Quality Indicators for the Care of Osteoporosis in Vulnerable Elders

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Osteoporosis is a systemic skeletal disease characterized by the loss of bone mass and disruption of the normal bone architecture that results in greater fracture risk.1 Osteoporosis is a common condition occurring in an estimated 25 million people in the United States and is the underlying cause in more than 1.5 million fractures each year.2 It affects elderly people of all races and ethnicities. In 1995, osteoporotic fractures cost an estimated $13.8 billion in the United States.3 Of individuals with osteoporotic hip fractures, 20% to 50% are unable to return to independent living and 12% to 20% die within 1 year.4

A variety of strategies to prevent fractures have been shown to be useful but depend on the recognition of the risks of developing bone loss and diagnosing osteoporosis. Bone mineral density (BMD) is the best available tool for assessing risk of osteoporotic fracture, but other factors, in particular, a history of a previous fragility fracture, are useful. Use of preventive interventions could reduce morbidity and mortality in vulnerable elders (VEs).

METHODS

A total of 590 articles were considered in this review: 21 identified through a Web search, 230 through reference mining, and 315 through the Assessing Care of Vulnerable Elders (ACOVE)-3 literature searches. Twenty-four additional articles were included after peer review.

RESULTS

Of the 19 potential quality indicators (QIs), 13 were judged valid by the expert panel process (see the QIs on pages S464–S487 of this supplement); six indicators were rejected. The literature summaries that support each of the indicators judged to be valid in the expert panel process are described.

Counseling About Diet, Weight-Bearing Exercise, and Alcohol Intake

1. ALL VEs at an initial primary care visit should be counseled about intake of calcium and vitamin D and weight-bearing exercise, BECAUSE such measures may prevent osteoporosis and decrease the risk of fractures.

Supporting Evidence

The search did not identify any randomized, clinical trials (RCTs), case-control studies, or cohort studies of preventive counseling for osteoporosis. Four guidelines recommend preventive counseling.5–8 The U.S. Preventive Services Task Force (USPSTF) recommended counseling about calcium and vitamin D intake, weight-bearing exercise, and smoking cessation in the second edition of Clinician’s Handbook of Preventive Services,9 and the American Academy of Family Physicians recommends calcium supplementation.10 One guideline states that it is reasonable to make recommendations for preventive counseling but that the benefits should not be overstated, because there are minimal data to support them.11

Three guidelines recommend counseling women who are at higher risk of osteoporosis on exercise and calcium and vitamin D supplementation.1,12,13

Screening Dual X-Ray Absorptiometry Scan

2. ALL female VEs without a diagnosis of osteoporosis should have documentation that they were offered a dual x-ray absorptiometry (DXA) scan, BECAUSE the results of the DXA may affect treatment decisions.

Supporting Evidence

Several lines of evidence support this indicator. First, one cohort study suggested that screening DXA scans decrease the incidence of hip fractures.14 Screening resulted in a lower risk of hip fracture (Cox proportional hazard ratio (HR) = 0.64, 95% confidence interval (CI) = 0.41–0.99). Participants in the screened group were more likely to start using calcium or bisphosphonates in the year after screening if their BMD was below average for their age than if it was
at or above average for their age. Persons with a BMD that was below the age-matched average who were started on any type of therapy to treat osteoporosis had a lower incidence of hip fracture than those with no use, but the results were not statistically significant.

A second source of support is that screening DXA scans affect treatment decisions. Four cohort studies and one RCT demonstrated that women who had a bone density study and were found to have low BMD were more likely to start osteoporosis therapy.15–19

The third line of evidence stems from studies finding that BMD is a good surrogate marker of fracture risk. The search identified five prospective studies20–25 and four review articles26–29 that showed that BMD predicted fracture risk. Several studies focusing on nursing home residents also demonstrated an association between BMD and fracture risk.30–32

Numerous guidelines for the diagnosis and treatment of osteoporosis recommend bone density studies to better assess fracture risk,5–7,13,33 although some recommend testing only under specific situations.8,12,34 The USPSTF recommends that women aged 65 and older be screened for osteoporosis with a DXA scan and that women at greater risk of osteoporosis be screened with a DXA scan starting at age 60.35 This recommendation is considered to be Grade B, meaning that the USPSTF found at least fair evidence that a DXA scan improves important health outcomes and concludes that the benefits outweigh the harms. This recommendation notes that there are no data to determine at what age to halt screening.

**Screening DXA Scan for Men**

3. **IF** a male VE without a diagnosis of osteoporosis has primary hyperparathyroidism, osteoporosis in a first-degree relative, hypogonadism, gonadotropin-releasing hormone antagonist use, osteopenia on x-ray, or has received more than 3 months of systemic glucocorticoid treatment, **THEN** a DXA scan should be performed, **BECAUSE** identification of osteoporosis or osteopenia will alter treatment decisions.

**Supporting Evidence**

The literature review did not identify any clinical trials that assessed the utility of DXA scans for screening for osteoporosis in men, although in a prospective cohort, the MINOS study, BMD scores were found to be predictive of fracture risk in men even after controlling for age, weight, and prevalent fractures. For each standard deviation decrease of 1, the odds ratio for fracture was significantly greater and varied from 1.28 to 1.89.36 Other studies have identified additional risk factors for osteoporosis in men.

A meta-analysis of corticosteroid use and fracture risk found that previous and current use of corticosteroids was associated with a significantly greater risk of any fracture and hip fracture.37 A review notes that primary hyperparathyroidism is associated with two times the risk of hip fracture and 1.5 times the risk of any fracture and that BMD results are often used to guide surgical decisions,38 although in a retrospective study of 464 Turkish men, parathyroid hormone levels were not associated with risk of osteoporosis.39

In a meta-analysis, a parental history of fracture (in particular, a family history of hip fracture) was associated with greater risk of fractures independent of osteoporosis (risk ratio = 1.16 for any fracture, 95% CI = 1.07–1.28 and 1.49 for hip fracture, 95% CI = 1.17–1.28).40 No significant difference was seen between men and women in this study. This association has been inconsistent, with the finding confirmed in some male-only cohorts41 but not others.42

Testosterone deficiency is present in approximately 30% of men with osteoporosis.43 Also, serum testosterone levels correlate with BMD in men in some studies44–46 but not others.47,48 One of the larger studies, the Framingham Study, evaluated the association between testosterone levels and BMD in 405 men, mean age 75.7, 17.5% of whom were hypogonadal, and did not find differences in BMD between the hypogonadal and eugonadal men at any site.48

Gonadotropin-releasing hormone antagonist therapy, which is used to treat prostate cancer, has been shown to result in loss of bone density.49–52

The search did not identify any studies of the relationship between osteopenia on x-ray and bone density or fracture risk in men.

One small study suggested that BMD results affected men’s health behavior in terms of initiating calcium and vitamin D supplementation.35 Although few guidelines address osteoporosis in men, one recommends BMD testing for men aged 70 and older, as well as for those with risk factors.33 Two guidelines recommend testing men with some of the risk factors that are included in this indicator.8,34

**Osteoporosis Considerations After Fracture**

4. **IF** a female VE has a new nonpathological fracture, **THEN** she should be treated for osteoporosis, or a DXA scan should be performed, **BECAUSE** nonpathological fractures are likely to be due to osteoporosis.

5. **IF** a VE has a new hip fracture or undergoes kyphoplasty or vertebroplasty, **THEN** a DXA scan should be performed or pharmacological therapy for osteoporosis should be prescribed within 6 months, **BECAUSE** the identification and treatment of osteoporosis will reduce the risk of another fracture.

**Supporting Evidence**

There are three lines of evidence that support these indicators. First, those with a history of a fracture are at greater risk for further fracture; second, those with a prior history of fracture have been shown to have less risk of fracture when treated; and third, osteoporosis is underdiagnosed in people who have had a fracture.

One meta-analysis included 15,259 men and 44,902 women from 11 cohorts to quantify the risk of subsequent fracture in those with a prior fracture history.53 Women with prior fracture had a significantly greater risk of any future fracture than those with no prior fracture (risk ratio (RR) = 1.84, 95% CI = 1.72–1.96). The RR for hip fracture for those with a previous fracture was 1.77 (95% CI = 1.49–2.11). The magnitude of the difference decreased only slightly and remained significant when BMD was taken into account for any fracture (RR = 1.73, 95% CI = 1.59–1.88) and for hip fracture (RR = 1.56, 95% CI = 1.23–1.98). Another study found that a history of fracture in men aged 50 and older was associated with
lower BMD ($P < .001$ for spine and $P < .006$ for distal radius).\(^4\)

The Fracture Intervention Trial showed that alendronate substantially reduced the risk of subsequent vertebral fractures.\(^5\) Risedronate was also effective in decreasing the RR = of hip fractures to 0.4 (95% CI = 0.2–0.8) in those with vertebral fractures at baseline.\(^6\) Raloxifene reduced the risk of new vertebral fractures irrespective of prevalent fracture status.\(^7\)

Numerous studies have evaluated the underdiagnosis of osteoporosis in patients with fractures. The search identified one systematic review of practice patterns in the diagnosis and treatment of osteoporosis after a fragility fracture.\(^8\) In the 13 studies that did not use BMD or laboratory tests as inclusion criteria, fewer than 32% of subjects received a BMD evaluation after a fragility fracture, and in five of the studies, fewer than 10% received a BMD test. Eleven studies reported on calcium and vitamin D use, with rates varying from 8% to 62%. Twenty studies described bisphosphonate use, with rates varying from 0.5% to 38% and only six studies reporting rates greater than 10%. The use of hormone therapy for the treatment of osteoporosis was reported in 19 studies and ranged from 0.5% to 55%, with a median of 10% and only three studies with more than 15%. Twelve studies reported on calcitonin use, all with rates of use less than 10%. Further evidence of the underdiagnosis and undertreatment of osteoporosis in women who have sustained fractures comes from the National Committee on Quality Assurance (NCQA). Only 17% of U.S. women aged 65 and older enrolled in health plans that participated in the National Committee on Quality Assurance’s accreditation process were treated for osteoporosis or underwent BMD testing after sustaining a nontraumatic fracture in 2004.\(^9\)

One retrospective study evaluated the effect of post-hip fracture treatment of osteoporosis on morbidity and mortality.\(^10\) Four hundred forty-nine patients aged 65 and older hospitalized for a hip fracture in 1996/97 were followed prospectively until 2001. Eight percent were receiving treatment for osteoporosis prefracture, whereas 23% were treated postfracture. Although the risk of subsequent hip fracture was not different for the treated (6%) versus untreated (4%), those in the treatment group had a significantly lower mortality rate.

The National Institutes of Health (NIH) consensus statement recommends that physicians who treat an acute fracture initiate an outpatient evaluation of the patient for osteoporosis and treatment if indicated.\(^11\) The National Osteoporosis Foundation recommends a bone density test and treatment for any woman with a hip or vertebral fracture.\(^12\)

### Osteoporosis Prophylaxis for Corticosteroids

6. **IF** a VE without osteoporosis is taking 7.5 mg per day or more of prednisone (or equivalent) for 1 month or longer, **THEN** he or she should be prescribed calcium and vitamin D supplements, **BECAUSE** this will retard the rate of bone loss and decrease the risk of fracture.

**Supporting Evidence**

A Cochrane review of the effects of calcium and vitamin D supplementation in patients taking corticosteroids\(^13\) identified five clinical trials (4 of which were randomized) of vitamin D (cholecalciferol) or di-hydroxy vitamin D (Calcitrol) with calcium versus calcium or placebo. The meta-analysis found that supplementation had a beneficial effect on BMD of the lumbar spine and radius but not the hip and that the effects on risk of nontraumatic fractures were not statistically significant.

Two additional meta-analyses on the use of vitamin D and corticosteroid-induced osteoporosis were identified, both of which found that supplementation had a beneficial effect on BMD of the lumbar spine.\(^14,15\) One also evaluated the effects of supplementation on fracture risk and did not find any significant benefit.\(^16\)

No study was identified that evaluated the use of calcium alone for the management of glucocorticoid osteoporosis. In most studies in which calcium served as the control therapy, bone loss was not stopped, suggesting that calcium alone is insufficient to prevent glucocorticoid induced osteoporosis.\(^17\)

Four guidelines support the use of calcium and vitamin D supplementation for individuals taking corticosteroid therapy.\(^18-20\)

### Corticosteroids and Bisphosphonate Therapy

7. **IF** a VE without osteoporosis is taking 7.5 mg per day or more of prednisone (or equivalent) for 3 months or longer, **THEN** he or she should be prescribed bisphosphonate therapy, **BECAUSE** this will retard the rate of bone loss and decrease the risk of fracture.

**Supporting Evidence**

A Cochrane meta-analysis\(^21\) of 13 controlled clinical trials published up to 1997 on the use of bisphosphonates found that bisphosphonates prevented bone loss at the spine and hip and yielded a statistically nonsignificant 24% reduction in the risk of a vertebral fracture. A second meta-analysis reported that bisphosphonates had a greater effect than vitamin D on lumbar spine BMD.\(^22\)

One meta-regression of 45 trials of drug therapy for corticosteroid-induced osteoporosis found that, relative to no therapy or calcium alone, the effect size for increasing BMD with bisphosphonates was 1.03 (95% CI = 0.85–1.17).\(^23\)

The search identified four additional controlled clinical trials of bisphosphonates in the treatment of corticosteroid-induced osteoporosis published after the Cochrane meta-analysis. Two studies of etidronate demonstrated statistically significantly better improvement in bone density than with calcium and vitamin D therapy alone.\(^24,25\) In two additional studies,\(^26,27\) risedronate was associated with improvements in BMD of the spine and hip. Additionally, there was a significant reduction in vertebral fractures in one\(^22\) and a nonsignificant trend toward vertebral fracture reduction in the other.\(^28\) In the fourth study, alendronate was effective in preserving BMD and significantly reduced vertebral fractures.\(^29\)

Five guidelines support the use of bisphosphonates for the prevention of bone loss in patients receiving glucocorticoid therapy, although the corticosteroid dose and duration of therapy that would trigger the institution of bisphosphonate therapy varied.\(^18-21,29\)
Identifying Secondary Osteoporosis
8. IF a female VE is newly diagnosed with osteoporosis, THEN she should receive a workup including questions about medication use and alcohol use and tests for complete blood count, liver function, renal function, calcium, phosphorus, vitamin D 25-OH, and thyroid-stimulating hormone, BECAUSE this may identify a treatable cause of osteoporosis and improve bone density.

Supporting Evidence
The literature search did not identify any trials that evaluated the utility of screening for medication and alcohol use in women identified with osteoporosis. Five studies that evaluated the effect of laboratory testing in women with osteoporosis were identified.76–80 Three studies found that screening for hypothyroidism was useful in identifying secondary osteoporosis.76–78 Two studies found that previously undiagnosed disorders of bone and mineral metabolism were identified in patients with osteoporosis,77,79 suggesting that screening parathyroid hormone (PTH), calcium, and vitamin D levels are useful in newly diagnosed osteoporosis. One prospective population-based study of 173 men and 143 women found that serum PTH and vitamin D levels did not predict bone loss.80

One review that suggested that the prevalence of secondary osteoporosis was less than 20% was identified.81 The study found that, in a cohort of 384 women with osteoporosis, 8.6% had a secondary cause (hyperthyroidism (n = 10), hyperparathyroidism (n = 10), glucocorticoid use (n = 10), anticonvulsant therapy (n = 2), and prolactinoma (n = 1)).82

The reported association between alcohol use and osteoporosis has been variable. In the Nottingham Early Postmenopausal Intervention Cohort study, lifetime alcohol consumption did not have an independent association with osteoporosis. In the Nottingham Early Postmenopausal Intervention Cohort study, lifetime alcohol consumption did not have an independent association with osteoporosis.83

Calcium and Vitamin D for Osteoporosis
10. IF a VE has osteoporosis, THEN he or she should be prescribed calcium and vitamin D supplements, BECAUSE this may decrease the risk of fractures.

Supporting Evidence
A meta-analysis including prevention and treatment trials of calcium supplementation on bone loss in postmenopausal women found that calcium was more effective than placebo in reducing the rate of bone loss in the spine and hip after 2 or more years of treatment. The RR of fractures of the vertebrae associated with calcium supplementation was 0.79 (95% CI = 0.54–1.09) and the RR of nonvertebral

Exercise for Osteoporosis
9. IF an ambulatory VE has a new diagnosis of osteoporosis, THEN there should be documentation of advice to exercise within 3 months, BECAUSE exercise may reduce the risk of falls and fractures, increase bone density, and decrease pain.

Supporting Evidence
Five meta-analyses of RCTs suggest that exercise improves BMD to varying degrees in postmenopausal women. These analyses included prevention and treatment trials, although most studies did not specifically select subjects with osteoporosis. In a Cochrane systematic review, aerobic, weight-bearing, and resistance exercises all increased BMD of the spine, although the quality of the studies in the meta-analysis was low, and the duration were short. No effect was seen on fractures.

A meta-analysis limited to aerobic exercise interventions demonstrated better hip BMD in exercisers than in nonexercisers.88 A third meta-analysis using a variety of exercise interventions, some with other concurrent therapies, found that those in the exercise group had less bone loss.89 A fourth meta-analysis of the effects of at least 17 weeks of exercise found that exercise training programs prevented or reversed almost 1% of bone loss per year in the lumbar spine and femoral neck of pre- and postmenopausal women.

The fifth meta-analysis reported that impact and nonimpact exercise prevented bone loss of the lumbar spine in postmenopausal women. Impact exercises also prevented bone loss in the femoral neck. In a systematic review of exercise for early postmenopausal women,12 of 16 studies showed more improvement in BMD in the exercise group than in controls.

The effect of exercise on osteoporosis has been evaluated in numerous cohort and longitudinal studies. In the Study of Osteoporotic Fractures, self-reported walking was associated with 30% less risk of fractures,93 and BMD was positively associated with physical activity.94

Data on the effects of exercise on osteoporosis treatment or prevention in men are scarce. One 4-year RCT of physical exercise in 140 men aged 53 to 62 did not demonstrate any effect on age-related bone loss of the hip.95 Several cohort studies have suggested that physical activity is associated with better BMD or lower fracture risk or that an inactive lifestyle is associated with lower BMD.98 Other studies have not been able to demonstrate any association between exercise and BMD or risk of hip fracture.92,99

Several guidelines recommend weight-bearing exercises, but not necessarily physical therapy alone, for all women as part of the prevention of osteoporosis.5,6,13,100,101 The NIH Consensus Development Panel on osteoporosis recommends physical therapy for the treatment of osteoporosis.1 In the Guide to Clinical Preventive Services published in 1996, the USPSTF guidelines noted that non-randomized, controlled trials and a limited number of RCTs provide evidence that exercise can retard bone loss.9

Supporting Evidence
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Pharmacological Treatment of Female Osteoporosis

11. IF a female VE has osteoporosis, THEN she should be treated with bisphosphonates, raloxifene, calcitonin, hormone replacement therapy (HRT), or teriparatide (if this is a new diagnosis, within 3 months), BECAUSE this will decrease the rate of bone loss and decrease the risk of fracture.

Supporting Evidence

Bisphosphonates. Numerous RCTs have evaluated the effect of bisphosphonates on BMD and fracture. Improvements in BMD have been demonstrated for alendronate, risedronate, etidronate, pamidronate, ibandronate, and zoledronic acid (Table 1). Reductions in fractures have been demonstrated for each of these agents except zoledronic acid (Table 1).

Teriparatide. Teriparatide is a synthetic, recombinant polypeptide hormone consisting of the first 34 amino acids of human PTH. In one study of 1,637 postmenopausal women with osteoporosis, teriparatide use was associated with significantly lower risk of new vertebral fractures (RR = 0.31–0.35, depending on teriparatide dose).129 New nonvertebral fractures occurred in 6% of the placebo group and in 3% of each of the teriparatide groups (RR = 0.47, 95% CI = 0.25–0.88 and RR = 0.46, 95% CI = 0.25–0.86, for the 20- and 40-μg doses, respectively). Although the different doses did not affect fracture risk reduction, a larger gain in BMD was seen with the 40-μg dose.

Two studies have compared teriparatide with other osteoporosis therapies. In one small study of teriparatide at 25 μg daily plus HRT compared with HRT alone, teriparatide significantly increased BMD while those on HRT alone had no significant change in BMD from baseline.130 An RCT comparing teriparatide 40 μg daily with alendronate daily found significantly fewer nonvertebral fractures with teriparatide than with alendronate (4.1% vs 13.7%, P = .04).131 Lumbar spine BMD was also greater with teriparatide than with alendronate at 2 years (15.1% vs 6.6%, P < .001).

Calcitonin. Three meta-analyses of calcitonin were identified.132-134 The first meta-analysis, which included 30 RCTs, evaluated the efficacy of calcitonin in the treatment of postmenopausal osteoporosis.132 Calcitonin reduced the incidence of vertebral fractures with a pooled RR of 0.46 (95% CI = 0.25–0.87). This part of the meta-analysis was based on four trials with 1,404 participants. The RR for nonvertebral fractures was 0.52 (95% CI = 0.22–1.23). In the second meta-analysis,133 the pooled change in BMD at the end of the study was 1.97 (95% CI = 1.77–2.17) at the spine and 0.32 (95% CI = −0.27–0.91) at the proximal femur. This meta-analysis had significant limitations, including heterogeneity of the treatment regimens and duration, and different inclusion criteria. The third meta-analysis,134 which included 14 RCTs, reported nonsignificantly lower risk for calcitonin than for placebo for vertebral (RR = 0.80, 95% CI = 0.64–1.01) and nonvertebral fractures (RR = 0.48, 95% CI = 0.20–1.15).

Raloxifene. The search identified three systematic reviews that evaluated the effect of raloxifene on fractures.135-137 These reviews identified the same two studies56,138 and came to the same conclusions. Of the two studies, one was significantly larger,56 with 7,705 subjects, compared with 103 in the other.138 The risk of vertebral

factors was 0.86 (95% CI = 0.43–1.72). The calcium was given with or without vitamin D.

In a recent RCT,103 1,460 community-dwelling women aged 70 and older were randomized to calcium carbonate 600 mg twice per day or placebo for 5 years. In the intention-to-treat analysis, calcium supplementation did not significantly reduce fracture risk (HR = 0.87, 95% CI = 0.67–1.12), although 830 patients (56.8%) who took 80% or more of their tablets (calcium or placebo) per year had lower fracture incidence in the calcium group than in the placebo group (10.2% vs 15.4%; HR = 0.66; 95% CI = 0.45–0.97).

Data on the efficacy of calcium supplementation in men are more limited. In one study of 111 men and 282 women aged 60 and older randomized to calcium supplements (750 mg), 25 OH vitamin D (15 μg), or placebo104 calcium was more effective than 25 OH vitamin D or placebo at preventing bone loss at 4 years. The number of fractures did not differ between the groups. In a study of 176 men and 213 women aged 65 and older randomized to 500 mg of calcium plus 700 IU of vitamin D3 daily or placebo for 3 years,105 total body, lumbar spine, and femoral neck BMD was statistically better in the treatment than the placebo group for men and women. Other studies have failed to demonstrate efficacy of calcium supplementation on BMD in men.106,107

Three meta-analyses have suggested that vitamin D can reduce fracture risk to varying degrees. One systematic review of RCTs and quasi-randomized trials of vitamin D and analogs108 reported that vitamin D alone had no statistically significant effect on hip, vertebral, or any new fracture. Vitamin D with calcium marginally reduced hip fractures (RR = 0.81, 95% CI = 0.68–0.96) but did not have any effect on vertebral fractures. The effect appeared to be restricted to those living in institutional care. In a meta-analysis of the efficacy of vitamin D treatment in preventing postmenopausal osteoporosis using 25 RCTs of standard or hydroxylated vitamin D with or without calcium supplementation, vitamin D reduced the risk of vertebral fractures (RR = 0.63, 95% CI = 0.45–0.88).109 A nonsignificant trend was seen for nonvertebral fractures (RR = 0.77, P = .09). The third meta-analysis evaluated fracture prevention with vitamin D supplementation and included studies with men.110 A vitamin D dose of 700 to 800 IU daily was associated with lower risk of hip fracture (RR = 0.74, 95% CI = 0.61–0.88) and of any nonvertebral fracture (RR = 0.77, 95% CI = 0.68–0.8). Doses of 400 IU daily were not effective in preventing hip and nonvertebral fractures. Two of these studies found that vitamin D supplementation was associated with greater risk of symptomatic adverse events or laboratory abnormalities.108,109

Four RCTs of vitamin D or vitamin D and calcium supplementation in institutionalized individuals had inconsistent results. One found that vitamin D supplementation reduced the risk of nonvertebral fractures.111 Two studies did not demonstrate fracture prevention.112,113 One RCT evaluated the effects of calcium and vitamin D on BMD as assessed according to ultrasound and found that broadband ultrasound scores but not speed-of-sound measures were improved significantly at 2 years.114 Numerous guidelines recommend the use of calcium and vitamin D supplements at varying doses.5,6,8,13
Table 1. Summary of Trials of Bisphosphonates for the Treatment of Postmenopausal Osteoporosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranney115</td>
<td>Alendronate</td>
<td>Meta-analysis</td>
<td>For subjects treated with at least 5 mg/d of alendronate, the pooled RR for vertebral fractures was 0.52 (95% CI = 0.43–0.65). The RR of nonvertebral fractures in patients given 10 mg/d or more was 0.51 (95% CI = 0.38–0.69)</td>
</tr>
<tr>
<td>Papapoulos116</td>
<td>Alendronate</td>
<td>Meta-analysis</td>
<td>For women with a T score &lt; − 2.0 or with a vertebral fracture, alendronate was associated with a 45% reduction in risk of hip fracture (95% CI = 16–64%, P = .007). For those with a T score of ≤ − 2.5 or vertebral fractures, the overall risk reduction in hip fracture was 55% (95% CI = 29–72%, P = .001)</td>
</tr>
<tr>
<td>Greenspan117</td>
<td>Alendronate</td>
<td>RCT in long-term care facilities</td>
<td>Bone density was 4.4% (95% CI = 3.3–5.5%) greater in the spine with alendronate than with placebo and 3.4% (95% CI = 2.3–4.4%) greater in the femoral neck. Eleven percent of placebo subjects and 8% of alendronate subjects experienced fractures, which was not statistically different. Routine spine radiographs were not part of the study.</td>
</tr>
<tr>
<td>Bone118</td>
<td>Alendronate vs premarin vs combination therapy vs placebo</td>
<td>RCT</td>
<td>Bone density of the lumbar spine was 6.0% greater with alendronate than with placebo, 6.0% greater for conjugated equine estrogens, and 8.3% greater for the combination; no difference in fracture rates</td>
</tr>
<tr>
<td>Cranney119</td>
<td>Risedronate</td>
<td>Meta-analysis</td>
<td>The pooled RR for vertebral fracture was 0.64 (95% CI = 0.52–0.77)</td>
</tr>
<tr>
<td>Boonen120</td>
<td>Risedronate</td>
<td>Pooled analysis of women aged ≥80 from three studies</td>
<td>Reduction in the risk of vertebral fractures of 81% (95% CI = 0.09–0.40) in the treatment group. A reduction in the risk of nonvertebral fractures was not seen</td>
</tr>
<tr>
<td>Sato121</td>
<td>Risedronate</td>
<td>RCT of women aged ≥70 with Alzheimer’s disease</td>
<td>Five hip fractures in the treatment group and 19 in the control group (P &lt; .001), BMD also improved in the risedronate group</td>
</tr>
<tr>
<td>Rosen122</td>
<td>Alendronate vs risedronate</td>
<td>RCT</td>
<td>Significantly greater bone density of the lumbar spine (3.4% vs 2.1%, P &lt; .001) and of the total hip (2.2% vs 1.2%, P &lt; .001) was seen with alendronate than with risedronate; no difference in fracture rates</td>
</tr>
<tr>
<td>Cranney123</td>
<td>Etidronate</td>
<td>Meta-analysis</td>
<td>The pooled RR of vertebral fracture was 0.60% (95% CI = 0.41–0.88), but no effect on nonvertebral fractures was seen</td>
</tr>
<tr>
<td>Harris124</td>
<td>Etidronate</td>
<td>RCT</td>
<td>BMD improved, but the risk of vertebral fractures was lower only for those at greater risk, defined as baseline BMD &lt; 50th percentile for the study group or three vertebral fractures</td>
</tr>
<tr>
<td>Hecht125</td>
<td>Etidronate</td>
<td>RCT</td>
<td>Reduced rate of bone loss with etidronate</td>
</tr>
<tr>
<td>Tano126</td>
<td>Ibandominate</td>
<td>RCT</td>
<td>20 mg weekly dose of ibandronate significantly increased BMD at the spine and hip (4.0% and 2.7%, respectively, more than placebo)</td>
</tr>
<tr>
<td>Chesnut127</td>
<td>Ibandronate</td>
<td>RCT</td>
<td>Daily and intermittent oral ibandronate significantly reduced the risk of new vertebral fractures 62% and 50%, respectively, and improved BMD. The incidence of nonvertebral fractures was not different between the three groups</td>
</tr>
<tr>
<td>Reid128</td>
<td>Zoledronic acid</td>
<td>RCT</td>
<td>BMD improvement of the lumbar spine 4.3% to 5.1% compared with placebo (P &lt; .001)</td>
</tr>
</tbody>
</table>

RR = relative risk; CI = confidence interval; RCT = randomized, controlled trial; BMD = bone mineral density.

Fractures was significantly lower for raloxifene than for placebo using data only from the larger study (RR = 0.60, 95% CI = 0.52–0.69) but not when data from both studies were pooled (RR = 0.61, 95% CI = 0.43–1.51). Lower risk was not demonstrated for nonvertebral fractures.135–137

Hormone Replacement Therapy. Several meta-analyses and numerous randomized clinical trials, prospective studies, case-control studies, and cohort studies have shown that HRT is effective in preserving BMD and decreasing fracture risk. In one meta-analysis of the use of HRT in six case-control and five cohort studies, the pooled relative risk of hip fracture was 0.75 (95% CI = 0.68–0.84).139 The second meta-analysis showed a trend toward fewer vertebral (RR = 0.66, 95% CI = 0.41–1.07) and nonvertebral (RR = 0.87, 95% CI = 0.71–1.08) fractures and consistently demonstrated more improvements in BMD than with placebo.140 In a third meta-analysis, HRT use was associated with 33% fewer vertebral fractures (P = 0.04).141 Although these studies were included in some of the meta-analyses, two randomized placebo-controlled trials that demonstrated a lower risk of fracture for women taking estrogen replacement therapy deserve further mention. In the Women’s Health Initiative, the use of conjugated equine estrogen 0.625 mg plus medroxyprogesterone acetate 2.5 mg a day for more than 5.2 years resulted in 33% fewer vertebral fracture, 33% fewer hip fractures, and 24% fewer fractures overall than with placebo, all of which were statistically significant.142,143 In the Heart and Estrogen/Progestin Replacement Study, a large RCT designed to examine the effect of estrogen plus progestin therapy on postmenopausal women with heart disease, there was no evidence for a reduction in the risk of wrist, hip, or vertebral fractures or height loss used as a surrogate marker for vertebral fracture with 10,554 person-years of follow-up.144 These two trials also highlighted the risks of HRT, and because of adverse effects of HRT on breast cancer, thromboembolic disease, dementia, stroke and coronary artery disease, most guidelines no longer recommend the routine use of HRT for the prevention or treatment of postmenopausal osteoporosis. In these studies, HRT was initiated a number of years after menopause, and whether these

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RR = relative risk; CI = confidence interval; RCT = randomized, controlled trial; BMD = bone mineral density.
findings are applicable to women with long-term continuous use of HRT since menopause remains to be determined.

Although some guidelines recommend HRT for the treatment of osteoporosis, others no longer recommend routine use of HRT for treatment or prevention of osteoporosis but recommend the other therapies.  

### Testosterone for Male Osteoporosis

12. IF a male VE has osteoporosis and is hypogonadal and has no history of prostate cancer, THEN he should be prescribed testosterone therapy, BECAUSE testosterone therapy has been shown to improve bone density and therefore may decrease fracture risk.

### Supporting Evidence

No direct evidence showed that treatment with testosterone would reduce fracture risk in elderly hypogonadal men with osteoporosis. Three small RCTs of testosterone therapy in hypogonadal, but not necessarily osteoporotic, men demonstrated modest benefits in BMD for those receiving treatment. Additionally, a chain of indirect evidence further supports this indicator. First, testosterone deficiency is present in approximately 30% of men with osteoporosis. Second, serum testosterone levels correlate with BMD in men in some studies but not others. One small case-control study of elderly men in nursing homes found that hypogonadal men were 6.5 times as likely to have a minimal-trauma hip fracture (95% CI = 2.0–20.6). Third, two small studies were identified that demonstrated the benefit of testosterone therapy in osteoporotic men with normal testosterone levels. Fourth, in a convenience sample of 72 men with low serum testosterone levels, testosterone replacement maintained BMD in the normal range and resulted in the greatest increases for participants with the lowest BMD at initiation of therapy. Furthermore, hypogonadal men have been found to have a greater risk of falls, which is a risk factor for fracture. Additionally, a 36-month randomized, placebo-controlled trial of the effect of testosterone replacement therapy on BMD in 108 men aged 65 and older with low serum testosterone reported no difference in the change in lumbar spine BMD between the treatment and control groups, although for those with a pretreatment serum testosterone level less than 6.94 nmol/L (&lt;200 ng/dL), the increase in BMD was significantly greater for testosterone recipients than for placebo recipients.

The use of testosterone for osteoporosis in men is relatively unaddressed in guidelines, although two position statements support the use of testosterone treatment in hypogonadal men with osteoporosis or on corticosteroid therapy.

### Pharmacological Treatment of Male Osteoporosis

13. IF a male VE has osteoporosis, THEN he should be treated with bisphosphonates, calcitonin, PTH, or if hypogonadal, testosterone (if this is a new diagnosis, within 3 months), BECAUSE this will reduce the rate of bone loss and decrease the risk of fracture and fracture rate.

### Supporting Evidence

Although clinical trials of osteoporosis in men lag behind those for women, there are data to support the use of these agents in osteoporosis. These are summarized in Table 2. Several guidelines recommend the use of these agents for the treatment of male osteoporosis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orwoll</td>
<td>Alendronate</td>
<td>Alendronate vs placebo</td>
<td>Less incidence of vertebral fractures with alendronate than with placebo (0.8% vs 7.1%, P = .02) (N = 241 men, mean age 63, range 31–87)</td>
</tr>
<tr>
<td>Ringe</td>
<td>Alendronate</td>
<td>Alendronate 10 mg daily vs 1 μg of alfalcacidol</td>
<td>New vertebral fractures in 18.2% and 7.4% (P = .07) at 2 years and in 24.2% and 10.3% (P = .04) at 3 years for alfalcacidol and alendronate, respectively</td>
</tr>
<tr>
<td>Sato</td>
<td>Risedronate</td>
<td>Risedronate vs placebo in 280 post-stroke men</td>
<td>Relative risk of hip fracture for risedronate relative to placebo 0.19 (95% CI = 0.04–0.89). BMD increased 2.5% in the risedronate group and decreased 3.5% in the placebo group (P &lt; .001)</td>
</tr>
<tr>
<td>Ringe</td>
<td>Risedronate</td>
<td>316 men with primary or secondary osteoporosis</td>
<td>60% fewer new vertebral fractures with risedronate than in controls (P = .03)</td>
</tr>
<tr>
<td>Trovas</td>
<td>Calcitonin</td>
<td>28 men</td>
<td>Significantly greater increase in BMD in the calcitonin group than with placebo at vertebrae but not hip; fracture rates not reported</td>
</tr>
<tr>
<td>Toth</td>
<td>Calcitonin</td>
<td>71 men with idiopathic osteoporosis</td>
<td>Greater BMD of the spine (3.5% vs 0.8% in controls, P = .04) and of the femoral neck (3.2% vs 0.7%, P = .004)</td>
</tr>
<tr>
<td>Orwoll</td>
<td>Teriparatide</td>
<td>By the end of therapy, BMD in the spine increased 5.9% (20 μg) and 9.0% (40 μg) from baseline compared to placebo for both; study prematurely discontinued because of osteosarcoma in rats noted. Eighteen months after study termination, the risk of vertebral fracture was 51% lower for the combined teriparatide group than for placebo (P = .07). Approximately 29% of the men in the placebo group and 18% of the men in the teriparatide group had started bisphosphonates</td>
<td></td>
</tr>
<tr>
<td>Finkelstein</td>
<td>Teriparatide vs alendronate vs the combination of the two</td>
<td>Teriparatide alone was significantly more effective than alendronate or combination therapy at improving BMD at the femoral neck and spine. The combination group had a greater effect than alendronate on spine BMD (P &lt; .001). Fracture data were not reported</td>
<td></td>
</tr>
</tbody>
</table>

BMD = bone mineral density.
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