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Managing Osteoporosis Patients after Long-Term Bisphosphonate Treatment:

Report of a Task Force of the American Society for Bone and Mineral Research

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Abstract

Bisphosphonates (BPs) are the most commonly used medications for osteoporosis, but optimal duration of therapy is unknown. This ASBMR report provides guidance on BP therapy duration with a risk benefit perspective.

Two trials provided evidence for long-term BP use. In the Fracture Intervention Trial Long-term Extension (FLEX), postmenopausal women receiving alendronate for 10 years had fewer clinical vertebral fractures than those switched to placebo after 5 years. In the HORIZON extension, women who received 6 annual infusions of zoledronic acid had fewer morphometric vertebral fractures compared with those switched to placebo after 3 years. Low hip T-score between −2 and −2.5 in FLEX and below −2.5 in HORIZON extension predicted a beneficial response to continued therapy. Hence, the Task Force suggests that after 5 years of oral BP or 3 years of intravenous BP, women should be reassessed. Women with previous major osteoporotic fracture, those who fracture on therapy, or others at high risk should generally continue therapy for up to 10 years (oral) or 6 years (intravenous), with periodic risk-benefit evaluation. Older women, those with a low hip T-score or high fracture risk score are considered high risk. The risk of osteonecrosis of the jaw and atypical femoral fracture increases with BP therapy duration, but such rare events are far outweighed by fracture risk reduction with BPs in high risk patients. For women not at high fracture risk after 3–5 years of BP treatment, a drug holiday of 2–3 years can be considered, with periodic reassessment.

The algorithm provided for long term BP use is based on limited evidence in mostly Caucasian postmenopausal women and only for vertebral fracture reduction. It is probably applicable to men and patients with glucocorticoid-induced osteoporosis, with some adaptations. It is unlikely that future osteoporosis trials will provide data for formulating definitive recommendations.

Keywords

Bisphosphonates; long term-bisphosphonate use; risk benefit; drug holiday; other osteoporosis therapies

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INTRODUCTION

A fracture due to osteoporosis occurs every 3 seconds around the world, with the hallmark fractures at the spine and hip leading to substantial mortality, morbidity, and huge societal costs worldwide.[1, 2] One in three older women and one in five older men will experience a fragility fracture[2] after age 50. Solid evidence from randomized placebo-controlled trials of 3–4 years duration, supports the efficacy of amino-bisphosphonates (BPs) in decreasing the risk of vertebral fractures (by 40–70%), hip fractures (by 20–50%) and non-vertebral fractures (by 15–39%), depending on the drug, skeletal site, and individual risk profile. These drugs have therefore dominated the landscape of osteoporosis therapies for the last two decades. They are approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of postmenopausal, glucocorticoid-induced, and male osteoporosis. Between 2005 and 2009, approximately 150 million prescriptions were dispensed in the United States (US) for the oral BPs, alendronate, risedronate or ibandronate, and 5.1 million patients over the age of 55 received a prescription for these drugs in 2008.[3] Extension trials have suggested efficacy of prolonged BP therapy in maintaining bone density, for up to 10 years with alendronate,[4, 5] 7 years with risedronate[6] and 6 years with zoledronic acid,[7] but evidence regarding fracture risk reduction with prolonged therapy is less convincing.

However, less than a decade after the publication of the first pivotal clinical trial with alendronate in 1995, reports regarding serious complications, potentially related to the cumulative intake of such drugs, began to appear in the literature. The most alarming to physicians and patients alike are osteonecrosis of the jaw (ONJ), first reported by dentists and oral surgeons in 2003, and atypical femoral fractures (AFFs), first reported in 2007. Many subsequent publications have appeared on both conditions, including 3 major reports from American Society for Bone and Mineral Research (ASBMR) Task Forces.[8–10] While ONJ was first described over 160 years ago, its association with the intake of BPs was new, and it occurs more commonly in the setting of cancer treatment in which high doses of intravenous BPs are used. AFFs can occur in patients not receiving any anti-fracture medications; they account for about 1% of all femoral fractures[11, 12] and about 3% of all femoral shaft fractures.[13] The incidence of AFFs seems to increase in patients taking long-term BPs for osteoporosis. This led the FDA to request information from all BP drug manufacturers regarding this potential safety signal and to assess long-term efficacy.[14] On October 13, 2010, the FDA reviewed all available data, including data summarized in the ASBMR Task Force initial report on Atypical Subtrochanteric and Diaphyseal Femoral Fractures,[10] and determined that new "*Warnings and Precautions*" information regarding the risk of AFFs should be added to the labels of all BP products approved for the prevention or treatment of osteoporosis. In September 2011, the FDA held a hearing to review the long-term safety and efficacy of BPs, and subsequently recommended that physicians re-assess the indication for continued BP therapy beyond 3–5 years,[14, 15] but noted that in high risk patients, drug discontinuation may not be advisable. Currently, all FDA approvals of BPs for the treatment of osteoporosis contain the following *"Important Limitation of Use"* statement: "The optimal duration of use has not been determined. All patients on BP therapy should have the need for continued therapy re-evaluated on a periodic basis."[16]

With additional reports, the association between BPs and AFFs has become more compelling. In its second report on Atypical Subtrochanteric and Diaphyseal Femoral Fractures,[9] the ASBMR Task Force revised the original case definition of AFFs, summarized the updated relevant literature, and underscored the significant association with BP use, although with differing strengths and magnitude. While the relative risk for BP use varied widely (between 2 and 128-fold), the absolute risk was consistently low, ranging between 3.2–50 cases/100,000 person-years, an estimate that appeared to double with prolonged duration of BP use (> 3 years, median duration 7 years), and seemed to decline with discontinuation. The incidence of ONJ in patients with osteoporosis is estimated to be between 1/10,000 and 1/100,000, and is only slightly higher than the ONJ incidence in the general population.[8, 17] Collectively, however, these rare yet serious harmful events have received wide coverage in the media and have resulted in perceived risks by the public that may be out of proportion to the absolute risks, leading patients to not fill or refill prescriptions for these drugs. Such behavior is likely to result in fractures that could have been prevented, given that patients need to take at least 75% of doses in order to prevent fractures.[18]

The persistent effect of BPs on bone, albeit with differing temporal resolution upon discontinuation due to differential avidity to bone,[19] coupled with concerns regarding perceived harms from such therapy, led to the concept of a drug holiday. The drug holiday is designed to minimize side effects and maximize benefits, and is an approach that has been successfully applied in other chronic disease states, such as rheumatoid arthritis and Parkinson's disease.[20, 21] Organizations have provided guidance regarding the risks and benefit of BP drug holidays in individuals who have received BPs for 3–5 years. The American Association of Clinical Endocrinologists (AACE) guideline suggests a drug holiday after 4 to 5 years of BP treatment in patients at moderate risk of fractures, and after 10 years for high-risk patients, but the terms high and moderate risk were not defined.[22] The National Osteoporosis Guideline Group (NOGG) in the UK developed a care path algorithm that suggests a drug holiday in individuals who have no history of fracture, whose FRAX risk falls below the NOGG intervention threshold, and whose hip bone mineral density (BMD) T-score is above −2.5; in such patients, repeating FRAX with BMD in 1.5–3 years was recommended.[23]

In 2013, in response to increasing concerns about prolonged BP therapy in osteoporosis patients, ASBMR leadership convened a multidisciplinary international task force on Managing Osteoporosis Patients after Long-Term Bisphosphonate Treatment. Experts in osteoporosis management, epidemiology, endocrinology, geriatrics, and drug surveillance were appointed to the Task Force. A bone scientist not in the osteoporosis field and an ethicist were also members of the Task Force. Task Force members were vetted by the ASBMR Ethics Committee, and approved by the ASBMR Executive Committee.[24] Task Force member Conflicts of Interest are listed at the end of this document.

CHARGES TO THE TASK FORCE

The main charges were determined by the ASBMR Professional Practice Committee, approved by Council, and subsequently modified by Task Force members to follow complementary themes and facilitate work amongst members. These were to:

- Provide guidance on duration of BP therapy in patients with postmenopausal osteoporosis, developing an algorithm that incorporates risk assessment (efficacy).
- Determine how potential harms may affect duration of therapy (safety), with a risk/benefit perspective.
- Discuss how the algorithm may apply to men and to glucocorticoid-induced osteoporosis.

Additional relevant points, namely risk factors for harms, resolution of benefits and harms upon BP discontinuation, monitoring on and off therapy, differential effects and costs of BPs, and alternative therapies, were also to be reviewed. Case studies were also included to illustrate the applicability of the algorithm to challenging clinical cases, where available evidence falls short of providing strong guidance and recommendations, and are discussed in Appendix I.

Details regarding the original and modified charges can be found in Appendix II.

METHODS

Methodology for the Literature Search

Three parallel systematic literature searches were implemented on the following terms: randomized controlled trials with long-term bisphosphonates, bisphosphonates and drug holidays, and bisphosphonates and guidelines. The databases searched included Ovid Medline, EmBASE, Cochrane and PubMed. The three searches were constructed, conducted with input and oversight from an expert medical librarian, and implemented by a research assistant at the American University of Beirut under supervision of one of the Task Force co-chairs (GE-HF). A detailed description of the search strategy and its yield is found in Appendix III.

Task Force Process

The Task Force met by multiple teleconferences and emails, in addition to 2 face-to-face meetings attended by several but not all task force members and at least one co-Chair. Two subgroups were formed, one charged with assessing BP effectiveness over time and the other BP safety. By consensus, the first subgroup constructed an algorithm containing the essential findings and recommendations of the Task Force. The second subgroup addressed side effects of BP therapy, constructing a figure relating the probability of serious adverse outcomes with osteoporotic fracture risk and other serious life events. It also reviewed risks of alternative therapies to BPs. The Task Force Co-Chairs wrote the first and subsequent drafts of the manuscript with input from all members, who provided sections to address specific questions raised during the teleconferences. The algorithm, figure, and text

underwent multiple revisions based on emails and discussions and were circulated to all task force members. The entire Task Force unanimously approved the final report.

EVIDENCE FOR LONG-TERM BP TREATMENT OF OSTEOPOROSIS

EXTENSION STUDIES USING BPs

Pivotal registration trials have unequivocally demonstrated the anti-fracture efficacy of commonly used BPs, namely alendronate, risedronate, zoledronic acid and ibandronate.[6, 25–31] Fracture reduction for vertebral, non-vertebral and hip fractures has been established for the first three, and hip fracture was a primary outcome only for the risedronate and zoledronic acid trials.[26, 30] The long-term efficacy of these BPs in extension studies is primarily based on trials conducted in a sub-set of trial participants and focused primarily on bone density changes. In these studies, subjects were re-randomized, (after a 1–2 year period of open label alendronate in FLEX) and fracture reduction was evaluated as an exploratory outcome. Ibandronate was not studied beyond 5 years,[32] and the extension study for risedronate, had no placebo group, and only included a small number of subjects followed for up to 7 years (N=74).[6] Additional details on currently used BPs are provided under the section below entitled "Differences among Bisphosphonates." Therefore, evidence supporting long-term BP therapy beyond 5 years is derived from two randomized, double-blind discontinuation trials conducted in the US and Europe, with alendronate (FLEX study) or zoledronic acid (HORIZON extension study).

The FLEX study was an extension of the alendronate Fracture Intervention Trial, including both of its sub-studies, the Vertebral Fracture Study[25] and the Clinical Fracture Study.[33] The extension study randomized 1099 postmenopausal women who had already received 4–5 years of oral alendronate (ALN), 5–10 mg/day, including up to one year open label ALN (10 mg/d), to either continue ALN 5 mg (n = 321), 10 mg (n = 322), or switch to placebo (n = 428),[4, 34] (see Appendix IVA-McNabb 2013 Figure 1 for study flow). All women also received 500 mg of calcium and 250 IU of vitamin D3 daily.

At entry into the extension study, the mean age was 73 (±5.7) years, and over 96% were white. The mean total hip T-score was −1.9 and the mean femoral neck T-score was −2.2. Importantly, women with a total hip BMD T-score <−3.5 or whose total hip BMD was lower than at FIT baseline were excluded from the extension. Sixty percent of women had a history of clinical fracture after age 45 years, and one-third had already suffered a vertebral fracture. The primary endpoint was the change in femoral neck BMD; secondary measures were BMD at other sites and bone turnover markers. Fracture incidence was an exploratory objective, captured as adjudicated vertebral and non-vertebral fractures, as done in FIT. Morphometric vertebral fractures were ascertained through lateral radiographs, obtained at entry and after 36 and 60 months of the extension. A semi-quantitative method was used, and mild fractures (20% height loss) were included.

After an additional 5 years of follow-up, those who continued on ALN (5 or 10 mg, N=662) had significantly less bone loss at all skeletal sites, (for example, femoral neck bone change by DXA was 0.46% in combined ALN versus −1.48% in placebo, p<0.001), and fewer clinical vertebral fractures (RR=0.45, 95% CI [0.24, 0.85], compared with those who were

switched to placebo, N=437,[4] (see Appendix IVA, Black 2006, Table 3). However, non-spine fracture risk was similar among those who continued ALN for approximately 10 years compared to women who received 5 years of ALN, followed by 5 years of placebo (RR=1.00, 95% CI [0.76,1.32]. There was no significant reduction in morphometric vertebral fractures with continued therapy beyond 5 years, (RR=0.86, 95% CI 0.60–1.22) [4]. (Appendix IVA, Black 2006, Table 3 provides details regarding number of subjects and fractures in each arm, by fracture type). Further analyses for risk stratification in the FLEX trial are discussed in the section below entitled "Risk stratification from the alendronate and zoledronic acid extension studies," and illustrated in the rest of Appendix IVA.

In the HORIZON study extension, 1233 postmenopausal women who had already received 3 annual IV infusions of zoledronic acid (ZOL) 5 mg, were randomized to either continue yearly ZOL (Z6) for an additional three years, or switch to placebo (Z3P3), in a blinded manner. All women received 1000–1500 mg of oral calcium and 400–1200 IU of vitamin D daily. The mean age was 75.5 (± 5) years, over 95% were from primarily Western populations, and 5% were Asians. The subjects had a mean total femoral neck T-score of −2.6 (± 0.6); women over age 93 years or on other bone active drugs were excluded. Approximately 60% of the women had at least one prevalent vertebral fracture at entry into the extension.[7] The primary endpoint was percent change in femoral neck BMD between the 2 arms; secondary endpoints included BMD at other sites, fractures, bone turnover markers, and safety. Clinical fractures were identified similarly to the core study, self-reported with central adjudication. The incidence of morphometric fractures was assessed by comparison of radiograph at 3 years and 6 years.[7]

Subjects randomized to the Z3P3 arm had significantly greater femoral neck bone loss (−0.80 vs. 0.24 %; p=0.0009), and those in the Z6 arm had fewer morphometric spine fractures (RR=0.51, 95% CI 0.26 to 0.95; p=0.035,[7] (see Appendix IVB, Black JBMR 2012, Figure 4). However, non-spine fracture risk did not differ among those who did and did not continue ZOL (RR=0.99, 95% CI 0.7 to 1.5), and the same applied to hip fractures. This may be explained by low statistical power as shown in Appendix IVB, Black JBMR 2012[7], where Figure 4 provides details regarding number of subjects and fractures in each arm, by fracture type. Further analyses for risk stratification in this trial extension are discussed in the section below entitled "Risk stratification from the alendronate and zoledronic acid extension studies", and illustrated in the rest of Appendix IVB.

DIFFERENCES AMONG BISPHOSPHONATES

Persistence of beneficial effects of BPs—Elevated bone turnover markers (BTMs) have been associated with low BMD and increased fracture risk in untreated postmenopausal women.[35] In pivotal studies of BPs, a significant decrease in BTMs has been demonstrated.[25–28,31, 33, 36] Persistence of low BTMs may be a potential indication of continued beneficial effects after discontinuation of long-term BP use.[37] Withdrawal of BP treatment is associated with decreases in BMD and increases in bone turnover, changes which differ among BPs. Based on these criteria, beneficial effects of ALN persist for 2–3 years and possibly 1–2 years for ibandronate and risedronate.[4, 37–39] In the case of three years of ZOL therapy, it extends for at least another three years.[7] These findings are

consistent with the relative binding affinities of BPs for hydroxyapatite and human bone tissue.[19, 40–43]

Cost and Convenience—Oral BPs are most frequency prescribed in part due to their low cost and convenience, and the costs of ALN, risedronate and ibandronate were found to be similar in a 2011 study.[44] Generic ALN, risedronate, and ibandronate are now available in many countries worldwide. The availability of generic BPs may alter total health care costs. ZOL may also be a cost-effective first-line option compared to other branded BPs and, in some cases, even in comparison with generic ALN; however, these comparisons are limited by a paucity of compliance and persistence data, as well as by incomplete country-specific data.[45] Generic ZOL became available in the US in 2013, and in the UK in 2014, which may also change previous cost-effective analyses. Cost and availability of generic BPs varies among countries.

Adherence—Adherence to osteoporosis therapies is essential to treatment efficacy, even with BPs, despite their long bone retention. Better adherence to BP therapy is associated with larger increases in BMD,[46] and - when exceeding 75% - with lower rates of fracture.[18] A meta-analysis of 171,063 subjects followed for 1–2.5 years revealed a 46% increased fracture risk in non-compliant subjects versus compliant ones.[47] However, adherence is a major problem with currently available oral anti-osteoporosis therapies, with less than 50% of those starting oral BPs continuing them for more than one year. Major determinants of adherence to oral BPs are comorbidities and health plan costs. Reasons for discontinuation include side effects, concern about side effects, poor understanding of benefits, inconvenience, and use of multiple medications.[48–54] Persistence with intravenous BPs is not far superior to oral drugs, including the once yearly regimen. In a random sample of 5% of new users of IV ZOL in the Medicare database, (N=846), 30% did not receive a second infusion.[55] Older age and receiving the infusion in a separate outpatient infusion center as opposed to a physician office predicted low adherence.[55] To date, evidence to establish superiority of intravenous vs oral BP is scarce and limited to short follow-up.[56]

RISK STRATIFICATION FROM THE ALENDRONATE AND ZOLEDRONIC ACID EXTENSION STUDIES

In an attempt to identify subgroups of subjects who may benefit most from longer term therapy, investigators from both extension trials performed additional post-hoc analyses.

Potential Risk Stratification by BMD, prevalent or incident fractures—In the FLEX study, there was no significant effect of low BMD (stratified into 3 categories), nor of prevalent fractures, on the reduction in non-vertebral and clinical vertebral fracture with continued ALN versus placebo (N=10 subgroup comparisons), the only exception being a reduction in clinical vertebral fractures in subjects with femoral neck T-score >-2.5 to ≤ -2, RR=0.22 [0.05–0.74], [4] (see Appendix IVA, Black 2006, Table 4). However, in these analyses, the subgroups categorized by T-scores may have had prevalent vertebral fractures. Similarly, those with prevalent fractures may have had a wide range of BMD. Therefore, additional analyses were conducted to evaluate the effect of continued ALN for 10 years in FLEX women with or without previous vertebral fractures at entry into FLEX, stratified by

BMD categories, on morphometric and non-spine fractures.[5] Out of a total of 12 subgroup analyses, the only significant finding was a reduction in non-spine fractures in women who did not have vertebral fractures and with femoral neck T-score ≤−2.5 at FLEX baseline, who continued ALN for an additional 5 years compared with women who were switched to placebo (RR=0.50; 95% CI 0.26 to 0.96) [5], (see Appendix IVA, Schwartz 2010, Table 2). Finally, in the most recent post-hoc analyses from FLEX, both femoral neck and total hip T-scores, entered as tertiles at study extension, predicted the occurrence of any clinical fracture after ALN discontinuation in subjects randomized to placebo in extension, proportions increasing from less than 10% to 30% from highest to lowest tertile,[57] (see Appendix IVA, Bauer 2014, Figure 2). Similarly, age (as a continuous variable) and hip BMD T-score (lowest versus other 2 tertiles), at time of ALN discontinuation, predicted clinical vertebral fractures during the subsequent 5 years,[57] (see Appendix IVA, Bauer JAMA Int Med 2014, Table 3).

In the HORIZON extension, additional analyses were performed to identify predictors of fractures in subjects who were randomized to placebo at three years.[58] By univariate analysis, the incidence of morphometric vertebral fractures in the Z3P3 group was predicted by femoral neck and total hip T-score ≤ −2.5,[58] (see Appendix IVB, Cosman 2014, Figure 1). The OR for femoral neck T-score ≤−2.5 was 3.3 [CI: 1.4–8], for total hip T-score ≤−2.5, 4.0 [CI: 1.8–8.9] and for incident morphometric fractures during the core study, 4.8 [CI: 1.4–16.8],[58] (see Appendix IVB, Cosman 2014, Table 2). Similarly, the incidence of non-vertebral fractures was predicted by total hip T-score as a continuous but not categorical variable, prevalent vertebral fracture (HR 3.0 [1.4–6.3]), and incident non-vertebral fractures during the core study, (HR 2.5 [1.2–5.3], [58] (see Appendix IVB, Cosman 2014, Table 3). Finally, neither age ≥ 75 yr, nor weight ≤ 60 kg, when entered as single categorical variables, was predictive of new morphometric or non-vertebral fractures in the Z3P3 subjects. The absolute risk of morphometric vertebral fracture in subgroups defined by single or combined risk factors is shown in Appendix IVB, Cosman 2014 Table 4[58]. The absolute risk of such fracture remained low (3.1%) in women who only had one risk factor, e.g., only a femoral neck BMD T-score ≤ −2.5.

In summary, the extension studies reveal that 10 years of therapy with ALN and 6 years with ZOL resulted in a decrease in bone loss at multiple skeletal sites, and a reduction in vertebral fractures compared with stopping ALN after 5 years or ZOL after 3 years. Subjects who seemed to benefit most from long-term ALN or ZOL therapy are those categorized as high risk, best captured by a persistent low T-score at hip (≤−2.5 in HORIZON for total hip or femoral neck T-score, and above 2.5 but ≤ −2 for femoral neck in FLEX), incident fracture during the core study or prevalent vertebral fracture at entry into the extension in HORIZON. However, the benefit in terms of fracture reduction was not entirely consistent across the two studies. Continued ALN resulted in a lower risk of clinical vertebral fractures, whereas ZOL resulted in a lower risk of morphometric vertebral fractures. The reason for this discrepancy is unclear, but possible factors include different baseline characteristics at entry into the extensions and in fracture incidence after treatment discontinuation. These data must be viewed with caution because of potential selection bias, small sample sizes, low numbers of fractures, post-hoc exploratory nature of many analyses, and lack of correction for multiple comparisons.

Based on these findings, continued BP therapy should be considered beyond three years with ZOL and beyond 5 years with ALN in high risk individuals, based on evidence for reductions in the risk of vertebral fractures only. In lower risk patients and in light of lack of evidence for fracture reduction with long-term therapy, discontinuation of treatment beyond 3–5 years, with monitoring, seems prudent.

Potential Risk Stratification by Bone Turnover Markers—Bone turnover markers (BTMs) are affected by BP therapy and are potentially useful in determining fracture risk before and after therapy has commenced. The 2010 AACE Clinical Practice Guideline stated that BTMs may be used at baseline to identify patients with high bone turnover and can be used to follow the response to therapy, although this was supported by Grade C level evidence.[22] Recently, the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommended serum procollagen type I N-terminal peptide (P1NP) to assess bone formation and serum C-terminal cross-linking telopeptide (CTX) to assess bone resorption.[59]

Although the IOF and IFCC recommended the use of specific BTMs, it remains unclear how such BTMs should be used in clinical practice. Clinical studies have suggested their use as a primary fracture prediction tool, but many clinicians use BTMs to monitor osteoporosis treatment. A post-hoc analysis of the Fracture Intervention Trial reported that greater suppression of serum P1NP, bone-specific alkaline phosphatase (BSAP), and CTX in ALN-treated subjects was positively associated with fewer vertebral fractures.[60] Similar data were reported with risedronate when suppression of markers was assessed by changes exceeding the least significant change,[61] but not for ZOL when a discrete cut off above or below the lower limit of premenopausal age was used.[62]

The bone turnover markers CTX, PINP, and BSAP, measured in 76 women who took part in the FLEX trial, did not predict bone loss at the lumbar spine, total hip, or femoral neck over a 5 years treatment free period, in women who discontinued ALN after a mean of 5 years.[34] Similarly, a change in BSAP or urinary NTX/Cr was not associated with fracture risk when measured 1 year post drug discontinuation in 437 study subjects.[57] Fasting serum PINP, measured in 1140 women at entry in the HORIZON extension, was not a predictor of morphometric or non-vertebral fractures in the Z3P3 group.[58] BTM changes reported in large groups of patients may not be observed in individuals because of the variability in BTM tests.

At this time, based on the limited evidence from FLEX and HORIZON extension studies, there is no evidence to support the measurement of BTMs to assess fracture risk after long-term BP use, or in offset periods. However, some experts use BTMs to determine whether a discontinued BP is still exerting its effects, and resume therapy when they exceed the lower half of the premenopausal range. This approach is based on the evidence that maintenance of BTMs in the lower range is associated with lower risk of fracture, and the rationale that such observations can be extended to patients who discontinue BPs after long term therapy.[59]

Potential Risk Stratification by Fracture Risk Calculators, Age and Weight—In untreated patients, fracture risk calculators have been developed to identify individuals who

may not have osteoporosis by DXA but are at high fracture risk nonetheless. The algorithm-based calculators that have been validated in at least one independent cohort from the original derivation cohort are the World Health Organization FRAX tool, the Garvan Risk Calculator, and the QResearch Database Qfracture.[63] To date, FRAX has been incorporated in some national osteoporosis guidelines and care pathways, but the evidence for its usefulness in treated patients is limited. In one study using the Manitoba database,[64] Leslie et al. demonstrated that FRAX score in patients on osteoporosis therapies predicted 10 year risk of major osteoporotic fractures and hip fractures, except for the subgroup of adherent patients at highest risk, where hip fracture risk was overestimated by 30%.[65] The same authors also demonstrated in a subsequent publication that FRAX scores slowly increased over time. This increase was attenuated but not prevented by treatment, and a change in FRAX score on therapy did not independently predict incident fracture.[64] This is not surprising, because FRAX includes both age and femoral neck BMD, which will likely affect the FRAX calculation in opposite directions over time in the treated patient.

Age and body mass index (BMI) are two of the most powerful predictors of fractures in general and play a key role in FRAX. These factors were independently evaluated in the FLEX study, and while older age and low BMI were predictors of bone loss at the spine and hip after discontinuation of ALN therapy, no model based on these risk factors was able to identify women likely to lose more bone over the next 5 years.[34] However, age and hip BMD at discontinuation predicted clinical fracture in the 5 years after discontinuation.[57] In contrast, in the HORIZON extension study,[58] neither age (≥75 yrs) nor weight (≤ 60 kg) at entry into the extension, or weight loss during the core trial, were predictors for the occurrence of morphometric or non-vertebral fractures in the group that discontinued ZOL after 3 years.

STOPPING BISPHOSHONATES AND RE-STARTING THERAPY

As described above, after 3 years of intravenous ZOL and 5 years of oral ALN treatment, high risk postmenopausal Caucasian women, such as those with recent incident or prevalent vertebral fractures in the HORIZON extension, or with hip T-scores of ≤−2.5 appeared to benefit the most from continued BP treatment. The evidence for this benefit is limited to reducing the risk of vertebral fractures, and data for other BPs are lacking. Furthermore, tools to identify subjects who will fracture when therapy is discontinued are limited. History and physical examination can provide information about additional clinical risk factors that may further increase fracture risk, such as older age, low BMI, weight loss, fall history, or the intake of drugs that have adverse effects on bone. Attention to causes of secondary osteoporosis, calcium intake, and vitamin D levels may also affect response to therapy. Two observational studies suggest that the serum 25-hydroxyvitamin D level should be 30 ng/ml or more to ensure an adequate response to BPs.[66–68] However, vitamin D status did not affect the bone density response to alendronate in in FIT.[66]

After treatment for 5 years with ALN and 3 years with ZOL, in postmenopausal women who have a low fracture risk, with a hip T-score higher than −2.5, discontinuation of BP therapy should be considered. These patients should be re-assessed at 2–3 years after discontinuation to determine if new risk factors are present. Patients treated with risedronate may need

earlier reassessment because of the shorter biologic half-life of this BP.[69] Repeat DXA or BTM measurements may be considered during this 'holiday,' but there are no data to guide the clinician regarding re-institution of therapy, because neither 1 year change in BMD nor 1 year change in BTMs predicted fractures post-BP discontinuation.[57] It would be reasonable to consider withholding therapy as long as BMD is stable, and to re-start BP therapy (or an alternate osteoporosis medication) if the BMD T-score is ≤ −2.5, or if other new/additional risk factors for fractures emerge. However, this approach is based on expert opinion. Furthermore, the use of a T-score cut-off of −2.5 for risk stratification and decision-making regarding therapy discontinuation is based on studies conducted almost exclusively in community-dwelling, postmenopausal Caucasian women. Although the relative risk for fracture/standard deviation decrease in BMD is best described by an inverse exponential relation that is similar across populations worldwide, the absolute fracture risk incurred by the same BMD T-score may be higher in more frail postmenopausal women or lower in non-Caucasian subjects than in robust Caucasian women.

SAFETY OF BISPHOSPHONATES AND EFFECT OF DISCONTINUATION ON AEs

Although some side effects of BPs, such as gastro-esophageal irritation and nephrotoxicity (see below), were recognized early as potential adverse effects, subsequent reports indicate that BP use may be associated with clinically serious but rare safety concerns including osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF). These are not unique to BPs and have been reported with denosumab, another potent antiresorptive agent, and also occur in people who have not been treated with any of these agents.

Osteonecrosis of the Jaw (ONJ)—ONJ was first associated with bisphosphonate therapy was in a report in 2003, in patients with metastatic cancer receiving high-dose intravenous BP therapy. ONJ is characterized by a) exposed necrotic bone in the maxillofacial region that has been present for at least 8 weeks of appropriate therapy; b) exposure to potent anti-resorptive agents (BPs or denosumab) or anti-angiogenic agents; c) no history of radiation therapy to the jaw.[70] In one study,[71] the incidence in patients not on BPs was 1/3,000 patient-years. The pathogenesis of ONJ remains unclear[17, 72] but several potential mechanisms, which are not necessarily mutually exclusive, have been proposed. These include over-suppression of bone remodelling, infection, inhibition of angiogenesis, soft tissue toxicity, and immune dysfunction. In patients receiving BP therapy for osteoporosis, current estimates of the incidence of ONJ range from approximately 1/10,000 to 1/100,000 patient treatment years.[8] Potential factors increasing the risk for BP-treated patients to develop ONJ include poor oral hygiene, smoking, diabetes mellitus, concomitant glucocorticoid and/or chemotherapy use, and invasive dental procedures, such as dental extractions or implants. The incidence may be higher in Asian populations, pointing to a genetic predisposition, as recently reported in Taiwanese subjects.[73] For the vast majority of patients with osteoporosis treated with BPs who develop ONJ, the clinical course is mild and self-limited, and is most often can be treated conservatively.[8, 17, 74] Preventive practices that may reduce the incidence of ONJ include prophylactic dental care and avoidance of invasive dental procedures. Detailed recommendations for management have been provided by the ASBMR[8], American Dental Association,[74] the American

Association of Oral and Maxillofacial Surgeons,[75] and the recently updated report of an International Task Force.[17]

Atypical Femur Fractures (AFFs)—The relationship between AFFs and BPs was first reported in 2008 in patients receiving oral BPs for osteoporosis. In a large retrospective analysis of > 1.8 million adults, including approximately 10% who had been treated with BPs, 142 AFF were identified, including 128 in subjects with prior BP exposure.[11] These fractures usually occur with little or no antecedent trauma, are often preceded by thigh or groin pain, and may occur bilaterally.[10, 76] Updated diagnostic criteria were published in 2014.[9] The diagnosis of AFF is made based on subtrochanteric or femoral shaft location and the presence of at least 4 of 5 major criteria: minimal trauma, fracture originating at the lateral cortex and being substantially transverse, complete fractures extending through both cortices, localized periosteal or endosteal cortical thickening, and minimal comminution at most. Minor criteria are not required for the diagnosis but include increased cortical thickness of the femoral diaphysis, bilaterality, a prodrome of thigh or groin pain, and delayed fracture healing. In terms of incidence rates, some but not all studies suggest a dose response relationship, with a rise in age-adjusted incidence rates from 1.8/100,000/year with a 2 year exposure, to 113/100,000/year with exposure from 8 to 9.9 years.[11] Such results strongly suggest that although a rare potential complication of BP use, AFF risk increases with prolonged duration of BP treatment, and that this should be taken into consideration when continuing BPs beyond 5 years However, it is important to note that for the vast majority of patients treated for osteoporosis, the BP-associated benefit of reduced fracture risk is greater than the risk of developing either ONJ or an AFF (see Figure 1).

Other Risk Factors for AFF—Limited data exist regarding AFF risk factors other than BPs. Documented AFFs have also been described among individuals treated with denosumab.[77, 78] An increased risk of AFF has been postulated in glucocorticoid and proton pump inhibitor users, individuals with diabetes and rheumatoid arthritis, and individuals of Asian ancestry. One study found AFF was particularly increased in individuals with low bone mass (osteopenia) compared to those with osteoporosis.[79]

Reports of AFF with denosumab therapy should be kept in mind when considering switching from BP to denosumab therapy, and a careful scrutiny of the relevant risk factors for AFF should be performed.[80] Importantly, documented AFFs have also occurred in individuals without any history of anti-resorptive therapy.

Other adverse events associated with BP Therapy—Other potential adverse events that have been reported to be increased in patients receiving BP therapy, but which are not included in this review include: esophageal cancer, atrial fibrillation, acute kidney injury, acute phase reaction (mostly noted after the first administration of an intravenous BP), musculoskeletal pain, and gastrointestinal intolerance. The strength of the association between BP use and atrial fibrillation and with esophageal carcinoma is weak at best,[81] and the FDA has not ordered warnings for either atrial fibrillation or esophageal carcinoma in package inserts for oral BPs. It is usually possible to avoid renal injury by only using BPs in patients with CrCl >. 30–35 ml/min,[82] and intravenous BPs can be used in those patients with gastrointestinal intolerance or contraindications to oral BPs.

Side-Effect Risks after Stopping Bisphosphonate Treatment

Effect of Bisphosphonate Discontinuation (Holiday) on AFF Risk: There are few data estimating the risk of AFF after stopping BPs. Of the 3 large cohort studies, only the Swedish study by Schilcher included information about the risk of AFF after stopping treatment.[12] Among the 45 women with confirmed AFF after stopping BPs, the risk fell by 70% each year after discontinuation (odds ratio 0.28, 95%CI: 0.21–0.38) but the most dramatic reduction in risk occurred after the first year of discontinuation. Specifically, compared to those without BP exposure, the relative risk of confirmed AFF was 43 in the first year following discontinuation and 3.5 after the first year, but these analyses were based upon a total of 46 AFF events and only 4 AFFs occurred >1 yr after discontinuation of BP. The derived estimates may have been overestimated in of view of short term follow-up in this cohort.[13]

Effect of Bisphosphonate Discontinuation on ONJ Risk: Because of the long-terminal half-life of BPs, the American Dental Association,[74] and the American Association of Oral and Maxillofacial Surgeons[75] do not recommend routine discontinuation of BP treatment for osteoporosis in most patients about to undergo invasive dental procedures. There are no studies of the incidence of ONJ in patients at different times after discontinuation of BP treatment for osteoporosis.

Potential Use of BTMs to determine safety risks: The value of BTMs to predict which patients on long-term BPs are at risk for AFFs is unclear. Markedly suppressed bone turnover leading to an inability to repair skeletal micro-fractures, followed by propagation of these small fractures, has been proposed as the mechanism underlying AFFs.[9, 10, 83, 84] The second report of a task force convened by the ASBMR to examine atypical subtrochanteric and diaphyseal femur fractures identified published reports in which AFFs had been confirmed by radiologic review.[9] Of these reports listed, none included BTMs. However, two reports examined the association of BTMs with AFFs.[85, 86] Odvina et al reported nine patients with “spontaneous nonspinal fractures” on long-term (range of 3–8 years) BPs. By dynamic histomorphometry, all had suppressed bone formation and eight of nine had low resorption. The correlation of bone histomorphometric parameters with BTMs was poor. Urine NTX was low to mid-normal in 7 subjects, and although serum BSAP levels ranged widely, serum osteocalcin was low or at lower limit of the reference range at the time of bone biopsy.[85] Visekruna et al reported on 3 subjects who experienced spontaneous “minimal-trauma chalk-stick type metadiaphyseal femoral fractures” while on long-term BPs. Serum NTX was low in only one of the subjects.[86] Similarly, both the American Dental Association recommendations[74] and the American Association of Oral and Maxillofacial Surgeons[75] conclude that measurement of BTMs does not help in the assessment of risk of ONJ in patients on BPs for osteoporosis.

Bisphosphonate Safety Concerns in Perspective with Other Medical and Non-Medical Safety Issues: To provide a perspective of the safety concerns associated with BP therapy, Figure 1 illustrates the incidence of ONJ and AFF and that of typical osteoporotic fractures in various countries, as well as some other important outcomes and serious events. The age-standardized incidence rate of hip fractures (after age 50 years) is elevated across all

continents.[87] Among women in the US, the age-adjusted annualized rates for fracture greatly exceeds that of other diseases in the elderly, such as heart attack (2 fold), breast cancer (4.7 fold) and stroke (8.5 fold).[88] For other health outcomes, CDC data outcome is expressed as crude rates for pedestrian injuries and murder.[89, 90] The risk of fractures is substantially decreased by BPs, and remains much higher than that of developing risk of ONJ (185 fold) or AFF (4835 fold) (Figure 1).[11, 71] As a comparison, the risk of stroke is decreased by aspirin therapy, but the risk of intracerebral bleed is increased to a comparable degree.[91]

Management of Adverse Events Related to Bisphosphonates: When ONJ or an AFF occurs in a patient on chronic BPs for osteoporosis, discontinuation of the BP is recommended. In the past few years, numerous case reports[92–101] and small prospective studies[102, 103] have reported healing of AFF or ONJ typically occurs within a few months of starting teriparatide therapy.

The American Association of Oral and Maxillofacial Surgeons recommends treatments based on the stage of ONJ[75]. Such treatment may include anti-bacterial mouth rinse, oral antibiotics, and surgical debridement. Good dental hygiene and patient education are emphasized for all patients on anti-resorptive drugs.[74] Specific recommendations for prevention, operative and medical management of ONJ have been reviewed recently.[74, 75]

In addition, a few reports have demonstrated beneficial effect of strontium ranelate or teriparatide in AFF.[92, 97, 104] Based on available reports, a limited course of teriparatide may be considered to accelerate healing of BP-related AFFs or ONJ, consistent with the recommendations of the ASBMR Task Force on Atypical Femoral Fractures and the International Consensus report on ONJ.[9, 17]

EFFICACY AND SAFETY PROFILE OF ALTERNATE DRUGS

Alternatives to BP therapy include nasal calcitonin[105], which is no longer approved for osteoporosis by the EMA, raloxifene,[106] denosumab,[107] teriparatide,[108] or strontium renelate.[109, 110] See Table for information on efficacy of osteoporosis approved medications by approval indication and site of fracture reduction.

The protective skeletal effects of all of these non-bisphosphonate agents are reversible upon discontinuation of the medication, and bone loss is expected to resume after the agent is stopped.[111–114]

Nasal calcitonin has been shown to reduce vertebral fractures by 36%,[105] but there are no conclusive data showing a reduction in non-spine or hip fractures with this agent. Calcitonin is well tolerated with approximately 6–8% of treated patients noting nasal irritation, which is generally mild in nature. During trials of an oral preparation of calcitonin in men with osteoarthritis, concern was raised regarding a possible increased risk of prostate cancer. The EMA's Committee has recommended limiting the use of calcitonin-containing medicines only for short-term treatment (hypercalcemia of cancer and Paget's disease of bone) in light of concerns that long-term use is associated with an increased risk of cancer.[115] After extensive review, the FDA has concluded there may be an increased absolute risk of

malignancy of approximately 1%, but causality could not be established. Thus, calcitonin remains on the market in the U.S. with inclusion of a new safety warning, and recommendations that risks and benefits be discussed for each individual patient.

Raloxifene is the only FDA-approved selective estrogen receptor modulator approved for the treatment of osteoporosis and has been shown to reduce vertebral fractures by 30–35% [106] with no effects on hip or non-spine fractures. The combination of conjugated estrogens and bazedoxifene has been FDA-approved for prevention of osteoporosis. Raloxifene has also been shown to decrease the risk of breast cancer in high risk individuals. Administered as a daily pill, raloxifene side effects include exacerbation of hot flashes and an increased risk of thromboembolic complications,[116] the latter is reflected by a box warning for fatal stroke.[117]

Denosumab is administered as a subcutaneous injection every six months and reduces vertebral fractures by 68% and hip fractures by approximately 40%.[107] Reported side effects include skin reactions such as eczema or rash and an approximately 1% increased risk of infections such as urinary tract infections, bronchitis, or erysipelas. Denosumab is a potent inhibitor of bone resorption, and both ONJ and AFFs have been reported during treatment with this agent. Incidence of these rare events during denosumab treatment appears similar to those seen with BP therapy,[77, 118, 119] although there are no large studies to determine the relative incidence of these complications in denosumab versus BPs in patients with osteoporosis. There is evidence that patients who have been on BPs have a further increase in bone mineral density when switched to denosumab, but effects on subsequent fracture risk are unknown.[120] Teriparatide (parathyroid hormone (PTH) 1–34) reduces vertebral fractures by approximately 65% and non-vertebral fractures by approximately 50%.[108] PTH (1–84) reduces vertebral fracture by approximately 58% with no effect on non-vertebral fractures.[121] Administered as a daily subcutaneous injection, these are the only available anabolic osteoporosis therapies. PTH (1–84) is not available in the U.S. and was withdrawn from market in Europe. Teriparatide is limited to a total of two years use in an individual's lifetime. Reported side effects include local injection site reactions, nausea, hypercalcemia, and hypercalciuria.[122] In animal studies, one rat strain, the Fischer 344 rat, that was treated with high doses of teriparatide from birth developed osteosarcomas, but an increased incidence of this rare tumor has not been seen in humans treated with teriparatide,[123] at least as measured by long-term surveillance studies.

Unlike bisphosphonates, calcitonin, raloxifene, and denosumab do not have long terminal half-lives. Hence, stopping these alternative therapies will lead to resumption of previous loss of bone density, within a few months of drug discontinuation.

Strontium ranelate is available outside of North America for the treatment of osteoporosis and has been shown to decrease vertebral fracture risk by 41% and non-vertebral fracture risk by 16%. In addition, in a subgroup analysis, hip fracture risk was decreased by 36% in women over age 74 years who had a femoral neck T-score < −3.[109, 110] However, there have been recent concerns about potential cardiovascular side effects supported by some[124] but not all[125] studies. In light of the above, and in its latest and final decision issued in March 2014, the EMA has restricted conditions of use of strontium ranelate to

postmenopausal women with severe osteoporosis for whom treatment with other products approved for osteoporosis is not possible, due to contraindications or intolerance. Cardiovascular contraindications are in place and other precautions include venous thromboembolism and impaired renal function. Rare serious Stevens-Johnson's skin reactions have also been reported with strontium ranelate.[126]

For detailed reviews on alternative osteoporosis therapies the reader is directed to published reviews.[127, 128]

Potential Additional Benefits of Bisphosphonate Treatment—Side effects of BPs may include beneficial effects, although most evidence is from observational studies. As example, previous studies have reported that some types of cancer may be found less commonly in BP users, such as breast cancer,[129] colon cancer,[130] and gastric cancer.[131] A recent review of osteoporosis registration trials, however, did not show reduced incidence of breast cancer in patients treated with ALN or ZOL,[132] although there may be potential positive effects of BPs in women with established breast cancer.[133] In addition, there is some evidence that vascular disease may be decreased in patients treated with BPs, as manifested by lower risk of stroke[134] and myocardial infarction.[135] There are also some reports that mortality is reduced in patients treated with BPs, although not all studies are positive.[54, 136–141] The mechanisms underlying such putative beneficial effects are unclear. Finally, there is some evidence that decreased pneumonia and arrhythmia after hip fracture may play a role in the reduced mortality noted in patients treated with ZOL.[142]

ALGORITHM: LONG-TERM OSTEOPOROSIS MANAGEMENT WITH BPs

Explanation of the Algorithm

After review of the efficacy and safety data for BP treatment of osteoporosis, the ASBMR Task Force created an algorithm for the management of patients with osteoporosis on long-term BP therapy, as shown in Figure 2. Because registration trials that demonstrated the anti-fracture efficacy of BPs,[25, 26, 28–31] and their corresponding extension studies with continuation or discontinuation of therapy thereafter,[4, 7, 58] have been exclusively conducted in postmenopausal women, the algorithm pertains to the management of this specific patient population. Based on these trials and post-hoc analyses of data from trials that exclusively used ALN and ZOL,[4, 5, 57, 58] the Task Force determined that for postmenopausal women who have been on oral BP therapy for 5 years or intravenous ZOL for 3 years, but less than 10 years, a major consideration was whether the particular patient had experienced a hip, spine, or multiple other osteoporotic fractures prior to therapy, or experienced a major osteoporotic fracture (spine, hip, humerus, or forearm) while on therapy. Because such fractures, especially when recent, i.e. experienced within 3–5 years, increase future fracture risk, the Task Force suggests that oral BP therapy be continued for up to a total of 10 years. For IV BP use, the algorithm pertains to ≤ 6 years of ZOL. Patients who sustain a major osteoporotic fracture while on therapy should also undergo evaluation for causes of secondary osteoporosis, new risk factors, and assessment of adherence with medication. In addition, switching to alternative therapies may be considered, although there have not been adequate studies to evaluate the efficacy of such an approach. The optimal

length of therapy for the patient who suffers a fracture while on treatment has not been established, and clinical judgment will be needed to determine each patient's specific fracture risk. In addition, the potential contributions of poor compliance or adherence to therapy, inadequate vitamin D status, high fall risk or new risk factors should be taken into consideration.

In addition to recent fracture, other potential variables that may signal increased fracture risk should be used for the decision on whether to continue therapy and may include older age (for example > 70–75 years), medication use (e.g. aromatase inhibitors, glucocorticoid therapy), or new diagnosis of a disorder associated with secondary osteoporosis. If the clinician determines that the patient remains at elevated fracture risk, based on femoral neck T-score, age, or other risk factors, the Task Force suggests that BP treatment be continued for another 2 to 3 years with reassessment at that time. For those women who are not considered to be at high fracture risk by these limited tools, a drug holiday should be considered with reassessment at 2 to 3 years, perhaps with earlier assessment for those women treated with risedronate. Alternative anti-fracture therapy could also be considered for those patients remaining at high risk for fracture. Alternative treatments would include the agents described above: teriparatide and denosumab as first options, then raloxifene, and strontium ranelate, depending on patient risk profile.

The algorithm was constructed to reflect the data from clinical trials in which the majority of subjects were Caucasian American and European women. Country-specific thresholds and those for non-Caucasian women for initial treatment vary, and so may thresholds for continuation or re-institution of therapy.

Limitations of the Proposed Algorithm

Risk Stratification by Prevalent Fractures—Risk stratification determined by history of fractures in the algorithm is based on evidence that this subgroup represents a high risk category, and one in which benefit may be derived from continued therapy for up to 10 years using ALN and 6 years with ZOL. This conclusion is derived from the HORIZON extension study only.[58] However, many patients with a history of major osteoporotic fractures are older, have experienced multiple osteoporotic fractures, and may have received BPs for more than 10 years. Although such patients remain at high risk for future fractures as they continue to age, with a consistent increase in fracture risk even when on treatment,[64] there is no evidence to guide clinicians on the best therapeutic option beyond 10 years. Such scenarios therefore could not be adequately addressed in the included algorithm (see illustrative cases in Appendix I).

Risk stratification in patients without a history of fracture—In untreated patients, increasing age and decreasing bone density T-scores at the hip are well-established independent risk factors for fractures, and predictive of response to therapy. The evidence for continued BP treatment efficacy based on a hip T-score ≤ −2.5 is limited to the FLEX and HORIZON extension trials that were conducted in older post-menopausal Caucasian women.[4, 5, 58] The evidence for age, BMI, and other risk factors from these studies is also

quite limited. Age, entered as a continuous variable at entry into FLEX extension, was predictive of future clinical fractures[57] after discontinuation of ALN therapy.

To date there are no trials that have tested the anti-fracture efficacy of switching therapies after 3–5 years of BP treatment, nor have any trials extended beyond 10 years, or assessed the utility of re-initiation of treatment following a drug holiday. The lack of good evidence for continued drug efficacy for prolonged periods is not unique to the field of osteoporosis and stems from the fact that most drug registration trials for chronic diseases last only 3–5 years, while approved therapies for such diseases are used for many more years. However, in the case of BPs, the increase in the risk of harms constitutes an additional challenge in the management of high risk patients. The algorithm therefore only constitutes a framework for decision making in patients on BP therapy for less than 10 years. This lack of solid evidence is unlikely to change, and implies that a tailored approach, which includes assessment of each patient's individual risk profile, must be adopted. A thoughtful risk benefit analysis, shared decision making with the patient, and careful follow-up are strongly recommended. Referral of the most challenging patients, such as those who are considered high risk and have been on BPs for more than 10 years, or who fracture after several years of BP therapy, to an osteoporosis expert should also be considered. The illustrative cases described in Appendix I provide some examples of challenges encountered in practice that could not all be addressed by the algorithm and illustrate how clinical decisions may be reached. Lastly, the data available do not allow for a similar assessment for men with osteoporosis or for subjects with glucocorticoid-induced osteoporosis, topics discussed in the following section.

APPLICATION OF ALGORITHM TO PATIENTS ON GLUCOCORTICOID THERAPY OR MEN

Long-term Bisphosphonate Therapy in Individuals Taking Continuous Oral Glucocorticoids

Glucocorticoid-induced osteoporosis is a common cause of secondary osteoporosis and often requires long-term bone protective therapy. Although bone loss and low BMD contribute to fracture in individuals treated with glucocorticoids, the increased fracture risk is partially independent of BMD, and fractures occur at a higher BMD than in other forms of osteoporosis.[143] As a consequence, most guidelines recommend that treatment should be started at a higher T-score in women receiving long-term glucocorticoid therapy than in those not receiving glucocorticoids.[144, 145]

The efficacy of BP therapy in women and men taking glucocorticoids has mostly been studied for only 1–2 years, with the exception of the comparator study of teriparatide versus ALN, for which 3 year data are available.[146–152] Furthermore, fracture has not been a primary end-point of any of the treatment studies in glucocorticoid-induced osteoporosis. Post-hoc or safety analyses have shown a reduction in morphometric vertebral fracture for ALN, etidronate and risedronate; in the comparator study of teriparatide versus ALN, teriparatide treatment was significantly more effective than ALN in reducing both morphometric and clinical vertebral fractures.[151] There is no evidence from any of the

studies for a reduction in non-vertebral or hip fractures, but the number of subjects studied was small. See Table for approved BPs in glucocorticoid-induced osteoporosis.

Long-term safety data for BP therapy in women treated with oral glucocorticoids are also lacking. However, the increased prevalence of co-morbidities and co-medications in women treated with glucocorticoids might be expected to increase the risk of adverse events, particularly gastrointestinal side effects. In addition, there is evidence from some studies that glucocorticoid therapy may increase the risk of BP-associated AFF and ONJ, although this has not been a consistent finding.[81]

There is evidence that following cessation of glucocorticoid therapy, fracture risk decreases, although it is unclear whether it returns to baseline values.[153] If glucocorticoid therapy is withdrawn, cessation of BP therapy can therefore be considered depending on BMD, fracture history and other risk factors. If fracture risk remains high based on these factors, the Task Force suggests that treatment be continued. In women who continue to take glucocorticoids long-term in a dose >5 mg/day of oral prednisolone or equivalent, continuation of bone protective therapy is generally indicated.[145]

Current guidelines on the management of glucocorticoid-induced osteoporosis do not specifically address the issue of duration of therapy in patients treated with BPs.[144, 145] However, in those women who require continued bone protective therapy and who have received BPs for more than 5 years, switching to teriparatide may be considered. The ability of BMD measurements and/or fracture risk algorithms such as FRAX to predict fracture in individuals taking glucocorticoids and treated with bone protective therapy has not been tested. However, higher T-score thresholds than those used in postmenopausal osteoporosis, including the −2.5 hip T-score cut-off used in the proposed algorithm, may be appropriate in such patients given the higher BMD at which fractures occur.

Most BP trials in patients on glucocorticoids were conducted in women and men. Thus, men aged above 50 years who are treated with long-term glucocorticoids >5mg/day are also at increased risk of fracture and may benefit from continuation of therapy.[144]

Long-term Bisphosphonate Therapy in Men

The efficacy of BP therapy in men has mostly been studied for 2–3 years, with extension studies proceeding as long as 4 years.[154–159] ALN, risedronate, and ZOL have been approved for treatment of osteoporosis in men, but not ibandronate (see Table). The optimal duration of therapy in men has not been determined. Unlike for postmenopausal women, fractures have not been the primary end-point for any of the BP treatment studies in men except for a single ZOL trial.[160] There is no evidence from any of the studies for a reduction in non-vertebral or hip fractures in men (see Table), although men were included in the ZOL post-hip fracture trial[140] in which a reduced fracture risk was demonstrated in the overall study population. Long-term safety data for BP therapies in men are also lacking. The prevalence of co-morbidities and co-medications in men might be expected to lead to similar risk of adverse events as in women. There is no evidence from studies that long-term BP therapy increases the risk of BP-associated AFF and ONJ more in men than women. There is no evidence that cessation of BP therapy in men leads to greater or more rapid

increase in fracture risk than in women. It remains unclear how long it takes in men for fracture risk to return to baseline values before treatment, but presumably this is similar to postmenopausal women. If fracture risk remains high based on post-treatment BMD or other risk factors as suggested for post-menopausal women, continued treatment should be considered. In men who require continued bone protective therapy and who have received BPs for more than 5 years, switching to teriparatide may be considered.

In light of these considerations, the algorithm developed by the ASBMR Task Force on Long-Term Bisphosphonates can be considered generally applicable to older men, although evidence in men is much scarcer than in postmenopausal women. Men on long-term BP therapy presumably have similar safety issues as postmenopausal women, with no greater risks identified in men. It should be reasonable to continue treatment in men on long-term therapy with a history of hip, spine, or multiple other osteoporotic fractures or major osteoporotic fracture while on therapy. For other men who have hip BMD T-score above −2.5, and who are not considered high risk due to age or other risk factors such as androgen deprivation therapy for prostate cancer, consideration of a drug holiday is reasonable for 2–3 years. Again, those men on risedronate may need earlier re-assessment. On the other hand, for men who have these types of fractures, or have a hip BMD T-score at or below −2.5, or who are high risk it is reasonable to continue treatment, with reassessment for possible drug holiday in 2–3 years. This conclusion is based on the evidence that changes in surrogates for fracture (BMD) in response to BPs are similar in men and women. The IOF and ISCD recommend that a white female database should be used for calculation of the T-score in men, as does the FRAX on-line calculator, while the NOF and Endocrine Society recommend the use of a white male database. The former approach would decrease the number of men who would be considered eligible for continued treatment after 3–5 years of BP. The impact of database selection in men on fracture prediction and actual fracture incidence was investigated by Ensrud et al in treatment naive men from the Mr Os cohort in the US.[161] The authors demonstrated that in the subgroup of men with osteoporosis exclusively defined by T-score using a female reference database, the proportion of subjects who actually experienced osteoporotic fractures (major or hip) were highest, compared to those in the subgroup identified by the use of a male database, or other subgroups.

CONCLUSIONS

It is obvious that there is relatively little evidence from which the Task Force can base recommendations, and indeed we have presented management suggestions based on limited data and clinical experience. The cases presented in Appendix I demonstrate how individualization of management is achieved. They also show that even if there were multiple randomized controlled studies on which the algorithm could be based, clinical judgment will still play an important role in taking care of patients with osteoporosis. As has been discussed in a series of papers on guidelines[162] basing guidelines on randomized trials does not address the impact of coexisting conditions in many patients with a given disorder. This is particularly true for osteoporosis because most patients are older and very often have many co-morbidities.

It is unlikely that there will ever be randomized controlled trials of osteoporosis patients of sufficient size and duration to provide clear evidence that a given strategy for long-term management leads to fewer osteoporotic fractures. Observational studies may provide some information, but they are always affected by potential unmeasured confounders and by the fact that many patients are not adherent to osteoporosis therapy. With new medications in development, it may be possible to treat patients with a sequence of therapeutic agents in the hopes that such a strategy will lead to fewer adverse events but improved fracture risk reduction. Nonetheless, the new drugs will likely be approved based on registration trials similar to the ones for existing approved drugs, and no trials are anticipated to address sequential therapies over extended periods of times. The clinician caring for the patient with the chronic disorder of osteoporosis will need to use the art in addition to the science of medicine. The algorithm created by the Task Force will be only one tool to help in clinical decision-making.

Research Needs and Future Directions

It is unlikely that additional evidence from the FLEX and HORIZON extension studies will result in major changes in the suggested algorithm in the near future. However, there is a pressing need to validate the use of FRAX or other fracture risk calculators in individuals on BP therapy, as suggested in the algorithm. Similarly, investigations of additional tools or different approaches to use bone turnover markers, to identify high risk individuals while on or off therapy, and to monitor individuals off therapy are also needed. Studies of sequential therapy may identify new long-term strategies for fracture risk reduction. Finally, lessons learned from the prolonged BP therapy experience should be taken into account when developing protocols for extension studies for current and future therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

The American Society for Bone and Mineral Research (ASBMR) is well served by the fact that many of those responsible for policy development and implementation have diverse interests and are involved in a variety of activities outside of the Society. Accordingly, the ASBMR requires all ASBMR Officers, Councilors, Committee Chairs, Editors-in-Chief, Associate Editors, and certain other appointed representatives to disclose any real or apparent conflicts of interest (including investments or positions in companies involved in the bone and mineral metabolism field), as well as any duality of interests (including affiliations, organizational interests, and/or positions held in entities relevant to the bone and mineral metabolism field and/or the American Society for Bone and Mineral Research).

The committees, task forces, and editorial boards of the ASBMR and its publications carry out the work of the Society on behalf of the membership. The distinct functions of the committees, task forces, and editorial boards are intended to address the broad mission of the ASBMR: to promote excellence in research and education, to integrate basic and clinical science in the field of bone and mineral metabolism, and to facilitate the translation of research into clinical practice and the betterment of human health. Chairs and members of committees, task forces, and editorial boards must assure that they act in these roles in a manner free from commercial bias and that they resolve any conflict or duality of interest or disclose them and then recuse themselves from related deliberations and voting. Below is a summary of disclosures from each task force member.

Robert Adler	McGuire VA Medical Center	Amgen	Consulting Fees (other than Advisory Board or Board of Directors)	Individual	Under $6,000	Current	Research consultant on 2 academic studies of osteoporosis treatment.
		Genentech	Research Grants	Institution	$6,000 – $20,000	Past	PI for investigator-initiated study of pituitary dysfunction in military traumatic brain injury. Study has ended.
		Merck	Research Grants	Institution	$6,000 – $20,000	Past	Completed study of odanacatib in men.
		Novartis	Research Grants	Institution	$6,000 – $20,000	Past	Completed extension study of zoledronic acid treatment of postmenopausal osteoporosis.
		Eli Lilly	Research Grants	Institution	$6,000 – $20,000	Past	Completed surveillance study of growth hormone replacement in adults.
		Amgen	Research Grants	Institution	$6,000 – $20,000	Past	Completed study of bisphosphonate adherence using large administrative databases.
Ghada El-Hajj Fuleihan	American University of Beirut-Medical Center	Leis Laboratoires Services	Other	Institution	$6,000 – $20,000	Current	Educational Grant to hold a densitometry ISCP Academy Course.
Douglas Bauer	University of California, San Francisco						No past disclosures reported
Bart Clarke	Mayo Clinic College of Medicine						No past disclosures reported
Gregory Clines	University of Michigan						No past disclosures reported
Juliet Compston	University of Cambridge School of Clinical Medicine	GSK	Consulting Fees (other than Advisory Board or Board of Directors)	Individual	Under $6,000	Past	Advisory Board attendance
		Servier	Honoraria or Royalties	Individual	Under $6,000	Past	Speaker at several national meetings

Warner Chilcott/University of Massachussets	Research Grants	Institution	> $100,000	Past	Participation in GLOW study (Global Longitudinal study of Osteoporosis in Women)
Sanofi-Aventis/University of Massachussetts	Research Grants	Institution	> $100,000	Past	Participation in GLOW study
Nycomed	Research Grants	Institution	> $100,000	Past	Research grant for histomorphometric analysis of biopsies from PEAK study FINISHED
Amgen	Honoraria or Royalties	Individual	Under $6,000	Past	Speaker at several national meetings
Warner Chilcott	Honoraria or Royalties	Individual	Under $6,000	Past	Speaker at national meetinmg
MSD	Consulting Fees (other than Advisory Board or Board of Directors)	Individual	Under $6,000	Past	Attendance at Advisory Board
Amgen	Honoraria or Royalties	Individual	Under $6,000	Past	Speaker at one national and one international meeting
GlaxoSmithKline	Research Grants	Institution	> $100,000	Past	Histomorphometric analysis of bone biopsies from HIV positive individuals
Gilead	Honoraria or Royalties	Individual	Under $6,000	Past	Speaker at national and international meetings
Amgen	Consulting Fees (other than Advisory Board or Board of Directors)	Institution	> $100,000	Past	Member of Data Monitoring Committee for FREEDOM study Advisory Board attendance
Acuitas	Research Grants	Institution	> $100,000	Past	Study of MRI-based analysis of trabecular bone structure - no longer active
Medtronic	Consulting Fees (other than Advisory Board or Board of Directors)	Individual	Under $6,000	Past	Advice on submission to NICE HTA for vertebroplasty and kyphoplasty FINISHED
Nycomed	Honoraria or Royalties	Individual	Under $6,000	Past	Speaker at several international meetings
Novartis	Consulting Fees (other than Advisory Board or Board of Directors)	Institution	> $100,000	Past	Member of Data Safety Monitoring Board for HORIZON studyAttendance at Advisory Board meeting
Sanofi-Aventis	Research Grants	Institution	Under $6,000	Past	Participation in GLOW study
MSD	Honoraria or Royalties	Institution	Under $6,000	Past	Speaker at national meeting
Acuitas	Research Grants	Institution	> $100,000	Past	Study of MRI-based analysis of trabecular bone structure - no longer active

		Sanofi-Aventis	Research Grants	Institution	Under $6,000	Past	Participation in GLOW study
Matthew Drake	Mayo Clinic College of Medicine						No past disclosures reported
Beatrice Edwards	MD Anderson Cancer Center						No past disclosures reported
Murray Favus	University of Chicago	CVS/Caremark	Consulting Fees (other than Advisory Board or Board of Directors)	Individual	Under $6,000	Current	I provide educational information to professional advisory board and pharmaceutical staff on current information on osteoporosis inlcuding bone metabolism, pathophysiology, medication effects, FDA approved medications.
Susan Greenspan	University of Pittsburgh	Merck	Advisory Board	Individual	Under $6,000	Current	Scientific advisory board for osteoporosis studies
		Amgen	Research Grants	Institution	$20,000 – $50,000	Current	PI for a research grant on osteoporosis therapy.
		Lilly	Research Grants	Institution	$20,000 – $50,000	Current	PI for a research grant on therapy for osteoporosis
Ross McKinney	Duke University School of Medicine	American Journal of Bioethics	Other	Individual	$0	Current	Member of the editorial board of the American Journal of Bioethics, as well as its conflict of interest committee.
		Gilead Sciences	Other	Individual	Under $6,000	Current	Member of several data safety monitoring boards for Gilead Sciences studies.
		Janssen Pharmaceuticals	Advisory Board	Individual	$6,000 – $20,000	Current	Member of a Pediatric Advisory Board, to help develop appropriate strategies for evaluating new agents in children.
Robert Pignolo	University of Pennsylvania						No past disclosures reported
Deborah Sellmeyer	The Johns Hopkins Bayview Medical Center	Amgen, Inc.	Other	Individual	$0	Current	Member, Data Safety Monitoring Board.

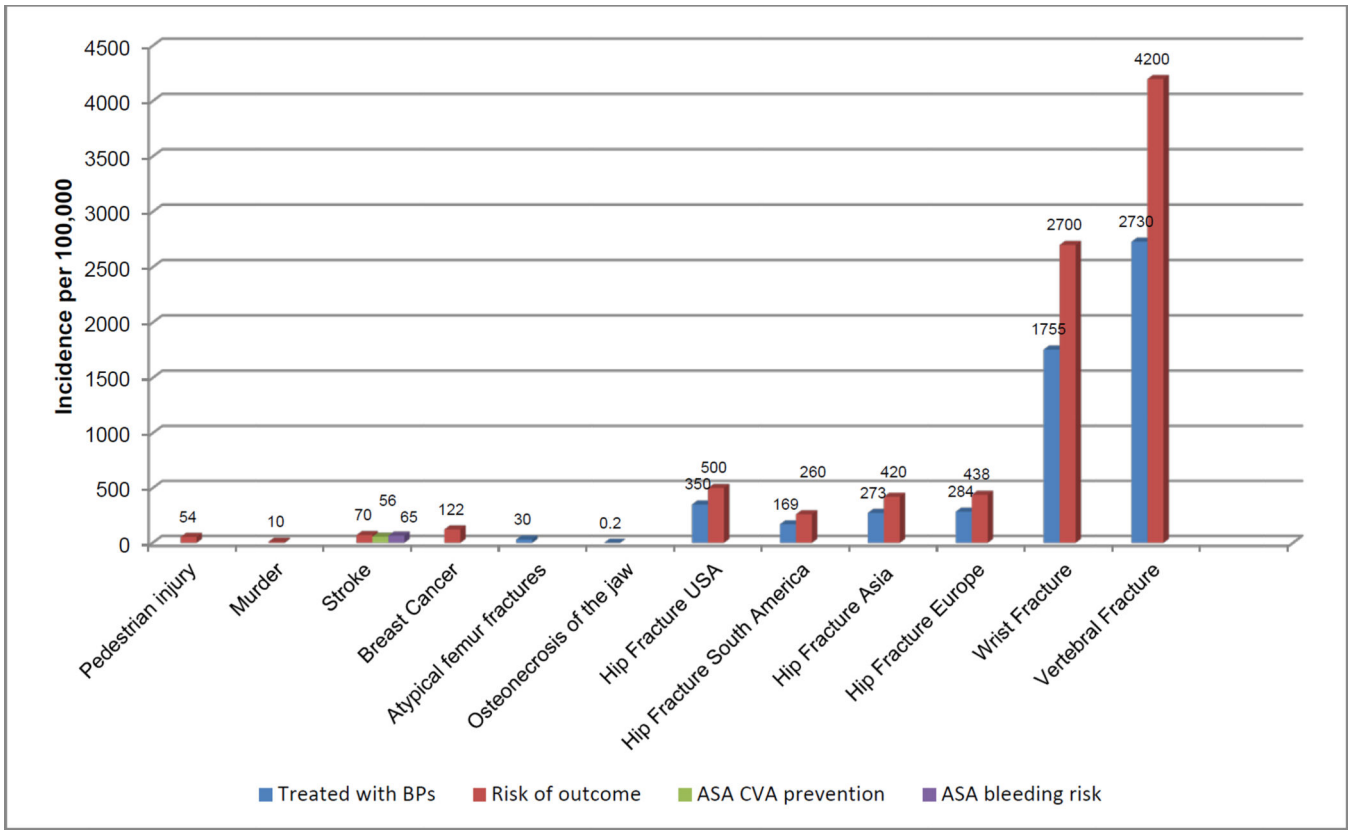

Figure 1. Risks Associated with Bisphosphonate Use and Other Health Outcomes

Likelihood of suffering fractures and other adverse events in adult patients. For fractures, the risk of fractures on BP therapy, and for stroke, the risk on aspirin therapy is illustrated. Fracture incidence rates are age-standardized, while for others they represent crude rates in the US. For ONJ and AFF the risks represent those reported while on BP therapy for 10 years.

Likelihood of suffering fractures and other adverse events in adult patients.[1–4] For fractures, the risk of fractures on BP therapy, and for stroke the risk on aspirin therapy is also illustrated. For ONJ[5] and AFF[6] the risks represent those reported while on BP therapy for 10 years.

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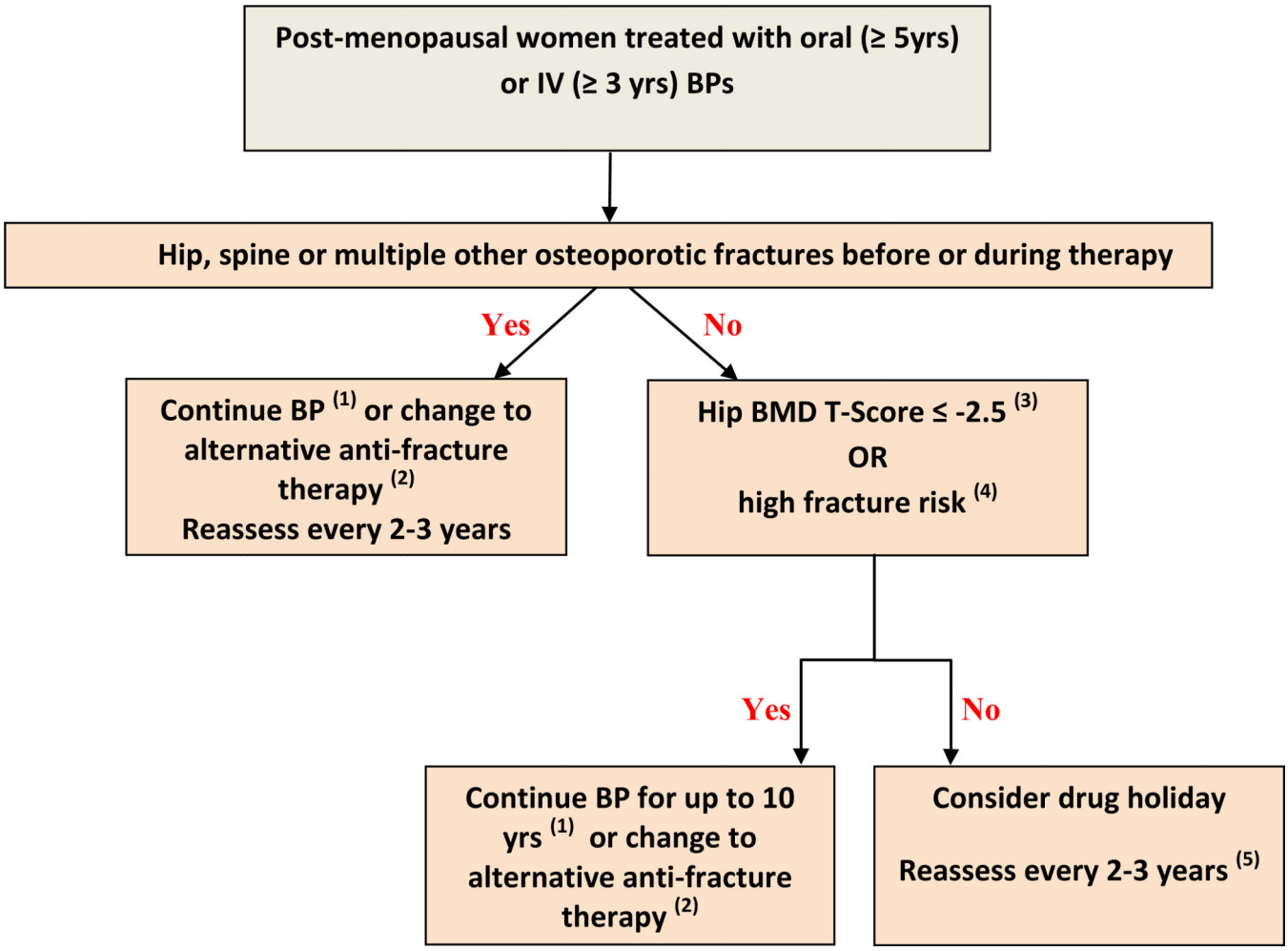

Figure 2. Algorithm for the Management of Postmenopausal Women on Long-Term Bisphosphonate Therapy

(1) Based on evidence for vertebral fracture reduction in FLEX and Horizon extension studies, continue BP therapy for up to 10 years with oral or up to 6 years with intravenous BPs. For patients who fracture on therapy, assess adherence and rule out secondary causes of osteoporosis. Management in high risk patients after 10 years of BP therapy is discussed in the text.

(2) The benefits of switching to an alternative anti-fracture therapy after prolonged bisphosphonate treatment have not been adequately studied.

(3) Based on FLEX and Horizon extension study (Caucasian women), may not apply to other populations.

(4) High fracture risk: defined by older age (70–75 yrs), other strong risk factors for fracture, or FRAX fracture risk score that is above country specific thresholds. The use of FRAX in patients on therapy was only assessed in the Manitoba observational cohort.(1)

(5) Reassessment includes clinical evaluation, risk assessment including risk factors, and may include bone density measurement by DXA. The monitoring interval with DXA should be based upon changes that are detectable and clinically significant. Reassessment may be

necessary at less than 2 years in patients with a new fracture, or in light of anticipated accelerated bone loss (e.g. institution of aromatase inhibitor or glucocorticoid therapy).

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Table

Efficacy of Osteoporosis Approved Medications in North America and Europe by Approval Indication and by Skeletal Site for Fracture Reduction (Updated December 2014, http://www.aub.edu.lb/fm/cmop/downloads/e-summary.pdf)

	Postmenopausal Osteoporosis				Fracture Risk Reduction		
	Prevention	Treatment	Men	GIO*	Vertebral fracture	Hip fracture	Non Vertebral fracture
ANTI-REMODELING AGENTS							
Alendronate	✓	✓	✓	✓	PMW	PMW	PMW
Ibandronate	✓	✓	-	-	PMW	-	PMW[a]
Risedronate	✓	✓	✓	✓	PMW	PMW	PMW
Zoledronic acid	✓	✓	✓	✓	PMW and M[b]	PMW and M[b]	PMW and M[b]
Bazedoxifene**	✓	✓			PMW	-	PMW[c]
Lasofoxifene**	✓	✓			PMW	-	PMW
Raloxifene	✓	✓	-	-	PMW	-	-
Denosumab	-	✓	✓	-	PMW and M[d]	PMW	PMW
Estrogen	✓	-	-	-	PMW	PMW	PMW
Conjugated estrogen/ Bazedoxifene***	✓	-	-	-	-	-	-
Calcitonin&	-	✓	-	-	PMW	-	-
Tibolone**	✓	-	-	-	PMW	-	PMW
ANABOLIC AGENTS							
Teriparatide	-	✓	✓	✓	PMW and M[e]	-	PMW
OTHERS							
Strontium ranelate[f]	✓	✓	✓	-	PMW	PMW[g]	PMW

PMW=Post-menopausal women; M=Men

*GIOP fracture data: One alendronate and one risedronate trial each showed a significantly reduction in vertebral fractures compared to placebo; one trial showed that teriparatide significantly reduced vertebral fractures compared to alendronate. One trial compared zoledronic acid with risedronate and showed no significant difference in vertebral fracture reduction. There are no studies comparing zoledronic acid or teriparatide with placebo.

**Only approved in Europe.

***Approval indication: FDA approval for osteoporosis prevention and European Medicines Agency approval for estrogen deficiency symptoms.

[a] Post hoc analysis, in women with FN BMD T-score <-3.

[b] Same study included men and women and there was no treatment by gender interaction; there was a lack of a statistically significant fracture reduction in men sub-population, as the gender-based subset analysis was powered for a BMD endpoint and not for anti-fracture efficacy. Vertebral fracture reduction has been demonstrated in another trial conducted exclusively in men.

[c] Post hoc analysis.

[d] Trial in men with prostate cancer on androgen deprivation therapy (ADT)

[e] In all the study group there was a significant reduction in moderate to severe fractures in the combined group (Teriparatide 20 mcg and 40 mcg). In the subgroup of men who had prevalent fracture at baseline, there was a significant reduction in all vertebral fractures in the combined group (Teriparatide 20 mcg and 40 mcg) and a significant reduction in moderate to severe vertebral fractures in each group separately.

[f] Approved by EMEA with restrictions: “Strontium ranelate is now restricted to the treatment of severe osteoporosis in postmenopausal women and adult men at high risk of fracture who cannot use other osteoporosis treatments due to, for example, contraindications or intolerance. The risk of developing cardiovascular disease should be assessed before starting treatment. Treatment should not be started in people who have or have had: ischemic heart disease or peripheral arterial disease or cerebrovascular disease or uncontrolled hypertension. Cardiovascular risk should be monitored every 6–12 months. Treatment should be stopped if the individual develops ischemic heart disease, peripheral arterial disease, or cerebrovascular disease, or if hypertension is uncontrolled”.

[g] Subgroup of high risk post-menopausal women, age ≥74 years and femoral neck bone mineral density T score ≤−3, corresponding to −2.4 according to NHANES reference.

[&] Calcitonin withdrawn from EU market, available in US for restricted conditions. See main text and FDA link.