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1. Introduction

Osteoporosis can be divided into two principle strands, clinical osteoporosis and densitometric osteoporosis. Clinical osteoporosis involves the identification of a fragility fracture and does not need densitometry for treatment to begin. Densitometric osteoporosis is identified via an assessment of bone mineral density. Approaches to treatment depend on the global fracture risk and the outcomes of densitometric tests.

The initial stage of the pharmacological treatment of osteoporosis is to identify the pathology of the primary condition or to determine whether the loss of bone density is a secondary symptom of a separate condition. Where secondary osteoporosis is identified, priority is given to the treatment of the primary condition. The option of pharmacological therapy must only be contemplated if the risk of fracture is too elevated, given that the intention behind pharmacological treatment in osteoporosis is to reduce the fracture risk. Based on World Health Organization figures, less than half of patients presenting a fragility fracture have been diagnosed with densitometric osteoporosis [1]. Once a course of medication has begun, long-term management must address improvements to lifestyle and take aspects of, security, cost, and compliance into account. As such, it is absolutely necessary to assess and make determinations on the basis of cost, assessment of cost-efficiency, and the adaptability of patients to drug security.

2. Antiresorptives

2.1. Calcitonin

Calcitonin binds to osteoclasts and hinders bone resorption. The use of salmon calcitonin has previously been widespread as a result of its extreme potency in humans, a result of its greater affinity for the human calcitonin receptor.
Calcitonin is now no longer a treatment for osteoporosis, having been supplanted by other treatments. Following a European risk-benefit analysis, the scientific committee of the European Medicines Agency (CHMP) advised that treatments using calcitonin should only be deployed in short-term scenarios. Treatments using injectable calcitonin should be confined to the short-term in Paget’s disease, the prevention of acute bone loss as a result of sudden immobilization and hypercalcemia resulting from cancer. In addition to this, calcitonin has been proven to be effective in treating pain resulting from fractures of the vertebral column. [2-4]

2.2. Hormonal Replacement Therapy (HRT)

HRT is a form of treatment which deploys varying doses of estrogen, sometimes on its own, sometimes in combination with progestagens. The calculated risk of fracture, based on principal cohort trials of postmenopausal women treated with HRT over the long term, indicate an appreciable lowering of the likelihood of both vertebral fracture (RR=0.6; CI 95%: 0.36 to 0.99) and wrist fracture (RR=0.39; CI 95%: 0.24 to 0.64), but a non-significant lowering of the likelihood of hip fracture (RR=0.64; CI 95%; 0.32 to 1.04). The WHI trial (Women’s Health Initiative), a randomised clinical trial (RCT) that assessed postmenopausal women randomly assigned to combined HRT (combined equine estrogen 0.625mg daily plus medroxyprogesterone 2.5mg daily) or a placebo, recorded, following 5.2 years of treatment, a decrease in hip fracture risk of 34% (hazard ratio [HR]=0.66; CI 95%: 0.45 to 0.98), in clinical vertebral fractures of 34% (HR=0.66; CI 95%: 0.44 to 0.98) and in any fracture of 24% (HR=0.76; CI 95%: 0.69 to 0.85) [5,6]. In the same investigation, the cohort taking estrogen on its own demonstrated comparable outcomes, however the treatment was put on hold as a result of an adverse risk-benefit ratio. In two meta-analyses of RCT’s, a decrease of 27% (RR=0.73; CI 95%: 0.56 to 0.94) in non-vertebral fractures and a trend towards a reduction of vertebral fractures (RR=0.66; CI 95%: 0.41 to 1.07) was recorded [7]. Nonetheless, neither the HERS (The Heart and Estrogen + Progestin Replacement Study) RCT nor the subsequent group, the HERS II study (Hulley et al., 1998), were able to register a decrease of the risk of hip fractures or of other locations (RR=1.04; CI 95%: 0.87 to 1.25) in patients with a history of cardiovascular disease [8].

The British National Institute of Health and Clinical Excellence published a meta-analysis of RCTs on HRT efficacy (with estrogen alone or combined) compared with placebo/non-treatment in postmenopausal women or those with surgical menopause [9]. The outcomes were organised according to the location of the fracture and the RCT used as the basis for the calculation of the relative risk was also identified. The outcomes are outlined in table 1.

<table>
<thead>
<tr>
<th>Fracture Location</th>
<th>Nr of RCTs</th>
<th>n</th>
<th>RESULTS</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral fracture</td>
<td>4 RCTs</td>
<td>11,842</td>
<td>RR=0.55; CI 95%: 0.46 to 0.66</td>
<td>[10-13]</td>
</tr>
<tr>
<td>Non-vertebral fracture</td>
<td>3 RCTs</td>
<td>11,774</td>
<td>RR=0.73; CI 95%: 0.65 to 0.81</td>
<td>[10, 11,14]</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>2 RCTs</td>
<td>11,745</td>
<td>RR=0.63; CI 95%: 0.42 to 0.93</td>
<td>[11,14]</td>
</tr>
<tr>
<td>Any type of fracture</td>
<td>3 RCTs</td>
<td>11,556</td>
<td>RR=0.70; CI 95%: 0.63 to 0.78</td>
<td>[14-16]</td>
</tr>
</tbody>
</table>

Table 1. Relative fracture risk in NICE meta-analysis
2.2.1. Security

2.2.1.1. Vascular illness

A thorough and methodical review of five RCTs looking at HRT with estrogen and two looking at combined HRT estrogen plus progesterone, failed to display compelling variance in the occurrence of acute coronary events (including acute myocardial infarction) between the cohort subject to intervention and the control cohort [7]. A combination of the outcomes of three studies contrasting estrogenic therapy to a placebo [11, 17] reported an odds ratio (OR) of 1.34 (IC 95%: 1.07 to 1.68) for cerebral vascular events. The combined outcomes of the studies that contrasted estrogen plus progesterone combined treatment with a placebo [5, 18], indicated an elevated risk of ictus (OR=1.28; CI 95%: 1.05 to 1.57) in the cohort subject to intervention. Out of four thorough and methodical reviews of observational trials looking at women treated with HRT [19-22], three of these indicated a significant decrease in the global mortality risk for acute coronary events. A recently published, thorough and methodical review, that compensated for selection bias of inclusion and analysis, did not reveal any link between the THS and the incidence, and mortality of acute coronary events [22].

The WHI primary prevention trial indicated a distinct elevation of the risk of acute coronary events (41%), starting the second year of treatment (29 instances in the treatment cohort, compared with 21 instances for 10,000 women per year in the general population) [5]. This elevated risk was greater in non-mortal coronary incidents (RR=1.50; CI 95%: 1.08 to 2.08) than in the mortal coronary incidents (RR=1.20; CI 95%: 0.58 to 2.50). The RCTs of HRT with estrogens alone, in both primary and secondary prevention, failed to indicate any positive impact on cerebrovascular illness [23]. In addition, the WHI study cohort with estrogen indicated an elevated risk of cerebrovascular incidents.

2.2.1.2. Venous thrombotic events

In a thorough and methodical review, McLean et al. indicated that estrogen patients treated with estrogen demonstrate an elevated risk of major venous thromboembolic incidents (OR=1.36; CI 95%: 1.01 to 1.86) compared to the placebo cohort [7]. A further thorough and methodical review assessing the impact of HRT (estrogen with or without progestagens) encompassed 12 studies (3 RCTs, 8 case-control studies and 1 cohort study) and indicated an elevated risk of thromboembolism (RR=2.14; CI 95%: 1.64 to 2.81). This risk was elevated in the first two years of the therapy and it varied according to the dose [24].

2.2.1.3. Breast cancer

A thorough and methodical review of 4 RCTs proved that patients treated with estrogens alone have a lower risk of breast cancer (OR=0.79; CI 95%: 0.66 to 0.93) than those treated with the placebo [7]. On the other hand, patients treated with estrogen and progestin have a higher risk of breast cancer (OR=1.28; CI 95%: 1.03 to 1.60) than those treated with the placebo [5, 18, 24]. Nonetheless the combined HRT cohort of the WHI study presented an elevated risk of invasive breast cancer [5]. This elevated risk occurred following the fourth year of treatment (RR=1.26;
CI 95%: 1.0 to 1.59), with a propensity to rise in line with the treatment’s longevity (38 instances compared with 30 for 10,000 women per year).

2.2.1.4. Endometrial cancer
The treatment of estrogen alone elevates the risk of subsequent endometrial hyperplasia and cancer [25,26]. A meta-analysis including 29 observational studies reported a demonstrable elevation of the risk of endometrial cancer, with or without combined estrogens (RR=2.3; CI 95%: 2.1 to 2.5) [20]. This risk is directly related to the treatment’s longevity and continues to be raised for a maximum of 5 years or more following the termination of treatment.

2.2.1.5. Ovarian cancer
Recently published thorough and methodical reviews of observational trials indicate an elevated incidence of ovarian cancer amongst women undergoing treatment, particularly long-term therapies (more than 10 years) [28,28]. Two cohort trials of postmenopausal women who underwent treatment for a period of more than 10 years corroborate this elevated risk of ovarian cancer (RR=2.2; CI 95%: 1.53 to 3.17), as well as an elevated mortality risk (RR=1.59; CI 95%: 1.13 to 2.25) [29,30].

We can conclude that HRT is an effective therapy both for postmenopausal osteoporosis and for the management of fracture risk. Nevertheless, even taking this conclusion into account, the use of combined HRT is not recommended for periods greater than 5 years, given the possible risk factors linked with treatments using a daily dose equivalent to 50 pg of estradiol. When HRT treatment is indicated, it should be prescribed at a low dosage (equivalent to estrogen transdermal patches of 25 mcg), only using higher doses if it is absolutely essential to do so. Estrogens and progestagens are only advised for the treatment of women with intact uteri. The level of the progestagen dose should be determined on the basis of the estrogen dose. In instances where a hysterectomy was carried out as a result of endometrial cancer, HRT should not involve combined estrogen and progestagens. Continuous combined HRT treatment should only commence following one whole year of menopause.

2.3. Selective Estrogen Receptor Modulators (SERMs)
Selective estrogen receptor modulators are medications with a selective impact on the estrogen receptor. They can function as estrogen receptor (ER) agonists in some tissues while in other tissues functioning as estrogen receptor antagonists. As a result of their selective estrogen-agonist behaviour within a variety of tissues, SERMs may be indicated as an alternative option for the prevention or treatment of conditions like osteoporosis, which are the result of a deficiency of estrogen, where avoiding the negatives effects of estrogens is a priority.

2.3.1. Differences between SERMs
At present there are two forms of SERM, which are distinguished by their chemical structure: triphenylethylene derivatives, for example tamoxifen and toremifene, and benzothiophene derivatives, for example raloxifene and bazedoxifene. Tamoxifen and toremifene on the one
hand are indicated for use in the treatment of breast cancer. Raloxifene on the other hand is used for the prevention and treatment of osteoporosis and in addition the prevention of breast cancer. All SERMs have been linked with an elevated occurrence of pulmonary thromboembolism and with the start of hot flushes, however they also impact in a positive manner on the lipid profile.

The SERMs vary distinctively with regards to tissue specificity. Bazedoxifene appears to have a lower impact on the uterus than estradiol jointly with raloxifene in animal experiments as a result of reduced estrogen receptor alpha agonistic effects.

2.3.2. Raloxifene

Raloxifene acts as estrogen agonist in bone and other systems but not in reproductive tissue. Many trials have proved the effectiveness of raloxifene for preserving bone in the early postmenopausal phase. In a meta-analysis of seven studies (four treatment and three prevention studies) which looked at the impact of raloxifene versus a placebo on bone mineral density, raloxifene augmented bone mineral density within the lumbar spine following a two year period of treatment [31]. A trial of 601 women, five years following the menopause, who were given a daily dose of 30, 60 or 150mg of raloxifene over two years, indicated an augmentation of their bone mineral density in spine and hip, whereas those subjected to the placebo presented reduced bone mineral density in the same locations [32]. In contrast with the results from the placebo, the average alteration in BMD with 60mg of raloxifene was 2.4% in the spine and 2.4% at the total hip (p<0.001 versus placebo). Postmenopausal women presenting low bone mass and osteoporosis were monitored over eight years in the study entitled ‘Multiple Outcomes of Raloxifene Evaluation’ (MORE, n=7,705) and its sister trial entitled ‘Continuing Outcomes Relevant to Evista’ (CORE, n=4,011) [33]. In relation to fractures, whilst raloxifene treatment led to a decreased risk of vertebral fracture, it failed to demonstrate a reduced risk of non-vertebral fractures. Nevertheless, in a meta-analysis of RCTs contrasting the effects of raloxifene with those of a placebo, raloxifene typically led to a decreased risk of vertebral fractures in postmenopausal women (OR=0.6; CI 95%: 0.5-0.7).

The results of the MORE trial indicated that, following a raloxifene treatment period of four years, at 60mg per day, the cumulative relative risk of one or more vertebral fractures was 0.64 (IC 95%: 0.53 - 0.76), compared with treatment using a placebo.

Verus placebo, treatment with 60mg of raloxifene was also linked to a decrease of 65% to 78% in occurrences of invasive breast cancer and invasive breast cancer with positive estrogen receptor (both p <0.05).

2.3.2.1. Adverse Effects

The MORE and CORE studies reported a link between raloxifene and an elevated incidence (1.7 times) of thromboembolism (TE), versus treatment using a placebo (95% CI: 0.93-3.14; risk difference total of 0.9/1,000 women-years) [34]. In a meta-analysis of nine trials, raloxifene treatment was linked with an elevated incidence of deep venous thrombosis and pulmonary embolism (OR=1.5; CI 95%: 1.1-2.1 and OR=1.9; 95% CI: 1.0-3.5, respectively) [35]. The RUTH
trial (‘Raloxifene Use for The Heart’), which studied 10,101 postmenopausal women with an average age of 68 and presenting with coronary heart disease, indicated a link between raloxifene and an elevated incidence of fatal stroke (HR=1.49; 95% CI: 1.00-2.24, a rise in the absolute risk of 0.7/1,000 women-years) as well as an elevated risk of thromboembolism (HR=1.44; 95% CI: 1.06-1.95, a rise in the absolute risk of 1.2/1,000 women-years) in comparison with the placebo results. No elevated risk of myocardial infarction or other coronary events was indicated in the RUTH trial. Nevertheless, in line with the observations regarding thromboembolism and pulmonary embolism, the outcomes of a recent review of a sub-cohort of the trial indicated that age had an impact on the occurrence of coronary events. For women of 60 years or under, the rate of occurrence of coronary events was distinctly reduced with raloxifene (50 cases), compared with the placebo group (84 cases; HR=0.59; 95% CI: 0.41 to 0.83, p=0.003). Raloxifene was also linked with an elevated occurrence of hot flushes, especially amongst women with recent menopause onset [36].

We can conclude that raloxifene provides an alternative option within osteoporosis therapies for specific patients. The drug’s profile relating to heart disease and breast cancer is sound but its links to an elevated risk of venous thrombosis should be taken into account in its use as a treatment.

2.3.2.2. Bazedoxifene

Bazedoxifene is a third-generation SERM. Some key differences have been demonstrated between the generations regarding their impact on the uterus and on breast tissue in particular [37]. The drug was developed with raloxifene as a template and by replacing the benzothio‐phene core with an indole ring [38].

In a phase II trial of healthy postmenopausal women, oral doses of bazedoxifene 2.5, 5, 10, 20, 30, or 40mg per day were as a rule well-tolerated and did not aggravate the endometrium. In addition, bazedoxifene 30 and 40 mg resulted in a notably reduced increase in the thickness of the endometrium and distinctly lowered the occurrence of uterine bleeding versus results from the placebo. In a two-year phase III trial of postmenopausal women at risk of osteoporosis, bazedoxifene 10, 20, and 40mg were proven to prevent bone loss and decrease bone turnover and were linked with a positive endometrial, ovarian, and breast security profile [39, 40].

A phase III, multi-centre, double-blind, randomised, controlled trial was formulated with the sole purpose of assessing the effectiveness of bazedoxifene in fracture prevention. The trial looked at 7,492 healthy postmenopausal women presenting with osteoporosis both with or without prevalent vertebral fractures. The women were randomly assigned to 20 or 40mg per day of bazedoxifene, 60mg of raloxifene, or to a placebo plus 1200mg of calcium and 400IU of vitamin D. The primary outcome was the occurrence of new vertebral fractures following a three-year treatment period. Secondary indicators included clinical vertebral fractures, worsening of vertebral fractures, non-vertebral fractures, breast cancer incidence, and variations in height. Both bazedoxifene 20 and 40mg reduced the occurrence of vertebral fractures to a similar extent as raloxifene versus the placebo. The occurrence at 36 months of new vertebral fractures was 2.3%, 2.5%, 2.3%, and 4.1% in the bazedoxifene 20mg, bazedoxifene 40mg, raloxifene 60mg, and placebo cohorts, respectively, with a distinct lowering of the
relative incidence for new vertebral fractures of 42%, 37%, and 42%, respectively, versus placebo. There was no overall impact on non-vertebral fractures, with incidence rates of 5.7% and 5.6% for the bazedoxifene 20 and 40mg cohorts, respectively, versus 5.9% for the raloxifene cohort and 6.3% for the placebo cohort. Nevertheless, in a later review of women with elevated fracture risk (poor femoral neck T-score and multiple vertebral fractures, n=1,772), bazedoxifene 20mg reduced the incidence of non-vertebral fracture by 50% and 44% reduction relative to the placebo (HR=0.50; 95% CI: 0.28–0.90; p=0.02) and raloxifene 60mg (HR=0.56; 95% CI: 0.31–1.01; p=0.05), respectively [41].

2.3.2.3. Safety

Miller et al. demonstrated that deep venous thromboembolism was uncommon with bazedoxifene (0% to 0.6% with varying dosage levels after two years) and similar to the placebo (0.3%). The rate of occurrence and the intensity of hot flushes were comparable with raloxifene, but slightly elevated versus placebo [40]. In the trial by Silverman et al., leg cramps (10.9% to 11.7% with varying dosage after three years) and deep venous thromboembolism (0.4% to 0.5% with varying dosage after three years) were decidedly more prevalent with bazedoxifene compared with the placebo (8.2% for leg cramps and 0.2% for deep venous thromboembolism), while fibrocystic breast disease was markedly less frequent. No distinction in risk levels between bazedoxifene and placebo was noted for myocardial infarction, strokes (ischemic or hemorrhagic), or retinal vein thrombosis [40-43].

We can conclude that bazedoxifene appears to have improved selectivity in contrast with other SERMs. The impact of bazedoxifene on the skeleton is not dissimilar to raloxifene, and bazedoxifene may be employed in the same way as raloxifene. The usefulness of bazedoxifene possibly lies in its risk profile being distinct to that of raloxifene, particularly with regards to uterine safety, and bazedoxifene may therefore present another option for the prevention and treatment of osteoporosis.

2.3.3. Lasofoxifene

Lasofoxifene is a powerful third-generation SERM. It has a distinct structure compared to first- and second-generation SERMs (raloxifene, tamoxifen and clomiphene or idoxifene). Lasofoxifene displays powerful estrogenic and anti-estrogenic activity in vitro and in vivo, targeting any areas with estrogens receptors, including bone, uterus, breast, blood vessels, and liver. Lasofoxifene has been analysed in postmenopausal women with regards to the prevention and treatment of osteoporosis. Security and tolerance levels of lasofoxifene is similar to that of raloxifene, however nonadherence rates as a result of adverse events are greater with lasofoxifene. Despite these indications, results demonstrate that lasofoxifene treatment may lead to greater endometrial thickness versus the placebo, despite there being no evidence of an elevated incidence of endometrial hyperplasia or cancer.

The PEARL study, a three-year pivotal fracture study, showed that lasofoxifene elevated lumbar spine and femoral neck BMD by approximately 3%. Furthermore, vertebral fractures
saw a decrease of 42%, and non-vertebral fractures of 27%, with a decrease in markers of bone turnover. Nevertheless, lasofoxifene did not reduce the risk of hip fractures [43].

2.4. Bisphosphonates

2.4.1. Analysis and mode of action

Bisphosphonates are a member of a class of antiresorptive agents whose antifracture action is well-documented through randomised controlled studies. There have been no studies to compare different bisphosphonates, a fact which has prevented the identification of a definite order of effectiveness for treatment.

Bisphosphonates lower fracture risk as a result of its inhibitory action of osteoclasts, which enables the osteoblasts to synthesize bone in the resorption spaces and some bone lacunae. This produces an augmentation in bone mass. However, the bisphosphonates also increase bone quality, by conserving the bone architecture, as demonstrated in studies which have analysed the biopsies of treated patients and control subjects.

Bisphosphonates comprise pyrophosphate analogs in which the central oxygen has been replaced by a carbon atom and two side chains (R1 and R2). Two phosphate chains are vital to enable the drug to bind to bone and to have an antiresorptive effect.

2.4.2. Etidronate

Etidronate was the original bisphosphonate used in osteoporosis therapy. It is no longer used in current practice. Its greatest asset is most likely its cost. It augments bone mass in the spine and femur and lowers the risk of vertebral fractures, however it has not demonstrated a reduction in the incidence of femoral fractures [44,45].

2.4.3. Clodronate

Clodronate has been deployed in postmenopausal osteoporosis therapy in oral and intravenous treatments. The trials indicate that it reduces the risk of bone loss in the vertebral spine in comparison to control subjects, and it presents similar results to estrogens after two years. In a six-year long study, it was also demonstrated to lower the incidence rate of vertebral fractures. McCloskey et al. carried out a three-year, double-blind, controlled study to observe the impact of oral clodronate (800mg per day) on fracture rates. In this study, clodronate was linked with a distinct improvement in the mean lumbar spine and hip BMD. Furthermore, it significantly lowered the risk of vertebral fracture (relative risk, 0,54; 95% CI, 0,37-0,80; p<0,0001). Despite these outcomes, subsequent to the introduction of powerful nitrogen bisphosphonates, the first-generation bisphosphonates have been reduced to a therapy of last resort [46].

2.4.4. Alendronate (alendronic acid)

Alendronate is one of the most commonly deployed bisphosphonates. It augments vertebral bone mass approximately 6-8% and 3-6% at the hip in postmenopausal osteoporotic women
after a three-year treatment. It demonstrates a reduction in vertebral and non-vertebral fractures of around 50% in this time period. In male osteoporosis, it has demonstrated improvements in bone mass of 5% after two years of treatment.

Alendronate is given orally, in doses of 70mg/week, fasting with 200 ml of water. The patient is prohibited from consuming solids or liquids for 30 minutes after treatment and must remain standing for this time.

The decisive study of alendronate, the FIT (Fracture Intervention Trial), demonstrated that the incidence of clinical fracture was reduced for the alendronate cohort compared to the control cohort (139 (13.6%) versus 183 (18.2%); relative hazard=0.72 (0.58-0.90)). The corresponding risk of hip and wrist fracture for the alendronate cohort when compared to the placebo cohort were 0.49 (0.23-0.99) and 0.52 (0.31-0.87) [47]. Ensrud et al. provided an assessment of a subset of FIT subjects who were patients with an elevated risk of fracture. The outcomes of this analysis demonstrate a decisive 47% lowering of the risk of new vertebral fractures in the alendronate cohort when set against the control cohort. A number of other papers have been generated from the FIT study, addressing multiple symptomatic fractures, bone mineral density, biochemical markers of formation and resorption, fracture prevention in osteopenic women, impact of alendronate continuation versus discontinuation, and the impact on women who lost bone over the course of treatment [48-51].

We can conclude that alendronate is a well-tolerated, secure and efficacious treatment method for postmenopausal osteoporosis, male osteoporosis, and glucocorticoid induced osteoporosis (GIOP).

2.4.5. Risedronate

This treatment has been proven to improve bone mass in spine and hip and to considerably lower the incidence of fracture in postmenopausal women. Treatment of postmenopausal women with osteoporosis with risedronate over a three-year period has produced a reduction in the risk of vertebral fractures in roughly 50% and non-vertebral fractures in 39% of subjects. At the hip, the fracture reduction rate is between 40 and 60%. After a five-year period, the outcomes are comparable. The treatment has demonstrated its anti-fracture efficacy after a six-month course. In other trials it has been proven that this reduction in risk was still present following a seven-year period of treatment, and was accompanied by a positive security profile. One of the principal studies of risedronate [52] looked at 5,445 women aged 70 to 79 years with osteoporosis (T-score at the femoral neck greater than -4 SD below the mean or lower than -3 plus a non-skeletal risk factor for hip fracture, such as poor gait or a tendency to fall) and 3,886 women aged at least 80 years with a minimum of one non-skeletal risk factor for hip fracture or poor BMD at the femoral neck (T-score below -4 or below -3 plus a hip-axis length of 11.1cm or greater). The subjects were given a treatment at random of either oral risedronate (2.5 or 5.0mg per day) or a placebo, over a three-year period. The outcomes indicated that the risk of hip fracture among subjects given risedronate was 2.8%, versus 3.9% among those given the placebo (relative risk, 0.7; 95% CI, 0.6 to 0.9; p=0.02). In the cohort of women with osteoporosis (70 to 79 years old), the risk of hip fracture among subjects given risedronate was 1.9%, versus 3.2% among subjects given the placebo (relative risk, 0.6; 95% CI,
In the cohort of subjects chosen principally for non-skeletal risk factors (those at least 80 years old), the risk of hip fracture was 4.2% for subjects given risedronate and 5.1% for those given the placebo (p=0.35) [52].

To assess the impact on vertebral fracture risk, Reginster et al. carried out a randomised, double-blind, controlled trial to evaluate the effectiveness and security of risedronate for reducing the risk of vertebral fractures in postmenopausal women with established osteoporosis. The trial was carried out at 80 locations in Europe and Australia. In total, 1,226 postmenopausal women with two or more prevalent vertebral fractures were given risedronate 2.5mg or 5mg per day or a placebo. Whilst the trial was carried out over three years, the 2.5mg cohort was ended by protocol amendment after two years. Risedronate 5mg lowered the incidence of new vertebral fractures by 49% over three years in comparison with the placebo (p<0.001). A distinct decrease of 61% was witnessed over the initial year alone (p<0.001). The decreased incidence of fracture was comparable in both cohorts after two years. The incidences of non-vertebral fracture saw a decrease of 33% in relation to the placebo figures over three years (p=0.06). Risedronate produced a distinct elevation in BMD at the spine and hip within a six-month period. We can conclude that risedronate 5mg was an efficacious and well-tolerated treatment for severe postmenopausal osteoporosis, decreasing the risk of vertebral fractures and increasing bone density in women with chronic osteoporosis [53].

### 2.4.6. Ibandronate

In trials lasting three years, ibandronate has been proven to decrease the risk of vertebral fractures (52%) and improve vertebral BMD (6.5%) whilst not having a substantial negative impact on bone histology. It has also shown to be very efficacious in reducing bone loss in GIOP (glucocorticoid induced osteoporosis). In women with severe osteoporosis T scores (<-3), it decreases the risk of non-vertebral fractures up to 69% [54].

Randomised clinical studies such as MOPS (Monthly Oral Pilot Study) or MOBILE (Monthly Oral Ibandronate in Ladies) have indicated that the ibandronate monthly dosage is just as efficacious and safe as the daily dosage. Amongst the general population of the pivotal trial (BONE, Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe), the likelihood of adverse incidents of the gastrointestinal tract in both the daily and the intermittent treatment cohorts was similar to the control cohort. Dyspepsia was the only adverse incident with a marginally greater rate in subjects undergoing therapy with ibandronate [55].

### 2.4.7. Zoledronate (zoledronic acid)

Zoledronic acid is a third-generation bisphosphonate. It is roughly as powerful as alendronate, risedronate and ibandronate, however the application of this drug intravenously prevents any negative impact and in fact augments the bioavailability, whilst also improving compliance to 100%.

The HORIZON trial (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial) was a global, multi-centre, double-blind, controlled study of
postmenopausal women with osteoporosis, whose goal was to demonstrate the increase efficacy of intravenous zoledronic acid 5mg compared with a control. Subjects presented with densitometric osteoporosis or densitometric osteopenia with a minimum of 2 mild to moderate vertebral fractures [56]. Over 7,700 women were involved in the trial and were monitored over a three-year period; particular scrutiny was made of new fractures, bone remodeling biochemical markers and densitometric developments. On completion of the trial, subjects that had been treated with zoledronic acid presented a decrease in the vertebral fracture risk of 70%. The decrease was comparable for the first two years of the trial, varying from 60% to 71%. In addition, subjects given zoledronate presented a decrease of 41% in hip fracture incidence and 25% in non-vertebral fracture incidence. The outcomes of bone density and biochemical bone remodeling markers were also markedly improved for the cohort given zoledronic acid. Furthermore, bone mineral density was elevated to over 6% in the lumbar spine and total hip, and to over 5% in the femoral neck. The biochemical markers of bone remodeling, after the initial transfusion of zoledronic acid, decreased significantly as anticipated, and stayed stable throughout the remainder of the trial [57].

Many subjects experienced adverse effects over the course of the trial, with a greater occurrence of these in the zoledronate cohort. This variance was explained by post-infusion syndrome, which commonly manifested itself 24-48 hours after the zoledronic acid infusion and dissipated three days after infusion. The syndrome presented with mild fever, myalgias, flu-like symptoms, headache and/or arthralgias and was dissipated with analgesic, non-steroid anti-inflammatory drugs or acetaminophen. A few subjects presented with passing renal function deterioration 9 to 11 days post-infusion, however these instances were of no clinical transience [57].

Perhaps the most significant conclusion in relation to zoledronate therapy is the 28% decrease in mortality of any cause, which was demonstrated in a cohort of over 2,000 subjects with femur fracture [56].

We can conclude that zoledronate therapy is extremely efficacious in the reduction of vertebral, non-vertebral and hip fractures. It reduces mortality, independent of the cause, following a femur fracture. Moreover, it is a low-risk therapy that avoids the gastrointestinal adverse events and high nonadherence rates that are commonly encountered with other bisphosphonates, but it should be dispensed and regulated with great caution when treating individuals with severe renal function impairment.

2.4.8. Safety of bisphosphonates

This class of treatments is usually well-tolerated, provided that they are administered carefully and that patients adhere to the instructions for their use. Esophageal ulcerations been encountered in situations where these treatments are given orally and on a daily basis. They must not be given to patients with gastric or esophageal ulcerations, or to patients with pyrosis (heartburn) which requires treatment. They must not be administered to pregnant women, or to individuals with chronic renal impairment. The intravenous bisphosphonates normally give rise to acute phase reactions with fever, arthromyalgia and flu-like symptoms that commonly dissipate before the second dosage and which can be mitigated by giving acetaminophen or
ibuprofen concurrently. Hypocalcaemia can present more frequently, so it is advisable to give calcium and vitamin D concurrently. The renal function has to be regulated both prior to and following treatments of intravenous bisphosphonates.

The avascular necrosis of the jaw, also called osteonecrosis of the jaw, is a condition which has concerned many practitioners since Marx identified it for the first time in 2003 and it ought to be outlined more completely in another chapter [58].

2.4.9. Long-term impact of bisphosphonate therapies: Atypical hip fractures

Research linking atypical fractures of the femur with longstanding treatments of bisphosphonates caused the American Society for Bone and Mineral Research (ASBMR) to launch an enquiry to consider the important queries raised by the conclusions of this research. The enquiry’s committee identified both major and minor features of incomplete and complete atypical femoral fractures and advised that all significant features, including their location in the subtrochanteric region and femoral shaft, transverse or short oblique orientation, little or no associated trauma, a medial spike when the fracture is complete, and lack of comminution, be discernible in order to designate a femoral fracture as atypical. Minor features include the fracture’s relationship with cortical thickening, a periosteal reaction of the lateral cortex, prodromal pain, bilaterality, delayed healing, co-morbid conditions, and concurrent drug usage, including bisphosphonates, other antiresorptive agents, glucocorticoids, and proton pump inhibitors. On the strength of published and unpublished information and the wide application of bisphosphonates, the occurrence of atypical femoral fractures linked with bisphosphonate use for osteoporosis seems to be decidedly uncommon, especially in relation to the extent to which vertebral, hip, and other fractures are in turn prevented. Moreover, a causal link between bisphosphonates and atypical fractures has not been demonstrated. Nevertheless, new investigations infer that the incidence rate increases with longer periods of therapy, and there is a feeling of unease that a lack of understanding and underreporting could be hiding the true extent of the issue.

A 2008 trial of 12,777 Swedish women aged 55 years or more with a fracture of the femur was made public recently. Radiographs of 1,234 of 1,271 women presenting a subtrochanteric or shaft fracture were analysed. Fifty-nine subjects with atypical fractures were isolated. The relative and absolute incidence of atypical fractures linked with bisphosphonate treatment was calculated using a national cohort analysis. The 59 subjects were also subject to a comparison with 263 control subjects who presented typical subtrochanteric or shaft fractures. The cohort analysis indicated an age-adjusted proportional risk of atypical fracture of 47.3. The rise in global risk was 5 instances per 10,000 patient-years. In total, 78% of the fractured patients and 10% of the controls had been given bisphosphonates (multivariable-adjusted odds ratio of 33.3). The incidence level was independent of coexisting ailments. Following cessation of treatment, the incidence level was reduced by 70% per year from the time of last use (odds ratio, 0.28; 95% CI, 0.21 to 0.38) [59].
2.5. Biological agents

Conditions that give rise to bone loss, like osteoporosis, are caused by the imbalance in the cycles of bone remodeling favouring bone resorption. The receptor activator of the nuclear factor κB (RANK), and its ligand (RANKL) are critical for the differentiation, activation and survival of osteoclasts and, as a result are the most simple intermediary in the regulating of bone remodeling (Burgess et al.1999). It has been proven that the signaling of the RANKL is inherent to the pathophysiology of many bone loss conditions, such as primary and many secondary forms of osteoporosis.

2.5.1. Denosumab

Denosumab is a fully human monoclonal IgG2 antibody to RANKL that imitates the effects of osteoprotegerine (OPG), endogenous inhibitor of RANKL that blocks bone resorption.

Comercial denosumab is sold as a sterile, uncolored solution administered via subcutaneous injection.

2.5.1.1. Denosumab in human clinical studies

Data is accessible from more than 50 clinical studies in healthy adults and patients with osteoporosis, bone loss linked with hormone-ablation treatments, rheumatoid arthritis, advanced cancer (multiple myeloma and advanced malignancies that involve bone and giant cell tumor of the bone collected since June 2001).

In the Denosumab Fortifies Bone Density (DEFEND) trial, a phase III, randomised, controlled trial of 332 postmenopausal women with osteopenia sorted by the length of menopause (<5 years, >5 years), denosumab showed a distinctive rise in lumbar BMD (6.5%) at the two-year point, in relation to the control (-0.6%). It also raised BMD in other sites including total hip, distal third of the radius, and whole body (p>0.001) in the two cohorts. The rate of side effects was comparable between the control cohort and the denosumab cohort [60].

In a comparative clinical study, the DECIDE (Determining Efficacy: Comparison of Initiating Denosumab vs. Alendronate) trial of 1,189 postmenopausal women with low BMD (T-score: ≤-2 SD), subjects were randomly allocated 1:1 to two groups, one to be given subcutaneous denosumab (60mg per 6 months) plus an oral alendronate placebo weekly or oral alendronate weekly (70mg) plus a subcutaneous denosumab placebo injection every 6 months. Denosumab raised total hip BMD in relation to alendronate (3.5% versus 2.5%, p<0.00001). A more significant increase in BMD could be witnessed with denosumab than with alendronate in other locations, as in the trochanter (4.5% vs. 3.5%), distal radius (1.1% versus 0.6%), lumbar spine (5.3% versus 4.2%) and femoral neck (2.2% versus 1.6%); p<0.0003. The security profile was comparable for the two cohorts. No subject in the trial developed antibodies in reaction to denosumab [61].

Another phase III, multi-centre, double-blind trial, named STAND (Study of transitioning from Alendronate to Denosumab) was carried out to assess the impact of denosumab in subjects who were undergoing alendronate treatment. Five hundred and four postmenopausal women ≥ 55
years old with a BMD T-score of <-2.0 and >-4 SD, who were taking weekly oral alendronate for a minimum of six months, were randomly assigned to the treatment for 44±33 months. Alterations to BMD and bone biochemical markers were assessed. After a year, the cohort taking denosumab (and had been given alendronate before the trial) presented a markedly elevated total hip BMD in comparison with the cohort which continued to take alendronate (1.9% versus 1.05%; p<0.00012). Markedly elevated BMD readings with denosumab in comparison with alendronate were also noted after one year at the lumbar spine, femoral neck, and distal radius (all p<0.0125). The side effects and serious side effects were comparable in both cohorts [62].

Lastly, the principal phase III study, the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months) study, involved 7,868 postmenopausal women with osteoporosis and a BMD T-score between <-2.0 and >-4 SD and assessed the effectiveness in fracture reduction of denosumab. Subjects were given 60mg subcutaneous denosumab or placebo every six months for three years. Approximately 23% of the subjects had experienced a prior vertebral fracture. The trial’s retention rate of subjects was 83%. The decrease in relative risk of fracture was 68% (2.3% versus 7.2%; p<0.0001) for vertebral fractures, 20% (6.5% versus 8.0%) for non-vertebral fractures and 40% (0.7% versus 1.2%) for hip fractures. In comparison to patients in the control cohort, patients in the denosumab cohort saw a proportional elevation of 9.2% in bone mineral density at the lumbar spine and 6.0% at the total hip at three years. No distinctive dissimilarities were apparent between patients who were given denosumab and those who were given a placebo in the overall rate of side effects, serious side effects, or nonadherence to the trial as a result of side effects. No instances of osteonecrosis of the jaw were found in either cohort during this decisive study (Cummings et al. 2009). Lastly, the positive effects of denosumab therapy were generally discernible following the first treatment and remained so over the course of up to eight years of denosumab therapy in an open-ended extension trial [63].

We can conclude that denosumab provides an extremely efficacious substitute for osteoporosis therapy through the reduction of bone resorption and the elevation of bone mineral density via the inhibition of RANKL. A distinct benefit of denosumab is its route of administration and dosage. A subcutaneous injection every 6 months is comparatively free of discomfort and improves the therapy retention levels.

3. Anabolic agents

3.1. Fluoride

A series of observations were published indicating a low occurrence of fracture in subjects residing in locations with elevated fluoride levels. Fluoride was first employed in osteoporosis therapy in 1961. It was authorised for the prevention of osteoporosis in several European countries, but was never given authorisation by the American Federal Drug Administration (FDA) [64,65].
The outcomes of studies into the impact of fluoride on the reduction of fracture risk are ambiguous. Some trials have shown a reduction in the risk of vertebral fractures under monofluorophosphate, or sodium fluoride treatment, whereas other trials, giving patients the same preparations and dosage, did not. In addition, one meta-analysis extends these investigations and identifies an elevated fracture risk with increasing dosages after four years [66-68]. As a result, fluoride is not employed in the treatment of osteoporosis any longer.

3.2. Teriparatide (1-34 parathohormone)

Within the range of treatment options available, teriparatide or recombinant human PTH (1-34), has a significant role to play. It is a member of the group of anabolic bone-forming drugs rather than the anti-resorptive or catabolic group. It is a catalyst for fresh bone formation by accelerating bone turnover in favour of formation. Teriparatide therapy improves trabecular connectivity and cortical bone thickness [69] and augments the mechanical properties of bone causing a marked reduction in vertebral and non-vertebral fractures in postmenopausal women with osteoporosis, male osteoporosis and corticosteroid-induced osteoporosis [70]. For this reason its application is deemed to be suitable mostly for individuals at high risk of fracture and for those for whom other drugs have been unsuccessful [71].

The original indication for teriparatide first made public was the treatment of established osteoporosis in postmenopausal women. Amongst the varying trials which have been carried out on this treatment, the FPT (Fracture Prevention Trial) is the most significant. It assessed teriparatide at dosages of 20 or 40μg/day in controlled conditions in 1,637 postmenopausal women with vertebral fractures. Subjects taking teriparatide presented a marked decrease in the rate of fresh vertebral and non-vertebral fractures. They also experienced elevated lumbar and femoral neck bone density. Whilst the 40μg/day dose had a greater impact on BMD, the risk of fracture did not vary to any marked extent between the two dosage levels, while the higher dosage was less tolerated (11% nonretention due to adverse events with 40μg/day compared with 6% with 20 μg/day or with the placebo). The dosage of 20μg/day presented a decreased risk of vertebral fracture of 65% and a decreased risk of non-hip non-vertebral fracture risk reduction of 35%. This trial was originally supposed to run over a 36-month period, but it was terminated when subjects had undergone on average 21 months of treatment for safety reasons following osteosarcomas witnessed in rats during drug toxicity trials [72]. In other trials it transpired nevertheless that this effect presented only in juvenile rats given with elevated doses of PTH [73]. In addition, no instances of osteosarcomas have been noted in humans.

A subset of subjects were monitored for a maximum of 18 months following the termination of the therapy. This subset, which had been given teriparatide, demonstrated an enduring 40% decrease in vertebral fracture risk at 18 months versus the control sample. These outcomes indicate that the drug’s positive impact on the rate of non-vertebral fractures continues beyond the termination of treatment [74].

3.2.1. Combination therapy: Teriparatide plus antiresorptives.

Despite bisphosphonates being the current benchmark for the treatment of osteoporosis, several studies exist that have assessed whether the combination of teriparatide and BP can
produce a positive impact. The trials indicate that, if both treatments are given at the same time, bisphosphonates reduce rather than increase the anabolic action of teriparatide [75].

Combined teriparatide and denosumab, on the other hand, improves spine and hip BMD to a greater extent than either treatment does when administered in isolation. In the DATA-HRpQCT study, subjects underwent high-resolution peripheral QCT assessments at the distal tibia and radius (postmenopausal osteoporotic women randomly assigned to take teriparatide 20μg daily (n=31), denosumab 60mg every 6 months (n=33), or both (n=30) for 12 months). In the teriparatide cohort, the overall volumetric BMD (vBMD) did not vary at either anatomic location but was improved in both other cohorts at both locations. The elevated vBMD at the tibia showed an increase in the combination cohort (3.1±2.2%) compared with either the denosumab (2.2±1.9%) or teriparatide cohort (-0.3±1.9%) (p<0.02). Cortical vBMD was reduced by 1.6±1.9% at the tibia and by 0.9±2.8% at the radius in the teriparatide cohort whilst it was elevated in both other cohorts at both anatomic locations. Tibia cortical vBMD saw greater increases in the combination cohort (1.5±1.5%) than in the other two cohorts (p<0.04 for both comparisons). Cortical thickness was not affected in the teriparatide cohort, but was elevated in the other cohorts. Elevations in cortical thickness at the tibia was more marked in the combination cohort (5.4±3.9%) than the other cohorts (p<0.01 for both comparisons). In the teriparatide cohort, radial cortical porosity was raised by 20.9±37.6% and by 5.6±9.9% at the tibia but was not affected in the other two cohorts. Bone stiffness and failure load, as calculated through finite element analysis, was not affected in the teriparatide cohort but was elevated in the other two cohorts at both locations. These results suggest that the application of denosumab combined with teriparatide has a positive impact on HR-pQCT indices of bone quality to a greater extent than either treatment in isolation and may be of significant clinical benefit in the management of postmenopausal osteoporosis [76].

3.2.2. Teriparatide in individuals formerly given antiresorptives

The EUROFORS study was a prospective, open-label, randomised study of 865 postmenopausal women with established osteoporosis and aimed to assess a variety of consecutive applications of teriparatide over a two-year period. Subjects were split into several subsets based on their former therapies. The outcomes of the BMD variations and biochemical markers of bone formation indicated that the application of teriparatide has a beneficial impact on bone mass and osteoblast function in postmenopausal women with established osteoporosis whatever the extent or type of former long-term exposure to antiresorptive treatments has been.

The length of the antiresorptive treatment and the length of pause in treatment between the former therapy and the teriparatide had no impact on BMD levels at any anatomic location. The skeletal reaction at the lumbar spine was comparable among former antiresorptive treatment cohorts at every point in time over the course of the trial, however subjects who had previously been given etidronate presented a greater increase, most likely a factor of its poorer anti-remodeling action. At six months, overall hip and femoral neck BMD showed a marked reduction in the former alendronate subset, and total hip BMD showed a marked reduction in the former risedronate subset. Overall hip and femoral neck BMD was statistically reduced...
from baseline in all other subsets at the six-month point. Nevertheless, this short-term reduction was contradicted over longer-term teriparatide therapy. All subsets demonstrated a numerically distinctive rise in BMD versus baseline after 18 and 24 months of therapy, and without variations between the cohorts at any point in the trial [77].

3.2.3. Sequential treatment

In a further non-randomised trial, 59 postmenopausal women with osteoporosis formerly given raloxifene or alendronate over an 18-36 month period, were treated with teriparatide over 18 months. Variations in BMD and bone-turnover markers were analysed. Subjects who had formerly been given alendronate saw a delayed rise in bone-turnover markers with results more than a third lower than those of subjects who had formerly been given raloxifene. Over the initial six-month period there were marked variations in the rise in BMD at the lumbar spine and hip. Subjects formerly given raloxifene saw more significant rises in BMD at the two sites. After 18 months of therapy marked variations continued in the lumbar spine, with greater improvement in subjects previously given raloxifene, however the variations in the hip were not as decisive. This proves that this application of teriparatide augments bone turnover in subjects formerly given raloxifene or alendronate, and that this improvement comes sooner and is more significant with the raloxifene pretreatment cohort [78].

3.2.4. Corticosteroid-induced osteoporosis and male osteoporosis

Studies have also been published which demonstrate the effectiveness of teriparatide in the management of GIOP. In a randomised, double-blind study, 428 subjects both male and female from 22 to 89 years old, who had been given corticosteroids for a minimum of three months were randomly assigned to be treated with either alendronate 10mg/day or teriparatide 20μg/day over an 18 month period. After a year, the overall femur BMD was greater in the teriparatide cohort and on termination of the trial there were fewer vertebral fractures in the teriparatide cohort [79].

Teriparatide has also been employed as a treatment in men with osteoporosis. The trial analysed results from men with idiopathic or secondary osteoporosis being treated with teriparatide in comparison with a control group. The trial indicated elevated results, independent of gonadal status and other influential elements in the teriparatide cohort [80].

3.2.5. Adverse Effects

Overall, teriparatide (recombinant human PTH (1-34)) injections are well-tolerated. It disappears from the bloodstream in less than four hours following subcutaneous administration. Injections on a daily basis are required and a passing reddening at the injection site has been observed. Headache and nausea have been noted in under 10% of patients treated with a daily dose of 20μg. Mild, early, short-term hypercalcemia can transpire, but severe hypercalcemia is uncommon. Higher levels of urinary calcium (up 30μg per day) and serum uric acid concentrations (up 13%) are witnessed, however these do not seem to have clinical ramifications.
We can conclude that teriparatide is an appropriate and effective drug for the management of osteoporosis. It is efficacious in addressing a variety of clinical conditions, e.g. male osteoporosis or corticosteroid-induced osteoporosis.

3.3. 1-84 Parathormone

Intact PTH (PTH 1-84) has been reported to have a beneficial impact on bone micro-architecture and to reduce incidence of fresh fractures as a result of its bone-forming mode of action [81]. PTH 1-84 is not procurable any more due to the withdrawal of its marketing licence at the behest of the regulating authority.

4. Dual action agents

4.1. Strontium ranelate

The possible clinical applications of strontium were revealed in approximately 1940, when strontium-89 was deployed as an analgesic treatment for bone metastases caused by prostate cancer [82,83].

In-vitro, strontium ranelate augments collagen and non-collagen protein synthesis through mature osteoblasts. The bone-forming action has been demonstrated by the higher levels of replication amongst pre-osteoblastic cells. This catalytic action on the duplication of pre-osteoblastic cells and the higher levels of collagen and non-collagen proteins have caused strontium ranelate to be regarded as a dual effect bone agent, because it does not simply reduce resorption [84]. The principal tool that can determine bone resorption at a molecular level is the RANK/RNAKL/OPG system outlined above. Solutions of 0.1mM to 2nM of strontium ranelate reduce the capacity of human osteoblasts to cause osteoclast differentiation, by reducing expression of mRNA of RANK-L and boosting mRNA expression of OPG, as reported in the trials carried out by Brennan et al. in 2006 [85, 86].

4.1.1. Impact of Strontium ranelate in fracture reduction

Studies have shown that the chemical properties of strontium ranelate cause the, densitometric values of subjects given the compound to be greater than the true values. Complex mathematical formulas exist to cut out the statistical impact of this from the DMO value, however it is more straightforward and sufficiently accurate to assume instead that half of the DMO achieved in the first year of therapy with strontium ranelate is a result of elevations in BMD and the remainder is a result of the basis caused by the heavier strontium measured by the DXA [87].

Information from the SOTI (Spinal Osteoporosis Therapeutic Intervention) study and the TROPOS (Treatment of Peripheral Osteoporosis) study looked at 1,649 postmenopausal subjects (SOTI trial) and 5,091 subjects (TROPOS trial) [88,89]. The initial three-year outcomes demonstrated a decrease in vertebral fractures of 41% with a NNT of 9. Moreover, an im-
Improvement in BMD of 12.7% was recorded. The decrease in vertebral fractures at the end of the four- and five-year periods was 33% and 24% respectively. In relation to non-vertebral fractures, the reduction in the relative incidence of fracture with strontium ranelate was 16% at the end of the three-year period and 15% at the end of the five-year period. A later assessment of these results in a subset of 1,977 subjects with high fracture risk (≥74 years old and a T-score of ≤-2.4) indicated a decrease in the incidence of vertebral fracture of 36% at the end of the three-year period and 43% at the end of the five-year period [87, 90].

4.1.2. Security

Strontium ranelate was deployed in a widespread manner across Europe up to February 2014, when the European Medicines Agency (EMA) advised that the use of the drug be limited to cases which cannot use other treatments approved for osteoporosis, and that subjects with high risk for ischemic cardiac disorders should be excluded from this treatment option. This decision was grounded in a study carried out by the Pharmacovigilance Risk Assessment Committee (PRAC) that highlighted doubts about cardiovascular security which went beyond the risk, already known, of venous thromboembolism. On the basis of the PRAC analysis, an elevated incidence of serious cardiac disorders (including myocardial infarction) was pinpointed and steps were put forward to minimize the risk, specifically targeting the highlighted issue, in April 2013.

5. Overview of current treatments

As set out in this review, there are several treatment options for osteoporosis. Unfortunately the choices are more restricted in daily clinical practice as treatments have been removed or their use restricted. Table 2 provides a summary of those treatments currently available to practitioners.

Table 2. Current available osteoporosis therapies
6. Future treatment options

6.1. Cathepsine K (CatK) inhibitors

Cathepsin K is expressed in the main in osteoclasts and a variety of other multinucleated cells including giant foreign body cells and Langhans cells. To a lesser extent it is present in macrophages, synovial fibroblasts, and fibroblasts at sites of wound repair or inflammation, chondrocytes, various epithelial cells of the human fetus, adult lung airway epithelium, thyroid epithelium, and potentially in low levels within smooth muscle cells. When the enzyme has been synthesised, it is separated into lysosomes and can be introduced into the extracellular environment. It is introduced particularly into the resorption lacuna below actively resorbing osteoclasts where it is causes the degradation of the collagen type I dominated organic bone matrix. Thus, in a similar manner to pycnoidisostosis, removal of cathepsin K from osteoclasts prevents bone resorption. Inhibitors of cathepsin K are reported to have a less significant impact on osteoclast–osteoblast interaction, causing a lower inhibition of bone formation than available bisphosphonate antiresorptive drugs. Human cathepsin K inhibitors have been proven to stop bone loss in ovariectomized mice without reducing the anabolic effectiveness of parathyroid hormone (PTH) [91].

Whilst no CatK inhibitor is licensed for osteoporosis treatment or prevention at the present time, trials of three CatK inhibitors for the management of osteoporosis have been published: balicatib, relacatib, and odanacatib.

6.1.1. Balicatib

Balicatib is extremely selective for CatK in enzyme potency tests but has a reduced selectivity in living tissue. Clinical trials of balicatib have shown elevated BMD in postmenopausal women, but the drug was linked with cutaneous adverse effects. The first presentation of the efficacy of cathepsin K inhibitors on human bone density was witnessed with balicatib. This study, released by Adami et al. at an ASBMR meeting in 2009 (Denver, CO, USA), was a multi-centre, randomised, controlled, 12 month, dose-range identifying trial of 675 postmenopausal subjects with lumbar spine T-score less than 2.0. In the cohort treated with 50mg of balicatib daily, markers of bone resorption were reduced by over 55% with no reduction in markers of bone formation (osteocalcin, bone-specific alkaline phosphatase and N-terminal propeptide of type I collagen). The lumbar spine BMD was elevated 4.46%, that of the total hip was elevated 2.25%. Cutaneous reactions, including pruritus and morphea-like alterations, were observed in a low number of subjects. In a limited Japanese study, intact PTH levels were demonstrated to be elevated by 50% with balicatib treatment [92].

6.1.2. Relacatib

Relacatib is a powerful but nonselective inhibitor of cathepsins K, L, V, and S for which no clinical data in humans has been made public. The use of relacatib with ovariectomized and control monkeys caused an acute and rapid decrease in bone markers, and the impact of this lasted for a maximum of 48 hours, according to the dosage administered [93].
On the basis of the adverse effects, especially the cutaneous reactions, the production of all cathepsin K inhibitor drugs has been discontinued or put on hold, with the exception of odanacatib and, at present, ONO 5334.

6.1.3. Odanacatib

Odanacatib is a potent, selective inhibitor with an ability to inhibit cathepsin K in osteoclasts [91].

Two trials have been undertaken to assess the effectiveness and security of odanacatib, a phase I study to determine the dosage and a phase II study to assess the security and effectiveness.

In the Phase I study a cohort of 49 women was used to assess a weekly dose. Doses of 5mg, 25mg, 50mg, and 100mg were used and 12 subjects were placed in the control cohort. A cohort of 30 women was created to enable the evaluation of the daily dosage. Doses of 0.5, 2.5, and 10mg were deployed, with six subjects placed in the control cohort. All treatments were given under fasting conditions. Odanacatib had an extended half-life of between 66 and 93 hours for all the treatments and dosages assessed. The effectiveness of both weekly and daily dosages in altering the markers was assessed. The impact was dose-dependant but not in proportion to the dosage level. Decreases in resorption markers were highest for weekly doses >50mg and daily doses ≥2.5mg. The greatest suppression was witnessed between days 3 and 5 with the weekly dose and this level remained elevated until the subsequent treatment [95].

The Phase II trial presented by Cusick et al. at the ASBMR meeting in 2009 (Denver, Co, USA), was a double-blind, randomised, controlled study lasting one year, with an expected extension period of two years. It looked at 399 postmenopausal women (postmenopausal (5yr) or bilateral oophorectomy) aged 45 to 85 years, presenting a T-score <-2 but not less than -3.5 in any one location. Subjects were assigned to five different cohorts with differing dosage levels: placebo, 3mg/week, 10mg/week, 25mg/week and 50mg/week. The variations in BMD at the lumbar spine were analysed and taken as the main outcome. In addition, variations in bone remodeling, variations in BMD in other locations and side effects were assessed in turn. The data indicated a elevation in BMD in all locations, which was related to the dose level. The more significant improvement was achieved with the highest dose. Weekly treatments of 50mg of odanacatib augmented bone mass by 5.7% in the lumbar spine, 4.1% in the total hip, 4.7% in the femoral neck, 5.2% in the trochanter and 2.9% in the distal third of the radius at the two-year point. Resorption markers dropped relative to the dose from the start of the therapy and stayed lower over the initial six-month period, at which point they increased to a similar level as those in the control group.

The data from the extension period of the phase II study to the three-year point (reported by Eisman et al. at the ASBMR meeting 2009 in Denver), looked at 169 women randomly assigned to weekly doses of odanacatib 50mg or a placebo. In the odanacatib cohort, BMD continued to rise (lumbar spine 7.5%, total hip 5.5%, femoral neck 5.5% and trochanter 7.4%). The urine NTX resorption marker was reduced by 50% versus the placebo, while the BSAP (bone specific alkaline phosphatase) formation marker remained unchanged. At the three-year point, formation markers had not only not decreased, but had in fact risen by 18% above baseline values.
6.1.4. ONO5334

ONO5334 is a new cathepsin K inhibitor. An initial trial has been carried out to assess its effectiveness and security in the treatment of postmenopausal osteoporosis. This was a year-long, randomised, double-blind, placebo and active-controlled parallel-group trial carried out across 13 locations in six European states. The study looked at 285 postmenopausal women from 55 to 75 years old with osteoporosis. Patients were randomly assigned to one of five dosage groups: placebo; 50mg twice daily, 100mg once daily, or 300mg once daily of ONO-5334; or alendronate 70mg once a week. After 12 months of monitoring all ONO-5334 doses and alendronate demonstrated a marked elevation of BMD at the lumbar spine, total hip (except the 100mg/day cohort), and femoral neck. There was little or no evidence that ONO-5334 suppressed bone-formation markers versus the alendronate, however the suppressive action on bone-resorption markers were comparable. There were no security issues of any clinic consequence. With a marked elevation in BMD, ONO-5334 also heralds a new mechanism in the treatment of osteoporosis. This new agent increases the range of treatments available both in the class of cathepsin K inhibitors as the second apparently available agent, and also across the full range of osteoporosis treatment [94].

We can conclude that Cathepsine K inhibitors are a new class of treatment that adds to the range of therapies available for the treatment and prevention of fractures, the most hazardous consequence of osteoporosis. Being able treat this condition at a variety of points along the resorption pathway is an asset and it provides clinicians with the opportunity to reduce the risk of fractures more effectively than before.

6.2. Sclerostin

Sclerostin is a protein encoded by the SOST gene [96, 97]. It is identified as an important inhibitor of osteoblast-mediated bone formation [98, 99]. Loss-of-function mutations in this gene are linked with sclerosteosis, which results in progressive bone overgrowth and elevated bone mass and BMD.

A similar condition is van Buchem disease, a less severe form of sclerostosis resulting from a deletion downstream of this gene, and leading to reduced sclerostin expression. SOST gene knockout mice no longer produce sclerostin and have an elevated bone mass, which demonstrates the impact this protein has on bone mass and BMD levels. In addition to elevated bone mass and BMD levels resulting from sclerostin deficiency, it is notable that no fractures have been reported in patients with either sclerosteosis or van Buchem disease [99, 100].

Sclerostin binds to low-density lipoprotein receptor-related protein (LRP) 5/6 and intercepts Wnt-signaling, governing bone formation in a negative manner and preventing osteoblast differentiation, proliferation, and activity [101].

6.2.1. Anti-sclerostin monoclonal antibodies

At the present there are three separate humanized sclerostin antibodies under investigation: romosozumab (AMGEN & UCB), blozozumab (Eli Lilly) and BPS804 (Novartis). Romosozumab...
mab is a high affinity immunoglobulin G2 (IgG2) monoclonal antibody. It is produced through the humanisation of a mouse sclerostin monoclonal antibody that neutralizes sclerostin. The first-in-human single-dose trial in healthy men and postmenopausal women was carried out to assess pharmacokinetics, pharmacodynamics, tolerance and security of romosozumab doses of 0.1, 0.3, 1, 3, 5 or 10 mg/kg delivered sub-cutaneously and 1 or 10 mg/kg delivered intravenously. Seventy-two subjects in total took part in the trial and were subsequently monitored for a maximum of 85 days. The pharmacokinetics of this agent were not relative to the dosage levels. Dose-related rises in bone formation markers and falls in bone resorption markers were noted. A small proportion of subjects presented anti-investigational product bodies however the majority of these were non-neutralizing antibodies. The data indicated that the agent was well-tolerated [102].

In a phase II, multi-centre, multi-dose, controlled, parallel groups clinical study, 419 postmenopausal women with poor BMD were randomly assigned to the treatment to assess the effectiveness of romosozumab versus alendronate, teriparatide and a placebo, over a one year course of therapy. The main outcome was BMD change. All the dosage levels of romosozumab causes a marked elevation in the BMD at the lumbar spine, femoral neck and total hip together with a short-term rise in the bone formation markers and a durable fall in the bone resorption markers [103]. Data from the phase III studies is to be published soon.

A randomised, double-blind, controlled phase II clinical study of blosozumab in postmenopausal women with poor BMD was recently made available. Subjects were given subcutaneously administered blosozumab 180 mg Q4W, 180 mg Q2W, 270 mg Q2W or equivalent placebo over a period of one year. In total, 120 women took part. Dosage levels across the range of blosozumab augmented lumbar spine and total hip BMD. Bone formation markers rose rapidly during the therapy while bone resorption markers fell at an early point in the therapy and continued at low level through to the end of the trial [104].

A comparable study was carried out using BPS804 with a similar cohort, however no data is yet published from this trial.

We can conclude that anti-sclerostin antibodies may be the most efficacious agent in the treatment of osteoporosis and bone defect related conditions.

7. Conclusion

Over the last decade, new drugs have come forward as potential pharmacological treatments for osteoporosis. More recent options are part of new classes of agent which present optimised modes of action, allowing practitioners to replace patients’ lost bone mass more quickly and efficaciously than with older treatments. Nonetheless, it is important to be aware that all drugs have their appropriate uses and also a wide range of side effects, factors which must be considered in any clinical decision-making process. Furthermore, it is vital that practitioners ensure that, as required by the majority of therapies, treatments for osteoporosis are administered alongside adjustments in a patient’s lifestyle and/or calcium and vitamin D supple-
mentation. New treatments are now coming into use that are likely to enable practitioners to opt for shorter courses of therapy which result in better outcomes for patients.

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