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Assessment and management of bone health in women with oestrogen receptor-positive breast cancer receiving endocrine therapy: Position statement of the Endocrine Society of Australia, the Australian and New Zealand Bone & Mineral Society, the Australasian Menopause Society and the Clinical Oncology Society of Australia

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Abstract

Objective: To formulate clinical consensus recommendations on bone health assessment and management of women with oestrogen receptor-positive early breast cancer receiving endocrine therapy.

Methods: Representatives appointed by relevant Australian Medical Societies used a systematic approach for adaptation of guidelines (ADAPTE) to derive an evidence-informed position statement addressing five key questions.

Results: Women receiving adjuvant aromatase inhibitors and the subset of premenopausal woman on tamoxifen have accelerated bone loss and increased fracture risk. Both bisphosphonates and denosumab prevent bone loss, additionally denosumab has proven anti-fracture benefit. Women considering endocrine therapy need fracture risk assessment, including clinical risk factors, biochemistry and bone mineral density (BMD) measurement, with monitoring based on risk factors. Weight-bearing exercise, vitamin D and calcium sufficiency is recommended routinely. Antiresorptive treatment should be considered in women with prevalent or incident clinical or morphometric fractures, a T-score (or Z-scores in women <50 years) of <-2.0 at any site, or if annual bone loss is ≥5%, considering baseline BMD and other fracture risk factors. Duration of antiresorptive treatment can be individualised based on absolute fracture risk. Relative to their skeletal benefits, risks of adverse events with antiresorptive treatments are low.

Conclusions: Skeletal health should be considered in the decision-making process regarding choice and duration of endocrine therapy. Before and during endocrine therapy, skeletal health should be assessed regularly, optimised by nonpharmacological intervention and where indicated antiresorptive treatment, in an individualised, multidisciplinary approach. Clinical trials are needed to better delineate long-term fracture risks of adjuvant endocrine therapy, and to determine the efficacy of interventions designed to minimise these risks.

Introduction

Adjuvant endocrine therapy improves oncologic outcomes in women with oestrogen receptor (ER)-positive early breast cancer. Consequent to the induced oestradiol depletion with aromatase inhibitors, bone loss is accelerated, which predisposes to increased fracture risk. In contrast, tamoxifen in postmenopausal women acts as an oestrogen on bone and retards bone resorption and prevents fractures. While there has been rapidly accumulating evidence on this topic, some evidence-based best practice knowledge gaps remain regarding the optimisation of bone health in women with early breast cancer. Moreover, existing evidence may not always be adopted into clinical practice.

In this joint position statement, the Endocrine Society of Australia, the Australian and New Zealand Bone & Mineral Society, the Australasian Menopause Society and the Clinical Oncology Society of Australia review and adapt guidelines using a systematic approach to formulate clinical consensus recommendations on assessment and management of bone health in women with ER-positive breast cancer receiving endocrine therapy. We aim to address key gaps, and to inform clinical management.

Background

Adjuvant endocrine therapies for ER-positive breast cancer include aromatase inhibitors (anastrozole, exemestane, letrozole) or selective oestrogen receptor modulators (SERM), usually tamoxifen. Aromatase inhibitors block the conversion of androgens to oestradiol. In postmenopausal women, this results in near complete (>98%) deprivation of circulating oestradiol. As aromatase inhibitors inhibit the oestradiol-mediated negative feedback on gonadotropin production, they cannot be used as breast cancer treatment in premenopausal women unless ovarian function is suppressed, typically by pharmacological means (e.g. gonadotropin releasing hormone agonists) or by bilateral oophorectomy. SERMs act as ER antagonists in the breast but have partial agonistic activity in tissues such as bone and endometrium, and may be used in both pre- and postmenopausal women. Women who become menopausal during the course of their adjuvant therapy may switch from tamoxifen to an aromatase inhibitor[1].

In postmenopausal women, aromatase inhibitors are preferred because of modest but significant improvements in breast cancer outcomes, including lower 10-year breast cancer mortality compared to tamoxifen (12.1% vs. 14.2% relative risk (RR) 0.85; 95% confidence interval (CI) 0.75-0.96, $p<0.01$)[2]. In premenopausal women, tamoxifen has traditionally been first line treatment, although a combined analysis of two large randomised controlled trials (RCT), Tamoxifen and Exemestane Trial (TEXT) and Suppression of Ovarian Function Trial (SOFT), reported improved 5-year disease free survival with ovarian suppression plus the aromatase inhibitor exemestane compared to ovarian suppression plus tamoxifen (91.1% vs. 87.3%, hazard ratio (HR) 0.72; 95% CI, 0.60-0.85; $p<0.001$)[3]. The benefit was significant in premenopausal women with high risk ER-positive, HER2-negative breast cancer, as defined by clinicopathological characteristics and in patients <35 years of age[4].

Increasing the duration of endocrine therapy from five to ten years can further reduce the risk of recurrence[5,6]. While the absolute benefit in reducing recurrence risk is modest, there has been no overall survival benefit with an extended adjuvant endocrine therapy approach reported to date. Further, extended treatment is associated with a significant increase in the incidence of adverse effects including endometrial cancer and venous thrombosis with tamoxifen, and osteoporosis and fracture risk with aromatase inhibitors. Compared to five years of aromatase inhibitor treatment followed by five years of placebo, ten years of

aromatase inhibitor treatment significantly increased the incidence of osteoporosis (10 vs. 7%, p=0.02) and of clinical fractures (133 vs. 86, p=0.001), despite 50% of women in both groups receiving bisphosphonates during the study[6]. Whereas women receiving extended treatment had a mean total hip BMD loss of 3.2%, there was a 22.4% increase in women receiving placebo.

Due to earlier detection and advances in adjuvant systemic treatment, most women with a diagnosis of early ER-positive breast cancer now have good prognosis with 10-year survival greater than 90%. Survivorship issues and the management of unfavourable treatment effects are of paramount importance. The adverse effects of endocrine therapy may have a marked negative impact on quality of life, treatment compliance, and on short- and long-term health consequences. Contemporary management involves multidisciplinary input from medical specialties (including oncologists, endocrinologists, breast surgeons, gynaecologists), allied health practitioners (physiotherapists, dieticians, exercise physiologists, psychologists) and general practitioners.

In randomised trials among postmenopausal women with early breast cancer, antiresorptive agents have not only demonstrated prevention of cancer treatment-induced bone loss but also reductions in the risk of disease recurrence and metastasis. An individual patient data meta-analysis[7] included 18,766 women with early breast cancer participating in 26 RCTs. Overall, 83% of all women received systemic chemotherapy, and 66% were node positive. Most studies included in this meta-analysis used zoledronic acid or clodronate. In the entire population, bisphosphonates reduced the risk of distant bone recurrence (RR=0.83, p=0.004), with less certain effects on time to any breast cancer recurrence (RR=0.94, p=0.08) or breast cancer mortality (RR=0.91, p=0.04). In the postmenopausal subgroup (n=11,767), bisphosphonates provided greater benefits, improving not only distant bone recurrence (RR=0.72, p=0.002), but also any breast cancer recurrence (RR=0.86, p=0.002) and breast cancer mortality (RR=0.82, p=0.002). In the premenopausal subgroup, bisphosphonates had no significant effects on any of these outcomes. The absolute benefits in postmenopausal women were modest (10-year absolute benefit 2.2% for bone recurrence, 1.6% for non-bone recurrences, and 3.3% for breast cancer mortality)[7]. While denosumab has demonstrated prevention of bone density loss and reductions in fracture rates[8], data on long-term oncological outcomes including survival are yet to be reported. Therefore, current practice guidelines in the US and Europe[9,10] recommend that adjuvant bisphosphate therapy should be

considered in postmenopausal women to improve breast cancer outcomes, especially in patients deemed to be at high enough recurrence risk to receive adjuvant chemotherapy. For women considered at low risk of recurrence, such as a small, node-negative tumour, bisphosphonates may not provide a clinically meaningful oncologic benefit. The choice of bisphosphonate treatment regimen, if indicated may depend on patient preference, side effect profile, country-specific availability, and on costs and funding mechanisms by government or insurer. Especially where generic bisphosphonates are available, costs may be offset by savings on bone mineral density (BMD) assessments. For women not receiving adjuvant bisphosphonates, the use of antiresorptive agents for prevention of bone loss will be the primary reason for their use.

Purpose and Scope

This position statement focuses on the optimal approaches to prevention and management of bone loss associated with endocrine therapy in ER-positive breast cancer, a common side effect of aromatase inhibitors and ovarian suppression. Accelerated bone loss can be further aggravated by the effects of chemotherapy, which is often given in addition to adjuvant endocrine therapy in high-risk patients with ER-positive breast cancer.

Specifically, we address the following key questions:
In women with early ER-positive breast cancer receiving adjuvant endocrine therapy,
(1) Does accelerated bone loss and increased fracture rates occur during endocrine therapy?
(2) What is the efficacy of non-pharmacological measures and pharmacotherapy in reducing the risk of adverse bone outcomes during endocrine therapy?
(3) How and when can fracture risk be assessed and monitored?
(4) When should pharmacotherapy with antiresorptive treatment be considered, which agent could be used, and how long can it be used?
(5) What is the risk of adverse effects with antiresorptive treatment?

This position statement is targeted towards health professionals involved in the clinical management of women with early breast cancer, including endocrinologists, oncologists, and general practitioners.

Methodology

The Councils of the Endocrine Society of Australia (ESA), the Australian and New Zealand Bone & Mineral Society (ANZBMS), the Australasian Menopause Society (AMS), and the Clinical Oncology Society of Australia (COSA) invited expert representatives of the respective societies: ESA, MG; ANZBMS, FM; AMS, AV; COSA, EL; and additional authors with expertise in this field, to participate in a working group in 2017. A distinguished endocrinologist with experience leading national and international guidelines (HT) was appointed to advise the working group. A consumer representative (JH) was invited to participate and highlight priorities, and to write a perspective (see Supplementary text).

Regular communication within the working group was accomplished by email prior to and subsequent to a face-to-face meeting held in October 2017. All potential conflicts of interests of participating authors were declared prior to commencing drafting of the manuscript (Supplementary Table 1). Position statement development used the process proposed by the ADAPTE working group[11] which includes; (step 1) definition of the clinical questions; (step 2) search for source guidelines; (step 3) assess clinical content of source guidelines; (step 4) evaluation of the quality and coherence of source guidelines; (step 5) adaption of the recommendations; (step 6) external review of the adapted guideline and (step 7) adoption, endorsement and implementation of the adapted guideline. The members of the working group were tasked to develop questions to be answered and to identify, consider and cite relevant evidence. Evidence was obtained from existing international evidence-based guidelines, systematic reviews, relevant publications, supplemented by the multi-disciplinary expertise of the expert working group. To identify and appraise contemporary evidence-based guidelines, we performed a systematic search of medical databases (PubMed, Cochrane Register and EMBASE) from 2012 to June 2017 with the assistance of a professional librarian. Assessment of previously published guidelines, using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument was conducted (*Ramchand et al, manuscript in preparation*).

All authors contributed to the writing of the manuscript and the final draft statement was agreed to by all authors. The draft statement was then submitted to the Councils of the ESA, ANZBMS, AMS and COSA who provided feedback. The working group responded to feedback and the final version was approved and submitted to Clinical Endocrinology in April 2018.

Evidence

(1) Does accelerated bone loss and increased fracture rates occur during endocrine therapy?

In postmenopausal women, aromatase inhibitors are associated with increased bone remodelling, a two-to-three-fold acceleration in BMD decline, and increased fracture rates. In the bone substudy of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, hip BMD declined by 7.2% after five years of aromatase inhibitor treatment, and the magnitude of bone loss was greatest within the first two years[12]. In a meta-analysis of seven RCTs enrolling 30,023 patients, aromatase inhibitor use was associated with a 47% increased fracture risk compared with tamoxifen (odds ratio 1.47; 95% CI 1.34-1.61; p<0.001)[13]. The absolute difference between the two groups was 2.2%, with a number needed to harm (i.e. to cause one fracture) of 46. Fracture rates were not uniformly collected and varied from 0.9% to 11.0% in these RCTs[13]. Fractures were not adjudicated as primary endpoints and the true risk is likely underestimated; indeed, in a recent dedicated fracture endpoint RCT, 10% of placebo-treated patients had a new clinical fracture within three years of aromatase inhibitor treatment[8].

It is important to note that aromatase inhibitor-associated fracture rates reported in these studies may be confounded by the lack of placebo controls, and beneficial bone health effects of tamoxifen in postmenopausal women may confound interpretation of data on aromatase inhibitor use. Given the established benefit of tamoxifen on breast cancer outcomes, there is limited RCT evidence comparing the effects of aromatase inhibitor treatment on bone health with placebo. However, clinical data do support the notion that aromatase inhibitors accelerate bone loss. In a bone sub-study of a breast cancer prevention RCT in high risk postmenopausal women without osteoporosis at baseline (T score of at least -2.5 at both spine and femoral neck) not receiving antiresorptive treatment, women randomized to anastrozole (n=310) had a significantly greater BMD decrease after 3 years of follow-up compared to women receiving placebo (n=342), both the at lumbar spine (-4.0% [-4.5 to -3.4] vs -1.2% [-1.7 to -0.7], p<0·0001) and at the total hip (-4·0% [-4.4 to -3.6] vs -1.8% [-2.1 to -1.4], p<0·0001)[14]. In one RCT of 147 postmenopausal women with early breast cancer, 2-year aromatase inhibitor treatment, compared with placebo, increased bone loss at the femoral neck 2.72% vs. 1.48% (p=0.024), but not at the lumbar spine, 2.17% vs. 1.84% (p= 0.57)[15]. In an RCT of 1,579 postmenopausal women randomised to aromatase inhibitor treatment vs. placebo after 5-year treatment with tamoxifen, with a median follow-up of 5.3 years, self-reported new diagnoses of osteoporosis were increased and significantly more clinical

fractures occurred in the women who received aromatase inhibitors (5.2% v 3.1%, p = 0.02)[16]. In the aforementioned RCT of 1,918 postmenopausal women with early breast cancer, 10 years of aromatase inhibitor treatment compared to 5 years of aromatase inhibitor treatment followed by 5 years of placebo led to a higher incidence of osteoporosis (10 vs. 7%, p=0.02) and clinical fractures (133 vs. 86, p=0.001), despite 50% of women in both groups receiving bisphosphonates during the study[6]. A recent meta-analysis combining RCTs and cohort studies estimated that aromatase-inhibitor treatment increased fracture risk by 17% [95% CI 1.07-1.28] compared to no endocrine treatment[17].

The largest magnitude of bone loss, 7-9% at the lumbar spine in the first 12 months, occurs in premenopausal women with chemotherapy-induced menopause or concurrent ovarian suppression and aromatase inhibition (Figure 1, adapted from Gralow et al[18]). Alkylating chemotherapy and age >40 years are associated with the highest risk of ovarian failure. In SOFT/TEXT, the use of ovarian suppression and aromatase inhibitor was associated with twice the prevalence of osteoporosis compared to ovarian suppression and tamoxifen use (13.2% vs. 6.4% at 68 months)[3].

In contrast to its antagonistic actions on ER signalling in the breast, tamoxifen acts at a partial ER agonist at the bone. Therefore, tamoxifen has differential effects on BMD depending on ovarian oestradiol production, acting as an anti-oestrogen when endogenous concentrations of oestrogen are high but as an oestrogen when circulating oestrogen concentrations are low. In postmenopausal women with early breast cancer tamoxifen modestly increased BMD (+1.2% at the lumbar spine at two years vs. -2.0% with placebo)[19]. In a 5-year RCT of more than 13,000 women at high risk of breast cancer, tamoxifen not only reduced the risk of invasive cancer but, after follow-up for an additional 7 years, reduced osteoporotic fracture risk by 32% (RR=0.68, 95% CI=0.51 to 0.92)[20]. By contrast, in women who continue to menstruate after chemotherapy, tamoxifen (being less potent than native oestradiol) reduced lumbar spine BMD by 4.6% at three years of follow-up[21]. In a 2-year RCT of 89 premenopausal women with breast cancer receiving Gonadotrophin releasing-hormone (GnRH) agonist therapy, tamoxifen reduced goserelin-associated bone loss (-5% with goserelin alone compared to -1.4% goserelin and tamoxifen, p=0.02)[22]. In a study of 404 premenopausal women, 3-year lumbar spine BMD loss was 9.0% with goserelin plus tamoxifen compared to 13.6% with goserelin plus anastrozole[8]. Therefore, premenopausal women have increased of bone loss during tamoxifen treatment, with the opposite observed in postmenopausal women.

(2) What is the efficacy of non-pharmacological measures and pharmacotherapy in reducing the risk of adverse bone outcomes during endocrine therapy?

The evidence regarding benefits of non-pharmacological measures specific to breast cancer survivors is limited. A recent systematic review and meta-analysis including seven RCTs enrolling 1,199 women with breast cancer in various exercise programs consisting of either progressive resistance training alone or in combination with impact loading exercises for at least 12 months did not demonstrate a benefit on bone density in postmenopausal women[23]. However, evidence from one large RCT (n = 498)[24] included in the meta-analysis[23] reported that exercise combining step aerobic- and circuit-training reduced bone loss in premenopausal women at the femoral neck [mean BMD difference = 1.2%; (95% CI 0.2–2.2); p = 0.02], but not at the lumbar spine. Moreover, accumulating evidence shows that exercise leads to multiple benefits in women with breast cancer, including improved quality of life, reduced aromatase inhibitor-associated arthralgia, and possible improved breast cancer outcomes[25,26]. Ongoing clinical trials are evaluating the effects of weight loss on oncological outcomes in obese women[27], but effects on bone density and fracture are not known. Evidence regarding vitamin D and calcium supplementation specific to breast cancer survivors is not available.

In RCTs of postmenopausal women with early breast cancer, bisphosphonates consistently prevent endocrine therapy-induced bone loss. The data are strongest for zoledronic acid (Table 1). However, fracture outcome data for bisphosphonates are lacking. By contrast, the ABCSG-18 trial reported a 50% reduction in clinical fracture rates with denosumab (60 mg given 6-monthly for 3 years) compared to placebo (HR 0.50; 95% CI 0.39-0.65; p<0.0001) in postmenopausal women receiving aromatase inhibitor treatment[8]. Although fracture numbers were small (overall n=268), the 55% of participants with normal baseline lumbar spine T-score (≥-1.0) had similar benefit from treatment with denosumab (HR 0.44; 95% CI 0.31-0.64; p<0.0001) compared to women with T-scores of <-1.0 (HR 0.57; 95% CI 0.40-0.82; p<0.0001)[8]. Placebo fracture incidence (clinical vertebral and non-vertebral) in this trial[8] was 162/10,000 person-years, comparable to placebo groups seen in recent placebo-controlled trials in established postmenopausal osteoporosis, 149/10,000 person-years in the HORIZON Recurrent Fracture Trial[28] and 209/10,000 person-years in the FREEDOM trial[29]. This was despite participants in the aromatase inhibitor study[8] being five to ten years younger than the

osteoporosis trial participants[28,29] and having bone density in the normal to osteopaenic ranges rather than osteoporosis.

In premenopausal women receiving aromatase inhibitor and ovarian suppression, marked bone loss was observed in women not receiving antiresorptive treatment (11% at the lumbar spine over three years) but this was completely prevented by 6-monthly administration of zoledronic acid[30].

(3) How and when can fracture risk be assessed and monitored?

Clinical risk factors for osteoporosis and fragility fractures are common in women with breast cancer. Vitamin D insufficiency/deficiency has been reported in 64% of Australian[31], and in 76% of American breast cancer survivors, with lower vitamin D levels observed in African American and Hispanic women[32]. Chemotherapy-induced neuropathy may increase falls risk. An Australian study[31] investigating secondary causes of osteoporosis in 200 women with breast cancer older than 50 years reported that 37% were current/previous smokers, 21% had elevated parathyroid hormone (PTH) levels (3% primary hyperparathyroidism), 5.5% had a history of hyperthyroidism, and 11.5% were taking oral/inhaled glucocorticoids. As in the general population, age and PTH levels were significantly associated with lower BMD in this study[31].

Clinical risk factors including age (>65 years), race (Caucasian), low body mass index (<20 kg/m^2), history of osteoporosis or prior fragility fractures, parental history of hip fracture, menopausal status, oral glucocorticoid use, smoking and alcohol consumption should be ascertained in all women commencing endocrine therapy (Table 2, Figure 2). In addition, basic laboratory testing (including full blood examination, electrolytes and creatinine, calcium, phosphate, alkaline phosphatase/liver function tests, thyroid-stimulating hormone, and 25-OH vitamin D) and dual energy x-ray absorptiometry (DXA) imaging are advised in all women. If reduced bone mass (T or Z scores < 1.0) is present, individualised assessment is needed to identify and exclude other causes of secondary osteoporosis (Figure 2). As in the general population, women considered to be high fracture risk, those with a history of ≥ 4cm of height loss or kyphosis and/or those with long-term glucocorticoid use should also be assessed for vertebral fractures. Lateral radiographs of the thoracolumbar spine can be used to assess for vertebral fractures (Figure 2). Vertebral fracture assessment (VFA) on DXA imaging may also be used for fracture screening; however, VFA may miss vertebral fractures

associated with mild height loss; thus, lateral radiographs would be preferential in individuals with a history of back pain or height loss.

In women with early breast cancer, there is insufficient evidence regarding the clinical usefulness of measuring bone remodelling markers in predicting fracture risk and monitoring treatment effects of antiresorptive agents. Routine monitoring of markers of bone remodelling (serum C-telopeptide [CTX]) and bone formation (N-terminal propeptide of type 1 procollagen [P1NP]) is not recommended. The utility of bone imaging other than DXA, such as high resolution peripheral quantitative computed tomography[33] also requires further evaluation.

The World Health Organisation Fracture Risk Assessment Tool (FRAX) does not take aromatase inhibitor treatment or chemotherapy into consideration and is not validated for use in women <40 years. Therefore, FRAX may substantially underestimate fracture risk in women receiving these treatments.

DXA should be repeated 12 months after commencement of endocrine therapy, with subsequent individualised monitoring frequency (Table 2, Figure 2).

(4) When should pharmacotherapy with antiresorptive treatment be considered, which agent could be used, and how long can these it be used?

Despite the lack of rigorous evidence specific to breast cancer survivors, general measures to prevent bone loss are recommended for all women starting endocrine therapy including ensuring calcium and vitamin D sufficiency (Figure 2). Exercise, including impact and resistance training, has multiple benefits for women with breast cancer in addition to bone health[25,34], and weight bearing exercise is recommended in all guidelines (Table 3). All women with breast cancer are advised to stop smoking and minimise alcohol consumption. Where possible, medications with adverse effects on BMD should be avoided.

In line with recommendations of the National Osteoporosis Foundation for the general population[35], women with a fragility fracture (including subclinical vertebral fracture) or women ≥ 70 years with a BMD T-score ≤-2.5 could commence antiresorptive therapy unless contraindicated. There is limited evidence specific to women receiving endocrine therapy to guide recommendations outside these criteria. Although recommendations differ slightly

between guidelines (Table 3), antiresorptive therapy can be considered in aromatase inhibitor-treated women not fulfilling the National Osteoporosis Foundation criteria if the BMD T-score is <-2.0 at any site, ≥ 2 fracture risk factors are present, there is a ≥5% and/or ≥0.05g/cm^2 decrease in BMD in one year, considering baseline BMD and other fracture risk factors, or if the FRAX 10-year risk for major fracture is >20% or hip fracture is >3% (Figure 2). Other commentators have suggested that antiresorptive treatment may be warranted in women with T scores between -1.5 and-2.0, if two or more clinical risk factors of fracture are present[36]. Notably, governmental subsidy for the use of antiresorptive therapy in these circumstances varies in different countries.

In premenopausal women, accelerated bone loss with cancer therapies occurs predominantly through treatment-induced suppression/failure of ovarian function and through the inhibition of oestrogen effect on bone. In women who receive GnRH analogues for ovarian suppression or experience ovarian failure, some recovery of bone density occurs in those who subsequently resume menses. In women receiving concurrent aromatase inhibitors and GnRH analogues, bone loss is most pronounced (Figure 1). Current guidance from expert groups for premenopausal women recommends that all premenopausal women be informed about the potential for bone loss during anticancer therapy. Premenopausal women commonly have normal baseline BMD with low short-term fracture risk yet lose bone more rapidly than older postmenopausal women. Decisions regarding antiresorptive treatment should be carefully discussed with each woman. In premenopausal women, if the Z-score is <-2.0, or if the Z-score is < -1.0 and there has been an annual decrease in BMD of 5%, antiresorptive therapy may be considered[37]. Zoledronic acid is the only bisphosphonate which has been shown to prevent bone loss associated with ovarian suppression and tamoxifen/anastrozole therapy[38] or with chemotherapy-induced ovarian failure[39], and data regarding denosumab are lacking in this setting. There is a lack of long-term follow-up of premenopausal women who experience bone loss during breast cancer therapy to guide fracture risk assessment. The uncertainties regarding optimal fracture risk assessment and management in premenopausal women treated for breast cancer is an area deserving of further research.

The duration of antiresorptive treatment should be individualised based on absolute fracture risk. In most untreated women, bone loss is most marked in the 12-24 months post aromatase inhibitor initiation, and limited data suggest partial BMD recovery after cessation of endocrine therapy. Most guidelines (Table 3) comment on the uncertainty regarding the

duration of antiresorptive treatment during endocrine therapy. In women with the highest baseline risk of fracture, antiresorptive treatment may need to be continued until the adjuvant breast cancer treatment is complete or even longer.

Zoledronic acid trials in this population have used 4 mg every 6 months (Table 1). Alternative dosing schedules using 5 mg every 12 months, with anti-fracture efficacy in other populations[40] may be relevant here but are yet to be trialled in this population.

The bisphosphonates alendronate and zoledronic acid persist in the bone matrix for years after therapy is discontinued. In contrast, there may be an increased risk of multiple vertebral fractures soon after discontinuation of denosumab, particularly among those with pre-existing vertebral fractures[41], including case reports of women treated with aromatase inhibitors[42]. Preclinical evidence suggests that accelerated bone remodelling may promote the development of skeletal metastasis[43]. Denosumab should be given strictly 6-monthly, and a delay in dosing should be avoided. Based on currently available data, it is recommended that denosumab should not be stopped without considering alternative treatment with a bisphosphonate to decrease the rebound BMD loss and vertebral fracture risk. The optimal timing of initiation and mode and duration of bisphosphonate administration following cessation of denosumab is unclear.

Currently, the use of antiresorptive treatment in this population is generally off label. However off label use is supported by evidence in this and the general population and is allowed in many countries. Where it is allowed, health professionals should inform women and discuss the evidence, possible concerns and side effects of treatment.

(5) What is the risk of adverse effects with antiresorptive agents?

Antiresorptive therapies are generally well tolerated, especially if dosing regimens used in osteoporosis studies are prescribed. However, discussion with the individual woman regarding potential side effects is necessary. Zoledronic acid is associated with an acute-phase reaction (typically within 24 to 72 hours of the first infusion), and treatment with antipyretic agents generally improves these symptoms. In addition, all bisphosphonates carry a warning regarding use in patients with severe renal impairment (creatinine clearance <35 mL/min). Severe hypocalcaemia has been observed in patients with chronic kidney disease stage 4-5, treated with denosumab despite 25-hydroxyvitamin D sufficiency, with

recommendations for caution in this group[44].

Osteonecrosis of the jaw is a potential complication of bisphosphonate and denosumab therapy. Osteonecrosis of the jaw is rare (estimated risk 1:10,000 to 1:100,000) when antiresorptives are prescribed in doses approved for osteoporosis treatment[10].

Another concern arising from longer-term antiresorptive use is atypical femoral fracture. Atypical femoral fractures are more common in patients exposed to long-term bisphosphonates, with higher risk (113 per 100,000 person-years) in patients who receive more than seven to eight years of therapy[45]. Therefore, especially in women with extended aromatase inhibitor treatment who have received antiresorptive treatment for five years or longer, have had no fragility fractures, and have maintained stable bone density in the osteopaenic range, consideration of treatment cessation and a period of monitoring should be given (see considerations for denosumab above). Of note, the risk of a subsequent atypical femoral fracture is reduced following 12 months of bisphosphonate cessation[45].

In women who desire future pregnancy, the risks and benefits of antiresorptive therapy should be assessed on an individual basis, particularly in those in whom resumption of menses occurs following breast cancer treatment cessation. Long-acting bisphosphonates accumulate and persist in the maternal skeleton for years, even following drug cessation. Limited data suggest that maternal use of bisphosphonates during or prior to pregnancy does not have serious foetal or neonatal adverse effects[46]. However, bisphosphonates should ideally be ceased at least one year prior to pregnancy.

Conclusions

Prior to commencement of adjuvant endocrine therapy all women should be counselled about associated side effects. Adverse effects on skeletal health should be considered in the decision-making process especially in women at high risk for fractures. Treating clinicians should be assiduous in ascertaining treatment related adverse effects and pursue interventions known to mitigate these effects and enhance treatment adherence. Management is best individualised, using a multidisciplinary approach. Key priorities for future research include the conduct of future clinical trials to delineate better the long-term fracture risks of adjuvant endocrine therapy and to determine the efficacy of interventions designed to mitigate these

risks. Availability of robust data on fracture rates and their prevention are also important to generate health economic data to inform health policy.

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References:

1. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst.* 2005;97(17):1262-1271.
2. Early Breast Cancer Trialists' Collaborative G, Dowsett M, Forbes JF, et al. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet.* 2015;386(10001):1341-1352.
3. Pagani O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med.* 2014;371(2):107-118.
4. Saha P, Regan MM, Pagani O, et al. Treatment Efficacy, Adherence, and Quality of Life Among Women Younger Than 35 Years in the International Breast Cancer Study Group TEXT and SOFT Adjuvant Endocrine Therapy Trials. *J Clin Oncol.* 2017;35(27):3113-3122.
5. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet.* 2013;381(9869):805-816.
6. Goss PE, Ingle JN, Pritchard KI, et al. Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years. *N Engl J Med.* 2016;375(3):209-219.
7. Early Breast Cancer Trialists' Collaborative G, Coleman R, Powles T, et al. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet.* 2015;386(10001):1353-1361.
8. Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet.* 2015;386(9992):433-443.
9. Dhesy-Thind S, Fletcher GG, Blanchette PS, et al. Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2017;35(18):2062-2081.
10. Hadji P, Coleman RE, Wilson C, et al. Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel. *Ann Oncol.* 2016;27(3):379-390.
11. Fervers B, Burgers JS, Haugh MC, et al. Adaptation of clinical guidelines: literature review and proposition for a framework and procedure. *Int J Qual Health Care.* 2006;18(3):167-176.

12. Eastell R, Adams JE, Coleman RE, et al. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. *J Clin Oncol.* 2008;26(7):1051-1057.
13. Amir E, Seruga B, Niraula S, Carlsson L, Ocana A. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. *J Natl Cancer Inst.* 2011;103(17):1299-1309.
14. Sestak I, Singh S, Cuzick J, et al. Changes in bone mineral density at 3 years in postmenopausal women receiving anastrozole and risedronate in the IBIS-II bone substudy: an international, double-blind, randomised, placebo-controlled trial. *Lancet Oncol.* 2014;15(13):1460-1468.
15. Lonning PE, Geisler J, Krag LE, et al. Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer. *J Clin Oncol.* 2005;23(22):5126-5137.
16. Goss PE, Ingle JN, Pater JL, et al. Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen. *J Clin Oncol.* 2008;26(12):1948-1955.
17. Tseng OL, Spinelli JJ, Gotay CC, Ho WY, McBride ML, Dawes MG. Aromatase inhibitors are associated with a higher fracture risk than tamoxifen: a systematic review and meta-analysis. *Ther Adv Musculoskelet Dis.* 2018;10(4):71-90.
18. Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force Report: Bone Health In Cancer Care. *J Natl Compr Canc Netw.* 2013;11 Suppl 3:S1-50; quiz S51.
19. Love RR, Mazess RB, Barden HS, et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med.* 1992;326(13):852-856.
20. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst.* 2005;97(22):1652-1662.
21. Vehmanen L, Elomaa I, Blomqvist C, Saarto T. Tamoxifen treatment after adjuvant chemotherapy has opposite effects on bone mineral density in premenopausal patients depending on menstrual status. *J Clin Oncol.* 2006;24(4):675-680.
22. Sverrisdottir A, Fornander T, Jacobsson H, von Schoultz E, Rutqvist LE. Bone mineral density among premenopausal women with early breast cancer in a randomized trial of adjuvant endocrine therapy. *J Clin Oncol.* 2004;22(18):3694-3699.

23. Fornusek CP, Kilbreath SL. Exercise for improving bone health in women treated for stages I-III breast cancer: a systematic review and meta-analyses. *J Cancer Surviv.* 2017;11(5):525-541.
24. Saarto T, Sievanen H, Kellokumpu-Lehtinen P, et al. Effect of supervised and home exercise training on bone mineral density among breast cancer patients. A 12-month randomised controlled trial. *Osteoporos Int.* 2012;23(5):1601-1612.
25. Casla S, Lopez-Tarruella S, Jerez Y, et al. Supervised physical exercise improves VO2max, quality of life, and health in early stage breast cancer patients: a randomized controlled trial. *Breast Cancer Res Treat.* 2015;153(2):371-382.
26. Ligibel J. Lifestyle factors in cancer survivorship. *J Clin Oncol.* 2012;30(30):3697-3704.
27. Ligibel JA, Barry WT, Alfano C, et al. Randomized phase III trial evaluating the role of weight loss in adjuvant treatment of overweight and obese women with early breast cancer (Alliance A011401): study design. *NPJ Breast Cancer.* 2017;3:37.
28. Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med.* 2007;357(18):1799-1809.
29. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med.* 2009;361(8):756-765.
30. Gnant M, Mlineritsch B, Luschin-Ebengreuth G, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. *Lancet Oncol.* 2008;9(9):840-849.
31. Mann GB, Kang YC, Brand C, Ebeling PR, Miller JA. Secondary causes of low bone mass in patients with breast cancer: a need for greater vigilance. *J Clin Oncol.* 2009;27(22):3605-3610.
32. Neuhouser ML, Sorensen B, Hollis BW, et al. Vitamin D insufficiency in a multiethnic cohort of breast cancer survivors. *Am J Clin Nutr.* 2008;88(1):133-139.
33. Ramchand SK, Seeman E, Wang XF, et al. Premenopausal women with early breast cancer treated with estradiol suppression have severely deteriorated bone microstructure. *Bone.* 2017;103:131-135.
34. Winters-Stone KM, Dobek J, Nail LM, et al. Impact + resistance training improves bone health and body composition in prematurely menopausal breast cancer survivors: a randomized controlled trial. *Osteoporos Int.* 2013;24(5):1637-1646.

35. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporos Int.* 2014;25(10):2359-2381.
36. Santen RJ. Clinical review: Effect of endocrine therapies on bone in breast cancer patients. *J Clin Endocrinol Metab.* 2011;96(2):308-319.
37. Hadji P, Gnant M, Body JJ, et al. Cancer treatment-induced bone loss in premenopausal women: a need for therapeutic intervention? *Cancer Treat Rev.* 2012;38(6):798-806.
38. Gnant M, Mlineritsch B, Stoeger H, et al. Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozol plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12. *Ann Oncol.* 2015;26(2):313-320.
39. Shapiro CL, Halabi S, Hars V, et al. Zoledronic acid preserves bone mineral density in premenopausal women who develop ovarian failure due to adjuvant chemotherapy: final results from CALGB trial 79809. *Eur J Cancer.* 2011;47(5):683-689.
40. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med.* 2007;356(18):1809-1822.
41. Cummings SR, Ferrari S, Eastell R, et al. Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension. *J Bone Miner Res.* 2018;33(2):190-198.
42. Anastasilakis AD, Polyzos SA, Makras P, Aubry-Rozier B, Kaouri S, Lamy O. Clinical Features of 24 Patients With Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: Systematic Review and Additional Cases. *J Bone Miner Res.* 2017;32(6):1291-1296.
43. Croucher PI, McDonald MM, Martin TJ. Bone metastasis: the importance of the neighbourhood. *Nat Rev Cancer.* 2016;16(6):373-386.
44. Dave V, Chiang CY, Booth J, Mount PF. Hypocalcemia post denosumab in patients with chronic kidney disease stage 4-5. *Am J Nephrol.* 2015;41(2):129-137.
45. Adler RA, El-Hajj Fuleihan G, Bauer DC, et al. Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* 2016;31(10):1910.
46. Green SB, Pappas AL. Effects of maternal bisphosphonate use on fetal and neonatal outcomes. *Am J Health Syst Pharm.* 2014;71(23):2029-2036.

Table 1. Summary of major RCTs evaluating the efficacy of anti-resorptive therapies for aromatase inhibitor induced bone loss (AIBL) in women with ER+ early breast cancer

Study	Population at study entry	Intervention	n	Dose, Route of Administration & Duration of Follow-up	Primary Outcomes	Results
PARENTAL THERAPIES						
Safra T et al.[1] 2011	Postmenopausal Median age 59y, range 43 - 84y T-score ≥ -2.5 No prevalent fractures	Zoledronate Untreated Control	47 43	4mg Q6M, IV 60 months	LS BMD up to 60 months	24m (n=57): Difference of 0.98 g/cm^2 and 0.63 g/cm^2 at spine and hip 48m (n=19): Difference of 0.87g/cm^2 and 0.60 g/cm^2 at spine and hip Primary end point at 60m not evaluable (n=15)
Gnant M et al.[2] 2008 ABCSG-12 Bone Sub-study	Premenopausal, OFS + AI Median age 45y, range 26 - 56y T-score ≥ -2.5 No prevalent fractures	Zoledronate Untreated Control	105 96	4mg Q6M, IV 60 months (ET + ZOL/Placebo for 36 months and then stopped for 24 months)	BMD at 12 months	4 arm study: OS + Tam/AI and OS + Tam/AI + ZOL (total n = 414) - only AI results presented here 12m: LS: +2.1% vs -5.6% in ZOL vs Control TH: no significant difference 36m: LS +1.0% vs -9.0% in ZOL vs Control TH: +0.8% vs -7.3% in ZOL vs Control
Gnant M et al.[3] 2015 ABCSG-18	Postmenopausal >60 or BSO or <60y + FSH and E2 in postmenopausal range Median age 64y, range 38-91y No T-score exclusion	Denosumab Placebo Control	1711 1709	60mg Q6M, SC 36 months	Time to first clinical fracture	Time to first clinical fracture delayed in Denosumab vs Placebo HR 0·5 [95% CI 0·39–0·65], p<0·0001 Fractures 92 vs 176 Fracture reduction irrespective of baseline BMD 36m: LS: +7.27% vs -2.75% in Denosumab vs Placebo

						TH: +4.60% vs -3.32% in Denosumab vs Placebo
Ellis GK et al.[4,5] 2008	Postmenopausal Mean age 59y, range 35-84y T-score -1.0 to -2.5	Denosumab Placebo Control	127 125	60mg Q6M, SC 24 months	BMD at 12 months	12m: Difference of +5.5% at LS in Denosumab vs Placebo 24m: Difference +7.6% at LS, +4.7% at TH, +3.6% at FN in Denosumab vs Placebo
ORAL THERAPIES						
Greenspan SL et al.[6] 2015	Postmenopausal Mean age 65(R) and 64(P) T-score -1.0 to -2.5 T-score <-2.5/prior FF allowed if treating team and patient agreeable after counselling about treatment options	Risedronate Placebo	55 54	35mg QW, PO 24 months	LS and TH BMD at 24 months	12m: LS: +2.0% vs -1.2% in Risedronate (n=50) vs Placebo (n=50) TH: +0.5% vs -1.6% in Risedronate (n=50) vs Placebo (n=50) 24m: LS: +2.3% vs -1.7% in Risedronate (n=48) vs Placebo (n=47) TH: +0.6% vs -2.7% in Risedronate (n=48) vs Placebo (n=47)
Sestak I et al.[7] 2014 IBIS-II Bone Sub-study	Postmenopausal or BSO Median age 60y T-score -1.0 to -2.5	Risedronate Placebo Allowed to reduce frequency to fortnightly or drug holiday if severe adverse events	137 123	35mg QW, PO 36 months	LS and TH BMD at 36 months	36m: LS: +1.1% vs -2.6% in Risedronate (n=77) vs Placebo (n=73) TH: -0.7% vs -3.5% in Risedronate (n=77) vs Placebo (n=73)
Van Poznak C et al.[8] 2010 SABRE	Postmenopausal Mean age 64y (R) and 65y (P) T-score -1.0 to -2.0	Risedronate Placebo	77 77	35mg QW, PO 24 months	LS BMD at 12 months	12m: LS: +1.2% vs -1.2% in Risedronate (n=72) vs Placebo (n=62) TH: +0.9% vs -0.4% in Risedronate (n=72) vs Placebo (n=62) 24m: LS: +2.2% vs -1.8% in Risedronate (n=60) vs Placebo (n=54) TH: +1.8% vs -1.1% in Risedronate (n=60) vs Placebo (n=54)
Markopoulos C et al.[9] 2010 ARBI	Postmenopausal Mean age 65 (R) and 63y (P) T-score -1.0 to -2.5	Risedronate Placebo	37 33	35mg QW, PO 24 months	LS and TH BMD at 12 months	12m: LS and TH not significant (n=57) 24m: LS 5.7% vs -1.5% in Risedronate (n=26) vs Placebo (n=21) TH 1.6% vs 3.9% in Risedronate(n=26) vs Placebo (n=21)

Lester JE et al.[10] 2008 ARIBON	Postmenopausal Median age 68y T-score -1.0 to -2.5	Ibandronate Placebo	25 25	150mg Q4W, PO 24 months	LS and TH BMD at 12 and 24 months	12m: LS: +3.11% vs -2.35% in Risedronate (n=23) vs Placebo (n=25) TH: +0.98% vs -2.27% in Risedronate (n=23) vs Placebo (n=25) 24m: LS: +2.98% vs -3.22% in Risedronate (n=21) vs Placebo(n=19) TH: +0.60% vs -3.90% in Risedronate (n=21) vs Placebo (n=19)
IMMEDIATE VS. DELAYED THERAPY						
Bundred NJ et al.[11] 2008 ZO-FAST	Postmenopausal Median age 57 (I) and 58 (D), range 36-87y T-score ≥ -2.0 No prevalent fractures n =1065 at baseline	Zoledronate - Immediate Zoledronate - Delayed[a]	533 532	4mg Q6M, IV 12 months	LS BMD at 12 months	12m: LS: +2.1% vs -3.5% in Immediate (n=467) vs Delayed (n=464) TH: Difference +3.6% in Immediate (n=467) vs Delayed (n=464)
Eidtmann H et al.[12] 2010 ZO-FAST	Postmenopausal Median age 57 (I) and 58 (D), range 36-87y T-score ≥ -2.0 No prevalent fractures n =1065 at baseline	Zoledronate - Immediate Zoledronate - Delayed[b]	533 532	4mg Q6M, IV 36 months	LS BMD at 12 months	36m: LS: +4.39% vs -4.9% in Immediate (n=314) vs Delayed (n=319) TH: Difference +5.41% in Immediate (n=314) vs Delayed (n=319)
Coleman R et al.[13] 2013 ZO-FAST	Postmenopausal Median age 57 (I) and 58 (D), range 36-87y T-score ≥ -2.0 No prevalent fractures n =1065 at baseline	Zoledronate - Immediate Zoledronate - Delayed[b]	533 532	4mg Q6M, IV 60 months	LS BMD at 12 months	60m: LS: +4.3% vs -5.7% in Immediate (n=264) vs Delayed (n=264) TH: +1.6% vs -4.2% in Immediate (n=264) vs Delayed (n=264)
Brufsky A et al.[14] 2007 Z-FAST	Postmenopausal Median age 60y, range 35-89y T-score ≥ -2.0	Zoledronate - Immediate Zoledronate - Delayed[a]	301 301	4mg Q6M, IV 12 months	LS BMD at 12 months	The least squares mean difference between groups in percentage change of BMD from baseline to month 12 for LS = 4.3% and total hip = 3.2% (Immediate n=251, Delayed n=256)
Brufsky A et al.[15] 2009	Postmenopausal Median age 60y, range 35-89y	Zoledronate - Immediate Zoledronate - Delayed[b]	301 301	4mg Q6M, IV	LS BMD at 12 months	The least squares mean difference between groups in percentage change of BMD from baseline to month 36 for LS = 6.7% and total hip = 5.3%

Z-FAST	T-score ≥ -2.0			36 months		(Immediate n=189, Delayed n=189)
Brufsky A et al.[16] 2012 Z-FAST	Postmenopausal Median age 60y, range 35-89y T-score ≥ -2.0	Zoledronate - Immediate Zoledronate - Delayed[b]	301 301	4mg Q6M, IV 61 months	LS BMD at 12 months	The least squares mean difference between groups in percentage change of BMD increased from baseline to month 61 for LS (4.3% to 8.9%) and total hip (3.2% to 6.7%)
Brufksky A et al.[17] 2008 Combined Z-FAST and ZO-FAST	Postmenopausal Median age 58(I) and 59(D), range 35-89y T-score ≥ -2.0	Zoledronate - Immediate Zoledronate - Delayed[a]	833 834	4mg Q6M, IV 12 months	LS BMD at 12 months	The least squares mean difference between groups in percentage change of BMD from baseline to month 12 for LS = 5.2% and total hip = 3.5%
Llombart A et al.[18] 2012 E-ZO-FAST	Postmenopausal Median age 58, range 40-81 T-score ≥ -2.0 No prevalent fractures	Zoledronate - Immediate Zoledronate - Delayed[b]	252 270	4mg Q6M, IV 12 months	LS BMD at 12 months	12m: LS: +2.72 vs -2.71 in Immediate vs Delayed TH: +1.72 vs -1.59 in Immediate vs Delayed
Hines SL et al.[19] 2009 NCCTG - NO3CC	Postmenopausal starting aromatase inhibition after tamoxifen; >55y with cessation of menses or <55 with 1yr cessation of menses or BSO Mean age 59y T-score ≥ -2.0 No prevalent fractures	Zoledronate - Immediate Zoledronate - Delayed[c]	274 277	4mg Q6M, IV 24 months	LS BMD at 12 months	12m: LS: +3.66 vs -1.66% in Immediate (n=208) vs Delayed (n=221) TH: +1.02% vs 1.41% in Immediate (n=208) vs Delayed (n=221) FN: +2.08% vs -0.09% in Immediate (n=208) vs Delayed (n=221) 24m: LS: +4.94% vs -2.28% in Immediate (n=179) vs Delayed (n=198) TH: +1.22% vs -3.34% in Immediate (n=179) vs Delayed (n=198) FN: +3.36% vs +0.54% in Immediate (n=179) vs Delayed (n=198)
Wagner-Johnston ND et al.[20] 2015 NCCTG - NO3CC	Postmenopausal starting aromatase inhibition after tamoxifen; >55y with cessation of menses or <55 with 1yr cessation of menses or BSO Mean age 59y T-score ≥ -2.0 No prevalent fractures	Zoledronate - Immediate Zoledronate - Delayed[c]	274 277	4mg Q6M, IV 60 months	LS BMD at 12 months	60m: Difference in LS +9.42% in Immediate (n=118) vs Delayed (n=119) Significant differences at TH in Immediate (n=118) vs Delayed (n=119) (values not given)

BMD = bone mineral density; BSO = bilateral salpingo-oophorectomy; E2 = oestradiol; ET = endocrine therapy; FN = femoral neck; FSH = follicle stimulating hormone; IV = intravenous; LS = lumbar spine; M = months; OFS = ovarian function suppression (with goserelin); PO = oral; SC = subcutaneous; TS = T-score; TH = total hip; Q = every; W = week; ZOL = zoledronic acid

[a] Delayed: ZOL started if fragility fracture or on study T-score <-2.0

[b] Delayed: ZOL started if fragility fracture or on study T-score <-2.0 or morphometric LS fracture detected at 36 months

[c] Delayed: ZOL started if fragility fracture or on study T-score <-2.0 or morphometric LS fracture detected at any point

Table 2. Summary of recommendations for evaluation of bone health in women with early breast cancer

Guideline	Baseline DXA	Frequency of subsequent scans	Details of fracture risk assessment	Assessment for morphometric fractures
Canadian Guidelines[21]	Yes	No treatment with BMAs: every 5 years if low risk (FRAX 10yr <10%) or 1-3 years if moderate risk (FRAX 10yr 10-20%). Treated with BMAs: every 2 years or annually if osteopaenia	FRAX tool	No recommendation
EMAS position statement[22]	Yes	No details	age > 65 years, BMI <24 kg/m ^{2}, a personal history of fragility fracture >50years, family history of hip fracture, glucocorticoid use > 6 months, prior/current history of smoking, alcohol consumption, Ca, PTH, 25OHD	No recommendation
ESMO guidelines[23]	Yes	1-2 years	FRAX tool, Ca, PO4, 25OHD, PTH, Cr Cl, SPEP	No recommendation
European Panel guidelines[24]	Yes	No recommendation	FRAX tool but only in postmenopausal women	No recommendation

Joint position statement of the IOF/CABS/ECTS/IEG/ESCEO/IMS/SIOG[25]	Yes	1-2 years	Smoking history, BMI < 20kg/m2, parental history of hip fracture, fragility fracture above age 50 years, oral glucocorticoid use > 6 months, 25OHD	No recommendation
Lithuanian Guidelines[26]	Yes	As per Lithuanian Ministry of Health recommendations – not specified	Prior history of FF. If no FF +TS <-1.5 evaluate falls risk. If no FF + TS <-1.5 and >-2.5 + ≥ 1 falls risk factor detailed evaluation of fracture risk factors: age > 65 years, low BMI < 20kg/m2, parental history of hip fracture, AI therapy >6 months, tamoxifen in the premenopausal period, premature menopause (natural or medically induced), radiotherapy, oral glucocorticoids > 7.5mg per day over 3 months, alcohol consumption, smoking	Yes. All patients at baseline
NCCN Task Force Report[27]	Yes	2 years; consider repeat scan in 1 year if bone loss risks have changed significantly or for a major therapeutic intervention	FRAX tool and annual height measurement	Vertebral fracture assessment (VFA) at time of DXA in everyone, if not available consider lateral T-L x-ray
Singapore Cancer Network Guidelines[28]	Yes	1-2 years	Personal history of FF as an adult, hip fracture in a first degree relative, chronic corticosteroid use, immobility and inadequate physical activity, cigarette smoking, > 2 standard drinks of alcohol daily, low body weight, lifelong low calcium intake, 25OHD, chronic illness (hyperthyroidism, hyperparathyroidism, inflammatory bowel disease)	No recommendation

25OHD = 25-hydroxy vitamin D; BL = baseline; BMAs = bone modifying agents; Ca = serum calcium; Cr Cl = creatinine clearance; DXA = dual energy x-ray absorptiometry scan; FF = fragility fracture; PO4 = phosphate; PTH = parathyroid hormone; SPEP = serum protein electrophoresis; TS = T-score (based on bone mineral density data)

Guidelines developed within the last 5 years were included.

Table 3. Summary of recommendations for management of bone health in women with early breast cancer

Guideline	Weight bearing exercise	Total daily calcium intake	Daily 25-OH vitamin D dose and target level	T-score to initiate anti-resorptive therapy	Other recommendations for starting anti-resorptive therapy	Recommended anti-resorptive agents and dose

Canadian Guidelines[21]	Yes	1200mg	1000IU daily; target level not specified	< -2.0 in postmenopausal women only	Postmenopausal FRAX 10yr 10-20% of major fracture; Premenopausal or postmenopausal FRAX 10 yr risk >20% of major fracture; Prevalent hip/spine FF or >1 FF	Zoledronate 4mg q6mo, denosumab 60mg q6mo, any oral bisphosphonate. No recommendations made favouring one agent over the other.
EMAS position statement[22]	Yes	1000mg	800 -1000IU; target level not specified	≤ -2.0	2 or more clinical risk factors for fracture (specific risk factors not specified – reference made to other guidelines); Women at intermediate or high risk of fracture	Bisphosphonates. Consider denosumab.
ESMO guidelines[23]	Yes, moderate intensity	1000mg	1000 - 2000IU; target level not specified	< -2.0	2 or more of the following risk factors: TS < -1.5, age >65, current/previous smoking history, BMI < 20, parental history of hip fracture, fragility fracture above age 50yo, oral glucocorticoid use > 6 months; annual BMD loss ≥ 10% or ≥ 4-5% if osteopaenic at baseline	Zoledronate 4mg q6mo, denosumab 60mg q6mo, any oral bisphosphonate. No recommendations made favouring one agent over the other.
European Panel guidelines[24]	Yes	1000mg	1000 - 2000IU; target level not specified	< -2.0	In postmenopausal women (natural/induced) if 2 or more clinical risk factors (risk factors not specified in guideline – reference made to other guidelines)	Premenopausal: Zoledronate 4mg q6mo. Postmenopausal women: Zoledronate 4mg q6mo, denosumab 60mg q6mo, any oral bisphosphonate.
Joint position statement of the IOF/CABS/ECTS/IEG/ESCEO/IMS/SIOG[25]	Yes, moderate intensity	1200mg for postmenopausal women	800 - 2000IU; target level not specified	< -2.0	2 or more of the following risk factors: TS < -1.5, age >65, current/previous smoking history, BMI < 20, parental history of hip fracture, fragility fracture above age 50 yo, oral glucocorticoid use > 6 months; Annual BMD loss ≥ 5-10%	Denosumab 60mg q6mo and zoledronate 4mg q6mo are the preferred agents - denosumab when fracture risk is a concern and zoledronate when disease recurrence is the main priority
Lithuanian Guidelines[26]	Yes	1000mg	800 - 1000IU; target level not specified	≤ -2.5 and at least 1 fall risk factor	Osteoporotic fracture (clinical or morphometric) within the previous year; TS ≤ -1.5 and > -2.5 + ≥ 2 RF for fracture + ≥ 1 fall RF	Denosumab 60mg q6mo. Bisphosphonates not approved for cancer-treatment induced bone loss in Lithuania.
NCCN Task Force Report[27]	Yes, 30 minutes per day of moderate intensity	1200mg	800 - 1000IU; target level not specified	≤ -2.0, consider if TS between -1.5 and -2.0	FRAX 10 yr fracture risk >20% for major fracture and > 3% for hip fracture	No recommendations made favouring one agent over the other (oral BP or zoledronate or denosumab). Consider parental therapy in patients who are non-adherent to oral therapy.

Singapore Cancer Network Guidelines[28]	Yes	1200 – 1500mg	800IU; target level not specified	< -2.0	Consider if TS between -1.5 and -2.0 and 2 additional clinical risk factors for fracture (advanced age, FF as an adult, hip fracture in a first degree relative, chronic corticosteroid use, immobility and inadequate physical activity, cigarette smoking, > 2 standard units of alcohol daily, low body weight, lifelong low calcium intake, vitamin D deficiency, chronic illness (hyperthyroidism, hyperparathyroidism, inflammatory bowel disease)	No recommendations made favouring one agent over the other (oral BP or zoledronate). Denosumab not covered by this guideline.

FF = fragility fracture; TS = T-score (based on bone mineral density data)

References

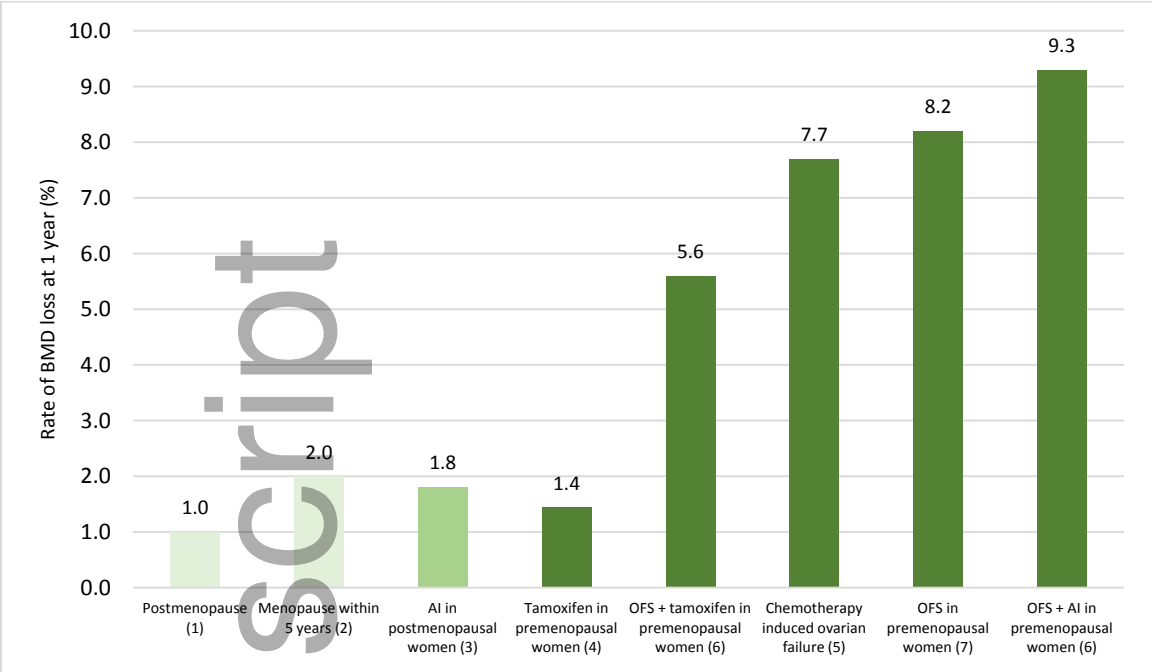
1. Safra T, Bernstein-Molho R, Greenberg J, et al. The protective effect of zoledronic acid on bone loss in postmenopausal women with early breast cancer treated with sequential tamoxifen and letrozole: a prospective, randomized, phase II trial. Oncology. 2011;81(5-6):298-305.
2. Gnant M, Mlineritsch B, Luschin-Ebengreuth G, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. Lancet Oncol. 2008;9(9):840-849.
3. Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2015;386(9992):433-443.
4. Ellis GK, Bone HG, Chlebowski R, et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. J Clin Oncol. 2008;26(30):4875-4882.
5. Ellis GK, Bone HG, Chlebowski R, et al. Effect of denosumab on bone mineral density in women receiving adjuvant aromatase inhibitors for non-metastatic breast cancer: subgroup analyses of a phase 3 study. Breast Cancer Res Treat. 2009;118(1):81-87.
6. Greenspan SL, Vujevich KT, Brufsky A, et al. Prevention of bone loss with risedronate in breast cancer survivors: a randomized, controlled clinical trial. Osteoporos Int. 2015;26(6):1857-1864.
7. Sestak I, Singh S, Cuzick J, et al. Changes in bone mineral density at 3 years in postmenopausal women receiving anastrozole and risedronate in the IBIS-II bone substudy: an international, double-blind, randomised, placebo-controlled trial. Lancet Oncol. 2014;15(13):1460-1468.
8. Van Poznak C, Hannon RA, Mackey JR, et al. Prevention of aromatase inhibitor-induced bone loss using risedronate: the SABRE trial. J Clin Oncol. 2010;28(6):967-975.
9. Markopoulos C, Tzoracoleftherakis E, Polychronis A, et al. Management of anastrozole-induced bone loss in breast cancer patients with oral risedronate: results from the ARBI prospective clinical trial. Breast Cancer Res. 2010;12(2):R24.
10. Lester JE, Dodwell D, Purohit OP, et al. Prevention of anastrozole-induced bone loss with monthly oral ibandronate during adjuvant aromatase inhibitor therapy for breast cancer. Clin Cancer Res. 2008;14(19):6336-6342.
11. Bundred NJ, Campbell ID, Davidson N, et al. Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST Study results. Cancer. 2008;112(5):1001-1010.
12. Eidtmann H, de Boer R, Bundred N, et al. Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST Study. Ann Oncol. 2010;21(11):2188-2194.
13. Coleman R, de Boer R, Eidtmann H, et al. Zoledronic acid (zoledronate) for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study): final 60-month results. Ann Oncol. 2013;24(2):398-405.

14. Brufsky A, Harker WG, Beck JT, et al. Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. J Clin Oncol. 2007;25(7):829-836.
15. Brufsky AM, Bosserman LD, Caradonna RR, et al. Zoledronic acid effectively prevents aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: Z-FAST study 36-month follow-up results. Clin Breast Cancer. 2009;9(2):77-85.
16. Brufsky AM, Harker WG, Beck JT, et al. Final 5-year results of Z-FAST trial: adjuvant zoledronic acid maintains bone mass in postmenopausal breast cancer patients receiving letrozole. Cancer. 2012;118(5):1192-1201.
17. Brufsky A, Bundred N, Coleman R, et al. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. Oncologist. 2008;13(5):503-514.
18. Llombart A, Frassoldati A, Paija O, et al. Immediate Administration of Zoledronic Acid Reduces Aromatase Inhibitor-Associated Bone Loss in Postmenopausal Women With Early Breast Cancer: 12-month analysis of the E-ZO-FAST trial. Clin Breast Cancer. 2012;12(1):40-48.
19. Hines SL, Mincey B, Dentchev T, et al. Immediate versus delayed zoledronic acid for prevention of bone loss in postmenopausal women with breast cancer starting letrozole after tamoxifen-N03CC. Breast Cancer Res Treat. 2009;117(3):603-609.
20. Wagner-Johnston ND, Sloan JA, Liu H, et al. 5-year follow-up of a randomized controlled trial of immediate versus delayed zoledronic acid for the prevention of bone loss in postmenopausal women with breast cancer starting letrozole after tamoxifen: N03CC (Alliance) trial. Cancer. 2015;121(15):2537-2543.
21. Paterson AH, Shea-Budgell MA. Bone Health in Patients with Breast Cancer: Recommendations from an Evidence-Based Canadian Guideline. J Clin Med. 2013;2(4):283-301.
22. Tremollieres FA, Ceausu I, Depypere H, et al. Osteoporosis management in patients with breast cancer: EMAS position statement. Maturitas. 2017;95:65-71.
23. Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J, Group EGW. Bone health in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2014;25 Suppl 3:iii124-137.
24. Hadji P, Coleman RE, Wilson C, et al. Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel. Ann Oncol. 2016;27(3):379-390.
25. Hadji P, Aapro MS, Body JJ, et al. Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG. J Bone Oncol. 2017;7:1-12.
26. Juozaityte E, Aleknavicius E, Janciauskiene R, et al. Guidelines for diagnostics and treatment of aromatase inhibitor-induced bone loss in women with breast cancer: a consensus of Lithuanian medical oncologists, radiation oncologists, endocrinologists, and family medicine physicians. Medicina (Kaunas). 2014;50(4):197-203.

27. Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force Report: Bone Health In Cancer Care. J Natl Compr Canc Netw. 2013;11 Suppl 3:S1-50; quiz S51.

28. Singapore Cancer Network Breast Cancer W. Singapore Cancer Network (SCAN) Guidelines for Bisphosphonate Use in the Adjuvant Breast Cancer Setting. Ann Acad Med Singapore. 2015;44(10):368-378.

Figure 1. Annual rates of bone density loss at the lumbar spine (%)



AI = aromatase inhibitor; OFS = ovarian function suppression with GnRH analogues

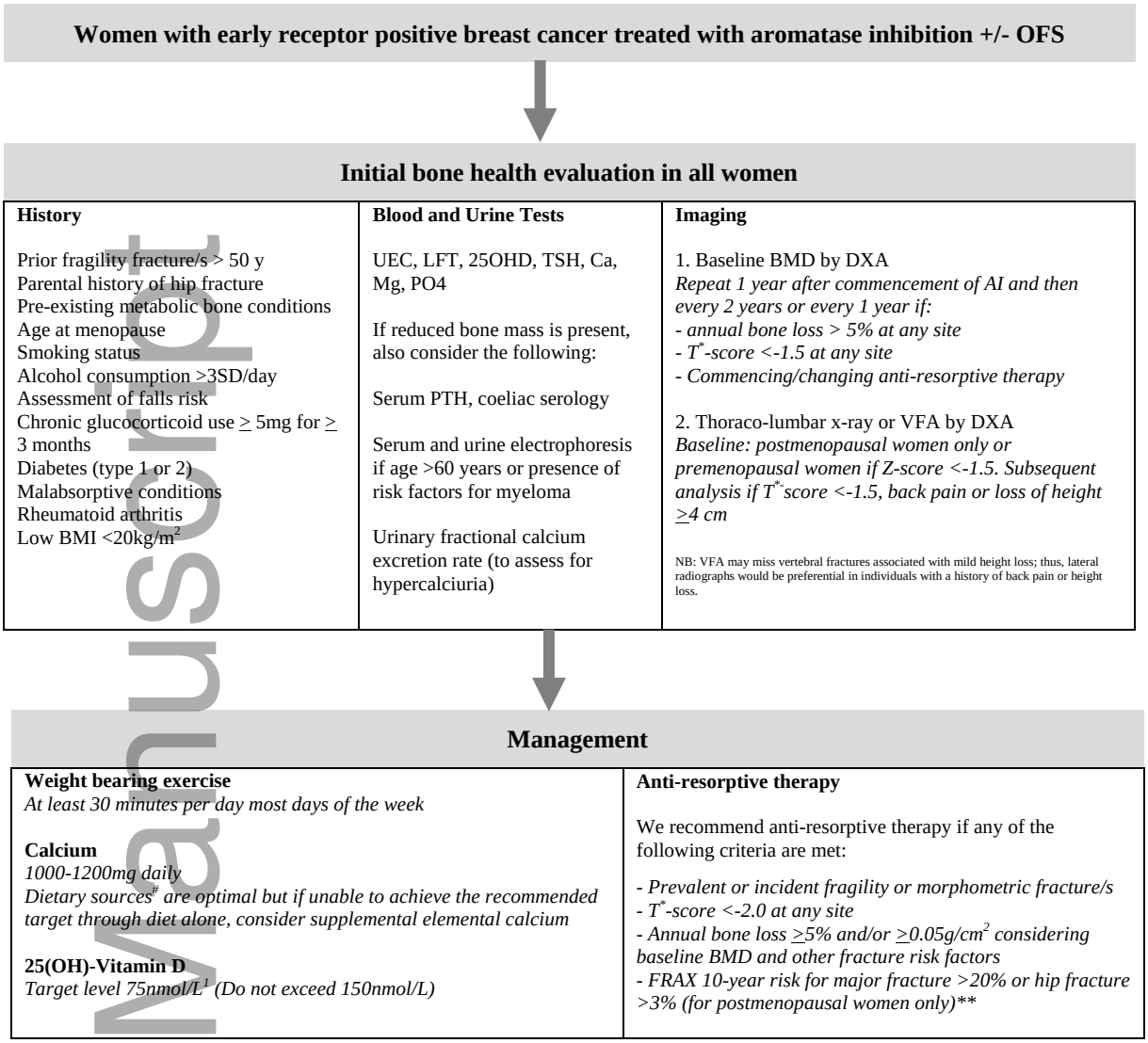
Adapted and updated from NCCN Taskforce Report: Bone Health in Cancer Care[1]

1. Kanis JA. Pathogenesis of osteoporosis and fracture. In: Kanis Ja, ed. *Osteoporosis*. London, United Kingdom: Blackwell Healthcare Communications; 1997: 22-55.
2. Finkelstein JS et al. Bone mineral density changes during the menopause transition in a multiethnic cohort of women. *J Clin Endocrinol Metab*. 2008; 93(3): 861-868.
3. Gnant M et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2015; 386(9992): 433-443.
4. Powles TJ et a. Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. *J Clin Oncol*. 1996; 14(1): 78-84.
5. Shapiro CL et al. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. *J Clin Oncol*. 2001; 19(14): 3306-3311.
6. Gnant et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow up of the ABSCG-12 bone-mineral density substudy. *Lancet Oncol*. 2008; 9(9): 840-849.
7. Fogelman I et al. Bone mineral density in premenopausal women treated for node-positive early breast cancer with 2 years of goserelin or 6 months of cyclophosphamide, methotrexate and 5-flourouracil (CMF). *Osteoporos Int*. 2003; 14(12): 1001-1006.

References

1. Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force Report: Bone Health In Cancer Care. *J Natl Compr Canc Netw*. 2013;11 Suppl 3:S1-50; quiz S51.

Figure 2. Management algorithm



25OHD = 25-hydroxy vitamin D; AI = aromatase inhibitor; Ca = calcium; LFT = liver function test; Mg = magnesium; PTH = parathyroid hormone; PO4 = phosphate; TSH = thyroid stimulating hormone; SD = standard drinks, OFS = ovarian function suppression (either bilateral oophorectomy or use of GnRH analogues; UEC = urea, electrolytes, creatinine; VFA = vertebral fracture analysis, BMI = body mass index

*For women <50 years Z-score should be used instead of T-score

** FRAX tool not validated for women <40 years old. FRAX may also underestimate fracture risk in women being treated with AI as this is not included in the algorithm.

#https://osteoporosis.org.au/sites/default/files/files/Calcium Fact Sheet 2nd Edition.pdf

The recommendations do not apply to women who are receiving adjuvant bisphosphonates to improve breast cancer outcomes, or to women with natural menopause receiving endocrine treatment with tamoxifen alone.

1 Holick, M.F., Binkley, N.C., Bischoff-Ferrari, H.A., Gordon, C.M., Hanley, D.A., Heaney, R.P., Murad, M.H., Weaver, C.M. & Endocrine, S. (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* **96**, 1911-1930.