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► **To cite this version:**

Christian Roux, Karine Briot. The crisis of inadequate treatment in osteoporosis. The Lancet Rheumatology, 2020, 2, pp.e110 - e119. 10.1016/S2665-9913(19)30136-5 . hal-03490127

**HAL Id: hal-03490127**

**<https://hal.science/hal-03490127v1>**

Submitted on 21 Jul 2022

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# **OSTEOPOROSIS: INADEQUATE CARE OF A POTENTIALLY SEVERE DISEASE**

**OR:**

## **THE CRISIS OF INADEQUATE TREATMENT IN OSTEOPOROSIS**

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**Conflict of interest statement:**

**CR : personal fees from Alexion, Amgen, Lilly, UCB ; research grants from Alexion, Kyowa Kirin, Regeneron.**

**KB : personal fees from Amgen, Lilly, Pfizer, UCB.**

#### Search strategy and selection criteria.

We searched PubMed and the Cochrane library for articles and reviews in the English language published between Jan 1, 2015 and June 30, 2019. We used the search terms “osteoporosis” and “fracture”, and limited the search to human, clinical studies, clinical trials, and meta-analysis. We also used older references, indicated in identified articles and authors’ own files, when appropriate.

The final reference list was generated on the basis of relevance to the concepts the authors aimed to highlight in the manuscript.

The number of fractures related to osteoporosis is expected to increase dramatically in the next few decades because of an increase in the number of osteoporotic elderly patients at high risk of falls and thus of fractures. Recent data and current developments in the diagnosis and treatment of osteoporosis may change our strategies of management of osteoporotic patients: the imminent risk fracture concept, the matter of treatment sequences, the potential effectiveness of screening, the goal-directed treatment strategy... Despite these remarkable advances, few patients receive appropriate treatment for osteoporosis, even after a fracture. The crisis in the treatment of osteoporosis is related to several factors, including the fears and beliefs that patients, as well as physicians hold about the adverse effects of current treatments. Strategies to address this crisis are important challenges. Careful selection of patients at high risk of fracture, selection of the best therapeutic strategy and accurate communication about fracture risk and bone fragility must be improved for optimizing population care, as the prevention of fragility fractures is within our reach.

## **INTRODUCTION**

Osteoporosis is a generalised bone disease characterised by a decrease in bone mass and a deterioration of bone microarchitecture resulting in an increased risk of fracture (1). Thus osteoporosis is both a disease, and a risk factor for fracture. Fragility fractures are a significant health concern, some of them being associated with increased morbidity, and mortality, and result in a considerable global economic burden. The number of osteoporotic elderly patients at high risk of falls and fractures is expected to increase dramatically in the next few decades, and in some countries the number of centenarians climbs sharply (2). The delay in human senescence has profound implications for both societies and individuals, who expect to reach old age in good health.

The objective of the treatment of osteoporosis is to decrease the risk of fracture. Guidelines are now available worldwide for screening of patients at high risk of fragility fracture, and for diagnosing and treating osteoporosis. Detailed reports have been published recently on bone biology (3) and epidemiology, pathogenesis, and management of osteoporosis (1). A number of recent data and current developments can change profoundly our strategies of management of osteoporotic patients: the clustering in time of fractures, the matter of treatment sequences, the potential effectiveness of screening, the goal-directed treatment...This paper reviews these concepts and challenges with the aim to raise awareness within clinicians to change their practices accordingly, so that sustained reductions in fracture risk can be achieved. .

## **THE CRISIS IN THE TREATMENT OF OSTEOPOROSIS**

Prescription of anti-osteoporotic drugs varies throughout the world but is dramatically decreasing in most countries in contrast to the general significant increase in overall prescription drug use and polypharmacy (4). Limitations in DXA reimbursement could contribute to the treatment gap. . The decline is not only the consequence of stopping treatments in low risk patients, or in patients who received prolonged therapies; it is observed also in patients who should be treated. From 2001 through 2009, initiation of osteoporosis pharmacotherapy following fragility fractures declined in US, even if only an average of 19% of these fractured patients were initially treated (5). After hip fracture, osteoporosis medication use in US within 12 months after discharge was 40% in 2002, and 20% in 2011 (6). This result is confirmed in other countries, including European countries, and after various incident fractures. Even in women with more than one incident fracture over 1 year, only 35% had a prescription of an anti-osteoporotic treatment (7).

Among the reasons of this “crisis” in the treatment of osteoporosis are the scarcity awareness of osteoporosis among health-care providers and the fear of side effects of some of the treatments: osteonecrosis of the jaw, atypical femoral fractures, atrial fibrillation, hypocalcemia. These side-effects are rare, but their perception is high (4). The incidence of osteonecrosis of the jaw is estimated to 1/10,000 bisphosphonate users i.e. an absolute risk of 0.001% to 0.01% (8). In

60,000 alendronate users, over a mean of 6.8 years of use, the incidence of osteonecrosis (and osteomyelitis) of the jaw was 2.53/10,000 patient-years (9). This open nationwide register based cohort study gives also the incidence of these events in untreated osteoporotic women (i.e. in the year preceding initiation of alendronate treatment): 1.13/10,000 patient years. In patients treated with denosumab over 10 years (10), the incidence of osteonecrosis of the jaw was 5.2/10,000 participant-years. Importantly, the American Dental Association underlined the importance of oral hygiene, dental health and routine dental care in treated patients, and recommended to not alter osteoporosis therapy before dental procedures. According to this Association, the decision to stop anti-resorptive therapy must be weighted against the risks associated with the underlying bone fragility (11). The incidence of atypical femoral fractures is between 3/100,000 to 5/10,000 among bisphosphonate users (12, 13) and 0.8/10,000 for long-term use of denosumab (10). Incidence of these fractures in bisphosphonate-treated patients increases with duration of treatment, and drops dramatically in the year following discontinuation (12). Careful attention must be paid in patients with chronic use of an anti-resorptive treatment to sudden or chronic thigh pain with or after weight-bearing activities: imaging (either magnetic resonance imaging, extended DXA scans, or bone scintigraphy) should be promptly performed, checking for any periosteal or endosteal thickening involving the lateral cortex of the femoral diaphysis (stress fracture), before the occurrence of a spontaneous transverse fracture. Placebo-controlled studies assessing anti-fracture efficacy of bisphosphonates have been of 3-5 years duration, and this is the duration of treatment with the highest benefit and minimal risks. At 3 or 5 years of bisphosphonate treatment, risk must be reassessed, and prolonged treatment must be given only for patients who are still at high risk of fracture (13).

According to numbers of events reported in clinical studies and cohorts, the number of subjects needed to harm is dramatically higher than the number needed to treat in a population of osteoporotic patients at high risk of fracture. Nevertheless, patients and practitioners are wary of these side effects. This could be the consequence of negative publicity in press and media (14). US Google search activity for the term “Fosamax®” (alendronate) from 2004 to 2015 shows huge spikes in 2006, 2008, and 2010, coincidental with press releases of side effects of the drug, and no peak of activity in the months following Food and Drug Administration and American, Society for Bone and Mineral Research reports (15). Even a follow-up to rectify (on a scientific basis) a biased presentation on television did not attenuate the effect of decreased prescriptions (16). But next to patients' concerns, physicians' views of osteoporosis can raise new barriers for treatment. Osteoporosis may be not perceived as a disease, but rather as natural, inevitable, bone deterioration (17). Fracture is considered as secondary to a fall, an event which is rare and random, and fragility fracture can be a misnomer. Finally the patients' perception of risk is both unpredictable and unchanged even by using different presentations (absolute or relative risk) (18). Accurate communication about fracture risk and bone fragility must be improved for optimizing population care.

## **FRAGILITY FRACTURES**

### **a) Consequences of fractures**

Hip fracture is the most devastating osteoporotic fracture because of the proportion of patients who do not regain previous mobility, or have severely chronic impaired mobility, requiring long-term nursing care. An increased risk for death after hip fracture is well established in both women and men. This has been shown early after the fracture, i.e. in the first 3 months (with a 5 to 8 fold increased risk for all-cause mortality) (19). This excess annual mortality persists over time, markedly in the youngest patients (aged 65-79 years), for up to 5 to 10 years (20). Hip fracture incidence varies within geographical regions, and changed over the past decades; it has been declining in some world regions since the mid-70s. However, the secular trend diverges according to countries, decreasing in some (21) (but not all (22)) Western countries, and increasing in Asia. Reasons for changing rates in fracture trends are unclear, and could be changes in lifestyle, obesity, birth period cohort effects, and in screening and treatment of osteoporosis. The women-to-men incidence rate ratio of major osteoporotic fractures decreased in Denmark between 1995 and 2010; in men was observed a lower rate of decrease of hip fracture but an increasing trend in vertebral fracture (23). In United States, hip fracture rates declined, but a plateau was observed recently (24) for which causation cannot be established; it is coincidental to both changes in population demographics in the country, and profound decline in osteoporosis care.

Vertebral fractures are the hallmark of osteoporosis. They differ from non-vertebral fractures by several characteristics. They usually occur during daily activities (lifting, bending forwards...), and thus without evidence of trauma or fall. In contrast to non-vertebral fractures, they are not a binary phenomenon (yes/no) but can be of graded severity, and classified in mild, moderate and severe fractures. This classification is clinically relevant, as the greater the number of prevalent vertebral fractures, and the greater their severity, the higher is the risk of incident vertebral and non-vertebral fractures. Even mild vertebral fractures indicate a high risk of sustaining shortly another vertebral fracture in osteoporotic elderly women (25). Attention must be paid to these mild fractures; some of them are missed because some physicians consider that they are only an expected effect of age. Others are not diagnosed and considered wrongly as an osteoarthritis-related deformity or a congenital short vertebral height. At any given value of bone mineral density, the risk of incident vertebral, and actually any fracture, depends heavily on the presence of prevalent radiographic vertebral fracture, even if they did not come to clinical attention (26). Thus assessment of vertebral fracture status by imaging technics, including the use of lateral thoracic and lumbar spine views by dual-energy X-ray absorptiometry (fig 1), to detect previously unrecognized vertebral fractures must be considered in individuals at risk for such fractures (such as chronic use of glucocorticoid therapy). This is a convenient way to avoid under-recognition of vertebral fractures. Whether or not they are symptomatic at time of diagnosis, vertebral fractures are associated with an increased mortality rate (27) which rises with greater number of vertebral fractures.

Among non-hip, non-vertebral fractures, some can have severe consequences such as those of the proximal humerus and pelvis (27); one-year excess mortality after fracture of a pelvis is 20 to 25%, and 5 to 10% after humerus fracture (28). The causes of excess mortality after fractures are poorly understood. However individuals with comorbidities have worse survival than those individuals who fracture but are comorbidity-free (29). This observation allows a selection of a population who should receive highest priority for early therapeutic intervention.

Men with osteoporosis have higher re-fracture and mortality risk than women (30). The difference may be related to poorer health and difference in co-morbidity profiles.

### **b) Imminent fracture risk**

The presence of prevalent fractures is the main risk factor for sustaining an incident one. But the risk of subsequent fracture is time-dependent, with much higher fracture risk in the first 2 years after an index fracture, a period defining an imminent fracture risk (31). In a prospective population-based study of post-menopausal women (without information on underlying osteoporosis), 924 sustained a first fracture from menopause onwards; 23% of all subsequent fractures occurred within 1 year and 54% within 5 years after the first one. Thus, the relative risk of sustaining a new fracture is 2, but reaches 5 in the first 2 years (32). In individuals with a recurrent fracture following a hip fracture, 45 % sustained the first further fracture one year after the sentinel fracture. Relative risks for fracture recurrence are highest immediately after the sentinel fracture (2.6-5.3, depending on the site of fracture) and fall progressively over 10 years (1.5-2.2) (33). Determinants for imminent fracture risk include advancing age, fracture site (major osteoporotic fracture i.e. hip, vertebrae, wrist, humerus), bone mineral density, falls and specific comorbidities (central nervous system (CNS) diseases, concomitant medications targeting the CNS) (34, 35). Advancing age is a determinant for imminent subsequent fractures: early intervention should be a priority in the very old patients with recent fracture (36).

The imminent risk of refracture can be related to different factors. The postfracture care can, paradoxically, increase the risk, through an increasing risk of falls during rehabilitation, impaired coordination and immobilization. Moreover, the underlying conditions may not be appropriately managed: in a total of 168,133 patients with a fragility fracture, mean age 80 years, roughly 70% of patients were exposed to at least one drug associated with increased fracture risk, and this proportion was unchanged at the time of discharge (37). Thus, the fracture was a missed opportunity for secondary prevention.

This transiency suggests that treatment given to such patients immediately after fracture might avoid a higher number of new fractures compared with treatment given at a later date providing that the drugs are potent and rapidly acting. However, randomised studies which have shown the effectiveness of pharmaceutical intervention do not give the information on the recency of fractures before inclusion, and these studies were not powered to assess the short term benefit of the treatment. In pivotal studies of currently approved anti-osteoporotic drugs, regardless of



statistical significance, divergence of curves of fracture incidence in treated and placebo groups occurs at month 12. The risk of a clinical fracture has been shown to decrease by 35% (median follow-up of 19 months) when zoledronic acid was given to patients (mean age of 74 years) within 90 days after a hip fracture (38). In a post hoc analysis, significant divergence in the fracture-free survival curves between the placebo and the zoledronic acid groups for all clinical fractures was seen as early as 12 months. In a post-hoc analysis of the trial comparing teriparatide and risedronate in post-menopausal women with prevalent vertebral fractures (VF), the recency of the VF (in the previous year) did not change the result of the reduction of new VFs (39). These data suggest the relevance of an early intervention.

## **FRACTURE RISK ASSESSMENT**

A low bone mineral density (BMD) is a strong risk factor for fragility fractures, and a densitometric threshold (T-score < - 2.5) can be used for osteoporosis definition (thus using a risk factor to define a disease); its specificity is high, but its sensitivity is low, as the majority of fragility fractures occurs in patients with T-score which does not reach this threshold. Thus, BMD is only one of the determinants of fracture: the combination of bone density with other risk factors (including age) improves detection of at risk-patients. Three tools using different risk factors, with or without bone density have been validated in independent cohorts (1); they calculate an individual absolute risk (not relative risk). The Garvan fracture risk calculator includes information on number of previous fractures and falls, and calculates 5 or 10 year osteoporotic fractures risk. The Q Fracture Score includes dose response for smoking and alcohol intake, and a larger list of risk factors than FRAX<sup>®</sup>. FRAX<sup>®</sup> ([www.shef.ac.uk/frax/](http://www.shef.ac.uk/frax/)) is the most frequently used worldwide to estimate the individual 10-year probability of hip or major osteoporotic fracture. FRAX<sup>®</sup> uses age, sex, body-mass index, parental hip fracture, previous fragility fracture, glucocorticoid use  $\geq 3$  months, rheumatoid arthritis, secondary osteoporosis, current smoking, alcohol intake  $\geq 3$  units per day; femoral neck BMD or T-score is optional. The therapeutic intervention threshold is the probability of having a fracture equivalent as the one of a woman of the same age who has already had a fragility fracture. FRAX<sup>®</sup> calculation does not take into account some risks of fracture, such as the recency, location, severity and number of previous fractures, falls and type 2 diabetes. Three prospective randomized controlled studies assessed the effectiveness of a screening of osteoporosis, as compared to usual management. The primary outcome was the proportion of individuals who had osteoporotic fractures. SCOOP study was conducted in women aged 70-85 years recruited by general practitioners (40). In the screening group treatment was recommended in women with a high risk of hip fracture using FRAX<sup>®</sup>, and the follow-up was 5 years. Screening did not reduce the incidence of all osteoporosis-related fractures, but reduced the incidence of hip fracture (hazard ratio 0.72 (0.59-0.89)). The ROSE study was conducted in women aged 65-80

years (41). Participants who were randomized to the screening group had a two-step screening program: FRAX<sup>®</sup> tool was used to select women for a bone densitometry. No significant difference was found in the intention-to-treat analysis, but the per protocol analysis showed a risk reduction in the group that underwent bone densitometry compared to women in the control group with a FRAX  $\geq$  15%. The best result was observed for hip fractures (sub hazard ratio 0.74 (0.58-0.95)). SALT study assessed a group of women 65-90 years with at least 1 clinical risk factor for fractures (42). Over a mean follow-up 3-7 years, screening and subsequent treatment had no statistically significant effect on the primary outcome fracture (nor major osteoporotic fracture nor hip fracture), as compared to controls.

Screening efforts for osteoporosis are expanding, by opportunistic use of data from computed tomography (CT) scans. A huge number of thoracic and abdominal CT scans are performed daily for various medical reasons, and information on spine (vertebral deformities, CT attenuation in Hounsfield units) are available, without added time, cost, and radiation. An opportunistic screening for osteoporosis can thus be easily implemented, and could be used in clinical practice to identify patients with an increased risk of fractures (43).

## **MANAGEMENT OF OSTEOPOROSIS**

### **a) Fracture liaison services**

One of the main reasons for the care gap existence is that postfracture management is considered as a low priority, because of the lack of awareness of the seriousness of the disease by physicians, policy makers, health administrators and the general public. Fracture Liaison Services (FLS) emerged for secondary fracture prevention targeted to patients with recent fractures. According to non-randomized studies, implementation of an FLS reduces the risk of subsequent fracture as compared to usual care. A prospective comparative observational study showed in patients with a recent non vertebral fracture that those followed in an FLS had a significant lower mortality risk of 35% over 2 years after adjustment for age, sex and baseline fracture risk (44). In a meta-analysis of 74 studies (16 controlled; 58 observational), FLS was associated with improvements in all outcomes versus non-FLS controls, with a 20% increase in initiation of an antiosteoporotic treatment, a 22% improvement in treatment adherence, a 5-point decrease in the absolute risk of new fracture and a 3-point decrease in the risk of death (45). The C-STOP randomized trial compared the efficacy of high-intensity FLS care (nurse care manager, BMD measurement and, if appropriate, initiation of therapy) to a low- intensity FLS care (information of the patient and physician about a possible link between the fracture and osteoporosis, with a reminder about management recommendations) (46). The proportion of patients taking osteoporosis medications after 6 months was significantly lower in the low-intensity than in the high-intensity group (28 vs 48%,  $p < 0.0001$ ). Within 6 months of the fracture, 76% of the high-

intensity group were considered to have received an appropriate management compared to only 44% in the low-intensity group (46). FLSs are cost-effective compared with usual care for the prevention of further fractures; the finding is consistent across randomized and non-randomized trials (45).

### **b) Treatment of vertebral fractures**

Restoration of shape is usual for non-vertebral fractures, using orthopedic and surgery procedures, but not for vertebral fractures. Acute pain associated with vertebral fractures needs analgesics and bracing, but these procedures do not always alleviate pain. In the 1990s, vertebroplasty was proposed to reduce both pain and vertebral body deformity (fig 2). During this procedure polymethyl-methacrylate is injected percutaneously in the fracture, with the objective to fuse the fragments of vertebral body, thus reducing local motion and pain; this can be done with or without using a balloon before the injection (kyphoplasty). Positive results on pain have been published in many retrospective or uncontrolled prospective studies. However among the 5 prospective randomized trials that compared vertebroplasty and placebo procedure, 4 showed that vertebroplasty conferred no clinically benefits with respect to pain and disability (47). In a recent Cochrane review; there is no evidence that subgroups could benefit more from the procedure, including those with very recent pain. This has been rebutted by the authors of the randomized trial which showed efficacy of vertebroplasty in elderly patients with acute vertebral fractures of less than 6 weeks' in duration (48). In the placebo groups, the procedures included skin incision, subcutaneous lidocaine, use of short needle, regular tapping on the needle, and preparation of the cement (smell of it permeating the room)... Interestingly in open trials which compare percutaneous vertebroplasty with standard medical care (i.e. without such "placebo" procedures), the analyses favour vertebroplasty for pain (6 trials) and disability (5 trials) (49). Beyond the technical differences, other characteristics such as proportion of inpatients and fracture duration are different among trials. In patients with very painful acute osteoporotic vertebral fracture of less than 6 weeks in duration, vertebroplasty should be considered providing that appropriate anti osteoporotic medication is started

### **c) Non pharmacological interventions**

Recommendations are available worldwide for calcium, protein and vitamin D intakes and weight-bearing physical activity, which are potential modifiable risk factors for osteoporosis (2). In community-dwelling people, aged 65 years and over, 1.9% of persons injured as the result of a recent fall reported a fractured hip, femur or pelvis, (2.7% for ribs or sternum, and 3.4% for lower leg and feet fractures) (50). Reducing fall frequency can help in prevention of a proportion of non-vertebral fractures; but fall is not a proven risk factor for vertebral fractures (51), which are usually spontaneous, and secondary to daily life movements. Correction of visual impairment (such as cataract surgery) has been associated to less hip fractures in a large retrospective study (52). In

community dwelling older adults, home based exercise programs reduce the risk of falls in primary fall prevention (i.e. in subjects selected on age alone) and secondary prevention (i.e. subjects selected after a fall) (53). Exercise alone, and combined exercise with various measures (vision assessment and treatment, environmental assessment and modification...) are associated with lower risk of injurious falls compared with usual care in subjects aged 78 years on average (54). Whether such programs can prevent injuries induced by falls, including fractures, has also been suggested in a meta-analysis of randomised controlled trials (55), but with significant heterogeneity between studies assessing injurious falls. In subjects 60 years and older (mean 73 years), long-term exercise training is associated with a significant decrease in the risk of fall and injurious falls, with a trend (RR = 0.84, p = 0.05) for a reduced risk of fractures (56). Providing that these exercises are adapted to patients' general health and fragility, with programs of 30 to 60 minutes 2 to 3 times per week, there is no side-effects related to this treatment.

Patients with low intakes of calcium and or vitamin D must be supplemented and these supplementations are adjuncts to osteoporosis therapies. The correction of deficiencies must ensure a total daily intake of calcium of 800-1200mg, and serum 25 hydroxyvitamin D of 50-75nmol/l (1). Calcium supplementation alone, or vitamin D supplementation alone cannot be recommended for fracture prevention in the general population. High doses of vitamin D can have deleterious effect on bone (57, 58). Meta analyses using different inclusion criteria show different results of vitamin D supplementation on fracture prevention, either a benefit (59) or absence of benefit (after exclusion of trials that combined vitamin D with calcium and compared with placebo (60)). Discrepancies can also be related to inclusion of subjects with, or without calcium or vitamin D deficiencies. None of the meta-analyses showed a benefit on the risk of vertebral fractures. The largest reduction in hip fracture incidence has been shown in 1992, in a large randomized study conducted in elderly women who were nursing home residents, and had a very low 25-hydroxy vitamin D serum levels at baseline (59). In the most recent meta analysis of 33 randomized clinical trials, the use of supplements that included calcium, vitamin D, or both, compared with placebo or no treatment was not associated with a decreased risk of fractures in community-dwelling older adults (61). The potential benefit of vitamin D supplementation on cardiovascular and cancer risks has not been confirmed (62).

Non pharmacologic interventions are not sufficient therapy for patients at high risk of fracture.

#### **d) Pharmacological interventions**

Several pharmaceutical treatments are effective in reducing the risk of vertebral, non-vertebral, and hip fractures, based on clinical trials of optimal methodology (table 1). These trials have been conducted in patients having low BMD and/or osteoporotic fractures. There is no evidence of anti-fracture effect of drugs in patients having only increased risk of fall, without proven underlying bone fragility. Treatments are recommended in patients with a high risk of fracture. Most of the pharmacological interventions available for women are also approved in men, based on

studies assessing the BMD changes induced by these treatments in men, with the underlying hypothesis that the similar changes in BMD could induce a similar decrease in fracture risk. The most commonly used osteoporosis drugs are anti-resorptive drugs: bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid), selective estrogens receptor modulators (SERMs), and denosumab (fully human monoclonal antibody against RANK-Ligand). Estrogen therapy with or without progestines is effective in prevention of bone loss and fractures, and can be used in early post-menopausal women when other drugs are not appropriate. The effects of the drugs on bone remodelling and modelling are different (1) and this explains differences of effects on trabecular and cortical components of bone, and pattern of changes on bone mineral density. Poor adherence to oral anti-osteoporotic treatments is well documented (1).

Long-term bone retention is a pharmacology property of bisphosphonates, meaning that these drugs are still active after discontinuation, for periods of time which are different among the molecules. This is not true for estrogens, SERMs and denosumab. An accelerated bone loss has been shown after withdrawal of denosumab: most of the decrease occurs during the first year after the last injection. This is concomitant to changes in bone turnover parameters that increase above baseline values within 3 to 6 months of discontinuation, i.e. after cessation of the drug effect on inhibition of osteoclasts formation, function, and survival. The risk of multiple vertebral fractures during this bone loss has been reported in case reports (63). After discontinuation of denosumab or placebo in the pivotal trial of the drug (64) there is a higher increased risk of multiple vertebral fractures in the previously denosumab treated patients, as compared to previously placebo treated patients (risk of 3.4% and 2.2% respectively). Thus it is recommended to anticipate the duration of treatment with denosumab. When discontinuation is decided, bone resorption markers must be assessed on a regular basis, and anti resorptive drug introduced accordingly (65). Teriparatide is an anabolic therapy, administered daily for 18-24 months, which reduces the risk of vertebral and non-vertebral fracture. Upon discontinuation of teriparatide, use of an anti-resorptive treatment prevents any decrease in BMD.

Extension studies have been conducted up to 10 years for denosumab (10); reliability of these extension studies is low because the absence of placebo group precludes any definitive conclusion on prolonged anti-fracture efficacy of the drug as compared to natural history of the disease. However these studies give relevant information about management of patients who require long-term treatment, and show that these prolonged treatments are associated with low rates of fracture, similar to the observed rate of the initial placebo-controlled trials (10). In the context of publicity about adverse events linked with long-term anti-osteoporotic treatments, it is a common practice to use "drug holidays" for bisphosphonates therapy, i.e. discontinuation therapy after 3 (zoledronic acid) or 5 (oral bisphosphonates) years. There is no clinical trial data which can be used to validate such a strategy. According to a recent systematic review (66), risk factors for fracture after stopping treatment are actually those that provide indication for treatment: low bone

mineral density and prevalent fractures. The duration of treatment must be discussed and shared with the patient based on analysis of risk factors for fractures.

The treat to target strategy plays an important role in several fields of medicine, and management of patients based on targets of blood pressure (hypertension), glycated haemoglobin (diabetes), or disease activity score (rheumatoid arthritis) is recommended. Such a strategy could help in the management of patients with osteoporosis. Fracture prevention is the goal of the treatment but it is not possible at the individual level to use the absence of fracture as an efficacy criterion. The treatment induced change in BMD is in theory the ideal candidate and can now be discussed in line with availability of new drugs which have a higher effect on BMD than oral bisphosphonates. A registry-based cohort study showed that treatment related increases in total hip BMD are associated with reduced fracture risk compared with absence of change in BMD (67). A recent meta regression of 38 placebo controlled trials of 19 therapeutic agents showed that the greater the improvement in bone density, the greater is the reduction in vertebral and hip fractures (not non vertebral fractures). For a 2 or 6% increase in total hip bone density, the expected decrease is 28 or 66%, and 16 or 40% for vertebral and hip fracture risk respectively (68). Thus improving bone density in patients with baseline low BMD is an objective of the treatment, and switching to another class of treatment must be considered if this objective is not reached. The problem however is to determine an optimal threshold to attain. This threshold is unknown, and may vary according to baseline value, age and associated risk factors. Continuous increase in hip BMD is associated with further fracture risk reduction (69), thus therapeutic intervention target must be decided on an individual basis.

Fracture prevention in patients with T-score higher than  $-2.5$  has been a debate; hormone replacement therapy showed both prevention of bone loss and reduced risk of vertebral and hip fractures in a low risk population. Most of the studies of anti-osteoporotic treatments have been conducted in post-menopausal women with osteoporosis (i.e. low bone mineral density with a T-score below  $-2.5$ ) and/or vertebral fractures. Prevention is a challenge, because of the risk of exposing to treatment subjects without fracture risk. The majority of post menopausal women does not have osteoporosis, and thus the majority of fractures occur in subjects with T-scores higher than  $-2.5$ . The association between bone density and fractures is a gradient and the threshold of  $-2.5$  is somewhat arbitrary: it produces a prevalence of osteoporosis in the femoral neck among post-menopausal women equivalent to the life-time risk of hip fracture for a 50-year old white woman (15-20%) (70). Osteopenia, i.e. a T-score between  $-1$  and  $-2.5$  is not a bone disease, but such T-scores can be observed in patients with a fragility fracture, because they have added risk factors. Patients with chronic inflammatory conditions (including without glucocorticoid therapy), renal insufficiency, obesity, diabetes, use of glucocorticoids, aromatase inhibitors, are more prone to have fractures although they don't have densitometric osteoporosis (71). Thus other determinants of bone strength, beyond bone density, must not be ignored. This was the rationale of the study of zoledronic acid 5mg against placebo at 18 month intervals over 6 years, in women

aged (71 years in average) and having a femoral neck T-score of -1.6. A fragility fracture occurred in 190 women in the placebo group and in 122 women in the zoledronate group, which represents a statistically significant reduction of risk (72). This result suggests the possibility of a primary prevention in women 65 years or older having fracture risk factors: the number of women that would need to be treated to prevent the occurrence of a fracture in one woman was 15, which is dramatically lower than the estimated number of patients to treat in the population 50-65 years (70).

The choice of first-line therapy has long been based on clinical judgment and local guidelines. However a number of studies suggest that sequence actually matters. Teriparatide is more effective than risedronate, as first line therapies, in decreasing the risk of new vertebral and clinical fractures, over 2 years, in post-menopausal women (72 years on average), with a mean lumbar spine T-score of -2.2, and with at least one vertebral fracture (and for 65% of them at least 2) (73). Thus, in such a population with severe osteoporosis, an anabolic agent must be used first, before switching to an anti-resorptive. Two other anabolic agents are now available in some countries. Abaloparatide is a parathyroid hormone related protein analogue, administered daily (80µg) as subcutaneous injections which has been compared to teriparatide and placebo in a 18 months study; both abaloparatide and teriparatide decrease significantly the risk of vertebral fractures (by roughly 80%); there were few non-vertebral fractures in the abaloparatide group (74). BMD increases from baseline to 6 months were greater in the abaloparatide group than in the teriparatide group at the total hip and femoral neck. The overall incidence of hypercalcemia was lower in the abaloparatide group (3.4%) than in the teriparatide group (6.4%). The results of this trial, assessing time to first event, suggest an early anti-fracture efficacy. Abaloparatide is not available in Europe. Romosozumab is a humanized monoclonal antibody against sclerostin (an osteocyte derived inhibitor of bone formation), given as monthly subcutaneous injections. The drug increases bone mineral density at the lumbar spine by 13.3% within 1 year in post-menopausal osteoporotic women, which is roughly one standard deviation, i.e. equivalent to +1 in T-score. The anti-fracture efficacy has been studied according to 2 different strategies. In one study, post-menopausal women with osteoporosis were randomized to romosozumab or placebo for 12 months, followed by an open label extension during which all women received denosumab 60mg every 6 months for 12 months (75). During the first 12 months, there was a significant reduced risk of vertebral fractures (1.8% in the placebo group versus 0.5% in the treated group), but not on non-vertebral fractures. In the second study, patients with severe osteoporosis were randomized to romosozumab monthly or alendronate 70mg weekly for 12 months; all patients received alendronate during the second year. The primary end point was at 2 years of treatment; over 24 months of treatment a 48%, 38% and 19% lower risk of vertebral hip, and non vertebral fractures was observed in the romosozumab-to-alendronate group as compared to the alendronate only group. (76). Knowing that previous bisphosphonate treatment attenuates the bone-forming effect of teriparatide, a prospective randomized study compared the effects of teriparatide and romosozumab on bone mineral density in post-menopausal women with osteoporosis transitioning

from oral bisphosphonate therapy (77). Through 12 months the difference in hip bone mineral density changes was statistically significant, being higher in the romosozumab group(3.2%). Current investigations are on-going to explain a numeric imbalance in serious adverse events affecting the cardiovascular system during the first 12 months of the alendronate-controlled study (76). The drug has been approved by the US Food and Drug Administration and is being evaluated by the European Medicines Agency.

The different mechanisms of action of anti-osteoporotic drugs (anti-resorptive versus anabolic) suggest that combinations of therapies may be useful. Initially the results were disappointing for combination of oral bisphosphonates and parathyroid anabolic agent (78). However one single infusion of zoledronate acid in combination with daily teriparatide has a better effect on bone mineral density than each drug alone (79). The combination of teriparatide 20µg daily and denosumab 60mg every 6 months has also a better densitometric effect than either treatment alone (80). These combination treatments may help in situation of very low bone density, recognizing however that there is no evidence of their anti-fracture efficacy.

There is a need for identifying novel therapeutic approaches for prevention and treatment of osteoporosis. A role for senescent cells in age-related bone loss has been investigated recently (81). These cells accumulate in the bone micro environment with aging; they are associated with a decrease in bone formation and increase in bone resorption. Under experimental conditions senolytic compounds reduce the burden of senescent cells and suppress bone resorption, but without the coupling effect on bone formation: actually it is observed an increase (cortical bone) or maintenance (trabecular bone) in bone formation. This suggests a complete different treatment strategy for osteoporosis, targeting a mechanism which is also involved in other age-related comorbidities.

## **CONCLUSION**

Our practices can change, by implementing systems of care such as FLS, improving screening of high risk patients, and improving therapeutic strategies, to provide sustained reductions in osteoporotic fractures risk. Prevention of fragility fractures is within our reach.



**Table 1: Type of fracture risk reduction of approved anti osteoporotic treatments**

Type of treatment	Vertebral fracture réduction	Non vertebral fracture reduction	Hip fracture reduction	Phase 3 studies duration (vs placebo)	Long term studies duration (extension studies)
<b>Antiresorptive treatments</b>					
Selective oestrogen receptor modulators					
Raloxifene (82)	Yes	No	No*	4 years	8 years
Basedoxifene (83)	Yes	No	No*	5 years	7 years
Bisphosphonates					
Alendronate (84)	Yes	Yes	Yes	5 years	10 years
Risedronate (85)	Yes	Yes	Yes	4 years	7 years
Ibandronate (86)	Yes	No	No*	3 years	5 years
Zoledronic acid (87)	Yes	Yes	Yes	3 years	9 years
Denosumab (10)	Yes	Yes	Yes	3 years	10 years
<b>Anabolic treatments</b>					
Teriparatide (88)	Yes	Yes	No*	2 years	
Abaloparatide (74)	Yes	Yes	No*	18 months	
Romozozumab (76)	Yes	Yes	Yes	1 year (vs alendronate)	

\*These studies were not powered for this assessment

**Figure 1: Vertebral Fracture Assessment (VFA) using dual-energy-X-ray absorptiometry.**

**This image is obtained at the time of bone mineral density measurement.**

**A – VFA of 68-year old subject**

**B – incident lumbar vertebral fracture in the same patient**

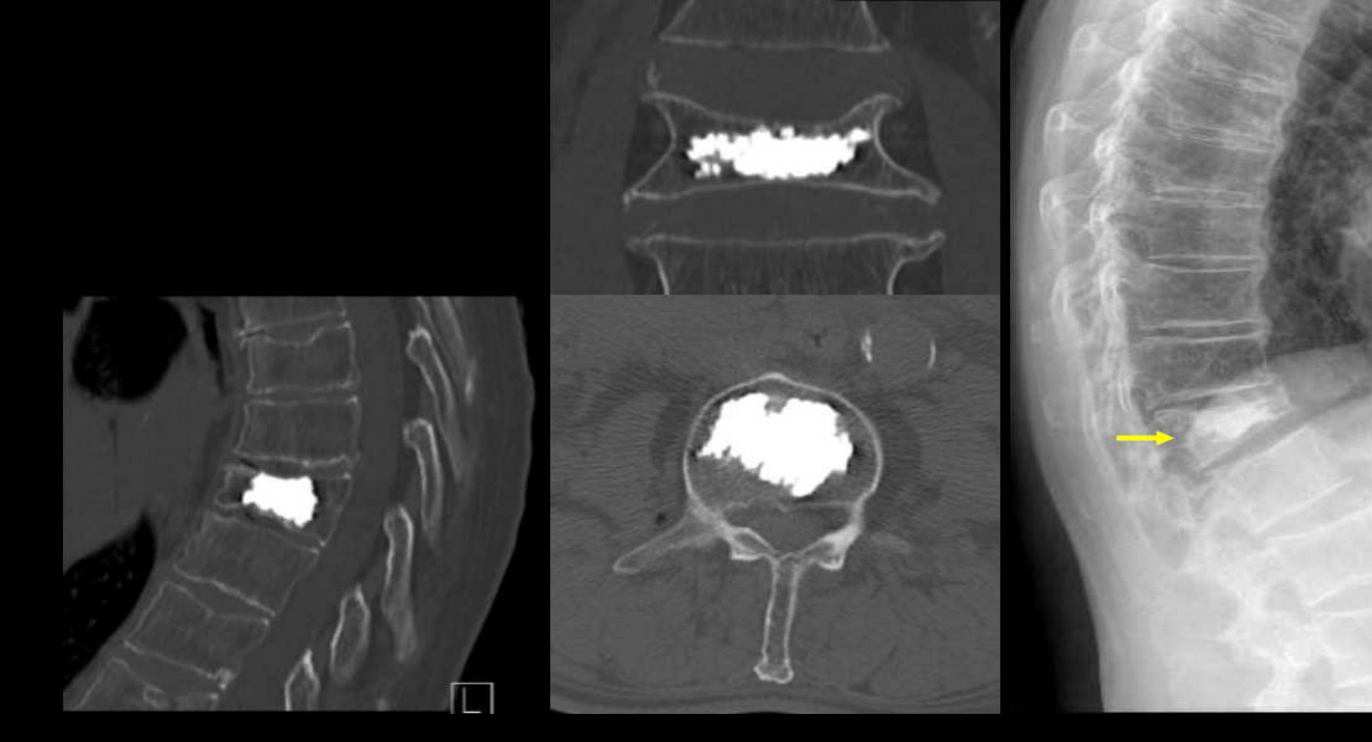


**A**



**B**

Figure 2: vertebroplasty of a severe painful vertebral fracture.



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