Practical guidance for the management of aromatase inhibitor-associated bone loss

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Background: Recent studies indicate that women with breast cancer are at increased risk of fracture compared with their age-matched peers. Current treatment guidelines are inadequate for averting fractures in osteopenic women, especially those receiving aromatase inhibitor (AI) therapy. Therefore, we sought to identify clinically relevant risk factors for fracture that can be used to assess overall fracture risk and to provide practical guidance for preventing and treating bone loss in women with breast cancer receiving AI therapy.

Methods: Systematic review of pertinent information from published literature and meeting abstracts through December 2007 was carried out to identify factors contributing to fracture risk in women with breast cancer. An evidence-based medicine approach was used to select risk factors that can be used to determine when to initiate bisphosphonate treatment of aromatase inhibitor-associated bone loss (AIBL).

Results: Fracture risk factors were chosen from large, well-designed, controlled, population-based trials in postmenopausal women. Evidence from multiple prospective clinical trials in women with breast cancer was used to validate AI therapy as a fracture risk factor. Overall, eight fracture risk factors were validated in women with breast cancer: AI therapy, T-score < −2.0, age 65 years, low BMI (<20 kg/m2), family history of hip fracture, personal history of fragility fracture after age 50, oral corticosteroid use >6 months, and smoking. Treatment recommendations were derived from randomized clinical trials.

Conclusions: The authors recommend the following for preventing and treating AIBL in women with breast cancer. All patients initiating AI therapy should receive calcium and vitamin D supplements. Any patient initiating or receiving AI therapy with a T-score < −2.0 and no additional risk factors should be monitored every 1–2 years for change in risk status and bone mineral density (BMD). Any patient initiating or receiving AI therapy with a T-score < −2.0 should receive bisphosphonate therapy. Any patient initiating or receiving AI therapy with any two of the following risk factors—T-score < −1.5, age >65 years, low BMI (<20 kg/m2), family history of hip fracture, personal history of fragility fracture after age 50, oral corticosteroid use >6 months, and smoking—should receive bisphosphonate therapy. BMD should be monitored every 2 years, and treatment should continue for at least 2 years and possibly for as long as AI therapy is continued. To date, the overwhelming majority of clinical evidence supports zoledronic acid 4 mg every 6 months to prevent bone loss in women at high risk. Although there is a trend towards fewer fractures with zoledronic acid, studies completed to date have not been designed to capture significant differences in fracture rate, and longer follow-up is needed.

Key words: Fracture risk, zoledronic acid, bisphosphonates, treatment recommendations, postmenopausal

Introduction

Bone turnover requires a delicate balance between bone resorption and formation, and any perturbation of these interconnected processes can increase the risk of fracture. A variety of genetic, pathologic, and environmental risk factors can contribute to increased bone loss, and breast cancer survivors may have multiple additional risk factors for bone loss, including their primary cancer and treatments. Indeed, several studies have demonstrated that women with breast cancer are at increased risk for bone loss and fracture [1–3]. Furthermore, breast cancer therapies, except tamoxifen in postmenopausal women, are known to erode bone quantity and quality in both...
Aromatase inhibitors (AIs) block estrogen production in peripheral tissues and are replacing tamoxifen as the adjuvant therapy of choice for postmenopausal women with ER+ breast cancer because of superior efficacy and a more favorable side-effect profile [8–11]. However, because all AIs effectively deplete residual estrogen levels, they are associated with accelerated bone loss and increased risk of fracture [10–14]. As AIs become the adjuvant treatment of choice for early breast cancer, bone health management in these patients will increasingly need to be addressed.

Current American Society of Clinical Oncology (ASCO) treatment guidelines for maintaining bone health in women with breast cancer rely solely on bone mineral density (BMD) as an indicator of the need for antiresorptive therapy [15]. Additional risk factors, however, have been demonstrated in postmenopausal women that significantly increase fracture risk [16], indicating that an osteoporotic T-score (≤ −2.5) alone may fail to identify a large number of patients who are at increased risk. This is highlighted by the fact that the annual risk of hip fracture is independently influenced by the number of risk factors (Figure 1) [16]. Osteoporosis treatment guidelines from the National Osteoporosis Foundation (NOF) and World Health Organization (WHO) indicate that it is important to include other risk factors along with BMD when assessing patient fracture risk and making treatment decisions [17, 18]. Furthermore, because BMD measurements may not always be available or reimbursed, other risk factors must be considered when assessing a patient's overall fracture risk. Therefore, fracture risk identification has become an important aspect of breast cancer patient management and an evidence-based algorithm is needed to assess risk and guide treatment or prevention in this setting.

**methods**

**systematic literature review**

Published literature was reviewed to identify factors that contribute to fracture risk in women with breast cancer. PubMed® searches of Medline® (National Library of Medicine, Bethesda, MD) and other databases were carried out to identify relevant articles from 1950 through December 2007. Additional information was obtained from abstracts presented at international meetings including the biannual St Gallen Breast Cancer Conference and European Breast Cancer Conference and the San Antonio Breast Cancer Symposium and ASCO annual meetings.

**risk factors for fracture in women with breast cancer**

Overall, risk factors for fracture were chosen from the available literature on the basis of their validation in large, prospective, population-based studies in healthy postmenopausal women and are listed in Table 2. In general, AI treatment studies were restricted to postmenopausal women with hormone receptor-positive breast cancer.

**AI therapy**

**level of evidence: I.** Several studies have shown that both steroidal and nonsteroidal AIs increase bone loss and fracture risk (Table 3) [10–14, 22, 23]. The Arimidex®, Tamoxifen, Alone or in Combination (ATAC; N = 6186) study [11]...
normal BMD at baseline experienced a shift to osteopenic
After 5 years, 17% of patients receiving anastrozole who had

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Type of evidence</th>
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<tbody>
<tr>
<td>I</td>
<td>Evidence from meta-analysis of multiple, well-designed, controlled studies (randomized trials with low false-positive and low false-negative errors)</td>
</tr>
<tr>
<td>II</td>
<td>Evidence from at least 1 well-designed, quasi-experimental study (randomized trials with high false-positive and high false-negative errors)</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from well-designed, quasi-experimental studies (nonrandomized, controlled single-group, pre-post, cohort, and time or matched case-control series)</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence from well-designed, nonexperimental studies (comparative and correlational descriptive and case studies)</td>
</tr>
<tr>
<td>V</td>
<td>Evidence from case reports</td>
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</tbody>
</table>

Table 1. Levels of evidence and grades of recommendation [19–21]

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>A</td>
<td>Level I evidence or consistent findings from multiple studies (level II, III, or IV)</td>
</tr>
<tr>
<td>B</td>
<td>Level II, III, or IV evidence with generally consistent findings</td>
</tr>
<tr>
<td>C</td>
<td>Level II, III, or IV evidence with inconsistent findings</td>
</tr>
<tr>
<td>D</td>
<td>Little or no systematic empirical evidence</td>
</tr>
</tbody>
</table>

Table 2. Fracture risk factors in women with breast cancer

<table>
<thead>
<tr>
<th>Validated risk factorsa</th>
<th>Possible risk factorsb</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI therapy</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>T-score &lt; -1.5</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>Age &gt; 65 years</td>
<td>Low weight</td>
</tr>
<tr>
<td>Low BMI (&lt;20 kg/m²)</td>
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<tr>
<td>Family history of hip fracture</td>
<td></td>
</tr>
<tr>
<td>Personal history of fragility fracture after age 50</td>
<td></td>
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<tr>
<td>Oral corticosteroid use ≥ 6 months</td>
<td></td>
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<tr>
<td>Smoking (current and history of)</td>
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</tbody>
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compared the efficacy of 2 types of endocrine therapy (AI versus selective ER modulator) in postmenopausal women with early breast cancer. After 5 years of therapy, fracture incidence had increased significantly in the anastrozole group compared with the tamoxifen group (11% versus 7.7%; \( P < 0.0001 \)) [11]. Furthermore, in the prospectively designed bone substudy of ATAC (\( n = 308 \)), 2 years of anastrozole significantly reduced lumbar spine BMD by 4.1% and total hip BMD by 3.9% compared with tamoxifen (\( P < 0.001 \)) [24]. After 5 years, 17% of patients receiving anastrozole who had normal BMD at baseline experienced a shift to osteopenic BMD, although no patients in this group became osteoporotic. Five percent of patients who were osteopenic at baseline became osteoporotic after 5 years of treatment [25]. Overall, patients receiving anastrozole for 5 years experienced a significant decrease in BMD and lost \( \sim 8\% \) BMD at the spine and hip relative to patients receiving tamoxifen (\( P < 0.0001 \) for both).

The Breast International Group 1-98 study compared letrozole with tamoxifen (\( N = 8010 \)) [14]. After a median of 26 months of follow-up, women in the letrozole group experienced significantly more fractures than women in the tamoxifen group (5.7% versus 4.0%; \( P < 0.001 \)). In the Intergroup Exemestane Study, women received 2–3 years of tamoxifen and were switched to exemestane or remained on tamoxifen for the remainder of the 5 years of therapy (\( N = 4724 \)) [10]. After a median follow-up of \( \sim 56 \) months, significantly more fractures were reported in women receiving exemestane compared with women receiving tamoxifen (7.0% versus 4.9%, respectively; \( P = 0.003 \)). This resulted in a relative 27% increased risk of fracture after patients switched to exemestane [10] and a median loss of 4% in lumbar spine BMD after 24 months [26].

The combined analysis of the Austrian Breast and Colorectal Cancer Study Group (ABCSG)-8 and Arimidex®-Novaldex® (ARNO)-95 study compared women who received 2 years of tamoxifen followed by either anastrozole or tamoxifen (\( N = 3224 \)) [13]. After a median follow-up of 28 months, women who switched to anastrozole had significantly more fractures than women who remained on tamoxifen (2% versus 1%, respectively; \( P = 0.015 \)).

Women enrolled in the National Cancer Institute of Canada Clinical Trials Group MA.17 study received tamoxifen for 5 years (\( N = 5187 \)) and then were randomized to receive 5 additional years of letrozole (\( n = 2593 \)) or placebo (\( n = 2594 \)) [12]. During 30 months of follow-up, patients receiving letrozole experienced a significant increase in newly diagnosed osteoporosis (8.1% versus 6.0%; \( P = 0.003 \)) and more fractures than patients in the placebo group (5.3% versus 4.6%); however, the difference in fracture incidence between the groups did not reach statistical significance (\( P = 0.25 \)). After 24 months of therapy, women enrolled in a bone substudy of the MA.17 study (\( n = 226 \)) experienced significant BMD loss at both lumbar spine (−5.4% versus −0.7%; \( P = 0.008 \)) and total hip (−3.6% versus −0.7%; \( P = 0.044 \)) compared with patients in the placebo group [27].

Taken together, the results from 6 large, well-designed, randomized, controlled clinical trials and the associated bone substudies provide strong evidence that both steroid and nonsteroid AI therapy can result in significant bone loss and increased risk of fracture. Indeed, the annual fracture rate observed for patients receiving anastrozole in the ATAC study is nearly 2-fold higher than the fracture rate in healthy, age-matched postmenopausal women with osteopenia (2.2% versus 1.3%, respectively) [11, 28].

BMD T-score \( < -1.5 \)

\textit{level of evidence: I}. The WHO and NOF use BMD T-scores to define normal bone density (T-score \( \geq -1.0 \)), osteopenia
(T-score between $-1.0$ and $-2.5$), and osteoporosis (T-score $\leq -2.5$) [17, 18]. In general, international treatment guidelines use these BMD categories to gauge fracture risk. The importance of BMD in evaluating fracture risk can be seen in the results of the National Osteoporosis Risk Assessment (NORA) study of >200,000 healthy postmenopausal women. In a subanalysis of 149,524 women, the fracture rate increased as the BMD T-score decreased [29]. However, 82% of fractures occurred in women with T-scores $>-2.5$ (i.e., non-osteoporotic women), and 52% of fractures occurred in women with osteopenia (T-score $-1.0$ to $-2.5$) [29]. In another NORA subanalysis of 170,083 women between 50 and 99 years of age, low BMD (T-score $<-1.0$) imparted a similar relative risk of fracture that was independent of the woman's age [30]. In total, these analyses indicate that women with BMD in the osteopenic range (T-score $-1.0$ to $-2.5$) are at increased risk of fracture and that treatment may be necessary before women become osteoporotic (T-score $<-2.5$).

**age**

*Level of evidence: I.* As women age, the natural decline in ovarian estrogen production that occurs during menopause produces rapid bone loss during the first few years and then the rate of bone loss slows to $\sim 1\%$–$2\%$ per year thereafter [31]. It is this slow, persistent bone loss that increases a woman’s risk of fracture. In a substudy of the Os des Femmes de Lyon study, 672 healthy postmenopausal women 50–85 years of age were evaluated for independent fracture risk factors. Fractures occurred more often in women who were older than 65 years, and multivariate analysis identified age (265 years) as an independent predictor of fracture [32]. Among women aged 65 and older, the 5-year fracture risk was increased 2-fold compared with women younger than 65 years [32]. In a prospective study of 521 women, the fracture rate profoundly increased with age and the risk of fracture was higher in older women at any given BMD [33]. Thus, women who are older than 65 years appear to be at increased risk of fracture.

**body mass index**

*Level of evidence: I.* Low body mass index (BMI) has long been associated with increased risk of fracture. A meta-analysis of data from 12 prospective studies enrolling a combined 14,887 men and 44,757 women examined the relationship between BMI and fracture risk [34]. The fracture risk associated with low BMI was similar for both men and women and increased at lower BMI values, especially when BMI was $<20$ kg/m$^2$. However, the risk was not linear throughout the BMI distribution. For example, a 5-U decrease in BMI at the low end of the spectrum (from 25 to 20 kg/m$^2$) resulted in a 2-fold increase in the risk of hip fracture, whereas a 10-U decrease in the middle of the BMI spectrum (from 35 to 25 kg/m$^2$) only increased fracture risk by 25%. Overall, the fracture risk associated with low BMI ($<20$ kg/m$^2$) was strongest for hip fracture and independent of age, sex, and BMD [34].

### family and personal history of fracture

*Level of evidence: I.* Genetic factors that may contribute to lifetime fracture risk have been examined in a variety of population studies. A genetic predisposition to fractures is well documented in the osteoporosis literature. For example, a meta-analysis of data from 7 multinational, prospective studies in 22,361 women revealed that a parental history of hip fracture was associated with a 34% increased risk of any fracture and a 75% increased risk of hip fracture [35]. In the same analysis, a sibling history of hip fracture resulted in an even larger 2.5-fold increase in the risk of hip fracture. In a study of 9516 postmenopausal women who were 65 years of age or older, maternal history of hip fracture increased the risk of hip fracture 2-fold [16]. Therefore, it appears that a family history of hip fracture is strongly associated with an increased risk of fracture.

In a similar manner, it is well established that a personal history of fragility fracture increases the likelihood of experiencing additional fractures in the future. This is supported by a report from Cummings et al. [16], in which postmenopausal women who had experienced any fracture after the age of 50 had a 1.5-fold increased risk of hip fracture. Similarly, a prospective study in 6787 women 66 years of age or older demonstrated that any previous fracture after the age of 50 was associated with increased risk of hip fracture and was independent of BMD status [36]. Furthermore, a meta-analysis of >45,000 women with information on prior fractures from 11 multinational, prospective trials quantified the risk associated with a history of prior fractures [37]. A previous history of adult fragility fracture increased the risk of any fracture by 84% and hip fracture by 77% compared with no

### Table 3. Fracture incidence in aromatase inhibitor (AI) trials

<table>
<thead>
<tr>
<th>AI study</th>
<th>N</th>
<th>Median follow-up (months)</th>
<th>Fracture incidence (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC [11]</td>
<td>6186</td>
<td>68</td>
<td>11.0</td>
<td>7.7</td>
</tr>
<tr>
<td>BIG 1-98 [14]</td>
<td>8010</td>
<td>26</td>
<td>5.7</td>
<td>4.0</td>
</tr>
<tr>
<td>IES [10]</td>
<td>4724</td>
<td>56</td>
<td>7.0</td>
<td>4.9</td>
</tr>
<tr>
<td>ABCSG-8/ARNO 95 [13]</td>
<td>3224</td>
<td>28</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>MA.17 [12]</td>
<td>5187</td>
<td>30</td>
<td>5.3</td>
<td>4.6</td>
</tr>
</tbody>
</table>

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ATAC, Arimidex®; Tamoxifen, Alone or in Combination; BIG, Breast International Group; IES, Intergroup Exemestane Study; ABCSG, Austrian Breast and Colorectal Cancer Study Group; ARNO, Arimidex®-Nolvadex®.
history of fracture. In women with prior fractures, low BMD was only responsible for ~8% of the increased risk of fracture. Taken together, a personal history of fragility fracture after age 50 contributes to fracture risk in postmenopausal women.

oral corticosteroid use

*level of evidence: I.* Increased bone loss and fracture risk are generally accepted consequences of long-term corticosteroid use. In a meta-analysis of 66 publications with data on patient BMD and 23 publications with data on patient fractures, a strong association was found between oral corticosteroid use and fracture risk. This analysis included ~250 000 male (28.5%) and female (71.5%) patients with an average age of 55.2 years and included patients from the General Practice Research Database (GPRD) study, among others [38]. Bone loss occurred at a rapid rate during the first 6 months of therapy and slowed slightly after 1 year. Fracture risk also increased quickly. Within 3–6 months of beginning corticosteroid therapy, patients receiving daily corticosteroids (27.5 mg prednisolone/day) had a 54% increased risk of nonvertebral fracture during the first year compared with their risk at baseline. In the GPRD study, corticosteroid use resulted in a 33% increased risk of any fracture, a 61% increased risk of hip fracture, and a 2.6-fold increased risk of vertebral fracture [38]. In a retrospective analysis of 20 896 women that compared patients who received oral corticosteroids (n = 10 448) with a matched group of patients who did not (n = 10 448), fracture risk increased with age [39]. Overall, women receiving oral corticosteroids had a 2.2-fold increased relative risk of any fracture, and fracture risk increased with dose, duration of therapy, and continuous corticosteroid use. Kanis and colleagues also performed a meta-analysis of 42 542 men and women from 7 prospective studies to ascertain the role of corticosteroid use in relative fracture risk [40]. For women in this study, corticosteroid use was found to be an independent predictor of fracture risk and increased the risk of any fracture by 39% and the risk of hip fracture by 2.1-fold [40]. Overall, oral corticosteroid use of > 6 months appears to significantly increase fracture risk. Currently available data indicate that short-term, low-dose oral or inhaled corticosteroid use does not increase fracture risk; however, long-term data are still forthcoming [41].

current and history of smoking

*level of evidence: I.* Several meta-analyses indicate that smoking is an independent risk factor for fracture. An analysis of 29 published studies of 2156 smokers and 9705 nonsmokers found that smoking increased the cumulative risk of hip fracture by ~50% in postmenopausal women [42]. The combined results from 10 independent studies that included 43 832 women found that after adjusting for BMD, current female smokers had a 55% increased risk of hip fracture [43]. Fracture risk was not limited to current smokers because women with a history of smoking still had a 42% increased risk of hip fracture that was independent of age and BMD. A meta-analysis of 50 published studies estimated that women who are current smokers have a 33% increased risk of any fracture and that previous smokers have an 18% increased risk compared with women who had never smoked [44]. Furthermore, the Study of Osteoporotic Fractures in 5822 women 265 years of age found that current smokers had a 61% increased risk of vertebral fractures that was independent of BMD [45]. Kanis and colleagues have recently performed a meta-analysis of 9 population-based studies in an effort to develop a fracture risk assessment tool and identified smoking as a strong fracture risk factor [46]. Therefore, available data indicate that current smoking is a strong independent fracture risk factor and that a history of smoking may also contribute to fracture risk.

other possible risk factors

*level of evidence: II–III.* In addition to the risk factors listed above, the literature search identified fracture risk factors that may ultimately prove to be significant if additional data become available (Table 2). However, the level of evidence currently available is insufficient for them to be identified as important risk factors in women with breast cancer. These risk factors include chemotherapy [5], radiotherapy [47], and low weight [48].

selecting a treatment to prevent AIBL: role of bisphosphonates in the adjuvant therapy setting

The available evidence from clinical trials and population-based studies indicates that women with breast cancer receiving AI therapy may already have several risk factors that elevate their fracture risk. As such, the selection of a therapeutic intervention strategy should also be on the basis of results from large clinical trials. Dietary calcium and vitamin D supplementation and exercise have been shown to maintain BMD in healthy postmenopausal women. Oral and intravenous (IV) bisphosphonates have shown efficacy for preventing bone loss associated with postmenopausal osteoporosis and with cancer treatment–associated bone loss in patients with breast or prostate cancer [49–51].

calcium and vitamin D supplementation and exercise

*level of evidence: I–III.* Evidence from the osteoporosis literature supports the use of calcium and vitamin D supplementation in postmenopausal women to maintain BMD. Recent analyses from the NORA study in >36 000 women determined the influence of dietary calcium and vitamin D intake on the risk of becoming osteoporotic (T-score ≤ −2.5) and the risk of experiencing a fracture [52]. A higher lifetime calcium intake reduced the risk of osteoporosis by 20%; however, calcium and vitamin D intake did not significantly affect the 3-year fracture risk in this study. A meta-analysis of 45 509 patients found that vitamin D combined with calcium supplementation in postmenopausal women and older men reduced the risk of hip fracture by 18% [53]. Another study in 36 282 healthy postmenopausal women enrolled in the World Health Initiative trial found that calcium and vitamin D supplementation caused a small 1% increase in hip BMD, but did not significantly reduce the incidence of hip fractures [54].
Overall, adequate dietary calcium and vitamin D intake is important for maintaining BMD, but supplementation alone is not sufficient to prevent the rapid bone loss that occurs during AI therapy.

Evidence from several small controlled studies indicates that exercise can help maintain BMD in healthy postmenopausal women and may slow bone loss in women receiving adjuvant therapy for breast cancer. A 4-year study in 68 postmenopausal women determined that BMD was maintained in women who participated in high-impact aerobic and resistance exercise, and there was a significant 2%–3% BMD loss during the same period in the control group ($P < 0.001$) [55]. A meta-analysis of 18 small, randomized, controlled trials found that aerobic, weight bearing, and resistance exercises increased lumbar spine BMD [56]. A small study in 66 pre- and postmenopausal women with early breast cancer beginning adjuvant chemotherapy found that resistance and aerobic exercise slowed BMD loss compared with standard care [57]. However, even with exercise the average BMD loss was $-0.76\%$ for the aerobic exercise group and $-4.92\%$ for the resistance exercise group. Although the available evidence is still very limited, it appears that regular exercise may help slow bone loss in women with breast cancer.

**oral bisphosphonates**

**level of evidence: II–III.** Randomized clinical trials have been initiated to determine whether oral and IV bisphosphonates can prevent bone loss during AI therapy. Data from studies of oral bisphosphonates are emerging; however, these have been from small clinical trials or from published abstracts only. For example, 2 small studies of postmenopausal women with breast cancer receiving oral clodronate ($N = 121$) and premenopausal women with chemotherapyn-induced menopause receiving oral risendronate ($N = 53$) showed respective 2.9% and 2.5% increases in BMD after 2 years of bisphosphonate treatment [58, 59]. The 10-year follow-up of women receiving oral clodronate, however, found that BMD loss was slowed but not prevented [60]. In the Study of Anastrozole with the Bisphosphonate Risedronate in postmenopausal women with hormone receptor-positive early breast cancer ($N = 234$), 12-month results indicate that oral risendronate reduces bone marker levels and prevents bone loss in osteopenic patients receiving anastrozole [61]. Another study, in Japanese women with breast cancer ($N = 92$) receiving anastrozolone and alendronate, found that bone resorption was reduced in patients receiving alendronate [62]. A 1-year analysis of the Arimidex®-Bonderonate® study found that monthly ibandronate prevented bone loss in osteopenic women ($n = 25$) compared with placebo ($n = 25$) and in a small number of patients with preexisting osteoporosis ($n = 13$) [63]. The primary limitation of these studies is that they were inadequately powered and the duration was too short to provide sufficient evidence to make firm recommendations in this patient population. Additionally, oral bisphosphonates have poor bioavailability, and patient compliance may be low. For instance, a large study ($N = 35\,537$) of women receiving bisphosphonate therapy for postmenopausal osteoporosis found that 57% of patients receiving oral bisphosphonates were noncompliant with therapy during the 2-year study period [64]. Noncompliance with oral bisphosphonate therapy resulted in a 37% increased risk of hip and vertebral fractures compared with compliant patients. Taken together, emerging evidence indicates that some oral bisphosphonates may have efficacy in preventing AIBL, but additional evidence is required before their use can be recommended in this setting.

**IV bisphosphonates**

**level of evidence: I.** To date, the largest concentration of data in support of bisphosphonate therapy to prevent AIBL is derived from 4 independent IV bisphosphonate studies that encompass $~2600$ pre- and postmenopausal women with early breast cancer. Data from the bone substudy of the ABCSG-12 trial ($n = 401$) indicate that zoledronic acid (4 mg IV every 6 months) prevents bone loss associated with ovarian suppression and endocrine therapy in premenopausal women with hormone receptor-positive breast cancer [65]. During 3 years of goserelin (3.6 mg every 28 days) combined with endocrine therapy, patients receiving zoledronic acid maintained baseline BMD, whereas those receiving anastrozole (1 mg/day) or tamoxifen (20 mg/day)alone had significant overall bone loss at the lumbar spine ($-17.4\%$ and $-11.6\%$, respectively; $P < 0.0001$ for both) and hip ($-8.2\%$ combined; $P < 0.0005$) [65].

In postmenopausal women with early breast cancer, the three companion Zometa®-Femara® Adjuvant Synergy Trials (Z-FAST, $N = 602$; ZO-FAST, $N = 1066$; E-ZO-FAST, $N = 527$) were designed to compare the efficacy of zoledronic acid treatment (4 mg IV every 6 months) administered concomitantly with AI therapy (up-front group) or after a BMD decrease to $<-2.0$ or a nontraumatic fracture (delayed group) [66–68]. During the first 12 months of the Z-FAST study, delaying zoledronic acid treatment resulted in 2.4% and 2.0% losses in BMD at lumbar spine and total hip, respectively [66]. In contrast, women who received up-front zoledronic acid during the same period experienced significant gains in lumbar spine and total hip BMD (1.9% and 1.3%, respectively; $P < 0.0001$ for both). The effect of up-front zoledronic acid on bone resorption was rapid and sustained, and patients experienced significant decrease in serum NTx levels from baseline to 12 months ($P < 0.0001$). Similar results for the 12- and 24-month analyses of the ZO-FAST study confirmed that up-front zoledronic acid prevents bone loss [67, 69]. The recent 12-month results from E-ZO-FAST are consistent with the other 2 studies and showed that patients receiving up-front zoledronic acid experienced a 2.7% increase in lumbar spine BMD and a 1.7% increase in total hip BMD [68]. Furthermore, results from the 24- and 36-month analyses of the Z-FAST trial indicate that women receiving up-front zoledronic acid continue to gain BMD during the 3 years of therapy [70, 71]. In fact, there was a larger overall difference in BMD between the up-front and delayed groups after 36 months compared with the difference observed at 12 and 24 months [71]. Although the studies were not powered to detect differences in fracture rate, there appears to be a trend towards fewer fractures in patients who received up-front zoledronic acid [71]. Taken together, evidence from 4 well-designed,
randomized, controlled studies indicates that zoledronic acid 4 mg administered every 6 months can prevent AIBL in both pre- and postmenopausal women.

In the AIBL setting, administration of zoledronic acid appears to be well tolerated, and the most common transient adverse events are infusion-site reaction and mild flu-like symptoms [65, 66, 70]. To date, twice-yearly dosing of zoledronic acid has proven safe. Out of a total of 2195 patients, 6 cases of osteonecrosis of the jaw (ONJ) have been reported and only 1 (<0.05%) case has been confirmed by the ONJ Adjudication Committee. Only 3 patients had impaired renal function that was suspected to be related to bisphosphonate treatment [65, 66, 70]. In general, adverse events common to all IV bisphosphonates are mild and easily manageable, and the risk of rare adverse events can be further reduced with preventive measures and proper patient surveillance [72–74].

Fractures can significantly decrease patient functional independence and health-related quality of life [75]. Therefore, addressing bone loss before patients experience debilitating fractures is of great importance for women with breast cancer. In addition to the negative effect on quality of life, fractures also result in substantial healthcare costs. Therefore, the goal of therapy is to preserve patient physical function and reduce the total costs of treatment by preventing bone loss and fractures. The cost savings of preventive therapy are borne out by a recent analysis from the UK using 24-month follow-up data from the Z-FAST trial [76]. In this exploratory analysis, zoledronic acid was shown to be cost-effective for prevention of fractures in women with early breast cancer receiving AI therapy using a threshold of £30 000 per quality-adjusted life year (QALY). The cost per QALY gained in patients receiving zoledronic acid was estimated to be £17 867 in patients with a high risk of fracture (on the basis of BMD status). Patients considered to have a low fracture risk had an estimated cost of £29 661 per QALY gained, also below the threshold. When all fractures were included, the cost per QALY gained was £19 302 for low-risk patients and £7724 for high-risk patients [76]. Therefore, in addition to reducing morbidity and maintaining patient quality of life, administering zoledronic acid before patients experience significant bone loss appears to be cost-effective in patients with breast cancer.

**fracture risk identification and treatment recommendations for patients receiving AIs**

*level of evidence: I*  
*grade of recommendation: A.*  
*Our guidance for the treatment and prevention of AIBL in women with early breast cancer initiating AI therapy is derived from well-designed, randomized, controlled studies. The identification of women who require antiresorptive therapy is on the basis of validated risk factors with or without BMD measurements (Figure 2). All patients beginning AI therapy should receive calcium and vitamin D supplements as recommended by previous ASCO guidelines for bone health in women with breast cancer [15]. Any patient initiating or receiving an AI with a T-score ≥−2.0 and no other fracture risk factors should be monitored every 1–2 years for change in risk status or BMD loss. If these patients experience an annual BMD decrease ≥5% (using the same machine), secondary causes of bone loss such as vitamin D deficiency should be evaluated and bisphosphonate therapy considered (zoledronic acid 4 mg IV every 6 months is the best-established therapy). Any patient initiating or

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**Figure 2.** Recommended management strategy for patients with breast cancer receiving aromatase inhibitor (AI) therapy. These recommendations are on the basis of results from trials in breast cancer patients and healthy populations. The largest body of evidence for treatment of AI-associated bone loss is for zoledronic acid 4 mg every 6 months. *If patients experience an annual decrease in bone mineral density (BMD) of ≥5% (using the same dual energy X-ray absorptiometry machine), secondary causes of bone loss such as vitamin D deficiency should be evaluated and bisphosphonate therapy considered. Use lowest T-score from 3 sites. BMI, body mass index.
Evidence from recent trials demonstrates that bisphosphonates, specifically zoledronic acid, can maintain bone health in patients receiving adjuvant AI therapy. Up-front zoledronic acid prevents bone loss associated with AI therapy in both pre- and postmenopausal women and will likely provide the greatest clinical benefit for patients with breast cancer. Although not sufficient to be included in our current recommendations, data for other bisphosphonates are emerging and may ultimately provide additional treatment options for patients receiving AI therapy.

The benefits of zoledronic acid treatment in the adjuvant setting may extend beyond preserving BMD and preventing fractures. Furthermore, evidence from preclinical and clinical studies indicates that early zoledronic acid therapy may have additional antitumor and antimetastatic properties. Ongoing clinical trials will evaluate the potential role of bisphosphonates in extending disease-free survival in women with breast cancer [82]. If the results from these studies are positive, they will lend additional support for up-front zoledronic acid therapy to not only prevent AIBL but also prolong disease-free and metastasis-free survival in patients with early breast cancer. Thus, adjuvant bisphosphonate therapy provides bone-protective effects to early breast cancer patients receiving AIs and may possibly offer these patients antitumor and antimetastatic utility as well.

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conflict of interest

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references


