CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will prescribe bisphosphonates appropriately and not keep patients on them indefinitely

SUSAN M. OTT, MD
Professor, Department of Medicine,
University of Washington, Seattle

What is the optimal duration of bisphosphonate therapy?

ABSTRACT

It is reasonable to stop bisphosphonates after 5 years of use and then to follow patients with markers of bone turnover. As long as the levels of these markers remain reduced, adding an antiresorptive drug does not make physiologic sense.

KEY POINTS

Bisphosphonates reduce the risk of osteoporotic fractures, including devastating hip and spine fractures.

As with any drugs, bisphosphonates should not be used indiscriminately. They are indicated for patients at high risk of fracture, especially those with vertebral fractures or a hip bone density T score lower than –2.5.

There is little evidence to guide physicians about the duration of bisphosphonate therapy beyond 5 years. One study with marginal power did not show any difference in fracture rates between those who continued taking alendronate and those who discontinued after 5 years (JAMA 2006; 296:2927–2938).

Evidence is accumulating that the risk of atypical fracture of the femur increases after 5 years of bisphosphonate use.

Anabolic drugs are needed; the only one currently available is teriparatide (Forteo), which can be used when fractures occur despite (or perhaps because of) bisphosphonate use.

doi:10.3949/ccjm.78a.11022

Almost all the data about the safety and efficacy of bisphosphonate drugs for treating osteoporosis are from patients who took them for less than 5 years.

Reports of adverse effects with prolonged use have caused concern about the long-term safety of this class of drugs. This is particularly important because these drugs are retained in the skeleton longer than 10 years, because there are physiologic reasons why excessive bisphosphonate-induced inhibition of bone turnover could be damaging, and because many healthy postmenopausal women have been prescribed bisphosphonates in the hope of preventing fractures that are not expected to occur for 20 to 30 years.

Because information from trials is scant, opinions differ over whether bisphosphonates should be continued indefinitely. In this article, I summarize the physiologic mechanisms of these drugs, review the scant existing data about their effects beyond 5 years, and describe my approach to bisphosphonate therapy (while waiting for better evidence).

MORE THAN 4 MILLION WOMEN TAKE BISPHOSPHONATES

The first medical use of a bisphosphonate was in 1967, when a girl with myositis ossificans was given etidronate (Didronel) because it inhibited mineralization. Two years later, it was given to patients with Paget disease of bone because it was found to inhibit bone resorption.[1] Etidronate could not be given for longer than 6 months, however, because patients developed osteomalacia.

Adding a nitrogen to the molecule dra-

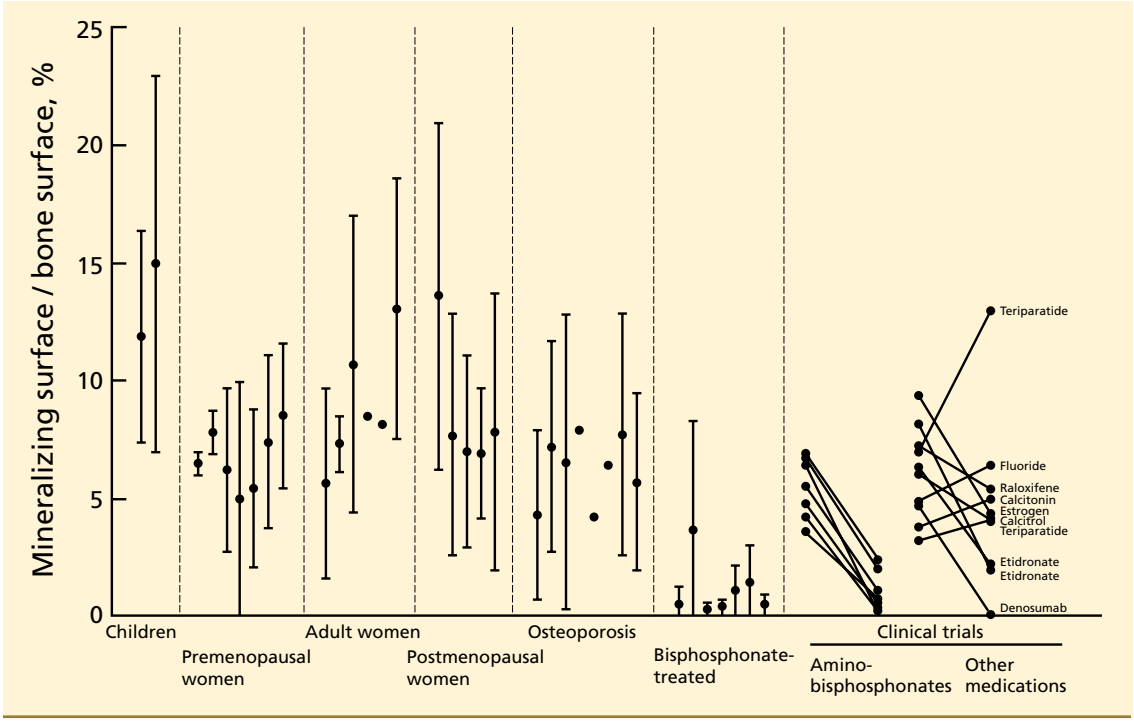

FIGURE 1. Mineralization surfaces in studies of normal people and with osteoporosis therapies. Mineralization (tetracycline-labelled) surfaces are directly related to the bone formation rate. Each point is the mean for a study, and error bars are one standard deviation. The clinical trials show the values before and after treatment, or in placebo vs medication groups. A list of the references is at http://courses.washington.edu/bonephys/physop.html.

Patients taking bisphosphonates long-term are forming very little new bone, and one-third of them are not forming *any* new bone

matically increased its potency and led to the second generation of bisphosphonates. Alendronate (Fosamax), the first amino-bisphosphonate, became available in 1995, It was followed by risedronate (Actonel), ibandronate (Boniva), and zoledronic acid (Reclast). These drugs are potent inhibitors of bone resorption; however, in clinical doses they do not inhibit mineralization and therefore do not cause osteomalacia.

Randomized clinical trials involving more than 30,000 patients have provided grade A evidence that these drugs reduce the incidence of fragility fractures in patients with osteoporosis.[2] Furthermore, observational studies have confirmed that they prevent fractures and have a good safety profile in clinical practice.

Therefore, the use of these drugs has become common. In 2008, an estimated 4 million women in the United States were taking them.[3]

BISPHOSPHONATES STRENGTHEN BONE BY INHIBITING RESORPTION

On a molecular level, bisphosphonates inhibit farnesyl pyrophosphate synthase, an enzyme necessary for formation of the cytoskeleton in osteoclasts. Thus, they strongly inhibit bone resorption. They do not appear to directly inhibit osteoblasts, the cells that form new bone, but they substantially decrease bone formation indirectly.[4]

To understand how inhibition of bone resorption affects bone physiology, it is necessary to appreciate the nature of bone remodeling. Bone is not like the skin, which is continually forming a new layer and sloughing off the old. Instead, bone is renewed in small units. It takes about 5 years to remodel cancellous bone and 13 years to remodel cortical bone[5]; at any one time, about 8% of the surface is being remodeled.

The first step occurs at a spot on the sur-

face, where the osteoclasts resorb some bone to form a pit that looks like a pothole. Then a team of osteoblasts is formed and fills the pit with new bone over the next 3 to 6 months. When first formed, the new bone is mainly collagen and, like the tip of the nose, is not very stiff, but with mineral deposition the bone becomes stronger, like the bridge of the nose. The new bone gradually accumulates mineral and becomes harder and denser over the next 3 years.

When a bisphosphonate is given, the osteoclasts abruptly stop resorbing the bone, but osteoblasts continue to fill the pits that were there when the bisphosphonate was started. For the next several months, while the previous pits are being filled, the bone volume increases slightly. Thereafter, rates of both bone resorption and bone formation are very low.

A misconception: Bisphosphonates build bone

While semantically it is true that the bone formation rate in patients taking bisphosphonates is within the normal premenopausal range, this often-repeated statement is essentially misleading.

The most direct measurement of bone formation is the percentage of bone surface that takes a tetracycline label, termed the *mineralizing surface*. **FIGURE 1** shows data on the mineralizing surface in normal persons,[6] women with osteoporosis, and women taking various other medications for osteoporosis. Bisphosphonate therapy reduces bone formation to values that are lower than in the great majority of normal young women.[7] A study of 50 women treated with bisphosphonates for 6.5 years found that 33% had a mineralizing surface of zero.[8] This means that patients taking bisphosphonates are forming very little new bone, and one-third of them are not forming *any* new bone.

With continued bisphosphonate use, the bone gradually becomes more dense. There is no further new bone, but the existing bone matrix is packed more tightly with mineral crystals.[9] The old bone is not resorbed. The bone density, measured radiographically, increases most rapidly during the first 6 months (while resorption pits are filling in) and more gradually over the next 3 years (while bone is becoming more mineralized).

Another common misunderstanding is that the bone density increases because the drugs are "building bone." After 3 years, the bone density in the femur reaches a plateau.[10] I have seen patients who were very worried because their bone density was no longer increasing, and their physicians did not realize that this is the expected pattern. The spinal bone density continues to increase modestly, but some of this may be from disk space narrowing, harder bone edges, and soft-tissue calcifications. Spinal bone density frequently increases even in those on placebo.

Bisphosphonates suppress markers of bone turnover

These changes in bone remodeling with bisphosphonates are reflected by changes in markers of bone formation and resorption. The levels of markers of bone resorption—N-telopeptide cross-linked type I collagen (NTx) and C-telopeptide cross-linked type I collagen (CTx)—decrease rapidly and remain low. The markers of bone formation—propeptide of type I collagen, bone alkaline phosphatase, and osteocalcin—decrease gradually over 3 to 6 months and then remain low. As measured directly at the bone, bone formation appears to be more suppressed than as measured by biochemical markers in the serum.

Bone density is only a surrogate end point

In a risedronate trial,[11] the fracture rate decreased as the biochemical markers of bone turnover decreased, except when the markers were very low, in which case the fracture rate increased.

Without remodeling, cracks can accumulate

The bisphosphonates do not significantly increase bone volume, but they prevent microscopic architectural deterioration of the bone, as shown on microscopic computed tomographic imaging.[12] This prevents fractures for at least 5 years.

But bisphosphonates may have long-term negative effects. One purpose of bone remodeling is to refresh the bone and to repair the microscopic damage that accumulates within any structure. Without remodeling, cracks can accumulate. Because the development and repair of microcracks is complex, it is difficult to predict what will happen with long-term bisphosphonate use. Studies of biopsies from

women taking bisphosphonates long-term are inconsistent: one study found accumulation of microcracks,[13] but another did not.[8]

STUDIES OF LONG-TERM USE: FOCUS ON FRACTURES

For this review, I consider long-term bisphosphonate use to be greater than 5 years, and I will focus on fractures. Bone density is only a surrogate end point. Unfortunately, this fact is often not emphasized in the training of young physicians.

The best illustration of this point was in a randomized clinical trial of fluoride,[14] in which the bone density of the treated group increased by 8% per year for 4 years, for a total increase of 32%. This is more than we ever see with current therapies. But the patients had more fractures with fluoride than with placebo. This is because the quality of bone produced after fluoride treatment is poor, and although the bone is denser, it is weaker.

Observational studies of fracture incidence in patients who continued taking bisphosphonates compared with those who stopped provide some weak evidence about long-term effectiveness.

With fluoride, bone was denser but weaker

Curtis et al[15] found, in 9,063 women who were prescribed bisphosphonates, that those who stopped taking them during the first 2 years had higher rates of hip fracture than compliant patients. Those who took bisphosphonates for 3 years and then stopped had a rate of hip fracture during the next year similar to that of those who continued taking the drugs.

Meijer et al[16] used a database in the Netherlands to examine the fracture rates in 14,750 women who started taking a bisphosphonate for osteoporosis between 1996 and 2004. More than half of the women stopped taking the drug during the first year, and they served as the control group. Those who took bisphosphonates for 3 to 4 years had significantly fewer fractures than those who stopped during the first year (odds ratio 0.54). However, those who took them for 5 to 6 years had slightly more fractures than those who took them for less than a year.

Mellström et al[17] performed a 2-year uncontrolled extension of a 5-year trial of risedronate that had blinded controls.[18] Initially, 407 women were in the risedronate group; 68 completed 7 years.

The vertebral fracture rate in the placebo group was 7.6% per year during years 0 through 3. In the risedronate group, the rate was 4.7% per year during years 0 through 3 and 3.8% per year during years 6 and 7. Nonvertebral fractures occurred in 10.9% of risedronate-treated patients during the first 3 years and in 6% during the last 2 years. Markers of bone turnover remained reduced throughout the 7 years. Bone mineral density of the spine and hip did not change from years 5 to 7. The study did not include those who took risedronate for 5 years and then discontinued it.

Bone et al[19] performed a similar, 10-year uncontrolled extension of a 3-year controlled trial of alendronate.[20] There were 398 patients randomly assigned to alendronate, and 164 remained in the study for 8 to 10 years.

During years 8 through 10, bone mineral density of the spine increased by about 2%; no change was seen in the hip or total body. The nonvertebral fracture rate was similar in years 0 through 3 and years 6 through 10. Vertebral fractures occurred in approximately 3% of women in the first 3 years and in 9% in the last 5 years.

The FLEX trial: Continuing alendronate vs stopping

Only one study compared continuing a bisphosphonate vs stopping it. The Fracture Intervention Trial Long-Term Extension (FLEX)[10] was an extension of the Fracture Intervention Trial (FIT)[21,22] of alendronate. I am reviewing this study in detail because it is the only one that randomized patients and was double-blinded.

In the original trial,[21,22] 3,236 women were in the alendronate group. After a mean of 5 years on alendronate, 1,099 of them were randomized into the alendronate or placebo group.[10] Those with T scores lower than –3.5 or who had lost bone density during the first 5 years were excluded.

The bone mineral density of the hip in the placebo group decreased by 3.4%, whereas in the alendronate group it decreased by 1.0%. At the spine, the placebo group gained less than the alendronate group.

Despite these differences in bone density, no significant difference was noted in the rates of all clinical fractures, nonvertebral fractures, vertebral fractures as measured on radiographs taken for the study ("morphometric" fractures, 11.3% vs 9.8%), or in the number of severe vertebral fractures (those with more than a two-grade change on radiography) between those who took alendronate for 10 years and those who took it for 5 years followed by placebo for 5 years.

However, fewer "clinical spine fractures" were observed in the group continuing alendronate (2.4% vs 5.3%). A clinical spine fracture was one diagnosed by the patient's personal physician.

In FIT, these clinical fractures were painful in 90% of patients, and although the community radiographs were reviewed by a central radiologist, only 73% of the fractures were confirmed by subsequent measurements on the per protocol radiographs done at the study centers. About one-fourth of the morphometric fractures were also clinical fractures.[23] Therefore, I think morphometric fractures provide the best evidence about the effects of treatment—ie, that treatment beyond 5 years is not beneficial. Other physicians, however, disagree, emphasizing the 55% reduction in clinical fractures.[24]

Markers of bone turnover gradually increased after discontinuation but remained lower than baseline even after 5 years without alendronate.[10] There were no significant differences in fracture rates between the placebo and alendronate groups in those with baseline bone mineral density T scores less than –2.5.[10] Also, after age adjustment, the fracture incidence was similar in the FIT and the FLEX studies.

Several years later, the authors published a post hoc subgroup analysis of these data.[25] The patients were divided into six subgroups based on bone density and the presence of vertebral fractures at baseline. This is weak evidence, but I include it because reviews in the literature have emphasized only the positive findings, or have misquoted the data: Schwartz et al stated that in those with T scores of –2.5 or below, the risk of nonvertebral fracture was reduced by 50%[25]; and Shane[26] concluded in an editorial that the use of alendronate for 10 years, rather than for 5 years, was associated with significantly fewer new vertebral fractures and nonvertebral fractures in patients with a bone mineral density T score of −2.5 or below.[26]

What was actually seen in the FLEX study was no difference between alendronate and placebo in morphometric vertebral fractures in any subgroup. In one of the six subgroups

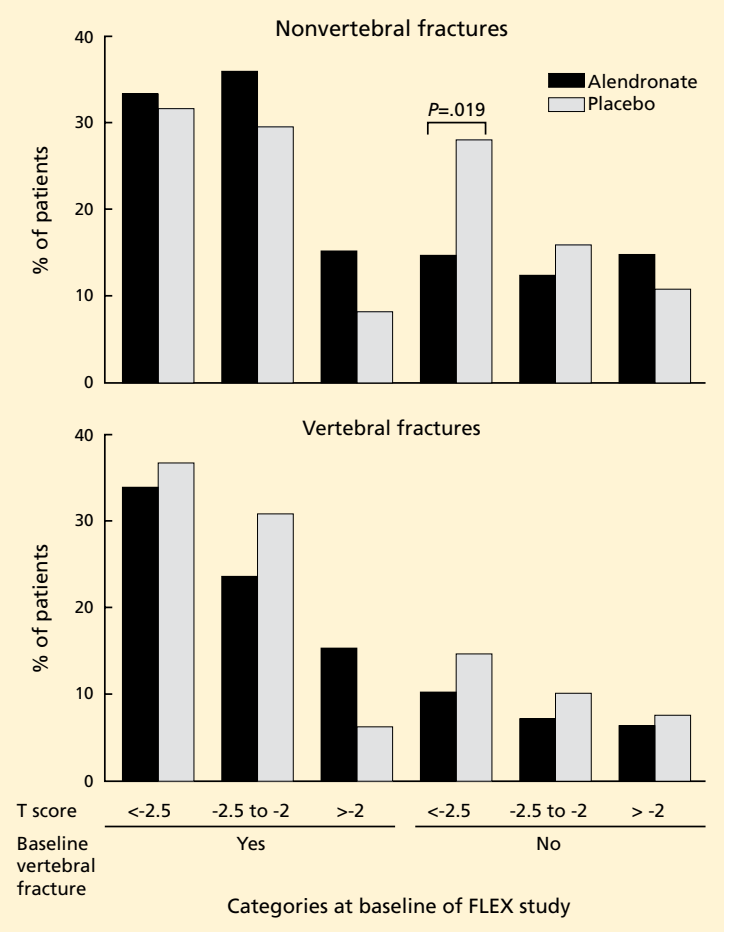

FIGURE 2. Fractures rates in the FLEX trial, a randomized double-blind study of women who took alendronate for 10 years (alendronate group) compared with women who took alendronate for 5 years followed by placebo for 5 years (placebo group). A post hoc analysis separated participants into six groups based on the presence of a vertebral fracture and the bone density (femoral neck T score) at the start of the trial, and the graph shows the percentage of women with a fracture during the last 5 years. The only significant difference was in the group with T scores below –2.5 who did not have a vertebral fracture at the outset.

DATA FROM SCHWARTZ AV, BAUER DC, CUMMINGS SR, ET AL; FLEX RESEARCH GROUP. EFFICACY OF CONTINUED ALENDRONATE FOR FRACTURES IN WOMEN WITH AND WITHOUT PREVALENT VERTEBRAL FRACTURE: THE FLEX TRIAL. J BONE MINER RES 2010; 25:976–982.

(N = 184), women with osteoporosis without vertebral fractures had fewer nonvertebral fractures with alendronate. There was no benefit with alendronate in the other five subgroups (FIGURE 2), not even in those with the greatest risk—women with osteoporosis who had a vertebral compression fracture, shown in the first three columns of FIGURE 2.[25] Nevertheless, several recent papers about this topic have recommended that bisphosphonates should be used continuously for 10 years in those with the highest fracture risk.[24,27–29]

ATYPICAL FEMUR FRACTURES

Recent reports, initially met with skepticism, have described atypical fractures of the femur in patients who have been taking bisphosphonates long-term (FIGURE 3).[28–30]

By March 2011, there were 55 papers describing a total of 283 cases, and about 85 individual cases (listed online in Ott SM. *Osteoporosis and Bone Physiology. http://courses.washington.edu/bonephys/opsubtroch.html.* Accessed 7/30/2011).

Recent reports have described atypical fractures of the femur in some patients on bisphosphnates long-term

The mean age of the patients was 65, bisphosphonate use was longer than 5 years in 77% of cases, and bilateral fractures were seen in 48%.

The fractures occur with minor trauma, such as tripping, stepping off an elevator, or being jolted by a subway stop, and a disproportionate number of cases involve no trauma. They are often preceded by leg pain, typically in the mid-thigh.

These fractures are characterized by radiographic findings of a transverse fracture, with thickened cortices near the site of the fracture. Often, there is a peak on the cortex that may precede the fracture. These fractures initiate on the lateral side, and it is striking that they occur in the same horizontal plane on the contralateral side.

Radiographs and bone scans show stress fractures on the lateral side of the femur that resemble Looser zones (ie, dark lines seen radiographically). These radiographic features are not typical in osteoporosis but are reminiscent of the stress fractures seen with hypophosphatasia, an inherited disease characterized by severely decreased bone formation.[31]

Bone biopsy specimens show very low bone formation rates, but this is not a necessary feature. At the fracture site itself there is bone activity. For example, pathologists from St. Louis reviewed all iliac crest bone biopsies from patients seen between 2004 and 2007 who had an unusual cortical fracture while taking a bisphosphonate. An absence of double tetracycline labels was seen in 11 of the 16 patients.[32]

The first reports were anecdotal cases, then some centers reported systematic surveys of their patients. In a key report, Neviaser et al[33] reviewed all low-trauma subtrochanteric fractures in their large hospital and found 20 cases with the atypical radiographic appearance; 19 of the patients in these cases had been taking a bisphosphonate. A similar survey in Australia found 41 cases with atypical radiographic features (out of 79 subtrochanteric low-trauma fractures), and all of the patients had been taking a bisphosphonate.[34]

By now, more than 230 cases have been reported. The estimated incidence is 1 in 1,000, based on a review of operative cases and radiographs.[35]

However, just because the drugs are associated with the fractures does not mean they caused the fractures, because the patients who took bisphosphonates were more likely to get a fracture in the first place. This confounding by indication makes it difficult to prove beyond a doubt that bisphosphonates cause atypical fractures.

Further, some studies have found no association between bisphosphonates and subtrochanteric fractures.[36,37] These database analyses have relied on the coding of the *International Classification of Diseases, Ninth Revision* (ICD-9), and not on the examination of radiographs. We reviewed the ability of ICD-9 codes to identify subtrochanteric fractures and found that the predictive ability was only 36%.[38] Even for fractures in the correct location, the codes cannot tell which cases have the typical spiral or comminuted fractures seen in osteoporosis and which have the unusual features of the bisphosphonate-associated fractures. Subtrochanteric and shaft fractures are about 10 times less common than hip fractures, and the atypical ones are about 10 times less common than typical ones, so studies based on ICD-9 codes cannot exonerate bisphosphonates.

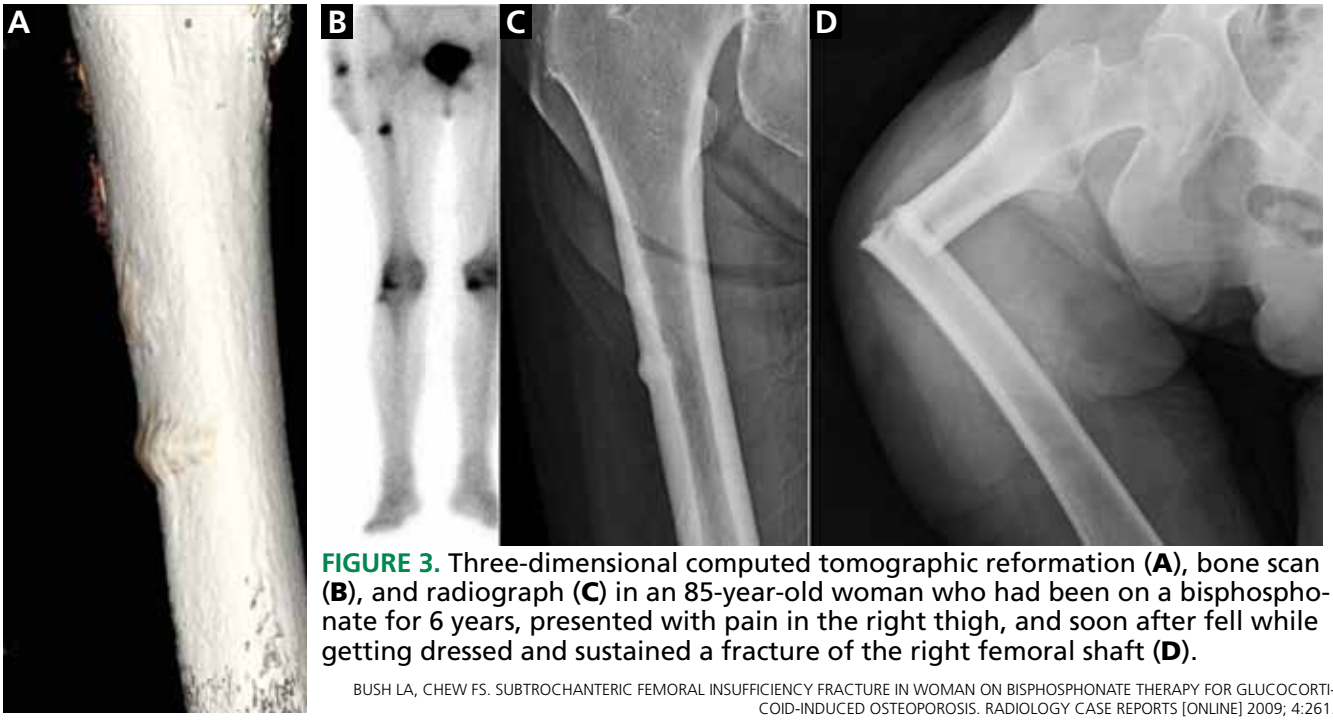

FIGURE 3. Three-dimensional computed tomographic reformation (**A**), bone scan (**B**), and radiograph (**C**) in an 85-year-old woman who had been on a bisphosphonate for 6 years, presented with pain in the right thigh, and soon after fell while getting dressed and sustained a fracture of the right femoral shaft (**D**).

BUSH LA, CHEW FS. SUBTROCHANTERIC FEMORAL INSUFFICIENCY FRACTURE IN WOMAN ON BISPHOSPHONATE THERAPY FOR GLUCOCORTICOID-INDUCED OSTEOPOROSIS. RADIOLOGY CASE REPORTS [ONLINE] 2009; 4:261.

A report of nearly 15,000 patients from randomized clinical trials did not find a significant incidence of subtrochanteric fractures, but the radiographs were not examined and only 500 of the patients had taken the medication for longer than 5 years.[39]

A population-based, nested case-control study using a database from Ontario, Canada, found an increased risk of diaphyseal femoral fractures in patients who had taken bisphosphonates longer than 5 years. The study included only women who had started bisphosphonates when they were older than 68, so many of the atypical fractures would have been missed. The investigators did not review the radiographs, so they combined both osteoporotic and atypical diaphyseal fractures in their analysis.[40]

At the 2010 meeting of the American Society for Bone and Mineral Research, preliminary data were presented from a systematic review of radiographs of patients with fractures of the femur from a health care plan with data about the use of medications. The incidence of atypical fractures increased progressively with the duration of bisphosphonate use, and was significantly higher after 5 years compared with less than 3 years.[28]

OTHER POSSIBLE ADVERSE EFFECTS

There have been conflicting reports about esophageal cancer with bisphosphonate use.[41,42]

Another possible adverse effect, osteonecrosis of the jaw, may have occurred in 1.4% of patients with cancer who were treated for 3 years with high intravenous doses of bisphosphonates (about 10 to 12 times the doses recommended for osteoporosis).[43] This adverse effect is rare in patients with osteoporosis, occurring in less than 1 in 10,000 exposed patients.[44]

BISPHOSPHONATES SHOULD BE USED WHEN THEY ARE INDICATED

The focus of this paper is on the duration of use, but concern about long-term use should not discourage physicians or patients from using these drugs when there is a high risk of an osteoporotic fracture within the next 10 years, particularly in elderly patients who have experienced a vertebral compression fracture or a hip fracture. Patients with a vertebral fracture have a one-in-five chance of fracturing another vertebra, which is a far higher risk than

Concern about long-term use should not discourage us from using these drugs when there is a high risk of fracture within the next 10 years

any of the known long-term side effects from treatment, and bisphosphonates are effective at reducing the risk.

Low bone density alone can be used as an indication for bisphosphonates if the hip T score is lower than –2.5. A cost-effectiveness study concluded that alendronate was beneficial in these cases.[45] In the FIT patients without a vertebral fracture at baseline, the overall fracture rate was significantly decreased by 36% with alendronate in those with a hip T score lower than –2.5, but there was no difference between placebo and alendronate in those with T scores between –2 and –2.5, and a 14% (nonsignificant) higher fracture rate when the T score was better than –2.0.[22]

A new method of calculating the risk of an osteoporotic fracture is the FRAX prediction tool (**http://www.shef.ac.uk/FRAX**), and one group has suggested that treatment is indicated when the 10-year risk of a hip fracture is greater than 3%.[46] Another group, from the United Kingdom, suggests using a sliding scale depending on the fracture risk and the age.[47]

It is not always clear what to do when the hip fracture risk is greater than 3% for the next decade but the T score is better than –2.5. These patients have other factors that contribute to fracture risk. Their therapy must be individualized, and if they are at risk of fracture because of low weight, smoking, or alcohol use, it makes more sense to focus the approach on those treatable factors.

In osteopenia, use of bisphosphonates to prevent fractures is based on hope, not evidence

Women who have osteopenia and have not had a fragility fracture are often treated with bisphosphonates with the intent of preventing osteoporosis in the distant future. This approach is based on hope, not evidence, and several editorial reviews have concluded that these women do not need drug therapy.[48–50]

MY RECOMMENDATION: STOP AFTER 5 YEARS

Bisphosphonates reduce the incidence of devastating osteoporotic fractures in patients with osteoporosis, but that does not mean they should be used indefinitely.

After 5 years, the overall fracture risk is the same in patients who keep taking bisphosphonates as in patients who discontinue them. Therefore, I think these drugs are no longer necessary after 5 years. The post hoc subgroup analysis that showed benefit in only one of six groups of the FLEX study does not provide compelling evidence to continue taking bisphosphonates.

In addition, there is a physiologic concern about long-term suppression of bone formation. Ideally, we would treat all high-risk patients with drugs that stop bone resorption and also improve bone formation, but such drugs belong to the future. Currently, there is some emerging evidence of harm after 5 years of bisphosphonate treatment; to date the incidence of serious side effects is less than 1 in 1,000, but the risks beyond 10 years are unknown. If we are uncertain about long-term safety, we should follow the principle of *primum non nocere*. Only further investigations will settle the debate about prolonged use.

While awaiting better studies, we use the approach shown in the algorithm in **FIGURE 4**.

Follow the patient with bone resorption markers

In patients who have shown some improvement in bone density during 5 years of bisphosphonate treatment and who have not had any fractures, I measure a marker of bone resorption at the end of 5 years.

The use of a biochemical marker to assess patients treated with anti-turnover drugs has not been studied in a formal trial, so we have no grade A evidence for recommending it. However, there have been many papers describing the effects of bisphosphonates on these markers, and it makes physiologic sense to use them in situations where decisions must be made when there is not enough evidence.

In FIT (a trial of alendronate), we reported that the change in bone turnover markers was significantly related to the reduction in fracture risk, and the effect was at least as strong as that observed with a 1-year change in bone density. Those with a 30% decrease in bone alkaline phosphatase had a significant reduction in fracture risk.[51]

Furthermore, in those patients who were compliant with bisphosphonate treatment, the reduction in fractures with alendronate treatment was significantly better in those who initially had a high bone turnover.[52]

Similarly, with risedronate, the change in

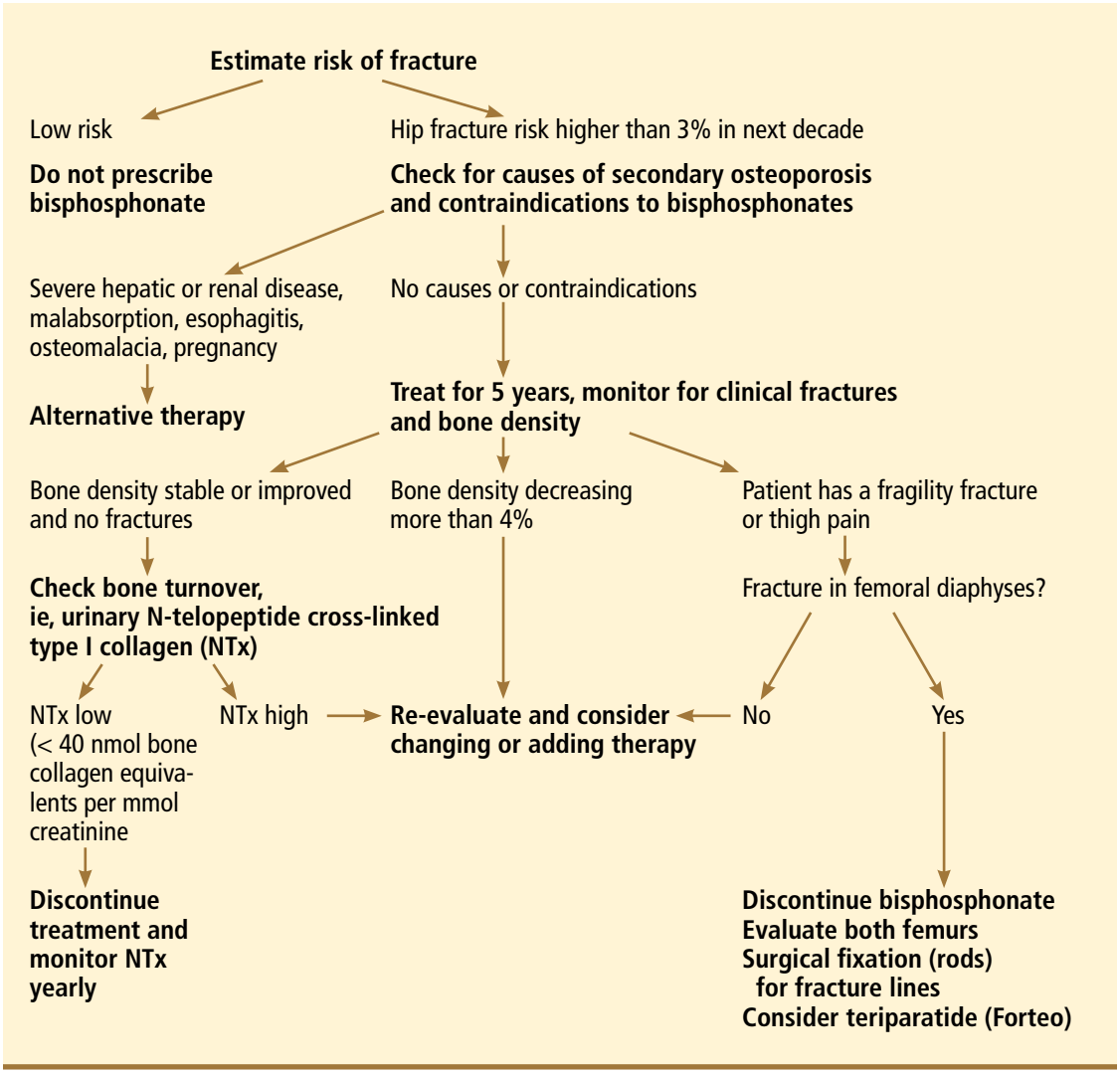

FIGURE 4. Suggested algorithm for bisphosphonate use, while awaiting better studies.

NTx accounted for half of the effect on fracture reduction during the clinical trial, and there was little further improvement in fracture benefit below a decrease of 35% to 40%.[10]

The baseline NTx level in these clinical trials was about 70 nmol bone collagen equivalents per millimole of creatinine (nmol BCE/mmol Cr) in the risedronate study and 60 in the alendronate study, and in both the fracture reduction was seen at a level of about 40. The FLEX study measured NTx after 5 years, and the average was 19 nmol BCE/mmol Cr. This increased to 22 after 3 years without alendronate.[53] At 5 years, the turnover markers had gradually increased but were still 7% to 24% lower than baseline.[10]

These markers have a diurnal rhythm and daily variation, but despite these limitations they do help identify low bone resorption.

In our hospital, NTx is the most economical marker, and my patients prefer a urine sample to a blood test. Therefore, we measure the NTx and consider values lower than 40 nmol BCE/mmol Cr to be satisfactory.

If the NTx is as low as expected, I discontinue the bisphosphonate. The patient remains on 1,200 mg/day of calcium and 1,000 U/day vitamin D supplementation and is encouraged to exercise.

Bone density tends to be stable for 1 or 2 years after stopping a bisphosphonate, and the biochemical markers of bone resorption remain reduced for several years. We remeasure the urine NTx level annually, and if it in-

NTx levels should stay lower than 40 for several years after stopping bisphosphonates

creases to more than 40 nmol BCE/mmol Cr an antiresorptive medication is given: either the bisphosphonate is restarted or raloxifene (Evista), calcitonin (Miacalcin), or denosumab (Prolia) is used.

Bone density is less helpful, but reassuring

Bone density is less helpful because it decreases even though the markers of bone resorption remain low. Although one could argue that bone density is not helpful in monitoring patients on therapy, I think it is reassuring to know the patient is not excessively losing bone.

Checking at 2-year intervals is reasonable. If the bone density shows a consistent decrease greater than 6% (which is greater than the difference we can see from patients walking around the room), then we would re-evaluate the patient and consider adding another medication.

If the bone density decreases but the biomarkers are low, then clinical judgment must be used. The bone density result may be erroneous due to different positioning or different regions of interest.

If we are unsure about long-term safety, we should follow the principle of *primum non nocere*

If turnover markers are not reduced

If a patient has been prescribed a bisphosphonate for 5 years but the NTx level is not reduced, I reevaluate the patient. Some are not taking the medication or are not taking it properly. The absorption of oral bisphosphonates is quite low in terms of bioavailability, and this decreases to nearly zero if the medication is taken with food. Some patients may have another disease, such as hyperparathyroidism, malignancy, hyperthyroidism, weight loss, malabsorption, celiac sprue, or vitamin D deficiency.

If repeated biochemical tests show high bone resorption and if the bone density response is suboptimal without a secondary cause, I often switch to an intravenous form of bisphosphonate because some patients do not seem to absorb the oral doses.

If a patient has had a fracture

If a patient has had a fracture despite several years of bisphosphonate therapy, I first check for any other medical problems. The bone markers are, unfortunately, not very helpful because they increase after a fracture and stay elevated for at least 4 months.[54] If there are no contraindications, treatment with teriparatide (Forteo) is a reasonable choice. There is evidence from human biopsy studies that teriparatide can reduce the number of microcracks that were related to bisphosphonate treatment,[13] and can increase the bone formation rate even when there has been prior bisphosphonate treatment.[55–57] Although the anabolic response is blunted, it is still there.[58]

If the patient remains at high risk

A frail patient with a high risk of fracture presents a challenge, especially one who needs treatment with glucocorticoids or who still has a hip T score below –3. Many physicians are uneasy about discontinuing all osteoporosis-specific drugs, even after 5 years of successful bisphosphonate treatment. In these patients anabolic medications make the most sense. Currently, teriparatide is the only one available, but others are being developed. Bone becomes resistant to the anabolic effects of teriparatide after about 18 months, so this drug cannot be used indefinitely. What we really need are longer-lasting anabolic medicines!

If the patient has thigh pain

Finally, in patients with thigh pain, radiography of the femur should be done to check for a stress fracture. Magnetic resonance imaging or computed tomography may be needed to diagnose a hairline fracture.

If there are already radiographic changes that precede the atypical fractures, then bisphosphonates should be discontinued. In a follow-up observational study of 16 patients who already had one fracture, all four whose contralateral side showed a fracture line (the "dreaded black line") eventually completed the fracture.[59]

Another study found that five of six incomplete fractures went on to a complete fracture if not surgically stabilized with rods.[60] This is an indication for prophylactic rodding of the femur.

Teriparatide use and rodding of a femur with thickening but not a fracture line must be decided on an individual basis and should be considered more strongly in those with pain in the thigh. ■

REFERENCES

1. **Francis MD, Valent DJ**. Historical perspectives on the clinical development of bisphosphonates in the treatment of bone diseases. J Musculoskelet Neuronal Interact 2007; 7:2–8.
2. **Bilezikian JP**. Efficacy of bisphosphonates in reducing fracture risk in postmenopausal osteoporosis. Am J Med 2009; 122(suppl 2):S14–S21.
3. **Siris ES, Pasquale MK, Wang Y, Watts NB**. Estimating bisphosphonate use and fracture reduction among US women aged 45 years and older, 2001-2008. J Bone Miner Res 2011; 26:3–11.
4. **Russell RG, Xia Z, Dunford JE, et al**. Bisphosphonates: an update on mechanisms of action and how these relate to clinical efficacy. Ann N Y Acad Sci 2007; 1117:209–257.
5. **Parfitt AM**. Misconceptions (2): turnover is always higher in cancellous than in cortical bone. Bone 2002; 30:807–809.
6. **Han ZH, Palnitkar S, Rao DS, Nelson D, Parfitt AM**. Effects of ethnicity and age or menopause on the remodeling and turnover of iliac bone: implications for mechanisms of bone loss. J Bone Miner Res 1997; 12:498–508.
7. **Chavassieux PM, Arlot ME, Reda C, Wei L, Yates AJ, Meunier PJ**. Histomorphometric assessment of the long-term effects of alendronate on bone quality and remodeling in patients with osteoporosis. J Clin Invest 1997; 100:1475–1480.
8. **Chapurlat RD, Arlot M, Burt-Pichat B, et al**. Microcrack frequency and bone remodeling in postmenopausal osteoporotic women on long-term bisphosphonates: a bone biopsy study. J Bone Miner Res 2007; 22:1502–1509.
9. **Boivin G, Meunier PJ**. Effects of bisphosphonates on matrix mineralization. J Musculoskelet Neuronal Interact 2002; 2:538–543.
10. **Black DM, Schwartz AV, Ensrud KE, et al; FLEX Research Group**. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA 2006; 296:2927–2938.
11. **Eastell R, Hannon RA, Garnero P, Campbell MJ, Delmas PD**. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate: review of statistical analysis. J Bone Miner Res 2007; 22:1656–1660.
12. **Borah B, Dufresne TE, Chmielewski PA, Johnson TD, Chines A, Manhart MD**. Risedronate preserves bone architecture in postmenopausal women with osteoporosis as measured by three-dimensional microcomputed tomography. Bone 2004; 34:736–746.
13. **Stepan JJ, Dobnig H, Burr DB, et al**. Histomorphometric changes by teriparatide in alendronate pre-treated women with osteoporosis (abstract). Presented at the Annual Meeting of the American Society of Bone and Mineral Research, Montreal 2008: #1019.
14. **Riggs BL, Hodgson SF, O'Fallon WM, et al**. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. N Engl J Med 1990; 322:802–809.
15. **Curtis JR, Westfall AO, Cheng H, Delzell E, Saag KG**. Risk of hip fracture after bisphosphonate discontinuation: implications for a drug holiday. Osteoporos Int 2008; 19:1613–1620.
16. **Meijer WM, Penning-van Beest FJ, Olson M, Herings RM**. Relationship between duration of compliant bisphosphonate use and the risk of osteoporotic fractures. Curr Med Res Opin 2008; 24:3217–3222.
17. **Mellström DD, Sörensen OH, Goemaere S, Roux C, Johnson TD, Chines AA**. Seven years of treatment with risedronate in women with postmenopausal osteoporosis. Calcif Tissue Int 2004; 75:462–468.
18. **Reginster J, Minne HW, Sorensen OH, et al**. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000; 11:83–91.
19. **Bone HG, Hosking D, Devogelaer JP, et al; Alendronate Phase III Osteoporosis Treatment Study Group**. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 2004; 350:1189–1199.
20. **Liberman UA, Weiss SR, Bröll J, et al**. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995; 333:1437–1443.
21. **Black DM, Cummings SR, Karpf DB, et al; Fracture Intervention Trial Research Group**. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1996; 348:1535–1541.
22. **Cummings SR, Black DM, Thompson DE, et al**. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998; 280:2077–2082.
23. **Fink HA, Milavetz DL, Palermo L, et al**. What proportion of incident radiographic vertebral deformities is clinically diagnosed and vice versa? J Bone Miner Res 2005; 20:1216–1222.
24. **Watts NB, Diab DL**. Long-term use of bisphosphonates in osteoporosis. J Clin Endocrinol Metab 2010; 95:1555–1565.
25. **Schwartz AV, Bauer DC, Cummings SR, et al; FLEX Research Group**. Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: the FLEX trial. J Bone Miner Res 2010; 25:976–982.
26. **Shane E**. Evolving data about subtrochanteric fractures and bisphosphonates (editorial). N Engl J Med 2010; 362:1825–1827.
27. **Sellmeyer DE**. Atypical fractures as a potential complication of long-term bisphosphonate therapy. JAMA 2010; 304:1480–1484.
28. **Shane E, Burr D, Ebeling PR, et al; American Society for Bone and Mineral Research**. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2010; 25:2267–2294.
29. **Giusti A, Hamdy NA, Papapoulos SE**. Atypical fractures of the femur and bisphosphonate therapy: a systematic review of case/case series studies. Bone 2010; 47:169–180.
30. **Rizzoli R, Akesson K, Bouxsein M, et al**. Subtrochanteric fractures after long-term treatment with bisphosphonates: a European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, and International Osteoporosis Foundation Working Group Report. Osteoporos Int 2011; 22:373–390.
31. **Whyte MP**. Atypical femoral fractures, bisphosphonates, and adult hypophosphatasia. J Bone Miner Res 2009; 24:1132–1134.
32. **Armamento-Villareal R, Napoli N, Panwar V, Novack D**. Suppressed bone turnover during alendronate therapy for high-turnover osteoporosis. N Engl J Med 2006; 355:2048–2050.
33. **Neviaser AS, Lane JM, Lenart BA, Edobor-Osula F, Lorich DG**. Low-energy femoral shaft fractures associated with alendronate use. J Orthop Trauma 2008; 22:346–350.
34. **Isaacs JD, Shidiak L, Harris IA, Szomor ZL**. Femoral insufficiency fractures associated with prolonged bisphosphonate therapy. Clin Orthop Relat Res 2010; 468:3384–3392.
35. **Schilcher J, Aspenberg P**. Incidence of stress fractures of the femoral shaft in women treated with bisphosphonate. Acta Orthop 2009; 80:413–415.
36. **Abrahamsen B, Eiken P, Eastell R**. Cumulative alendronate dose and the long-term absolute risk of subtrochanteric and diaphyseal femur fractures: a register-based national cohort analysis. J Clin Endocrinol Metab 2010; 95:5258–5265.
37. **Kim SY, Schneeweiss S, Katz JN, Levin R, Solomon DH**. Oral bisphosphonates and risk of subtrochanteric or diaphyseal femur fractures in a population-based cohort. J Bone Miner Res 2010. [Epub ahead of print]
38. **Spangler L, Ott SM, Scholes D**. Utility of automated data in identifying femoral shaft and subtrochanteric (diaphyseal) fractures. Osteoporos Int 2010. [Epub ahead of print]
39. **Black DM, Kelly MP, Genant HK, et al; Fracture Intervention Trial Steering Committee; HORIZON Pivotal Fracture Trial Steering Committee**. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. N Engl J Med 2010; 362:1761–1771.
40. **Park-Wyllie LY, Mamdani MM, Juurlink DN, et al**. Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. JAMA 2011; 305:783–789.
41. **Green J, Czanner G, Reeves G, Watson J, Wise L, Beral V**. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. BMJ 2010; 341:c4444.
42. **Cardwell CR, Abnet CC, Cantwell MM, Murray LJ**. Exposure to oral

bisphosphonates and risk of esophageal cancer. JAMA 2010; 304:657–663.
43. **Stopeck AT, Lipton A, Body JJ, et al**. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol 2010; 28:5132–5139.
44. **Khosla S, Burr D, Cauley J, et al; American Society for Bone and Mineral Research**. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2007; 22:1479–1491.
45. **Schousboe JT, Ensrud KE, Nyman JA, Kane RL, Melton LJ 3rd**. Cost-effectiveness of vertebral fracture assessment to detect prevalent vertebral deformity and select postmenopausal women with a femoral neck T-score > -2.5 for alendronate therapy: a modeling study. J Clin Densitom 2006; 9:133–143.
46. **Dawson-Hughes B; National Osteoporosis Foundation Guide Committee**. A revised clinician's guide to the prevention and treatment of osteoporosis. J Clin Endocrinol Metab 2008; 93:2463–2465.
47. **Compston J, Cooper A, Cooper C, et al; the National Osteoporosis Guideline Group (NOGG)**. Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. Maturitas 2009; 62:105–108.
48. **Cummings SR**. A 55-year-old woman with osteopenia. JAMA 2006; 296:2601–2610.
49. **Khosla S, Melton LJ 3rd**. Clinical practice. Osteopenia. N Engl J Med 2007; 356:2293–2300.
50. **McClung MR**. Osteopenia: to treat or not to treat? Ann Intern Med 2005; 142:796–797.
51. **Bauer DC, Black DM, Garnero P, et al; Fracture Intervention Trial Study Group**. Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: the fracture intervention trial. J Bone Miner Res 2004; 19:1250–1258.
52. **Bauer DC, Garnero P, Hochberg MC, et al; for the Fracture Intervention Research Group**. Pretreatment levels of bone turnover and the antifracture efficacy of alendronate: the fracture intervention trial. J Bone Miner Res 2006; 21:292–299.
53. **Ensrud KE, Barrett-Connor EL, Schwartz A, et al; Fracture Intervention Trial Long-Term Extension Research Group**. Randomized trial of effect of alendronate continuation versus discontinuation in women with low BMD: results from the Fracture Intervention Trial long-term extension. J Bone Miner Res 2004; 19:1259–1269.
54. **Ivaska KK, Gerdhem P, Akesson K, Garnero P, Obrant KJ**. Effect of fracture on bone turnover markers: a longitudinal study comparing marker levels before and after injury in 113 elderly women. J Bone Miner Res 2007; 22:1155–1164.
55. **Cosman F, Nieves JW, Zion M, Barbuto N, Lindsay R**. Retreatment with teriparatide one year after the first teriparatide course in patients on continued long-term alendronate. J Bone Miner Res 2009; 24:1110–1115.
56. **Jobke B, Pfeifer M, Minne HW**. Teriparatide following bisphosphonates: initial and long-term effects on microarchitecture and bone remodeling at the human iliac crest. Connect Tissue Res 2009; 50:46–54.
57. **Miller PD, Delmas PD, Lindsay R, et al; Open-label Study to Determine How Prior Therapy with Alendronate or Risedronate in Postmenopausal Women with Osteoporosis Influences the Clinical Effectiveness of Teriparatide Investigators**. Early responsiveness of women with osteoporosis to teriparatide after therapy with alendronate or risedronate. J Clin Endocrinol Metab 2008; 93:3785–3793.
58. **Ettinger B, San Martin J, Crans G, Pavo I**. Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. J Bone Miner Res 2004; 19:745–751.
59. **Koh JS, Goh SK, Png MA, Kwek EB, Howe TS**. Femoral cortical stress lesions in long-term bisphosphonate therapy: a herald of impending fracture? J Orthop Trauma 2010; 24:75–81.
60. **Banffy MB, Vrahas MS, Ready JE, Abraham JA**. Nonoperative versus prophylactic treatment of bisphosphonate-associated femoral stress fractures. Clin Orthop Relat Res 2011; 469:2028–2034.

***ADDRESS**: Susan Ott, MD, Department of Medicine, University of Washington, Box 356426, Seattle, WA 98195; e-mail smott@u.washington.edu.*