Reumatología Clínica

Special Article

Recommendations by the Spanish Society of Rheumatology on Osteoporosis☆

Antonio Naranjo Hernández,[a,][*] Petra Díaz del Campo Fontecha,[b] María Pilar Aguado Acín,[c] Luis Arboleya Rodríguez,[d] Enrique Casado Burgos,[e] Santos Castañeda,[f] Jordi Fiter Aresté,[g] Laia Gifre,[h] Carmen Gómez Vaquero,[i] Gloria Candelas Rodríguez,[k,l] Félix Manuel Francisco Hernández,[a,l] Núria Guañabens Gay[j]

[a] Servicio de Reumatología, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain
[b] Unidad de Investigación, Sociedad Española de Reumatología, Madrid, Spain
[c] Servicio de Reumatología, Hospital Universitario La Paz, Madrid, Spain
[d] Sección de Reumatología, Hospital Universitario Central de Asturias, Oviedo, Spain
[e] Servicio de Reumatología, Hospital Universitari Parc Taulí (UAB), Sabadell, Barcelona, Spain
[f] Servicio de Reumatología, IIS Princesa, Madrid, Spain
[g] Servicio de Reumatología, Hospital Universitario Son Espases, Palma de Mallorca, Spain
[h] Servicio de Reumatología, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain
[i] Servicio de Reumatología, Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Barcelona, Spain
[j] Servicio de Reumatología, Hospital Clínic, Barcelona, Spain
[k] Servicio de Reumatología, Hospital Universitario Clínico San Carlos, Madrid, Spain
[l] Grupo de Revisores de Evidencia de la SER, Madrid, Spain

ARTICLE INFO

ABSTRACT

Objective: To update the recommendations on osteoporosis (OP) of the Spanish Society of Rheumatology (SER) based on the best possible evidence.

Methods: A panel of nine expert rheumatologists in OP was created, previously selected by the SER through an open call. The phases of the work were: identification of the key areas for updating the previous consensus, analysis and synthesis of the scientific evidence (using the SIGN levels of evidence) and formulation of recommendations based on this evidence and consensus techniques.

Results: This revision of the recommendations implies an update in the diagnostic evaluation and treatment of OP. It proposes some criteria to consider the high risk of fracture and some indications to start treatment. The recommendations also address issues related to the safety of treatments and the management of special situations such as inflammatory diseases and treatment with glucocorticoids.

Conclusions: We present an update of SER recommendations on OP.

© 2018 Elsevier España, S.L.U. and Sociedad Española de Reumatología y Colegio Mexicano de Reumatología. All rights reserved.

Recomendaciones de la Sociedad Española de Reumatología sobre osteoporosis

RESUMEN

Objetivo: Actualizar las recomendaciones sobre osteoporosis (OP) de la Sociedad Española de Reumatología (SER) basadas en la mejor evidencia posible.

Métodos: Se creó un panel formado por nueve reumatólogos expertos en OP previamente seleccionados por la SER mediante una convocatoria abierta. Las fases del trabajo fueron: identificación de las áreas claves para la actualización del consenso anterior, análisis y síntesis de la evidencia científica (utilizando los niveles de evidencia del SIGN) y formulación de recomendaciones a partir de esta evidencia y de técnicas de consenso.

* Corresponding author.
  E-mail address: anarher@gobiernodecanarias.org (A. Naranjo Hernández).

Resultados: Esta revisión de las recomendaciones comporta una actualización en la evaluación diagnóstica de la OP y de su tratamiento. Propone unos criterios para considerar alto riesgo de fractura y unas indicaciones para iniciar tratamiento. Las recomendaciones abordan también cuestiones relativas a la seguridad de los tratamientos y al manejo de situaciones especiales como las enfermedades inflamatorias y el tratamiento con glucocorticoides.

Conclusiones: Se presenta la actualización de las recomendaciones SER sobre OP.

Introduction and objectives

Osteoporosis (OP) is a diffuse skeletal disorder characterised by a general reduction in bone strength leading to a higher risk of fracture due to fragility.

In Spain and in other countries the rate of fragility fractures is increasing, mainly due to higher life expectancies.[1] One study reported that in 2010 2.4 million Spaniards (1.9 million women and 0.5 men) over 50 suffered from OP,[2] and as a consequences of this there were 204,000 new fractures at a cost of 2842 million euros (2.8%of the total healthcare costs in Spain).[3] It has been estimated that in 2025 there will be an 40% increase in the rate of fractures and a 30% increase in costs.[3]

Recent years have witnessed advances in the diagnosis and treatment of OP but only a minority of patients with high fracture risk are being accurately assessed and treated in keeping with the recommendations of clinical practice guidelines.[4]

This document contains the updated recommendations of the Spanish Society of Rheumatology (Spanish acronym: SER) on OP from the previous ones of 2011.[5] These recommendations aim at helping physicians take decision for the management of postmenopausal OP and secondary OP (glucocorticoids, inflammatory diseases, OP of the male and other clinical forms).

Methodology

Design

Qualitative synthesis of scientific evidence and consensus techniques have been used in this project which reflect the agreement by experts based on their clinical experience and scientific evidence.

Procedural stages

A series of steps were taken during the development of the recommendations document, which were:

1. *Creation of the work group.* The document began with the formation of a panel of experts formed by 9 SER member rheumatologists. They were selected through an open call to all SER members. The Clinical practice Guideline and Recommendations Committee (Spanish acronym: GPC) of the SER assessed the curriculum vitae of all applicants, in accordance with objective criteria of contribution to knowledge on OP, taking into consideration publications in significant journals over the last 5 years. Coordination of clinical and methodological aspects was made, respectively, by one of these rheumatologists as the main researcher (MR) and a methodology specialist executive from the Research Unit of the SER.
2. *Identification of the key areas for updating of the previous agreement.* All workgroup members were involved in giving shape to the document, and in establishing its content and key aspects. First they identified the clinical questions of research which could have the greatest impact in offering information on OP management: diagnosis, assessment, prevention, treatment and special circumstances. After this, they decided which of these required a response through the formulation of a PICO question (patient, intervention, comparison, and outcome). The methodology to be followed in the recommendation creation process was also defined.
3. *Literature review search.* To respond to the non PICO clinical questions an updated systematic review (SR) search and GPC was made in MEDLINE and specialised sources in guidelines. The other clinical questions were reformatted in four questions with the PICO format. To respond to the PICO questions a search strategy was designed and a review of scientific evidence was made of studies published up until May 2017. The following databases were used: PubMed (MEDLINE), EMBASE and Cochrane Library (Wiley Online). The process was completed with a reference manual, posters and congress abstracts search which the reviewers and experts considered to be of interest.
4. *Analysis and synthesis of scientific evidence.* The SR and GPC identified for the non PICO questions were assessed by the methodology coordinator. It was agreed that only those of high quality were considered apt for their incorporation as a source of evidence. Two rheumatologists from the workgroup of SER evidence reviewers were responsible for systematically reviewing the scientific evidence available for the PICO questions. After a critical reading of the complete test of the selected studies for each review, they drew up a summary using a homogenised formula including tables and texts to describe the methodology, results and quality of each study. They made in-depth notes on the reasons for exclusion of articles not included in the selection. The overall level of the scientific evidence was assessed using the *Scottish Intercollegiate Guidelines Network* (SIGN) (see Appendix 1) evidence levels.
5. *Formulation of recommendations.* When the critical reading was completed, the MR and the panel of experts proceeded with the formulation of specific recommendations based on the available scientific evidence. This formulation was based on "formal assessment" or "reasoned judgement," previously summarising the evidence for each of the clinical questions. They also took into account quality, quantity and consistency of the scientific evidence, the generality of the results, its applicability and its clinical impact. For the formulation of the recommendations two rounds of consensus were used. First, with the "reasoned judgement" system, where all of the experts drafted and discussed the recommendations. Then, in the presence of the methodologist, using the modified technique of nominal consensus, the level of agreement of the experts with the drafting of each recommendation was agreed upon. It was established that there was a high level of consensus when the percentage of experts who agreed with the recommendation draft was 75% or above. The agreement was evaluated using a dichotomous reply (yes: agreed with the wording; no: disagreed with the wording). Grading of the recommendations was made with the SIGN system (see Appendix 1). The recommendations were divided into four main areas: diagnosis and evaluation; treatment; special circumstances; new treatments.

6. *Public exposure.* The draft of this document of SER recommendations was submitted to a process of public exposure by the members of SER and different interest groups (pharmaceutical industry, other scientific societies and patient associations) aimed at receiving scientific evaluation and discussion of its methodology and recommendations. The complete information of this process is found in the appendix to the SER web site (www.ser.es), in the section under SER Research and Recommendations.

Structure

The document includes all the formulated recommendations subdivided into the different above-mentioned areas. Management algorithms were formulated from the recommendations and these offer a summarised approach to the treatment of OP.

Results

There is a total of 28 formulated recommendations on OP (Table 1).

Diagnosis and evaluation

Definition and diagnosis

OP is a diffuse skeletal disease characterised by a reduction in bone resistance which leads to a higher risk of fragility fractures. The concept of "bone resistance" encompasses factors relating both to bone mineral density (BMD) and the quality of the bone tissue.[6]

A fragility fracture is that brought on by a low impact trauma. A fall, standing up or being seated would be included in this concept. The most frequent and relevant fractures are those of the proximal femur, the spine and the distal forearm.[7]

OP may be defined in any of the following circumstances:

a) *T*-score in spine columnar, femoral neck or total hip ≤ -2.5 SD.
b) Femoral fracture due to fragility, regardless of the BMD value, in postmenopausal women and in men >50 years of age.
c) Fracture due to fragility of the spine, proximal humerus or pelvis in postmenopausal women and in men >50 years of age, if there is a low BMD (*T*-score <−1.0 SD).

The conceptual definition of OP by the World Health Organisation (WHO) is solely based on the results of the BMD. An individual has OP if the *T*-score in lumbar spine, femoral neck or total hip is equal to or under −2.5 standard deviation (SD) compared with the population peak bone mass.[8,9]

In normal clinical practice this definition fails to be operative due to many fragility fractures occurring in patients with a *T*-score >−2.5 SD. For this reason the *National Bone Health Alliance* has proposed the consideration diagnosing OP in postmenopausal women and in men >50 years of age with femoral fracture caused by fragility, regardless of the BMD value, and also when there is a low impact spinal fracture, of the proximal humerus or the pelvis, if the *T*-score <−1.0 SD.[10] Doubts exist regarding forearm fracture, which in some cases could be included depending on age or the mechanism of the fracture. The authors also included OP diagnosis for the American population a quantified risk with the *Fracture Risk Assessment* (FRAX®) for the primary fracture ≥20% (proximal humerus, forearm, hip or clinical spine fracture) or a risk of femoral fracture ≥3%.[10]

In view of the recommendations of these groups of experts and in accordance with clinical experience, the panel of experts considered it appropriate to include postmenopausal women and men >50 years of age with fragility fracture of the femur (regardless of BMD) in the OP diagnosis, as well as spinal fracture, fracture of the humerus or the pelvis, if it was accompanied by low bone mass (AL: 89%).

Fracture risk factors

The main aim in OP management is fracture prevention and it is therefore essential to identify those individuals with the highest risk of presenting with them.[11]

Table 2 describes high fracture risk factors (RF) (relative risk ≥2) and moderate RF (relative risk 1–2).[5]

Several risk factors, such as age, fracture history and the use of glucocorticoids, among others contribute to the risk of fracture regardless of the BMD. Patients with a recent fracture are at a particularly high risk of suffering from a new fracture.[11]

The term "imminent fracture risk" has recently been proposed to refer to patents with a short term highs risk, such as those with a recent fracture, elderly fragile people with frequent falls or people treated with glucocorticoids at high level doses.[12,13]

Recommendation: *It is recommended that evaluation of fracture risk due to fragility should not be exclusively based on BMD figures but also bear in mind clinical risk factors* (RR: B; AL: 100%).

The combination of the BMD with clinical RF provides the best estimation of fracture risk.[14,15] This has led to the development of fracture risk calculation tools which are able to include many factors. Among the most popular and widely used is the FRAX®.[9]

Evaluation of fracture risk

Recommendation: *It is recommended that the tool FRAX® be used, with or without BMD, to assess the fracture risk* (RR: √; AL: 78%).

The FRAX® calculates the probability of presenting a primary fracture (this include hip, clinical spine, humerus and forearm) or a hip fracture in the following 10 years, with the inclusion or non inclusion of the BMD score. When the BMD is included in the FRAX® tool the prediction of fracture risk is more precise and reliable.[16,17]

FRAX® limitations are mostly determined by insufficiencies in the data from which it was calculated. Thus the FRAX® does not consider the dose-response factor for several RF, nor lumbar BMD, nor the greater risk of fracture in patients with a recent fracture, and it does not encompass falls.[9,16–18]

The Spanish version of the FRAX® underestimates the risk of the primary fracture.[19] However, the application of a decision algorithm with bone densimetry threshold indication (DXA) and treatment based on FRAX® has been shown to be cost-effective with regard to the exclusive use of *T*-score −2.5 SD.[20] Despite its limitations, the current version of the Spanish FRAX® may help to classify patients better with regard to fracture risk.

Recommendation: *It is recommended that patients be classified as high fracture risk when the risk quantified by FRAX® for hip fracture is ≥3%* (RR: √; AL: 100%).

Recommendation: *To classify patients as high risk using the FRAX® for the primary fracture it is suggested that the threshold ≥10% without BMD be used or ≥7.5% with BMD* (RR: √; AL: 78%).

The validity of the Spanish FRAX® was analysed in two prospective cohorts studies and in both the primary fracture risk was underestimated. The relationship between observed fractures and expected fractures was 2.2 in the FRIDEX[20] study and 1.5 in the ECOSAP[21] Study. However, the estimation of the Spanish FRAX® for hip fracture appears to be appropriate. A workgroup estimated the thresholds of the FRAX® in the Spanish population[20,22,23] defining high primary fracture risk as a FRAX®, with or without BMD, ≥7.5% and intermediate risk between 5% and 7.5%. This was a single study which defined risk thresholds in Spain and had methodological

Table 1
SER recommendations on osteoporosis.

Recommendations	RR	AL
Diagnosis and evaluation		
Recommendation: It is recommended that fragility fracture risk assessment should not be based exclusively on the measurement of BMD but should also take into account clinical risk factors.	B	100%
Recommendation: The use of the FRAX®, tool is recommended, with or without BMD, to assess fracture risk.	√	78%
Recommendation: The classification of patients into high fracture risk is recommended when the risk quantified by FRAX® for hip fracture is ≥3%.	√	100%
Recommendation: To classify high risk patients using FRAX® for primary fracture it is recommended that the threshold used is ≥10% without BMD or ≥7.5% with BMD.	√	78%
Recommendation: the use of densitometry is recommended in the following cases:	D	
1. Fragility fracture		100%
2. Presence of two or more high fracture risk factors		100%
3. FRAX® for primary fracture ≥5%		78%
4. Treatment with aromatase inhibitor drugs, antiandrogen drugs and glucocorticoids		100%
5. Disease associated with secondary OP		100%
Recommendation: A basic analytical study is recommended to rule out secondary causes of osteoporosis.	√	100%
Recommendation: The routine example of bone turnover markers is not established. However, they could be considered in the initial assessment and in follow-up of patients with osteoporosis.	B	89%
Recommendation: Assessment of the presence of vertebral fractures is recommended in the high fracture risk patient or the patient with osteoporosis when kyphosis or significant height loss is perceived and when there is back pain or low back pain of recent onset.	D	100%
Treatment		
Recommendation: A healthy lifestyle is recommended for the prevention of primary and secondary osteoporosis and fractures, including a balanced diet and regular physical exercise, avoidance of tobacco, limitation of alcohol consumption and the use of preventative measures for falls.	√	100%
Recommendation: A daily intake of calcium between 1000 and 1200 mg, most of which should be included in the regular diet.	D	100%
Recommendation: The daily intake of 800 UI of vitamin is recommended in the following cases:	D	100%
1. Patients with osteoporosis		
2. People over 65 years of age with fracture risk		
3. People with vitamin D deficiency		
4. People with limited exposure to sunlight		
5. People with inadequate calcium intake (under 700–800 mg per day)		
Recommendation: Initiation of pharmacological treatment is recommended to reduce the risk of osteoporotic fracture in the following situations.	√	
1. Fragility fracture of vertebra or hip in patients >50 years of age		100%
2. Other fragility fractures in patients >50 years of age and with low bone mass (*T*-score <−1 SD)		89%
3. OP defined by *T*-score ≤−25 SD in spine, femoral neck or hip, always considering age, BMD figures and other risk factors		100%
4. Patients with high risk of hip fracture according to FRAX® with BMD ≥3%		100%
5. Men being treated with androgen deprivation and *T*-score ≤−2.5 SD		100%
6. Women in treatment with aromatase inhibitors and *T*-score ≤−2 SD or with a *T*-score <−1.5 SD and an additional risk factor, or with ≥2 risk factors without BMD		78%
7. Patients who are going to receive glucocorticoids for over 3 months in the following cases: (a) initial dose ≥30 mg/day of prednisone; (b) postmenopausal women and men >50 years of age with dose ≥5 mg/day and previous fragility fracture or *T*-score ≤−1.5 SD or high risk of fracture: FRAX® for hip ≥3% or for primary fracture ≥10% without BMD or ≥7.5% with BMD		100%
Recommendation: When selecting treatment, among other factors, it is recommended to consider:	√	100%
1. The efficacy and safety of the drugs		
2. The cost/effectiveness ratio		
3. The BMD value		
4. The presence of fractures, particularly vertebral or multiple fragility fractures		
5. Previous treatments and adherence to the same		
6. Age		
7. Comorbidities and polymedication		
8. Limitations for oral administration		
Recommendation: It is recommended that fracture risk be reassessed after 5 years of treatment with oral bisphosphonates or after 3 years of treatment with zoledronic acid.	D	100%
Recommendation: When treatment with denosumab is suspended an alternative treatment for the osteoporosis must be considered.	D	100%
Recommendation: In high fracture risk patients, including those with previous fragility fracture, or with a T-score of proximal femur <−.5 SD, it is not recommended to discontinue the osteoporosis treatment.	D	89%
Recommendation: A periodical clinical assessment is recommended to confirm adherence to and efficacy of treatment, incidence of fractures and the possible appearance of adverse effects.	√	100%
Recommendation: If the patient with OP has been subjected to any invasive dental procedure (extraction or implant) it is advised to postpone antiresorptive treatment initiation until the surgical wound has completely healed.	D	100%
Recommendation: In patients treated with antiresorptives who are going to have a dental procedure it is not recommended to discontinue treatment with BP or denosumab. If risk factors additional to osteonecrosis of the jawbones exist or the surgical procedure is to be extensive temporary discontinuation of treatment with BP may be considered.	D	78%

Table 1 (*Continued*)

Recommendations	RR	AL
Recommendation: In patients with high fracture risk and prolonged treatment with bisphosphonates (>5 years for orals or >3 years for intravenous) it is recommended not to suspend treatment, since the risk of atypical femur fracture is very low and the benefits of fracture reduction greatly outweigh the risk of atypical fracture.	D	100%
Special situations		
Recommendation: It is recommended that all patients ≥50 years of age with a recent fragility fracture be assessed systematically to prevent further fractures.	D	100%
Recommendation: The treatment of choice for an acute vertebral fracture is rest, rapidly scaled analgesics to control pain, and if necessary the use of a brace.	√	100%
Recommendation: Vertebroplasty and kyphoplasty are recommended for the treatment of vertebral fracture only in cases of serious refractory pain on a WHO analgesic scale, including opiates.	D	100%
Recommendation: In patients who receive or who are going to receive treatment with glucocorticoids fracture risk must be assessed and the initiation of treatment for osteoporosis as soon as possible.	D	100%
Recommendation: It is recommended that pharmacological treatment be initiated to prevent OP in patients who are going to receive glucocorticoids for over 3 months in the following cases:	D	
1. Patients with an initial dose ≥30 mg/day of prednisone. In these cases it is recommended that treatment be imitated for OP immediately		100%
2. Postmenopausal women and men >50 years of age with a prednisone dose ≥5 mg/day who also present with some of the following conditions:		100%
a) Previous fragility fracture		89%
b) Low BMD (*T*-score ≤−1.5 SD in spine or hip)		78%
c) High fracture risk: FRAX® for hip ≥3% or for primary fracture ≥10% without BMD or ≥7.5% with BMD		100%
3. Premenopausal women and men <50 years of age and daily dose ≥7.5 mg/of prednisone who also present with one of the following conditions:		78%
a) Previous fragility fracture		78%
b) Low BMD (*Z*-score ≤−3 SD)		
Recommendation: It is advisable to assess the risk of fracture and consider performing DXA in patients with rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis especially those over 50 years of age and who are being treated with glucocorticoids or with a severe or evolved disease.	√	100%
Recommendation: The study of the causes of secondary osteoporosis in all men with low bone mass or fragility fracture is recommended.	D	100%
Recommendation: It is recommended that a study of secondary osteoporosis causes be made in all premenopausal women with a low bone mass or with a fragility fracture.	√	100%

BMD: bone mineral density; FRAX®: Fracture Risk Assessment; AL: agreement level; RR: Recommendation rating (see Appendix 1).

Table 2
Clinical fracture risk factors.

Higher risk (relative risk ≥2)
Over 65 years of age
Low weight: body mass index <20 kg/m²
Personal history of fragility fracture
Maternal history of femur fracture
Glucocorticoids (>5 mg/day of prednisone or equivalent for >3 months)
More than 2 falls in the last year
Moderate risk (relative risk between 1and 2)
Active smoker
Consumes >3 units of alcohol per day[a]
Early menopause (<45 years of age), primary and secondary amenorrhea, hypogonadism in the male
Diseases which may reduce BMD: rheumatoid arthritis and other inflammatory arthropathies, intestinal pathology, celiac disease, malabsorption, hepatopathies, hyperparathyroidism, anorexia and bulimia, solid organ transplant, etc.
Drugs with the ability to reduce BMD/increases the risk of fractures: hydantoins, antiretrovirals, anticonvulsants, aromatase inhibitors, androgen deprivation drugs, etc.
Conditions related to falls: eye conditions, neurological diseases (stroke, Parkinson), use of psychodrugs

[a] One unit of alcohol is equal to 200 ml of beer or 100 ml of wine or 25 ml of a spirit.

limitations such as not being validated in regions other than Catalonia, including only 8.9% of subjects with intermediate risk and 8.5% with high fracture risk, as well as overlapping in the confidence interval of the high risk threshold. In this sense, the panel considers that a women aged around 70 years with a prior fracture (is approximately equivalent to as Spanish FRAX® for the principal fracture without BMD of 10%) is an example of high fracture risk.

From the scarce evidence and low level of agreement in classifying the patient as high fracture risk based on the FRAX®, the panel of experts agreed to consider a high risk fracture as FRAX® ≥3% for a hip fracture. Since no further studies on the FRAX® thresholds and/or national official positioning were available, the panel of experts also considered high fracture risk a FRAX® for primary fracture ≥10% without BMD or ≥7.5% with BMD.

The panel of experts also considered as high fracture risk, but without reaching an acceptable level of agreement (AL: 55%), the combination of two or more high RF. Should the FRAX® tool not be used, the presence of two high risk factors may serve as the starting point for assessing the BMD.

Bone densimetry

The technique of choice today for measuring BMD is the DXA dual energy X-ray absorptiometry.[6,10,11] The measurement is made in the lumbar spine and the proximal femur (femoral neck and total hip). According to the experts, measurement using DXA of the distal third of the forearm should only be performed when measurement in the lumbar spine or the proximal femur is not feasible and/or in specific pathologies such as hyperparathyrodism.[24]

The DXA has a high specificity for the reduction of fracture risk, but a low sensitivity. The risk increases exponentially as the BMD descends.[25] However, the majority of fragility fractures occur in patients with a *T*-score above −2.5 SD. Studies made in patients diagnosed with OP using DXA and without other RF of fractures conclude that it could be appropriate to estimate risk using FRAX® before evaluating treatment.[26,27]

Different groups of experts agree that the BMD determined in the peripheral skeleton using DXA of the phalanx and heel spur and the ultrasound technique of the heel spur may be useful for prediction of fracture risk but not for diagnosing OP.[28,29]

Bone densitometry indications

Criteria for requesting a DXA vary widely nationally and internationally. The majority of international guidelines on OP recommend evaluation of BMD in postmenopausal women ≥65 years of age, regardless of other RF.[30–32] There is controversy regarding the screening age in males. The *National Osteoporosis Foundation* (NOF) and the *International Society for Clinical Densitometry* (ISCD) recommend measurement in males ≥70 years of age, whilst the Canadian guidelines put the threshold at ≥65 years of age.[31]

According to the conclusions of a cross-sectional study the aim of which was to evaluate DNX indication criteria in postmenopausal Spanish women based on the FRAX® tool, the indication of the test should be based on clinical criteria to allow for patients to be selected where its evaluation is more efficient.[33] The authors conclude that the strategy should begin with calculation of the fracture risk according to clinical RF, and in this setting using FRAX®[33] could be helpful.

Based on the accepted international recommendations on DXA indications, the panel of experts considers that its main applications in clinical practice are: OP diagnosis, evaluation of fracture risk, evaluation of treatment and monitorisation of response to treatment.

In patients with an imminent risk of fracture performing a DXA should not impede treatment initiation. Thus patients with a high fracture risk may be treated without the need to carry out a DXA, although it seems appropriate to know the baseline BMD for evaluation of treatment effectiveness at a later date. The panel of experts agree that when the fracture risk is low no DXA should be performed and that a DNA should not be recommended to all women going through the menopause.

Recommendation: *It is recommended to perform a densitometry in the following cases* (RR: D):

1. *Fragility fracture (AL: 100%).*
2. *Presence of two or more high risk fracture factors (AL: 100%).*
3. *FRAX® for primary fracture ≥5% (AL: 78%).*
4. *Treatment with aromatase inhibitor drugs, antiandrogens and glucocorticoids (AL: 100%).*
5. *Diseases associated with secondary OP (AL: 100%).*

Based on these international studies, the panel of experts considered the use of FRAX® without BMD as initial assessment of fracture risk. When the risk calculated using the Spanish FRAX® without BMD, for the principal fracture is ≥5% it is advisable to perform DXA.[34] Low risk patients are therefore not recommended to have DXA.

The panel also considered measuring in BMD, regardless of age, in the population which present with RF for fragility fractures such as: previous fragility fracture, women who begin treatment with aromatase inhibitors for breast cancer,[35] males treated with androgen deprivation therapy for prostate cancer and patients treated with glucocorticoids. The recent guideline of the *American College of Rheumatology* (ACR) for the prevention and treatment of OP using glucocorticoids recommends performing DXA in patients who start chronic treatment with glucocorticoids in the following cases: (1) adults <40 years of age when there is a background of fracture or high RF of fracture and (2) adults ≥40 years of age in all cases and calculate the FRAX® with BMD.[36] the oncology guidelines and those of the *International Osteoporosis Foundation* (IOF) recommend DXA to decide whether to initiate treatment for OP in women receiving aromatase inhibitors[35] and in males in androgen deprivation therapy.[37]

In cases of recent fracture due to fragility or treatment with high doses of glucocorticoids, studies concluded that performing a DXA should not delay initiation of treatment to prevent new fractures.[12,13]

Other patients who are eligible for DXA due to presenting with high OP and fragility fracture risks are those suffering from diseases associated with secondary OP, such as chronic inflammatory arthropathies, inflammatory bowel disease, intestinal malabsorption syndromes, chronic liver disease or advanced chronic kidney disease. In these cases the panel considers BMD reasonable in order to establish prevention measures and appropriate treatment for each individual patient.

Trabecular Bone Score

The *Trabecular Bone Score* (TBS) is an analysis of the bone texture obtained from the DXA which evaluates parameters related to the bone micro architecture of the lumbar spine and has good correlation with computerised tomography.[38,39] Low TBS values are associated with an increased risk of primary osteoporotic fracture, regardless of BMD.[38] The combination of TBS and lumbar BMD increases the reduction of the risk of developing fractures.[39] Furthermore, the introduction of the TBS in the FRAX® algorithm enables a better prediction of the development of future fractures.[38,40,41] As a result, according to studies, the TBS could be an additional tool for the evaluation of fracture risk in patients with OP[38–40] and in some causes of secondary OP (diabetes, hyperparathyroidism, glucocorticoids). However, its usefulness in the monitorisation of the therapeutic response has not yet been established.[38]

To sum up, the panel of experts consider that although TBS could have several advantages in the evaluation of fracture risk, further studies are required to recommend its use in clinical practice.

Analysis

Recommendation: *It is recommend that a basic analytical study be performed to rule out secondary causes of osteoporosis* (RR: √; AL: 100%).

Basic laboratory tests to identify secondary OPs and make the differential diagnosis with other bone disease include[30,42,43]: haemogram, serum calcium and phosphate tests, alkaline phosphatase, test, proteingram, albumin, creatinine, liver function tests, calciuria and 25-hydroxy vitamin D tests.

Different scientific societies[30,42,43] have produced documents with the following recommendations:

- Additional tests will be carried out if there is suspicion of an associated condition:
  1. PTH (primary or secondary hyperparathyroidism).
  2. TSH (hyperthyroidism).
  3. Immunoelectrophoresis (myeloma).
  4. Antitransglutaminase antibodies (celiac disease).
  5. Urinary cortisol (Cushing's).
  6. Serum tryptase (mastocytosis).
  7. Sexual hormone study (young people).
  8. Genetic study (imperfect osteogenesis, hypophosphatase and others).

Bone turnover markers

Recommendation: *The routine use of bone turnover markers has not been established. However, they could be considered in initial assessment and in follow-up of patients with osteoporosis* (RR: B; AL: 89%).

The reductions of the greatest magnitude in markers of bone turnover (MBT) are significantly associated to more marked reductions in the non vertebral fracture risk,[44] and the initial changes in a formation marker predict the efficacy of the bisphosphonates

(BP) in the reduction of vertebral fracture risk.[45] However, there is not sufficient evidence to conclude that MBT are able to identify a reduction in risk fracture unequivocally.[46]

The majority of GPC recommend the consideration of the use of MBT in the initial evaluation and in follow-up, as an additional test. In the initial evaluation, the high levels may predict a faster loss of bone mass and a higher risk of fracture. But their main indication is in follow-up, since they can contribute to assessing treatment adherence and efficacy, and also contribute to monitoring the duration of therapeutic holidays.[30,42,43,47] The groups of international experts conclude that further research studies are required prior to making a recommendation based on the evidence.[43] To conclude, although the use of bone turnover markers has not been established as a routine, the panel of experts suggest that they could provide additional information in the initial evaluation and in the patient follow-up with OP.

The two main serum references of MBT which are recommended to use by the IOF and the *International Federation of Clinical Chemistry and Laboratory Medicine* (IFCC) are the precollagen type I N-terminal propeptide (PINP), bone turnover marker and the Carboxyl-terminal telopeptide of type I collagen (CTX), a reabsorption marker.[48]

Vertebral fracture screening

Recommendation: *It is recommended that the presence of vertebral fractures be assessed in the patient with a high fracture risk or with osteoporosis, when kyphosis or significant loss of height has presented and when there is back pain or low back pain of recent onset* (RR: D; AL: 100%).

Chest and lumbar spine X-rays (focused on T7 and L3, respectively) are the method of choice for diagnosis of a vertebral fracture. A side projection is usually sufficient, thus minimising the radiation the patient receives.[49] These are useful in the initial evaluation of all patients diagnosed with OP when there is a significant loss of height or a change in relevant statics (especially thoracic kyphosis) and dorsolumbar pain of recent onset with or without a history of trauma[50] in a patient with a risk of OP or fracture. Height loss which is significantly associated with the presence of vertebral fractures is not defined, varying between 2 cm compared with measurement in previous years to 4 cm of historic loss since youth.[30,51] The presence of a vertebral fracture, the number of them and their degree of severity are highly relevant indicators of the risk of new vertebral fractures, even those of the hip.[52]

The panel of experts has thus considered that the presence of vertebral fractures should be assessed in the evaluation of the patient with OP or with a high risk of fracture when kyphosis or significant loss of height is present and there are clinical features of vertebral fracture. Some DXA teams also use the *Vertebral Fracture Assessment* (VFA) to assess fractures.

Treatment

Non pharmacological therapies

Recommendation: *Included in the prevention of primary and secondary osteoporosis and fractures is the recommendation for a healthy lifestyle, consisting of a balanced diet and regular physical exercise, not smoking, limiting alcohol consumption and using preventative measures against falls* (RR: √; AL: 100%).

Several studies have concluded that the first step to the prevention of OP and the avoidance of fractures is to maintain healthy life habits.[53–57] Evidence suggests that exercise has a modest effect on reducing fractures and preventing falls.[57] Table 3 contains a

summary of the most important measures to be taken into consideration.

Studies show that the adoption of fall prevention measures, in which exercise programmes and actions on environmental safety and minimisation of the use of drugs such as hypnotics, diuretics, antihypertensives and others which impair balance, also contribute both to primary and secondary fragility fracture prevention.[57,58]

In contrast, exercises which require great effort or are abrupt and those which involve repeated flexion or twisting of the trunk and abdominals are ill-advised.

Regarding specific measures for the patient who has kyphosis, studies have proven the effectiveness of exercise, and training in muscular strength and balance.[59]

The effectiveness of hip protectors in the prevention of fractures is inconclusive, and adherence to their use is very low.[60] Finally, vibratory platforms have not demonstrated any consistent efficacy.[61]

Calcium and vitamin D

Recommendation: *It is recommended that a daily intake of calcium between 1000 and 1200 mg be taken and that it should mainly originate from a regular diet* (RR: D; AL: 100%).

Recommendation: *In the following cases a daily intake of 800 UI of vitamin D is recommended* (RR: D; GA: 100%):

1. *Patients with osteoporosis.*
2. *People over 65 years of age with fracture risk.*
3. *People with a vitamin D deficit.*
4. *People with limited exposure to the sun.*
5. *People with an insufficient calcium intake (under 700–800 mg daily).*

Studies coincide in the need to ensure an adequate provision of calcium as an essential feature in any OP treatment programme.[47] Thus patients in pharmacological treatment for OP must use calcium and vitamin D supplements because practically all clinical trials which have demonstrated the efficacy of the antiosteoporotic drugs routinely include calcium supplements and cholecalciferol (vitamin D_3). When the calcium provided in the diet is insufficient, it is recommended that calcium and vitamin D supplements be taken. In postmenopausal women with OP the international expert groups advise an intake of 800–1.200 mg/of calcium per day and 800 UI/of vitamin D per day.[62,63]

In primary prevention a daily intake of calcium of 1000–1200 mg for women >50 years of age and men >70 years of age is advised, preferably in the diet, and 1000 mg/of calcium per day in women <50 years of age and men aged between 51 and 70.

Some foods are rich in calcium, such as milk products (milk, cheese, and yoghurt) tinned oily fish, beans and almonds. A list of foods and an online calculator are available in the IOF website.[64,65] if supplements are used, the experts advise bearing in mind the

Table 3
Main habits of a healthy lifestyle.[53–57]

Cover nutritional requirements with a healthy diet which includes an adequate intake of proteins (0.8 g per kilo of body weight), calcium, fruit and vegetables
Limit caffeine intake
Prudent exposure to sunlight
Avoid consumption of tobacco and limited intake of alcohol to under 3 units per day[a]
Encourage physical activity with regular exercise both own weight bearing (examine: walking, dancing, practising taichi 30–40 min per session) and muscle and postural strengthening, 3–4 days per week

[a] One unit of alcohol is equal to 200 ml of beer or 100 ml of wine or 25 ml of a spirit.

optimum dose for calcium absorption which is situated in 500 mg of calcium, and if larger doses are administered they should be spread over time.[66]

With regard to the possible side effects of calcium supplements, constipation and dyspeptic upsets are the most notable. An increased risk of nephrolithiasis was demonstrated (RR 1.17) in the *Women's Health Initiative*[67] study, attributed to a diet rich in calcium of the women studied. However, a systematic review concluded that the calcium supplements in OP treatment, alone or in combination with other types of treatment, did not significantly increase the risk of nephrolithiasis or renal colic.[68] Controversy exists regarding the possible increased cardiovascular risk associated with calcium supplements, particularly if the recommended maximum dose is exceeded. The available evidence suggests that a total daily intake of calcium (obtained by adding up dietary intake plus supplements) under 2000 mg did not increase cardiovascular risk.[69,70]

Regarding vitamin D, in OP patients, the conclusion reached by the experts is to maintain minimum serum concentrations of 25-hydroxy cholecalciferol (calcidiol) of 30 ng/ml. They therefore recommend measuring the calcidiol levels in patients with a risk of vitamin D deficiency and in patients with OP. Given the essential role of sunlight as a source of vitamin D, they advise an exposure to the sun of 10–15 min per day.[62,63] When necessary; they advise vitamin D supplements with a dose between 800 and 2000 UI/day, depending on baseline levels. In patients with hepatopathies, malabsorption syndromes, treatment with anticonvulsives or other situations where the vitamin 25D hydroxylation may be compromised, administration of the metabolite calcidiol is recommended.

Current scientific evidence enables us to state that neither the increase of dietary calcium nor the isolated intake of calcium supplements is able to protect against the presence of fractures.[71,72] Vitamin D administered as a monotherapy is not effective in reducing fragility fractures either, in non institutionalised elderly people.[72,73] Calcium and vitamin D supplements have been show to be effective in the population >65 years of age who reside in care homes, reducing the risk of non vertebral fracture and marginally of hip fracture.[72,74] This effect depends to a large extent on the vitamin D dose (≥800 UI daily) and is more obvious at a greater age and with lower vitamin D levels.[72] Calcium and vitamin D supplements do not reduce the risk of vertebral fracture.[72]

The efficacy of calcium and vitamin D supplements in the non institutionalised population >65 years of age (residents in the community) is questionable, as evidenced by the high number required to treat (NNT) to prevent fracture in this low risk population group[74] and the results of a recent meta-analysis.[75]

There are contradictory data on the efficacy of vitamin D in the prevention of falls. Some results indicate that vitamin supplements, with and without calcium, would be effective in the prevention of falls,[76] and especially in the elderly with vitamin D deficit.[77] Other studies do not show this beneficial effect of vitamin D,[78] and even the administration of annual high doses could increase the risk of falls.[79]

Treatment to prevent fractures

Recommendation: *It is recommended that pharmacological treatment be initiated to reduce the Risk of osteoporotic fracture in the following situations* (RR: √):

1. *Fragility fracture of vertebra or hip in patients >50 years of age (AL: 100%).*
2. *Other fragility fractures in patients >50 years of age and with low bone mass (T-score <−1 S) (AL: 89%).*

3. *OP defined by T-score ≤−2.5 SD in spine, femoral neck or total hip, always evaluating age, BMD figures and other risk factors (AL: 100%).*
4. *Patients with a high hip fracture risk according to FRAX® with BMD ≥3% (AL: 100%).*
5. *Males in androgen deprivation treatment and T-score ≤−2.5 SD (AL: 100%).*
6. *Women in treatment with aromatase inhibitors and T-score ≤−2 or with a T-score <−1.5 SD and an additional risk factor, or with ≥2 risk factors without BMD (AL: 100%).*
7. *Patients in treatment with glucocorticoids and: (a) initial dose ≥30 mg/day of prednisone; (b) postmenopausal women and men >50 years of age with a dose of ≥5 mg/day and previous fragility fracture or T-score ≤−1.5 SD or high risk of fracture: FRAX® for hip ≥3% or for primary fracture ≥10% without BMD or ≥7.5% with BMD (AL: 78%).*

The drugs used for the treatment of OP have been shown to be more effective in patients with a high risk of fracture and in those with an existing fracture or with a T-score ≤−2.5 SD.[80]

The NOF recommendations and those of other expert groups support the use of FRAX® in selecting candidates for treatment, including cases without OP using DXA.[30,80]

The panel thus considers that treatment is indicated in patients with fragility fracture, OP from DXA T-score ≤−2.5 SD, high fracture risk (FRAX® for hip fracture with BMD ≥3%)[23,34] and in sub-groups of patients who take glucocorticoids, aromatase inhibitors[35] or antiandrogens.[37] The specific circumstances where osteoporotic antifracture treatment should be assessed is commented upon in detail in other sections.

Regarding patients with fragility fractures, the NOF recommends treating all hip and vertebra fractures, whilst the other fractures would be treated depending on the results of the DXA and the risk of new fractures calculated using the FRAX®.[30]

Regarding the evaluation of treatment based on the DXA outcome with a T-score ≤−2.5 SD, the panel wishes to highlight that in these cases clinical risk factors and the FRAX® should also be considered when decision are to be taken.

Prophylaxis and treatment of OP induced by glucocorticoids are dealt with in a separate section.

Several international guidelines, including those on oncology, advise that treatment be indicated for OP in women who receive aromatase inhibitors and have a T-score below or equal to −2 SD or with a T-score <−1.5 SD with an additional risk factor, or with ≥2 risk factors without BMD.[35] For men in androgen deprivation therapy, the IOF fixes the threshold for treating OP in a T-score of −2.5 SD or a raised fracture risk by FRAX®[37] (Fig. 1).

Antifracture treatment choice

Recommendation: *When selecting treatment, among other factors, it is recommended to take the following into consideration* (RR: √; AL: 100%):

1. *The efficacy and safety of the drugs.*
2. *Cost-effectiveness ratio.*
3. *The value of the BMD.*
4. *The presence of fractures, particularly vertebral or multiple fractures due to fragility.*
5. *Treatments prior to this and adherence to them.*
6. *Age.*
7. *Comorbidities and polymedication.*
8. *Limitations for oral administration.*

The final aim of OP treatment is the prevention of fractures. Table 3 contains the efficacy in primary and secondary prevention
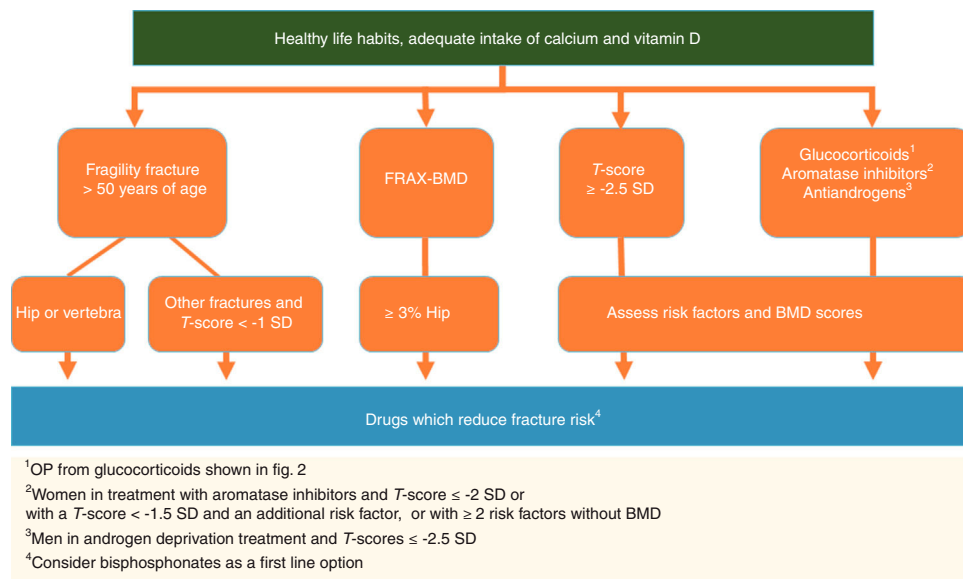
Fig. 1. Recommendations for initiating treatment for the prevention of fractures in patients with osteoporosis or risk of osteoporosis.

of vertebral and non vertebral fractures of the drugs used in Spain.[81–94]

In the main studies conducted with drugs in patients who only had osteopenia without prevalent fracture (primary prevention) no fracture reduction occurred in primary outcome.

In primary fracture prevention in patients with OP, the drugs which demonstrated a reduction of vertebral fracture were: alendronic acid, zoledronic acid, raloxifene, bazedoxifene and denosumab, whilst denosumab also reduced non vertebral fracture and hip fracture in this group.

In patients with OP and vertebral fracture, alendronic acid, risedronic acid and zoledronic acid reduced new vertebral, non vertebral and hip fractures, whilst teriparatide reduced vertebral and non vertebral fractures and denosumab reduced vertebral fractures. For their part, ibandronic acid, raloxifene and bazedoxifene reduced vertebral fractures in patients with previous fracutre.[81–94] With regard to forearm fractures, alendronic acid demonstrated a significant reduction of new wrist fractures in meta-analysis in patients with previous vertebral fracture.[81]

Tables 4–7 contain details of the risk reduction for different fractures in the published studies.[83–94]

In patients with at least two moderate vertebral fractures or at least one severe fracture teriparatide was significantly more effective than risedronic acid for reducing new morphometric and clinical vertebral fractures after 24 months of treatment. There were no significant differences in the rate of new non vertebral fractures.[95]

Strontium renalate has not been included in these recommendations because its production has been suspended, nor calcitonin, because of the limitation its technical record has in treatment indication and duration. However, therapy with oestrogens reduces vertebral and hip fractures, but is currently not used due to its poor risk/benefit profile and because safer treatments exist.

The following aspects have to be taken into consideration when integrating trial outcomes into clinical practice: (1) the patient profile included is a postmenopausal woman with a high baseline risk due to age and the presence of previous fractures; (2) the populations of the trials are different to one another, and therefore may not be directly compared; (3) the studies were conducted with calcium and/or vitamin D supplements and (4) real treatment adherence is lower than that reported in the trials. Moreover, treatment should be individualised according to the circumstances of each patient.

Another aspect to take into account is the cost/effectiveness ratio of treatment. The studies undertaken in other countries fix the threshold of FRAX® for primary fracture, so that the cost-effectiveness of the treatment is 8.8% (Portugal),[96] 13.8% (Switzerland)[97] and 10%–15% (Greece).[98] For estimation the cost of alendronic acid was considered (Portugal and Switzerland) and the average cost of treatment for OP (Greece). When drugs other than alendronic acid were considered, the FRAX® threshold for cost effectiveness was higher.[96–98] Despite no cost-effectiveness studies existing for Spain based on fracture risk, the panel of experts advised taking into account BP as first line option in OP treatment.

The panel of experts therefore consider that when choosing treatment to prevent fractures the efficacy and safety of the drugs, cost-effectiveness ratio, BMD figures, and presence of previous features (location, number and time passed since fracture) and oral administration route limitations should be contemplated. Other factors which also were to be taken into account were previous treatments and adherence to them, co morbidities and patient preferences. Thus, in patients with several fractures, oral intolerance, dementia, malabsorption and poor adherence, parenteral therapy could be considered.

Sequential and combined therapy

The risk of long-term complications in OP treatments[99–101] and the increase in the risk of fracture after their suspension[102,103] often obliges physicians to put forward a sequential treatment strategy.

Although there are currently no outcomes on fracture reduction with sequential treatment,[104,105] the bone forming sequence (teriparatide) followed by antiresorptive sequence (denosumab or BP)[104–106] is the most effective in terms of gaining BMD. Teriparatide followed by denosumab appears to be more effective than teriparatide followed by BP.[107]

The administration of teriparatide after an antiresorptive drug is also effective, although its anabolic effect may slow down (less change in bone markers and lower increase of BMD),[108] and if administered after denosumab it has been described as a loss of initial BMD in the hip.[106] Sequential treatment with romosozumab followed by an antiresorptive drug is dealt with in the section relating to new treatments.

Little information exists on the use of one antiresorptive drug followed by another, especially if the first was administered for

Table 4
Efficacy of the drugs to reduce vertebral, non vertebral and hip fracture.

	Vertebral			Non vertebral		Hip	
	Osteopenia	Osteoporosis (no previous vertebral fracture)	Established Osteoporosis (with previous vertebral fracture)	Osteoporosis (no previous vertebral fracture)	Established Osteoporosis (with previous vertebral fracture)	Osteoporosis (no previous vertebral fracture)	Established Osteoporosis (with previous vertebral fracture)
Alendronic acid[83,84]	ND	SI	SI	ND	SI	SG	SI
Risedronic acid[85,86]	ND	PH	SI	ND	SI	ND	SI
Zoledronic acid[87]	ND	SI	SI	ND	SI	ND	SI
Denosumab[88]	ND	SI	SG	SI	ND	SI	ND
Teriparatide[89]	ND	ND	SI	ND	SI	ND	ND
Ibandronic acid[90]	ND	NA	SI	ND	PH	ND	ND
Raloxifene[91]	PH	SI	SI	ND	PH	ND	ND
Bazedoxifene[92]	ND	SI	SI	PH	PH	ND	ND

ND: not demonstrated; PH: post hoc analysis by subgroups (designed after knowledge of the trial outcome); SG: subgroup analysis designed prior to knowing the trial outcome; SI: ITT (intention to try) analysis.

Table 5
Efficacy of treatments to reduce vertebral fracture. Reference studies used for the approval of each drug.

Study (duration)	Drug	Baseline risk profile	Mean age (years)	RRR (%)	RRA (%)	NNT
FIT-1[83] (3 years)	Alendronic acid	Vertebral Fr	71	47	7	14
FIT-2[84] (3 years)	Alendronic acid	Without Vertebral Fr	68	44	1.7	60
BONE[90] (3 years)	Ibandronic acid	Vertebral Fr	69	62	4.9	27
VERT NA[85] (3 years)	Risedronic acid	Vertebral Fr	69	41	5	20
VERT MN[86] (3 years)	Risedronic acid	Vertebral Fr	71	49	10.9	10
HORIZON[87] (3 years)	Zoledronic acid	$T < -1.5$ SD + Vertebral Fr or $T < -2.5$ SD $\pm$ Vertebral Fr	73	70	7	14
MORE[91] (3 years)	Raloxifene	Vertebral Fr or $T < -2.5$ SD	67	35	3.5	16
Silverman et al.[92] (3 years)	Bazedoxifene	Sin Vertebral Fr $T < -2.5$ SD and > -4 SD With Vertebral Fr $T > -4$ SD	67	38	1	82
FPT[89] (2 years)	Teriparatide	Vertebral Fr	70	65	9.3	11
FREEDOM[88] (3 years)	Denosumab	T between -2.5 and -4 SD	72	67	4.9	20

SD: standard deviation; RF: risk factor; Fr: fracture; NNT: necessary number to treat; ARR: absolute risk reduction; RRR: relative risk reduction; T: T-score.

Table 6
Efficacy of treatments to reduce non vertebral fracture. Reference studies used for the approval of each drug.

Study (duration)	Drug	Baseline risk profile	Mean age (years of age)	RRR (%)	ARR (%)	NNT
FIT-1 (3 years)[83]	Alendronic acid	Vertebral Fr	71	20	3	–
FIT-2 (3 years)[84]	Alendronic acid	Sin Vertebral Fr	68	12	1.8	–
VERT NA (3 years)[85]	Risedronic acid	Vertebral Fr	69	40	3.2	31
VERT MN (3 years)[86]	Risedronic acid	Vertebral Fr	71	33	5.1	–
HIP (3 years)	Risedronic acid	Group 1 $T < -4$ SD < -3 SD and RF	74	20	1.8	55
HORIZON (3 years of age)[87]	Zoledronic acid	$T < -1.5$ SD + Vertebral Fr or $T < -2.5$ SD $\pm$ Vertebral Fr	73	28	2.7	37
HORIZON-R[93]	Zoledronic acid	Hip Fr	75	27	3.3	30
FPT (2 years)[89]	Teriparatide	Vertebral Fr	70	35	2.9	34
FREEDOM (3 years)[88]	Denosumab	T between -2.5 and -4 SD	72	20	1.5	66

SD: standard deviation; RF: risk factor; Fr: fracture; NNT: necessary number to treat; ARR: absolute risk reduction; RRR: relative risk reduction; T: T-score.

Table 7
Efficacy of treatments to reduce hip fracture. Reference studies used for the approval of each drug.

Study (duration)	Drug	Baseline risk profile	Age (years)	RRR (%)	ARR (%)	NNT
FIT-1[83] (3 years)	Alendronic acid	Vertebral Fr	71	51	1	90
HIP[94] (3 years)	Risedronic acid	Group 1 $T < -4$ SD or < -3 SD and RF	74	40	1.3	77
HORIZON[87] (3 years)	Zoledronic acid	Vertebral Fr + $T < -1.5$ SD or $T < -2.5$ SD $\pm$ Fr vertebral	73	41	0.9	109
FREEDOM[88] (3 years)	Denosumab	$T < -2.5$ and > -4 SD	72	39	0.4	230

SD: standard deviation; RF: risk factor; Fr: fracture; NNT: necessary number to treat; ARR: absolute risk reduction; RRR: relative risk reduction; T: T-score.

years. A review of 11 prospective studies of patients previously treated with alendronic acid or risedronic acid showed that the change to ranelate from strontium or denosumab achieved an additional increase in BMD.[109] However, no data were available on fracture reduction either.[109] In one study denosumab showed increases in BMD in patients who had been treated with zoledronic acid.[110]

There are studies which show greater efficacy in combined therapy (bone formation and antiresorptive) compared with monotherapy. The combination of zoledronic acid and teriparatide has been associated with a higher increase in femoral BMD one year after treatment compared with teriparatide in monotherapy.[104,111] The combination of denosumab and teriparatide has been associated with a greater increase in lumbar spine and proximal femur BMD, compared with both drugs in monotherapy.[112] Notwithstanding, there is no evidence of reduction of fractures with these combinations. After a review of the literature, the panel concluded that combined (bone formation and antiresorptive) treatment did not appear to be an option to recommend in general, although its use could be justified in highly selected serious cases of OP.

Treatment duration

OP is a chronic disease, and treatment must therefore be maintained indefinitely or at least for several years. However, there is no recommended maximum treatment for each drug used.[42,100]

The antiresorptive drugs (selective oestrogen receptor modulators, SERM, BP and denosumab) generally reduce fracture risk from 12 to 18 months[88,91,113] and have no maximum approved duration.

In the case of BP, its efficacy, in terms of BMD and fracture risk reduction is maintained for at least 3 years of treatment.[114,115] Some studies show that from the 4th or 5th year BMD slightly rises or remains stable and the risk of some complications increases so that after 5 years of treatment with oral BP or 3 years with zoledronic acid it is advisable to evaluate the risk/benefit of continuing with treatment.[116] The Groups of experts agrees in recommending maintaining treatment (up to 10 years for oral BP or up to 6 years for zoledronic acid) in patients with a high fracture risk (fractures prior or during treatment, age >75 years or T-score ≤ -2.5 SD in femoral neck or total hip).[42,100,117,118]

Denosumab produces a progressive increase of BMD for at least 10 years of treatment, maintaining its ant fracture efficacy over time.[119] Although there is no consensus regarding the duration of this treatment, some authors indicate that it could be established according to a predefined objective (treat to target strategy), i.e. after reaching a certain BMD value.[120] however, they should not suspend treatment with denosumab without establishing other treatment for OP (see section "Suspension or discontinuation of treatment").

Although data exist on efficacy and safety of SERM (raloxifene and bazedoxifene) up to 8 years, maximum duration of the treatment is conditioned by the risk of complications such as thromboembolism, which is more frequent in patients over 70.[121]

Regarding patients who receive glucocorticoids, aromatase inhibitors or androgen deprivation therapy, the panel of experts consider that antiresorptive treatment should be maintained at least whilst the patient receives the inductor drug of OP (see "Osteoporosis by glucocorticoids").

Teriparatide has been shown to reduce the risk of fracture after 6–12 months of treatment initiation. However, to achieve maximum efficacy, both in trabecular and cortical bones, different groups of experts agree that it is recommendable to maintain it for 2 years, which is the maximum period approved.[42,100,108]

Treatment suspension or discontinuation

Recommendation: *It is recommended that fracture risk be reassessed after 5 years of treatment with oral bisphosphonates or after 3 years of treatment with zoledronic acid* (RR: D; AL: 100%).

Recommendation: *When treatment with denosumab it is suspended an alternative treatment for osteoporosis should be contemplated* (RR: D; AL: 100%).

Recommendation: *In patients with high fracture risks like those with a previous fragility fracture, or with a T-score of proximal femur <−2.5 SD, it is not recommended to discontinue osteoporosis treatment* (RR: D; AL: 89%).

OP treatment implies that the patient will receive medication for years, although in some cases it is possible to have interruptions. The so-called "therapeutic holidays" are a temporary suspension of treatment with BP to reduce the presence of adverse effects, because they accumulate in the bone tissue and maintain their effect even years after having been suspended.[115,122–124] This residual effect is not observed with other drugs such as SERM, denosumab or teriparatide.

Although the decision to discontinue treatment with BP must be individualised, the consensus of experts advise reassessing treatment in patients with low fracture risk and who have not presented with incident fractures after 5 years of treatment with oral BP or 3 years with zoledronic acid.[100] The duration of this discontinuation is unknown and has been calculated to be between 2 and 3 years, depending on the BP used.[100,125] Although there is little evidence, the changes in BMD and bone turnover markers could help with decision-making.[100]

The majority of international guidelines advise not to suspend treatment with BP in high fracture risk patients, like those with previous fragility fractures, a low T-score in hip or in those who present with a fragility fracture during treatment.[100,126,127] Regarding the value of the BMD capable of predicting a high fracture risk on suspending treatment, the post hoc analysis of the FLEX and HORIZON studies state this as a femoral T-score <−2.5 SD.[122,124] If treatment with BP is prolonged, it seems reasonable to reassess after 5 years of treatment with oral BP or 3 years with zoledronic acid.[100,126]

According to different scientific societies and groups of experts, the concept of treatment suspension should not be applied to other drugs such as denosumab, since its removal may lead to an increase in bone remodelling, with a decrease in BMD and an increase in fracture risk, including multiple fractures after its suspension.[127–130] For this reason, they concluded that if it is decided to suspend treatment for any reason with denosumab, an alternative treatment should always be considered.[128] The panel of experts, despite little evidence regarding the consequences of suspension of denosumab and its alternative treatment efficacy, recommend that when treatment is suspended with denosumab an alternative OP treatment be sought.

Follow-up, monitorisation and adherence

Recommendation: *Periodical clinical evaluation for confirming compliance and efficacy of treatment, incidence of fractures and the possible presence of adverse effects is recommended* (RR: $\checkmark$; AL: 100%).

Adherence. Low OP treatment adherence is a frequent problem, after 12 months of treatment less than half of the patients stick to the therapy they were prescribed.[131] Low adherence is also associated with an increased fracture risk.[132]

The efficacy of different measures has been studied to improve adherence, such as telephone calls or meetings with patients, but none of them appear to have been truly effective.[133] In a systematic review of 20 studies it was observed that the simplification of posology, electronic prescription and the intervention of the pharmacist improved adherence or persistence of OP treatment. Patient education has demonstrated its effectiveness in several studies, but

not in all of them, whilst monitorisation and supervision had no significant impact on adherence.[134] However, the *Fracture Liaison Service* (FLS) units for secondary fracture prevention reported an adherence >70% at 1–2 years, which was related partly to the educational efforts made by the nurse.[135,136]

MBT could help with follow-up and adherence. The IOF and *European Calcified Tissue Society* (ECTS), in a workgroup for analysing the usefulness of the MBT in oral BP adherence, recommended measuring PINP and CTX at the beginning of treatment and after 3 months, to verify whether there was a greater reduction to the minimum significant change of the MBT.[137] The same workgroup considered a significant change to be a reduction that was higher than 38% for PINP and above 56% for CTX, whilst absence of change suggested the need for reassessment to identify problems with treatment, mainly low adherence.[137] In one meta-analysis of 6 studies which assessed the efficacy of the MBT to improve treatment adherence, compliance was a high average, and it was difficult to assess the repercussion of the act of informing of the outcomes of the MBT.[46] In the meta-analysis one study stood out where higher persistence was observed if the patient was informed of their response to treatment (HR for discontinuation 0.71; 95% CI: .53–.95), whilst informing of the poor response to the drug reduced it (HR for discontinuation 2.22; 95% CI: 1.27–3.89).[138] The reinforcement using the outcomes of the MBT thus had an influence on persistence, depending on the response of the MBT.

Monitorisation

OP treatment monitorisation includes the analytical determinations and the DXA, as well as asking the patient about new fractures. Several studies conclude that the bone remodelling markers could be useful for early monitoring of compliance and response to treatment,[139] but the panel of experts consider that they cannot recommend their systematic determination in patient follow-up. The panel recommends monitoring the response to treatment through central DXA, bearing in mind patient characteristics.

There are no controlled, good quality studies on the frequency with which measurement of the BMD should be repeated during treatment.[140] Possible variation in BMD with current treatments is slow to occur and usually of little magnitude. Given the risk of DXA measurement error, international experts concluded that measurement should be made when the expected change is equal to or higher than the minimum significant difference.[32] For this reason, in general, it is not advised to repeat measurement of the BMD before 2–3 years.[5,141] Other guidelines advise lengthening this time period to 3 years for zoledronic acidy and up to 5 years for oral BP.[126,142,143] In situations of high fracture risk,[5] in treatment with high doses of glucocorticoids or when there is a suspicion of failure in therapy, such as when a new fracture occurs, the period for repeating DXA may be shortened.[144] The aim is to detect the patients who, despite treatment, suffer from a significant drop in BMD. It is also advised to carry out a DXA when planning temporary suspension of the drug for "therapeutic holidays".[124] Although the greatest changes in BMD are detected in the lumbar spine, it is useful to also monitor the hip, as it is less dependent on artefacts impacted by degenerative changes.

Several authors propose using a treat to target strategy in OP where the objectives would be to reach a certain value of the *T*-score (for example, *T*-score: −2.5 SD) or BMD. If this occurred, monitorisation of the BMD would enable the knowledge of whether the therapeutic aim had been reached. However, not all drugs lead to an improvement of BMD proportional to the reduction of fracture risk, and the real value of this strategy in clinical practice is also yet to be defined.[117]

Determination of TBS provides information on the changes which treatment may produce on bone microarchitecture,[145] but insufficient data is available to recommend its use in clinical follow-up.

Therapy failure

The definition of therapeutic failure in the treatment of OP is complex and there are no established criteria. Experts agree that it is advisable to ensure that treatment adherence is correct, confirm an adequate supply of calcium and vitamin D and rule out secondary OP causes. With regard to treatment failure, after one year of treatment with any antiosteoporotic drug, a group of international experts suggest the following criteria of assessment for treatment changes[144]:

1. Two or more fragility fractures during treatment.
2. One fragility fracture together with one of the following factors:
   - Significant loss of BMD (>5% in lumbar spine or >4% in proximal femur).
   - Absence of significant changes in the MBT (reduction of PINP or CTX >25% with antiresorptive treatment, or increase >25% with bone turnover treatment after 6 months).
3. Absence of significant changes in the MBT together with a significant loss of BMD.

Treatment safety

In general the drugs approved for OP treatment are safe and present with good tolerability.[146] Oral BP may lead to a series of adverse digestive effects (pyrosis, dyspepsia, esophagitis, dysphagia or abdominal pain) and oral effects (conjuntivitis, anterior uveitis), of minor intensity in most cases, which disappear when the drug is withdrawn. After the first infusion of zoledronic acids symptoms of unclarified origin have been described characterised by fever, myalgias and bone pains and this occurs in between 20% and 30% of patients. In subsequent infusions the symptoms tend to disappear. This effect may occur rarely with oral BP.

Treatment with BP does not increase cardiovascular risk. No association has been demonstrated between the development of auricular fibrillation and treatment with oral BP. In one study an increased risk of auricular fibrillation was observed with the use of intravenous zoledronic acid.[147] Isolated cases of cancer of the oesophagus have been published in patients on oral BP, but the most recent studies have not confirmed this relationship.[148] Osteomuscular pain, kidney damage and hepatotoxicity from BP are exceptional and will rarely lead to withdrawal of the drug.[149] Use of BP is not advised in patients with glomerular filtration rate <30 ml/min, since there are no available studies that have demonstrated a reduction in fractures in these patients and on the contrary, they increase the risk of impairment of a reduced remodelling osteodystrophy.

Denosumab, in the guideline approved for the treatment of OP, is a drug which is generally well tolerated. A higher rate of infections has been observed, and in particular cutaneous[88] and urinary,[150] but their overall rate is very low.[151] However, due to their structure, they are not eliminated by the kidney, which is an advantage for patients with kidney diseases where a higher risk of hypocalcaemia must be monitored. As with BP, denosumab should not be used when there is clinical suspicion or histomorphometric evidence of reduced remodelling osteodystrophy.

Adverse reactions to teriparatide are generally not serious. Muscle pain, cramps and dizziness are frequent. Treatment with teriparatide may raise calcaemia and calciuria, and it is therefore advisable to determine the levels of calcium in the blood and urine prior to initiating treatment.

In recent years complications have appeared which are associated with prolonged treatment with antiresorptives (BP and

denosumab) and which have generated uncertainty about safety. The relative importance of these rare adverse effects (osteonecrosis of the jawbones and atypical femur fracture) in the treatment of OP is a highly controversial issue.

The fear of patients in suffering these complications may be an impediment for adherence and therapeutic compliance, although the benefit–risk balance of maintaining treatment is highly favourable for high fracture risk patients. A brief analysis will now be made of both complications, based on the systematic reviews carried out to complete this document.

Osteonecrosis of the jawbones

Recommendation: *If any invasive dental procedures has been indicated to the OP patient (dental extraction or implant) it is recommended that antiresorptive treatment initiation be postponed until the surgical wound has completely healed* (RR: D; AL: 100%).

Recommendation: *In patients treated with antiresorptives who are going to carry out a dental procedure it is not recommended that they discontinue treatment with BP or denosumab. If other additional osteonecrosis of the jawbone risks prevail or the surgical procedure is to be extensive, temporary suspension of the treatment with BP may be considered* (RR: D; AL: 78%).

Osteonecrosis of the jawbones has been associated with the prolonged use of BP or denosumab, although its rate in patients with OP is very low (between 1/10,000 and 1/100,000).[152–154]

According to the outcomes of a previous review, published in 2013, available evidence on BP is scarce and of low quality.[154] There is insufficient data to confirm that oral BP or intravenous BP used for OP treatment confers any significant risk of osteonecrosis of the jawbones. There have not been enough studies to assess the role of denosumab in the development of osteonecrosis of the jawbones (level of evidence 3).[152,153] Several systemic factors such as previous treatment with BP or dental extractions are associated with the development of osteonecrosis of the jawbones in patients treated with denosumab (level of evidence 3).[153]

Several medical associations have published recommendations to reduce the risk of this complication. In general, guidelines include correct dental hygiene in their proposals and dental check-up if poor dental health is observed. If any invasive dental procedures has been indicated (dental extraction or implant) it is recommended that treatment initiation be postponed until the surgical wound has completely healed.[155] The use of CTX marker thresholds have been suggested to assess the baseline risk of osteonecrosis of the jawbones. However, available evidence does not endorse its use.[156]

There is some controversy regarding the which approach to take in patients who are already taking BP or denosumab. The majority of guidelines advise not to suspend antiresorptive treatment in non oncological patients. In 2011, the *American Dental Association* guide recognised that the risk of osteonecrosis of the jawbones was very low in patients with OP, and it was therefore not necessary to suspend an oral BP prior to a dental procedure.[157] However, and according to the recommendations made by the international panel of experts, in patients who have undergone extensive oral surgery and with associated risk factors (diabetes, periodontal disease, immunodeficiency, tobacco habit), clinical judgement may suggest temporal suspension of treatment.[155] In this situation, and given that withdrawal of denosumab leads to a bone remodelling and the risk of appearance of multiple vertebral fractures, the panel considers that treatment with denosumab should not be interrupted.

During OP treatment, invasive dental procedures may be made only after careful consideration of their necessity. In the case of denosumab, and whenever possible, surgery must be avoided in periods close to drug administration.[158] In this situation a prolonged unnecessary suspension should be avoided, especially in patients

treated with denosumab. Should a relevant adverse event occur such as osteonecrosis of the jawbones, and although no scientific evidence demonstrates withdrawal of the drug will help the process evolve, the same document considers it prudent to suspend treatment and assess drug indication with a different mechanism of action.[155]

Atypical femur fracture

Recommendation: *In patients with high fracture risk and prolonged treatment with bisphosphonates (>5 years for orals or >3 years for intravenous) it is recommended not to suspend treatment, since the risk of atypical femur fracture is very low and the benefits of fracture reduction greatly outweigh the risk of atypical fracture* (RR: D; AL: 100%).

Atypical fracture of the femur is a potential complication from prolonged treatment with BP or denosumab, although real incidence is very low.

According to the definition proposed by the *American Society for Bone and Mineral Research* (ASBMR),[159] the atypical fracture of the femur is located between the lesser trochanter and the suprachondylar crest and should present with a minimum of 4 out of the following 5 criteria: (1) minimum or absent trauma; (2) origin of the fracture in the external cortical and directed cross-sectionally or obliquely; (3) without comminution or, if this exists, it must be minimal; (4) periostic or endostic thickening of the external, localised cortical, and (5) involvement of the external side cortical (incomplete fracture) or both corticals (complete fracture). Minor criteria are not essential for diagnosis, but they increase it: (a) cortical thickness increased diffusely in femoral diaphysis; (b) pain in thighs or groin area, prior to fracture; (c) bilateral fracture of similar characteristics, and (d) delay in consolidation.

Apart from prolonged treatment with antiresorptives, the atypical fracture of the femur has also been associated with several comorbidities or with taking medication such as proton pump inhibitors or glucocorticoids.

According to the results of a previous 2011 review, the rate of atypical fracture of the femur was very low and it could not be confirmed that there was a significant increase in the risk of atypical fracture of the femur in patients with Op treated with BP. Since then several poor quality studies have been published which show that the rate of atypical fracture of the femur as very low. Two of the 3 published meta-analyses,[160,161] based on randomised clinical trials (RCT), cohort, case and control studies, with a high degree of overlapping, demonstrated a significant increase in the risk of subtrochanteric or diaphysary fracture with the use of BP ranged between 1.70 and 1.99, although with a high level of heterogeneity. In a third meta-analysis which only explored alendronic acid,[162] the relative risk of atypical fracture of the femur with this drug was 3.23 (95% CI: .88–11.84), but the differences were not significant. When a stratified analysis was made with the studies to assess the effect of alendronic acid over 5 years, heterogeneity was insignificant. Using a model of fixed effects, the relative risk was 2.55 (95% CI: 2.26–2.88), concluding that the alendronic acid did not increase the risk of atypical fracture of the femur short-term, but it did in the long term (>5 years).[162]

A recent systematic review[162] concluded that the rate of atypical fracture of the femur associated with BP was very low, but that the relative risk (RR) increased with prolonged use (especially if it was over 3 years). According to the authors, the benefits of BP in reduction of OP fractures greatly outweigh the risk of atypical femur fracture. A limiting feature highlighted was that almost all studies were retrospective and of variable duration (4–9 years), limiting the interpretation of long term exposure.

Regarding the RCT,[163,164] isolated cases have been reported on atypical femur fractures, but these studies present with relevant

limitations, such as the short duration of the same, the non-inclusion of this outcome as a main variable or the losses in follow-up, which impede the obtainment of reliable outcomes. If we analyse observational studies,[165,166] the incidence and absolute risk of atypical fracture of the femur in patients treated with BP have very low rates (between 10.8 and 19.1 per 100,000 patients per year).

The rate of atypical femur fracture represents 0.3% of the total of femur fractures or 5% of the total of subtrochanteric/diaphyseal fractures. Women represent 80% of all diaphyseal fractures and 95% of the atypical fractures of the femur, with a relative risk which is higher in men. The outcome of recent review studies and meta-analyses suggest a favourable benefit/risk ratio to maintain treatment up until 10 years with antiresorptives.

Regarding denosumab, the systematic review results on the risk of atypical femur fracture are very limited due to the scarcity of high quality studies. The studies included were one RCT,[147] two follow-up studies[167,168] and one cohort study.[169]

According to observational studies, long-term treatment with denosumab (between 7 and 10 years) is associated with a nil[168] or very low rate of atypical fracture of the femur (.8 per 10,000 patients per year).[167] A clinical trial of postmenopausal women with OP who had switched from BP to denosumab was unable to demonstrate that the rare cases of atypical fracture of the femur which appeared early on could be attributable to the use of denosumab, in contrast they appeared to be derived from prior use of BP.[160]

Although cases of atypical femur fracture have been described in patients treated with denosumab, the panel of experts decided not to make a specific recommendation on the risk of atypical femur fracture with denosumab due to low evidence and the need for further studies with a higher number of cases and longer time period.

To reduce the clinical impact of atypical femur fracture, in patients under prolonged treatment with BP or denosumab attention must be paid to the presence of pain in the thighs. In these cases it is recommended that X-rays be performed to detect stress fractures or cortical thickening and for early determination of atypical femur fracture. It may also be useful to use magnetic resonance or a bone scan to confirm diagnosis.

Treatment of an atypical femur fracture is surgical. When this complication arises, studies conclude that antiresorptive treatment should be withdrawn, the pain treated, an adequate provision of calcium and vitamin D ensured and a drug with a different mechanism of action be indicated.[170] No control studies exist On the efficacy of teriparatide in patients who have suffered an atypical femur fracture. In a short series of cases, treatment with teriparatide increased the bone mass and the bone remodelling markers, but with no consistent effect on fracture consolidation.[170]

Special situations

Fragility fracture

Recommendation: *It is recommended that all patients' ≥50 years of age with a recent fragility fracture be assessed systematically to prevent further fractures* (RR: D; AL: 100%).

Patients with fragility fracture have a significant increase in the risk of further fractures. However, it is normal that fewer than 25% of them start treatment for OP after a fracture.[4] The term "imminent fracture risk" has recently been introduced to refer to patients with recent fractures, fragile elderly people with frequent falls and fracture patients who have started treatment with high doses of glucocorticoids.[12]

In keeping with the EULAR[171] recommendations the panel of experts suggested that all patients with recent osteoporotic fracture aged ≥50 years of age should be systematically assessed to prevent new fractures.

The FLS model, or Fracture Unit appears to be the most effective[172] in terms of evaluation and treatment initiation. It is also cost-effective[173] and positive experiences have been had with it in Spain.[136] The central element of a Fracture Unit is the coordinator (in Spain this is usually a medical bone metabolism expert), who works in close collaboration with a specialised nurse. The keys to success in the Fracture Unit are: (a) identification of all cases, usually from a list of emergencies and of hospitalised patients; (b) study of the patients, including determination of risk factors, DXA and analysis; (c) the advice of the nurse on non pharmacological measures and adherence to medication; (d) early initiation of antifracture treatment and (e) the drawing up of a report with precise indications for the primary care physician.

In patients with fragility fracture the panel of experts concludes that it would be useful to assess fracture risk factors and falls and identify secondary OP. They advise the carrying out of DXA and assessment of the presence of vertebral fractures.

Vertebral fracture

Recommendation: *The treatment of choice for an acute vertebral fracture is rest, rapidly scaled analgesics to control pain, and if necessary the use of a brace* (RR: √; AL: 100%).

Acute vertebral fracture may lead to serious pain and disability, lasting for several months.[174] General measures that have been shown to be useful and shorten the recovery period are bedrest (for 4 days or less) and rapidly scaled analgesics (including the use of powerful opiates when necessary).[175]

Ortheses (rigid or semi-rigid brace) are useful for acute episode in combination with analgesic treatment, as they help to immobilise the fracture, reduce load and improve spinal alignment in patients who can tolerate them. The type of orthesis will depend on fracture location. Prolonged use is not advisable. It has not been demonstrated that the rate of new fractures will decrease.[176]

In patients with persistent and highly intense pain (visual analogue scale [VAS] ≥7), after 4–6 weeks of treatment as described above, some studies concluded that facet infiltrations could be considered or radiofrequency ablation of the lumbar medial branch,[177] before prescribing a vertebroplasty or kyphoplasty. According to other studies, in the sub-acute and chronic phase it would be beneficial to have physical therapy using heat applied techniques, ultrasound or hydrotherapy and a progressive initiation of an exercise programme to strengthen the paravertebral and thoracoabdominal muscles.[178] Weight-bearing exercises and balance training prevent falls and fractures and improve the patient's quality of life.[59,176]

Vertebroplasty and kyphoplasty
In which cases would vertebroplasty and kyphoplasty be indicated?

Recommendation: *Vertebroplasty and kyphoplasty are recommended for the treatment of vertebral fracture only in cases of serious refractory pain on a WHO analgesic scale, including opiates* (RR: D; AL: 100%).

Systematic reviews of the clinical efficacy of vertebroplasty in patients with fractures due to OP, with pain which is refractory to analgesic treatment, conclude that in open trials vertebroplasty has better results than an optimum analgesic treatment in improving quality of life and reducing pain and disability.[179,180] However, in double blind trials there is no evidence that vertebroplasty is superior to placebo with local anaesthesia. Also, after a month, the average pain, according to the VAS, was 5 points in the placebo group and 4.3 points in the vertebroplasty group, with an absolute reduction in pain of 7% and a relative reduction of 10%.[179] Evidence of its clinical efficacy is not consistent. The complications associated with the procedure are rare, but may be serious. Notwithstanding, it

cannot be determined with certainty whether vertebroplasty leads to an increased risk of new fractures in adjacent vertebra.[179,180]

Systematic reviews of the clinical efficacy of kyphoplasty conclude that in open studies it has better outcomes than conservative treatment in improving quality of life and reducing pain and disability, but the evidence of its clinical efficacy is not consistent as there are no available double blind studies to compare with placebo.[179,181]

Reduction in pain associated with kyphoplasty analysed through VAS, compared with conservative treatment, was −1.82 after 30 days, −1.45 after 3 months and −1.48 after 6 months, but −.84 and −.69 after 12 and 24 months, respectively.[181] The authors conclude that vertebroplasty and kyphoplasty could improve quality of life and reduce pain in vertebral fractures refractory to analgesic treatment, with a doubtful increase in the rate of new fractures in the adjacent vertebra. There is therefore not sufficient evidence for their recommendation in standard clinical practice.

Osteoporosis from glucocorticoids

Recommendation: *In patients who receive or who are going to receive treatment with glucocorticoids fracture risk must be assessed and the initiation of treatment for osteoporosis as soon as possible* (RR: D; AL: 100%) (Fig. 2).

Recommendation: *It is recommended that pharmacological treatment be initiated to prevent OP in patients who are going to receive glucocorticoids for over 3 months in the following cases* (RR: D):

1. *Patients with an initial dose ≥30 mg/day of prednisone. In these cases it is recommended that treatment be imitated for the OP immediately (AL: 100%).*
2. *Postmenopausal women and men >50 years of age with doses of prednisone ≥5 mg/day who also present with some of the following conditions:*
   a) *Previous fragility fracture (AL: 100%).*
   b) *Low BMD (T-score ≤−1.5 SD in spine or hip) (AL: 89%).*
   c) *High fracture risk: FRAX® for hip ≥3% or for primary fracture ≥10% without BMD or ≥7.5% with BMD (AL: 78%).*
3. *Premenopausal women and men <50 years of age and dose ≥7.5 mg/day of prednisone who also present with some of the following conditions:*
   a) *Previous fragility fracture (AL: 100%).*
   b) *Low BMD (Z-score ≤−3 SD) (AL: 78%).*

OP induced by glucocorticoids is the most frequent cause of secondary OP, and is associated with the presence of fractures in up to 30%–50% of cases.[182] The risk of fracture depends on factors such as age, prior BMD, daily accumulated dose of glucocorticoids and baseline disease. The loss of BMD is fast, especially in the first 6–12 months, even with low doses of glucocorticoids, with trabecular bone being the most affected.[182] According to studies, the fractures associated with treatment with glucocorticoids appear with BMD which is not too low, due to the fact that the glucocorticoid mainly affects the whole bone micro architecture, and the TBS and FRAX® adjusted with TBS could have a certain additional usefulness in the assessment of the risk of these patients.[183] However, the application of the FRAX® in OP through glucocorticoids has certain limitations and underestimates the real risk of fracture, since it does not adjust from accumulated dose from daily dose or treatment duration.

ACR recommendations consider that in patients who receive or are going to receive treatment with glucocorticoids the fracture risk must be assessed (preferably using FRAX®) and treatment initiation as soon as possible should be assessed. Furthermore, general preventative OP measures would have to be used in all patients, such as healthy life habits for bones and diet (see section on non pharmacological treatment, calcium and vitamin D). Furthermore, the lowest possible dose of glucocorticoid should be used and for as short a time as possible, and using immunosuppressants if necessary.[36]

In patients with an intermittent corticoid regime and who have an accumulated dose of prednisone >5 g/year or those with annual losses of BMD above 10% the panel of experts consider that treatment for OP would also be indicated.

Premenopausal women or men <50 years of age are at a lower fracture risk. There are also fewer data on efficacy and safety or OP treatments for this population group and treatment indications appear to be more restrictive.

The pharmacological treatment of choice is oral BP (risedronic acid and alendronic acid) or intravenous zoledronic acid since they stabilise or increase the BMD and reduce the risk of vertebral fractures in comparison with control groups.[184] According to the technical specifications, the drugs which currently have an glucocorticoid OP indication in Spain are teriparatide, risedronic acid and zoledronic acid.

In women with established OP, teriparatide has been demonstrated to be more effective than risedronic acid in reducing vertebral fractures and clinical fractures, regardless of having received previous treatment with BP.[185] In fact, teriparatide has demonstrated superiority against alendronic acid in both gain in BMD and reduction in morphometric vertebral fractures, in premenopausal, postmenopausal women and men treated with glucocorticoids after 18 months of follow-up.[186] As a result, the panel of experts consider that high risk patients or those refractory or who have contraindications to antiresorptive treatment could evaluate the treatment with teriparatide.[47]

In patients who start or have already received glucocorticoids, the administration of denosumab for 12 months has shown an increase in BMD which is significantly higher than with risedronic acid,[187] and the *European Medicines Agency* (EMA) has recommended that denosumab be added into the technical specification as a new indication: for treatment of the loss of BMD associated with the prolonged use of glucocorticoids in adult patients at high risk of fracture.

According to the recommendations of the International Groups, the treatment of choice should be maintained for as long as treatment with glucocorticoids lasts and for at least 6 months after suspending the glucocorticoid, unless fractures exist, in which case it would be continued.[36]

Rheumatic, inflammatory and systemic diseases

Recommendation: *It is advisable to assess the risk of fracture and consider performing DXA in patients with rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis especially those over 50 years of age and who are being treated with glucocorticoids or with a severe or evolved disease* (RR: √; AL: 100%).

Patients with rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis are at greater risk of *OP* and/or fractures.[188–194] One study reported an increased fracture risk in psoriasis arthritis and in severe psoriasis.[195] The conclusions of some studies in patients with rheumatoid arthritis advise screening for fragility fracture and performing rheumatoid DXA, especially in patients >50 years of age in those with severe disease or evolved disease or those treated with glucocorticoids.[188,189] Moreover, several documents of consensus on the management of comorbidities in rheumatoid arthritis, psoriasis arthritis and systemic lupus erythematosus suggested making an accurate prophylaxis of OP.[196–198] In relation to antifracture treatments, all the drugs approved for OP were used. In the case of denosumab, safety data was limited in patients treated with biologic agents for their baseline disease, although according to the outcome of some studies there does not
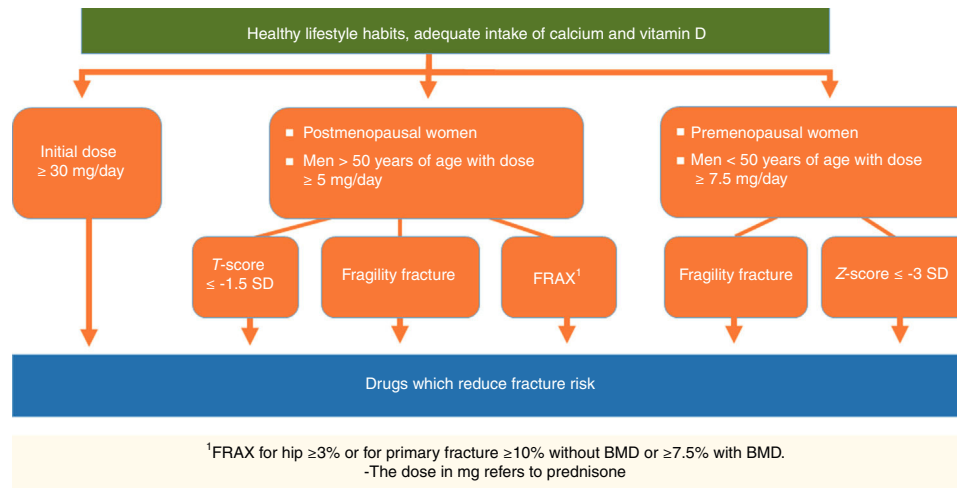
Fig. 2. Recommendations to initiate prophylaxis or Op treatment in patients who will receive glucocorticoids in the following 3 months.

appear to be a different safety profile from the postmenopausal OP one.[199]

Osteoporosis in the male

Recommendation: *The study of the causes of secondary osteoporosis in all men with low bone mass or fragility fracture is recommended* (RR: D; AL: 100%).

It has been observed in different studies that OP in the male is underdiagnosed.[200] in fact it has been estimated that a third of hip fractures worldwide occur in males, especially after the age of 70 years. Furthermore, mortality after a hip fracture (over 37% in the first year) is higher than that in women.[201] Also, in the male secondary OP is more frequent and studies therefore conclude that appropriate, accurate clinical assessment is needed for systematic exclusion. The most frequent OP causes and risk factors in the man are hypogonadism, alcohol consumption, tobacco and glucocorticoids. Fracture risk assessment in the male would include clinical risk factors, the existence of previous fractures and the measurement of BMD by DXA (if indicated) to better stratify those patients more susceptible for treatment.[202] With regard to DXA, the same reference values are used in men as in women.[203]

With regard to non pharmacological prevention measures, the same may be considered as for OP in women. For hormonal treatment, there are no data on fracture reduction efficacy with testosterone treatment, and the experts therefore only indicate treatment in males with symptomatic hypogonadism and also advising it should be combined with another antiosteoporotic treatment.[204] The drugs which have shown improvement of BMD and reduction of vertebral risk fracture both in eugonadal and hypogonadal males are oral BP (alendronic acid and risedronic acid),[205,206] zoledronic acid (the only one which was established as the primary aim)[207] and teriparatide.[208,209] Denosumab was also approved in males with a high fracture risk and to reduce the loss of BMD in the patient with prostate cancer in androgen deprivation treatment.[210] All these drugs, except the alendronic acid, have an indication in Spain for OP in the male.

Osteoporosis in premenopausal women

Recommendation: *It is recommended that a study of secondary osteoporosis causes be made in all premenopausal women with a low bone mass measured by DXA or with a fragility fracture* (RR: √; AL: 100%).

According to the different scientific societies and expert groups, in the premenopausal woman a DXA should be carried out when there are fragility fractures and/or risk factors associated with the loss of bone mass.[42,211] In this patient group the Z-score would have to be used (which compares with individuals of the same age and sex) instead of the T-score.[42,211,212] Thus, "low bone mass" is considered when the Z-score is lower than −2 SD.[211] The presence of fragility fractures and particularly when associated with low bone mass, means that OP diagnosis may be established in the premenopausal woman.[212]

Considering that over 50% of premenopausal women with OP present with a secondary OP[212,213] the experts recommend making an exhaustive study to rule out an underlying cause,[212,213] with the most frequent being the following: treatment with glucocorticoids, oestrogen deficit, malabsorption diseases and OP associated with pregnancy or breast feeding.[212] Idiopathic forms are frequent in premenopausal women and may be associated with hypercalciuria and with a family history of OP.[213]

The therapeutic approach in the premenopausal woman includes optimum calcium and vitamin D intake, regular physical exercise, suspending tobacco consumption, limiting alcohol consumption and treating the underlying cause.[212]

For premenopausal OP experts, the specific antiosteoporotic drugs (BP, teriparatide, denosumab) will be considered in patients with fragility fracture or for certain secondary causes such as treatment with glucocorticoids.[213] The drugs which they have studied in premenopausal OP are BP (alendronic acid and risedronic acid) and teriparatide.[212] According to experts, in young women certain caution should be used in the administration of BP given its long

retention in the bone tissue, particularly in women who wish to get pregnant in the future. They also conclude that none of these drugs should be used in pregnancy (BP and teriparatide are in the C category according to the FDA).[214,215] With regard to the SERM, it seems reasonable to avoid its use in premenopausal women, whilst with denosumab there is only an indication in postmenopausal OP (according to the FDA: category in pregnancy).[212]

Some experts suggests that in fertile women anti conceptive measures should be prescribed if any antiosteoporotic treatment is initiated.[213]

Other special situations: kidney disease, liver disease and digestive problems

Chronic renal disease

In patients with chronic renal disease (CRD) certain differential aspects should be taken into consideration with postmenopausal OP: (1) DXA does not discriminate the type of underlying bone disease and (2) renal osteodystrophy should be excluded, particularly dynamic bone disease (very low osteodystrophy with remodelling) in chronic dialysis patients, since this contraindicates the use of antiresorptives. PTH levels <120 pg/ml with low alkaline phosphatase suggest the presence of dynamic bone disease.[216]

With regard to a deficiency of vitamin D in the CRD, in states 3–5D, the experts consider the use of therapeutic strategies similar to those accepted for the general population to be appropriate.

Regarding antifracture treatments for stage 1–2 patients and filtered >35 ml/min, its use is mostly similar to that of patients without CRD.[217,218]

The technical specifications of the drugs indicates that BP, teriparatide and raloxifene are not recommended when filtration is <30 ml/min (<35 ml/min for alendronic acid and zoledronic acid). However, some post hoc studies conducted with risedronic acid[219] and raloxifene[220,221] in patients with glomerular filtration between 15 and 30 ml/min (stage 4) have shown these drugs demonstrate most efficacy and safety. Notwithstanding, the limited evidence of this type of post hoc study must be borne in mind. Bazedoxifene has not been sufficiently documented in patients with filtration <30 ml/min. Denosumab does not require dose adjustment in kidney failure, but the risk of hypocalcaemia is higher, and it is therefore advised to optimise calcium and vitamin D supplements. Evidence of their safety in patients with stage 4 CRD and in haemodialysis is also limited due to the post hoc studies having a limited number of patients.[222]

Chronic liver disease

According to the experts, patient management with chronic liver disease includes evaluation of factors which lead to bone loss and the increase in fracture risk such as malnutrition, vitamin D deficit, intensity of cholestasis, glucocorticoids and hypogonadism. The pharmacological studies of reduction in patients with liver disease are limited, with no contraindications existing for the use of BP, which increase BMD.[223] There is not enough experience with other treatments.

Digestive diseases

Studies conclude that management of patients with celiac disease, inflammatory bowel disease, and bariatric surgery should consider malabsorption and malnutrition (evaluate calcium and vitamin D supplements), as well as the use of glucocorticoids. In inflammatory bowel disease the BP reduce the risk of vertebral fracture.[224]

According to the data sheet, oral BP are contraindicated in patients with esophageal anomalies and other factors which may delay emptying, such as stenos is and acalasia. The panel of experts consider that when oral antiresorptive therapy is contraindicated,

it is regarded as ineffective due to serious malabsorption is not tolerated, and parenteral route treatment may be considered.[47]

New treatments

Two new drugs for OP treatment: romosozumab and abaloparatide are currently in an advanced phase of clinical development.

Romosozumab is a humanised IgG2 monoclonal antibody which links and blocks sclerostin. It is administered monthly subcutaneously for a year, followed by denosumab or alendronic acid for a further year and has shown a significant reduction in the incidence of new vertebral and non vertebral fractures.[225,226] in one of the studies an increase in the rate of serious adverse cardiovascular events was observed compared with alendronic acid,[226] which motivated a requirement by the US Food and Drug Administration (FDA) to provide the results of additional studies.

Abaloparatide is a synthetic peptide which activate the type 1 receptor of the PTH, approved by the FDA in 2017 and rejected by the EMA in 2018. In daily subcutaneous administration it obtained a significant reaction in the rate of vertebral and non vertebral fractures compared with placebo, with no differences to teriparatide.[227] Its safety and tolerability profile was similar to teriparatide, but with a lower rate of hypercalcaemia.

Conclusion

As mentioned in the introduction, the aim of this document was to provide an update on the new advances in the different aspects of OP relating to clinical practice: diagnosis, evaluation, treatment and follow-up.

The document is based on a critical review of the previous consenus,[5] the best available scientific evidence and expert clinical experience. This was a joint task between panel members and the SER Unit of Research which, together with SER reviewers, carried out an extensive systematic review on the different areas of interest and provided the necessary scientific rigour to produce the recommendations with their level of evidence and also their level of consensus, to provide the reader with the most objective evaluation of these recommendations.

The new definition of OP is incorporated into the diagnostic assessment of this document, and which encompasses patients with fragility fractures and low bone mass, the concept of imminent risk of fracture and the utility of TBS.

With regard to treatment, the effectiveness of each drug for the prevention of fractures together with several selection criteria such as cost-effectiveness, the existence of multiple fractures or the limitations for oral use are presented. The panel members assessed the possibility of including an extensive treatment decision algorithm no agreement was reached on this.

The SER reviewers for their part have updated osteonecrosis of the jawbone and atypical femur fracture guidelines. Special situations were maintained in keeping with the 2011 recommendations, adding OP of inflammatory rheumatisms and a few precautions which should be taken into account in patients with kidney disease and gastrointestinal and hepatic problems. Finally, a section on the new treatments (romosozumab and abaloparatide) was produced.

We would like to highlight from these recommendations that fracture risk and treatment indication were the issues most debated among panel members. The use of the FRAX® was unanimously accepted for hip fracture with the threshold of 3% whilst the level of agreement for primary fracture was somewhat lower. In the document the reason why of this discrepancy was exposed, which was basically derived from the absence of sufficient studies on the calibration of the FRAX® for the Spanish population.

To conclude, we may say that the recommendations of this document are a draft consultation framework for OP management. They are general regulations which require individualisation in each case and this is the role we must accept as professionals.

Conflict of interests

Acknowledgements

Annex 1. Levels of evidence and SIGN recommendations

Levels of evidence	
1++	High quality meta-analysis, systematic reviews of clinical trials or high quality clinical trials with very low risk of bias.
1+	Well executed meta-analysis, systematic reviews of clinical trials or well executed clinical trials with low risk of bias.
1−	Meta-analysis, systematic reviews of clinical trials or clinical trials with high risk of bias.
2++	Systematic reviews of high quality cohort studies or cases and controls. Cohort studies or case and control studies with a very low risk of bias and high probability of establishing a causal relationship.
2+	Well executed cohort studies or case and control studies with low risk of bias and a moderate probability of establishing a causal relationship.
2−	Cohort studies or case and control studies with high risk of bias and significant risk that there will be no causal relationship.
3	Non analytical studies, such as case reports and case series.
4	Expert opinions.

Recommendation rates	
A	At least one meta-analysis, systematic review or clinical trial classified as 1++ and directly applicable to the target population of the guide; or a volume of scientific evidence composed by studies classified as 1+ and with major agreement between them.
B	A volume of scientific evidence composed by studies classified as 2++, directly applicable to the target population of the guide and which show major concordance between them; or scientific evidence extrapolated from studies classified as 1++ or 1+.
C	A volume of scientific evidence composed by studies classified as 2+, directly applicable to the target population of the guide and which shows major consistency between them; or scientific evidence extrapolated from studies classified as 2++.
D	Scientific evidence level 3 or 4; or scientific evidence extrapolated from studies classified as 2+.

Studies classified as 1− and 2− should not be used in the production of recommendations due to their high possibility of bias.

Good clinical practice	
√	Recommended practice based on clinical experience and consensus of the drafting team

[a]On occasions the drafting group notices an important practical aspect which has to be highlighted and for which there is probably no supporting evidence. In general, these cases concern some aspect of treatment which is considered good clinical practice and which nobody would usually question. These aspects are valued as points of good clinical practice. These messages are not an alternative to the recommendations based on evidence but should only be considered when there is no other way of highlight this aspect.

References

1. Azagra R, Lopez-Exposito F, Martin-Sanchez JC, Aguye A, Moreno N, Cooper C, et al. Changing trends in the epidemiology of hip fracture in Spain. Osteoporos Int. 2014;25:1267–74.

2. Hernlund E, Svedbom A, Ivergard M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos. 2013;8:136.

3. Kanis JA, Borgstrom F, Compston J, Dreinhofer K, Nolte E, Jonsson L, et al. SCOPE: a scorecard for osteoporosis in Europe. Arch Osteoporos. 2013;8:144.

4. Kanis JA, Svedbom A, Harvey N, McCloskey EV. The osteoporosis treatment gap. J Bone Miner Res. 2014;29:1926–8.

5. Perez Edo L, Alonso Ruiz A, Roig Vilaseca D, Garcia Vadillo A, Guanabens Gay N, Peris P, et al. 2011 Up-date of the consensus statement of the Spanish Society of Rheumatology on osteoporosis. Reumatol Clin. 2011;7: 357–79.

6. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. JAMA. 2001;285:785–95.

7. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A. The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int. 2001;12:417–27.

8. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organ Tech Rep Ser. 1994;843:1–129.

9. Kanis JA, on behalf of the World Health Organization Scientific Group. Assessment of osteoporosis at the primary health-care level. Technical report. UK: World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield; 2007.

10. Siris ES, Adler R, Bilezikian J, Bolognese M, Dawson-Hughes B, Favus MJ, et al. The clinical diagnosis of osteoporosis: a position statement from the National Bone Health Alliance Working Group. Osteoporos Int. 2014;25:1439–43.

11. Black DM, Rosen CJ. Clinical practice. Postmenopausal osteoporosis. N Engl J Med. 2016;374:254–62.

12. Roux C, Briot K. Imminent fracture risk. Osteoporos Int. 2017;28:1765–9.

13. Johansson H, Siggeirsdottir K, Harvey NC, Oden A, Gudnason V, McCloskey E, et al. Imminent risk of fracture after fracture. Osteoporos Int. 2017;28:775–80.

14. Kanis JA, Oden A, Johnell O, Johansson H, de Laet C, Brown J, et al. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. Osteoporos Int. 2007;18:1033–46.

15. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 1995;332:767–73.

16. Rubin KH, Friis-Holmberg T, Hermann AP, Abrahamsen B, Brixen K. Risk assessment tools to identify women with increased risk of osteoporotic fracture: complexity or simplicity? A systematic review. J Bone Miner Res. 2013;28:1701–17.

17. Marques A, Ferreira RJ, Santos E, Loza E, Carmona L. The accuracy of osteoporotic fracture risk prediction tools: a systematic review and meta-analysis. Ann Rheum Dis. 2015;74:1958–67.

18. Kanis JA, Hans D, Cooper C, Baim S, Bilezikian JP, Binkley N, et al. Interpretation and use of FRAX in clinical practice. Osteoporos Int. 2011;22:2395–411.

19. Tebé C, Espallargues M, Estrada MD, Kotzeva A, del Río LM, di Gregorio S. Validación del modelo predictivo de fractura osteoporótica FRAX. Plan de Calidad para el Sistema Nacional de Salud del Ministerio de Sanidad, Política Social e Igualdad. Agència d'Informació, Avaluació i Qualitat en Salut; 2011. Informes de Evaluación de Tecnologías Sanitarias, AIAQS núm. 2010/01.

20. Azagra R, Roca G, Encabo G, Aguye A, Zwart M, Guell S, et al. FRAX® tool, the WHO algorithm to predict osteoporotic fractures: the first analysis of its discriminative and predictive ability in the Spanish FRIDEX cohort. BMC Musculoskelet Disord. 2012;13:204.

21. Gonzalez-Macias J, Marin F, Vila J, Diez-Perez A. Probability of fractures predicted by FRAX® and observed incidence in the Spanish ECOSAP Study cohort. Bone. 2012;50:373–7.

22. Azagra RRG, Roca G, Martín-Sánchez JC, Casado E, Encabo G, Zwart M, et al. Umbrales de FRAX para determinar personas con alto y bajo riesgo de fractura osteoporótica en población femenina española. Med Clin (Barc). 2015;144:1–8.

23. Azagra R, Zwart M, Aguye A, Martin-Sanchez JC, Casado E, Diaz-Herrera MA, et al. Fracture experience among participants from the FROCAT study: what thresholding is appropriate using the FRAX tool? Maturitas. 2016;83:65–71.

24. Schousboe JT, Shepherd JA, Bilezikian JP, Baim S. Executive summary of the 2013 International Society for Clinical Densitometry Position Development Conference on Bone Densitometry. J Clin Densitom. 2013;16:455–66.

25. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ. 1996;312:1254–9.

26. Wainwright SA, Marshall LM, Ensrud KE, Cauley JA, Black DM, Hillier TA, et al. Hip fracture in women without osteoporosis. J Clin Endocrinol Metab. 2005;90:2787–93.

27. Lespessailles E, Cortet B, Legrand E, Guggenbuhl P, Roux C. Low-trauma fractures without osteoporosis. Osteoporos Int. 2017;28:1771–8.

28. Cummings SR, Bates D, Black DM. Clinical use of bone densitometry: scientific review. JAMA. 2002;288:1889–97.

29. Lewiecki EM, Watts NB, McClung MR, Petak SM, Bachrach LK, Shepherd JA, et al. Official positions of the international society for clinical densitometry. J Clin Endocrinol Metab. 2004;89:3651–5.

30. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014;25:2359–81.

31. Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ. 2010;182:1864–73.

32. Bouman C, Maas A, Herwaarden N, Segurado OG, Sasso EH, Hoogen F, et al. Predictive value of a multi-biomarker disease activity score for successful dose reduction of TNF inhibitors in rheumatoid arthritis: results of the dress study. Ann Rheum Dis. 2015;74:973–4. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/823/CN-01162823/frame.html

33. Gomez-Vaquero C, Roig-Vilaseca D, Bianchi M, Santo P, Narvaez J, Nolla JM. Assessment of a set of FRAX®-based criteria for the indication of bone densitometry in Spanish postmenopausal women. Med Clin (Barc). 2013;140:439–43.

34. Azagra R, Roca G, Martin-Sanchez JC, Casado E, Encabo G, Zwart M, et al. [FRAX® thresholds to identify people with high or low risk of osteoporotic fracture in Spanish female population]. Med Clin (Barc). 2015;144:1–8.

35. Hadji P, Aapro MS, Body JJ, Gnant M, Brandi ML, Reginster JY, et al. Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG. J Bone Oncol. 2017;7:1–12.

36. Buckley L, Guyatt G, Fink HA, Cannon M, Grossman J, Hansen KE, et al. 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheumatol. 2017;69:1521–37.

37. Cianferotti L, Bertoldo F, Carini M, Kanis JA, Lapini A, Longo N, et al. The prevention of fragility fractures in patients with non-metastatic prostate cancer: a position statement by the international osteoporosis foundation. Oncotarget. 2017;8:75646–63.

38. Silva BC, Leslie WD. Trabecular bone score: a new DXA-derived measurement for fracture risk assessment. Endocrinol Metab Clin North Am. 2017;46:153–80.

39. Del Rio LM, Winzenrieth R, Cormier C, di Gregorio S. Is bone microarchitecture status of the lumbar spine assessed by TBS related to femoral neck fracture? A Spanish case-control study. Osteoporos Int. 2013;24:991–8.

40. Martineau P, Leslie WD. Trabecular bone score (TBS): method and applications. Bone. 2017;104:66–72.

41. McCloskey EV, Oden A, Harvey NC, Leslie WD, Hans D, Johansson H, et al. Adjusting fracture probability by trabecular bone score. Calcif Tissue Int. 2015;96:500–9.

42. Camacho PM, Petak SM, Binkley N, Clarke BL, Harris ST, Hurley DL, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis—2016. Endocr Pract. 2016;22 Suppl. 4:1–42.

43. Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2013;24:23–57.

44. Hochberg MC, Greenspan S, Wasnich RD, Miller P, Thompson DE, Ross PD. Changes in bone density and turnover explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. J Clin Endocrinol Metab. 2002;87:1586–92.

45. Bauer D, Black D, Bouxsein M, Lui L, Cauley J, de Papp A, et al. Bisphosphonate-related changes in bone turnover are associated with vertebral, but not nonvertebral fracture risk reduction: a meta-regression. J Bone Miner Res. 2016;31 Suppl. 1. S51.

46. Burch J, Rice S, Yang H, Neilson A, Stirk L, Francis R, et al. Systematic review of the use of bone turnover markers for monitoring the response to osteoporosis treatment: the secondary prevention of fractures, and primary prevention of fractures in high-risk groups. Health Technol Assess. 2014;18: 1–180.

47. Gonzalez-Macias J, del Pino-Montes J, Olmos JM, Nogues X. Clinical practice guidelines for posmenopausal, glucocorticoid-induced and male osteoporosis. Spanish Society for Research on Bone and Mineral Metabolism (3rd updated version 2014). Rev Clin Esp. 2015;215:515–26.

48. Vasikaran S, Eastell R, Bruyere O, Foldes AJ, Garnero P, Griesmacher A, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporos Int. 2011;22:391–420.

49. Wall BF, Hart D. Revised radiation doses for typical X-ray examinations. Report on a recent review of doses to patients from medical X-ray examinations in the UK by NRPB. National Radiological Protection Board. Br J Radiol. 1997;70:437–9.

50. Adams JE. Opportunistic identification of vertebral fractures. J Clin Densitom. 2016;19:54–62.

51. Xu W, Perera S, Medich D, Fiorito G, Wagner J, Berger LK, et al. Height loss, vertebral fractures, and the misclassification of osteoporosis. Bone. 2011;48:307–11.

52. Siris ES, Genant HK, Laster AJ, Chen P, Misurski DA, Krege JH. Enhanced prediction of fracture risk combining vertebral fracture status and BMD. Osteoporos Int. 2007;18:761–70.

53. Hallstrom H, Wolk A, Glynn A, Michaelsson K. Coffee, tea and caffeine consumption in relation to osteoporotic fracture risk in a cohort of Swedish women. Osteoporos Int. 2006;17:1055–64.

54. Giampietro PF, McCarty C, Mukesh B, McKiernan F, Wilson D, Shuldiner A, et al. The role of cigarette smoking and statins in the development of postmenopausal osteoporosis: a pilot study utilizing the Marshfield Clinic Personalized Medicine Cohort. Osteoporos Int. 2010;21:467–77.

55. Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, et al. Alcohol intake as a risk factor for fracture. Osteoporos Int. 2005;16:737–42.

56. Choi M, Hector M. Effectiveness of intervention programs in preventing falls: a systematic review of recent 10 years and meta-analysis. J Am Med Dir Assoc. 2012;13, 188.e13–21.

57. Goodwin VA, Abbott RA, Whear R, Bethel A, Ukoumunne OC, Thompson-Coon J, et al. Multiple component interventions for preventing falls and fall-related injuries among older people: systematic review and meta-analysis. BMC Geriatr. 2014;14:15.

58. Tricco AC, Thomas SM, Veroniki AA, Hamid JS, Cogo E, Strifler L, et al. Comparisons of interventions for preventing falls in older adults: a systematic review and meta-analysis. JAMA. 2017;318:1687–99.

59. Li WC, Chen YC, Yang RS, Tsauo JY. Effects of exercise programmes on quality of life in osteoporotic and osteopenic postmenopausal women: a systematic review and meta-analysis. Clin Rehabil. 2009;23:888–96.

60. Santesso N, Carrasco-Labra A, Brignardello-Petersen R. Hip protectors for preventing hip fractures in older people. Cochrane Database Syst Rev. 2014. CD001255.

61. Oliveira LC, Oliveira RG, Pires-Oliveira DA. Effects of whole body vibration on bone mineral density in postmenopausal women: a systematic review and meta-analysis. Osteoporos Int. 2016;27:2913–33.

62. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1911–30.
63. Dawson-Hughes B, Mithal A, Bonjour JP, Boonen S, Burckhardt P, Fuleihan GE, et al. IOF position statement: vitamin D recommendations for older adults. Osteoporos Int. 2010;21:1151–4.
64. Haschka J, Englbrecht M, Hueber AJ, Manger B, Kleyer A, Reiser M, et al. Retro-study of reduction of therapy in patients with rheumatoid arthritis in ongoing remission. Ann Rheum Dis. 2015;74:668. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/859/CN-01162859/frame.html
65. Yazici Y, Gandhi K, Alemao E, Furst DE. Routine assessment of patient index data 3 (RAPID3)-defined remission is as stringent as ACR/eular Boolean-defined remission in a clinical trial of patients with early rheumatoid arthritis treated with abatacept. Arthritis Rheumatol. 2015;67. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/615/CN-01162615/frame.html
66. Harvey JA, Zobitz MM, Pak CY. Dose dependency of calcium absorption: a comparison of calcium carbonate and calcium citrate. J Bone Miner Res. 1988;3:253–8.
67. Wallace RB, Wactawski-Wende J, O'Sullivan MJ, Larson JC, Cochrane B, Gass M, et al. Urinary tract stone occurrence in the Women's Health Initiative (WHI) randomized clinical trial of calcium and vitamin D supplements. Am J Clin Nutr. 2011;94:270–7.
68. Candelas G, Martinez-Lopez JA, Rosario MP, Carmona L, Loza E. Calcium supplementation and kidney stone risk in osteoporosis: a systematic literature review. Clin Exp Rheumatol. 2012;30:954–61.
69. Lewis JR, Calver J, Zhu K, Flicker L, Prince RL. Calcium supplementation and the risks of atherosclerotic vascular disease in older women: results of a 5-year RCT and a 4.5-year follow-up. J Bone Miner Res. 2011;26:35–41.
70. Chung M, Tang AM, Fu Z, Wang DD, Newberry SJ. Calcium intake and cardiovascular disease risk: an updated systematic review and meta-analysis. Ann Intern Med. 2016;165:856–66.
71. Bolland MJ, Leung W, Tai V, Bastin S, Gamble GD, Grey A, et al. Calcium intake and risk of fracture: systematic review. BMJ. 2015;351:h4580.
72. Moyer VA. Vitamin D and calcium supplementation to prevent fractures in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2013;158:691–6.
73. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005;293:2257–64.
74. Avenell A, Mak JC, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. Cochrane Database Syst Rev. 2014. CD000227.
75. Zhao JG, Zeng XT, Wang J, Liu L. Association between calcium or vitamin D supplementation and fracture incidence in community-dwelling older adults: a systematic review and meta-analysis. JAMA. 2017;318:2466–82.
76. Weaver CM, Alexander DD, Boushey CJ, Dawson-Hughes B, Lappe JM, LeBoff MS, et al. Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. Osteoporos Int. 2016;27:367–76.
77. Michael YL, Whitlock EP, Lin JS, Fu R, O'Connor EA, Gold R. Primary care-relevant interventions to prevent falling in older adults: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med. 2010;153:815–25.
78. Gillespie LD, Robertson MC, Gillespie WJ, Lamb SE, Gates S, Cumming RG, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev. 2009. CD007146.
79. Uusi-Rasi K, Patil R, Karinkanta S, Kannus P, Tokola K, Lamberg-Allardt C, et al. Exercise and vitamin D in fall prevention among older women: a randomized clinical trial. JAMA Intern Med. 2015;175:703–11.
80. Crandall CJ, Newberry SJ, Diamant A, Lim YW, Gellad WF, Suttorp MJ, et al. AHRQ comparative effectiveness reviews. Treatment to prevent fractures in men and women with low bone density or osteoporosis: update of a 2007 report. Rockville, MD: Agency for Healthcare Research and Quality (US); 2012.
81. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008. CD001155.
82. Wells G, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008. CD004523.
83. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet. 1996;348:1535–41.
84. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA. 1998;280:2077–82.
85. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. JAMA. 1999;282:1344–52.
86. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int. 2000;11:83–91.
87. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356:1809–22.
88. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361:756–65.
89. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344:1434–41.
90. Chesnut CH 3rd, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res. 2004;19:1241–9.
91. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA. 1999;282:637–45.
92. Silverman SL, Christiansen C, Genant HK, Vukicevic S, Zanchetta JR, de Villiers TJ, et al. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. J Bone Miner Res. 2008;23:1923–34.
93. Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med. 2007;357:1799–809.
94. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med. 2001;344:333–40.
95. Kendler DL, Marin F, Zerbini CAF, Russo LA, Greenspan SL, Zikan V, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet. 2018;391:230–40.
96. Marques A, Lourenco O, Ortsater G, Borgstrom F, Kanis JA, da Silva JA. Cost-effectiveness of intervention thresholds for the treatment of osteoporosis based on FRAX® in Portugal. Calcif Tissue Int. 2016;99:131–41.
97. Lippuner K, Johansson H, Borgstrom F, Kanis JA, Rizzoli R. Cost-effective intervention thresholds against osteoporotic fractures based on FRAX® in Switzerland. Osteoporos Int. 2012;23:2579–89.
98. Makras P, Athanasakis K, Boubouchairopoulou N, Rizou S, Anastasilakis AD, Kyriopoulos J, et al. Cost-effective osteoporosis treatment thresholds in Greece. Osteoporos Int. 2015;26:1949–57.
99. Dell RM, Adams AL, Greene DF, Funahashi TT, Silverman SL, Eisemon EO, et al. Incidence of atypical nontraumatic diaphyseal fractures of the femur. J Bone Miner Res. 2012;27:2544–50.
100. Adler RA, el-Hajj Fuleihan G, Bauer DC, Camacho PM, Clarke BL, Clines GA, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a Task Force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2016;31:16–35.
101. Lo JC, O'Ryan FS, Gordon NP, Yang J, Hui RL, Martin D, et al. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. J Oral Maxillofac Surg. 2010;68:243–53.
102. McClung MR, Wagman RB, Miller PD, Wang A, Lewiecki EM. Observations following discontinuation of long-term denosumab therapy. Osteoporos Int. 2017;28:1723–32.
103. Kaufman JM, Orwoll E, Goemaere S, San Martin J, Hossain A, Dalsky GP, et al. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. Osteoporos Int. 2005;16:510–6.
104. Cosman F, Nieves JW, Dempster DW. Treatment sequence matters: anabolic and antiresorptive therapy for osteoporosis. J Bone Miner Res. 2017;32:198–202.
105. Cosman F. Anabolic and antiresorptive therapy for osteoporosis: combination and sequential approaches. Curr Osteoporos Rep. 2014;12:385–95.
106. Leder BZ, Tsai JN, Uihlein AV, Wallace PM, Lee H, Neer RM, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet. 2015;386:1147–55.
107. Ebina K, Hashimoto J, Kashii M, Hirao M, Kaneshiro S, Noguchi T, et al. The effects of switching daily teriparatide to oral bisphosphonates or denosumab in patients with primary osteoporosis. J Bone Miner Metab. 2017;35:91–8.
108. Obermayer-Pietsch BM, Marin F, McCloskey EV, Hadji P, Farrerons J, Boonen S, et al. Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior antiresorptive treatment. J Bone Miner Res. 2008;23:1591–600.
109. Eiken P, Vestergaard P. Treatment of osteoporosis after alendronate or risedronate. Osteoporos Int. 2016;27:1–12.
110. Anastasilakis AD, Polyzos SA, Efstathiadou ZA, Savvidis M, Sakellariou GT, Papatheodorou A, et al. Denosumab in treatment-naive and pre-treated with zoledronic acid postmenopausal women with low bone mass: effect on bone mineral density and bone turnover markers. Metabolism. 2015;64:1291–7.
111. Cosman F, Eriksen EF, Recknor C, Miller PD, Guanabens N, Kasperk C, et al. Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1–34)] in postmenopausal osteoporosis. J Bone Miner Res. 2011;26:503–11.

112. Leder BZ, Tsai JN, Uihlein AV, Burnett-Bowie SA, Zhu Y, Foley K, et al. Two years of denosumab and teriparatide administration in postmenopausal women with osteoporosis (The Data Extension Study): a randomized controlled trial. J Clin Endocrinol Metab. 2014;99:1694–700.

113. Inderjeeth CA, Chan K, Kwan K, Lai M. Time to onset of efficacy in fracture reduction with current anti-osteoporosis treatments. J Bone Miner Metab. 2012;30:493–503.

114. Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC, et al. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. J Clin Endocrinol Metab. 2000;85:4118–24.

115. Black DM, Reid IR, Boonen S, Bucci-Rechtweg C, Cauley JA, Cosman F, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res. 2012;27:243–54.

116. Ensrud KE, Barrett-Connor EL, Schwartz A, Santora AC, Bauer DC, Suryawanshi S, et al. Randomized trial of effect of alendronate continuation versus discontinuation in women with low BMD: results from the Fracture Intervention Trial long-term extension. J Bone Miner Res. 2004;19:1259–69.

117. Cummings SR, Cosman F, Lewiecki EM, Schousboe JT, Bauer DC, Black DM, et al. Goal-directed treatment for osteoporosis: a progress report from the ASBMR-NOF Working Group on Goal-Directed Treatment for Osteoporosis. J Bone Miner Res. 2017;32:3–10.

118. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA. 2006;296:2927–38.

119. Bone HG. Late-breaking abstract presentations. Ten years of denosumab treatment in postmenopausal women with osteoporosis: results from the FREEDOM extension trial. In: Presented at: American Society for Bone and Mineral Research (ASBMR) 2015 annual meeting. 2015.

120. Ferrari S, Adami S, Brown JP, Cosman F, Czerwinski E, de Gregorio LH, et al. Relationship between total hip (TH) BMD T-score and incidence of nonvertebral fracture (NVFX) with up to 10 years of denosumab (DMAb) treatment. In: Presented at: European Calcified Tissue Society (ECTS) 2016 annual meeting. 2016.

121. Siris ES, Harris ST, Eastell R, Zanchetta JR, Goemaere S, Diez-Perez A, et al. Skeletal effects of raloxifene after 8 years: results from the continuing outcomes relevant to Evista (CORE) study. J Bone Miner Res. 2005;20:1514–24.

122. Bauer DC, Schwartz A, Palermo L, Cauley J, Hochberg M, Santora A, et al. Fracture prediction after discontinuation of 4 to 5 years of alendronate therapy: the FLEX study. JAMA Intern Med. 2014;174:1126–34.

123. Black DM, Reid IR, Cauley JA, Cosman F, Leung PC, Lakatos P, et al. The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res. 2015;30:934–44.

124. Cosman F, Cauley JA, Eastell R, Boonen S, Palermo L, Reid IR, et al. Reassessment of fracture risk in women after 3 years of treatment with zoledronic acid: when is it reasonable to discontinue treatment? J Clin Endocrinol Metab. 2014;99:4546–54.

125. Moro Alvarez MJ, Neyro JL, Castaneda S. Therapeutic holidays in osteoporosis: long-term strategy of treatment with bisphosphonates. Med Clin (Barc). 2016;146:24–9.

126. Compston J, Bowring C, Cooper A, Cooper C, Davies C, Francis R, et al. Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013. Maturitas. 2013;75:392–6.

127. Anagnostis P, Paschou SA, Mintziori G, Ceausu I, Depypere H, Lambrinoudaki I, et al. Drug holidays from bisphosphonates and denosumab in postmenopausal osteoporosis: EMAS position statement. Maturitas. 2017;101:23–30.

128. Tsourdi E, Langdahl B, Cohen-Solal M, Aubry-Rozier B, Eriksen EF, Guanabens N, et al. Discontinuation of denosumab therapy for osteoporosis: a systematic review and position statement by ECTS. Bone. 2017;105:11–7.

129. Leder BZ, Neer RM, Wyland JJ, Lee HW, Burnett-Bowie SM, Finkelstein JS. Effects of teriparatide treatment and discontinuation in postmenopausal women and eugonadal men with osteoporosis. J Clin Endocrinol Metab. 2009;94:2915–21.

130. Anastasilakis AD, Polyzos SA, Makras P, Aubry-Rozier B, Kaouri S, Lamy O. Clinical features of 24 patients with rebound-associated vertebral fractures after denosumab discontinuation: systematic review and additional cases. J Bone Miner Res. 2017;32:1291–6.

131. Weycker D, Macarios D, Edelsberg J, Oster G. Compliance with drug therapy for postmenopausal osteoporosis. Osteoporos Int. 2006;17:1645–52.

132. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. Bone. 2006;38:922–8.

133. Bianchi ML, Duca P, Vai S, Guglielmi G, Viti R, Battista C, et al. Improving adherence to and persistence with oral therapy of osteoporosis. Osteoporos Int. 2015;26:1629–38.

134. Hiligsmann M, Salas M, Hughes DA, Manias E, Gwadry-Sridhar FH, Linck P, et al. Interventions to improve osteoporosis medication adherence and persistence: a systematic review and literature appraisal by the ISPOR Medication Adherence & Persistence Special Interest Group. Osteoporos Int. 2013;24:2907–18.

135. Eekman DA, van Helden SH, Huisman AM, Verhaar HJ, Bultink IE, Geusens PP, et al. Optimizing fracture prevention: the fracture liaison service, an observational study. Osteoporos Int. 2014;25:701–9.

136. Naranjo A, Ojeda-Bruno S, Bilbao-Cantarero A, Quevedo-Abeledo JC, Diaz-Gonzalez BV, Rodriguez-Lozano C. Two-year adherence to treatment and associated factors in a fracture liaison service in Spain. Osteoporos Int. 2015;26:2579–85.

137. Diez-Perez A, Naylor KE, Abrahamsen B, Agnusdei D, Brandi ML, Cooper C, et al., International Osteoporosis Foundation and European Calcified Tissue Society Working Group. Recommendations for the screening of adherence to oral bisphosphonates. Osteoporos Int. 2017;28:767–74.

138. Delmas PD, Vrijens B, Eastell R, Roux C, Pols HA, Ringe JD, et al. Effect of monitoring bone turnover markers on persistence with risedronate treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab. 2007;92:1296–304.

139. Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. J Bone Miner Res. 2003;18:1051–6.

140. Combs BP, Rappaport M, Caverly TJ, Matlock DD. "Due" for a scan: examining the utility of monitoring densitometry. JAMA Intern Med. 2013;173: 2007–9.

141. Buttgereit F, Strand V, Lee EB, McCabe D, Kolluri S, Tammara B, et al. Efficacy and safety of PF-04171327, a novel dissociated agonist of the glucocorticoid receptor (DAGR): results of a phase 2, randomized, double-blind study. Ann Rheum Dis. 2015;74:737–8. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/840/CN-01162840/frame.html

142. Qaseem A, Forciea MA, McLean RM, Denberg TD. Treatment of low bone density or osteoporosis to prevent fractures in men and women: a clinical practice guideline update from the American College of Physicians. Ann Intern Med. 2017;166:818–39.

143. Sun TY, Wang D, Salvadore G, Singh J, Hsu B, Curran M, et al. The effect of IL-6 neutralizing agents on depressed mood and anhedonia in immunology and oncology clinical. Neuropsychopharmacology. 2015;40:S181–2. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/263/CN-01163263/frame.html

144. Diez-Perez A, Adachi JD, Agnusdei D, Bilezikian JP, Compston JE, Cummings SR, et al. Treatment failure in osteoporosis. Osteoporos Int. 2012;23:2769–74.

145. Senn C, Gunther B, Popp AW, Perrelet R, Hans D, Lippuner K. Comparative effects of teriparatide and ibandronate on spine bone mineral density (BMD) and microarchitecture (TBS) in postmenopausal women with osteoporosis: a 2-year open-label study. Osteoporos Int. 2014;25:1945–51.

146. Crandall CJ, Newberry SJ, Diamant A, Lim YW, Gellad WF, Booth MJ, et al. Comparative effectiveness of pharmacologic treatments to prevent fractures: an updated systematic review. Ann Intern Med. 2014;161:711–23.

147. Kim DH, Rogers JR, Fulchino LA, Kim CA, Solomon DH, Kim SC. Bisphosphonates and risk of cardiovascular events: a meta-analysis. PLOS ONE. 2015;10:e0122646.

148. Wright E, Schofield PT, Molokhia M. Bisphosphonates and evidence for association with esophageal and gastric cancer: a systematic review and meta-analysis. BMJ Open. 2015;5:e007133.

149. Arboleya L, Alperi M, Alonso S. Adverse effects of bisphosphonates. Reumatol Clin. 2011;7:189–97.

150. Silva-Fernandez L, Rosario MP, Martinez-Lopez JA, Carmona L, Loza E. Denosumab for the treatment of osteoporosis: a systematic literature review. Reumatol Clin. 2013;9:42–52.

151. Watts NB, Roux C, Modlin JF, Brown JP, Daniels A, Jackson S, et al. Infections in postmenopausal women with osteoporosis treated with denosumab or placebo: coincidence or causal association? Osteoporos Int. 2012;23: 327–37.

152. Bagan J, Peydró A, Calvo J, Leopoldo M, Jiménez Y, Bagan L. Medication-related osteonecrosis of the jaw associated with bisphosphonates and denosumab in osteoporosis. Oral Dis. 2016;22:324–9.

153. De Oliveira CC, Brizeno LA, de Sousa FB, Mota MR, Alves AP. Osteonecrosis of the jaw induced by receptor activator of nuclear factor-kappa B ligand (Denosumab)—review. Med Oral Patol Oral Cir Bucal. 2016;21:e431–9.

154. Chamizo E, Santamaría EL, Olea AH, Lozano R. Revisión sistemática de la literatura sobre la osteonecrosis maxilar con el uso de bisfosfonatos en pacientes con osteoporosis. Reumatol Clin. 2013;9:172–7.

155. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res. 2015;30:3–23.

156. Enciso R, Keaton J, Saleh N, Ahmadieh A, Clark GT, Sedghizadeh PP. Assessing the utility of serum C-telopeptide cross-link of type 1 collagen as a predictor of bisphosphonate-related osteonecrosis of the jaw: a systematic review and meta-analysis. J Am Dent Assoc. 2016;147, 551–60.e11.

157. Hellstein JW, Adler RA, Edwards B, Jacobsen PL, Kalmar JR, Koka S, et al. Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis: executive summary of recommendations from the American Dental Association Council on Scientific Affairs. J Am Dent Assoc. 2011;142:1243–51.

158. European Medicines Agency: prolia (denosumab). Available from: http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/001120/WC500093526.pdf.

159. Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2014;29:1–23.

160. Lee S, Yin RV, Hirpara H, Lee NC, Lea A, Llanos S, et al. Increased risk for atypical fractures associated with bisphosphonate use. Fam Pract. 2015;32:276–81.

161. Gedmintas L, Solomon DH, Kim SC. Bisphosphonates and risk of sub-trochanteric, femoral shaft, and atypical femur fracture: a systematic review and meta-analysis. J Bone Miner Res. 2013;28:1729–37.

162. Liu L, Li C, Yang P, Zhu J, Gan D, Bu L, et al. Association between alendronate and atypical femur fractures: a meta-analysis. Endocr Connect. 2015;4:58–64.

163. Miller PD, Pannacciulli N, Brown JP, Czerwinski E, Nedergaard BS, Bolognese MA, et al. Denosumab or zoledronic acid in postmenopausal women with osteoporosis previously treated with oral bisphosphonates. J Clin Endocrinol Metab. 2016;101:3163–70.

164. Bianchi G, Czerwinski E, Kenwright A, Burdeska A, Recker RR, Felsenberg D. Long-term administration of quarterly IV ibandronate is effective and well tolerated in postmenopausal osteoporosis: 5-year data from the DIVA study long-term extension. Osteoporos Int. 2012;23:1769–78.

165. Pazianas M, Abrahamsen B, Wang Y, Russell RG. Incidence of fractures of the femur, including subtrochanteric, up to 8 years since initiation of oral bisphosphonate therapy: a register-based cohort study using the US MarketScan claims databases. Osteoporos Int. 2012;23:2873–84.

166. Geada N, Mafra I, Barroso R, Franco J. [Atypical femoral fractures and bisphosphonates treatment: is it a risk factor?]. Acta Med Port. 2014;27:704–9.

167. Bone HG, Wagman RB, Brandi ML, Brown JP, Chapurlat R, Cummings SR, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. Lancet Diabetes Endocrinol. 2017;5:513–23.

168. Sugimoto T, Matsumoto T, Hosoi T, Miki T, Gorai I, Yoshikawa H, et al. Three-year denosumab treatment in postmenopausal Japanese women and men with osteoporosis: results from a 1-year open-label extension of the Denosumab Fracture Intervention Randomized Placebo Controlled Trial (DIRECT). Osteoporos Int. 2014;26:765–74.

169. Silverman SL, Siris E, Kendler DL, Belazi D, Brown JP, Gold DT, et al. Persistence at 12 months with denosumab in postmenopausal women with osteoporosis: interim results from a prospective observational study. Osteoporos Int. 2015;26:361–72.

170. Watts NB, Aggers D, McCarthy EF, Savage T, Martinez S, Patterson R, et al. Responses to treatment with teriparatide in patients with atypical femur fractures previously treated with bisphosphonates. J Bone Miner Res. 2017;32:1027–33.

171. Lems WF, Dreinhofer KE, Bischoff-Ferrari H, Blauth M, Czerwinski E, da Silva J. EULAR/EFORT recommendations for management of patients older than 50 years with a fragility fracture and prevention of subsequent fractures. Ann Rheum Dis. 2017;76:802–10.

172. Ganda K, Puech M, Chen JS, Speerin R, Bleasel J, Center JR, et al. Models of care for the secondary prevention of osteoporotic fractures: a systematic review and meta-analysis. Osteoporos Int. 2013;24:393–406.

173. McLellan AR, Wolowacz SE, Zimovetz EA, Beard SM, Lock S, McCrink L, et al. Fracture liaison services for the evaluation and management of patients with osteoporotic fracture: a cost-effectiveness evaluation based on data collected over 8 years of service provision. Osteoporos Int. 2011;22:2083–98.

174. Fink HA, Ensrud KE, Nelson DB, Kerani RP, Schreiner PJ, Zhao Y, et al. Disability after clinical fracture in postmenopausal women with low bone density: the fracture intervention trial (FIT). Osteoporos Int. 2003;14:69–76.

175. Bonner FJ Jr, Sinaki M, Grabois M, Shipp KM, Lane JM, Lindsay R, et al. Health professional's guide to rehabilitation of the patient with osteoporosis. Osteoporos Int. 2003;14 Suppl. 2:S1–22.

176. Newman M, Minns Lowe C, Barker K. Spinal orthoses for vertebral osteoporosis and osteoporotic vertebral fracture: a systematic review. Arch Phys Med Rehabil. 2016;97:1013–25.

177. Solberg J, Copenhaver D, Fishman SM. Medial branch nerve block and ablation as a novel approach to pain related to vertebral compression fracture. Curr Opin Anaesthesiol. 2016;29:596–9.

178. Kendler DL, Bauer DC, Davison KS, Dian L, Hanley DA, Harris ST, et al. Vertebral fractures: clinical importance and management. Am J Med. 2016;129, 221.e1–10.

179. Stevenson M, Gomersall T, Lloyd Jones M, Rawdin A, Hernandez M, Dias S, et al. Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for the treatment of osteoporotic vertebral fractures: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2014;18:1–290.

180. Buchbinder R, Golmohammadi K, Johnston RV, Owen RJ, Homik J, Jones A, et al. Percutaneous vertebroplasty for osteoporotic vertebral compression fracture. Cochrane Database Syst Rev. 2015. CD006349.

181. Rodriguez AJ, Fink HA, Mirigian L, Guanabens N, Eastell R, Akesson K, et al. Pain, quality of life, and safety outcomes of kyphoplasty for vertebral compression fractures: report of a Task Force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2017;32:1935–44.

182. Whittier X, Saag KG. Glucocorticoid-induced osteoporosis. Rheum Dis Clin North Am. 2016;42:177–89.

183. Van Staa TP, Laan RF, Barton IP, Cohen S, Reid DM, Cooper C. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. Arthritis Rheum. 2003;48:3224–9.

184. Allen CS, Yeung JH, Vandermeer B, Homik J. Bisphosphonates for steroid-induced osteoporosis. Cochrane Database Syst Rev. 2016;10. CD001347.

185. Geusens P, Marin F, Kendler DL, Russo LA, Zerbini CA, Minisola S, et al. Effects of teriparatide compared with risedronate on the risk of fractures in subgroups of postmenopausal women with severe osteoporosis: the VERO trial. J Bone Miner Res. 2018;33:783–94.

186. Saag KG, Shane E, Boonen S, Marin F, Donley DW, Taylor KA, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. N Engl J Med. 2007;357:2028–39.

187. Saag KG, Wagman RB, Geusens P, Adachi JD, Messina OD, Emkey R, et al. Denosumab versus risedronate in glucocorticoid-induced osteoporosis: a multicentre, randomised, double-blind, active-controlled, double-dummy, non-inferiority study. Lancet Diabetes Endocrinol. 2018;6:445–54.

188. Gough AK, Lilley J, Eyre S, Holder RL, Emery P. Generalised bone loss in patients with early rheumatoid arthritis. Lancet. 1994;344:23–7.

189. Cooper C, Coupland C, Mitchell M. Rheumatoid arthritis, corticosteroid therapy and hip fracture. Ann Rheum Dis. 1995;54:49–52.

190. Chen B, Cheng G, Wang H, Feng Y. Increased risk of vertebral fracture in patients with rheumatoid arthritis: a meta-analysis. Medicine (Baltimore). 2016;95:e5262.

191. Xue AL, Wu SY, Jiang L, Feng AM, Guo HF, Zhao P. Bone fracture risk in patients with rheumatoid arthritis: a meta-analysis. Medicine (Baltimore). 2017;96:e6983.

192. Pray C, Feroz NI, Nigil Haroon N. Bone mineral density and fracture risk in ankylosing spondylitis: a meta-analysis. Calcif Tissue Int. 2017;101:182–92.

193. Wang X, Yan S, Liu C, Xu Y, Wan L, Wang Y, et al. Fracture risk and bone mineral density levels in patients with systemic lupus erythematosus: a systematic review and meta-analysis. Osteoporos Int. 2016;27:1413–23.

194. Ramirez J, Nieto-Gonzalez JC, Curbelo Rodriguez R, Castaneda S, Carmona L. Prevalence and risk factors for osteoporosis and fractures in axial spondyloarthritis: a systematic review and meta-analysis. Semin Arthritis Rheum. 2018;48:44–52.

195. Ogdie A, Harter L, Shin D, Baker J, Takeshita J, Choi HK, et al. The risk of fracture among patients with psoriatic arthritis and psoriasis: a population-based study. Ann Rheum Dis. 2017;76:882–5.

196. Mosca M, Tani C, Aringer M, Bombardieri S, Boumpas D, Brey R, et al. European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. Ann Rheum Dis. 2010;69:1269–74.

197. Roubille C, Richer V, Starnino T, McCourt C, McFarlane A, Fleming P, et al. Evidence-based recommendations for the management of comorbidities in rheumatoid arthritis, psoriasis, and psoriatic arthritis: expert opinion of the Canadian Dermatology-Rheumatology Comorbidity Initiative. J Rheumatol. 2015;42:1767–80.

198. Loza E, Lajas C, Andreu JL, Balsa A, Gonzalez-Alvaro I, Illera O, et al. Consensus statement on a framework for the management of comorbidity and extra-articular manifestations in rheumatoid arthritis. Rheumatol Int. 2015;35:445–58.

199. Curtis JR, Xie F, Yun H, Saag KG, Chen L, Delzell E. Risk of hospitalized infection among rheumatoid arthritis patients concurrently treated with a biologic agent and denosumab. Arthritis Rheumatol. 2015;67:1456–64.

200. Jain S, Bilori B, Gupta A, Spanos P, Singh M. Are men at high risk for osteoporosis underscreened? A quality improvement project. Perm J. 2016;20:60–4.

201. Ebeling PR. Osteoporosis in men. Curr Opin Rheumatol. 2013;25:542–52.

202. Watts NB, Adler RA, Bilezikian JP, Drake MT, Eastell R, Orwoll ES, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012;97:1802–22.

203. Johnell O, Kanis JA, Oden A, Johansson H, de Laet C, Delmas P, et al. Predictive value of BMD for hip and other fractures. J Bone Miner Res. 2005;20:1185–94.

204. Kanis JA, Bianchi G, Bilezikian JP, Kaufman JM, Khosla S, Orwoll E, et al. Towards a diagnostic and therapeutic consensus in male osteoporosis. Osteoporos Int. 2011;22:2789–98.

205. Xu Z. Alendronate for the treatment of osteoporosis in men: a meta-analysis of randomized controlled trials. Am J Ther. 2017;24:e130–8.

206. Zhong ZM, Chen JT. Anti-fracture efficacy of risedronic acid in men: a meta-analysis of randomized controlled trials. Clin Drug Investig. 2009;29:349–57.

207. Orwoll ES, Miller PD, Adachi JD, Brown J, Adler RA, Kendler D, et al. Efficacy and safety of a once-yearly i.v. infusion of zoledronic acid 5 mg versus a once-weekly 70-mg oral alendronate in the treatment of male osteoporosis: a randomized, multicenter, double-blind, active-controlled study. J Bone Miner Res. 2010;25:2239–50.

208. Niimi R, Kono T, Nishihara A, Hasegawa M, Matsumine A, Kono T, et al. Analysis of daily teriparatide treatment for osteoporosis in men. Osteoporos Int. 2015;26:1303–9.

209. Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, et al. The effect of teriparatide [human parathyroid hormone (1–34)] therapy on bone density in men with osteoporosis. J Bone Miner Res. 2003;18:9–17.

210. Langdahl BL, Teglbjaerg CS, Ho PR, Chapurlat R, Czerwinski E, Kendler DL, et al. A 24-month study evaluating the efficacy and safety of denosumab for the treatment of men with low bone mineral density: results from the ADAMO trial. J Clin Endocrinol Metab. 2015;100:1335–42.

211. Lewiecki EM, Gordon CM, Baim S, Leonard MB, Bishop NJ, Bianchi ML, et al. International Society for Clinical Densitometry 2007 adult and pediatric official positions. Bone. 2008;43:1115–21.

212. Cohen A. Premenopausal osteoporosis. Endocrinol Metab Clin North Am. 2017;46:117–33.

213. Peris Bernal P. Osteoporosis in young individuals. Reumatol Clin. 2010;6:217–23.

214. McNicholl DM, Heaney LG. The safety of bisphosphonate use in premenopausal women on corticosteroids. Curr Drug Saf. 2010;5:182–7.

215. FDA. Ficha técnica de FORTEO®. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021318s015lbl.pdf [accesssed 03.12.17].

216. Torres PU, Canaud B. [How to slow down parathyroid hormone (PTH) secretion without the risk of inducing an adynamic bone disease]. Nephrol Ther. 2005;1 Suppl. 4:S337–41.

217. Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) guideline update: what's changed and why it matters. Kidney Int. 2017;92:26–36.

218. Schipper LG, Fleuren HW, van den Bergh JP, Meinardi JR, Veldman BA, Kramers C. Treatment of osteoporosis in renal insufficiency. Clin Rheumatol. 2015;34:1341–5.

219. Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. J Bone Miner Res. 2005;20:2105–15.

220. Ishani A, Blackwell T, Jamal SA, Cummings SR, Ensrud KE. The effect of raloxifene treatment in postmenopausal women with CKD. J Am Soc Nephrol. 2008;19:1430–8.

221. Melamed ML, Blackwell T, Neugarten J, Arnsten JH, Ensrud KE, Ishani A, et al. Raloxifene, a selective estrogen receptor modulator, is renoprotective: a post-hoc analysis. Kidney Int. 2011;79:241–9.

222. Jamal SA, Ljunggren O, Stehman-Breen C, Cummings SR, McClung MR, Goemaere S, et al. Effects of denosumab on fracture and bone mineral density by level of kidney function. J Bone Miner Res. 2011;26:1829–35.

223. Guanabens N, Monegal A, Cerda D, Muxi A, Gifre L, Peris P, et al. Randomized trial comparing monthly ibandronate and weekly alendronate for osteoporosis in patients with primary biliary cirrhosis. Hepatology. 2013;58:2070–8.

224. Melek J, Sakuraba A. Efficacy and safety of medical therapy for low bone mineral density in patients with inflammatory bowel disease: a meta-analysis and systematic review. Clin Gastroenterol Hepatol. 2014;12, 32–44.e5.

225. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med. 2016;375:1532–43.

226. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med. 2017;377:1417–27.

227. Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA. 2016;316:722–33.