Osteoporosis Guidelines and Clinical Practice

Andrea J. Singer. MD, FACP, CCD
Director, Women's Primary Care
Medical Director, Bone Densitometry and Fracture Liaison Service
MedStar Georgetown University Hospital
Washington, DC

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  - Radius Health (paid to Georgetown University)
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- Board positions with the NOF
- Guideline committees with NOF

Osteoporosis Guidelines – What's all the Fuss About Anyway?

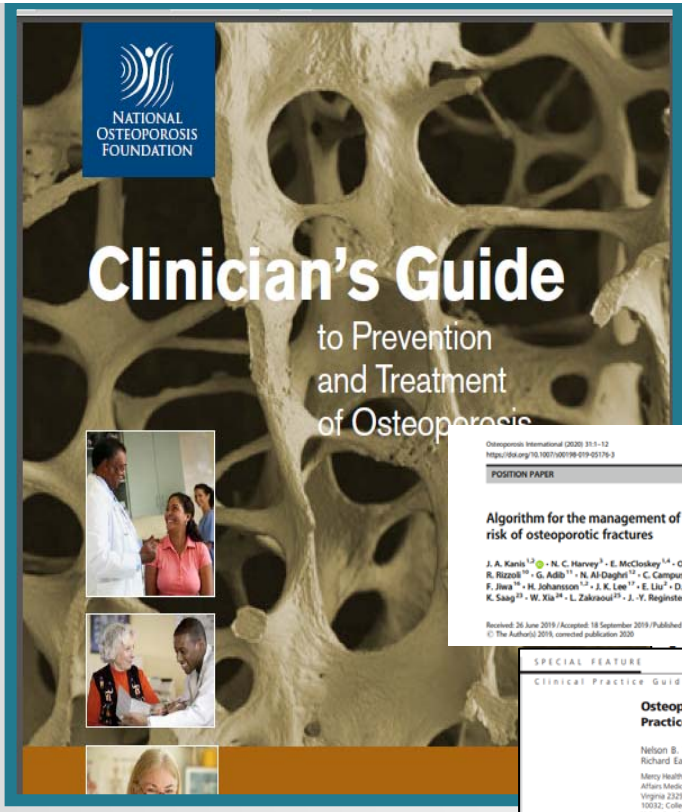
- "All guidelines are wrong, but good ones are useful"[1]

- Too many?
- Different methodologies
- Different patient populations
- Difficult to include patients' values and preferences
- Variable strategies for updates as new data emerge

1. E. Michael Lewiecki, MD
2. Lewiecki, EM et al. *Osteoporos Int* **31,** 2073–2076 (2020).

Muddying the Waters

- Many do not distinguish or fully distinguish the advantages, disadvantages, and mechanism of action of different treatment options
- Not all address sequence of therapy
- Not all differentiate or define levels of risk or definitions of risk levels vary
- Confusion about duration of therapy



CLINICAL PRACTICE GUIDELINE

Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society* Clinical Practice Guideline

Richard Eastell,[1] Clifford J. Rosen,[2] Dennis M. Black,[3] Angela M. Cheung,[4] M. Hassan Murad,[5] and Dolores Shoback[6,7]

[1]University of Sheffield, Sheffield S10 2TN, United Kingdom; [2]Maine Medical Center Research Insti Scarborough, Maine 04074; [3]University of California San Francisco, San Francisco, California 9410 [4]University of Toronto, Toronto, Ontario M5S 1A1, Canada; [5]Mayo Clinic Evidence-Based Practice Ce Rochester, Minnesota 55905; [6]Endocrine Research Unit, San Francisco Veterans Affairs Medical Center Francisco, California 94121; and [7]De Francisco, California 94143

ORCiD numbers: 0000-0003-3436-8

CLINICAL PRACTICE GUIDELINE UPDATE

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

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

[1]Endocrine Research Unit, San Francisco Veterans Affairs Medical Center, Department of Medicine, San Francisco, California 94121; [2]Department of Medicine, University of California San Francisco, San Francisco, California 94143; [3]The Maine Medical Center Research Institute, Scarborough, Maine 04074; [4]University of California San Francisco, San Francisco, California 94107; [5]Department of Medicine, University Health Network, Toronto, Ontario, M5G 2C4 Canada; [6]University of Toronto, Toronto, Ontario, M5G 2C4 Canada; [7]Mayo Clinic, Rochester, Minnesota 55905; and [8]The University of Sheffield, Sheffield, S10 2TN United Kingdom

ORCiD number: 0000-0003-3436-8199 (C. J. Rosen, (Chair)).

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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

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 abalopa-ratide, teriparatide or romosozumab

ABBREVIATIONS GUIDE

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

* 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.

Osteoporosis International (2020) 31:1–12
https://doi.org/10.1007/s00198-019-05176-3

POSITION PAPER

Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures

J. A. Kanis[1,2] · N. C. Harvey[3] · E. McCloskey[1,4] · O. Bruyère[5] · N. Veronese[6] · M. Lorentzon[7,7,8] · C. Cooper[3,9] · R. Rizzoli[10] · G. Adib[11] · N. Al-Daghri[12] · C. Campusano[13] · M. Chandran[14] · B. Dawson-Hughes[15] · K. Javaid[9] · F. Jiwa[16] · H. Johansson[1,2] · J. K. Lee[17] · E. Liu[2] · D. Messina[18] · O. Mkinsi[19] · D. Pinto[20,21] · D. Prieto-Alhambra[9,22] · K. Saag[23] · W. Xia[24] · L. Zakraoui[25] · J.-Y. Reginster[12,26]

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SPECIAL FEATURE
Clinical Practice Guideline

Osteoporosis in Men: An Endocrine Society Clinical Practice Guideline

Nelson B. Watts, Robert A. Adler, John P. Bilezikian, Matthew T. Drake, Richard Eastell, Eric S. Orwoll, and Joel S. Finkelstein

Mercy Health Osteoporosis & Bone Health Services (N.B.W.), Cincinnati Ohio 45236; McGuire Veterans Affairs Medical Center and Virginia Commonwealth University School of Medicine (R.A.A.), Richmond, Virginia 23298; Columbia University College of Physicians and Surgeons (J.P.B.), New York, New York 10032; College of Medicine, Mayo Clinic (M.T.D.), Rochester, Minnesota 55905; Medical School at the University of Sheffield (R.E.), Sheffield S10 2RX, United Kingdom; Oregon Health & Sciences University (E.S.O.), Portland, Oregon 97239; and Massachusetts General Hospital, Harvard Medical School (J.S.F.), Boston, Massachusetts 02114

ACP American College of Physicians
Leading Internal Medicine, Improving Lives

CLINIC

Treatment of Low Bone Density or Osteoporosis to Prev Men and Women: A Clinical Practice Guideline Update from the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Mary Ann Forciea, MD; Robert M. McLean, MD; and Thomas D. Denberg, MD, PhD; for the Clinical Guidelines Committee of the American College of Physicians*

Description: This guideline updates the 2008 American College of Physicians (ACP) recommendations on treatment of low bone density and osteoporosis to prevent fractures in men and women. This guideline is endorsed by the American Academy of Family Physicians.

Methods: The ACP Clinical Guidelines Committee based these recommendations on a systematic review of randomized controlled trials; systematic reviews; large observational studies (for

Recommendation 2: *ACP recommends that clinicians treat osteoporotic women with pharmacologic therapy for 5 years. (Grade: weak recommendation; low-quality evidence)*

Recommendation 3: *ACP recommends that clinicians offer pharmacologic treatment with bisphosphonates to reduce the risk for vertebral fracture in men who have clinically recognized osteoporosis. (Grade: weak recommendation; low-quality evidence)*

Menopause: The Journal
Vol. 17, No. 1, pp. 23-24
DOI: 10.1097/gme.0b013
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NAMS co

Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

NUMBER 129, SEPTEMBER 2012
(Reaffirmed 2016)
(Replaces Practice Bulletin No. 50, January 2004)

Osteoporosis

Osteoporosis has a fivefold greater prevalence in women than in men. In the United States, although women only have twice the fracture rate of men, they sustain 80% of hip fractures because older women far outnumber older men. In 2005, the cost for direct care of the estimated 2 million osteoporosis-related fractures was projected to be $17 billion, with hip fractures accounting for approximately 72% of the cost (1). Morbidity and loss of function can occur with all fractures and consequently present a significant burden to the patient, the family, and society. Morbidity and mortality are especially high with hip fractures. Of women older than 80 years who have had a hip fracture, only 56% could walk independently after 1 year (2). Approximately 3–6% of women die of complications while hospitalized for hip fracture, an outcome often correlated with comorbidity and age (2, 3). Many aspects of gynecology and obstetrics can affect bone health. Obstetrician–gynecologists have the opportunity to play a key role in the prevention of osteoporosis and osteoporotic fractures. The purpose of this practice bulletin is to review the diagnosis, evaluation, and treatment of osteoporosis.

Updated NOF Clinician's Guide:Preview

The 2021 edition contains updates on:

- Current and projected fracture incidence, disability, and death attributed to persistent underdiagnosis and undertreatment of osteoporosis.
- Implications of wrist fractures for morbidity and risk of other osteoporotic fractures.
- Expanded clinical diagnostic criteria to better identify individuals at risk for fracture.
- Risk stratification for optimizing treatment outcomes.
- Recommendations for screening and care of patients at high risk for fractures.
- Special issues related to osteoporosis in men.
- Management recommendations for glucocorticoid-induced osteoporosis.
- Current evidence on use of calcium and/or vitamin D supplementation for bone health.
- Vertebral imaging to diagnose subclinical spinal fractures.
- New bone imaging techniques.
- Novel FDA-approved drugs to prevent fractures.
- Bisphosphonate holiday in the context of long-term treatment.
- Impact of sequence on use of osteoporosis medications.
- Insights from NOF survey of patient treatment priorities and preferences.
- Evaluations recommended prior to orthopedic surgery in patients with osteoporosis.
- Post-fracture pain management, rehabilitation and fracture prevention.
- Exercise to improve function, preserve independence, and prevent falls and fractures.
- Organizational strategies, including fracture liaison services (FLS), for secondary fracture prevention.

LeBoff, M, et al. Osteoporos Int. Accepted

2021NOF Clinician's Guide

- "Where possible, recommendations in this guide are based on evidence from RCTs; however, relevant published data and guidance from expert clinical experience provides the basis for recommendations in those areas where RCT evidence is currently deficient or not applicable to the many osteoporosis patients not considered for RCT participation due to age and morbidity."

Guideline Goals

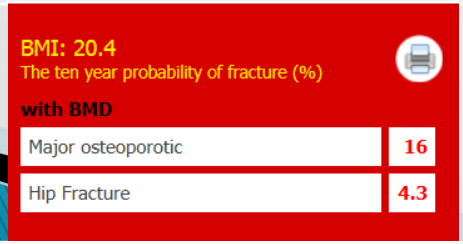
- Provide recommendations for the evaluation, treatment and management of osteoporosis
  - mainly in postmenopausal women, some in men
- Refine characterization of risk to direct appropriate intervention
- Emphasize assessment after being on treatments to determine if and when further treatments are necessary

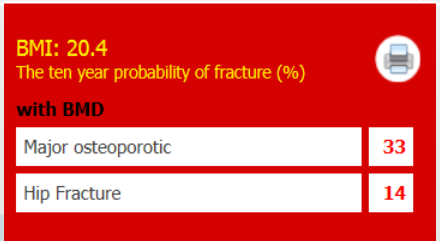
Challenges in Formulation of Guidelines: Target Patient Population

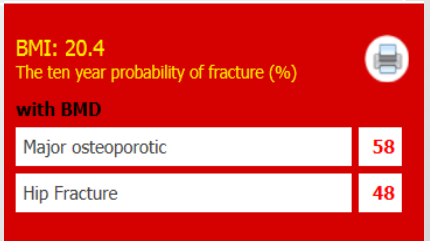
Fracture risk and risk categories among "unequivocally" osteoporotic patients

Caucasian female, height 63", weight 115 lbs, + family h/o osteoporosis

Patient	1	2	3
Age	58	68	78
Prior fracture	wrist	no	humerus
Parent fractured hip	no	yes	yes
Current smoking	yes	no	no
Lumbar spine BMD T-score	-2.8	-2.5	-3.1
Femoral neck BMD T-score	-2.2	-3.5	-3.3







Challenges in Formulation of Guidelines: Target Patient Population

- Osteoporosis encompasses men and women with fragile bones, but very different levels of fracture risk.
- Consideration of patient diversity is critical for effective treatment of osteoporosis.
- Patient diversity, particularly with respect to level of fracture risk, is important in determining initial osteoporosis therapy as well as duration of therapy.*

*Endocrine Society 2019, AACE/ACE 2020, NOF 2021, IOF 2020

Family history

- Mother – osteoporosis; hip, wrist, elbow, rib and vertebral fractures
- Brother – 2 vertebral compression fractures

Fracture history

- 4/2016 – Acute L1 fracture, L2 fracture noted – URI, cough and "muscle pull"
- 1/2018 – acute T10 and T11 fractures – coughed and heard a "pop"
- X-ray also showed a sacral insufficiency fracture
- 4/2018 – acute T12 fracture, no inciting event

DXA

- Lumbar spine (L3-L4) T-score -3.8
- Left total hip -2.0; femoral neck -2.7

- VFA = Vertebral Fracture Assessment.

Who are the Highest Risk Patients?

- Prior fracture is the most important risk factor for future fracture[1]
  - Recent fracture(s) suggests very high risk (osteoporosis emergency/urgency)[2,3]
    - In over 377,000 women with first fracture[2], absolute risk of another fracture:
      - 10% first year
      - 18% first 2 years
      - 31% first 5 years
  - Multiple fractures also indicate very high risk[4,5]
  - Proactive spine imaging required to find morphometric vertebral fractures
    - NHANES VFA Study 2017[6]
      - Vertebral Fracture Prevalence 5% in 60s, 10% in 70s, 20% in 80s[3]

1. Kanis J Bone 2004
2. Balasubramanian A et al OI 2018
3. Van Geel TA, et al Ann Rheum Dis 2009
4. Gehlbach et al OI 20007
5. van Helden S, et al OI 2006
6. Cosman F et al OI 2017

Family history

- Mother with bilateral hip fractures

Past medical history

- Healthy
- Remote former smoker

Fracture history

- Acute T11 compression fracture – leaned over in shower and could not stand up.
- Fracture has been life altering

DXA

- Lumbar Spine T-score -2.8 Right hip -2.5; FN -2.7
- Compared with 2 years prior, BMD decreased by 6.2% and 6.4% at LS and total hip, respectively

- VFA = Vertebral Fracture Assessment.

Family history

- No known osteoporosis or fractures

Past medical history

- Healthy
- Menopause age 53
- BMI 22.3 kg/m^2 (weight 121 pounds, height 5'2")

Medications

- No prescriptions
- Multivitamin and vitamin D3 1000 IU daily

DXA

- Lumbar Spine T-score -3.3 Left hip -2.5; FN -2.7

- VFA = Vertebral Fracture Assessment.

Who are the Highest Risk Patients?

- Other considerations for very high risk (vary by guideline)
  - **Very low T-score: <-3.0**
  - **Very high fracture probability: FRAX MOF >30% or hip fracture >4.5%** (or other validated fracture risk algorithm to be at very high fracture risk)
  - Fractures while on approved osteoporosis therapy
  - Fractures while on drugs causing skeletal harm (ie, long-term glucocorticoids)
  - High risk for falls or history of injurious falls

AACE Guidelines. Endocrine Practice. 2020;26(Suppl 1).

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*

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High risk/no prior fractures**

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

Reassess yearly for response to therapy and fracture risk

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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
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Very high risk/prior fractures**

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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.

Endocrine Society Updated Algorithm for Management of Postmenopausal Osteoporosis 2020

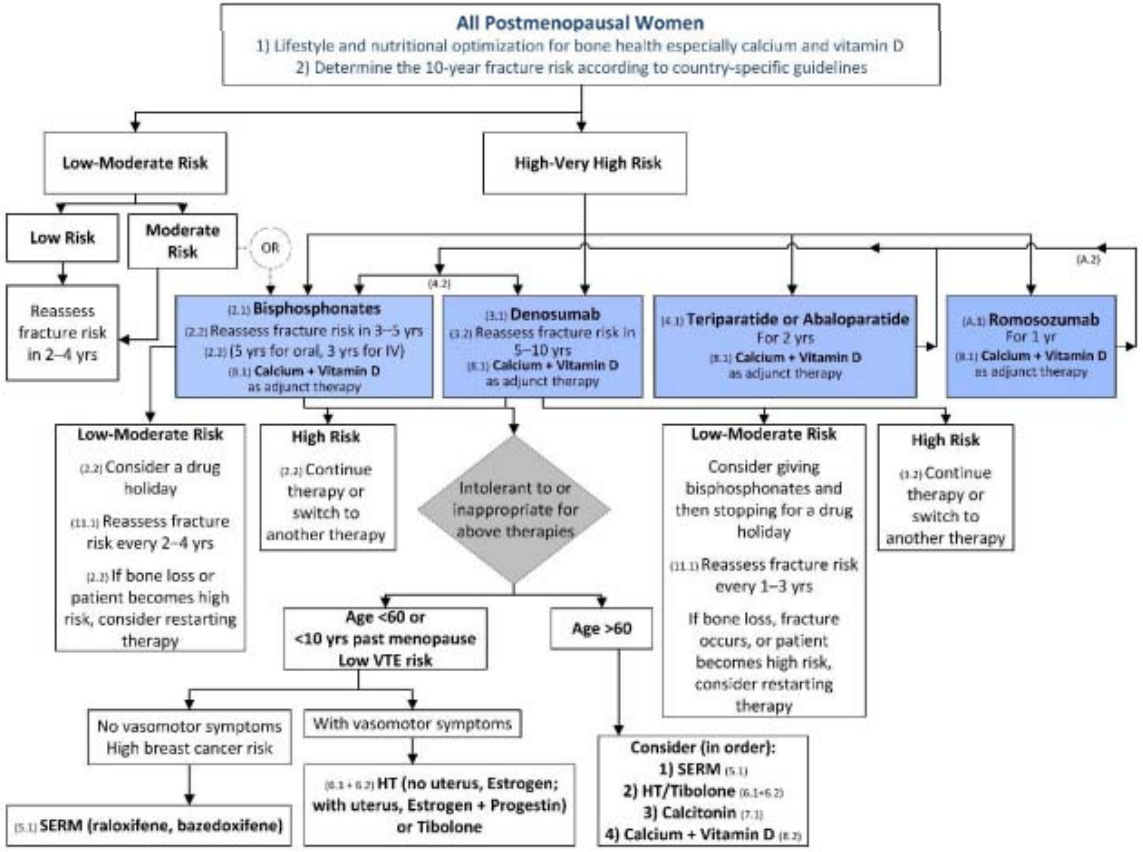


Figure 1. Updated algorithm for management of postmenopausal osteoporosis. Note: We considered that a determination of fracture risk would include measurement of lumbar spine and hip BMD and inserting femoral neck BMD value into the fracture risk assessment (FRAX) tool. Using that FRAX algorithm, we define the following risk categories: "low risk" includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above –1.0, and 10-year hip fracture risk <3% and 10-year risk of major osteoporotic fractures <20%; "moderate risk" includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above –2.5, and 10-year hip fracture risk <3% or risk of major osteoporotic fractures <20%; "high risk" includes a prior spine or hip fracture, or a BMD T-score at the hip or spine of –2.5 or below, or 10-year hip fracture risk ≥3%, or risk of major osteoporotic fracture risk ≥20%; and "very high risk" includes multiple spine fractures and a BMD T-score at the hip or spine of –2.5 or below.

Pharmacologic Treatment Recommendations – NOF Clinician's Guide

- No uniform recommendation applies to all patients. Management plans must be individualized.

- Consider initiating pharmacologic treatment in postmenopausal women and men ≥50 years of age who have:
  - Primary Fracture Prevention:
    - T-score ≤ -2.5 at the femoral neck, total hip, lumbar spine, 33% radius by DXA.
    - Low bone mass (osteopenia: T-score between -1.0 and -2.5) at the femoral neck or total hip by DXA **with** a 10-year hip fracture risk ≥3% or a 10-year major osteoporosis-related fracture risk ≥20% (clinical vertebral, hip, forearm, or proximal humerus) based on the U.S. adapted FRAX® model.
  - Secondary Fracture Prevention:
    - Fracture of the hip or vertebra regardless of BMD
    - Fracture of proximal humerus, pelvis, or distal forearm in persons with low bone mass (osteopenia: T-score between -1.0 and -2.5). The decision to treat should be individualized in persons with a fracture of the proximal humerus, pelvis, or distal forearm who *do not have osteopenia or low BMD*.

- Supports the Endocrine Society's treatment algorithm for the management of postmenopausal osteoporosis according to fracture risk

LeBoff M, et al. Osteoporos Int 2021, accepted.

What Else Helps to Inform Treatment Decisions?

- Comparative Fracture Data
- Treatment Sequence Considerations
- Goal Directed Therapy or Treat-to-Target

- Emphasis on the aforementioned and prominence in executive summary or body of report varies between guidelines, though all include (NOF, AACE, Endo)
- ACP does not really consider risk stratification or the above:
  - Recommendation 1 Treat with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral compression fractures in women who have known osteoporosis *(grade: strong recommendation; high-quality evidence)*
  - Recommendation 3 Treat with bisphosphonates to reduce the risk for vertebral fracture in men who have clinically recognized osteoporosis. *(Grade: weak recommendation; low-quality evidence)*

Bone Forming versus Anti-resorptive Agents

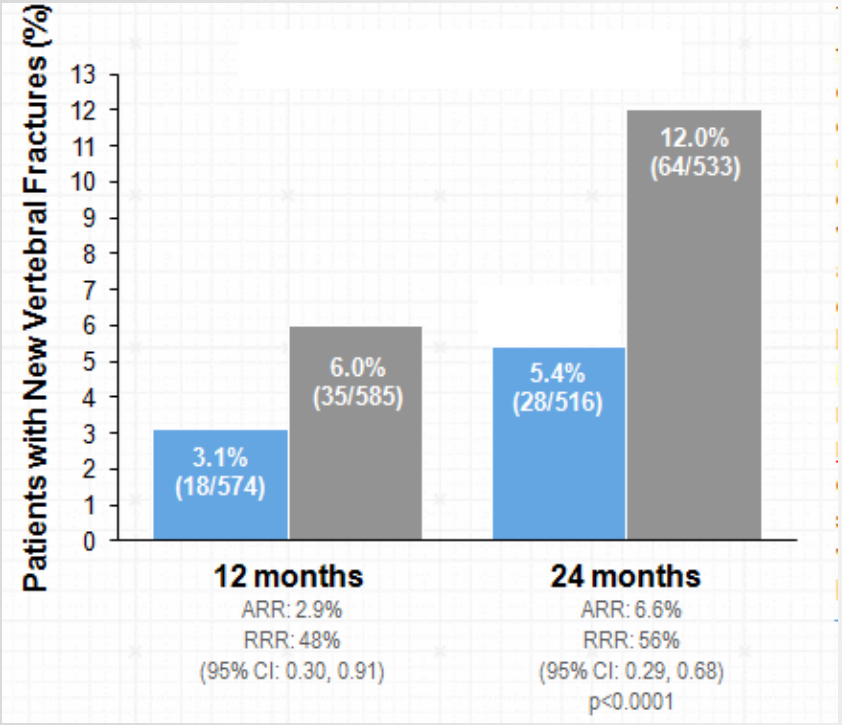
Bone forming agents

- Reduce vertebral and non-vertebral fracture risk
- Romosozumab reduces hip fracture risk vs alendronate (RRR 38%)
- Significant compared to anti-resorptive agents (head-to-head fracture trials: VERO, ARCH)
- ***Appropriate for high/very high-risk patients in need of skeletal rescue; large, rapid increases in BMD and rapid reduction in fracture risk***
- ***To be followed by a bisphosphonate or denosumab***

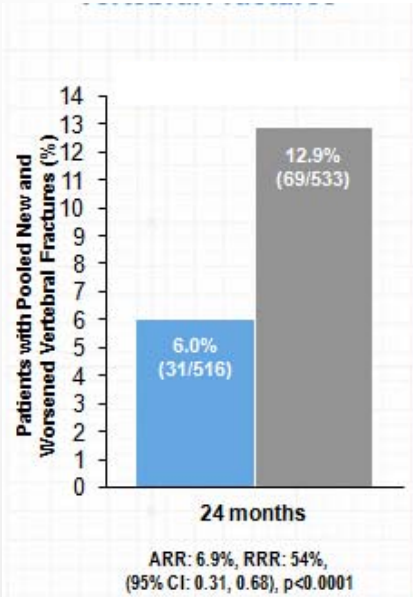
VERO - Kendler DL et al. *Lancet* 2017 Nov 9. pii: S0140-6736(17)32137-2
ARCH - Saag K et al. *N Engl J Med.* 2017;377:1417-27

Head-to-Head Fracture Study (VERO): Teriparatide vs Risedronate

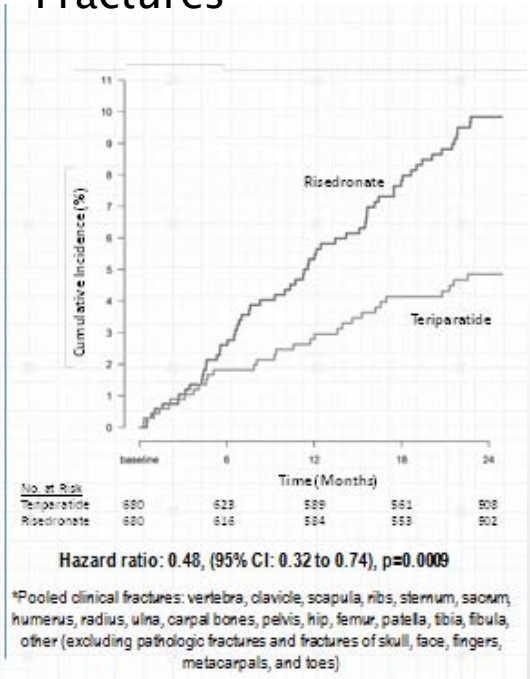
Incidence of New Vertebral Fractures



Incidence of New & Worsened VFs



Cumulative Incidence of Pooled Clinical Fractures



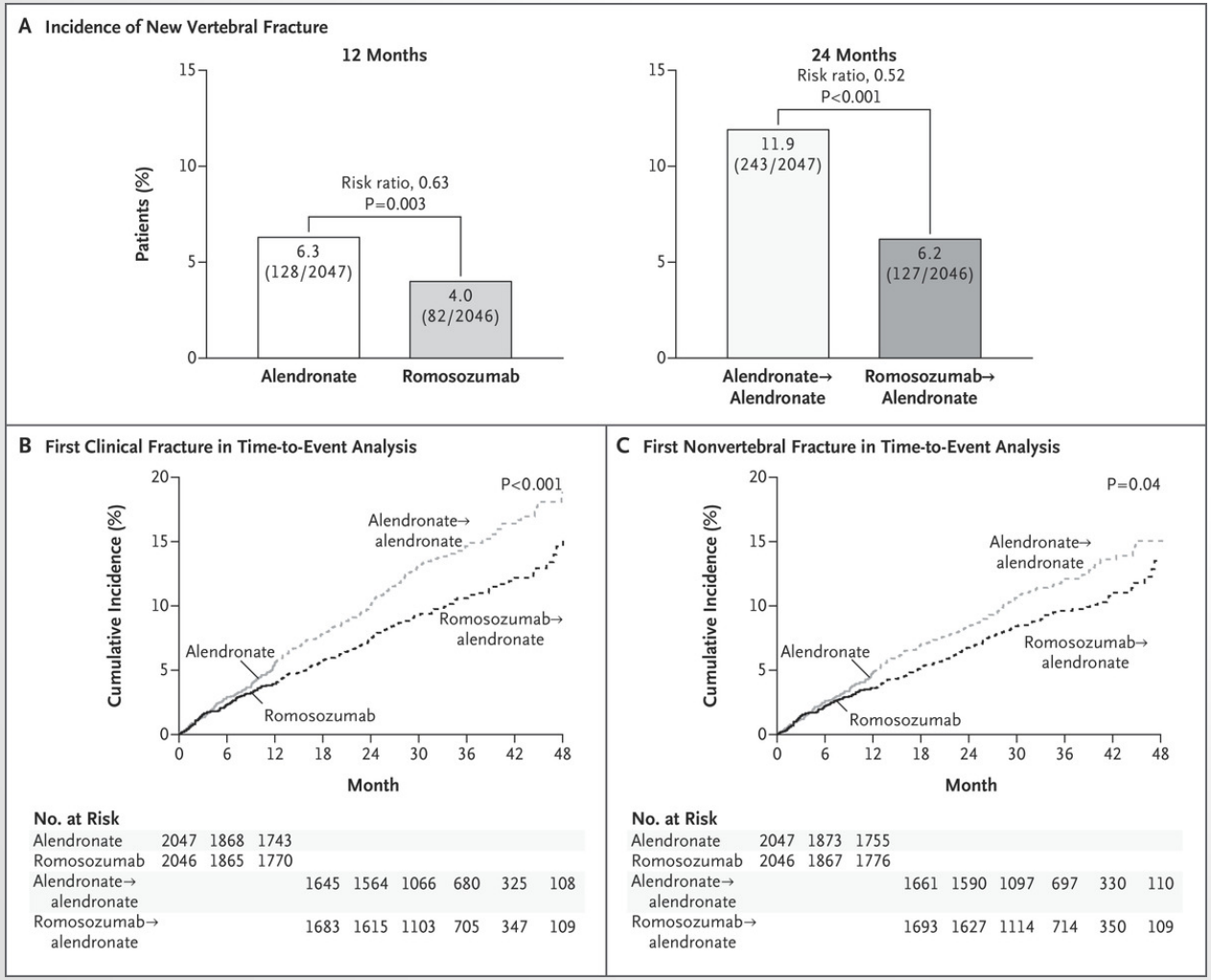
Teriparatide

Risedronate

Comparison of cumulative incidence of non-vertebral fractures did not meet statistical significance

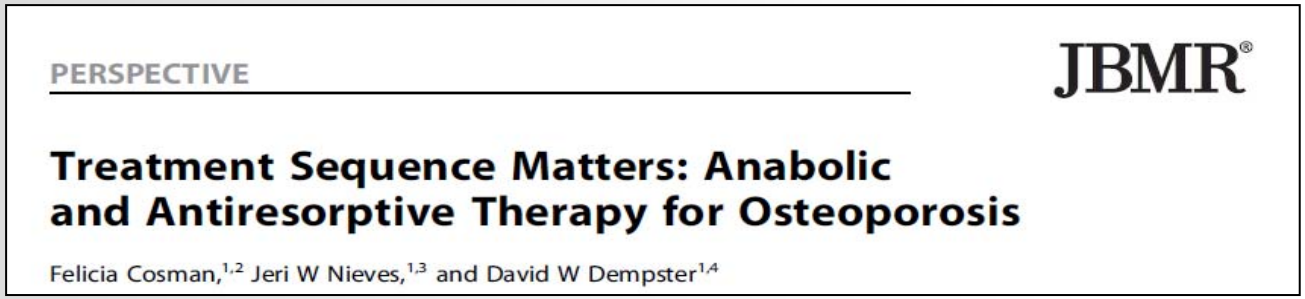
Kendler, DL et al. The Lancet 2017; 391:230-240

Head-to-Head Fracture Study (ARCH): Romosozumab vs Alendronate



Saag KG et al. N Engl J Med 2017;377:1417-1427

Osteoporosis Treatment Sequence: Sequence Matters



PERSPECTIVE

JBMR®

Treatment Sequence Matters: Anabolic and Antiresorptive Therapy for Osteoporosis

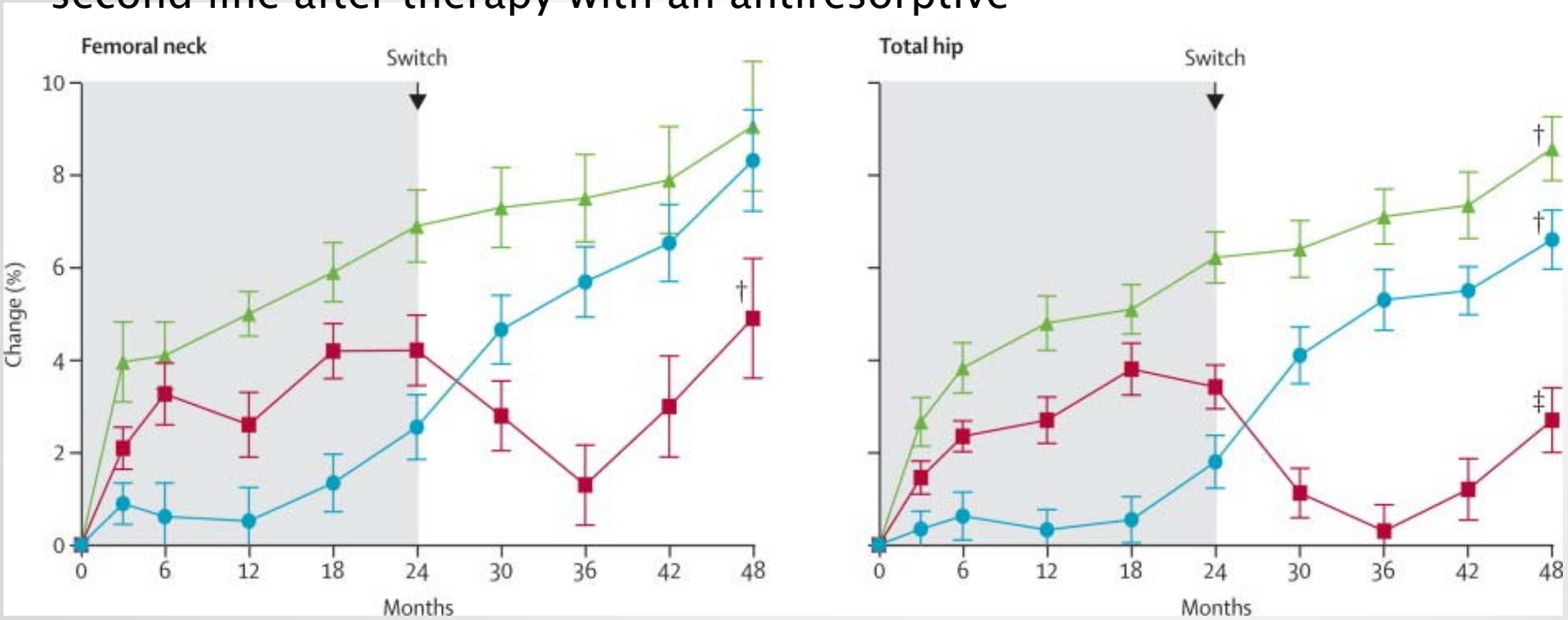
Felicia Cosman,[1,2] Jeri W Nieves,[1,3] and David W Dempster[1,4]

- There is accumulating evidence that BMD and fracture outcomes are significantly influenced by the order in which antifracture agents are administered
- When sequential treatment is considered, **anabolic therapy followed by an antiresorptive agent is preferred.**
- An anabolic agent administered following antiresorptive therapy has demonstrably less impact on BMD and fracture risk than if the anabolic is administered first
- Anabolic therapy after a potent antiresorptive agent may be followed by a delay or attenuation of effect or even bone loss (hip BMD loss and strength)

NOF Clinician's Guide 2021; AACE Guidelines 2020

Osteoporosis Treatment Sequence:
4 Year Sequential Treatment with Teriparatide and Denosumab (DATA-Switch)

Greater BMD gains when an anabolic agent is used first followed by a potent antiresorptive agent, as compared to when an anabolic is used second line after therapy with an antiresorptive



Green: Combination Teriparatide +Denosumab for 2 years followed by Denosumab for 2 years
Red: Denosumab for 2 years followed by Teriparatide for 2 years
Blue: Teriparatide for 2 years followed by Denosumab for 2 years

Leder BZ et al. Lancet 2015, 386:1147–55

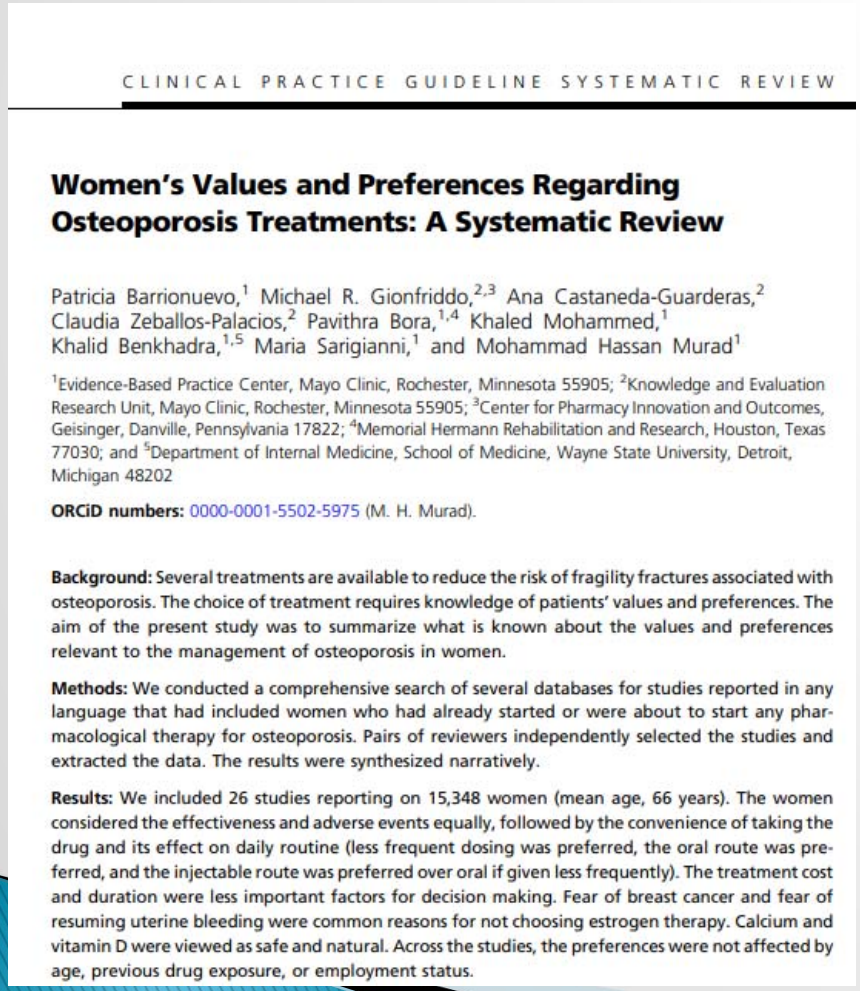
Setting and Reaching Goals of Therapy: Treat-to-Target

- Stratify patients according to level of fracture risk
- Identify a treatment target that represents an acceptable level of risk
- Initiate treatment with an agent most likely to reach the target
- Site-specific vulnerabilities can be factored in, such as recent wrist or vertebral fracture, as well as fracture reduction data for each of the treatments.
- Speed of effect onset should also be considered in relation to a patient's imminent fracture risk.
- Monitor for response to treatment and to track progress in reaching the target
- If patient is not responding or not on track to reach the target, then consider altering treatment plan
- Fundamental to the concept of "treat-to-target" is the principle that response to therapy is not necessarily sufficient to achieve an acceptable level of risk. A patient may reach their "target" BMD and still be at unacceptably high risk for fracture.

Cummings SR et al. J Bone Min[illegible] Res. 2017;32:3–10. NOF Clinician's Guide 2020

Patient Preferences Are Important

The ideal medication may be the one best able to sufficiently reduce risk, while accommodating a patient's needs and preferences.



CLINICAL PRACTICE GUIDELINE SYSTEMATIC REVIEW

Women's Values and Preferences Regarding Osteoporosis Treatments: A Systematic Review

Patricia Barrionuevo,[1] Michael R. Gionfriddo,[2,3] Ana Castaneda-Guarderas,[2] Claudia Zeballos-Palacios,[2] Pavithra Bora,[1,4] Khaled Mohammed,[1] Khalid Benkhadra,[1,5] Maria Sarigianni,[1] and Mohammad Hassan Murad[1]

[1]Evidence-Based Practice Center, Mayo Clinic, Rochester, Minnesota 55905; [2]Knowledge and Evaluation Research Unit, Mayo Clinic, Rochester, Minnesota 55905; [3]Center for Pharmacy Innovation and Outcomes, Geisinger, Danville, Pennsylvania 17822; [4]Memorial Hermann Rehabilitation and Research, Houston, Texas 77030; and [5]Department of Internal Medicine, School of Medicine, Wayne State University, Detroit, Michigan 48202

ORCiD numbers: 0000-0001-5502-5975 (M. H. Murad).

Background: Several treatments are available to reduce the risk of fragility fractures associated with osteoporosis. The choice of treatment requires knowledge of patients' values and preferences. The aim of the present study was to summarize what is known about the values and preferences relevant to the management of osteoporosis in women.

Methods: We conducted a comprehensive search of several databases for studies reported in any language that had included women who had already started or were about to start any pharmacological therapy for osteoporosis. Pairs of reviewers independently selected the studies and extracted the data. The results were synthesized narratively.

Results: We included 26 studies reporting on 15,348 women (mean age, 66 years). The women considered the effectiveness and adverse events equally, followed by the convenience of taking the drug and its effect on daily routine (less frequent dosing was preferred, the oral route was preferred, and the injectable route was preferred over oral if given less frequently). The treatment cost and duration were less important factors for decision making. Fear of breast cancer and fear of resuming uterine bleeding were common reasons for not choosing estrogen therapy. Calcium and vitamin D were viewed as safe and natural. Across the studies, the preferences were not affected by age, previous drug exposure, or employment status.

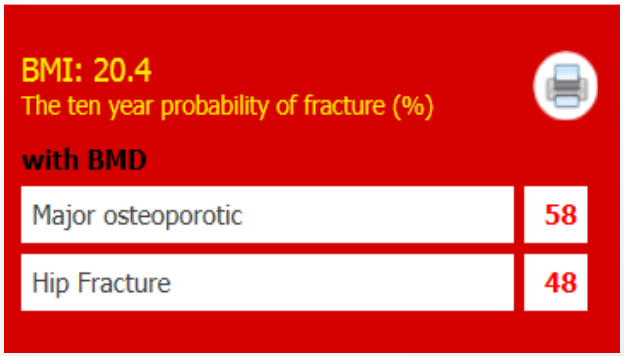
- Conclusions
  - Women value effectiveness and side effects equally
  - Medications given less frequently are preferred
  - Injectable drugs appear acceptable if given less frequently
  - More research is needed

Barrioneuvo P, et al. J Clin Endocrinol Metab 2019; 104:1631-1636

Duration of Treatment

- Balance between benefit and risk depends on:
  - Individual patient characteristics
  - Initial fracture risk
  - Residual fracture risk

78 yo WF
63”, 115 lbs
Humerus fracture
Parent hip fracture
Spine T-score -3.1; FN -3.3



Treatment beyond five years may be recommended, as residual fracture risk likely remains high, and benefits of treatment would be expected to outweigh risks.

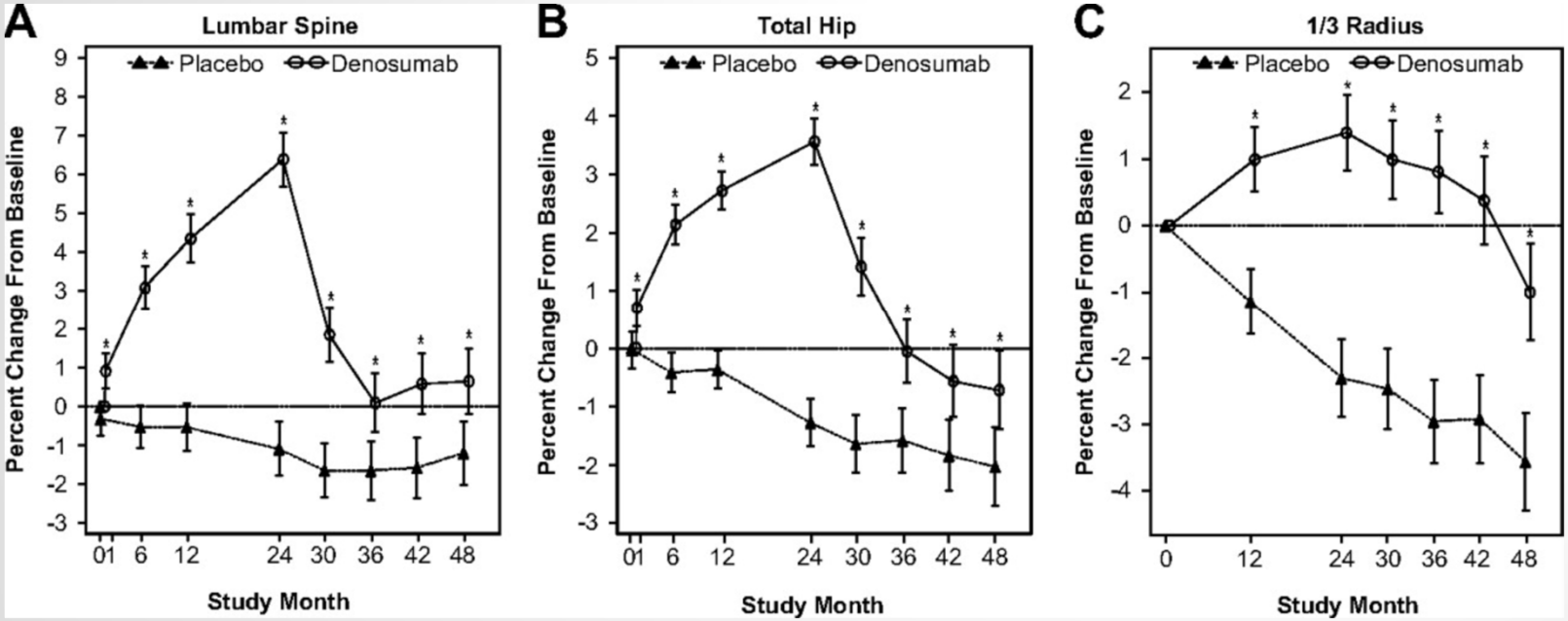
Duration of Treatment

	ACP	ASBMR Task Force, AACE/ACE, Endocrine Society, NOF	
Pharmacologic agent(s) discussed	Treat osteoporotic women with "pharmacologic therapy" for 5 years	Bisphosphonates (BPs): •Oral BPs: consider a holiday after 5 years of stability in moderate-risk patients and 6-10 years in higher-risk patients •IV ZA: consider a holiday after 3 years/doses in moderate-risk patients and 6 years/doses in higher-risk patients. •A drug holiday is not recommended with denosumab	
Continuation of treatment recommended	"Continuing treatment after 5 years may be beneficial for some patients and may be appropriate after reassessing the risks and benefits of continuing therapy." In text only	Consider up to 10 years of BP (or alternative) treatment for: •Hip, spine or multiple other OP fractures before/during treatment •Hip BMD T-score ≤-2.5 •High fracture risk defined by older age (70–75 years), other strong risk factors for fracture, •FRAX fracture risk score that is above country specific thresholds	• Bone forming agents or raloxifene may be used during BP holiday for higher-risk patients • Other agents should be continued for as long as clinically appropriate
Assessment of fracture risk after discontinuation of treatment		• Every 2-3 years, including DXA • Ending of BP "holiday" based on individual patient – fracture occurrence or fracture risk or change in BMD (DXA) or biochemical markers of bone turnover	

Adler R et al. *J Bone Miner Res* 2016; 31:16–35

ASBMR – American Society for Bone and Mineral Research; AACE/ACE – American Association of Clinical Endocrinologists/American College of Endocrinology; DXA – dual-energy X-ray absorptiometry; ZA – zoledronic acid

Effects of Denosumab Discontinuation



- Effects of 60 mg denosumab every 6 months for 24 months on BMD is reversible upon treatment discontinuation for 24 months, reflecting the biological mechanism of action of denosumab.
- Continued therapy is required to maintain treatment effects.

Bone HG, et al. J Clin Endocrinol Metab. 2011;96(4):972-980.

Duration of Therapy: What Does This Mean in Clinical Practice?

- The duration of therapy needs to be individualized
- Discontinuation of therapy or a "drug holiday" is a bisphosphonate specific concept
- Drug holidays may be appropriate for some patients taking bisphosphonates, but not all, and abrupt cessation of other medications is not appropriate.
- Newer guidelines address transitions from therapeutic agents with particular attention to denosumab.
- Osteoporosis is a chronic disease and as such, requires lifelong *management*
- Monitoring after discontinuation of bisphosphonate treatment and re-initiation of anti-fracture therapy need to be addressed and individualized to provide the best patient outcomes.
- A drug holiday does **not** equal drug retirement

Assessing Response to Therapy and Reassessing Fracture Risk

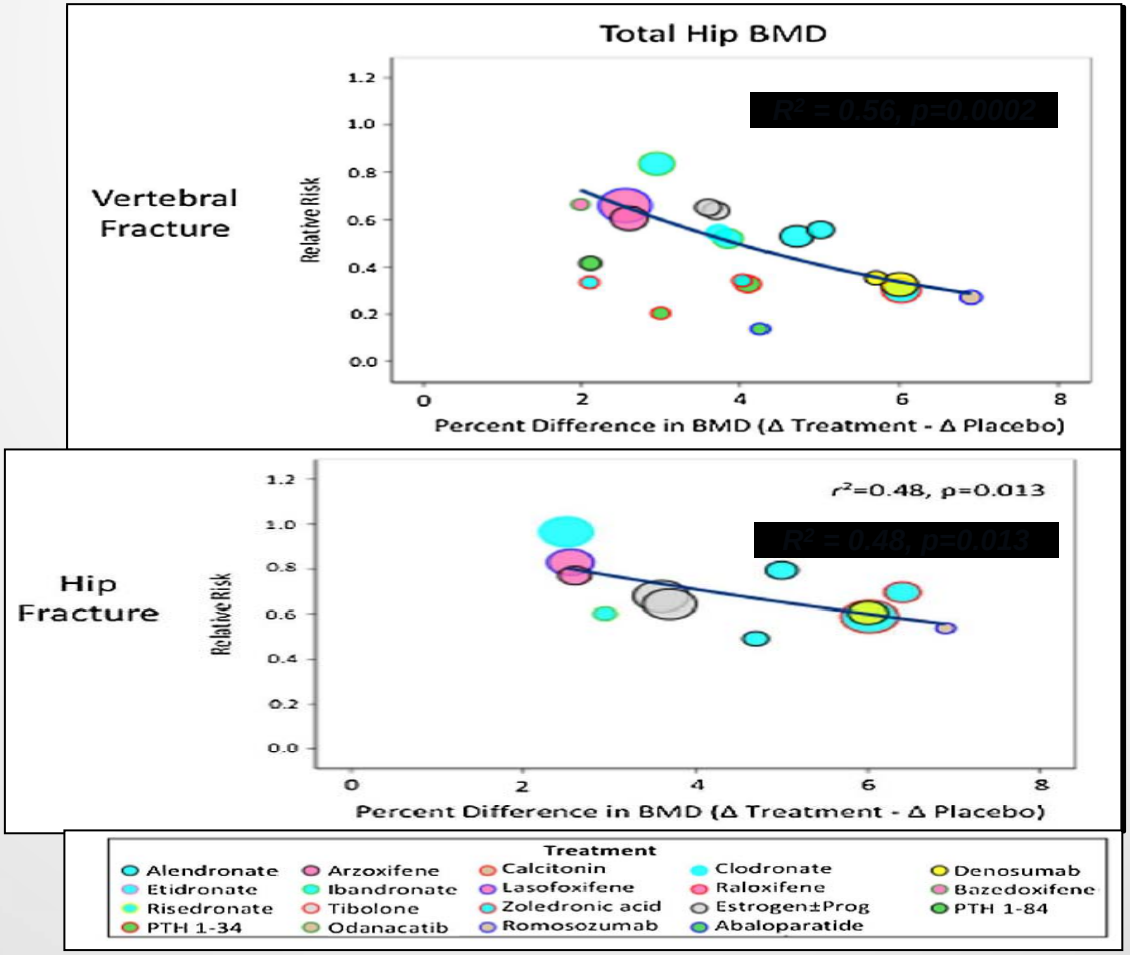
- NOF, AACE/ACE: Baseline axial DXA and repeat DXA every 1-2 years until stable. Continue with follow-up DXA every 1-2 years or at a less frequent interval depending on clinical circumstances.
- Endocrine Society: In those being treated, axial DXA every 1 to 3 years to assess the response to treatment.
- ACP: Recommends against bone density monitoring during the five-year pharmacological treatment period

Why Monitor?

- Variability of response to medications, poor adherence.
- Relationship between BMD gains and fracture reduction appear to be more consistent across therapies than previously appreciated (FINH database)
- Individual gains in BMD appear to be much better correlated with efficacy in “real world” experience than in clinical trials.
- May not be feasible or acceptable to patients to start therapy and provide no concrete follow-up.

Relationship Between Change in Hip BMD On-treatment and Fracture Risk

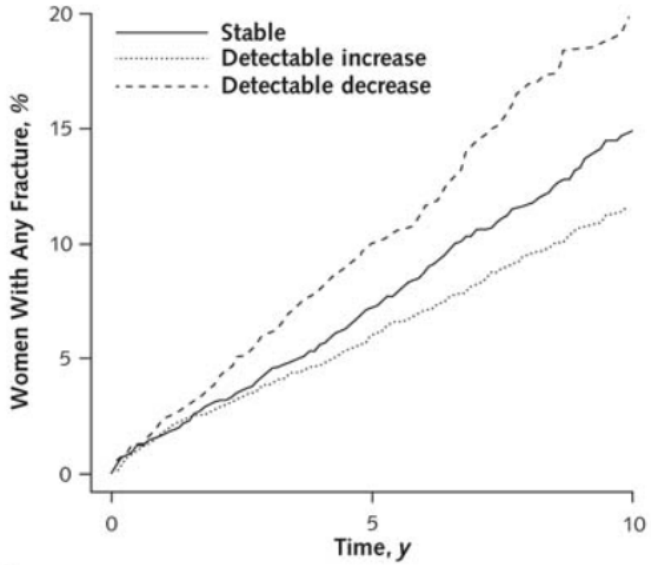
Larger increases in hip BMD were associated with greater reduction in vertebral and hip fracture risk



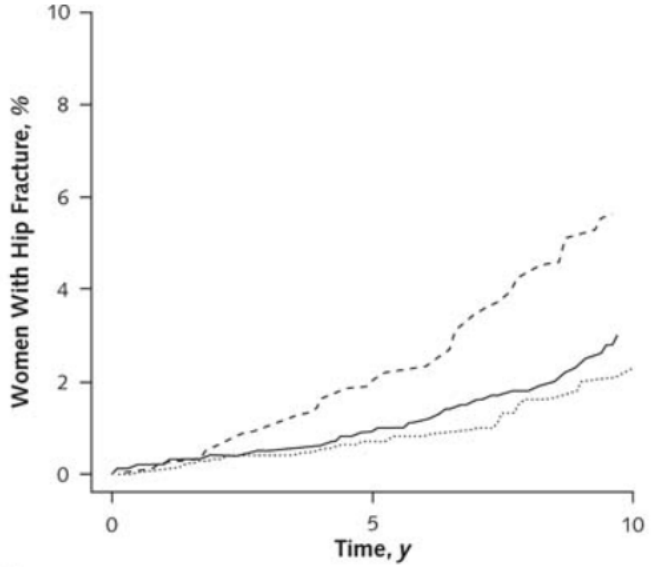
Bouxsein M et al. *J Bone Miner Res* 2019;34:632-42

BMD Changes and Anti-Fracture Efficacy: Routine Clinical Practice

Cumulative fracture risk, by change in total hip BMD



Women at risk, *n*			
Stable	3333	2762	1277
Detectable increase	1995	1717	796
Detectable decrease	1235	1036	557



Women at risk, *n*			
Stable	3333	2945	1447
Detectable increase	1995	1812	889
Detectable decrease	1235	1115	628

6629 women 40+ initiating therapy with 2 consecutive DXAs (mean interval 4.5 years)

Leslie WD, et al. Ann Intern Med. 2016;165(7):465-472.

What Does This Mean in Clinical Practice?

- The frequency of BMD re-evaluation should be individualized.
- Patients with osteoporosis may have undiagnosed disorders contributing to bone loss or may have absorption or adherence issues.
- Obtaining a follow-up DXA scan to identify an individual who is not responding to therapy may be crucial to be able to change therapy before the occurrence of a fracture that could be life altering.

57-year-old woman:

Family history

- Mother – osteoporosis, vertebral fracture

History

67 inches
130 pounds

Menopause at 53

No prior fracture

Evaluation:
Lumbar spine T-score -2.7
Left total hip -2.2; femoral neck -2.1

Estrogen and the Guidelines

- Estrogen deficiency is the main pathophysiological mechanism of bone loss in both women and men
- Estrogen is approved for preventing osteoporosis in postmenopausal women but this indication is not fully endorsed by all guidelines
- Reduced fracture risk by ~34% in low-risk women in WHI
- Rapid loss of BMD and fracture protection upon stopping therapy
- *Ideal therapy to prevent relatively rapid bone loss in early menopause – especially in women with vasomotor symptoms – to be followed by a bisphosphonate to maintain the benefit when estrogen therapy is stopped*
- NAMS endorses use; also considers extended use of HT as an option. Awaiting updated guidelines
- AACE, NOF, and Endocrine Society endorse use of estrogen or estrogen plus progestogen with some caveats
- ACP guideline (recommendation 5) recommends against using menopausal estrogen therapy or menopausal estrogen plus progestogen therapy or raloxifene for the treatment of osteoporosis in women. *(Grade: strong recommendation; moderate-quality evidence)*

62-year-old woman:

Family history

- Mother – osteoporosis
- Breast cancer

History

67 inches
130 pounds

Menopause at 51

No prior fracture

Evaluation:
Lumbar spine T-score -2.7
Left total hip -2.2; femoral neck -2.1

Raloxifene and the Guidelines

- Weak anti-remodeling effects
- Small BMD effect, not sustained
- Reduced vertebral fracture risk by 30-50%
- No hip or non-vertebral fracture reduction
- Increased risk of venous thrombosis (AR 1.2/1000 woman-yrs)
- Increased risk of stroke in older women at risk for heart disease (AR 0.7/1000 woman-yrs)
- Can worsen vasomotor symptoms

- *Appropriate for younger postmenopausal women at risk for vertebral but not hip fracture, especially with risk factors/increased risk for breast cancer*

- Approved by the FDA for prevention and treatment of postmenopausal osteoporosis (PMO) as well as for the reduction of risk of breast cancer in women with PMO or at high risk of breast cancer.

- NAMS endorses use. Awaiting updated guidelines

- AACE/ACE, NOF and Endocrine Society endorse these indications with some caveats

- ACP guideline (recommendation 5) recommends against using menopausal estrogen therapy or menopausal estrogen plus progestogen therapy or raloxifene for the treatment of osteoporosis in women.

What Does This Mean in Clinical Practice?

- Unless contraindicated, women with early menopause or primary ovarian insufficiency who require prevention of bone loss are likely best served with ET/HT or oral contraceptives rather than other bone-specific treatments until average age of menopause, at which time treatment may be reassessed.

- HT (estrogen, estrogen-progestin, or conjugated estrogens-bazodoxefine) may be the most appropriate bone-active therapy in women with bothersome vasomotor symptoms, without contraindications, and with elevated risk of bone loss, who are < age 60 or within 10 years of menopause.

- HT may be used in women at increased risk for fracture when alternate osteoporosis therapies are not appropriate, cause adverse effects or intolerance, or have shown lack of efficacy.

- Although raloxifene is not effective in reducing hip fracture risk, it may be appropriate initial therapy in some women, particularly those in younger years, who are at risk for vertebral fractures, especially when other antiresorptive medications are contraindicated or not tolerated or in women at elevated risk for breast cancer, who are seeking the potential additional “benefit” of reducing breast cancer risk.

Patient Phone Message

- **Situation:**
  - Pt asking for next steps since PCP informed her that she no longer has osteoporosis.

- **Background/Assessment:**
  - Pt states that her PCP, Dr. Smith, informed her that she no longer has osteoporosis. She is asking how she needs to follow up.
  - Last denosumab injection 4/13/2021. Last DXA was 2019.

Patient: Lucy

- 73 year-old woman
- Initial DXA with Lumbar spine T-score -3.0, total hip -1.9; FN -2.5
- History of distal radius fracture
- Initially treated elsewhere with oral bisphosphonates and had GI intolerance. Switched to denosumab.
- DXA 2 years later showed Lumbar spine T-score -2.4, Total hip -1.6, FN -2.3
- She is pleased that she no longer has osteoporosis and wants to know if she can stop treatment

How Do You Respond?

- Two major questions:
  - Does this patient still have osteoporosis?
  - Can treatment be stopped?
- No drug holiday with denosumab
  - Stopping treatment leads to increased remodeling and decreased BMD
  - Increased risk for multiple vertebral fractures seen
  - Prior vertebral fracture is greatest predictor of off-treatment multiple vertebral fractures

Cummings SR et al. J Bone Miner Res. 2018;33:190-198.

PERSPECTIVE

JBMR®

Treated Osteoporosis Is Still Osteoporosis

E Michael Lewiecki,[1] Neil Binkley,[2] and John P Bilezikian[3]

- Osteoporosis is a lifelong disease that warrants lifelong attention
- There is no known "cure" for osteoporosis
- Retaining the diagnosis is consistent with other chronic diseases (diabetes, hypertension, etc)
- Adverse consequences of changing diagnosis to "osteopenia" include
  - False sense of security
  - Stopping medication that is still needed
  - Potential loss of insurance coverage for medication
  - Change in allowable frequency of BMD testing

Lewiecki EM et al. J Bone Miner Res. 2019;34(4):605-606.

Osteoporosis is a Chronic Disease Requiring Long-term Management

- NOF Clinician's Guide
  - *Maintain diagnosis of osteoporosis in patient diagnosed by fracture in adulthood or T-score (-2.5 or below), even if subsequent DXA T-score is above -2.5.*
- AACE/ACE Guidelines
  - *When the initial diagnosis of osteoporosis is made according to a T-score of $\leq$ -2.5, the diagnosis persists even when a subsequent DXA measurement shows a T-score better then -2.5*
- Helps providers and patients focus on concept that osteoporosis can be treated effectively, fracture risk can be reduced, but there is no cure and therefore ongoing management is necessary

Conclusions

- While guidelines must be concise and easy to implement, they must be balanced with a consideration of:
  - the wide range of patient presentations
  - the differing properties of osteoporosis therapies
- Though it may be aspirational, harmonization of the guidelines is an important goal to help guide clinicians and patients in management of osteoporosis and post-fracture care.
  - Complete harmonization may be difficult because of regional differences in healthcare priorities, variability in resources, availability of diagnostic tools, and variability in treatment options around the world.
- Open discussion and debate regarding the evaluation and treatment of osteoporosis are essential as is ongoing research to define optimal diagnostic and therapeutic approaches.
- Guidelines are meant to guide, not take the place of clinical judgement.
- Individualization of patient goals and targets should be placed at the center of discussion.

Lewiecki, EM et al. *Osteoporos Int* **31,** 2073–2076 (2020).