Reumatología Clínica

Original Article

2011 Up-Date of the Consensus Statement of the Spanish Society of Rheumatology on Osteoporosis[☆]

Lluis Pérez Edo,[a] Alberto Alonso Ruiz,[b] Daniel Roig Vilaseca,[c] Alberto García Vadillo,[d]
Nuria Guañabens Gay,[e] Pilar Peris,[e] Antonio Torrijos Eslava,[f] Chesús Beltrán Audera,[g]
Jordi Fiter Aresté,[h] Luis Arboleya Rodríguez,[i] Jenaro Graña Gil,[j] Jordi Carbonell Abelló,[a]
Joan Miquel Nolla,[k] Susana Holgado Pérez,[l] Esteban Salas Heredia,[m] Jaime Zubieta Tabernero,[n]
Javier Del Pino Montes,[o] Josep Blanch i. Rubió,[a] Manuel Caamaño Freire,[p] Manuel Rodríguez Pérez,[q]
Santos Castañeda,[d] Dacia Cerdá,[e] Carmen Gómez Vaquero,[k] Javier Calvo Catalá,[r] Manel Ciria,[a]
Estíbaliz Loza[s,*]

[a] Servicio de Reumatología, Hospital del Mar, Barcelona, Spain
[b] Servicio de Reumatología, Hospital de Cruces, Barakaldo, Bizkaia, Spain
[c] Servicio de Reumatología, Hospital de Sant Joan Despí Moisès Broggi, Sant Joan Despí, Barcelona, Spain
[d] Servicio de Reumatología, Instituto de Investigación Sanitaria Hospital La Princesa, Hospital Universitario de La Princesa, Madrid, Spain
[e] Servicio de Reumatología, Hospital Universitari Clínic de Barcelona, Barcelona, Spain
[f] Servicio de Reumatología, Hospital Universitario La Paz, Madrid, Spain
[g] Servicio de Reumatología, Hospital universitario Miguel Servet, Zaragoza, Spain
[h] Servicio de Reumatología, Hospital Universitari Son Espases, Palma de Mallorca, Spain
[i] Servicio de Reumatología, Hospital Universitario Central de Asturias, Oviedo, Spain
[j] Servicio de Reumatología, Complexo Hospitalario Universitario A Coruña, A Coruña, Spain
[k] Servicio de Reumatología, Hospital Universitari de Bellvitge, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain
[l] Servicio de Reumatología, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain
[m] Servicio de Reumatología, Clínica Mediterránea de Neurociencias, Alicante, Spain
[n] Servicio de Reumatología, Hospital Virgen de la Salud, Toledo, Spain
[o] Servicio de Reumatología, Hospital Universitario de Salamanca, Salamanca, Spain
[p] Servicio de Reumatología, Complexo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain
[q] Servicio de Reumatología, Hospital Regional Universitario Carlos Haya, Málaga, Spain
[r] Servicio de Reumatología, Consorci Hospital General Universitari Valencia, Valencia, Spain
[s] Unidad de Investigación, Sociedad Española de Reumatología, Madrid, Spain

ARTICLE INFO

ABSTRACT

Objective: Due to increasing improvement in the diagnosis, evaluation and management of osteoporosis and the development of new tools and drugs, the Spanish Society of Rheumatology (SER) has promoted the development of recommendations based on the best evidence available. These recommendations should be a reference to rheumatologists and other health professionals involved in the treatment of patients with osteoporosis.

Methods: Recommendations were developed following a nominal group methodology and based on a systematic review. The level of evidence and the degree of recommendation were classified according to the model proposed by the Center for Evidence Based Medicine at Oxford. The level of agreement was established through Delphi technique. Evidence from previous consensus and available clinical guidelines was used.

Results: We have produced recommendations on diagnosis, evaluation and management of osteoporosis. These recommendations include the glucocorticoid-induced osteoporosis, premenopausal and male osteoporosis.

Conclusions: We present the SER recommendations related to the biologic therapy risk management.

© 2011 Elsevier España, S.L. All rights reserved.

Actualización 2011 del consenso Sociedad Española de Reumatología de osteoporosis

R E S U M E N

Palabras clave:
Consenso
Guía
Osteoporosis
Recomendaciones

Objetivo: Dado el creciente avance en el diagnóstico como evaluación y tratamiento de la osteopososis, y la incorporación de nuevas herramientas y medicamentos, desde la Sociedad Española de Reumatología (SER) se ha impulsado el desarrollo de recomendaciones basadas en la mejor evidencia posible. Estas deben de servir de referencia para reumatólogos y otros profesionales de la salud implicados en el tratamiento de pacientes con osteoporosis.

Métodos: Las recomendaciones se emitieron siguiendo la metodología de grupos nominales. El nivel de evidencia y el grado de recomendación se clasificaron según el modelo del Center for Evidence Based Medicine de Oxford y el grado de acuerdo se extrajo por técnica Delphi. Se utilizó toda la información de consensos previos y guías de práctica clínica disponibles.

Resultados: Se realizan recomendaciones sobre el diagnóstico, evaluación y tratamiento en pacientes con osteoporosis. Estas recomendaciones incluyen la osteopososis secundaria a glucocorticoides, la osteoporosis premenopáusica y la del varón.

Conclusiones: Se presentan las recomendaciones SER sobre el diagnóstico, evaluación y manejo de pacientes con osteoporosis.

© 2011 Elsevier España, S.L. Todos los derechos reservados.

Introduction

Updating knowledge on the different aspects of osteoporosis (OP) is still needed because of its high prevalence, its complications, and the associated health and social spending. At a time when the rational use of resources is important, this document is, in reality, a corporate reflection in which we analyze new evidence on diagnosis, risk factors for fracture, follow up and treatment of OP.

These recommendations are intended as a reference for therapeutic decision making to rheumatologists and all professionals who, from the different levels of care, are implicated in the treatment of OP.

Methodology

Tasks were distributed for the elaboration of this document and commentary to each part. The structure of the document is based on questions relevant to clinical practice in OP.

Each panelist was first assigned one or several parts of the consensus for write up. Once completed, the whole panel was distributed for comment. After that, members of the research unit (RU) of the Spanish Society of Rheumatology (SER) unified, categorized, classified and summarized all of the comments for their evaluation prior to the panel getting together.

A meeting of the nominal group was carried out, moderated by members of the RU of SER. In this meeting, modification proposals in relation to format and content, including the recommendations, were performed.

Then, a Delphi survey was performed and consensus recommendations were voted on (anonymously online). The aggregated results were shown to all the panelists (modified Delphi). Recommendations with a degree of agreement (DA) of less than 70% were reedited and voted for a second time. Agreement is defined if, on a scale of 1 (complete disagreement) to 10 (complete agreement), the vote is 7 or more. The level of evidence (LE) and degree of recommendation (DR) are classified according to the model proposed by the Center for Evidence Based Medicine of Oxford[1] by members of the RU of SER.

With all of this information the definite document was written up.

Results

Diagnosis and Evaluation

What Is Osteoporosis?

OP has been defined in the consensus conference of the National Institute of Health as a skeletal disease characterized by reduced bone resistance that predisposes an increase in the risk of fracture (LE 5; DR D; DA 100%).

Bone resistance reflects the integration of bone density and bone quality. At the same time, bone density is determined by the peak value of bone mass and the magnitude of its loss, while bone quality depends on architecture, bone exchange, the accumulation of microlesions and mineralization.[2]

When Should I Suspect a Case of Osteoporosis?

There is no current population survey protocol that is universally accepted for the identification of persons with OP. Patients are identified by a strategy of case by case search based on a history of one or more fragility associated fractures or the presence of significant clinical risk factors.[3]

In certain groups of patients, mainly the elderly and postmenopausal women, we must maintain a high degree of suspicion and actively search for risk factors (LE 5; DR D; DA 100%).

What Is Considered an Osteoporotic Fracture?

An osteoporotic fracture or fragility fracture is conditioned by low impact trauma. A fall from a standing or sitting position is included in this concept. Fractures that occur as a consequence of sports or accidents are excluded (LE 5; DR D; DA 100%).

It is estimated that close to 40% of Caucasian women will have at least one fracture after the age of 50.[4–9] The most frequent and relevant are those of the proximal femur, the spinal column and the distal forearm. On the other hand, we must point out that fractures of the cranium or face are excluded from this definition.[10]

What Is High Risk of Osteoporotic Fracture?

As occurs with OP, there is no universally accepted survey to identify the population with a high risk of fracture.

The risk of osteoporotic fracture is determined by the presence of one or more risk factors including low bone mineral density (BMD). The combination of risk conferred by a low BMD with clinical risk factors[11] allows for a better estimate of risk. We consider a

Table 1
Risk Factors for Fracture.

High risk (≥2)
  1. Advanced age (65 years)
  2. Low weight (BMI < 20 kg/m^2)
  3. Personal history of fractures
  4. Maternal history of fractures
  5. Steroids[a]
  6. Falls[b]

Moderate risk (>1 < 2)
  7. Tobacco and/or alcohol consumption[c]
  8. Early menopause (45 years)
  9. Primary and secondary amenorrhea
  10. Hypogonadism in the male
  11. Diseases and drugs with a capacity to reduce BMD: rheumatoid arthritis and other inflammatory arthropathies, inflammatory intestinal disease, celiac disease, malabsorption, liver disease, hyperparathyroidism, hyperthyroidism, anorexia and bulimia,[d] patients with solid organ transplants, use of hydantoin, antiretrovirals, antiepileptics, etc.)
  12. Factors related to falls: visual disturbances, psychopharmacology, stroke, Parkinson's disease

[a] More than 5 mg/prednisone/day for over 3 months.
[b] More than 2 falls in the past year.
[c] Tobacco use and alcohol consumption >3 units a day: one unit of alcohol is equivalent to 8–10 g.
[d] If untreated it may be considered as a risk factor for fracture.

high risk for fracture when there are at least 2 high risk factors (Table 1). Having a tool for the calculation of osteoporotic fracture risk would permit the identification of persons with a high risk who would merit early intervention and reduce the number of unnecessary treatments administered to low risk patients.

Different instruments that estimate the risk of fracture based on risk factors have been developed (Table 2). Of them, the most important is the FRAX tool[©], a software tool sponsored by the WHO,[12] which can be applied with and without BMD. The FRAX® algorithms calculate the absolute 10 year probability of fracture into a group of "major fractures" (clinical vertebral, forearm, hip and humeral fractures) and isolated hip fractures. It is currently the most recommended instrument used to calculate the risk of osteoporotic fracture. However, as everything, it has limitations and the medical judgment of the clinician is still fundamental. The risk of a major fracture calculated by FRAX[©] in the Spanish population over 15% is very specific for osteoporosis.

There is no consensus in the medical literature on the threshold above which the risk for a fracture would be considered "high" in the Spanish population. An approximation would be:

– Absolute 10 year risk of fracture <10%: low.
– Absolute 10 year risk of fracture ≥10% and <20%: moderate.
– Absolute 10 year risk of fracture ≥20%: low.

If FRAX[©] is employed, its systemic application is recommended in patients in whom: (a) the indication of a BMD is being evaluated; (b) the onset of treatment is being evaluated for OP, and (c) they are over 65 years of age.

What History and Examination Data Are Important?

If OP is suspected, with the aim of evaluating the risk of fracture and the cause of OP, we recommend obtaining the following data: age, ethnicity, history of toxic habits (tobacco, alcohol), dietary intake of calcium and vitamin D, degree of exposure to sunlight, menstrual history (age at menopause and menarche), obstetric history (interventions, surgical menopause, hypogonadism), osteopenia associated diseases and drugs, previous trauma, family or personal history of fragility fractures and conditions associated

to falls, as well as data regarding recent or prior fractures (LE 5; DR D; DA 95%).

The presence of present or prior fractures should be evaluated determining episodes of acute and/or chronic back pain, progressive reduction in height, etc.[13,14] It is important to remember that OP is asymptomatic and that more than half of the vertebral fractures are also asymptomatic.[15]

It is recommended that physical examination record weight, height, the existence of skeletal deformities and palpation/percussion of the spine be carried out (LE 5; DR D; DA 90%).

The relationship between the body mass index and BMD is well known.[16] The possible existence of skeletal deformities should be established by the presence of dorsal kyphosis, a reduction of the space between the ribs and the pelvis, etc., and palpation/percussion should be directed to the localization of painful zones of the locomotor system.[14] General physical examination may provide data on other diseases associated to a reduction in bone mass.

What Laboratory Data Is Important?

Laboratory tests are performed to identify associated processes and perform a differential diagnosis with other diseases associated to bone fragility.[17–21]

When OP is suspected, one should request: complete blood count, alkaline phosphatase, creatinine, serum proteins, erythrocyte sedimentation rate, serum calcium and phosphorus and 24 h urinary calcium excretion (LE 5; DR D; DA 100%).

It is advisable to determine during the initial visit what the levels of 25-hydroxyvitamin D (25-[OH]-D$_3$), parathyroid hormone (PTH) and thyroid stimulating hormone are (LE 5; DR D; DA 80%).

In case an associated disease is suspected, pertinent laboratory tests should be performed (LE 5; DR D; DA 95%).

The systematic determination of bone markers is not recommended for the diagnosis and evaluation of patients with OP. Their measurement is useful to identify subjects with a greater risk of fracture and especially to evaluate in an early manner response to, both antiresorptive as well as bone forming treatments (LE 2c; DR C; DA 80%).

Bone remodeling markers provide additional and complementary information to the study of BMD. Osteocalcin, bone alkaline phosphatase and type I procollagen aminoterminal propeptide stand out as bone formation markers and pyridinolynes, carboxy and aminoterminal telopeptides of type I collagen (serum CTX and urine NTX) and tartrate 5b resistant acid phosphatase stand out among those associated to resorption. These are more sensitive and specific than classic markers such as total alkaline phosphatase and hydroxyproline. It is important to take into account biological variability and circadian rhythm in their correct interpretation and therefore establish an adequate schedule to obtain samples.[22–24]

When Is it Advisable to Request Spinal X-rays?

Spine radiographs are not useful to assess the decrease in BMD, but allow the diagnosis of fractures, including asymptomatic ones. We must remember that the presence of prior vertebral fracture is a significant risk factor for new fractures, both vertebral and nonvertebral.[25–29]

In patients with suspected or diagnosed OP, it is recommended to perform an initial spinal X-ray for detecting fractures (LE 2b; DR B; DA 95%).

If there is suspicion of vertebral fracture during follow up, a spinal X-ray is recommended (LE 2b; DR B; DA 100%).

The panel believes that for the diagnosis of spinal fractures, lateral, dorsal and lumbar spine X-rays, with focus on D8 and L2, respectively[30] are sufficient (LE 2a; DR C; DA 100%).

Table 2
Characteristics of the Different Scales Evaluating Risk of Osteoporotic Fracture.

	Fracture	Catalan Agency	EPESE	Minimal Data Group	Community of Madrid	Díez	WHI	NORA	Garvan Institute		FRAX	Qfracture	Body Weight[d]	ABONE[d]	ORAI[d]	DOE Score[d]
Year	2001	2001	2002	2002	2007	2007	2007	2007	2008		2008	2009	1996	2000	2000	2004
Reference	4	3	5	6	7	8	9	10	11		12	13	14, 15	15, 16	15, 17	18
Population	MP ≥ 65 y		≥65 y		MP ≥ 50 y	MP ≥ 65 y	MP 50–79 y	MP 50–64	≥60 y		40–90 y	30–85 y			M ≥ 50 y	
Time limit, years	5	ND	3		10	3	5	3	5 and 10		10	10				
Fracture evaluated	F, V, NV	ND	F, all	All	F, V	NV	F	All	All		F, major	F, all	All	All	All	
General data																
Age	X	X	X	X	X	X	X		X	X	X	X	X		X	X
Gender		X	X						X	X	X	X				
Ethnicity			X				X					X				
Weight/height/BMI	X	X	X	X	X		X				X	X	X	X	X	X
BMD	(FT)					US	X[i]		CF		(CF)					
Markers of bone remodeling																
Health habits																
Previous fracture	X	X			X	X	X	X	X	X	X	X				X
Tobacco		X					X				X	X				
Alcohol		X									X	X				
Caffeine																
Calcium intake		X				X										
Sunlight exposure		X														
Vitamin D deficit																
Protein rich diet																
Poor physical activity		X					X									
Activities of daily living			X	X												
Cognitive alterations			X	X												
Self assessed health							X	X	X							
Urinary incontinence				X												
Falls																

	1	2	3	4	5	6	7	8	9	10	11	12	13
Visual acuity			X										
Walking speed				X									
Difficulty getting up	X												
Falls in the previous year				X		X			X	X		X	
Family history of fracture	X[b]	X			X[c]	X[c]	X[e]				X	X	
Hormonal status													
Hypogonadism		X											
Early menopause		X											
Amenorrhea		X											
Prior use of estrogens								X				X	X
Fertility		X											
Lactation		X											
No. of offspring													
OP secondary to disease													
Chronic hepatitis											X	X	
CRF													
Intestinal malabsorption		X[a]									X	X	
Chronic lung disease												X[j]	
Cushing's disease													
Hyperparathyroidism		X									X		
Hyperthyroidism		X									X		
Diabetes mellitus[g]		X									X	X	
Pernicious anemia		X											
Multiple myeloma													
Rheumatoid arthritis		X									X	X	
Other			X[f]									X[i]	

Table 2 (*Continued*)

	Fracture Risk Scales (1, 2, 3)														
	Fracture	Catalan Agency	EPESE	Minimal Data Group	Community of Madrid	Díez	WHI	NORA	Garvan Institute	FRAX	Qfracture	Body Weight[d]	ABONE[d]	ORAI[d]	DOE Score[d]
OP secondary to drugs															
Steroids		X					X			X	X				
Thyroid hormones/low TSH															
Diuretics[l]															
Antiandrogens															
Antiestrogens															
Antiepileptics		X	X												
Organ transplant															
Others							X[h]				X[k]				

CF: Femoral neck; DMO: Bone densitometry; F: femoral fracture; FT: total femur; FV: vertebral fracture; H: humeral fracture; CRF: chronic renal failure; MP: postmenopausal women; ND: no defined/no determined; NV: non-vertebral fracture; OP: osteoporosis; R: fracture of the distal third of the radius; US: ultrasound.

[a] Gastrectomy.

[b] Femoral fracture in the mother.

[c] Femoral fracture in the mother, father or sister.

[d] Index developed to identify persons with low bone mass; it has been evaluated for fracture risk.

[e] Femoral fracture in the father or mother.

[f] Stroke.

[g] Hypoglycemic drugs.

[h] Peripheral densitometry: distal forearm, fingers, calcaneus, by DXA or ultrasound.

[i] Cardiovascular disease.

[j] Asthma.

[k] Trycyclic antidepressants.

[l] Thyazide diuretics have osteoprotective effects.

Anteroposterior projections are not essential for diagnosis but can provide additional information.

When Is it Indicated to Perform a Bone Densitometry?

A densitometric survey of the general population is not cost-effective[31] and there is great variability regarding indications for densitometry.[3,32–37] Until today there are no validated tools that satisfactorily quantify the risk of fracture or a consensus on the definition of risk of fracture that helps determine a therapeutic intervention. The evaluation of BMD along with other risk factors is useful for the diagnosis and follow up of patients.

The indication for performing a densitometry should be based on clinical criteria that allow the selection of patients in which the use of this technology is efficient (LE 2b; DR B; DA 95%).

Before requesting for it is essential to be certain that the result will help determine the therapeutic decision to be taken.[38]

A baseline densitometry is recommended in the following (LE 5; DR D; DA 75%):

1. Women with early menopause and any major risk factors for fracture.
2. Postmenopausal women of any age and men over 50 with at least one major risk factor for fracture.
3. A history of fragility fracture in patients over 50.
4. Underlying disease or chronic treatment with medication associated to bone loss, especially glucocorticoids.
5. Women over 65 years of age and men >70 without known risk factors at least in one occasion if patient request it.
6. Evaluation of pharmacologic treatment.
7. If the FRAX© is employed, a densitometry is recommended in women 65 and older and those younger but with a major risk factor for fracture according to the FRAX©, equivalent to a 65 year old woman with no risk factors de riesgo (Spanish FRAX 3.6%).[39,40]

To detect significant changes with a confidence interval (CI) of 95%, these should be, at least, 2.8 times the variation coefficient (minimum significant change). In clinical practice its application is difficult because very strict precision measures are needed.[41] The use of another concept is more practical, "the smallest detectable difference" which is established in 2% (change in lumbar BMD ± 0.05 g/cm^2, total femur ± 0.04 g/cm^2).[42] Although major changes in BMD are detected on the lumbar spine, it is also useful to monitor the hip because it is less dependent on artifacts produced by degenerative change.

Which Densitometric Technique Is the Most Adequate?

Dual energy X-ray absorciometry (DXA) is recommended as the reference technique for measuring BMD (LE 2b; DR B; DA 100%).

DXA is a technique that has good precision, low radiological exposure and allows for measurement of BMD both in the axial as well as in the peripheral skeleton. It is considered the best technique to evaluate BMD.[28,41,42]

What Is Dual Energy X-ray Absorciometry Good for?

Results of BMD obtained through DXA predict the future risk of fracture due to OP, both in postmenopausal women as in elderly males.[43–49] But in addition, according to WHO, to diagnose OP it is necessary to know the value of the BMD in the femur and lumbar spine through a central DXA.[50,51] Currently, central DXA is the only validated technique to follow up and for evaluation of therapeutic response.

To perform a diagnosis of OP, we recommend carrying out a DXA, as long as it is possible on the hip and lumbar spine (LE 2b; DR B; DA 95%).

A lateral projection of the spine should not be used for the diagnosis of OP.

If DXA of the lumbar spine or hip is impossible, it is recommended that DXA be performed on the distal third of the radius of the non-dominating forearm (LE 2b; DR B; DA 90%).

This may occur in case of anatomical alterations (scoliosis, degenerative problems, multiple vertebral fractures, morbid obesity) or technical problems (presence of metallic elements after spinal surgery, hip arthroplasty).[52]

When necessary, control DXA of the hip and the spine should be performed with the same equipment (LE 1b; DR A; DA 90%).

Long-term precision or reproducibility of DXA; expressed as a variation coefficient, varies according to the measurement area and the equipment used from 1 to 2%.[53–55] In women undergoing treatment for postmenopausal OP, densitometric controls should be performed every 2–3 years.[32] In general, codensitometric controls are not recommended before 2 years because it has been seen that some patients who lose bone mass during the first year may regain it during the second.[55]

Ultrasound, peripheral DXA equipment and central or peripheral quantitative computerized tomography are useful to predict an elevated risk of fracture but should not be used for diagnosis, follow up or evaluation of therapeutic response in patients with OP (LE 1a; DR A; DA 95%).

There are other techniques to measure BMD in the peripheral skeleton, such as phalangeal, knee and calcaneus DXA, and calcaneus ultrasound. They are cheaper, easier to handle and faster in comparison to central DXA but, among other limitations, their precision is low.[49,52,56,57] They are useful to predict the future risk of fracture and may have some value when it is impossible to perform a central DXA.[49,52,56] Peripheral quantitative computed tomography is a rapidly developing imaging technique. It allows for volumetric BMD measurement of the lumbar spine, hip and distal radiums, but its results are not comparable to those obtained through DXA.[58]

How Is Osteoporosis Diagnosed?

Diagnosis of OP is based on the densitometric criteria established by WHO for white postmenopausal women (BMD values under −2.5 standard deviations (SD) (T-score inferior to −2.5) and/or the presence of fragility fractures (LE 2c; DR B; DA 90%).

Cutpoints for BMD measured by DXA on the lumbar spine and hip[59–61] correspond to normal, values of BMD > −1 SD in relation with the mean of young adults (T-score > −1); osteopenia or low bone mass, BMD values between −1 and −2.5 SD (T-score between −1 and −2.5); OP, BMD values of <−2.5 DE (T-score < −2.5), and established OP when the previous condition is associated to ≥1 osteoporotic fracture. The same cutpoints have been proposed for adult males.[60]

Treatment

What Non-pharmacologic Methods Should we Use?

The following general measures should be recommended to all of the population, with special emphasis on osteoporotic patients: physical exercise, elimination of toxic habits, balanced diet, adequate intake of calcium and vitamin D, preventing falls (LE 1a; DR A; DA 100%).

Moderate to intense physical exercise increases bone mass in young patients,[62–66] as well as in adults, although less intensely.[67] There is no consistent evidence on the effect over bone mass in elderly patients, but performing it reduces the risk of fractures, probably by reducing falls.[68–70]

Avoidance of sedentarism and the performance of moderate physical activity are recommended, taking into account the

Table 3
Degree of Recommendation of Non-pharmacologic Interventions.[a]

Intervention	DMO	Vertebral Fractures	Hip Fractures
Exercise	A[b]	B–C	B–C
Dietary calcium	B	No effect	No effect
Calcium supplements	A	No effect	No effect
Vitamin D and calcium supplements	A	B[c]	B
			A in the elderly
Hip protectors	No studies	No studies	B–C[c]

BMD: Bone.

[a] Degree of recommendation according to CEMB: A: extremely recommended; B: favorable recommendation; C: favorable recommendation but non-conclusive; D: not recommended nor disproved.

[b] Except the elderly.

[c] Contradictory results.

patients' age, physical status and other diseases (LE 5; DR D; DA 100%).

A balanced diet with an adequate consumption of proteins, avoidance of excess salt and moderate sun exposure are also recommended (LE 5; DR D; DA 100%).

A daily calcium intake of 1000 mg and serum 25-OH vitamin D levels of ≥30 ng/ml (75 mmol/l) is recommended (LE 5; DR D; DA 100%).

Sometimes, common diets do not provide these calcium requirements and therefore must be modified or supplemented with pharmacological calcium which, if taken isolatedly, has not shown a significant effect on the reduction of fractures in post-menopausal OP, but help reduce the loss of bone mass.[71–73] In healthy women it has been suggested to increase cardiovascular risk[74,75] and renal lithiasis,[76] but this is a controversial and unclear subject.

Approximately 50% of the osteoporotic population presents low serum concentrations of vitamin D and it is advisable to supplement it with 800–1000 U in all patients. The efficacy of vitamin D supplements in the prevention of fractures is controversial.[77–82] There is evidence that it reduces fractures in institutionalized elderly patients when administered with calcium.[77–82] Additionally, some studies indicate that vitamin D supplements may reduce falls[81] but other do not.[82]

In patients receiving anticatabolic treatment, we recommend an intake of 1000 mg of calcium and 800–1000 U of vitamin D is recommended (LE 1a; DR A; DA 95%).

In the elderly, measures directed at reducing the risk of falls, promoting the use of canes, avoiding psychopharmacologic agents, correcting visual disturbances and adapting living spaces are recommended. In high risk populations, hip protectors may be employed.[83–85]

For more information consult Table 3.

How to Treat an Acute Vertebral Fracture?

The goals of treatment of a vertebral fracture are acute pain control and functional recovery (LE 2b; DR B; DA 100%).

It is very important to inform patients that fractures may take up to 3 months to consolidate and that pain will gradually decrease and improve function.[86]

Oral analgesics, relative rest, orthoses and rehabilitation are the mainstays of treatment (LE 2b; DR B; DA 90%).

Oral analgesics are first-line drugs to reduce the pain of vertebral fractures. The choice should be appropriate to the magnitude of pain. In cases where the pain reaches a significant intensity and conventional painkillers failed, we recommend using opioids.[87,88]

If complete rest is indicated, return to sitting and walking should be accomplished in the shortest possible time. During the acute episode there may be a need for prescription orthotics and, once control of acute pain is achieved, rehabilitation may be useful (LE 5; DR B; DA 95%).

A back brace should be used with caution as excessive spinal immobility could increase OP,[89] and rehabilitation should be directed by a specialist.[90]

In patients with acute vertebral fractures with pain that does not respond to the above measures, vertebroplasty or kyphoplasty may be indicated (LE 1c; DR B; DA 95%).

Several observational studies have shown rapid analgesic effect and reduced period of immobilization in a high percentage of patients, in the short to medium term, but this does not exempt these procedures from secondary.[91–96] Recently, two controlled clinical trials have not shown that vertebroplasty was more effective than other conservative options.[97,98] Another controlled trial has found benefit with the use of vertebroplasty in a subgroup of patients with persistent intense symptoms.[99] Based on the above, patients who are going to undergo these interventions should be carefully selected.[100]

Currently, no generalization can be recommended for vertebroplasty or kyphoplasty to treat osteoporotic vertebral fractures (LE 5; DR D; DA 100%).

What Drugs Should Be Recommended in Osteoporosis?

The objective of pharmacologic treatment of OP is to reduce the risk of fracture (LE 1a; DR A; DA 100%).

Pharmacological intervention is performed with therapeutic agents capable of acting in both phases of bone remodeling. At present, there are three categories of anti-osteoporotic drugs, antiresorptive and anti-catabolic, which inhibit bone resorption by acting on osteoclasts and their precursors, decrease the rate of activation of bone remodeling, increase bone mineral density and preserve the microarchitecture of the bone; and anabolic drugs, which act on osteoblasts or their precursors resulting in increased bone remodeling, with bone formation increased to a greater extent than resorption, which in time increases mass and bone strength, as well as agents with a double mechanism of action where there is a combination of both.[101,102]

For more information regarding their indications, efficacy in relation to the prevention of fractures and adverse events, see Tables 4 and 5.

Antiresorptive Drugs or Anti-catabolic.

Hormone Replacement Therapy. Currently, HRT should not be recommended for the treatment of postmenopausal OP, except for women with early menopause, intense climacteric symptoms or in the case of not being able to administer other OP drugs due to adverse effects or ineffectiveness (LE 1c; DR B; DA 95%).

Estrogens may reduce the incidence of vertebral and peripheral fractures, although drugs such as alendronate are superior.[103,104] There is evidence that hormone replacement therapy (HRT) increases the risk of breast cancer, heart disease, stroke and venous thromboembolism.[105]

Table 4
Characteristics of the Main Drugs Commercialized for Osteoporosis in Spain (According to the Data Sheet, Current to January 2010).[a]

Active Ingredient	Dose and Administration	Indications	Contraindications	Adverse Events[c]
Estrogens	Dose: 1–2 tab Oral Freq: Daily	Prevention of OP in postmenopausal women and increased risk of fractures, who do not tolerate other drugs or have contraindications	Allergies to estrogens or contents. Personal history or suspicion of breast cancer. Malignant estrogen dependent tumors or suspicion Undiagnosed vaginal hemorrhage Untreated endometrial hyperplasia Idiopathic venous thromboembolism or history Known thrombophilia Active arterial or recent thromboembolic disease Pregnancy and lactation Acute liver disease or history of liver disease with altered liver function tests Porphyria	Frequent: vomiting, abdominal pain, anorexia, depression, vaginal hemorrhage, breast discharge, gynecomastia, breast pain, amenorrhea, dismenorrhea, cholestatic hepatitis, jaundice, endometrial hyperplasia, dizzyness, alopecia, headache, ↑ weight Infrequent: changes in libido and humor, edema, alteration in menstrual fluid, vertigo, venous thromboembolism, migraines, breast cancer, vaginitis Rare: pancreatitis, stroke, ovarian cancer, allergic reactions, glucose intolerance, asthma exacerbation, hirsutism
Calcitonin	Dose: 100–200 UI Nasal Freq: daily	Postmenopausal OP and established to ↓ risk of vertebral fractures	Allergy to calcitonin/contents Hypocalcemia Pregnancy and lactation	Very frequent: rhinitis, nasal irritation Frequent: vertigo, headache, disgeusia, ulcerative rhinitis, epistaxis, sinusitis, pharyngitis, diarrhea, abdominal pain, musculoskeletal pain, flushing, fatigue Infrequent: alteration in vision, cough, HTA Rare: neutralizing antibodies to calcitonin, generalized *rash*
Alendronate	Dose: 70 mg Oral Freq: weekly At least 30 min before 1st meal or medication of the day, using only water	Postmenopausal OP	Allergy to alendronate/contents Esophageal abnormalities or other factors delaying esophageal emptying (stenosis, achalasia) Impossibility to remain seated or standing ≥ 30 min) Hypocalcemia Severe renal failure Pregnancy and lactation	Frequent: abdominal pain, dyspepsia, headache, constipation, diarrhea, flatulence, esophageal ulcer, dysphagia, musculoskeletal pain Infrequent: gastritis, esophagitis, esophageal ulcers, GI bleeding Rare: symptomatic hypocalcemia, uveitis, esophageal stenosis, PUH, ON jaw
Etidronate[b]	Dose: 400 mg Oral Freq: 2 week/3 months Empty stomach, at least 2 h before or after food or medication	Postmenopausal vertebral OP with no hormone replacement therapy	Allergy to alendronate/contents Severe renal failure Osteomalacia Pregnancy and lactation	Frequent: abdominal pain, constipation, diarrhea, flatulence, vomiting, muscle cramps in legs Rare: hypersensitivity reactions, pancytopenia, leukopenia, agranulocytosis

Table 4 (*Continued*)

Active Ingredient	Dose and Administration	Indications	Contraindications	Adverse Events[c]
Ibandronate	Dose: 150 mg Oral Freq: monthly After nocturnal fasting (minimum 6 h) and 1 h before breakfast or 1st beverage (different from water) of the day or other drug or oral supplement (including calcium)	Postmenopausal OP and increased risk of fracture	Allergy to ibandronate/contents Esophageal abnormalities or other factors delaying esophageal emptying (stenosis, achalasia) Impossibility to remain seated or standing ≥ 60 min Hypocalcemia Severe renal disease Pregnancy and lactation Special attention if esophageal abnormalities or other factors delay esophageal emptying (stenosis, achalasia), upper gastrointestinal problems or active or recent esophageal bleeding	Frequent: headache, skin rash, esophagitis, gastritis, GERD, dyspepsia, diarrhea, abdominal pain, musculoskeletal pain, cold-like symptoms Infrequent: esophagitis with ulcers or stenosis and dysphagia, vomiting, flatulence, fatigue Rare: duodenitis, urticaria, angioedema
Risedronate	Dose/frequency: 5 mg/d 35 mg/week 75 mg 2 d followed/month Oral At least 30 min before the first food or liquid of the day except water	Postmenopausal OP, for a ↓ risk of vertebral and hip fractures Prevention of OP in women with ↑ tisk of osteoporosis Maintain/↑ bone mass in postmenopausal women and prednisone use for >3 months and ≥7.5 mg/d OP in men with ↑ risk of fractures	Allergy to risedronate/contents Hypocalcemia Severe renal failure Pregnancy and lactation Special attention if: esophageal alterations or other factors delaying esophageal emptying (stenosis, achalasia), active or recent upper gastrointestinal problems, impossibility to remain seated or standing ≥30 min	Frequent: headache, constipation, dyspepsia, abdominal pain, diarrhea, musculoskeletal pain Infrequent: iritis, gastritis, esophagitis, dysphagia, duodenitis, esophageal ulcer Rare: glositis, esophageal stenosis, abnormal liver function tests
Raloxifen	Dose: 60 mg Oral Freq: daily It may be administered at any hour of the day, independent of meals	Treatment and prevention in postmenopausal women OP	Allergy to raloxifen/contents Women who may become pregnant, pregnancy or lactation History/current venous thromboembolic episode (DVT, pulmonary embolism, retinal thrombosis) Liver failure, including cholestasis Severe renal insufficiency Unexplained uterine bleeding Patients with signs or symptoms of endometrial cancer or in treatment for breast cancer	Very frequent: vasodilatation (hot flashes), cold like symptoms Frequent: leg cramps, peripheral edema Infrequent: deep venous thromboembolism, pulmonary embolism, retinal thrombosis, superficial venous thrombosis Rare: thrombocytopenia, nausea, vomiting, abdominal pain, dyspepsia, headache, rash, arterial thrombosis, ↑ blood pressure, breast pain
Bazedoxifen	Dose: 20 mg Oral Freq: daily May be administered at any hour of the day, independent of meals	OP in postmenopausal women with ↑ of risk of fracture	Allergy to bazedoxifen/contents Presence or history of deep venous thromboembolism, lung embolism, and retinal vein thrombosis Potentially fertile women Unexplained uterine bleeding Patients with signs or symptoms of endometrial cancer	Infrequent: hot flashes, muscle spasms Frequent: hypersensitivity, fatigue, oral dryness, urticaria, peripheral edema, ↑ triglycerides, ALT, AST Infrequent: DVT, lung embolism
Teriparatide	Dose: 20 μg SC Freq: daily	OP in postmenopausal women and men with ↑ risk of fracture OP due to steroids in women and men with ↑ risk of fracture	Allergy to calcitonin/contents Pregnancy and lactation Preexistent hypercalcemia Severe renal failure Bone metabolic disease (hyperparathyroidism, Paget) different from primary or steroid associated OP Unexplained elevation of alkaline phosphatase History of external radiation or radiotherapy on the skeleton Bone tumors or bone metastasis	Infrequent: limb pain Frequent: palpitations, anemia, dizzyness, muscle paresthesia, cyatica, vertigo, dyspnea, GERD, ↑ sweating, fatigue, hypercholesterolemia, hypotension, thoracic pain, injection site reaction, headache, depression Infrequent: tachycardia, ↑ weight, heart murmur, ↑ alkalyne phosphatase, enphysema, hemorrhoids, muscle pain, joint pain, hypercalcemia >2.76 mmol/l, hyperuricemia Rare: allergic reaction

Table 4 (*Continued*)

Active Ingredient	Dose and Administration	Indications	Contraindications	Adverse Events[c]
Parathyroid hormone	Dose: 100 μg SC Freq: daily	OP in postmenopausal women with ↑ risk of fracture	Allergy to parathyroid hormone/contents Pregnancy and lactation Preexisting hypercalcemia and other phosphorous calcium metabolic abnormalities Bone metabolic diseases (hyperparathyroidism, Paget) different from primary OP Unexplained elevation of alkaline phosphatase History of external radiation or radiotherapy on the skeleton Severe renal or liver failure	Infrequent: hypercalcemia, hypercalciuria, nausea Frequent: headache, dizzyness, palpitations, injection site erythema, astenia, fatigue, vomiting, constipation, diarrhea, limb pain, paresthesias Infrequent: ↑ alkaline phosphatase, disgeusia, parosmia, abdominal pain, hyperuricemia, anorexia
Strontium ranelate	Dose: 2 g Oral Freq: daily Between meals preferably when going to sleep, minimum 2 h after dinner	Postmenopausal OP to ↓ risk of vertebral and hip fractures	Allergy to ranelate/contents Pregnancy and lactation Severe renal insufficiency Special attention if: ↑ risk of venous thromboembolism	Frequent: Headache, cognition impairment, memory loss, diarrhea, dermatitis, venous thromboembolism, blood creatin-phosphokinase Infrequent: convulsiones Unknown frequency‡: joint pain, fever, peripheral edema, ↑ transaminases, abdominal pain, vomiting, bronchial hyperreactivity
Zolendronic acid	Dose: 5 mg IV Freq: annual	OP in postmenopausal women and males with ↑ risk of fracture OP due to steroid use in postmenopausal women and men with ↑ risk of fracture	Allergy to the active ingredient, any bisphosphonate or any content Hypocalcemia Severe renal failure Pregnancy and lactation	Frequent: hypocalcaemia, headache, dizzyness, hyperemia ocular, atrial fibrillation, vomitus, diarrhea, joint pain Infrequent: infections, fatigue, insomnia, lethargy, paresthesia, anemia, tremors, syncope, vertigo, disgeusia, conjunctivitis, gastritis, esophagitis, dyspepsia, GERD, abdominal pain, constipation Rare: uveitis, episcleritis, iritis Unknown frequency[d]: ON jaw
Denosumab (not marketed)	Dose: 60 mg SC Freq: 6 months	OP in postmenopausal women with ↑ risk of fractures Bone mass loss associated to hormone suppression in men with prostate cancer and ↑ risk of fractures	Allergy to denosumab/contents Hypocalcemia Pregnancy and lactation	Frequent: limb pain, respiratory and urinary tract infection, cyatica, cataracts, constipation, skin rash Infrequent: diverticulitis, cellulitis, otitis, eczema, Rare: hypocalcemia

Tab: tablets; Freq: frequency; HTA: arterial hypertension; iv: intravenous; mg: milligram; μg: microgram; w: weekly; ON: osteonecrosis; OP: osteoporosis; PUH: perforation, ulcers, hemorrhage; GER: gastroesophageal reflux; sc: subcutaneous; DVT: deep venous thrombosis.

[a] Data in this table is obtained from the Data Sheet of the Spanish Drug Agency.

[b] Information unavailable in data sheet. Obtained from Vademecum, Food and Drug Administration (FDA).

[c] Adverse events: very frequent (1 in 10 patients); frequent (1 in 100 patients); infrequent (1 in 1000 and less than 1 in 100); rare (1 in 10,000 and less than 1 in 1000 patients).

[d] Unknown frequency: postmarketing experience.

Table 5
Antifracture Efficacy of Antiosteoporotic Drugs.

Study	Population	Intervention	% FV PLC	% FV INT	RR (CI 95%)	RRR	RAR	NNT
Morphometric vertebral fracture								
Black et al.,[a] 1996, CT double blind placebo controlled, 3 years	n = 2027 ♀ with ↓ BMD and ≥1 FV	Aln = 5 mg/day → 10 mg/day	15%	8%	0.53 (0.40–0.68)	47%	7%	14
Cummings et al.,[b] 1998, CT double blind placebo controlled, 4 years	n = 4432 ♀ with ↓ BMD no FV	Aln = 5 mg/day → 10 mg/d	14.1%	12.3%	0.86 (0.73–1.1)	14%	1.8%	55
Harris et al.,[133] 1999, CT double blind placebo control, 3 years	n = 2458 ♀ pom and ≥1 FV	Ris = 2.5 mg/d	16%	11%	0.36 (0.12–0.60)	64%	5%	20
Reginster et al.,[134] 2000, CT double blind, placebo controlled, 3 years	n = 1226 ♀ and OP pm and ≥2 FV	Ris = 5 mg/d Ris = 2.5 mg/d			0.40 (0.17–0.65)	60%	10%	10
Chesnut et al.,[c] 2005, CT double blind placebo controlled	n = 2946 ♀ and OP pm and 1–4 FV	Ris = 5 mg/d Ibn = 2.5 mg/d	9.6%	4.7%	0.49 (0.22–0.76)	51%	4.9%	20
		Ibn = 20 mg/2 d 12, dose/3 months			0.47 (0.19–0.76)	53%	4.7%	21
Black et al.,[148] 2007, CT double blind placebo controlled, 3 years	n = 7765 ♀ and OP pm (62% FV)	Zol = 1 annual infusion (5 mg)	10%	3.3%	0.30 (0.24–0.38)	70%	7.6%	13
Lyles et al.,[149] 2007, CT double blind placebo controlled, 1,9 years*	n = 2127 patients with FC	Zol = 1 annual infusion (5 mg)	3.8%	1.7%	0.54 (0.32–0.92)	46%	2.1%	48
Chesnut et al.,[107] 2000, CT randomized, 5 years	n = 1255 ♀ and OP pm and FV	Calciton = 100, 200, 300 U/d			0.67 (0.47–0.97)	33%	6.2%	16
Ettinger et al.[111], 1999, CT blind placebo controlled, 3 years	n = 7705 ♀ and OP pm (30% FV)	Ral = 60 mg/d	4.5%	2.3%	0.45 (0.29–0.71)	55%	2.2%	45
Silverman et al.,[116] 2008, CT blind placebo/active controlled, 3 years	n = 7492 ♀ and OP pm (56% FV)	Ral = 120 mg/d Baz = 20 mg/d	21.2% 4.1%	14.7% 2.3%	0.70 (0.56–0.86) 0.58 (0.38–0.89)	30% 42%	6.5% 1.8%	16 55
Cummings et al.,[d] 2010, CT blind placebo controlled, 5 years	n = 8556 ♀ and OP (28% FV)	Baz = 40 mg/d Las = 0.25 ng/d	9.3%	5.6%	0.36 (0.12–0.60)	41%	3.7%	27
Neer et al.,[179] 2001, CT randomized placebo controlled, 21 months*	n = 1637 ♀ pm and FV	Las = 0.50 ng/d Trp = 20 μg/d	14.3%	5%	0.35 (0.22–0.55)	65%	9.3%	11
Greenspan et al.,[182] 2007, EC double blind placebo controlled, 18 months	n = 2532 ♀ and OP pm (20% FV)	Trp = 40 μg/d PTH (1–84) = 100 μg/d	3.4%	1.4%	0.42 (0.24–0.72)	59%	2%	51
Meunier et al.,[e] 2004, CT phase III placebo controlled, 3 years	n = 1649 ♀ and OP pm and ≥1 FV	rSr = 2 g/s	32.8%	20.9%	0.41 (0.48–0.73)	59%	12%	8
Cummings et al.,[163] 2009, EC placebo controlled, 3 years	n = 7868 ♀ and OP pm (23% FV)	Den = 60 mg/6 months	7.2%	2.3%	0.32 (0.26–0.41)	68%	4.9%	20
Hip fracture								
Black et al.,[a] 1996, EC double blind placebo controlled, 3 years	n = 2027 ♀ with ↓ BMD and ≥1 FV	Aln = 5 mg/d → 10 mg/d			0.49 (0.23–0.99)	47%	1%	91

McClung et al.,[f] 2001, CT randomized placebo controlled, 3 years	n = 5445 ♀ (70–79 years) OP and 1 FR no hip fx	Ris = 2.5 mg/d	0.50 (0.30–0.90)	50%	1%	99
		Ris = 5 mg/d				
	n = 3886 ♀ ≥80 years and ≥1 FR no hip fx or ↓ BMD		0.80 (0.60–1.20)	NS	NS	NA
Black et al.,[148] 2007, CT double blind placebo controlled, 3 years	n = 7765 ♀ and OP pm (62% FV)	Zol = 1 annual infusion (5 mg)	0.59 (0.42–0.83)	41%	1.1%	91
Lyles et al.,[149] 2007, CT double blind placebo controlled, 1.9 years[*]	n = 2127 patients with FC	Zol = 1 annual infusion (5 mg)	NS	NS	NS	NA
Reginster et al.,[196] 2005, CT double blind placebo controlled, 5 years[**]	n = 5091 ♀ and OP pm (55% FV)	rSr = 2 g/d	NS	NS	NS	NA
Cummings 2009,[13] CT randomized placebo controlled, 3 years	n = 7858 ♀ and OP pm	Den = 60 mg/6 months	0.60 (0.37–0.97)	40%	0.5%	200

Aln: alendronate; Baz: bazadoxifene; Calciton: calcitonin; BMD: bone mineral density; CT: Clinical trial; FC: fractura de cadera; no hip FR: nkeletal risk factor for hip fracture; FV: vertebral fracture; CI: confidence interval; INT: intervention; mg: milligram; μg: microgram; ng: nanogram; Las: lasofoxifene; NA: not applicable; NNT: number needed to treat; NS: no statistical significance; OP: osteoporosis; PLC: placebo; pm: posmenopausal; Ral: raloxifen; Ris: risedronate; RR: relative risk; RRA: Absolute risk reduction; RRR: relative risk reduction; rSr: strontium ranelate; Trp: teriparatide; Zol: zoledronate.

RR: incidence in exposed/incidence in non-exposed; the probability of an event occurring (i.e. fractures). If <1, the intervention is protective.

RRR: (1-RR)100; if an intervention reduces the risk of an event, the RRR expresses the percentage in which the intervention would contribute to the reduction of the risk of the event relative to that occurring in the control group.

RAR: (incidence in non-exposed – incidence in exposed) × 100; refers to the percentage of events that could be avoided by intervention. If 0.40 (i.e. 40%), of every 100 persons treated with the intervention could lead to the avoidance of 40 events.

NNT: 1/RAR; necessary number of patients that should be treated to avoid an event.

[*] Mean of follow up.

[**] In a subgroup of 1.977 women with a very elevated risk of fracture (mean age 80) there was a reduction in risk of 36% (P = .046).

[a] Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomized 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.

[b] 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.

[c] Chesnut CH, Ettinger MP, Miller PD, Baylink DJ, Emkey R, Harris ST, et al. Ibandronate produces significant, similar antifracture efficacy in North American and European women: new clinical findings from BONE. Curr Med Res Opin 2005;21:391–401.

[d] Cummings SR, Ensrud K, Delmas PD, LaCroix AZ, Vukicevic S, Reid DM, et al. Lasofoxifene in postmenopausal women with osteoporosis. N Engl J Med 2010;362:686–96.

[e] Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004;350:459–68.

[f] 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.

Table 6
Preventive Measures of Osteonecrosis of the Jaw of the Spanish Agency of Drugs and Health Products.

It is important that the decision to start treatment with BF be performed after benefits are evaluated (prevention of fragility fractures) and risks for the individual patient taken into account when the treatment is to be maintained in the long term, a situation that can be a risk factor for OJ
The recommendations of existing clinical guidelines published by the health services of the autonomous communities and scientific societies must be considered
Having decided on the need for treatment with BF, for dental preventive measures are to be carried out:
 – An initial assessment of the oral health status of the patient and regular dental checks must be performed. In addition, dental attention should occur as soon as symptoms such as pain or oral inflammation appear
 – When dental work is needed, it should be as conservative as possible
 – If extractions or invasive procedures are necessary it is recommended that the dentist refer the patient to centers experienced in this type of problem
Patients who develop OJ should receive appropriate treatment by experienced professionals
For effective implementation of these recommendations it is essential to develop local guidelines and protocols shared by different means and levels of care involved in patient monitoring

BF: bisphosphonates; OJ: osteonecrosis of the jaw.

Calcitonin. Calcitonin can be administered as a preventive measure and as a second line treatment of postmenopausal OP, after bisphosphonates, and may be indicated in the treatment of recent symptomatic vertebral fractures (LE 1c; DR B; DA 70%).

Calcitonin prevents loss of BMD in the spine,[106] reduces the risk of new vertebral fractures in postmenopausal women with a history of vertebral fractures, but not the risk of peripheral fractures.[107] It also has an analgesic effect in patients with vertebral fractures.[108] Its effectiveness seems to be maintained in the long term.

Raloxifene. Raloxifene is recommended as second line treatment of postmenopausal OP (LE 1a; DR A; DA 90%).

Raloxifene decreases the loss of BMD[109] and reduces vertebral fracture risk in women with postmenopausal OP with and without fractures, but does not reduce the risk of non-vertebral fractures.[110,111] In addition, it decreases serum cholesterol and low-density lipoprotein cholesterol, although it does not seem to reduce the risk of heart disease. It also decreases the incidence of estrogen receptor positive breast cancer,[112] but is associated with increased thromboembolic events.[113,114]

Bazedoxifene. Bazedoxifene is an alternative to raloxifene in the treatment of postmenopausal OP (LE 1c; DR B; DA 83%).

Bazedoxifene has demonstrated its protective action in BMD loss and reducing vertebral fractures in postmenopausal women with OP and, like raloxifene, has shown efficacy in reducing vertebral fractures, except in high-risk fracture population (post hoc). At a dose of 20 mg the most common side effects, cramps and hot flashes, were matched to raloxifene and deep vein thrombosis was observed in 0.4 and 0.2% of patients receiving bazedoxifene and placebo,[115,116] respectively.

Bisphosphonates. The panel recommends bisphosphonates (BF) as first-line drugs in the treatment of OP (LE 1a; DR A; DA 100%).

BF are currently the most widely used drugs in the treatment of OP.[117] Its anti-fracture effectiveness has been amply demonstrated[118–121] and are generally well tolerated. On the other hand, the rate of adherence to treatment in the medium or long term (1 year) is low, between 47% in the monthly presentation and 30% in the weekly presentation. Therefore, measures aimed at improving patient compliance must be implemented.[122]

We do not have enough evidence to recommend one drug over another, so the choice will be based on other factors such as dosage, characteristics, patient preferences and physician experience with the use of BF.

There is no general agreement on the optimal duration of treatment, although an average period of 5 years is advised, after which its continuation, suspension or discontinuation or replacement by another drug should be evaluated, taking into account the estimated residual risk of fracture at the time.[123]

Before starting treatment, an adequate calcium and vitamin D supplementation should be ensured as well as basic guidelines to follow: BF should be taken in the morning (standing or seated with a glass of 200 ml of water), fasting since the previous day and waiting at least half an hour (1 h for monthly dose) before eating solid foods or drinking (except water).

The different BF approved for use in OP will now be discussed. For more information, see Tables 4 and 5.

Etidronate. Etidronate increases bone mass and moderately reduces the risk of vertebral fractures in women with OP, with a duration of 4 years,[124,125] but does not significantly reduce the risk of hip and non-vertebral fractures. Its continued use can cause osteomalacia.[126]

Alendronate. Alendronate significantly reduces the risk of vertebral and non-vertebral fractures, including the hip. Currently, the most common form of administration is a once weekly dosing of 70 mg. Although optimal duration of treatment[127] was observed when the drug was discontinued after 5 years of treatment, 5 years later a decrease in lumbar and hip BMD was seen, 3.7 and 2.4% compared with when it was continued for 10 years and remodeling markers increased, with no differences in fracture incidence between groups (except clinical vertebral fractures), so treatment may be maintained for 10 years,[128] but this also opens the possibility of a "therapeutic holiday" at 5 years due to the residual effect of the drug on the risk of fracture.

There is a presentation containing alendronate and vitamin D, and generic alendronate sodium with a similar bioequivalence with the brand product. Slight differences were observed in the in vitro decay[129] and esophageal transit,[130] raising doubts about some generic formulations, which may have lower bioavailability and potency, and greater ability to cause esophageal adverse effects.[131] Because generic prescribing is a central objective of health systems, independent studies are needed for the clinician to prescribe generics without reserve.[132]

Risedronate. Risedronate is effective in reducing the risk of vertebral and non-vertebral fractures, including hip and postmenopausal OP in women with and without previous fractures.[133–137] The most commonly used dosage is 35 mg/week orally[138] and there is also a presentation that allows its administration in doses of 75 mg monthly given in 2 consecutive days. There is also a generic preparation.

Ibandronate. Ibandronate is effective in preventing vertebral fractures at a dose of 2.5 mg/day orally in postmenopausal women with OP with and without prior fractures. Efficacy in non-vertebral fractures is significant only in the subgroup with higher risk. It has no efficacy in hip fracture. The bioequivalent single dose of 150 mg may be used monthly.[120,139–144] It may also be administered as an intravenous injection of 3 mg every 3 or 4 months,[145] which has an acceptable safety profile and may be performed as an outpatient procedure,[146] as an option for patients with obvious risk of compliance failure.[147]

Zoledronate. This BF is marketed for intravenous use only. Its standard dose is annually, 5 mg, day. It is effective in reducing

the incidence of clinical vertebral fractures, morphometric, non-vertebral and hip fractures over 3 years.[148] It also reduces overall mortality in patients with hip fractures,[149] without a clear explanation in this respect.[150] It is an alternative for patients with OP and increased risk of fractures or those who do not tolerate or are contraindicated oral BF.

Adverse Events of Bisphosphonates. The overall safety profile of BF is acceptable (see Table 4). However, a number of adverse events potentially related to BF have been reported, which may be serious.[151] Although it is not the purpose of this paper to perform a comprehensive review on the subject, we will discuss some relevant aspects.

The panel, on the basis of available evidence does not believe that there is a need to stop BF for dental procedures in relation to the risk of osteonecrosis (LE 2a; DR B; DA 95%).

There have been reports of osteonecrosis of the jaw (OJ), but its incidence in patients with OP is very low (1/10 000 1:100 000), and it has been associated with prolonged use of BF.[152,153] Among the recommendations issued in this regard, we point out those published by AEMyPS (Table 6), to which we refer the reader.[154] These include a proper oral hygiene and review, and if invasive dental procedures are contemplated (tooth extraction or implant), it is better to complete the healing process before initiating BF. On the other hand, there is controversy about the approach to be followed in those patients already taking BF. The panel believes that discontinuation of 3–6 months should be assessed individually, weighing risks and benefits, since the benefit of this practice has not been evaluated scientifically. It has also suggested the use of marker CTX, which above a certain threshold may be associated with increased risk of OJ,[155] but there is no consistent evidence to support it.[156]

Attention should be paid to the occurrence of thigh pain, especially in patients with prolonged treatment with BF, and X-rays used to rule out stress fractures (and try to prevent progress) or identify atypical fractures (LE 2a; DR B; DA 95%).

There have been reports of atypical fractures (sub-trochanteric/femur shaft), with a very low incidence (although it could be underestimated). They are usually bilateral, often accompanied of pain of the thighs and/or groin, and are sometimes associated with some comorbidities and/or medications such as HRT, proton pump inhibitors or glucocorticoids.[157–159]

There is an association between the development of atrial fibrillation and the use of intravenous zoledronate. There are isolated cases of esophageal cancer in patients taking oral BF, though this association has not been confirmed. Musculoskeletal pain, kidney damage and hepatotoxicity associated to BF are exceptional and rarely cause drug withdrawal.[160]

If significant adverse events occur with the use of BF, the panel recommended suspending BF and evaluating the start of a drug with a different mechanism of action (LE 5; DR D; DA 95%).

If adverse events are significant, such as OJ, occur and although there is no scientific evidence indicating that the withdrawal of the drug improves the outcome of the process, it is prudent to suspend and evaluate the indication of drugs with different mechanisms of action from BF.

Denosumab. Denosumab may be recommended as first-line therapy for the treatment of postmenopausal OP with risk of fracture (LE 1b; DR A; DA 95%).

Denosumab is a monoclonal antibody that inhibits the formation, activation and survival of osteoclasts. It is therefore, an antiresorptive drug approved for the treatment of postmenopausal OP with a high risk of fracture, at a dose of 60 mg/6 months subcutaneously[161,162] (Table 4).

Denosumab has been reported to reduce the risk of new vertebral fractures by 68% compared to placebo after 3 years of treatment (RR = 0.32, 95%, 0.26–0.41), the risk of hip fractures in 40% (RR = 0.60, 95% CI, 0.37–0.97), non-vertebral fractures by 20% (RR = 0.80, 95% CI, 0.67–0.95) and multiple fractures (≥2)[163] (see Table 5). Its effect is reversible since the inhibition that occurs in bone resorption disappears rapidly as serum levels decline.[164,165] It is effective in patients previously treated with alendronate, even without a rest interval,[166] and reduced levels of biomarkers of bone turnover, particularly resorption markers, fall faster and more intensely than with alendronate.[167,168] It also produces marked increases in BMD at the lumbar spine, total hip and femoral neck, distal radius and total body, from 12 months of treatment onward, with an effect greater than alendronate and far superior to placebo.[163,164,167–171]

The overall incidence of adverse events was similar to placebo in terms of general infections, cancer, hypocalcemia and cardiovascular events,[163,164,167–170] but described a slight increase in urinary tract and skin infections[163,172] (see Table 4).

Anabolic Drugs.

Parathyroid Hormone Analogs. PTH analogs can be recommended as first-line drugs for the treatment of OP with a high risk of fracture (LE 1b; DR A; DA 90%).

PTH's osteoforming[173,174] effects can prolong the life of osteoblasts, whether administered complete[175] or as an amino fraction.[176] There are two molecules on the market (see Table 4): teriparatide (Trp) or 1–34 rhPTH used at doses 20 mg/day subcutaneously, and the rhPTH 1–84 (PTH 1–84) at doses of 100 mg/day subcutaneously. They are, therefore, osteoforming drugs whose effect is primarily anabolic. The main difference is that Trp pharmacokinetics are found elevated within 3 h, while the PTH 1–84 lasts up to 9 h.[177,178]

PTH 1–34 reduces the incidence of vertebral and nonvertebral fractures but not hip fractures, both as monotherapy and associated with HRT.[179,180,181] PTH 1–84 shows effectiveness in reducing vertebral fractures in women with and without previous fracture.[182] Both are superior to alendronate in increasing BMD[183–186] (Table 5).

There is a limit of the duration of therapy to 2 years, both for Trp as for PTH 1–84, due to the occurrence of osteosarcomas in Fischer rats treated with Trp[179,187] for 2 years, although in humans this association is not proven.[188–190]

Adverse reactions generally are not serious with either drug. Mainly hypercalcemia and hypercalciuria[177–179,182,191,192] occur, so it is advisable to monitor the levels of calcium in blood and urine in patients starting treatment. This monitoring of serum and urinary calcium during treatment is necessary only with PTH 1–84. For more information, see Table 4.

Mixed Action Drugs.

Strontium Ranelate. Strontium ranelate (RSR) may be recommended as a first-line drug for the treatment of postmenopausal OP to reduce the risk of vertebral, non-vertebral and hip fractures in a subgroup at high risk (>70 years and femoral neck DXA T ≤3) (LE 1b; DR A; DA 90%).

RSR produces increased bone formation and decreased resorption in moderation, which translates into an actual increase in bone mass and strength.[193–195] It is indicated for the treatment of OP in postmenopausal women (Table 4).

BMD increased from 12.7% to 14.4% in the lumbar spine, 5.7% to 8.2% in the femoral neck and 7.1% to 9.8% in the total hip.[196,197] However, some of this increase is due to the deposition of strontium in bone, so the increase is 50% of what is referred. This effect is maintained for 5 years.[198] RSR reduces vertebral fractures by 41% (effect detected in the first year), not 16% vertebral, non-vertebral fractures by 19% higher and hip fractures by 36% in a high-risk subgroup after 3 years of treatment (Table 5). This benefit remains up to 8 years afterward.[199]

Although the possibility of an increased tendency for deep vein thrombosis and pulmonary embolism exists, it is not clearly

Table 7
Drugs in Development.

Resorption inhibiting drugs
1. Cathepsin K inhibition
Odanacatib
Relacatib
MK-0674
2. Integrin inhibition
3. Src-kinase inhibition
4. Acidification mechanism inhibition
Anabolic drugs
1. Wnt signaling pathway modulation
Anti-sclerostin antibodies (AMG-785)
sFRP inhibitors
2. Activin inhibition (ACE-011)

demonstrated.[200] The data sheet recommends caution in patients at risk for these events. There have also been cases reported of DRESS syndrome[201,202] and, although very rare, it is recommended that patients be informed to discontinue treatment if a rash appears and seek medical attention. The rest of the adverse events are generally mild and transient[203] (see Table 4).

Drugs in Development

Table 7 shows the drugs that can potentially increase the currently available arsenal against OP. Antiresorptive drug development is more advanced than that of anabolic drugs.

Some seem to inhibit cathepsin K, whose main function is to degrade bone matrix, rapidly, selectively and reversibly[204–206]: odanacatib and MK-0674.[207]

Also in development are drugs capable of inhibiting integrins,[208] Src kinase[209] or interfere with the acidification process (chloride channel, vacuolar ATP-ase).[210]

Developing anabolic drugs act on two regulatory elements of osteoblastic activity: the Wnt signaling pathway and activins.[211–217]

Combination and Sequential Therapy

We recommend antiresorptive therapy is instituted at the end of the 24 months cycle of anabolic drug administration and it is not recommended concomitantly with BF (LE 1b; DR A; DA 100%).

PTH analogs may be administered sequentially with bone resorption inhibitors or mixed-acting drugs.[180,181,184,218–222] However, the use of raloxifene or estrogen[180,181,220] does not seem to inhibit their action. The fact of having received prior treatment with antiresorptive does not appear to alter the anabolic effect of Trp.[223,224]

Combined treatment with antiresorptives cannot be recommended across the board, although their use might be justified in highly selected cases (LE 5; DR D; DA 85%).

Multiple associations were tested: etidronate and estrogen,[225] alendronate,[226] risedronate[227] or Trp,[180,221] raloxifene plus alendronate,[109] Trp[228] or PTH (1–84) with raloxifene[184,218] and Trp.[220] The combined administration of these drugs achieved, in most cases, a greater increase in BMD than monotherapy, but there is no clear evidence that it improves anti-fracture efficacy. Only the concomitant use of estrogen and Tpr has shown a significant reduction of new vertebral fractures.[180] However, combinations of these drugs are well-tolerated and no adverse effects could be seen on bone tissue.

What Patients Should Undergo Drug Treatment?

Initiate pharmacological treatment (LE 5; DR D; DA 74%):

1. Postmenopausal women:
– Low-trauma fracture intensity, regardless of the value of BMD.

– OP (BMD below −2.5 SD in the *T*-score of the spine and/or femur) with or without fractures, assessing risk factors.
– The use of FRAX algorithm[A] may help in decision making when considering the establishment of drug treatment.

Evaluate pharmacologic treatment:

– Early menopause (<45 years) by DXA and/or other risk factors.
– Osteopenia (BMD between −1 and −2.5 SD on the *T*-score) Treatment is reserved for very specific cases, as would be intense osteopenias near the OP range in younger women with high risk factors for fracture.

Table 1 shows the most important risk factors[12]; some may be by themselves an indication for treatment, such as administration of glucocorticoids in doses higher than 5 mg/day for over 3 months.

How Long Should Treatment Be Maintained and How Does One Assess its Effectiveness?

Treatment of OP, unless contraindicated, should be maintained for years (LE 5; DR D; DA 100%).

The two PTH analogs can be administered only for 24 months. The rest have maintained their efficacy and safety for varying periods: 10 years for alendronate, risedronate and etidronate up to 7 years ibandronate 3 years,[139,148] raloxifene 8 years,[229] zoledronate 6 years,[230] calcitonin 5 years,[107] denosumab 3 years,[163] and rSr 8 years.[199] We must remember that there have been reports of atypical fractures with prolonged treatment with BF.[231]

Anti-osteoporotic drugs reduce but do not eliminate the risk of new fractures, so that treatment can be effective even though the patient has new fractures.

It is recommended to assess response to treatment by central DXA every 2–3 years regardless of the type of drug (LE 5; DR D; DA 75%).

At the beginning of treatment it may be desirable to repeat a central DXA at one year and, in situations of high risk for fracture such as transplanted patients, high dose steroids and multiple vertebral fractures, every 6 or 12 months (LE 5; DR D; DA 75%).

Bone turnover markers may be useful to assess the effectiveness of early treatment and to help improve its persistence (LE 2c; DR C; DA 80%).

It is recommended to evaluate the therapeutic response to anti-osteoporotic drugs with central DXA, taking into account the characteristics of each patient.[22,23,232–235] Bone turnover markers may be useful to assess its early efficacy.[22–24]

The appearance of new fractures with a decrease in BMD values over 2%, which corresponds to the minimum significant change after at least one year of treatment, may be seen as an inadequate therapeutic response. If there is only one of those two situations, the response is probably inadequate. By contrast, an appropriate response to treatment will be defined by the absence of these negative circumstances.[24]

What Is the Most Appropriate Anti-osteoporotic Drug?

The selection of a specific drug for a patient with OP should be based on: (a) evidence of efficacy in patients with the same characteristics, (b) absence of contraindications, (c) real possibility of compliance; (d) adverse events, and (e) efficiency of prescription.

Efficiency should be considered as a requirement in its entirety and not just by the price of the drug, given that factors such as costs associated with its administration or affect its anti-fracture effectiveness reflect on treatment costs. The prescription must be viable and take into account other associated treatments and empower the patient to achieve optimal compliance.

The patient must be informed to participate in decisions making regarding the selection of a particular drug (LE 5; DR D; DA 100%).

Male Osteoporosis

In the male, the densitometic diagnostic approach of OP is the same as in women (LE 5; DR D; DA 95%).

OP is a common male problem, and has a similar or higher morbidity than in women. The prevalence of densitometry OP in Spanish men >20 years of age is estimated between 2.5% and 4.2%,[236,237] that of radiographic vertebral fractures is 20% in men <65 years and in 25% >65 years,[238] and the incidence of hip fracture is 73–115/100 000 inhabitants >50 years.[239,240] However, its diagnostic suspicion is usually low, unless there are clear risk factors (steroids, chronic liver disease, chronic obstructive pulmonary disease, etc.).

In males, it is advisable to perform a basic study of the most common causes of secondary OP through a clinical history and the required laboratory tests (LE 5; DR D; DA 100%).

There are differences in etiopathogenesis[241] and in risk factors between men and women. Secondary OP is more common in males.[241–244] In Spain, the most common cause is hypogonadism (10%–20%),[242] followed by chronic corticosteroid therapy and alcohol abuse, usually associated with liver disease.[245,246]

In the treatment of male OP the same general measures as in women, and the use of drugs approved for this purpose are recommended (LE 5; DR D; DA 75%).

Currently, drugs that have indications for male OP are risedronate,[247] zoledronate[248] and Trp,[249] with the same dosage and schedule as in female OP.

It is recommended that monitoring, evaluation and duration of treatment be the same as in female OP (LE 5; DR D; DA 95%).

Premenopausal Osteoporosis

In premenopausal women, the diagnostic criteria differ according to DXA. Thus, the value of BMD should be applied using the Z scale and the diagnosis of "low bone mass" is set if Z scale <-2 SD. The presence of fragility fractures, particularly associated with low bone mass, allows the diagnosis of OP (LE 5; DR D; DA 87%).[250,251]

About 50% of cases are associated processes, and a comprehensive study is recommended to identify the underlying cause (LE 5; DR D; DA 91%).

The most common causes are glucocorticoid treatment or Cushing's disease, pregnancy, osteogenesis imperfecta or estrogen deficiency, anorexia nervosa and/or intestinal malabsorptive diseases. In addition, it is known that idiopathic forms are frequent associated with hypercalciuria and a family history of OP.

The therapeutic approach includes an adequate intake of calcium and vitamin D, exercise, avoidance of tobacco and alcohol,[252] and treating the underlying cause.

In patients who only show a decrease in BMD with no other risk factors, pharmacologic intervention is usually not required, although it is advisable to monitor these patients (LE 5; DR D; DA 96%).

Drug therapy is considered in specific cases such as in patients with fractures or in those with associated factors, especially treatment with glucocorticoids and hypogonadism. In these cases, BF, estrogen, calcitonin, PTH treatment or Trp may be indicated.

BF in women of childbearing potential should be used with caution, as there is few data on its safety (LE 5; DR D; DA 96%).

Therefore, contraceptive measures should be indicated in patients undergoing such treatment.[7,253]

Glucocorticoid-induced Osteoporosis

Glucocorticoids (GC) are the most common cause of secondary OP, representing up to 25% of all cases of OP.[254] It is also estimated that fractures occur in one third of those treated after one year and 50% at some point in their evolution.[255]

The risk of fracture caused by GC depends on several factors: BMD at the beginning of treatment, daily and accumulated dose, and underlying disease. BMD loss is rapid, especially during the first year, even at low doses, and trabecular bone is most affected.[256] There are individual characteristics that make these patients more vulnerable to lower doses of corticosteroids and develop osteoporosis more than others with higher doses.[257] Due to the great changes that occur on the bone microarchitecture, fractures produced by GC appear with BMD values that are higher than in other types of OP, so that the threshold for intervention should be located above the T-score of postmenopausal OP.

The prevention and treatment of OP should begin as soon as possible. Preventive measures should be undertaken in patients using doses equivalent to ≥ 5 mg/day of prednisone for more than 3 months. If there is a history of fragility fractures or the patient is over 65, the start of drug treatment is recommended. In those that do not have fractures and are less than 65 years old, a DXA is indicated and if this presents a $T < -1.5$ SD, drug treatment is indicated.[258]

Preventive measures: in patients who are to take prolonged GC the following should be considered: (a) use the lowest GC dose possible and as suspend it as quickly as possible, (b) avoidance of the use of tobacco/alcohol, a balanced diet with adequate calcium intake, etc., (c) prevention of muscle loss and falls with a program of proper nutrition and exercise, (d) supplementation with calcium and vitamin D (LE 5; DR D; DA 90%).

Drug therapy: BF (alendronate, risedronate or zoledronate) and Trp have proven effective in the prevention and treatment of OP due to GC.[258–267] All treatments should always be supplemented with adequate doses of calcium and vitamin D. In patients at a high risk of fracture, treatment may be started with osteoforming agents (Trp) followed by BF. Treatment with thiazides (25 mg/day) should be considered in patients with hypercalciuria.

According to technical data, drugs for corticosteroid associated OP are Trp, risedronate and zoledronate (see Table 4).

Discussion

As commented in the introduction, the objective of this document is to update on advances in the different clinical aspects of osteoporosis: diagnosis, evaluation, follow up and treatment. This has been a joint effort by members of the panel and the RU of SER and has entailed a large systematic review on different topics of interest and has provided the necessary scientific strength to emit recommendations with a degree of evidence but also of consensus, providing the reader a more objective evaluation of these recommendations.

This paper highlights a number of new contributions in the field and the inclusion of some tables that complement the various recommendations. On the one hand, we have expanded the areas of clinical interest with pre-menopausal osteoporosis, male osteoporosis and osteoporosis secondary to steroids. Furthermore, we have added two new antiresorptive drugs: bazedoxiphen and denosumab. We have also included the results of systematic reviews aimed at answering the following questions: the relationship of biphosphonates to osteonecrosis of the jaw and atypical fractures of the femur, the relationship between calcium supplementation and the occurrence of kidney stones, and the degree of evidence of different algorithms to calculate the risk of fracture. And finally, we

have joined the tables that summarize the effectiveness of different drugs in reducing fractures and current approved indications (data sheets), dosage, adverse events and interactions with other drugs.

It is also important to emphasize some observations in this document. The first is the fact that the evaluation of the risk for fracture was one of the topics that generated a greater debate among the panel members, because it had been intended that the same criteria as previous documents or the FRAX© algorithm were to be used. The panel's solution was to expose both options so that the reader may have the largest information possible and so that it may help in identifying patients at risk for osteoporosis.

The degree of evidence of the different drugs is based on its "main studies" and in most of them the primary objective was the reduction in vertebral fractures, noting that the efficacy in the reduction of non-vertebral and hip fractures does not represent the same degree of evidence. Only rSr and risedronate have carried out studies in which the primary objective has been non-vertebral and hip fractures, respectively.

As stated in this document and, according to the European Drug Agency, indications for the use of bazedoxiphen and denosumab are for women with high risk of fracture, contrasting with the analysis of their main studies which were based in populations with a majority of patients without previous fracture, making them moderate in risk. It is necessary to take this into account when choosing appropriate treatment.

In conclusion, the recommendations of this document constitute a background for management of OP. They are general norms that must be individualized in a role we, as professionals, must assume.

Disclosures

References

1. CEBM CfEBM. Oxford centre for evidence-based medicine-levels of evidence (March 2009). Available from: http://www.cebm.net/index.aspx?o=1025; 2009 [updated March 2009; cited in November 2009].
2. NIH Consensus Development Panel on Osteoporosis Prevention D, and Therapy. Osteoporosis prevention, diagnosis, and therapy. JAMA. 2001;285:785–95.
3. National Osteoporosis Guideline Group. NOGG. Sheffield: World Health Organization Collaborating Centre for metabolic bone diseases; Available from: http://www.shef.ac.uk/NOGG/; 2010 [updated January 2010; cited in March 2011].
4. Robinson CM, Royds M, Abraham A, McQueen MM, Court-Brown CM, Christie J. Refractures in patients at least forty-five years old. A prospective analysis of twenty-two thousand and sixty patients. J Bone Joint Surg Am. 2002;84-A:1528–33.
5. World Health Organization. Guidelines for preclinical evaluation and clinical trials in osteoporosis. 1998.
6. Melton 3rd LJ, Thamer M, Ray NF, Chan JK, Chesnut 3rd CH, Einhorn TA, et al. Fractures attributable to osteoporosis: report from the National Osteoporosis Foundation. J Bone Miner Res. 1997;12:16–23.
7. Brown JP, Josse RG. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ. 2002;167 Suppl. 10:S1–34.
8. Scottish Intercollegiate Guidelines Network. Available from: www.sign.ac.uk [updated May 2011; cited in May 2011].
9. Melton 3rd LJ. How many women have osteoporosis now? J Bone Miner Res. 1995;10:175–7.
10. Herrera A, Cáceres E, Caeiro JR, Canales V, Curto JM, Fernández N, et al. Recomendaciones de manejo clínico del paciente mayor de 50 años con fractura osteoporótica. REEMO. 2003;12:125–8.
11. 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.
12. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int. 2008;19:385–97.
13. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet. 2002;359:1929–36.
14. Kanterewicz E. Anamnesis. Exploración física. Estudio analítico. In: Arboleya L, Pérez L, editors. Manual de enfermedades óseas Sociedad Española de Reumatología. Madrid: Editorial Médica Panamericana; 2010. p. 65–70.
15. Cooper C, O'Neill T, Silman A. The epidemiology of vertebral fractures. European Vertebral Osteoporosis Study Group. Bone. 1993;14 Suppl. 1:S89–97.
16. De Laet C, Kanis JA, Oden A, Johanson H, Johnell O, Delmas P, et al. Body mass index as a predictor of fracture risk: a meta-analysis. Osteoporos Int. 2005;16:1330–8.
17. Brown JP, Fortier M. Canadian consensus conference on osteoporosis, 2006 update. JOGC. 2006:S95–112.
18. Tannenbaum C, Clark J, Schwartzman K, Wallenstein S, Lapinski R, Meier D, et al. Yield of laboratory testing to identify secondary contributors to osteoporosis in otherwise healthy women. J Clin Endocrinol Metab. 2002;87:4431–7.
19. Cerda Gabaroi D, Peris P, Monegal A, Albaladejo C, Martinez MA, Muxi A, et al. Search for hidden secondary causes in postmenopausal women with osteoporosis. Menopause. 2010;17:135–9.
20. Eastell R, Hannon RA. Biomarkers of bone health and osteoporosis risk. Proc Nutr Soc. 2008;67:157–62.
21. Garnero P. Bone markers in osteoporosis. Curr Osteoporos Rep. 2009;7:84–90.
22. Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J. The use of biochemical markers of bone turnover in osteoporosis. Committee of Scientific Advisors of the International Osteoporosis Foundation. Osteoporos Int. 2000;11 Suppl. 6:S2–17.
23. Eastell R, Krege JH, Chen P, Glass EV, Reginster JY. Development of an algorithm for using PINP to monitor treatment of patients with teriparatide. Curr Med Res Opin. 2006;22:61–6.
24. Diez-Perez A, Gonzalez-Macias J. Inadequate responders to osteoporosis treatment: proposal for an operational definition. Osteoporos Int. 2008;19:1511–6.
25. Klotzbuecher CM, Ross PD, Landsman PB, Abbott 3rd TA, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res. 2000;15:721–39.
26. Naves M, Diaz-Lopez JB, Gomez C, Rodriguez-Rebollar A, Rodriguez-Garcia M, Cannata-Andia JB. The effect of vertebral fracture as a risk factor for osteoporotic fracture and mortality in a Spanish population. Osteoporos Int. 2003;14:520–4.
27. Naves M, Diaz-Lopez JB, Gomez C, Rodriguez-Rebollar A, Cannata-Andia JB. Determinants of incidence of osteoporotic fractures in the female Spanish population older than 50. Osteoporos Int. 2005;16:2013–7.
28. Kanis JA, Borgstrom F, De Laet C, Johansson H, Johnell O, Jonsson B, et al. Assessment of fracture risk. Osteoporos Int. 2005;16:581–9.
29. Hasserius R, Karlsson MK, Nilsson BE, Redlund-Johnell I, Johnell O. Prevalent vertebral deformities predict increased mortality and increased fracture rate in both men and women: a 10-year population-based study of 598 individuals from the Swedish cohort in the European Vertebral Osteoporosis Study. Osteoporos Int. 2003;14:61–8.
30. Grados F, Fechtenbaum J, Flipon E, Kolta S, Roux C, Fardellone P. Radiographic methods for evaluating osteoporotic vertebral fractures. Joint Bone Spine. 2009;76:241–7.
31. U.S. Preventive Services Task Force. Guide to clinical preventive services. Available from: http://www.ahrq.gov/clinic/uspstfix.htm; 2010 [updated 2010; cited in May 2011].
32. National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. Available from: www.nof.org; 2008 [updated 2008; cited in April 2011].
33. International Society for Clinical Densitometry (ISCD). Canadian physician pocket guide to BMD testing. Available from: http://www.iscd.org/Visitors/PDFs/ISCD-CANADIANPanelOfficialPositions-BMDcard.pdf; 2004 [updated 2004; cited in April 2011].
34. Lewiecki EM, Baim S, Langman CB, Bilezikian JP. The official positions of the International Society for Clinical Densitometry: perceptions and commentary. J Clin Densitom. 2009;12:267–71.
35. Panel de expertos del Documento de Consenso 2006 de la SER sobre la osteoporosis posmenopáusica. Documento de Consenso 2006 de la Sociedad Española de Reumatología sobre la osteoporosis posmenopáusica. Reumatol Clin. 2007;3 Suppl. 1:26–32.
36. Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster JY, Borgstrom F, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2008;19:399–428.
37. González Macías J, Guañabens Gay N, Gómez Alonso C, Del Río Barquero L, Muñoz Torres M, Delgado M, et al. Guías de práctica clínica en la osteoporosis postmenopáuisca, glucocorticoidea y del varón. Sociedad Española de Investigación Ósea y del Metabolismo Mineral. Rev Clin Esp. 2008;28 Suppl. 1:1–24.
38. Kanis JA, Melton 3rd LJ, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res. 1994;9:1137–41.
39. Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A. Case finding for the management of osteoporosis with FRAX – assessment and intervention thresholds for the UK. Osteoporos Int. 2008;19:1395–408.
40. Kanis JA, McCloskey EV, Johansson H, Oden A, Strom O, Borgstrom F. Development and use of FRAX in osteoporosis. Osteoporos Int. 2010;21 Suppl. 2:S407–13.
41. Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. Osteoporos Int. 1994;4:368–81.

42. Kanis JA, Gluer CC. An update on the diagnosis and assessment of osteoporosis with densitometry. Committee of Scientific Advisors, International Osteoporosis Foundation. Osteoporos Int. 2000;11:192–202.

43. 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.

44. Stone KL, Seeley DG, Lui LY, Cauley JA, Ensrud K, Browner WS, et al. BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. J Bone Miner Res. 2003;18:1947–54.

45. Schuit SC, Van der Klift M, Weel AE, De Laet CE, Burger H, Seeman E, et al. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. Bone. 2004;34:195–202.

46. 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.

47. Cummings SR, Cawthon PM, Ensrud KE, Cauley JA, Fink HA, Orwoll ES. BMD and risk of hip and nonvertebral fractures in older men: a prospective study and comparison with older women. J Bone Miner Res. 2006;21:1550–6.

48. Leslie WD, Tsang JF, Caetano PA, Lix LM. Effectiveness of bone density measurement for predicting osteoporotic fractures in clinical practice. J Clin Endocrinol Metab. 2007;92:77–81.

49. Nelson HD, Haney EM, Dana T, Bougatsos C, Chou R. Screening for osteoporosis: an update for the U.S. Preventive Services Task Force. Ann Intern Med. 2010;153:99–111.

50. Hans D, Downs Jr RW, Duboeuf F, Greenspan S, Jankowski LG, Kiebzak GM, et al. Skeletal sites for osteoporosis diagnosis: the 2005 ISCD Official Positions. J Clin Densitom. 2006;9:15–21.

51. Baim S, Binkley N, Bilezikian JP, Kendler DL, Hans DB, Lewiecki EM, et al. Official Positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD Position Development Conference. J Clin Densitom. 2008;11:75–91.

52. Hans DB, Shepherd JA, Schwartz EN, Reid DM, Blake GM, Fordham JN, et al. Peripheral dual-energy X-ray absorptiometry in the management of osteoporosis: the 2007 ISCD Official Positions. J Clin Densitom. 2008;11:188–206.

53. Baim S, Wilson CR, Lewiecki EM, Luckey MM, Downs Jr RW, Lentle BC. Precision assessment and radiation safety for dual-energy X-ray absorptiometry: position paper of the International Society for Clinical Densitometry. J Clin Densitom. 2005;8:371–8.

54. Lewiecki EM, Binkley N, Petak SM. DXA quality matters. J Clin Densitom. 2006;9:388–92.

55. Bell KJ, Hayen A, Macaskill P, Irwig L, Craig JC, Ensrud K, et al. Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data. BMJ. 2009;338:b2266.

56. Krieg MA, Barkmann R, Gonnelli S, Stewart A, Bauer DC, Del Rio Barquero L, et al. Quantitative ultrasound in the management of osteoporosis: the 2007 ISCD Official Positions. J Clin Densitom. 2008;11:163–87.

57. Nayak S, Olkin I, Liu H, Grabe M, Gould MK, Allen IE, et al. Meta-analysis: accuracy of quantitative ultrasound for identifying patients with osteoporosis. Ann Intern Med. 2006;144:832–41.

58. Engelke K, Adams JE, Armbrecht G, Augat P, Bogado CE, Bouxsein ML, et al. Clinical use of quantitative computed tomography and peripheral quantitative computed tomography in the management of osteoporosis in adults: the 2007 ISCD Official Positions. J Clin Densitom. 2008;11:123–62.

59. 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.

60. Kanis JA, McCloskey EV, Johansson H, Oden A, Melton 3rd LJ, Khaltaev N. A reference standard for the description of osteoporosis. Bone. 2008;42:467–75.

61. WHO Scientific Group. Assessment of osteoporosis at the primary health care level Geneva (Switzerland). World Health Organization; Available from: http://www.who.int/chp/topics/Osteoporosis.pdf; 2007 [updated 2007; cited in May 2011].

62. Hind K, Burrows M. Weight-bearing exercise and bone mineral accrual in children and adolescents: a review of controlled trials. Bone. 2007;40:14–27.

63. Rizzoli R, Bianchi ML, Garabedian M, McKay HA, Moreno LA. Maximizing bone mineral mass gain during growth for the prevention of fractures in the adolescents and the elderly. Bone. 2010;46:294–305.

64. Chevalley T, Rizzoli R, Hans D, Ferrari S, Bonjour JP. Interaction between calcium intake and menarcheal age on bone mass gain: an eight-year follow-up study from prepuberty to postmenarche. J Clin Endocrinol Metab. 2005;90:44–51.

65. Rowlands AV, Ingledew DK, Powell SM, Eston RG. Interactive effects of habitual physical activity and calcium intake on bone density in boys and girls. J Appl Physiol. 2004;97:1203–8.

66. Chevalley T, Bonjour JP, Ferrari S, Rizzoli R. High-protein intake enhances the positive impact of physical activity on BMC in prepubertal boys. J Bone Miner Res. 2008;23:131–42.

67. Martyn-St James M, Carroll S. Effects of different impact exercise modalities on bone mineral density in premenopausal women: a meta-analysis. J Bone Miner Metab. 2010;28:251–67.

68. Bonaiuti D, Shea B, Iovine R, Negrini S, Robinson V, Kemper HC, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Rev. 2002:CD000333.

69. Korpelainen R, Keinanen-Kiukaanniemi S, Heikkinen J, Vaananen K, Korpelainen J. Effect of impact exercise on bone mineral density in elderly women with low BMD: a population-based randomized controlled 30-month intervention. Osteoporos Int. 2006;17:109–18.

70. Sherrington C, Whitney JC, Lord SR, Herbert RD, Cumming RG, Close JC. Effective exercise for the prevention of falls: a systematic review and meta-analysis. J Am Geriatr Soc. 2008;56:2234–43.

71. Shea B, Wells G, Cranney A, Zytaruk N, Robinson V, Griffith L, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. Endocr Rev. 2002;23:552–9.

72. Prince RL, Devine A, Dhaliwal SS, Dick IM. Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. Arch Intern Med. 2006;166:869–75.

73. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Burckhardt P, Li R, Spiegelman D, et al. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. Am J Clin Nutr. 2007;86:1780–90.

74. Bolland MJ, Barber PA, Doughty RN, Mason B, Horne A, Ames R, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. BMJ. 2008;336:262–6.

75. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ. 2010;341:c3691.

76. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354:669–83.

77. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet. 2007;370:657–66.

78. Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med. 2009;169:551–61.

79. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA. 2010;303:1815–22.

80. Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and postmenopausal osteoporosis. Cochrane Database Syst Rev. 2009:CD000227.

81. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ. 2009;339:b3692.

82. 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.

83. Parker MJ, Gillespie WJ, Gillespie LD. Effectiveness of hip protectors for preventing hip fractures in elderly people: systematic review. BMJ. 2006;332:571–4.

84. Robinovitch SN, Evans SL, Minns J, Laing AC, Kannus P, Cripton PA, et al. Hip protectors: recommendations for biomechanical testing – an international consensus statement (part I). Osteoporos Int. 2009;20:1977–88.

85. Cameron ID, Robinovitch S, Birge S, Kannus P, Khan K, Lauritzen J, et al. Hip protectors: recommendations for conducting clinical trials – an international consensus statement (part II). Osteoporos Int. 2010;21:1–10.

86. Agulnek AN, O'Leary KJ, Edwards BJ. Acute vertebral fracture. J Hosp Med. 2009;4:E20–4.

87. Sheon RP, Rosen H. Clinical manifestations and treatment of osteoporotic thoracolumbar vertebral compression fracture. Available from: www.uptodate.com/online/content/topic.do?topicKey=spinaldi/6255&selectedTitle=1%7E114&source=search_result [cited in May 2011].

88. Mazanec DJ, Podichetty VK, Mompoint A, Potnis A. Vertebral compression fractures: manage aggressively to prevent sequelae. Cleve Clin J Med. 2003;70:147–56.

89. Stadhouder A, Buskens E, Vergroesen DA, Fidler MW, De Nies F, Oner FC. Nonoperative treatment of thoracic and lumbar spine fractures: a prospective randomized study of different treatment options. J Orthop Trauma. 2009;23:588–94.

90. Francis RM, Aspray TJ, Hide G, Sutcliffe AM, Wilkinson P. Back pain in osteoporotic vertebral fractures. Osteoporos Int. 2008;19:895–903.

91. Rousing R, Andersen MO, Jespersen SM, Thomsen K, Lauritsen J. Percutaneous vertebroplasty compared to conservative treatment in patients with painful acute or subacute osteoporotic vertebral fractures: three-months follow-up in a clinical randomized study. Spine (Phila Pa 1976). 2009;34:1349–54.

92. Wardlaw D, Cummings SR, Van Meirhaeghe J, Bastian L, Tillman JB, Ranstam J, et al. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. Lancet. 2009;373:1016–24.

93. Voormolen MH, Mali WP, Lohle PN, Fransen H, Lampmann LE, Van der Graaf Y, et al. Percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures. The VERTOS study. AJNR Am J Neuroradiol. 2007;28:555–60.

94. Kasperk C, Hillmeier J, Noldge G, Grafe IA, Dafonseca K, Raupp D, et al. Treatment of painful vertebral fractures by kyphoplasty in patients with primary osteoporosis: a prospective nonrandomized controlled study. J Bone Miner Res. 2005;20:604–12.

95. Diamond TH, Bryant C, Browne L, Clark WA. Clinical outcomes after acute osteoporotic vertebral fractures: a 2-year non-randomised trial comparing percutaneous vertebroplasty with conservative therapy. Med J Aust. 2006;184:113–7.

96. Alvarez L, Alcaraz M, Perez-Higueras A, Granizo JJ, De Miguel I, Rossi RE, et al. Percutaneous vertebroplasty: functional improvement in patients with osteoporotic compression fractures. Spine (Phila Pa 1976). 2006;31:1113–8.

97. Kallmes DF, Comstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. N Engl J Med. 2009;361:569–79.

98. Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt C, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. N Engl J Med. 2009;361:557–68.

99. Klazen CA, Lohle PN, De Vries J, Jansen FH, Tielbeek AV, Blonk MC, et al. Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial. Lancet. 2010;376:1085–92.

100. Pérez-Nuñez MI, Riancho del Corral JA. Vertebroplastia y cifoplastia como tratamiento de las fracturas vertebrales osteoporóticas. Rev Osteopor Metab Miner. 2010;2:27–33.

101. Hosking DJ, Geusens P, Rizzoli R. Osteoporosis therapy: an example of putting evidence-based medicine into clinical practice. QJM. 2005;98:403–13.

102. Riggs BL, Parfitt AM. Drugs used to treat osteoporosis: the critical need for a uniform nomenclature based on their action on bone remodeling. J Bone Miner Res. 2005;20:177–84.

103. Lufkin EG, Wahner HW, O'Fallon WM, Hodgson SF, Kotowicz MA, Lane AW, et al. Treatment of postmenopausal osteoporosis with transdermal estrogen. Ann Intern Med. 1992;117:1–9.

104. Greenspan SL, Resnick NM, Parker RA. Combination therapy with hormone replacement and alendronate for prevention of bone loss in elderly women: a randomized controlled trial. JAMA. 2003;289:2525–33.

105. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288:321–33.

106. Overgaard K, Riis BJ, Christiansen C, Hansen MA. Effect of salcatonin given intranasally on early postmenopausal bone loss. BMJ. 1989;299:477–9.

107. Chesnut 3rd CH, Silverman S, Andriano K, Genant H, Gimona A, Harris S, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med. 2000;109:267–76.

108. Lyritis GP, Paspati I, Karachalios T, Ioakimidis D, Skarantavos G, Lyritis PG. Pain relief from nasal salmon calcitonin in osteoporotic vertebral crush fractures. A double blind, placebo-controlled clinical study. Acta Orthop Scand Suppl. 1997;275:112–4.

109. Johnell O, Scheele WH, Lu Y, Reginster JY, Need AG, Seeman E. Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2002;87:985–92.

110. Cranney A, Tugwell P, Zytaruk N, Robinson V, Weaver B, Adachi J, et al. Meta-analyses of therapies for postmenopausal osteoporosis. IV. Meta-analysis of raloxifene for the prevention and treatment of postmenopausal osteoporosis. Endocr Rev. 2002;23:524–8.

111. 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.

112. Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med. 2006;355:125–37.

113. Adomaityte J, Farooq M, Qayyum R. Effect of raloxifene therapy on venous thromboembolism in postmenopausal women. A meta-analysis. Thromb Haemost. 2008;99:338–42.

114. Barrett-Connor E, Cox DA, Song J, Mitlak B, Mosca L, Grady D. Raloxifene and risk for stroke based on the framingham stroke risk score. Am J Med. 2009;122:754–61.

115. De Villiers TJ, Chines AA, Palacios S, Lips P, Sawicki AZ, Levine AB, et al. Safety and tolerability of bazedoxifene in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled phase 3 trial. Osteoporos Int. 2011;22:567–76.

116. 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.

117. Siris ES, Pasquale MK, Wang Y, Watts NB. Estimating bisphosphonate use and fracture reduction among U.S. women age 45 and older, 2001–2008. J Bone Miner Res. 2011;26:3–11.

118. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al. Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008:CD003376.

119. 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.

120. Cranney A, Wells GA, Yetisir E, Adami S, Cooper C, Delmas PD, et al. Ibandronate for the prevention of nonvertebral fractures: a pooled analysis of individual patient data. Osteoporos Int. 2009;20:291–7.

121. Jansen JP, Bergman GJ, Huels J, Olson M. Prevention of vertebral fractures in osteoporosis: mixed treatment comparison of bisphosphonate therapies. Curr Med Res Opin. 2009;25:1861–8.

122. Cotte FE, Fardellone P, Mercier F, Gaudin AF, Roux C. Adherence to monthly and weekly oral bisphosphonates in women with osteoporosis. Osteoporos Int. 2010;21:145–55.

123. Arboleya L. Bisfosfonatos. In: Manual de enfermedades óseas de la SER. Madrid: Editorial Médica Panamericana; 2010. p. 319–30.

124. Watts NB, Harris ST, Genant HK, Wasnich RD, Miller PD, Jackson RD, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. N Engl J Med. 1990;323:73–9.

125. Harris ST, Watts NB, Jackson RD, Genant HK, Wasnich RD, Ross P, et al. Four-year study of intermittent cyclic etidronate treatment of postmenopausal osteoporosis: three years of blinded therapy followed by one year of open therapy. Am J Med. 1993;95:557–67.

126. Ott SM, Woodson GC, Huffer WE, Miller PD, Watts NB. Bone histomorphometric changes after cyclic therapy with phosphate and etidronate disodium in women with postmenopausal osteoporosis. J Clin Endocrinol Metab. 1994;78:968–72.

127. 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.

128. Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med. 2004;350:1189–99.

129. Dansereau RJ, Crail DJ, Perkins AC. In vitro disintegration studies of weekly generic alendronate sodium tablets (70 mg) available in the US. Curr Med Res Opin. 2009;25:449–52.

130. Perkins AC, Blackshaw PE, Hay PD, Lawes SC, Atherton CT, Dansereau RJ, et al. Esophageal transit and in vivo disintegration of branded risedronate sodium tablets and two generic formulations of alendronic acid tablets: a single-center, single-blind, six-period crossover study in healthy female subjects. Clin Ther. 2008;30:834–44.

131. Ringe JD, Moller G. Differences in persistence, safety and efficacy of generic and original branded once weekly bisphosphonates in patients with postmenopausal osteoporosis: 1-year results of a retrospective patient chart review analysis. Rheumatol Int. 2009;30:213–21.

132. Body JJ, Bergmann P, Boonen S, Boutsen Y, Devogelaer JP, Goemaere S, et al. Evidence-based guidelines for the pharmacological treatment of postmenopausal osteoporosis: a consensus document by the Belgian Bone Club. Osteoporos Int. 2010;21:1657–80.

133. 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.

134. 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.

135. Watts NB, Josse RG, Hamdy RC, Hughes RA, Manhart MD, Barton I, et al. Risedronate prevents new vertebral fractures in postmenopausal women at high risk. J Clin Endocrinol Metab. 2003;88:542–9.

136. Harrington JT, Ste-Marie LG, Brandi ML, Civitelli R, Fardellone P, Grauer A, et al. Risedronate rapidly reduces the risk for nonvertebral fractures in women with postmenopausal osteoporosis. Calcif Tissue Int. 2004;74:129–35.

137. Cranney A, Tugwell P, Adachi J, Weaver B, Zytaruk N, Papaioannou A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. III. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. Endocr Rev. 2002;23:517–23.

138. Brown JP, Kendler DL, McClung MR, Emkey RD, Adachi JD, Bolognese MA, et al. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. Calcif Tissue Int. 2002;71:103–11.

139. Chesnut IC, 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.

140. Reginster JY, Adami S, Lakatos P, Greenwald M, Stepan JJ, Silverman SL, et al. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. Ann Rheum Dis. 2006;65:654–61.

141. Stakkestad JA, Lakatos P, Lorenc R, Sedarati F, Neate C, Reginster JY. Monthly oral ibandronate is effective and well tolerated after 3 years: the MOBILE long-term extension. Clin Rheumatol. 2008;27:955–60.

142. Harris ST, Blumentals WA, Miller PD. Ibandronate and the risk of nonvertebral and clinical fractures in women with postmenopausal osteoporosis: results of a meta-analysis of phase III studies. Curr Med Res Opin. 2008;24:237–45.

143. Sebba AI, Emkey RD, Kohles JD, Sambrook PN. Ibandronate dose response is associated with increases in bone mineral density and reductions in clinical fractures: results of a meta-analysis. Bone. 2009;44:423–7.

144. Harris ST, Reginster JY, Harley C, Blumentals WA, Poston SA, Barr CE, et al. Risk of fracture in women treated with monthly oral ibandronate or weekly

bisphosphonates: the eValuation of IBandronate Efficacy (VIBE) database fracture study. Bone. 2009;44:758–65.

145. Delmas PD, Adami S, Strugala C, Stakkestad JA, Reginster JY, Felsenberg D, et al. Intravenous ibandronate injections in postmenopausal women with osteoporosis: one-year results from the dosing intravenous administration study. Arthritis Rheum. 2006;54:1838–46.

146. Von Moos R, Caspar CB, Thurlimann B, Angst R, Inauen R, Greil R, et al. Renal safety profiles of ibandronate 6 mg infused over 15 and 60 min: a randomized, open-label study. Ann Oncol. 2008;19:1266–70.

147. Boonen S, Vanderschueren D, Venken K, Milisen K, Delforge M, Haentjens P. Recent developments in the management of postmenopausal osteoporosis with bisphosphonates: enhanced efficacy by enhanced compliance. J Intern Med. 2008;264:315–32.

148. 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.

149. 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.

150. Colon-Emeric CS, Mesenbrink P, Lyles KW, Pieper CF, Boonen S, Delmas P, et al. Potential mediators of the mortality reduction with zoledronic acid after hip fracture. J Bone Miner Res. 2010;25:91–7.

151. Arboleya L, Alperi M, Alonso S. Efectos adversos de los bisfosfonatos. Reumatol Clin. 2011;7:189–97.

152. Abrahamsen B. Adverse effects of bisphosphonates. Calcif Tissue Int. 2010;86:421–35.

153. Edwards BJ, Gounder M, McKoy JM, Boyd I, Farrugia M, Migliorati C, et al. Pharmacovigilance and reporting oversight in US FDA fast-track process: bisphosphonates and osteonecrosis of the jaw. Lancet Oncol. 2008;9:1166–72.

154. Agencia Española del Medicamento y productos Sanitarios. Nota informativa de la AEMPS: recomendaciones para la prevención de la osteonecrosis del maxilar asociada al tratamiento con bisfosfonatos. Available from: http://www.aemps.es/actividad/alertas/usoHumano/seguridad/NI_2009-10_bisfosfonatos.htm; 2009 [updated 2009; cited in 2010].

155. Marx RE, Cillo Jr JE, Ulloa JJ. Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment. J Oral Maxillofac Surg. 2007;65:2397–410.

156. Baim S, Miller PD. Assessing the clinical utility of serum CTX in postmenopausal osteoporosis and its use in predicting risk of osteonecrosis of the jaw. J Bone Miner Res. 2009;24:561–74.

157. Abrahamsen B, Eiken P, Eastell R. Cumulative alendronate dose and the long-term absolute risk of subtrochanteric and diaphyseal femur fractures: a register-based national cohort analysis. J Clin Endocrinol Metab. 2010;95:5258–65.

158. Black DM, Kelly MP, Genant HK, Palermo L, Eastell R, Bucci-Rechtweg C, et al. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. N Engl J Med. 2010;362:1761–71.

159. Koh JS, Goh SK, Png MA, Kwek EB, Howe TS. Femoral cortical stress lesions in long-term bisphosphonate therapy: a herald of impending fracture? J Orthop Trauma. 2010;24:75–81.

160. Pazianas M, Cooper C, Ebetino FH, Russell RG. Long-term treatment with bisphosphonates and their safety in postmenopausal osteoporosis. Ther Clin Risk Manag. 2010;6:325–43.

161. Rheumatology ACo. Denosumab. Available from: http://www.rheumatology.org/publications/hotline/2010_10_18_denosumab.asp; 2010 [updated October 2010; cited in April 2011].

162. Lewiecki EM. Denosumab update. Curr Opin Rheumatol. 2009;21:369–73.

163. 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.

164. McClung MR, Lewiecki EM, Cohen SB, Bolognese MA, Woodson GC, Moffett AH, et al. Denosumab in postmenopausal women with low bone mineral density. N Engl J Med. 2006;354:821–31.

165. Miller PD, Bolognese MA, Lewiecki EM, McClung MR, Ding B, Austin M, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. Bone. 2008;43:222–9.

166. Kendler DL, Roux C, Benhamou CL, Brown JP, Lillestol M, Siddhanti S, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. J Bone Miner Res. 2010;25:72–81.

167. Brown JP, Prince RL, Deal C, Recker RR, Kiel DP, De Gregorio LH, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. J Bone Miner Res. 2009;24:153–61.

168. Seeman E, Delmas PD, Hanley DA, Sellmeyer D, Cheung AM, Shane E, et al. Microarchitectural deterioration of cortical and trabecular bone: differing effects of denosumab and alendronate. J Bone Miner Res. 2010;25:1886–94.

169. Lewiecki EM, Miller PD, McClung MR, Cohen SB, Bolognese MA, Liu Y, et al. Two-year treatment with denosumab (AMG 162) in a randomized phase 2 study of postmenopausal women with low BMD. J Bone Miner Res. 2007;22:1832–41.

170. Bone HG, Bolognese MA, Yuen CK, Kendler DL, Wang H, Liu Y, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. J Clin Endocrinol Metab. 2008;93:2149–57.

171. Genant HK, Engelke K, Hanley DA, Brown JP, Omizo M, Bone HG, et al. Denosumab improves density and strength parameters as measured by QCT of the radius in postmenopausal women with low bone mineral density. Bone. 2010;47:131–9.

172. Reid IR, Miller PD, Brown JP, Kendler DL, Fahrleitner-Pammer A, Valter I, et al. Effects of denosumab on bone histomorphometry: the FREEDOM and STAND studies. J Bone Miner Res. 2010;25:2256–65.

173. Tam CS, Heersche JN, Murray TM, Parsons JA. Parathyroid hormone stimulates the bone apposition rate independently of its resorptive action: differential effects of intermittent and continuous administration. Endocrinology. 1982;110:506–12.

174. Hock JM, Gera I. Effects of continuous and intermittent administration and inhibition of resorption on the anabolic response of bone to parathyroid hormone. J Bone Miner Res. 1992;7:65–72.

175. Whitfield J, Morley P, Willick G. The parathyroid hormone, its fragments and analogues – potent bone-builders for treating osteoporosis. Expert Opin Investig Drugs. 2000;9:1293–315.

176. Ma YL, Cain RL, Halladay DL, Yang X, Zeng Q, Miles RR, et al. Catabolic effects of continuous human PTH (1–38) in vivo is associated with sustained stimulation of RANKL and inhibition of osteoprotegerin and gene-associated bone formation. Endocrinology. 2001;142:4047–54.

177. European Medicines Agency. Forsteo. Available from: www.emea.eu.int/humandocs/humans/EPAR/forsteo; 2010 [updated 2010; cited in May 2011].

178. Schwietert HR, Groen EW, Sollie FA, Jonkman JH. Single-dose subcutaneous administration of recombinant human parathyroid hormone [rhPTH(1–84)] in healthy postmenopausal volunteers. Clin Pharmacol Ther. 1997;61:360–76.

179. 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.

180. Cosman F, Nieves J, Woelfert L, Formica C, Gordon S, Shen V, et al. Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal. J Bone Miner Res. 2001;16:925–31.

181. Lindsay R, Nieves J, Formica C, Henneman E, Woelfert L, Shen V, et al. Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. Lancet. 1997;350:550–5.

182. Greenspan SL, Bone HG, Ettinger MP, Hanley DA, Lindsay R, Zanchetta JR, et al. Effect of recombinant human parathyroid hormone (1–84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. Ann Intern Med. 2007;146:326–39.

183. Body JJ, Gaich GA, Scheele WH, Kulkarni PM, Miller PD, Peretz A, et al. A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1–34)] with alendronate in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2002;87:4528–35.

184. Black DM, Greenspan SL, Ensrud KE, Palermo L, McGowan JA, Lang TF, et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med. 2003;349:1207–15.

185. SEIOMM. Guías de práctica clínica en la osteoporosis postmenopáusica glucocorticoidea y del varón. Rev Clin Esp. 2008;8 Suppl. 1:1–24.

186. SEIOMM. Guías de práctica clínica en la osteoporosis postmenopáusica glucocorticoidea y del varón. Rev Osteoporos Metab Miner. 2009;1:53–60.

187. Jolette J, Wilker CE, Smith SY, Doyle N, Hardisty JF, Metcalfe AJ, et al. Defining a noncarcinogenic dose of recombinant human parathyroid hormone 1–84 in a 2-year study in Fischer 344 rats. Toxicol Pathol. 2006;34:929–40.

188. Tashjian Jr AH, Chabner BA. Commentary on clinical safety of recombinant human parathyroid hormone 1–34 in the treatment of osteoporosis in men and postmenopausal women. J Bone Miner Res. 2002;17:1151–61.

189. Subbiah V, Madsen VS, Raymond AK, Benjamin RS, Ludwig JA. Of mice and men: divergent risks of teriparatide-induced osteosarcoma. Osteoporos Int. 2010;21:1041–5.

190. Peris P. Toxicidad de la teriparatida. Rev Esp Reum. 2004;3:19–23.

191. Bevilacqua M, Dominguez L, Chebat E, Barrella M, Righini V, Gandolini G, et al. Teriparatide (1–34) vs. Parathyroid hormone (1–84) in women with severe postmenopausal osteoporosis: a randomized, head-to-head study. In: ASBMR 30th Annual Meeting. 2008. p. 48.

192. Piemonte S, Romagnoli E, Cipriani C, Fassino V, Del Fiacco R, Carnevale V, et al. The effect of recombinant PTH(1–34) and PTH(1–84) on serum ionized calcium, 1,25-dihydroxyvitamin D, and urinary calcium excretion: a pilot study. Calcif Tissue Int. 2009;85:287–92.

193. Marie PJ, Hott M, Modrowski D, De Pollak C, Guillemain J, Deloffre P, et al. An uncoupling agent containing strontium prevents bone loss by depressing bone resorption and maintaining bone formation in estrogen-deficient rats. J Bone Miner Res. 1993;8:607–15.

194. Chattopadhyay N, Quinn SJ, Kifor O, Ye C, Brown EM. The calcium-sensing receptor (CaR) is involved in strontium ranelate-induced osteoblast proliferation. Biochem Pharmacol. 2007;74:438–47.

195. Caverzasio J. Strontium ranelate promotes osteoblastic cell replication through at least two different mechanisms. Bone. 2008;42:1131–6.

196. Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab. 2005;90:2816–22.

197. Meunier PJ, Reginster JY. Design and methodology of the phase 3 trials for the clinical development of strontium ranelate in the treatment of women with postmenopausal osteoporosis. Osteoporos Int. 2003;14 Suppl. 3:S66–76.

198. Reginster JY, Felsenberg D, Boonen S, Diez-Perez A, Rizzoli R, Brandi ML, et al. Effects of long-term strontium ranelate treatment on the risk of nonvertebral and vertebral fractures in postmenopausal osteoporosis: results of a five-year, randomized, placebo-controlled trial. Arthritis Rheum. 2008;58:1687–95.

199. Reginster JY, Bruyere O, Sawicki A, Roces-Varela A, Fardellone P, Roberts A, et al. Long-term treatment of postmenopausal osteoporosis with strontium ranelate: results at 8 years. Bone. 2009;45:1059–64.

200. Breart G, Cooper C, Meyer O, Speirs C, Deltour N, Reginster JY. Osteoporosis and venous thromboembolism: a retrospective cohort study in the UK General Practice Research Database. Osteoporos Int. 2010;21:1181–7.

201. Jonville-Bera AP, Crickx B, Aaron L, Hartingh I, Autret-Leca E. Strontium ranelate-induced DRESS syndrome: first two case reports. Allergy. 2009;64:658–9.

202. Pernicova I, Middleton ET, Aye M. Rash, strontium ranelate and DRESS syndrome put into perspective. European Medicine Agency on the alert. Osteoporos Int. 2008;19:1811–2.

203. Grosso A, Douglas I, Hingorani A, MacAllister R, Smeeth L. Post-marketing assessment of the safety of strontium ranelate; a novel case-only approach to the early detection of adverse drug reactions. Br J Clin Pharmacol. 2008;66:689–94.

204. Bone HG, McClung MR, Roux C, Recker RR, Eisman JA, Verbruggen N, et al. Odanacatib, a cathepsin-K inhibitor for osteoporosis: a two-year study in postmenopausal women with low bone density. J Bone Miner Res. 2010;25:937–47.

205. Eisman JA, Bone HG, Hosking DJ, McClung MR, Reid IR, Rizzoli R, et al. Odanacatib in the treatment of postmenopausal women with low bone mineral density: three-year continued therapy and resolution of effect. J Bone Miner Res. 2011;26:242–51.

206. Stroup GB, Kumar S, Jerome CP. Treatment with a potent cathepsin K inhibitor preserves cortical and trabecular bone mass in ovariectomized monkeys. Calcif Tissue Int. 2009;85:344–55.

207. Isabel E, Bateman KP, Chauret N, Cromlish W, Desmarais S, Duong le T, et al. The discovery of MK-0674, an orally bioavailable cathepsin K inhibitor. Bioorg Med Chem Lett. 2010;20:887–92.

208. Murphy MG, Cerchio K, Stoch SA, Gottesdiener K, Wu M, Recker R. Effect of L-000845704, an alphaVbeta3 integrin antagonist, on markers of bone turnover and bone mineral density in postmenopausal osteoporotic women. J Clin Endocrinol Metab. 2005;90:2022–8.

209. Hannon RA, Clack G, Rimmer M, Swaisland A, Lockton JA, Finkelman RD, et al. Effects of the Src kinase inhibitor saracatinib (AZD0530) on bone turnover in healthy men: a randomized, double-blind, placebo-controlled, multiple-ascending-dose phase I trial. J Bone Miner Res. 2010;25:463–71.

210. Schaller S, Henriksen K, Sveigaard C, Heegaard AM, Helix N, Stahlhut M, et al. The chloride channel inhibitor NS3736 [corrected] prevents bone resorption in ovariectomized rats without changing bone formation. J Bone Miner Res. 2004;19:1144–53.

211. Ominsky MS, Vlasseros F, Jolette J, Smith SY, Stouch B, Doellgast G, et al. Two doses of sclerostin antibody in cynomolgus monkeys increases bone formation, bone mineral density, and bone strength. J Bone Miner Res. 2010;25:948–59.

212. Li X, Warmington KS, Niu QT, Asuncion FJ, Barrero M, Grisanti M, et al. Inhibition of sclerostin by monoclonal antibody increases bone formation, bone mass and bone strength in aged male rats. J Bone Miner Res. 2010;25:2647–56.

213. Padhi D, Jang G, Stouch B, Fang L, Posvar E. Single-dose, placebo-controlled, randomized study of AMG 785, a sclerostin monoclonal antibody. J Bone Miner Res. 2011;26:19–26.

214. Bodine PV, Stauffer B, Ponce-de-Leon H, Bhat RA, Mangine A, Seestaller-Wehr LM, et al. A small molecule inhibitor of the Wnt antagonist secreted frizzled-related protein-1 stimulates bone formation. Bone. 2009;44:1063–8.

215. Lotinun S, Pearsall RS, Davies MV, Marvell TH, Monnell TE, Ucran J, et al. A soluble activin receptor Type IIA fusion protein (ACE-011) increases bone mass via a dual anabolic-antiresorptive effect in Cynomolgus monkeys. Bone. 2010;46:1082–8.

216. Fajardo RJ, Manoharan RK, Pearsall RS, Davies MV, Marvell T, Monnell TE, et al. Treatment with a soluble receptor for activin improves bone mass and structure in the axial and appendicular skeleton of female cynomolgus macaques (*Macaca fascicularis*). Bone. 2010;46:64–71.

217. Ruckle J, Jacobs M, Kramer W, Pearsall AE, Kumar R, Underwood KW, et al. Single-dose, randomized, double-blind, placebo-controlled study of ACE-011 (ActRIIA-IgG1) in postmenopausal women. J Bone Miner Res. 2009;24:744–52.

218. Black DM, Bilezikian JP, Ensrud KE, Greenspan SL, Palermo L, Hue T, et al. One year of alendronate after one year of parathyroid hormone (1–84) for osteoporosis. N Engl J Med. 2005;353:555–65.

219. Rittmaster RS, Bolognese M, Ettinger MP, Hanley DA, Hodsman AB, Kendler DL, et al. Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate. J Clin Endocrinol Metab. 2000;85:2129–34.

220. Deal C, Omizo M, Schwartz EN, Eriksen EF, Cantor P, Wang J, et al. Combination teriparatide and raloxifene therapy for postmenopausal osteoporosis: results from a 6-month double-blind placebo-controlled trial. J Bone Miner Res. 2005;20:1905–11.

221. Ste-Marie LG, Schwartz SL, Hossain A, Desaiah D, Gaich GA. Effect of teriparatide [rhPTH(1–34)] on BMD when given to postmenopausal women receiving hormone replacement therapy. J Bone Miner Res. 2006;21:283–91.

222. Anastasilakis AD, Polyzos SA, Avramidis A, Papatheodorou A, Terpos E. Effect of strontium ranelate on lumbar spine bone mineral density in women with established osteoporosis previously treated with teriparatide. Horm Metab Res. 2009;41:559–62.

223. 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.

224. Boonen S, Marin F, Obermayer-Pietsch B, Simoes ME, Barker C, Glass EV, et al. Effects of previous antiresorptive therapy on the bone mineral density response to two years of teriparatide treatment in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2008;93:852–60.

225. Wimalawansa SJ. Combined therapy with estrogen and etidronate has an additive effect on bone mineral density in the hip and vertebrae: four-year randomized study. Am J Med. 1995;99:36–42.

226. Lindsay R, Cosman F, Lobo RA, Walsh BW, Harris ST, Reagan JE, et al. Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoporosis: a randomized, controlled clinical trial. J Clin Endocrinol Metab. 1999;84:3076–81.

227. Harris ST, Eriksen EF, Davidson M, Ettinger MP, Moffett Jr AH, Baylink DJ, et al. Effect of combined risedronate and hormone replacement therapies on bone mineral density in postmenopausal women. J Clin Endocrinol Metab. 2001;86:1890–7.

228. Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. N Engl J Med. 2003;349:1216–26.

229. 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.

230. Maricic M. The role of zoledronic acid in the management of osteoporosis. Clin Rheumatol. 2010;29:1079–84.

231. Lenart BA, Neviaser AS, Lyman S, Chang CC, Edobor-Osula F, Steele B, et al. Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. Osteoporos Int. 2009;20:1353–62.

232. 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.

233. Chen P, Miller PD, Delmas PD, Misurski DA, Krege JH. Change in lumbar spine BMD and vertebral fracture risk reduction in teriparatide-treated postmenopausal women with osteoporosis. J Bone Miner Res. 2006;21:1785–90.

234. International Society for Clinical Densitometry (ISCD). 2007 ISCD official positions. Middletown; Available from: http://www.iscd.org/; 2007 [updated 2007; cited in May 2011].

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

236. Grupo de Trabajo en Osteoporosis (GTO). In: Rorer R-P, editor. Estudio de la densidad ósea en la población española. Madrid: Edimsa; 1992.

237. Ciria M, Laiz A, Benito P. Osteoporosis y grado de conocimiento de la misma en la población española. In: Reumatología SEd, editor. Estudio EPISER Prevalencia e impacto de las enfermedades reumáticas en la población española. Madrid: Sociedad Española de Reumatología; 2001. p. 101–24.

238. Cannata JB, Naves ML, Virgós MJ, Gómez Alonso C, Díaz López JB. Epidemiología de las fracturas vertebrales. Rev Esp Enf Metab Oseas. 1993;2 Suppl. B:2.

239. Olmos JM, Martinez J, Garcia J, Matorras P, Moreno JJ, Gonzalez-Macias J. Incidence of hip fractures in Cantabria. Med Clin (Barc). 1992;99:729–31.

240. Sosa M. La fractura osteoporótica de cadera en España. Rev Esp Enf Metab Oseas. 1993;2:189–92.

241. Peris P, Guanabens N, Monegal A, Suris X, Alvarez L, Martinez de Osaba MJ, et al. Aetiology and presenting symptoms in male osteoporosis. Br J Rheumatol. 1995;34:936–41.

242. Peris P, Guanabens N. Male osteoporosis. Curr Opin Rheumatol. 1996;8:357–64.

243. Blanch J, Pacifici R, Benito P, Ciria M, Perez-Edo L, Pros A, et al. Osteoporosis in men. J Bone Min Res. 1996;11:S231.

244. Jackson JA, Kleerekoper M. Osteoporosis in men: diagnosis, pathophysiology, and prevention. Medicine (Baltimore). 1990;69:137–52.

245. Goldray D, Weisman Y, Jaccard N, Merdler C, Chen J, Matzkin H. Decreased bone density in elderly men treated with the gonadotropin-releasing hormone agonist decapeptyl (D-Trp6-GnRH). J Clin Endocrinol Metab. 1993;76:288–90.

246. Morrison D, Capewell S, Reynolds SP, Thomas J, Ali NJ, Read GF, et al. Testosterone levels during systemic and inhaled corticosteroid therapy. Respir Med. 1994;88:659–63.

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

248. 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.

249. 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.

250. 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.

251. Peris P, Guanabens N, Martinez de Osaba MJ, Monegal A, Alvarez L, Pons F, et al. Clinical characteristics and etiologic factors of premenopausal osteoporosis in a group of Spanish women. Semin Arthritis Rheum. 2002;32:64–70.

252. Bhalla AK. Management of osteoporosis in a pre-menopausal woman. Best Pract Res Clin Rheumatol. 2010;24:313–27.

253. Peris P. Osteoporosis en individuos jóvenes. Reumatol Clin. 2010;6:217–23.

254. Van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int. 2002;13: 777–87.

255. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int. 2007;18:1319–28.

256. Sambrook PN. Osteoporosis inducida por glucocorticoides. In: Favus MJ, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. 6th ed. Barcelona: Amer Society For Bone & Mineral; 2007. p. 361–8.

257. Huizenga NA, Koper JW, De Lange, Pols HA, Stolk RP, Burguer H, et al. A polimorphism in the glucocorticoid receptor gene may be associated with and increased sensitivity to glucocorticoids in vivo. J Clin Endocrinol Metab. 1998:144–51.

258. Sosa Henriquez M, Díaz Curiel M, Díez Pérez A, Gómez Alonso C, González Macías J, Farrerons Minguella J, et al. Guía de prevención y tratamiento de la osteoporosis inducida por glucocorticoides de la Sociedad Española de Medicina Interna. Rev Clin Esp. 2008;208:33–45.

259. Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group. N Engl J Med. 1998;339:292–9.

260. Wallach S, Cohen S, Reid DM, Hughes RA, Hosking DJ, Laan RF, et al. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. Calcif Tissue Int. 2000;67:277–85.

261. Reid DM, Devogelaer JP, Saag K, Roux C, Lau CS, Reginster JY, et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet. 2009;373:1253–63.

262. 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.

263. Sambrook PN. Anabolic therapy in glucocorticoid-induced osteoporosis. N Engl J Med. 2007;357:2084–6.

264. Silverman SL, Lane NE. Glucocorticoid-induced osteoporosis. Curr Osteoporos Rep. 2009;7:23–6.

265. Adler RA. Glucocorticoid-induced osteoporosis: management update. Curr Osteoporos Rep. 2010;8:10–4.

266. Compston J. Management of glucocorticoid-induced osteoporosis. Nat Rev Rheumatol. 2010;6:82–8.

267. Condon JR, Nassim IR, Dent CE, Hilb A, Staihorpe EM. Possible prevention and treatment of steroid-induced osteoporosis. Postgrad Med J. 1978;54: 249–52.