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Critical points in strategies for the diagnosis and treatment of osteoporosis

Punkty krytyczne strategii rozpoznawania i leczenie osteoporozy

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Abstract

Current treatment decisions for osteoporosis depend on the fracture risk calculated based on the results of comprehensive diagnostic procedures [clinical risk factors (CRF), densitometry (BMD), morphometry, and bone turnover markers (BTM)]. Recently developed fracture risk assessment tool (FRAX™) represents an important new achievement as a 10-year fracture risk calculation based on femoral neck densitometry and age combined with independent clinical fracture risk factors. FRAX™ presents several options: FRAX™ BMI (body mass index) is advocated as a helpful screening tool to identify the group of patients with high fracture risk, independently of access to densitometry and FRAX™, utilizing hip densitometry. In both cases, the probability of major fractures or hip fractures are calculated during performed diagnostic evaluations. Operating FRAX™ algorithm does not include spinal bone mineral density, which is its main limitation. With the aim of improvement of anti-fracture efficacy of therapeutic management of osteoporosis, we have extended our discussion to three integral elements of existent strategy: 1) screening outlines, 2) principles of drug selection, and 3) treatment benefit evaluation.
Since osteoporosis is a chronic disease, long-term adherence to the treatment is important. The suitability of the drug, the patient's preference, tolerability, and convenience should all be considered. Anti-catabolic drugs are most appropriate in patients with high bone turnover, while anabolic drugs demonstrate efficacy irrespective of bone turnover. BMD measurement is most widely used for long-term assessment of the efficacy of osteoporosis treatment. The measurements of bone turnover markers (BTMs) can be considered a useful short-term (at 3 months) monitoring tool in selected patients. In both BTM and BMD, the least significant change (LSC) method should be used for interpretation of the results. Fractures are not a reliable clinical endpoint for evaluating the effectiveness of therapy in individual patients because of their stochastic nature. If fractures occur, however, the need for drug change and additional non-pharmacological treatment (fall prevention, balance training, muscle strengthening) should always be considered.

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Key words: *fractures, BMD, bone turnover markers, osteoporosis, FRAX™, bisphosphonates, PTH*

Streszczenie

Kryterium interwencji farmakoterapeutycznej w osteoporozie bez złamań stanowi ocena indywidualnego bezwzględnego 10-letniego ryzyka złamań, określonego na podstawie kompleksowej analizy czynników ryzyka złamań. Kompleksowa ocena ryzyka złamań w perspektywie 10-letniej integruje wyniki badań diagnostycznych (densytometria, ocena bezobjawowych złamań kręgów, ocena metabolizmu kostnego) oraz wybranych klinicznych czynników ryzyka złamań. Wprowadzony w 2008 roku kalkulator FRAX™ (*WHO Fracture Risk Assessment Tool*) pozwala na szybkie i proste obliczanie 10-letniego ryzyka złamań, które u indywidualnego pacjenta powinno być podstawą do podejmowania dalszych decyzji diagnostycznych i terapeutycznych. FRAX™ opracowany jako kalkulator obliczający 10-letnie ryzyko złamań może być stosowany z uwzględnieniem densytometrii bliższej nasady kości udowej wraz z innymi niezależnymi czynnikami ryzyka złamań. FRAX™ oparty na wskaźniku masy ciała (BMI, *body mass index*), gęstości mineralnej kości (BMI, bez uwzględnienia pomiaru BMD [*bone mineral density*]) może być przydatnym narzędziem przesiewowym dla lekarzy pierwszego kontaktu oceniających ryzyko złamań (*case finding strategy*), zwłaszcza w przypadku ograniczonego dostępu do densytometrii. W obu przypadkach FRAX™ może oceniać 10-letnie ryzyko złamania bliższej nasady kości udowej oraz wszystkich złamań osteoporotycznych. Głównym ograniczeniem algorytmu FRAX™ jest brak możliwości wykorzystania wyników badań densytometrycznych w lokalizacji kręgosłupa lędźwiowego. O ile decyzja, co do potrzeby leczenia farmakologicznego osteoporozy opiera się głównie na wielkości przewidywanego 10-letniego ryzyka złamania, to zasadniczymi kryteriami wyboru leku u indywidualnego pacjenta powinny być skuteczność przeciwzłamaniowa leku, oceniana w randomizowanych, kontrolowanych badaniach klinicznych, oraz potencjalne działania niepożądane, dostępność i łatwość stosowania. Na wybór leku wpływa także mechanizm jego działania: leki przeciwresorpcyjne są najbardziej skuteczne u chorych z zaawansowanym zanikiem kostnym i szybkim obrotem metabolicznym kości, podczas gdy leki anaboliczne lub podwójnym punkcie uchwytu (ranelinian strontu) działają niezależnie od wyjściowych wartości BMD czy aktywności obrotu kostnego. „Złotym standardem" leczenia osteoporozy pozostają bisfosfoniany. Ocena efektywności prowadzonej farmakoterapii jest jednym z ważniejszych elementów strategii w postępowaniu przeciwzłamaniowym. Pomiar BMD jest uznanym długoterminowym wskaźnikiem zastępczym oceny wytrzymałości mechanicznej kości. Wskaźnikiem krótkoterminowym oceny efektywności terapii (3 miesiące) jest pomiar poziomu markerów obrotu

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kostnego w surowicy. W obu przypadkach podstawowym kryterium interpretacyjnym powinna być najmniejsza znacząca zmiana (LSC, *least significant change*). Interpretacja znaczenia złamania kości w trakcie terapii antyzłamaniowej jest niejednoznaczna. Złamań nie należy interpretować jako bezwzględnego wskaźnika braku efektywności stosowanej farmakoterapii, należy jednak ponownie zanalizować dane pacjenta, wprowadzając zwłaszcza modyfikację postępowania niefarmakologicznego. **(Endokrynol Pol 2009; 60 (2): 124–133)**

Słowa kluczowe: *złamania, BMD, markery obrotu kostnego, osteoporoza, FRAX™, bisfosforany, PTH*

Introduction

To improve the antifracture efficacy of therapeutic management of osteoporosis, three key issues are overviewed.

1. Selection of the most effective screening strategy to identify patients at high risk of osteoporotic fractures with the aim of achieving the best sensitivity, with use of clinical risk factors (CRF), bone mineral density (BMD) or bone turnover markers (BTM) compromised in the form of a semi quantitative or quantitative model of FRAX™, in both cases directed to hip or to all osteoporotic fractures.
2. Improvement and evaluation of pharmacological management with a focus on the mechanisms of the action of drugs used in osteoporosis, such as anticatabolic treatments (bisphosphonates, hormonal therapy, SERMs, calcitonin), proanabolic treatments (teriparatide), or dual-action treatments (strontium ranelate).
3. To overcome problems of low compliance and persistence in osteoporosis therapy, the development of short and long-term monitoring strategies for the evaluation of proper use of drugs utilized in therapy, and evaluation of their effectiveness.

Limitations of definition of osteoporosis and its consequences

Osteoporosis is defined as a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures [1]. The definition of osteoporosis based on low bone mass is invalidated by several problems, principally because of the lack of a clear-cut discrimination point. It does not provide explicit diagnostic criteria that allow one to decide whether an individual is osteoporotic, nor does it specify the cause or the pathogenesis mechanisms of low bone mass or poor microarchitectural state. It also does not refer to the underlying mechanisms concerning relation to inactivity, aging, or developed material properties [1–6].

Osteoporosis is a common and debilitating disease. Worldwide, the lifetime risk for women having an osteoporotic fracture is estimated at 30–40%. Furthermore, new studies have shown the prevalence of osteoporosis in men as higher than previously thought — with approximately one in five men affected. Generally, osteoporosis can be diagnosed in one of two ways — clinically, especially in the presence of fragility fractures, and in more difficult situations when related to the prefracture stage. In the latter, with use of clinical risk factors densitometry when necessary extended with morphometry and bone metabolism estimations for establishing the potential fragility and fracture risk of analyzed subjects.

Osteoporotic fracture

The definition of an osteoporotic fracture is not straightforward [1–3]. A widely adopted approach is to consider fractures from low energy trauma as being osteoporotic. Low energy may variously be defined as a fall from a standing height, or trauma that in a healthy individual would not give rise to fracture. This characterization of low trauma indicates that the vast majority of hip and forearm fractures are low energy injuries. At the age of 50 years, approximately 75% of people hospitalized for vertebral fractures have fractures that are attributable to low energy injuries, increasing to 100% by the age of 90 years.

The rising incidence of fractures with age does not provide direct evidence for osteoporosis, since a rising incidence of falls could also be a cause. By contrast, a lack of increasing incidence of fractures with age is reasonable presumptive evidence that a fracture is unlikely to be osteoporosis related.

In women, fracture incidence begins to increase around the age of fifty (time of menopause), and in men the increase begins later, in about the mid sixties. These fractures in the older age groups are typically the result of minimal trauma and occur at the hip, spine, and wrist (the most common sites of osteoporotic fractures) with incidence of them higher in women than in men.

Despite a large number of studies that have examined the incidence of fractures by age and sex, our knowledge of the incidence and the pattern of fractures worldwide is incomplete.

Hip fractures, the second most common osteoporotic fracture, are usually caused by a fall from standing height usually with a subsequent requirement of hospitalization and surgery. Nevertheless, it should be pointed out that most falls do not result in fracture, with only about 1–2% of falls in the elderly causing a hip fracture.

Vertebral fracture prevalence is very difficult to ascertain, as it is estimated that only about 30% of "morphometric" fractures are clinically apparent. The third

Table I. *WHO/NOF diagnostic criteria (DXA)*
Tabela I. *Kryteria diagnostyczne WHO/NOF (DXA)*

	T-score
Normal	> –1.0
Osteopenia (low bone mass)	–1.0 to –2.5
Osteoporosis	< –2.5
Established osteoporosis	< –2.5 + fracture

most common osteoporotic fractures are distal forearm fractures, caused mostly by a fall on an outstretched hand. These fractures tend to occur at younger ages, and about 20% result in hospitalization.

Osteoporosis, even with fractures, frequently goes unrecognized in the clinical setting, with many studies showing that fewer than 20% of patients with osteoporotic fractures receive a diagnosis of osteoporosis. An even smaller percentage of those diagnosed are treated for osteoporosis.

Diagnosis of non-fracture patients and limitations of traditional WHO definitions

Diagnosis of non-fractures patients, until recent years, was based on densitometry, the most widely validated technology for the assessment of skeletal health, and used the T-score expressed as standard deviation (SD) difference between the BMD of a patient and that of a young adult female reference population [4, 5].

The widespread clinical use of DXA, particularly at the proximal femur and lumbar spine (central DXA), arises from many prospective studies that have documented a strong gradient of risk for fracture prediction. The following four general descriptive categories are given for adult men and women using measurements of DXA at the femoral neck, spine, and forearm, summed up in the so-called WHO criteria (Table I).

From one side, operationally, BMD when assessed by dual-energy X-ray absorptiometry (DXA). DXA of central skeletal sites (spine and hip) is considered the "gold-standard" method for the diagnosis of osteoporosis and monitoring changes in BMD because:

— biomechanical studies have shown a strong correlation between mechanical strength and BMD measured by DXA;
— large epidemiological studies have established a strong relationship between fracture risk and BMD measured by DXA;
— the World Health Organization (WHO) classification of BMD for the diagnosis of osteoporosis and osteopaenia is largely based on reference data obtained by DXA;
— most randomized clinical trials showing a benefit with pharmacological intervention have selected subjects based on low BMD measured by DXA;
— there is a relationship between reduction in fracture risk with pharmacological therapy and BMD increase measured by DXA;
— DXA accuracy and presentation are excellent. A T-score of –2.5 or less at the femoral neck, total hip, lumbar spine, or one-third (33%) radius is considered a diagnosis of osteoporosis [4].

On the other, it appeared that although bone mass is an important component of the risk of facture, other abnormalities occur in the skeleton that contribute to fragility. It has become apparent that the presence of several risk factors used to trigger a BMD test are associated with a fracture risk much greater than can be accounted for by BMD alone. In addition, the vast majority of fractures appeared in the range of T-*score* lower than –2.5.

Since BMD forms just one component of fracture risk, accurate assessment of fracture risk should ideally take into account other readily measured indices of fracture risk that add information to that provided by BMD. Many cross-sectional prospective population studies indicate that the risk of fracture increases by a factor of 1.5 to 3.0 for each standard deviation decrease in BMD. Low sensitivity is one of the reasons why widespread population-based screening with BMD is not widely recommended in women at the time of menopause. There are also a number of limitations in the general application of DXA for diagnosis that should be recognised. The presence of osteomalacia, a complication of poor nutrition in the elderly, will underestimate total bone mass because of decreased mineralisation of bone. Osteoarthritis and osteoarthrosis of the spine and/or hip are common in the elderly, and contribute to the density measurement, but not necessarily to skeletal strength. Heterogeneity of density also appears due to osteoarthrosis. Presently there are no satisfactory clinical tools available to assess bone quality independently of bone density, so for practical purposes the assessment of osteoporosis depends upon the measurement of skeletal mass, as assessed by measurements.

Lately a large number of additional risk factors for fracture have been identified. For the purposes of risk assessment, interest is centred around factors that contribute significantly to fracture risk over and above that provided by BMD measurements or age.

Moreover, BMD measurements lack sensitivity over clinical assessment of fracture risk, i.e., the detection rate is low. For example, at the age of 50 years the proportion of women with osteoporosis is approximately 5%; however, the proportion of these who will fracture in the next 10 years is about 20%. The detection rate for

Table II. *Most frequently analyzed risk factors*
Tabela II. *Najczęstsze czynniki uwzględniane w ocenie ryzyka*

Low body mass index (BMI)
A history of fragility fracture is an important risk factor for further fracture
A family history of fragility fractures is a significant risk factor that is largely independent of BMD
Cigarette smoking
Glucocorticoids
Alcohol
Rheumatoid arthritis

these fractures (sensitivity) is low, and in fact, up to 96% of fragility fractures would arise in women without osteoporosis diagnosed, according to WHO BMD diagnostic criteria. Low sensitivity is one of the reasons why widespread population screening is not widely recommended in women during menopause [7].

The development of FRAX ™

Over the past few years a series of meta-analyses has been undertaken to identify clinical risk factors that could be used in case finding strategies, with or without the use of BMD (Table II).

The WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield has developed algorithms to compute age-specific fracture probabilities in men and women, from CRFs and BMD measurement at the femoral neck. The algorithms (FRAX™) are based on a series of meta-analyses using several identified CRFs for fracture. The performance characteristics of these CRFs have been validated in independent, population-based, prospectively studied cohorts with over a million person-years of observation. The FRAX™ tools calculate the 10-year probability of a major osteoporotic fracture (clinical spine, hip, forearm, or proximal humerus) or hip fracture calibrated to the fracture and death hazards [7–10].

A fracture risk assessment tool (FRAX™ trademark) was developed based on the use of clinical risk factors with or without bone mineral density tests applied. The aim of this was to apply an assessment tool for the prediction of fractures in men and women with the use of clinical risk factors (CRFs) for fractures with and without the use of femoral neck bone mineral density (BMD). The clinical risk factors, identified from previous meta-analyses, comprised body mass index (BMI, as a continuous variable), a prior history of fracture, a parental history of hip fracture, use of oral glucocorticoids, rheumatoid arthritis and other secondary causes of osteoporosis, current smoking, and alcohol intake of 3 or more units daily.

BMD and skeletal risk factors — semi quantitative model

In circumstances of limited adaptation of FRAX™ to routine clinical practice, patients in the presence of risk factors and low bone mass at the spine can alternatively use an algorithm based on that developed by the Osteoporosis Society of Canada's "Recommendations for Bone Mineral Density Reporting", which estimates the 10-year probability of fracture using the lowest BMD measured in alternative central sites (lumbar spine [LS], femoral neck [FN], total hip, and distal 1/3 radius, if indicated). Demonstration of an established high 10-year probability of major osteoporotic fracture is an indication to initiate drug treatment [11]. In patients with moderate risk, the presence of any of the following risk factors [family history of fractures, demonstration of vertebral fractures on X-ray or VFA, long-term glucocorticosteroid treatment: (prednisone at more than 5 mg/day for more than 3 months), increased bone metabolism in postmenopausal women measured by bone turnover markers], which undoubtedly doubles the estimated fracture risk, shifts the fracture probability from the moderate level to the high level, and suggests that initiation of pharmacological treatment should be considered. According to the estimated prevalence of fractures in Poland, demonstration of a 10-year probability of more than 20% should be considered as high, and between 10% and 20% as moderate (Table III). Ten-year fracture risk values of more than 20% are recognized in this case as an indication for treatment.

Bone turnover markers

One important determinant of bone strength that is not assessed by either BMD or clinical factors is the rate of bone remodelling measured by BTMs [12].

BTMs help to detect postmenopausal women who are at high risk of all osteoporotic fractures independently of age, BMD, and prior fracture [12–15]. This association has been assessed prospectively in longitudinal cohort studies and case-control studies. Osteopenic women with high BTM levels have a risk of fracture similar to that of osteoporotic women based on BMD, whereas osteopenic women with normal BTM levels have a fracture risk that is comparable to that of postmenopausal women with normal BMD [15].

Whether the pre-treatment (baseline level) BTM concentrations are predictive of a greater response to any of the anti-osteoporotic drugs remains controversial [12].

Table III. *Ten-year fracture risk (FR) depending on sex, age, and BMD T-score (according to 2005 OSC Recommendations for Bone Mineral Density Reporting)*

Tabela III. *Dziesięcioletnie ryzyko złamania w zależności od płci, wieku i T-score dla BMD*

Women						
Age (years)	**T-score**					
	> –2.0	**–2.0 to –2.5**	**–2.5 to –3.0**	**–3.0 to –3.5**	**–3.5 to –4.0**	**< –4.0**
50	Low	Moderate	Moderate	Moderate	Moderate	High
55	Low	Moderate	Moderate	Moderate	High	High
60	Low	Moderate	Moderate	High	High	High
65	Moderate	Moderate	High	High	High	High
70	Moderate	Moderate	High	High	High	High
75	Moderate	High	High	High	High	High
80	Moderate	High	High	High	High	High
85	Moderate	High	High	High	High	High
Men						
Age (years)	**T-score**					
	> –2.0	**–2.0 to –2.5**	**–2.5 to –3.0**	**–3.0 to –3.5**	**–3.5 to –4.0**	**< –4.0**
50	Low	Low	Low	Low	Moderate	Moderate
55	Low	Low	Low	Moderate	Moderate	Moderate
60	Low	Low	Low	Moderate	Moderate	Moderate
65	Low	Low	Moderate	Moderate	Moderate	Moderate
70	Low	Moderate	Moderate	Moderate	Moderate	High
75	Moderate	Moderate	Moderate	High	High	High
80	Moderate	Moderate	Moderate	High	High	High
85	Moderate	Moderate	Moderate	High	High	High
	FR <10%		FR 10–20%		FR >20%	

FR — fracture risk; Low risk of fracture (<10%); Moderate risk of fracture (10–20%); High risk of fracture (>20%)

In post-hoc analysis of the Fracture Intervention Trial (FIT) alendronate non-spine fracture efficacy was greater among women with high pre-treatment N-terminal propeptide of type I collagen (P1NP) [16]. For osteoporotic woman in the lowest tertile of pre-treatment P1NP, the alendronate versus placebo, the relative hazard for non-spine fracture, was 0.88 compared to the relative hazard of 0.54 among those in the highest tertile of P1NP. Similar results were observed among women without osteoporosis at baseline. A pharmacoeconomic study (Markov model) [14] concluded that measurement of BTMs has the potential to identify a subset of postmenopausal women (top BTM quartile), without osteoporosis by BMD criteria, for whom alendronate therapy to prevent fracture is cost-effective.

Additional information provided by BTMs can affect clinical decisions, increasing identification, sensitivity, and specifity of subjects at risk of fractures.

The large biological variability of BTM determinations by different methods was previously a significant obstacle to its broader use in clinical settings. However, automated immunoassays with ECLIA devices for serum determination of OC, P1NP, and CTX and diagnostic standards of GLP in pre-laboratory steps introduced in the last 2 years have made bone turnover marker determination a routine endocrinological diagnostic procedure [17,18].

In order to make use of the clinical potential of BTM, appropriate reference ranges are crucially important. Recommended normal reference ranges for premenopausal women were recently published for OC, CTX, and P1NP determined with ECLIA automated immunoassay as standard procedure [19–21] as well as a scatter plot identifying postmenopausal woman belonging to an elevated bone turnover marker subgroup using two markers in the Polish population [22]. With these tools, the appropriate identification of postmenopausal women with high and low bone turnover is possible.

Therapeutic threshold

Diagnostic thresholds differ from intervention thresholds in several ways. When diagnostic values combi-

Table IV. *Effect of various factors on anti-fracture efficacy of registered antiosteoporotic drugs in pivotal RCT's*

Tabela IV. *Wpływ różnych czynników na skuteczność w zapobieganiu złamaniom zarejestrowanych leków przeciwosteoporotycznych w najważniejszych badaniach z randomizacją i grupą kontrolną*

	BMD osteopenia		BMD osteoporosis		Previous fracture			Bone tumover	
	VFx risk	HipFx risk	VFx risk	HipFx risk	Previous VFx (–)	Previous VFx (+)	Previous HipFx (+)	High	Normal (premenopausal)
ALN	+	ø	+	+	+	+	ND	+	ø
RIS	ND	ND	+	+[1]	ND	+	ND		
IBN	ND	ND	+	+[2]	ND	+	ND		
ZOL	ND	ND	+	+	+	+	+		
CT	ND	ND	+	ø	ND	+	ND		
RAL	+	ø	+	ø	+	+	ND		
PTH	ND	ND	+	+	ND	+	ND		
RS	+	ND	+	+	+	+	ND	+	+

ND — no data; [1]in high-risk population (age > 70, FN T-score < –4.0 or –3.5 and clinical risk factors); [2]FN T-score < –3.0; VFx (+) — vertebral fracture; HipFx (+) — hip fracture

ne estimated fracture probabilities and are based on the presence of clinical risk factors: densitometry, morphometry, and high bone turnover data, intervention thresholds will also be focused on the determination of the cost and benefits of treatment. The fact that fracture risk varies markedly in different populations and different nations is important for establishing therapy. For example, in women with a T-score of –2.5 SD, the probability of hip fracture is 5 times greater at the age of 80 years than at the age of 50 years. Moreover, it seems that multiplicative relation of fracture risk to BMD is acceptable for low risk, but not for moderate/high risk. This observation is inline with the estimation of Kanis et al. [7], showing that absolute risk increases linearly with RR in young women (i.e. multiplicatively), but slower than RR in older women. There also significant differences in absolute fracture risk in different countries. Since the present approaches to the identification of patients at risk for fracture focus selection on a few clinical factors and estimation of femoral neck BMD, more information is required.

A potential list of other significant risk factors, the validity of which would permit further refinements to the models available, would include clinical risk factors for falls, the use of DXA at other skeletal sites such as the total hip and lumbar spine, indices of bone turnover and the use of other technologies such as quantitative ultrasound, and secondary causes of osteoporosis other than rheumatoid arthritis. Assessment algorithms should also be further validated in male and non-Caucasian populations.

Case-finding strategies also require broader validation in clinical trials, to test whether pharmacological agents reduce fracture risk in individuals identified by the use of clinical risk factors, with and without the selective use of BMD.

Principles for drug selection in osteoporosis

Treatment decisions in osteoporosis should be based on the absolute risk of fracture (FRAX™) calculated by means of a patient's clinical risk factors and BMD, and in selected cases on the assessment of bone metabolic rate using biochemical markers of bone turnover. In all cases of low bone mass or low-trauma fractures, differential diagnosis should be performed to rule out secondary causes; however, causative management of secondary osteoporosis does not exclude the need for symptomatic anti-fracture pharmacotherapy [11].

The successful fracture prevention trial of alendronate, a little over ten years ago, documented the drug's efficacy in fracture prevention [23]. This was a landmark event in bone research, and was followed by successful trials of other bisphosphonates, selective oestrogen receptor modulators (SERMs), calcitonin, strontium ranelate, and parathormone analogues [24–35]. Consequently, drug selection in osteoporosis treatment started to be based on the results of randomized, placebo-controlled clinical trials demonstrating the effects of a given intervention on fracture risk (Table IV). However, it is worth remembering that no studies have directly compared these therapies head-to-head for anti-fracture efficacy [36–38].

The mechanism of action of the drug is the subject of critical evaluation. Anti-catabolic drugs seem to be the most appropriate in patients with high bone turnover, while anabolic drugs demonstrate efficacy irrespective of bone turnover. Anabolic treatment should be

particularly indicated in patients with low bone formation in the elderly, in patients with glucocorticoid-induced osteoporosis, and in patients with extremely low bone mass, or after multiple fractures, where preservation of bone mass and bone architecture by anti-catabolic drugs is not sufficient to reduce efficiently high absolute risk of fracture [11].

Co-morbidities and safety for bone and other tissues (non-skeletal risks and benefits) of the drug were considered when registered, and utilized.

Calcium and vitamin D supplements are the mainstay of prevention and are the necessary complement of osteoporosis treatment. The recommended daily doses of vitamin D_3 and calcium are 800–2000 IU and 500–1500 mg, respectively [39–40].

Treatment of choice

All oral N-containing bisphosphonates showed a similar relative rate of vertebral fracture reduction in the placebo-controlled, randomized clinical trials [36–38]. Modest differences in hip or nonvertebral fracture risk reduction are difficult to compare due to differences in the baseline patient characteristics and marked differences in the dropout rate in those studies, and seem to be of small clinical importance (Table IV) [41]. Moreover, recent observational studies including the evaluation of a large number of community-based persons initiating oral bisphosphonates therapy, based on administrative claims databases of large commercial health care systems, showed similar absolute rates of both vertebral and nonvertebral fractures between new users of weekly alendronate vs. weekly risedronate [42, 43], and weekly alendronate and risedronate vs. monthly ibandronate [44]. Bisphosphonates are the most effective in postmenopausal women and aging males with established osteoporosis, especially with high bone turnover. Present evidence does not prove the efficacy of bisphosphonates in osteopenia (Table IV).

In fact, the main difference among various oral bisphosphonates relates mostly to compliance and persistence (adherence-to therapy). A once-a-month schedule is better accepted by patients than a once-a-week scedule [45, 46], which in turn seems to be better than a daily schedule [47].

Intravenous bisphosphonates (ibandronate 3 mg every 3 months, zoledronic acid 5 mg once a year) may be particularly useful in the treatment of patients with gastrointestinal pathologies and patients intolerant of oral bisphosphonates, as well as patients chronically immobilised (as a result of vertebral or hip fractures or stroke), or those with dementia [30, 48, 49]. Once-yearly zoledronic acid therapy not only maintains bone microarchitecture, but also enables sufficient bone renewal. Moreover, apart from the bone preserving effect, zoledronic acid administered once a year guarantees 100% adherence to therapy.

Bisphosphonates are considered the treatment of choice for the prevention of osteoporotic fractures in postmenopausal women and men with prevalent low-trauma vertebral or hip fractures, and in patients with high 10-year fracture probability, particularly those with advanced bone loss and/or high activity of bone turnover markers [11].

Strontium ranelate, with its synchronous antiresorptive and pro-anabolic effects, shows anti-fracture efficacy in all types of osteoporotic fractures, both vertebral and nonvertebral, regardless of the initial BMD or bone turnover (Table IV) [50]. It significantly reduces the incidence of vertebral fractures in women with osteopaenia, and the probability of hip fractures in women older than 80 years with low bone mineral density [51, 52]. Strontium ranelate is an alternative recommended therapeutic option in postmenopausal women. It should be considered as the treatment of choice in postmenopausal women with BMD values consistent with osteopaenia, independently of the bone turnover and in women over the age of 80 [11].

Second-line treatment options

Raloxifene (SERM) may be considered in postmenopausal women with low bone mass or younger postmenopausal women with osteoporosis, who are at greater risk of vertebral fracture than hip fracture. It prevents bone loss and reduces the risk of vertebral fractures, but its effectiveness in reducing other fractures is uncertain (Table IV). Extraskeletal risk and benefits are important when considering raloxifene therapy [53–55].

Calcitonin is definitely not a first-line drug for osteoporosis treatment, as its fracture efficacy is not strong and its BMD effects are less than those of other agents. It is, however, recommended for treating bone pain from acute vertebral compression fracture.

Teriparatide is a highly effective bone anabolic agent, which produces a highly significant reduction of osteoporotic fractures of any type in patients with severe osteoporosis (Table IV). Nowadays, this is the only medication to restore bone structure independently of the degree of initial disarrangement. However, the relative fracture reduction with anabolic treatment with PTH differs only a little from that with adequately studied resorption inhibitors. For safety reasons, the duration of treatment has been restricted to 24 months. In order to maintain the achieved therapeutic effects, continuation of treatment with bisphosphonates should be considered [56–59].

Combining anti-catabolic drugs

The addition of bisphosphonates (alendronate, risedronate) to long-term hormone therapy in postmenopausal women results in a greater increase of bone mineral density. Alendronate increases BMD by 3% at 2 years in women receiving hormone therapy [60, 61]. Co-administration of calcitonin and oestrogens, raloxifene, and alendronate also increases BMD, although the effect of this treatment on the risk of fractures has not been investigated. Due to the increased treatment costs, multiplication of potential side effects, and the lack of data on the potential superiority of the combined use of antiresorptive drugs, this treatment is not recommended [11].

Treatment with teriparatide and anti-catabolic drugs

Bisphosphonates used prior to, or in combination with, PTH preparations reduce the anabolic effect of parathormone. However, the inclusion of bisphosphonates after completion of treatment with a PTH preparation maintains the previously achieved therapeutic effect and promotes further increase of BMD. Conclusions from the existing data should be drawn cautiously, due to the lack of prospective studies, the small size of the study population, and, especially, the lack of evaluation of the effects of anti-catabolic treatment following completion of teriparatide treatment on the incidence of fractures. It seems, however, that anti-catabolic treatment, which prevents bone loss after discontinuation of teriparatide, should be recommended, and sequential treatment with anabolic-followed by anti-catabolic drugs offers the desirable benefits needed for long-term efficacy [56–59].

Osteoporosis is a chronic disease; therefore, long-term adherence (compliance and persistence) to the treatment is most important. The suitability of the drug for long-term administration, and factors such as patient preference, tolerability, and convenience are important factors influencing the final efficacy of the treatment. Adherence to therapy in osteoporosis is poor. In studies of 6 months to 1 year, adherence rates for prescription drugs ranged from below 25% to 80%, depending on the therapy [42, 62]. Ensuring adherence to the treatment plan is perhaps the most important follow-up measure for clinicians. It is important to identify barriers to adherence. If drug-related adverse effects occur, appropriate management strategies should be instituted. If adverse effects persist, switching to another agent may be required. The decision to discontinue or suspend therapy is based on the patient's risk of fracture and response to treatment, as well as the likelihood of diminishing beneficial effects from the agent used. Fracture risk after discontinuing therapy has not been adequately evaluated.

Assessing response to osteoporosis therapy

Patients treated with pharmacological agents to improve bone strength and reduce fracture risk may not achieve optimal skeletal benefit. Monitoring the effects of therapy can inform the patient and physician whether or not the drug is having its expected skeletal response [63, 64].

Lacking direct tools for bone strength measurement in living patients, we are presently limited to existing surrogate ones [63, 64]. The available surrogate measurements of bone strength, with the aim of osteoporosis treatment benefit evaluation, are focused in literature on the following four items:

1. BMD measurement is, to date, the most widely used and probably the best long-term assessment of efficacy of anti-fracture treatment.
2. The measurements of bone turnover markers (BTMs: CTX, P1NP, OC) can be considered as a short-term (at 3 months) surrogate monitoring tool in patients treated with anti-catabolic (bisphosphonates, raloxifene, hormone therapy, calcitonin) as well as anabolic (PTH) drugs [65, 66, 12].
3. In both BTMs and BMD measurement, the least significant change (LSC) method should be used for interpretation of the results. Only compliant patients may be defined as "nonresponders" or "suboptimal responders". In these cases, no significant changes (according to LSC) of BMD or BTMs are observed during treatment. A patient is defined as compliant when she/he correctly takes at least 80% of the presented doses of the treatment in a minimal time interval of one year [18, 17, 67].
4. The most controversial point appears to be the question of whether an incident fracture is a reliable clinical endpoint for the evaluation of the effectiveness of therapy [63, 64].

The practical guidelines of monitoring therapy with BMD are implemented to everyday good clinical practice by ISCD and IOF using LSC as an interpretation tool, and extended for BTM use. BTM is evidenced as the best short time surrogate marker to identify nonresponders and/or non-compliers to therapy. A dose-dependent decrease of BTMs has been consistently found for HRT, SERMs, bisphosphonates, and denosumab. Teriparatide induced a marked increase in BTMs. Reduction in bone turnover has been demonstrated as an independent predictor of therapeutic efficacy on fracture risk reduction in different studies. A meta-analysis of several randomised clinical trials on osteoporosis tre-

atment estimated that a 70% reduction in resorption markers corresponds to a 40% reduction in the risk of nonvertebral fractures, while a 50% reduction in bone formation markers was associated with a 44% nonvertebral fracture risk reduction. The concept of LSC differences, commonly applied to DXA measurements to establish statistical significance of bone density changes in individual patients, is now also introduced for BTM when using automated ECLIA machines for OC, P1NP, and CTX measurements [18, 17, 67].

Fractures has not been shown as a reliable clinical endpoint for evaluating the effectiveness of therapy in individual patients because of its stochastic nature (i.e. subject to randomness) that may or may not occur, regardless of fracture probability [63, 64]. However, fracture prevention is the primary aim of osteoporosis treatment, and incident fracture frequency has been defined as the primary endpoint in all relevant osteoporotic clinical trials (but with potential limits when judged in a single patient). For this reason, incident fracture is not necessarily a pharmacological treatment failure. However, when a fracture occurs, other non-pharmacological intervention should be analysed (fall prevention, balance training, muscle strengthening). A patients is defined as a "nonresponder" or "suboptimal responder" when, during treatment, a significant decrease in BMD (below LSC) is observed and/or the patient does not have the expected change in BTMs (below or above LSC).

Conclusions

Current treatment decisions in osteoporosis are based on the results of comprehensive diagnostic procedures (BMD, absolute risk of fracture, BTM). Since osteoporosis is a chronic disease, long-term adherence to treatment is important. Suitability of the drug, patient preference, tolerability and convenience should all be considered. Anti-catabolic drugs are most appropriate in patients with high bone turnover, while anabolic drugs demonstrate efficacy irrespective of bone turnover. Treatment benefit evaluation in patients is crucial for improving individual anti-fracture efficacy. BMD measurement is most widely used for long-term assessment of the efficacy of osteoporosis treatment. Measurements of bone turnover markers (BTMs) can be considered a useful short-term (at 3 months) monitoring tool in selected patients. In both BTM and BMD the LSC method should be used for interpretation of the results. Fractures are not a reliable clinical endpoint for evaluating the effectiveness of therapy in individual patients because of their stochastic nature; however, if fractures occur, the need for drug change and additional non-pharmacological treatment (fall prevention, balance training, muscle strengthening) should always be considered.

References

1. Kanis JA, Borgstorm F, De Laet C et al. Assessment of fracture risk. Osteoporosis Int 2005; 16: 581–589.
2. Engelke K, Glüer CC. Quality and performance measures in bone densitometry Part 1: Errors and diagnosis. Osteoporosis Int 2006; 17: 1283–1292.
3. Glüer CC, Engelke K. Quality and performance measures in bone densitometry Part 2: Fracture risk. Osteoporosis Int 2006; 17: 1449–1458.
4. Watts NB, Lewiecki EM, Miller PD et al. National Osteoporosis Foundation 2008 clinical guide to prevention and treatment of osteoporosis and the World Health Organization fracture risk assessment tool (FRAX): what they mean to the bone densitometrists and bone technologist. Assessment of Skeletal Health. J Clin Densitometry 2008; 11: 473–477.
5. Kanis JA, Johnell O, De Laet C et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone 2004; 35: 375–382.
6. Kanis JA, Oden A, Johnell O. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. Osteoporosis Int 2007; 18: 103–1046.
7. Kanis JA, McCloskey EV, Johansson H et al, and National Osteoporosis Guideline Group. Case finding for the management of osteoporosis with FRAX® — assessment and intervention thresholds for the UK, Osteoporosis Int 2008; 1395–1408.
8. Kanis JA on behalf of the World Health Organization Scientific Group. Assessment of osteoporosis at the primary health care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases. University of Sheffield, UK. Summary Report. Fracture Risk Assessment Tool (FRAX™), 2008.
9. Kanis JA, Burlet N, Cooper C et al. on behalf of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis 2008. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporosis Int 2008; 19: 388–428.
10. Zethraeus N, Borgström F, Ström O et al. Cost-effectiveness of the treatment and prevention of osteoporosis - a review of the literature and a reference model. Osteoporosis Int. 2007; 18: 9–23.
11. Lorenc R.S, Głuszko P, Karczmarewicz E et al. National Guidelines — Poland http://www.iofbonehealth.org, Recommendation on the diagnosis and treatment of osteoporosis in Poland. Reducing the incidence of fractures through effective prevention and treatment. 2008.
12. Civitelli R, Armamento-Villareal R, Napoli N. Bone turnover markers: understanding their value in clinical trials and clinical practice. Osteoporosis Int February 2009 (Epub ahead of print).
13. Bouxsein M, Delmas PD. Perspective considerations for development of surrogate endpoints for antifracture efficacy of new treatments in osteoporosis: a perspective. J Bone Miner Res 2008; 23: 1155–1167.
14. Reginster JY, Collette J, Neuprez A et al. Editorial. Role of biochemical markers of bone turnover as prognostic indicator of successful osteoporosis therapy. Bone 2008; 42: 832–836.
15. Sornay-Rendu E, Munoz F, Garnero P et al. Identification of osteopenic women at high risk of fracture: The OFELY study. J Bone Miner Res 2007; 22: S1, S21.
16. Bauer DC, Garnero P, Hochberg MC et al. Pretreatment levels of bone turnover and the antifracture efficacy of alendronate: the fracture intervention trial. J Bone Miner Res 2006; 21: 291–298.
17. Garnero P, Vargnaud P, Hoyle N. Evaluation of a fully automated serum assay for total N-terminal propeptide of type I collagen in postmenopausal osteoporosis. Clinical Chemistry 2008; 54: 188–196.
18. Hannon R, Blumsohn A, Naylor K. Response of biochemical markers of bone turnover to hormone replacement therapy: impact of biological variability. J Bone Min Res. 1998; 13: 1124–1133.
19. Glover SJ, Garnero P, Naylor K et al. Establishing a reference range for bone turnover markers in young, healthy women. Bone 2008; 42: 623–630.
20. Adami S, Bianchi G, Brandi ML et al. Determinants of bone turnover markers in healthy premenopausal women. Calcif Tissue Int 2008; 82: 341–347.
21. Glover S, Gall M, Schoenborn-Kellenberger O et al. Establishing a reference internal for bone turnover in 637 healthy, young, pre-menopausal women from UK, France, Belgium and the USA. J Bone Miner Res 2008; 29 (Epub ahead of print).
22. Łukszkiewicz J, Karczmarewicz E, Płudowski P et al. Feasibility of simultaneous measurement of bone formation and bone resorption markers to assess bone turnover rate in postmenopausal women: an EPOLOS study. Med Sci Monitor 2008; 14, 12: PH65–70.
23. Liberman UA, Weiss SR, Bröll J et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995; 333: 1437–1443.
24. Black DM, Cummings SR, Karpf DB et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996; 348: 1535–1541.

25. Black DM, Thompson DE, Bauer DC et al. Fracture Intervention Trial. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. J Clin Endocrinol Metab 2000; 85: 4118–4124.
26. Harris ST, Watts NB, Genant HK et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA rok? 282: 1344–1352.
27. Chestnut CH 3rd, Silverman S, Andriano K et al. 2000 A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. Am J Med 2000; 109: 267–276.
28. Chestnut CH 3rd, Skag A, Christiansen C et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res 2004; 19: 1241–1249.
29. Reginster J-Y, Adami S, Lakatos P et al. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. Ann Rheum Dis 2006; 65: 654–661.
30. Black DM, Delmas PD, Eastell R. Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis. N Engl J Med 2007; 356: 1809–1822.
31. Ettinger B, Black DM, Mitlak BH et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene. Results from a 3-year randomized clinical trial. JAMA 1999; 282: 637–645.
32. Chestnut CH 3rd, Silverman S, Andriano K et al. 2000 A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. Am J Med 2000; 109: 267–276.
33. Meunier PJ, Roux C, Seeman E et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004; 350: 459–468.
34. Reginster JY, Seeman E, De Vernejoul MC et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: treatment of peripheral osteoporosis (TROPOS) study. J Clin Endocrinol Metab 2005; 90: 2816–2822.
35. Neer RM, Arnaud CD, Zanchetta JR et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001; 344: 1434–1441.
36. MacLean C, Alexander A, Carter J, Chen S, Desai SB, Grossman J et al. Comparative Effectiveness of Treatments to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis. Comparative Effectiveness Review No. 12. (Prepared by the Southern California/RAND Evidence-based Practice Center under contract 290-02-0003). Rockville, MD: Agency for Healthcare Research and Quality; December 2007. Available at http://www.effectivehealthcare.ahrq.gov/reports/final.cfm.
37. MacLean C, Newberry S, Margaret Maglione M et al. Systematic Review: Comparative Effectiveness of Treatments to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis. Arch Int Med 2008; 148: 197–213.
38. Boonen S, Laan RF, Barton IP et al. Effect of osteoporosis treatments on risk of non-vertebral fractures: review and meta-analysis of intention-to-treat studies. Osteoporos Int 2005; 16: 1291–1288.
39. Bischoff-Ferrari HA, Willett WC, Wong JB et al. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA 2005; 293: 2257–2264.
40. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC et al. Effect of vitamin D on falls: a meta-analysis. JAMA 2004; 291: 1999–2006.
41. Nguyen ND, Eisman JA, Nguyen TV. Anti-hip fracture efficacy of biophosphonates: a Bayesian analysis of clinical trials. J Bone Miner Res. 2006; 21: 340–349.
42. Silverman SL, Watts NB, Delmas PD et al. Effectiveness of bisphosphonates on nonvertebral and hip fractures in the first year of therapy: the risedronate and alendronate (REAL) cohort study. Osteopor Int 2007; 18: 25–34.
43. Curtis JR, Westfall AO, Cheng H et al. RisedronatE and ALendronate Intervention over Three Years (REALITY): minimal differences in fracture risk reduction. Osteoporos Int. On-line First doi 10.1007/s00198-008-0772-2.
44. Harris ST, Reginster J-Y, Harley C et al. Risk of fracture in women treated with monthly oral ibandronate or weekly bisphosphonates: The eValuation of IBandronate Efficacy (VIBE) database fracture study Bone (2009), doi:10.1016/j.bone.2009.01.002.
45. Emkey R, Koltun W, Beusterien W et al. Patient preference for once-monthly ibandronate versus once-weekly alendronate in randomized, open-labeled, cross-over trial: the Bonviva Alendronate Trial in Osteoporosis (BALTO) Curr Med Res Opin 2005; 21: 1895–1903.
46. Recker RR, Gallagher R, MacCosbe PE. Effect of dosing frequency on bisphosphonate medication adherence in a large longitudinal cohort of women. Mayo Clin Proc 2005; 80: 856–861.
47. Lewiecki E.M, Rosen C, Bockman RS et al. 2001 Alendronate 70 mg Once Weekly and Alendronate 10 mg Once Daily Preference Study in Postmenopausal Women with Osteoporosis. ASBMR 2001, Phoenix.
48. Delmas PD, Adami S, Strugala C et al. Intravenous ibandronate injections in postmenopausal women with osteoporosis: one year results from the Dosing Intravenous Administration Study. Arthritis Rheum 2006; 54: 1838–1846.
49. Lyles KW, Colón-Emeric CS, Magaziner JS et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007; 357: 1799–1809.
50. Christian Roux C, Jean-Yves Reginster J-Y, Jacques Fechtenbaum J et al. Vertebral Fracture Risk Reduction With Strontium Ranelate in Women With Postmenopausal Osteoporosis is Independent of Baseline Risk Factors. J Bone Miner Res 2006; 21: 536–542.
51. Seeman E, Vellas B, Benhamou C et al. Strontium ranelate reduces the risk of vertebral and non-vertebral fracture in women eighty years of age and older. J Bone Miner Res 2006; 7: 1113–1120.
52. Seeman E, Devogelaer J-P, Lorenc R et al. Strontium Ranelate Reduces the Risk of Vertebral Fractures in Patients With Osteopenia. J Bone Miner Res 2008; 23: 433–438.
53. Martino S, Cauley JA, Barrett-Connor E et al. Invasive breast cancer risk reduction in postmenopausal women with osteoporosis treated with raloxifene for 8 years: results from the Continuing Outcomes Relevant to Evista Trial. J Natl Cancer Inst 2004; 96: 1751–1761.
54. Vogel VG, Costantino JP, Wickerham DL et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial. JAMA 2006; 295: 2727–2741.
55. Barrett-Connor E, Mosca L, Collins P et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med 2006; 355: 125–137. http://jcem.endojournals.org/cgi/ijlink?linkType=ABST&journalCode=nejm&resid=355/2/125
56. Black DM, Greenspan SL, Ensrud KE et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med 2003; 349: 1207–1215.
57. Finkelstein JS, Hayes A, Hunzelman JL et al. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. N Engl J Med 2003; 349: 1216–1226. http://jcem.endojournals.org/cgi/ijlink?linkType=ABST&journalCode=nejm&resid=349/13/1216
58. Finkelstein JS, Leder BZ, Burnett S-A et al. Effects of teriparatide, alendronate, or both on bone turnover osteoporotic men. J Clin Endocrinol Metab 2006; 91: 2882–2887.
59. Black DM, Bilezikian JP, Ensrud KE et al. One year of alendronate after one year of parathyroid hormone (1–84) for osteoporosis. N Engl J Med 2005; 353: 555–565.
60. Greenspan SL, Resnick NM, Parker RA. Combination therapy with hormone replacement and alendronate for prevention of bone loss in elderly women: a randomized controlled trial. JAMA 2003; 289: 2525–2533.
61. Bone HG, Greenspan SL, McKeever C et al. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. Alendronate/Estrogen Study Group. J Clin Endocrinol Metab 2000; 85: 720–726.
62. Cramer JA, Amonkar MM, Hebborn A et al. Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis. Curr Med Res Opin 2005; 21: 1453–1460.
63. Lewiecki EM, Watts NB. Assessing response to osteoporosis therapy. Osteoporosis Int 2008; 19: 1363–1368.
64. Diez-Perez A, Gonzalez-Macias J. Inadequate responders to osteoporosis treatment: proposal for an operational definition. Osteoporosis Int 2008; 19: 1511–1516.
65. Eastel R, Krege JH, Chen P et al. Development of an algorithm for using P1NP to monitor treatment of patients with teriparatide. Current Med Research and Opinion 2006; 22: 61–66.
66. Chen P, Satterwhite JH, Licata AA et al. Early changes in biochemical markers of bone formation predict BMD response to teriparatide in postmenopausal women with osteoporosis. J Bone Miner Res 2005; 20: 962–970.
67. Clowes JA, Hannon RA, Yap TS et al. Effect of feeding on bone turnover markers and its impact of biological variability of measurements. Bone 2002; 30: 886–890.