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Guideline for diagnostic, prevention and treatment of postmenopausal osteoporosis

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Abstract. ***Background.*** Postmenopausal osteoporosis (PMO), which is developed due the estrogen deficiency in women after menopause, is the most common type of systemic osteoporosis. The latest Ukrainian recommendation for its management requires revision due to new data from high-quality research performed in recent years. ***The purpose*** was to develop a guideline on the diagnosis, prevention, and treatment of PMO based on an analytical analysis of modern literary sources in order to improve the awareness of the medical community of Ukraine. ***Methodology.*** To develop the guideline, an expert group of 13 leading Ukrainian scientists of various specialties was created who conducted a thorough review of modern literature on this topic, assessed the level of existing evidence using the GRADE system, proposed and voted on 15 recommendations of the guideline. ***Results.*** The guideline contains chapters on diagnosis and differential diagnosis of PMO, assessment of the osteoporotic fracture risk, the role of bone turnover markers in the management of PMO, and modern strategies of antiosteoporotic treatment. ***Conclusions.*** The Ukrainian guideline on the diagnosis, prevention, and treatment of PMO, which contains 15 main recommendations, created on the basis of a thorough analysis and synthesis of modern literature data, is an important tool for the management of PMO and is recommended by Ukrainian Association of Osteoporosis for use in Ukrainian medical community.

Keywords: guideline; recommendations; Ukraine; postmenopausal osteoporosis; diagnostics; prevention; treatment

Introduction

Osteoporosis is a systemic skeletal disease, characterized by low bone mass and micro-architectural deterioration associated with a decreased number of bone trabeculae, their thinning and loss of connection, a decreased thickness of the cortical bone, and an increased porosity, which leads to decreased bone strength, increased bone fragility and risk of fractures (*WHO*, 1994) [1, 2]. According to *International Statistical Classification of Diseases and Related Health Problems (ICD) 10 (Appendix 1 and 2)*, the diagnosis of osteoporosis is classified in chapter XIII (Diseases of the musculoskeletal system and connective tissue, M00-M99, coded as M80-M82) [3].

The medical and social significance of osteoporosis is determined by its consequences — fragility fractures, which lead to decreased average life expectancy of the patients, an

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increased disability, pain syndromes of various localizations, and a deterioration in the quality of life [4]. The typical localizations of osteoporotic fractures (OPFs) are the hip, spine, distal forearm, and proximal humerus.

The recently published results of the *SCOPE (Scorecard for osteoporosis in Europe)* project [5], conducted in 29 European countries by the *International Osteoporosis Foundation (IOF)* have demonstrated that more than 23 million men and women in the European Union (EU) have a high risk of OPFs. In 2019, 4.3 million fractures were registered in 29 European countries, in 2034 their number can increase by almost a quarter (24.8 %) compared to 2019 (5.34 million). Eight new OPFs occur every minute, and one in three women and at least one in six men will experience OPF during their lifetime. Annually, almost a quarter of a million deaths in the EU are a direct result of hip or vertebral fractures.

Research conducted at the Ukrainian Scientific and Medical Center of Osteoporosis using dual-photon X-ray absorptiometry (DXA) revealed osteoporosis in 8.4 % of the total female population, 20 % of the women at the age 50 years and older [6]. Taking into account the fact that almost 22 million women (53.6 % of the entire population of the country) were registered in Ukraine on January 1, 2022 [7], the number of females with osteoporosis can be more than 1.8 million.

Nowadays, there is significant variability in the epidemiology of OPFs in the world. According to the data of the multicenter epidemiological study *STOP (System of registration of osteoporotic fractures)*, conducted by the Ukrainian Association of Osteoporosis with the support of the Ukrainian Association of Orthopedics and Traumatologists, it was established that the incidence of hip fractures in Ukraine was 255.5 per 100,000 women at the age of 50 years and older and 197.8 per 100,000 in men of the same age [8, 9]. Considering the fact that according to the data of the *State Statistics Service of Ukraine* on January 1, 2022, subjects aged 50 years and older accounted for 38.2 % of the total population [7], the annual number of patients only with hip fractures may be more than 35 thousand.

Postmenopausal osteoporosis (PMO, type 1 of the primary osteoporosis), which is developed due the estrogen deficiency in women after menopause, is the most common type of systemic osteoporosis. Estrogen deficiency is a key factor that leads to increased rates of bone turnover with progressive bone loss, more pronounced in trabecular bone. In postmenopausal women, OPFs occur more often than stroke, myocardial infarction, and breast cancer taken together, and they are a significant cause of increased disability and mortality [10–12].

The population of the world, in general, and Ukraine, in particular, is steadily aging. Due to current demographic trends, the number of elderly people, in particular, postmenopausal women, is increasing, so the medical and social significance of osteoporosis and its complications will increase in the coming years. In 2021, women aged 50 years and older were 26 % of all females in the world [13]. If in 1990 there were 467 million postmenopausal women in the world, whose average age was about 60 years, in 2030 this number can increase to 1.2 billion, while 47 million new postmenopausal females will appear every year [14].

The first guidance for the management of osteoporosis in the world was published in 1997 by the *European Foundation for Osteoporosis and Bone Disease* (later the *International Osteoporosis Foundation, IOF)*, the following recommendations for the management of PMO, published by the *IOF* and the *European Society for Clinical and Economic Evaluation of Osteoporosis and Osteoarthritis (ESCEO)*, appeared in 2008, 2013, and 2019 [15]. The latest Ukrainian recommendation [16] on this topic currently requires revision due to new data and results of high-quality research about the diagnosis of osteoporosis and strategies for its prevention and treatment.

The ***aim*** was to develop a guideline on the diagnosis, prevention, and treatment of PMO based on an analytical analysis of modern literary sources in order to improve the awareness of the medical community of Ukraine.

Methodology

For the development of this guideline, an expert group of 13 leading Ukrainian scientists of various specialties (rheumatologists, obstetricians-gynecologists, orthopedic traumatologists, biologists) was created, who are experts on this issue, board members of the Ukrainian Association of Osteoporosis or its active members with extensive experience in diagnosis and treatment of PMO. Experts have studied the following issues: 1) diagnosis of PMO, assessment of risk factors of OPFs and determination of their risk; 2) prevention of PMO; 3) treatment of PMO and monitoring of the effectiveness and safety of antiosteoporotic therapy.

Two or three experts conducted a thorough review of literary sources on each of the above-mentioned issues, after which the recommendations of the guideline were proposed for consideration by the expert group. Meta-analyses, systematic reviews and results of randomized controlled trials (RCTs) became the basis for formulating the recommendations of the guideline. An analytical search was conducted in the *Cochrane, PubMed, MEDLINE, Embase, Scopus, Web of Science* databases from January 1, 2013 to June 1, 2023. During the creation of the list of used and recommended literary sources, the experts did not exclude the most important meta-analyses, systematic reviews and some studies, published before the start of the analytical search.

A systematic and comprehensive synthesis of the evidence for this guideline was carried out using the adopted by the *Committee on the Development of WHO Recommendations* [17] *Grading of Recommendations, Assessment, Development and Evaluation (GRADE)* [18]. This approach was also recommended by the *State Expert Center of the Ministry of Health of Ukraine* [19]. A critical assessment of the quality of the guideline recommendations was carried out using the *AGREE II tool (Appraisal of Guideline ResEarch and Evaluation, Questionnaire on Expertise and Evaluation of Guidelines II)* using grades from 1 to 7 points (1 — completely disagree, 7 — completely agree) [20] *(Appendix 3)*.

Voting for the guideline recommendations was held in July 2023. As a result of the work of the expert group, 15 re-

commendations were formulated and successfully voted on *(Appendix 4)*. Thirteen authors of this article are 13 members of the expert group who participated in the vote.

Diagnosis and differential diagnosis of postmenopausal osteoporosis

Diagnosis of PMO is based on the quantitative assessment of bone mineral density (BMD), which is one of the main determinants of bone strength and determines the risk of OPFs. Bone mineral density is the amount of bone mass per unit of volume (volume density) or area (area density), both of which can be measured *in vivo* using densitometric techniques.

Nowadays, various methods are used in clinical practice to assess bone density (ultrasound densitometry (USD), quantitative computer tomography (CT), digital X-ray radiogrammetry, etc.); however, dual-energy X-ray absorptiometry (DXA) is the most widely used for the diagnosis of osteoporosis. Due to the two-dimensional image of densitometers, the planar but not the true volume bone density is measured (in g/cm^2, not g/cm^3), however, it accounts for about 2/3 of the dispersion of its strength determined *in vitro* isolated on the vertebral bodies and proximal part of the femur (hip). Indications for DXA in accordance with the latest *International Society of Clinical Densitometry (ISCD)* recommendations [21] are given in *Appendix 5*.

Modern densitometers also contain other programs (*Vertebral fracture assessment (VFA), Trabecular bone score (TBS), Hip strength analysis (HSA)*, etc.), which, together with BMD measurement, can significantly improve the prediction of OPFs. In general, all densitometric technologies have high specificity and low sensitivity, so they require careful interpretation.

The interpretation of BMD indices in postmenopausal women is carried out according to *WHO* recommendations (Table 1) based on the T-score [2, 21], which describes the number of standard deviations (SD) by which BMD that is measured at the femoral neck of a person differs from the average value expected in young healthy subjects [15, 22]. According to the *ISCD* and *IOF* guidelines [21, 22], measurement of femoral neck BMD is more important due to its higher predictive value for fracture risk *(evidence level 1++)*, especially in elderly subjects, in general, and postmenopausal women, in particular. BMD measurement at the lumbar spine is less informative due to the prevalence of degenerative changes in elderly people, which, as an artifact, increases BMD indices.

Today, BMD measurements using DXA are performed at the total hip and femoral neck, the lumbar spine (L_1-L_4) and the distal radius (33 % radius or 1/3 radius), although not all studies demonstrated the advantages of the combined use of these measurements [23, 24]. According to the latest *ISCD* recommendations, the diagnosis of PMO is established based on the lower T-score measured at the proximal femur (total hip or femoral neck) or at the lumbar spine. Assessment of BMD indices of the radius should be carried out under the following circumstances: 1) measurement or interpretation of proximal femur and/or lumbar spine BMD is impossible; 2) in patients with hyperparathyroidism; 3) in persons with severe obesity (body weight restriction) [21].

Low bone mass (osteopenia) according to ICD-10 [3] is not a separate diagnosis, but ICD-11 [25] considers the possibility of its inclusion *(Appendix 2)*.

It should be noted that the interpretation of BMD indices should be carried out individually in subjects with hip osteoarthritis, degenerative changes of the spine, scoliosis, fractures, suspicion of osteomalacia, etc. Quantitative comparison of BMD indices between different densitometers without cross-calibration is not possible, and ensuring strict quality control of measurements with proper calibration of densitometers using phantoms is mandatory [21].

According to the latest *ISCD* recommendations [26], repeated measurement of BMD in combination with clinical assessment of fracture risk, bone turnover markers (BTMs), and other factors can be used to make a decision to assess the rate of bone loss, initiate antiosteoporotic therapy in untreated patients, monitor the effectiveness of therapy, or monitor the persons who have stopped the treatment for osteoporosis. For a dynamic evaluation of bone loss or assessment of the antiosteoporotic therapy effectiveness, BMD measurements should be performed using the same DXA device. Intervals between BMD measurements should be determined according to the clinical situation (usually, one year after the initiation or change of the antiosteoporotic therapy, with longer intervals after establishing a therapeutic effect). In cases associated with rapid bone loss (for example, glucocorticoid therapy), more frequent BMD measurements may be used.

Table 1. Classification of BMD according to WHO criteria

Bone state	Bone mineral density	T-score
Norm	Within 1 SD compared to the reference sample of young subjects*	–1.0 or higher
Low bone mass (osteopenia)	Between 1.0 and 2.5 SD lower than the indices of the reference sample of young subjects*	Between –1.0 and –2.5
Osteoporosis	By 2.5 SD or lower than the indices of the reference sample of young subjects*	–2.5 or lower
Severe or established osteoporosis	By 2.5 SD or lower than the indices of the reference sample of young subjects*	–2.5 or lower and one or more fractures

Note: * — reference values of a sample of young people (20–29 years old) of the Caucasian race, determined on the basis of the NHANES III study (The Third National Health and Nutrition Examination Survey) [22].

Recommendation 1. ***Instrumental confirmation of the diagnosis of PMO is recommended using DXA with the measurement of BMD indices of the femoral neck, total hip or lumbar spine* according to WHO criteria (T-score = –2.5 SD or lower)*** **(grade B recommendation, level of agreement (LA) — 100 %).**

Note: * — the lowest index of the measured regions. If it is impossible to assess the BMD of the specified regions, the BMD of the distal part of the radius can be used.

As the clinical manifestations of osteoporosis are nonspecific, and its first symptom may be a fragility fracture, the diagnostic algorithm for suspected PMO should include not only the BMD measurement, but also the exclusion of diseases and conditions that may be the reason for secondary osteoporosis.

Important results on the physical examination of a patient with osteoporosis may be the consequences of previous fractures (for example, increased thoracic kyphosis, the decreased distance between the lower ribs and the pelvic brim), a recent fracture (for example, localized tenderness of the spinous process of the vertebra), or abnormalities that indicate a secondary cause of osteoporosis (for example, thyromegaly, Cushing's syndrome, etc.). Accurate height measurement is also useful (a height loss of ≥ 4.0 cm in comparison with the historical maximum) may indicate a high probability of a vertebral fracture. Measurement of body weight with body mass index (BMI) calculation is a part of the clinical evaluation of the patient with osteoporosis because low body weight and BMI ≤ 20 kg/m^2 or a 5 % loss of body weight are associated with an increased risk of OPFs. Abnormalities in posture, gait, balance, muscle strength, signs of postural hypotension, or impaired consciousness may be associated with an increased risk of falling.

In this regard, a comprehensive examination of a patient suspected of PMO should include a number of general clinical and some special methods of laboratory and instrumental research [15] (Table 2).

Recommendation 2. ***We recommend basing a comprehensive examination of a person with suspicion of PMO on the assessment of OPF risk factors, DXA indices, and the determination of possible causes of bone loss*** **(grade B recommendation, LA —** ***98.9 %*****).**

Assessment of the osteoporotic fracture risk (OPFs)

As mentioned above, a decreased BMD is a significant predictor of the OPF risk (each SD decrease leads to an increase of the OPF risk twice (*evidence level 1++*)) [28]. However, the risk gradient differs depending on the place of measurement, device, subject age, fracture location, etc. [29]. The low sensitivity of the BMD index determines that the majority of OPFs occur in women who, according to BMD indices, do not have osteoporosis (T-score ≤ –2.5 SD) [30, 31]. Therefore, current guidelines for the management

Table 2. Program of examination for a person suspected of PMO

Routine examination methods	Evaluation of complaints and history taking into account the presence of clinical risk factors for OPFs
	Calculation of the 10-year probability of a major OPFs (hip, clinical spine, humerus or foream fractures) and hip fractures separately according to the Ukrainian version of the FRAX®
	Physical examination of the patient: assessment of posture (increased thoracic kyphosis, tenderness of the spinous processes of the vertebrae), measurement of the main anthropometric indices (height, body weight) with BMI calculation, assessment of gait and balance, muscle strength and risk of falls
	DXA of proximal femur, lumbar spine, and distal radius
	General (clinical) blood analysis with formula
	Biochemical analysis of blood: — total (ionized) calcium, phosphorus, magnesium, parathyroid hormone (PTH), alkaline phosphatase, 25(OH)D; — liver transaminases (ALT, AST); — glucose; — urea, creatinine with calculation of glomerular filtration rate (GFR); — thyroid-stimulating hormone (thyrotropic hormone, TSH)
	X-ray of the thoracic and/or lumbar spine. Indications: 1) acute/intense vertebral pain syndrome, especially in persons who are taking glucocorticoids in a dose equivalent to ≥ 5 mg/d of prednisolone for ≥ 3 months; 2) if a vertebral fracture is suspected; 3) decrease in height by > 4 cm; 4) increased thoracic kyphosis
Special examination methods	Gonadotropic (FSH, LH), sex (estradiol, progesterone) hormones, prolactin
	Triiodothyronine (T_3), thyroxine (T_4)
	Electrophoresis of blood and urine proteins
	Daily excretion of cortisol
	BTMs
	VFA. Indications for women with a T < –1.0 SD and the presence of one or more criteria: 1) the woman's age ≥ 70 years; 2) loss of height > 4 cm; 3) suspicion of vertebral fracture; 4) glucocorticoid therapy (equivalent to ≥ 5 mg/day of prednisolone for ≥ 3 months) [21, 27]
	TBS
	Scintigraphy
	Specialist consultations

of osteoporosis recommend determining BMD in combination with the assessment of other fracture risk factors [15, 32]. One of the most significant risk factors for OPFs is age [33, 34] and BMD [29, 35–37] *(evidence level 1++)*.

However, to date, a number of factors have been found to have a significant impact on the risk of OPFs *(evidence level 1++ and 1+):* previous fragility fracture [38, 39], hip fracture in parents [40], low body mass index (BMI) [41, 42], smoking [43, 44], excessive alcohol consumption [45–48], increased predisposition to falls [34, 49], early or premature menopause [37, 50], some diseases (rheumatoid arthritis [51–53]), endocrine diseases (type I [54, 55] and type II diabetes mellitus [56, 57]), thyroid diseases [58, 59], inflammatory bowel diseases [60, 61], osteogenesis imperfecta [62], anorexia nervosa [63], etc.

According to the data of the *World Health Organization pharmacovigilance database (VigiBase®)* [64], a number of drugs contribute to the development of osteoporosis and an increase in the risk of OPFs, namely glucocorticoids, analogs of gonadotropin-releasing hormone, aromatase inhibitors, androgen receptor blockers, thyroid hormones, proton pump inhibitors, thiazolidinediones, vitamin K antagonists, loop diuretics, protease inhibitors, nucleoside and nucleotide reverse transcriptase inhibitors and inducing enzymes, antiepileptics, including barbiturates and their derivatives, derivatives of hydantoin, carboxamide and fatty acids. The negative impact of a number of drugs on the development of osteoporosis and its complications has been demonstrated in numerous meta-analyses and systematic reviews [64, 65] *(evidence level 1++ and 1+)* (for glucocorticoids [66–68], sugar-lowering agents [69–71], antidepressants [72], antipsychotic [73], antiparkinsonian drugs [74], lithium drugs [75], benzodiazepines [76], proton pump inhibitors [77], etc.).

Some of these factors increase the risk of OPFs by reducing BMD, others by affecting not only the density, but also the micro- and macroarchitectonics (quality) of bone. Some of these factors (smoking, excessive alcohol consumption, low BMI, some drugs, etc.) are modifiable, so their identification and correction may be important in the management of PMO.

Today, one of the most widely used and researched algorithms for fracture risk assessment, based on the evaluation of risk factors for OPFs and BMD, is the FRAX *(Fracture Risk Assessment Tool, Fig. 1)* [78]. FRAX® is an algorithm for the calculation of the 10-year probability of the major OPFs (clinical spine, hip, forearm and humerus fracture) and separately the 10-year probability of hip fractures in men and women aged 40–90 years old. It takes into account the age, subject BMI and existing clinical risk factors for OPFs (previous fragility fractures, hip fractures in parents, smoking, alcohol consumption (more than 3 units/day), taking glucocorticoids, the presence of rheumatoid arthritis, type I diabetes mellitus, osteogenesis imperfecta in adults, long-term untreated hyperthyroidism, hypogonadism, or early menopause (< 45 years), malabsorption syndromes, or chronic liver disease) together with an optional femoral neck BMD measurement. In Ukraine, the FRAX® has been used in the risk assessment of OPFs since 2009 [79], in June 2016, its Ukrainian-language version appeared. Since October 2016 the Ukrainian model FRAX®, which was created based on the results of epidemiological studies in Ukraine [10, 11], appeared on the FRAX online resource *(https://www.sheffield.ac.uk /FRAX/tool.aspx?country=66)*. In 2019, the thresholds of the Ukrainian FRAX® [80] were obtained, which are currently recommended by the Ukrainian Association of Osteoporosis for the stratification of patients with regard to the OPF risk and the choice of further management *(Appendix 6)* [80]. Nowadays, the FRAX is included in most of the recommendations for the management of osteoporosis, including PMO.

Since not all significant risk factors of OPFs are included in the FRAX®, in recent years, studies have been accumulating on the underestimation of OPF risk in patients with various diseases (type II diabetes mellitus [81, 82], systemic lupus erythematosus [83], spondyloarthritis [84]) and in subjects, who are receiving high doses of glucocorticoids [85]. Modern studies and guidelines demonstrate the need to consider the dose of glucocorticoids when assessing the OPF risk [15, 86]. Work is currently underway to include other clinical risk factors in the FRAX®. The FRAXplus® algorithm *(https://www.fraxplus.org)* allows to modify the FRAX® results, additionally taking into account the fracture location (vertebral, hip, humerus, forearm fractures, etc.) and the post-fracture time (from 0 to 24 months), higher doses of oral glucocorticoids (≥ 7.5 mg/d prednisone equivalent), TBS, number of falls in the previous year, duration of type II diabetes mel-

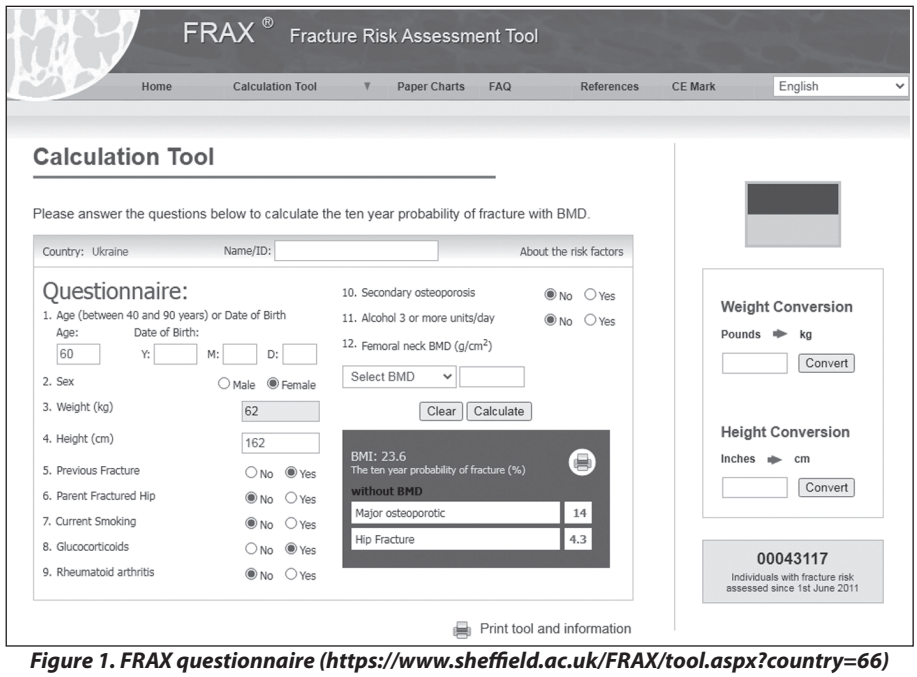

Figure 1. FRAX questionnaire (https://www.sheffield.ac.uk/FRAX/tool.aspx?country=66)

litus (less than 5 years, 5–10 years, more than 10 years), as well as additional indices (hip axis length (HAL) and lumbar spine BMD). Obviously, the assessment of the 10-year probability of OPFs should be carried out individually based on the available clinical risk factors of OPFs, in particular, those that are not included in the FRAX® [87].

Recommendation 3. ***We recommend assessing the 10-year probability of major OPFs and hip fractures in postmenopausal women based on the Ukrainian FRAX® version using cut-off values for the Ukrainian population for further management decisions (in particular, DXA or the appointment of antiosteoporotic treatment)*** **(grade C recommendation, LA — 100 %).**

Recommendation 4. ***We recommend interpreting the risk of OPFs taking into account other diseases and states that affect bone loss, but are not included in FRAX® and FRAXplus®*** **(grade D recommendation, LA — 96.7 %).**

Bone turnover markers (BTM) in the management of postmenopausal osteoporosis

The processes of modeling and remodeling in bone occur throughout a person's life and are responsible for maintaining mineral homeostasis; recovery from micro- and macroinjuries and fractures. The development of PMO is characterized by an increase in the rate of bone turnover, which reliably reflects BTMs [88–91].

According to some recommendations, BTMs cannot be used to establish the diagnosis of PMO [92–94] due to their low sensitivity and specificity, however, they can be useful *(evidence level 1++)* for predicting the fracture risk [95, 96], assessing BMD changes during long-term treatment of osteoporosis [97], monitoring of patients after cessation of antiosteoporotic treatment [96, 98]. In addition, BTMs have clinical value in the study of the causes of secondary osteoporosis.

Today, the best markers for assessing the rate of bone turnover in clinical cases are the marker of bone formation — *procollagen type 1 N-terminal propeptide (P1NP)* and its resorption marker — the *carboxy-terminal telopeptide of collagen type I (C-terminal cross-linking telopeptide of type 1 collagen, CTX-I, or* β*-CTX, or* β*-CTX-I)*, determined in blood serum [90, 91].

Meta-analyses conducted by the expert group of the *International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)* and *IOF* demonstrated an increased level of BTMs with an increased risk of OPFs (for each SD increased PINP, the fracture risk increased by approximately 23 %, for CTX-I — 18 %) [95] and may be useful in the prediction of the fractures [96], however, recent fracture significantly complicates the interpretation of BTMs [99, 100].

According to the conclusion of the *ESCEO* Consensus Group [92], BTMs are not useful for predicting bone loss or evaluating the effectiveness of treatment in an individual subject, but the measurement of *P1NP* and *CTX-I* in blood serum is appropriate for monitoring adherence to the treatment with oral bisphosphonates (BPs). Their dynamics after 3 months after the initiation of antiresorptive treatment (decrease of *PINP* and *CTX-I* more than a significant level (more than 38 % for *PINP* and 56 % for *CTX-I*)) is a reason to continue treatment. In the absence of achieving a significant level, a reassessment of the therapy is recommended (control of adherence to the therapy, establishment of other causes leading to bone loss, in particular, the presence of secondary osteoporosis) [92]. Another algorithm [93] for monitoring the effectiveness of antiresorptive therapy using BTMs suggested that the optimal response is to decrease the *PINP* level by 10 μg/L to a level below 35 μg/L and to decrease the *CTX-I* level by 100 ng/L to a level below 280 ng/L. Ensuring strict quality control of laboratory research is important in providing of the informativeness of BTMs [101].

Recommendation 5. ***We don't recommend using BTMs (PINP and CTX-I) in the diagnosis of osteoporosis, but recommend them for use in predicting the risk of OPFs and monitoring antiosteoporotic therapy*** **(grade A recommendation, LA — 96.7 %).**

Alternative methods of diagnosing osteoporosis and fracture risk

Central and peripheral computed tomography (CT)

According to the latest *ISCD* recommendations [21], the T-score of the hip and femoral neck, calculated from two-dimensional CT images, are equivalent to the corresponding T-scores of DXA for the diagnosis of osteoporosis (according to WHO criteria), and the trabecular BMD of the spine, measured by CT, has a similar to DXA prognostic value in assessing the risk of vertebral fractures in postmenopausal women. CT and DXA provide comparable information about the state of the bone, but when both methods are available, DXA is preferable because of less X-ray exposure. Antiosteoporotic treatment should be started if it is impossible to perform DXA and there is a high risk of OPFs according to the relevant criteria of central (measurement at the lumbar spine) or peripheral CT (measurement at the ultradistal radius) and the presence of risk factors of OPFs [21]. In postmenopausal women, peripheral CT of the ultradistal radius is an informative method for predicting a hip fracture, but not a vertebral fracture. Indices of trabecular BMD of the lumbar spine, integrated and trabecular BMD of the proximal femur measured by central CT, and indices of trabecular and total BMD of the ultradistal radius, measured by peripheral CT, are recommended by the *ISCD* for the monitoring of bone status and treatment efficacy [21].

Recommendation 6. ***Central and peripheral CT (measurement at the lumbar spine or ultradistal radius, respectively) is a reliable alternative to DXA in the diagnosis of PMO and predicting the risk of OPFs, however, we don't recommend it for dynamic monitoring of the bone state due to a higher dose of X-ray irradiation*** **(grade C recommendation, LA — 95.6 %).**

Trabecular bone score

The TBS can be obtained from a two-dimensional DXA image of the lumbar spine. To date, numerous systematic reviews [102–104] have demonstrated that this index, regard-

less of BMD, is informative in predicting OPFs and correlates with the quality (microarchitectonics) of the bone. According to the latest *ISCD* recommendations [21], TBS is associated with the risk of vertebral, hip fractures, and other OPFs in postmenopausal women. In addition, it is associated with the risk of OPFs in postmenopausal women with type II diabetes mellitus. However, it should not be used alone to determine the recommendations for osteoporosis treatment. In patients receiving antiosteoporotic therapy, the role of TBS in monitoring the effectiveness of antiresorptive therapy has not been definitively established, although it may be potentially useful for monitoring of osteoanabolic therapy [21]. Modern meta-analyses [105] confirmed that in postmenopausal women, TBS can be used together with FRAX® and BMD to increase the informativeness of the prediction of OPFs.

Recommendation 7. ***In postmenopausal women, we recommend using TBS together with FRAX® and BMD to increase the informativeness of the prediction of OPF risk*** **(grade A recommendation, LA — 97.8 %).**

Hip strength analysis

Another method of assessing the OPF risk, implemented in modern densitometers, is the assessment of hip strength based on its geometry parameters [106]. According to the latest *ISCD* recommendations [21], the *hip axis length*, measured using DXA, is associated with the risk of hip fractures in postmenopausal women. In contrast to the above, other indices (*CSA, OD, SM, BR, CSMI, NSA*) measured by DXA should not be used for the assessment of the hip fracture risk, decision about the initiation of antiosteoporotic therapy and monitoring of its effectiveness. Today, the reference values for this methodology have been received for the Ukrainian population and can be used for scientific research and comprehensive assessment of the risks of hip fractures [107].

Ultrasound densitometry (USD)

Ultrasound densitometry is another diagnostic methodology for determining the risk of OPFs and BMD. In addition to the last one, USD measures the coefficient of *Broadband Ultrasonic Attenuation (BUA)* when passing through bone and the speed of propagation of ultrasound in the bone *(Speed of Sound, SOS)*. Measurement is possible at the calcaneus, tibia, or phalanges of the fingers. Despite the meta-analyses [108–110], and recent systematic reviews [111] regarding the value of USD in predicting the risk of OPFs according to the latest *ISCD* recommendations [21], this method was not recommended for establishing the diagnosis of osteoporosis, evaluation the effectiveness of preventive and therapeutic measures in patients with PMO.

Lifestyle modification and diet correction in the management of postmenopausal osteoporosis

According to current concepts, correction of the modifiable risk factors for OPFs [112] and falls [113], especially in persons with increased risk, may be an effective strategy for the management of osteoporosis and its complications *(evidence level 1++)*. An adequate level of physical activity, smoking cessation and limiting alcohol consumption, rational consumption of calcium, vitamin D, and protein are important components of saving the bone strength and fracture prevention.

Immobilization in various somatic diseases and after fractures leads to bone loss and increased fracture risk [114]. Instead of this, rational physical activity with the inclusion of exercises of various orientations is an important strategy for the management of PMO.

To date, the positive effect of various physical exercises on BMD in postmenopausal women has been demonstrated [115–118]. High-intensity non-weight-bearing exercises and strength exercises with resistance for lower extremities are most effective in improving femoral neck BMD, while combined exercise programs are most effective in increasing spine BMD *(evidence level 1++)* [119]. However, the effect of various physical exercises in reducing the risk of OPFs is contradictory [119–121] and depends on the type, intensity and duration of programs, localization of OPFs, etc. [122]. Exercises are important in the rehabilitation of patients with vertebral fractures *(evidence level 1++)* [123], hip fractures *(evidence level 1++)* [124] and for reducing the risk of falls *(evidence level 1++)* [125, 126]. Today, the use of weight-loading physical exercises, exercises for the improvement of muscle strength and coordination [127], in particular with the use of oriental gymnastics (Tai-Chi, etc.) [128, 129] is an important strategy for reducing the risk of falls *(level of evidence 1++)* and prevention of OPFs [126].

Today, the expediency of using various types of orthoses (external medical and technical devices of various constructions, which include corsets, bandages, etc.), aimed at correcting the position of individual motor segments of the skeleton, preventing falls and fractures, restoring lost motor functions, etc., continues to be studied. Spinal orthoses and hip protectors are the most studied among them in patients with osteoporosis and its complications.

The effectiveness of the orthoses used in patients with vertebral compression fractures in reducing kyphotic deformation, improving postural stability and better functional results have been demonstrated in a number of RCTs [130–132]. However, systematic reviews [133–135] and meta-analyses of RCTs [136] indicated the low quality of this evidence *(evidence level 2++)*. In addition, compliance with the use of spinal orthoses is low and demonstrates a high variability, particularly by gender, although associated with BMI, age, and level of spinal pain syndrome [137].

The effectiveness of hip protectors in reducing the risk of hip fractures is also not significant *(evidence level 1++)*, while low adherence of the patients to the use of this strategy was also noted [138].

Recommendation 8. ***We recommended the optimization of lifestyle (correction of modified risk factors for OPFs, prevention of falls, rational physical activity with the use of physical exercise complexes) as a mandatory component of programs for the prevention and treatment of PMO*** **(grade B recommendation, LA — 100 %).**

Today, diet optimizing with sufficient calcium, vitamin D, and protein intake is important both for the formation of peak

bone mass and rates of bone loss in postmenopausal women [139]. Various guidelines for the management of osteoporosis recommend a daily intake of 700–1200 mg of calcium and 400–800 IU of vitamin D [15, 16, 32, 33]. It is obvious that the need for these nutrients, which are necessary for bone, increases with age, in particular, in postmenopausal women. According to the Norms of physiological needs of the Ukrainian population in basic food substances and energy [140], the daily calcium intake for adult women should be 1100 mg/d (increases to 1300 mg/d for females aged 60 and older), vitamin D — 5 μg/d (200 IU/d; increasing to 10 μg/d (400 IU/d) for persons at the age 60 years old and older). Research conducted in recent years in Ukraine established a low rate of calcium consumption in the diet of the population regardless of age and gender (the average level of consumption in women at the age of 50 years old and older was 515.3 mg/d) [141] and a large share of vitamin D deficiency [142, 143].

Sufficient levels of calcium and vitamin D intake can be ensured both due to diet and additional intake of dietary supplements. To date, a small but reliable effect of calcium on BMD has been established *(evidence level 1++)* [144], but its effects in reducing the risk of OPFs are doubtful [145]. The results of meta-analyses of RCTs regarding the effect of vitamin D supplements on fracture risk and falls in elderly people are also contradictory [146–149]. However, the results of modern high-quality meta-analyses demonstrated a small but reliable effect of the combined use of calcium and vitamin D in reducing the risk of OPFs *(evidence level 1++)* [148–153].

The combined use of calcium and vitamin D in order to optimize the level of their consumption, together with antiresorptive agents, can affect the effectiveness of antiosteoporotic therapy and reduce the risk of possible side effects [143, 154–157].

According to modern meta-analyses, sufficient protein consumption is also an important strategy in preserving bone mass in postmenopausal women and in patients with OPFs [158–160]. According to the Norms of physiological needs of the Ukrainian population in basic food substances and energy [140], the daily need for protein consumption for women at the age 40–59 years old is 58–82 g/d depending on the group (I–IV) of physical activity. Modern guidelines for osteoporosis management [15] and the conclusions of the *ESCEO* and *IOF* expert group [161] indicated the positive effect of sufficient protein consumption in the prevention of osteoporosis and its complications, reducing the recovery time of the patients after OPFs.

Recommendation 9. ***We recommend consuming calcium (1000–1200 mg/d), vitamin D (400–800 IU/d) and proteins (1.0–1.2 mg/kg of body weight per day) for the effective prevention and treatment of PMO and reducing the risk of OPFs*** **(grade A recommendation, LA — 98.9 %).**

Pharmacological treatment of postmenopausal osteoporosis

Strategies of antiosteoporotic therapy in Ukraine

Currently, drugs with antiresorptive and anabolic effects on bone are used for the treatment of PMO [88, 89]. The first group includes BPs, denosumab (antibody to *RANKL*), menopausal hormone therapy (MHT), selective estrogen receptor modulators *(SERMs):* raloxifene, bazedoxifene, and others, tibolone (selective tissue regulator of estrogen activity, *STEAR*), to others — PTH fragments (teriparatide (PTH 1–34) and abaloparatide (an analog of the protein bound to PTH), as well as an antibody to sclerostin (romosozumab). Drugs from the second group are currently not registered in Ukraine, and drugs of the first group are represented by oral (alendronic acid, risedronic acid and ibandronic acid) and parenteral (ibandronic acid and zoledronic acid) BPs, denosumab and MHT (in the form of estrogen monotherapy or combined estrogen-progestogen drugs). The choice of antiosteoporotic drugs, the form of their administration (oral or parenteral) and the duration of the treatment courses depends on the clinical situation and should take into account their benefit and risk profiles, as well as the patients' adherence to the treatment.

Bisphosphonates

BPs are the most studied drugs with antiresorptive effects on bone [163, 164]. Due to their affinity to hydroxyapatite, they are embedded in the bone, and due to the effect on the proton vacuolar adenosine triphosphatase (ATPase), disruption of the cytoskeleton and corrugated border of osteoclasts, which leads to the loss of their motor activity and death, BPs lead to inhibition of the rate of bone resorption. When entering the human body, up to 50 % of BPs are accumulated in the bone, the other 50 % are excreted in the urine. BPs remain in the bone matrix in an inactive state for many years and are gradually released in the process of bone resorption. Their positive effect persists for several years after stopping treatment, which makes it possible to consider the possibility of drug "holiday" in antiosteoporotic treatment and distinguishes them from other drugs for osteoporosis treatment.

Alendronic acid is registered in Ukraine in oral form at a dose of 70 mg once a week. It really reduces the risk of vertebral and non-vertebral fractures, including hip fractures *(evidence level 1++)* [165] in postmenopausal women and is the most widely used BPs in the world. When taking alendronate, certain instructions should be followed (taking in the morning on an empty stomach at least 30 minutes before eating or drinking (except water) in a sitting or standing position, drinking a sufficient amount of water in an upright position and avoiding taking other medicines at the same time).

Risedronic acid is another oral BP, which is used at a dose of 35 mg once a week and has similar features to alendronate when taking it. To date, the effectiveness of risedronate in reducing the risk of vertebral and non-vertebral fractures has been demonstrated *(evidence level 1++)* [166].

Ibandronic acid is currently available in two forms: oral (150 mg 1 time per month) and parenteral (3 mg quarterly intravenously). A significant effect of ibandronate has been demonstrated in reducing the risk of vertebral fractures [167, 168], as well as non-vertebral fractures in women with a femoral neck T-score (DXA –3.0 SD) *(evidence level 1+)* [169, 170], but increasing of the risk of hip fractures has not been proven. Oral ibandronate has similar instructions for use to other oral BPs.

A comparison of the efficacy and safety of three oral BPs in the 2-year RCT *TRIO* [171] demonstrated a more pronounced effect of alendronate and ibandronate on spine BMD and comparable dynamics at the peripheral skeleton. However, a monthly mode of ibandronic acid taking can significantly improve the patient's adherence to antiosteoporotic treatment.

The most frequent side effects of oral BPs are manifestations from the gastrointestinal tract (abdominal pain, dysphagia, dyspepsia, nausea, heartburn, constipation, or diarrhea) and musculoskeletal pain, less often skin reactions.

Zoledronic acid is used to treat PMO at a dose of 5 mg once a year intravenously. The results of the RCTs confirmed the effectiveness of zoledronic acid in reducing the risk of vertebral, non-vertebral fractures and hip fractures [172] and mortality in patients after hip fractures *(evidence level 1+)* [173].

Among the side effects of zoledronic acid, the most frequent are acute-phase reactions, which can be aggravated by insufficient calcium supply and vitamin D deficiency [157], therefore it is important to measure their levels in blood serum before the administration of zoledronic acid. Gastrointestinal disorders are less often.

BPs are contraindicated for patients with hypocalcemia, increased sensitivity to them, during pregnancy and lactation period, significant renal dysfunction (GFR ≤ 35 ml/min for alendronic and zoledronic acids and ≤ 30 ml/min for risedronic and ibandronic acids). Before initiation of BP therapy, creatinine clearance should also be determined and creatinine level should be monitored in persons at risk of chronic kidney disease. Oral BPs are contraindicated in subjects with esophagus pathology that delays normal food passages (e.g., achalasia of the esophagus), with diaphragmatic hernia, or in persons with the inability to stand or sit upright for at least 30–60 minutes (for example, expressed vertebral pain syndrome after vertebral fractures).

Rare but extremely important and dangerous side effects of BPs are the osteonecrosis of the jaw [174, 175] and atypical femoral fractures [176–178]. The risk of these side effects is quite low [176, 178], differs from the type of BPs, increases with their long-term use, especially in patients from the risk group (glucocorticoid therapy, chemotherapy, smoking, alcohol intake, etc.). Cancellation of BPs leads to a rapid decrease in the risk of these adverse reactions. Patients receiving BPs and planning surgical dental procedures should be aware of the possible risks of osteonecrosis of the jaw [179]. Also, during the treatment of BPs, monitoring of symptoms associated with atypical femoral fractures (prodromal pain in the groin, thigh, buttock, or lower back) should be carried out. Additionally, it should be noted that the absolute risk of atypical femoral fractures during the use of BPs remains low compared to their effective reduction of the risk of OPFs.

Denosumab

Denosumab is another antiosteoporotic drug with an antiresorptive effect. It is a fully monoclonal human antibody, and its mechanism of action is related to the regulation of the chain: the ligand of the receptor of nuclear factor kappa-B — the receptor of the nuclear factor kappa-B (RANK) — osteoprotegerin (OPG). Denosumab binds with high affinity and specificity to RANKL, similar to OPG, one of the important regulators of bone resorption expressed by osteoblasts, preventing the activation of its receptor (RANK) on the surface of osteoclast progenitors, which leads to inhibition of proliferation and formation of mature osteoclasts. Unlike BPs, denosumab does not have a prolonged effect, because it is not accumulated as BPs in the bone, but circulates in the intercellular substance.

Modern studies demonstrate a reliable effect of denosumab in reducing the risk of vertebral and non-vertebral fractures in general and hip fractures in particular evidence level 1+ [180, 181]. Denosumab is prescribed at 60 mg once every 6 months, subcutaneously.

The most common side effects of denosumab are musculoskeletal and extremity pain, less commonly infectious skin diseases (mainly cellulitis) and hypocalcemia. Osteonecrosis of the jaw and atypical fractures may also occur after denosumab treatment, but their risk remains low [178]. Sufficient calcium and vitamin D intake during the denosumab therapy can reduce the risk of hypocalcemia and improve the long-term results of antiosteoporotic treatment [155, 156].

Due to the lack of accumulation of denosumab in bone, it, unlike BPs, has no after-effect and has a "rebound" effect [182–184], which is characterized by progressive bone loss and an increased risk of fractures. Therefore, after the end of denosumab therapy, the question of continuing antiosteoporotic therapy, in particular with the use of BPs, which can slow bone loss, should be considered.

Menopausal hormone therapy

Menopausal hormone therapy (hormone replacement therapy) involves the use of estrogen-progestogen drugs (combined therapy in females with natural menopause) or estrogens (monotherapy, for women with surgical menopause) [185–187]. The results of systematic reviews [188, 189] and meta-analyses [190–192] confirm the positive MHT effect in the prevention of OPFs *(evidence level 1+)*. Numerous RCTs have demonstrated the positive effect of MHT on BMD [193–196]. In addition to the positive effect of MHT on the risk of vertebral and non-vertebral fractures, it has a positive influence on the severity of vegetative-vascular and urogenital manifestations of postmenopause, reduces the risk of colorectal cancer, but increases the risk of thromboembolism, gallstone disease, bronchial asthma, cardiovascular and cerebrovascular diseases, breast cancer, etc. [186, 187].

In general, MHT is considered effective in the prevention of OPFs, however, due to the need for its long-term use and a number of the above-mentioned side effects, it is usually recommended only to women with a high risk of OPFs, for whom other antiosteoporotic therapy (BPs, denosumab) is unusable [15, 212].

Tibolone (STEAR)

Tibolone, which belongs to the STEAR group, is a synthetic steroid with a structure different from estrogens and

SERMs. Tibolone has a multidirectional effect in various tissues after the formation of active metabolites with estrogen-, progestogen-, and androgen-like qualities [197]. To date, a meta-analysis of controlled studies has shown a positive effect of tibolone on BMD of the lumbar spine and femoral neck *(evidence level 1+)*, but no beneficial effect on BMD compared to estrogen therapy has been established [197]. The results of available RCTs confirm the positive effect of tibolone in reducing the risk of vertebral and non-vertebral fractures [198]. Other positive effects of tibolone include reducing the risk of invasive breast and colon cancer [199].

Tibolone is prescribed at a dose of 2.5 mg/d (tablet for oral administration) daily.

Side effects of tibolone include lower abdominal pain, postmenopausal bleeding, breast discomfort, skin and subcutaneous tissue disorders, swelling, weight gain, and others. Important, although infrequent, side effects of tibolone include an increased risk of stroke [198, 199] and recurrence of breast cancer [200].

Conducted network meta-analyses, which compared the effectiveness of various antiosteoporotic strategies [201, 202], indicate the greatest effectiveness of osteoanabolic therapy in reducing OPF risk. The comparison of the effectiveness of antiresorptive agents revealed the specific features depending on age, the degree of risk of OPFs, and the fracture localization. According to a recent network meta-analysis [201], a reduction in the risk of hip fractures was demonstrated for alendronate, zoledronate, risedronate, denosumab, MHT and calcium in combination with vitamin D [201], non-vertebral fractures — for denosumab, alendronate, risedronate, zoledronate, tibolone, MHT and vitamin D [201], vertebral fractures — denosumab, zoledronate, risedronate, alendronate, ibandronate, MHT and tibolone [201]. Meta-analyses and systematic reviews devoted to the comparison of financial costs of treatment [203–206] confirmed a greater economic burden in cases of denosumab and osteoanabolic therapies, which substantiates the feasibility of using oral BPs as "first-line" drugs for the treatment of PMO.

The choice of an antiosteoporotic treatment strategy depends on the risk of OPFs

Today, the feasibility of initiating antiosteoporotic therapy and the choice of a drug for the treatment of osteoporosis and its complications is based, in particular, on the assessment of the OPF risk. The FRAX® calculated the 10-year probability of major OPFs and hip fractures is most often used for this. There are 4 categories of risk of OPFs: low, moderate, high, and very high [207–209]. Patients at low risk of OPFs (FRAX® below the lower intervention threshold for a specific population, *Appendix 6*) do not need antiosteoporotic therapy. Optimizing the calcium and vitamin D consumption in the diet and adequate physical activity are recommended for them [208–213]. Some guidelines recommend that in the presence of other complaints of menopausal syndrome in a woman at low risk of OPFs, MHT should be recommended. Re-evaluation of BMD [208, 212] is recommended after 5–10 years.

Subjects with a moderate risk of OPFs (FRAX® between the lower and upper limits of the intervention, *Appendix 6*) should be referred to the DXA for additional examination, re-assessment of the risk of OPFs and making decisions regarding further management [15, 79, 80, 208–213]. Persons with a risk of OPFs below the "treatment threshold" are classified into a group of low-risk OPFs and do not require further treatment. Subjects with a risk of OPFs above the "treatment threshold" or the upper limit of intervention according to FRAX® *(Appendix 6),* depending on their results, are classified into a group of high or very high risk, respectively [208–212] and require the antiosteoporotic treatment.

For persons from a group of high-risk OPFs, against the background of optimization of calcium and vitamin D intake, and physical activity, and use of strategies aimed at preventing falls, it is advisable to use oral BPs (first line therapy) or other antiresorptive agents (injectable BPs or denosumab when there are restrictions for prescription or side effects of oral BPs). According to current recommendations for the management of osteoporosis, the effectiveness of antiosteoporotic therapy with DXA should be evaluated after 2 years of treatment [208, 212].

Today, discussions regarding the definition of "very high risk" of OPFs are ongoing. In various guidelines, it is proposed the various criteria, in particular:

— FRAX® (using an age-dependent or hybrid partially age-associated approach, namely when the "intervention limit" is exceeded by 20 or 60 %) [15, 32, 208, 211, 212];

— the T-score according to DXA (T-score ≤ –3.5 SD [213] or T ≤ –4.0 SD [214] regardless of the presence of fractures);

— previous fracture (recent primary OPFs [185], vertebral fracture during the past 2 years [213] or history of ≥ 2 fragility vertebral fractures at any time [213]);

— combinations of several of the abovementioned criteria:

1) OPFs and T-score according to DXA (more than 1 previous vertebral fracture and T-score ≤ –2.5 SD [215] or 1 severe or 2 or more moderate vertebral fractures and T-score ≤ –1.5 SD [214]);

2) OPF and FRAX® (recent OPFs and FRAX® for OPFs ≥ 30 %) [216].

For patients with a very high risk of OPFs, on the background of optimization of calcium and vitamin D intake, physical activity and the use of strategies focused on the prevention of falls, osteoanabolic agents should be used to initiate antiosteoporotic therapy, followed by continuation of antiresorptive therapy. A similar approach is based on the results of recent RCTs that demonstrated significant advantages of osteoanabolic agents compared with antiresorptive agents [217-219] as for the dynamics of lumbar spine and hip BMD during the treatment.

However, osteoanabolic agents for the treatment of osteoporosis are not registered in Ukraine today, which is a challenge for the adequate management of PMO. However, in the absence of opportunities to use osteoanabolic agents for the treatment of a patient from the group of a very high risk of OPFs, the "drugs of choice" may be parenteral BPs

(in particular, zoledronic acid) or denosumab [212]. To date, there are no clear recommendations regarding the timing of re-evaluation of BMD in patients at very high risk of OPFs, however, according to ISCD recommendations [21], the need for DXA should be determined by the doctor's reasoned opinion.

Recommendation 10. ***We recommend choosing the drug for the treatment of PMO and its complications (Fig. 2) based on the OPF risk, side effects of drugs, the presence of concomitant pathology, and preferences of patients*** **(grade D recommendation, LA — 98.9 %).**

Recommendation 10.1. ***For persons with a low risk of OPFs according to FRAX® we recommend optimizing the calcium, vitamin D, and protein intake, physical activity with DXA control after 3–5 years*** **(grade BA recommendation, LA — 100 %).**

Recommendation 10.2. ***For persons with a moderate risk of OPFs according to FRAX® we recommend performing DXA with a reassessment of the OPF risk and making a decision on further management*** **(grade B recommendation, LA — 100 %).**

Recommendation 10.3. ***For persons at high risk of OPFs we recommend prescribing oral bisphosphonates (first line of therapy), injectable bisphosphonates or denosumab (second line of therapy), or MHT (third line of therapy) in combination with sufficient calcium, vitamin D, and protein intake, physical therapy programs with DXA control after 1–2 years*** **(grade B recommendation, LA — 97.8 %).**

Recommendation 10.4. ***Persons with a T-score ≤ ≤ –4.0 SD, hip or vertebral fractures during the last year, and a FRAX® score above the upper intervention limit (Appendix 6) are persons at very high risk of OPFs. We recommend prescribing them zoledronic acid or denosumab in combination with sufficient calcium, vitamin D and protein intake, a physical therapy program with DXA control after 1 year*** **(grade D recommendation, LA — 97.8 %).**

Duration and monitoring of effectiveness and safety of antiosteoporotic therapy

Due to the increase in the frequency of such disabling side effects of antiosteoporotic therapy as osteonecrosis of the jaw and atypical fractures of the femur, in the long-term treatment of osteoporosis, not only reducing the OPF risk but also the safety of the therapy is relevant [220]. Today, it is known, that BPs due to the mechanism of their action accumulate in bone for a long period of time and have an after-effect. This important effect allows us to consider possible "drug holidays" in the treatment of patients with osteoporosis. Since most RCTs on the effectiveness and safety of antiosteoporotic therapy have been performed for 3–5 years, and only a few of them lasted for 9–10 years, the question of the feasibility of the treatment should be decided individually, taking into account the benefits and risks for the patient. To date, the effectiveness and safety of continuing antiosteoporotic therapy for more than 10 years has not been studied in RCTs, so its feasibility should be substantiated individually. Taking into account the above, a duration of BPs therapy of 3–5 years (3 years for zoledronic acid and 5 years for alendronate, ibandronate, and risedronate) is currently justified *(evidence level 1+)*, which is displayed in other guidelines for the management of osteoporosis [32, 221, 222].

According to current views, changes in antiosteoporotic treatment can be justified:

1) side effects of antiosteoporotic drugs (see above);

2) inadequate effect of the treatment (in particular, due to violation of adherence);

3) achieving the effect of the treatment.

Today, according to *IOF* experts' proposals [223], the adequacy of the response to antiosteoporotic treatment is assessed using the presence of two criteria: fracture during the course of treatment and BMD dynamics (providing the patient adheres to treatment during all treatment courses):

1) inadequate response: incident of fracture and reduction in BMD by more than 2 %;

2) possible inadequate response — an incident of a fracture or a decrease in BMD of more than 2 %;

3) an adequate response is the absence of a fracture and the absence of a decrease in BMD of more than 2 %.

The decision to cancel antiosteoporotic treatment should be made based on a comprehensive assessment of the patient with the assessment of the OPF risk (according to FRAX® and other risk factors), BMD, the presence of OPFs before the initiation of therapy and during the antiosteoporotic treatment.

In persons with a high and very high risk of OPFs: 1) in accordance with Ukrainian FRAX®; 2) systemic osteoporosis (T ≤ –2.5 SD); 3) a history of hip or vertebral fractures; 4) a fragility fracture during the antiosteoporotic treatment (if adherence to it is confirmed); 5) diseases and conditions that lead to bone loss (development of secondary osteoporosis) and taking drugs that negatively affect the bone (medium and high doses of glucocorticoids, etc.), antiosteoporotic therapy should be continued taking into account the risks and benefits.

Cancellation of BPs therapy leads to negative BMD dynamics, increased rate of bone turnover and risk of OPFs after 2–3 years when using alendronate [224, 225], risedronate [226, 227] and ibandronate [228]. A somewhat smaller BMD dynamic was established when zoledronate therapy was canceled [229]. In contrast to the abovementioned, cancellation of denosumab leads to a pronounced loss of BMD and an increase in the risk of OPFs [182, 230]. Due to the well-known properties of BPs accumulate in bone after the end of the treatment, their prescription may be interrupted if the treatment effect is achieved. In contrast, the use of other antiosteoporotic treatment strategies (demosumab, MHT, etc.) due to the so-called "rebound effect" [230] requires the prescription of other antiosteoporotic strategies (in particular, BPs), which can partially reduce this effect [231–234].

After the completion of the antiosteoporotic treatment course, in case of a low OPF risk and the absence of osteoporosis (T ≤ –2.5 SD) according to the DXA, a re-assessment of the OPF risk and BMD measurement should

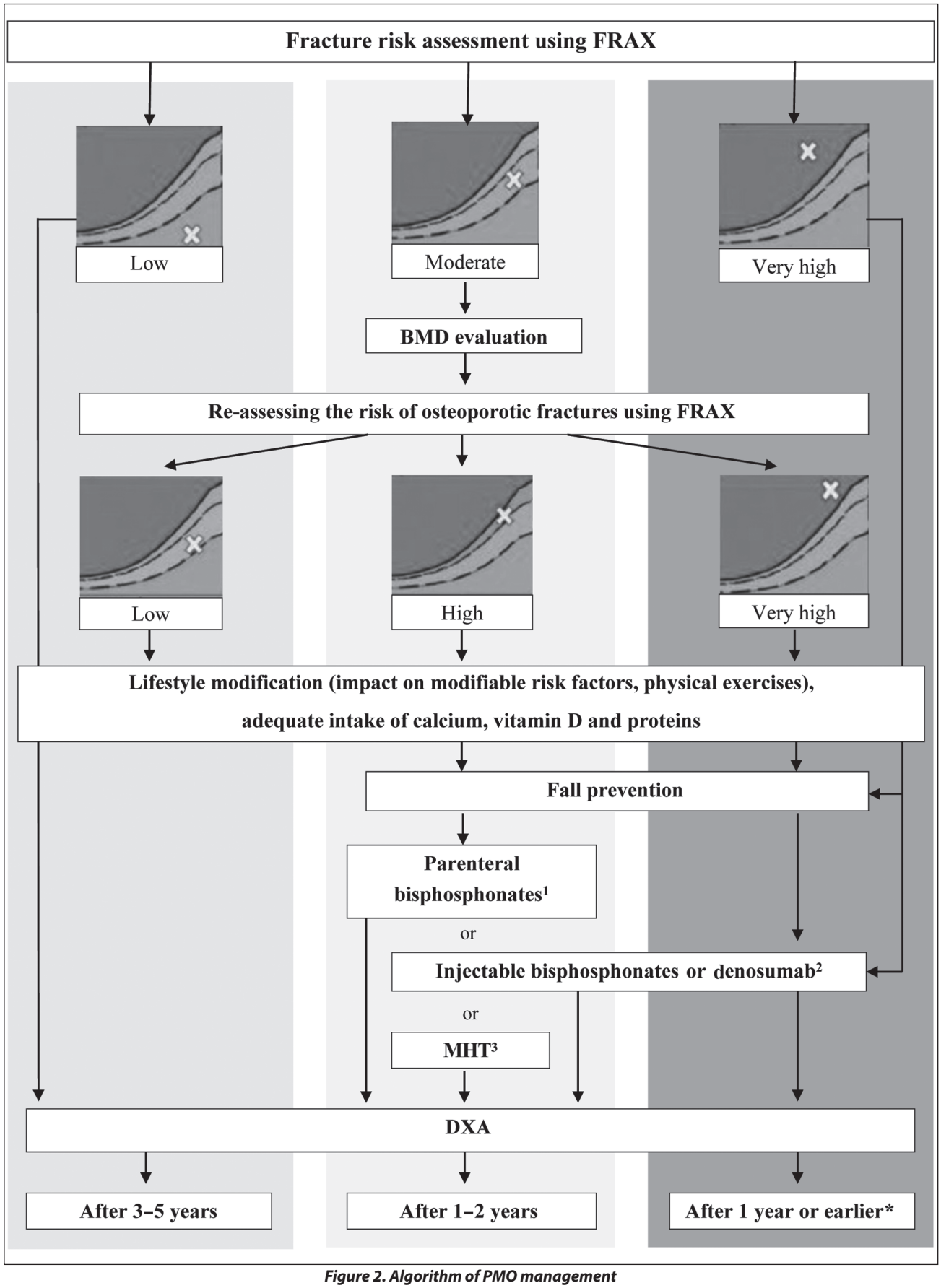

Figure 2. Algorithm of PMO management

Notes: *[1] — first line therapy; [2] — second line therapy; [3] — third line therapy; * — determined by the doctor's reasoned opinion.*

prescribed individually after 1–2 years. If it is necessary to continue the treatment course, the choice of the antiosteoporotic drug should be performed taking into account the OPF risk, BMD, incident of the fracture before and during the treatment, concomitant diseases and conditions that lead to the development of osteoporosis and its complications.

Recommendation 11. ***The duration of antiosteoporotic therapy should be based on the OPF risk at the start of the treatment and during dynamic observation, the presence of diseases and conditions with a proven negative effect on bone, and should last up to 5 years for oral BPs and 3 years for parenteral BPs and denosumab, however its duration can be continued in subjects with high risk of OPFs*** **(grade B recommendation, LA — 97.8 %).**

Recommendation 12. ***We recommend the continuation of BP therapy after completion of denosumab treatment*** **(grade A recommendation, LA — 98.9 %).**

Recommendation 13. ***Changes in the therapy of PMO and its complications are recommended to be justified by side effects of drugs, low adherence of patients to antiosteoporotic treatment, the ineffectiveness of the selected treatment strategy, or achievement of the treatment effect*** **(grade C recommendation, LA — 98.9 %).**

Surgical methods of treatment of osteoporotic fractures

Due to the significant negative impact on survival and quality of life of patients with OPFs, in particular hip fractures, some surgical strategies are important in the management of patients with PMO [235–237]. Modern systematic reviews and meta-analyses [237–240] evidence the important role of surgical treatment methods, in particular, total hip arthroplasty in reducing mortality rates, restoring function, and preserving the quality of life of patients with hip fractures.

The most common surgical method for the treatment of vertebral compression fractures is percutaneous vertebroplasty (PVP, which is based on the intervention of bone cement into the vertebral body) and percutaneous balloon kyphoplasty (a procedure similar to vertebroplasty, but before the intervention of bone cement into the damaged vertebral body, a balloon is inserted, which is spreading there).

To date, the positive results of PVP in the treatment of patients with vertebral fractures are unconvincing. A meta-analysis of RCTs [241] did not confirm its advantages compared to simulation of surgery in reducing pain syndrome, impairment of work capacity and quality of life in patients in the acute and sub-acute periods after vertebral fractures *(evidence level 1++)* with an increase in the frequency of side effects. Later published meta-analyses of RCTs [242, 243] with an analysis of the *VAPOUR* (*Vertebroplasty for Acute Painful OPFs*) study [244] demonstrated that PVP was effective only in patients in the acute period after vertebral fracture that had stable and pronounced pain syndrome. A recent Bayesian meta-analysis conducted for the identification of the optimal surgical method for the treatment of vertebral fractures (PVP, balloon kyphoplasty and non-surgical methods) [244] had demonstrated the greatest effectiveness of PVP in reducing pain syndrome and improving the quality of life of patients, balloon kyphoplasty — in reducing the risk of repeated fractures at the operated level of the spine, and non-surgical methods of treatment in reducing the risk of adjacent vertebral fractures.

Recommendation 14. ***In patients with femoral neck fractures we recommend surgical treatment, preference should be given to hip arthroplasty*** **(grade A recommendation, LA — 100 %).**

Recommendation 15. ***Solving the issue of the possibility of surgical treatment of OPFs of vertebral fractures is recommended to be considered in case of ineffective treatment of persistent vertebral pain syndrome using conservative methods of treatment. Decisions should be made after a detailed understanding of the patient's risks and the benefits of surgical treatment; preference should be given to PVP*** **(grade A recommendation, LA — 97.8 %).**

Conclusions

The updated Ukrainian Guideline on the diagnosis, prevention, and treatment of PMO, which was created based on the thorough analysis and synthesis of modern literature data, contains sections devoted to the diagnosis and differential diagnosis of PMO, risk assessment of OPFs, the role of BTMs in the management of PMO, modern strategies of antiosteoporotic treatment. The Guideline consisted of 15 main Recommendations, is an important tool for the management of PMO, and is recommended for use in practical health care by doctors of various specialties.

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Appendix 1

Abbreviations

BMD	Bone mineral density
BMI	Body mass index
BPs	Bisphosphonates
BTMs	Bone turnover markers
CTX-I	C-terminal cross-linking telopeptide of type 1 collagen
CT	Computer tomography
DXA	Dual-energy X-ray absorptiometry
ESCEO	European Society for Clinical and Economic Evaluation of Osteoporosis and Osteoarthritis
FRAX®	Fracture Risk Assessment Tool
ICD	International Classification of Diseases
IOF	International Osteoporosis Foundation
ISCD	International Society of Clinical Densitometry
MHT	Menopausal hormone therapy
OPF(s)	Osteoporotic fracture(s)
P1NP	Procollagen type 1 N-terminal propeptide
PMO	Postmenopausal osteoporosis
PTH	Parathyroid hormone
PVP	Percutaneous vertebroplasty
RCT(s)	Randomized controlled trial(s)
SD	Standard deviation
TBS	Trabecular bone score
USD	Ultrasound densitometry
WHO	World Health Organization

Appendix 2

Terminology of osteoporosis, coding according to ICD

Osteoporosis is a systemic disease of the skeleton, which is characterized by low bone mineral mass, a deterioration of its microarchitectonics, associated with a decreased number of trabeculas, their thinning and loss of connection, decreased thickness of the cortical bone and increased its porosity, which leads to an increased bone fragility and risk of fractures (WHO, 1994) [1, 2].

Postmenopausal osteoporosis is one of the most common types of systemic osteoporosis, associated with decreased level of sex hormones after natural or artificial menopause [12–14].

Menopause is the last menstruation in a woman's life, caused by the loss of ovarian follicular function and decreased level of estrogens in blood (WHO [5]).

Severe (established) osteoporosis is characterized by reduced BMD indices (T-score ≤ –2.5 SD) and the presence of at least one fragility fracture (WHO, 1994) [1, 2].

Fragility (low-energy or low-trauma) fracture (WHO, 1994) — a fracture caused by trauma that would not be sufficient to fracture a healthy bone. Occurs as a result of reduced bone strength with minimal trauma (fall from height or less, or in the absence of identifiable trauma). The most frequent localizations are hip, spine, distal forearm, proximal humerus, proximal tibia, ribs [1, 2].

Coding of the diagnosis of osteoporosis according to ICD-10 [3]

Code	Definition
M80	**Osteoporosis with pathological fracture**
M80.0	Postmenopausal osteoporosis with pathological fracture
M80.1	Post-oophorectomy osteoporosis with pathological fracture
M80.2	Osteoporosis of disuse with pathological fracture
M80.3	Postsurgical malabsorption osteoporosis with pathological fracture
M80.4	Drug-induced osteoporosis with pathological fracture
M80.5	Idiopathic osteoporosis with pathological fracture
M80.8	Other osteoporosis with pathological fracture
M80.9	Unspecified osteoporosis with pathological fracture
M81	**Osteoporosis without pathological fracture**
M81.0	Postmenopausal osteoporosis
M81.1	Post-oophorectomy osteoporosis
M81.2	Osteoporosis of disuse
M81.3	Postsurgical malabsorption osteoporosis
M81.4	Drug-induced osteoporosis
M81.5	Idiopathic osteoporosis
M81.6	Localized osteoporosis (Lequesne)
M81.8	Other osteoporosis. Senile osteoporosis
M81.9	Osteoporosis, unspecified
M82	**Osteoporosis in diseases classified elsewhere**
M82.0	Osteoporosis in multiple myelomatosis
M82.1	Osteoporosis in endocrine disorders
M82.8	Osteoporosis in other diseases classified elsewhere

Note: an additional code of external causes (class XX) is used to identify the medicinal product.

Coding of the diagnosis of osteoporosis according to ICD-11 [25]

Code	Definition
FB83.0	**Osteopenia**
FB83.00	Premenopausal idiopathic osteopenia
FB83.01	Postmenopausal osteopenia
FB83.02	Senile osteopenia
FB83.03	Osteopenia of disuse
FB83.04	Drug-induced osteopenia
FB83.0Y	Other specified osteopenia
FB83.0Z	Osteopenia, unspecified
FB83.1	**Osteoporosis**
FB83.10	Premenopausal idiopathic osteoporosis
FB83.11	Postmenopausal osteoporosis
FB83.12	Osteoporosis of disuse
FB83.13	Drug-induced osteoporosis
FB83.14	Osteoporosis due to malabsorption
FB83.1Y	Other specified osteoporosis
FB83.1Z	Osteoporosis, unspecified

Appendix 3

Evidence levels for the significance of potential risk factors and intervention studies, and the corresponding gradation of recommendations [19]

Evidence level for research about potential risk factors	
1++	High-quality meta-analysis (MA), systematic review (SR) of RCTs or RCTs with a very low risk of systematic error
1+	Well-conducted MA, SR of RCTs or RCT with low risk of systematic error
1–	MA, SR of RCTs or RCT with a high risk of systematic error
2++	High-quality SR of case-control or cohort studies OR high-quality case-control or cohort studies with low risk of false information, systematic errors, and high probability that connections are causal
2+	Well-conducted case-control or cohort studies with a low risk of false information, systematic errors or misinformation and a reasonable probability that the connection is causal
2–	Case-control studies or cohort studies with a high risk of false information, systematic errors or misinformation and a significant risk that the connection is not causal
3	Non-analytical studies such as case reports, case series reports
4	Expert opinion
Evidence level for intervention studies	
1++	High-quality meta-analysis (MA), systematic review (SR) of RCTs or RCTs with a very low risk of systematic error
1+	Separate RCTs (with narrow confidence intervals)
2++	SR of at least one non-randomized controlled trial or well-designed cohort study
2+	One cohort study or low-quality RCT
3++	SR of at least one case-control study

End of the table

3+	One case-control study
4	Expert reports and/or case series (low-quality cohort studies and case-control studies)
Gradation of recommendations	
A	At least 1 MA, SR or RCTs graded as 1++ and applicable to the target population or SR of RCT or body of evidence mainly from 1+ studies that can be directly applied to the target population and that have consistent results
B	The complex of evidence includes 2++ studies that can be directly applied to the target population and that have consistent results or results from 1++ or 1+ studies that can be extrapolated to the target population
C	The complex of evidence includes 2+ studies with consistent results that can be directly applied to the target population or extrapolated evidence from 2++ studies
D	Evidence 3 or 4 or extrapolated data from 2+ studies

Notes: MA — meta-analysis; SR — systematic review; RCT — randomized controlled trial.

Appendix 4

Guideline for diagnostic, prevention and treatment of postmenopausal osteoporosis

No.	Recommendation	Grade/ level*
1	2	3
1	Instrumental confirmation of the diagnosis of PMO is recommended using DXA with the measurement of BMD indices of the femoral neck, total hip or lumbar spine# according to WHO criteria (T-score = –2.5 SD or lower)	B/100 %
2	We recommend basing a comprehensive examination of a person with suspicion of PMO on the assessment of OPF risk factors, DXA indices, and the determination of possible causes of bone loss	B/98.9 %
3	We recommend assessing the 10-year probability of major OPFs and hip fractures in postmenopausal women based on the Ukrainian FRAX® version using cut-off values for the Ukrainian population for further management decisions (in particular, DXA or the appointment of antiosteoporotic treatment)	C/100 %
4	We recommend interpreting the risk of OPFs taking into account other diseases and states that affect bone loss, but are not included in FRAX® and FRAXplus®	D/96.7 %
5	We don't recommend to use of BTMs (PINP and CTX-I) in the diagnosis of osteoporosis, but recommend them for use in predicting the risk of OPFs and monitoring antiosteoporotic therapy	A/96.7 %
6	Central and peripheral CT (measurement at the lumbar spine or ultradistal radius, respectively) is a reliable alternative to DXA in the diagnosis of PMO and predicting the risk of OPFs, however, we don't recommend them for dynamic monitoring of the bone state due to a higher dose of X-ray irradiation	C/95.6 %
7	In postmenopausal women, we recommend using TBS together with FRAX® and BMD to increase the informativeness of the prediction of OPF risk	A/97.8 %
8	We recommended the optimization of lifestyle (correction of modified risk factors for OPFs, prevention of falls, rational physical activity with the use of physical exercise complexes) as a mandatory component of programs for the prevention and treatment of PMO	B/100 %
9	We recommend consuming calcium (1000–1200 mg/d), vitamin D (400–800 IU/d) and proteins (1.0–1.2 mg/kg of body weight per day) for the effective prevention and treatment of PMO and reducing the risk of OPFs	A/98.9 %
10	We recommend choosing the drug for the treatment of PMO and its complications (Fig. 2) based on the OPF risk, side effects of drugs, the presence of concomitant pathology, and preferences of patients	D/98.9 %
10.1	For persons with a low risk of OPFs according to FRAX® we recommend optimizing the calcium, vitamin D, and protein intake, physical activity with DXA control after 3–5 years	A/100 %
10.2	For persons with a moderate risk of OPFs according to FRAX® we recommend performing DXA with a reassessment of the OPF risk and making a decision on further management	B/100 %
10.3	For persons at high risk of OPFs we recommend prescribing oral bisphosphonates (first line therapy), injectable bisphosphonates or denosumab (second line therapy), or MHT (third line therapy) in combination with sufficient calcium, vitamin D, and protein intake, physical therapy programs with DXA control after 1–2 years	B/97.8 %
10.4	Persons with a T-score≤ –4.0 SD, hip or vertebral fracture during the last year, and a FRAX® score above the upper intervention limit (Appendix 4) are persons at very high risk of OPFs. We recommend prescribing them zoledronic acid or denosumab in combination with sufficient calcium, vitamin D and protein intake, a physical therapy program with DXA control after 1 year	D/97.8 %
11	The duration of antiosteoporotic therapy should be based on the OPF risk at the start of the treatment and during dynamic observation, the presence of diseases and conditions with a proven negative effect on bone, and should last up to 5 years for oral BPs and 3 years for parenteral BPs and denosumab, however its duration can be continued in subjects with high risk of OPFs	B/97.8 %
12	We recommend the continuation of BP therapy after completion of denosumab treatment	A/98.9 %
13	Changes in the therapy of PMO and its complications are recommended to be justified by side effects of drugs, low adherence of patients to antiosteoporotic treatment, the ineffectiveness of the selected treatment strategy, or achievement of the treatment effect	C/98.9 %

End of the table

1	2	3
14	In patients with femoral neck fractures we recommend surgical treatment, preference should be given to hip arthroplasty	A/100 %
15	Solving the issue of the possibility of surgical treatment of OPFs of vertebral fractures is recommended to be considered in case of ineffective treatment of persistent vertebral pain syndrome using conservative methods of treatment. Decisions should be made after a detailed understanding of the patient's risks and the benefits of surgical treatment; preference should be given to PVP	A/97.8 %

Notes: * — strength of recommendations and evidence level; # — the lowest index of the measured regions. If it is impossible to assess the BMD of the specified regions, the BMD index of the distal part of the radius can be used; the strength of the recommendations was determined according to the evidence level [17, 19].

Appendix 5

Indications for BMD testing according to *ISCD* recommendation [21]

1. Women aged 65 and older.
2. For postmenopausal women younger than age 65 a bone density test is indicated if they have a risk factor for low bone mass such as:
— low body weight;
— prior fracture;
— high risk medication use.
3. Disease or condition associated with bone loss.
4. Women during the menopausal transition with clinical risk factors for fracture, such as low body weight, prior fracture, or high-risk medication use.
5. Adults with a fragility fracture.
6. Adults with a disease or condition associated with low bone mass or bone loss.
7. Adults taking medications associated with low bone mass or bone loss.
8. Anyone being considered for pharmacologic therapy.
9. Anyone being treated, to monitor treatment effect.
10. Anyone not receiving therapy in whom evidence of bone loss would lead to treatment.

Appendix 6

10-year probability of major OPFs in women depending on age with intervention thresholds for the Ukrainian FRAX® model, % [80]

Age (years)	Lower limit of intervention	"Threshold" of treatment	Upper limit of intervention
40	2.4	5.5	6.6
45	2.7	6.1	7.3
50	3.1	6.7	8.1
55	3.5	7.5	9.1
60	4.0	8.3	10
65	4.4	8.8	11
70	5.0	9.6	12
75	6.0	11	13
80	6.7	11	13
85	6.9	11	13
90	6.0	10	12

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Рекомендації щодо діагностики, профілактики та лікування постменопаузального остеопорозу

Резюме. ***Актуальність.*** Постменопаузальний остеопороз (ПМП ОП), який виникає внаслідок дефіциту естрогенів у жінок після настання менопаузи, — найбільш поширений тип системного остеопорозу. Українські рекомендації щодо його менеджменту потребують перегляду у зв'язку з отриманням останніми роками нових даних і результатів високоякісних досліджень. ***Мета дослідження*** — на основі аналізу сучасних літературних джерел розробити Рекомендації щодо діагностики, профілактики та лікування постменопаузального остеопорозу задля поліпшення обізнаності медичної спільноти України. ***Методологія.*** Для розробки Рекомендацій була створена експертна група з 13 провідних українських вчених різного фаху, які провели ретельний огляд сучасних літературних джерел щодо цієї проблеми, за допомогою системи GRADE оцінили рівень наявних доказів, запропонували 15 положень Рекомендацій та проголосували за них. ***Результати.*** Ці Рекомендації містять розділи щодо діагностики та диференційної діагностики ПМП ОП, оцінки ризику остеопоротичних переломів, ролі біохімічних маркерів кісткового ремоделювання в менеджменті ПМП ОП, сучасних стратегій антиостеопоротичного лікування. ***Висновки.*** Українські Рекомендації щодо діагностики, профілактики та лікування ПМП ОП, які містять 15 основних положень, розроблених на ґрунті ретельного аналізу й синтезу сучасних літературних даних щодо цього питання, є важливим інструментом для менеджменту ПМП ОП і рекомендовані до використання у практичній охороні здоров'я лікарями різного фаху.

Ключові слова: рекомендації; постменопаузальний остеопороз; діагностика; профілактика; лікування