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Clinical practice guidelines for postmenopausal, glucocorticoid-induced and male osteoporosis: 2022 update

Spanish Society for Bone and Mineral Metabolism Research (SEIOMM)

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Summary
This update incorporates the most relevant information that has emerged during the seven years since the publication of the previous version, with a particular focus on diagnostic procedures and therapeutic options. Among the diagnostic procedures, we highlight the use of the Trabecular Bone Score (TBS) and densitometry for identifying the risk of vertebral fractures. Novel therapeutic modalities include the use of anabolic drugs with comparative studies focused on their efficacy for the treatment of severe osteoporosis. Guidelines for actions to be taken after discontinuation of antiresorptive agents, sequential therapy and current recommended treatment schemes are included

Key words: osteoporosis, fractures, densitometry, anabolic, antiresorptive.

Introduction

Seven years have passed since the publication of the previous version of the Osteoporosis Guidelines of the Spanish Society for Bone Research and Mineral Metabolism (SEIOMM) that was created in accordance with the standard methodology of evidence-based medicine[1]. This update incorporates the most essential information that has appeared since the publication of the previous version, with particular reference to new diagnostic procedures and therapeutic options. Novel diagnostic modalities discussed in these guidelines include the Trabecular Bone Score (TBS) and the detection of vertebral fractures by densitometry. Among the therapeutic options, we discuss the use of novel anabolic drugs (abaloparatide and romosozumab). Studies that compare the efficacy of various drug regimens for the treatment of severe osteoporosis are also considered. Likewise, the guidelines for action after the withdrawal of antiresorptive drugs and other sequential and combined treatment schemes are assessed.

To prepare this update, a group of experts (see author listing) reviewed each of the sections and incorporated new findings from reports published in recent years. The initial draft of the manuscript was then critically examined by a group of experts. Once their comments were considered, the new text was distributed to other interested parties, including SEIOMM partners, patient associations, the Spanish Agency for Medicines and Health Products, and pharmaceutical industries so that each might provide additional comments and contributions to the document. The document was then re-analyzed again by the group of experts tasked with drafting the guidelines. The recommendations were graded according to the level of evidence as indicated in Tables S1 and S2.

The topics reviewed in this document include (1) diagnostic and therapeutic aspects of primary osteoporosis in postmenopausal women, (2) specific findings associated with osteoporosis in males, and (3) new information on the diagnosis and treatment of glucocorticoid-induced osteoporosis.

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ASSESSMENT OF PATIENTS AT RISK FOR OSTEOPOROSIS

1. Fracture risk factors

The main factors associated with the risk of bone fractures in patients presenting with osteoporosis include gender, age, bone mineral density (BMD), history of fragility fracture, history of hip fracture in a first-degree relative, and low body weight (i.e., body mass index [BMI] <20 kg/m^2). Paradoxically, obesity can also be a risk factor for some peripheral fractures, including those of the humerus and distal third of the radius. Recognised risk factors also include various diseases including hypogonadism, early menopause, prolonged amenorrhea, anorexia nervosa, malabsorption, rheumatoid arthritis, diabetes (particularly type 1), immobilization, as well as their treatments, e.g., glucocorticoids, inhibitors of aromatase or gonadotropin-releasing hormone agonists[2,3]. Other disorders and medications that may be associated with the development of osteoporosis, (although probably less strongly) are hyperparathyroidism, hyperthyroidism, selective serotonin reuptake inhibitors, proton pump inhibitors, and anticonvulsants, as well as smoking and excessive alcohol consumption. Calcium deficiency and vitamin D deficiency have traditionally been considered risk factors for osteoporosis, although their precise role continues to be a subject of debate (Table 1).

Factors associated with an increased risk of falls, including postural instability, inability to get up from a chair, visual impairment, and some neurological problems are also associated with an increased risk of fractures.

After a first fracture, the greatest risk of sustaining a new fracture occurs within the first two years, particularly if the first fracture was vertebral[4-6]. This has led to the concept of an "imminent risk" of fracture. The main factors that have been associated with imminent risk are older age, female gender, white race, recent fracture, falls, and some comorbidities and treatments (e.g., very low bone mass, cardiovascular disease, obstructive pulmonary disease, chronic and depression, and anxiety, as well as the use of sedatives, hypnotics, glucocorticoids, and muscle relaxants).

In conclusion, recent evidence suggests that an assessment of clinical risk factors combined with the measurement of BMD is an effective method for assessing fracture risk (Recommendation A).

2. Bone densitometry and related techniques

Dual-energy X-ray absorptiometry (DXA) can be used to quantify BMD and is thus the procedure most commonly used to estimate fracture risk[7]. The results are expressed in terms of T-score, which is the number of standard deviations (SDs) by which the BMD value obtained differs from that of the normal young adult population (i.e., 20–29 years of age). The World Health Organization (WHO) guidelines state that osteoporosis can be diagnosed when the BMD is less than -2.5 T[8]. The organization has since clarified that this value must correspond to a measurement made on the neck of the femur using data from the National Health and Nutrition Examination Survey (NHANES III) study as a reference[9]. By contrast, the International Society for Clinical Densitometry (ISCD)[10] states that this diagnosis can be established based on a -2.5 T value detected in the lumbar spine or total hip as well as the femoral neck. The WHO also defined normal bone density, osteopenia (i.e., low bone mass), as well as established or severe osteoporosis (Table 2).

BMD measured at the mid-third of the radius may also be used to diagnose osteoporosis when the hip and lumbar spine cannot be used or interpreted[11].

In, The ISCD recommends that instead of T-scores, Z-scores adjusted for ethnicity or race be used when diagnosing osteoporosis in premenopausal women, men younger than 50 years of age, and children. Z-scores ≤-2.0 are identified as "low bone mineral density for age chronological" or "below expected range for age". Z-scores >-2.0 are identified as"within expected range for age".

Evaluation of therapeutic efficacy is an indication for densitometry. This examination might be repeated after two to three years of treatment.

Other measurement techniques, including quantitative ultrasonometry and quantitative computed tomography, among others, also provide values that are related to fracture risk. However, they are not recommended as diagnostic procedures at this time.

Lateral projections of DXA studies can be used to identify vertebral fractures (i.e., VFA, or “vertebral fracture assessment”). However, the accuracy of this procedure is lower than that of conventional radiography, most notably for the diagnosis of fractures of the upper thoracic vertebrae.

The Trabecular Bone Score (TBS) is a parameter that describes bone texture based on data obtained from a DXA image of the lumbar spine. TBSs are typically reduced in patients who have sustained fragility fractures, and it is a useful value for assessing fracture risk in women and men over 50 years of age, independent of BMD findings. The combination of BMD and TBS is superior to BMD alone for the prediction of fracture risk. A TBS may be particularly useful in assessing fracture risk in patients diagnosed with diabetes or primary hyperparathyroidism as well as those treated with glucocorticoids. The TBS is also expressed in absolute terms and as a T- score.

A TBS value <1.230 (T <-3) is indicative of a degraded trabecular microstructure and a high risk of fracture. The TBS has been included in the Fracture Risk Assessment Tool (FRAX) which can be used to calculate the absolute risk of fracture in a given patient.

Despite the proven usefulness of DXA for assessing patients with an elevated risk of sustaining a fracture, the sensitivity and specificity of this modality remain limited. DXA does not identify all subjects at risk of fracture; more than 50% of peripheral fractures occur in patients with a T-score >-2.5[12,13]. Current trends suggest that BMD measurements might be considered together with the clinical risk factors when calculating an absolute fracture risk[14,15].

There are no universally accepted criteria regarding when to perform densitometry. The general recommendation is that this procedure might be performed when risk factors that are strongly associated with osteoporosis or fractures emerge (Table 1), including:

a) Disorders frequently associated with osteoporosis, such as rheumatoid arthritis, early menopause, hyperparathyroidism, hyperthyroidism, malabsorption, and anorexia nervosa, among others.

b) Treatments with negative effects on the bone, such as glucocorticoids, antiestrogens, and antiandrogens, among others.

c) Other factors (especially if two of them are observed in a single patient): age over 65 years (according to some authors), low weight (BMI <20 kg/m^2), family history of osteoporosis, alcoholism, and smoking, among others.

In conclusion, DXA can be used to measure BMD in the proximal femur and lumbar spine to assess the risk of fracture (Recommendation A). A TBS can provide additional information on the risk of fracture in an individual patient (Recommendation B).

3. Markers of bone turnover

Bone turnover markers (BTMs) provide information on the dynamics of bone turnover. Among the markers of bone formation, significant research has focused on levels of osteocalcin, bone alkaline phosphatase, and the carboxy –and amino-terminal propeptides of type I procollagen (PICP and P1NP). Markers of bone resorption include the carboxy– and amino-terminal telopeptides of collagen I (CTX in blood, s-CTX and NTX in urine) and tartrate-resistant acid phosphatase 5b (FATR 5b). Various international organizations (for example, the International Federation of Clinical Chemistry) have recommended the use of P1NP and s-CTX as markers of bone formation and resorption, respectively, for ongoing and future clinical studies. It is important to control the variability of these measurements by obtaining biological samples consistently between 08:00 and 10:00 hrs after an overnight fast.

While BTMs are not useful for diagnosing osteoporosis, this information may be combined with other risk factors to identify, patients with a higher risk of sustaining a fracture. These values are particularly useful for the early assessment of responses to both antiresorptive and anabolic therapy (Evidence 2a)[16,17]. For example, measurements of s-CTX and PINP are recommended as an effective means to monitor bone turnover after discontinuation of denosumab[18].

In conclusion, BTMs can be useful for evaluating therapeutic responses (Recommendation B), but they must be measured under standardised conditions. They are not used routinely to diagnose osteoporosis.

4. Identification of vertebral fractures

Conventional radiography is not sufficiently sensitive or specific when used to assess changes in bone mass[8]. However, the use of this modality is essential when attempting to identify fractures.

A diagnosis of a vertebral fracture requires a decrease of at least 20–25% in height[19]. This is because slight wedging can be confused with deformities of another origin (e.g., sequelae of Scheuermann's disease, small wedging of a degenerative type)[20]. Thus, VFA by DXA may be useful as a first step. Spinal radiography (or DXA) is recommended for patients over the age of 70 years with suspected osteoporosis who present with back pain, glucocorticoid treatment, or a significant decrease in height (>4 cm based on historical data or >2 cm in confirmed height)[21].

In conclusion, reliable identification of vertebral fractures is important in decision-making because these lesions represent a risk for future fractures. Evaluation can be done by radiography or by VFA. However, radiography should not be used as a method of assessing bone mass to establish a diagnosis of osteoporosis (Recommendation A).

Table 1. Diseases and treatments that constitute risk factors for osteoporosis

1. Factors clearly associated with osteoporosis
   - Hypogonadism
   - Early menopause, amenorrhea
   - Anorexia nervosa
   - Malabsorption
   - Rheumatoid arthritis
   - Diabetes (particularly type 1)
   - Immobilization
   - Cushing's disease
   - Drugs
     - Glucocorticoids
     - Aromatase inhibitors
     - Gonadotropin-releasing hormone agonists

2. Other factors associated with less consistency
   - Hyperparathyroidism. Hyperthyroidism
   - Calcium deficiency
   - Vitamin D deficiency
   - Drugs and toxic
     - Selective serotonin reuptake inhibitors
     - Proton-pump inhibitor
     - Anticonvulsants
     - Antiretrovirals
     - Alcohol, tobacco

Table 2. WHO diagnostic criteria for osteoporosis

- Normal: BMD T ≥−1
- Osteopenia or low bone mineral density: BMD T <−1 and >−2.49
- Osteoporosis: BMD T ≤−2.5
- Severe osteoporosis: BMD T ≤−2.5 + fracture

BMD: bone mineral density; T (T-score or T index): comparison with the BMD value reached in a young reference population.

5. Study protocol

In addition to anamnesis and a physical examination, an evaluation of a patient with suspected osteoporosis should include a complete blood count and determination of basic biochemical parameters (kidney and liver function and serum levels of calcium, albumin, phosphorus, alkaline phosphatase, thyrotropin (TSH), and 25-hydroxyvitamin D, as well as a serum protein electrophoresis study). It is useful to quantify calciuria. These tests should be performed before starting treatment and then repeated if clinically indicated. The usefulness of parathyroid hormone (PTH) levels and BTMs remains controversial (see the previous section). Bone densitometry and an assessment of potential vertebral fractures by VFA or radiology will almost always be required. Pertinent studies should be performed to rule out secondary causes of osteoporosis (e.g., hypercortisolism, celiac disease, and systemic mastocytosis, among others) in younger patients (Recommendation C).

6. Risk prediction tools

Various scoring scales have been developed to assess either the risk of developing osteoporosis (i.e., low DXA), or sustaining osteoporotic fractures. Current scoring scales used to assess the risk of densitometric osteoporosis do not include BMD but are useful in deciding when densitometry evaluations should be performed.

The simplest method, known as the Osteoporosis Self-assessment Tool [OST])[22,23] includes only patient age and weight which are variables included in all assessment strategies.

To assess the risk of fractures, the addition of findings from DXA to the clinical data results in their improved predictive value. Several instruments have been developed for this purpose, including FRAX[24], the Garvan Medical Research Institute scale[25], and the QFracture Index[26]. All three have similar discriminatory capacities albeit with only moderate performance[27,28]. FRAX is the most widely used of these instruments on a worldwide basis. Unfortunately, its adaptation in Spain has been inadequate[29] and it underestimates the risk of fracture, most notably major osteoporotic fractures. Other tools, such as EPIC, which has been adjusted to the Spanish population, are currently undergoing validation.

In conclusion, although fracture risk prediction tools may be helpful in decision-making in some cases, their predictive value for our population is limited. Adaptations of FRAX may be used with caution pending the development and validation of newer and more precise instruments (Recommendation C).

AVAILABLE TREATMENTS FOR POSTMENOPAUSAL OSTEOPOROSIS

1. Non-pharmacological interventions

A balanced diet should be maintained by all patients diagnosed with postmenopausal osteoporosis. This would include a protein intake of 1–1.5 g/kg/day. While sun exposure will promote essential vitamin D synthesis, additional supplementation may be needed (see below)[30]. Furthermore, recent evidence suggests that physical exercise that loads the skeleton has a positive effect with respect to preventing falls and reducing the risk of fracture[31]. Routine exercise is recommended, for example, walking every day for at least 30 minutes.

Smoking and excessive alcohol consumption should be avoided, as both are factors associated with decreased bone mass and an increased risk of fractures[32,33].

Although the efficacy of fall prevention programs (beyond basic physical exercise) remains controversial, recent evidence suggests that they are useful in institutionalised elderly patients who undergo repeated falls[34,35].

Hip protectors are slightly effective at reducing the risk of hip fracture. However, poor tolerance by some patients, poor adherence, and a slight increase in the risk of pelvic fractures limit its application[36].

2. Calcium and vitamin D

Patients treated with antiresorptive or anabolic drugs for osteoporosis should be certain to maintain an adequate intake of calcium and vitamin D[37,38]. Serum levels of 25-hydroxyvitamin D (25(OH)D) should be maintained above 20–25 ng/ml, preferably above 30 ng/ml[39]. The recommended daily dose of vitamin D is generally between 800–1200 IU/day, although some patients may need higher doses to maintain adequate serum levels of 25(OH)D. While bi-weekly or monthly equivalents can be considered, administration of large amounts of vitamin D in a single dose (e. g., 500,000 IU/year)[40] is not recommended. The standard dose of calcifediol (25(OH)D3) is 0.266 micrograms every 15–30 days. This form of vitamin D may be preferable in patients with advanced liver disease or problems with intestinal absorption. Occasionally, these patients may require parenteral administration.

Daily intake of calcium should be maintained at 1000-1200 mg/day[30]. While it is preferable to obtain this amount from dietary sources, supplements can be added as necessary. The general population, particularly the elderly, should be advised to maintain adequate nutrient intake, including appropriate levels of calcium and vitamin D. However, the isolated effects of calcium and vitamin D on the progression of osteoporosis are not well-understood; if they exist at all, their impact seems to be limited[41-43].

In conclusion, patients at risk for developing osteoporosis and those undergoing treatment with antiresorptive or anabolic drugs should receive and be certain that they are taking in an adequate supply of calcium and vitamin D. However, these nutrients alone are insufficient treatments in patients who have developed osteoporosis (Recommendation A).

3. Calcitonin

Although treatment with calcitonin was associated with a slight reduction in the risk of vertebral fractures, it has no impact on the risk of peripheral fractures. Furthermore, long-term calcitonin use has been associated with an increased risk of tumors. Thus, calcitonin is not approved for the treatment of osteoporosis[44,45].

4. Thiazides

Although numerous observational studies suggested that treatment with thiazides resulted in increased bone mass and a concomitant reduction in the risk of fracture[46], we have no data that can be construed as recommending its use as a treatment for osteoporosis. Thiazide treatment (e. g., 12–50 mg/day of hydrochlorothiazide or chlorthalidone) can be considered for patients presenting with hypercalciuria[47] (Recommendation D).

5. Estrogen therapy

The results of several clinical trials have revealed the efficacy of estrogens for the prevention of fractures. A recent network meta-analysis revealed that estrogen therapy (with or without progesterone) reduced the risk of vertebral fracture by 34% (hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.49–0.89); hip fracture by 29% (HR, 0.71; 95% CI, 0.52–0.98); and non-vertebral fractures by 21% (HR, 0.79; 95% CI, 0.70-0.90)[48]. However, the side effects of estrogen therapy revealed by the Women's Health Initiative (WHI) study and other trials include an increase in cardiovascular events and breast cancer. Thus, estrogen is not recommended as a treatment for osteoporosis ex cept in women with early menopause or at a high risk of fracture in which there is no other therapeutic option available[49]. Estrogens may be an effective treatment for osteoporosis in women already receiving these drugs as therapy for the climacteric syndrome.

In conclusion, although estrogen therapy is effective in preventing osteoporotic fractures, it is not recommended for routine use given the possibility of serious side effects (Recommendation A). Estrogens can be considered in patients exhibiting early menopause who have no other contraindications and/or in cases in which no other therapeutic options are available (Recommendation D).

6. Selective Estrogen Receptor Modulators (SERMs)

Results from several recent studies document that these drugs can increase BMD in the spine over follow-up pe-

riods as long as eight years[50,51]. A recent meta-analysis revealed that raloxifene and bazedoxifene reduce the risk of vertebral fracture by 40%, although neither drug has any impact on non-vertebral fractures[48]. The main complication associated with this class of drugs is an increased risk of venous thromboembolic disease.

In conclusion, SERMs may be indicated for the treatment of osteoporosis because they reduce vertebral fractures, but they do not reduce the risk of non-vertebral fractures (Recommendation A).

7. Tibolone

Although the use of this drug will reduce the risk of both vertebral and non-vertebral fractures in women under 60 years of age (or <10 years of menopause)[52,53], its cardiovascular side effects limit its use. At this time, tibolone may be prescribed for patients who are not at high risk for cardiovascular disease or breast cancer who cannot be treated with other drugs (Recommendation B). This drug has not been approved for the treatment of osteoporosis in Spain.

8. Phytoestrogens and isoflavones

Isoflavones may have a favorable effect on BMD[54]. However, they are not currently recommended for the treatment of osteoporosis due to the lack of data focused on their efficacy in preventing fractures.

9. Bisphosphonates (BPs)

9.1. Etidronate

While etidronate reduces the incidence of vertebral fractures by about 40%[55], it has no impact on non-vertebral fractures (Evidence 1a; Recommendation A). This drug has fallen into disuse as more effective BPs have become available.

9.2. Alendronate

Alendronate increases BMD at the lumbar spine and the hip in both treatment and prevention studies performed in osteoporotic women (Evidence 1a). Both daily and weekly administration of this drug result in similar efficacy (Evidence 1a). At a dose of 70 mg/week, alendronate reduces the incidence of vertebral, non-vertebral, and hip fractures by ~45%, 25–30%, and 45–55%, respectively[56,57] (Evidence 1a). Most clinical trials focused on this drug included a treatment period of three to five years. However, administration over longer periods may sometimes be recommended. One extension study revealed that patients who discontinued treatment after five years had a higher risk of suffering clinical vertebral fractures than those who continued on this drug[58]. Older patients with low BMDs at the femoral neck at the time of treatment withdrawal exhibit a greater risk of fracture, including non-vertebral fractures[59,60]. Several meta-analyses and studies with data from real-world practice documented efficacy findings that were similar to those reported previously[48,61]. Alendronate is generally well tolerated, although it can result in some side effects (described below). Long-term use of this drug has been associated with an increase in atypical fractures. Recently, there has been speculation as to its possible beneficial cardiovascular ef fects[62].

In conclusion, alendronate has a definitive role in the treatment of osteoporosis as it reduces the risk of vertebral, non-vertebral, and hip fractures in susceptible individuals (Recommendation A).

9.3. Risedronate

A recent systemic review and network meta-analysis documented the efficacy of risedronate in preventing vertebral, non-vertebral, and hip fractures in postmenopausal women with osteoporosis or osteopenia. The reduction in risk of fracture compared to placebo was 39% for vertebral fracture, 27% for hip fracture, and 22% for non-vertebral fractures[48,63] (Evidence 1a). Risedronate can be administered in single doses of 35 mg per week or 75 mg on two consecutive days per month[64,65]. A new gastro-resistant formulation has been developed that does not require fasting before its administration[64]. Risedronate is well tolerated with side effects similar to those of other BPs as described below.

In conclusion, administration of risedronate results in reductions in the incidence of vertebral, non-vertebral, and hip fractures. Thus, this drug has a definite role in the treatment of osteoporosis (Recommendation A).

9.4 Ibandronate

Ibandronate can be administered orally at 150 mg/dose once a month or intravenously at 3 mg every 3 months intravenously (NB: the intravenous formulation is not marketed in Spain). Ibandronate reduces the risk of vertebral fractures by ~60% but has no impact on non-vertebral fractures (Evidence 1b). In a meta-analysis that included 107 trials focused on drugs that can be used to treat osteoporosis, ibandronate was identified as somewhat less efficacious at reducing the incidence of fractures than other BPs[48].

In conclusion, ibandronate reduces the risk of vertebral fractures (Recommendation A), although had no apparent effect on non-vertebral fractures.

9.5. Zoledronate

Zoledronate administered intravenously at a dose of 5 mg/year reduces the incidence of vertebral, non-vertebral, and hip fractures by 70%, 25%, and 40%, respectively[66] (Evidence 1b). Patients who, continue treatment with zoledronate for an additional three years after completion of an initial three years of treatment benefit from an additional 50% reduction in the risk of vertebral fracture compared to those who are not maintained on this regimen[67]. In a clinical trial that included women with what was called “osteopenia” who were older than 65 years of age, administration of this drug every 18 months also reduced the incidence of vertebral and non-vertebral fractures[68]. The side effects of this drug are described in the section to follow. While one network meta-analysis identified no differences between zoledronate and any of the other BPs studied in terms of fracture prevention[69], two other studies revealed that zoledronate was shown to be more effective than the other formulations[70,71].

In conclusion, zoledronate also reduces the incidence of vertebral, non-vertebral, and hip fractures, and thus plays an important role in osteoporosis treatment (Recommendation A).

9.6. Adverse effects of bisphosphonates[72,73]

BPs are generally safe and well-tolerated drugs. However, given their central role in the treatment of osteoporosis, possible adverse effects are discussed in detail below. It should be noted that other beneficial effects of these drugs have been described, including a decrease in mortality, especially that associated with cardiovas-

cular events, and a reduction in the incidence of some cancers. However, the actual extent of these effects remains controversial[74-76].

a) Adverse effects on the upper digestive tract have been described in patients taking oral BPs (i.e., esophagitis and esophageal ulcers). These responses can be largely avoided if the drug is ingested with a glass of water with an upright position maintained for the following 30–60 minutes. Contrary to what was suggested in some of the initial studies, these drugs do not increase the incidence of cancer of the esophagus or stomach[77,78]. However, BPs should not be prescribed for patients with disorders of the upper digestive tract, notably those with difficulty swallowing or Barrett's esophagus.

b) Acute-phase response or flu-like symptoms have been described mainly in response to intravenous BPs. This reaction typically appears within 24–36 hours of drug administration, can be relieved with acetaminophen, and usually disappears within three days[79]. This response had been reported in 25–35% of patients receiving intravenous zoledronate for the first time. The intensity typically diminishes in response to subsequent injections.

c) Studies regarding the association of BP treatment (especially intravenous) with atrial fibrillation have led to discordant results[80]. This has not been identified as a potential limitation for treatment in cases in which these drugs are indicated. Of note, several studies documented a reduced incidence of cardiovascular events in patients treated with BPs[81,82].

d) BPs are not recommended in patients with renal failure with glomerular filtration rates (GFRs) ≤30 ml/min. However, even in patients with normal GFRs, BPs can promote the development of renal failure if administered via the intravenous route without due caution. Overly rapid administration (i.e., over a period of <15 minutes for zoledronate), simultaneous use of potentially nephrotoxic agents (NSAIDs, diuretics), and drug administration to dehydrated patients must be avoided[83,84].

e) Intravenous BPs can result in clinically significant hypocalcaemia, especially when administered to patients with decreased GFRs, vitamin D deficiency, insufficient calcium intake, or very high bone turnover.

f) The risk of developing osteonecrosis of the jaw (ONJ) among patients treated with BPs for osteoporosis is very low (1/1,500 –1/100,000 patient-years, depending on the specific study)[85,86]. The incidence of this complication is related to the patient's state of oral health (i.e., periodontitis) and a history of dental trauma; a decrease in bone turnover is most likely involved. However, BTM measurements are not useful for identifying people at risk. Temporary suspension of drug treatment does reduce the frequency of this complication.

g) The incidence of atypical fractures of the femur (AFF) is very low[87,88]. In a recent study from the United States, 1.7 patients with AFF were identified for every 10,000 treated with BPs. The relative risk (RR), compared with those not treated, increased with the time of exposure to BPs (RR = 2.5 with treatments < three years; RR = 8.9 with treatment for three to five years; RR = 19.9 with five to eight years of treatment, and RR = 43.5 for treatments lasting longer than eight years). Despite the observed increase in RR, the absolute risk is very low compared to the risks associated with osteoporotic fractures. Current estimates suggest that for each atypical fracture appearing during the first three years of treatment, ~270 clinically-relevant fragility fractures are prevented, including 70 hip fractures[89]. Risk factors for AFF include Asian race, low weight, and femoral curvature. The incidence of AFF appears to decline rapidly after drug withdrawal. The usefulness of the synthetic parathyroid hormone, teriparatide, for the treatment of AFF remains controversial.

h) Various types of inflammatory reactions of the eye have been described in association with the use of BP (e.g., episcleritis, keratitis, and uveitis). These adverse effects are very infrequent but would require discontinuation of treatment[90].

i) Diffuse osteoarticular and muscular pain can develop in patients undergoing BP drug treatment. The discomfort typically disappears after the drug has been withdrawn[91].

10. Denosumab

Denosumab is a monoclonal antibody with a powerful antiresorptive effect that translates into a reduction in the risk of fracture. In general, it has shown greater antiresorptive potency and results in a greater increase in BMD than achieved with BPs.

Denosumab therapy results in reductions in the risk of vertebral, non-vertebral, and hip fractures of ~70%, 20%, and 40% respectively[92] (Evidence 1b). A post hoc analysis of these data suggests that its efficacy in reducing hip fracture may be greater in subjects older than 75 years of age[93] (Evidence 2b). Its beneficial impact on fracture risk appears to be maintained during treatment and persists for at least 10 years[94].

In the months following drug withdrawal, an increase in BTMs and a loss of the bone mass gained with subsequent stabilization at baseline values are observed. In some patients, these responses have been associated with multiple vertebral fractures[95]. Therefore, any interruption of denosumab therapy should be followed by the administration of a BP for six months following the final dose. However, the ideal regimen has not yet been established (see below)[18].

Denosumab is generally well tolerated. It is not associated with an increased risk of neoplasms, cardiovascular events, or infections and is safe to use in patients with diabetes[96]. As with BPs, the risk of AFF and ONJ is very low. In a study performed with patients treated for a prolonged period (up to 10 years), the risk of AFF was determined to be ~1/10,000 patient-years. The risk of developing ONJ was 1/2,000 patient-years[94]. Furthermore, denosumab can be used safely in patients with GFRs <30 ml/min and even in those on dialysis with no need for dose adjustment. However, hypocalcaemia may develop, especially in patients with advanced renal failure. Close follow-up will be necessary for these patients, together with an adequate supply of calcium and vitamin D.

In conclusion, denosumab therapy can reduce the incidence of vertebral, non-vertebral, and hip fractures. Thus, this agent has a definitive role in the treatment of osteoporosis (Recommendation A).

11. Strontium ranelate

Strontium ranelate reduces the incidence of vertebral and non-vertebral fractures by ~40% and 16%, respectively[97]. However, the administration of this agent results in an increased incidence of cardiovascular events. It is not currently available for use in Spain or any other European country.

12. Parathyroid hormone (PTH) 1-34 (teriparatide)
Teriparatide is the amino-terminal (1-34) peptide fragment of human parathyroid hormone (PTH) that promotes bone formation. Administration of teriparatide reduces the risk of vertebral fracture by 65% and non-vertebral fracture by 50%[98] (Evidence 1a). While teriparatide has not yet been evaluated in trials designed to assess its specific impact on hip fractures, a review of observational studies suggested reductions of ~56%[99]. A more recent meta-analysis found that teriparatide therapy resulted in no significant reductions in hip fractures[48], although another three reviews concluded that it reduced hip fractures between 56% and 65%[61,100,101]. One study directly compared the effects of the BP, risedronate, and teriparatide in postmenopausal women with severe osteoporosis and vertebral fractures; the teriparatide-treated group experienced fewer vertebral and clinical fractures than the BP-treated group (5.4% versus 12.0% and 4.8% versus 9.8%, respectively)[102]. Teriparatide is administered as a daily subcutaneous injection for two years. The benefits with respect to BMD that are achieved with this drug decrease progressively after its withdrawal; thus, sequential treatment with an antiresorptive drug is recommended. Teriparatide is generally well tolerated. Several biological and biosimilar drugs have been approved for clinical use because they have met the standard bioequivalence requirements established for these drugs.

In conclusion, teriparatide reduces both vertebral and non-vertebral fractures and, although it is not approved for this indication, it probably also reduces the incidence of hip fractures (Recommendation A).

13. PTH (1-84)
This formulation is not currently licensed for osteoporosis treatment.

14. Abaloparatide
Abaloparatide is an analog of the 1-34 region of PTH and is a PTHrP (PTH-related peptide). The results of a clinical trial found that administration of abaloparatide reduced the risk of vertebral and non-vertebral fractures by 86% and 43%, respectively, compared to placebo[103]. A recent meta-analysis revealed that the use of

this drug resulted in 87%, 50%, and 61% reductions in vertebral, non-vertebral, and wrist fractures respectively[104]. Abaloparatide is approved for use in the US but not in Europe. It is not available in Spain.

15. Romosozumab
Romosozumab is a sclerostin-neutralizing monoclonal antibody. Sclerostin is a small protein pathway which is essential for osteoblastic activity. Various experimental and clinical studies have shown that romosozumab has a dual effect. Administration of romosozumab increases bone formation and also decreases the rate of bone resorption. The latter effect has been associated with the impact of this drug on levels of the osteoclast NKL. Consistent with its dual effect, romosozumab increases the levels of bone formation markers, such as PINP, and decreases the levels of resorption markers, such as CTX. Romosozumab induces notable increases in BMD in both the spine and the hip. The anabolic effects of this drug disappear after 6–12 months of treatment. Therefore, it is typically administered for periods of one year, after which an antiresorptive agent must be used to maintain or increase BMD.

The results of three pivotal trials and several meta-analyses[48,105-108] reveal that treatment with romosozumab for 12 months reduces the incidence of vertebral fractures in postmenopausal women and men with osteoporosis (relative risk reduction [RRR], 66%–73%)[109]. Likewise, the combined analysis revealed that romosozumab therapy decreases the risk of non-vertebral (RRR 33%) and hip fractures (RRR 56%). In postmenopausal women with severe osteoporosis and a history of previous fragility fractures, treatment with romosozumab for one year followed by alendronate significantly reduced the risk of new vertebral, hip, and clinical fractures, compared with treatment over the entire period with alendronate alone[107].

Romosozumab is generally well-tolerated, although the results of several studies suggested that it may increase the incidence of cardiovascular events[110]. While this difference was small in absolute terms (1.3% of events versus 0.9% in the control group), romosozumab is not indicated in patients with a history of myocardial infarction or stroke and should be carefully considered in patients presenting with multiple cardiovascular risk factors.

In conclusion, romosozumab has a defined role in the treatment of osteoporosis as it reduces the risk of both vertebral and peripheral fractures (Recommendation A). Potential cardiovascular risks and specific contraindications should be assessed in each patient.

16. Vertebroplasty and kyphoplasty
Although many uncontrolled studies have shown that these procedures are associated with a marked analgesic effect, randomised clinical trials have offered contradictory results[111-114] and controversy regarding a potential increased risk of fracture in the adjacent vertebrae remains. Therefore, these procedures are not routinely recommended[87] for patients with asymptomatic vertebral fractures, mild pain, or those with symptoms that have persisted for more than one year. These procedures can be considered in patients who present with fractures that are less than six weeks old and severe pain despite appropriate medical treatment and in patients with fractures that have evolved over six weeks to one year ago with persistent pain that responds poorly to analgesics and evidence of edema on magnetic resonance imaging studies[115]. These procedures may also be useful in patients who present with contraindications or poor tolerance to analgesics. Vertebroplasty and kyphoplasty are similar in terms of effectiveness and safety[116]. There is insufficient evidence on the relative usefulness of procedures that include the insertion of expanding implants specifically when compared to vertebroplasty and balloon kyphoplasty (Recommendation B).

In conclusion, vertebroplasty, kyphoplasty, and related techniques are not routinely recommended for the treatment of vertebral fractures, although these procedures may help to control symptoms in carefully selected patients (Recommendation C). In any case, its use must be accompanied by medical treatment of osteoporosis to prevent new fractures.

INITIATION AND FOLLOW-UP OF TREATMENT
1. Decision to commence treatment
There is no internationally agreed or apstandard on when to initiate treatment for osteoporosis. SEIOMM suggests that, in general, patients that present with the following attributes should be treated:

1. Patients who present with one or more fragility fractures, especially those of the vertebrae, hip, humerus, and pelvis, regardless of whether their T-scores indicate "osteoporosis".

2. Patients with a BMD <-2.5T at the lumbar spine, femoral neck, or total hip.

3. Women with osteopenia (particularly with T < -2.0) who also present with factors that are strongly- associated with an increased risk of fracture (e. g., hypogonadism or early menopause, treatment with glucocorticoids or antiestrogens, among others).

However, we recognise that some situations may require exceptions to these recommendations. All patients must undergo a careful, individualised assessment that considers the risk factors for fracture as well as other clinical characteristics. For example, it may be possible to delay the start of treatment in young women who present with only slightly low BMD, without fractures or other risk factors. By contrast, a patient who presents with several important risk factors may require early treatment. Scales that help estimate fracture risk (e. g., FRAX) may be helpful, although these instruments have not yet been fully validated for use in the Spanish population, as mentioned above.

2. Control of the therapeutic response

Adherence and therapeutic responses to treatment regimens can be assessed by changes in BTMs.

The beneficial effect of a given treatment regimen can be confirmed by increases in BMD and the absence of new fractures. However, it is critical to recognise that a single fracture while on a treatment regimen is not necessarily indicative of therapeutic failure. Elderly patients and those with dementia, poor quality of life, and/or multiple fractures are at greater risk for therapeutic failure. In cases where oral BPs have failed, parenteral drugs (zoledronate, denosumab, and [de- pending on patient characteristics] teriparatide or romosozumab) may represent good therapeutic alternatives.

Changes to treatment regimens due to a potential inadequate response may be considered in the following circumstances[117]:

a) development of two successive fractures; or

b) coincidence of two of the following three factors, including the de velopment of a new fracture; decrease in BMD greater than the minimum significant change (nb: this varies based on the densitometer and the skeletal region studied but is usually between 4–5%); or decrease in BTMs below the minimum significant change, usually ~25% (Recommendation D).

Before proceeding with a therapeutic change, the following factors should be considered as possible causes of an inadequate response: a) vitamin D deficiency; b) secondary forms of osteoporosis; c) in- adequate compliance; d) tendency to fall; e) defective techniques used to measure BMD and/or BTMs; f) serious bone deterioration, leading to the likelihood of new fractures despite active drug treatment.

If the reasons for the changes observed include an apparent lack of an appropriate response, the following options are recommended[117,118] (Recommendation D):

- Select the drug with the highest anti-fracture effect.
- Select a drug that is anabolic rather than antiresorptive.
- Select an injectable drug rather than one that is taken orally.

3. Duration of treatment

Interruption of treatment is justified when the risk/benefit ratio becomes unfavourable. These situations can include: a) therapeutic objectives have been achieved; b) loss of effectiveness; or c) increased risk of developing secondary effects.

a) Attainment of objectives

Although the "treat to target" strategy is theoretically an attractive approach, the objectives to be achieved in the treatment of osteoporosis are not well defined, which limits its practical application. For some experts, the absence of new fractures and the increase in BMD would be the most appropriate objectives to consider. Other experts have recommended objectives that include reaching a T-score greater than -2.0 or -2.5, especially in studies focused on the hip[119-121].

b) Loss of effectiveness

The increase in BMD induced by antiresorptive drugs is more marked during the first years of treatment. However, that does not mean that these drugs subsequently lose effectiveness. Although there is no general agreement, the results of several studies have revealed that fracture risk reduction persists with treatment with zoledronate for six years and with alendronate or denosumab for 10 years, especially in patients who maintain a high baseline risk.

c) Increased risk of developing undesirable long-term side effects

ONJ and AFF induced by BPs and denosumab are particularly relevant to this concern. The absolute risk of ONJ in patients treated with antiresorptive agents for osteoporosis is very low and similar to that reported for the general population. Likewise, there is currently no evidence that short-term discontinuation of treatment reduces the risk of ONJ or disease progression in patients who need dental procedures. The absolute risk of AFF is also very low, although the relative risk increases with the duration of exposure to BPs (see the previous section).

Based on these facts, the following recommendations are proposed. These recommendations represent expert consensus, albeit without published studies to provide definitive support[122-126] (Recommendation D):

1. Patients treated with BPs should be evaluated after three (zoledronate) or five years (oral BP) of treatment. Patients treated with denosumab should be evaluated after 5–10 years of treatment.

2. After this evaluation, treatment should be continued (with the same or another drug) if any of the following circumstances occur:

a. BMD at the femoral neck at <-2.5 T.

b. The appearance of fragility fractures in the 3–5 years prior to evaluation.

c. Some experts also recommend continuing treatment if the patient has a history of hip or vertebral fracture at any time.

If none of these circumstances arise, BP treatment can be withdrawn, at least temporarily.

If treatment is maintained, the possibility of its withdrawal should be periodically reassessed at various intervals thereafter. There is currently no guidance as to how often each patient should be reassessed, nor if there is a defined maximum duration of treatment. A limit of 10 years is often set, as there are no studies that have evaluated the impact of these drugs over the longer term. However, if the patient remains at risk, anti-osteoporotic treatment should not be withdrawn. If anti-resorptive treatment is withdrawn, and the patient remains at risk for fracture, a drug from another class should be administered, for example, an anabolic.

When BP treatment is withdrawn, the suspension must be temporary (i.e., a "drug holiday"). It is not known how long the treatment regimen can be safely suspended or fully discontinued. Typically, the drug can be suspended for a period of 1 to 3 years, depending on the BP used (e. g., perhaps one year for risedronate, two years for alendronate, and three years for zoledronate). Some experts have suggested that BTMs and BMD measurements can help with this decision, although we are not in a position to confirm this. In theory, if the BMD remains above a "target" value (e. g., T >-2 or -2.5), drug withdrawal can be considered.

"Drug holidays" should not be scheduled for patients treated with denosumab, because after its withdrawal, not only is there no residual effect, but bone turnover increases to levels above baseline values (i. e., a "rebound effect"). This increased bone turnover has been associated with a rapid loss of bone mass and an increased risk of developing multiple vertebral fractures. Therefore, continuing denosumab therapy in- definitely is recommended. In cases in which denosumab must be discontinued, it should be replaced with a potent BP (see below)[18].

There are some data available that address the efficacy and safety of SERMs (raloxifene and bazedoxifene) for up to eight years. In these cases, the treatment regimen can be maintained through this time or until the risk of hip fracture or complications, such as thromboembolic disease, increases. It is not usually recommended in patients older than 65-70 years of age.

Treatment with teriparatide or romosozumab should be maintained for 24 and 12 months, respectively, followed in both cases by an antiresorptive drug.

4. Sequential and combined treatment

4.1. Bisphosphonates (BPs) after denosumab

As stated above, a BP must be administered after discontinuation of denosumab to limit the rebound effect (Recommendation A). Pending the results of ongoing trials focused on the optimal BP regimen, patients with a low risk of fracture and who have been treated with denosumab for a relatively short period (up to 2.5 years), can be treated for another two years with an oral BP, such as alendronate. IV zoledronate is another alternative. Zoledronate is preferable in cases of prior intolerance to oral BPs, foreseeable poor adherence, or polypharmacy. Patients who have been treated with denosumab for a longer period (i. e., more than 2.5 years) or who remain at high risk of fracture should be treated with zoledronate for 1–2 years. The first dose of zoledronate should be administered once denosumab has been discontinued (i. e., six months after the last dose) and repeated when elevations in BTMs are detected, generally at 6 or 12 months later. If BTM measurements are not available, zoledronate administration can be repeated 6 and 12 months after the first dose[18,127]. The need for additional doses should be considered on an individual basis (Recommendation D).

There are no trials that established the best therapeutic options for patients who have sustained a vertebral fracture after discontinuation of denosumab. However, the following options have been recommended in this situation:

a) restart denosumab;
b) administer zoledronate;
c) administer teriparatide together with denosumab (Recommendation D)[18]. In the months following the discontinuation of denosumab, treatment with teriparatide alone should be avoided, because it causes a transient loss of bone mass[128].

4.2. Antiresorptive agents after anabolics

Progressive loss of BMD will follow after discontinuing treatment with teriparatide[129]. Several studies have shown that this loss of bone mass could be prevented by the sequential administration of an antiresorptive agent; additional increases in BMD might also result from this new drug regimen[130], although there are no data available on fracture prevention. Likewise, after completion of treatment with romosozumab, current recommendations include that the patient shouldontinue with an antiresorptive agent[131,132].

In conclusion, after completion of treatment with anabolic drugs, such as teriparatide or romosozumab, further treatment with powerful antiresorptive drugs, such as a BP or denosumab, is recommended (Recommendation A).

4.3. Anabolic after antiresorptive drugs

The anabolic effects of PTH depend on the type of antiresorptive drug used in the previous treatment regimen. Several studies have confirmed that the previous use of a BP result in an overall decrease and slightly reduces the rate of increase in BMD that resulted from teriparatide treatment[133,134]. However, the reduction in fracture risk associated with the use of teriparatide is not affected by prior treatment with a BP[135].

One study focused on the impact of switching to romosozumab or teriparatide among women previously treated with a BP (particularly alendronate). Both groups exhibited increases in spine BMD, but those who switched to romosozumab exhibited these increases 12 months or more after those achieved in patients who switched to teriparatide; this was especially notable in the hip[136].

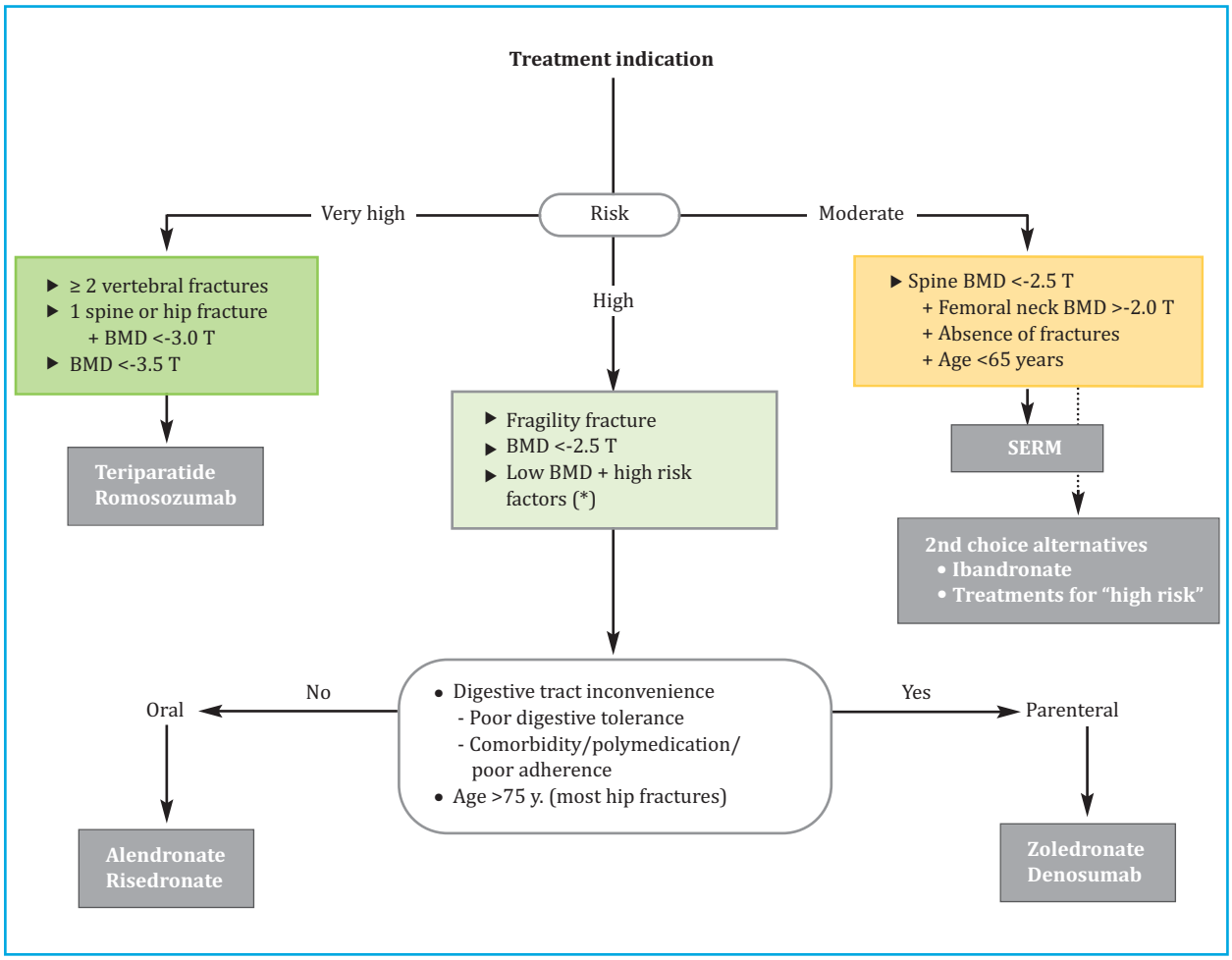
By contrast, initiation of teriparatide in postmenopausal women who had completed a course of treatment with denosumab resulted in a transient decrease in BMD[128]. Therefore, teriparatide should not be administered after discontinuation of denosumab.

In conclusion, although the preferred sequence is an anabolic followed by an antiresorptive drug, prior treatment with a BP is not a contraindication for subsequent administration of teriparatide or romosozumab and is considered adequate to reduce the risk of fracture. (Recommendation A). Teriparatide in the months following denosumab suspension should be avoided, given the risk of accelerated bone loss (Recommendation A).

4.4. Combination treatments

- The combination of two antiresorptive drugs (e.g., estrogens and a BP) can enhance the gain in bone mass achieved individually[137], but there are doubts regarding the risk-benefit ratio of this association compared to results achieved with each drug alone. This combination is not recommended.
- Studies focused on the combination of a BP and teriparatide have not shown clear benefits over individual administration of each drug. Thus, this combination is not recommended. However, in one study, the combination of zoledronate and teriparatide resulted in a higher value for hip BMD than what was achieved in response to teriparatide alone[138].

Figure 1. Algorithm for selecting the initial treatment in postmenopausal osteoporosis



SERM: selective estrogen receptor modulator; (*): especially if T ≤-2 and factors strongly associated with fracture risk, such as hypogonadism, early menopause, or treatment with glucocorticoids or sex hormone antagonists. These general criteria may need to be adapted based on other clinical determinants of fracture risk, the characteristics of individual patients, and their preferences.

• In one trial, the use of denosumab combined with teriparatide resulted in greater increases in BMD at the hip and spine than those achieved with each drug alone[139].

In conclusion, given the lack of data on fracture prevention and the higher costs and side effects associated with these types of regimens, combination therapy is not generally recommended at this time. However, combinations of denosumab or zoledronate with teriparatide can be considered on an individual basis in particularly severe cases associated with a very high risk of hip fracture. In these cases, it may be preferable to delay the start of antiresorptive for one to two months after initiating teriparatide to take advantage of the anabolic effect (Recommendation grade D).

5. Therapeutic decision algorithms

The proposed algorithm is based on data from published trials and considerations that are summarised below.

5.1. Initial treatment (Choice of a drug; Figure 1)

The main criterion for choosing the initial drug is the risk of fracture. We distinguish three levels of risk, including "moderate", "high", and "very high".

1) Moderate risk. This category corresponds to the risk profile of a woman under 65 years of age, with no history of fracture, a spinal T-score between -2.5 and -3.0, and a relatively preserved hip BMD (T-score >-2). In this situation, a SERM is recommended because one can then delay the use of prolonged treatment strategies that can elicit AFF or ONJ. However, ibandronate and antiresorptive agents that are typically recommended for high-risk situations are the second choice in this situation. These drugs represent acceptable alternatives if for some reason SERMs are to be avoided.

2) High risk. Most of the cases seen in the clinic will present this level of risk (see section above "Decision to start treatment"). These patients do not meet the criteria that define either moderate or very high-risk cohorts as described further below. Alendronate, risedronate, zoledronate, or denosumab are indicated for the treatment of patients in the high-risk cohort. Oral BPs are considered preferable for patients <75 years of age when there are no inconveniences with respect to oral administration (digestive problems, polypharmacy, adherence). Injectable antiresorptive drugs are considered preferable in all other cases. As most individuals who have sustained hip fractures are over 75 years of age and belong to the second group, injectable antiresorptive agents are generally preferred for this group. Given the rebound effect after discontinuation of denosumab, zoledronate may be the preferred agent if there are doubts regarding compliance.

3) Very high risk. We consider women to be at very high risk in any of the following situations: a) two or more vertebral fractures, or an equivalent risk (i.e., T-score <-3.5); or b) vertebral or hip fracture with a T-score <-3.0. There may be other clinical situations that suggest that a patient is at a very high risk of fracture; these will require individualised consideration. For this level of risk, bone-forming drugs such as teriparatide or romosozumab should be used. Romosozumab may have a better cost-benefit ratio (although its marketing price was not known at the time that these guidelines were written), albeit a less favorable risk-benefit ratio due to the potential increase in cardiovascular events. Romosozumab should be avoided in all patients with or at high risk of developing cardiovascular disease. However, these guidelines and recommendations should be understood as provisional at this time, pending marketing in Spain and further experience with this drug in our population.

Although some authors have suggested that all patients with a recent fracture, especially a vertebral fracture, might benefit from treatment with a bone-forming drug. However, there is currently no consensus on this point among our panel of experts. Regardless of the treatment that is ultimately selected, therapy should be initiated as soon as possible given that these patients are at very high risk for new fractures.

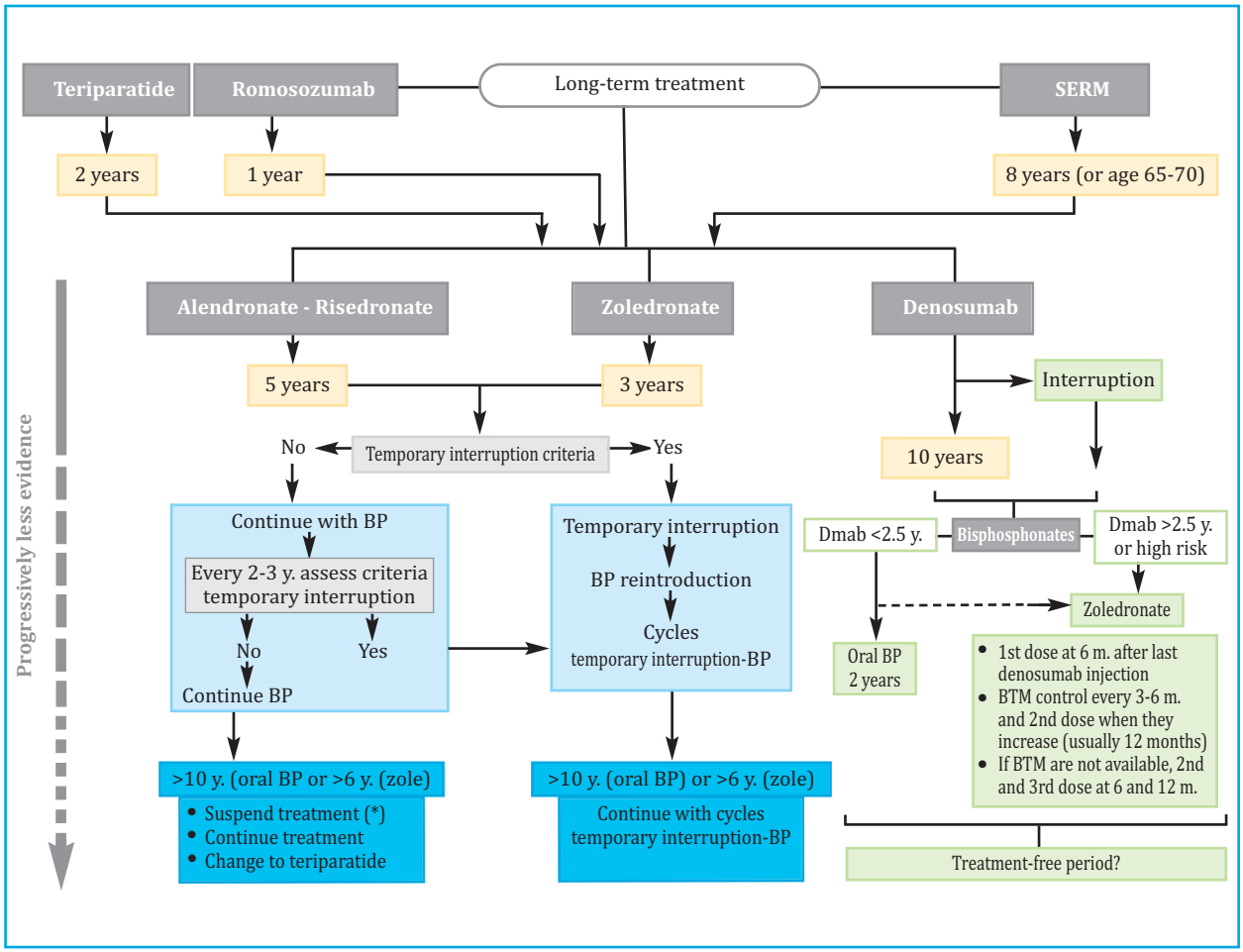
5.2. Long-term treatment (Figure 2)

Romosozumab should only be administered for one year; teriparatide therapy is limited to two years. Likewise, given that efficacy and safety data are available for up to eight years of treatment only, withdrawal of SERMs should be considered after that period, when the patient reaches 65-70 years of age or if the risk of fracture increases. After one or more of these milestones are reached, it will likely be necessary to administer another antiresorptive. The discussion on long-term treatment is thus restricted to a consideration of BPs and denosumab. One key differentiating factor at this time is the potential impact of a temporary interruption or "therapeutic vacation" or "drug holiday". While this is discouraged for individuals undergoing treatment with denosumab, it is currently accepted for BP regimens.

1) Denosumab. This agent can be administered continuously for 5–10 years. No information is currently available regarding longer periods of use. Thus, the decision to continue or discontinue drug treatment should be made carefully. Once administration of denosumab has been interrupted, the patient should be treated with a BP, for example, alendronate or zoledronate. Zoledronate is preferred if denosumab treatment was prolonged for more than 2–3 years. (See section 4.1).

2) Bisphosphonates (BPs). Three periods of use have been described:

Figure 2. Long-term treatment continuation algorithm



BP: bisphosphonates; SERM: selective estrogen receptor modulators; BTM: bone turnover markers; (*): there are not enough data to establish a recommendation after that treatment time, so the possible options are listed before a decision that must be individualized.

• First period: Current recommendations suggest that these drugs should be administered without interruption for five years (for oral BPs) or three years for zoledronate.

• Second period: After the first period (above), treatment can be temporarily interrupted if the requirements for a "drug holiday" are met (see above). The need to reinstate treatment should be periodically assessed. Once reinstated, the possibility of a second temporary suspension can be reassessed at frequent intervals.

• Third period (after 10 years of continuous or intermittent treatment with an oral BP, or six years of treatment with zoledronate): No high-quality studies are available that can be used to guide decision-making. By extrapolation of what was proposed for the second period, it is reasonable to assume that a patient that meets the appropriate requirements can be converted to a "drug holiday" regimen. Otherwise, one of the following three options should be chosen depending on context and clinical judgement:

a) Maintain treatment: This increases the risk of complications but may keep the risk of osteoporotic fractures comparatively low;

b) Withdraw treatment: This strategy reduces the risk of complications but could increase the risk of developing osteoporotic fractures;

c) Change the regimen: Teriparatide can be prescribed. This drug can reduce the risk of complications as well as the risk of developing osteoporotic fractures.

MALE OSTEOPOROSIS

There is very little evidence available to guide the treatment of male osteoporosis. Of the information that does exist, most of the studies focus on increasing BMD as a primary objective. The results are largely similar to those obtained from studies in women and suggest that drug efficacy in men is similar with respect to the prevention of fractures. Interestingly, administration of BPs such as alendronate, risedronate, and zoledronate resulted in a decrease in vertebral fractures in male patients[140-144]. Denosumab reportedly increases BMD in men and reduces the risk of fracture specifically in those undergoing androgen deprivation therapy[145,146]. Teriparatide also has beneficial effects in men[147,148]. For this reason, a drug selection strategy similar to that designed initially for women might be proposed for men:

a) Risedronate or alendronate (nb: the latter drug is not approved in Spain for male osteoporosis) for patients who have no restrictive criteria for oral administration, as described for women with postmenopausal osteoporosis;

b) Zoledronate or denosumab in patients with these restrictive criteria or who are older and therefore are at a higher risk of hip fracture;

c) Teriparatide in patients with established osteoporosis and with a high risk of fracture. Although, as in women, romosozumab also induces gains in BMD in men[109], its use to treat osteoporosis in men is not currently approved.

Proper calcium intake is also recommended, preferably through diet and vitamin D supplements in cases of insufficiency. Androgens are only justified if there is associated hypogonadism and no contraindications for their use. Even in cases of hypogonadism, some of the aforementioned drugs might have significant anti-fracture efficacy. Lastly, when hypercalciuria is detected, administration of thiazides may be considered (Recommendation D).

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

BPs are the drugs of choice for glucocorticoid-induced osteoporosis[149-151]. However, if a patient presents with vertebral fractures, treatment with teriparatide is justified due to its greater anti-fracture effect[152,153] (Recommendation A). Calcium and vitamin D should also be administered. The active metabolites of vitamin D by themselves have some preventive effect on bone loss, but we do not have convincing evidence regarding their role in fracture prevention at this time[154].

Postmenopausal women and men over the age of 50 years who receive or are about to receive doses of prednisone equal to or greater than 5 mg/day (or the equivalent dose of other corticosteroids) for more than three months should receive treatment for this condition. In premenopausal women and men under 50 years of age, treatment is indicated only in cases of previous fractures, low BMD, or very high glucocorticoids dose (e. g., >30 mg/day of prednisone for more than 3 months).

Drug treatment should be maintained while the patient remains on corticosteroids. Once they are withdrawn, the risk of fracture must be evaluated in each patient. If the risk is not overly high, it may be possible to stop osteoporosis therapy entirely.

Denosumab results in a greater increase in BMD than that achieved by BPs in patients receiving corticosteroids. However, the reduction in fracture risk is similar with both drugs, as are the adverse effects[155-157]. Given, on the one hand, the rebound effect observed in some patients when denosumab is discontinued[158] and, likewise, the possibility of withdrawing antiresorptive treatment when discontinuing corticosteroids, denosumab should be indicated when it is not possible to use other antiresorptive agents and the risk of fracture is high.

In patients receiving corticosteroids, densitometric evaluation performed at shorter intervals may be justified (Recommendation D).

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Annex I
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Annex II
Conflicts of interests

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Cannata Andía, Jorge					
Cano, Antonio		Gedeon Richter			Theramex
Carbonell Abella, Cristina		Amgen, UCB, Stada, Theramex, Angelini Pharma, Gebro	Amgen, Rubio		
Casado Burgos, Enrique		UCB, Gedeon Richter, Stada, Grünenthal, Lilly, Amgen, Theramex, Gebro, Italfarmaco, Angelini Pharma	Lilly, Amgen, Stada		Theramex, Bayern, Gp-Pharm, Gebro, Gedeon Richter, Stada
Ciria Recasens, Manuel		Grünenthal, Angelini Pharma, Gedeon Richter, Theramex, Rubio, Gebro Pharma	Amgen, Lilly, Rubio		
Corral-Gudino, Luis					
Del Pino Montes, Javier		Gedeon Ritcher, Grünenthal, UCB	Amgen		
Del Río Barquero, Luis Miguel		Amgen, Gedeon Richter			
Díaz Curiel, Manuel			Rubio		
Díez Pérez, Adolfo	Active Life Sci	Amgen, Lilly, Theramex			
García Vadillo, Alberto		Lilly, Amgen, Gebro Pharma, Theramex	UCB, Lilly, Amgen		
Gómez Alonso, Carlos	Faes	Stada, Grünenthal, Amgen, UCB	Amgen	Stada, Kyowa Kirin, Faes	Amgen, Kyowa Kirin
Gómez de Tejada Romero, María Jesús					
González Macías, Jesús		Amgen-UCB, Gedeon Richter, Menarini, Theramex	Lilly	Faes	
Guañabens, Nuria		Eli Lilly, Amgen, UCB	Eli Lilly, Amgen, UCB		Amgen, UCB
Hawkins Carranza, Federico					
Jodar Gimeno, Esteban	SICAM SL, Cajal PME, H&B	Amgen, Asofarma, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Faes, Janssen, Lilly, MSD, Novartis, Novo Nordisk, Viatrix	Amgen, Lilly, Novo Nordisk, UCB	Amgen, AstraZeneca, Boehringer Ingelheim, Faes, Janssen, Lilly, MSD, Novo Nordisk Pfizer & Sanofi	Amgen, AstraZeneca, Faes, Fresenius, Italfármaco, Janssen, Lilly, MSD, Mundipharma, Novo Nordisk, Shire & UCB

Annex II (cont.)
Conflicts of interests

Author	Shares, employee	Conference fees	Travel costs	Research grants	Advisory councils
Malouf Sierra, Jorge		Theramex, Amgen, Angelini Pharma	Lilly		Amgen, UCB
Martínez Díaz-Guerra, Guillermo		Lilly, Amgen, UCB, Angelini Pharma, Italfarmaco, Kyowa Kirin	Lilly, Amgen, UCB	Amgen	Lilly, Amgen, UCB, Alexion, Shire, Kyowa Kirin
Monegal Brancos, Ana			Amgen, Lilly		
Muñoz Torres, Manuel		Amgen, UCB, Grünenthal Pharma, Stada, Meiji, Gedeon Richter, Ferrer			Amgen, UCB, Meiji
Naves Díaz, Manuel		Grünenthal, Gedeon Richter	Amgen, UCB		
Nogues, Xavier		UCB, Amgen, Lilly, Faes, Italfarmaco	Amgen		UCB, Amgen
Nolla, Joan M		Amgen, Lilly	Amgen, Lilly		
Pérez-Castrillón, José Luis		MSD, Lilly, Amgen, UCB, Gedeon-Ritcher, Grünenthal	Gedeon-Ritcher, MSD, Amgen, Italfarmaco	Pfizer	Faes
Peris Bernal, Pilar		Amgen, UCB, Lilly, Kyowa Kirin			
Quesada Gómez, José Manuel		Amgen, Faes, Ferrer, Gebro Pahrma, Grünenthal, Procare Health Iberia, S.L, Theramex	Amgen, Faes	Faes	Amgen, Shire
Riancho, José A.		Amgen, UCB, Lilly, Merck	Amgen, UCB, Lilly, Merck, Takeda	Alexion, Kyowa Kirin	
Rodríguez García, Minerva		Amgen, Kiowa Kyrin	Rubió, Amgen, Vifor Pharma		
Sosa Henríquez, Manuel					
Torrijos Eslava, Antonio					
Valero Díaz de Lamadrid, Carmen		Amgen			

Annex III
Supplementary tables

Table S1. Levels of evidence according to the Oxford Center for Evidence-Based Medicine for studies evaluating therapy, prevention or harm

Level	
1a	Systematic reviews of RCTs with homogeneity between individual studies or several RCTs with similar results
1b	Single RCT with narrow confidence interval
2a	Systematic review of cohort studies with homogeneity between individual studies
2b	Individual cohort study or a low-quality RCT
2c	'Results' research; ecological studies
3a	Systematic review of case-control studies with homogeneity between individual studies
3b	Individual case-control study
4	Case series and low-quality cohort and case-control studies
5	Expert opinions without explicit critical appraisal, or based on physiology, basic research or "first principles"

RCT: randomized clinical trial.

Table S2. Grades of recommendation from the Oxford Center for Evidence-Based Medicine according to levels of evidence

Recommendation	Type of studies
A	Consistent level 1 studies (randomized clinical trials). By consistency we mean homogeneity (concordance) in the results of the different individual studies
B	Consistent level 2 (cohort studies) or 3 (case-control studies) studies or extrapolations from level 1 studies
C	Level 4 studies (case series and low-quality cohort or case-control studies) or extrapolations from level 2 or 3 studies
D	Level 5 evidence (inconclusive expert opinions or studies or problematic inconsistency between them, whatever their level)

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