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ORIGINAL ARTICLE

The 2018 Guidelines for the diagnosis and treatment of osteoporosis in Greece

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Abstract

Summary We report the updated guidelines for the management of osteoporosis in Greece, which include guidance on fracture risk assessment, diagnosis-pharmacological treatment-follow-up of osteoporosis based on updated information, and national evidence from Greek clinical practice and the healthcare setting.

Purpose The purpose of this report was to update the Guidelines for the Management of Osteoporosis in Greece that was published in 2011.

Methods In line with the GRADE system, the working group initially defined the main clinical questions that should be addressed when dealing with the diagnosis and management of osteoporosis in clinical practice in Greece. Following a literature review and discussion on the experience gained from the implementation of the 2011 Guidelines transmitted through the national electronic prescription network, the Hellenic Society for the Study of Bone Metabolism (HSSBM) uploaded an initial draft for an open dialogue with the relevant registered medical societies and associations on the electronic platform of the Greek Ministry of Health. After revisions, the Central Health Council approved the final document.

Results The 2018 Guidelines provide comprehensive recommendations on the issues of the timing of fracture risk evaluation and dual-energy X-ray absorptiometry (DXA) measurement, interpretation of the DXA results, the diagnostic work-up for osteoporosis, the timing as well as the suggested medications for osteoporosis treatment, and the follow-up methodology employed during osteoporosis treatment.

Conclusions These updated guidelines were designed to offer valid guidance on fracture risk assessment, diagnosis-pharmacological treatment-follow-up of osteoporosis based on updated information and national evidence from clinical practice and the healthcare setting. Clinical judgment is essential in the management of every individual patient for the purpose of achieving the optimal outcome in the safest possible way.

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Introduction

Osteoporosis is a covert chronic disease which remains asymptomatic until it is complicated by fragility fractures. Fractures, especially those of the hip, represent a major cause of disability, morbidity, and mortality for older people and pose an enormous economic burden on healthcare systems, this applying equally to the Greek healthcare setting [1, 2]. Population aging, particularly in the developed countries, further inflates the problem, making projections about the coming decades even more ominous [3].

To date, several management strategies have been developed to prevent, tools to diagnose, as well as efficacious and safe agents to treat osteoporosis and decrease the risk of fractures. However, and despite the publication of guidelines by several scientific national and international societies worldwide and their constant updates [4–6], it is a common belief that the disease is still under-diagnosed and under-treated, while, on the other hand, there are many individuals with low fracture risk who are needlessly treated for several years. These facts reflect either the inability of healthcare providers to accurately identify individuals at high risk or to adequately convince them of the necessity to receive treatment in the long term for this asymptomatic condition.

For this purpose, Guidelines for the Management of Osteoporosis in Greece was published some years ago [7]. The current manuscript details the 2018 update of these guidelines in line with the decision of the Greek Ministry of Health and in view of the 2015 Greek population-specific FRAX-based treatment thresholds [8] and developments in osteoporosis pharmaceutical market.

Methods

The Guidelines aimed to provide guidance to all physicians dealing with osteoporosis in Greece while also evaluating Greek patients with an increased risk for fragility fractures. In Greece, patients with a heightened risk of fractures can be treated in either a private or a public healthcare setting. Moreover, they can switch settings should they so desire and still be reimbursed by the National Healthcare System, given that both therapeutic and diagnostic procedures are prescribed through the national electronic prescription network and also according to the current Guidelines regarding treatment and diagnosis. Specifically, outpatients are reimbursed at 85% for any diagnostic procedure performed in a private setting, while the total cost (100%) is covered whenever a public service is used. Furthermore, any osteoporosis treatment received as an outpatient is reimbursed at 75%, while all relevant diagnostic and treatment (e.g., i.v. bisphosphonates) costs for osteoporosis are covered during admissions to either public or private hospitals.

In order for the previous Guidelines [7] to be updated, the working group defined the major clinical questions that are currently addressed when dealing with the diagnosis and management of osteoporosis in Greece. More specifically, the six major clinically relevant questions that were finally defined were the following:

- When and how should individuals be evaluated regarding their fracture risk?
- When should individuals be evaluated with dual-energy X-ray absorptiometry (DXA) scan?
- How should the results of the DXA scan be interpreted?
- What should the diagnostic work-up for osteoporosis include?
- When and how should patients be treated for osteoporosis?
- How should patients be followed during osteoporosis treatment?

Following the clarification of these clinical questions, a systematic literature review was performed in PubMed Medline concerning articles published between 2011 and 2017 using the keywords: osteoporosis, treatment, guidelines, recommendations, fragility fractures, bone mineral density, assessment of fracture risk, treatment failure, and bone markers. The following article types were included in the review process: clinical guidelines, meta-analyses of randomized controlled trials, randomized controlled trials, non-randomized controlled trials, prospective cohort studies, retrospective case-control studies, and cross-sectional studies, while consecutive case series and single case reports were scrutinized for adverse events. During three meetings, organized by the Hellenic Society for the Study of Bone Metabolism (HSSBM) and conducted among specialists treating patients with osteoporosis, an in-depth discussion took place concerning both the literature review and the accumulated experience from the implementation of the 2011 Guidelines in ongoing clinical practice via the national electronic prescription network.

Starting from January 2011, the national electronic prescription network has been the only pathway enabling prescription for treatment and diagnostic procedures to be formulated and subsequently reimbursed by the Greek National Healthcare System. Several therapeutic protocols are included in this network for almost any chronic disease such as diabetes, hypertension, and hyperlipidemia. Each therapeutic protocol follows an algorithmic process involving several steps regarding the personal history and medical exams of the

subject in order to reach the proposed medication for each case. Following the registration of a case to a therapeutic protocol, the network allows the continuation of the specific treatment for at least a year without requiring new data input at every prescription. Therefore, significant information was gathered, especially regarding the use of osteoporosis medications, which has been previously presented and analyzed in an effort to evaluate the cost-effective FRAX thresholds for osteoporosis treatment in Greece [8]. The working panel consisted of four endocrinologists, four orthopedic surgeons, and three rheumatologists; a ten-point numerical rating scale (1 = no agreement, 10 = full agreement) was used to measure agreement. In the case of issues with weak evidence in the literature, a modified Delphi technique was used. The draft document (in Greek), including the proposed recommendations for the update of the existing Guidelines and the summaries of evidence, was uploaded on the electronic platform for the "Disease and Patient Registries" of the Greek Ministry of Health in order to facilitate an open dialogue with the registered medical societies and associations. Patient or pharmaceutical associations were not involved in the formulation of the Guidelines. Taking into account the comments raised and following the relevant revisions, the final draft was submitted for approval to the Central Health Council, a committee of the Greek Ministry of Health with the authority to plan and approve treatment protocols of various diseases, as part of the formation of the national strategy on health, among other tasks.

The approved 2018 Guidelines for the diagnosis and treatment of osteoporosis replaced the previous Guidelines of 2011, and, as from November 2018, have been in use through the national electronic prescription network. The herein included description is the English version of the updated Guidelines and was developed and structured through a translation of the original Greek document by exactly the same working panel of experts.

During the transition from the 2011 to the 2018 Guidelines, there was a 2-month period during which physicians could use either the old or the new version of the Guidelines; after this period, all prescriptions had to be drawn up according to the latest Guidelines. No formal feedback can be currently provided from the users' point of view, and the authors are not aware of any process evaluating this aspect. However, although we cannot provide hard evidence, it is our conviction that any transition period between old and new guidelines should be quite short, as physicians tend to use the older versions, preferring to switch to the new ones only when they are obliged to.

Results

The six questions discussed below provide information with regard to screening (questions 1, 2), diagnosis (question 3), diagnostic work-up (question 4), treatment (question 5), and follow-up during treatment of osteoporosis (question 6).

Question 1: When and how should individuals be evaluated regarding their fracture risk?

The identification of individuals with high fracture risk is of paramount importance [3, 4, 6, 9]. Age and menopausal status are critical cutoff points which indicate the need for screening for osteoporosis. Specifically, in the absence of a previous fragility fracture, there is no need to assess fracture risk in a premenopausal woman or in a man < 50 years old [8], unless there exists one of the indications for BMD testing stated below in response to Question 2. A baseline clinical assessment is recommended in all perimenopausal or postmenopausal women and men ≥ 50 years old regardless of previous fragility fractures in order to identify, evaluate, and possibly correct existing clinical risk factors (CRFs). The risk of fracture at younger ages is typically low among generally healthy individuals, justifying the age limits set above as indicative for fracture risk assessment [10].

The Fracture Risk Assessment (FRAX) tool (http://www.shef.ac.uk/FRAX/) estimates the absolute 10-year fracture risk for individuals ≥ 40 years, who are naive to any antiosteoporotic treatment, depending on their risk factors and their BMD measurement, if available [11]. Essential information for FRAX calculation includes age, gender, prevalent osteoporotic fractures, weight and height, exposure to glucocorticoids, diagnosis of rheumatoid arthritis, secondary osteoporosis, parental hip fracture, and smoking and alcohol consumption. Hip BMD is optional in the calculation of fracture risk, making FRAX an ideal tool for the initial risk assessment of an individual. A Greek database for the calculation of fracture risk has been validated and is available for the general Greek population aged between 40 and 90 years old. Despite its known limitations [12], FRAX is currently regarded as the best tool to assess fracture risk among the population of Greece. Moreover, given that almost all diagnostic tests and prescriptions should come from the national web-based prescription network, FRAX can be considered as readily accessible to every physician dealing with osteoporosis in Greece.

In the case of a patient who has been receiving glucocorticoids for 3 months or more, FRAX needs to be adjusted according to the dose, which can be divided into low (< 2.5 mg of prednisolone or equivalent daily), medium (2.5–7.5 mg daily), and high (> 7.5 mg daily). With the exception of medium-dose exposure, which does not need adjustment, in patients with low exposure, the unadjusted FRAX value should be decreased by 20% for major osteoporotic and by 35% for hip fractures, respectively, while in the event of high-dose exposure, it should be upwardly revised by 15% and 20% for major osteoporotic and hip fractures, respectively

[13]. Should both lumbar spine (LS) and femoral neck (FN) BMD scores be available, the FRAX-based risk prediction for major osteoporotic fractures could be further corrected by a respective 10% increase or decrease of the relevant FRAX estimate for a major fracture for each LS-rounded *T* value below or above that of the FN *T* score [14].

Question 2: When should individuals be evaluated with a DXA scan?

The current Guidelines have not modified the previous indications for BMD testing [7]. The recommended skeletal sites include LS (L1–L4) and hip (at the femoral neck and total hip sites). The Greek National Healthcare System currently reimburses the measurement of a single skeletal site on each assessment of an individual. However, the simultaneous measurement of both sites (LS and hip) is strongly recommended (whenever this is available and is also financially possible), this due to possible wide differences, especially among younger individuals. Forearm BMD should be measured in cases of patients with primary hyperparathyroidism, obese patients with a weight exceeding the limit of the scan table, difficulties in measurement for anatomic reasons (e.g., scoliosis and spondylarthritis), and/or interpretation of hip and/or LS results [15, 16].

Indications for BMD testing (men and women) reimbursed by the National Healthcare System, include

Age < 50 years:

- Fragility fracture(s) (e.g., arising from a fall from standing height)
- Hypogonadism
- Premature menopause (< 45 years)
- Malabsorption syndromes
- Primary hyperparathyroidism
- Medications known to induce bone loss and/or fractures (e.g., glucocorticoids, aromatase inhibitors, anticonvulsants, anticoagulants, antiretroviral therapy, etc.)
- Other conditions/diseases related with bone loss and/or fractures (e.g., rheumatoid arthritis, type 1 diabetes, Cushing's syndrome, HIV infection, etc.)

Age 50–64 years:

- Any of the conditions and/or diseases applying for patients of age < 50 years
- Fragility fracture(s) after the age of 40 years
- Parent hip fracture (at any age)
- Vertebral fracture and/or "osteopenic" imaging of skeleton (radiographs)
- Low weight (< 60 kg) and/or weight loss > 10% of weight at the age of 20 years
- Alcohol consumption (≥ 25–30 g daily) and/or smoking

Age ≥ 65 years:

- All men and women.

Question 3: How should the results of the DXA scan be interpreted?

BMD testing remains the main tool for the diagnosis of osteoporosis and still sets the diagnostic thresholds for the definition of osteoporosis and osteopenia [17, 18], although the treatment intervention thresholds might differ according to the existing CRFs. Therefore, the following BMD interpretation terms should be applied:

Postmenopausal women, women in menopausal transition, men ≥ 50 years:

- Normal BMD: *T* score ± 1.0
- Osteopenia: − 2.5 < *T* score < − 1.0
- Osteoporosis: *T* score > − 2.5
- Established osteoporosis: *T* score > − 2.5 in the presence of one or more fragility fractures

Premenopausal women and men < 50 years:

In this age group, the diagnosis of osteoporosis cannot be solely based on BMD measurements, additional indications of compromised bone strength being needed (e.g., prior fragility fracture and disease related to increased fracture risk). *Z* scores are preferred over *T* scores, while the terminology for these ages should be [19]

- BMD below the expected range for age: *Z* score < − 2.0,
- BMD within the expected range for age: *Z* score > − 2.0.

However, the *T* scores of these young adults may prove useful during the long-term follow-up, especially if these patients will eventually receive treatment, which will last until after the age of 50 years old. In addition, and according to the working group of IOF, a *T* score below − 2.5 at the LS and/or hip in association with a chronic disease known to affect bone metabolism may also indicate osteoporosis among young adults [20].

Question 4: What should the diagnostic work-up for osteoporosis include?

Collection of information associated with the patient's medical history and lifestyle as well as clinical examination are indispensable for the evaluation of each person and for the differential diagnosis of secondary osteoporosis. At a minimum, the information obtained should at least address the FRAX-related questions regarding personal medical history, including co-morbidities and medication as well as family history of fractures. In addition, the clinical examination

should include weight and height measurements as well as evaluation of the patient's posture: kyphosis and/or a decrease in height might indicate presence of vertebral deformities.

Minimum baseline laboratory assessment should include

- Serum calcium (corrected for albumin).
- Serum phosphate.
- Complete blood count.
- Erythrocyte sedimentation rate (ESR).
- Serum creatinine.
- Serum total alkaline phosphatase (ALP).
- Thyroid stimulating hormone (TSH).
- 25(OH) vitamin D.
- 24-h urine calcium.

The combination of the above laboratory tests is considered capable of giving clear indications of disease or even of yielding the diagnosis in more than 90% of cases with secondary osteoporosis [21]. Additionally, it will provide important information concerning the status of the individual's calcium and vitamin D metabolism, which are crucial in the therapeutic management of osteoporosis [22]. Depending on medical history, clinical examination, and the results of the initial laboratory assessment, additional laboratory tests might be required, including parathyroid hormone (PTH), serum testosterone (men), serum tryptase, and tissue transglutaminase (tTG) antibodies.

Bone markers are indicators of the overall bone remodeling status of the skeleton and offer useful information before and during osteoporosis treatment. However, they exhibit considerable individual variability, and to date, adequate evidence as to their utility in the selection of the most suitable treatment is lacking [23]; therefore, they are considered optional in the baseline diagnostic and therapeutic approach. As both the IOF and the International Federation of Clinical Chemistry (IFCC) Bone Marker Standards Working Group have already stated, serum N-terminal propeptide of type I procollagen (PINP) and C-terminal telopeptide of type I collagen (CTX-I) should be preferred as reference markers of bone turnover for fracture risk prediction and monitoring of osteoporosis treatment [24], although they are not currently reimbursed by the Greek National Healthcare System. In the event that a bone marker value is available immediately prior to treatment initiation, a decrease of less than 38% and 56% for PINP and CTX-I, respectively, at 3 months of bisphosphonate administration could signify poor compliance or defective absorption of the administered medication, or even the presence of an under-diagnosed secondary cause [25].

Plain lateral X-rays of the thoracic and lumbar spine are indicated when the *T* score at any site is ≤ -1.0, while they are considered mandatory in the baseline assessment of osteoporosis in the case of

- Prevalent vertebral fractures.
- Persistent back pain.
- Progressive kyphosis.
- Height loss more than 4 cm from maximum height or more than 1.5 cm during the last year.

Vertebral fracture assessment (VFA) by DXA scan could also provide adequate information if available. The identification of morphometric vertebral fractures is fundamental in the assessment of future fracture risk, while a baseline depiction of the individual's spine allows an accurate follow-up.

Question 5: When and how should patients be treated for osteoporosis?

The antifracture efficacy of several agents has been tested in numerous randomized control trials (RCTs) and meta-analyses in postmenopausal women. Though RCTs in men using fractures as the primary endpoint are as yet lacking, the working group has developed the treatment algorithm (Fig. 1) in order to include the therapeutic strategy for male osteoporosis as well [26], with the exception of ibandronate (no indication for male osteoporosis) and selective estrogen receptor modulators (SERMs), which can only be used among female patients. The antifracture efficacy of the currently available medications in Greece is briefly outlined in Table 1. The indications for treatment initiation, treatment re-initiation, or continuation of the current treatment (all reimbursed by the Greek National Healthcare System) are depicted in Fig. 1. The recommended treatment strategy is deployed in four therapeutic steps: the first two steps involve patients not currently treated, while the latter two apply to those under treatment for osteoporosis. As in the previous Guidelines [7], the working group recognizes that the most common causes of defective adherence to treatment in Greece as regards oral bisphosphonates are either treatment-induced adverse effects of the upper gastrointestinal (GI) tract or aggravation of already existing GI symptoms and signs. Thus, the treatment algorithm allows the use of oral bisphosphonates only among patients lacking any upper GI problem, and this is the case in each therapeutic step.

Per os and i.v. bisphosphonates, denosumab, and SERMs (for females) are recommended for patients not currently treated, including those with at least one vertebral and/or hip fragility fracture, and/or with at least two non-vertebral fragility fractures regardless of their BMD values, and those with a BMD value ≤ -2.5 at any skeletal site with or without a fragility fracture. This is also the case among patients up to 75 years old with osteopenia and a FRAX score $\geq 10\%$ for major osteoporotic fracture and/or $\geq 2.5\%$ for hip fracture or $\geq$

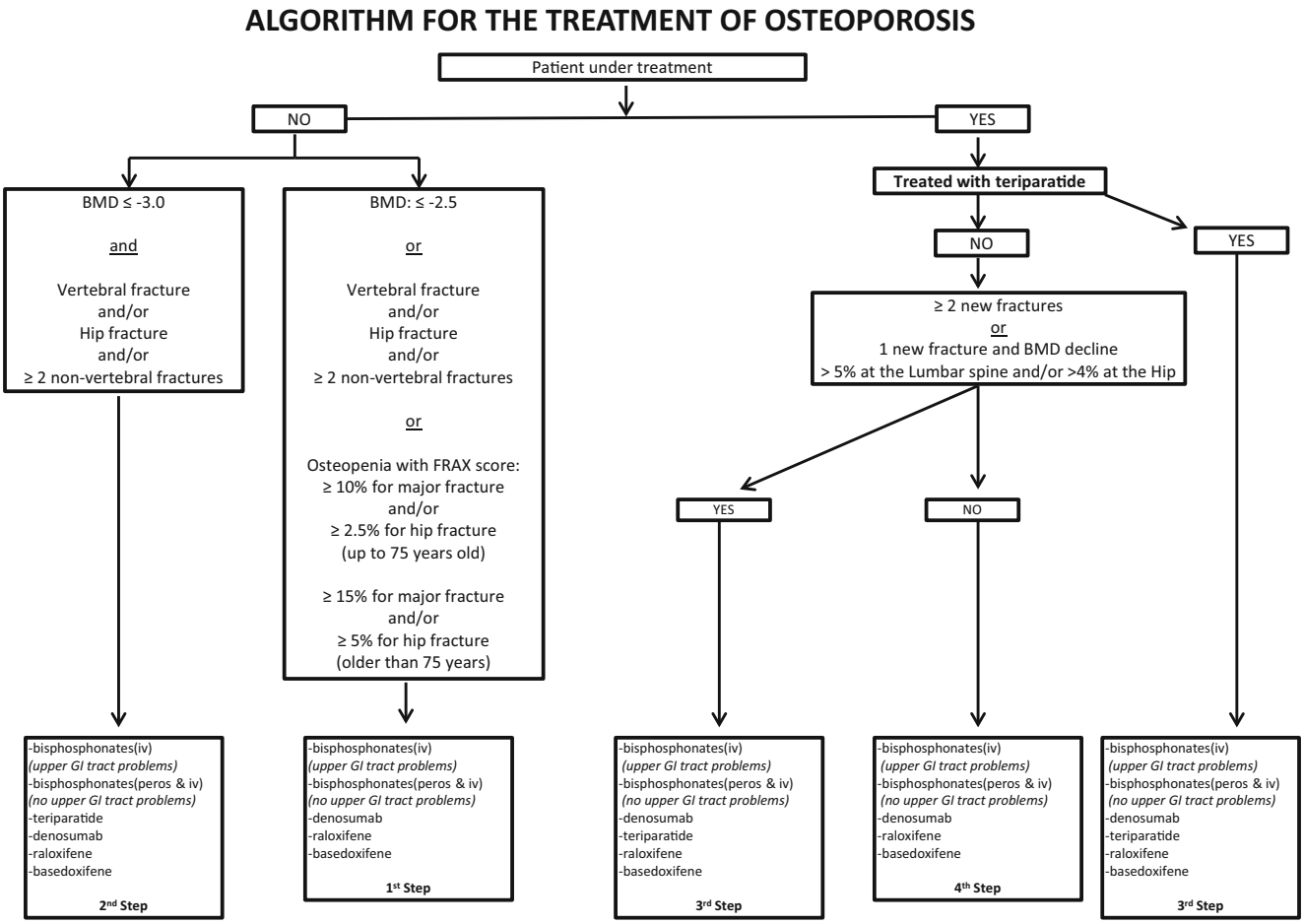

Fig. 1 Defining the need for initiation of treatment (postmenopausal women and men ≥ 50 years). Raloxifene and basedoxifene are indicated only for female patients. Since August 2017, strontium ranelate is no longer available in Greece or worldwide following a decision by its manufacturer (for commercial reasons); strontium ranelate was deleted from the 2017 algorithm. Ibandronate is not recommended for men

15% for major fracture and/or ≥ 5% for hip fracture among subjects older than 75 years [8]. These are the specific for the Greek population treatment thresholds that came up following a cost-effectiveness analysis as detailed in Makras et al. [8]. Treatment with per os and i.v. bisphosphonates, denosumab, SERMs (females only), and teriparatide is allowed for patients not currently treated and with a BMD ≤ − 3.0 at any skeletal site and an additional history of a low-energy vertebral fracture and/or a hip fracture and/or two or more non-vertebral fractures. Although the selection of a BMD ≤ − 3.0 in combination with the abovementioned fragility fractures is an arbitrarily set threshold, the working group strongly believes that it describes the cases of severe osteoporosis who will significantly benefit from the use of teriparatide be it as a first-line treatment, and thus, it is also included as an option in this second therapeutic step.

Among cases already under treatment, the therapeutic algorithm takes into consideration the current use of teriparatide in order to determine the subsequent therapeutic steps. Patients on teriparatide are allowed to follow a specific branch within the algorithm in order either to continue this treatment for up to 2 years or to subsequently receive per os and i.v. bisphosphonates, denosumab, and SERMs (females only) (third therapeutic step, Fig. 1). Patients not currently on

Table 1 Antifracture efficacy of osteoporosis treatment in postmenopausal women

Medication	Antifracture efficacy		
	Vertebral	Non-vertebral	Hip
Alendronate	+	+	+
Risedronate	+	+	+
Ibandronate	+	+(1)	
Zolendronic acid	+	+	+
Denosumab	+	+	+
Raloxifene	+		
Bazedoxifene	+	+(2)	
Teriparatide	+	+	

Post hoc analysis [27]. Post hoc analysis among female patients with a femoral neck BMD *T* score < − 3.0 and/or ≥ 1 vertebral fracture [28]

teriparatide should be evaluated for the efficacy of the current treatment. According to these updated Guidelines, treatment failure after at least 1 year of treatment is defined as the incidence of (a) at least two new fragility fractures or (b) one new fragility fracture and a BMD decrease (measured with the same DXA equipment) of more than 5% at the LS and/or 4% at the hip [25]. If the definition of treatment failure is met, patients are allowed to follow the already described third therapeutic step (Fig. 1) including teriparatide, even in the case of a hip fracture [29]. Finally, patients on treatment, excluding those on teriparatide, who do not fulfill the criteria for treatment failure can follow the fourth therapeutic step, which includes per os and i.v. bisphosphonates, denosumab, and SERMs (females only).

As in the previous Guidelines, several regimens can be used through the four therapeutic steps; however, the treating physician should choose the most suitable treatment for the patient based on medical history, fracture risk, previous treatment for osteoporosis and concomitant medications, treatment-induced risks and benefits, weighting of the financial cost and potential benefit, as well as future follow-up [7].

In all the above cases, daily co-administration of 400–800 IU of vitamin D3 is strongly recommended. In addition, total calcium intake (dietary and/or through supplements) of 1200 mg per day must be ensured [30].

Question 6: How should patients be followed during osteoporosis treatment?

It is recommended that treatment effectiveness be evaluated annually by DXA at one site (the site with the lower *T* score at baseline evaluation) or every 2 years by DXA at two sites (including that with the lower *T* score at baseline evaluation). Most guidelines recommend follow-up DXA scans every 2–5 years to reduce the cost and to reveal greater BMD changes that could clearly differentiate actual gains from variations within the least significant change (LSC) [4, 5]. However, we recommend annual DXA scans to maintain the patient's perception of treatment necessity and improve adherence in view of the asymptomatic nature of the disease, as poor adherence results in adverse skeletal outcomes [31]. Given that both PINP and CTX-I are not currently reimbursed by the Greek National Healthcare System, we do not propose their use as a means to monitor treatment efficacy and adherence.

Treatment should be changed in the case of adverse events or treatment failure (Fig. 1). Deprescription should also be considered if this would lead to an overall improvement of the patient's health; however, this therapeutic strategy should be tailored on an individual basis, and no further recommendations are provided within this document.

For individuals at low fracture risk not currently under treatment, with or without a history of previous osteoporosis treatment, it is recommended that monitoring should include

- Clinical examination (back pain, height, falls, incident fractures), including prescription of calcium and vitamin D regimens, every 6 months.
- FRAX calculation every 6 months in the event of any differentiation in CRFs.
- BMD scans (at the site with the lower *T* score at baseline evaluation, plus one more site) at intervals of not less than 2 years, depending on the age, BMD status, and the agent that has previously been administered.

When there is the need for treatment re-initiation, the algorithm of Fig. 1 is once more implemented.

For patients who have completed five consecutive years of oral or denosumab treatment as well as for those who have had three consecutive years of i.v. bisphosphonates, the full initial diagnostic work-up, described in question 4, is recommended in order to

- Classify the patient as low or high risk and come to a decision regarding treatment discontinuation [32].
- Identify laboratory/hormonal changes and/or morphometric vertebral fractures.
- Confirm the initial diagnosis and the appropriateness of the administered treatment approach.
- Re-evaluate the patient's perception of the current therapy in order to form a decision as to the next steps in an effort to achieve optimal adherence.

Following the above and in the event of a decision for current treatment discontinuation, clinical and BMD re-evaluation is recommended 1 year after bisphosphonates or SERM resumption. In the case of denosumab discontinuation, further therapeutic actions are needed, which are described in "Discussion—other working group recommendations" section.

Discussion—other working group recommendations

The current Guidelines provide updated information regarding the treatment of osteoporosis within the Greek healthcare setting. Although the recommendations for the evaluation and management of bone fragility are universal, the implementation of the knowledge in each country is a crucial issue that needs to take into account several factors, including the national healthcare system, the baseline fracture risk of the general population, and the economic status of the country. The working group further discusses several additional recommendations that cannot be readily incorporated within the discussion of the six listed questions.

Among women ≤ 55 years old lacking risk factors (e.g., history of thromboembolism, breast and/or ovarian cancer,

or liver disease) and experiencing menopausal symptoms, estrogens with or without progestogen (hormonal replacement therapy (HRT)) could be considered as a therapeutic option since they reduce the risk of all osteoporotic fractures (vertebral, non-vertebral, and hip) [9]. In addition, among women at increased risk of breast cancer, raloxifene might have an advantage as a therapeutic choice as it reduces the incidence of invasive breast cancer [33].

In contrast to the previous Guidelines [7], nasal calcitonin is no longer indicated for the treatment of osteoporosis [34]. However, it could be considered either as an injection or an infusion with the following indications: prevention of acute bone loss because of immobilization for up to 4 weeks, cancer-induced hypercalcemia, Paget's disease, and among patients not responding to or not eligible for alternative treatment for up to 3 months [34]. In patients with recent osteoporotic fractures, especially those with vertebral fractures, resulting in sudden short-term immobilization, co-administration of calcitonin can be considered for analgesia as well. As concerns back pain resulting from vertebral fractures, teriparatide has also been reported to have an analgesic effect [35, 36]. However, the analgesic effects on fracture related pain of both calcitonin and teriparatide have not been confirmed in all studies; therefore, physicians should carefully consider a relevant therapeutic decision.

Denosumab should be considered among patients with up to stage IV renal insufficiency; however, the risk of severe hypocalcemia should be carefully evaluated in these cases [37]. In contrast to bisphosphonates, denosumab is a circulating agent which does not become embedded in the skeleton, and therefore, there is no protective effect following discontinuation. Instead, a rapid loss of the therapeutic effect should be expected, which is also characterized by a rebound increase of bone turnover markers above baseline for up to 48 months and a concomitant decrease of BMD towards pretreatment levels within a time period of 12 months [38]. While the overall fracture risk was not found to be increased during the early discontinuation period [39], significant concerns have recently been raised regarding the risk of multiple fragility vertebral fractures following denosumab discontinuation [40]. In a post hoc analysis of the core study (FREEDOM) and its extension, the risk of multiple vertebral fractures was significantly higher among those who discontinued denosumab than placebo, and this was even more prominent in patients with prior vertebral fractures sustained before or during treatment [41]. No increase in the overall non-vertebral fracture rate is expected after stopping denosumab [41]. For all the above reasons, treatment with bisphosphonates for a period of 12–24 months is suggested following denosumab discontinuation, although the optimal regimen and scheme is yet to be defined [42, 43].

Anabolic treatment with teriparatide should be immediately followed by antiresorptive treatment (bisphosphonates or denosumab) [43].

Among patients switching from oral bisphosphonates to parenteral antiresorptive treatment, denosumab is more effective than zoledronic acid in terms of BMD accrual and bone turnover suppression [44].

Patients showing poor compliance to treatment should be treated with medications administered at longer between-treatment intervals [5].

Currently, there are no data available on the efficacy and safety of continuing any agent used in osteoporosis treatment for more than ten consecutive years. In these cases, treatment should be individualized according to previous therapy, medical history, and fracture risk [30].

New therapeutic approaches, such as abaloparatide and romosozumab, were not assessed in the construction of the current Guidelines and therefore are not discussed in this document.

Finally, physicians should offer continual consultation regarding protection from falls, especially among older patients, and encourage in all cases physical exercise, smoking cessation, and avoidance of alcohol consumption. Since all the above information may not be applicable in every single case, clinical judgment is always crucial, the physician needing to deal with every individual patient in a personalized manner, aiming for the best possible outcome and using the safest means.

Compliance with ethical standards

Conflict of interest -PM has received lecture fees and research grants from Amgen and lecture fees from Glaxo, Eli-Lilly, Pfizer, Leo, Genesis, ELPEN, VIANEX, Rafarm, Galenica, and UniPharma.

-ADA has received lecture fees from Amgen, Eli-Lilly, ELPEN, ITF Hellas, Rafarm, and VIANEX.

-GA has nothing to disclose.

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-KDS has received lecture fees and advisory board fees from Amgen Hellas and honoraria and lecture fees from Pharmaserve Lilly, Specifar a Teva, and VIANEX.

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