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CONSENSUS STATEMENT

Evidence-based guidelines for the pharmacological treatment of postmenopausal osteoporosis: a consensus document by the Belgian Bone Club

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Abstract Several drugs are available for the management of postmenopausal osteoporosis. This may, in daily practice, confuse the clinician. This manuscript offers an evidence-based update of previous treatment guidelines, with a critical assessment of the currently available efficacy data on all new chemical entities which were granted a marketing authorization. Osteoporosis is widely recognized as a major public health concern. The availability of new therapeutic agents makes clinical decision-making in osteoporosis more complex. Nation-specific guidelines are needed to take into consideration the specificities of each and every health care environment. The present manuscript is the result of a National Consensus, based on a systematic review and a critical appraisal of the currently available literature. It offers an evidence-based update of previous treatment guidelines, with the aim of providing clinicians with an unbiased assessment of osteoporosis treatment effect.

Keywords Bisphosphonate · Osteoporosis · Raloxifene · Strontium · Teriparatide

Introduction

Osteoporosis is widely recognized as a major public health concern. The cumulative lifetime fracture risk for a 50-year

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woman with osteoporosis is as high as 60% [1]. In Belgium, the annual costs of osteoporotic fractures are currently estimated in the range of 150 million euros, on a societal perspective [2]. Effective fracture prevention would have a major impact on women's morbidity and, to a lesser extent, mortality. The availability of new therapeutic agents has made clinical decision-making in osteoporosis more complex [3]. Because individual clinicians cannot systematically collect all the evidence bearing on the efficacy of osteoporosis therapies, they require summaries for consistent therapeutic patterns [3]. As recommended by the recently published European guidance for the diagnosis and management of osteoporosis in postmenopausal women [4], nation-specific guidelines are needed to take into consideration the specificities of each and every health care environment. The present document is the result of a national consensus, based on a systematic review and a critical appraisal of the currently available literature. It offers an evidence-based update to previous Belgian Bone Club treatment guidelines [5], with the aim of providing clinicians with an unbiased assessment of osteoporosis treatment effect. Currently in Belgium, reimbursement of antiosteoporosis medications is granted to postmenopausal women with low bone mineral density (BMD; T-score<−2.5 at the lumbar spine or at the hip) or with a prevalent vertebral fracture. Nevertheless, taking into account the new development of validated tools, assessing the 10-year absolute fracture risk of postmenopausal women, based on the presence of clinical risk factors, it can reasonability be expected that within a few months or years, reimbursement of antiosteoporosis medications will be open to all women who really deserve treatment [6, 7]. These guidelines address only postmenopausal women, and glucocorticoid-induced osteoporosis is not included. Whereas most compounds have proven to significantly reduce the occurrence of vertebral fractures, discrepancies remain regarding the level of evidence related to their nonvertebral or hip antifracture effect.

Methods

This paper expands and updates our previously published Consensus [5]. We included meta-analyses or randomized controlled trials (RCTs) in postmenopausal women, comparing interventions currently registered in Belgium for the management of osteoporosis with a placebo. However, for some registered drugs like calcitonin and etidronate, the reader is referred to our previous Consensus publication [5] because no new data have been generated since and because these drugs are no longer considered first-line treatment options for the management of osteoporosis. The intervention could be given in conjunction with a calcium and vitamin D supplement, provided the comparison group received the same supplements. Furthermore, the results had to be reported with a follow-up of at least 1 year on one or more of the outcomes of interest: radiological or clinical evidence of fractures of the vertebra, wrist, or hip. We searched MEDLINE from 1966 to 2009 and databases such as the Cochrane Controlled Register for citations of relevant articles. After this extensive search of the literature, a critical appraisal of the data was obtained through a consensus experts meeting.

Calcium and vitamin D

Maintaining adequate calcium and vitamin D intake, through diet modification and/or supplementation, is recommended as part of standard care for osteoporosis. A recent expert panel concluded that combined calcium and vitamin D supplementation should be recommended in patients with osteoporosis or those at increased risk of developing osteoporosis [8]. Calcium and vitamin D reverses secondary hyperparathyroidism with resultant beneficial effects on bone density; additionally, calcium and vitamin D supplementation significantly improves body sway and lower extremity strength, reducing the risk of falls [9].

Calcium deficiency related to inadequate intake of calcium leads to increased serum parathyroid hormone (PTH) concentrations and bone loss. The guidelines issued by the consensus conference of the National Institutes of Health in the USA recommend a dietary intake of 1 g/day in postmenopausal women on hormone-replacement therapy and 1.5 g/day in other postmenopausal women and in all individuals over 65 years of age [10]. Although calcium deficiency can be corrected by adjusting the dietary intake of calcium, most individuals—and particularly older women at risk of osteoporosis—are unable or unwilling to change their lifestyle practices and will require calcium supplementation. In line with the assumption that calcium as citrate is better absorbed than calcium as carbonate in the fasting state, a recent comparative trial concluded that the use of calcium citrate may reduce bone resorption at lower doses than calcium carbonate, lead to less adverse effects, and potentially improve long-term compliance [11, 12].

Several serum 25-hydroxyvitamin D (25(OH)D) cut-offs have been proposed to define vitamin D insufficiency (as opposed to adequate vitamin D status), ranging from 30 to 100 nmol/l. Based on the relationship between serum 25 (OH)D, BMD, bone turnover, lower extremity function, and falls, 50 nmol/l is likely to be the appropriate serum 25(OH)D threshold to define vitamin D insufficiency [13]. Supplementation should therefore generally aim to increase 25(OH)D levels within the 50–75-nmol/l range. In most individuals, this level can be achieved with a dose of 800 IU/day vitamin D, the dose that was used in successful fracture prevention studies to date; a randomized clinical trial assessing whether higher vitamin D doses achieve a

greater reduction of fracture incidence would be of considerable interest.

The efficacy of combined calcium and vitamin D supplementation in reducing nonvertebral fracture rates has been demonstrated in three large, randomized, placebo-controlled, multicenter studies. Two of these studies involved institutionalized elderly patients, the Decalyos I [14, 15] and Decalyos II [16] studies, and one involved community-living elderly patients [17].

Decalyos I enrolled 3,270 women, aged 69–106 years (mean, 84 years), all of whom were able to at least walk indoors with a cane [14]. All had inadequate dietary calcium intake (<800 mg/day; mean, 513 mg/day) at study entry, while 44% had vitamin D insufficiency—serum 25 (OH)D level <30 nmol/ml, by radioimmunoassay (RIA). Randomization was 1:1 to 1,200 mg of calcium as tricalcium phosphate plus 800 IU of vitamin D daily (n=1,634) or to double placebo (n=1,636). In the women completing 18 months' therapy (n=1,765), supplementation reduced hip fracture incidence by 43% (risk ratio (RR), 0.57; 95% confidence interval (CI) not indicated; p=0.043) and nonvertebral fracture incidence by 32% (RR, 0.68; 95% CI not indicated; p=0.015) [14]. Similar benefits were seen in the intention-to-treat analysis. The reduction in hip fracture risk was apparent after 10 months' therapy, while an effect on all nonvertebral fractures was seen within 2 months. Furthermore, it was noted that the incidence of hip fracture increased markedly with time in the placebo group but remained stable in the calcium and vitamin D group. Changes in BMD at the proximal femur at 18 months (+2.7% in calcium and vitamin D group vs. −4.6% in the placebo group) were consistent with the reported differences in fracture risk between the two treatment groups [14]. Similar differences were seen in BMD at the femoral neck and in the trochanteric region. Secondary hyperparathyroidism also improved in the supplement group, with the majority of the improvement noted within 6 months. Further analysis of Decalyos I at 36 months' follow-up confirmed the continued preventive effect of calcium and vitamin D on fracture risk. For patients remaining on treatment, risk of hip and nonvertebral fractures continued to be significantly reduced (RR, 0.61 and 0.66, respectively; 95% CI not indicated; both p<0.01). In the intent-to-treat analysis, similar risk reductions were observed (RR, 0.77 and 0.83, respectively; 95% CI not indicated; both p<0.02) [15].

Decalyos II had a similar design to Decalyos I, with the exception that randomization was 2:1 to calcium and vitamin D vs. placebo and that the study duration was 2 years [16]. Of the 639 enrolled patients (610 randomized), 66% had an inadequate intake of both calcium (<800 mg/day) and vitamin D (serum 25(OH)D level (by RIA) <30 nmol/ml). Hip fractures occurred in 27 out of 393 (6.9%) women in the calcium and vitamin D group, compared with 21 out of 190 (11.1%) in the placebo group. The difference in the cumulative probability of hip fracture did not achieve statistical significance (RR, 0.69; 95% CI not indicated; p=0.07). Hip fracture risk was reduced in the calcium and vitamin D group from about 9 months, a finding consistent with that in Decalyos I. The magnitude of reduction in hip fracture risk was also similar to that seen in Decalyos I. The incidence of nonvertebral fractures was comparable in the two treatment groups. Femoral neck BMD remained unchanged in the calcium and vitamin D group (mean change, +0.29%/year) but decreased in the placebo group (−2.36%/year). The mean difference between the two treatment groups was not statistically significant (95% CI, 0.44–5.75%). Biochemical indices of calcium homeostasis normalized within 6 months of commencement of supplementation.

In contrast to the Decalyos studies, the study by Dawson-Hughes et al. [17] involved healthy, elderly, ambulatory men and women aged over 65 years (n=389; mean age, 71 years) living in the community. Levels of insufficiency were not as profound as those documented in the Decalyos studies. Randomization was 1:1 to calcium 500 mg as calcium citrate malate plus vitamin D 700 IU or placebo, with follow-up and treatment planned for 3 years. Nonvertebral fractures were sustained by 11 (5.6%) patients in the calcium and vitamin D group, compared with 26 (13.3%) in the placebo group (RR of first fracture, 0.5; 95% CI, 0.2–0.9; p=0.02). As in the Decalyos studies, supplementation also led to significant improvements in biochemical parameters and BMD.

Results of trials assessing fracture reduction with vitamin D alone have been equivocal [18–20]. In a recent randomized, double-blind, placebo-controlled study, vitamin D 100,000 IU every 4 months reduced the risk of first hip, wrist or forearm, or vertebral fractures by 33% (RR, 0.67; 95% CI, 0.48–0.93; p=0.02) [19]. Similarly, in a controlled trial in elderly Finnish subjects, annual intramuscular injections of high doses of vitamin D (150,000–300,000 IU) reduced fracture rates by approximately 25% (RR, 0.75; 95% CI not indicated; p=0.03) [20], although the benefits were limited to fractures of the upper limbs and ribs and to women only. No reduction in the risk of hip fractures was seen in a randomized, double-blind, placebo-controlled trial of vitamin D (400 IU/day) alone in an elderly community-dwelling population (n=2,578; mean age, 80 years) in the Netherlands (RR, 1.18; 95% CI, 0.81–1.71; p=0.31) [18].

More recently, meta-analyses have confirmed that the combination of calcium and vitamin D supplementation decreases the fracture risk for postmenopausal women [21, 22]. The analyses provided evidence that these beneficial effects were not attributable to either calcium or vitamin D alone with, for example, Bischoff-Ferrari et al. and Boonen et al., suggesting that oral vitamin D appears to reduce the

risk of hip fractures only when calcium supplementation is added [21, 22].

In the meta-analysis by Bischoff-Ferrari et al., the effectiveness of vitamin D supplementation in preventing hip and nonvertebral fractures in older persons was estimated [21]. Heterogeneity among studies for both hip and nonvertebral fracture prevention was observed, which disappeared after pooling RCTs with low-dose (400 IU/day) and higher-dose vitamin D (700–800 IU/day), separately. A vitamin D dose of 700 to 800 IU/day reduced the relative risk (RR) of hip fracture by 26% (three RCTs with 5,572 persons; pooled RR, 0.74; 95% CI, 0.61–0.88) and any nonvertebral fracture by 23% (five RCTs with 6,098 persons; pooled RR, 0.77; 95% CI, 0.68–0.87) vs. calcium or placebo. No significant benefit was observed for RCTs with 400 IU/day vitamin D (two RCTs with 3,722 persons; pooled RR for hip fracture, 1.15; 95% CI, 0.88–1.50; pooled RR for any nonvertebral fracture, 1.03; 95% CI, 0.86–1.24), supporting the concept that vitamin D supplementation between 700 and 800 IU/day reduces fracture risk in elderly persons and that an oral vitamin D dose of 400 IU/day is not sufficient for fracture prevention. In a more recent meta-analysis on the efficacy of oral supplemental vitamin D in preventing nonvertebral and hip fractures, Bischoff-Ferrari et al. confirmed that fracture prevention with vitamin D is dose dependent [23].

Boonen et al. analyzed over 45,000 patients from six randomized placebo-controlled trials to examine the effect of combined vitamin D with calcium supplementation in hip fracture prevention [22]. The pooled RR for hip fracture was 0.82 (95% CI, 0.71–0.94), showing a significant 18% risk reduction with the combined use of calcium and vitamin D supplementation compared with no supplementation. An adjusted indirect comparison for combined calcium and vitamin D supplementation also demonstrated a statistically significant 25% reduction in hip fracture risk with calcium and vitamin D compared with vitamin D alone (95% CI, 0.58–0.96). Taken together, these analyses, designed to extend the findings of Bischoff-Ferrari et al. [21], provided evidence that oral vitamin D appears to reduce the risk of hip (and any nonvertebral) fractures only when calcium is added. Thus, to optimize clinical efficacy, vitamin D 700–800 IU/day should be complemented with calcium, using a dose of 1,000–1,200 mg/day of elemental calcium.

The meta-analysis by Tang et al. evaluated almost 64,000 patients aged 50 years or older from 29 randomized trials to assess calcium or calcium in combination with vitamin D for the prevention of fracture and osteoporotic bone loss [24]. Supplementation was associated with a 12% reduction in all fractures, which was greater in trials with higher compliance. In trials that reported BMD, reduced rates of bone loss of 0.54% (95% CI, 0.35–0.73; $p<0.001$) at the hip and 1.19% (95% CI, 0.76–1.61; $p<0.001$) at the spine were reported in association with supplementation. For the best therapeutic effect, the authors recommended minimum doses of 1,200 mg of calcium and 800 IU of vitamin D.

Combined supplementation has also been recommended as an effective adjunct to osteoporosis therapy. In elderly patients taking bisphosphonates for the treatment of osteoporosis, studies have demonstrated an incremental benefit of vitamin D on BMD at the lumbar spine [8]. More recent evidence for the role of calcium and vitamin D as an essential component of the medical management of osteoporosis came from the ICARO study, a multicenter, observational study [25]. The study has been designed to analyze, in postmenopausal women with established osteoporosis, the risk factors for an "inadequate clinical response" to drug therapy, defined as the occurrence of new vertebral or nonvertebral fragility fractures in patients prescribed, for at least 1 year, alendronate, risedronate, or raloxifene (RAL), with a compliance over 50%. In 880 patients treated with antiresorptive agents for a median of 2.0 (95% CI, 1.0–4.5)years, the incidence of fractures during treatment with antiresorptive agents in a clinical setting is considerably higher than that observed in randomized clinical trials. Moreover, in adjusted analyses, inadequate compliance to treatment and lack of supplementation of calcium and vitamin D were found to be major determinants of this poor response.

Calcium and vitamin D supplementation is frequently perceived by patients and sometimes by their physicians as an excessive medication and is easily dismissed to avoid polypharmacy, especially in elderly patients. Lack of motivation is the most common reason for nonadherence to calcium and vitamin D3 supplementation, emphasizing the need for an active role of physicians in prescribing supplements and motivating patients [26].

In conclusion, calcium and vitamin D should be considered as an essential (but not sufficient) component of the treatment of osteoporosis, although most patients will derive further benefit in terms of fracture prevention from the addition of an antiresorptive or anabolic agent. However, antifracture efficacy with antiresorptive or anabolic osteoporosis medications has only been documented in calcium and vitamin D supplemented individuals. The available evidence suggests that, in many patients, combined supplementation with 1,000–1,200 mg of elemental calcium and 800 IU of vitamin D may be required.

Hormone replacement therapy

Estrogen deficiency is the most frequent risk factor for osteoporosis. Although randomized trials provide strong evidence that bone loss can effectively be prevented even

with rather small doses of hormone replacement therapy (HRT) and that fracture risk can be reduced with conventional doses, even in postmenopausal women who do not suffer from osteoporosis [27], the consensus has changed since the Women Health Initiative (WHI) studies. These randomized controlled trials evaluated, however, only two regimens of HRT: either the daily dose of 0.625 mg conjugated equine estrogen (CEE) alone in hysterectomized women or CEE combined with medroxyprogesterone acetate in women with an intact uterus. Following the first publications of these studies, HRT is no longer recommended as a first-line therapy for osteoporosis. Indeed, the WHI studies have reported that prolonged use of HRT especially in elderly women pertains an increased risk of breast cancer, thromboembolic disease, and cerebrovascular accidents [28], confirming that the presence of a history of one of these affections should be considered as an absolute contraindication to HRT prescription and that the presence of important risk factors of breast cancer, thromboembolic disease, and cerebrovascular accidents should be viewed as relative contraindications. The latter two risks may be lower when using a transdermal administration of estrogen rather than an oral one, and especially so in women with a genetic predisposition of thrombosis [29, 30]. Similarly, tibolone should not be viewed as a first line therapy for osteoporosis treatment. In an RCT in elderly women suffering from osteoporosis at the hip or spine or osteopenia and radiologic evidence of a vertebral fracture, Cummings et al. [31] evaluated tibolone (1.25 mg/day, i.e., half the conventional dosis) as compared to placebo. After a median time of 34 months of treatment, the tibolone group, as compared with the placebo group, had a decreased risk of vertebral fracture (70 cases vs. 126 cases per 1,000 person-years; RR, 0.55; 95% CI, 0.41–0.74; $p<0.001$) and a decreased risk of nonvertebral fracture (122 cases vs. 166 cases per 1,000 person-years; RR, 0.74; 95% CI, 0.58–0.93; $p=0.01$). Interestingly the tibolone group also had a decreased risk of invasive breast cancer (RR, 0.32; 95% CI, 0.13–0.80; $p=0.02$) and colon cancer (RR, 0.31; 95% CI, 0.10–0.96; $p=0.04$). However, because the tibolone group had an increased risk of stroke (RR, 2.19; 95% CI, 1.14–4.23; $p=0.02$), the study was stopped prematurely.

Although prolonged use of HRT may reduce the risk of fracture in healthy postmenopausal women, these data have to be strongly weighted against the other reported effects of HRT on disease outcomes (breast cancer risk, thromboembolic disease, risk of stroke, etc.) and with the possibility of treating women for osteoporosis with other therapeutic regimens [32]. Given these possibilities, our view is that, currently, HRT should not be prescribed for osteoporosis in women who do not experience menopausal symptoms. In symptomatic women, the potential adverse effects should be explained, and the treatment should be prescribed for short periods of time. Indeed, Lekander et al. [33], using a Markov cohort simulation model and using results taken from the WHI and containing hip, vertebral, and wrist fracture, breast and colorectal cancer, coronary heart disease, stroke, and venous thromboembolic events, found that it was cost-effective to treat women with menopausal symptoms with HRT and even where symptoms were mild HRT remained cost-effective [33]. The question remains unanswered whether HRT prescribed for a few years to suppress menopausal symptoms offers also long-lasting benefits for the prevention of postmenopausal bone loss and osteoporotic fracture. While most observational studies reported that past HRT users had the same osteoporosis risk as never users after a few years of HRT withdrawal, Bagger et al. [34] reported in 347 healthy postmenopausal women with normal bone mass who had earlier participated in placebo-controlled HRT trials that compared to placebo-treated women, HRT-treated women had a significantly reduced risk of osteoporotic fractures (RR=0.48 (95% CI, 0.26–0.88)). There are only short-term randomized trials available about the effect of phytoestrogens on osteoporosis. Most of these data evaluated either the bone turnover or the modification of the bone mass, and they have found inconsistent results. With the exception of a prospective trial assessing the effects of ipriflavone on osteoporotic fractures, which concluded in an absence of significant effect [35], we were unable to find randomized trials that evaluated the fracture efficacy of phytoestrogens [36–40].

In conclusion, when prescribing HRT, benefits need to be balanced against potential risks, and these should be explained to women. Although HRT significantly decreases bone loss and risk of osteoporotic fractures, its main indication in postmenopausal women remains the relief of menopausal symptoms. In younger women (50–59-year-old women), and when used during short periods of time (less than 5 years), the risk of stroke and of breast cancer are mild, and a "window of opportunity" for a benefit in cardiovascular disease may even exist.

Selective estrogen-receptor modulators

Since the publication of our former evidence-based guidelines for the treatment of postmenopausal osteoporosis [5], few papers dealing with selective estrogen-receptor modulators (SERMs) have been published.

In a meta-analysis taking into account data from the studies with RAL therapy in which vertebral fractures were prospectively collected, it was shown that in seven clinical studies pooled together, RAL 60 mg reduced the risk for vertebral fracture by 40% (RR, 0.60; 95% CI, 0.49–0.74) and RAL 120/150 mg by 49% (RR, 0.51; 95% CI, 0.41–0.64) [41]. A tentative trial aimed at comparing the

antifracture efficacy of RAL and alendronate in postmenopausal women with low bone mass had to be stopped after 1 year, due to the too slow enrolment of treatment-naïve women to meet the planned timeline [42]. This resulted in insufficient power to demonstrate non-inferiority between treatments. When the study was stopped, the women were in the study for a mean of 312 days and a median of 190 days, without any significant difference in treatment duration nor in incidence of vertebral and nonvertebral fractures between the treatment groups [42]. No difference in adverse events leading to treatment discontinuation was observed either. The only adverse events significantly more frequent in the alendronate group as compared to the RAL group ($p<0.05$) were colonoscopy (1.1% vs. 0.1% of women), diarrhea (3.8% vs. 1.0%), and nausea (5.3% vs. 3.1%). Women with ≥1 hot flush or leg cramp were more numerous in the RAL group than in the alendronate group (10.3% vs. 7.3%; $p=0.049$), whereas women with ≥1 upper gastrointestinal adverse event were more numerous in the alendronate group (14.5% vs. 10.9%; $p=0.046$) [42].

The Continuing Outcomes Relevant to Evista (CORE) trial was planned as a 3-year extension of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial in a double-blind mode [43, 44]. This study was started on average 10.6 months after the end of the MORE study, because the code could evidently not be broken immediately at the end of the MORE study. Four thousand eleven women could resume the very same treatment assigned at the start of MORE in a double-blind manner with the exception that only the 60-mg dose of RAL was compared with placebo. The patients initially assigned to the 120-mg dose in MORE continued on 60 mg in CORE. The primary objective of CORE was to evaluate the risk of breast cancer [43], with peripheral, but not the vertebral fractures, recorded as adverse effects. Furthermore, other treatments aimed at improving bone status were allowed, bisphosphonate therapy being more frequent in the former RAL group than in the placebo group. Only 386 women took no bone-acting drug during 8 years, and 259 were on RAL. The latter ones maintained their BMD values both at the spine and at the hip [44]. After 8 years (4 years in MORE, 3 years in CORE, plus nearly 1 year in between without SERM therapy), RAL therapy led to BMDs higher by 2.2% at the spine and by 3% at the total hip, comparatively with placebo. There was no statistically significant difference in the incidence of nonvertebral fractures between both groups [44]. In a post hoc analysis, the risk of new nonvertebral fractures at six skeletal sites (clavicle, humerus, wrist, pelvis, hip, and lower leg) was statistically significantly decreased in CORE patients suffering from prevalent vertebral fractures at MORE baseline and in women with semiquantitative grade 3 vertebral fractures in the combined MORE and CORE trials on RAL [44]. It is interesting to note that during the time interval between the end of MORE and the start of CORE (on average 337±85 (SD) days), a significant bone loss was observed at the spine and the femoral neck in the RAL group, correlated at the spine with the length of time off of study drug [44]. Moreover, in another study, treatment discontinuation for 1 year after 5 years of continuous therapy with RAL was also accompanied with significant BMD declines both at the lumbar spine (−2.4±2.4%) and the hip (−3.0±3.0%), an effect comparable with estrogen weaning [45]. There is no data available, however, on fracture incidence following RAL discontinuation [45].

At the end of the 8-year study period of MORE+CORE, the reduction in invasive breast cancer amounted to 66% (RR, 0.34; 95% CI, 0.22–0.50) and in invasive estrogen-receptor-positive breast cancers to 76% as compared with placebo (RR, 0.24; 95% CI, 0.15–0.40) [43]. In contrast, there was no statistically significant difference in the incidence of invasive estrogen-receptor-negative breast cancer between groups. Regardless of invasiveness, the overall incidence of breast cancer decreased by 58% in the RAL group (RR, 0.42; 95% CI, 0.29–0.60) compared with the placebo group. Endometrial tolerance (hyperplasia, cancer, or vaginal bleedings) was not different from placebo [43]. A nonsignificant increase in the risk of deep venous thrombosis persisted in the CORE study (RR, 2.17; 95% CI, 0.83, 5.70) [43].

In another study vs. placebo, concerning 10,101 postmenopausal women (mean age, 67.5 years) with coronary heart disease or multiple risk factors for coronary heart disease, RAL (60 mg/day) did not modify significantly the risk of primary coronary events but confirmed a reduction in the risk of invasive breast cancer (RR, 0.56; 95% CI, 0.38–0.83) [46]. The risk of clinical vertebral fractures (RR, 0.65; 95% CI, 0.47–0.89) was also reduced. However, RAL therapy was associated with an increased risk of fatal stroke (RR, 1.49; 95% CI, 1.0–2.24) and venous thromboembolism (RR, 1.44; 95% CI, 1.06–1.95). In the STAR study involving 19,647 postmenopausal women with increased 5-year breast cancer risk, RAL was shown to be as effective as tamoxifen in reducing the risk of invasive breast cancer [47]. In this study, RAL demonstrated a lower risk of thromboembolic events and cataracts, but a nonsignificant higher risk of noninvasive breast cancer as compared with tamoxifen [47].

In conclusion, RAL at a daily dose of 60 mg is able to prospectively induce a significant decrease in the vertebral fracture risk in postmenopausal women with both densitometric osteoporosis (T-score≤−2.5) and established osteoporosis. Data on nonvertebral fracture are only positive in post hoc analyses in a subgroup of patients with prevalent vertebral fractures. Another clinical advantage is that a

reduced risk of invasive breast cancer, chiefly of estrogen-receptor-positive invasive breast cancers was observed, similar to that conferred by tamoxifen. On the other hand, RAL does not confer any cardiovascular prevention. On the contrary, it provoked a small but significant increase in the risk of fatal stroke as well as of venous thromboembolism. In his decision for antiosteoporotic therapy with RAL, the clinician should weigh the benefits observed on the reduction in invasive breast cancer and vertebral fracture risk and the drawbacks of this treatment, which are the lack of effect on nonvertebral fracture risk, and the increased risks of venous thromboembolism and fatal stroke.

Bisphosphonates

Alendronate, risedronate, ibandronate, and zoledronic acid (ZA) are currently registered in Belgium for the treatment of osteoporosis. Oral bisphosphonates may be associated with gastrointestinal complaints, and therapeutic schemes are mandatory constraining. Inconvenience and complexity of required dosing procedures with oral bisphosphonate therapy are factors that hinder medication persistence leading to suboptimal health care outcomes. These are reasons why alternative approaches have been developed. Repeated infusions of potent bisphosphonates at large time intervals could circumvent these constraints and greatly simplify the current treatment of osteoporosis.

The antifracture efficacy of alendronate has been established in large populations of postmenopausal women [48–50]. In the study including 2,027 women with prevalent vertebral fracture(s) at baseline, alendronate reduced the incidence of new vertebral fractures by 47% (RR, 0.53; 95% CI, 0.41–0.68) [49]. The incidence of vertebral fractures with clinical symptoms was similarly reduced (RR, 0.46; 95% CI, 0.28–0.75). There was no reduction in the overall risk of nonvertebral fractures (RR, 0.80; 95% CI, 0.63–1.01), but hip fracture incidence was also reduced (RR, 0.49; 95% CI, 0.23–0.99) as was wrist fracture risk (RR, 0.52; 95% CI, 0.31–0.87) [49]. Estimation of the effect on hip fracture was not precise and the CI correspondingly wide, reflecting that the number of fractures (33 in total) was small. The antifracture efficacy of alendronate was also demonstrated in 4,432 women with low bone mass but without vertebral fractures at baseline treated for 4 years (5 mg daily during the first 2 years, then 10 mg daily). The reduction in the incidence of radiological vertebral fractures was 44% (RR, 0.56; 95% CI, 0.39–0.80). However, the reduction in clinical fractures was not statistically significant in the whole group but well among women with initial T-scores below −2.5 at the femoral neck (RR, 0.64; 95% CI, 0.50–0.82). No reduction was observed in the risk of nonvertebral fractures (RR, 0.88; 95% CI, 0.74–1.04) [50].

The effect of alendronate on nonvertebral fractures has been best estimated in a meta-analysis of five placebo-controlled trials of at least 2 years duration including postmenopausal women with a T-score<−2.0. The estimated cumulative incidence of nonvertebral fractures after 3 years was 12.6% in the placebo group and 9.0% in the alendronate group (RR, 0.71; 95% CI, 0.502–0.997) [51]. Another meta-analysis estimated that alendronate reduced vertebral fracture incidence by 48% when given at 5 mg daily or more (RR, 0.52; 95% CI, 0.43–0.65) and nonvertebral fracture rate by 49% when given at 10 mg daily or more (RR, 0.51; 95% CI, 0.38–0.69) [52]. However, data from one of the largest trials with alendronate [53] were excluded from this meta-analysis [52]. Data on BMD and biochemical markers of bone remodeling have been reported from patients discontinuing alendronate treatment after 3 to 5 years or continuing for 10 years [53, 54]. As primary outcome, women who discontinued alendronate showed, after 5 years, a 3.7% (95% CI, 3–4.5) and 2.4% (95% CI, 1.8–2.9) decline in lumbar and hip BMD, respectively, as compared with patients continuing alendronate [54]. Similarly, biochemical markers gradually increased over 5 years in patients discontinuing alendronate (55.6% for serum C-terminal telopeptide of type 1 collagen (sCTX) and 59.5% for N-propeptide of type 1 collagen). There was no evidence that discontinuation of alendronate for up to 5 years increases fracture risk, but the optimal duration of treatment remains unknown, although these data provide evidence for 10 years safety of alendronate therapy.

Alendronate was well tolerated in these different placebo-controlled trials, but patients at risk for upper gastrointestinal events were excluded from the trials, and subsequent experience has undoubtedly demonstrated that esophageal and, to a lesser extent, gastric toxicity can be troublesome adverse events, especially if proper intake instructions are not respected. Several cases of esophageal ulcerations have thus been described [55].

Daily compliance with 10 mg alendronate is uncertain and difficult to maintain in routine clinical practice. The efficacy and safety of treatment with oral once-weekly alendronate 70 mg, twice-weekly alendronate 35 mg, and daily alendronate 10 mg have been compared in a double-blind, 1-year study involving a total of 1,258 postmenopausal osteoporotic women. The increases in BMD at the lumbar spine, hip, and total body were similar for the three dosing regimens, and the fall in bone turnover markers was also quite similar. The gastrointestinal tolerance of the once-weekly regimen and the daily dosing were similar [55]. The antifracture efficacy of the weekly formulation is supposed to be similar to the daily formulation, but this has not been formally tested.

Generic alendronate sodium tablets are now available with a theoretical bioequivalence to the branded product.

Differences in in vitro disintegration and esophageal transit with generic formulations of alendronic acid 70-mg tablets have been reported [56, 57]. Some concern remains for the clinician that the pharmaceutical properties of the various generic formulations may affect the potential for esophageal irritation and tolerability, the bioavailability, and the potency of generic alendronate [58]. In a retrospective 1-year observational analysis, the persistence of patients treated with generic alendronate and the increases of lumbar spine and total hip BMD were significantly lower as compared to each of the two originals branded alendronate and risedronate [59]. The question of lower bioavailability or potency of generic alendronate remains open.

Risedronate at the dose of 5 mg daily for 3 years has been shown to significantly reduce the vertebral fracture risk in established osteoporosis as compared with placebo. In women with at least one vertebral fracture at baseline, the relative reduction of new vertebral fractures was 41% (RR, 0.59; 95% CI, 0.42–0.82) and 39% for nonvertebral fractures (RR, 0.61; 95% CI, 0.39–0.94) [60]. In women with at least two vertebral fractures at baseline, the risk of new vertebral fractures was reduced by 49% (RR, 0.51; 95% CI, 0.36–0.73) but, in this study, the effect on new nonvertebral fractures was not significant (RR, 0.67; 95% CI, 0.44–1.04) [61]. Pooling of both studies showed that after 1 year of treatment, the risk of new vertebral fracture was reduced by 62% (RR, 0.38; 95% CI, 0.25–0.56) and of multiple new vertebral fractures by 90% (RR, 0.10; 95% CI, 0.04–0.26) [62]. Reduction of clinical vertebral fractures and nonvertebral fractures has been reported within 6 months of risedronate treatment [63]. The European study [61] was continued blindly in a subset of the population, and the antifracture efficacy was maintained for at least 5 years [64], the longest available double-blind fracture data for an antiresorptive. Vertebral fracture risk reduction with risedronate was confirmed in women over 80 with documented osteoporosis (RR, 0.56; 95% CI, 0.39–0.81), providing post hoc evidence that even in patients 80 years of age or older, reducing bone resorption rate remains an effective osteoporosis treatment strategy [65].

Risedronate has also been shown to decrease the incidence of hip fractures in a controlled trial specifically designed for that purpose. Hip fracture reduction was only observed in women with documented osteoporosis, however. In this placebo-controlled study involving 5,445 women 70–79 years old who had osteoporosis and risk factors for falls, it was shown that risedronate at 2.5 or 5 mg/day for 3 years (the actual mean duration of treatment was 2 years) lowered the RR of hip fracture by 40% (RR, 0.60; 95% CI, 0.40–0.90). There was no dose effect and, interestingly, the effect was greater in the group of women who had a vertebral fracture at baseline (RR, 0.40; 95% CI, 0.20–0.80). In the same study, however, there was no significant effect of risedronate in 3,886 women ≥80 years old (RR, 0.80; 95% CI, 0.60–1.20), but these patients were essentially selected on the basis of the presence of at least one risk factor for hip fracture, such as difficulty standing from a sitting position and a poor tandem gait, rather than on the basis of low BMD or prevalent fractures [66]. The antifracture efficacy of risedronate has been confirmed in a meta-analysis [67]. The pooled RR for vertebral fractures in women given 2.5 mg or more of risedronate daily was 0.64 (95% CI, 0.54–0.77), whereas for nonvertebral fractures, it was 0.73 (95% CI, 0.61–0.87). Like alendronate, risedronate also had a safe profile in clinical trials. The safety profile of risedronate was similar to that of placebo, despite the fact that unlike in the alendronate trials, patients with a history of gastrointestinal disease or chronic use of nonsteroidal anti-inflammatory drugs were not excluded from the risedronate studies. A weekly formulation of risedronate has also been developed and, as for alendronate, has been shown to be therapeutically equivalent to the daily formulation as judged by the effects on bone density and on bone turnover [68].

The iBandronate Osteoporosis trial in North America and Europe (BONE) has been the first study to prospectively demonstrate a reduction of vertebral fracture risk on an intermittent bisphosphonate regimen [69]. A 2.5-mg daily oral ibandronate and an intermittent oral ibandronate dosage (20 mg every other day for 12 doses every 3 months) were assessed in a 3-year placebo-controlled trial including 2,946 osteoporotic women with prevalent vertebral fracture. The RR reductions of new morphometric vertebral fracture, compared with placebo, were 62% (RR, 0.38; 95% CI, 0.25–0.59) and 50% (RR, 0.50; 95% CI, 0.34–0.74) for the daily and intermittent groups, respectively. The incidence of nonvertebral fractures was similar between the ibandronate and placebo groups after 3 years (9.1%, 8.9%, and 8.2% in the daily, intermittent, and placebo groups, respectively; difference between arms was not significant). The overall population was at low risk for osteoporotic fractures (mean total hip BMD T-score, −1.7), but post hoc analysis, in higher-risk subgroups, showed that the daily regimen reduced the risk of nonvertebral fractures (femoral neck BMD T-score<−3.0, 69%; $p=0.012$; lumbar spine BMD T-score<−2.5 and history of a clinical fracture, 62%; $p=0.025$).

The oral 150-mg dose of monthly ibandronate has been evaluated in the Monthly Oral Ibandronate in Ladies (MOBILE), a 2-year, multicenter, double-blind, noninferiority bridging study comparing the efficacy and safety of once-monthly ibandronate with daily ibandronate in 1,609 postmenopausal women [70]. The 150-mg once-monthly dose of ibandronate consistently produced greater sCTX suppression and greater increase in lumbar and total hip BMD ($p<0.05$) than the daily regimen, but the cumulative

dose was larger. Once-monthly ibandronate was as well tolerated as daily treatment. These results were confirmed in the MOBILE 3-year extension study [71].

The Dosing Intravenous Administration trial (DIVA) trial is a randomized, double-blind, double dummy, non-inferiority, international multicenter trial comparing daily 2.5 mg oral ibandronate and intermittent intravenous ibandronate, given 2 mg every 2 months or 3 mg every 3 months, in 1,395 postmenopausal women [72]. All patients had osteoporosis (lumbar spine T-score<−2.5). The primary end point was change from baseline in lumbar spine BMD at 1 year. At 1 year, mean lumbar spine BMD increases were 5.1%, 4.8%, and 3.8% in the intravenous 2 mg, the intravenous 3 mg, and the oral daily 2.5 mg groups, respectively. Both of the intravenous regimens not only were noninferior but also were superior ($p<0.001$) to the oral regimen. Hip BMD increases were also significantly greater in both intravenous groups. After 1 year, the median reduction from baseline in the sCTX level was similar in the three treatment groups.

The ibandronate dose response for the prevention of nonvertebral fractures has been evaluated in a pooled analysis of individual patient data from eight randomized trials [73]. This study was conducted to assess the effect of high vs. lower doses of ibandronate on nonvertebral fractures based on annual cumulative exposure (ACE). ACE was defined as the total annual dose of bisphosphonate absorbed and therefore available to the bone tissue taking into account the fact that 100% of an intravenous bisphosphonate and 0.6% of an oral dose are absorbed. The results were adjusted for clinical fracture, age, and bone density. High ACE doses defined as ≥10.8 mg (150 mg once monthly, 3 mg i.v. every 3 months, and 2 mg i.v. every 2 months) were compared to ACE doses ≤7.2 mg (100 mg oral monthly, 50/50 mg monthly, and 2.5 mg oral daily) and to low 5.5 mg ACE dose (oral 2.5 mg daily). A dose–response effect on nonvertebral fractures was observed when comparing high with low ACE doses. The comparison resulted in a 0.62 RR (95% CI, 0.396–0.974; $p=0.038$) for ACE doses ≥10.8 mg vs. to 5.5 mg ACE doses and in a 0.64 RR (95% CI, 0.43–0.94) for ≥10.8 mg ACE doses vs. ≤7.2 mg ACE doses, leading to the conclusion that higher ibandronate dose levels (150 mg monthly or 3 mg i.v. quarterly) significantly reduced nonvertebral fracture risk in postmenopausal women.

In a similar analysis, Harris et al. compared reduction in fracture risk for high (≥10.8 mg), mid (7.2–5.5 mg), and low (≤4.0 mg) ACE relative to placebo [74]. It was observed that doses of ibandronate resulting in ACEs ≥10.8 mg, including the marketed oral 150 mg monthly and i.v. 3 mg thrice monthly, significantly reduce the risk of all clinical, vertebral, and nonvertebral fractures with a 0.712 RR (95% CI, 0.55–0.92; $p=0.01$). The risk of nonvertebral fractures was also significantly reduced with a 0.701 RR (95% CI, 0.50–0.99; $p=0.04$). Data from the four phase III clinical trials of ibandronate (8,710 patients) were pooled in a meta-analysis to assess the relationship between ibandronate dose, BMD changes, and rates of both clinical and nonvertebral fractures [75]. It was observed that both lumbar spine and total hip BMD increased with increasing ibandronate dose. A statistically significant inverse linear relationship has been reported between percent change in lumbar spine BMD and the rate of clinical fractures ($p=0.005$).

There is no evidence, from placebo-controlled trials, for a reduction of nonvertebral fracture with ibandronate, but data from the MOBILE bridging study, from meta-analysis and from ACE evaluations, suggest a significant effect of the marketed oral 150 and the 3 mg i.v. ibandronate on the risk reduction of nonvertebral fractures. Hip, nonvertebral, or clinical fracture rates were not statistically different between patients receiving monthly oral ibandronate, weekly oral alendronate, or risedronate in a 12-month observational study, but patients on oral ibandronate had a significantly 64% lower risk of vertebral fractures than patients on weekly bisphosphonates (RR, 0.36; 95% CI, 0.18–0.75; $p=0.006$) [76].

Both oral 2.5 mg daily and intermittent oral ibandronate dosage (20 mg every other day for 12 doses every 3 months) were well tolerated with an incidence of adverse events similar to placebo in the BONE trial [69]. Once-monthly oral ibandronate was well tolerated, with a similar safety profile to placebo in a 3-month, double-blind, placebo-controlled, phase I study (Monthly Oral Pilot Study) [77] and with a similar incidence of adverse events across groups (oral 50+50, 100, and 150 mg) in the MOBILE study [70]. The incidence of upper gastrointestinal adverse events was similar for the once-weekly 70-mg alendronate and the once-monthly 150-mg ibandronate in a 12-month comparative study [78]. After 1 year, the incidence of proportion of patients all adverse events, treatment-related adverse events, and treatment-related adverse events that led to withdrawal was similar for the i.v. 2-mg twice monthly, 3-mg thrice monthly, and oral 2.5-mg ibandronate in the DIVA trial [72]. Renal safety has been confirmed, without clinically relevant changes in serum creatinine, creatinine clearance, or microalbuminuria, in patients with breast cancer and bone metastases receiving ibandronate 6 mg every 3–4 weeks for 6 months given over 15 min [79] or for 2 years given every 3–4 weeks over 1–2 h [80].

To date, oral alendronate, risedronate, and ibandronate have not been studied in head-to-head comparative trials with fracture endpoints. Because of evidence that differences exist in the BMD–fracture risk relationship between different agents and that the relationship between fracture risk reductions and BMD is not a simple linear one [77, 81], BMD endpoint trials cannot substitute for fracture endpoint trials and do not allow a formal comparison of the magnitude of the treatment effects of different osteoporosis agents.

ZA is the latest of the aminobisphosphonates available for parenteral osteoporosis treatment. It has the highest affinity among bisphosphonates for bone surfaces, the maximum inhibition potency to inhibit the activity of the farnesyl diphosphate synthesis, and the highest antiresorptive activity [82]. One intravenous dose of ZA (4 to 20 μg/kg) attenuated trabecular and cortical bone loss for 32 weeks in ovariectomized rats. At 100 μg/kg, bone loss was completely suppressed. ZA was ten times more potent than alendronate in this model [83]. The increase of bone resorption postovariectomy, measured by TRAP5b, was suppressed until the 32nd week, even for the lowest dose of ZA (0.8 μg/kg). In human, one intravenous injection of ZA decreased bone turnover for at least 1 year [84], and perhaps even for 2 years [85], opening the road for a yearly treatment in osteoporosis. A once-yearly intravenous injection of ZA was tested in two controlled studies. In the Health Outcome and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial (HORIZON PFT), a yearly injection of ZA (5 mg over 15 min) given at 0, 12, and 24 months was compared to a placebo infusion in more than 7,500 postmenopausal women with osteoporosis who were followed up for 3 years. All patients received daily calcium and vitamin D supplements (1,000–1,500 mg/400–1,200 IU). The markers of bone turnover were decreased by 30% to 59% at 12 months. BMD increased significantly ($p<$ 0.001) at the femoral neck (5.06%; 95% CI, 4.76 to 6.28), total hip (6.02%; 95% CI, 5.77 to 6.28), and lumbar spine (6.71%; 95% CI, 5.69 to 7.74). The 3-year risk of morphometric vertebral fracture was reduced by 70% (RR, 0.30; 95% CI, 0.24–0.38) and that of hip fracture by 41% (RR, 0.59; 95% CI, 0.42–0.83). Nonvertebral fractures were decreased by 25% (RR, 0.75; 95% CI, 0.64–0387). Clinical vertebral fractures were reduced by 77% (RR, 0.23; 95% CI, 0.14–0.37), and all clinical fractures were reduced by 33% (RR, 0.67; CI, 0.58–0.77; $p<0.001$) [86]. A subgroup of around 150 patients included in the HORIZON trial had a bone biopsy at the end of the observation period [87]. The microCT and histological analysis showed the expected reduction of the activation frequency and increased length of the remodeling cycle, an increased trabecular bone volume and trabecular number, and a decreased trabecular separation. There was no alteration of osteoblast function, and even a significant increase of mineral apposition rate.

In a second study including more than 2,100 patients (HORIZON Recurrent Fracture Trial), men and women over 50 years old received ZA or a placebo infusion within 90 days after repair of a hip fracture. In this only trial conducted to study the risk of fracture in patients with a prevalent hip fracture, not only was the risk of a new clinical fracture reduced by 35% (RR, 0.65; 95% CI, 0.50–0.84; $p<0.001$) in the ZA group during the 1.9 years follow-up but the risk of death was also reduced by 28% (RR, 0.72; 95% CI, 0.56–0.93) in this arm [88]. A significant reduction of fracture risk was already observed at 12 months. The decreased mortality is only partly explained by the reduction of fracture rates [89].

In these two controlled studies, the profile was safe, with a number of serious adverse events or deaths not significantly different in the groups treated with ZA or with placebo. The main problem with ZA was the postinfusion syndrome, which is classical with all intravenous bisphosphonates following the first infusion, usually mild, and can be reduced by acetaminophen [90]. Intriguingly, an unexpected number of episodes of atrial fibrillation described as severe adverse events occurred in the ZA-treated group. The fact that the total incidence of atrial fibrillation was not increased, that the episodes occurred late after the injection, and that an increased frequency of AF was not found in the HORIZON-RFT trial suggests that this occurred by chance [82, 91]. A recent meta-analysis provided no evidence for an excess risk of atrial fibrillation in patients treated with bisphosphonates [91]. This study did not reveal any increase in the risk of stroke or cardiovascular mortality. Asymptomatic hypocalcaemia occurred in a few patients treated with ZA, most frequently 9 to 11 days after the infusion. Serum creatinine increased transiently in some patients of the ZA group. However, in the long term, there was no alteration of the renal function [92].

Adherence to treatment is crucial to reach high-level efficiency and low level of side effects. In clinical practice, adherence is poor in osteoporotic patients. It has been measured that approximately 75% of women who initiate osteoporosis drug therapy are nonadherent within 12 months, almost 50% having discontinued their therapy by this time [93]. This is not only observed in asymptomatic osteoporotic patients but also after such a severe event as a hip fracture. Prescription rate and compliance with bisphosphonates or SERMs after hip fracture have been measured in 23,146 patients who had sustained a hip fracture. Of these patients, 6% received treatment during the study period (4.6% alendronate, 0.7% risedronate, and 0.7% RAL). At 12 months, the rate of persistence was 41%, and the median duration of persistence was 40.3 weeks [94]. An important factor is the frequency of drug administration. Medication persistence has been compared for patients receiving weekly oral or daily oral bisphosphonates in a large, longitudinal cohort of female patients ($n=$211,319) receiving prescriptions for alendronate or risedronate from approximately 14,000 US retail pharmacies. Only 56.7% of patients receiving the weekly regimen and only 39.0% of patients receiving the daily regimen continued to take bisphosphonate therapy at month 12 of the study period ($p<0.0001$) [95].

A recent study, based on an analysis of the French national prescription database, evaluate whether monthly

bisphosphonate treatment provided superior adherence than weekly treatment. Both compliance (medication possession ratio (MPR)) and persistence (time to discontinuation) were superior in the monthly ibandronate treatment group. Twelve-month persistence rates were 47.5% for monthly ibandronate and 30.4% for weekly bisphosphonates. Compliance was significantly higher in the monthly cohort (MPR= 84.5%) than in the weekly cohort (MPR=79.4%). After adjustment for potential confounding variables, women with monthly regimens were 37% less likely to be nonpersistent (RR=0.63 (0.56–0.72)) and presented a 5% higher mean MPR (84.5% vs. 79.3%, $p<0.001$) than women with weekly regimens [96]. Besides avoidance of the gastrointestinal side effects, an advantage which could be expected from intravenous administration is an improved adherence.

Osteonecrosis of the jaw (ONJ) is frequently presented as a "classical complication" of bisphosphonate treatment, thereby generating anxiety in osteoporotic patients and interrogations in practitioners dealing with osteoporotic treatment. According to a recent systematic review of the literature for relevant studies on bisphosphonates-associated ONJ in oncology and treated osteoporotic patients, it appears that ONJ is rare in osteoporotic patients, with an estimated incidence <1 case per 100,000 person-years of exposure [97]. At the opposite, in oncology patients receiving high-dose intravenous bisphosphonates, ONJ appears to be dependent of the dose and duration of therapy, with an estimated incidence of 1–12% at 36 months. The authors underline that ONJ incidence in the general population is unknown. To date, pathogenesis of bisphosphonate-related ONJ remains an enigma [98].

Unusual mid-shaft long bone fractures have been reported in some patients receiving bisphosphonates, mainly alendronate, for the treatment of osteoporosis [99–102]. It has been hypothesized that this could be due to prolonged suppression of bone turnover, leading to accumulation of microdamage and development of hypermineralized bone, but this remains to be confirmed. Two recent histologic studies did not show indeed an increased prevalence of microcracks in patients who had received alendronate for more than 5 years [103, 104], though it appears in the study by Stepan et al. that cracks become significantly more prevalent in the alendronate-treated patients with the lowest bone mineral densities. A recently published epidemiological study also suggests that these fractures are more linked to osteoporosis itself than to bisphosphonate treatment [105]: this registered-based cohort study has shown that the distribution of these atypical fractures was identical in an alendronate-treated cohort and in an untreated cohort, and that in a small number of patients who remained on alendronate for more than 6 years, there was no shift from typical to atypical femur fractures, which is reassuring. Further investigation is mandatory to precise the usefulness of stopping bisphosphonate (after 5 or 10 years of treatment?) or monitoring bone markers to avoid oversuppression of bone turnover.

Anabolic agents

The pharmacologic armamentarium available to clinicians to reduce fracture risk in women with postmenopausal osteoporosis consists essentially of antiresorptive agents, i.e., drugs acting through inhibition of osteoclastic bone resorption and lowering of global bone turnover. The only exceptions are peptides from the PTH family, which, under specific modalities of administration, act as anabolic agents stimulating bone formation, and strontium ranelate, which acts as an uncoupling agent effecting a stimulation of bone formation with reduction of bone resorption. The interest generated by these alternatives to antiresorptive treatment resides in their greater potential for restoration of bone mass and possibly also bone structure in osteoporotic subjects who have already suffered substantial skeletal deterioration.

Peptides of the PTH family have been investigated in the management of osteoporosis since more than 30 years [106]. Their proposed use in the treatment of osteoporosis is based on the observation that intermittent exposure to low dose PTH is anabolic to the bone, in contrast to the catabolic effects on cortical bone resulting from continuous exposure to supraphysiological levels of PTH from either endogenous or exogenous origin. The anabolic effects of PTH are exerted through stimulation on the cells of osteoblastic lineage of the PTH-1 receptor, which is shared by both PTH and PTH-related peptide (PTHrP) and is therefore also known as the PTH–PTHrP receptor. For either molecules, it is the N-aminoterminal region that activates the receptor as is more in particular the case for PTH (1–34) also known as teriparatide. The anabolic actions of the intermittently administered peptides from the PTH family involve augmentation of the number of osteoblasts through stimulation of cell replication and inhibition of osteoblast apoptosis, and probably also stimulation of osteoblast activity. The molecular mechanisms underlying these anabolic effects are still poorly understood, but appear to include both direct actions on osteoblastic cells as well as indirect effects such as through stimulation of IGF-1 production and downregulation of sclerostin, a physiologic antagonist of the important anabolic Wnt-β-catenin pathway. The anabolic effects of PTH and related peptides appear to be more pronounced on cancellous than on cortical bone [107].

The efficacy and safety of self-administered daily subcutaneous injections of 20 μg teriparatide, the dosing regimen presently proposed for clinical use in postmenopausal osteoporosis, has been evaluated in an RCT

involving 1,637 postmenopausal women with prior vertebral fracture (mean T-score, −2.6 at the lumbar spine), assigned to receive daily s.c. injections of 20 or 40 μg of teriparatide or placebo. Vertebral radiographs were obtained at baseline and at the end of the study (median duration of observation, 21 months), and serial measurements of bone mass by dual energy X-ray absorptiometry (DXA) were performed. New vertebral fractures occurred in 14% of the women in the placebo group and in 5% of the women in the 20-μg teriparatide group. The RR of fracture as compared with the placebo group was 0.35 (95% CI, 0.22–0.55). New nonvertebral fragility fractures occurred in 6% of the women in the placebo group and in 3% of the women in the 20-μg teriparatide group (RR, 0.47; 95% CI, 0.25–0.88). Over the 21-month observation period, compared to placebo, the 20-μg teriparatide group increased BMD by 9 and 3 percentage points in the lumbar spine and femoral neck, respectively. At the shaft of the radius, BMD decreased by 2.1±4.2% in the 20-μg teriparatide group as compared to a decrease by 1.3±3.3% in the placebo group (p=0.09). Total body bone mineral content increased by 2 to 3 percentage points in the 20-μg teriparatide group as compared to placebo as measured on Hologic or Lunar DXA equipment, respectively. Nine percent of the women in the 20-μg teriparatide group reported dizziness, and 3% reported leg cramps, as compared to 6% and 1% of the women in the placebo group, respectively (p=0.05 and p=0.02, respectively); the frequency of these complaints was not higher than in the placebo group for the higher teriparatide dosage. A limited increase of the report of nausea and headache in the higher teriparatide dose group was not different from placebo in the 20-μg teriparatide group. Mild hypercalcemia (defined as a calcium concentration that exceeded 10.6 mg/dl) occurred at least once in 11% of the patients treated with 20 μg teriparatide daily (95% were less than 11.2 mg/dl) as compared to 2% hypercalcemia in the women in the placebo group; 3% of the women on the 20-μg teriparatide treatment required dose reduction because of persistent hypercalcemia, and treatment had to be discontinued in a single patient. Treatment resulted in a limited increase of calciuria without increase of the prevalence of hypercalciuria. Compared to the 20-μg teriparatide treatment, a treatment with a higher daily dose of 40 μg teriparatide resulted in a larger increase of BMD at the lumbar spine and the femoral neck, a larger decrease of BMD at the shaft of the radius, a similar reduction in the risk of vertebral and nonvertebral fracture, and a higher incidence of hypercalcemia [108, 109].

In contrast with the effects of antiresorptive drugs on biochemical markers of bone turnover, the treatment effects of teriparatide on BMD and fracture risk reduction are underlied by marked and sustained increases in the biochemical markers of bone turnover, an initial rapid and marked increase of the markers of bone formation being followed with a delay of about 1 month by a less pronounced increase of the markers of bone resorption [110]. The magnitude of early changes in markers of bone formation has been shown to correlate with increases of BMD at 18 months of treatment [111] and with improvements in bone structure as shown by histomorphometry and including augmentation of cancellous bone with increased trabecular thickness and connectivity [112]. The antifracture efficacy of teriparatide on spinal fracture does not seem to be modulated by age of the subjects (<65, 65–75, or >75 years), prevalent spinal BMD values (T-score <−2.5 or >−2.5), or the number of prevalent fractures (one or two or more fractures) [113], and the response to treatment does not appear different in postmenopausal patients with baseline 25 (OH)D insufficiency (serum 25(OH)D >10 but ≤75 nmol/ml) or sufficiency (>75 nmol/ml) [114].

At the end of the randomized placebo controlled trial having demonstrated the efficacy of 20 μg daily subcutaneous injections of teriparatide in postmenopausal osteoporosis [108], the patients were followed for an additional 18-month period without teriparatide, during which they were allowed to use any antiosteoporotic medication considered appropriate by their treating physician. While the proportion of patients having received an inhibitor of bone resorption was slightly higher in patients previously in the placebo group than in the patients having been treated with 20 μg/day teriparatide, the reduction of vertebral fractures observed in this particular group during the initial trial was confirmed during this 18-month follow-up observation period (RR, 0.59; 95% CI, 0.42–0.85) [115]. Since the efficacy and safety of teriparatide in postmenopausal osteoporosis has been studied for a mean duration of only 21 months of active treatment, this compound has been released for clinical use for treatments of limited duration, set at 18 and 24 months according to the European and US regulatory agencies, respectively. Moreover, treatment duration tend to be also limited by the relatively high cost of treatment. However, interruption of treatment is followed by a rapid decrease of BMD, which can be prevented by subsequent treatment with a biphosphonate [115]. Furthermore, from theoretical considerations, it had been proposed that concomitant treatment of teriparatide with an antiresorptive agent might possibly allow for improved therapeutic efficacy, compared to teriparatide alone, considering the different mechanisms of action. For these reasons, there has been considerable interest for combination therapies combining teriparatide with an antiresorptive agent administered either concomitantly or consecutively. Available data on biochemical markers of bone turnover and BMD indicate that concomitant treatment of teriparatide with a strong antiresorptive drug, such as alendronate, does not result in a synergestic effect with the biphosphonate rather mitigating the effect of teriparatide [116]. In a trial of only 6 months duration,

combination of teriparatide with the weaker antiresorptive drug RAL did result in greater gain of BMD at the hip [117]. Taken the rapid bone loss after cessation of treatment, subsequent treatment with an antiresorptive agent seems advisable to preserve the gains achieved during teriparatide treatment. On the other hand, patients who are candidate for treatment with teriparatide have not uncommonly previously been treated with an antiresorptive agent. In fact, in Belgium, as well as in some other countries, failure of treatment with an antiresorptive drug is a condition for reimbursement of treatment with teriparatide. The available data suggest that prior treatment with antiresorptive drugs does not compromise the ultimate treatment effects of teriparatide, although the treatment effects may be initially blunted in women previously treated with some antiresorptive agents [107, 118].

Anabolic effects in postmenopausal osteoporosis with stimulation of bone turnover and increases of BMD have also been documented for PTH (1–84) [119, 120]. However, documentation of antifracture efficacy is limited to vertebral fractures and with some methodological reservations, whereas the rate of adverse events was rather high [120]. The efficacy and safety of 18 months daily s.c. injections of 100 μg human recombinant (1–84) PTH was assessed in an RCT in postmenopausal osteoporosis [120]. Women with low BMD (mean lumbar spine T-score around −3) without or with (only 18.6%) prevalent vertebral fracture were randomized to receive PTH (n=1,286) or placebo (n=1,246) with daily supplemental calcium (700 mg) and vitamin D (400 IU) in both groups. Overall dropout was high (n=831) with only 70% and 64% completing the study in the placebo and PTH group, respectively. Moreover, at discontinuation or completion of the study, only 66% in the PTH group as compared to 91% in the placebo group had received daily injection with or without supplemental calcium. The RR of new or worsened vertebral fracture in women treated with PTH was 0.42 (95% CI, 0.24–0.72; p<0.001); this is assuming no fracture in the women who did not complete the study. In sensitivity analyses, the RR was 0.60 (95% CI, 0.36–1.0; p=0.05) if the patients who prematurely discontinued had a fracture rate similar to that in all patients completing the trial and was 0.62 (95% CI, 0.37–1.04; p=0.07) if they had a fracture rate similar to that in placebo recipients who completed the trial. In this study, PTH (1–84) treatment resulted in a rather substantial increase if the incidence of hypercalcemia is 23% (95% CI, 21–26%) and hypercalciuria is 24% (95% CI, 20–27%).

Strontium ranelate

Strontium ranelate is a new treatment of postmenopausal osteoporosis that reduces the risk of vertebral and hip fractures. It is the first antiosteoporotic agent that appears to simultaneously increase bone formation and decrease bone resorption, thus uncoupling the bone remodeling process [121]. Specifically, the dual mode of action of strontium ranelate is due to direct effects on both osteoblasts and osteoclasts, as reflected by the changes in bone markers in clinical trials [122]. Several studies in various models have demonstrated that strontium ranelate increases osteoblast replication, differentiation, and activity [123], while in parallel, it downregulates osteoclast differentiation and activity [124–126]. A recent study has shown that strontium ranelate increases the expression of the bone-specific alkaline phosphatase (bALP; osteoblast differentiation) and the number of the bone nodules (osteoblast activity) of murine osteoblasts. In parallel, strontium ranelate decreases the tartrate resistant acid phosphatase activity (osteoclast differentiation) and the capability of murine osteoclasts to resorb (osteoclast activity), probably by acting on the cytoskeleton of these cells [127]. In addition to these direct effects on osteoblasts and osteoclasts, strontium ranelate also modulates the level of osteoprotegerin (OPG) and RANKL, two molecules strongly involved in the regulation of osteoclastogenesis by osteoblasts. Other studies have demonstrated the involvement of the calcium-sensing receptor in the effects of strontium ranelate on osteoblasts, osteoclasts, and OPG/RANKL regulation [126]. Finally, strontium ranelate administration decreased bone resorption and maintained bone formation in adult ovariectomized rats, which resulted in prevention of bone loss, an increase in bone strength, and a positive effect on intrinsic bone properties [128]. It should be kept in mind, however, that strontium ranelate reduces resorption and stimulates formation to a lesser extent than bisphosphonates and teriparatide, respectively [127].

Strontium ranelate has been investigated in a large phase 3 program, initiated in 1996, which includes two extensive clinical trials for the treatment of established osteoporosis [122, 129, 130]. The Spinal Osteoporosis Therapeutic Intervention (SOTI) study was aimed at assessing the effect of strontium ranelate on the risk of vertebral fractures [122]. The Treatment of Peripheral Osteoporosis (TROPOS) trial aimed to evaluate the effect of strontium ranelate on peripheral (nonspinal) fractures [129]. Both studies were multinational, randomized, double-blind, and placebo-controlled, with two parallel groups (strontium ranelate 2 g/day, taken orally 2 h apart from the meals vs. placebo) [122, 129]. The study duration was 5 years, with main statistical analysis planned after 3 years of follow-up. One thousand six hundred forty-nine patients were included in SOTI (mean age 70 years), and 5,091 patients were included in TROPOS (mean age 77 years) [130].

The primary analysis of SOTI [122] (ITT, n=1,442), evaluating the effect of strontium ranelate 2 g/day on vertebral fracture rates, revealed a 41% reduction in RR of

experiencing a new vertebral fracture (semiquantitative assessment) with strontium ranelate throughout the 3-year study compared with placebo (139 patients with vertebral fracture vs. 222, respectively (RR, 0.59; 95% CI, 0.48–0.73; $p<0.001$). The RR of experiencing a new vertebral fracture was significantly reduced in the strontium ranelate group as compared with the placebo group for the first year. Over the first 12 months, RR reduction was 49% (RR, 0.51; 95% CI, 0.36–0.74; Cox model $p<0.001$).

The primary analysis of TROPOS (ITT, $n=4,932$), evaluating the effect of strontium ranelate 2 g/day on nonvertebral fracture, showed a 16% RR reduction in all nonvertebral fractures over a 3-year follow-up period (RR, 0.84; 95% CI, 0.702–0.995; $p=0.04$) [129]. Strontium ranelate treatment was associated with a 19% reduction in risk of major nonvertebral osteoporotic fractures (RR, 0.81; 95% CI, 0.66–0.98; $p=0.031$). In the high-risk fracture subgroup ($n=1,977$; women; mean age≥74 years; femoral-neck BMD T-score of less than or equal to −2.4 according to National Health and Nutrition Examination Survey normative value), treatment was associated, in a post hoc analysis requested by the European regulatory authorities, with a 36% reduction in risk of hip fracture (RR, 0.64; 95% CI, 0.412–0.997; $p=0.046$).

Of the 5,091 patients, 2,714 (53%) completed the study up to 5 years [130]. The risk of nonvertebral fracture was reduced by 15% in the strontium ranelate group compared with the placebo group (RR, 0.85; 95% CI, 0.73–0.99). The risk of hip fracture was decreased by 43% (RR, 0.57; 95% CI, 0.33–0.97), and the risk of vertebral fracture was decreased by 24% (RR, 0.76; 95% CI, 0.65–0.88) in the strontium ranelate group. After 5 years, the safety profile of strontium ranelate remained unchanged compared with the 3-year findings [131].

In addition, the very long-term efficacy of strontium ranelate has been investigated in an extension of the SOTI and TROPOS studies, in which a total of 879 patients were entered into a 3-year open-label extension to examine the impact of administration over 8 years [132]. The cumulative incidence of vertebral fractures over the extension was 13.7%, compared with 11.5% in the combined original trials, while the cumulative incidence of nonvertebral fractures over the TROPOS extension was 12.0%, compared with 9.6% in the first 3 years of the study [132]. Despite an increased fracture risk with aging, there was no significant difference in vertebral and nonvertebral fracture risk between the original trial periods and the open-label extensions suggesting the maintenance of antifracture efficacy of this agent [132]. There were no additional safety concerns [132].

In order to assess the efficacy of strontium ranelate according to the main determinants of vertebral fracture risk (age, baseline BMD, prevalent fractures, family history of osteoporosis, baseline body mass index, and addiction to smoking), data from SOTI and TROPOS ($n=5,082$) were pooled (strontium ranelate 2 g/day group ($n=2,536$); placebo group ($n=2,546$); average age 74 years; 3-year follow-up) [133]. This study showed that a 3-year treatment with strontium ranelate leads to antivertebral fracture efficacy in postmenopausal women independently of baseline osteoporotic risk factors [133].

To determine whether strontium ranelate also reduces fractures in elderly patients, an analysis based on pre-planned pooling of data from the SOTI and TROPOS trials included 1,488 women between 80 and 100 years of age followed for 3 years [134]. In the ITT analysis, the risk of vertebral, nonvertebral, and clinical (symptomatic vertebral and nonvertebral) fractures was reduced within 1 year by 59% ($p=0.002$), 41% ($p=0.027$), and 37% ($p=0.012$), respectively. At the end of 3 years, vertebral, nonvertebral, and clinical fracture risks were reduced by 32% ($p=0.013$), 31% ($p=0.011$), and 22% ($p=0.040$), respectively. The medication was well tolerated, and the safety profile was similar to that in younger patients.

Strontium ranelate was studied in 1,431 postmenopausal women, from the SOTI and TROPOS studies, with osteopenia [135]. In women with lumbar spine osteopenia, strontium ranelate decreased the risk of vertebral fracture by 41% (RR, 0.59; 95% CI, 0.43–0.82; $p=0.002$), by 59% in women with no prevalent fractures (RR, 0.41; 95% CI, 0.17–0.99; $p=0.039$), and by 38% in women with prevalent fractures (RR, 0.62; 95% CI, 0.44–0.88; $p=0.008$). In women with osteopenia both at the lumbar spine and the femoral neck, strontium ranelate reduced the risk of fracture by 52% (RR, 0.48; 95% CI, 0.24–0.96; $p=0.034$).

After 3 years of strontium ranelate 2 g/day, each percentage point increase, without correction for SR adsorption to hydroxyapatite crystals, in femoral neck, and total proximal femur BMD was associated with a 3% (95% adjusted CI, 1–5%) and 2% (1–4%) reduction in risk of new vertebral fracture, respectively. The 3-year changes in femoral neck and total proximal femur BMD explained 76% and 74% of the reduction in vertebral fractures observed during the treatment, respectively [135, 136].

In the SOTI and TROPOS trials, the incidence of adverse events, serious adverse events, and withdrawals due to adverse events was similar in the strontium ranelate and placebo groups [137, 138]. During the first 3 months of treatment, nausea, diarrhea, headache, dermatitis, and eczema were more frequently associated with strontium ranelate compared to placebo, but, thereafter, there was no difference in incidence between strontium ranelate and placebo groups concerning nausea and diarrhea.

In pooled data from the SOTI and TROPOS trials, there was an apparent increased risk of venous thromboembolism in the strontium ranelate group (0.6% vs. 0.9% per year), although the annual incidence was similar in the strontium ranelate and placebo groups in the individual trials [122,

129]. A recently published study used the UK General Practice Research Database to assess the risk of several recently reported adverse events linked to the use of strontium ranelate for osteoporosis in postmenopausal women [139]. Age-adjusted rate ratios for venous thromboembolism, gastrointestinal disturbance, minor skin complaint, and memory loss were 1.1 (95% CI, 0.2–5.0), 3.0 (95% CI, 2.3–3.8), 2.0 (95% CI, 1.3–3.1), and 1.8 (95% CI, 0.2–14.1), respectively. No cases of ONJ, Stevens–Johnson syndrome, or drug rash with eosinophilia and systemic symptoms were found.

Recently, the postmarketing experience of patients treated with strontium ranelate reported cases of the drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome (<20 for 570,000 patient-years of exposure) [138]. This incidence is in the vicinity of what has been previously reported as severe skin reactions, with most of the other currently marketed antiosteoporosis medications. A causative link has not been firmly established, as strontium is a trace element naturally present in the human body, and ranelic acid is poorly absorbed. Due to the possible fatality linked to this syndrome, however, it seems reasonable to discontinue immediately strontium ranelate and other concomitant treatment known to induce such a syndrome in case of suspicious major skin disorders occurring within 2 months of treatment initiation [140] and to introduce adapted treatment and follow-up to avoid systemic symptoms. Anecdotic cases of alopecia were also reported, but no causative link was formally established [141]. Strontium ranelate is not indicated in patients with severe kidney failure (i.e., with creatinine clearance below 30 ml/min).

New therapeutic perspectives

Blockade of the RANK—RANK ligand (RANKL) pathway

The discovery of the OPG—RANK ligand (RANKL)—RANK system has allowed unraveling the mechanisms whereby osteoblastic cells regulate bone resorption. The most critical molecules for the differentiation, activation, and survival of osteoclasts are indeed the receptor activator of nuclear factor NF-κB (RANK), its ligand RANKL, a member of the tumor necrosis factor (TNF) superfamily, and OPG that acts as a decoy receptor for RANKL. RANKL and OPG are principally produced by osteoblasts and marrow stromal cells [142, 143]. OPG competitively inhibits the binding of RANKL to RANK on osteoclasts and their precursors. This results in inhibition of the fusion of osteoclast precursor cells, blockade of the activation of mature osteoclasts, and induction of osteoclast apoptosis. OPG is a powerful inhibitor of bone resorption that could have been used clinically [144, 145]. However, because OPG also binds to the cytotoxic ligand TRAIL and other members of the TNF family, a specific fully human antibody against RANKL has been developed (Amgen). This antibody, named denosumab, has been shown to specifically bind to RANKL with a very high affinity, preventing its interaction with the receptor RANK. Moreover, animal studies showed that this antibody had pharmacokinetic and pharmacodynamic advantages as compared to an OPG construct. Denosumab has a very long circulating half-life (1–1.5 months), and administration of a single dose by the subcutaneous route induces a rapid (12 h), marked (decrease in uNTX >80%) and prolonged (>6 months) inhibition of bone resorption in postmenopausal women [146]. The interest for using denosumab to counteract postmenopausal bone loss was enhanced by the knowledge that disequilibrium of the balance between RANKL and OPG plays a major role in the pathogenesis of osteoporosis. RANKL expression is increased after menopause, whereas estrogens stimulate OPG production [147]. RANKL expression is indeed significantly higher in bone marrow cells isolated from early untreated postmenopausal women than in cells obtained from pre- or postmenopausal women treated with estrogens [148].

A phase 2 study has been conducted in 412 postmenopausal women with low bone mass. Various therapeutic schedules of denosumab were tested against placebo and against alendronate as a positive control. After 1 and 2 years, BMD changes with denosumab 30 mg every 3 months and >60 mg every 6 months were similar to, or in some cases greater than, the changes obtained with alendronate. Denosumab tended to produce greater bone density increments than alendronate at skeletal sites enriched for cortical bone. The drug was well tolerated. The only concern was the occurrence of six cases (in 314 patients) of infections associated with hospitalizations [149, 150]. This concern was not confirmed in a phase III study where there were no significant differences between denosumab and placebo in prespecified adverse events, including infections [151]. The antifracture efficacy of denosumab has been evaluated in a placebo-controlled phase 3 trial including 7,868 postmenopausal osteoporotic women who received 60 mg denosumab every 6 months or matching placebo for a total of 3 years (the FREEDOM trial). Both groups of patients also received 1 g of calcium and 400–800 IU of vitamin D; 83% of the population completed the study. The primary endpoint was the occurrence of new vertebral fractures. There was a 68% (95% CI, 59–74%) reduction in the incidence of new vertebral fractures (7.2% in the placebo group vs. 2.3% in the denosumab group). The incidence of clinical vertebral fractures was similarly reduced by 69% (95% CI, 53–80%). The incidence of nonvertebral fractures was reduced by

20% (95% CI, 5–33%) and one of hip fractures (total number 69) by 40% (95% CI, 3–63%). As determined in a substudy including 441 patients, lumbar spine BMD increased by 9.2% at 3 years and total hip BMD by 6% compared to placebo, whereas serum CTX decreased by 72% compared to placebo [151].

The effects of denosumab and alendronate on BMD and biochemical markers of bone turnover have been compared in a randomized, blinded, phase 3 trial. One thousand one hundred eighty-nine postmenopausal women with a T-score <−2.0 at the lumbar spine or total hip were randomized 1:1 between s.c. denosumab 60 mg every 6 months plus oral placebo weekly or oral alendronate 70 mg weekly plus s.c. placebo injections every 6 months for 1 year. There were larger gains in BMD at all measured skeletal sites (lumbar spine, total hip, femoral neck, trochanter, and one third radius) in denosumab-treated patients than in alendronate-treated patients. Thus, the least squares mean (95% CI) treatment difference between the denosumab and alendronate groups were 1.1% (0.7–1.4%) at the lumbar spine, 1.0% (0.7–1.2%) at the total hip, and 0.6% (0.3–1.0%) at the femoral neck. Denosumab treatment also led to a significantly greater reduction in bone turnover markers compared with alendronate therapy. The overall safety profile was similar for both treatments [152].

Other molecules in development

New SERMs are in different development phases, notably lasofoxifene and arzoxifene. The Postmenopausal Evaluation and Risk-reduction with Lasofoxifene placebo-controlled trial enrolled 8,566 osteoporotic women treated during 3 years. Compared with placebo, the 0.5-mg daily dose significantly reduced the risk of new vertebral fractures (RR, 0.58; 95% CI, 0.45–0.73) and of non-vertebral fractures as well (RR, 0.78; 95% CI, 0.64–0.96). Lasofoxifene reduced the risk of estrogen receptor positive breast cancer (RR, 0.24; 95% CI, 0.09–0.65). There was an increased risk of venous thromboembolism (RR, 2.40, 95% CI, 1.21–4.74) but neither of endometrial cancer nor stroke [153]. The full publication is awaited. Despite favorable initial data [154], the development of arzoxifene, another new SERM, has been stopped. Bazedoxifene is another new SERM with beneficial effects on bone without undesirable effects on the endometrium and breast. The phase III study was a double-blind, randomized, placebo- and RAL-controlled randomized 3-year multinational study that included 6,847 osteoporotic women aged 55 years or more (intent-to-treat population). Patients were treated with bazedoxifene 20 or 40 mg/day, RAL 60 mg/day, or placebo. Relative to placebo, bazedoxifene 20 and 40 mg and RAL 60 mg reduced the risk of new vertebral fractures (primary endpoint) by 42% (RR, 0.58; 95% CI, 0.38–0.89), 37% (RR, 0.63; 95% CI, 0.42–0.96), and 42% (RR, 0.58; 95% CI, 0.38–0.89), respectively. The treatment effect was similar among subjects with or without prevalent vertebral fracture. Overall, there were no significant differences in the incidence of nonvertebral fractures among treatment groups. In post hoc analyses, bazedoxifene reduced the risk of nonvertebral fractures in subjects at higher fracture risk [155].

Other potentially useful inhibitors of bone resorption include cathepsin K inhibitors, src kinase inhibitors, integrin inhibitors, chloride channel inhibitors, and PTHrP antibodies. Cathepsin K inhibitors are the only ones of these candidate drugs currently in phase 3 development. Cathepsin K is a lysosomal protease that is highly expressed in osteoclasts and plays a pivotal role in the degradation of bone collagen. Cathepsin K inhibitors have been shown in preclinical studies to reverse ovariectomy-induced bone loss and to restore bone strength [156]. As with src inhibitors, cathepsin K inhibitors appear to decrease bone resorption without substantially decreasing bone formation, which could lead to greater increases in bone density than are observed in response to presently available antiresorptive agents. Odanacatib is a highly selective, nonlysosomotropic cathepsin K inhibitor, structurally distinct from other inhibitors that occasionally induced “morphea-like” skin changes. Various doses of odanacatib, given orally once weekly, were tested against placebo in a 2-year study in 399 previously untreated postmenopausal women with low BMD (T-score <−2). Odanacatib treatment resulted in dose-related increases in BMD vs. baseline at trabecular and cortical bone sites. Lumbar spine and total hip BMD increased by 5.5% and 3.2%, respectively [157]. The safety profile of 50 mg given weekly appears to be similar to placebo, and the antifracture efficacy of odanacatib 50 mg once weekly is currently being tested in a phase 3 trial. New agents to stimulate bone formation are also in development, among which, a human antibody against sclerostin will soon enter phase 3 clinical trials. Pharmacodynamic studies have shown that this antibody can increase BMD and bone formation markers [158].

Conclusions

During the last decade, several new therapeutic options have emerged, characterized by the unequivocal demonstration of their antifracture efficacy and an improved safety profile, leading to a positive risk/benefit balance. Whereas most of them have proven to significantly reduce the occurrence of vertebral fractures (Table 1), some discrepancies remain regarding the level of evidence related to their nonvertebral or hip antifracture effect (Table 2). Based on a systematic review and a critical appraisal of the current literature, the

Table 1 Effect on vertebral fracture rates (from randomized controlled trials)

	Osteopenia	Osteoporosis (without prevalent vertebral fractures)	Established osteoporosis (with prevalent vertebral fractures)
Raloxifene	●	■	■
Alendronate	NA	■	■
Risedronate	NA	●	■
Ibandronate	NA	■	■
Zoledronate	NA	■	■
Teriparatide	NA	NA	■
Strontium ranelate	●	■	■
Denosumab	NA	■	■

NA No evidence available

■ Denotes a preplanned analysis in the entire study population

● Denotes a post hoc analysis

following recommendations are made for the management of postmenopausal osteoporosis in Belgium.

- Calcium and vitamin D supplementation should be a first-line strategy for the management of osteoporosis. Based on the very low mean dietary intake of calcium in the Belgian population, a systematic pharmacological supplementation (1,000–1,200 mg of calcium ion daily) in postmenopausal women appears to be an appropriate strategy (unless an individual dietary assessment reveals a satisfactory intake). The high prevalence of vitamin D deficiency in elderly Belgian subjects, combined with the low marginal cost of a calcium–vitamin D supplementation compared with calcium alone, suggest that, after the age of 65, calcium and (800–1,000 IU) vitamin D should be systematically offered to all postmenopausal women, either alone or, if needed, in combination with another therapeutic regimen.
- HRT can no longer be considered as a first-line treatment for osteoporosis. It should only be considered in women experiencing climacteric symptoms, for the shortest possible duration and with the lowest effective doses.
- Selective-estrogen receptor modulators are a first-line option for women with low BMD, with or without fractures. Their effect on vertebral fracture is unequivocal, across different degrees of skeletal fragility, ranging from osteopenia to severe osteoporosis. Evidence of antifracture efficacy against nonvertebral fractures is limited to a post hoc analysis performed in a high-risk subset of the population. Breast benefits have been documented and should be taken into account when assessing the overall risk/benefit ratio of SERMs.
- Bisphosphonates reduce vertebral, nonvertebral, and hip fractures in women with established osteoporosis (low BMD and prevalent fractures). Due to their beneficial effect on hip fractures, bisphosphonates are first-line agents in the treatment of elderly subjects. There is currently no compelling evidence for significant differences in the magnitude of the treatment effects between alendronate, risedronate, ibandronate, and zoledronate more especially as the dosage regimens usually pre-

Table 2 Effect on nonvertebral/hip fracture rates (from randomized controlled trials)

	Nonvertebral		Hip	
	Osteoporosis (without prevalent vertebral fractures)	Established osteoporosis (with prevalent vertebral fractures)	Osteoporosis (without prevalent vertebral fractures)	Established osteoporosis (with prevalent vertebral fractures)
Raloxifene	NA	●	NA	NA
Alendronate	■	■	NA	■
Risedronate	NA	■	NA	■
Ibandronate	NA	●	NA	NA
Zoledronate	■	NA	■	NA
Teriparatide	NA	■	NA	NA
Strontium Ranelate	●	■	●	▲
Denosumab	■	NA	■	NA

NA no evidence available

■ Denotes a preplanned analysis in the entire study population

▲ Denotes a preplanned analysis on a subset of the study population

● Denotes a post hoc analysis

scribed for weekly and monthly oral bisphosphonates have been indirectly adapted from bridging studies based on BMD end points. From an evidence-based perspective, the duration of bisphosphonate treatment should not exceed the duration of randomized controlled clinical trials having unequivocally demonstrated a fracture reduction compared with a placebo. Concerns have been raised that prolonged use of certain bisphosphonates may be harmful for bone strength by oversuppressing bone resorption, hence preventing removal of spontaneously occurring microcracks and inducing excessive mineralization. However, these concerns come only from studies performed in animals, and their relevance to human subjects remains to be clarified.

- Teriparatide decreases vertebral and nonvertebral fractures in subjects with both low bone density and prevalent vertebral fractures. In order to optimize the cost-benefit ratio of this drug, its use should be confined to this high-risk population.
- Strontium ranelate reduces vertebral fractures in women with osteopenia, osteoporosis, and severe osteoporosis. Reduction of nonvertebral and hip fracture has been shown, over 5 years, in elderly subjects with low femoral density, making this drug a first-line therapy in this population.
- Except for strontium ranelate, there is no linear relationship between increases in BMD or reductions in bone turnover and fracture risk reductions. Different osteoporosis agents should not be compared on the basis of their respective impact on surrogate endpoints like BMD or bone turnover. The regular assessment (yearly) of BMD is an appropriate option to follow patients treated with bisphosphonates or strontium ranelate. For RAL-treated patients, biochemical markers of bone turnover, brought back to normal values for premenopausal women, may be a better indication of efficacy. The optimal monitoring tools for teriparatide remain to be defined.
- Combination use of antiresorptive agents cannot be recommended, because of the associated cost without documented additional antifracture benefits, the increased potential for side effects, and the risk of inducing oversuppression of bone turnover. However, if low doses of estrogen, used for the management of climacteric symptoms, are insufficient to normalize bone turnover, the addition of a bisphosphonate to HRT may be considered.
- Current data discourage the concomitant use of alendronate and PTH since the bisphosphonate appears to blunt the anabolic action of PTH.
- Risk factor alterations, including fall prevention strategies, are recommended.
- Denosumab significantly reduces spinal, nonvertebral, and hip fractures in women with postmenopausal osteoporotic women. It could be a first-line treatment, in this particular indication, providing no safety concerns emerge after longer follow-up and more extensive use.

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