Guidance for the Management of Breast Cancer Treatment-Induced Bone Loss

A consensus position statement from a UK Expert Group

Reviewed and supported by the National Osteoporosis Society (NOS), the National Cancer Research Institute (NCRI) Breast Cancer Study Group and the International Osteoporosis Foundation (IOF)

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Executive summary

Understanding osteoporosis and its diagnosis and management

- Osteoporosis is defined as a skeletal disorder characterised by compromised bone strength predisposing to an increased risk of fracture.
- Well-established risk factors for fracture include older age, female gender, corticosteroid use, secondary osteoporosis, family history of fracture, prior fragility fracture, low body mass index, smoking, excess alcohol consumption and low bone mineral density (BMD).
- In terms of BMD, osteoporosis is defined by the World Health Organization as a BMD that is 2.5 standard deviations (SD) or more below the average value for young healthy women (a T-score of <–2.5 SD). This criterion has been widely accepted and, in many countries, provides both a diagnostic and intervention threshold.

Breast cancer treatments associated with ovarian suppression

- A number of breast cancer treatments are associated with premature ovarian suppression, including treatment with gonadotrophin-releasing hormone inhibitors, chemotherapy, or surgical ablation.
- The rate of bone loss may exceed 5% per year (compared with 2–5% in women undergoing a natural menopause), thereby increasing the risk of osteoporosis and fractures for the women being treated.

Adjuvant breast cancer treatments associated with bone loss

- Tamoxifen is the most widely used endocrine treatment for breast cancer, and, until recently, was the gold standard for the adjuvant treatment of patients with oestrogen receptor-positive (ER+) operable breast cancer.
- There is increasing use of aromatase inhibitors for the adjuvant treatment of postmenopausal women with ER+ breast cancer instead of, or following, initial tamoxifen therapy; this has been due to proven increased efficacy at reducing the risk of disease recurrence.

Tamoxifen: effect on bone health

- Despite pre and postmenopausal women having a similar anticancer response to tamoxifen, a differential effect on bone health is observed between the two patient groups.
- In premenopausal women with high levels of circulating oestrogen from the ovaries, tamoxifen predominantly has an anti-oestrogenic effect, causing increased loss of BMD for 1–2 years; however, this is not persistent through 5 years of tamoxifen therapy.
- By contrast, in low oestrogen states tamoxifen has an oestrogen agonist effect. In premenopausal women with ovarian suppression or ablation, tamoxifen may marginally reduce the bone loss associated with the rapid loss of ovarian function. In postmenopausal women, tamoxifen has an oestrogen agonist effect causing a small but significant increase in BMD, and this may lead to a significant reduction in the risk of fractures.

Aromatase inhibitors: effect on bone health

- Despite the overall favourable tolerability profile of aromatase inhibitors, an adverse effect on bone health has been demonstrated.
- In postmenopausal women, the use of aromatase inhibitors increases bone turnover and induces bone loss at sites rich in trabecular bone at an average rate of 1–3% per year leading to an increase in fracture incidence compared with that seen during tamoxifen use. The bone loss is much more marked in young women with treatment-induced ovarian suppression followed by aromatase inhibitor therapy (average 7–8% per annum).
- Randomised clinical trials in postmenopausal women indicate that bisphosphonates prevent the bone loss and accelerated bone turnover associated with aromatase inhibitor therapy and are a promising strategy for the prevention and treatment of osteoporosis in this setting.
- Pre-treatment with tamoxifen for 2–5 years may reduce the clinical significance of the adverse bone effects associated with aromatase inhibitors, particularly if this leads to a shortening in the duration of exposure to an aromatase inhibitor. However, skeletal status should still be assessed at the commencement of aromatase inhibitor therapy.

Recommendations for managing treatment-induced bone loss

- The rate of bone loss in women who experience a premature menopause before the age of 45 or are receiving ovarian suppression therapy is accelerated by the concomitant use of aromatase inhibitors. These patients are considered to be at high risk of clinically important bone loss and should have a baseline dual energy X-ray absorptiometry (DXA) assessment of BMD.
- Treatment initiation recommendations are based on a combination of risk factors for osteoporotic fracture and BMD levels.
- Bisphosphonates, along with a healthy lifestyle and adequate intake of calcium and vitamin D are the treatments of choice to prevent bone loss.
- Owing to the rate of bone loss associated with breast cancer treatments, and uncertainties about the interaction between aromatase inhibitor use and BMD for fracture risk, the threshold for intervention has been set at a higher level than that generally recommended for postmenopausal osteoporosis.
- Management recommendations have been summarised in two algorithms, one for women experiencing a premature menopause and the other for postmenopausal women requiring adjuvant aromatase inhibitor therapy.

Introduction

Randomised clinical trials show that many of the therapies used in breast cancer are associated with bone loss, which in turns leads to an increased risk of fracture. Advances in treatments have improved long-term survival in women diagnosed with breast cancer, which means that it is increasingly important to ensure that bone health is maintained both during and after anticancer treatments.

The majority of women being treated for breast cancer are not under the care of a bone specialist. Therefore, the aim of this guidance is to provide non-bone specialists with a rationale for treating cancer treatment-induced bone loss.

Methodology

Selection of Expert Group

The guidance was developed by a UK Expert Group selected from clinical stakeholders in the management of breast cancer (medical/clinical oncologists and breast surgeons) and bone experts (rheumatologists and endocrinologists) with an interest in the identification of those at risk, and management of, postmenopausal and secondary osteoporosis, especially corticosteroid-induced osteoporosis. When the project started, the chairman of the group, David Reid, was chair of the Medical Board of the National Osteoporosis Society and, with the help of members of the board, selected the other members of the UK Expert Group.

Definition of scope

At the start of this project, a face-to-face meeting of the UK Expert Group was convened to define the scope of the guidance. The agreed objective was to provide guidance on appropriate management of bone loss associated with cancer treatments. Initially, it was planned to complete guidance for the prevention of bone loss associated with the treatment of both breast and prostate cancer. However, it became clear that the most urgent demand for guidance was in the field of treatment-induced bone loss in breast cancer, and so the group decided to focus on this first. It was agreed that the target audience for the guidance document would be health-care professionals involved in the management of patients with cancer treatment-induced bone loss, and that the final document would be available in hard copy as well as an electronic download. The group also agreed that it would be useful to produce leaflets summarising the treatment algorithms as a quick reference guide.

Search strategy

The group decided that a systematic literature search would be conducted, followed by assimilation of the evidence. The PubMed and MEDLINE databases were searched from 1960 to 2005 using search terms outlined by the section lead authors. Randomised controlled trials, observational studies and meta-analyses were assessed. A further search of the grey literature and an updated search of PubMed and MEDLINE were under-taken by individual members of the Expert Group up to the date of publication.

Assimilation and grading of the evidence

Assessments of the abstracts, and where appropriate full papers, were conducted by at least two members of the Expert Group (Appendix I). Where there was disagreement on the quality score of the paper, the two group members reached a consensus after discussion.

Understanding osteoporosis and its diagnosis and management

Osteoporosis is defined as a skeletal disorder characterised by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features, namely bone density and bone quality.[1]

Peak bone density is achieved in early adulthood with subsequent age-related decreases in both sexes that can be accelerated by extrinsic and/or intrinsic factors such as hormonal changes, of which the menopause is the prime example. Age-related bone loss appears to be asymptomatic, and the morbidity of osteoporosis is secondary to the fractures that occur.

The definition of an osteoporotic fracture is not straightforward, but a widely adopted approach is to consider fractures from low energy trauma as being osteoporotic. 'Low energy' may be defined as a fall from a standing height or less, or trauma that would not give rise to a fracture in a healthy individual. Osteoporotic fractures most commonly occur at the hip, spine and forearm, but many other fractures that occur in individuals over 50 years of age are related, at least in part, to low bone mineral density (BMD) and should be regarded as osteoporotic.[2-4] In the Western World, the estimated lifetime risk for a wrist, hip or vertebral fracture is 30–40%, which is similar to that observed for coronary heart disease.

Hip fracture is the most serious osteoporotic fracture and usually occurs as a result of a fall from the standing position, although it sometimes occurs spontaneously.[3] The risk of falling increases with age and is somewhat higher in elderly women than in elderly men. Approximately one-third of elderly individuals fall annually, 5% sustain a fracture and 1% suffer a hip fracture.[5] Hip fracture nearly always requires hospitalisation, and there is a high degree of associated morbidity and appreciable mortality that depends partly on age, the treatment received and co-morbidities of the patient.[6] Up to 20% of patients die in the first year following hip fracture, mostly as a result of serious underlying medical conditions,[7] and less than half of survivors regain the level of function that they had prior to the fracture.[8]

Vertebral fracture is the most difficult osteoporosis-related fracture to define, as the diagnosis is made on the sometimes-subtle changes in the shape of the vertebral body. Furthermore, not all vertebral fractures come to clinical attention[9,10] and may remain undiagnosed in as many as 60–75% of affected individuals. These so-called asymptomatic fractures are none the less associated with significant morbidity, impaired quality of life and an increased risk of future fractures.[11]

Distal forearm fracture is usually caused by a fall on the outstretched hand.[12] Although fractures of the wrist cause less morbidity than hip fractures, are rarely fatal, and seldom require hospitalisation, the consequences are often underestimated. Fractures are painful, usually require one or more reductions, and need 4–6 weeks in plaster. Approximately 1% of patients with a forearm fracture become dependent on a caregiver as a result of the fracture,[13] but nearly one-half of patients report only fair or poor functional outcome at 6 months.[14] Moreover, the risk of other osteoporotic fractures in later life is considerably increased.[15] The greatest evidence that skeletal fragility is increased in the future is the previous occurrence of skeletal failure, i.e. a low trauma fracture. The future risk of fracture is considerably enhanced by a previous fracture, which at least doubles the risk of subsequent fracture, partially independent of BMD, this being especially true for vertebral fractures.[16]

Bone mineral density

Osteoporosis has been operationally defined on the basis of BMD assessment. According to the World Health Organization (WHO) criteria, osteoporosis is defined as a BMD that is 2.5 standard deviations or more below the average value for young healthy women (a T-score of ≤–2.5 SD) (Figure 1).[12,17] This criterion has been widely accepted and, in many countries, provides both a diagnostic and intervention threshold.

BMD testing using dual energy X-ray absorptiometry (DXA) is not always easily available or accessible. Another problem

is that BMD tests have high specificity but low sensitivity,[12] which means that BMD measurement alone is not optimal for the detection of individuals at high risk of fracture. In other words, the risk of fracture is very high when osteoporosis is present, but by no means negligible when BMD is normal. Indeed, the majority of fragility fractures will occur in individuals with a T-score of above –2.5.

In the past decade, a great deal of research has taken place to identify factors other than BMD that contribute to fracture risk. Examples include age, gender, the degree of bone turnover, a prior fracture, a family history of fracture, and lifestyle risk factors such as physical inactivity, excess alcohol intake and smoking. Some of these risk factors are partially or wholly independent of BMD. Independent risk factors used with BMD could, therefore, enhance the information provided by BMD alone. Conversely, some strong BMD-dependent risk factors can, in principle, be used for fracture risk assessment in the absence of BMD tests. For this reason, the consideration of well-validated risk factors, with or without BMD, is likely to improve fracture prognostication and the selection of individuals at high risk for treatment.

Risk factors for fracture

The WHO working group has carried out a mega-analysis of many cohort studies to identify the following key risk factors for fracture: increasing age, female gender, personal history of fracture (after age 50), parental history of hip fracture, low body mass index, current smoker, excess alcohol consumption (4 or more units per day), diseases (such as rheumatoid arthritis), glucocorticoid use (tablets or suppository for more than a few weeks), and low femoral neck BMD ($T \leq -2.5$).[18] This list is not exhaustive and excludes many risk factors for falling, such as frailty, cerebrovascular disease, or Parkinson's disease, since there is some doubt whether the identified risk would be modified by a pharmaceutical intervention targeted at the skeleton. Such risks are more appropriately managed through interaction with local multidisciplinary falls services.

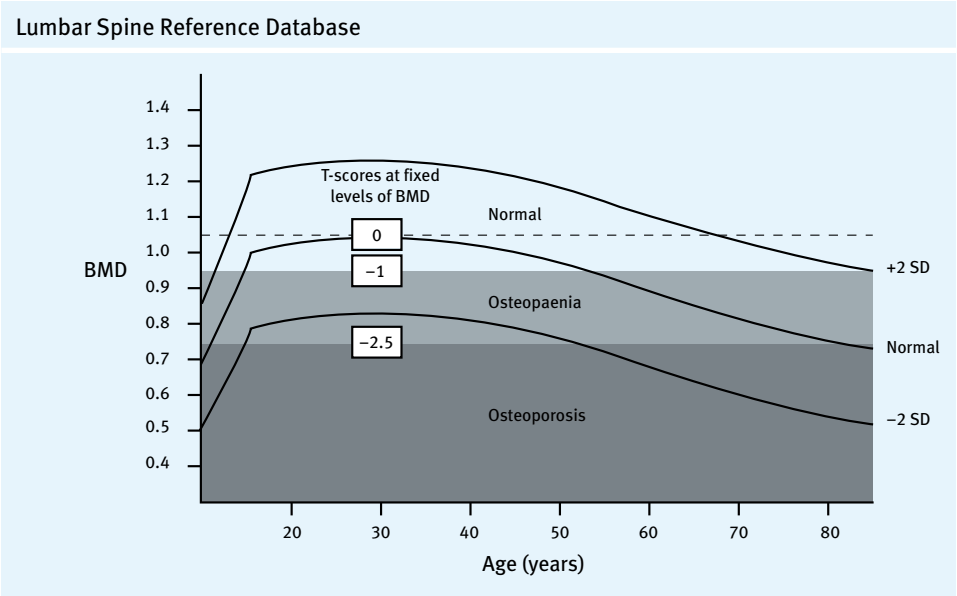


Figure 1. Reference curve for spine BMD (by Hologic scanner) in women from the age of 10 to 85 years showing the WHO classification of BMD

Breast cancer and bone loss

Breast cancer is the most common malignant tumour in women, with over 40,000 new cases and approximately 12,000 deaths per year in the UK alone. The cure rate from the disease is high and increasing, in part as a result of the wider use and increased effectiveness of systemic adjuvant therapies given at the time of diagnosis. Many therapies, particularly those that induce a therapeutic premature menopause or lower postmenopausal oestrogen concentrations, may result in appreciable bone loss and increased skeletal morbidity. Since most women are likely to be long-term survivors after breast cancer diagnosis, it is of vital importance to maintain bone health during and after anticancer treatments that affect the skeleton.

Breast cancer treatments associated with ovarian suppression

There are a number of ways in which women treated for breast cancer may have premature ovarian suppression and hence be at increased risk of osteoporosis and fractures. The section that follows examines each in turn, with the recommendations for assessment and management, drawn from a systematic review of the literature.

Ovarian suppression as a result of gonadotrophin-releasing hormone agonists

Gonadotrophin-releasing hormone (GnRH) agonists are a group of compounds (including goserelin, nafarelin, triptorelin and leuprolide) that lead to super stimulation of the GnRH receptors on the anterior pituitary. After an initial increase in gonadotrophin secretion, this leads to down-regulation of receptor activity with suppression of gonadotrophin secretion and reversible inhibition of gonadal activity. These agents have well accepted roles in the management of benign conditions such as endometriosis, uterine fibroids, and ovarian regulation prior to ovulation induction. In oncology, they are used in prostate cancer and in the management of breast cancer in premenopausal women.

Most of the information regarding the effect of these agents on the skeleton is derived from studies in premenopausal women with benign indications. Here, there is a consistent induction of a menopause-like state, with typical climacteric symptoms and a rapid increase in bone turnover leading to a reduction in bone mass. Most studies demonstrate a consistent loss of 4–5% in lumbar spine BMD over the first 6 months of therapy. In most benign indications for GnRH therapy, treatment is limited to a few months and so information about longer-term bone loss and associated fracture incidence is not available. Following cessation of therapy, there is resumption of ovarian function and restoration of much of the lost bone. Several therapies have been shown to reduce the bone loss associated with GnRH inhibitor therapy in premenopausal women. These include oestrogen replacement, tibolone, raloxifene, etidronate and zoledronic acid.

GnRH inhibition is used to induce reversible ovarian suppression in premenopausal women with oestrogen receptor-positive (ER+) breast cancer. There is little information regarding the skeletal effect of GnRH inhibition in breast cancer but it seems reasonable to assume the same effects as in underlying benign disease states, due to similar early effects on the skeleton. Importantly, in breast cancer, the treatment is continued for several years (usually 2–5 years) and so the effect on the skeleton would be expected to be more marked than that observed in the benign indications, where treatment duration is limited.

In a subset of patients from a large study (the ZEBRA study) of 1640 women receiving goserelin as part of early breast cancer treatment, bone density was measured in 53 women treated with goserelin and compared with 43 women treated with standard cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy.[19] At the end of the first year, the goserelin-treated group had lost 8.2% of bone density from the lumbar spine and 4.5% from the femoral neck. The lumbar spine loss associated with goserelin was significantly greater than that observed with chemotherapy (4.5%), but the femoral loss was similar in the two treatment

groups. After 2 years, bone loss was significantly greater in the goserelin group at both measurement sites compared with those receiving chemotherapy (spine: –10.5% vs. –6.5%; femoral neck: –6.4% vs. –4.5%). After the second year of therapy, goserelin was stopped, as required by the protocol. Menses returned in 72.7% of goserelin recipients upon cessation of therapy, and this was associated with a partial recovery of bone density at 3 years, whereas amenorrhoea was permanent in the majority of CMF recipients (76.5% of patients at 3 years). As a result, no significant differences in BMD were observed between the goserelin group and those receiving chemotherapy at the 3–year assessment (spine: –6.2% vs. –7.2%; femoral neck: –3.1% vs. –4.6%).

In a small, randomised, controlled trial, bone density results were evaluated in 13 patients treated with goserelin alone, and compared with 14 patients receiving goserelin plus tamoxifen, 18 patients receiving tamoxifen alone, and 21 patients not receiving any endocrine therapy.[20] At the end of the 2-year treatment period, the goserelin treatment group had lost 5.0% of their total body bone density compared with 0.3% in the group receiving no endocrine therapy. The bone loss was reduced by the co-administration of tamoxifen; patients treated with goserelin plus tamoxifen experienced a bone loss of 1.4%. Following cessation of goserelin, there was a 1.5% recovery of bone mass 1 year after treatment was finished.

More recently, a larger study investigating the combination of goserelin and tamoxifen showed rapid bone loss during the first year, which continued at a slower rate in years 2 and 3 to give an estimated loss of 11.6% in lumbar spine bone density at the end of 3 years.[21] This compared with an estimated loss at 3 years of 17.3% if goserelin was combined with the aromatase inhibitor anastrozole. Bone loss in both of these groups was prevented by the administration of zoledronic acid; this was initially given at a dose of 8 mg by intravenous infusion every 6 months, but early in the study the dose was reduced to 4 mg every 6 months. Similar but less marked changes were seen in the proximal femur. Partial recovery was seen on cessation of goserelin and endocrine treatment, but significant bone loss persisted at 5 years.[22]

None of these studies were of sufficient size or had sufficient follow up to allow any insight into fracture rates during or following GnRH therapy. Furthermore, it must be remembered that this treatment is primarily aimed at premenopausal women that are likely to start off with a low absolute fracture risk.[23] However, comparison with the findings in older men treated with GnRH agonists for prostate cancer, where similar changes in bone density are seen, would indicate that absolute fracture risk will be increased following this treatment.[24]

Ovarian suppression as a result of chemotherapy

Cytotoxic chemotherapy used in the treatment of breast cancer can result in temporary amenorrhoea or, especially in older premenopausal women, irreversible damage to the ovarian tissues, leading to premature ovarian failure. Although there is no agreed definition of chemotherapy-induced ovarian failure, irreversible amenorrhoea lasting for several months (6–12 months) following chemotherapy and an elevated follicle-stimulating hormone seems to be widely accepted.[25] An early menopause has been demonstrated in diseases other than breast cancer where chemotherapy is used.

Few studies were identified specifically examining the effects of an early menopause associated with chemotherapy for breast cancer. However, in Hodgkin's disease[26,27] and lymphoma,[28] studies have demonstrated that premature menopause is associated with reduced bone density especially in those who did not receive hormone replacement therapy (HRT).

In breast cancer, the changes in BMD resulting from a chemotherapy-induced menopause have been similar to those seen in other diseases. In a cohort study of 27 women with early breast cancer who had received adjuvant chemotherapy at least 2 years before, 11 became amenorrhoeic.[29] The amenorrhoeic women, who might have received up to 12 months of

tamoxifen as part of their chemotherapy, had approximately a 14% reduction in their spine BMD compared with those who remained premenopausal. In a step-wise multiple regression analysis, the only significant variable accounting for 28% of the variation in BMD was menopausal status.

A rapid and significant bone loss has been demonstrated in women with breast cancer treated with adjuvant chemotherapy.[30] In a prospective cohort study to determine the baseline predictors of ovarian failure in initially premenopausal women with breast cancer, 35 of 49 patients evaluated developed ovarian failure after 6 months of follow-up.[31] At 6 months, the only significant predictors of ovarian failure in a multivariate model were age and alcohol intake in the past year.

Few studies have examined how the effects of an early menopause induced by chemotherapy can be abrogated, although the bisphosphonates are thought to play a role. Saarto *et al* reported on 113 women who were premenopausal before chemotherapy.[32] Of these, 38% became amenorrheoic in the first year, with a further 36% developing irregular menses and only 22% retaining regular menses. The likelihood of loss of regular menstruation increased with age. In this trial a total of 148 patients were randomised to receive oral clodronate or placebo (although the randomisation method lacked clarity and resulted in unequal numbers), and at 2 years of follow-up, overall bone loss was abrogated by the use of the bisphosphonate clodronate at the lumbar spine (placebo: –5.9%, clodronate: –2.2%; p=0.005) and femoral neck (placebo: –2.0%, clodronate: +0.9%; p=0.017). Those women who became amenorrhoeic lost bone density in both treatment groups, although the magnitude of loss was significantly less if receiving clodronate (lumbar spine: 9.5% vs. 5.9%; femoral neck: 4.6% vs. 0.4%).

A small but well conducted randomised, controlled trial carried out in 53 women with an artificially induced menopause and a mean age of 47 years evaluated the effects of a non-standard regimen of risedronate, 30 mg/day for 2 weeks, every 3 months.[33] Of the 53 women, 36 had been pre-treated with tamoxifen. The BMD was maintained at the lumbar spine and hip sites in risedronate-treated women, compared with significant losses in the placebo group. At 2 years, the mean differences between the two treatment groups were 2.5% at the lumbar spine and 2.6% at the femoral neck. Both bone resorption and formation rates fell in the risedronate group compared with the placebo group. The BMD fell in a third year of follow-up, i.e. when risedronate was stopped.

An analysis of a 12-month randomised, controlled trial (with a 12-month pre-planned extension) has been conducted in 87 women with breast cancer who had experienced a premature menopause a mean of 3.2 to 3.4 years earlier. In this analysis, risedronate 35 mg weekly was associated with increased BMD at the lumbar spine (+1.2%) and total hip (+1.3%), compared with mean losses in the placebo group (lumbar spine: –0.9%; total hip: –0.8%); the differences between the two groups were significant ($p<0.01$).[34] Furthermore, bone markers (urinary N-telopeptide of type 1 collagen [NTX] and serum procollagen type 1 N-propeptide [P1NP]) were significantly reduced in the risedronate treatment group at 6 months in comparison with baseline.

Ovarian suppression as a result of surgical ablation

Oophorectomy before the menopause

In premenopausal individuals, the effect of oophorectomy on bone has been examined in two retrospective studies. In the first of these, a case-control study of 146 patients with a mean age at oophorectomy of 25 years,[35] there was a greater than two-fold increase in the risk of developing any subsequent fracture when compared with age-matched controls. More specifically, there was an increased risk of developing a hip or radial forearm fracture (2-fold and 3.7-fold, respectively).

In the second study,[36] describing a cohort of 463 patients with a median age of 43.8 years, there was a significantly increased risk of developing either a vertebral fracture (standardised

morbidity ratio [SMR] 1.9; 95% CI 1.3–2.8) or a forearm fracture (SMR 1.4; 95% CI 1.0–2.0). There was no increased risk of hip fracture. However, confounding factors were that 60% of women had taken HRT at some time, with 80% doing so within the first year after oophorectomy. Younger women were more likely to develop fractures and were more likely to be taking HRT.

Effects of HRT on bone in individuals who have undergone oophorectomy

One hundred women who had taken part in a prospective controlled trial of oestrogen therapy for the prevention of post-oophorectomy bone loss were reviewed after a median follow-up period of 9 years. A significant reduction in height occurred among the placebo-treated group, but not in the group treated with mestranol (mean 23 x 3 µg/day). The placebo-treated group had a higher spine score, lower central vertebral height, and larger wedge-angle than the oestrogen group. Within each group, none of these spinal morphometric changes correlated with changes in mineral content of metacarpal or radial bones as measured by photon absorptiometry or X-ray densitometry, although both peripheral and central measurements showed highly significant differences between the two groups. Oestrogen treatment, therefore, prevents against central, as well as peripheral, bone loss, and reduces the incidence of vertebral compression.[37]

Three case-control and two case series have attempted to evaluate what effect the provision of HRT has on bone density following oophorectomy. Interpretation of the studies is difficult as they are small studies of less than 88 patients.[38-42] The mean ages of patients studied have ranged from 40 to 50 years, with one case series reporting two patients of 12 years of age.[42]

These studies have indicated that, following oophorectomy, there is a reduction in bone density of up to 10% in the 3 years afterwards. However, in the setting of breast cancer, HRT is *not* recommended for bone protection due to the adverse effects of HRT on breast cancer recurrence and the availability of alternative therapies.

Adjuvant breast cancer treatments associated with bone loss

Tamoxifen

Tamoxifen is probably the most widely used endocrine treatment for breast cancer worldwide. It is only effective in women with ER+ breast cancer, and most patients with these cancers will receive the drug at some time. Until recently, it was the gold standard for the adjuvant endocrine treatment of patients with ER+ operable breast cancer. In spite of high levels of circulating oestrogen from the ovaries in premenopausal women, compared with relatively low levels from non-ovarian tissue in postmenopausal women, the anticancer response to tamoxifen in pre and postmenopausal women with metastases is similar.[43]

Tamoxifen is an oestrogen antagonist that competitively inhibits oestrogen binding to the oestrogen receptor. However, tamoxifen may become a tumour agonist, thereby reducing or reversing its antiproliferative activity.

With respect to bone, tamoxifen has a differential effect in pre and postmenopausal women.[44,45] In premenopausal women with high levels of circulating oestrogen from the ovaries, tamoxifen predominantly has an anti-oestrogenic effect causing increased loss of BMD for 1–2 years. However, this loss is only about 1–2% and is not persistent through 5 years of tamoxifen therapy. No special monitoring or treatment to prevent this loss would be required. In postmenopausal women, tamoxifen is known to increase BMD of the spine,[46-50] hip,[48,50,51] but not the forearm[51-53] or total body.[46] It also reduces biochemical markers of bone resorption[46,48,51] and bone formation[46,48,51,52] to a similar extent to raloxifene.[54]

In summary, the bone loss caused by tamoxifen in premenopausal women does not present a clinical problem requiring bone-protecting medication, and tamoxifen protects against bone loss in postmenopausal women. However, following ovarian suppression with luteinizing hormone-releasing hormone analogues, the oestrogen agonist action of tamoxifen is insufficient to counteract the rapid bone loss associated with medical castration.[21]

Aromatase inhibitors

Aromatase inhibitors are highly potent inhibitors of oestrogen production that suppress circulating oestradiol levels to almost undetectable levels. Possibly because there is no associated agonist effect, aromatase inhibition is a more effective treatment than tamoxifen. In particular, the third generation non-steroidal (anastrozole and letrozole) and steroidal (exemestane) aromatase inhibitors inhibit the aromatase enzyme by 96–99%. Overall, aromatase inhibitors have a favourable side-effect profile but, owing to the known relationships between residual oestrogen levels and bone loss[55] and also fracture risk,[56,57] this associated marked reduction in oestradiol would be expected to have significant effects on bone physiology.

Clinical indications for aromatase inhibitors

Advances in adjuvant therapy have led to improvements in the long-term survival of women with early breast cancer; the 10-year probability of survival is now 80–85%. Tamoxifen has been the cornerstone of adjuvant endocrine therapy of breast cancer for several decades, a role that has largely been unchallenged until now. Recently, the aromatase inhibitors have been shown to further reduce the risk of recurrence after a diagnosis of ER+ breast cancer, either when given in place of the previous standard of care (tamoxifen), or when administered in sequence after a few years of tamoxifen therapy.[58-62] As a result of these trials, the aromatase inhibitors are now recommended in the adjuvant treatment setting,[63] such that many women with breast cancer will be exposed to several, and possibly many years of treatment with an aromatase inhibitor.

Table 1. Effects of aromatase inhibitors on fracture risk from five clinical trials

	Aromatase Inhibitor (%)	Tamoxifen / Placebo (%)	% Increase	Reference
ATAC (Anastrozole)	375 (12.0%)	234 (7.5%)	55%*	Forbes *et al.*[64]
BIG 1-98 (Letrozole)	211 (8.6%)	141 (5.8%)	50%	Coates *et al.*[68]
IES (Exemestane)	162 (7.0%)	115 (4.9%)	41%	Coombes *et al.*[60]
ABCSG (Anastrozole)	34 (2.0%)	16 (1.0%)	113%	Jakesz *et al.*[61]
MA17 (Letrozole)	137 (5.3%)	119 (4.6%)	15%	Perez *et al.*[69]

*On-treatment fracture excess. Post-treatment the fracture incidences were similar in ATAC.

Anastrozole and bone

Anastrozole has been shown to be at least as effective as tamoxifen in the treatment of metastatic breast cancer. In the adjuvant setting, the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial has demonstrated a significant advantage for anastrozole over tamoxifen.[58] A recent update has shown not only an improvement in disease-free survival, but also a reduction in distant metastases.[64]

The ATAC trial also demonstrated a favourable adverse event profile for anastrozole, compared with tamoxifen, with the exception of effects on the musculoskeletal system. In the anastrozole group, there were more musculoskeletal side effects and fractures, most frequently affecting the spine and fractures other than the hip and wrist. The incidence of all fractures in the 2007 update was 12% in the anastrozole group and 7.7% in the tamoxifen group ($p<0.0001$)[64] (Table 1). To date, there has been no significant increase in fractures occurring at the hip, and the excess fracture incidence seen for anastrozole over tamoxifen during the 5-year treatment period appears to resolve on withdrawal of endocrine treatment. However, further data are required on the long-term effects of aromatase inhibitor treatment on bone health.

It is uncertain how much of the excess fracture risk can be attributed to the increase in bone turnover caused by anastrozole, as opposed to the loss of the bone protective effects of tamoxifen.

Within the ATAC trial, a bone sub-protocol investigated 308 patients for changes in BMD and bone turnover markers.[65,66]

Patients entering this part of the study had a DXA scan of the lumbar spine and hip, at baseline and after 12, 24 and 60 months on treatment. Bone turnover markers were also measured at baseline, 3, 6 and 12 months. A small increase in BMD at the spine and hip was observed in patients treated with tamoxifen, whereas anastrozole therapy was associated with a decrease in BMD at these sites. This was obvious at 1 year and further increased during the second year of therapy, with approximately a 2% loss of bone density annually (Figure 2). Over the course of the 5-year treatment programme, an average BMD loss of 7–8% was observed. Despite these changes, no patient with normal BMD at baseline developed osteoporosis.

The decrease in BMD observed in the ATAC trial was associated with an increase in bone remodelling, as demonstrated by an increase in markers of bone resorption and formation in the anastrozole group. There was a 26% increase in the bone resorption marker serum C-terminal telopeptide of type I collagen (CTX) and a 20% increase in the bone formation marker bone alkaline phosphatase (bone ALP). Conversely, tamoxifen therapy was associated with a decrease in markers of bone turnover.[65]

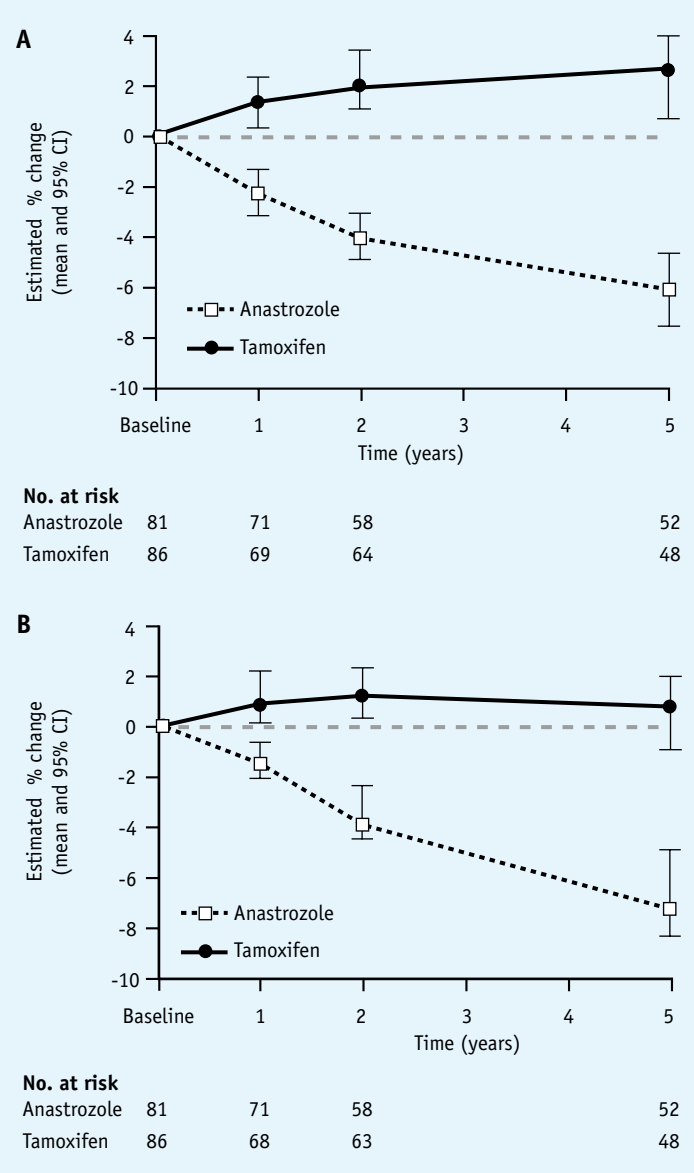
Letrozole and bone

Letrozole has been shown to be superior to tamoxifen in advanced breast cancer, while in early breast cancer, The Breast International (BIG) 1-98 Collaborative Group showed superiority of letrozole over tamoxifen, with a risk reduction very similar to that observed with anastrozole in the ATAC trial.[59] Additionally, a study investigating the role of letrozole after standard treatment with 5 years of adjuvant tamoxifen therapy has shown a highly significant improvement in disease-free survival with letrozole.[62]

Letrozole is known to increase bone turnover, and its effects have been investigated in healthy postmenopausal women; after 3 months of letrozole therapy, CTX, a marker of bone resorption, had increased by around 20% ($p < 0.005$).[67]

In the BIG 1-98 study, a 50% excess of fractures was

Figure 2. Mean percentage change in BMD after 1, 2 and 5 years of treatment. Bars represent 95% CI. **(A)** Lumbar spine change over time; **(B)** total hip change over time



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observed with a median follow-up of 30 months (8.6% vs. 5.8%).[68] In the MA-17 study, patients were randomised to letrozole or placebo after completing 5 years of adjuvant tamoxifen therapy. More diagnoses of osteoporosis were made in the letrozole group, compared with the placebo group, at 5.8% and 4.5% of patients, respectively (p=0.07), and the fracture rate was also slightly increased.[62] Recently, the first data from 226 patients evaluated in the MA-17 bone sub-protocol were presented.[69] Patients receiving letrozole had a significant decrease in BMD at 24 months at both the lumbar spine (p=0.008) and hip (p=0.044); these results strongly suggest that letrozole has similar effects on bone health to that of anastrozole.

Exemestane and bone

Exemestane is superior to tamoxifen in the first-line treatment of advanced breast cancer, and has also been evaluated in the adjuvant treatment setting. Although results from direct comparisons with tamoxifen are not expected for some time, data from the Intergroup Exemestane Study (IES), evaluating sequential therapy with tamoxifen for 2–3 years followed by exemestane for 2–3 years, compared with 5 years of tamoxifen therapy, have shown a significant advantage in favour of the sequential treatment option, with improvements in both disease-free and overall survival.[60]

Exemestane, in contrast to the non-steroidal agents, has weak androgenic activity. It was postulated that this might result in less adverse effects on bone.[70] This provided some support for the potentially different mechanism of action of exemestane. However, in another biochemical study, exemestane was found to increase levels of bone turnover markers[71] and in the Letrozole, Exemestane, and Anastrozole Pharmacodynamics (LEAP) study, which compared the effects of all three clinically available aromatase inhibitors in postmenopausal women, no significant differences in the profile of biochemical markers of bone metabolism were seen. Of note, changes in parathyroid hormone were similar with all three agents, arguing against an anabolic effect of exemestane.[72]

Results of a placebo-controlled trial of exemestane in early breast cancer have recently been published.[73] In this study, 147 patients with low risk early breast cancer were randomised to receive treatment with exemestane 25 mg/day or placebo. Patients had a baseline DXA scan of the spine and hip, and follow-up assessments occurred annually. After 1 year, the BMD of patients in the exemestane group decreased by 2.17% and 2.72% at the spine and hip, respectively. However, bone loss in the placebo group was somewhat greater than expected, at 1.84% and 1.48% at the spine and hip, respectively. As a result, there was no significant difference between the two treatment groups at the lumbar spine, although the difference in hip BMD did reach statistical significance (p=0.024). None of the women were taking calcium or vitamin D supplements, and recent analysis has confirmed that many of these women were vitamin D deficient.[74] In a 1-year follow up to the study after discontinuation of exemestane, the loss of BMD was partially reversed.[73]

The effect of exemestane on markers of bone turnover was also assessed in this study. Exemestane was associated with significant increases in both markers of formation and resorption. In the exemestane group, levels of P1NP and CTX increased from baseline by 44% and 35%, respectively. However, levels of P1NP and CTX in the placebo group decreased by only 4% (p<0.001) and 5% (p=0.012), respectively. The increase in bone resorption was consistent with the bone loss observed, while the increase in bone formation markers can be attributed to the coupling of bone formation to bone resorption.

Data from the bone sub-protocol of the IES study have recently become available.[75] This study measured BMD and bone markers of resorption and formation in 206 patients at baseline, 6, 12 and 24 months. Patients who remained on tamoxifen showed no significant change from baseline in BMD. In patients who switched to exemestane, the mean rates of bone loss 6 months after tamoxifen cessation were 2.7% and 1.2% at the

spine and hip, respectively. Thereafter, bone loss continued but at a slower rate of 0.5–1% per year. After 2 years, the change from baseline in BMD was 3.6% at the spine and 2.4% at the hip. Despite the more modest rate of bone loss seen in this bone sub-study, a significant increase in the incidence of fractures was observed in the IES study as a whole. With a median follow-up in all participants of 58 months and median exposure to exemestane of 30 months, 162 (7%) of patients in the exemestane group experienced a fracture compared with 115 (5%) patients in the tamoxifen group (odds ratio 1.45 [1.13–1.87]; p=0.003).[60]

Treatment of aromatase inhibitor-induced bone loss

As in other forms of increased bone loss, the bisphosphonates are the preferred treatment for aromatase inhibitor-induced bone loss. The results of several intervention studies with zoledronic acid have been published recently; there are also ongoing studies with a number of oral bisphosphonates, such as anastrozole and risedronate in the SABRE trial, and anastrozole and ibandronate in the ARIBON trial. In SABRE, 138 women receiving anastrozole who were osteopaenic at baseline were randomised to risedronate 35 mg weekly or placebo. Risedronate led to a mean increase of 1.7% in BMD at 12 months compared with a 0.41% loss in the placebo arm. In this study, risedronate also improved BMD in a cohort of women with osteoporosis at baseline.[76] In ARIBON, 50 osteopaenic women were randomised to monthly oral ibandronate 150 mg monthly or placebo during treatment with anastrozole. As expected, ibandronate prevented the bone loss observed in the placebo group. BMD changes at 12 months were +2.78% at the spine and +1.35% at the hip versus -2.61% at the spine and -2.34% at the hip for ibandronate and placebo treated patients, respectively (p<0.001).[77] These two studies suggest that bisphosphonates at the dose and schedule used in postmenopausal osteoporosis are effective in the setting of aromatase inhibitor bone loss.

The Austrian Breast Cancer Study Group (ABCSG) reported on 400 patients with early breast cancer undergoing ovarian suppression with goserelin plus either anastrozole or tamoxifen, with or without bone-protecting therapy comprising a 6-monthly schedule of zoledronic acid 4 mg.[21] Without zoledronic acid, clinically important and significant bone loss occurred; the mean reductions in BMD at 3 years were 8% and 16% with tamoxifen and anastrozole, respectively. However, the addition of zoledronic acid prevented bone loss with either endocrine strategy. The effects of zoledronic acid on bone turnover and fracture rates have not been reported.

The Zometa-Femara Adjuvant Synergy Trials (Z-FAST [US])/(ZO-FAST [Europe]) (n=1668) recruited postmenopausal breast cancer patients with normal bone density or osteopaenia (T-score of >–2). Patients were treated with adjuvant letrozole and randomised either to immediate intravenous zoledronic acid (4 mg by intravenous infusion every 6 months) or to a delayed phase of treatment based on changes in BMD. In the Z-FAST study, the mean difference in BMD between the immediate and delayed groups at 12 months was 5.1% and 3.6% at the spine and hip, respectively (p≤0.001). Bone turnover was increased in the delayed group but reduced with zoledronic acid therapy.[78] Similar results were seen in the ZO-FAST study.[79] Follow-up is currently too short for a reliable assessment of the effect of prophylactic zoledronic acid on the incidence of fragility fractures, but the increase in BMD coupled with reduced bone turnover would be expected to prevent any increase in fractures associated with aromatase inhibitor use.

Raloxifene is an effective treatment for the prevention of osteoporosis. Unlike HRT, it does not increase the risk of recurrent breast cancer. However, in view of the interaction between tamoxifen and anastrozole, with the combination behaving like tamoxifen alone,[58] the addition of raloxifene to an aromatase inhibitor cannot be recommended in the adjuvant treatment setting.

Strontium ranelate is licensed in most of the world for the treatment of postmenopausal osteoporosis. However, there is currently no research using this agent in cancer treatment-induced bone loss and so we cannot recommend its use.

Monitoring the effects of treatment for breast cancer treatment-induced bone loss

The response to anti-resorptive therapy can be monitored in the individual by the use of bone turnover markers or BMD. The goal of monitoring the individual is to identify non-response. This might indicate inadequate compliance with therapy, underlying secondary osteoporosis or simply failure of the drug to be effective.

Bone turnover markers can be used to monitor response to treatments such as the once weekly (or once monthly) bisphosphonates risedronate, alendronate and ibandronate.[80] The primary mechanism of action of these drugs is to reduce bone resorption, and so it is logical to use bone resorption markers. The most commonly used markers are urinary NTX expressed as a ratio to creatinine and measured on a second morning void urine sample, serum CTX on a serum sample collected between 8 and 10am with the patient in the fasting state. These markers decrease on average by 55–75%, and the maximal response is complete by about 3 months of treatment. It may be helpful to have two measurements of bone resorption marker before the treatment is started and then further measurements can be made at 3 and 6 months.

The goal of anti-resorptive treatment is to reduce the bone resorption marker by more than the least significant change, into the lower half of the reference range for healthy young women.[81] Bone turnover markers do vary from day to day, and the least significant change approach takes this into account. A decrease of 50% or more in bone resorption markers usually indicates that the least significant change has been exceeded. It is helpful to plot out the graph to show to the patient. The lower half of the reference range is taken as the second target. Women between the age of 35 and 45 years have reached peak bone mass and have not yet started to lose bone, and so this can be considered to be a period of stable bone health. The lower part of the reference range has been associated with the lowest risk of fracture. This approach is helpful when bone turnover markers are being measured for the first time once the patient has started treatment. Care needs to be taken when interpreting bone turnover markers, as there may be changes due to intercurrent diseases or to recent fracture.[82]

BMD can also be used to monitor response to anti-resorptive treatments.[83] It is usual to recommend an 18-month to 2-year interval before making the second measurement, as the increase in BMD is quite small, even at the lumbar spine (the optimal site for measurement). The only published study of bisphosphonates in aromatase inhibitor-associated bone loss is the use of zoledronic acid in women receiving letrozole. In this study, zoledronic acid therapy was associated with a mean increase in the spine and total hip at 1 year of 4% and 3%, respectively.[78] The best site in the proximal femur for monitoring therapy is the total hip, as this shows the least variability. Care needs to be taken in interpreting change in BMD as there may have been changes to vertebral anatomy in the intervening period, for example degenerative changes in the spine, differences in the positioning of the femur or large changes in weight. The least significant change for the spine is about 5%.[83]

Algorithms and recommendations

The American Society of Clinical Oncology (ASCO) has suggested an algorithm for the management of treatment-induced bone loss.[84] In patients with a history of breast cancer, postmenopausal women receiving aromatase inhibitors are considered as "high-risk" and recommended to undergo annual DXA assessment of the spine and hip, and receive calcium and vitamin D supplements. Those with BMD above the T-score threshold for a diagnosis of osteoporosis (T-score of >–2.5) are reassured and monitored on an annual basis, while those with a T-score of ≤2.5 are recommended to receive a bisphosphonate in addition to calcium and vitamin D supplementation and continue with annual DXA scans.

We have modified this algorithm to reflect the more recent findings summarised previously and the importance of risk factors other than BMD in selection of patients for intervention. Elderly (>75 years of age) women with one or more risk factors for osteoporotic fracture should receive bone protection with a bisphosphonate irrespective of BMD. Additionally, to reflect the speed of cancer treatment-induced bone loss, we suggest a more cautious BMD level for intervention. In postmenopausal women we recommend intervention when the T-score falls below –2 or if the rate of bone loss in women with pre-existing osteopaenia exceeds 4% per year. Similar recommendations apply to women with a premature menopause, with the exception of those receiving ovarian suppression plus an aromatase inhibitor in whom the recommended T-score threshold for intervention is –1, due to the very rapid losses of bone which occurs in this group of women averaging 16% over 3 years.[21]

Where bisphosphonate therapy has been recommended, local protocols and funding arrangements should be taken into consideration when choosing the most appropriate product to use. Weekly oral alendronate 70 mg or risedronate 35 mg, monthly oral ibandronate 150 mg, 3-monthly intravenous ibandronate 3 mg, or 6-monthly intravenous zoledronic acid 4 mg are all considered appropriate. The dose of zoledronic acid used in postmenopausal osteoporosis is 5 mg annually given by the intravenous route. However the studies referenced in this document where zoledronic acid has been used to prevent breast cancer treatment-induced bone loss have used 4 mg biannually. The 4 mg dose every 6 months has thus been included in the algorithm, but individual clinicians may wish to use 5 mg annually.

Treatment algorithms proposed by the Expert Group

The choice of endocrine therapy should be based on the characteristics and prognosis of the underlying breast cancer, rather than pre-existing bone health, provided that appropriate monitoring and treatment of bone loss can be ensured.

Two algorithms for the management of bone loss in early breast cancer are proposed.

Algorithm 1: Women who experience premature menopause due to chemotherapy or ovarian suppression, ablation or removal.

Algorithm 2: Postmenopausal women receiving treatment with aromatase inhibitors.

There are no specific monitoring or treatment requirements for:

- women who continue to menstruate after treatment for early breast cancer; or
- postmenopausal women above 45 years of age who do not require endocrine treatment or who are receiving tamoxifen therapy.

Any patient, regardless of age, with a baseline T-score of <–2 should be assessed for other causes of osteoporosis, based on erythrocyte sedimentation rate (ESR), full blood count (FBC), bone and liver function tests (calcium, phosphate, alkaline phosphatase, albumin, aspartate aminotransferase [AST] / γ-glutamyl transferase [γGT]), serum creatinine and thyroid function tests, and the serum protein electrophoretic strip.

Algorithm 1: Women who experience premature menopause

The development of a treatment-induced menopause or planned ovarian suppression treatment before the age of 45 years are indications for evaluation of BMD by DXA.

BMD assessments should be done at the lumbar spine and at one or both total hip sites. There is no requirement to obtain a DXA before starting treatment, but a baseline assessment should be obtained within 3 months of commencing ovarian suppression therapy or oophorectomy and within 12 months of developing postchemotherapy amenorrhoea.

Monitoring and treatment thereafter depends on the baseline BMD and the type of any concomitant endocrine treatment. Owing to the very rapid bone loss observed with the use of ovarian suppression therapy plus an aromatase inhibitor, a different threshold for follow-up, monitoring and intervention is recommended.

Any patient with a documented vertebral fragility fracture or previous low trauma hip fracture should receive prophylactic bisphosphonate treatment irrespective of baseline BMD.

For patients who are not receiving a concomitant aromatase inhibitor, three groups of patients are defined based on baseline BMD:

High-Risk Group: Patients with a baseline T-score of <–2 at the lumbar spine or either hip site or whose BMD falls below this threshold should receive bisphosphonate therapy at osteoporosis doses in addition to lifestyle advice, calcium and vitamin D supplementation.

- The choice of bisphosphonate should be based on local protocols and funding arrangements. Weekly oral alendronate 70 mg or risedronate 35 mg, monthly oral ibandronate 150 mg, 3-monthly intravenous ibandronate 3 mg, or 6-monthly intravenous zoledronic acid 4 mg are all considered appropriate.
- Bisphosphonates are contraindicated in patients with a low glomerular filtration rate (<30 ml/min/1.73m²) or hypocalcaemia. Such patients who require bone sparing therapy should be referred to the local bone service. Oral bisphosphonates must be used with caution in patients with oesophageal disease, although intravenous bisphosphonates will usually be appropriate in such patients.
- Follow-up of patients requiring bisphosphonate treatment should include a repeat DXA after 24 months and/or measurement of a bone resorption marker, if desired, as an aid to judging compliance and response. If there is bone loss associated with bisphosphonate therapy, first check that the compliance with instructions is correct, then re-evaluate for secondary osteoporosis. Poor compliance and secondary osteoporosis explain most cases of poor response. However, some patients may be true non-responders and a switch of therapy, for example to an intravenous bisphosphonate, or a referral to the local bone service should be considered in these patients.

Medium-Risk Group: For those patients with a T-score between –1 and –2, lifestyle advice plus calcium (1 g/day) and vitamin D (400–800 IU) supplementation are recommended unless dietary intake of calcium exceeds 1 g/day and serum 25-hydroxyvitamin D is known to be >20 µg/L.

- A follow-up DXA scan should be performed at 24 month intervals to exclude a clinically significant reduction in BMD (T-score of <–2 or >4% per annum decline in BMD at either the spine or hip [the forearm is not suitable for repeat assessments within such timeframes]).
- Patients who exceed these limits should commence bone protection therapy as described in the high-risk group.

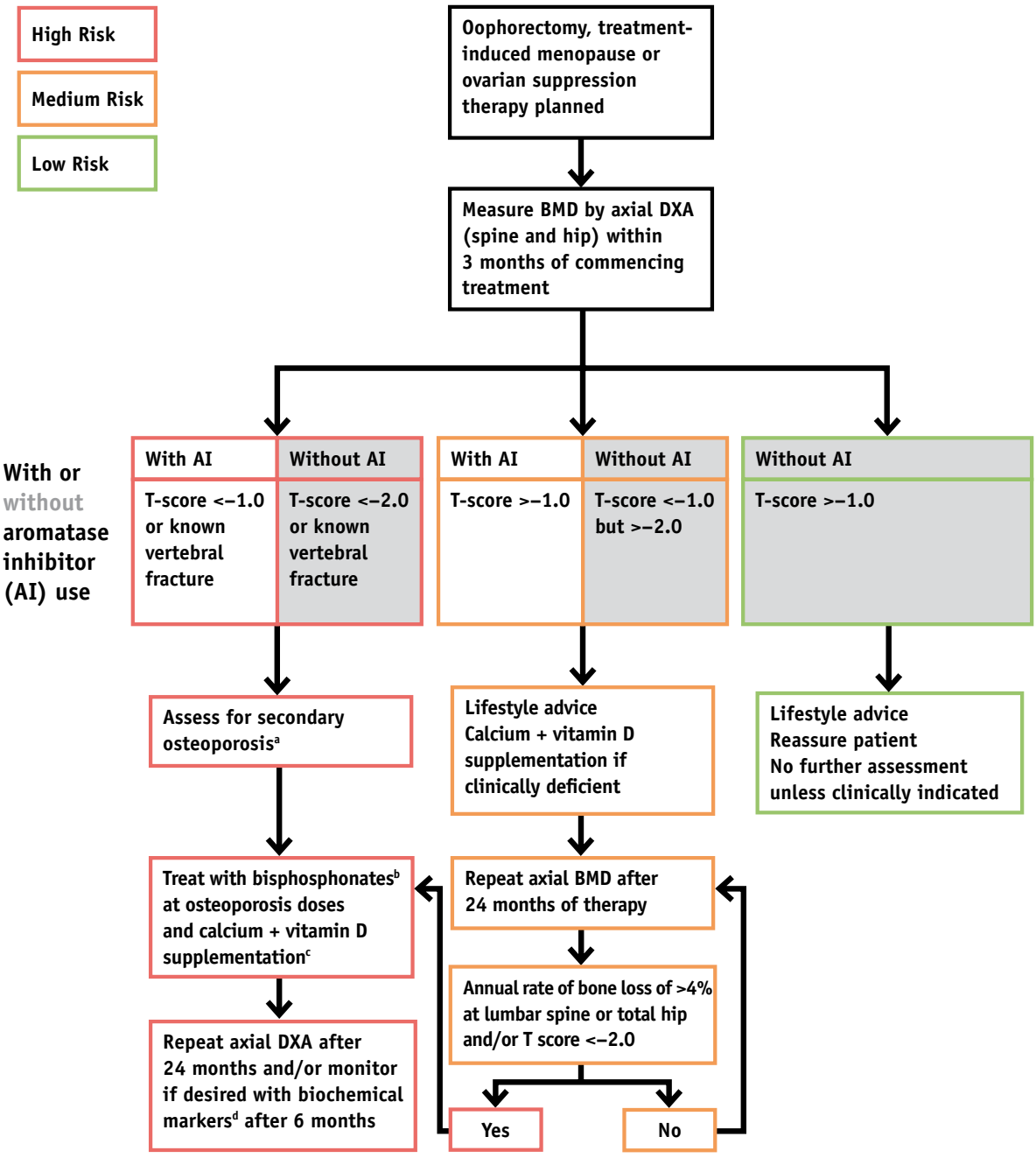
Low-Risk Group: For those patients with normal BMD (T-score of >–1), the risk of developing osteoporosis over a 5-year treatment and follow-up period is very low. Advice on lifestyle (diet, weight-bearing exercise, reduced alcohol consumption and cessation of smoking) is sufficient and no specific intervention or follow-up assessment of BMD is required.

For patients receiving a concomitant aromatase inhibitor, only two groups are defined:

High-Risk Group: Those patients with a T-score of <–1 should receive bone protection therapy with a bisphosphonate as described above.

Medium-Risk Group: Those patients with a T-score of >–1 should be monitored as indicated for all medium-risk groups.

Algorithm 1: Adjuvant treatment associated with ovarian suppression/failure with or without concomitant aromatase inhibitor use in women who experience premature menopause



a ESR, FBC, bone and liver function (calcium, phosphate, alkaline phosphatase, albumin, AST / γGT), serum creatinine, endomysial antibodies, serum thyroid-stimulating hormone

b Alendronate 70 mg per week, risedronate 35 mg per week, ibandronate (150 mg po monthly or 3 mg iv 3-monthly), zoledronic acid 4 mg iv 6-monthly

c To be given as ≥1 g of calcium + ≥800 IU of vitamin D

d Biochemical markers such as serum C-terminal telopeptide of type I collagen or urinary N-telopeptide of type I collagen

Algorithm 2: Postmenopausal women

The use of an aromatase inhibitor (steroidal or non-steroidal) is an indication for evaluation of BMD by DXA.

BMD assessments should be done at the lumbar spine and at one or both total hip sites. There is no requirement to obtain a DXA before starting treatment, but a baseline assessment should be obtained within 3 months of commencing an aromatase inhibitor.

Monitoring and treatment thereafter depends on the baseline BMD, age, and presence of any major risk factors for osteoporotic fracture. These are defined as:

- previous fragility fracture above the age of 50 years;
- parental history of fracture;
- a body mass index (BMI) of <22;
- alcohol consumption of 4 or more units per day;
- diseases known to increase fracture risk such as premature menopause, rheumatoid arthritis;
- ankylosing spondylitis, immobility, and Crohn's disease; and
- prior oral corticosteroid use for more than 6 months.

For women over the age of 75 years with one or more major risk factors, bone protection therapy with a bisphosphonate is recommended irrespective of baseline BMD.

For women aged under 75 years or without major risk factors, three groups of patients are defined based on baseline BMD:

High-Risk Group: Patients with a baseline T-score of <–2 at the lumbar spine or either hip site or whose BMD falls below this threshold should receive bisphosphonate therapy at osteoporosis doses in addition to lifestyle advice, calcium and vitamin D supplementation.

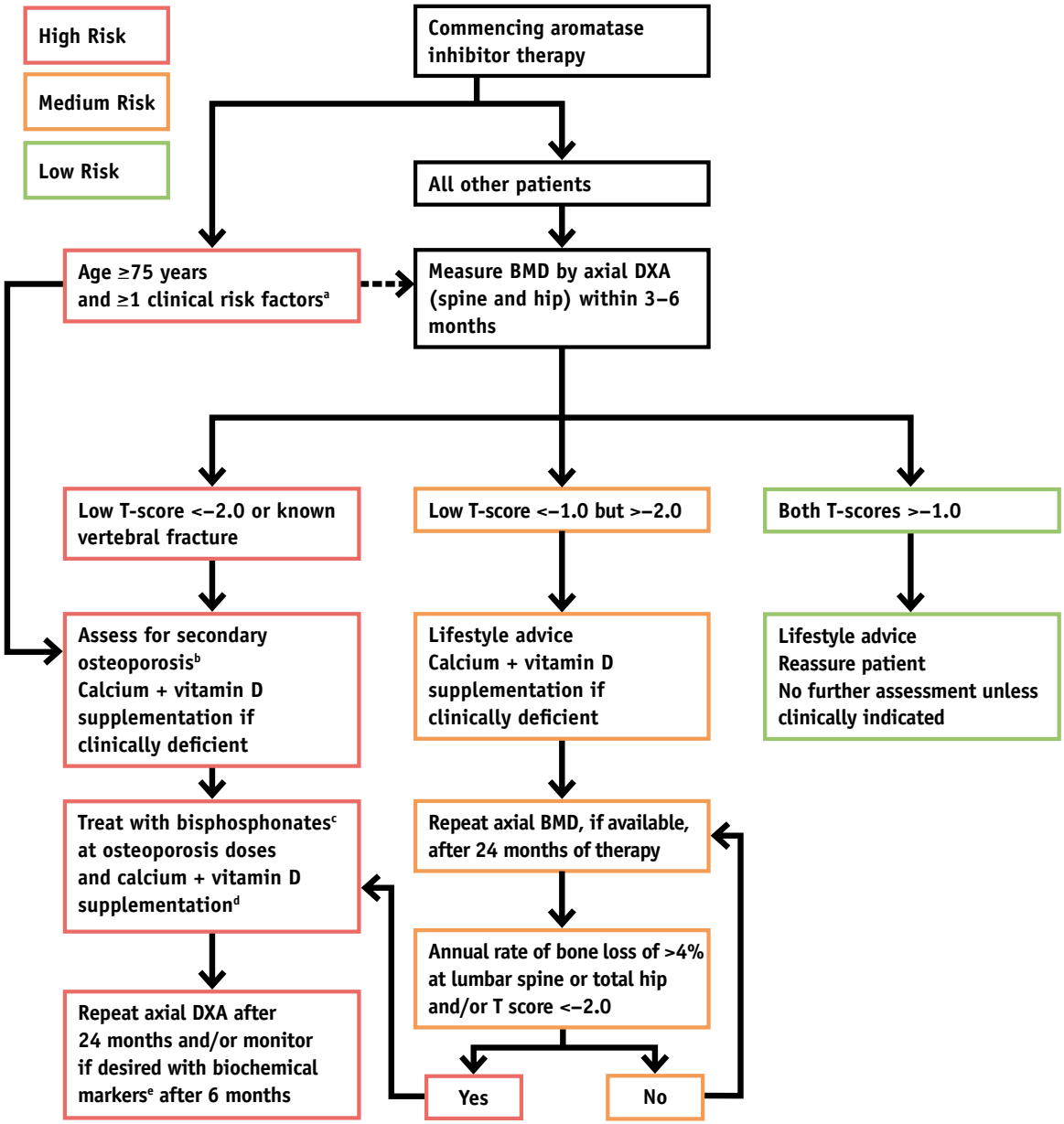
- The choice of bisphosphonate should be based on local protocols and funding arrangements. Weekly oral alendronate 70 mg or risedronate 35 mg, monthly oral ibandronate 150 mg, 3-monthly intravenous ibandronate 3 mg, or 6-monthly intravenous zoledronic acid 4 mg are all considered appropriate.
- Bisphosphonates are contraindicated in patients with a low glomerular filtration rate (<30 ml/min/1.73m^2) or hypocalcaemia. Such patients who require bone sparing therapy should be referred to the local bone service. Oral bisphosphonates must be used with caution in patients with oesophageal disease, although intravenous bisphosphonates will usually be appropriate in such patients.
- Follow-up of patients requiring bisphosphonate treatment should include a repeat DXA after 24 months and/or measurement of a bone resorption marker, if desired, as an aid to judging compliance and response. If there is bone loss associated with bisphosphonate therapy, first check that the compliance with instructions is correct, then re-evaluate for secondary osteoporosis. Poor compliance and secondary osteoporosis explain most cases of poor response. However, some patients may be true non-responders and a switch of therapy, for example to an intravenous bisphosphonate, or a referral to the local bone service should be considered in these patients.

Medium-Risk Group: For those patients with a T-score between –1 and –2, lifestyle advice plus calcium (1 g/day) and vitamin D (400–800 IU) supplementation are recommended unless dietary intake of calcium exceeds 1 g/day and serum 25-hydroxyvitamin D is known to be >20 µg/L.

- A follow-up DXA scan should be performed at 24 month intervals to exclude a clinically significant reduction in BMD (T-score of <–2 or >4% per annum decline in BMD at either the spine or hip [the forearm is not suitable for repeat assessments within such timeframes]).
- Patients who exceed these limits should commence bone protection therapy as described in the high-risk group.

Low-Risk Group: For those patients with normal BMD (T-score >–1), the risk of developing osteoporosis over a 5-year treatment period is very low. Advice on lifestyle (diet, weight-bearing exercise, reduced alcohol consumption and cessation of smoking) is sufficient and no specific intervention or follow-up assessment of BMD is required.

Algorithm 2: Postmenopausal adjuvant treatment with aromatase inhibitors



a Previous low-trauma fracture after age 50, parental history of hip fracture, alcohol intake of ≥4 units/day, diseases associated with secondary osteoporosis, prior corticosteroids for >6 months, low BMI (<22)

b ESR, FBC, bone and liver function (calcium, phosphate, alkaline phosphatase, albumin, AST / γGT), serum creatinine, endomysial antibodies, serum thyroid stimulating hormone

c Alendronate 70 mg per week, risedronate 35 mg per week, ibandronate (150 mg po monthly or 3 mg iv 3-monthly), zoledronic acid 4 mg iv 6-monthly

d To be given as ≥1 g of calcium + ≥800 IU of vitamin D

e Biochemical markers such as serum C-terminal telopeptide of type I collagen or urinary N-telopeptide of type I collagen

Audit recommendations

Recommendation	Criterion	Exceptions	Definitions
All postmenopausal women receiving aromatase inhibitor therapy for the treatment of breast cancer should have an assessment of skeletal risk	i. All postmenopausal women receiving aromatase inhibitor therapy for the treatment of breast cancer should have clinical risk factors for fracture assessed ii. All women in whom bone sparing therapy is not indicated on the basis of clinical risk alone should have axial bone densitometry undertaken using DXA	Patients who refuse assessment of skeletal status Patients in whom prognosis is so poor as to make bone sparing treatment unjustified Patients already receiving bone sparing therapy With regard to criterion (ii): patients who are unable to undergo DXA for technical reasons	Aromatase inhibitors include: anastrozole, letrozole and exemestane Bone sparing therapy includes: bisphosphonates; strontium ranelate Calcium and vitamin D supplementation by itself is NOT considered bone sparing therapy Technical reasons for not undertaking DXA include: body weight in excess of limit for scanner; deformity sufficient to make positioning impossible; presence of orthopaedic implants or other disease to make it impossible to obtain meaningful measurements
Bone sparing therapy should be offered to all postmenopausal women receiving aromatase inhibitors for the treatment of breast cancer in whom the fracture risk is deemed to warrant it	Bisphosphonate therapy should be offered according to this guideline	Women who refuse to take bone sparing therapy Women in whom bisphosphonates (by any route) are contraindicated	Need for bone sparing therapy should be judged according to the algorithm with this guideline Bisphosphonates are contraindicated in patients with hypocalcaemia, renal impairment (GFR <30ml/min/1.73m²), and sensitivity to bisphosphonates Oral bisphosphonates should be used with caution, if at all, in patients with oesophageal disease. However, in the absence of other contraindications intravenous therapy can be used in such circumstances
All patients receiving bone sparing therapy should receive supplemental calcium and vitamin D unless the prescribing physician is sure of adequate calcium and vitamin D status	Evidence of prescription/ recommendation for calcium and vitamin D supplementation or documented assessment of calcium and vitamin D status	Women with hypercalcaemia or sarcoidosis Women with a history of renal stones	Minimum doses: calcium 500 mg elemental calcium and vitamin D 10 µg (400 international units) daily

External review

The derived treatment algorithms and subsequently the full guidance document were reviewed and endorsed by the National Cancer Research Institute Breast Cancer Group and the National Osteoporosis Society.

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Conflicts of Interest

The authors list the following conflicts of interest.

David Reid has received research funding from and/or acts in an advisory capacity to Procter & Gamble, Roche, Novartis and Merck.

Julie Doughty has received research funding from AstraZeneca and has acted in an advisory capacity to AstraZeneca, Novartis, Pfizer and Roche.

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Anthony Howell has received honoraria for speaking engagements and advising boards from AstraZeneca, Novartis and Pfizer, and has received research funds from AstraZeneca.

Eugene McCloskey has received research funding from and/or acts in an advisory capacity to Procter & Gamble, Roche, Novartis, AstraZeneca, Pfizer, Merck, Amgen, Eli Lilly and Bayer Schering Pharma.

Trevor Powles acts as a consultant to the advisory boards of Eli Lilly and Pfizer.

Peter Selby has received research funding from Novartis and acts in an advisory capacity to the Alliance for Better Bone Health, Roche and Servier.

Robert Coleman has received research funding from and/or acts in an advisory capacity to AstraZeneca, Novartis, Pfizer and Roche.

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APPENDIX I: EVIDENCE TABLES

The level of evidence was assessed according to the grades defined below.

1	Well-conducted meta-analyses, systematic reviews, or randomised controlled trials with a low risk of bias	**2–**	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
1–	Meta-analyses, systematic reviews, or randomised controlled trials with a high risk of bias	**3**	Non-analytic studies, e.g. case reports, case series
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationships are causal	**4**	Expert opinion

Effects of gonadotrophin-releasing hormone agonists on bone

AUTHORS	REFERENCE	LEVEL OF EVIDENCE	STUDY DESIGN	PATIENT CHARACTERISTICS	NUMBER OF PATIENTS	AGE	KEY FINDINGS	COMMENTS
Fogelman I *et al*	*Osteoporos Int* 2003; **14**:1001–6.	1–	Open-label, 2-year randomised controlled trial with a 1-year extended follow-up	Premenopausal women with node-positive early breast cancer	Goserelin (n=53) Cyclophosphamide, methotrexate + 5-fluorouracil (CMF) (n=43)	Mean age 43 yrs	• Mean BMD losses during goserelin vs CMF: lumbar spine BMD 10.5% vs 6.5% (p=0.0005); femoral neck BMD 6.4% vs 4.5% (p=0.04) • Off treatment, partial recovery of BMD after stopping goserelin but not CMF • Ovarian suppression resulting in amenorrhoea was closely related to BMD loss in both treatment groups	• A planned subprotocol of the ZEBRA study (Zoladex Early Breast Cancer Research Association)
Sverrisdottir A *et al*	*J Clin Oncol* 2004; **22**:3694–9.	1–	Randomised controlled trial with 2-year treatment phase and 1-year follow-up	Premenopausal women with node-positive or node-negative early breast cancer	Goserelin (n=13) Goserelin + tamoxifen (n=14) Tamoxifen (n=18) No endocrine therapy (n=21)	Mean age (yrs) 46 44 46 46	• Goserelin alone decreased total body bone density (TBBD) by 5.0% • Tamoxifen alone decreased TBBD by 1.5% • Goserelin and tamoxifen decreased TBBD by 1.4% • 1 year after cessation of treatment, the goserelin alone group showed a 1.5% increase from the 2-year time point	• A planned subprotocol of the Zoladex in Premenopausal Patients (ZIPP) study • 64–76% of the patients were oestrogen receptor-positive
Gnant MF *et al*	*J Clin Oncol* 2007; **25**: 820–8.	1–	3-year open-label randomised controlled trial	Premenopausal women with node-positive or node-negative early breast cancer	All patients received goserelin plus one of: Tamoxifen alone (n=103) Tamoxifen + zoledronic acid (n=100) Anastrozole alone (n=94) Anastrozole + zoledronic acid (n=104)	Median age (yrs) 47 44 46 45	• Lumbar Spine BMD: ◦ Goserelin + tamoxifen associated with 11.6% decrease ◦ Goserelin + anastrozole associated with 17.3% decrease • Trochanter BMD: ◦ Goserelin + tamoxifen associated with 5.1% decrease ◦ Goserelin + anastrozole associated with 11.3% decrease • BMD remained stable in zoledronic acid-treated patients (p<0.001)	• There was a high dropout rate in all groups, which meant that low numbers of BMD measurements were taken after 3 years (the reasons for this are not clear)

Effects of ovarian suppression as a result of chemotherapy on bone

AUTHORS	REFERENCE	LEVEL OF EVIDENCE	STUDY DESIGN	PATIENT CHARACTERISTICS	NUMBER OF PATIENTS	AGE	KEY FINDINGS	COMMENTS
Delmas PD *et al*	*J Clin Oncol* 1997; **15**:955–62.	1–	Randomised controlled trial	Women with breast cancer and artificially induced menopause	Women were stratified according to prior tamoxifen use (n=53): Pre-treated with tamoxifen (n=36) Risedronate (n=27) Placebo (n=26)	Mean age (yrs) 46 46 47	• BMD was maintained at the lumbar spine and hip sites in the risedronate group, compared with losses in the placebo group • At 2 years mean differences between groups at the lumbar spine and femoral neck were 2.5% and 2.6%, respectively • Bone resorption and formation fell in the risedronate group compared with the placebo group	• Non-standard risedronate regime used 30 mg/d for 2 weeks every 3 months for 2 years; BMD fell in the third year when treatment or placebo stopped

Headley JA *et al*	*Cancer Invest* 1998; **16**:6–11.	2–	Cohort of breast cancer patients	Breast cancer patients previously treated with adjuvant chemotherapy	Received adjuvant chemotherapy (n=27) Became amenorrhoeic (n=16)	Premenopausal: mean age 39 yrs Postmenopausal: mean age 47 yrs	• Women who became permanently amenorrhoeic as a result of chemotherapy had BMD 14% lower than women who maintained menses after chemotherapy • Chemotherapy-treated women who maintained ovarian function had normal BMD	• No data on controls shown, reductions in BMD derived from scanner normative data
Howell SJ *et al*	*Clin Endocrinol* 1998; **49**:397–402.	2–	Retrospective cohort study of patients treated for haematological malignancies or sarcoma	Women with ovarian failure following treatment with cytotoxic chemotherapy	Received combination chemotherapy (n=33) for: Hodgkin's disease (n=27) Non-Hodgkin's lymphoma (n=4) Sarcoma (n=1) Acute myeloid leukaemia (n=1)	Mean age 38 yrs	• Duration of amenorrhoea was 49 months • No significant differences in total cohort compared with normative reference data • Trend to lower values in chemotherapy patients when those taking HRT were excluded – only significant at proximal radius	• Patient data only compared with reference database – variety of scanners used
Kreuser ED *et al*	*Ann Oncol* 1992; **3**:S105–10.	2–	Cohort study	Men and women treated with chemotherapy (cyclophosphamide, vincristine, procarbazine, and prednisone [COPP]/doxorubicin, bleomycin, vinblastine, dacarbazine [ABVD] regimen +/– irradiation) for Hodgkin's disease 2–10 years earlier	Hodgkin's disease patients (n=49) Men (n=27) Women (n=22)	Median age 39 yrs; age at diagnosis 35 yrs	• Follicle-stimulating hormone (FSH) was elevated in 80% of men but testosterone levels and BMD were normal • FSH was elevated in 77% of women and spinal quantitative computed tomography (QCT) measurements of BMD were significantly lower in women with premature menopause compared with age-matched controls	• Age-matching not clear in paper
Ratcliffe MA *et al*	*Hematol Oncol* 1992; **10**:181–7.	2+	Case-control study	Women with chemotherapy-induced menopause treated for lymphoma	Post-treatment non-menopausal (n=26) Post-treatment menopausal (n=24) Post-treatment >18 months since menopause (n=16) Young controls (n=18) Older controls (n=60)	Mean age (yrs) 27 39 40 26 39	• BMD (lumbar and trochanter) was normal in post-treatment premenopausal patients compared with controls • BMD was significantly lower in post-treatment menopausal patients than in matched controls	• Matched controls used
Saarto T *et al*	*J Clin Oncol* 1997; **15**:1341–7.	1–	Prospective randomised clinical trial of oral clodronate 1600 mg daily for 3 years started with adjuvant chemotherapy	Premenopausal breast cancer patients without skeletal metastases	Clodronate (n=67) Controls (n=81)	Mean age (yrs) 43 44	Of 113 premenopausal patients: • 38% developed amenorrhoea in the first year after chemotherapy; 36% had irregular menstruation • 22% preserved regular menstruation – likelihood of loss of regular menstruation rose with age • At 2 years overall bone loss abrogated with clodronate at lumbar spine (–5.9% vs –2.2%) and femoral neck (–2.0% vs +0.9%) • Amenorrhoea group lost bone although significantly less if receiving clodronate at lumbar spine (9.5% vs 5.9%) and femoral neck (4.6% vs 0.4%)	• Randomisation method unclear • Unequal numbers in clodronate and control groups
Shapiro CL *et al*	*Breast Cancer Res Treat* 2005;**90**:41–6.	2+	Prospective cohort study to determine the baseline predictors of ovarian failure in premenopausal women with breast cancer	Premenopausal women receiving adjuvant chemotherapy	Patients (n=49) Developed ovarian failure (n=35) Maintained ovarian status (n=14)	Median age (yrs) 42 44 38	• At 6 months significant predictors of ovarian failure at baseline were age and alcohol intake in the past year	
Greenspan S *et al*	*J Clin Endocrinol Metab* 2007;**92**:131–6.	1	Randomised, double-blind, placebo-controlled trial of risedronate (35 mg weekly) in chemotherapy patients 3.2–3.4 years postmenopause	Postmenopausal women having received chemotherapy with or without tamoxifen or aromatase inhibitors	Risedronate (n=43) Placebo (n=44)	Mean age (yrs) 50 49	After 12 months: • Risedronate: +1.2% at lumbar spine; + 1.3% at total hip • Placebo: –0.9% at lumbar spine; –0.8% at total hip ($p<0.01$ for both) • Significant reduction in urinary N-telopeptide crosslinked type 1 collagen (NTX) and N-terminal propeptide of type 1 procollagen (P1NP) in risedronate group only	• Good retention (95%) • Permuted block randomisation

Effects of surgical oophorectomy on bone

AUTHORS	REFERENCE	LEVEL OF EVIDENCE	STUDY DESIGN	PATIENT CHARACTERISTICS	NUMBER OF PATIENTS	AGE	KEY FINDINGS	COMMENTS
Svanberg	*Acta Obstet Gynecol Scand* 1981; **106**:11–5.	2–	Retrospective case-control study	Women oophorectomised between the ages of 15 and 30 years because of advanced salpingitis	146 premenopausal women (age-matched controls)	Mean age 25 yrs	• Data for 57 women was available for analysis with respect to fractures and this was compared to 43 control patients • Complete oophorectomy was found to be followed by an increased incidence of fractures: ◦ increased total fractures (23/57 vs 10/43) ◦ increased hip fractures (8/57 vs 3/43) ◦ increased radial fractures (15/57 vs 3/43)	
Melton *et al*	*J Clin Epidemiol* 1996; **49**:1111–5.	2+	Retrospective cohort study	Premenopausal women who underwent bilateral oophorectomy for benign ovarian conditions in 1950–1979	Patients (n=463)	Median age 43.8 yrs	• Increased risk of distal forearm fracture (standardised morbidity ratio [SMR] 1.4; 95% CI 1.0–2.0) • Increased risk of vertebral fractures (SMR 1.9; 95% CI 1.3–2.8) • No increased risk of hip fracture (SMR 1.1; 95% CI 0.6–1.9)	• 60% of the women had taken HRT at some time, with 80% having taken it during the first year after oophorectomy • Women who had become oestrogen deficient at a younger age were more likely to develop a fracture but were also more likely to have been taking HRT for longer periods of time

Effects of HRT on bone after surgical oophorectomy

AUTHORS	REFERENCE	LEVEL OF EVIDENCE	STUDY DESIGN	PATIENT CHARACTERISTICS	NUMBER OF PATIENTS	AGE	KEY FINDINGS	COMMENTS
Yasuda M *et al*	*Int J Gynaecol Obstet* 1994;**47**:151–6.	2–	Case-control	Premenopausal women	HRT positive (n=39) HRT negative (n=15) Premenopausal control group (n=36)	Mean age (yrs) 41 42 39	• BMD decreased significantly in the HRT negative patients • No decrease in BMD was seen in the control or HRT positive patients • Osteocalcin and alkaline phosphatase were lower in the HRT positive group compared with the HRT negative group • Low-density lipoprotein cholesterol was lower in the HRT positive group compared with the HRT negative group	• HRT positive patients had had an oophorectomy and taken HRT for more than 6 months • HRT negative patients had had an oophorectomy but had not taken HRT • Control patients were premenopausal patients who had not had an oophorectomy and had no significant differences in baseline characteristics including BMD
Kurabayashi T *et al*	*Int J Gynaecol Obstet* 1998;**60**:271–7.	2–	Case-control	Premenopausal women ovariectomised for gynaecological malignancies	HRT positive (n=59) HRT negative (n=11)	Mean age (yrs) 40 47	• In the HRT negative group BMD of the lumbar vertebrae decreased significantly. Pre-operative BMD was 91.8%, 91.0%, 91.3% at 1, 2 and 3 years postovariectomy, respectively. • In the HRT positive group no decrease in BMD was seen. Pre-operative BMD was 98.4 %, 99.0%, 99.4%, 98.8%, 98.7% at 1, 2, 3, 4 and 5 years postovariectomy, respectively	• Nonrandomised study; basis for allocation into study groups unclear • Duration of HRT from 1 to 5 years • Mean age in the HRT positive group was 40 years versus 47 years in the HRT negative group
Hee P *et al*	*Acta Obstet Gynecol Scand* 1999;**78**:534–9.	3	Case series	Perimenopausal women having had hysterectomy and bilateral salpingo-oophorectomy for benign disease	Patients (n=88) Included in statistics (n=79)	Mean age (yrs) 40–55	• 89% of patients were still taking HRT at 1–3 years	• Patients concerned about breast cancer risk and weight gain
Castelo-Branco C *et al*	*Menopause* 1999; **6**:307–11.	1– and 2–	Randomised controlled trial part and case-control part	Surgical postmenopausal women	Total (n=165) Equine oestrogens (n=55) Oestradiol (n=55) Controls (n=55)	Mean age (yrs) 47 (oestrogens) 46 47 47	• HRT (both groups) resulted in no change from baseline in BMD at years 1, 3 and 5 • Controls showed a decrease from baseline at 1, 3 and 5 years	• Controls were a nonrandomised group after oophorectomy that did not want HRT • Only one third of patients continued HRT after 5 years. The main reason for discontinuation was fear of cancer • HRT patients showed a decrease in BMD at one or more bone density assessments
Kanaoka Y *et al*	*Gynecol Obstet Invest* 2003;**55**:168–72.	3	Case series	Oophorectomised adolescent girls	HRT (n=2)	Age 12 yrs	• Decreased BMD after 3 years • But after 5 years of HRT bone density was normal for their age	• Case report of two girls aged 12

Effects of tamoxifen on bone

AUTHORS	REFERENCE	LEVEL OF EVIDENCE	STUDY DESIGN	PATIENT CHARACTERISTICS	NUMBER OF PATIENTS	AGE	KEY FINDINGS	COMMENTS
Cuzick J *et al*	*Lancet* 2002; **360**:817–24.	1	Randomised, double-blind, placebo-controlled trial of tamoxifen, 20 mg/day for 5 years	Women who were at increased risk of breast cancer	Patients (n=7152)	35–70 yrs	• After median follow-up of 50 months: ◦ 69 breast cancers had been diagnosed in 3578 women in the tamoxifen group and 101 in 3566 in the placebo group (risk reduction 32%; p=0.013) ◦ Endometrial cancer was nonsignificantly increased (11 vs 5 events) and thromboembolic events were significantly increased with tamoxifen (43 vs 17; odds ratio 2.5; p=0.001), particularly after surgery ◦ There was a significant excess of deaths from all causes in the tamoxifen group (25 vs 11 events; p=0.028)	
The Breast International (BIG) 1-98 Collaborative Group	*N Engl J Med* 2005; **353**:2747–57.	1–	Randomised, double-blind phase 3 trial	Postmenopausal women with hormone receptor-positive breast cancer	Patients (n=8010) Letrozole (n=4003) Tamoxifen (n=4007)	Median age (yrs) 61 61 61	• Letrozole reduced the risk of recurrent disease compared with tamoxifen, particularly at distant sites	• Academic-led registration study
Fisher B *et al*	*J Natl Cancer Inst* 1998; **90**:1371–88.	1	Randomised, placebo-controlled trial of tamoxifen 20 mg/day for 5 years, for the prevention of breast cancer	Women at increased risk for breast cancer	Patients (n=13388) Tamoxifen (n=6681) Placebo (n=6707)		• Tamoxifen reduced the risk of invasive breast cancer by 49% (p<0.00001) • Tamoxifen reduced the risk of noninvasive breast cancer by 50% (p<0.002) • Tamoxifen reduced the occurrence of oestrogen receptor-positive tumors by 69%, but no difference in the occurrence of oestrogen receptor-negative tumour was seen • A reduction in hip, radius, and spine fractures was observed with tamoxifen	• The National Surgical Adjuvant Breast and Bowel Project initiated the Breast Cancer Prevention Trial (P-1) in 1992 • Women were at increased risk for breast cancer because they: ◦ were 60 years of age or older; ◦ were 35–59 years of age with a 5-year predicted risk for breast cancer of at least 1.66%; or ◦ had a history of lobular carcinoma in situ
Gnant MF *et al*	*J Clin Oncol* 2007; **25**:820–8.	1–	Randomised, open-label, phase 3 trial	Premenopausal women with hormone-responsive breast cancer	Patients (n=401) Tamoxifen alone (n=103) Tamoxifen + zoledronic acid (n=100) Anastrozole alone (n=94) Anastrozole + zoledronic acid (n=104)	Median age (yrs) 47 44 46 45	• Endocrine treatment without zoledronic acid led to significant overall bone loss after 3 years of treatment (BMD: –14.4%; mean T-score reduction: –1.4) • Zoledronic acid 4 mg every 6 months effectively inhibited the bone loss associated with endocrine therapy	• Bone subprotocol within evaluation of luteinizing hormone-releasing hormone (LHRH) agonist + tamoxifen or anastrozole +/– bone protection in premenopausal women
Powles TJ *et al*	*J Clin Oncol* 1996; **14**:78–84.	1–	Placebo-controlled trial of tamoxifen for the prevention of breast cancer	Premenopausal and postmenopausal healthy women	Data for this analysis was available for 179 women	Not mentioned in study	• In premenopausal women, BMD decreased progressively in the lumbar spine (p<0.001) and in the hip (p<0.05) for women on tamoxifen, but not for those on placebo • The mean annual loss in lumbar BMD per year over the 3-year study period in tamoxifen-treated compliant women who remained premenopausal throughout the study period was 1.44% compared with a small gain of 0.24% per annum for women on placebo (p<0.001) • The mean annual increase in BMD for women on tamoxifen was 1.17% in the spine (p<0.005) and 1.71% in the hip (p<0.001) compared with a nonsignificant loss for women on placebo	
Vehmanen L *et al*	*J Clin Oncol* 2006; **24**:675–80.	2	A prospective study of the effect of adjuvant chemotherapy followed by tamoxifen on BMD	Premenopausal women with early breast cancer	Patients (n=111)	Not mentioned in study	• Tamoxifen treatment and menopausal status correlated significantly with the changes in lumbar spine BMD (p<0.0001) • At 3 years of follow-up, menstruating patients on tamoxifen had lost a significant 4.6% of their baseline BMD values, while a modest gain of 0.6% was noted in the control group • In contrast, bone loss was reduced among tamoxifen-treated women as compared with controls in patients who developed chemotherapy-induced early menopause; the lumbar spine BMD values decreased 6.8% in tamoxifen users and 9.5% in the controls, respectively	• Patients with hormone receptor-positive tumors received tamoxifen 6 months after the beginning of the chemotherapy (tamoxifen group), while those with hormone receptor-negative tumors received no further therapy (control group)

Effects of aromatase inhibitors on bone

AUTHORS	REFERENCE	LEVEL OF EVIDENCE	STUDY DESIGN	PATIENT CHARACTERISTICS	NUMBER OF PATIENTS	AGE	KEY FINDINGS	COMMENTS
Howell A *et al* on behalf of the ATAC Trialists' Group	*Lancet* 2005; **365**:60–2.	1–	Double-blind randomised trial	Postmenopausal women with localised breast cancer	Patients (n=9366)	Median age 64 yrs	• Anastrozole significantly prolonged: ◦ disease-free survival (575 events with anastrozole vs 651 with tamoxifen); and ◦ time-to-recurrence (402 vs 498) • Anastrozole significantly reduced: ◦ distant metastases (324 vs 375); and ◦ contralateral breast cancers (35 vs 59 [42% reduction]) • Fracture incidence was 11% with anastrozole; 7% with tamoxifen	• Academic-led registration study
The Breast International (BIG) 1-98 Collaborative Group	*N Engl J Med* 2005; **353**:2747–57.	1–	Randomised, double-blind, phase 3 trial	Postmenopausal women with hormone receptor-positive breast cancer	Patients (n=8010) Letrozole (n=4003) Tamoxifen (n=4007)	Median age 61 yrs	• Letrozole reduced the risk of recurrent disease compared with tamoxifen, particularly at distant sites	• Academic-led registration study
Coombes RC *et al*	*Lancet* 2007; **369**:559–70. Erratum in: *Lancet* 2007;**369**:906	1-	International, phase 3 randomised controlled trial	Postmenopausal patients with unilateral invasive, oestrogen receptor-positive or oestrogen receptor unknown breast cancer who were disease-free after 2–3 years of tamoxifen therapy	Patients (n=4724) Exemestane (n=2352) Tamoxifen (n=2372)	<60 yrs: (n=1523) 60–69 yrs: (n=2021) ≥70 yrs: (n=1180) <60 yrs: (n=763) 60–69 yrs: (n=1005) ≥70 yrs: (n=584) <60 yrs: (n=760) 60–69 yrs: (n=1016) ≥70 yrs: (n=596)	• Patients who switched to exemestane after 2–3 years on tamoxifen showed early improvements in disease-free survival that persisted after treatment and resulted in a modest improvement in overall survival	• Academic-led registration study
Jakesz R *et al*	*Lancet* 2005; **366**:455–62.	1–	Combined analysis of data from two prospective, multicentre, randomised, open-label trials	Postmenopausal women with hormone sensitive early breast cancer who had completed 2 years of adjuvant oral tamoxifen therapy	Patients (n=3224) Tamoxifen (n=1606) Anastrozole (n=1618)	Median age (yrs): 62 62	• At 28 months there was a 40% decrease in the risk for an event (defined as local or distant metastasis, or contralateral breast cancer) in the anastrozole group as compared with the tamoxifen group (67 events with anastrozole vs 110 with tamoxifen)	• Academic-led registration study
Goss P *et al*	*N Engl J Med* 2003; **349**:1793–802.	1–	Randomised, double-blind, placebo-controlled phase 3 trial	Postmenopausal women with primary breast cancer who had completed approximately 5 years of adjuvant tamoxifen therapy	Patients (n=5157) Letrozole (n=2575) Placebo (n=2582)	Median age (yrs): 62 62	• After the completion of standard tamoxifen treatment, letrozole significantly improved disease-free survival • Diagnoses of osteoporosis was as follows: Letrozole: 5.8% Placebo: 4.5% • The rates of fracture were slightly higher in the letrozole group than in the placebo group	• Academic-led registration study
Winer E *et al* ASCO Technology Assessment	*J Clin Oncol* 2005; **23**:619–29.	2	Assessment of four phase 3 randomised, adjuvant trials: ATAC: double-blind ITA: open-label IES: double-blind MA-17: double-blind	Postmenopausal woman with hormone receptor-positive breast cancer	ATAC (n=9366) ITA (n=426) IES (n=4742) MA-17 (n=5187)	Not mentioned in study	• Panel recommends that adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer should include an aromatase inhibitor as initial therapy or after treatment with tamoxifen	• Practice guidance document
Cummings SR *et al* For the Study of Osteoporotic Fractures Research Group	*N Engl J Med* 1998; **339**:733–8.	2+	Prospective cohort study	Postmenopausal women	Hip Fracture: With fracture (n=133) Control (n=343) Vertebral Fracture: With fracture (n=138) Control (n=264)	Mean age (yrs) 75 72 73 72	• There is an increased risk of hip and vertebral fracture in postmenopausal women with undetectable serum oestradiol concentrations and high serum concentrations of sex hormone-binding globulin	• Established importance of residual postmenopausal oestrogen levels on bone health
Eastell R *et al* on behalf of the ATAC Trialists' Group	*J Bone Miner Res* 2006; **21**:1215–23.	1–	Bone sub-protocol of the ATAC trial (2-year data)	Postmenopausal women with invasive primary breast cancer	Patients (n=308) Anastrozole (n=81) Tamoxifen (n=86) Combination (n=80) Nonrandomised controls (n=39)	Median age (yrs) 65 64 64 65	• Adjuvant anastrozole treatment results in significant BMD loss and an increase in bone turnover • Tamoxifen (and the combination) results in increased BMD and decreased bone turnover	• Detailed substudy evaluating BMD and bone biomarkers
Eastell R *et al*	*J Clin Oncol* 2008; **26**:1051–7.	1–	Bone subprotocol of the ATAC trial (5-year data)	Postmenopausal women with invasive primary breast cancer	Patients (n=167) Anastrozole (n=81) Tamoxifen (n=86)		• In the anastrozole group, significant bone loss was seen throughout the 5 years • The rate of bone loss appeared to slow in years 2–5 at the spine. • No patient with normal BMD at baseline became osteoporotic	• Update of Eastell 2006 2-year data

Harper-Wynne C *et al*	*Cancer Epidemiol Biomakers Prev* 2002; **11**:614–21.	2–	Pilot volunteer study	Postmenopausal women	Patients (n=32)	Age of volunteers not available	• Mean C-terminal telopeptide of type 1 collagen (CTX) increases (from 2300 to 2828 pmol/l after 3 months) indicated a significant ($p<0.05$) effect of letrozole on bone resorption • There was no significant effect of letrozole on normal epithelial cell proliferation; mean (percent) Ki67 values were 1.48 and 1.64 pre- and post-treatment, respectively	• Detailed evaluation of biomarkers
Martinetti A	*Anticancer Research*, 2003;**23**:3485–91.	2+	Randomised, double-blind trial comparing exemestane with megestrol acetate	Patients with metastatic breast cancer	Patients (n=769)	Ages not available	• Anti-aromatase therapy was associated with increased osteoclast activity, suggesting the existence of possible differential effects of different hormonal therapies on bone remodelling markers regardless of the oestrogen suppression induced by exemestane	
Lonning P *et al*	*J Clin Oncol* 2005; **23**:5126–37.	1–	Randomised, double-blind, placebo-controlled trial	Postmenopausal women with early breast cancer	Patients (n=147) Exemestane (n=73) Placebo (n=74)	Median age (yrs) 60 59	• Exemestane modestly enhanced bone loss from the femoral neck without significant influence on lumbar spine bone loss • The mean annual rate of BMD loss was 2.17% vs 1.84% in the lumbar spine (not significant) and 2.72% vs 1.48% in the femoral neck ($p=0.024$) in the exemestane and placebo arms, respectively	• Unique placebo-controlled study in early breast cancer designed to evaluate bone biomarkers
Lonning P *et al*	*J Clin Oncol* 2006; **24**(18S), Abstract 554	1–	Randomised, double-blind, placebo-controlled trial	Postmenopausal women with early breast cancer	Patients (n=147) Exemestane (n=73) Placebo (n=74)	Median age (yrs) 60 59	• The mean levels of vitamin D were 22.6 ng/ml in the placebo group and 21.6 ng/ml in the exemestane group, with no significant between-group difference • Low serum calcium levels at baseline were significantly correlated to low BMD in the femoral neck in the exemestane group • Individual levels of vitamin D, parathormone and oestradiol at baseline were not correlated to BMD	• Update of Lonning 2005 publication
Coleman RE *et al*	*Lancet Oncol* 2007; **8**:119–27.	1–	Randomised controlled study	Postmenopausal women with historically confirmed and completely resected unilateral breast cancer	(n=206) Exemestane (n=101) Tamoxifen (n=105)	Age of substudy participants not available	• Within 6 months of switching to exemestane, BMD was lowered by: ◦ 2.7% at the lumbar spine ($p<0.0001$) ◦ 1.4% at the hip compared with baseline ($p<0.0001$) • BMD decreases were only 1.0% and 0.8% in year 2 at the lumbar spine ($p=0.002$) and hip ($p=0.003$), respectively • No patient with normal BMD at baseline became osteoporotic	• Bone subprotocol of IES study evaluating "switch" strategy
Gnant MF *et al*	*J Clin Oncol* 2007; **25**:820–8.	1–	Randomised, open-label, phase 3 trial	Premenopausal women with hormone-responsive breast cancer	Patients (n=401) Tamoxifen alone (n=103) Tamoxifen + zoledronic acid (n=100) Anastrozole alone (n=94) Anastrozole + zoledronic acid (n=104)	Median age (yrs) 47 44 46 45	• Endocrine treatment without zoledronic acid led to significant overall bone loss after 3 years of treatment (BMD: –14.4%; mean T-score reduction: –1.4) • Zoledronic acid 4 mg every 6 months effectively inhibited the bone loss associated with endocrine therapy	• Bone subprotocol within evaluation of luteinizing hormone-releasing hormone (LHRH) agonist + tamoxifen or anastrozole +/- bone protection in premenopausal women
Brufsky A *et al*	*J Clin Oncol* 2007; **25**:829–36.	1–	Randomised, open-label, multicentre study	Postmenopausal women with early breast cancer	Patients (n=602) Upfront (n=301) Delayed (n=301)	Median age (yrs) 60 60	• Upfront zoledronic acid therapy prevented bone loss in the lumbar spine in postmenopausal women receiving adjuvant letrozole for early-stage breast cancer • At month 12, lumbar spine BMD was 4.4% higher in the upfront group than in the delayed group ($p<0.0001$)	• Prospective evaluation of immediate versus delayed bone protection in postmenopausal women
Bundred N *et al*	*Cancer* 2008; **112**:1001–10.	1–	Randomised, multicentre study; patients were randomised to either begin receiving zoledronic acid at the same time as the letrozole regimen or to delay the start of zoledronic acid		1066 postmenopausal women with early breast cancer	Median age 58 yrs	• At 12 months, the delayed group had lost an average of 3.5% BMD at the lumbar spine and 2% at the hip, compared with a slight increase in BMD at those sites in the immediate treatment group ($p<0.0001$) • Among postmenopausal women, the average total BMD loss in the delayed group was 6%, with virtually no change in the immediate treatment group ($p<0.0001$)	• European companion study to Brufsky *et al* 2007 • The delay group were started on zoledronic acid: 1) when their BMD T score decreased to more than 2 SD below normal; 2) if they had a nontraumatic fracture; 3) if they were found to have an asymptomatic fracture when they were assessed at 36 months after starting letrozole
Hillner B *et al*	*J Clin Oncol* 2003; **21**:4042–57.	4	ASCO guidelines update	Women with breast cancer	n/a	n/a	• For patients with plain radiographic evidence of bone destruction, intravenous pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks is recommended • There is insufficient evidence supporting the efficacy of one bisphosphonate over the other • Starting bisphosphonates in women who demonstrate bone destruction through imaging but who have normal plain radiographs is considered reasonable treatment • Starting bisphosphonates in women with only an abnormal bone scan but without evidence of bone destruction is not recommended • The presence or absence of bone pain should not be a factor in initiating bisphosphonates	• Practice guidance

Trial names

ATAC: Arimidex, Tamoxifen Alone or in Combination. **IES**: Intergroup Exemestane Study. **ITA**: Italian Tamoxifen versus Anastrozole. **MA-17**: study of extended adjuvant therapy with letrozole after 5 years of standard tamoxifen therapy