

Pharmacologic Treatment of Primary Osteoporosis or Low Bone Mass to Prevent Fractures in Adults: A Living Clinical Guideline From the American College of Physicians

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Description: This guideline updates the 2017 American College of Physicians (ACP) recommendations on pharmacologic treatment of primary osteoporosis or low bone mass to prevent fractures in adults.

Methods: The ACP Clinical Guidelines Committee based these recommendations on an updated systematic review of evidence and graded them using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.

Audience and Patient Population: The audience for this guideline includes all clinicians. The patient population includes adults with primary osteoporosis or low bone mass.

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 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 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).

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).

Recommendation 3: ACP suggests that clinicians use the sclerostin inhibitor (romosozumab, moderate-certainty evidence) or recombinant PTH (teriparatide, low-certainty 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).

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 fractures (conditional recommendation; low-certainty evidence).

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P rimary osteoporosis (osteoporosis that is not secondary to a separate condition or medication) is characterized by decreasing bone mass and density and reduced bone strength leading to a higher risk for fracture (Appendix

Table 1, available at Annals.org) (1, 2). Fractures can occur in any bone, but hip and spine fractures are most common, accounting for 42% of all osteoporotic fractures. Fractures are associated with serious morbidity and mortality, and people with prevalent fractures are at much higher risk for future fractures (3-5). Overall, an estimated 10.2 million persons aged 50 years or older in the United States have osteoporosis, and about 43.3 million persons (>40% of older U.S. adults) have low bone mass associated with a high risk for progression to osteoporosis (6).

The clinical and economic burden of osteoporotic fractures is increasing over time in certain racial and ethnic

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* This article, written by Amir Qaseem, MD, PhD, MHA; Lauri A. Hicks, DO; Itziar Etxeandia-Ikobaltzeta, PharmD; Tatyana Shamliyan, MD, MS; and Thomas G. Cooney, MD, was developed for the Clinical Guidelines Committee of the American College of Physicians. Individuals who served on the Clinical Guidelines Committee from initiation of the project until its approval were Timothy J. Wilt, MD, MPH‡ (Chair); Carolyn J. Crandall, MD, MS‡ (Vice Chair); Devan Kansagara, MD, MCR‡ (Past Vice Chair); Pelin Batur, MD, NCMP‡; Thomas G. Cooney, MD†; J. Thomas Cross Jr., MD, MPH‡; Nick Fitterman, MD†; Lauri A. Hicks, DO†; Jennifer S. Lin, MD, MCR†; Michael Maroto, JD, MBA†§; Reem A. Mustafa, MD, PhD, MPH‡; Adam J. Obley, MD†; Douglas K. Owens, MD, MS‡; Jeffrey A. Tice, MD†; Janice E. Tufte†§; Sandeep Vijan, MD, MS‡; and John W. Williams Jr., MD, MHS‡. Kate Carroll, MPH, was a nonauthor contributor from ACP staff. Approved by the ACP Board of Regents on 25 April 2022.

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groups compared with White Americans, although differences in treatment effects for these populations remain unclear (7). Over the past decade, the prevalence of osteoporosis in the United States increased in females but not males (6, 8). However, males with osteoporotic hip fractures have greater morbidity and mortality than females with hip fractures and receive treatments aimed at fracture prevention less often than females (9–12). There is substantial burden for working patients due to absenteeism and loss of productivity (13–15).

The American College of Physicians (ACP) has previously published clinical recommendations on screening and pharmacologic interventions for osteoporosis (16, 17), with the most recent guideline, published in 2017, aimed at treatment of osteoporosis (18).

SCOPE AND PURPOSE

The purpose of this ACP guideline is to present a focused update on clinical recommendations for pharmacologic treatments (Table) of osteoporosis and low bone mass to prevent fractures in adults, based on the best available evidence of the benefits and harms of treatments and consideration of patient values, preferences, and costs (Figures 1 to 3). Since publication of the 2017 ACP guideline (18), evidence has emerged on the efficacy of human parathyroid hormone-related peptides (24, 25), sclerostin inhibitors (26, 27), the comparative effectiveness of treatments (28–30), and treatments in males. This update also adds key questions on values and preferences and costs of interventions and incorporates network meta-analysis. The update of the evidence regarding use of estrogen, treatment duration, drug discontinuation (31), and serial bone mineral density monitoring (32) was not addressed in this update but will be reevaluated by the Clinical Guidelines Committee (CGC) during the living review process.

We evaluated the following pharmacologic interventions: an analogue of human parathyroid hormone-related protein (PTHrP) (abaloparatide), bisphosphonates (alendronate, ibandronate, risedronate, zoledronate), a receptor activator of nuclear factor κ B (RANK) ligand inhibitor (denosumab), recombinant human parathyroid hormone (recombinant PTH) (teriparatide), a sclerostin inhibitor (romosozumab), and selective estrogen receptor modulators (SERMs) (bazedoxifene, raloxifene). Appendix Table 2 (available at [Annals.org](#)) summarizes definitions of fracture outcomes, and the Table provides an overview of medications licensed in the United States for treatment of osteoporosis. We focused on effectiveness and harms of active drugs compared with placebo or bisphosphonates.

POPULATION

The population is adults (premenopausal and postmenopausal females and males) with low bone mass (33) or primary osteoporosis as diagnosed in primary studies (34). In assessing baseline risk for fracture, we consider diagnosis of osteoporosis, history of osteoporotic fractures (clinical or incidental), multiple risk factors for fractures,

or failure or intolerability of osteoporosis medications rather than scores from available tools (35–39). The recommendations are based on biological sex assigned at birth because most studies reported sex rather than gender and the majority enrolled only older females.

INTENDED AUDIENCE

The intended audience is all clinicians. The management of secondary osteoporosis in people with cancer (40–43) and other serious illnesses is outside the scope of this guideline.

GUIDELINE DEVELOPMENT PROCESS

The CGC developed this guideline according to ACP's guideline development process (44) and its policy on disclosure of interests and management of conflicts of interest (45). The CGC used Evidence-to-Decision tables when reporting the evidence (Supplement Appendixes 1 to 3, available at [Annals.org](#)) and graded the recommendations using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (Appendix Figure, available at [Annals.org](#)) (46). Supplement Appendix 4 (available at [Annals.org](#)) presents baseline patient characteristics, and Supplement Appendix 5 (available at [Annals.org](#)) lists the key questions for the supporting systematic review and details about the methods for the guideline and systematic review. ACP completes a Guidelines International Network (GIN) standards reporting form for each guideline it publishes, which can be found in GIN's International Guideline Library or on ACP's website (www.acponline.org/clinical-information/guidelines/guideline-process).

Because there are many ongoing studies (Table 5c of Supplement Appendix 5), the CGC is planning to maintain this topic as a living guideline with quarterly literature surveillance and periodic updating of the systematic review and the clinical recommendations. The CGC will consider quantitative and qualitative factors, such as the certainty of the evidence, the balance between benefits and harms, and contextual considerations to assess whether the new evidence may lead to changes to the recommendations and the need for an update. The CGC may decide to retire the topic from living status if it is no longer considered a priority for decision making, when there is confidence that conclusions are not likely to change with new evidence, or if it becomes unlikely that new evidence will emerge (47).

SYSTEMATIC REVIEW AND SUMMARY OF FINDINGS

This guideline is based on an accompanying systematic review and network meta-analysis completed by the ACP Center for Evidence Reviews at the Portland Veterans Affairs Research Foundation and funded by ACP. The accompanying systematic review and the Supplement Appendixes provide the appraised evidence of benefits and harms of evaluated pharmacologic interventions (34).

Table. Medications Licensed in the United States for Treatment of Osteoporosis

Drug Name (Class)	Route; Frequency	Types of Fractures Examined in Randomized Clinical Trials at Long-Term Follow-up (>36 mo)				Average Annual Medicare Spending Per Beneficiary in 2019	FDA Warning
		Hip	Clinical Vertebral	Any Clinical	Radiographic Vertebral		
Antiresorptive drugs							
Alendronate (bisphosphonate)*†‡	By mouth (tablet or solution); once a day (10 mg) or once a week (70 mg)§	Yes	No	Yes	Yes	\$793-\$1306 (brand-name); \$39 (generic)	Upper gastrointestinal irritation; osteonecrosis of the jaw; atypical femur fractures; severe bone, joint, and muscle pain
Risedronate (bisphosphonate)*†‡	By mouth; once a day, once a week, or 2 d in a row once per month§	Yes	No	No	Yes	\$2036-\$2732 (brand-name); \$604 (generic)	Upper gastrointestinal irritation; osteonecrosis of the jaw; atypical femur fractures; severe bone, joint, and muscle pain
Ibandronate (bisphosphonate)*†‡	By mouth; once a month§	No	No	No	Yes	\$1379 (brand-name); \$220 (generic)	Upper gastrointestinal irritation; osteonecrosis of the jaw; atypical femur fractures; severe bone, joint, and muscle pain
Zoledronate (bisphosphonate)*†‡	Intravenous; once a year§	Yes	Yes	Yes	Yes	\$855 (brand-name); \$316-\$987 (generic)	Osteonecrosis of the jaw; atypical femur fractures; severe bone, joint, and muscle pain
Denosumab (RANK ligand inhibitor)†	By injection (subcutaneous); every 6 mo¶	Yes	Yes	Yes	Yes	\$1913-\$12 241 (brand-name)	Dermatologic reactions and serious infection, including skin infections; suppression of bone turnover contributing to adverse outcomes, such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing
Anabolic drugs							
Abaloparatide (parathyroid hormone-related protein)	By injection (subcutaneous); once a day	No	No	Yes**	Yes**	\$9873 (brand-name)	Hereditary osteosarcoma disorders††
Teriparatide (recombinant human parathyroid hormone) ‡‡	By injection (subcutaneous); once a day	Yes**	Yes**	Yes**	Yes**	\$22 156 (brand-name)	Hereditary osteosarcoma disorders††
Romosozumab (sclerostin inhibitor)	By injection (subcutaneous); once a month for 12 mo§§	No	Yes**	Yes**	Yes**	\$5574 (brand-name)	Cardiovascular risk Stroke history or risk
Estrogen agonist on bones							
Raloxifene (selective estrogen receptor modulator)*‡	By mouth; once a day	Yes	Yes	Yes	Yes	\$1730 (brand-name); \$593 (generic)	Stroke history or risk Thromboembolism history or risk¶¶

FDA = U.S. Food and Drug Administration; RANK = receptor activator of nuclear factor κB.
 * Indicated for treatment of osteoporosis in postmenopausal females.
 † Indicated for males. Bisphosphonates have been approved for males with primary osteoporosis based on improvement in bone mineral density, and denosumab is approved for males with secondary osteoporosis based on a reduction in risk for vertebral fractures (19).
 ‡ Indicated for the prevention of osteoporosis in postmenopausal females with low bone mass.
 § All patients receiving bisphosphonate therapy should have the need for continued therapy reevaluated periodically. Patients at low risk for fracture should be considered for drug discontinuation after 3 to 5 years of use. Patients who discontinue therapy should have their risk for fracture reevaluated periodically.
 || Indicated for postmenopausal females with osteoporosis who are at high risk for fracture, defined as a history of osteoporotic fracture or multiple risk factors for fracture or patients who have failed or are intolerant to other available osteoporosis therapy.
 ¶ Denosumab discontinuation is associated with multiple vertebral fractures in some patients (20).
 ** Short-term follow-up (12 to 36 months).
 †† Dose-dependent increase in incidence of osteosarcoma in preclinical studies.
 ‡‡ Indicated for males; increase in bone mass in males with primary or hypogonadal osteoporosis who are at high risk for fracture.
 §§ Use of romosozumab should be limited to 12 monthly doses because the anabolic effect wanes after 12 monthly doses (21).
 ||| The analysis of the FDA Adverse Event Reporting System suggested higher risk for major adverse cardiovascular events associated with romosozumab (22). The current FDA safety warnings recommend avoiding use of romosozumab in patients with high risk for major cardiovascular events (21).
 ¶¶ Higher risk for venous thromboembolism and fatal stroke in females who have documented coronary heart disease or are at increased risk for major coronary events (23).

OUTCOMES OF INTEREST
Benefits and Harms

Critical outcomes that were evaluated included patient-oriented clinical outcomes of fractures (Appendix Table 2), patient functional status, quality of life, and serious adverse events, and important outcomes included withdrawals due to adverse events. When evaluating the net

benefits of the various treatments, we looked at fracture rates at longer time (≥36 months) and shorter time (12 to <36 months) to outcome assessment (48). The CGC prioritized benefits and harms that lasted at least 36 months over those only assessed at 12 to less than 36 months (34).

Each study contributed to outcomes at 1 time point of fracture assessment (12 to <36 months or ≥36 months). In

Figure 1. Treatments to reduce fractures in postmenopausal females with primary osteoporosis.

Treatments to Reduce Fractures in Postmenopausal Females With Primary Osteoporosis



Recommendations

RECOMMENDATION: 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: 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).

RECOMMENDATION: ACP suggests that clinicians use the sclerostin inhibitor (romosozumab, moderate-certainty evidence) or recombinant PTH (teriparatide; low-certainty 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).

RATIONALE: 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. Evidence showed that 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 years) with osteoporosis and very high risk for fracture. Bisphosphonates were associated with higher risk for osteonecrosis of the jaw and atypical femoral fractures. Teriparatide may have resulted in no difference in risk for serious adverse events but probably increased the risk for withdrawal due to adverse events in RCTs after 36 months.



Patient Population

Postmenopausal females diagnosed with primary osteoporosis



Interventions Compared With Placebo

Bisphosphonates (alendronate, risedronate, zoledronate), denosumab, teriparatide, abaloparatide, romosozumab, raloxifene

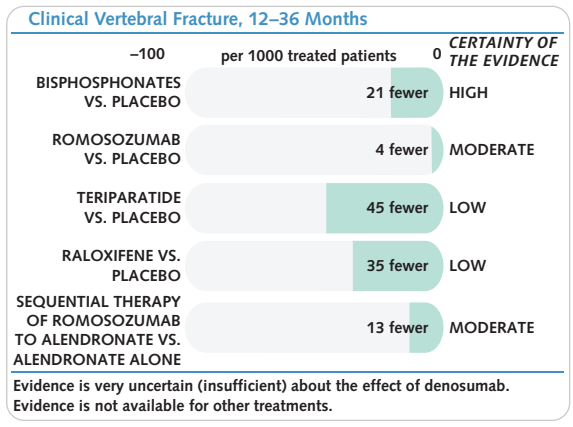
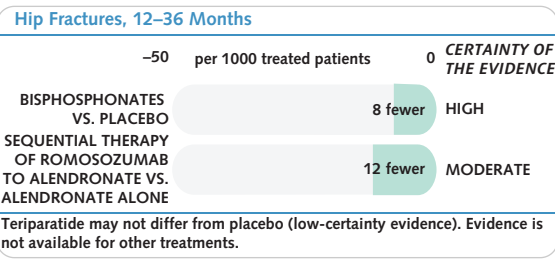
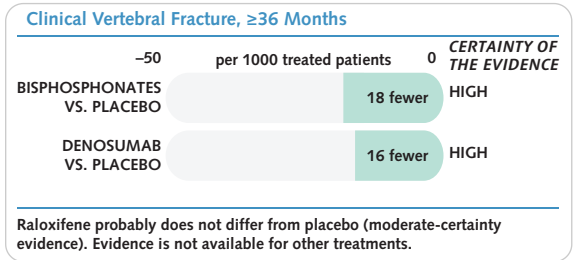
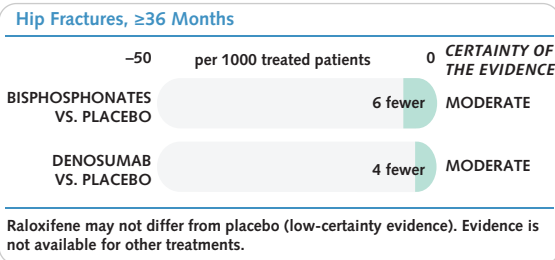


Key Outcomes Assessed at 12–36 and ≥36 Months

Hip fracture, any clinical and clinical vertebral fractures, radiographic vertebral fractures, harms (serious adverse effects and treatment withdrawal due to adverse effects)



Key Outcomes



Continued on following page

Figure 1—Continued

Serious Adverse Events, ≥ 36 Months

	CERTAINTY OF THE EVIDENCE
Bisphosphonates and denosumab resulted in no differences in serious adverse events and withdrawals due to adverse events in RCTs.	HIGH to MODERATE
Bisphosphonates were associated with higher risk for osteonecrosis of the jaw and atypical femoral or subtrochanteric fractures in observational studies, with higher risk after longer treatment duration.	LOW
Romosozumab followed by alendronate probably did not increase risk for serious harms or withdrawal due to adverse effects compared with bisphosphonate alone at 12- to 36-month outcome assessment in an RCT.	MODERATE to LOW
Teriparatide may have resulted in no difference in risk for serious adverse events but probably increased the risk for withdrawal due to adverse events in RCTs.	LOW to MODERATE



Clinical Considerations

- Clinicians should prescribe generic medications if possible rather than more expensive brand-name medications.
- Clinicians treating postmenopausal females with osteoporosis should encourage adherence to recommended drug treatments and healthy lifestyle modifications, including exercise, and counseling for evaluation and prevention of falls.
- Adequate calcium and vitamin D intake should be part of fracture prevention in all postmenopausal females with low bone mass or osteoporosis.
- Clinicians should assess baseline risk for fracture based on individualized assessment of bone density, history of fractures, response to prior treatments for osteoporosis, and multiple risk factors for fractures in postmenopausal females with primary osteoporosis.
- Current evidence suggests that increasing the duration of bisphosphonate therapy to longer than 5 years probably reduced risk for new vertebral fractures but not risk for other fractures at the expense of increased risk for long-term harms. Therefore, clinicians should consider stopping bisphosphonate treatment after 5 years unless the patient has a strong indication for treatment continuation.
- The decision of a temporary treatment discontinuation (holidays) should be individualized and based on baseline risk for fractures, type of medication and its half-life in bone, duration of discontinuation, benefits and harms of discontinuation, and higher risk for fracture due to drug discontinuation.
- Females initially treated with an anabolic agent should be offered an antiresorptive agent after discontinuation to preserve gains and because of serious risk for rebound and multiple vertebral fractures.
- Older postmenopausal females with primary osteoporosis who are at increased risk for falls and other adverse events due to polypharmacy or drug interactions need individualized treatment selection based on comorbidities and concomitant medications associated with higher risk for falls/fractures.



addition, we prioritized prevention of hip fractures and clinical vertebral fractures followed by prevention of any clinical or radiographic vertebral fractures based on the high risk for disability, institutionalization, morbidity, and mortality in people with clinical fractures (3, 4) and the high risk for future fractures in people with radiographic fractures (49). We also prioritized serious adverse events reported in randomized controlled trials (RCTs) and observational studies as more clinically important than withdrawals due to adverse events, which were usually available only from RCTs. Overall, we contextualized the balance between benefits and harms based on the direction and magnitude of treatment effects across all outcomes and the certainty of evidence.

Public and Patient Values and Preferences

The CGC considered values and preferences of the public and patients when assessing the value of the interventions.

Costs

The CGC considered costs and burden of care when assessing the value of the interventions.

RECOMMENDATIONS

Figures 1 to 3 summarize the recommendations.

Treatments to Reduce Fractures in Adults Diagnosed With Osteoporosis

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 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 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).

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).

Figure 2. Treatments to reduce fractures in males with primary osteoporosis.

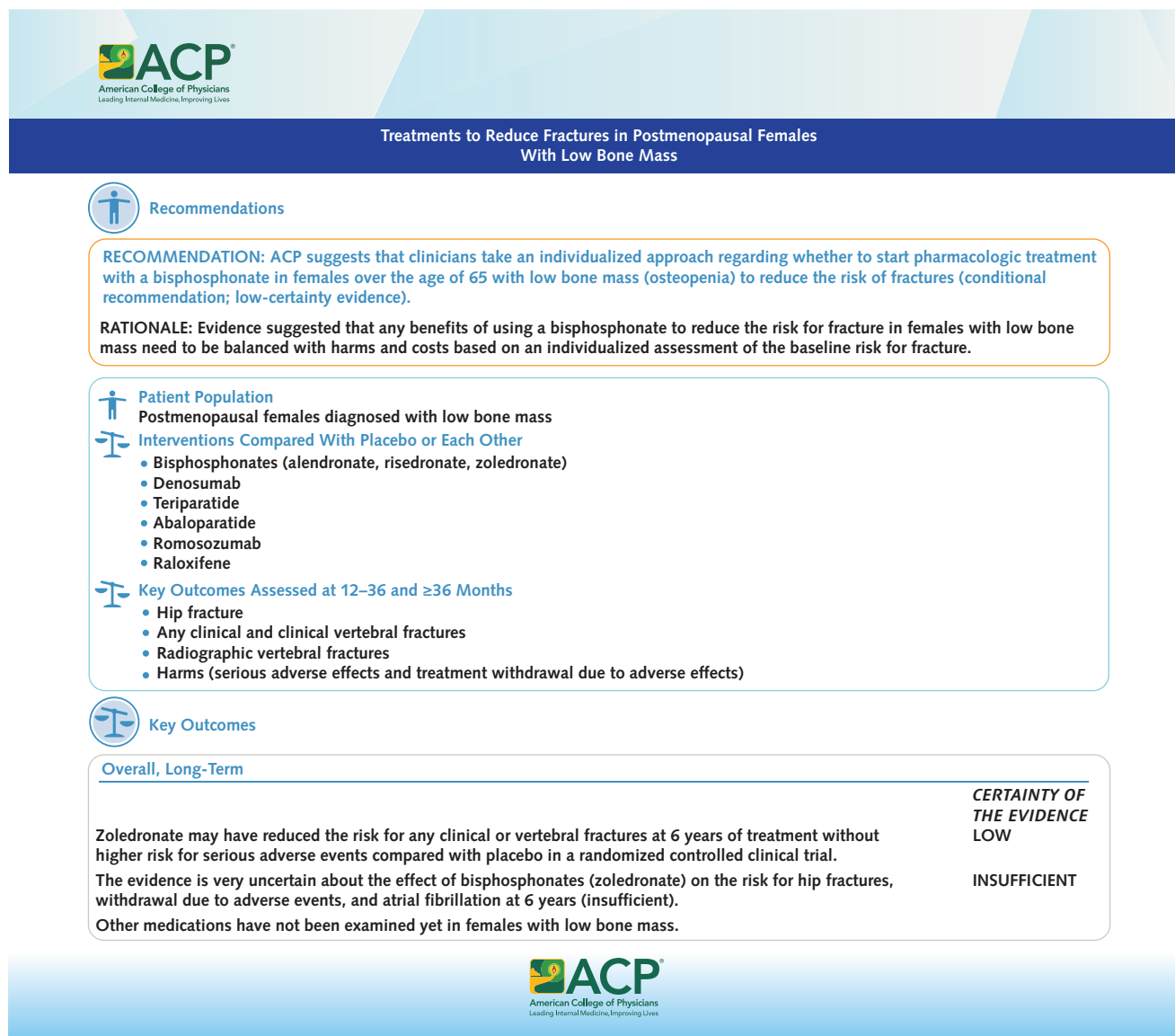


ACP = American College of Physicians; RANK = receptor activator of nuclear factor κB; RCT = randomized controlled trial.

Rationale

Bisphosphonates should be used as first-line treatment in both females and males with primary osteoporosis. In postmenopausal females and males with osteoporosis, bisphosphonates had the most favorable balance among benefits, harms, patient values and preferences, and cost among the drug classes we evaluated (Tables 1a to 1c of Supplement Appendix 1) (34). However, bisphosphonates

were associated with higher risk for osteonecrosis of the jaw and atypical femoral or subtrochanteric fractures in observational studies compared with people with osteoporosis who were not treated with bisphosphonates (low certainty of evidence) (Tables 1b.i to 1b.iii of Supplement Appendix 1) (34). In addition to net clinical benefits, bisphosphonates are much cheaper (Table) than other pharmacologic treatments and are available in generic formulations.

Figure 3. Treatments to reduce fractures in postmenopausal females with low bone mass.

ACP = American College of Physicians.

These recommendations are applicable to bisphosphonates studied in the eligible primary RCTs (alendronate, risedronate, or zoledronate), which were evaluated in the accompanying evidence review (34). There is no evidence that ibandronate reduces hip fractures (34). The RANK ligand inhibitor (denosumab) can be used as a second-line treatment in both females and males at high risk for fracture. Evidence from RCTs showed that denosumab had a favorable long-term net benefit in postmenopausal females with primary osteoporosis, a history of osteoporotic fractures, and a history of treatment with bisphosphonates (Table 4a of Supplement Appendix 4) (34). Use of denosumab was not associated with a higher risk for osteonecrosis of the jaw (34); however, events were detected in the extension trials and more data are needed to clarify the risk.

Benefits and Harms of Bisphosphonates

Evidence from the network meta-analysis suggested no greater benefits from other drug classes compared with bisphosphonates (Table 2a of Supplement Appendix 2) (34). High-certainty evidence showed that bisphosphonates reduced risk for hip fractures (absolute risk difference [ARD], 6 fewer events per 1000 patients), clinical vertebral fractures (ARD, 18 fewer events per 1000 patients), any clinical fracture (ARD, 24 fewer events per 1000 patients), and radiographic vertebral fractures (ARD, 56 fewer events per 1000 patients) compared with placebo in RCTs assessing outcomes at least 36 months after treatment initiation (Table 1a of Supplement Appendix 1). High-certainty evidence showed no differences between bisphosphonates and placebo in serious adverse events and withdrawals due to adverse events at least 3

years after initiation of treatment in included RCTs (Table 1a of Supplement Appendix 1) (34). However, evidence from observational studies showed that bisphosphonates were associated with higher risk for atypical femoral fractures and osteonecrosis of the jaw (pooled from 5 observational studies; adjusted risk ratio, 3.4 [95% CI, 1.9 to 5.2]; low certainty) at least 2 to 3 years after treatment initiation compared with people with osteoporosis who were not treated with bisphosphonates (Tables 1b.i to 1b.iii of Supplement Appendix 1), although observed events were uncommon (unadjusted incidence of osteonecrosis of the jaw was 0.01% to 0.3% of bisphosphonate users) (34). Longer treatment duration with bisphosphonates may have been associated with higher risk for osteonecrosis of the jaw (34) and atypical femoral fractures (34). Higher risk for atypical femoral fractures was observed in Asian females compared with non-Hispanic White females (595 vs. 109 per 100 000 person-years) (34).

Compared with other medications, evidence from RCTs suggested that there may be no differences between bisphosphonates and denosumab in fracture risk reduction at 36 months or beyond (low certainty; Table 2a of Supplement Appendix 2). Raloxifene probably reduced radiographic fractures compared with placebo but increased risk for withdrawal due to adverse events in RCTs and was associated with higher risk for venous thromboembolism in RCTs (34). Evidence from studies with shorter follow-up (12 to <36 months) showed no greater net benefit from other drug classes compared with bisphosphonates (Tables 2a and 2b of Supplement Appendix 2) (34).

Benefits and Harms of the RANK Ligand Inhibitor (Denosumab)

Currently, denosumab is the only available RANK ligand inhibitor. Evidence showed that denosumab reduced clinical vertebral fractures (ARD, 16 fewer events per 1000 patients; high certainty) and probably reduced risk for hip fractures (ARD, 4 fewer events per 1000 patients; moderate certainty), any clinical fracture (ARD, 14 fewer events per 1000 patients; moderate certainty), and radiographic vertebral fractures (ARD, 48 fewer events per 1000 patients; moderate certainty) in RCTs assessing outcomes at least 3 years after treatment initiation (Table 1a of Supplement Appendix 1). Denosumab probably reduced risk for radiographic vertebral fractures at shorter follow-up (12 to <36 months) (ARD, 64 fewer events per 1000 patients; moderate certainty) (Table 1a of Supplement Appendix 1).

Evidence from RCTs showed there are probably no differences in serious adverse effects and withdrawal due to adverse effects at 36 months between denosumab and placebo (moderate certainty; Table 1a of Supplement Appendix 1).

Treatment in Males

There was no evidence suggesting differences in treatment benefits and harms by sex (34). Evidence was limited on the effect of bisphosphonates and fracture prevention in males with primary osteoporosis (Table 1c of Supplement Appendix 1) (34). Therefore, we complemented low-certainty conclusions of the effect of bisphosphonate treatment for males by extrapolating results from trials that included females in order to recommend the same first- and second-line treatments for males and females.

We downgraded the overall certainty of evidence from the available data in females to low due to indirectness, and we downgraded the strength of the recommendation to conditional.

The systematic review identified 10 studies (6 RCTs and 4 observational studies) that included only males with osteoporosis or patients stratified by sex (34). Low-certainty evidence showed that bisphosphonates may have reduced radiographic vertebral fractures (ARD, 140 fewer events per 1000 patients) compared with placebo in RCTs assessing outcomes at least 36 months from treatment initiation in males (Table 1c of Supplement Appendix 1). No RCTs evaluated hip fractures. Bisphosphonates probably reduced radiographic vertebral but not any clinical fractures at 12 to less than 36 months (moderate certainty) (34). Evidence from RCTs assessing harms at 12 to less than 36 months showed no differences in the risk for serious adverse events (high certainty) and probably no difference in withdrawals due to adverse events (moderate certainty) and atrial fibrillation (low certainty) in males (Table 1c of Supplement Appendix 1) (34). Longer treatment with bisphosphonates was associated with higher risk for atypical femoral fractures and osteonecrosis of the jaw (34). For other harms, zoledronate increased the likelihood of pyrexia, myalgia, and arthralgia (50-52).

Applicability

Most studies enrolled adults at high risk for fracture, although definitions of baseline risk were heterogeneous due to different scoring scales used in the RCTs and different proportions of adults with prior vertebral fractures at baseline (Table 4a of Supplement Appendix 4) (34). Appendix Table 3 (available at Annals.org) summarizes risk factors for fractures (36-39). Primary studies did not consistently report on prior treatment response, although most allowed previous treatments with bisphosphonates (Table 4a of Supplement Appendix 4) (34). Only bisphosphonates have been tested as first-line treatment in treatment-naive patients (34). Primary studies enrolled adults with osteoporosis who were already taking vitamin D, calcium, or both supplements (Table 4a of Supplement Appendix 4) (34). Most studies included females and a very small number of males with primary osteoporosis (Table 4b of Supplement Appendix 4), but few RCTs assessed the effect of zoledronate in males with osteoporosis (34).

Values and Preferences

Limited evidence on values and preferences related to net benefit from oral or injectable medications (34, 53, 54) showed that females considered the effectiveness and adverse effects of treatments equally, followed by convenience of taking the medication and effect on daily routine (they preferred less frequent dosing, oral route of administration, and injectable route over oral if taken at a lower frequency) (34). Out-of-pocket costs were considered extremely important factors (34). Bisphosphonates can be taken through various routes and at various

frequencies, giving patients an opportunity to tailor treatment to their preferences (Table). Views from the CGC Public Panel reported preferences for use of bisphosphonates to treat osteoporosis. Similar to the research evidence, the Public Panel's preferences were also driven by the profile of benefits and harms.

Costs

We considered national data on resource use and published systematic reviews of economic analyses of lifetime horizon cost applicable to the United States (55). National Medicare data suggested that bisphosphonates are substantially less expensive than the other drug classes (Table 1d and Figures 1b and 1c of Supplement Appendix 1). Medicare data also showed that generic bisphosphonates (oral alendronate or intravenous zoledronate) were the least expensive compared with brand-name formulations (Table 1e of Supplement Appendix 1). The overall treatment cost was probably higher for injectable intravenous formulations because it included reimbursement for clinic visits, infusion costs (intravenous), and potential missed work hours for working patients. Systematic reviews concluded that the most cost-effective initial therapy for postmenopausal osteoporosis was generic zoledronate or oral alendronate (Table 1f of Supplement Appendix 1) (34, 56) and that the maximum net benefit from bisphosphonates is observed in patients with high baseline risk for fractures (Table 1g of Supplement Appendix 1) (34). These analyses did not address poor adherence to oral bisphosphonates or additional costs associated with injectable drugs or brand-name formulations. The absolute cost to use denosumab, romosozumab, or teriparatide is higher because discontinuation should be followed by an alternative sequential treatment to prevent rebound fractures.

Evidence from the published cost-effectiveness analysis (CEA) was insufficient to conclude economic value of drugs for osteoporosis (34). The most recent systematic review of CEAs of osteoporosis drugs included 12 CEAs, but only 1 was from the United States (57). The review suggested that baseline risk for fracture, the magnitude of medication effects on fracture prevention, medication adherence and persistence, and drug cost contributed to cost-effectiveness of available medications (58). A single CEA conducted in the United States (57) concluded that denosumab was cost-effective compared with other osteoporosis treatments in older U.S. males with osteoporosis, based on indirect evidence from a single RCT in postmenopausal females (59).

Recommendation 3: ACP suggests that clinicians use the sclerostin inhibitor (romosozumab, moderate-certainty evidence) or recombinant PTH (teriparatide, low-certainty 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).

Rationale

Evidence showed that the benefits after 24 months of treatment with recombinant PTH (teriparatide) or the sclerostin inhibitor (romosozumab) may have outweighed

harms only in a select population of postmenopausal females (mean age, >74 years) with osteoporosis and very high risk for fracture (Table 1a of Supplement Appendix 1 and Table 2a of Supplement Appendix 2) (34, 60–65). We developed our recommendations on the basis of the assessment of very high risk for fracture in primary RCTs (60, 65). Very high risk was based on older age, a recent fracture (for example, within the past 12 months), history of multiple clinical osteoporotic fractures, multiple risk factors for fracture (see Appendix Table 3), or failure of other available osteoporosis therapy (30, 66–68) (Table 4a of Supplement Appendix 4).

Currently, romosozumab is the only available sclerostin inhibitor and teriparatide is the only available recombinant PTH. Discontinuation of romosozumab or teriparatide treatment may result in rapid bone loss and higher fracture risk and should be followed by administration of an antiresorptive agent (69, 70).

Because this is a conditional recommendation for females, we did not make a recommendation for males because any further downgrading due to indirectness was not sufficient to support a clinical recommendation.

Benefits and Harms of Recombinant PTH (Teriparatide)

None of the included studies evaluated the long-term benefits of teriparatide (Table 1a of Supplement Appendix 1). Evidence showed that teriparatide reduced risk for any clinical fractures and radiographic vertebral fractures (ARD, 27 and 69 fewer events per 1000 patients, respectively; high certainty) and may have reduced clinical vertebral fractures (ARD, 45 fewer events per 1000 patients; low certainty) compared with placebo at 24-month outcome assessment (34) but may have resulted in no difference in risk for hip fractures (low certainty). Evidence from RCTs showed that teriparatide may have resulted in no difference in risk for serious adverse effects (low certainty) but probably increased risk for withdrawal due to adverse effects at 36- and 24-month follow-up (ARD, 127 and 17 more events per 1000 patients, respectively; moderate certainty), most commonly due to nausea, dizziness, vomiting, headache, palpitations, and leg cramps (34, 71).

Compared with bisphosphonates at 24-month outcome assessment, evidence showed that teriparatide probably reduced risk for radiographic vertebral fractures (ARD, 66 fewer events per 1000 patients; moderate certainty), may have reduced risk for any clinical fracture (ARD, 46 fewer events per 1000 patients; low certainty), and may have resulted in no differences in serious adverse events (low certainty) or withdrawal due to adverse events (moderate certainty). However, teriparatide increased risk for withdrawal due to adverse events in the longer term (36 months) (risk ratio, 3.1; low certainty) (Table 2a of Supplement Appendix 2) (34). There is not yet sufficient evidence on the benefits and harms of sequential therapy with bisphosphonates after 72 weeks of teriparatide (34, 72).

Benefits and Harms of the Sclerostin Inhibitor (Romosozumab)

None of the included studies evaluated the long-term benefits and harms of romosozumab or reported its effect on risk for hip fractures (34). Moderate-certainty evidence from RCTs assessing outcomes at 12 to 36 months after treatment initiation showed that romosozumab probably reduced clinical vertebral fractures (ARD, 4 fewer events per 1000 patients), radiographic vertebral fractures (ARD, 13 fewer events per 1000 patients), and any clinical fractures (ARD, 9 fewer events per 1000 patients) compared with placebo, but prevention of hip fractures was not reported (Table 1a of Supplement Appendix 1) (34). At 12 months, romosozumab compared with bisphosphonates may have resulted in no differences in clinical or radiographic vertebral fractures (low certainty) with no evidence about its effect in hip fractures (34). Evidence from RCTs showed that romosozumab may have resulted in no differences in serious adverse events (moderate certainty) or withdrawals due to adverse events (low certainty) compared with placebo (34). Romosozumab increased risk for cardiovascular events compared with alendronate (hazard ratio, 1.9 [CI, 1.1 to 3.1]) (21, 34, 60).

Benefits and Harms of Sequential Therapy

Evidence from RCTs that looked explicitly at sequential therapy with bisphosphonates after initial treatment with denosumab, romosozumab, or teriparatide was limited (34, 73). Moderate-certainty evidence from a single large RCT (60) showed that romosozumab followed by alendronate probably reduced all clinical fractures compared with placebo and probably reduced hip fractures (ARD, 12 fewer events per 1000 patients), clinical vertebral fractures (ARD, 13 fewer events per 1000 patients), any clinical fracture (ARD, 33 fewer events per 1000 patients), and radiographic vertebral fractures (ARD, 40 fewer events per 1000 patients) compared with a bisphosphonate alone at 12- to 36-month outcome assessment, without higher risk for serious harms or withdrawal due to adverse effects (Table 1a of Supplement Appendix 1 and Table 2a of Supplement Appendix 2) (34).

Applicability

Primary studies of romosozumab or teriparatide enrolled postmenopausal females (mean age, >74 years) with osteoporosis and very high risk for fracture (Table 1a of Supplement Appendix 1 and Table 2a of Supplement Appendix 2) (34). An estimated 10% of females older than 50 years in the general U.S. population would be characterized as being at very high risk (68) as defined by the level of risk in females enrolled in RCTs of romosozumab (Table 4a of Supplement Appendix 4). Primary studies enrolled postmenopausal females with osteoporosis who were already taking vitamin D, calcium, or both supplements (Table 4a of Supplement Appendix 4) (34). Because this is a conditional recommendation for females, we

did not make a recommendation for males because any further downgrading due to indirectness was not sufficient to support a clinical recommendation.

Values and Preferences

The systematic review did not identify any studies of patient values and preferences in adults treated with romosozumab or teriparatide (34).

Costs

Teriparatide is the most expensive of the reviewed treatments, with an average annual cost per Medicare beneficiary of \$22 156. Romosozumab is more expensive than bisphosphonates (average annual cost per Medicare beneficiary is \$5574 vs. a range of \$39 to \$2700) but may be less expensive than denosumab (range of \$1913 to \$12 241) (Figure 1c of Supplement Appendix 1). The systematic review did not identify any CEAs applicable to the United States for either treatment (34). The evidence from the published CEAs was insufficient to conclude economic value of sequential treatments for osteoporosis (34). Indirect evidence from a single RCT extension with high risk of bias was used in CEAs of sequential therapy with abaloparatide or teriparatide followed by alendronate (74–76). Because teriparatide and romosozumab should be followed by bisphosphonates after discontinuation, the absolute cost would be higher than the cost of monotherapy, although the cost-effectiveness of sequential therapy has not been examined (34). Romosozumab and teriparatide are administered by subcutaneous injection, but teriparatide can be administered by self-injection, whereas romosozumab is often injected by clinicians (Table), increasing the overall cost of treatment.

Treatments to Reduce Fractures in Adults With Low Bone Mass

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 fractures (conditional recommendation; low-certainty evidence).

Rationale

Evidence was limited on treatments in adults with low bone mass and was largely informed by a single trial in older females that showed zoledronate may reduce any clinical or vertebral fractures (34). Fracture prevention in females with low bone mass needs to be balanced with harms and costs of bisphosphonates based on an individualized assessment of baseline risk for fractures. Diagnostic criteria for low bone mass in females varied in the primary studies (Table 4c of Supplement Appendix 4). The effectiveness across different individual bisphosphonates has not been directly evaluated in females with low bone mass.

The systematic review did not identify any studies reporting on fracture outcomes for males with low bone mass or on differences in treatment outcomes by sex (34). Because the certainty of evidence was low in females, further extrapolation downgraded the certainty in males to insufficient due

to indirectness (34). Therefore, evidence was very uncertain to make a recommendation for or against treatment in males with low bone mass.

Benefits and Harms of Bisphosphonates

Low-certainty evidence from a long-term (6 years) RCT of older females with higher baseline risk for fracture (2.3%) than older females with low bone mass (34, 77) showed that zoledronate may have reduced any clinical or vertebral fractures, although evidence was very uncertain for the effect on hip fractures, withdrawals due to adverse events, or risk for atrial fibrillation (Table 3a of Supplement Appendix 3) (34, 77, 78). Evidence showed there may have been no differences in serious adverse events (34). The limited evidence on the effects of alendronate or risedronate on fractures was very uncertain (insufficient) (34).

Applicability

The RCT enrolled females aged 65 years or older diagnosed with low bone mass at either the total hip or the femoral neck on either side. Females with osteoporosis at 1 hip site, history of nonvertebral fracture (in 24%), prevalent vertebral fracture (in 13%), and a median 10-year risk for osteoporotic fracture of 12% were also eligible for the trial (77) (Table 4c of Supplement Appendix 4).

Values and Preferences

The systematic review did not identify any studies of patient values and preferences in adults with low bone mass (34).

Costs

The systematic review did not identify any CEAs applicable to the United States in adults with low bone mass, but as previously noted, bisphosphonates are a less expensive option and provide patients with choices for medication route and frequency (34).

CLINICAL CONSIDERATIONS

- Clinicians should prescribe generic medications if possible rather than more expensive brand-name medications.
- Clinicians treating adults with osteoporosis should encourage adherence to recommended treatments and healthy lifestyle modifications, including exercise, and counseling for evaluation and prevention of falls.
- Adequate calcium and vitamin D intake should be part of fracture prevention in all adults with low bone mass or osteoporosis.
- Clinicians should assess baseline risk for fracture based on individualized assessment of bone density, history of fractures, response to prior treatments for osteoporosis, and multiple risk factors for fractures (Appendix Table 3). There are many available risk assessment tools with varying predictive value, which were not evaluated in the systematic review (34) or in this guideline.
- Current evidence suggests that increasing the duration of bisphosphonate therapy to longer than 3 to 5 years reduces risk for new vertebral fractures but not risk for other fractures (34, 79-81). However, there is increased risk for

long-term harms (34). Therefore, clinicians should consider stopping bisphosphonate treatment after 5 years unless the patient has a strong indication for treatment continuation.

- The decision for a temporary bisphosphonate treatment discontinuation (holiday) and its duration should be individualized and should be based on baseline risk for fractures, type of medication and its half-life in bone, benefits, and harms (higher risk for fracture due to drug discontinuation).

- Females initially treated with an anabolic agent should be offered an antiresorptive agent after discontinuation to preserve gains and because of serious risk for rebound and multiple vertebral fractures (21, 69, 70, 82).

- Older adults (for example, those aged >65 years) with osteoporosis may be at increased risk for falls and other adverse events due to polypharmacy or drug interactions. Individualized treatment selection should address contraindications and cautions for drugs indicated to treat osteoporosis based on comorbidities and concomitant medications (Tables 1j and 1k of Supplement Appendix 1) as well as reassessment of other drugs associated with higher risk for falls and fractures.

- There is variable risk for low bone mass in transgender persons based on age at gonadectomy, therapy with sex hormones, distribution of comorbidities, and behavioral risk factors for osteoporosis and fractures. When considering the potential risk for fractures, history of gonadectomy (including age) and sex steroid therapy should be considered in treatment decisions for secondary osteoporosis.

EVIDENCE GAPS AND RESEARCH NEEDS

Future RCTs should be designed to shed light on long-term comparative benefits and harms from all available treatments in patients with primary osteoporosis or low bone mass, specifically in less-studied populations, such as premenopausal females, males, intersex persons, transgender persons after any transitioning treatment, residents of long-term care facilities, and people with multimorbidity and polypharmacy. More studies should assess whether fracture outcomes vary depending on baseline risk for fracture and prior response to treatments. Benefits and harms from delayed (83-85) or off-label longer treatment duration with denosumab or anabolic treatments should be examined in well-designed, real-world evidence studies.

Areas With Inconclusive Evidence

Evidence on benefits and harms was inconclusive to recommend for or against PTHrP (abaloparatide) or SERMs (raloxifene, bazedoxifene) (Table 1a of Supplement Appendix 1 and Table 2a of Supplement Appendix 2). Long-term safety of abaloparatide in humans has yet to be determined. The included studies provided sparse data to assess whether treatment benefits and harms varied according to baseline risk for fracture, age (Table 1h of Supplement Appendix 1 and Table 2c of Supplement Appendix 2), race, and ethnicity. Ongoing studies are expected to provide evidence on the benefits and harms of romosozumab and combined therapies in males with osteoporosis (86-91).

Areas With No Evidence

None of the included studies assessed long-term benefits and harms of pharmacologic therapy compared with nonpharmacologic therapy, abaloparatide, romosozumab, or sequential therapy with available drugs for adults with primary osteoporosis. Treatments to mitigate rebound bone loss in patients with contraindications to bisphosphonates or harms after bisphosphonate treatment are unknown. No included studies assessed effects of anabolic drugs on fracture prevention in patients with low bone mass and multiple risk factors for fractures. No included studies specifically examined fracture prevention in transgender persons with osteoporosis or low bone mass.

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Note: Clinical guidelines are meant to guide care based on the best available evidence and may not apply to all patients or individual clinical situations. They should not be used as a replacement for a clinician's judgment. Any reference to a product or process contained in a guideline is not intended as an endorsement of any specific commercial product. All ACP clinical guidelines are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

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Appendix Figure. Grading the certainty of evidence and strength of recommendations in ACP clinical guidelines using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

Grading Certainty of Evidence			
High	Confident that the true effect lies close to that of the estimate of the effect (the intervention “results in” the effect).		
Moderate	Moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a sizeable possibility that it is substantially different (the intervention “probably results in” the effect).		
Low	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect (the intervention “may result in” the effect).		
Grading Strength of Recommendations			
Strength	Balance of Benefits and Harms	Applicable Patient Population	Policy Implications
Strong (ACP recommends)	Confidence that the benefits clearly outweigh risks and burden or vice versa.	Applies to most patients in most circumstances.	Only strong recommendations could be considered as quality indicators to guide the development of accountability, reporting, and payment programs.
Conditional (ACP Suggests)	Benefits probably outweigh the risks and burden, or vice versa, but there is appreciable uncertainty.	Applies to many patients but may differ depending on circumstances or patients' values and preferences.	Policymaking will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Quality indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

ACP = American College of Physicians.

Appendix Table 1. Definitions of Low Bone Mass and Osteoporosis

Condition	Definition
Low bone mass (osteopenia)	A BMD value at the femoral neck, the lumbar spine, or both that is between 1 and 2.5 SDs below the mean BMD value for a young woman (18, 92, 93)
Osteoporosis	A BMD value at the femoral neck, the lumbar spine, or both that is ≥ 2.5 SDs below the mean BMD value for a young woman; osteoporosis may be diagnosed in postmenopausal women and in men aged ≥ 50 y if the T-score for the lumbar spine, total hip, or femoral neck is -2.5 or less (in certain circumstances, the 33% radius [also called the 1/3 radius] may be used) (18, 92, 93) The reference standard from which the T-score is calculated is the White female population aged 20–29 y in the NHANES III database A uniform White (not adjusted for race) female reference was used for men in all ethnic groups

BMD = bone mineral density; NHANES III = Third National Health and Nutrition Examination Survey.

Appendix Table 2. Osteoporotic Fracture Outcomes Reference Guide*

Fracture Outcome	Fracture Location	Definition	Example
Clinical†	Any fracture	Any fracture (vertebral or nonvertebral) discovered because the patient is symptomatic; verified by radiograph‡	A patient seeks care for symptoms that are suggestive of fracture after a fall from a standing height, and the clinician orders radiographs by which the fracture is subsequently confirmed.
Clinical vertebral	Spine	A vertebral fracture discovered because the patient is symptomatic; verified by radiograph	After a fall from a standing height, a patient seeks care due to symptoms highly suggestive of vertebral fracture, and the clinician orders radiographs confirming fracture.
Nonvertebral†	All nonspine	Clinical fractures outside the spine§, excluding fractures not considered to be related to osteoporosis (e.g., in the toes, skull, face, or fingers)	A patient breaks their tibia during a fall from a standing height, and fracture is subsequently confirmed by radiograph.
Hip	Hip	Clinical fracture at the top of the femur	A patient falls and cannot get up due to hip pain. Hip fracture is subsequently confirmed by radiograph.
Radiographic vertebral	Spine	Any vertebral fracture appearing on a radiograph , regardless of whether the patient is symptomatic	A study performs spinal radiographs on all participants entering the study and again after treatment.

* Most studies limited data to fragility fractures (i.e., fractures resulting from a fall from a standing height or lower) and radiographic vertebral fractures; pathologic and high-trauma fractures were generally excluded. A combined outcome of any clinical fracture was created specifically for the network meta-analysis (34).

† Not a GRADE (Grading of Recommendations Assessment, Development and Evaluation) outcome, but analyzed as any clinical fracture for network meta-analysis.

‡ Major osteoporotic fractures (fractures of hip, spine [clinical], wrist, or humerus) were included as any clinical fracture.

§ Several studies limited nonvertebral fractures to predetermined sites. For example, the MOVER (MONTHly intraVenous ibandronatE versus daily oral Risedronate) study defined nonvertebral fractures as those at 6 major sites: the femur, the forearm, the humerus, the clavicle, the tibia/fibula, and the pelvis (94).

|| Most studies used semiquantitative and/or quantitative morphometry assessment to determine prevalent and incident vertebral fractures.

Appendix Table 3. Risk Factors for Osteoporotic Fracture*

Increasing age
Female sex
Postmenopause (females)
Hypogonadism or premature ovarian failure
Low body weight
History of hip fracture in parent
Racial background (White persons are at higher risk than Black persons)
Previous clinical or morphometric vertebral fracture
Previous fracture due to minimal trauma (i.e., previous osteoporotic fracture)
Rheumatoid arthritis
Current smoking
Current alcohol intake (≥ 3 drinks daily)
Low bone mineral mass
Vitamin D deficiency
Low calcium intake
Hyperkyphosis
Falling and immobilization
Long-term use of certain medications, the most implicated being glucocorticoids, anticoagulants, anticonvulsants, aromatase inhibitors, cancer chemotherapeutic drugs, and gonadotrophin-releasing hormone agonists

* From references 36 to 39.