

OSTEOPOROSIS TREATMENT UPDATES
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DISCLOSURES

- Dr. Lindsey Reakes, presenter for this CE activity, has no relevant financial relationship(s) with ineligible companies to disclose.

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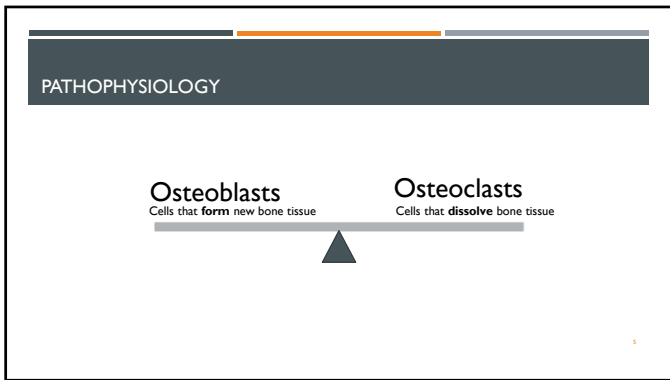
OBJECTIVES

- Identify risk factors for osteoporosis and implement plan for modifiable risk factors
- Recognize drugs that contribute to osteoporosis risk
- Appropriately identify and refer patients meeting criteria for bone mineral density screening
- Utilize bone mineral density and FRAX score to determine patients who require treatment
- Choose appropriate pharmacotherapy treatment in patients with diagnosis of osteopenia and osteoporosis

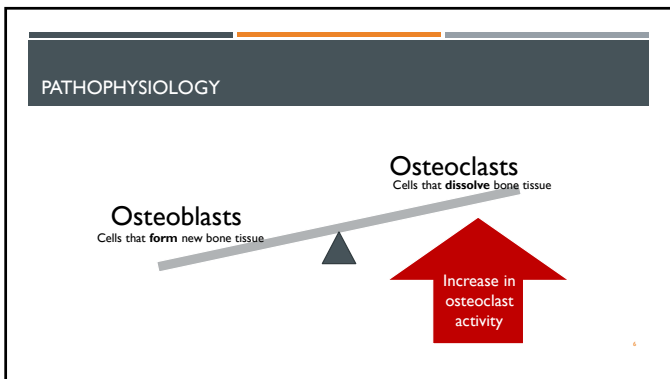
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GUIDELINES FOR OSTEOPOROSIS

Update expected late 2022

ACR (2017) NAMS (2021) NICE (2018)

NOF (2014) NOGG (2017) AACE (2020)

ACR: American College of Rheumatology
 NAMS: The North American Menopause Society
 NICE: National Institute for Health & Care Excellence

NOF: National Osteoporosis Foundation
 NOGG: National Osteoporosis Guideline Group
 USPSTF: United States Preventive Services Task Force

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NAMS UPDATES

Nearly 50% of women 50+ years of age will experience osteoporosis-related fracture in their lifetime

Primary cause of bone loss at menopause is estrogen deficiency

Hormone therapy is appropriate treatment at time of menopause

Osteoporosis is progressive with advancing age

NAMS 2021

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NAMS UPDATES

Once diagnosed, life-long management is required

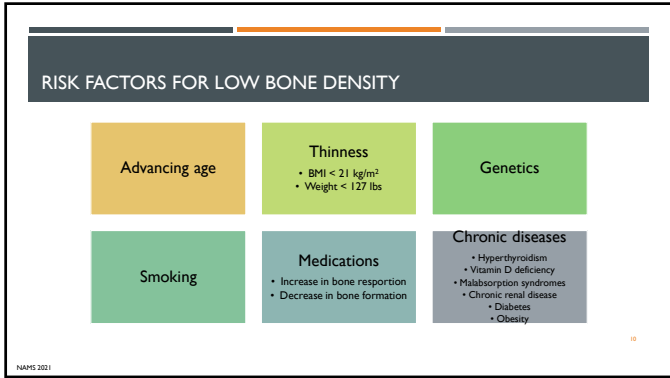
BMD (during treatment) is directly correlated with patient hip fracture risk

hip T-scores are the appropriate clinical targets upon which clinicians should base therapeutic choices

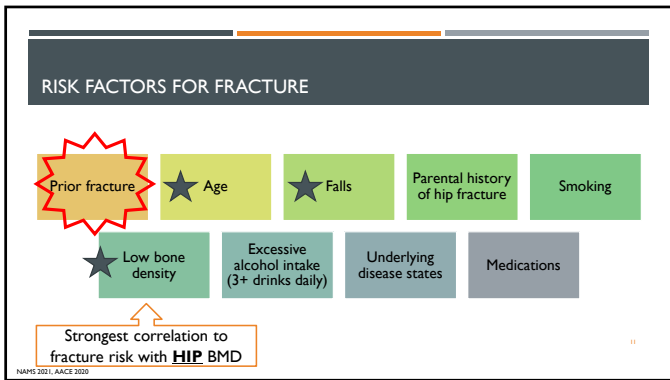
Recommendation for those at **very high fracture risk** focuses on treatment initiation with an osteoanabolic or bone-building agent, followed by an anti-remodeling agent.

NAMS 2021

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QUESTION 1

Which of the following is **NOT** a risk factor for low bone density?

- BMI of 24 kg/m²
- Advanced age
- Smoking
- Family history of osteoporosis

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MEDICATIONS ASSOCIATED WITH OSTEOPOROSIS

Associated with bone loss	Associated with fracture risk
<ul style="list-style-type: none"> Aromatase inhibitors Excess thyroid hormone Gonadotropin-releasing hormone Cytotoxic agents Glucocorticoids > 3 months IM medroxyprogesterone 	<ul style="list-style-type: none"> PPI SGLT₂-inhibitors SSRI/SNRI Thiazolidinediones

NAME 2021

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QUESTION 2

All of the following medications are associated with bone loss or fracture risk, EXCEPT:

- Omeprazole
- Jardiance
- Amlodipine
- Prednisone > 3 months

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USPSTF SCREENING RECOMMENDATION

Population	Recommendation	Grade
Women 65 years and older	The USPSTF recommends screening for osteoporosis with bone measurement testing to prevent osteoporotic fractures in women 65 years and older.	B
Postmenopausal women younger than 65 years at increased risk of osteoporosis	The USPSTF recommends screening for osteoporosis with bone measurement testing to prevent osteoporotic fractures in postmenopausal women younger than 65 years who are at increased risk of osteoporosis, as determined by a formal clinical risk assessment tool. See the Clinical Considerations section for information on risk assessment.	B
Men	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis to prevent osteoporotic fractures in men. See the Clinical Considerations section for suggestions for practice regarding the I statement.	I

U.S. Preventive Services Task Force. Screening for Osteoporosis. U.S. Preventive Services Task Force Recommendation Statement. JAMA. 2018;319 (24): 2521-2533

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INDICATIONS FOR BMD TESTING

- History of fracture post-menopause
- Known medical causes of bone loss or fracture
- 65 years or older Aligns with USPSTF
- 50 years or older with 1+ risk factor:
 - Weight < 127 lbs
 - History of hip fracture in parent
 - Current smoker
 - Discontinuing estrogen with additional risk factors for fracture

Peri or postmenopausal with additional risk factors:

- Excessive consumption of alcohol
- Long term systemic glucocorticoid use (3+ months)

NAMIS 2021, AACE 2020

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INDICATIONS FOR BMD TESTING (NOF 2014)

- Women age 65 or older & men age 70 and older, regardless of risk factors
- Younger postmenopausal women, in perimenopausal and men 50-69 with clinical risk factors for fracture
- Adults who have a fracture at or after age 50
- Adults with certain medication conditions or on medications known to result in bone loss
- Off medication for osteoporosis treatment for 1-2 years

NOF 2014

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QUESTION 3

Which of the following patients is **NOT** indicated for bone mineral density screening?

- 66 YO post-menopausal female who has never been screened
- 43 YO female who is a current every day smoker
- 56 YO post-menopausal female who is discontinuing estrogen therapy
- 59 YO post-menopausal female with history of fracture at age 57

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DIAGNOSIS

Dx based on T-score **persists** even when subsequent DXA shows improved T-score

- Diagnosed by DXA
- History of vertebral or hip fracture, irrespective of BMD or other risk factors
- Low bone mass AND any of the following:
 - History of fracture of proximal humerus, pelvis or distal forearm
 - History of multiple fractures at other sites (excluding face, feet, hands)
 - Increased fracture risk using FRAX country-specific thresholds

10-year hip fracture probability of $\geq 3\%$ or a 10-year major osteoporosis-related fracture probability $\geq 20\%$

NAMS 2021, AACE 2020, NOF 2014

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FRAX CALCULATOR

- Validated & accurate predictor in large US populations. Available online at www.shef.ac.uk/FRAX or as an application on smart phones

- Pearls of FRAX
 - Underestimates in patients with recent falls, diabetes, or those with low spine BMD, but not femoral neck BMD
 - Does not include all risk factors
 - RA may be entered into FRAX as a surrogate or fracture associated with T2DM

NOGG 2017, AACE 2020, www.shef.ac.uk/FRAX

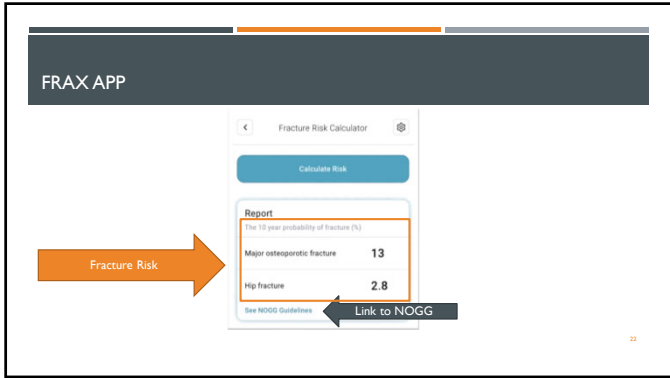
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FRAX APP

No quantification of risk factors such as:

- glucocorticoid dose
- alcohol intake
- smoking duration

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REPEAT SCREENING DXA

Population	Recommendation
Postmenopausal (50-64 y) and baseline T-score great than -1.5	Defer to age 65 (USPSTF screening recommendation)
Initial T-score less than -1.5 and within 5 years of menopause	"Earlier retesting should be considered"
Untreated postmenopausal women at low risk	Every 5 years, unless rapid bone loss anticipated
Important risk factors ^a	"Earlier retesting should be considered"

^a prior fracture, medical conditions or medications that predispose to bone loss

Interval between repeat BMD screenings may be longer for patients without major risk factors and who have initial T-score in the normal or upper low bone mass range

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PHYSICAL EXAM & LABORATORY MONITORING

- Physical exam should include detailed evaluation of risk factors, history of fractures or falls, and other family history. Annual height and weight should be recorded.
- Routine labs should be ordered to rule out secondary causes of bone loss or contraindications to specific therapy:

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NON-PHARMACOLOGICAL TREATMENT

- Correct any modifiable risk factors (i.e. smoking cessation, limiting alcohol)
- Regular physical activity to improve strength and balance
- Steps for fall prevention, including tapering high risk medications
- Adequate intake of calcium and vitamin D

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CALCIUM & VITAMIN D SUPPLEMENTATION

- Dietary intake preferred over supplementation
- Calcium may require multiple doses, only ~ 600 mg of elemental calcium can be absorbed with each dose
- Calcium formulations:
 - Carbonate – preferred, highest elemental calcium (40%), cheapest, more GI discomfort
 - Citrate – preferred with acid suppressing agents, lower elemental calcium (21%)
- Vitamin D₃ preferred for replacement

Age (y)	Calcium, mg		Vitamin D, IU	
	EAR	RDA	EAR	RDA
51-70	1000	1200	400	600
71+	1000	1200	400	800

EAR, estimated average requirement; RDA, recommended daily allowance

NAMS 2012, AACCE 2010
<http://www.bonin.nih.gov/health-info/bone-health/nutrition/calcium-and-vitamin-d-important-every-age>

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PHARMACOLOGICAL AGENTS

PREVENTION & TREATMENT OF OSTEOPOROSIS

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TRABECULAR STRUCTURE

Goal should be to prevent bone loss and development of osteoporosis and subsequent fractures

Normal bone Osteoporotic bone

NOF 2014

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TREATMENT OPTIONS

Antiresorptive

- Bisphosphonates
- Denosumab
- Raloxifene
- Calcitonin-salmon

Osteoanabolic

- PTH Receptor agonists
- Romosozumab

Osteoanabolic agent

↓

Antiresorptive agent

Correct low serum calcium before starting therapy

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PREVENTION vs TREATMENT

<p>Prevention</p> <ul style="list-style-type: none"> ■ Bisphosphonates ■ Estrogen receptor agonist-antagonist (EAA) ■ Hormone therapy 	<ul style="list-style-type: none"> ■ Bisphosphonates ■ Calcitonin-salmon ■ Denosumab ■ Estrogen receptor agonist-antagonist (EAA) ■ Hormone Therapy ■ PTH agonists ■ Raloxifene ■ Romosozumab 	<p>Treatment</p> <ul style="list-style-type: none"> ■ Bisphosphonates ■ Calcitonin-salmon ■ Denosumab ■ PTH agonist ■ Raloxifene ■ Romosozumab
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Evidence supporting the superiority of anabolic agents over antiresorptive agents in reducing vertebral fracture risk in very high risk patients

NAMS 2021, AACE 2020

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MONITORING TREATMENT WITH DXA

- Repeat DXA every 1-2 years until findings are stable
- If BMD decreases in treated patient, evaluate for:
 - Non-adherence
 - Secondary causes of osteoporosis
 - Use of medications that might cause bone loss

AAACE 2020 31

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PHARMACOLOGICAL AGENTS

PREVENTION OF OSTEOPOROSIS

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MEDICATION COVERAGE

Medication	Vertebral?	Non-vertebral?	Hip?	Prevention	Treatment
Alendronate					
Ibandronate					
Risedronate					
Zoledronic acid					
Raloxifene					
Denosumab					
Teriparatide					
Abaloparatide					
Romosozumab					
Calcitonin					

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HORMONE THERAPY - PREVENTION

- Primary indication is for treatment of vasomotor symptoms in select patients, with benefit of bone protection
- Several oral or transdermal options indicated for **prevention** of postmenopausal osteoporosis
 - Intact uterus → estrogen + progestin
 - No uterus → estrogen alone
- Estrogen therapy **NOT** approved for treatment
- Benefit rapidly declines with withdrawal of agent
- Adverse effects:
 - EPT: increased risk of breast cancer, VTE and stroke
 - ET: increased risk for DVT and stroke

Timing is KEY!

- Benefits outweighs risks for patients: **≤ 60 years and within 10 years of menopause**

NAMS 2021, AACE 2020

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ESTROGEN-BAZEDOXIFENE - PREVENTION

- Available in fixed dose combination of CE 0.45 mg + bazedoxifene 20 mg once daily
- MOA: combination of estrogen + EAA provides relief of vasomotor symptoms and maintenance of BMD in postmenopausal females with intact uterus
- Indicated for young postmenopausal women with VMS and **prevention** of osteoporosis
- Antagonist activity at uterus prevents endometrial hyperplasia – no progestin needed

Best Candidates

- Postmenopausal women with intact uterus
- Needing relief from hot flashes and prevention of bone loss

Caution use in

- Women > 60 years of age

NAMS 2021, AACE 2020

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BISPHOSPHONATE - PREVENTION

- MOA: impairs osteoclast function, resulting in decrease in bone remodeling and increase in bone mineral density
- Consider for prevention of bone loss in early menopause if estrogen cannot be taken or when hormone therapy is discontinued
- Approved agents include alendronate, risedronate, ibandronate, and zoledronate – discussed in next section

NAMS 2021, AACE 2020

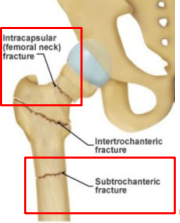
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PHARMACOLOGICAL AGENTS
TREATMENT OF OSTEOPOROSIS

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BISPHOSPHONATE - TREATMENT

- All agents approved for treatment, weekly doses based on BMD compared to daily use, not fracture endpoints
- Treatment plateaus after ~ 5 years
- Common adverse effects
 - Bone and/or muscle pain
 - Gastric distress (oral) – follow administration guidelines to help minimize
 - Flu like symptoms (zoledronic acid)
 - Osteonecrosis of jaw (ONJ)
 - Atypical femur or subtrochanteric fractures




NAMS 2021, AAACE 2020

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BISPHOSPHONATE - TREATMENT

- Contraindications to bisphosphonate therapy
 - Hypocalcemia
 - Severe renal impairment (eGFR < 30-35 mL/min depending on agent)
 - Pregnancy or lactation
 - Abnormalities of esophagus that lead to delayed emptying
 - Inability to remain in upright position for 30-60 minutes



NAMS 2021, AAACE 2020

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ALENDRONATE

- Approved for postmenopausal osteoporosis or osteoporosis in men, and for treatment of glucocorticoid induced osteoporosis
- Administer first thing in morning, 30+ minutes prior to food or drinks. Swallow whole.
- Remain upright for **30+ minutes** and until food has been eaten
- Renal adjustments:
 - Use not recommended in CrCl < 35 mL/min
- Available as tablet, solution, or effervescent tablet

	Weekly	Daily
Low Bone Mass	35 mg	5 mg
Osteoporosis	70 mg	10 mg

Fracture Reduction		
Vertebral	Nonvertebral	Hip
YES	YES	YES

NAMS 2021, AACF 2020

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IBANDRONATE

- Approved for postmenopausal osteoporosis
- Administer 60 minutes before first food, drink or medications. Swallow whole
- Remain upright for **60 minutes**
- Renal dose adjustments:
 - Use not recommended in CrCl < 30 mL/min
- Available as: oral tablet, IV solution

	Monthly	Q3 Months
Low Bone Mass	150 mg	NO
Osteoporosis	150 mg	3 mg (IV)

Fracture Reduction		
Vertebral	Nonvertebral	Hip
YES	NO	NO

NAMS 2021, AACF 2020

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RISEDRONATE

- Approved for postmenopausal osteoporosis, osteoporosis in men and for prevention of glucocorticoid-induced osteoporosis in postmenopausal women
- Administration:
 - IR: On empty stomach with 6-8 oz of water 30 minutes prior to food or drink.
 - DR: immediately after breakfast with 4 oz of water
- Remain upright for **30+ minutes**
- Renal dose adjustment:
 - Not recommended in CrCl < 30 mL/min
- Available as: IR tablet, DR tablet

	Monthly	Weekly	Daily
Low Bone Mass	150 mg	35 mg	5 mg
Osteoporosis	150 mg	35 mg	5 mg

Fracture Reduction		
Vertebral	Nonvertebral	Hip
YES	YES	YES

NAMS 2021, AACF 2020

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ZOLEDRONIC ACID

- Approved for postmenopausal osteoporosis and men at increased risk of fracture, and glucocorticoid-induced osteoporosis in men and women
- Administration: infused over 15 minutes in health care facility
 - May develop flu like symptoms; if needed may treat with acetaminophen
 - Ensure proper hydration PRIOR to infusion
- Renal dose adjustment:
 - Not recommended in CrCl < 35 mL/min or evidence of acute kidney injury
 - Use with caution in CrCl < 80 mL/min
- Available as: IV solution

	Yearly	Every 2 years
Low Bone Mass	NO	5 mg (or 1 x dose)
Osteoporosis	5 mg	NO

Fracture Reduction		
Vertebral	Nonvertebral	Hip
YES	YES	YES

NAMS 2021, AAACE 2020

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BISPHOSPHONATE DRUG HOLIDAYS

- Consider drug holiday after 3-5 years of treatment in low-moderate fracture risk and no longer meeting treatment criteria
 - 5 years with oral bisphosphonates
 - 3 years for IV zoledronate
- Bone turnover begins to increase after 2-3 years off of therapy

Restart if and when:

- Significant decline in BMD
- Intervening fracture
- Change in clinical risk
- After 18 months – 3 years

Those remaining at high risk:

- Continue bisphosphonate therapy or
- Switch to denosumab or osteoanabolic agent

NAMS 2021, AAACE 2020, NODG 2017

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BISPHOSPHONATE DRUG HOLIDAYS IN HIGH RISK

Recent fracture within 12 months

Age 75 or greater

History of hip or spine fracture

History of multiple low trauma fractures

Hip bone density < -2.5 or very low T-score (< -3)

Long term use of glucocorticoids

FRAX major fracture > 30% or hip > 4.5%

NAMS 2021, AAACE 2020, NODG 2017

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DENOSUMAB - TREATMENT

- MOA: monoclonal antibody that inhibits RANK ligand, a primary stimulator of bone resorption
- Approved for postmenopausal women, men at increased risk of fracture, and glucocorticoid induced osteoporosis
- Administered as 60 mg subcutaneous injection every 6 months in health care facility

Fracture Reduction		
Vertebral	Nonvertebral	Hip
YES	YES	YES

NAMS 2021, AACF 2020

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DENOSUMAB - TREATMENT

- Bone turnover rapidly returns after discontinuation
 - Doses should be completed on time
- Use okay in renal impairment
- Hypocalcemia more common, monitor levels prior to each dose and within 2 weeks after first dose if pre-disposed to hypocalcemia
- Rare occurrence of ONJ or atypical femur fractures

NO DRUG HOLIDAY!

NAMS 2021, AACF 2020

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RALOXIFENE – PREVENTION AND TREATMENT

- MOA: estrogenic agonist activity at bone to prevent bone loss and estrogenic antagonist activity at breast and uterine tissues. Decreases bone resorption, leading to increased BMD and decreased fracture incidence.
- Associated with bone loss when given to premenopausal women
- Reduces incidence of breast cancer by 76% at 3 years
- Adverse effects: increased hot flashes, leg cramps and increased risk of VTE

Best Candidates

- Low risk of hip fracture
- Elevated risk of breast cancer
- Low risk of stroke & VTE

Fracture Reduction		
Vertebral	Nonvertebral	Hip
YES	NO	NO

NAMS 2021, AACF 2020

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CALCITONIN SALMON - TREATMENT

- AACE recommends **limiting use** of calcitonin as long-term treatment due to availability of more effective agents
- Available subcutaneous daily injection or nasal spray
- Rapid bone loss on discontinuation within 1-2 years

Fracture Reduction	Fracture Reduction		
	Vertebral	Nonvertebral	Hip
	YES	NO	NO

NAMS 2021, AACE 2020

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PTH RECEPTOR AGONIST - TREATMENT

Anabolic agents

- Two agents available: teriparatide & abaloparatide
- Administered as daily subcutaneous injections
- Adverse events: orthostatic hypotension (with first dose), hypercalcemia, increased risk of tumors in rats
- Avoid use in:
 - Hypercalcemia
 - Osteosarcoma
 - Skeletal metastasis

Fracture Reduction	Fracture Reduction		
	Vertebral	Nonvertebral	Hip
	YES	YES	NO

Limit 2 years in a lifetime for most*

- Teriparatide updated Nov. 2020 to allow for one repeat course in appropriate patients
- Abaloparatide limited to 2 years in a lifetime

NAMS 2021, AACE 2020
*Formo. Package insert, Lilly USA, 2020

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ROMOSUZUMAB- TREATMENT

- Mechanism of action: monoclonal antibody that inhibits sclerostin
- Sclerostin inhibits bone formation by:
 - Inhibiting osteoblast formation from precursors
 - Inhibits function of mature osteoblasts
 - Inhibits new bone modeling
 - Secondarily, increases bone resorption

DUAL EFFECT

↑ INCREASES BONE FORMATION ↓ DECREASES BONE RESORPTION


<https://www.emoryhpq.com/mechanism-of-action>

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ROMOSUZUMAB- TREATMENT

- Indicated for post-menopausal osteoporosis at high risk of fracture

History of osteoporotic fracture → History of multiple fractures → Failed other treatment



- Administered as 210 mg (2 injections) once monthly for 12 months by healthcare provider
- Adverse effects:
 - injection site reactions
 - increased risk of cardiovascular events
- Avoid use if patient had MI or stroke in previous year. Discontinue if MI or stroke while on therapy

NAMS 2021, AAACE 2020

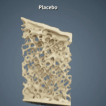

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ROMOSUZUMAB- TREATMENT

- Compared to alendronate, romosuzumab decreased vertebral fracture risk by 37%

Fracture Reduction		
Vertebral	Nonvertebral	Hip
YES	YES	YES

- 12 months of romosuzumab, followed by alendronate therapy compared to alendronate alone
 - Reduced nonvertebral fractures by 19%
 - Reduced hip fractures by 38%

NAMS 2021, AAACE 2020
<http://www.evenityhip.com/mechanism-of-action>

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QUESTION 4

Which of the following the best treatment option for a patient with osteopenia based on T-scores?

- Denosumab
- Romsozumab
- Teriparatide
- Bisphosphonate

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MEDICATION COVERAGE					
Medication	Vertebral?	Non-vertebral?	Hip?	Prevention	Treatment
Alendronate	✓	✓	✓	✓	✓
Ibandronate	✓	✗	✗	✓	✓
Risedronate	✓	✓	✓	✓	✓
Zoledronic acid	✓	✓	✓	✓	✓
Raloxifene	✓	✗	✗	✓	✓
Denosumab	✓	✓	✓	✗	✓
Teriparatide	✓	✓	✗	✗	✓
Abaloparatide	✓	✓	✗	✗	✓
Romosozumab	✓	✓	✓	✗	✓
Calcitonin	✓	✗	✗	✗	✓

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QUESTION 5

A 63 YO post-menopausal female (menopause ~ 8 years ago) had a recent diagnosis of *osteoporosis* based on T-score at FN of -2.5. She has not had any recent fractures and does not believe she has a family history of fractures. Her C-Cl is > 60 mL/min. Which of the following would be the best treatment option to provide hip, vertebral, and non-vertebral fracture reduction?

- A. Alendronate 35 mg once weekly
- B. Risedronate 35 mg once weekly
- C. Ibandronate 150 mg monthly
- D. Romosozumab 210 mg once monthly x 12 months

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CASE EXAMPLES

Table 9. Choosing an initial treatment for postmenopausal osteoporosis

Example	Fracture Risk	Recommended starting therapy
Age 65 y T-score: LS -2.6, FN -1.8 No other risk factors	Moderate	Raloxifene or bisphosphonate
Age 68 y, mother with hip fracture T-score: FN -2.8 Wrist fracture at 60	High	Bisphosphonate or denosumab
Age 72 y T-score: FN -3 Humerus fracture age 68 Two recent vertebral fractures	Very High	Osteoanabolic drug

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PEARLS

- Ensure normal calcium prior to start agents
- Many agents require dose adjustments for renal dysfunction
- Concomitant use is not recommended for prevention or treatment, but sequential therapy may be beneficial

NAMS 2021, AACE 2020

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OSTEOPOROSIS TREATMENT UPDATES

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FULL GUIDELINE REFERENCES

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