FACULTAD DE MEDICINA
PONTIFICIA UNIVERSIDAD
CATÓLICA DE CHILE

“Futuro de las Terapias de la Osteoporosis: Romosozumab”

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Depto. Endocrino UC

Sin conflictos de interés para la presente charla

Mujer 78 años

En seguimiento por osteoporosis de muy alto riesgo de fractura.

Antecedentes de múltiples esquemas terapéuticos.

Fracturas previas: Fractura vertebral clínica D12 (2002).

Antecedentes personales:

- Menopausia: 56 años
- Niega otras enfermedades relevantes.
- Vitamina D
- Calcio: 500mg citrato de calcio + 1000mg calcio con alimentación.
- Actividad Física: Solo caminatas 2500 pasos día.

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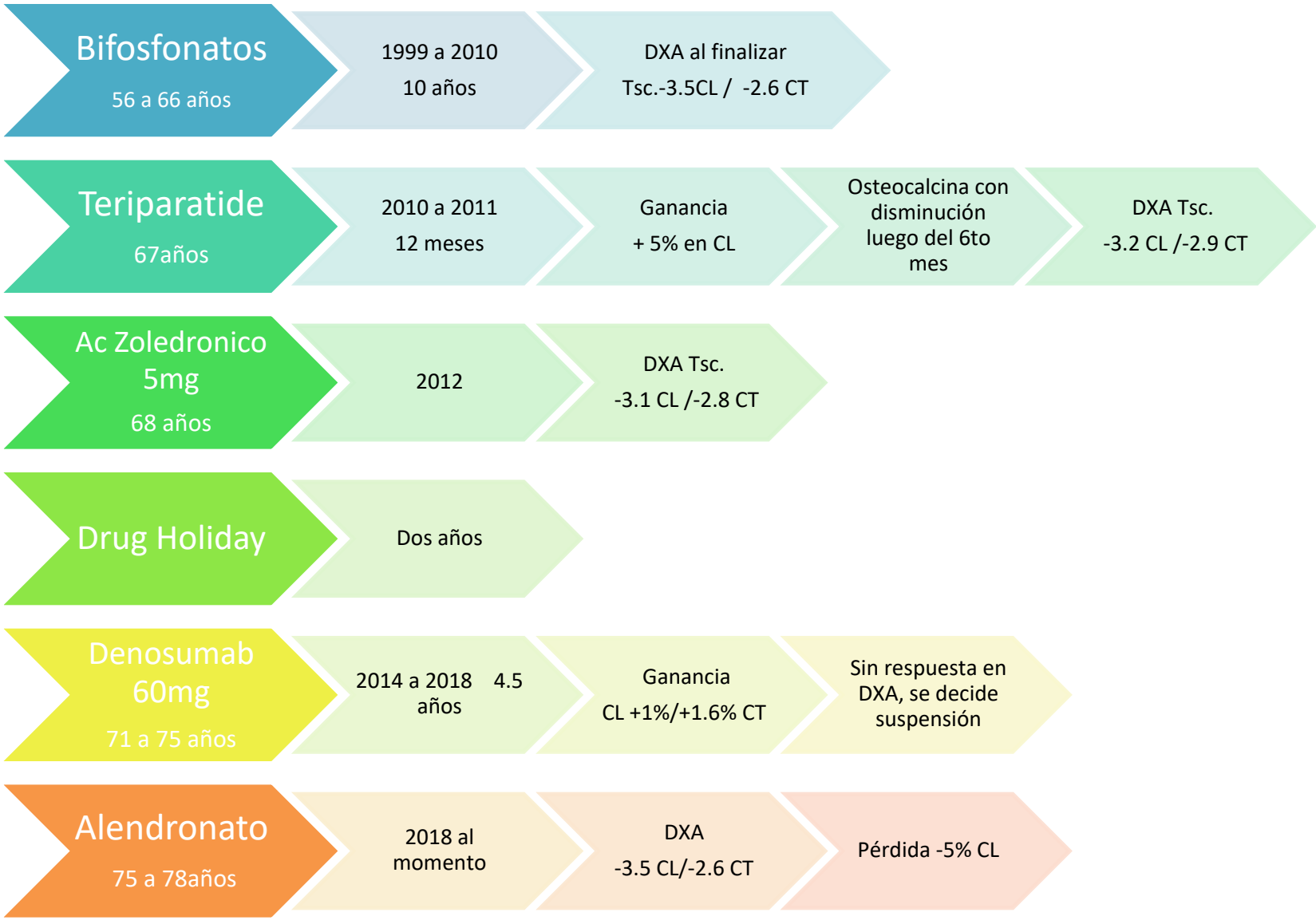
METABÓLICAS

Historia de Tratamiento



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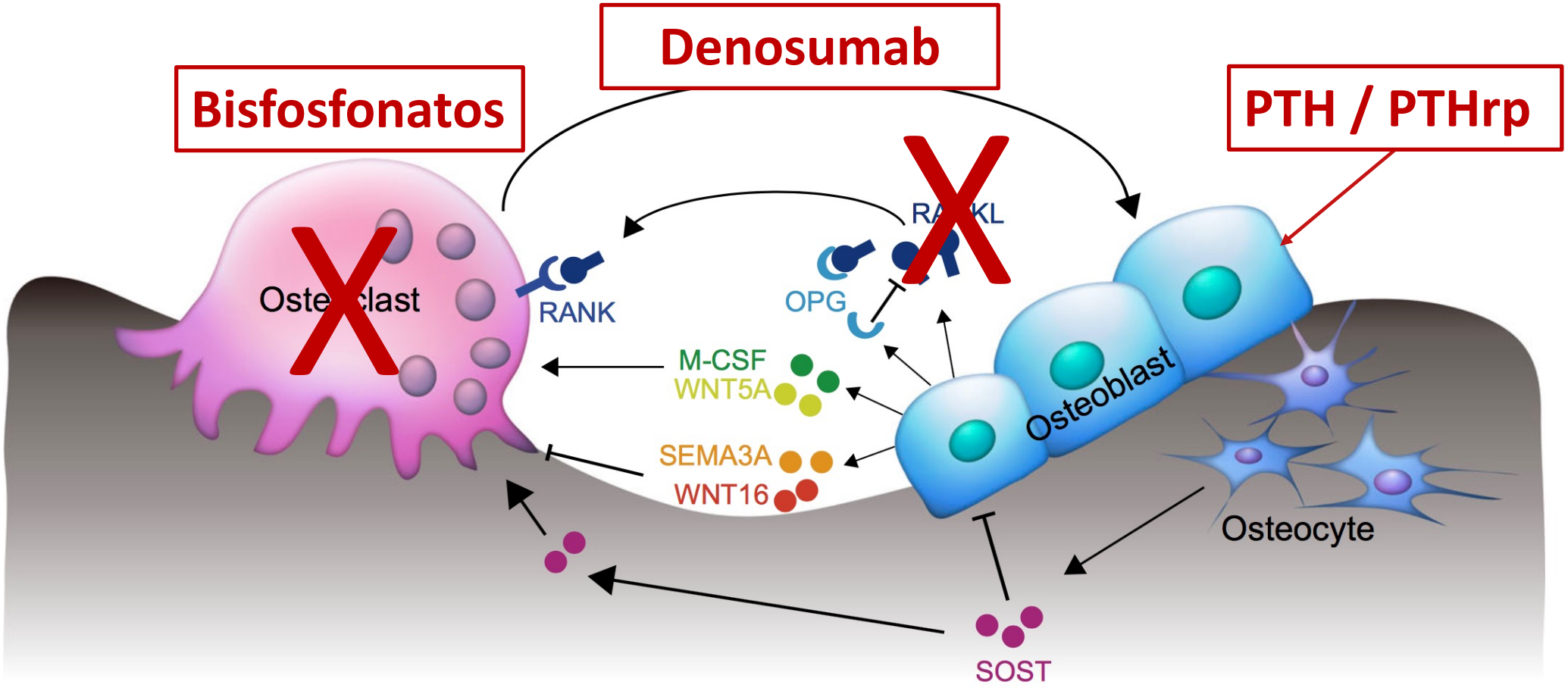

Han. Nature / Bone Research. 2018

- En febrero 2021, a raíz de dolor intenso lumbar le realizaron estudios por imágenes donde se evidencia fractura vertebral L2. Sin traumatismo previo (solo su marido le realizo un masaje fuerte)

- 22/9/21 Estudio secundario normal– Ca 9.1 P 3.6 Mg 2.1 TSH 3.13 T4 6.7 PTH 42.3 Vit D 33.4 CTX 381 OC 35.7

DXA	L3-L4	CFI	CT
Sep/2021	0.722 **-3.9** -1.7	0.686 -2.5 -0.3	0.674 **-2.7** -0.7

T153cm
P52kg

Se decide iniciar Romosozumab 210 mg sc mensual

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Evolución

LAB	Ca mg/d	P mg/dl	CTX pg/mL	OC ng/mL	FAO ug/L	VD ng/mL	PTH pg/mL	Indicación
BASAL	9.1	3.6	381	35.7		33.4	42.3	VD2 20g/s
30 días	8.4	3.8	313	67.4	23.3	35.5	48.2	2 comp Calcio
12 meses	8.9	3.4	197	30	11	38.1	88 (85)	

DXA	L3L4	CFI	CT
BASAL	0.722 **-3.9** -1.7	0.686 -2.5 -0.3	0.674 **-2.7** -0.7
12 meses	0.907 -2.5 -0.3	0.672 -2.6 -0.4	0.684 -2.6 -0.6

+ 25%CL

Al finalizar los 12 meses, se indica continuar con Denosumab 60mg

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Temario

- **Romosozumab:**
  - Mecanismo de acción
  - Beneficios en fracturas
  - Eventos adversos
  - Secuencia de tratamiento
  - Indicaciones según guías clínicas

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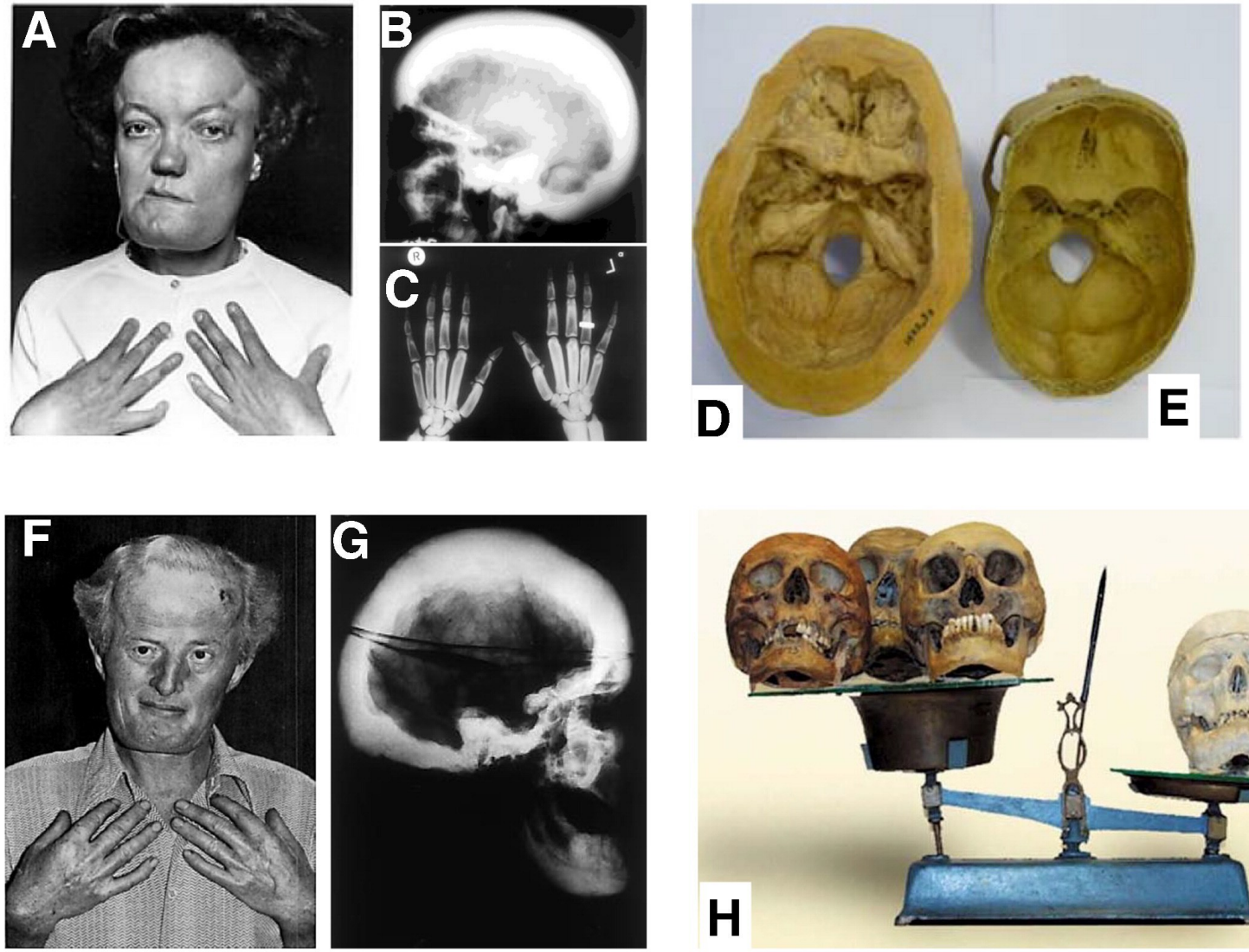
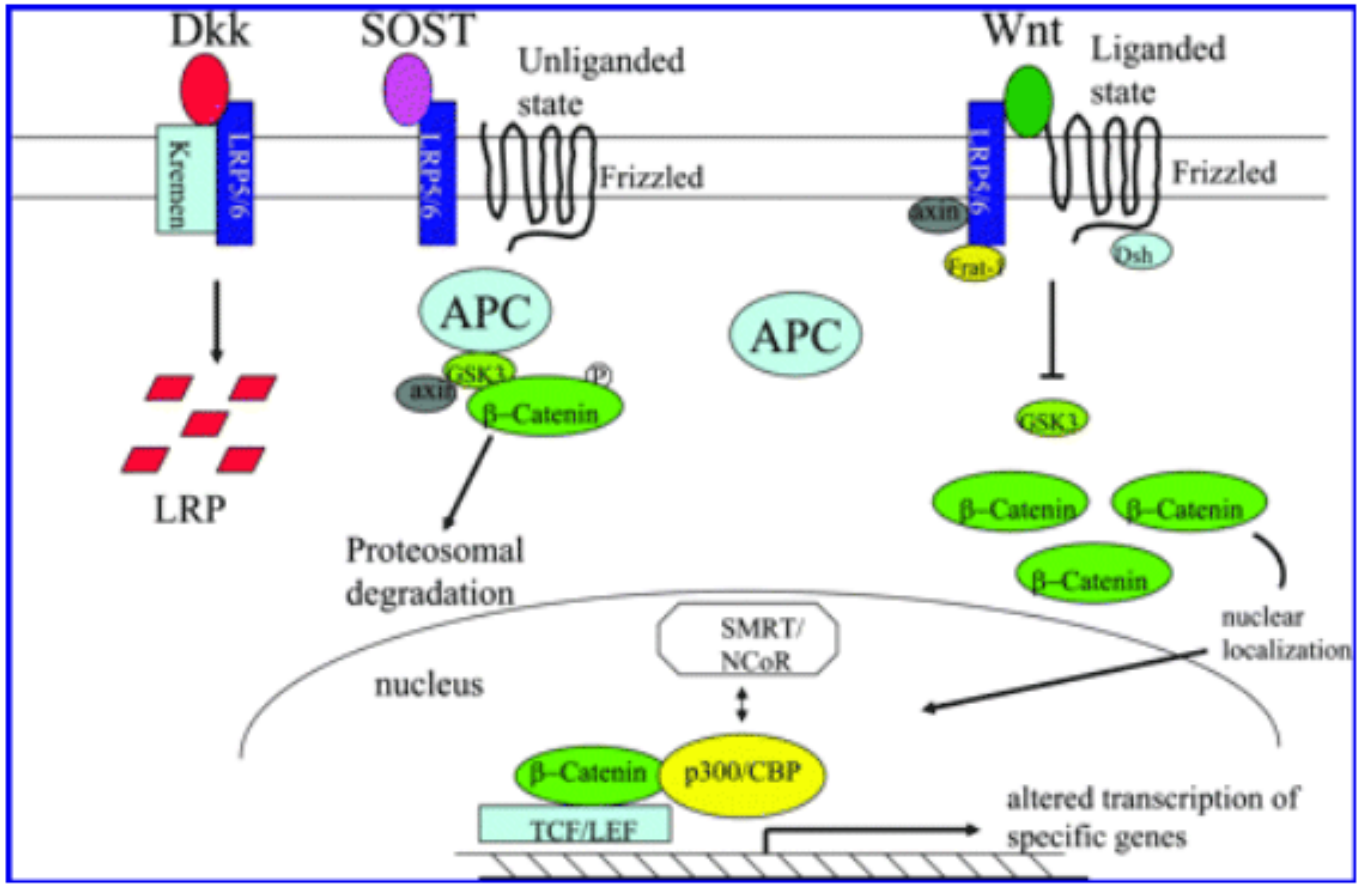
Esclerosteosis / Enfermedad de Van Buchem



Metabolism - Clinical and Experimental 2018 8038-47DOI: (10.1016/j.metabol.2017.10.005)

Vía Wnt

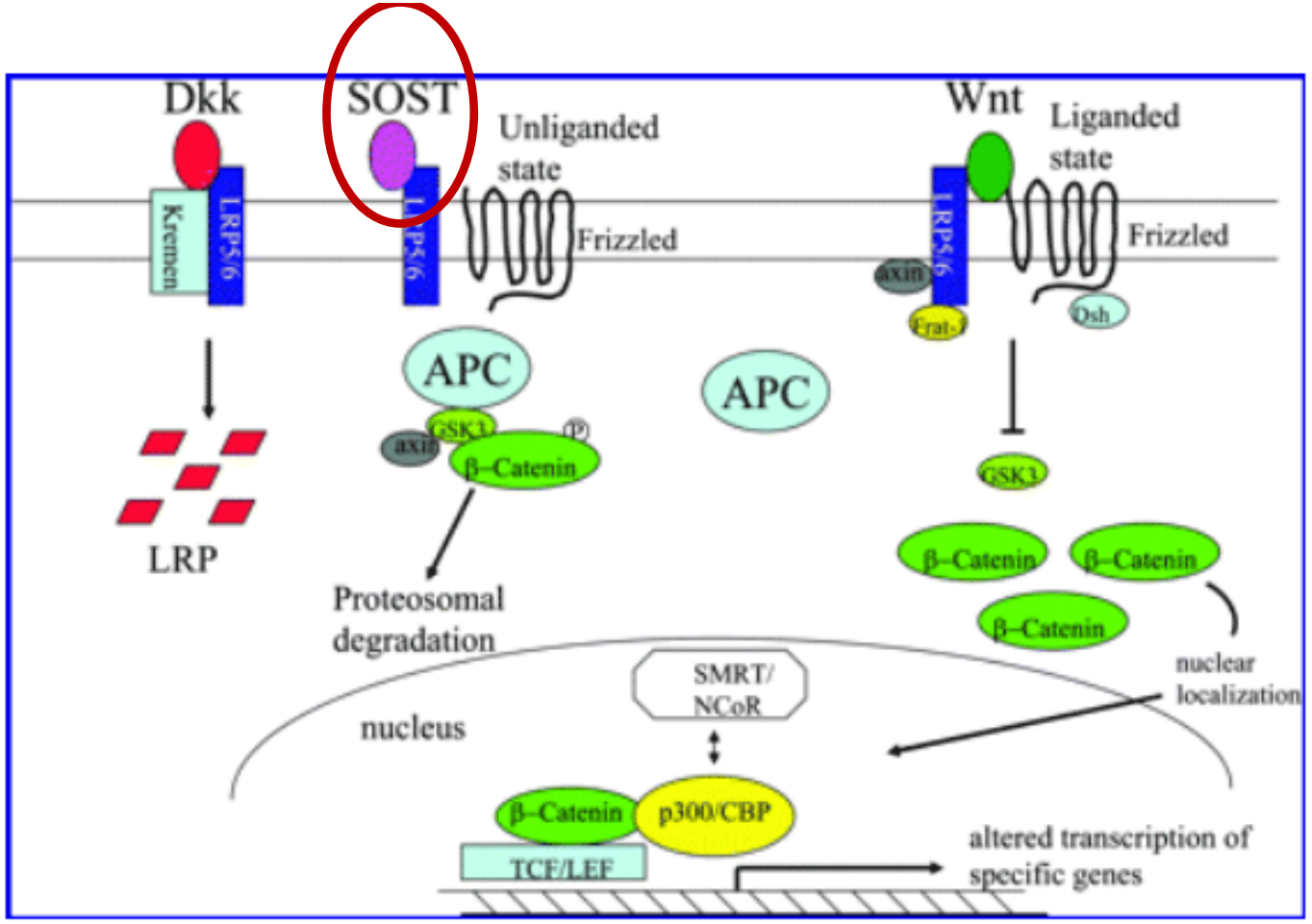


- **Via Wnt activada:**
  - Aumenta maduración y activación osteoblastos
  - Disminuye maduración y activación osteoclastos por aumento de OPG.

Modificado de Raisz. JCI. 2005

Krishnan. JCI. 2006

Vía Wnt

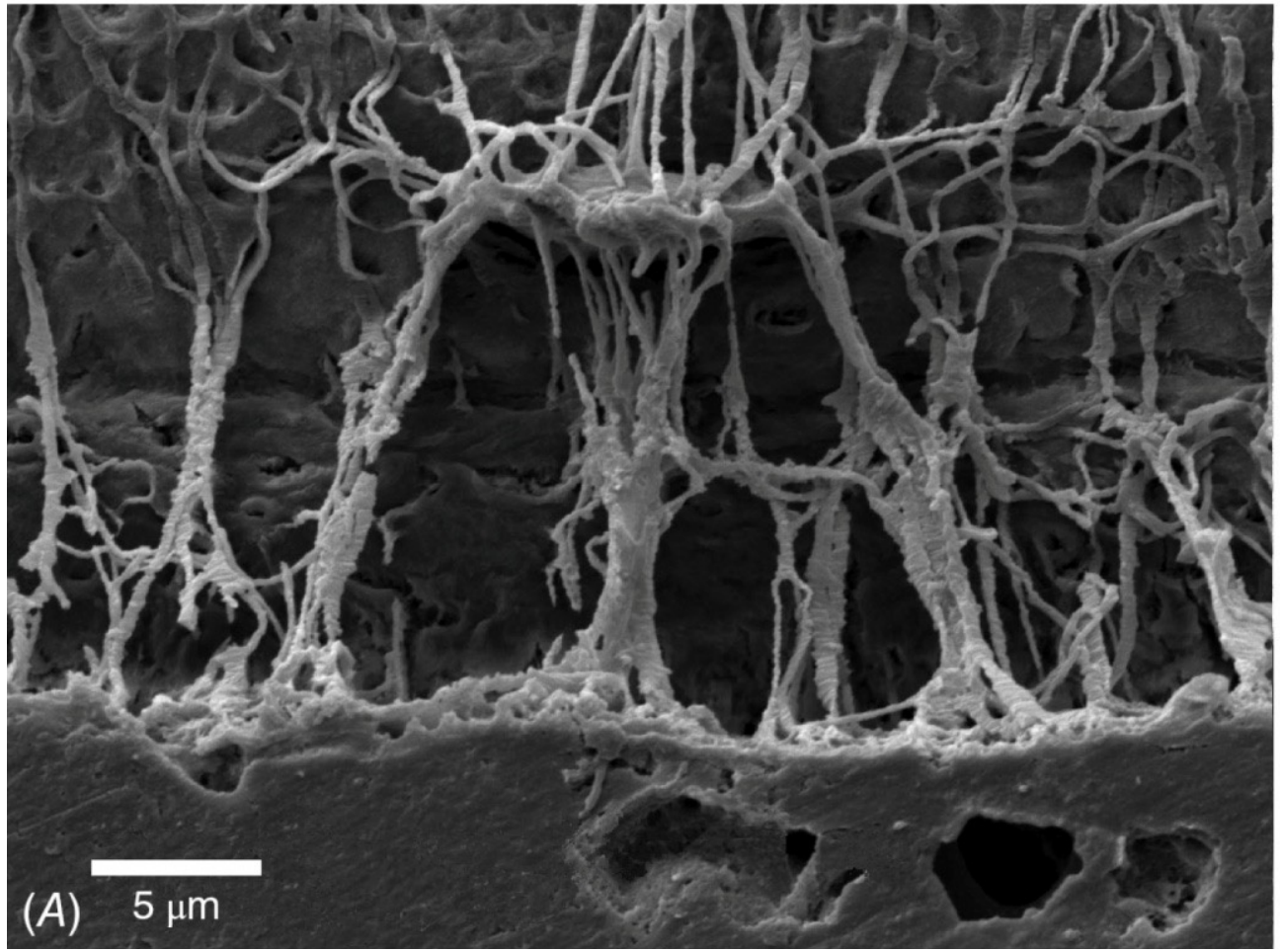


- **Esclerostina (SOST)**
  - Inhibe activación vía WNT
  - Disminuye maduración y activación osteoblastos
  - Aumenta maduración y activación osteoclastos por disminución OPG.

Modificado de Raisz. JCI. 2005

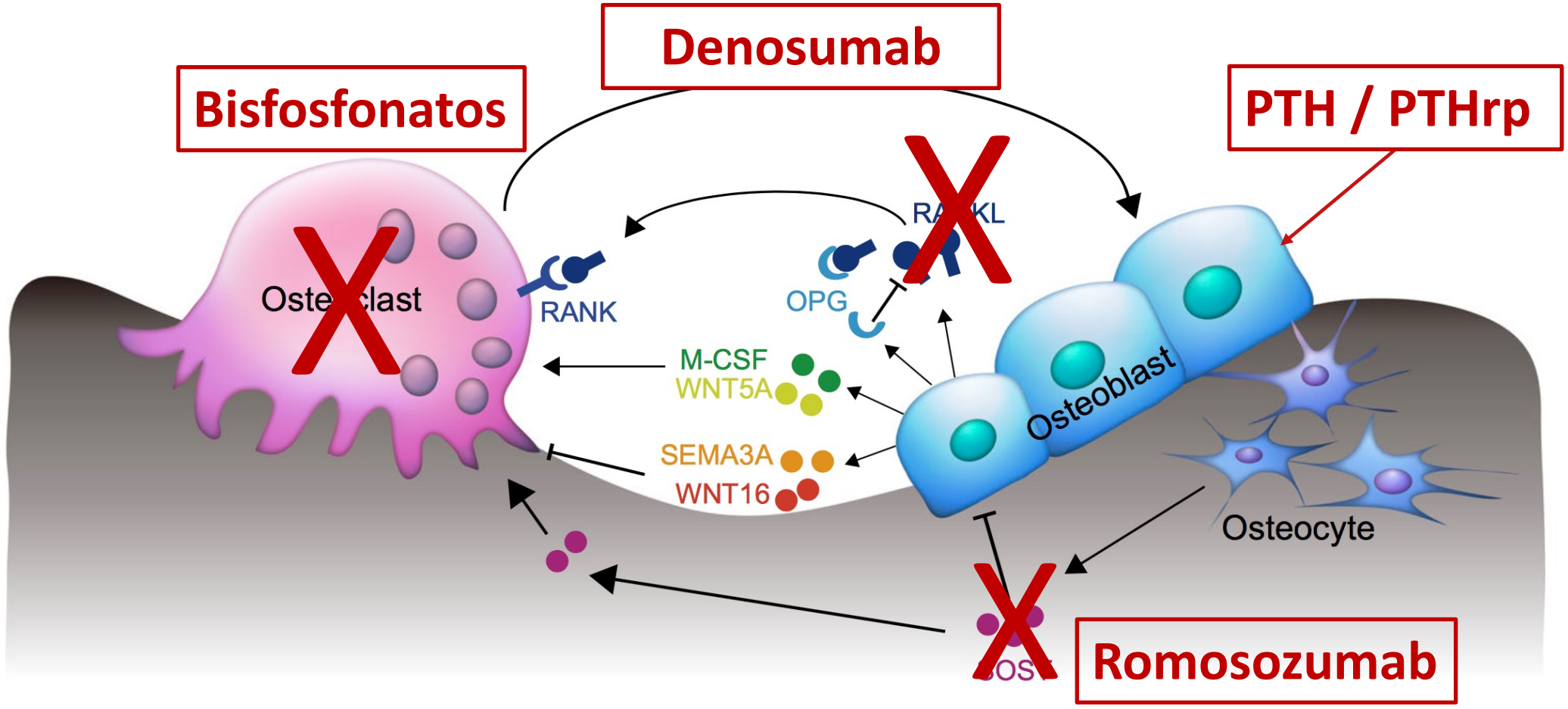
Krishnan. JCI. 2006

Osteocito

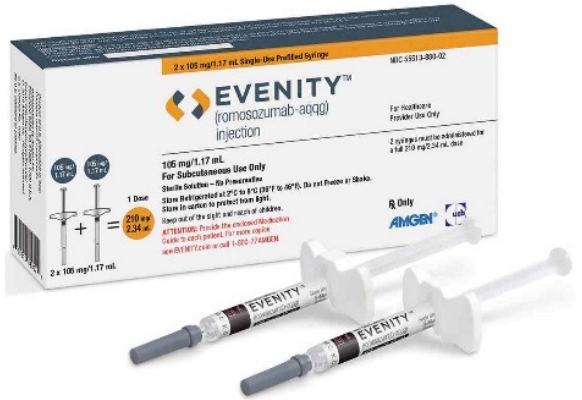


- **Osteoblastos maduros incluídos en matriz ósea**
- **Mecanoreceptores**
- **Al aumentar carga mecánica secretan menos esclerostina, con mayor activación Wnt.**

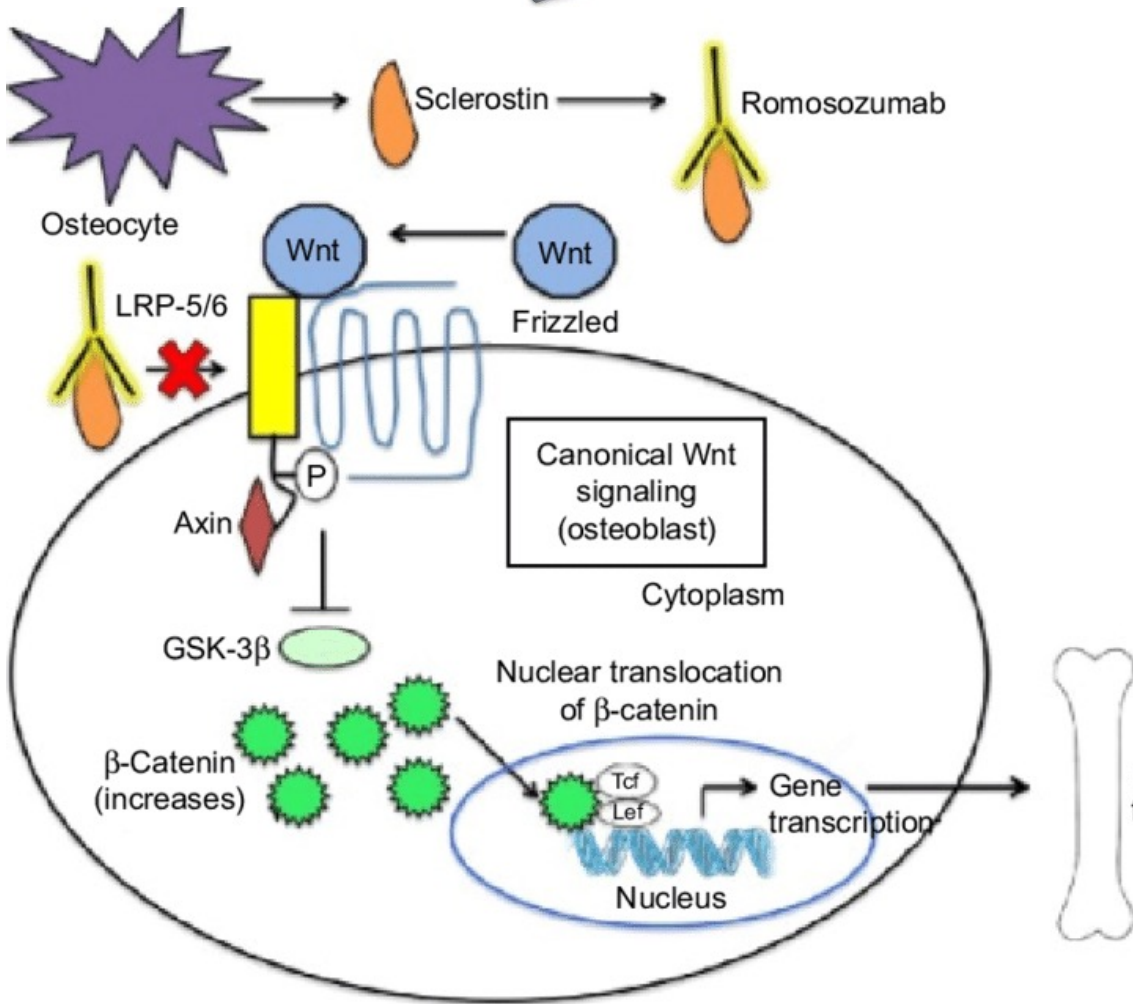
Primer on Bone Diseases. 9th edition



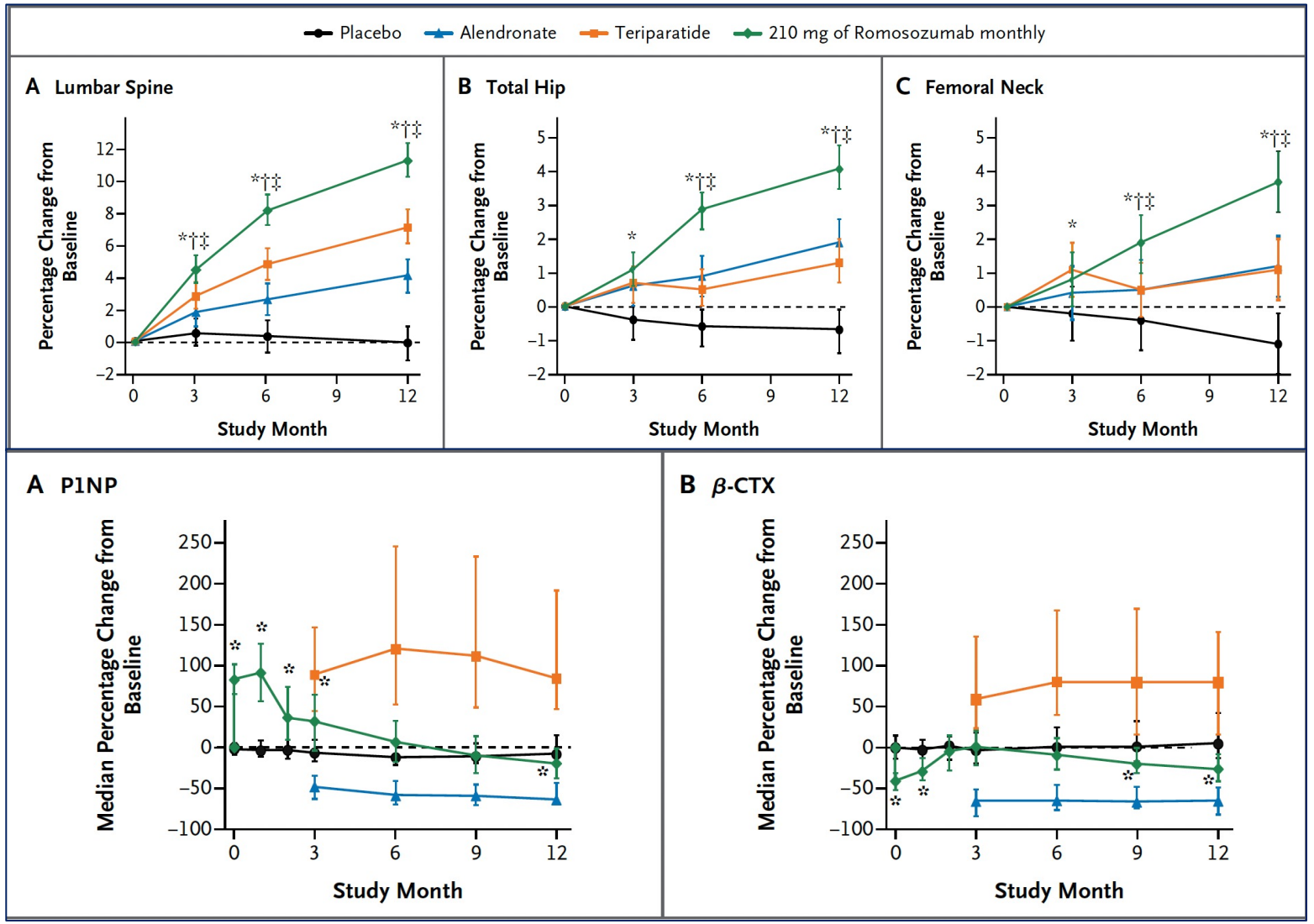
Han. Nature / Bone Research. 2018



- **Romosozumab:**
  - Anticuerpo monoclonal IgG antiesclerostina.
  - Wnt ubicua. SOST especifica
  - Aprobado por la FDA en 2019.
  - Dos inyecciones de 105 mg subcutánea c/u
  - El tratamiento limitado a 1 año.
  - Sin excreción renal
  - Catabolismo intracelular



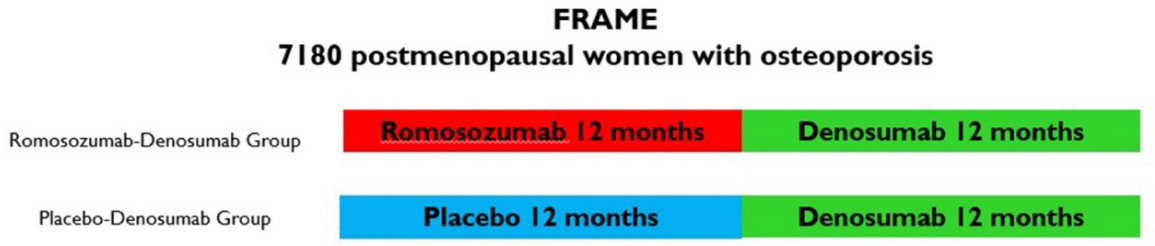
Romosozumab in Postmenopausal Women with Low Bone Mineral Density

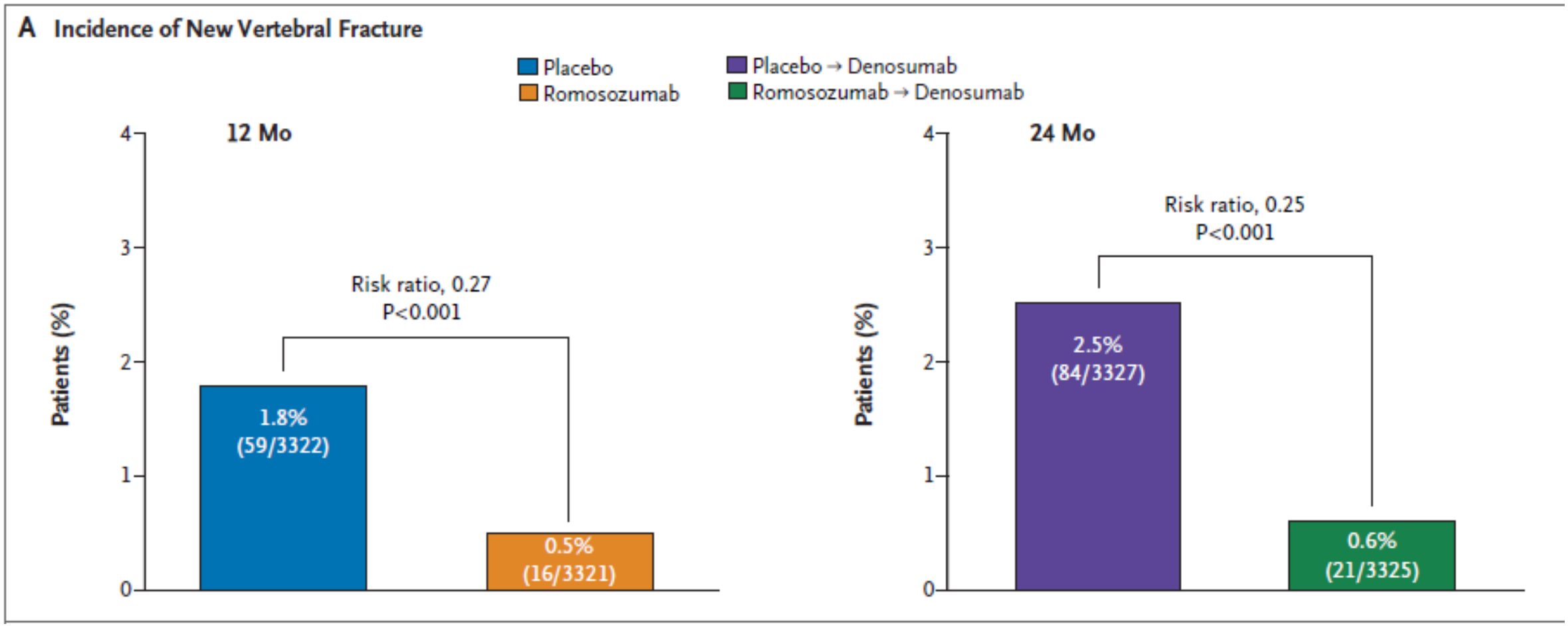


McClung et al. NEJM 370;5 : 2014

Romosozumab Treatment in Postmenopausal Women with Osteoporosis

F. Cosman, D.B. Crittenden, J.D. Adachi, N. Binkley, E. Czerwinski, S. Ferrari, L.C. Hofbauer, E. Lau, E.M. Lewiecki, A. Miyauchi, C.A.F. Zerbini, C.E. Milmont, L. Chen, J. Maddox, P.D. Meisner, C. Libanati, and A. Grauer





- RRR 36% fx clínicas (FV sintomaticas + no vertebrales)
- Protección a los 6 meses

NEJM, 2016, 375(16)

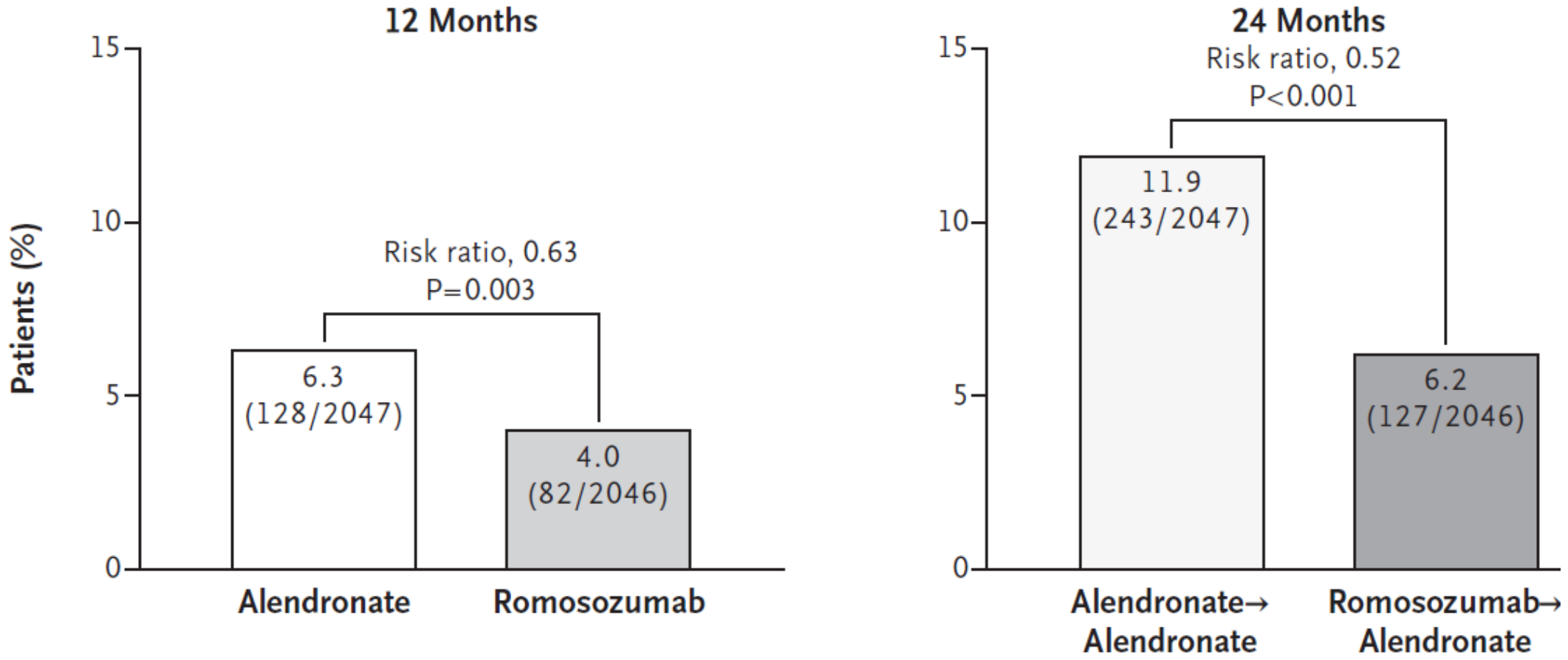
Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis

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

4093 postmenopausal women with osteoporosis and fragility fracture

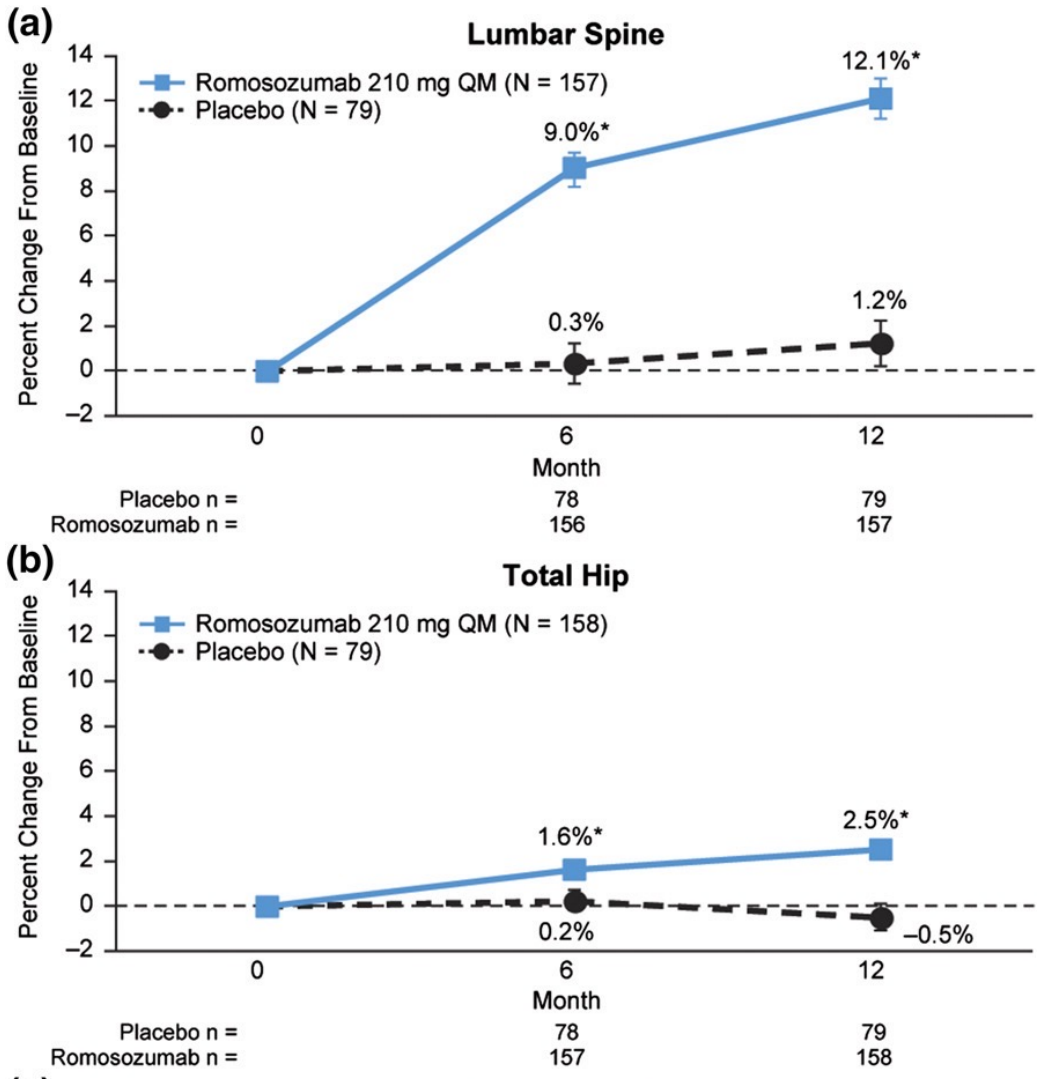
A Incidence of New Vertebral Fracture



N Engl J Med. 2017;377 (15):1417–1427.

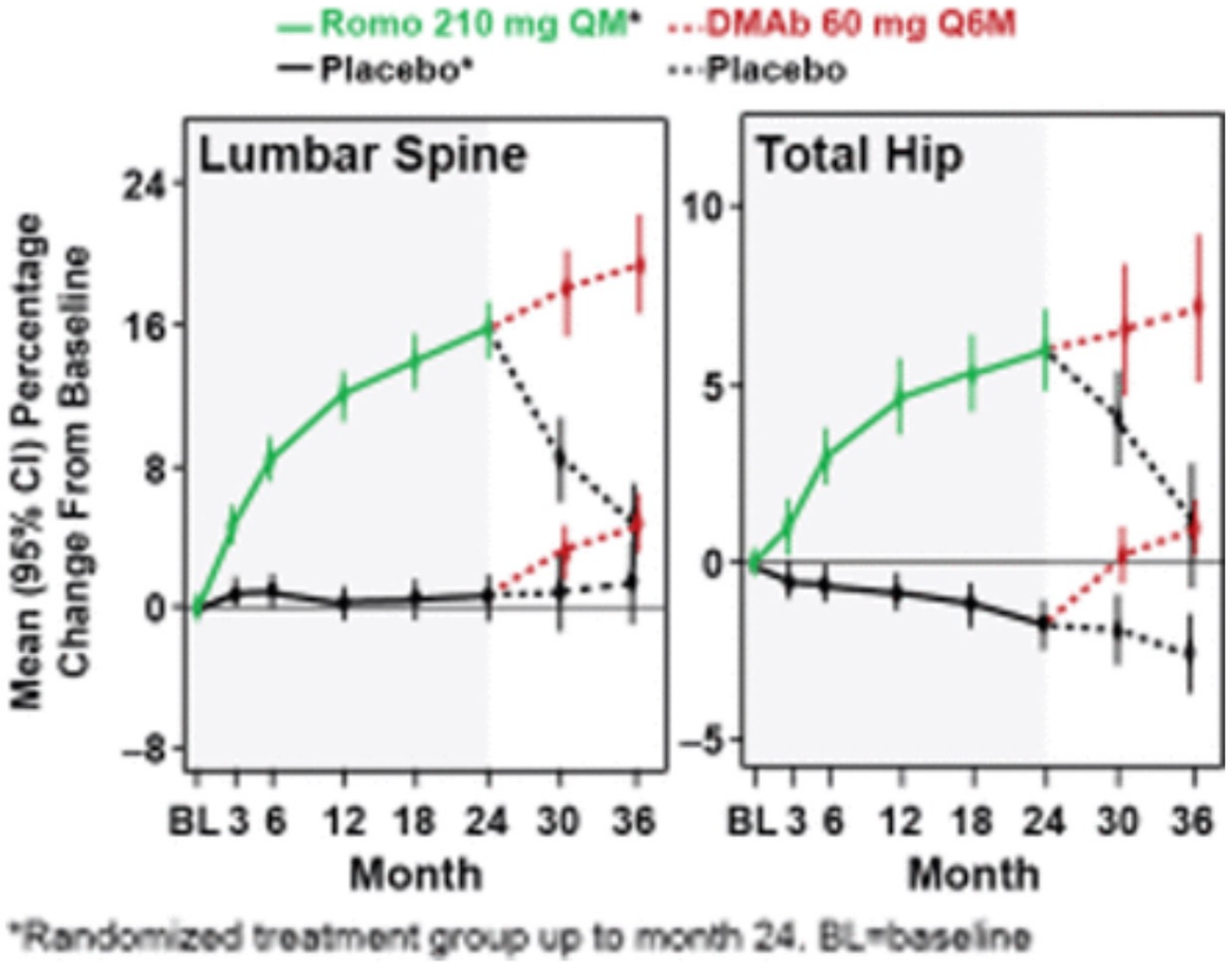
- RRR 27 % fx clínicas (FV sintomaticas + no vertebrales)

A Phase III Randomized Placebo-Controlled Trial to Evaluate Efficacy and Safety of Romosozumab in Men With Osteoporosis

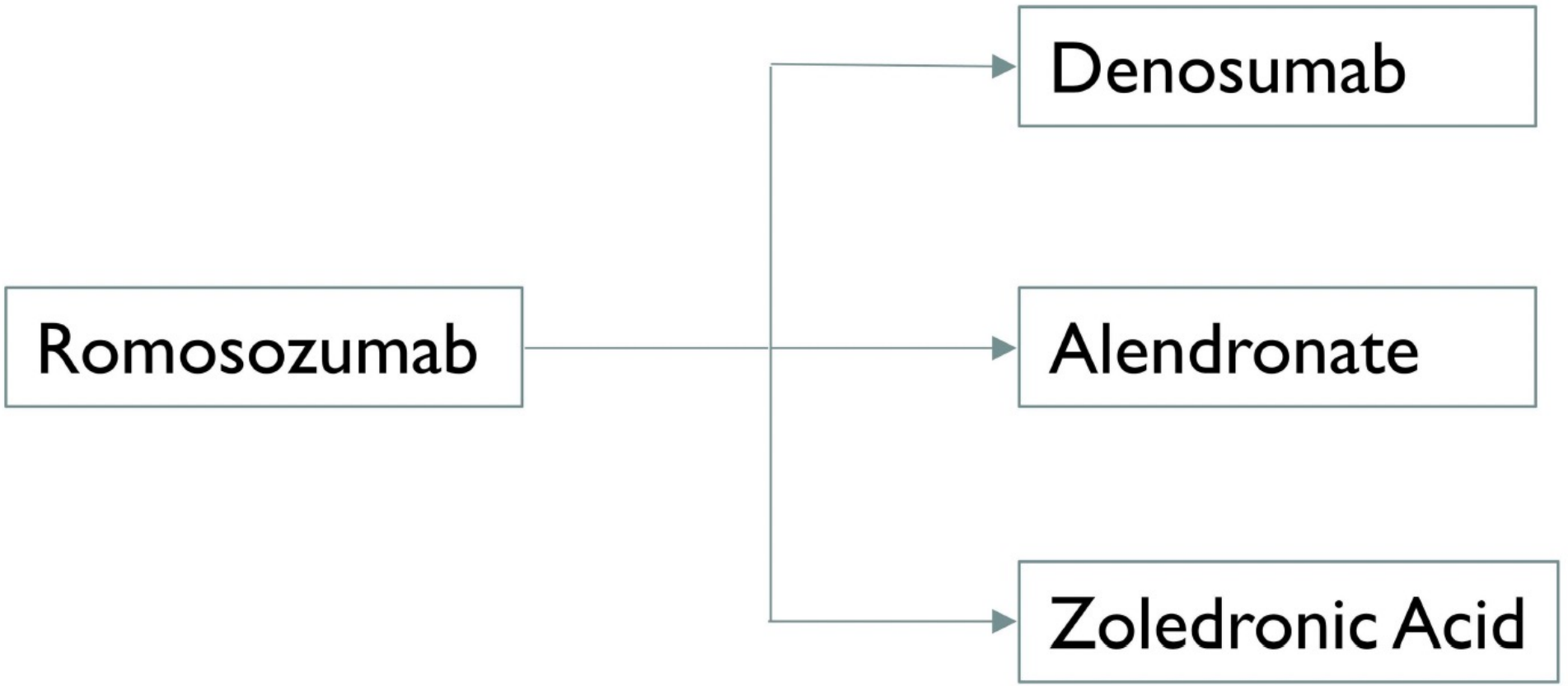


J Clin Endocrinol Metab, September 2018, 103(9):3183–3193

Manejo post Romosozumab



Ann Rheumatic Dis. 2015;(74):166–167.


Romosozumab
Denosumab
Alendronate
Zoledronic Acid

Treatment Sequence Matters: Anabolic and Antiresorptive Therapy for Osteoporosis

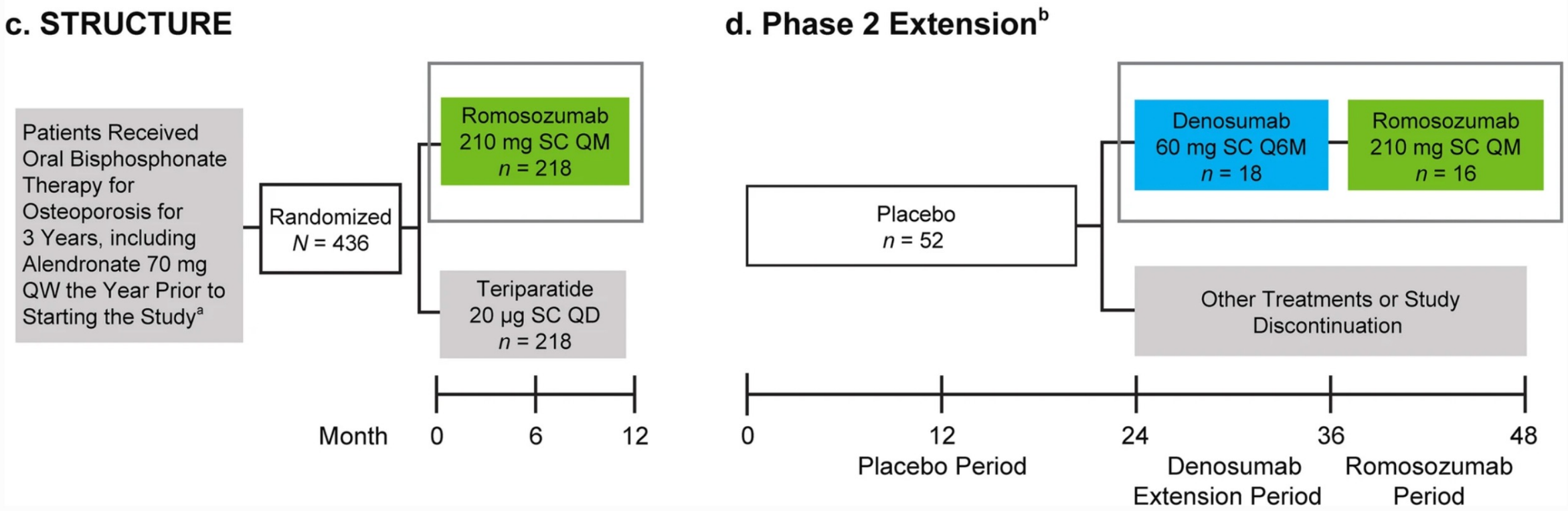
Felicia Cosman,[1,2] Jeri W Nieves,[1,3] and David W Dempster[1,4]

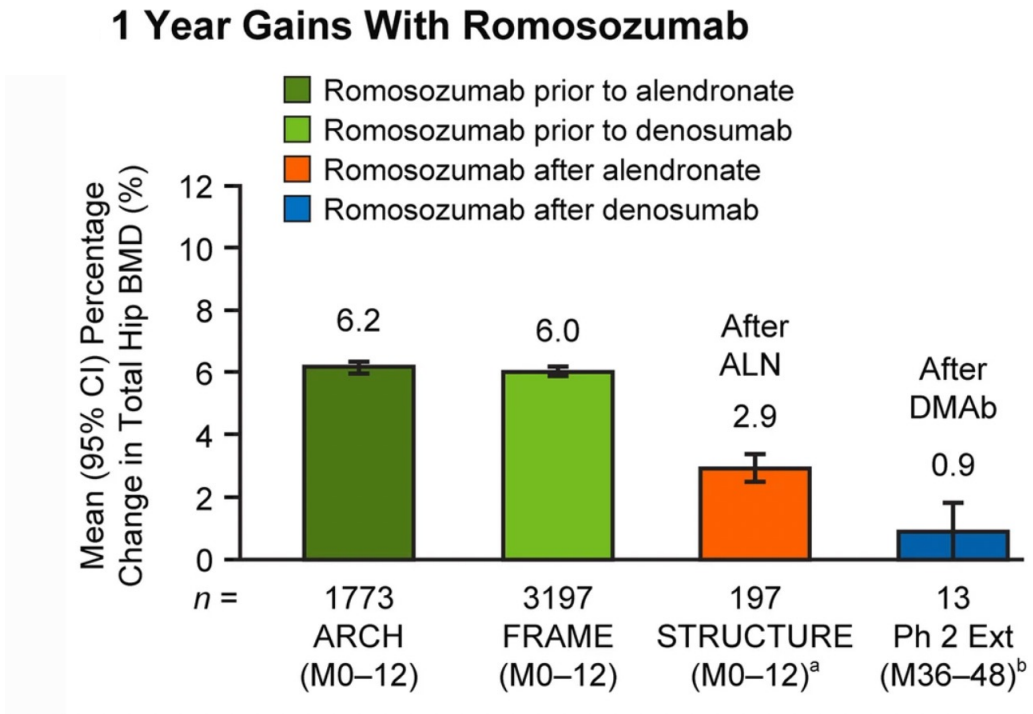
Table 1. Hip BMD Effect of Switching From Potent Antiresorptive Therapy to TPTD

Study	Sample size	Treatment paradigm	% Change in total hip BMD during TPTD/PTH treatment			
			6 mo	12 mo	18 mo	24 mo
Ettinger et al.[27]	33	Alendronate (mean 29.3 mo) → TPTD (18 mo)	−1.8%	−1.0%	+0.3%	–
Boonen et al.[24]	107	Alendronate (median 29.2 mo) → TPTD (24 mo)	−1.2%	−0.6%	+0.6%	+2.1%
Boonen et al.[24]	59	Risedronate (median 23.4 mo) → TPTD (24 mo)	−1.6%	−0.4%	+0.9%	+2.9%
Miller et al.[30]	158	Risedronate (mean 37.2 mo) → TPTD (12 mo)	−1.2%	−0.3%	–	–
Miller et al.[30]	166	Alendronate (mean 38.0 mo) → TPTD (12 mo)	−1.9%	−1.7%	–	–
Cosman et al.[26]	50	Alendronate (mean 45.7 mo) → TPTD (18 mo)	−0.8%	–	+0.9%	–
Leder et al.[28]	27	Denosumab (24 mo) → TPTD (24 mo)	−1.7%	−2.7%	−1.7%	−0.7%

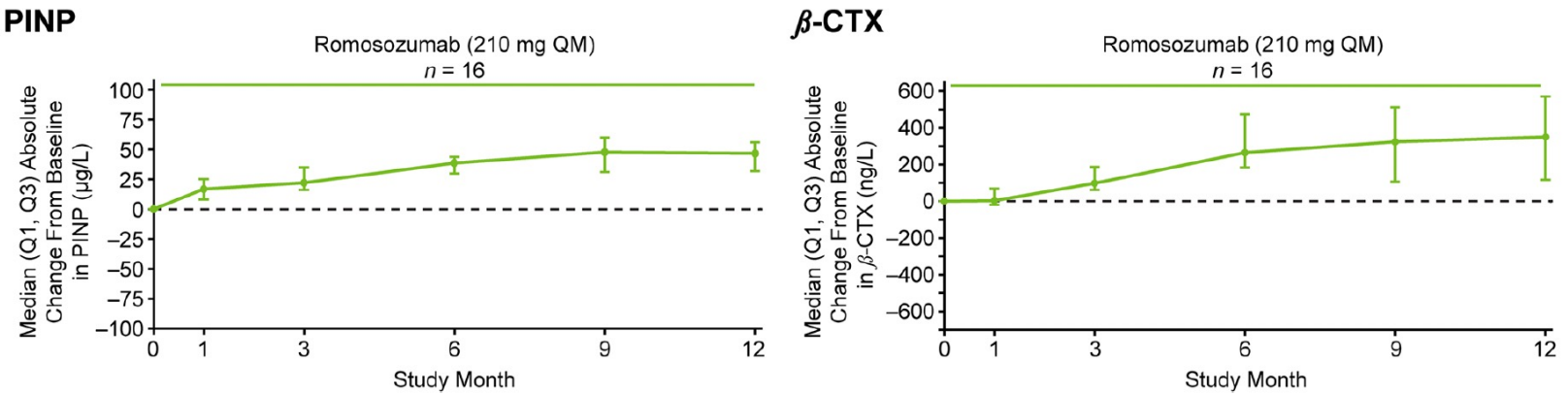
JCEM, 2019, 104: 11

Romosozumab in Women Treated With Antiresorptive Agents First



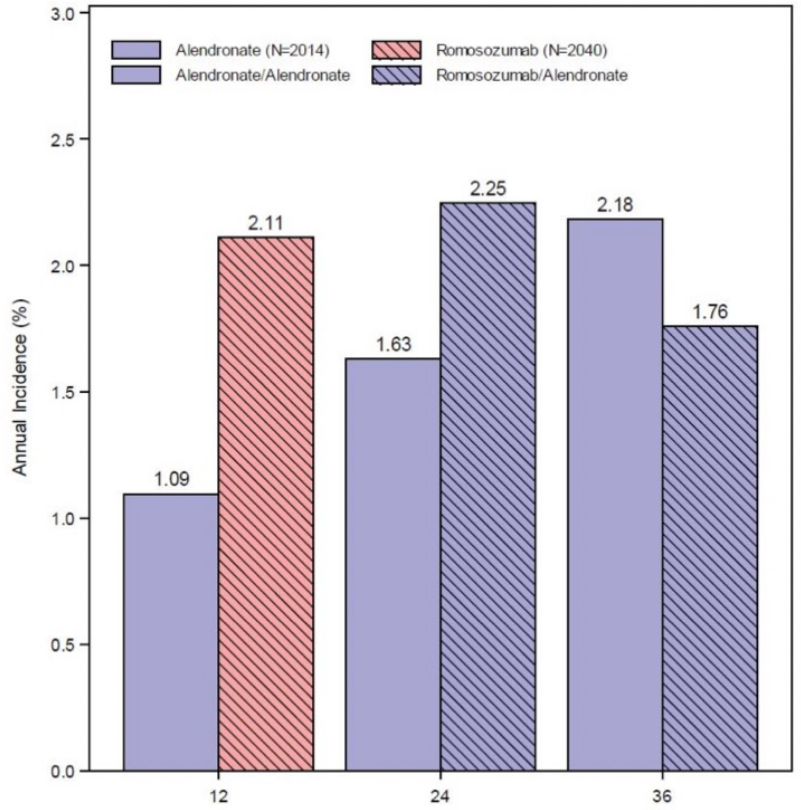


d. Phase 2 Extension (romosozumab after denosumab)



Efectos adversos

- FRAME: 2 casos de ONJ / 1 Fx atípica / Sin aumento MACE
- ARCH: 1 ONJ / 1 Fx atípica / Aumento MACE
- BRIDGE: Aumento MACE

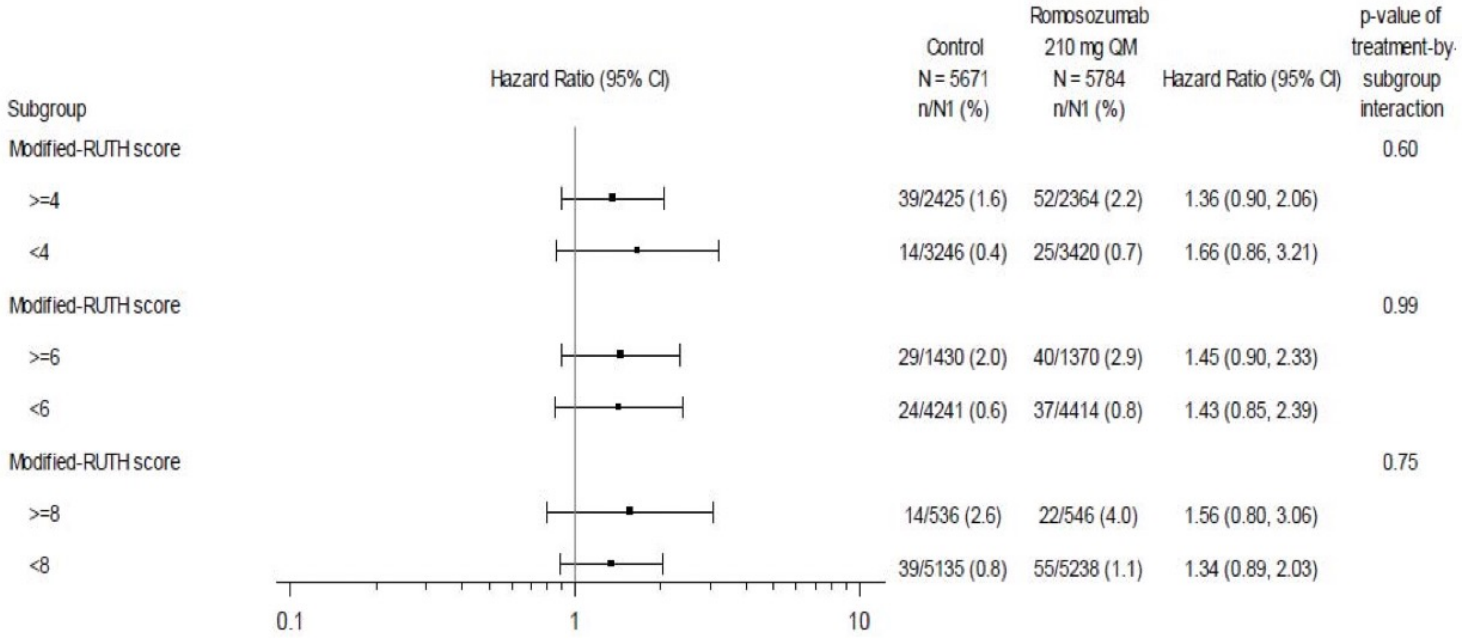


Food and Drug Administration. Division of bone, reproductive, and urologic products office of drug evaluation iii multidisciplinary review and evaluation document, 2018.

Efectos adversos

- FRAME: 2 casos de ONJ / 1 Fx atípica / Sin aumento MACE
- ARCH: 1 ONJ / 1 Fx atípica

Figure 7 Subgroup Analysis by Modified RUTH Score: Subject Incidence of MACE in the Double-blind Period (DCRI Adjudication of Studies 20070337, 20110142, and 20110174)



Food and Drug Administration. Division of bone, reproductive, and urologic products office of drug evaluation iii multidisciplinary review and evaluation document, 2018.

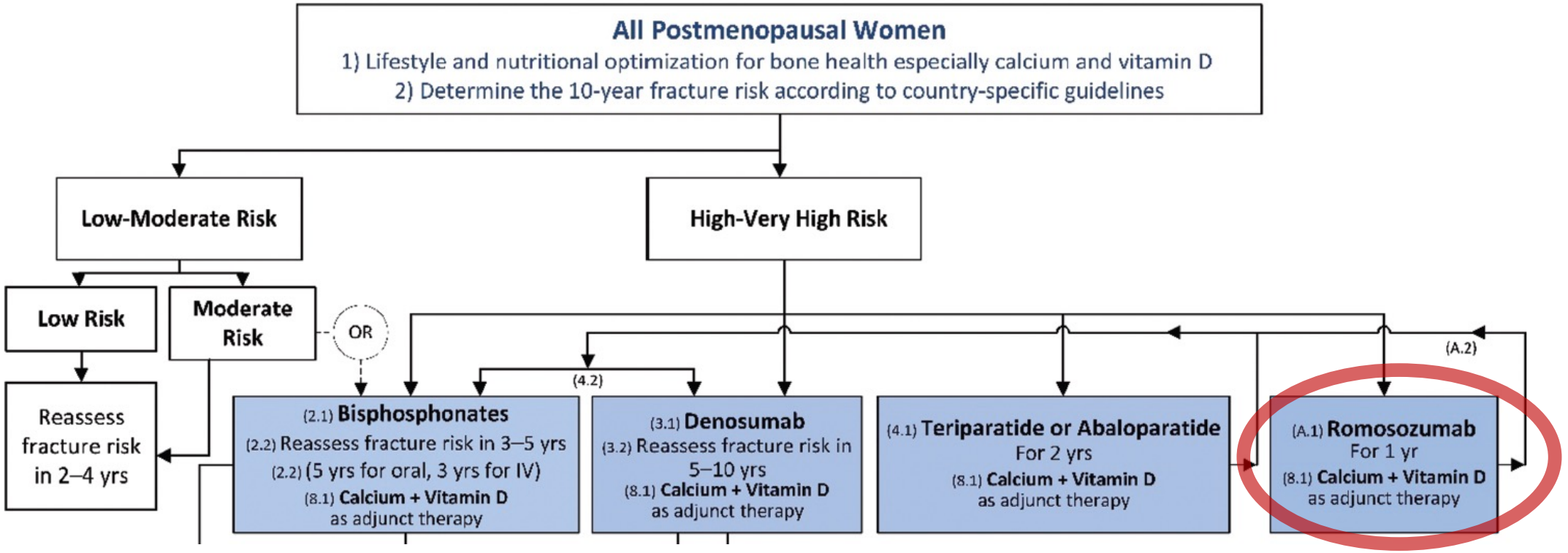
WARNING: POTENTIAL RISK OF MYOCARDIAL INFARCTION, STROKE AND CARDIOVASCULAR DEATH

See full prescribing information for complete boxed warning.

- **EVENITY may increase the risk of myocardial infarction, stroke and cardiovascular death. (5.1)**
- **EVENITY should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year. Consider whether the benefits outweigh the risks in patients with other cardiovascular risk factors. (5.1)**
- **If a patient experiences a myocardial infarction or stroke during therapy, EVENITY should be discontinued. (5.1)**

Food and Drug Administration. Division of bone, reproductive, and urologic products office of drug evaluation iii multidisciplinary review and evaluation document, 2018.

Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Guideline Update



J Clin Endocrinol Metab, March 2020, 105(3):587–594

AACE/ACE 2020 POSTMENOPAUSAL OSTEOPOROSIS TREATMENT ALGORITHM

Lumbar spine or femoral neck or total hip T-score of ≤ -2.5, a history of fragility fracture, or high FRAX® fracture probability*

Evaluate for causes of secondary osteoporosis

Correct calcium/vitamin D deficiency and address causes of secondary osteoporosis

- Recommend pharmacologic therapy
- Education on lifestyle measures, fall prevention, benefits and risks of medications

High risk/no prior fractures**

- Alendronate, denosumab, risedronate, zoledronate***
- **Alternate therapy:** Ibandronate, raloxifene

Reassess yearly for response to therapy and fracture risk

Increasing or stable BMD and no fractures

Consider a drug holiday after 5 years of oral and 3 years of IV bisphosphonate therapy

Resume therapy when a fracture occurs, BMD declines beyond LSC, BTM's rise to pretreatment values or patient meets initial treatment criteria

Progression of bone loss or recurrent fractures

- Assess compliance
- Re-evaluate for causes of secondary osteoporosis and factors leading to suboptimal response to therapy

- Switch to injectable antiresorptive if on oral agent
- Switch to abaloparatide, romosozumab, or teriparatide if on injectable antiresorptive or at very high risk of fracture
- Factors leading to suboptimal response

ABBREVIATIONS GUIDE

BMD – bone mineral density
LSC – least significant change
BTM – bone turnover marker

Very high risk/prior fractures**

- Abaloparatide, denosumab, romosozumab, teriparatide, zoledronate***
- Alternate therapy: Alendronate, risedronate

Reassess yearly for response to therapy and fracture risk

Denosumab	Romosozumab for 1 year	Abaloparatide or teriparatide for up to 2 years	Zoledronate
Continue therapy until the patient is no longer high risk and ensure transition with another antiresorptive agent.	Sequential therapy with oral or injectable antiresorptive agent	Sequential therapy with oral or injectable antiresorptive agent	• If stable, continue therapy for 6 years**** • If progression of bone loss or recurrent fractures, consider switching to abaloparatide, teriparatide or romosozumab

* 10 year major osteoporotic fracture risk ≥ 20% or hip fracture risk ≥ 3%. Non-US countries/regions may have different thresholds.
** Indicators of very high fracture risk in patients with low bone density would include advanced age, frailty, glucocorticoids, very low T scores, or increased fall risk.
*** Medications are listed alphabetically.
**** Consider a drug holiday after 6 years of IV zoledronate. During the holiday, an anabolic agent or a weaker antiresorptive such as raloxifene could be used.

Table 2 Definition of Very High Risk of Fracture American Association of Clinical Endocrinology Guidelines 2020, Endocrine Society Guidelines 2020

American Association of Clinical Endocrinology Guidelines 2020	**Endocrine Society Guidelines 2020**
Very High Risk • Recent fracture in the past 12 months. • Multiple fractures • Fractures while on approved osteoporosis therapy • Fractures while on drugs causing skeletal harm • High risk for falls or history of injurious falls • A very low T score (<-3.0) • A very high fracture probability by fracture risk assessment tool (major osteoporotic fracture >30%, hip fracture >4.5%)	Very High Risk • Multiple spine fractures and a BMD at the hip or spine of ≤ −2.5

Costo US y Argentina: Similar a Teriparatide. Chile > 6 millones de pesos (?)

Mensajes finales

- Esclerostina, secretada por osteocitos, es clave en la regulación del recambio óseo inducido por carga mecánica.
- Romosozumab por un año disminuye riesgo de Fx vertebrales (73%) y clínicas (36%)
- La terapia secuencial (anabólico → antiresortivo) optimiza la ganancia de DMO.
- En contraste con Teriparatide, ha demostrado ganancia en DMO en pacientes previamente tratados con antiresortivos.
- Posible aumento de riesgo cardiovascular. Contraindicado en pacientes con eventos en ultimo año.
- Guías clínicas lo recomiendan en muy alto riesgo de fracturas
- Fecha disponibilidad en Chile ?

“Presente de las Terapias de la Osteoporosis: Romosozumab”

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