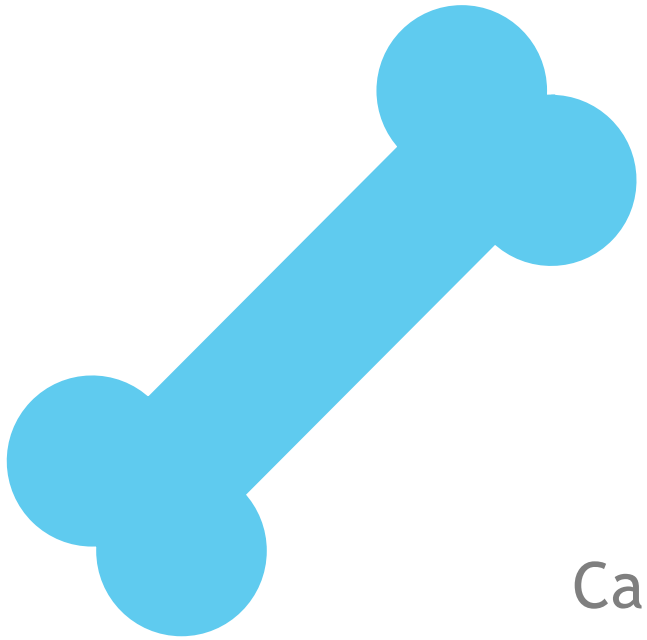

Osteoporosis: An Overview

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Disclosure of financial relationships

- None
- (I am Chair of the American College of Physicians Clinical Guidelines Committee)

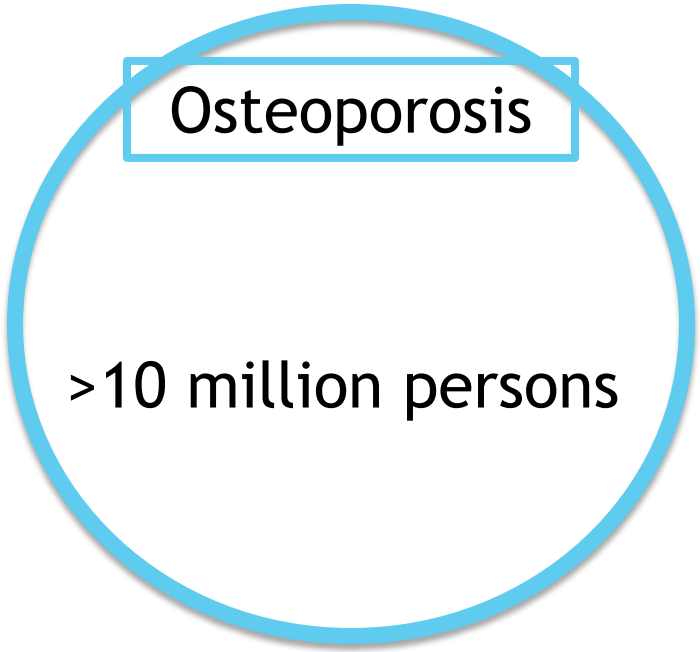
Objective

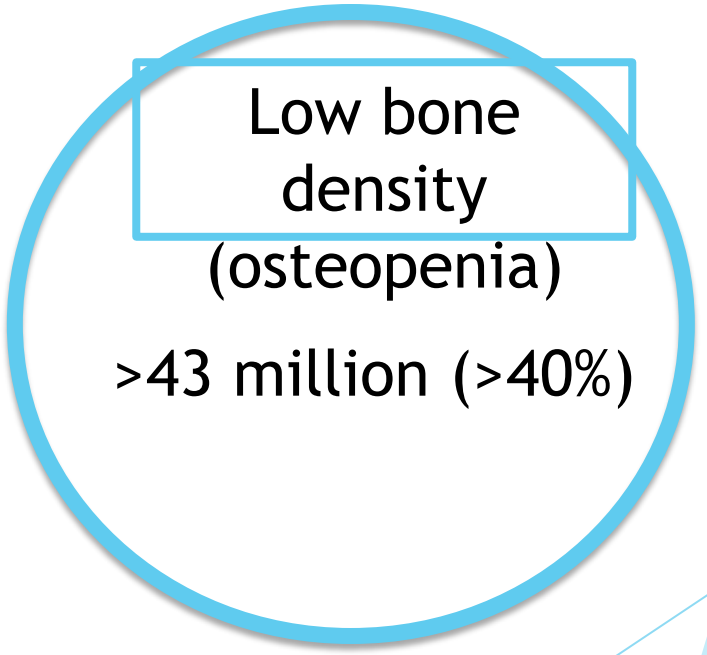
- Learn key “take-home messages” regarding:
  - Screening guidelines for persons aged ≥65 y/o
  - Medication management of osteoporosis.

Importance

Osteoporosis → fractures→ serious morbidity and mortality

In the U.S. age 50+:





Objective

- Learn key “take-home messages” regarding:
  - **Screening guidelines for persons aged ≥65 y/o**
  - Medication management of osteoporosis.

United States Preventive Services Task Force (USPSTF) 2018 screening recommendations

- Women 65 years and older:
  - screen with bone mineral density (BMD) test (B recommendation)

(JAMA. 2018;319(24):2521-2531

United States Preventive Services Task Force (USPSTF) 2018 screening recommendations

- Men:
  - current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis to prevent osteoporotic fractures in men. (I statement)

(*JAMA*. 2018;319(24):2521-2531

Men: Clinical considerations USPSTF 2018

- An estimated 1 to 2 million men in the United States have osteoporosis.
- Men account for 29% of osteoporotic fractures in the United States.
- But..
- In the absence of other risk factors, it is not until age 80 years that the prevalence of osteoporosis in White men starts to reach that of White women at age 65 years.
- Data on effectiveness of medications to treat osteoporosis in men are lacking. (*JAMA*. 2018;319(24):2521-2531)


Whom to screen
Effective treatments?

Objective

- Learn key “take-home messages” regarding:
  - Screening guidelines for persons aged ≥65 y/o
  - **Medication management of osteoporosis.**

Calcium and Vit. D: Institute of Medicine Recommended Dietary Allowance

Group		Dose	
Sex	Age	Calcium	Vitamin D
Women	51-70	1,200 mg/d	600 IU/d
Men	51-70	1,000 mg/d	600 IU/d
Women and Men	>70 y/o	1,200 mg/d	800 IU/d

GENERAL POPULATION!

Worthwhile!

http://www.iom.edu/reports/2010/dietary-reference-intakes-for-calcium-and-vitamin-d.aspx (report brief)

VITAL trial Vitamin D 2022

- RCT 25,871 participants
  - men 50 years of age or older
  - women 55 years of age or older
  - Vit. D3 supplement (2000 IU/d), n−3 fatty acids (1 g per day), or both
  - median follow-up of 5.3 years.
- Vit. D3 vs. placebo, did not have a significant effect on:
  - total fractures, nonvertebral fractures, or hip fractures.
- No fracture reduction in people with h/o fragility fx or low baseline vit. D level (LeBoff et al NEJM 2022)

U.S. FDA-approved prescription osteoporosis therapies 2023*

- Antiresorptive:
- Bisphosphonates
  - Alendronate
  - Risedronate (incl. delayed-rel. Atelvia)
  - Ibandronate (IV/PO)- postmeno. women
  - Zoledronic acid (IV)
- Monoclonal Ab: inhibitor of receptor activator of nuclear factor-kappa B
  - Denosumab
- Selective estrogen receptor modulator
  - Raloxifene- postmeno. women only
- Anabolic:
- Recombinant parathyroid hormone
  - Teriparatide subcut[1] (max. 2 yrs, exceptions)
- Parathyroid hormone-related peptide (1-34) analog (PTH1 rec agonist)
  - Abaloparatide[1] (> 2 yrs not recommended) subcut.
- Dual ↑ formation and ↓ resorption
- Sclerostin inhibitor (monoclonal Ab)
  - Romosozumab [1] (max 1 yr)-postmeno women

- [1]hx of osteoporotic fracture, multiple risk factors for fracture, or failed or intolerant to other therapy.

Case

- A 67-year-old female is evaluated after her baseline bone density test reveals osteoporosis.
- No prior fractures
- No other risk factors for fracture, otherwise healthy.
- Which of the following is the most appropriate initial treatment?
- A. raloxifene
- B. risedronate
- C. romosozumab
- D. abaloparatide

Case

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- B. **risedronate**
- C. romosozumab
- D. abaloparatide

American College of Physicians 2023 Guidelines

- Benefits evaluated (RCTs):
  - Fractures
    - Hip*
    - Clinical vertebral*
    - Any clinical fracture
    - Nonvertebral
    - Radiographic vertebral
  - Functional status
  - Quality of life

- Harms evaluated (RCTs, observational studies ≥ 1,000 ppts):
  - Serious adverse events*
  - Withdrawals due to adverse events

*prioritized

(prioritized ≥ 36 mo. vs. 12-<36 mo.)

(Ayers et al, Annals of Internal Medicine, 3 Jan. 2023)

Recommendations and rationale

- **1. Females with osteoporosis**
- 2. Males with osteoporosis
- 3. Persons with low bone density (osteopenia)
- Recommendation 1a: ACP recommends that clinicians use bisphosphonates for initial pharmacologic treatment to reduce the risk of fractures in postmenopausal females diagnosed with primary osteoporosis (strong recommendation; high-certainty evidence).
- Recommendation 2a: ACP suggests that clinicians use the RANK ligand inhibitor (denosumab) as a second-line pharmacologic treatment to reduce the risk of fractures in postmenopausal females diagnosed with primary osteoporosis who have contraindications to or experience adverse effects of bisphosphonates (conditional recommendation; moderate-certainty evidence). (Qaseem et al, Ann Intern Med. 2023 Jan 3)

Benefits in females ≥ 36 months

Fracture Type	Difference per 1000 treated patients (certainty of evidence)	
Hip fracture ≥ 36 mo		
Bisphosphonate vs. placebo*	6 fewer (high)	(11 fewer to 1 fewer)
Denosumab vs. placebo	4 fewer (mod.)	(8 fewer to 0 fewer)
Raloxifene vs. placebo	No sig. dif. (mod.)	
Evidence not available for other treatments.		
*There is no evidence from RCTs that ibandronate reduces hip fractures. Certainty of evidence rated based on GRADE.		

(Qaseem et al, Ann Intern Med. 2023 Jan 3)

Benefits in females ≥ 36 months, cont'd

Fracture type	Difference per 1000 treated patients (certainty of evidence)	
Clinical vertebral fracture ≥ 36 mo		
Bisphosphonate vs. placebo	18 fewer (high)	(26 fewer to 13 fewer)
Denosumab vs. placebo	16 fewer (high)	(22 fewer to 11 fewer)
Raloxifene vs. placebo	No sig. dif. (mod.)	(8 fewer, 29 fewer to 12 more)
Evidence not available for other treatments.		

(Qaseem et al, Ann Intern Med. 2023 Jan 3)

Harms in females ≥ 36 months

- Bisphosphonates:
  - higher risk of
    - osteonecrosis of the jaw (ONJ) (0.01% -0.3% of users).
    - atypical femoral or subtrochanteric fracture (AFFs) in observational studies (statistical heterogeneity, no estimate)
- Denosumab: ONJ and AFF events only evident in extension trials, not RCTs.
- Romosozumab vs. alendronate increased risk of adverse cardiovascular events. (Qaseem et al, Ann Intern Med. 2023 Jan 3)

Rationale: Postmenopausal females with primary osteoporosis

- Bisphosphonates :
  - had the most favorable balance among benefits, harms, patient values and preferences, and cost among the examined drugs in postmenopausal females with primary osteoporosis and should be used as first-line treatment.
- Denosumab:
  - also had a favorable long-term net benefit, but…
  - bisphosphonates are much cheaper than other pharmacologic treatments and available in generic formulations.
- Bisphosphonates were associated with higher risk for ONJ and AFFs, with higher risk after longer duration. (Qaseem et al, Ann Intern Med. 2023 Jan 3)

Rationale: Postmenopausal females with primary osteoporosis recombinant PTH (teriparatide) and sclerostin inhibitor (romosozumab)

- The primary RCTs enrolled participants had “very high risk”, for example:
  - Recent fracture (within past 12 months)
  - History of multiple clinical osteoporotic fractures
  - Multiple risk factors for fracture
  - Failure of other osteoporosis therapy

(Qaseem et al, Ann Intern Med. 2023 Jan 3) →

Rationale: Postmenopausal females with primary osteoporosis recombinant PTH (teriparatide) and sclerostin inhibitor (romosozumab)

- The benefits of recombinant PTH (teriparatide) or the sclerostin inhibitor (romosozumab) may have outweighed harms compared with placebo in a select population of postmenopausal females (mean age >74 yrs) with osteoporosis and very high risk for fracture.
- Teriparatide may have resulted in no difference in risk of serious adverse events, but probably increased the risk of withdrawal due to adverse events in RCTs (low to mod. certainty).
- Recommendation 3: ACP suggests that clinicians use the sclerostin inhibitor (romosozumab, moderate certainty of evidence) or recombinant PTH (teriparatide, low certainty of evidence), followed by a bisphosphonate, to reduce the risk of fractures only in females with primary osteoporosis with very high risk of fracture (conditional recommendation). (Qaseem et al, Ann Intern Med. 2023 Jan 3)

Recommendations and rationale

- **1. Females with osteoporosis**
- **2. Males with osteoporosis**
- 3. Persons with low bone density (osteopenia)
- Recommendation 1b: ACP suggests that clinicians use bisphosphonates for initial pharmacologic treatment to reduce the risk of fractures in males diagnosed with primary osteoporosis (conditional recommendation; low-certainty evidence).
- Recommendation 2b: ACP suggests that clinicians use the RANK ligand inhibitor (denosumab) as a second-line pharmacologic treatment to reduce the risk of fractures in males diagnosed with primary osteoporosis who have contraindications to or experience adverse effects of bisphosphonates (conditional recommendation; low-certainty evidence).

(Qaseem et al, Ann Intern Med. 2023 Jan 3)

Benefits in males ≥ 36 months*

Fracture type	Difference per 1000 treated patients (certainty of evidence)
Hip fractures ≥ 36 mo.	No RCTs
Clinical vertebral fractures ≥ 36 mo.	No RCTs
(Qaseem et al, Ann Intern Med. 2023 Jan 3)	

Benefits in males ≥ 36 months*

Fracture type	Difference per 1000 treated patients (certainty of evidence)
Hip fractures ≥ 36 mo.	No RCTs
Clinical vertebral fractures ≥ 36 mo.	No RCTs
Any clinical fracture ≥ 36 mo.	
Bisphosphonate vs. placebo	No sig. dif. (insufficient evidence, one RCT, RR 0.73, 0.27-1.98)
Radiographic vertebral fracture ≥ 36 mo.	
Bisphosphonate vs. plac.	140 fewer (low) (266 fewer to 13 fewer)
Evidence not available for other treatments.	*1 trial (alendronate, 134 ppts, Ringe 2004)
(Qaseem et al, Ann Intern Med. 2023 Jan 3)	

Rationale: Males with primary osteoporosis

- Limited evidence was available for the effect of bisphosphonates on radiographic vertebral fracture prevention in males with primary osteoporosis. No evidence on clinical vert. or hip fracture.
- CGC extrapolated results from bisphosphonate trials that included females.
- Because of the indirectness, the CGC downgraded:
  - certainty of evidence from the data in females to low
  - strengths of the recommendation to conditional.
- Why not sclerostin inhibitor (romosozumab) or teriparatide in males?
  - Recommendations for these drugs in females were already conditional, so no further downgrading was possible for males.

(Qaseem et al, Ann Intern Med. 2023 Jan 3)

Recommendations and rationale

- 1. Females with osteoporosis
- 2. Males with osteoporosis
- **3. Persons with low bone density (osteopenia)**
- Recommendation 4: ACP suggests that clinicians take an individualized approach regarding whether to start pharmacologic treatment with a bisphosphonate in females over the age of 65 with low bone mass (osteopenia) to reduce the risk of fracture(s) (conditional recommendation; low-certainty evidence).

(Qaseem et al, Ann Intern Med. 2023 Jan 3)

Benefits: Low bone mass (osteopenia) in females*

Fracture type	Difference per 1000 treated patients (certainty of evidence)
Hip fracture	
Bisphosphonate (zoledronate) ≥ 36 mo.	No sig. dif. (insuff.)
Clinical Vertebral fracture	
Bisphosphonate (zoledronate) ≥ 36 mo	Risk ratio (95% CI) = 0.41 (0.22-0.76); no evidence to calculate absolute risk reduction. (low)
Evidence not available for other treatments.	*1 RCT Reid NEJM 2002 zoledronic acid
(Qaseem et al, Ann Intern Med. 2023 Jan 3)	

Rationale: Low bone mass (osteopenia)

- Largely informed by single RCT of zoledronic acid vs. placebo:
  - Older females, ≥ 65 y/o
  - Included participants with:
    - Osteoporosis at hip
    - Prior nonvertebral fracture (in 24%), and/or
    - Prevalent vertebral fracture (in 14%).
    - Zoledronic acid may decrease any clinical and vertebral fractures (low certainty)
- No data in males, therefore:
  - Low certainty in females was downgraded to insufficient in males due to indirectness (Qaseem et al, Ann Intern Med. 2023 Jan 3)

Rationale: Low bone mass (osteopenia), cont'd

- Key points for counseling patients:
  - Benefits:
    - no treatments significantly reduce hip fracture
    - Bisphosphonates may ↓ any clinical fracture and clinical vertebral fx but low certainty
    - the RCT of zoledronic acid included many persons with previous fracture and osteoporosis
  - Harms:
    - evidence on serious harms with bisphosphonates in this population was either insufficient or low certainty.

(Qaseem et al, Ann Intern Med. 2023 Jan 3)

Areas with no evidence (examples)

- Long-term benefits and harms of:
  - Abaloparatide
  - Romosozumab
  - Sequential therapy with available drugs.

- Optimal treatment:
  - to mitigate rebound bone loss after bisphosphonate therapy
  - For persons with contraindications to bisphosphonates or harms after bisphosphonate treatment (Qaseem et al, Ann Intern Med. 2023 Jan 3)

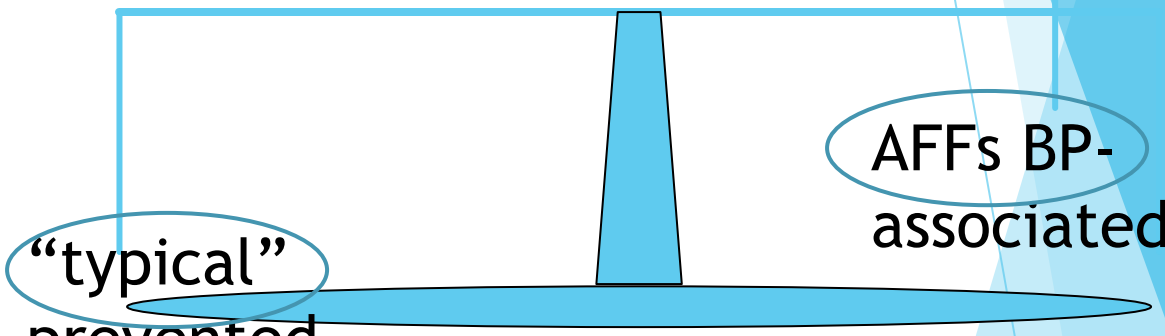
Treatment Duration: Optimal is unknown

- Increasing duration of bisphosphonate therapy to longer than 5 yrs:
  - reduces risk for new vertebral fractures but not risk for other fractures, but
  - at expense of other long-term harms.
- Clinicians should:
  - Consider stopping bisphosphonate after 5 yrs. unless strong indication for continuation.
  - Initiate an antiresorptive agent after cessation of an anabolic agent in females. (Qaseem et al, Ann Intern Med. 2023 Jan 3)

AFF and ONJ in detail

Update: Atypical vs. typical femoral fx

- 196,129 women ≥ 50 y/o in Kaiser Permanente healthcare system
- After 3 yrs:



White women	149	2
Asian women	91	8

(Black et al NEJM 2020)

Anti-resorptives and Osteonecrosis of the Jaw: International Task Force Recommendations

- 14 international societies, including ASBMR and AAOMS (maxillofacial surg.)
- Risk reduced by good oral hygiene, see dentist q6 mo. (or as recommended)

(Khan et al J Clin Densitom Jan-Mar 2017;20(1):8-24) →

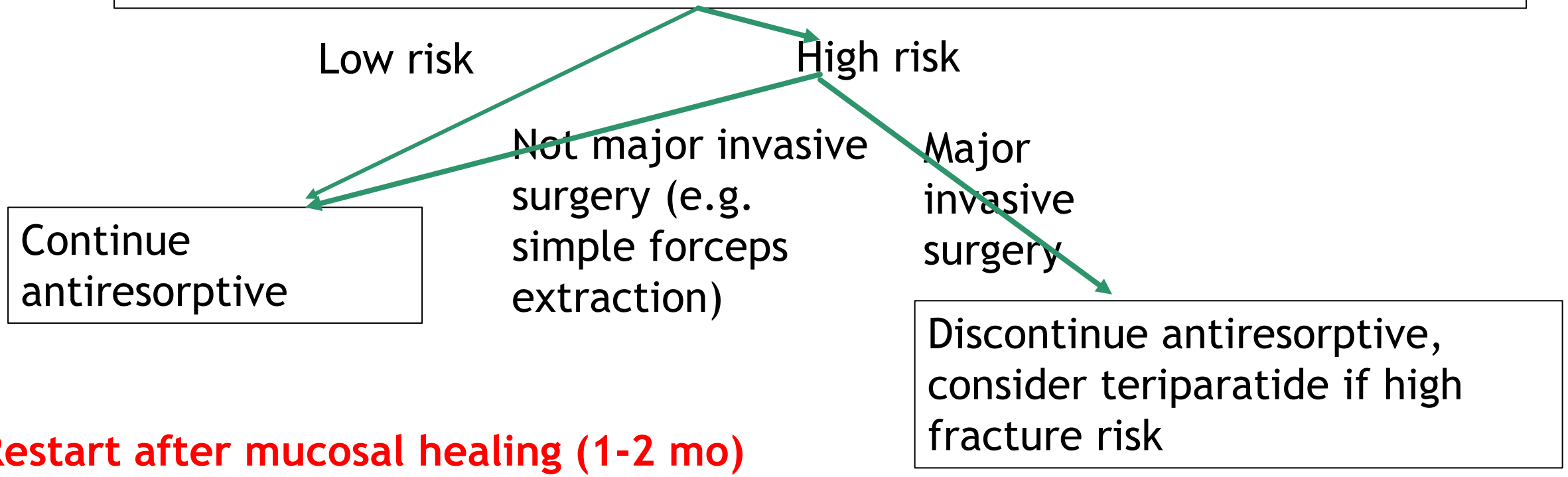
Anti-resorptives and Osteonecrosis of the Jaw: International Task Force Recommendations

- **“Routine dental work, such as dental cleaning, fillings or root canals should be performed as usual and do not require stopping osteoporosis treatment.”**
- If oral surgery is needed, ideally complete the surgery before starting low dose oral or yearly IV bisphosphonate therapy or denosumab.
- Periodontal disease should be managed before starting oncology doses of BP or denosumab.
- ONJ usually heals with appropriate treatment.
- Resumption of BP or denosumab therapy following healing of ONJ lesions is recommended, no reports of subsequent local recurrence

(Khan et al J Clin Densitom Jan-Mar 2017;20(1):8-24)

Anti-resorptives and Osteonecrosis of the Jaw: International Task Force Recommendations

ONJ risk (high risk is ≥1):
Major invasive oral surgery, diabetes, glucocorticoid therapy, periodontal disease, denture use, tobacco use, antiangiogenic agents



Restart after mucosal healing (1-2 mo)

(My own figure, based on text in Khan et al J Clin Densitom 2017;20(1):8-24)

Monitoring during therapy: key points

- Precision error <3-6% hip and 2-4% at spine-stay with same machine and look for “significance of change” on report.
- Fracture protection during therapy even if decrease in BMD in RCTs.
- RCTs have not been performed to show that BMD monitoring during therapy decreases fx risk.

- Monitor by asking how patient is doing with taking the medication, whether they have any new fractures.
- Check BMD after initial treatment period (5 yrs).

Denosumab “rebound fractures” saga continues

- post-hoc exploratory analysis (FREEDOM trial) in patients with ≥7 months follow-up after discontinuing placebo or DMAb.
- Recorded morphometric (radiographic) vert. fx

(Cosman et al JBMR 2022) →

Denosumab “rebound fractures” saga continues

	Annualized vertebral fracture rates per 100 patient-years		
	Placebo	Short-term DMAb (≤3 years)	Long-term DMAb (>3 years)
Any vert. fx			
Multiple vert. fx			
≥4 vert. fx			

(Table I created based on information in Cosman et al JBMR 2022)

Denosumab “rebound fractures” saga continues

	Annualized vertebral fracture rates per 100 patient-years		
	Placebo	Short-term DMAb (≤3 years)	Long-term DMAb (>3 years)
Any vert. fx	9.4 (6.4, 13.4)	6.7 (4.2, 10.1)	10.7 (7.4, 15)
Multiple vert. fx	3.6 (1.9, 6.3)	2.9 (1.4, 5.4)	7.5 (4.8, 11.1)
≥4 vert. fx	0.59 (0.1, 2.1)	0.57 (0.1, 2.1)	3.34 (1.7, 6.0)
*dmab duration associated with risk of multiple VF (risk for long-term > short-term, short-term not sig. dif. from plac.) Of 15 patients with ≥4 VF, 13 had DMAb exposure.			

(Table I created based on information in Cosman et al JBMR 2022)

Denosumab
“rebound fractures”

- Author conclusions:
- Patients transitioning off DMAb after 3 years may warrant more frequent administration of zoledronic acid or another bisphosphonate to maintain bone turnover and BMD and prevent multiple vertebral fractures.

(Cosman et al JBMR 2022)

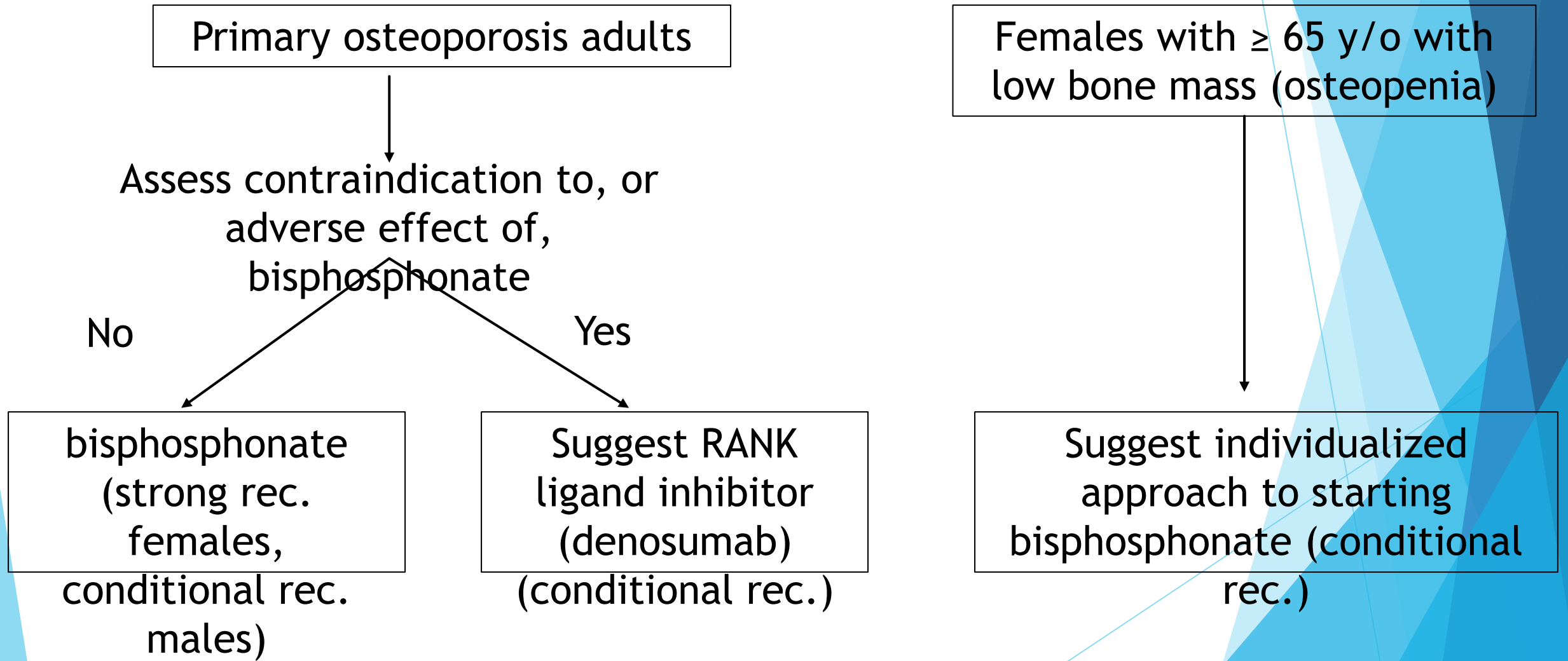
Adverse effects: FDA Drug Safety Communication 2022

- The FDA is investigating the risk of severe hypocalcemia with serious outcomes, including hospitalization and death, in patients with advanced kidney disease on dialysis treated with the osteoporosis medicine Prolia (denosumab).
- Patients should not stop Prolia treatment without first consulting your health care professional, as stopping may worsen your bone condition.
- Advise patients on dialysis to immediately seek help if they experience symptoms of hypocalcemia.
- https://www.fda.gov/safety/medical-product-safety-information/prolia-denosumab-amgen-drug-safety-communication-fda-investigating-risk-severe-hypocalcemia-patients 11/22/2022 →

Adverse effects: FDA Drug Safety Communication 2022

- Patients: “Tell your health care professional if you experience any symptoms of low blood calcium levels such as unusual tingling or numbness in the hands, arms, legs, or feet; painful muscle spasms or cramps; voice box or lung spasms causing difficulty breathing; vomiting; seizures; or irregular heart rhythm.”
- Ensure:
  - adequate calcium and vitamin D supplementation
  - frequent blood calcium monitoring.
- https://www.fda.gov/safety/medical-product-safety-information/prolia-denosumab-amgen-drug-safety-communication-fda-investigating-risk-severe-hypocalcemia-patients 11/22/2022

Upshot



(Created from information in guideline Qaseem et al Ann Intern Med. 2023 Jan 3)

Upshot cont'd

Female adult with "Very high risk"

Consider romosozumab or teriparatide followed by bisphosphonate (conditional rec.)

(Created from information in guideline Qaseem et al Ann Intern Med. 2023 Jan 3)

Important gaps

- **Optimal exercise type, intensity, frequency?**
- Benefits and risks of treatments in persons with T-score between -1 and -2.5?
- Bisphosphonate holiday: appropriate candidates, duration, monitoring?

Monitoring: Untreated older women

- Prospective large cohort postmenopausal women (Women's Health Initiative)
- Change in BMD (baseline to 3 yrs) in postmenopausal women (not taking osteoporosis medication) does not add meaningfully to baseline BMD alone to distinguish between women who do, and women who do not, experience subsequent fracture.
- Repeated BMD testing 3 years after baseline BMD among postmenopausal women should not be routinely performed. (Crandall et al, JAMA Internal Medicine online July 27, 2020)
- Related refs in same vein: Berry, JAMA 2013, Black et al JBMR 2017, Gourlay et al Am J Prev Med 2016, Hillier et al Arch Intern Med 2007