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CONSENSUS STATEMENT

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

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Introduction

Osteoporosis is widely recognized as a major public health concern. The cumulative lifetime fracture risk for a 50-year 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 extend 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 International Osteoporosis Foundation (IOF), nation-specific guidelines are requested 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 [4], with the aim of providing clinicians with an unbiased assessment of osteoporosis treatment effect.

Methods

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. 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 2004, 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

Calcium deficiency related to inadequate intake of calcium leads to increased serum parathyroid hormone 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 [5]. Although calcium deficiency can be corrected by adjusting the dietary intake of calcium [6], most individuals—and particularly older women at risk of osteoporosis—are unable or unwilling to change their lifestyle practices and will require calcium supplementation.

The efficacy of combined calcium and vitamin D supplementation in reducing non-vertebral fracture rates has been demonstrated in three large, randomized, placebo-controlled, multicenter studies. Two of these studies involved institutionalized elderly patients, the Decalyos I [7, 8] and Decalyos II [9] studies, and one involved community-living elderly patients [10].

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 [7]. All had inadequate dietary calcium intake (< 800 mg/day, mean 513 mg/day) at study entry, while 44% had vitamin D insufficiency—serum 25-hydroxyvitamin D [serum 25(OH)D] level < 12 ng/ml, by radioimmunoassay (RIA). Randomization was 1:1 to 1,200 mg of calcium 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 non-vertebral fracture incidence by 32% (*RR* 0.68; 95% CI not indicated; $p = 0.015$) [7]. 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 non-vertebral 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 [7]. 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 non-vertebral 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 $p < 0.02$) [8].

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 [9]. 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] < 12 ng/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 non-vertebral 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 and colleagues [10] involved healthy, elderly, ambulatory men and women aged ≥ 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 plus vitamin D 700 IU or placebo, with follow-up and treatment planned for 3 years. Non-vertebral 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 [11, 12, 13]. 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; $p = 0.02$) [12]. 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; $p = 0.03$) [13], 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; $p = 0.31$) [11].

In conclusion, calcium and vitamin D should be a first-line medication for the prevention and treatment of osteoporosis, although most patients will derive further benefit in terms of fracture prevention from the addition of an antiresorptive or anabolic agent. To date, there have been no head-to-head studies of calcium and vitamin D vs vitamin D alone to enable the incremental benefit provided by combined supplementation over vitamin D alone to be determined.

Hormone replacement therapy

Estrogen deficiency is considered a major risk factor for osteoporosis. It is also the most frequent risk factor from an epidemiological point of view. For years, the consensus has been to recommend hormone replacement therapy (HRT) as a first-line therapy to prevent bone loss in estrogen-deprived women [14], since randomized trials provide strong evidence that bone loss can be effectively prevented even with rather small doses of HRT [15]. Furthermore, studies evaluating other health endpoints, such as cardiovascular diseases, suggested, in the past, that HRT may have important beneficial effects. Recent publications, however, have challenged the efficacy of HRT in reducing cardiovascular diseases and, moreover, have reported increased risk of breast cancer, thromboembolic disease, and cerebrovascular accidents [16, 17]. This has changed the recommendations of many scientific or regulatory authorities with regards to HRT use [18]. Consequently, many patients have stopped the use of HRT and, instead, moved towards alternative therapies such as phytoestrogens to treat their climacteric symptoms. This paper is focused solely on the antifracture effect of HRT and phytoestrogens.

Since no large-scale prospective trials were ever performed to assess the efficacy of HRT in postmenopausal osteoporotic women, the reviewed studies that included data on vertebral and non-vertebral fractures showed a large heterogeneity in population samples and selections. The earliest data that are available from randomized studies were not designed to assess the efficacy of HRT on fracture rate. The fracture data were often extrapolated from subgroup analyses of studies assessing other therapeutic interventions. Moreover, most of these studies evaluated only a small number of patients (often less than 100) taking HRT. Not surprisingly, their lack of power resulted in nonsignificant results. In this respect also, the results obtained by Lufkin et al. (*RR* for vertebral fractures 0.39; 95% CI, 0.16–0.95) [43] are rather surprising. More recently, two large prospective studies were designed to assess the effect of estrogen plus progestin on the risk of coronary heart disease events (Heart and Estrogen/progestin Replacement Study—-HERS) [17] and on the major health benefits and risks of the most commonly used combined HRT in the USA (Women's Health Initiative—WHI) [15]. None of these studies included women based on the presence of osteoporosis or osteoporosis risk factors. In the HERS trial, no differences were observed for the rates of hip fractures (*RR*, 1.10; 95% CI, 0.49–2.50) or any fractures (*RR*, 0.95; 95% CI, 0.75–1.21) [17]. However in the WHI trial, a significant reduction in the risk of hip (*RR*, 0.66; 95% CI, 0.45–0.98), vertebral (*RR*, 0.66; 95% CI, 0.44–0.98) and all fractures (*RR*, 0.76; 95% CI, 0.69–0.85) was observed [15]. It should be stated that this significant effect disappeared when the calculation of the 95% CI took into account the multiple statistical testing issue [15]. When considering the effects of HRT on all disease outcomes in a global model, the authors concluded that there was an absence of net benefit, even in women considered to be at high risk for fracture [19].

In conclusion, prolonged use of estrogen with or without progestin may reduce the risk of fracture in healthy postmenopausal women. These evidence-based data can be used when evaluating the necessity to prescribe HRT to postmenopausal women. However, these data have to be strongly weighted with respect to 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. 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. There are only limited randomized data 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 [20], we were unable to find randomized trials that evaluated the fracture efficacy of phytoestrogens [21–25].

Calcitonin

Calcitonin is an endogenous polypeptidic hormone that inhibits osteoclastic bone resorption [26]. Salmon calcitonin is approximately 40–50 times more potent than human calcitonin, and the majority of clinical trials have been performed with salmon calcitonin [27]. For clinical use it can be administrated either by injection or nasal application, which provides a biological activity of 25–

50% compared with the injectable formulation (200 IU nasal calcitonin would be equivalent to 50 IU injectable). A number of randomized trials have proven that subcutaneous or intranasal calcitonin is effective in the prevention of trabecular bone loss in postmenopausal females [28, 29, 30]. In addition, calcitonin may have an analgesic effect in women with acute vertebral fracture, which appears to be independent of its effect on osteoclastic resorption [27, 31].

Although the development of antibodies to calcitonin generates a potential problem, the biological or clinical significance of antibody development remains speculative [30]. Down-regulation of calcitonin receptors on osteoclasts by long-term exposure has also been reported to decrease calcitonin activity [32]. Intermittent treatment has been advocated to avoid clinical resistance; however, such a regimen has not been unequivocally validated. Therefore, clinical trials have been performed with a great variation of calcitonin doses and regimens. The weekly doses of calcitonin ranged from 80 IU to 2,800 IU.

In a recent systematic review of the literature on calcitonin studies performed between 1966 and 2000 [33], 75 articles from the 770 initially retrieved manuscripts were retained for closer examination of the study entry criteria and subsequent meta-analysis. After this review 30 study reports were maintained fulfilling the following criteria: (1) randomized and controlled trial (comparing calcitonin vs placebo or calcium and/or vitamin D) of at least 1-year duration, (2) outcomes included bone mineral density (BMD) at the specified sites and /or fracture incidence, (3) postmenopausal females.

Most of these studies were of small frame (frequently less than 100 patients) and therefore only reported on BMD. These results will not be discussed here in detail, but can be briefly summarized as follows. In meta-analysis of the BMD effects [33], the data revealed an increase at the lumbar spine (24 studies) and the forearm (eight studies) but not at the femoral neck (nine studies). Compared with bisphosphonates and SERMs the BMD effect of calcitonin is small, mostly not exceeding a 1% increase, independently of treatment duration. However, the relation between bone density change and fracture reduction (see below) with calcitonin (compared with other agents) has not been established. The effect of calcitonin dose did not affect the overall results on BMD, except at the lumbar spine. Only at the lumbar spine did the nasal administration result in a lower BMD response compared with the parenteral injection.

Pooling the four trials ($n = 1{,}404$) reporting results for vertebral fracture [34, 35, 36, 37] using a random-effect model reveals an *RR* of 0.46 (95% CI, 0.25–0.87; $p = 0.02$). These results resulted mainly from three small trials that provide point estimates that suggest larger treatment effects (*RR*, 0.52, 0.23 and 0.27, respectively), two of which showed statistically significant reduction in vertebral fracture rates. The fourth study [34], PROOF (Prevent Recurrence of Osteoporotic Fracture) demonstrated a borderline significance with an *RR* of 0.79 (95% CI, 0.62–1.00; $n = 1{,}108$; $p = 0.05$) for the 200 IU/day group, while no effects were observed for 100 IU/day and 400 IU/day groups. The variability in the results between the three small and the fourth larger trial is illustrated in a significant test of heterogeneity ($p = 0.01$). Losses to follow-up in the four trials were 18.7%, 21%, 45% and 59.3%, respectively, with the greatest loss in the PROOF study. A larger loss of follow-up can bias the trial results against the active treatment, if those at greater risk of fracture were preferentially lost to follow-up in the control group. However, meta-analysis failed to find any systematic effect of loss to follow-up.

From three trials reporting data on non-vertebral fractures [34, 36, 38] a pooled estimate showed a non-significant *RR* of 0.52 (95% CI, 0.22–1.23; $n = 1{,}481$; heterogeneity $p = 0.087$, $p = 0.14$). It included two small trials, in which one showed a large statistically significant effect (*RR*, 0.25; 95% CI, 0.10–0.65), and the other provided a point estimate suggesting a large effect but not statistically significant (*RR*, 0.60; 95% CI, 0.08–4.31). The large trial PROOF [34] showed a much more modest treatment effect that did not reach statistical significance (*RR*, 0.80; 95% CI, 0.59–1.09; $n = 1245$; $p = 0.16$). Although the small number of trials available for fracture incidence prevents a strong inference, the observation for non-vertebral—as for vertebral—fractures that the single large trial yields a much smaller effect than the smaller trial raises the concern of publication bias, as is also suggested by the funnel plot for the lumbar spine BMD effects [33]. These highest evidence levels of overall negative data for non-vertebral fracture contrast with those of a low evidence level from an observational study [39] suggesting a 30% reduction in hip fractures in patients treated with injectable calcitonin.

In general, trials, because of their small size, were poor in their reporting of adverse events. It was difficult to confidently estimate pooled RRs for adverse effects, due to the inadequate reporting in the trials. Loss of follow-up was similar in treatment groups compared with controls. The *RR* for headache was 0.57 (95% CI, 0.34–0.93; $p = 0.02$) in the PROOF trial; the pooled *RR* for rhinitis from four trials was 1.72 (95% CI, 0.92–3.23; $p = 0.09$), and the pooled *RR* for climacteric symptoms for one trial was 0.20 (95% CI, 0.05–0.77; $p = 0.02$).

In conclusion, calcitonin likely increases bone mineral density at the lumbar spine and forearm, but the true effect may be smaller than the pooled estimates would suggest. Calcitonin likely reduces the risk of vertebral fracture; however, the magnitude of the impact on these fractures remains questionable. Its effect on non-vertebral fractures remains equivocal.

Selective estrogen-receptor modulators (SERMs)

SERMs are non-hormonal compounds that have the property of binding to estrogen receptors in various tissues. They behave like estrogen agonists towards some

target tissues (e.g., bone, liver), but they exert an estrogen-antagonistic action on the breast and/or, according to the drug, an agonistic action, or not, on other female sexual organs, such as the uterus [40].

SERMs of the first generation, such as tamoxifen, have been used widely in the secondary prevention of breast cancer [41]. This compound was shown incidentally to be protective against bone loss [42]. However, its estrogen-agonistic action on the uterus precluded its long-term use in osteoporosis prevention. A second-generation SERM, raloxifene, a benzothiophene, possesses a more selective activity, and has therefore been studied in large trials in prevention and treatment of osteoporosis.

Raloxifene at a dose of 60 mg/day or 120 mg/day vs placebo (calcium 700 mg and vitamin D 400 IU) was first administered to postmenopausal women with at least one prevalent vertebral fracture in a study of 1-year duration [43]. Biochemical markers of bone remodeling, such as bone-specific alkaline phosphatases (−30% to −36%), osteocalcin (−28% to −31%) and urinary CTx (−31% to −39%) decreased significantly as compared with baseline values. A significant increase in the total hip BMD and the 1/3 distal radius BMD was observed as compared with baseline. A non-significant trend towards increase over controls was observed in lumbar BMD, total body and total hip BMD [43].

In the MORE study (Multiple Outcomes of Raloxifene Evaluation), 7,705 postmenopausal women (at least 2 years postmenopausal) received 60 mg or 120 mg raloxifene/day or placebo. All women were on calcium (500 mg/day) and vitamin D (400 IU/day) supplementation [44]. The main endpoint of MORE was the reduction of the percentage of women developing a new vertebral fracture when on raloxifene. Secondary endpoints were: assessing the relative risk of non-vertebral facture, of breast cancer and of cardiovascular events. After the 3-year study period, by studying the spine radiographs obtained in 6,828 women, 503 (7.4%) had at least one incident of vertebral fracture (10.1% of women in the placebo group, 6.6 % of women in the 60 mg raloxifene group and 5.4% in those on 120 mg raloxifene). The relative risk of incident of vertebral fracture was significantly decreased in both groups on raloxifene [*RR*, 0.7 (95% CI, 0.5–0.8) and *RR*, 0.5 (95% CI, 0.4–0.7) in the 60 mg and 120 mg raloxifene groups, respectively]. Raloxifene at a dose of 60 mg/day reduced the risk of incident clinical vertebral fracture during the first year of therapy by 68% (*RR*, 0.32; 95% CI, 0.13–0.80) in the overall study population, and by 66% (*RR*, 0.34; 95% CI, 0.11–0.77) in the group of women with prevalent vertebral fractures. The corresponding decrease in fracture risk for the whole group was −46% (*RR*, 0.54; 95% CI, 0.34–0.86) after 2 years and −41% (*RR*, 0.59; 95% CI, 0.41–0.83) after 3 years [45]. The risk of non-vertebral fracture was not significantly different in the whole group of patients treated either by raloxifene 60 mg/day, 120 mg/day or by placebo (*RR*, 0.9; 95% CI, 0.8–1.1). It should be recalled, however, that the mean age of women in the MORE trial was 67 years, i.e., relatively young. From an epidemiologic point of view, the studied population in the MORE trial does not allow studying non-vertebral fractures, because their incidence at that mean age (including hip fractures) is not high enough to demonstrate a protecting effect by any medical intervention. However, in a post-hoc analysis, a subgroup of patients with a severe vertebral fracture (SQ3) before starting the study ($n = 614$) showed a significant risk of non-vertebral fracture within the 3 years of the study. In this group with severe osteoporosis, raloxifene 60 mg/day allowed a reduction of 26% of the relative risk of new vertebral fracture (*RR*, 0.74; 95% CI, 0.54–0.99) and of 47% of the non-vertebral fracture risk (clavicle, humerus, wrist, pelvis, hip and leg) (*RR*, 0.53; 95% CI, 0.29–0.99) [46]. Beyond their predictive value for future non-vertebral fracture, these vertebral fractures provoke a crippling loss of mobility, with severe back pain, leading to a dramatic decrease in the quality of life of the involved patients. During the 3 years of the MORE study, raloxifene led to a significant decrease (by 61%) in the incidence of one new moderate and severe vertebral fracture (*RR*, 0.39; 95% CI, 0.17–0.69) in women without any prevalent vertebral fracture, and by 37% (*RR*, 0.63; 95% CI, 0.49–0.83) in women with at least one prevalent vertebral fracture before initiation of therapy [47]. Raloxifene (60 mg/day) was also able to significantly decrease the risk of new vertebral fractures in women without prevalent vertebral fracture, but with a lumbar BMD lower than −2.5 *T*-scores, both in women with a femoral neck BMD between −1 and −2.5 *T* -scores to start with (so-called osteopenia) (*RR*, 0.53; 95% CI, 0.32–0.88) and in women with a lower femoral neck BMD (*T* -score < -2.5) (*RR*, 0.31; 95% CI, 0.06–0.71) [48]. Moreover, the extension of the MORE study to a fourth year confirmed the persistence of the anti-fracture efficacy of raloxifene 60 mg/day. During the fourth year, if the latter is considered separately, the risk of new vertebral fracture was reduced by 48% (*RR*, 0.52; 95% CI, 0.35–0.78) or by 35% (RR, 0.65; 95% CI, 0.52–0.81), according to the presence or non-presence of prevalent vertebral fracture before starting the study [49].

With antiresorbing agents such as raloxifene, it is difficult to monitor therapy with densitometry, because—in line with observations obtained with bisphosphonates [50]—there is no linear relationship between the changes in BMD observed after a few months of therapy with raloxifene in an individual patient, and the reduction of the fracture risk after 3–4 years of therapy. In the MORE study, only 4% of the anti-fracture effect after 3 years could be attributed to the changes in BMD observed after 1 year or 3 years [51]. On the contrary, the observed changes in biochemical marker of bone remodeling during the first 6 months or 12 months of therapy could explain nearly 33% of the anti-fracture efficacy of raloxifene [52].

Some extraskeletal effects have been observed with raloxifene. After 3 years of therapy, 13 cases of breast

cancer developed in the 5,129 women on raloxifene vs 27 in the 2,576 women on placebo (*RR*, 0.24; 95% CI, 0.13–0.44). Raloxifene reduced the risk of estrogen receptor-positive breast cancer by 90% (*RR*, 0.10; 95% CI, 0.04–0.24), but not estrogen receptor-negative invasive breast cancer (*RR*, 0.88; 95% CI, 0.26–3.0) [53]. In the MORE study, there was no significant difference in the incidence of combined coronary and cerebrovascular complications in the overall cohort ($n = 96$ (3.7%) in the placebo group; 82 (3.2%) in the 60 mg/day raloxifene group and 94 (3.7%) in the 120 mg/day raloxifene group). However, in 1,035 women with increased cardiovascular risk at baseline, a decrease of 40% of the risk of cardiovascular complications was observed on raloxifene (*RR*, 0.60; 95% CI, 0.38–0.95) [54]. Hot flashes were the most frequent side effect, leading to withdrawal from therapy in 0.1%, 0.7% and 0.5% of women on placebo, raloxifene 60 mg and raloxifene 120 mg, respectively. Leg cramps were more frequent on raloxifene (7% in the 60 mg group and 6.9% in the 120 mg group) vs 3.7% in the placebo group. After 3 years, raloxifene increased the risk of venous thromboembolic complications (*RR*, 3.1; 95% CI, 1.5–6.2) but did not increase the risk of endometrial cancer (*RR*, 0.8; 95% CI, 0.2–2.7) [44].

In conclusion, raloxifene at the dose of 60 mg/day, the dose unanimously recommended for therapy, is able to prospectively produce a significant decrease of the vertebral fracture risk in postmenopausal women suffering from osteoporosis (densitometric definition: −2.5 *T* -scores) as well as from established osteoporosis. There are some convergent, but retrospective, data tending to demonstrate that raloxifene could also prevent non-vertebral fracture in severe osteoporotic cases. Raloxifene might also confer some extraskeletal advantages, such as breast cancer and cardiovascular prevention. However, taking into account these extra-osseous potential advantages should wait until the results of dedicated, prospective controlled trials, which are still in progress.

Bisphosphonates

Etidronate, alendronate, risedronate and ibandronate are currently registered in Belgium for the treatment of osteoporosis. Oral bisphosphonates may be associated with gastrointestinal complaints, and strict adherence to constraining therapeutic schemes is mandatory. This is one of the reasons why alternative approaches are under active investigation. Repeated infusions of potent bisphosphonates at large time intervals could circumvent these constraints and greatly simplify the current treatment of osteoporosis.

Bisphosphonates are divided into two groups when considering their main mechanism of action, namely the nitrogen-containing bisphosphonates and the non-nitrogen-containing bisphosphonates, essentially etidronate and clodronate. Bisphosphonates localize preferentially to sites of active bone remodeling. They act directly on mature osteoclasts, decreasing their bone resorption activity, notably by lowering H^+ and Ca^{++} extrusion and modifying the activity of various enzymes [55]. Moreover, bisphosphonates can induce osteoclast apoptosis. Clodronate, but not the aminobisphosphonates, can be metabolized to an adenosine triphosphate (ATP) analog that is toxic for macrophages and for osteoclasts [56]. On the other hand, nitrogen-containing bisphosphonates, but not clodronate, interfere with the mevalonate pathway that is essential to maintaining cell-membrane integrity. Aminobisphosphonates are nanomolar inhibitors of farnesyl-pyrophosphate (PP) synthase. This leads to an inhibition of post-translational prenylation of proteins with farnesyl or geranyl-geranyl isoprenoid groups. Various cellular proteins have to be anchored to cell membrane by a prenyl (lipid) group to become active. Most of these proteins are guanosine 5'-triphosphate (GTP)-binding proteins, including the protein *Ras*, and prenylated proteins are essential for osteoclast function, notably cell activity and attachment [57]. The net result, regardless of the mechanism (clodronate vs aminobisphosphonates), is osteoclast apoptosis, notably through the induction of caspase-3 [58].

Etidronate is administered intermittently (400 mg daily for 2 weeks every 3 months) for 3–5 years. Several studies of similar design have examined the anti-fracture efficacy of cyclical etidronate in postmenopausal women with prevalent vertebral fractures [59]. Methodological problems in fracture assessment, the limited statistical power, the potential toxicity of the compound on bone mineralization, the necessity to perform post-hoc analyses to suggest that this form of treatment was effective in preventing new vertebral fractures in postmenopausal women with low bone mass and multiple prevalent vertebral fractures, all this led the Belgian Bone Club several years ago to conclude that etidronate was an outdated form of therapy [60]. A recent meta-analysis has also shown that etidronate does not have a significant anti-fracture efficacy in postmenopausal osteoporosis (95% CI, 0.45–1.5).

Oral alendronate has been extensively studied for the treatment of osteoporosis under randomized controlled trial conditions. In an initial 3-year study, when given in different doses to osteoporotic women, 20% of whom had prevalent vertebral deformities, alendronate significantly increased BMD and reduced the incidence of new vertebral deformities. At the end of 3 years, one or more new vertebral fractures had occurred in 6.2% of women in the placebo group and in 3.2% of women treated with alendronate. Alendronate reduced the vertebral fracture rate by 48% (*RR*, 0.52; 95% CI, 0.28–0.95) [61]. The anti-fracture efficacy of alendronate has been best established in two large populations of postmenopausal women, one with and one without preexisting vertebral fractures [62, 63]. The daily dose of alendronate was 5 mg for the first 2 years and 10 mg thereafter. In the study including 2,027 women with established osteopo-

rosis, i.e., 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). 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 non-vertebral 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) [62]. Estimation of the effect on hip fracture was not precise and the confidence interval correspondingly wide, reflecting that the number of fractures (33 in total) was small.

The anti-fracture 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 non-vertebral fractures (*RR*, 0.88; 95% CI, 0.74–1.04) [63].

The effect of alendronate on non-vertebral 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 non-vertebral 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) [64]. A more recent 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 non-vertebral fracture rate by 49% when given at 10 mg daily or more (*RR*, 0.51; 95% CI, 0.38–0.69) [65]. However, data from one of the largest trials with alendronate [63] were excluded from this meta-analysis [65].

The effect of alendronate on bone mass and turnover is gradually lost when treatment is stopped. BMD data for up to 10 years have recently been reported [66], but placebo-controlled fracture data beyond 3 years are not available. There is no evidence that prolonged therapy leads to a loss of benefit, but the optimal duration of treatment is unknown. Alendronate, an aminobisphosphonate, 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 [67]. 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 [68]. The anti-fracture efficacy of the weekly formulation is supposed to be similar to the daily formulation, but this has not been formally tested.

Risedronate efficacy has been extensively tested in double-blind placebo-controlled trials. Risedronate at the dose of 5 mg daily for 3 years has thus 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 non-vertebral fractures (*RR*, 0.61; 95% CI, 0.39–0.94) [69]. 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 non-vertebral fractures was not significant (*RR*, 0.67; 95% CI, 0.44–1.04) [70]. In both studies, the effect on vertebral fracture rate was significant already after 1 year. 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) [71]. The European study [70] was continued blindly in a subset of the population and the anti-fracture efficacy was maintained for at least 5 years [72], the longest available double-blind fracture data for an antiresorptive. More recently, 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 the first evidence that, even in patients 80 years of age or older, reducing bone resorption rate remains an effective osteoporosis treatment strategy [73].

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 mg/day or 5 mg/day for 3 years (the actual mean duration of treatment was 2 years) lowered the relative risk of hip fracture by 40% (*RR*, 0.6; 95% CI, 0.4–0.9). There was no dose effect and, interestingly, the effect was greater in the group of women who had a vertebral fracture at baseline (*RR*, 0.4; 95% CI, 0.2–0.8). In the same study, however, there was no significant effect of risedronate in 3,886 women ≥80 years old (*RR*, 0.8; 95% CI, 0.6–1.2), 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, a poor tandem gait, etc. rather than on the basis of low BMD or prevalent fractures [74]. The anti-fracture efficacy of risedronate has been confirmed in a recent meta-analysis [75]. The pooled relative risk 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 non-vertebral 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 (NSAID) 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 [76].

To date, alendronate and risedronate have not been studied in head-to-head comparative trials with fracture endpoints. Because of increasing 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, 78], 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. Meta-analyses cannot substitute for direct comparative fracture trials either. In the context of the treatment of osteoporosis with alendronate or risedronate, the confidence intervals around the magnitude of the treatment effects overlap, both for their effects on vertebral and non-vertebral fractures, even in recent meta-analyses [75]. Apparent differences in the point estimates should, therefore, not be interpreted as indicating true underlying differences in the magnitude of the effect. Available results from the published trials and from recent systematic reviews and meta-analyses provide convincing evidence for vertebral and non-vertebral fracture reduction for *both* agents, alendronate and risedronate, but *no* evidence for significant differences in the magnitude of the treatment effects.

Oral ibandronate at 2.5 mg daily and the intermittent administration of ibandronate delivering a similar cumulative exposure (20 mg every other day for 12 doses every 3 months) has been shown in a 3-year placebo-controlled trial in 2,946 osteoporotic women with prevalent vertebral fracture to significantly reduce vertebral fracture rate. The relative risk reductions 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. This difference was not statistically significant, and this trial is thus the first to show anti-fracture efficacy for the intermittent administration of a bisphosphonate. The overall population was at low risk for osteoporotic fractures. Consequently, the incidence of non-vertebral 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 not significant). A post-hoc analysis has suggested a 69% reduction in non-vertebral fractures in the daily group when considering high-risk patients with a femoral neck T-score < -3.0 [79], but the effect of ibandronate on non-vertebral fracture risk and, more specifically, hip fracture incidence remains to be clarified.

Anabolic agents

Inhibitors of bone resorption have demonstrated their interest in the management of osteoporosis. However, none of the currently registered anti-resorptive medications has unequivocally demonstrated its ability to fully prevent the occurrence of new vertebral or peripheral osteoporotic fractures, once the disease is established [80]. A major interest was subsequently shown in medications that stimulate osteoblast activity to such an extent that bone density can be brought back to values observed in normal subjects. However, for a positive effect of a drug on bone mineral content to translate into a decrease in facture rate, it is mandatory that pharmacologic intervention does not induce deleterious effects in the biomechanical properties of the skeleton.

Peptides from the parathyroid hormone family (PTH) have been investigated in the management of osteoporosis since more than 30 years [80]. A continuous endogenous production or exogenous administration of PTH, as is the case in primary or secondary hyperparathyroidism, can lead to deleterious consequences on the skeleton, particularly on cortical bone. However, daily administration of PTH, e.g., through daily subcutaneous injections, results in an increase of the number and activity of osteoblasts, leading to an increase in bone mass and an improvement in skeletal architecture, at both the trabecular and cortical skeleton. This treatment also increases cortical bone width.

In order to assess the effects of the 1–34 amino-terminal fragment of PTH on fractures, 1,637 postmenopausal women with prior vertebral fractures were randomly assigned to receive 20 μg or 40 μg of parathyroid hormone (1–34) or placebo, safety-administered subcutaneously daily. 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 were performed by dual-energy X-ray absorptiometry (DXA).

New vertebral fractures occurred in 14% of the women in the placebo group and in 5% and 4%, respectively, of the women in the 20-μg and 40-μg dose groups. The relative risk of fracture as compared with the placebo group were 0.35 and 0.31 (95% CI, 0.22–0.55 and 0.19–0.50), respectively. New non-vertebral fragility fractures occurred in 6% of the women in the placebo group and 3% of those in each parathyroid hormone

group (*RR*, 0.47 and 0.46, 95% CI, 0.25–0.88 and 0.25–0.86, respectively). As compared with placebo, the 20-μg and 40-μg doses of parathyroid hormone increased bone mineral density by 9% and 13% in the lumbar spine and by 3% and 6% in the femoral neck. The 40-μg dose decreased bone mineral density at the shaft of the radius by 2%. Both doses increased total body bone mineral by 2–4% more points than did placebo. Parathyroid hormone had only minor side effects (occasional nausea and headache) [81].

The anti-fracture efficacy of PTH on spinal fracture was not modulated by the age of the subjects (< 65 years, 65–75 years or more than 75 years), prevalent spinal BMD values (*T*-score < −2.5 or > −2.5) or number of prevalent fractures (one or two or more fractures) [82].

At the end of this trial, patients were followed for an additional 18-month period without PTH, during which they were allowed to use any anti-osteoporotic medication considered appropriate by their caregiver. 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 received 20 μg/day PTH, the reduction of vertebral fractures observed in this particular group during the initial trial was confirmed during this 18-month period of follow-up (*RR*, 0.59; 95% CI, 0.42–0.85) [83].

In direct comparison with alendronate during 14 months in osteoporotic women, a high dose (40 μg/day) PTH induces a statistically more pronounced increase in lumbar BMD (12.2% vs 5.6%). This effect was also observed at the level of the femoral or total body BMD. However, at the level of the distal radius, containing mainly cortical bone, BMD reached lower values on PTH than on alendronate. In this relatively small-sized study, the incidence of non-vertebral fractures was lower in the PTH group (4.1%) compared with the alendronate group (13.4%) [84].

Importantly, the concomitant administration of PTH and alendronate does not provide any significant benefit compared with the effect observed after PTH alone. The bisphosphonate appears to blunt, in males and females, the anabolic action of parathyroid hormone. Whether this also applies to other bisphosphonates or inhibitors of resorption remains unknown. [85, 86]

Treatment of postmenopausal osteoporosis with parathyroid hormone (1–34) decreases the risk of vertebral and non-vertebral fractures, increases vertebral, femoral and total body bone mineral density and is well-tolerated. The 40-μg dose increases bone mineral density more than the 20-μg dose but has similar effects on the risk of fractures and is more likely to have side effects (such as transient hypercalcemia, which was of no concern with the 20 μg/day).

Strontium ranelate appears to have a particular profile characterized by an inhibition of bone resorption and a stimulation of bone formation, suggesting that, for the first time, a chemical entity used in the treatment of osteoporosis could be targeted to an uncoupling of the bone remodeling process.

The effects of strontium ranelate in postmenopausal women with vertebral osteoporotic fractures were assessed during a double-blind, placebo-controlled trial (phase II STRATOS study). Either strontium ranelate (500 mg, 1 g/day or 2 g/day) or placebo was given to 353 Caucasian women (age: 66 years; lumbar BMD by DXA: 0.699 g/cm^2). All patients were also given a daily supplement of calcium (500 mg) and vitamin D_2 (800 I.U.). At the conclusion of this 2-year study, the mean annual increases in lumbar BMD values were: +1.2% for the placebo; +2.9% for 500 mg; +4.5% for 1 g and +7.3% for 2 g. Due to the distribution of strontium into the new bone formed, there is a large increase in BMD.

An adjustment of the BMD was performed in the phase II trial in order to determine the effective dose to treat postmenopausal osteoporosis. The mean annual increase in lumbar-adjusted BMD of the group receiving 2 g of strontium ranelate was +2.97%. This result was significantly different as compared with placebo. A significant decrease in pyridinium cross-links (NTX) and an increase in bone-specific alkaline phosphatase were evident after 3 months and 6 months of treatment, respectively, in the group receiving 2 g of strontium ranelate. During the second year of treatment, the dose of 2 g was associated with a 44% reduction in the number of patients experiencing a new vertebral deformity. Bone histomorphometry showed no mineralization defects. The same percentage of withdrawals following an adverse effect (10%) was observed for patients receiving placebo and for those receiving 2 g of strontium ranelate [87]. The 2 g dose of strontium ranelate per day was chosen for the phase III studies to confirm the anti-fracture efficacy of strontium ranelate in the treatment of postmenopausal osteoporosis.

Strontium ranelate has been investigated in a large phase III program that includes two extensive clinical trials for the treatment of severe osteoporosis: the first study (Spinal Osteoporosis Therapeutic Intervention), aimed at assessing strontium ranelate's effect on the risk of vertebral fractures, and the second study (Treatment of Peripheral Osteoporosis) aims at evaluating the effect of strontium ranelate on peripheral (non-spinal) fractures. Both studies were multinational, randomized, double-blind and placebo-controlled with two parallel groups (2 g/day strontium ranelate vs placebo) with a study duration of 5 years, with main statistical analysis planned after 3 years.

All patients included in these two studies had previously participated in a normalization of calcium and vitamin D study called FIRST (Fracture International Run-in Strontium Ranelate Trials). Throughout the studies, the patients received calcium/vitamin D supplements that were individually adapted according to their deficiencies (500 mg or 1,000 mg of calcium, and 400 IU or 800 IU of vitamin D_3). From more than 9,000 osteoporotic postmenopausal women having taken part

in FIRST, 1,649 patients were included in the vertebral fracture study, with a mean age of 69 years, and 5,091 patients were included in the peripheral fracture study, with a mean age of 77 [88].

The primary analysis of the vertebral study, evaluating the effect of 2 g of strontium ranelate on vertebral fracture rates, revealed a 41% reduction in relative risk (RR) of experiencing a first new vertebral fracture (semi-quantitative 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) in the intent-to-treat population. This anti-fracture efficacy of strontium ranelate was demonstrated from the first year, with a 49% reduction in relative risk (RR) of experiencing a first new fracture with strontium ranelate compared with placebo (*RR*, 0.51, 95% CI, 0.36–0.74). Bone-specific alkaline phosphatase increased while serum CTX decreased. The lumbar BMD increased by 14.4% in the treated group when compared with the placebo group) at 3 years. Strontium ranelate was well-tolerated, without any specific adverse event, and no deleterious effects were observed on rates of non-vertebral fractures [89].

The primary analysis of the peripheral study, evaluating the effect of 2 g/day of strontium ranelate on non-vertebral fracture, showed a significant reduction in the relative risk of experiencing a first non-vertebral fracture in the group treated with strontium ranelate throughout the 3-year study compared with placebo, in the intention-to-treat population. A 41% ($p = 0.025$) reduction in the relative risk of experiencing a hip fracture was demonstrated in the population that had regularly taken strontium ranelate for the first 18 months of the study (these patients had to have, at month 3, month 6, month 12 and month 18, blood strontium levels of at least 40 mol/l, corresponding to the minimum concentration after repeated daily dosing of strontium ranelate). The authors inferred that strontium ranelate is a new, effective and safe treatment of vertebral and non-vertebral osteoporosis, with a unique mechanism of action [90].

Non-pharmacological intervention and risk factor modification

Non-pharmacological prevention of fractures must be considered as a long-term treatment of osteoporosis, not only for postmenopausal women but also from childhood through adolescence, pre-menopause and peri-menopause.

Lifestyle habits including low calcium intake, general nutrition and weight-bearing exercise during adolescence and early adulthood contribute up to 20% of the observed variation in the attainment of peak bone mass, as well as to the rate of bone loss later in life [91, 92].

In 1988 C. Cooper et al. compared the physical activity of 300 elderly men and women with hip fractures with that of 600 controls matched for age and sex. Among women the risk of fracture increased significantly ($p < 0.05$) with shorter standing times, lower self-reported walking speeds and less-frequent muscle loading and productive activity. Furthermore, there was an almost fivefold increase in risk between the highest and lowest fifths of grip strength [93].

In 1995, risk factors for hip fracture were evaluated in a large prospective observational study [94]. These women were followed at 4-month intervals for 4.1 years. Besides expected risk factors like maternal history of hip fracture, personal history of any fracture, or low bone density, many lifestyle habits were significantly associated with a risk of hip fracture. Women who regularly walked for exercise had a 30% lower risk of fracture (*RR*, 0.7; 95% CI, 0.5–0.9). Those who spent 4 h per day or less on their feet had an increased risk of fracture (*RR*, 1.7; 95% CI, 1.2–2.4). Risk of hip fracture was also increased in women with: high caffeine intake (*RR*, 1.3; 95% CI, 1.0–1.5 per 190 mg/day); current use of long-acting benzodiazepines (*RR*, 1.6; 95% CI, 1.1–2.4) or inability to rise from a chair (*RR*, 2.1; 95% CI, 1.3–3.2). Some factors that were initially associated with a risk of hip fracture in age-adjusted models like current smoking or alcohol ingestion were no longer significant after adjustment for other variables.

The EPIDOS prospective study examined the risk factors for hip fracture in 7,575 women, aged 75 years or older, during an average of 1.9 years of follow-up [95]. In age-adjusted multivariate analysis, neuromuscular and visual impairments were significant and independent predictors of the risk of hip fracture: Slower gait speed (*RR*, 1.4; 95% CI, 1.1–1.6); difficulty walking (*RR*, 1.2; 95% CI, 1.0–1.5, for 1 point on the difficulty score); reduced visual acuity (*RR*, 2.0; 95% CI, 1.1–3.7, for acuity ≤ 2/10); small calf circumference (*RR*, 1.5; 95% CI, 1.0–2.2). Anxiolytic-drug use was significantly associated with the risk of hip fracture (*RR*, 1.4; 95% CI, 1.1–2.0) but this life habit was no longer significant in the multivariate analysis.

More recently, the OFELY study identified independent predictors of all osteoporosis-related fractures in a cohort of 672 healthy postmenopausal women aged 59.1 ± 9.8 years, prospectively followed for 5.3 ± 1.1 years [96]. Seven independent predictors of incident osteoporotic fractures were identified: age ≥65 years (odds ratio [*OR*], 1.9; 95% CI, 1.04–3.46); past falls (*OR*, 1.76; 95% CI, 1.00–3.09); total hip BMD ≤0.736 g/cm^2 (*OR*, 3.15; 95% CI, 1.75–5.66); left grip strength ≤0.60 bar (*OR*, 2.05; 95% CI, 1.15–3.64); maternal history of fracture (*OR*, 1.77; 95% CI, 1.01–3.09); low physical activity (*OR*, 2.08; 95% CI, 1.17–3.69) and personal history of fragility fracture (*OR*, 3.33; 95% CI, 1.75–5.66). Other lifestyle habits, i.e., smoking, alcohol, tea or coffee consumption were not associated with an increased fracture risk.

Low protein intake and malnutrition in the elderly have been associated with significant bone loss, at both femoral and spine sites, and increased risk of femoral fractures [97, 98]. Recently, the role of dietary protein

intake in osteoporotic hip fracture was evaluated in 1,167 patients 50–89 years of age (831 women) with hip fracture and 1,334 controls (885 women) [99]. Diet was assessed using a specific questionnaire. The odds ratios (OR) of hip fracture decreased across increasing quartiles of total protein intake for participants 50–69 years of age: (*OR*, 1.0; reference); (*OR*, 0.51; 95% CI, 0.30–0.87); (*OR*, 0.53; 95% CI, 0.31–0.89); (*OR*, 0.35; 95% CI, 0.21–0.59). No similar associations were observed in participants 70–89 years of age.

Sports activity and loading exercise may increase BMD up to 10% in adolescents and young adults, the early 20 s being the final opportunity to maximize the peak bone mass [92, 100, 101]. Promoting school physical education, sport and physical activity habits seems to be a reasonable starting point for prevention of osteoporosis. Nevertheless, the impact of the early exercise-induced rise in bone mass and bone strength on the risk for osteoporotic fractures later in life remains unknown, due to the lack of controlled trials of sufficient duration.

Several experimental studies have shown beneficial effects of physical training, mainly high-impact exercise regimens, on BMD, muscle mass, muscle strength and dynamic balance in postmenopausal women [102, 103]. Weight-bearing jumping exercise has been evaluated alone or in combination with alendronate in a randomized placebo-controlled 12-month trial [104]. In this trial, exercise was ineffective in increasing bone mass at the lumbar spine or femoral neck. However, at the distal tibia, exercise was effective in increasing the section modulus (3.6%; 95% CI, 0.3–7.1%), i.e., bone strength, and the ratio of cortical bone to bone area (3.7%; 95% CI, 0.1–7.3%). This exercise training was effective in increasing the mechanical properties of bone at the most-loaded bone sites, as well as improving muscular performance and dynamic balance. Fifteen months after withdrawal of intervention, physical performances had declined and were no longer statistically significant between exercisers and non-exercisers [105]. Based on these results, it seems evident that exercise therapy should be continued to maintain long-term benefits.

The long-term protective effect of resistive back-strengthening exercises on the spine (back-extensor strength; BMD; incidence of vertebral fractures) was evaluated in 50 healthy white postmenopausal women, aged 58–75 years, 8 years after they had completed a 2-year randomized controlled trial [106]. The difference in BMD was not significant between the two groups at baseline and 2-year follow-up, but was significant at 10-year follow-up ($p = 0.0004$). The incidence of vertebral fracture was six fractures in 378 vertebral bodies examined (1.6%) in the back-exercise group and 14 fractures in 322 vertebral bodies examined (4.3%) in the control group ($p = 0.029$). Mean back-extensor strength between the two groups was still significantly different at 10-year follow-up ($p = 0.001$). In summary, benefits from participation in a 2-year back-exercise course continued even 8 years after cessation.

In a recent review of non-pharmacological prevention of osteoporotic fractures, Deprez et al. emphasize the importance of falls as risk factor for non-vertebral and mainly hip fractures [6]. They remind us that falls occur at least once a year in 30% of individuals older than 65 years and in 50% of those older than 80 years of age, with a 5–6% fracture incidence. They consider environmental risk factors (inappropriate clothing, obstacles at home, slippery shower, the use of psychotropic agents with long half-lives, etc.) or patient-related factors (lower limb weakness, neurological disturbances, etc.) and review many clinical tools that can be used to evaluate the risk of falls. Lower-limb dysfunction deserves specific attention, because it is associated with increased risk for hip fracture in men (*OR*,3.4; 95% CI, 2.1–5.4) [107] and in women (*OR*,1.7; 95% CI, 1.1–2.8) [108] and can be largely modified by a therapeutic intervention. In 1,016 women and men aged 65 to 97, a program of muscle-strengthening and balance-retraining exercises performed at home in three weekly 30-minute sessions reduced by 35% both the number of falls (incident rate ratio [*IRR*], 0.65; 95% CI, 0.57–0.75) and the number of fall-related injuries (*IRR*, 0.65; 95% CI, 0.53–0.81) [109]. This program was most effective in patients aged 80 and older.

The increased risk for hip fracture associated with hitting the hip in a fall (*OR*, 97.8; 95% CI, 31.7–302) and the reduced risk associated with high body mass index (*OR*,0.60; 95% CI, 0.40–0.90, for each additional 4 kg/m^2) suggest that preventive efforts for older patients at high risk might include protective hip pads to reduce the force on the hip in a fall [110]. In 1997, Lauritzen et al. described a significant reduction of the hip fracture risk (*RR*, 0.44; 95% CI, 0.21–0.94) with the use of hip protectors in a randomized trial (444 women; 221 men) [111]. Similar results were published in 2000 with a 60% reduction of the hip fracture risk in the hip-protector group (*RR*, 0.4; 95% CI, 0.2–0.8) in 1,801 ambulatory, frail elderly patients with a mean age of 82 years [112]. These results were not confirmed in other trials that found hip protectors having no effect for the prevention of the first [113] or of a second hip fracture [114]. Deprez et al. underline that differences between these studies may be due to differences in randomization methods: most of the studies showing a positive effect of hip protectors used the study centers as the randomization unit, whereas most of the studies that found no benefit used individual randomization [6]. If an entire center uses hip protectors it increases the probability that the devices are properly positioned and worn with an optimal compliance, day and night.

In postmenopausal women, walking for exercise, back-strengthening exercises, avoiding long-acting sedative-hypnotic agents, in association with appropriate dietary calcium and protein intake, can be recommended to reduce fracture risk. In the very old, prevention of falls and correct positioning of hip protectors should probably be considered as important components of any

strategy to reduce the burden associated with osteoporosis.

Conclusion

During the last decade, several new therapeutic options have emerged, characterized by the unequivocal demonstration of their anti-fracture 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 non-vertebral or hip anti-fracture effect (Table 2). Based on a systematic review and a critical appraisal of the current literature, the 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 (500–600 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 (400–800 IU) vitamin D should be systematically offered to all postmenopausal women, either alone or, if needed, in combination with another therapeutic regimen
- Hormone replacement therapy 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
- Calcitonin appears to have a predominant effect on trabecular bone. The drawbacks of repeated injections and the high cost of the nasal formulation preclude its long-term use in the treatment of osteoporosis. Analgesic properties may be an interesting option for acute pain following a spinal fracture event
- Selective-estrogen receptor modulators are a first-line option for women with low bone mineral density, 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 anti-fracture efficacy against non-vertebral fractures is limited to a post-hoc analysis performed in a high-risk subset of the population. Major non-skeletal benefits have been documented or are under investigation (breast, heart, overall mortality) and should be taken into account when assessing the overall risk/benefit ratio of SERMs
- Bisphosphonates reduce vertebral (alendronate, risedronate, ibandronate) and hip fractures (alendronate, risedronate) in women with established osteoporosis (low bone mineral density 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 and risedronate. 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 over-suppressing bone resorption, hence preventing removal of spontaneously occurring micro-cracks 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 non-vertebral 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 non-vertebral and hip fracture has been shown in elderly subjects with low femoral density
- 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

Table 1 Effect on vertebral fracture rates (from randomized controlled trials) (*NA* no evidence available)

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

■A preplanned analysis in the entire study population
●A post-hoc analysis

Table 2 Effect on non-vertebral/hip fracture rates (from randomized controlled trials) (*NA* no evidence available)

	Non-vertebral		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	■
Teriparatide	NA	■	NA	NA
Strontium ranelate	●	■	●	▲
Calcitonin	NA	■	NA	●
Ibandronate	NA	●	NA	NA

■A preplanned analysis in the entire study population
▲A preplanned analysis on a subset of the study population
●A post-hoc analysis

impact on surrogate endpoints like BMD or bone turnover. The regular assessment (yearly) of bone mineral density is an appropriate option to follow patients treated with bisphosphonates. For raloxifene-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 and strontium ranelate remain to be defined

- Combination use of anti-resorptive agents cannot be recommended, because of the associated cost without documented additional anti-fracture benefits, the increased potential for side effects, and the risk of inducing over-suppression 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 parathyroid hormone since the bisphosphonate appears to blunt the anabolic action of parathyroid hormone. Whether this also applies to other bisphosphonates or inhibitors of resorption remains unknown
- Risk factor alterations, including fall prevention strategies, are recommended. However, no anti-fracture efficacy of such strategies has ever been demonstrated. Subsequently, fall prevention cannot be considered a substitute for pharmacological treatment of osteoporosis, not even in old age

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