KAISER PERMANENTE

Osteoporosis Screening, Diagnosis, and Treatment Guideline

Last guideline approval: November 2011

Guidelines are systematically developed statements to assist patients and providers in choosing appropriate health care for specific clinical conditions. While guidelines are useful aids to assist providers in determining appropriate practices for many patients with specific clinical problems or prevention issues, guidelines are not meant to replace the clinical judgment of the individual provider or establish a standard of care. The recommendations contained in the guidelines may not be appropriate for use in all circumstances. The inclusion of a recommendation in a guideline does not imply coverage. A decision to adopt any particular recommendation must be made by the provider in light of the circumstances presented by the individual patient.

Prevention

The following are effective strategies for preventing osteoporosis:

Consume adequate calcium and vitamin D. Grade A

Engage in weight-bearing exercise. Grade B
For more information, see the Adult Weight Management Guideline.

Avoid tobacco use. Grade B
For information on tobacco cessation, see the Tobacco Use Guideline.

Screening Recommendations and Tests

Table 1. Recommendations for when to order a DEXA

Population eligible for screening	Test(s)	Frequency
Women aged 65 years and older [1,2]	Dual energy X-ray absorptiometry (DEXA)	See Tables 6 and 7 for specific recommendations. [6]
Women under 65 whose 10-year fracture risk is greater than or equal to that of a 65-year-old woman without additional risk factors based on the FRAX tool (9.3%) [3]		
Women and men of any age who have suffered a low-impact fracture [4]		
Women and men of any age who are at increased risk as a result of selected medical conditions or treatment with specific medications [5]		

1 While there is not direct evidence to support screening for osteoporosis, DEXA is recommended for women aged 65 years and older because of strong evidence that bisphosphonates significantly reduce hip-fracture risk for older women who have met the diagnostic T score criteria of less than -2.5.

2 The USPSTF did not recommend an upper age limit at which to stop screening. GH recommends screening only those likely to benefit.

3 Factors that increase risk for osteoporosis that are included in the FRAX tool are: age, gender, weight, height, previous fracture, parent fractured hip, smoking status, glucocorticoid use, history of rheumatoid arthritis, secondary osteoporosis (see “Secondary causes of osteoporosis,” below), alcohol consumption.

4 Fractures are considered low-impact when due to a fall from a standing height or a lower level of trauma.

5 Many medical conditions and medications may confer increased risk for osteoporotic fractures, especially in the setting of a low BMI. See “Secondary causes of osteoporosis” and “Medications that increase the risk of osteoporosis” below for factors that increase the risk of low bone density.

6 Because of limitations in the precision of testing, a minimum of 2 years may be needed to reliably measure a change in bone density; however, longer intervals may be adequate for repeated screening to identify new cases of osteoporosis.

Secondary causes of osteoporosis

Endocrine disorders
Hyperparathyroidism
Diabetes mellitus, type 1
Hyperthyroidism (long duration)
Cushing syndrome
Hypogonadism
Hemochromatosis

Metabolic disorders
Rickets
Hypercalciuria
Hypophosphatasia
Anorexia nervosa

Malignancies
Multiple myeloma
Systemic mastocytosis

Congenital conditions
Cystic fibrosis
Gaucher's disease
Osteogenesis imperfecta

Other
Hepatic or renal disease (chronic)
Malabsorption syndrome
Rheumatologic disease
Spinal cord injury

Medications that increase the risk of osteoporosis

Consider the risk-to-benefit ratio when prescribing the following medications that affect bone density:

Anticonvulsants
Phenytoin
Primidone
Phenobarbital
Carbamazepine

Hormone therapy
Androgen deprivation therapy
Inhibitors of gonadal hormones, including aromatase inhibitors
Levothyroxine (high doses to treat thyroid cancer)
Depo-medroxyprogesterone

Disease-modifying antirheumatic drugs
Methotrexate (when used in high doses to treat cancer)
Cyclosporine
Corticosteroids

> ***Note:*** An individual receiving (or expecting to receive) glucocorticoid (steroid) therapy equivalent to an average of 5.0 mg of prednisone or greater, per day, for more than 3 months is considered to be at increased risk for low bone density or osteoporosis (*Medicare Benefit Policy Manual*).

Other
Heparin
Proton pump inhibitors (PPIs) longer than 5–7 years

Diagnosis

Table 2. Interpretation of bone density test results		
Test	**Results** [2]	**Interpretation** [3]
Bone density by dual energy X-ray absorptiometry (DEXA) [1]	**T-score** [4]	
	T-score -2.5 and lower	Osteoporosis
	T-score between -1 and -2.5	Low bone density (osteopenia)
	T-score -1 and higher	Normal
	Z-score [5]	
	Z-score -2.0 and lower	Below expected range for age
	Z-score above -2.0	Within expected range for age

1 May be measured and reported as a total hip score, the femoral neck score, and/or the L1 to L4 total lumbar score. Occasionally the distal radius is used if other sites are not practical or as an early indicator in hyperparathyroidism.

2 DEXA result is based on the worst score of the individual scores of the spine, total hip, femoral neck, and when applicable, the one-third radius (forearm). Premenopausal females and men younger than 50 will only have Z-scores.

3 Although these definitions are necessary to establish the presence of osteoporosis, they should not be used as the sole determinant of treatment decisions.

4 The T-score represents the number of standard deviations a patient's bone density differs from the average bone density of a healthy 30-year-old of the same sex and ethnicity.

5 The Z-score represents the number of standard deviations a patient's bone density from the average bone density of people their same age, sex, and ethnicity.

For patients with low bone density or osteoporosis, based on history, consider evaluation for secondary causes (see previous page).

Treatment

Goals

Prevention of fracture through both decreasing risk factors and improving bone density to a T-score greater than -2.5 (the T-score target may be higher or lower in high-risk patients).

Lifestyle Modifications/Non-Pharmacologic Options

Consume adequate calcium and vitamin D.
Fall prevention and precautions are critically important for patients with osteoporosis.

Pharmacologic Options for Osteoporosis

Patients with T-scores less than or equal to -2.5 (osteoporosis) or a hip or vertebral fracture should usually be offered treatment for osteoporosis.

Table 3a. Recommended baseline before initiating therapy

Eligible population	Test(s)	Frequency
Patients for whom pharmacotherapy for low bone density or osteoporosis is considered	25(OH) vitamin D level	At initial prescription
	Serum calcium	
	Creatinine	

Primary prevention strategies—particularly consuming adequate calcium and vitamin D and performing weight-bearing exercise—should be continued when initiating pharmacologic treatment for osteoporosis.

Table 3b. Recommended pharmacologic options for osteoporosis treatment

Eligible population	Line	Medication	Initial dose	Therapeutic/goal dose/ duration of treatment
Patients with osteoporosis	1st	Alendronate	70 mg once weekly or 10 mg daily	5 years. [1,2]
	or	Risedronate [PA] for intolerance to alendronate	35 mg once weekly or 5 mg daily	
	2nd	Zolendronic acid [PA] for GI intolerance to oral bisphosphonates	5 mg IV infused over at least 15 minutes every 12 months	No studies have evaluated the optimal duration of treatment.
	3rd	Denosumab [3]	60 mg as a single dose, once every 6 months	No studies have evaluated the optimal duration of treatment.
	or	Raloxifene [PA] [4]	60 mg once daily	No studies have evaluated the optimal duration of treatment.
	or	Calcitonin [PA] [5]	One spray (200 IU) daily in alternating nostrils	No studies have evaluated the optimal duration of treatment. The maximum duration of therapy evaluated was 3 years.
	4th	Teriparatide [NF] [3,6]	20 mcg SC once daily	No more than 2 years.
	5th	Estradiol [7]	0.5 mg daily	No studies have evaluated the optimal duration of treatment.

Table 3b annotations are on the following page.

Table 3b continued.

[1] There is insufficient evidence to guide treatment for more than 5 years. While many clinicians and patients like to measure bone density at the end of therapy, there is no evidence that knowing this value improves patient care. The advice below assumes that you have decided to measure bone density. Based on expert opinion, this guideline recommends the following:

- If the patient has achieved goal density, the bisphosphonate may be stopped and dietary and lifestyle modifications continued.
- If the patient has a T-score that is less than -2.5, explore adherence to treatment. If adherence is not an issue, consider one of the following:
  - Continue bisphosphonates for an additional 2–5 years. (Safety issues regarding long-term [more than 10-year] use of medicines used to treat osteoporosis is not known.)
  - Recommend a "drug holiday" for 2 years, followed by 3 more years of therapy.
  - Consider switching to another class of medication.
  - Consider stopping bisphosphonate treatment and continuing dietary and lifestyle modifications.
- If the patient has decreased bone density from baseline; consider consultation with a bone expert (e.g., endocrinologist or rheumatologist).

[2] See evidence summary and/or Pharmacy fact sheets for more information regarding: subtronchanteric femur fractures, osteonecrosis of the jaw and atrial fibrillation.

[3] Refer to an endocrinologist for use.

[4] Treatment with raloxifene, a selective estrogen-receptor modulator (SERM), has not been shown to decrease the risk of hip fractures, but has been shown to reduce the risk of vertebral fractures.

[5] Calcitonin is less effective for increasing bone density than estrogen or bisphosphonates. There is no evidence that calcitonin prevents hip fracture. Nasal calcitonin may be more useful in the first month after an acute vertebral compression fracture. After 1 month, it is no more effective than placebo for pain control (Lyritis 1997).

[6] Teriparatide (1-34 parathormone) may be beneficial in very selected circumstances and should only be prescribed by a specialist in bone disease. Currently it is **not** recommended that it be given for more than 2 years. There is no evidence that teriparatide prevents hip fracture.

[7] There is insufficient evidence to determine whether the combination of estrogen and bisphosphonates reduces the incidence of fractures.

Not recommended: Although tamoxifen may have a bone-sparing effect similar to HRT, it should not be used as a primary treatment for osteoporosis.

Pharmacologic Options for Low Bone Density (Osteopenia)

For women with higher T-scores and men, making decisions to treat should be made on a case by case basis; clinicians and patients should consider patient preferences, risk factors, and comorbidities.

Decision Support Aid: The FRAX calculator

The FRAX calculator was developed by the World Health Organization (WHO) and may be used to help determine which patients would benefit from starting FDA-approved medical therapies.

Limitations: The Osteoporosis Guideline team consensus opinion was to be cautious in interpreting results from the FRAX calculator.

- This tool applies only to previously untreated postmenopausal women and men aged 50 years and older.
- This tool may underestimate fracture risk in patients with a history of a vertebral fracture, a hip fracture, or multiple fractures.
- Some risk factors cannot be readily quantified and are not included in this calculation (such as frailty and dementia).
- This tool has not been validated in prospective studies as a decision-making tool for starting medication.

Table 4. Indications for pharmacologic therapy in patients with low bone density (osteopenia)

Tool	Estimated outcomes	Intervention to be considered
FRAX calculator [1]	10-year probability of a hip fracture is 3% or higher. [2]	Bisphosphonate or other osteoporosis treatment
	10-year probability of a major osteoporotic-related fracture is 20% or higher. [3]	

[1] The FRAX calculator is available online (http://www.shef.ac.uk/FRAX/), using the drop-down list under "Calculation Tool."

[2] The National Osteoporosis Foundation recommends initiating therapy when 10-year probability of a hip fracture is 3% or higher. This recommendation is based on cost-benefit analyses with generic alendronate.

[3] The National Osteoporosis Foundation recommends initiating therapy when 10-year probability of a major osteoporotic-related fracture is 20% or higher. This recommendation is based on cost-benefit analyses with generic alendronate.

Pharmacologic Options for Patients on Long-term Corticosteroid Therapy

Table 5. Pharmacologic options for patients on long-term corticosteroid therapy [1]

Eligible population	Line	Medication	Initial dose	Duration
Patients at high risk for steroid-induced osteoporosis: **prevention**	1st	Risedronate [PA] [2]	35 mg once weekly or 5 mg daily	No studies have evaluated the optimal duration of treatment.
	2nd	Zolendronic acid [PA] [2]	5 mg IV infused over at least 15 minutes every 12 months	
Patients with steroid-induced osteoporosis: **treatment**	1st	Alendronate [3]	5 or 10 mg daily [4,5]	No studies have evaluated the optimal duration of treatment.
	2nd	Risedronate [PA] [2]	5 mg daily [5]	
	3rd	Zolendronic acid [PA] [2]	5 mg IV infused over at least 15 minutes every 12 months	

1 Long-term use of corticosteroids is associated with increased risk of osteoporosis; consequently, it is reasonable to consider starting prophylactic therapy in patients on chronic steroids. The dose of steroid treatment for which the benefit of treatment with bisphosphonates is thought to outweigh the risk ranges from 5 to 7.5 mg/day. Consider a referral to a rheumatologist or endocrinologist for patients on chronic corticosteroid treatment. To decrease the risk of developing osteoporosis, assess patients on corticosteroids to see if it would be appropriate to:

- Reduce the dose.
- Switch to a topical or inhaled form.
- Switch to an alternative drug.

2 Risedronate and zolendronic acid are FDA-approved for both the treatment and prevention of steroid-induced osteoporosis.

3 Alendronate is FDA-approved for the **treatment** of steroid-induced osteoporosis; it is **not** approved for the **prevention** of steroid-induced osteoporosis.

4 Most patients should be prescribed alendronate 5 mg once daily. Postmenopausal women not receiving estrogen should be prescribed 10 mg once daily.

5 Only the daily dosing of alendronate and risedronate are FDA-approved for the treatment of steroid-induced osteoporosis.

Follow-up/Monitoring

Review clinical history for secondary causes, including medications (e.g., anticonvulsants, corticosteroids), malabsorption, hyperparathyroidism, hyperthyroidism, alcoholism, or cancer; see "Secondary causes of osteoporosis," p. 3. Refer as appropriate.

Follow-up/Monitoring: Patients Who Have *Not* Sustained a Fracture

Table 6. Recommended follow-up and monitoring for patients who have low bone density but have *not* sustained a fracture

Baseline or most recent DEXA score and/or clinical circumstances	Recommended screening interval
Patients not at high risk due to medications or chronic conditions and with a T-score of:	
Higher than -1.5	Repeat DEXA scan only if the number of risk factors increases or there is a clinical concern regarding osteoporosis.
-1.5 to -1.9	May choose to repeat DEXA scan in 5 years.
-2.0 to -2.4	May choose to repeat DEXA in 2 years.
-2.5 or lower, choosing no treatment	Repeat DEXA scan as clinically indicated but no more frequently than every 2 years.
-2.5 or lower, choosing bisphosphonates	May choose to repeat DEXA scan in 5 years
Patients on chronic steroids	Repeat the DEXA scan 6 months after the initiation of corticosteroid treatment and annually thereafter (expert opinion).
Patients at high risk due to comorbid conditions, and patients with fractures	Repeat DEXA scan after 2–3 years of treatment.

Follow-up/Monitoring: Patients Who *Have* Sustained a Fracture

Table 7. Recommended follow-up and monitoring for patients who have sustained a fracture

Eligible population	Workup	Treatment
Low-impact fracture [1]	Order a DEXA scan. Order within 3 months of fracture: • 25-OH vitamin D level • Calcium • Creatinine Think about secondary causes of osteoporosis (see p. 3), especially in young patients.	Basic preventions (e.g., calcium and vitamin D, minimize harmful medications, encourage regular exercise). Bisphosphonates or, if contraindicated, raloxifene, calcitonin, denosumab, teriparatide, or estrogen. [2] Manage any identified secondary causes of osteoporosis. Consider recommending hip protector pads.
New fracture in patients already on osteoporosis treatment	Do not repeat the DEXA scan for at least 2 years after initiation of medications. [3]	Consider: • Medication adherence • Change in medication • Fall prevention • Hip protector pads • Consulting or referring to endocrinology, rheumatology, or other specialty
Fractures associated with high levels of trauma	DEXA scan is not recommended, although it may be considered for patients with unexpected fractures from other falls, such as those involving a couple of steps or perhaps a dramatic slip with limbs flailing.	—

[1] Low-impact fractures are defined as fractures caused by a degree of trauma not expected to cause a fracture; for example, a fall from standing height or lower. Low-impact fractures, such as vertebral compression fractures and distal forearm fractures, are common in the elderly, but they can occur at any age.

[2] Exceptions include patients with hypocalcemia (until condition is corrected), renal failure, or severe esophageal problems, or patients who are pregnant or likely to become pregnant.

[3] Medications take about 2 years to be effective, so fractures during the first 2 years are least likely to represent treatment failure. A repeat test could lead to misinterpreting errors within the precision of the test. Medications are generally about 30–70% effective in preventing fractures, so the occurrence of a fracture on treatment does not necessarily indicate treatment failure.

Medication Monitoring

Table 8. Recommended monitoring for medication side effects		
Eligible population—patients taking:	**Test(s)**	**Frequency**
Alendronate	Creatinine Serum calcium Vitamin D	No studies have evaluated the optimal intervals for monitoring.
Risedronate	Creatinine Serum calcium Vitamin D	No studies have evaluated the optimal intervals for monitoring.
Zolendronic acid	Serum creatinine	Prior to each dose.
	Serum calcium Vitamin D	At baseline and then as needed; no studies have evaluated the optimal intervals for monitoring.
Calcitonin	None	No studies have evaluated the optimal intervals for monitoring.
Raloxifene	None	No studies have evaluated the optimal intervals for monitoring.

Comorbidity Screening

Table 9. Comorbidity screening: alcohol misuse	
Eligible population	**Test(s)**
Patients with osteoporosis	Consider screening with AUDIT [1]

[1] See the Unhealthy Drinking in Adults Guideline for additional guidance.

Other Organizations' Recommendations

U.S. Preventive Services Task Force (USPSTF)

The USPSTF recommends screening for osteoporosis in:

- Women aged 65 year or older
- Women younger than 65 years old whose fracture risk is greater than or equal to that of a 65-year-old white woman who has no additional risk factors

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis in men.

American College of Physicians

The American College of Physicians recommends screening with DEXA for men who are at increased risk for osteoporosis and are candidates for drug therapy. The most important risk factors for osteoporosis in men are age (greater than 70 years), low body weight (body mass index 25 kg/m^2 or lower), weight loss (greater than 10% [compared with the usual young or adult weight or weight loss in recent years]), physical inactivity (participates in no physical activity on a regular basis [walking, climbing stairs, carrying weights, housework, or gardening]), use of oral corticosteroids, and previous fragility fracture.

National Osteoporosis Foundation

The National Osteoporosis Foundation recommends bone density testing in:

- Women aged 65 and older
- Men aged 70 and older
- Postmenopausal women and men aged 50–69 when concerned with the risk factor profile
- Men and women who have had a fracture

Evidence Summary

Prevention

Calcium and vitamin D

The evidence suggests that calcium plus vitamin D or vitamin D alone is beneficial, but there is not evidence to support taking calcium alone. Three meta-analyses of randomized controlled trials (RCTs) were identified; two of these were limited to postmenopausal women. In pooled analyses (Shea 2005), researchers found a small, statistically significant increase in bone density (about 1%), with calcium alone compared to placebo, but no significant reduction in fracture rate.

Papadimitropoulos and colleagues (2002) found there were significantly fewer vertebral fractures, but not nonvertebral fractures, in women assigned to take either standard vitamin D or hydroxylated vitamin D. The third meta-analysis included both men and women aged ≥ 60 years (Bischoff-Ferrari 2005). A pooled analysis of five studies found a significant reduction of hip fractures and all nonvertebral fractures with doses of 700–800 IU vitamin D daily, with or without calcium supplementation (number needed to treat [NNT]=27). There was not a significant reduction in fracture with a dose of 400 IU daily.

Exercise

Several cohort studies have found an association between exercise and fracture risk. Cummings et al (1995) found that low levels of exercise and reduced quadriceps strength are both associated with an increased risk of hip fracture. A cohort study that included men only found a statistically significant association between participation in vigorous physical activity at baseline and a decreased risk of subsequent hip fracture over 20 years (Kujala 2000).

Tobacco

A meta-analysis of cohort studies, with a combined sample size of nearly 60,000 individuals, found a significantly increased risk of any fracture (adjusted RR=1.13) and hip fracture (RR=1.60, 95% CI, 1.27–2.02) in current smokers compared to non-smokers (Kanis 2005).

Screening

DEXA

There is no direct evidence from controlled studies that screening for osteoporosis improves health outcomes. The indirect evidence for screening is based on studies showing that women identified by dual energy X-ray absorptiometry (DEXA) scans as having low T-scores can successfully be treated with bisphosphonates (see evidence section on treatment).

FRAX

Development of the FRAX tool is based on extensive evaluation of epidemiological data and statistical modeling (e.g., Kanis 2008). No studies were identified that evaluated the FRAX tool in clinical practice or compared patient outcomes with and without the use of FRAX.

Treatment

Efficacy of Bisphosphonates

Alendronate

Two meta-analyses evaluated the effectiveness of alendronate in postmenopausal women. A pooled analysis of three placebo-controlled RCTs of at least 3 years' duration found that alendronate reduced the risk of nonvertebral fracture in postmenopausal women by 14% (95% CI, 3%–24%) (Boonen 2005). An earlier meta-analysis with less strict trial eligibility criteria included 11 placebo-controlled RCTs and found a 48% (95% CI, 31%–57%) reduction in vertebral fractures and a 37% (95% CI, 8%–57%) reduction in hip fractures with > 5 mg alendronate (Cranney 2002). The authors also found a 49% (95% CI, 31%–62%) reduction in nonvertebral fractures with > 10 mg alendronate.

Duration of alendronate therapy in postmenopausal women

The Fracture Intervention Trial Long-term Extension (FLEX) trial compared the effects of discontinuing alendronate after 5 years versus continuing for 10 years. Women with a very high risk of fracture (i.e., T-scores less than -3.5 or T-scores below their Fracture Intervention Trial [FIT] baseline) were excluded from the FLEX trial. Results from the FLEX trial suggest that women who discontinued alendronate after 5 years showed a moderate decline in bone mineral density and a gradual increase in biochemical markers of bone turnover, but no higher fracture risk other than for clinical vertebral fractures compared to women who continued alendronate (Black 2006). A post hoc subgroup analysis of the FLEX trial evaluated whether the antifracture efficacy of continued alendronate differed by femoral neck T-score and vertebral fracture status at FLEX baseline. Results suggest that women with femoral neck T-scores less than -2.5 with no vertebral fracture at baseline who continued alendronate had significant reductions in nonvertebral fracture compared to women who discontinued alendronate. This study also found that the relative risk reduction for all fracture outcomes was similar for participants who did and did not lose bone in the femoral neck from FIT baseline to FLEX baseline. Besides being a post hoc analysis, results of this study are limited by the small number of fractures (Schwartz 2010).

Two meta-analyses evaluated the effectiveness of alendronate treatment in men. Both excluded RCTs conducted in men with secondary causes of osteoporosis other than hypogonadism. In a pooled analysis of two RCTs (Sawka 2005—BMC Musculoskel Discord), 10 mg alendronate significantly reduced the risk of vertebral fractures (OR=0.44, 95% CI, 0.23–0.83) but not the risk of nonvertebral fractures. The same two RCTs, plus one additional study, were included in a meta-analysis on bone density (Sawka 2005—J Clin Densitom). In the pooled analysis, there was a statistically significant increase in bone mineral density with 10 mg alendronate compared to a control intervention. The pooled weighted mean difference in bone mineral density was 8% at the lumbar spine and 4% at the femoral neck over 2–3 years.

Risedronate

There are two meta-analyses of studies on the effectiveness of risedronate in postmenopausal women. A meta-analysis of placebo-controlled RCTs of at least 3 years' duration found that risedronate reduced the risk of nonvertebral fracture in postmenopausal women by 19% (95% CI, 8%–29%) (Boonen 2005). The Boonen analysis was based on intention to treat. An earlier meta-analysis with less strict trial eligibility criteria included eight placebo-controlled RCTs and found a 36% reduction (95% CI, 23%–46%) in the risk of vertebral fractures with risedronate (Cranney 2002, pp. 517–523).

One RCT on risedronate effectiveness in men was identified. In this single blind study (Ringe 2005), patients on risedronate 5 mg daily had significantly greater increases in bone mineral density and significantly lower incidences of new vertebral fracture after a year compared to men assigned to calcium and vitamin D only. There was no significant reduction in the incidence of nonvertebral fractures, but the study was likely underpowered for this comparison.

Zolendronic acid

The Health Outcomes and Reduced Incidence with Zolendronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial was a randomized, double-blind, placebo-controlled trial, that evaluated the effects of annual infusions of zolendronic acid (5 mg) on fracture risk over a 3-year period. Results from this

trial suggest that over a 3-year period, women who received zolendronic acid had a significantly reduced risk of vertebral, hip, and other fractures compared to women who received placebo. There was no significant difference in serious adverse events or discontinuation due to adverse events; however, subjects in the zolendronic acid group had a higher incidence of atrial fibrillation and post-infusion symptoms such as pyrexia, myalgia, influenza-like symptoms, and headache (Black 2007). The HORIZON Recurrent Fracture Trial was a randomized, double-blind, placebo-controlled trial, that evaluated the safety and efficacy of once yearly IV zolendronic acid (5 mg) in women and men who had undergone recent surgical repair of a hip fracture. After a median follow-up of 1.9 years, the incidence of any new fracture was significantly lower in the zolendronic acid group compared to the placebo group. Additionally, all-cause mortality was lower in the zolendronic acid group (Lyles 2007).

A post hoc subgroup analysis of the HORIZON Pivotal Fracture Trial and the HORIZON Recurrent Fracture Trial evaluated the safety and efficacy of once yearly IV zolendronic acid (5 mg) in postmenopausal women aged 75 years or older compared to placebo. Results from this analysis suggest that once-yearly IV zolendronic acid reduced the risk of any clinical fracture, clinical vertebral fracture, and nonvertebral fracture compared to placebo; however, results from this analysis should be interpreted with caution as this with a post hoc subgroup analysis that involved two difference populations (Boonen 2010).

Safety of bisphosphonates

Atrial fibrillation

Two meta-analyses evaluated the association between the use of bisphosphonates and atrial fibrillation. The first meta-analysis that included 266,761 subjects from 7 non-experimental studies did not find an association between bisphosphonates use and risk of atrial fibrillation (Kim 2010). Results from the second meta-analysis that included 26,342 subjects from 4 RCTs suggest that bisphosphonate use may be associated with an increase in the risk for atrial fibrillation (RR 1.53, 95% CI 1.17–2.00) (Bhuriya 2010). Neither of these meta-analyses evaluated the risk of atrial fibrillation relative to the type or dose of bisphosphonates.

Esophageal and gastric cancer

A recent cohort study that included 83,652 patients from the UK General Practice Research Database investigated the association between bisphosphonates and esophageal and gastric cancer. Results from this study suggest that bisphosphonate use was not associated with an incident esophageal or gastric cancer (Cardwell 2010). However, results from a case-control study that included 17,675 patients from the same database suggest that that oral bisphosphonates increase the risk for esophageal cancer (RR 1.30, 95% CI 1.02 to 1.66). Additionally, the risk for esophageal cancer appeared to be higher for subjects with a longer duration of use (Green 2010).

Atypical fractures of the femoral shaft

Results from several observational studies suggest that while bisphosphonate use is associated with an increased risk of atypical fractures of the femoral shaft the absolute risk is small (Park-Wyllie 2011, Schilcher 2011). The number needed to treat to harm per year of bisphosphonate use was 2000 (Schilcher 2011). A secondary analysis of three large randomized controlled trials (FIT, FLEX, and HORIZON) found no significant increase in risk of atypical fractures of the femoral shaft associated with bisphosphonate used; however, the study was underpowered for definitive conclusion (Black 2010). Another observational study found no significant association between bisphosphonate use and atypical fractures of the femoral shaft compared with raloxifene/calcitonin use; however, due to the small number of events the authors concluded that the association between atypical fractures of the femoral shaft and bisphosphonates could not be ruled out (Kim 2011).

Osteonecrosis of the jaw

A recent case-control study found an association between osteonecrosis of the jaw and bisphosphonate use. However, since this study had several methodological limitations (cases and controls were not similar at baseline, 38% (N=117) of cases refused to participate, and bisphosphonate use was determined using self-report) it was not selected for review (Barasch 2011).

Raloxifene
There is fair evidence from meta-analyses of RCTs (Seeman 2006, Stevenson 2005) that raloxifene is effective in preventing vertebral fractures. Most of the studies examined radiographic vertebral fractures. One placebo-controlled RCT that found a reduction in clinical vertebral fractures (Barrett-Connor 2006) also found a significant increase in fatal stroke and VTE. One large RCT, the CORE trial (Siris 2005) found no significant benefit of raloxifene in reducing nonvertebral fractures and another large RCT found no significant benefit for preventing hip fracture.

A sub-study of Multiple Outcomes of Raloxifene (MORE) trial that included 5,114 women from the placebo and raloxifene 60 mg/day group compared the safety and efficacy of raloxifene in postmenopausal women with or without baseline vertebral fracture. Findings suggest that there was no significant difference in the safety or efficacy of raloxifene based on vertebral fracture status at baseline. Results from this study should be interpreted with caution as the analysis may lack power (Sontag 2010).

A small pilot RCT that compared the safety and efficacy of raloxifene to placebo in 114 women receiving long-term glucocorticoids. After 12 months of follow-up, participants in the raloxifene group experienced significant increase in lumbar spine and total hip BMD compared to the placebo group. There were 3 vertebral fractures in the placebo group and none in the raloxifene group (P=0.24). No participant developed arterial or venous thromboembolism; however, follow-up may not have been long enough to assess the safety of raloxifene with regard to VTE (Mok 2011).

Calcitonin
There is no high-grade evidence that calcitonin prevents hip fractures. The primary study supporting an effect of calcitonin on vertebral fractures and nonvertebral fractures in postmenopausal women is the PROOF study (Chesnut 2000), which was found to have flawed methods, including a large loss to follow-up. A meta-analysis found that intranasal calcitonin 250–2800 units weekly increased lumbar spine bone density compared to placebo (weighted mean difference = 3.74; 95% CI, 2.04–5.43), but did not increase femoral neck bone density (Cranney 2002, pp. 540–551). Calcitonin has been found to be less effective than bisphosphonates at increasing bone density in postmenopausal women. A randomized controlled trial (Downs 2002) found that increases in bone density at the lumbar spine, trochanter, and femoral neck were significantly higher after 12 months of treatment with alendronate 10 mg daily than after treatment with calcitonin 200 units daily.

Testosterone therapy for men
One RCT was identified on the effect of testosterone on bone mineral density in healthy men aged > 65 (Snyder 1999). The study did not find a significant difference in the change in bone mineral density after 36 months between men assigned to testosterone versus placebo. The study was relatively small and may have been underpowered to detect clinically meaningful differences.

Denosumab
Results from a recent meta-analysis that included 3 RCTs and 940 subjects suggest that denosumab did not reduce fracture risk in postmenopausal women with osteoporosis or osteopenia compared to placebo. Serious adverse events were more common in women taking denosumab (number needed to harm [NNH]=20; 95% CI, 150–9). As there were only 3 studies included in the meta-analysis, results should be interpreted with caution (Anastasilakis 2009). A RCT published after the meta-analysis that included 7,868 postmenopausal women with osteoporosis found that denosumab given twice yearly for 36 months was associated with a statistically significant reduction in vertebral, nonvertebral, and hip fracture risk. There was no significant difference between the two groups in the total incidence of adverse events, serious adverse events, or discontinuation due to adverse events. Adverse events occurring more frequently in the denosumab group included eczema (3.0% vs. 1.7%, P<0.001), flatulence (2.2% vs. 1.4%, P=0.008), and cellulitis (0.3% vs. <0.1%, P=0.002) (Cummings 2009).

Teriparatide
Two RCTs have compared teriparatide (1-34 parathyroid hormone) to placebo. The first was in over 1,500 women with pre-existing vertebral fractures and low BMD (Neer 2001). The second was in over 400 men with low bone mineral density (Orwoll 2003). The studies found a 3–5% increase in hip BMD and 10–13% increase in vertebral BMD over 1 year (men's study) or 1.5 years (women's study), which is as good as or better than bisphosphonates (placebo increases were 0, plus or minus 1%). Teriparatide reduced the occurrence of new vertebral fractures by 65% and nonvertebral fragility fractures by about 50%. No reduction in hip fractures was seen, but the number of events was too few to draw conclusions. Osteosarcoma was seen in rat studies but not in clinical studies of humans taking teriparatide.

Estrogen

The Women's Health Initiative (WHI) RCT evaluated the effects of estrogen alone or in combination with progestin on fracture risk in healthy postmenopausal women. Results from this trial suggest that estrogen with or without progestin reduced fracture risk; however, the harms of estrogen therapy such as increased risk of thromboembolic events, stroke, coronary heart disease, and breast cancer may outweigh the benefits (Anderson 2004, Cauley 2003, Nelson 2010).

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Guideline Development Process and Team

Development Process

The Osteoporosis Guideline was developed using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis. For details, see Evidence Summary and References.

This edition of the guideline was approved for publication by the Guideline Oversight Group in November 2011.

Team

The Osteoporosis Guideline development team included representatives from the following specialties: endocrinology, family medicine, orthopedics, pharmacy, and radiology.

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Appendix 1. Recommendation Grade Labels

About the Labeling System

This labeling system is adapted from the U.S. Preventive Services Task Force (USPSTF). The label is based on the degree to which the evidence supports the specific clinical recommendation as written by the guideline team. In this system, *certainty* refers to the likelihood that the guideline team's assessment of net benefit (i.e., the benefit minus harm of the service as implemented in a general primary care population) is correct, based on the nature of the overall evidence available.

While the grades are useful tools in assessing recommendations, they are not meant to replace the clinical judgment of the individual provider or to establish a standard of care.

Recommendation Grade Definitions

Label	Definition
Grade A	**The service is recommended.** There is high certainty that the net benefit (i.e., benefits minus harms) is substantial.
Grade B	**The service is recommended.** There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.
Grade C	**The recommendation is against *routinely* providing the service.** There may be considerations that support providing the service to an individual patient. There is at least moderate certainty that the net benefit is small.
Grade D	**The recommendation is against providing the service.** There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.
I statement	**The current evidence is insufficient to assess the balance of benefits and harms of the service.** Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.
Expert opinion	**Expert opinion refers to the collective opinion of the guideline team. The language of the recommendation is at the team's discretion.** The evidence is assumed to be insufficient unless otherwise stated. In the rare case there is fair or good evidence, the evidence does not support the expert opinion recommendation put forth by the team.

Levels of Certainty Regarding Net Benefit

Level of certainty	Description
High	**The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations.** These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	**The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained** by such factors as: • The number, size, or quality of individual studies • Inconsistency of findings across individual studies • Limited generalizability of findings to routine primary care practice • Lack of coherence in the chain of evidence As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	**The available evidence is insufficient to assess effects on health outcomes.** Evidence is insufficient because of: • The limited number or size of studies • Important flaws in study design or methods • Inconsistency of findings across individual studies • Gaps in the chain of evidence • Findings that are not generalizable to routine primary care practice • A lack of information on important health outcomes More information may allow an estimation of effects on health outcomes.