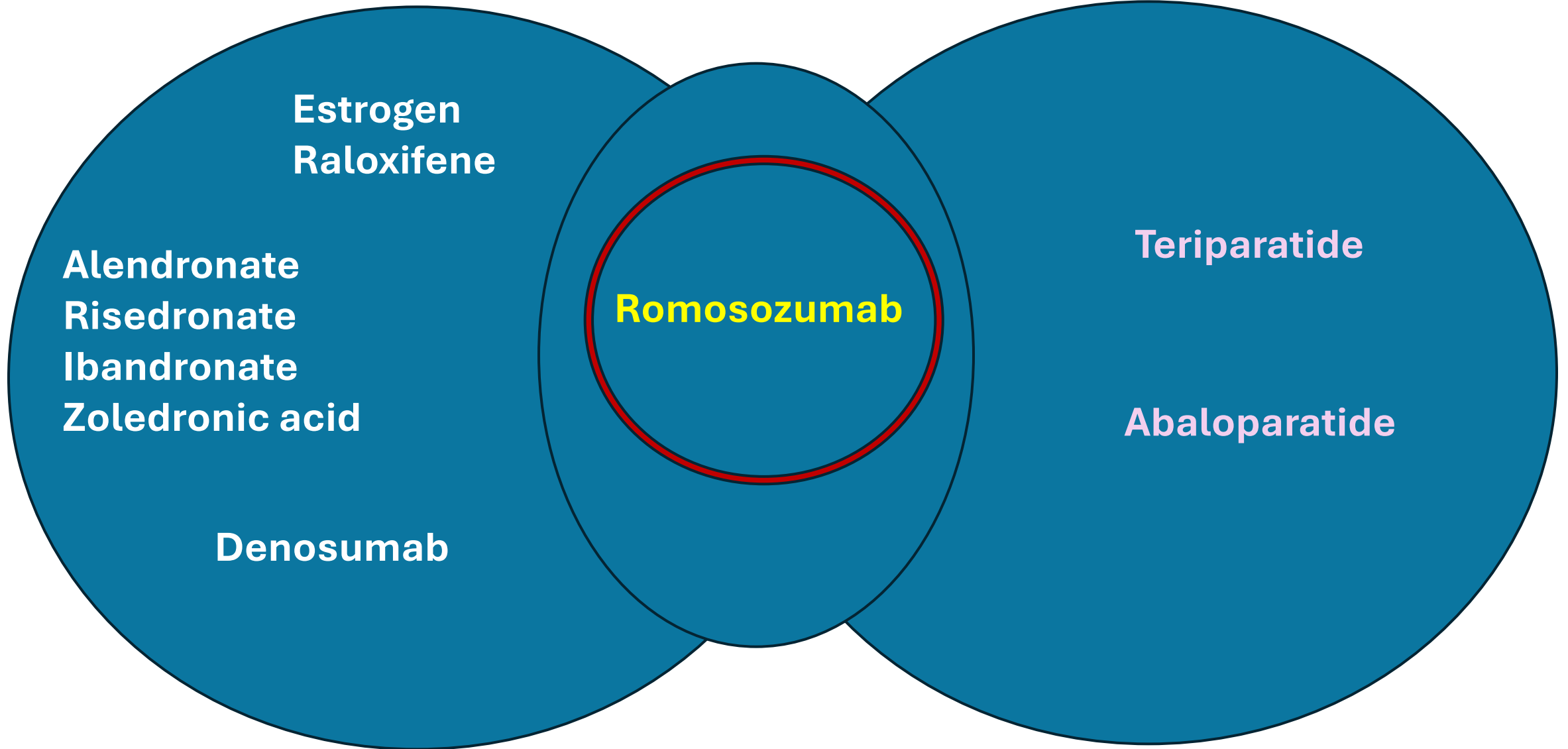
Alendronate
Risedronate
Ibandronate
Zoledronic acid

Denosumab

Romsozumab

Teriparatide

Abaloparatide



Romosozumab

Monoclonal
antibody

Binds and inhibits
sclerostin

Dual mechanisms
of action

- Builds bone!!!
- And decreases bone loss

Sclerostin and the Wnt Signaling Pathway

Osteoanabolic effects

✓ First 3 months

Antiresorptive effects

✓ Entire year of therapy

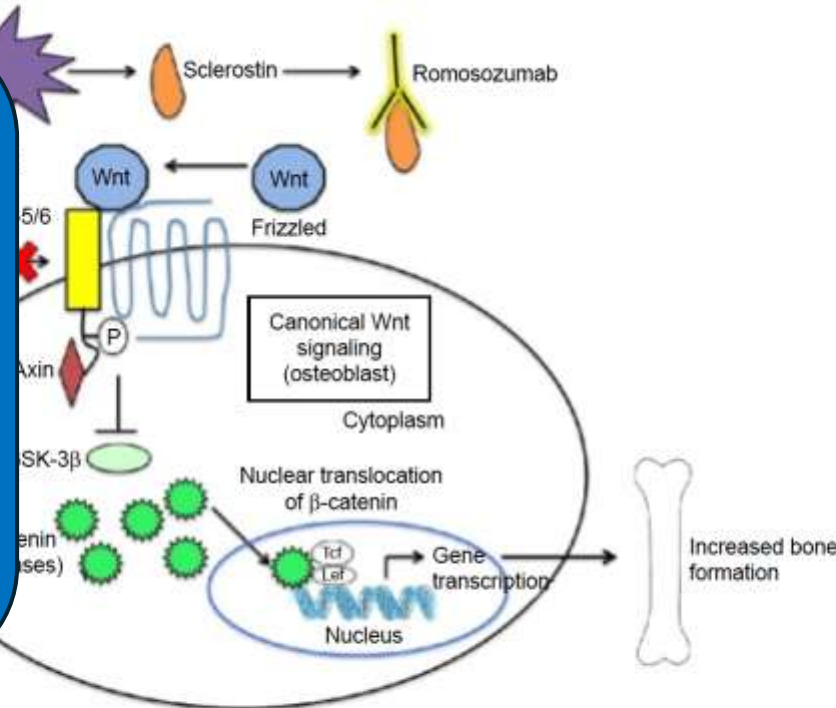


Figure 2 Mechanism of action of romosozumab.

Notes: Romosozumab is a human monoclonal antibody that binds sclerostin (an inhibitor of Wnt pathway signaling). When this monoclonal antibody binds to sclerostin, sclerostin cannot bind to the LRP-5 and LRP-6 receptors and is unable to exert its inhibitory effect. Wnt binds to LRP-5 or LRP-6 coreceptors and its receptor, leading to activation of the Wnt signaling pathway and bone formation. Copyright ©2015, Dove Medical Press. Shah AD, Shoback D, Lewinsohn D. Sclerostin inhibition: a novel therapeutic approach in the treatment of osteoporosis. *Int J Womens Health*. 2015;7:565–580.

Abbreviation: LRP, LDL-receptor-related protein.

Wnt pathway results in bone formation

Sclerostin inhibits the Wnt pathway

Romo = mAb to sclerostin

Increases bone formation

Osteoblast maturation and differentiation (anabolic)

Osteoclast inhibition through osteoprotegerin (OPG, antiresorptive)

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Romozumab or Alendronate for Fracture Prevention
in Women with Osteoporosis

Kenneth G. Saag, M.D., Jeffrey Petersen, M.D., Maria Luisa Brandi, M.D., Andrew C. Karaplis, M.D., Ph.D.,
Mattias Lorentzon, M.D., Ph.D., Thierry Thomas, M.D., Ph.D., Judy Maddox, D.O., Michelle Fan, Ph.D.,
Paul D. Meisner, Pharm.D., and Andreas Grauer, M.D.

ARCH
Trial

4093 postmenopausal women with OP and prior fragility fx

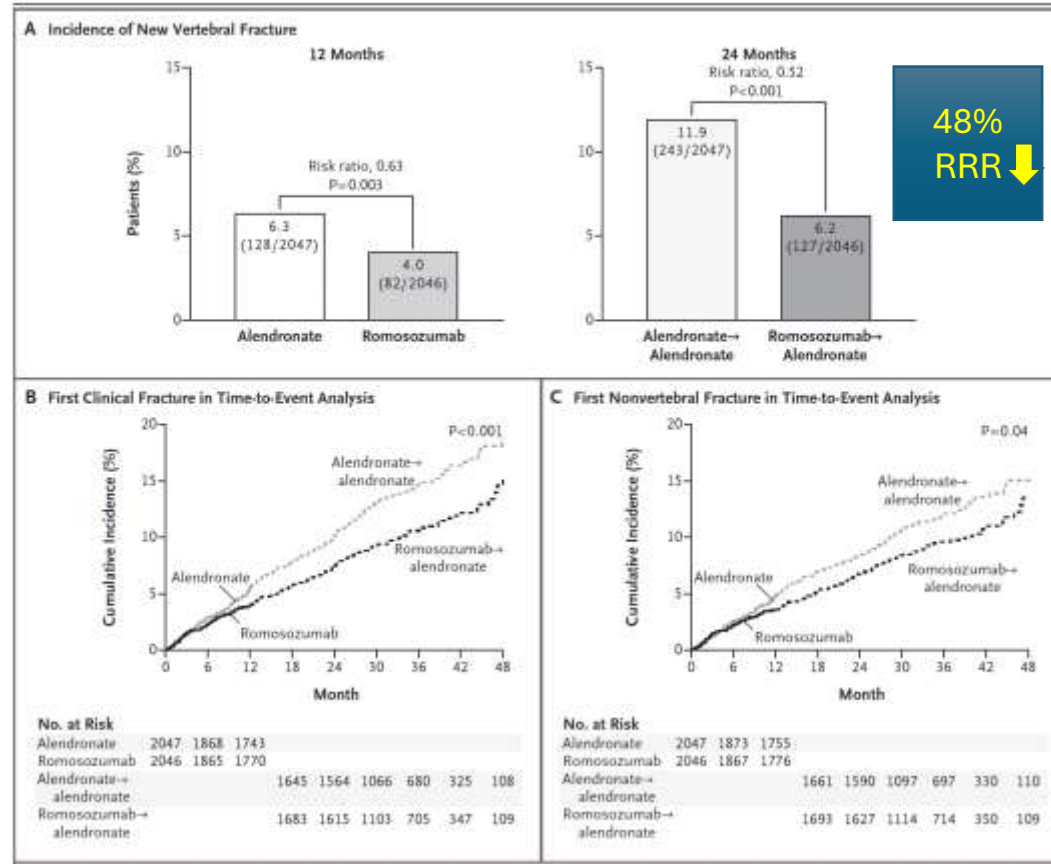
Romo vs. ALN x 12 mos

Then open label ALN x 12 mos

Primary endpoint of new vert fracture at 24 mos

Romo vs. ALN (12 mos) + ALN (12 mos)

ROMOSUZUMAB OR ALENDRONATE FOR FRACTURE PREVENTION



27%
RRR ↓

48%
RRR ↓



Romo --> ALN
ALN --> ALN

19%
RRR ↓

Hip fx 38%
RRR ↓

A Few Things to Know About Romo

Anabolic agents must be followed by antiresorptive treatment

- Prior studies of romosozumab in osteoporosis:
 - Reduced fracture risk compared to placebo (12-month study)
 - Leads to significant gains in BMD
 - More benefit when given prior to alendronate (vs. alendronate alone)
- **Black box warning** - increased risk of MI, stroke, and myocardial death

What about the Black Box Warning?

- Studies in over 11,000 women
- One of the studies
 - ~4000 postmenopausal women
 - Major CV event (heart attack, stroke, heart failure, revascularization procedure)
 - 2.5% who received romo
 - 1.9% who received alendronate
- Black box warning
 - Avoid prescribing romo to patients with MI, stroke, TIA in **past 12 months**
 - Consider prior ASCVD events
 - Consider significant risk factors
 - Shared decision-making



One Year of Romosozumab Followed by Two Years of Denosumab Maintains Fracture Risk Reductions: Results of the FRAME Extension Study

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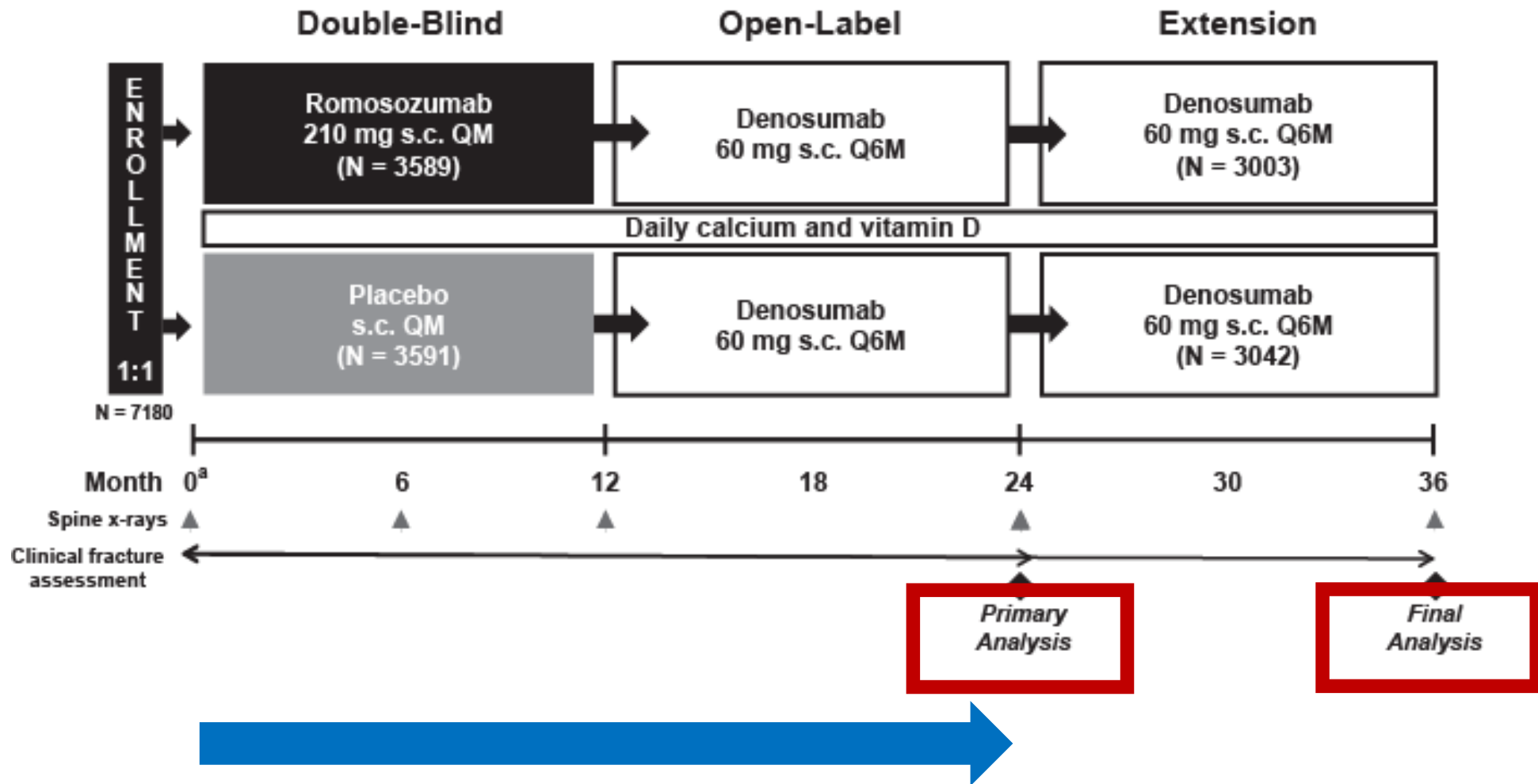
⁴Monash University, Melbourne, Australia

⁵McMaster University, Hamilton, ON, Canada

⁶Miyauchi Medical Center, Osaka, Japan

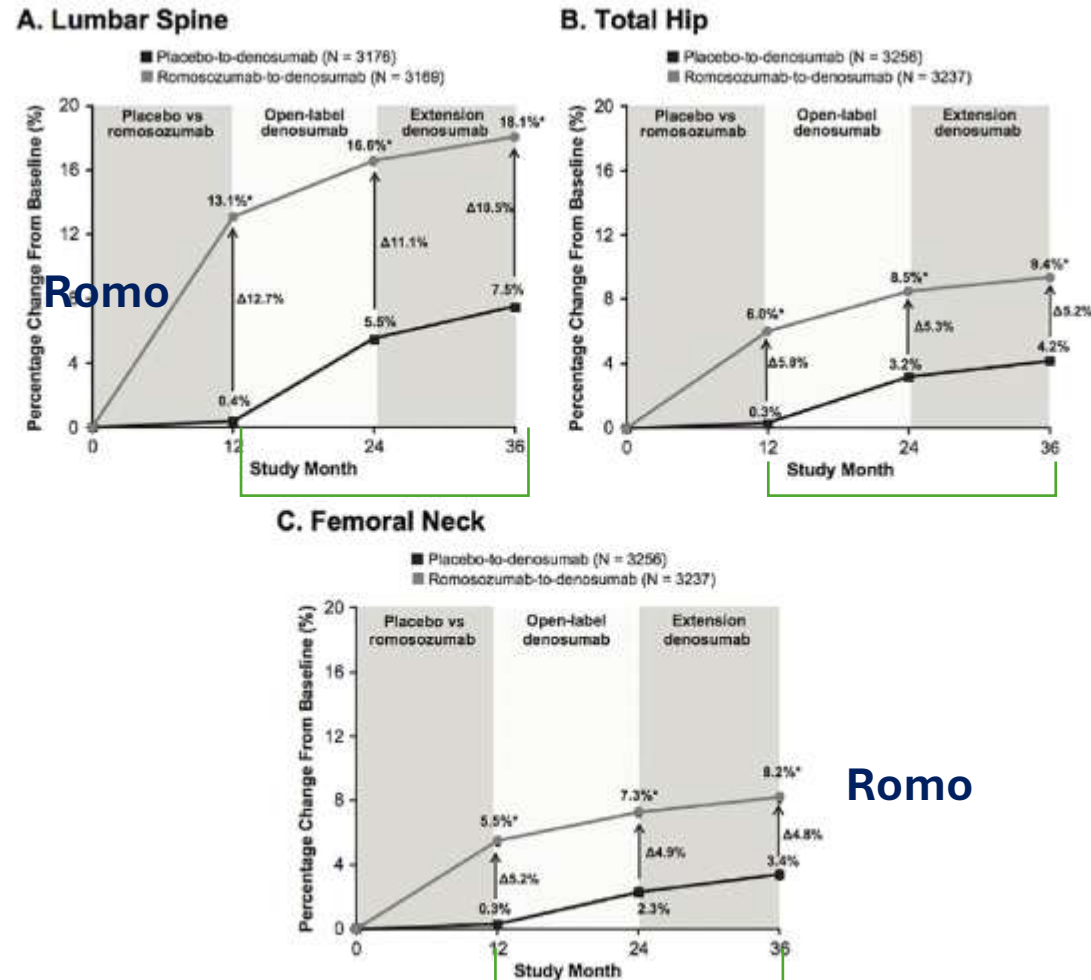
⁷University Hospitals Leuven, Leuven, Belgium

⁸UCB Pharma, Brussels, Belgium



**FRAME
Study**

FRAME Extension Study: BMD



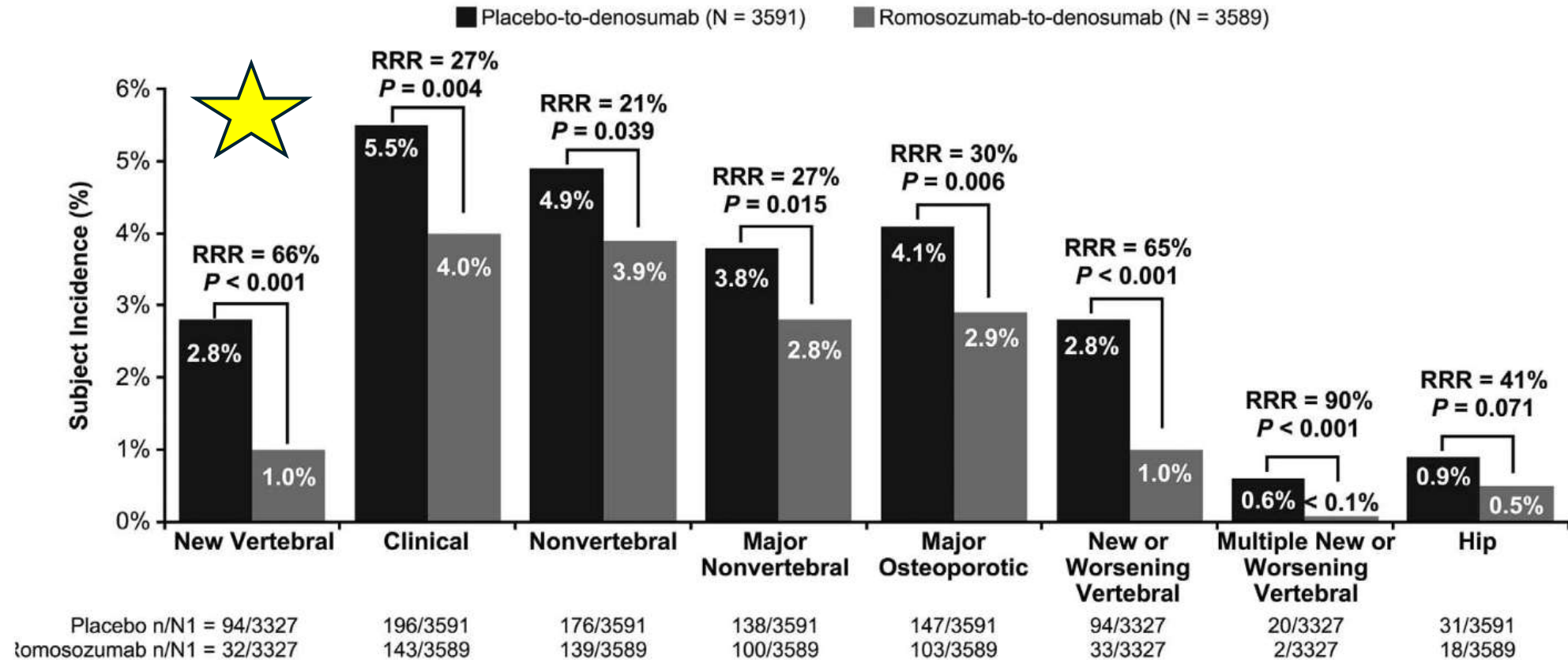
Romo + Denosumab

Romo

Fig. 3. Percentage change from baseline in BMD at the lumbar spine, total hip, and femoral neck at 36 months. Least-squares mean (95% CI) percentage changes in BMD at the lumbar spine (A), total hip (B), and femoral neck (C). Least squares mean percentage change from baseline in BMD and *p* values

FRAME Extension Study: Romo + Dmab

A. Key Fracture Endpoints Through 36 Months




FRAME Extension Study: Take-home Points

- Romo for 12 months led to rapid and significant increases in BMD
- Romo for 12 months followed by Dmab x 24 months is associated with decreased vertebral and clinical fracture risk
- The risk of fracture was lower in patients who received Romo followed by Dmab compared to Placebo followed by Dmab
- The relative risk reduction with Romo persisted throughout the 36 months
- Romo was well tolerated and was without increased risk of serious cardiovascular events or death compared to placebo
- Benefits of Romo + Dmab would be expected to decrease if not followed by another antiresorptive agent

Case 2

- 58 yo woman with psoriatic arthritis who is taking adalimumab
 - Has been doing well and presents for routine follow-up
 - History of breast cancer treated with lumpectomy, XRT
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- DXA scan is performed



	T-score
• Total lumbar	-3.5
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- Discussion of treatment options

Consider the role of
anabolic therapy

Case 2: Thoughts about Anabolic Therapy

- Window of opportunity
- No prior antiresorptive agent
- No history of MI, stroke, TIA
 - Low ASCVD risk profile
- History of
 - Bone malignancy
 - **Radiation therapy (XRT)**
 - Paget disease of bone
 - Unexplained elevation of PTH or alkaline phosphatase

 ✓ **Romosozumab**

✓ **Teriparatide**

✓ **Abaloparatide**

Bone Health Management: Shared Decision-making



- Romosozumab
 - 12 monthly SQ treatments
 - Follow anabolic therapy with antiresorptive agent
 - Plan for subsequent treatment with alendronate, zoledronic acid, or denosumab
 - Important to follow denosumab by an antiresorptive agent (7-8 months after last dmab dose)

Blunting of anabolic effect if antiresorptive agent is used prior to anabolic agent

Is a Shorter Course of Romo Possible?

Osteoanabolic effects

✓ First 3 months

Antiresorptive effects

✓ Entire year of therapy

3 months romo + 9 months denosumab

compared to

12 months romo

Is a Shorter Course of Romo Possible?

Mean age 69.6 years

High fracture risk

- ✓ T-score < -2.5
- ✓ Or prior fragility fx

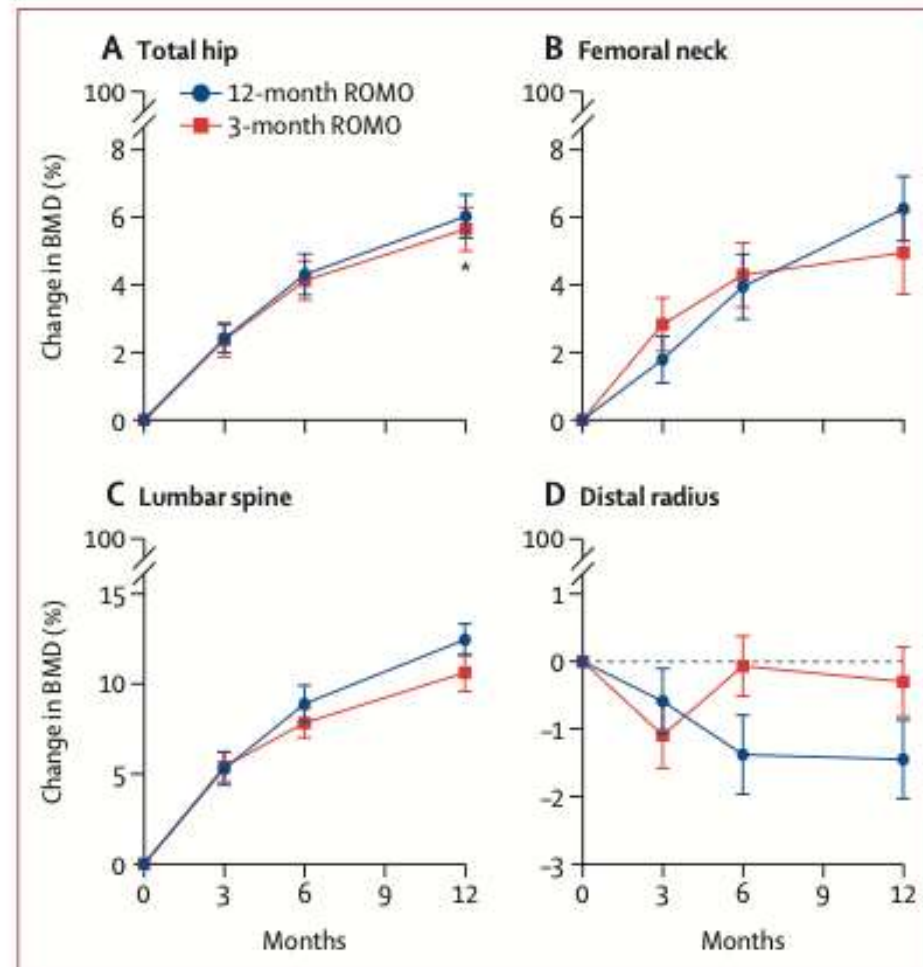


Figure 2: Change in BMD over the 12-month treatment period

Non-inferiority study

Primary endpoint
Change in total hip
BMD at 1 year

Take-home Points: Shorter Course of Romo

Osteoanabolic effects of romo are early and brief

3 months romo + 9 months denosumab non-inferior to 12 months romo

 Total hip BMD primary endpoint

- Similar increases between groups for BMD Spine, femoral neck, radius

Cost-effective approach

Enhance safety perception

- Potential to reduce cardiovascular risk

Improved medication access



Case 3

- 63 yo woman with osteopenia presents with right temporal headache, jaw claudication, scalp tenderness x 3 days.
- ESR 85, CRP 12 (<0.8)
- Prednisone 60 mg daily
- TA ultrasound with (+) halo sign
- Right TA biopsy c/w GCA



ACR 2022 GIOP Guidelines

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AMERICAN COLLEGE
of RHEUMATOLOGY
Empowering Rheumatology Professionals

2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

Mary Beth Humphrey,^{1*} Linda Russell,^{2*} Maria I. Danila,³  Howard A. Fink,⁴ Gordon Guyatt,⁵ Michael Cannon,⁶ Liron Caplan,⁷  Sara Gore,⁸ Jennifer Grossman,⁹ Karen E. Hansen,¹⁰ Nancy E. Lane,¹¹ Nina S. Ma,¹² Marina Magrey,¹³  Tim McAlindon,¹⁴ Angela Byun Robinson,¹⁵ Sumona Saha,¹⁰ Charles Womack,⁸ Basma Abdulhadi,³ Julia F. Charles,¹⁶ Jonathan T. L. Cheah,¹⁷ Sharon Chou,¹⁶ Itivrita Goyal,¹ Katherine Haseltine,² Lesley Jackson,³  Reza Mirza,⁵ Iram Moledina,³ Emma Punni,¹ Tim Rinden,¹⁸ Marat Turgunbaev,¹⁹ Katherine Wysham,²⁰  Amy S. Turner,¹⁹  and Stacey Uhl²¹

Key recommendations

**ASAP,
pred \geq 2.5 mg/d for
> 3 mos**

1. As soon as possible after initiation of ≥ 2.5 mg/day GC treatment for >3 months, screening for fracture risk in patients ≥ 40 years of age should be assessed by using FRAX and by performing BMD using dual-energy x-ray absorptiometry (DXA) with vertebral fracture assessment (VFA) testing or spinal x-rays. BMD with VFA testing or spinal x-ray is advised in patients <40 years, as FRAX is not validated in this population.
2. Adequate age-appropriate dietary and supplemental intake of calcium and vitamin D, weight-bearing exercise, and avoidance of smoking and excessive alcohol intake is encouraged for all patients receiving GCs.
3. All adult patients with medium, high, or very high fracture risk should be offered OP therapy.
4. Oral bisphosphonates (BP) are strongly recommended over no treatment in high or very high fracture risk adults.
5. For adults with very high fracture risk, anabolic agents (parathyroid hormone [PTH] and PTH-related protein

[PTHrP]) are conditionally recommended over antiresorptive agents (BP or denosumab [DEN]).

6. In adults ≥ 40 years of age at high risk of fracture, DEN or PTH/PTHrP are conditionally recommended over BP.
7. In adults at moderate risk of fracture, oral or intravenous (IV) BP, DEN, and PTH/PTHrP are conditionally recommended.
8. Include in decision-making that sequential OP treatment is recommended to prevent rebound bone loss and vertebral fractures after discontinuation of DEN, romosozumab, and PTH/PTHrP.

✓ **Anabolic prior to antiresorptive to avoid blunted effect**

✓ **Denosumab shows nice BMD increases**



Strong recommendation with low certainty of evidence

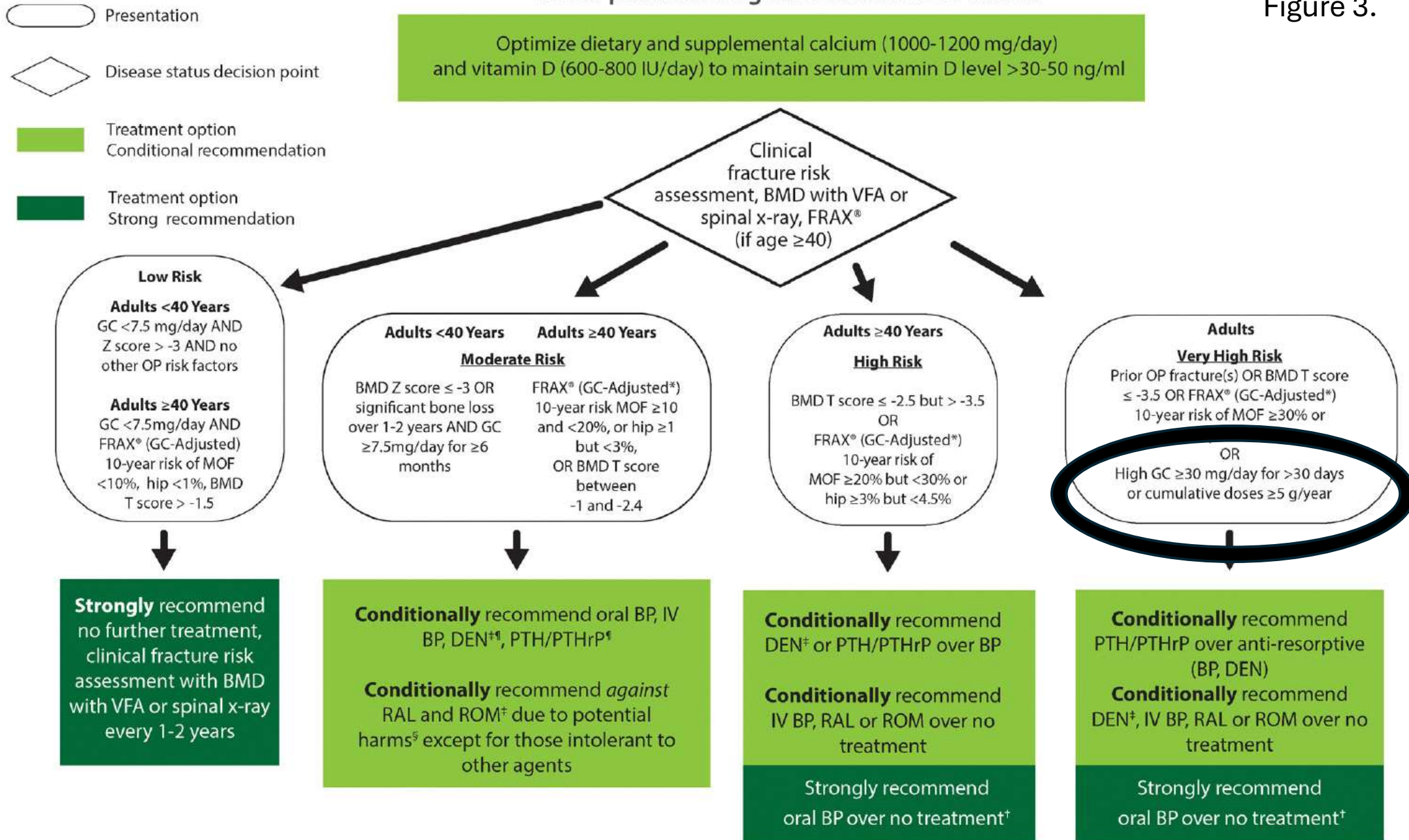
Initial assessment within 6 mos of GC initiation

Table 1. Definitions of selected terms used in the recommendations and upgraded position statements for GIOP*

Term	Adults ≥40 years of age	Adults <40 years of age
MOF	Nontraumatic or pathological fractures of the spine, hip, wrist, or humerus	Nontraumatic or pathological fractures of the spine, hip, wrist, or humerus
Clinical fracture risk assessment	History of GC use, evaluation for falls, fractures, frailty, secondary causes of OP, FRAX with GC adjustment, BMD with VFA or spinal x-ray	History of GC use, evaluation for falls, fractures, frailty, secondary causes of OP, BMD with VFA or spinal x-ray (FRAX not validated at age <40 years)
Follow-up risk assessment during GC treatment	BMD with VFA or spinal x-ray every 1–2 years during OP therapy; BMD with VFA or spinal x-ray every 1–2 years after OP therapy is discontinued	BMD with VFA or spinal x-ray every 1–2 years during treatment; BMD with VFA or spinal x-ray every 1–2 years after OP therapy is discontinued
FRAX GC correction	If GC dose is >7.5 mg/day, multiply the 10-year risk of MOF by 1.15 and the hip fracture risk by 1.2†	Not applicable as FRAX is not validated in this age group
Very high fracture risk	Prior OP fracture(s) OR BMD <i>t</i> -score ≤−3.5 OR FRAX (GC Adjusted) 10-year risk of MOF ≥30% or hip ≥4.5% OR high GC ≥30 mg/day for >30 days OR cumulative doses ≥5 g/y	Prior fracture(s) OR GC ≥30 mg/day OR cumulative ≥5 g/y
High fracture risk	BMD <i>t</i> -score ≤−2.5 but >−3.5 OR FRAX (GC Adjusted) 10-year risk of MOF ≥20% but <30% or hip ≥3% but <4.5%	–
Moderate fracture risk	FRAX (GC-Adjusted) 10-year risk of MOF ≥10 and <20%, hip >1 and <3% OR BMD <i>t</i> -score between −1 and −2.4	Continuing GC treatment ≥7.5 mg/day for ≥6 months AND BMD <i>z</i> -score < −3 OR significant BMD loss (more than the least significant change of DXA)
Low fracture risk	FRAX (GC-Adjusted) 10-year risk of MOF <10%, hip <1%, BMD >−1.0	None of the above risk factors other than GC treatment

Initial pharmacological treatment for adults

Figure 3.

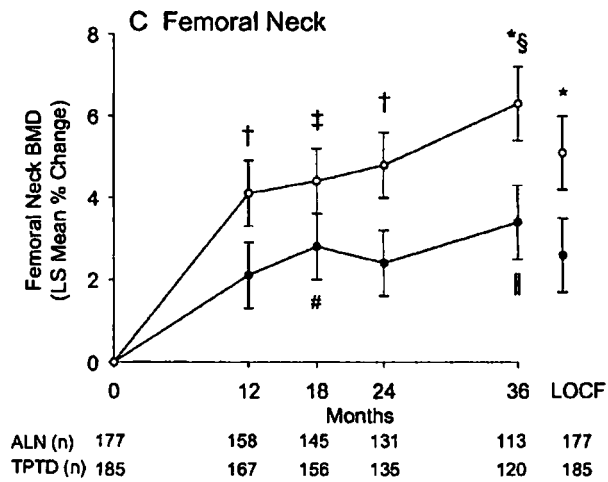
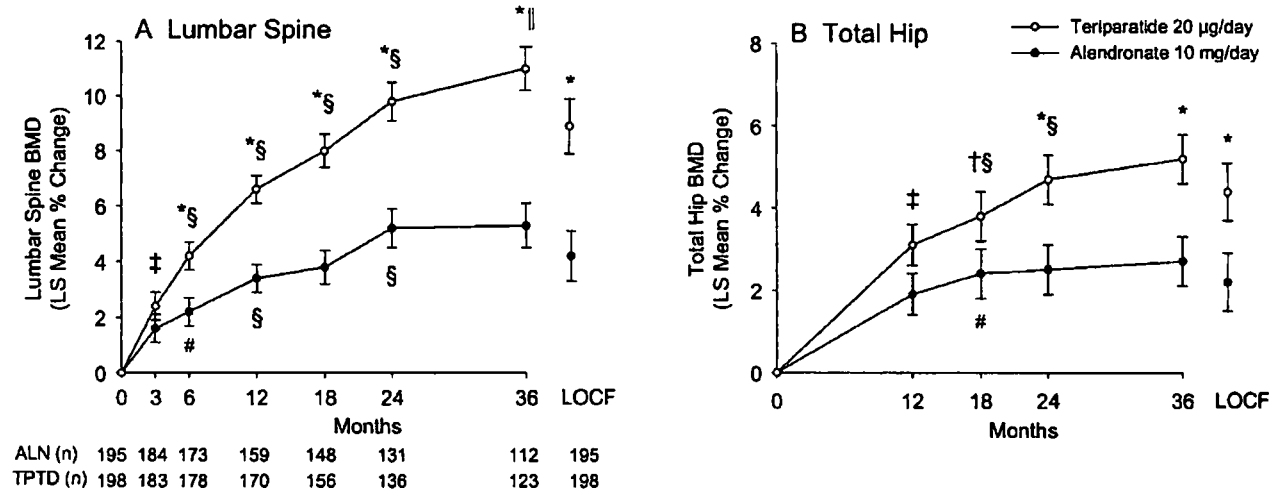


Teriparatide vs. Alendronate

- ❖ 18-month primary trial with 18-month extension (36 months total)
- ❖ 428 subjects
 - ❖ Mean prednisone dose 7.5 mg (\geq 3 months)
- ❖ TPD 20 ug daily vs. Alendronate 10 mg daily



Bone Mineral Density Changes over 36 months with Teriparatide vs. Alendronate



Incident Vertebral and Non-vertebral Fractures in Subjects with Glucocorticoid-Induced Osteoporosis

Fracture type	Subjects taking alendronate (n = 214)	Subjects taking teriparatide (n = 214)	P
≥1 radiographic vertebral†	13 (7.7)	3 (1.7)	0.007
≥1 clinical vertebral‡	4 (2.4)	0	0.037
≥1 nonvertebral	15 (7.0)	18 (7.5)	0.845
≥1 nonvertebral fragility	5 (2.3)	9 (4.2)	0.256

* Values are the number (%).

† Subjects with baseline and postbaseline spinal radiographs (n = 169 subjects in the alendronate group and 173 subjects in the teriparatide group).

‡ A clinical vertebral fracture (assessed in 169 subjects in the alendronate group and 173 subjects in the teriparatide group) was a new radiographically confirmed fracture that was associated with symptoms such as back pain.

Most vertebral fractures occurred in first 18 months (both groups)

BMD spine continued to significantly increase 24-36 months in TPTD group



Case 3

Very high fracture risk with
GiACTA prednisone taper

Conditional recommendation

- ❖ PTH analog
- ❖ Denosumab
- ❖ IV bisphosphonate, raloxifene, romo

Strong recommendation

Oral bisphosphonate over no therapy



When initiating therapy

Discuss benefits

Why anabolic as the first therapy?

Discuss adverse effects & risks

Delineate planned duration of treatment course

Take-home Points

Build bone first, then maintain bone

Blunting of anabolic effect if antiresorptive agent is first

All anabolic agents should be followed by antiresorptive agents to maintain the gains

PTH analog agents no longer have a black box warning

- Safe to use for more than 2 years in a patient's lifetime

Be aware of the ASCVD risk factor profile when choosing romo
(Black Box Warning)

In patients at very high fracture risk, consider anabolic therapy as the first choice

In patients taking glucocorticoids with very high fracture risk, consider teriparatide as first choice

Thank you!

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