

Korean Society for Health Promotion and Disease Prevention

2021년 대한임상건강증진학회 춘계학술대회

2021. 5. 30 (일)

# 골다공증 치료의 최신지견

김 정 환 (을지의대)





## 어떤 환자를 치료해야 하나?

폐경 후 여성, 50세 이상 남성

- 1) 대퇴골 골절 또는 척추 골절
- 2) BMD T-2.5이하 (요추, 대퇴골 경부/총대퇴골)
- 3) 골감소증 환자 중
  - 과거 골절력
  - 골절 위험이 증가된 이차성 원인 존재
  - FRAX 모델 10년 골절 위험도 대퇴골 3%, 주요 골절 20% 이상 (FRAX, Fracture Risk Assessment Tool - <https://www.shef.ac.uk/FRAX/>)

골다공증의 진단 및 치료지침 2015

## 폐경 여성에서 골절 위험 예방을 위한 1차 약제

Type of Fracture	Antiresorptive therapies						Bone formation therapy
	Bisphosphonates			Denosumab	Raloxifene	HRT	Teriparatide
	Alendronate	Risedronate	Zoledronate				
Vertebral	✓	✓	✓	✓	✓	✓	✓
Hip	✓	✓	✓	✓	-	✓	-
Non-vertebral	✓	✓	✓	✓	-	✓	✓

Ibandronate : only Vertebral Fx.  
Pamidronate : only Korea

## Bisphosphonate (경구용)

- 공복에 복용
- 물 200ml 이상 복용
- 30분 이상 공복 유지, 1시간 가량 눕지 않도록
- 흡수 방해 음식 – 유제품, 오렌지 주스, 보리차, 광천수
- 커피, 칼슘, 제산제 – 투약 후 1시간 이상 지난 후 섭취
- 장용제 – 식사와 상관없이 복용 가능
- 시럽제 – 최소 30mL 이상의 물과 함께 복용

## Bisphosphonate (경구용)

- 부작용
  - 1) 위장장애, 식도염, 위궤양
    - 일시 중단 후 증상 호전되면 재투약 고려
    - 지속되면 약제 종류, 투약 경로 변경
    - 위장장애 지속 시 내시경 확인 후 재투약 여부 결정
  - 2) 독감 유사 증상
    - 처음 투약, 과량 복용시
    - 수일 내 호전, 재투여시 빈도 감소
    - AAP 투여 고려
  - 3) 저칼슘혈증
    - 부갑상선 저하증, Vit D/Ca 섭취 부족
- 금기증
  - 식도협착, 중증신부전, 저칼슘혈증, 골연화증



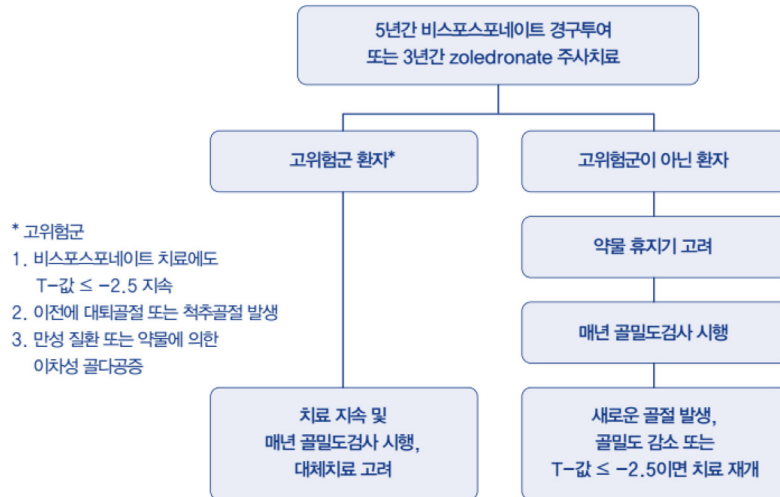
## Bisphosphonate (주사제)

- 반드시 정맥주사 (근육주사는 안됨)
- 천천히 투여
- 생리식염수 또는 5%포도당 수액에 혼합 (하트만 수액은 안됨)
- 이상반응
  - 독감 유사증상
  - 저칼슘혈증, 신기능 장애
- 금기
  - 중증 신부전, 저칼슘혈증, 골연화증, 임신, 수유

## MRONJ (Medication-Related Osteonecrosis of the Jaw)

- 국내 발생률 0.04%
- 위험요인
  - 국소적 요인 : 구강 내 수술, 해부학적 요인, 돌출된 골표면 자극, 구강질환, 틀니
  - 전신적 요인 : BP 사용기간, 스테로이드 사용, 고령, 당뇨병, 흡연, 유전적 인자
- BP 장기 복용으로 인한 발생 (3~5년 복용 후)
- 3~5년 후(골절력 있는 골절 고위험군 6~10년) 평가
  - 골절 위험도/ 턱뼈괴사 위험 여부에 따라 결정
  - 골절 고위험군일 경우 휴약기간 중 대체약제 고려 가능

## BP drug holiday



## HRT

- 자궁이 있는 여성 : Estrogen-Progesterone Therapy, EPT
- 자궁이 없는 여성 : Estrogen Therapy, EP

투여 방법	제제	1일 표준 용량
경구	conjugated equine estrogen	0.625 mg
	micronized estradiol	1~2 mg
	estropipate	0.625 mg
패치	estradiol	50 µg
젤	estradiol	1.5 mg

- 요추/대퇴골 골밀도 증가
- 첫 1년 간 대부분 상승, 첫 HRT 여성에서 더욱 증가
- 골절 감소
- 골표지자 감소

## SERM (Raloxifen)

- 뼈 - 에스트로겐 유사 작용, 뼈 강도 증가, 골절 감소
- 자궁내막, 유방 - 에스트로겐 길항작용
  - 침윤성 유방암 발생 감소
  - 자궁내막증/자궁내막암 위험 증가 안 함
- 심혈관계 효과
  - 뇌졸중, 혈전색전증 증가 위험
- 이상반응
  - 안면홍조 : ¼에서 치료 후 수개월간 발생 (증상 가벼움)
  - 다리통증
- 금기증
  - 정맥혈전 기왕력
  - 장기간 안정 필요 시
  - 수술 전후
  - 수술 등 장기간 부동상태 예상

: 최소 3일 전 중단. 보행가능까지 투약 보류



## SERM (Bazodoxifen)

- 3세대 SERM
- 요추/대퇴골 골밀도 증가
- Raloxifen 비교
  - 척추 골절 발생 감소
  - 비척추 골절 발생 감소시키지 못함
  - 고위험 군에서는 비척추골절도 감소
  - 심혈관 질환 부작용 : 위약군에 비해 증가 보이지 않음
- 자궁내막 두께 영향 없음
- 신부전 용량 조절 필요 없음
- 뇌졸중 발생이 위약군보다 적었음
- 콜레스테롤 개선 효과
- 이상반응 : 안면홍조, 다리통증(경련)

## TSEC

- Ideal SERM

### E-agonistic effect

Bone  
Cardiovascular system

### E-antagonistic effect

Endometrium  
Breast tissue

- TSEC

- absence of progestin, for managing postmenopausal osteoporosis and menopausal symptoms

Conjugated estrogens

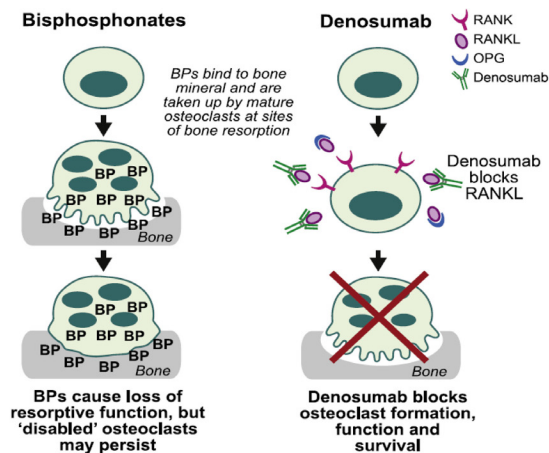


Bazedoxifene

**DUAVIVE™**  
CONJUGATED ESTROGENS/  
BAZEDOXIFENE 0.45 MG/20 MG TABLETS

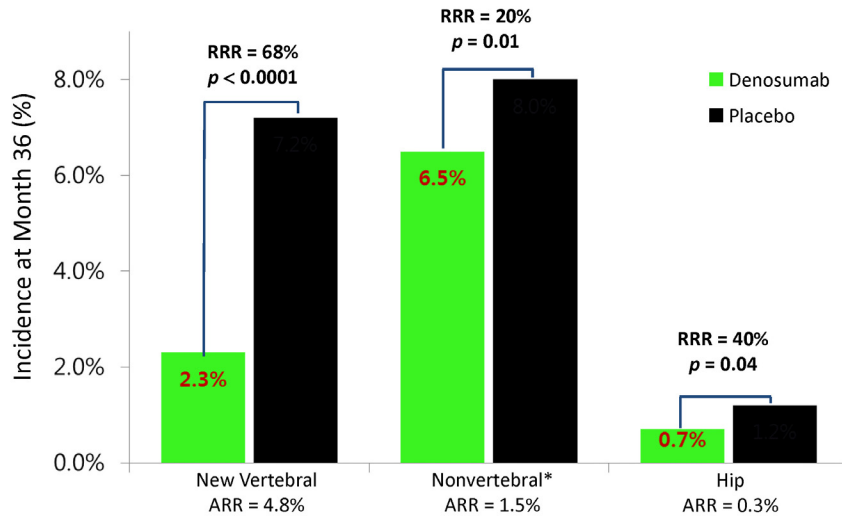
## Denosumab

- RANKL (Receptor Activator of Nuclear factor Kappa-B Ligand) 억제
- 파골전구세포에서 발현하는 RANKL과 결합
- 파골세포 생성, 활성화 억제 – 골흡수 감소

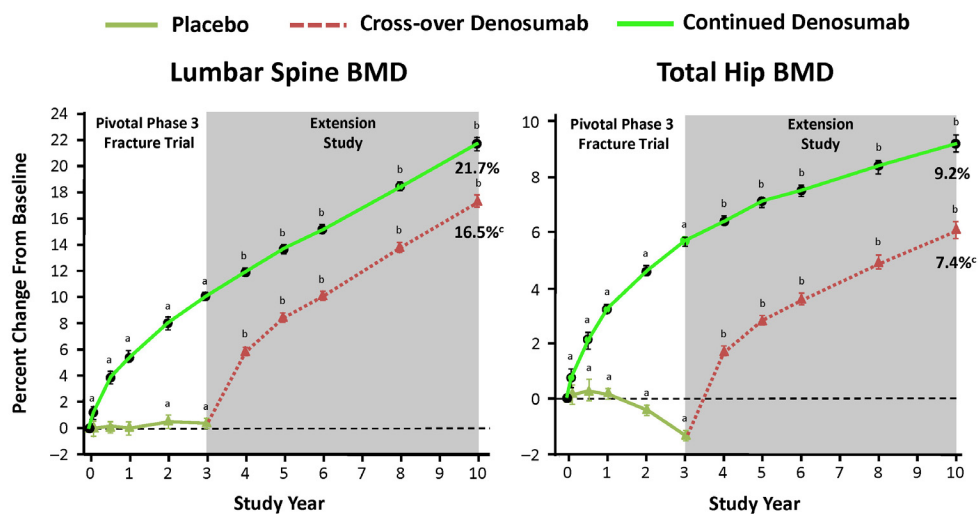


Baron R et al. Bone 2011; 48:677-692.

## Effect of Denosumab on Fracture Risk at 36 Months



## Change in Lumbar Spine and Total Hip BMD Through 10 Years With Denosumab Treatment



Data represents LS means and 95% CI.

\* $p < 0.05$  vs Pivotal Phase 3 study baseline; <sup>b</sup> $p < 0.05$  vs Pivotal Phase 3 study baseline and extension baseline; <sup>c</sup>Percentage change while on denosumab treatment. BMD = bone mineral density; LS = least-squares; CI = confidence interval

Adapted from: Bone HG, et al. Presented at: American Society of Bone and Mineral Research; October 12, 2015; Seattle, WA. Oral presentation LB-1157.



DENOSUMAB

## Incidence of Adverse Events (Rates per 100 Subject-Years)

	<u>FREEDOM Years 1–3</u>	<u>Extension Years 1–7</u>	
	Placebo (N = 3883)	Cross-over Denosumab (N = 2206)	Long-term Denosumab (N = 2343)
All AEs	156.1	96.8	97.0
Infections	30.7	20.7	19.9
Malignancies	1.6	2.0	2.0
Eczema	0.6	0.9	0.9
Hypocalcemia	< 0.1	< 0.1	< 0.1
Pancreatitis	< 0.1	< 0.1	< 0.1
Serious AEs	10.4	10.1	10.3
Infections	1.3	1.4	1.5
Cellulitis or erysipelas	< 0.1	< 0.1	< 0.1
Fatal AEs	0.8	0.8	0.8
Osteonecrosis of the jaw	0	< 0.1	< 0.1
Atypical femoral fracture	0	< 0.1	< 0.1

- No difference of Cellulitis in 3 groups
- Cumulative osteonecrosis of the jaw cases: 6 cross-over, 7 long-term
- Cumulative atypical femoral fracture cases: 1 cross-over, 1 long-term



의정부율지대학교병원  
UIJEONGBU EULJI MEDICAL CENTER, EULJI UNIVERSITY

## PTH

- 골형성 촉진제
- 조골세포 자멸사 억제, 조골세포 분화/활성화 촉진
- 골흡수억제제에 치료 반응이 불충분한 경우 (골절발생/골량 감소)

- PTH(1-34) – Teriparatide



매일 1회 피하주사



주1회 피하주사

- 골흡수억제제보다 골량 증가 효과 높음 (특히 척추 골량 증가)

## PTH

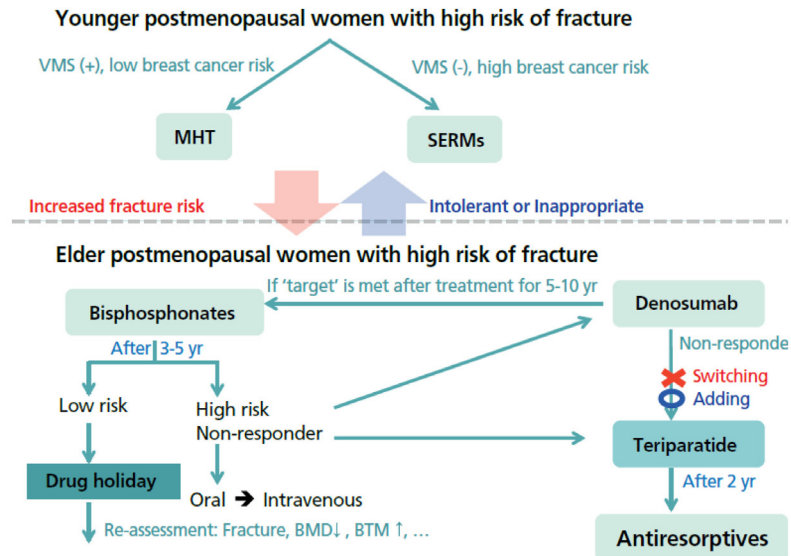
- 부작용
    - 오심, 두통, 경미한 다리경련, 고칼슘혈증
  - 금기
    - 파제트씨병
    - 알칼리인산분해효소가 증가했으나 원인이 명확하지 않은 환자
    - 소아
    - 뼈에 방사선 치료를 받은 환자
    - 골육종의 발생 위험이 높은 환자, 골전이암, 골의 악성종양
    - 골다공증 외의 대사성 골질환
    - 고칼슘혈증
    - 중증 신부전
    - 임신 또는 수유 시
- \* 요로결석이 있거나 digitalis 복용 중인 경우 주의

## PTH

- 급여기준
  - 가. 투여대상: 기존 골흡수억제제 중 한가지 이상에 효과가 없거나 사용할 수 없는 환자로 다음의 조건을 모두 만족하는 경우
    - 1) 65세 이상 (폐경여성)
    - 2) 중심골에서 DEXA로 측정한 T-score  $\leq -2.5$
    - 3) 골다공증성 골절이 2개 이상 발생
  - 나. 투여기간: 최대 24개월, 반복 불가, Teriparatide 교체투여 인정 안됨.
- 사용 시 주의점
  - PTH 중간 후 급격하게 골량 감소 (특히 남성)
  - 투약 종료 후 순차적으로 골흡수억제제로 전환
  - Denosumab 사용 중단 후 Teriparatide 투여하면 골소실이 증가
  - Denosumab 사용 후 Teriparatide 쓸 경우 Add 권고.



## 어떤 경우에 어떤 약을 골라야할까?



J Korean Med Assoc 2019 October; 62(10):542-550

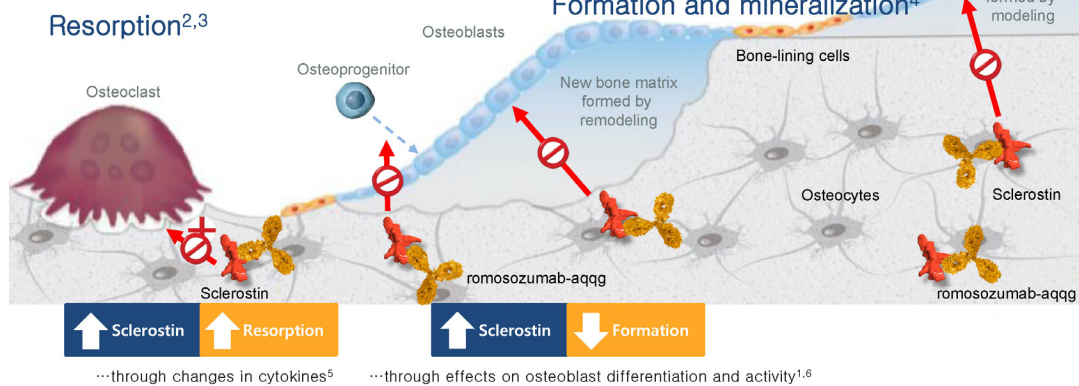
## Romosozumab

- 2019년 5월 KFDA 승인, 11월 출시
- Sclerosin 단일클론항체
  - 골형성 촉진, 일시적 골흡수 억제
- 12개월 투여 후,
  - 요추, 대퇴골 골밀도 증가, 골절 감소
- 12개월 후 골형성 효과 소실
  - 투여 1년 후 BP, Denosumab 투여

## Romosozumab exerts a dual effect through multiple molecular processes<sup>1-4</sup>

Sclerostin regulates bone formation and resorption through multiple molecular processes<sup>1-4</sup>

romosozumab increases bone formation and, to a lesser extent, decreases bone resorption<sup>1</sup>

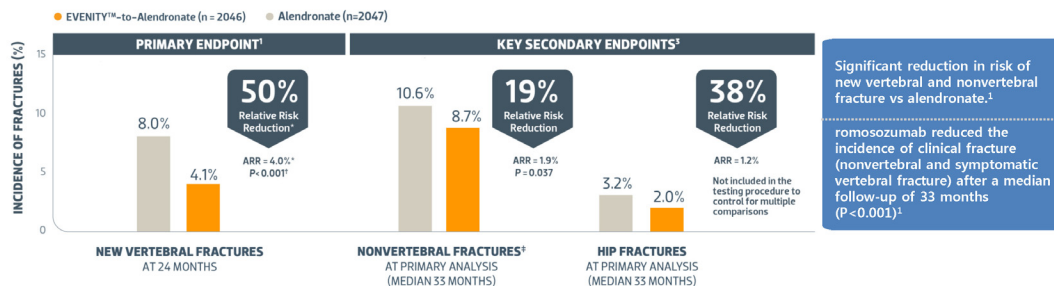


1. Romosozumab (romosozumab-aqqg) prescribing information, Amgen.
2. Crockett JC, et al. *J Cell Sci.* 2011;124(7):991-998.
3. Dempster DW, et al. *Clin Ther.* 2012;34:521-536.
4. Ominsky M, et al. *Bone.* 2017;96:63-75.
5. Chan BY, et al. *Osteoarthritis Cartilage.* 2011;19(7):874-885.
6. Winkler DG, et al. *EMBO J.* 2003;22(23):6267-6276.

## Romosozumab for 12 months followed by alendronate provided superior vertebral and nonvertebral fracture risk reduction vs alendronate alone<sup>1</sup>

ARCH

Consider romosozumab after fracture when your patients' risk of another is at its highest<sup>1,2</sup>



This was an event-driven trial and the duration of follow-up varied across subjects. The median duration of subject follow-up for the primary analysis period was 33 months.<sup>1</sup>

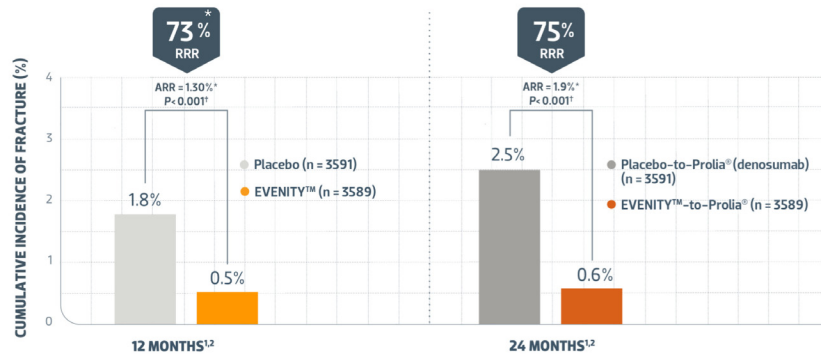
ARR = absolute risk reduction.

\*Absolute and relative risk reductions are based on the Mantel-Haenszel method adjusting for age strata, baseline total hip (BMD) T-score (< -2.5, > -2.5), and presence of severe vertebral fracture at baseline. †P value based on logistic regression model (new vertebral fracture) or Cox proportional hazards model (other fracture types) adjusting for age strata, baseline total hip (BMD) T-score, and presence of severe vertebral fracture at baseline. ‡Nonvertebral fractures excluded fractures of the skull, facial bones, metacarpals, fingers, and toes. Pathologic or high trauma fractures were also excluded.

1. romosozumab (romosozumab-aqqg) prescribing information, Amgen. 2. van Geel TA, et al. *Ann Rheum Dis.* 2009;68:99-102. 3. Saag KG, et al. *N Engl J Med.* 2017;377(15):1417-1427.

## Romsozumab rapidly reduced new vertebral fracture by 12 months<sup>1,2</sup>

FRAME

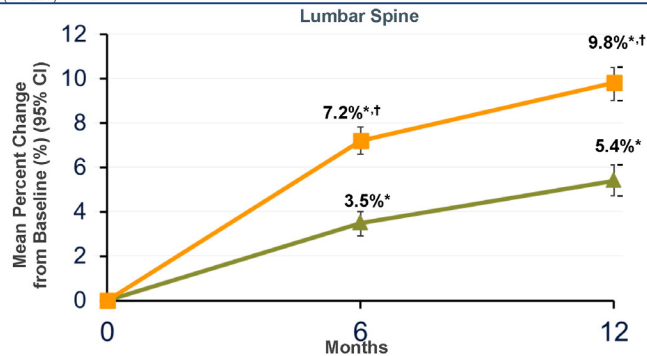


ARR = absolute risk reduction; RRR = relative risk reduction.  
For new vertebral fracture, n = Number of patients randomized. \*Absolute and relative risk reduction are based on the Mantel-Haenszel method adjusting for age and prevalent vertebral fracture strata. †P-value is based on logistic regression model adjusted for age and prevalent vertebral fracture strata.  
1. romsozumab (romsozumab-aqg) prescribing information, Amgen. 2. Cosman F, et al. *N Engl J Med*. 2016;375:1532-1543.

## Percent Change in Lumbar Spine BMD by DXA

STRUCTURE

Teriparatide (n = 209)  
Romsozumab (n = 206)

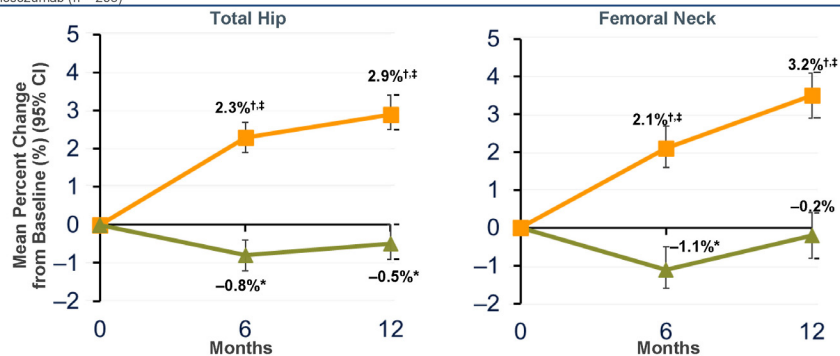


\*P < 0.0001 vs baseline. †P < 0.0001 vs teriparatide.  
Data are LS means and 95% CI.  
Langdahl BL, et al. *Lancet*. 2017;390:1585-1594.

## Percent Change in Total Hip and Femoral Neck BMD by DXA

STRUCTURE

Teriparatide (n = 209)  
Romosozumab (n = 208)

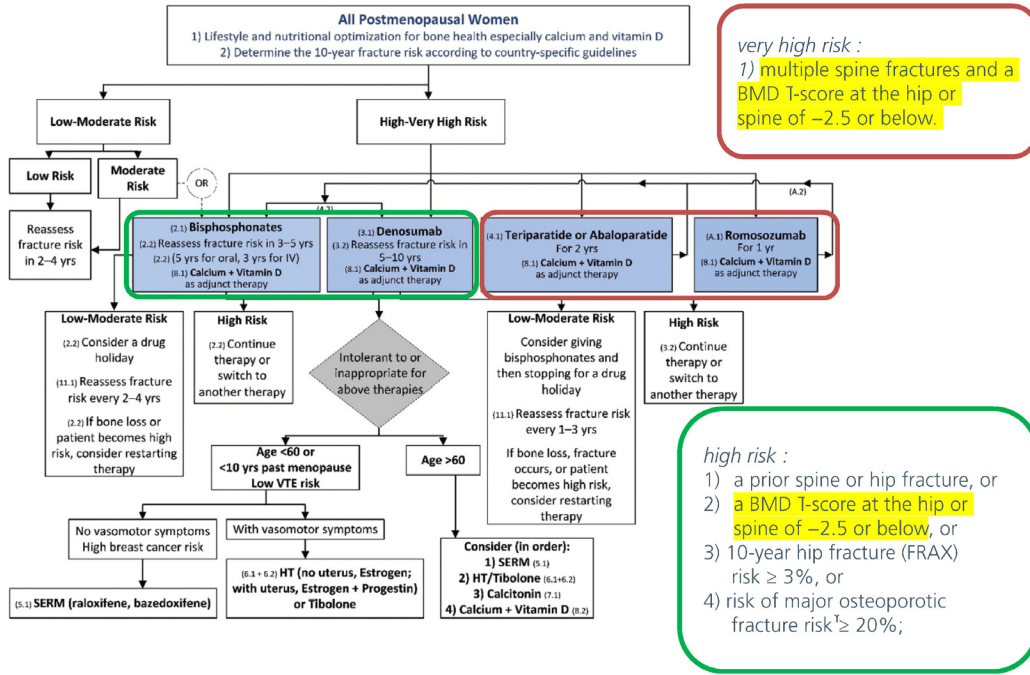


\*P < 0.05 vs baseline. †P < 0.0001 vs baseline. ‡P < 0.0001 vs teriparatide.  
Data are LS means and 95% CI.  
aBMD = areal bone mineral density.  
Langdahl BL, et al. *Lancet*. 2017;390:1585-1594.

## CLINICAL PRACTICE GUIDELINE UPDATE

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

Dolores Shoback,<sup>1,2</sup> Clifford J. Rosen,<sup>3</sup> Dennis M. Black,<sup>4</sup>  
Angela M. Cheung,<sup>5,6</sup> M. Hassan Murad,<sup>7</sup> and Richard Eastell<sup>8</sup>



## Clinical Practice Guidelines

### AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/ AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS— 2020 UPDATE

Pauline M. Camacho, MD, FACE<sup>1</sup>; Steven M. Petak, MD, JD, FACP, FCLM, MACE, CCD<sup>2</sup>;  
Neil Binkley, MD<sup>3</sup>; Dima L. Diab, MD, FACE, FACP, CCD<sup>4</sup>; Leslie S. Eldeiry, MD<sup>5</sup>;  
Azeez Farooki, MD<sup>6</sup>; Steven T. Harris, MD, FACP, FASBMR<sup>7</sup>; Daniel L. Hurley, MD, FACE<sup>8</sup>;  
Jennifer Kelly, DO, FACE<sup>9</sup>; E. Michael Lewiecki, MD, FACE, FACP, CCD<sup>10</sup>;  
Rachel Pessah-Pollack, MD, FACE<sup>11</sup>; Michael McClung, MD, FACP, FACE<sup>12</sup>;  
Sunil J. Wimalawansa, MD, PhD, MBA, FCCP, FACP, FRCP, DSc, FACE<sup>13</sup>;  
Nelson B. Watts, MD, FACP, CCD, FASBMR, MACE<sup>14</sup>

## AACE/ACE 2020 POSTMENOPAUSAL OSTEOPOROSIS TREATMENT ALGORITHM

Lumbar spine or femoral neck or total hip T-score of  $\leq -2.5$ , 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

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

### ABBREVIATIONS GUIDE

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

\* 10 year major osteoporotic fracture risk  $\geq 20\%$  or hip fracture risk  $\geq 3\%$ . 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.



COPYRIGHT ©2020 AACE. MAY NOT BE REPRODUCED IN ANY FORM WITHOUT EXPRESS WRITTEN PERMISSION FROM AACE.

Postmenopausal Osteoporosis Guidelines, Endocr Pract. 2020;26(Suppl 1)