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Recommendations and metaanalyses

2018 update of French recommendations on the management of postmenopausal osteoporosis

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ABSTRACT

Objectives: To update the 2012 recommendations on pharmacotherapy for postmenopausal osteoporosis, under the aegis of the Bone Task Force of the French Society for Rheumatology (SFR) and of the Osteoporosis Research and Information Group (GRIO), in collaboration with scientific societies (Collège national des généralistes enseignants, Collège national des gynécologues et obstétriciens français, Fédération nationale des collèges de gynécologie médicale, Groupe d'étude de la ménopause et du vieillissement hormonal, Société française de chirurgie orthopédique, Société française d'endocrinologie, and Société française de gériatrie et de gérontologie).

Methods: Updated recommendations were developed by a task force whose members represented the medical specialties involved in the management of postmenopausal osteoporosis. The update was based on a literature review and developed using the method advocated by the French National Authority for Health (HAS).

Discussion and conclusion: The updated recommendations place strong emphasis on the treatment of women with severe fractures, in whom the use of osteoporosis medications is recommended. All the available osteoporosis medications are suitable in patients with severe fractures; zoledronic acid deserves preference as the fist-line drug after a hip fracture. In patients with or without non-severe fractures, the decision to use osteoporosis medications is based on bone mineral density values and in challenging cases, on probabilities supplied by prediction tools such as FRAX®. All osteoporosis medications are suitable; raloxifene should be reserved for patients at low risk for peripheral fractures. The fracture risk should be reevaluated every 2 to 3 years to decide on the best follow-up treatment. These updated recommendations discuss the selection of first-line osteoporosis medications and treatment sequences.

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1. Objectives and methods

These updated recommendations are intended for all physicians involved in managing women who have, or are at risk for, postmenopausal osteoporosis. The objectives of the update are to review current epidemiological data on postmenopausal osteoporosis; identify the key criteria for evaluating patients at high risk for fractures; and clarify the principles of drug therapy for postmenopausal osteoporosis in the light of recent evidence about indications, efficacy and safety. The content of the recommendations was discussed and elaborated according to the method advocated by the French National Authority for Health (HAS) then validated by a multidisciplinary study group. When published data were inadequate or incomplete, expert consensus formed the basis for the recommendations, to give due weight to current practice and expert opinion.

No recommendations can encompass every specific situation, the full spectrum of comorbidities or all hospital care protocols. Therefore, the current update does not claim to cover all possible management strategies and should not serve as a substitute for individual physician responsibility regarding treatment decisions. The indications of the drugs and the information on reimbursement by the statutory health insurance system of drugs, bone absorptiometry and serum 25-OH-vitamin D assays are valid for France.

These updated recommendations were developed by a project manager and a scientific committee then discussed and revised by a multidisciplinary panel of reviewers. As part of the process of revising and validating the recommendations, advice was obtained from the following scientific societies: Collège national des généralistes enseignants, Collège national des gynécologues et obstétriciens français, Fédération nationale des collèges de gynécologie médicale, Groupe d'étude de la ménopause et du vieillissement hormonal, Groupe de recherche et d'information sur les ostéoporoses (GRIO), Société française de chirurgie orthopédique, Société française d'endocrinologie, Société française de gériatrie et de gérontologie, and Société française de rhumatologie (SFR).

2. Epidemiology of osteoporosis and fractures

2.1. Epidemiology

Osteoporosis is a generalized bone disease in which bone strength is diminished, resulting in a risk of fractures [1]. As a disease that increases the risk and frequency of several severe fractures associated with devastating consequences, osteoporosis is a major public health issue. The fracture risk increases substantially with age and the burden placed by osteoporosis on public health is therefore heaviest in countries with long life expectancies. The recommendations presented here apply to patients in whom causes of decreased bone strength other than postmenopausal osteoporosis have been ruled out.

Osteoporotic or fragility fractures are induced by low-energy trauma such as a fall from standing height while walking. The only bones where osteoporotic fractures do not occur are the skull, facial bones, cervical spine, first three thoracic vertebras, hand bones and toes; fractures at these sites are due to either injuries or tumors. Falls from standing height are the leading cause of non-vertebral fragility fractures. Among these falls, 5% are responsible for fractures at any site [2] and 2% for hip fractures in individuals older than 65 years of age [3].

2.1.1. Epidemiological data from France

Annual estimates for 2001 in France blame osteoporosis for about 70,000 vertebral fractures, 60,000 hip fractures and 35,000 wrist fractures [4]. The number of patients requiring surgery for hip fractures increased between 2002 and 2013 by 5% in females (from 49,287 to 50,215) and by 22% in males (from 12,716 to 15,482) [5]. According to a report issued in January 2016 by a French national research agency (*Direction de la recherche, des études, de l'évaluation et des statistiques*), among patients in France older than 55 years of age who sustain a hip fracture due to any cause, 23.5% die within the following year (www.data.drees.sante.gouv.fr).

A study by the French statutory health insurance system for salaried workers (*Caisse nationale d'assurance maladie*) assessed hospital admissions in France of patients older than 50 years with fractures in 2013 [6]. The number of patients admitted with osteoporotic fractures at any site was 177,000. Among these patients, three-quarters were female and two-thirds were older than 70 years. The number of admissions for fractures of any type increased by 9% between 2011 and 2013. Direct annual costs totaled 771 million Euros. During the year following the admission, 6325 (7%) patients died, 12% experienced another fracture and 40% were readmitted. The mortality rate was twice as high in males than in females. During the first year after the fracture, only 10% of patients underwent bone absorptiometry and only 15% were started on osteoporosis medication. Thus, over 80% of patients did not receive appropriate management after sustaining a fracture that required hospital admission. These data from France [6] are consistent with those reported worldwide [7].

2.1.2. Consequences of severe fractures

Severe fractures are associated with an increase in mortality. Fractures are severe at the following sites: hip, proximal humerus, spine, pelvis, sacrum, femoral shaft, distal femur, ribcage involving at least three ribs and proximal tibia [8–10]. The excess mortality compared to the general population occurs chiefly among patients younger than 70 years of age [8]. Epidemiological studies have confirmed that pelvic and humeral fractures are associated with increased mortality [11]. Furthermore, severe fractures are associated with a risk of further vertebral and non-vertebral fractures, which account for 25% of the excess mortality [12].

Other common fractures, such as forearm fractures, are classified as non-severe because they are not associated with an increase in mortality, although their impact may be substantial. Non-severe fractures can be the first manifestation of osteoporosis and are associated with a risk of further fractures, which may be severe [13].

2.2. Risk factors for fractures and short-term fracture risk

A recent fracture is a major risk factor for a further fracture in the short term. More specifically, after a vertebral fracture there is a 25% risk of sustaining another fracture within the following year [14]. The risk of fracture is also increased during the 2 to 3 years after a non-vertebral fracture [15,16]. In addition to a recent fracture, risk factors for a repeat fracture in the short term include risk factors for falls [17,18]. Patients who have these risk factors should be treated promptly to prevent further fractures.

2.3. Comorbidities and fracture risk

Patients with osteoporosis have an increased prevalence of chronic comorbidities such as dementia, Parkinson's disease, other neurological disorders, diabetes and cardiovascular disease and many are on multiple medications [19,20]. These comorbidities must receive appropriate attention, as they increase the fracture risk and the adverse impact of fractures. Examples of situations in which fractures are particularly deleterious include hip fractures in patients with dementia and vertebral fractures in those with chronic obstructive pulmonary disease. The risk/benefit ratio should be evaluated carefully in the event of comorbidities and

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the treatment options and administration modalities should be discussed with the patient.

3. Evaluation of the fracture risk and treatment decisions

Decisions about offering osteoporosis treatment are guided by the existence, type and date of previous fractures; patient age; risk factors for falls; bone mineral density (BMD) values; and comorbidity profile.

3.1. Fracture risk prediction tools

3.1.1. History of fractures in the patient

A history of fracture is the strongest predictor of further fractures [14,15,18,20,21], regardless of fracture location at the spine or at a peripheral site. The period of greatest risk increase is 2 to 3 years after the first fracture. However, the risk increase remains significant for 10 to 15 years (particularly after vertebral and humeral fractures) [22,23]. The time since the fracture is important to note, as only recent fractures are associated with an increased short-term risk of fractures.

Vertebral fractures are common, but their frequency is underestimated, as they are missed in two-thirds of cases due to the paucity of the symptoms or to a mistaken diagnosis of disk disease as the source of pain, in the absence of a radiographic assessment. Vertebral fractures are a key risk factor for vertebral and non-vertebral fractures. The risk of further fractures increases with the number and severity of the existing vertebral fractures. Even in the absence of symptoms, a radiographic vertebral fracture is associated with an increased relative risk of incident fractures during the first year and for up to 15 years after the diagnosis, after adjustment for age and BMD [21].

Vertebral fracture assessment (VFA) is a dual-energy X-ray densitometry technique for detecting vertebral fractures at the thoracic and lumbar spine. VFA is not reimbursed by the health insurance system in France. VFA is indicated in postmenopausal women with spinal pain or any of the following criteria: loss of height $\geq$ 4 cm compared to historical height (at 20 years of age), loss of height $\geq$ 2 cm as established prospectively during follow-up, previous vertebral fracture, chronic comorbidities and treatments associated with a high risk of vertebral fracture (glucocorticoids and aromatase inhibitors) (ISCD 2015) (www.iscd.org) (expert consensus).

3.1.2. Bone mineral density (BMD) measurement

Dual-energy X-ray absorptiometry (DXA) is the reference method for measuring BMD at the lumbar spine and hip. Bone strength correlates strongly with BMD. In postmenopausal women, BMD results are reported as T-scores. The T-score is the number of standard deviations (SDs) of the measured BMD value above or below the same-site mean BMD in young women. The World Health Organization defines osteoporosis as a T-score ≤ -2.5 at the femoral neck [24]. Since July 1, 2006, the French health insurance system reimburses DXA in women meeting the criteria listed in (Box 1).

3.1.2.1. Selecting the BMD measurement site and reference curve. BMD should be measured at two sites, the lumbar spine and proximal femur (femoral neck and total hip). BMD measurement at the radius is not indicated for the evaluation of postmenopausal osteoporosis [25]. According to the International Osteoporosis Foundation, if DXA is performed at a single site, the femoral neck or total hip should be selected and the NHANES III reference curve used [26,27]. BMD at the femoral neck correlates more strongly with the fracture risk in cohort studies overall, is used in the FRAX tool and can serve to monitor treatment effects.

Box 1: Criteria for reimbursement of dual-energy X-ray absorptiometry (DXA) in France (*Journal Officiel*, June 30, 2006: *Décision du 29 juin 2006 de l'Union nationale des caisses d'assurance maladie relative à la liste des actes et prestations pris en charge par l'assurance maladie*).

First DXA

In the general population, regardless of age and gender

- evidence of osteoporosis: vertebral fracture confirmed radiologically (vertebral body deformity) with no evidence of trauma or tumor; previous nonvertebral fracture without significant trauma (at sites other than the skull, fingers, toes, and cervical spine);
- disease or treatment known to induce osteoporosis: systemic glucocorticoid therapy prescribed for at least 3 months in a daily dosage > 7.5 mg of prednisone-equivalent; if possible, DXA should be performed at treatment-initiation;
- documented history of a disease or treatment known to induce osteoporosis: prolonged hypogonadism (including bilateral orchiectomy or prolonged anti-androgen therapy with a Gn-Rh analog), uncontrolled hyperthyroidism, hypercorticism, primary hyperparathyroidism, and osteogenesis imperfecta.

Additional criteria (vs. the general population) in postmenopausal women (including those taking hormone replacement therapy in doses below the values recommended for bone protection):

- history of hip fracture without significant trauma in a first-degree relative;
- Body mass index < 19 kg/m^2;
- menopause before 40 years of age, for whatever reason;
- history of glucocorticoid therapy for at least 3 consecutive months in a daily dosage > 7.5 mg prednisone-equivalent.

Second DXA:

- discontinuation of osteoporosis drug therapy in a postmenopausal woman, except if the drug is stopped prematurely because of adverse events;
- in postmenopausal women with no history of fracture, when the first DXA showed normal BMD values or osteopenia and no osteoporosis therapy was given, DXA can be repeated 3 to 5 years later.

3.1.2.2. Relation between a low T-score and the fracture risk. The fracture risk increases as BMD decreases: for each BMD decrease by 1 SD, the fracture risk increases 2-fold [28–30]. As the T-score value declines, the risk of osteoporotic hip fracture increases [31,32]. BMD decrease at any site is associated with a higher risk of fracture at any site. Nevertheless, a decline in BMD measured at the femur strongly predicts the risk of fracture at any site and at the femur [32,33].

3.1.2.3. Limitations of using a T-score cutoff. Defining osteoporosis based on BMD criteria fails to identify all women at risk for fractures. Thus, over 50% of non-vertebral fractures occur in women whose T-score is above -2.5 [30,34–36]. Among patients with osteoporosis diagnosed based on a fracture after a trivial trauma although they do not meet BMD criteria for the disease, bone tissue assessments show specific alterations responsible for decreased bone strength. For instance, obese individuals may have BMD values that are too low for their body weight, diabetic patients exhibit bone matrix abnormalities related to protein glycation and women starting aromatase inhibitor therapy experience excessive bone resorption [37–41].

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Table 1
Risk factors for falls.

Patient-related factors	Environmental factors
Age > 80 years	*Consumption of alcoholic beverages*
Fall within the past year	*Physical inactivity*
Musculoskeletal and neurological impairments	*Malnutrition*
decreased muscle strength in the lower limbs	*Physical environment*
decreased grip strength	fall hazards in the home (stairs, rugs)
difficulty walking	use or failure to use walking aids
impaired balance	fall hazards out of doors (uneven sidewalks, slippery surfaces)
Impaired visual acuity	cane used inappropriately or not at all
Hearing loss	Socioeconomic factors: education, income, living conditions, social integration
Use of psychotropic agents	
Polypharmacy (> 4 medications)	
Specific diseases	
Parkinson disease	
dementia	
depression	
residual impairments after a stroke	
vitamin D deficiency	

3.1.3. Evaluating the fall risk

Risk factors for falls play a central role in the occurrence of non-vertebral fractures in very elderly and/or frail patients [42]. Recommendations about identifying individuals at high risk for falls were issued by the HAS in 2005 (http://www.has-sante.fr/portail/upload/docs/application/pdf/prevention_des_chutes-argumentaire.pdf).

Numerous factors increase the risk of falls (Table 1). Routinely evaluating and managing risk factors for falls in elderly patients would raise major challenges. Therefore, HAS guidelines, together with guidelines issued in the UK and US in 2010 and recommendations by other scientific societies, support the use of simple tests and questions as screening tools for elderly patients. In practice, a history of falling, particularly within the last 3–6 months and regardless of the circumstances, or a fear of falling that restricts self-sufficiency should prompt an evaluation for causes of balance impairment, if needed during a specialized geriatric visit. In doubtful cases, dynamic balance impairments responsible for an up-and-go time above 14 seconds or static balance impairments with a single-leg stance time below 5 seconds and/or instability during the sternal push test indicate a need for an etiological workup and an appropriate management strategy [43,44].

3.2. Fracture risk prediction tools for specialists

These tools can be helpful to all physicians trained in interpreting their results and experienced in managing bone diseases.

3.2.1. Absolute fracture risk estimation using the FRAX®

The identification of individuals at risk for fractures requires a multifactorial assessment including BMD measurement and an evaluation of the clinical risk factors associated with the fracture risk (Box 2). The roles played by the various risk factors varies with age. The Fracture Risk Assessment Tool FRAX® was developed to quantify the fracture risk [45] (www.sheffield.ac.uk/FRAX). The tool estimates the 10-year probability of a hip fracture and of major fracture defined as a fracture of the hip, humerus, wrist or a clinical vertebral fracture. The FRAX® tool has been tested in several cohorts in France [46–50]. The recommendations set forth below (consensus of experts) are based on national validation and calibration studies [46–50] and on international recommendations (NOF, NOS, NOGG).

Box 2: Risk factors for fractures.

- Age*
- Caucasian ethnicity
- Menopause before 40 years of age
- Primary or secondary amenorrhea
- Family history of bone fragility fractures*
- History of fracture*
- Low body mass index*
- Visual acuity impairment*
- Neuromuscular disorders*
- Very long period of immobility*
- Smoking*
- Glucocorticoid therapy*
- Low calcium intake
- Vitamin D deficiency
- Excessive alcohol use

*increases the risk of osteoporotic fractures independently from bone mineral density.

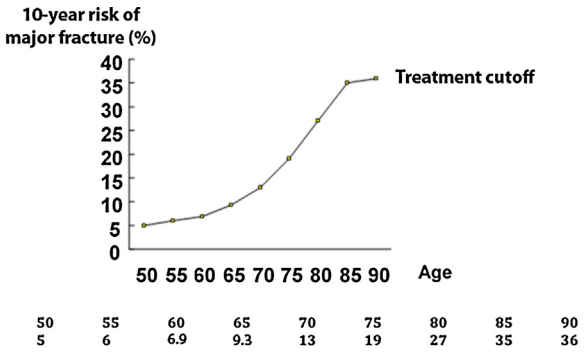

Fig. 1. FRAX® probability of major osteoporotic fracture cutoffs for osteoporosis drug therapy according to patient age in France.

The FRAX® tool is not useful when there is a clear indication to start osteoporosis therapy, for instance a history of severe fracture or a T-score ≤ -3 at the lumbar spine and at the total hip and/or femoral neck.

The FRAX® cutoff above which osteoporosis treatment is appropriate varies with age. For a given age, the FRAX® cutoff for treatment is the value in same-age women with a history of fracture (risk of repeat fracture) [45]. Fig. 1 shows the cutoffs according to age (consensus of experts).

3.2.2. The trabecular bone score (TBS)

The trabecular bone score (TBS) is a measure of bone texture that is automatically computed from DXA data at the lumbar spine. TBS values are lower in patients with than without fragility fractures and have been found effective in discriminating between these two groups. Combining the BMD and TBS values predicts the fracture risk more effectively than does the lumbar BMD value alone. Nevertheless, in prospective studies, femoral BMD was the strongest predictor. Routine TBS measurement for fracture risk prediction and treatment monitoring is not recommended, as the ability of the TBS to reclassify patients has not been firmly established [51,52]. The TBS is associated with the risk of osteoporotic hip fractures after adjustment on the FRAX® probability [53,54]. A metaanalysis of 14 prospective studies showed that adjustment on the TBS did not substantially improve the predictive performance of the FRAX® tool [55,56]. In situations where the appropriateness of osteoporosis therapy is not obvious, the TBS can be used in the same way as the FRAX® and with the same treatment-initiation cutoffs.

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3.2.3. Bone turnover markers

Several laboratory markers are available for noninvasively assessing bone turnover. Among them, some reflect bone formation (osteocalcin, bone alkaline phosphatase, procollagen I extension peptides) and others bone resorption (degradation peptides). However, the clinical meaning of bone marker levels must be interpreted in the light of potential confounders such as renal function or a recent fracture. No markers are available for predicting DXA results. In contrast, bone turnover markers can predict bone loss. Combining several markers and/or combining markers and risk factors might improve the prediction of bone fragility. No marker associated with an increased fracture risk was reproducibly identified in published studies. However, combining markers and BMD measurement may improve predictive performance. According to recommendations recently issued by experts, there is insufficient evidence that bone turnover markers help to predict the fracture risk in clinical practice [57]. Thus, routine bone turnover marker assays are not recommended for this purpose but may help specialists decide whether osteoporosis therapy is in order in difficult cases. Furthermore, marker assays are useful for monitoring the effects of anti-resorptive treatments.

4. Strategies for preventing and treating postmenopausal osteoporosis

The diagnosis of osteoporosis requires the elimination of other causes of bone fragility, which include metabolic diseases, malignancies and genetic disorders. This diagnostic step must be completed before starting osteoporosis therapy. Fracture prevention is the treatment goal. Therefore, osteoporosis therapy should aim both to increase bone strength and to decrease the risk of falls. The management strategy thus combines pharmacological and non-pharmacological components. The efficacy of available osteoporosis medications in preventing fractures was proven in populations with osteoporosis diagnosed based on BMD criteria or on a history of fracture (Tables 2 and 3) [58–75].

No head-to-head comparisons of the anti-fracture efficacy of osteoporosis medications are available. Neither BMD values nor

Table 2
Effect of treatments on the risk of vertebral fracture.

Treatment	Study	Duration	Relative risk	Comments
Hormone replacement therapy	WHI	5 years	All fractures (including vertebral fractures): 0.76 (0.69–0.85)	
Raloxifene	MORE (Delmas)	3 years	0.7 (0.5–0.8)	
		4 years	0.64 (0.53–0.76)	Decrease during the 4th year similar to the first 3 years
Alendronate	FIT 1 (Black)	3 years	0.53 (0.41–0.68)	Morphometric
			0.45 (0.27–0.72)	Clinical vertebral fractures
	FIT 2 (Cummings)	4 years	0.56 (0.39–0.80)	Secondary endpoint
	Metaanalysis (Cranney)	2–3 years	0.52 (0.43–0.65)	
	Metaanalysis (Wells)	≥ 1 year	0.55 (0.38–0.80)	Primary prevention
			0.55 (0.43–0.69)	Secondary prevention
Risedronate	Vert NA (Harris)	3 years	0.59 (0.42–0.82)	
	Vert MN (Reginster)	3 years	0.51 (0.36–0.73)	
	Pooled analysis VERT-NA et MN	1 year	0.38 (0.25–0.56)	High-risk women (≥1 vertebral fracture and T-score ≤ −2.5)
	Metaanalysis (Wells)	≥ 1 year	0.61 (0.50–0.76)	Secondary prevention
	Metaanalysis (Boonen)	3 years	0.19 (0.09–0.4)	Post-hoc analysis in individuals ≥ 80 years
Zoledronic acid	HORIZON PFT (Black)	3 years	0.3 (0.24–0.38)	
	HORIZON RFT (Lyles)	3 years	0.54 (0.32–0.92)	In hip fracture patients
	Pooled analysis in individuals ≥ 75 years	3 years	0.34 (0.21–0.55)	Post-hoc analysis (clinical vertebral fractures)
Teriparatide	PFT (Neer)	18 months	0.35 (0.45–0.78)	
Denosumab	FREEDOM (Cummings)	3 years	0.32 (0.26–0.41)	

Table 3
Effect of treatments on the risk of nonvertebral fracture.

Treatment	Study	Duration	Relative risk	Comments
Hormone replacement therapy	WHI (Cauley)	5 years	All fractures (including vertebral fractures): 0.76 (0.69–0.85)	Hip 0.66 (0.45–0.98)
Raloxifene	MORE (Ettinger)	3 years	0.92 (0.8–1.1) (NS)	Post-hoc in selected high-risk patients 0.53 (0.29–0.99)
Alendronate	FIT 1 (Black)	3 years	0.80 (0.63–1.01)	Hip: 0.49 (0.23–0.99) Wrist: 0.52 (0.31–0.87)
	FIT 2 (Cummings)	4 years	0.86 (0.73–1.01)	
	Metaanalysis (Karpf)	3 years	0.71 (0.50–0.997)	
	Metaanalysis (Cranney)	3 years	0.51 (0.38–0.69)	
	Metaanalysis (Wells)	≥ 1 year	0.77 (0.64–0.92)	Hip fracture: RR = 0.47 (0.26–0.85)
Risedronate	Vert NA (Harris)	3 years	0.61 (0.39–0.94)	Women with at least one vertebral fracture
	Vert MN (Reginster)	3 years	0.67 (0.44–1.04)	Women with at least two vertebral fractures
	Hip Study (McClung)	3 years	0.7 (0.6–0.9)	Only in women with osteoporosis aged 70–79 years 0.4 (0.6–0.9)
	Metaanalysis (Wells)	≥ 1 year	0.80 (0.72–0.90)	Hip fracture: RR = 0.74 (0.59–0.94)
	Metaanalysis (Boonen)	3 years	NS	Post-hoc analysis in individuals ≥ 80 years
Zoledronic acid	HORIZON PFT (Black)	3 years	0.75 (0.64–0.87)	Hip fracture: 0.59 (0.42–0.83)
	HORIZON RFT (Lyles)	3 years	0.73 (0.55–0.98)	In hip fracture patients: hip fracture 0.70 (0.41–1.19)
	Pooled analysis of individuals ≥ 75 years (Boonen)	3 years	0.73 (0.60–0.90)	Post-hoc analysis
Teriparatide	PFT (Neer)	18 months	0.47 (0.25–0.88)	
Denosumab	FREEDOM (Cummings)	3 years	0.80 (0.67–0.95)	Hip: RR = 0.60 (0.37–0.97)

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Box 3: Examples of treatment strategies in various clinical situations.

- In hip fracture patients, zoledronic acid should be considered for the first-line treatment as the only drug for which evidence of anti-fracture efficacy exists in this population (grade A).
- In patients with two prevalent vertebral fractures, teriparatide can be used as the first-line treatment at the time of diagnosis, in the absence of contraindications (grade A).
- In women younger than 70 years of age who have osteoporosis requiring drug therapy, raloxifene deserves considerations if the risk of nonvertebral fractures is low as indicated by absence of the following criteria: low T-score at the hip, risk factors for falls, and history of nonvertebral fracture (grade A).
- In women younger than 60 years of age who have menopausal symptoms and osteoporosis without severe fractures, hormone replacement therapy can be considered (grade A).
- In patients with severe fractures and very low BMD values (T-score ≤ -3) injectable drugs can be used to achieve the BMD target (T-score > -2.5 or -2 at the hip) by the end of the course of treatment; options include zoledronic acid, denosumab (in patients with intolerance or unresponsiveness to bisphosphonates), and teriparatide (reimbursed for patients with at least two vertebral fractures) followed by an anti-resorptive agent (consensus of experts).

biochemical parameters can serve to compare efficacy. Important considerations when selecting the drug include beneficial or undesirable extra-skeletal effects, specific contraindications of each drug, constraints for patients, and decision-sharing with patients. Taking the drugs exactly as ordered may contribute to minimize the risk of certain adverse events. Factors relevant to drug selection include age, the risk of vertebral and/or non-vertebral fractures, and fracture severity (consensus of experts). Finally, the conditions under which each drug is reimbursed by the health insurance system must be respected.

In every case, the patient should be informed about the disease and its treatments. Emphasis should be placed on treatment adherence as part of the process of shared decision making. Adherence should be monitored throughout follow-up.

If osteoporosis drug therapy fails or raises challenges, advice should be sought from a bone disease specialist (consensus of experts). Management by a multidisciplinary network for fracture patients has been shown to improve the quality of care [76,77]. The recommendations set forth here consider both the first treatment course and subsequent treatments. Box 3 gives examples of treatment recommendations for various clinical situations.

4.1. Osteoporosis medications

4.1.1. Recommendations for fracture patients

4.1.1.1. Severe fracture. DXA should be performed before making treatment decisions if allowed by the medical situation (grade A). Osteoporosis drug therapy is recommended in patients of all ages after a severe fragility fracture (hip, vertebra, distal femur, proximal humerus, pelvis, proximal tibia) if the T-score is ≤ -1 (consensus of experts) (Fig. 2). DXA provides a quantitative assessment of bone fragility, confirms that the T-score is ≤ -1, and serves as a reference for monitoring the treatment (Fig. 2). If the T-score is > -1, it may be best to seek advice from a bone disease specialist and to use fracture prediction tools (FRAX®, TBS and bone turnover markers).

In patients with severe non-vertebral fractures, the following drugs are reimbursed in France: alendronate, 70 mg/week or 10 mg/day; risedronate, 35 mg/week or 75 mg on 2 consecutive days once a month or 5 mg/day; zoledronic acid, 5 mg as a single intravenous infusion per year; and denosumab, 60 mg subcutaneously every 6 months (reimbursed only when used after a bisphosphonate). Zoledronic acid is the only osteoporosis drug that has been proven effective in postmenopausal patients with hip fractures [69].

The following treatments are recommended in patients with vertebral fractures:

- alendronate, 70 mg/week or 10 mg/day;
- risedronate, 35 mg/week or 75 mg on 2 consecutive days once a month or 5 mg/day;
- zoledronic acid, 5 mg as a single intravenous infusion per year;
- denosumab, 60 mg subcutaneously every 6 months (reimbursed only when used after a bisphosphonate);
- raloxifene, 60 mg/day (reimbursed in patients younger than 70 years);
- teriparatide (reimbursed in patients with at least two vertebral fractures);
- menopausal hormone replacement therapy in women aged 50 to 60 years of age who have menopausal symptoms.

Parenterally administered drugs (zoledronic acid and denosumab) can be given preference in patients with any of the following: hip fracture; very low BMD values; comorbidities and, more specifically, memory impairments; poor adherence; and polypharmacy (consensus of experts).

4.1.1.2. Non-severe fractures (wrist and other sites). DXA should be performed before making treatment decisions (grade A). Given the correlation between declining BMD values and rising fracture risk, the treatment indications depend on the T-score (consensus of experts). These indications are reported in Fig. 2 [29–31].

Treatment is recommended if the T-score is ≤ -2 at the lumbar spine and/or hip. If the T-score is > -2 and < -1, it may be best to seek advice from a bone disease specialist and to use fracture prediction tools (FRAX®, TBS and bone turnover markers). If the T-score is > -1, treatment is not recommended (consensus of experts).

When osteoporosis drug therapy is indicated, the following drugs may be used (in alphabetical order): alendronate, 70 mg/week or 10 mg/day; risedronate, 35 mg/week or 75 mg on 2 consecutive days once a month or 5 mg/day; zoledronate, 5 mg as a single intravenous infusion per year; denosumab, 60 mg subcutaneously every 6 months (reimbursed only when used after a bisphosphonate); raloxifene, 60 mg/day; and menopausal hormone replacement therapy in women aged 50 to 60 years of age who have menopausal symptoms. Raloxifene should be reserved for patients at only moderate risk for non-vertebral fractures (grade A), i.e., who are younger than 70 years of age and have none of the following risk factors: femoral T-score ≤ -3, high risk of falls, and history of non-vertebral fracture. Menopausal hormone replacement therapy is indicated in postmenopausal women who have menopausal symptoms and are younger than 60 years of age, as proof of efficacy exists only for the early postmenopausal period. The treatment duration should be determined based on the menopausal symptoms and on a discussion of the risk/benefit ratio with the patient. Patients without menopausal symptoms may be given hormone replacement therapy if they fail to tolerate or to respond to other osteoporosis drugs. In patients receiving dosages lower than those recommended for bone protection, repeat DXA should be performed 2 to 3 years after treatment-initiation (grade A). If the BMD values are still low, an osteoporosis drug can be added to the hormone replacement regimen.

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Based on T-score at site where the value is lowest	Severe fractures (femur, spine, humerus, pelvis, proximal tibia)	Non-severe fractures	No fracture but risk factors for osteoporosis and/or falls
>-1	Advice from a specialist	No treatment	No treatment
≤-1 and >-2	**Treatment**	Advice from a specialist	No treatment
≤-2 and >-3	**Treatment**	**Treatment**	Advice from a specialist
≤-3	**Treatment**	**Treatment**	**Treatment**

Fig. 2. Indications of drug therapy for postmenopausal osteoporosis.

4.1.2. Recommendations for patients without fractures

Osteoporosis screening using DXA is recommended in postmenopausal women with risk factors for osteoporosis (grade A). The test is reimbursed in this situation. Falls and osteoporosis are independent risk factors for non-vertebral fractures and osteoporosis is common in patients who fall. Therefore, screening DXA should be performed in elderly patients at risk for falls (consensus of experts) [78].

Given the correlation between declining BMD values and rising fracture risk, the treatment indications depend on the T-score (consensus of experts). These indications are reported in Fig. 2 [29–31]. Treatment is recommended if the T-score is ≤ -3 at the lumbar spine and/or hip. If the T-score is > -3 et ≤ -2, it may be best to seek advice from a bone disease specialist and to use fracture prediction tools (FRAX®, TBS, and bone turnover markers). If the T-score is > -2, treatment is not recommended (consensus of experts).

When osteoporosis drug therapy is indicated, the treatment options are those listed for non-severe fractures.

The criteria for using raloxifene and menopausal hormone replacement therapy are described in the previous section.

4.2. Treatment measures to be used in combination with osteoporosis drug therapy

4.2.1. Fall prevention

Preventing falls and their consequences is crucial in elderly and/or frail patients. The implementation of appropriate fall prevention measures has been reported to decrease falls in elderly patients who are at high risk for falls and who live at home [79]. Fall prevention measures include exercises to improve balance, vitamin D supplementation if serum 25-OH-vitamin D levels are low, decreasing the use of medications that impair alertness or induce postural hypotension, eliminating environmental hazards, improving vision and providing appropriate treatment for lower limb pain.

The assessment of risk factors for falls in individual patients and the provision of appropriate management requires collaboration among the networks involved in fracture care and in geriatric care, rehabilitation departments, and geriatric teams.

Participation in physical activity programs that include specific balance exercises is key to successful fall prevention. Also needed are muscle strengthening exercises; work on coordination and stamina; and activities to increase joint motion range, particularly at the ankle [79]. These exercises have been proven effective in decreasing the risk of falls and of complicated falls (grade A).

Patients older than 65 years of age should be advised to engage in moderate-to-high intensity exercises at least twice a week, preferably on nonconsecutive days, with 8 to 12 repeats of 8 to 10 exercises (updated recommendations by the French national health and nutrition program) (*Programme national nutrition santé-révisions des repères relatifs à l'activité physique et à la sédentarité* [PNNS] *2016*) (www.anses.fr).

Many barriers to engaging in physical activities have been reported. Patients often feel that their age or health problems make exercising difficult. However, these two factors indicate a strong need for exercise. Patients should be encouraged and supported in their efforts to develop an exercise routine. No specific exercise duration is recommended, but each exercise should be repeated until a further repeat would be difficult to perform without help. Both the quality and the intensity of the physical activity are important. That increasing the level of physical activity and participating in exercise programs act synergistically to decrease the fall risk and in some studies, the fracture risk should be clearly explained to elderly patients and their carers (grade B) [80–82].

4.2.2. Calcium intake

The recommended calcium intake for postmenopausal women older than 50 years of age is at least 1000 to 1200 mg. Preference should be given to dietary calcium (dairy products and calcium-rich mineral water) (consensus of experts). Calcium-deficient patients at risk for fractures should ingest at least 1000 mg of calcium per day according to the PNNS. In practice, the dietary calcium intake can be assessed using a food frequency self-questionnaire available online (www.grio.org) (Table S1; See the supplementary material associated with this article online). Calcium supplements alone have not been proven effective in decreasing the risk of osteoporotic fractures. Calcium supplementation was associated with a higher risk of cardiovascular events in older women [83–85]. This adverse effect occurred chiefly among women whose baseline dietary calcium intake was adequate [86]. Vitamin D-deficient patients should receive vitamin D supplements.

4.2.3. Vitamin D

Current recommendations state that the serum 25-OH-vitamin D level should be kept at or above 30 ng/mL (75 nmol/L) (consensus of experts) [45]. A serum 25-OH-vitamin D assay should be performed to rule out other causes of bone fragility (osteomalacia), as well as in patients who fall and are scheduled for osteoporosis medication therapy. In both these indications, the assay is reimbursed in France. The assay may need to be repeated during follow-up to check that the target is met, particularly in patients at high risk for vitamin D deficiency due to comorbidities, malabsorption, difficulty achieving therapeutic goals or initial profound vitamin D deficiency defined as serum 25-OH-vitamin D < 10 ng/mL. Follow-up assays are recommended in patients who require osteoporosis medication therapy (consensus of experts).

In patients with vitamin D deficiency or insufficiency, initial high-dose supplementation can rapidly increase the serum 25-OH-vitamin D level above 30 ng/mL [45]. The vitamin D dosage for maintenance therapy is 800 to 1200 IU/day. Instead of daily supplementation, a dose of 80,000 to 100,000 IU can be given every 2 to 3 months [46]. Currently available data suggest that high doses of 500,000 to 600,000 IU once or twice a year may be deleterious and consequently are not recommended [87] (consensus of experts).

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4.3. Elimination of modifiable risk factors

Whenever possible, risk factors for fractures and falls should be eliminated. Examples include smoking cessation and discontinuation of non-essential medications associated with falls such as opiates and hypnotic agents [88,89]. Oral glucocorticoid therapy should be discontinued or reduced to the minimal effective dosage. Restraint regarding alcohol consumption should be encouraged.

5. Follow-up of patients with postmenopausal osteoporosis

Table 4 lists the main follow-up measures needed according to the nature of the osteoporosis treatment.

5.1. Clinical follow-up

Patients must receive clinical follow-up (consensus of experts). Fractures must be recorded and evaluations performed to detect new risk factors and/or diseases associated with osteoporosis. Patients should be asked about falls, and their risk factors for falls should be assessed. Treatment adherence should receive careful attention. Finally, adverse drug effects should be sought.

Vertebral fractures are responsible for loss of height. Consequently, height should be measured once a year in patients with osteoporosis. A reduction in height is a nonspecific sign of vertebral disease [90–92].

As with all treatments for chronic disease, osteoporosis medications are effective only when taken as ordered. Several studies have established that poor treatment adherence is associated with decreased effectiveness [93]. Treatment adherence monitoring is therefore a crucial component of the clinical follow-up. In addition, in the oldest patients, adherence to fall prevention measures should be assessed.

Patients receiving treatment for postmenopausal osteoporosis should be informed about the very low risk of osteonecrosis of the jaw and of atypical femoral fractures associated with bisphosphonates and denosumab. Dental care should be provided as needed before treatment-initiation. If the patient receives regular care from a dentist and is not scheduled for a dental extraction or other invasive dental procedure in the short term, anti-resorptive treatment can be started. An evaluation by a dentist is recommended for patients who do not see a dentist regularly. If the short-term fracture risk is high, for instance after a severe fracture, the dental evaluation should not delay the initiation of osteoporosis therapy. The recommendations for oral care during treatment are the same as in the general population, i.e., a dentist visit at least once a year. Dental extractions can be performed if needed, with antibiotic therapy. Bisphosphonate or denosumab therapy for osteoporosis does not contraindicate dental implant surgery. (http://afssaps.sante.fr/htm/10/filltrpsc/lp071203.htm) (www.sscmfco.fr). These recommendations do not apply to patients taking bisphosphonate or denosumab therapy for osteolytic tumors.

5.2. Role for bone mineral density (BMD) measurement during follow-up

5.2.1. Frequency of BMD measurement

BMD measurements can be performed 2 to 3 years after treatment-initiation and whenever a treatment change is considered (discontinuation of osteoporosis drug therapy or switch to a different drug). The goal is to check the absence of bone loss (defined as a greater than 0.03 g/cm^2 BMD decrease) [94] (grade B). BMD measurement is also appropriate when the treatment must be stopped prematurely due to drug-related adverse events.

Recent data on zoledronic acid indicate that 40% to 61% of the decrease in the risk of vertebral and non-vertebral fractures is attributable to the BMD increase at the total hip [95]. With denosumab, the proportion of the anti-fracture effect ascribable to the same-site BMD increase is over 50% at vertebral and 72% at non-vertebral sites [96]. Similar results have been obtained with teriparatide. Given these data, serial BMD measurements during follow-up are now intended not only to detect non-responders, but also to assess the bone response to treatment with the goal of achieving tight disease control.

BMD values at the end of a treatment course is among the criteria used to assess the risk of fractures over the next few years. The femoral BMD value after 5 years of alendronate or 3 years of zoledronic acid has been shown to predict the fracture risk over the following years [97,98]. In women whose hip T-score is < -2.5 after 3 years of zoledronic acid, 5 years of alendronate, or 4 years of denosumab, further treatment is beneficial to decrease the risk of vertebral fractures with zoledronic acid or of non-vertebral fractures with alendronate and denosumab [99].

5.2.2. BMD target in patients with postmenopausal osteoporosis

Setting a BMD target may change current practice regarding the duration of the first treatment course. At present, the duration is determined in advance based on efficacy data from placebo-controlled trials. Recommended durations are thus 18 months with teriparatide, 3 years with zoledronic acid and denosumab and 5 years with other drugs. At the end of these periods, the decision to stop or continue the treatment is determined based on the residual fracture risk.

One possible BMD target is the value above which the fracture risk is decreased to an acceptable level. The target may vary with age and with the site at greatest risk for fracture. In all patients, the minimum treatment objective is absence of bone loss (BMD change ≤ 0.03 g/cm^2). After a severe fracture in a patient with a very low femoral BMD value, the goal is a significant BMD increase, to a T-score value ≥ -2.5 or -2 at the femur [97–99]. Achieving this goal may require treatment adjustments (consensus of experts).

5.3. Role for bone turnover markers during follow-up

When treatment is recommended with an anti-resorptive agent (bisphosphonate, denosumab, raloxifene, or menopausal hormone replacement therapy), a bone resorption marker (serum CTX) can be assayed 3 to 12 months after treatment-initiation depending on the drug. Pharmacological effectiveness results in serum CTX levels that are at least within the normal range for non-menopausal women. If the serum CTX levels remain high, treatment adherence and modalities should be reviewed with the patient. If appropriate, a treatment change should be considered. However, an important point is that CTX assays are interpretable only if performed in the morning after an overnight fast. Furthermore, in patients with a history of fracture, the assay must be performed at least 6 months after the event (grade B).

5.4. Spinal radiographs or vertebral fracture assessment

Radiographs or VFA to detect vertebral fractures are indicated in postmenopausal women during osteoporosis drug therapy who report spinal pain and/or whose height as measured prospectively decreases by at least 2 cm [90] (consensus of experts).

6. Treatment safety

For methodological reasons, extension studies of phase III randomized controlled trials supply only a low level of evidence

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Table 4
Follow-up of patients receiving osteoporosis drug therapy.

Treatments	No fracture	New risk factors	Height	Adherence	Safety	DXA	Bone turnover markers	Evaluation of vertebral morphology
Alendronate	+	+	Annually	+	+	2–3 years	3–12 months after treatment-initiation	If height loss and/or spinal pain
Risedronate	+	+	Annually	+	+	2–3 years	3–12 months after treatment-initiation	If height loss and/or spinal pain
Zoledronic acid	+	+	Annually	+	+	3 years	If delivery of the infusion is in doubt	If height loss and/or spinal pain
Denosumab	+	+	Annually	+	+	3 years	If delivery of the injection is in doubt	If height loss and/or spinal pain
Teriparatide	+	+	Annually	+	+	18 months	NON	If height loss and/or spinal pain
Raloxifene	+	+	Annually	+	+	2–3 years	3–12 months after treatment-initiation	If height loss and/or spinal pain
Hormone replacement therapy	+	+	Annually	+	+	2–3 years	3–12 months after treatment-initiation	If height loss and/or spinal pain

+: at each visit.

regarding anti-fracture efficacy. However, they show that prolonged therapy is safe both overall and for bone tissue. During bisphosphonate therapy for up to 10 years, the incidence of gastrointestinal and other adverse events was not higher than in the placebo group during the randomized controlled phases.

Exposure to bisphosphonates or denosumab is among the risk factors for osteonecrosis of the jaw. In patients with osteoporosis, the incidence of osteonecrosis of the jaw is extremely low and similar to that in the general population (see section 5 on follow-up). Thus, the ASBMR task force reported an incidence of 0.001% to 0.01% patient-years [100].

Bisphosphonate or denosumab therapy is also one of the risk factors for atypical femoral fractures. With bisphosphonates, the risk is very low, with an estimate of 3.2 to 50 cases/100,000 patient-years by the ASBMR task force [101]. The risk decreases after treatment discontinuation. Concomitant risk factors such as specific femoral and knee geometry features may be present. The diagnosis should be considered when a patient reports persistent pain in the groin or thigh. These data do not challenge the favorable risk/benefit ratio in patients at risk for osteoporotic fractures [101,102].

The body of evidence in the literature indicates that the risk of cancer is not increased in patients exposed to bisphosphonates [103]. Furthermore, data suggest an anti-tumor effect of anti-resorptive drugs (oral and injectable bisphosphonates and denosumab) in patients with breast cancer.

Patients should be informed of the risk of rare adverse events such as uveitis. Denosumab is associated with a risk of hypocalcemia, particularly in patients with vitamin D deficiency or kidney failure. An evaluation must be conducted to ensure that the bone fragility requiring denosumab therapy is not a complication of chronic kidney disease. In this situation, a serum calcium assay should be performed before each denosumab injection.

7. Treatment duration

7.1. Theoretical treatment duration

The duration of osteoporosis drug therapy depends on age, the BMD treatment response, bone and overall tolerance of the drug and occurrence of fractures during treatment (consensus of experts). The anti-fracture efficacy of available osteoporosis drugs was proven in randomized controlled trials lasting 3 to 5 years, or 18 months for teriparatide (grade A).

Studies have assessed the effects of longer treatment durations: 10 years for alendronate [104,105], 7 years for risedronate [106], 8 years for raloxifene [107], 9 years for zoledronic acid [108] and 10 years for denosumab [109]. As these studies had no control group, their results cannot establish long-term efficacy. However, they provide valuable data on long-term osseous and extraosseous treatment safety.

7.2. Course of action in clinical practice

Treatment discontinuation after the first drug course can be considered in patients meeting the following criteria (consensus of experts): no fracture during treatment; no new risk factors; no BMD decrease > 0.03 g/cm^2 at the spine or hip; and in patients with a history of severe fracture, a femoral T-score ≥ -2.5 or -2. Considering each specific situation is not feasible and these recommendations should be adapted to each individual patient.

An evaluation is recommended 2 years after treatment discontinuation. The interval between subsequent evaluations depends on the type of treatment. The carry-over effect on BMD after treatment discontinuation is more prolonged with zoledronic acid and alendronate than with the other drugs. No carry-over effect exists with denosumab; instead, a rebound bone resorption effect with loss of some of the BMD gains occurs at treatment discontinuation.

8. Treatment sequences

Several treatment sequences have been validated. BMD values decrease after the recommended 18-month-long course of teriparatide therapy. Consequently, teriparatide therapy should be followed immediately by treatment with an anti-resorptive agent (bisphosphonate or denosumab) [110–112]. Similarly, denosumab discontinuation is followed by bone loss with an increase in the risk of multiple vertebral fractures. There is some evidence that bisphosphonates may prevent bone loss after denosumab discontinuation. Therefore, oral or injectable bisphosphonate therapy should be given for 6 to 12 months when denosumab is stopped [113,114] (consensus of experts).

The oral bisphosphonate-denosumab sequence produces a larger BMD increase than does prolonged bisphosphonate therapy [115,116]. In contrast, taking zoledronic acid after oral bisphosphonates does not result in BMD values above those obtained with prolonged oral bisphosphonates [117,118].

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K. Briot: occasional interventions as an expert or speaker for Amgen, MSD, Lilly and Pfizer.

C. Roux: occasional interventions for ALEXION, AMGEN, PFIZER, and UCB; and clinical trial research contracts for ULTRAGENYX.

T. Thomas: occasional interventions for Amgen, Chugaï, Expanscience, Gilead, HAC-Pharma, LCA, MSD, Novartis, Pfizer, Thuasne, UCB, Abbvie, BMS, Lilly, TEVA and Medac.

H. Blain: occasional interventions as an expert or speaker for Lilly and Expanscience.

D. Buchon declares that he has no competing interest.

R. Chapurlat occasional interventions as an expert or speaker for Amgen, UCB, Radius and Lilly.

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G. Weryha Georges: occasional interventions for Novartis, Procter & Gamble, Lilly, Servier, Theramex, Daiichi Sankyo, and Ipsen; and clinical trial research contracts for Servier, Lilly, MSD, Amgen, Nycomed and Roche.

B. Cortet: occasional interventions as an expert or speaker for Amgen, Expansience, Ferring, Lilly, Meda, Medtronic, MSD, Novartis, Roche diagnostics, and UCB.

Appendix A. Supplementary data

Supplementary data (Table S1) associated with this article can be found in the online version at: https://doi.org/10.1016/j.jbspin.2018.02.009.

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