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Le linee guida: Indicazioni terapeutiche

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Guidelines for the Management of Osteoporosis and Fragility Fractures

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5.0 NON-PHARMACOLOGICAL MEASURES FOR OSTEOPOROSIS PREVENTION AND TREATMENT

5.1 Nutritional Approach

Calcium

An adequate intake of calcium increases the density of the bone matrix in children and adolescents, maintains it in adults and slows down its loss in women after menopause. The average calcium intake in the Italian population is insufficient, especially in the elderly. This dietary deficiency may contribute to negative calcium balance and to a condition of secondary hyperparathyroidism. Daily calcium requirements depend on age and certain conditions **(Table 3).**

Table 3 ***Calcium requirements at different ages and under different conditions***

CALCIUM REQUIREMENTS	mg/day
1-5 years	800
6-10 years	800-1200
11-24 years	1200-1500
25-50 years	1000
Pregnant or nursing	1200-1500
Postmenopausal women receiving oestrogen/Men 50-65 years of age	1000
Postmenopausal women without oestrogen treatment/Men aged> 65 years of age	1200

It has been reported that the sole administration of calcium did not produce a complete but only a slight reduction in fracture risk, particularly in the elderly, but the most convincing documentation of its anti-fracture efficacy has been shown when it is administered in combination with vitamin D. The efficacy of an adequate calcium intake, as well as vitamin D, is proportional to the severity and the frequency of the deficiencies in the population examined.

it is recommended that calcium supplementation adhere to the following guidelines:

1) Always estimate diet calcium intake by means of a brief questionnaire before prescription;
2) Always try to ensure an adequate intake of calcium from food and water rich in calcium;
3) Use dietary supplements only when calcium assumption is insufficient, indicating intake at meals and the minimum dose necessary to satisfy requirements, possibly dividing intake into a number of doses (for example, 500 mg at lunch and 500 mg at dinner).

Vitamin D

Vitamin D is contained almost exclusively in animal fats, fish, liver, milk and dairy products, while the amount of vitamin D in some vegetable fats is negligible; approximately 20% of circulating vitamin D derives from food, while it is largely produced by endogenous synthesis in the skin following exposure to UVB sun rays, a process increasingly less efficient with advancing age. Consequently, there is a frequent need for supplementation, especially in old age, with vitamin D (cholecalciferol or ergocalciferol, namely $_{D3}$ or $_{D2}$), which, if associated with an adequate intake of calcium has proved useful in the primary prevention of fractures, in the elderly.

Table 4 ***Interpretation of plasma levels of 25 (OH) D***

nmol/L	*ng/mL*	*Interpretation*
<25	<10	Severe Deficiency
25-50	10-20	Deficiency
50-75	20-30	Insufficiency
75-125	30-50	Ideal Range
125-375	50-150	Possible Side Effects
>375	>150	Intoxication

The aim of vitamin D deficiency and insufficiency therapy is to restore normal serum levels and thus of deposits of 25 (OH) D, in a brief time.

The cumulative dose to be administered within a few weeks may vary depending on the severity of the deficiency and the body mass. The weekly administration of 50,000 IU of cholecalciferol during 2-3 months can restore values to normal levels in severe deficiency cases. This must be followed by a maintenance dose of up to 2,000 IU daily, or equivalent doses administered weekly or monthly. These doses should be reduced accordingly if basal values are achieved, for example, or in the case of insufficiency.

As to the use of alternative hydroxylated metabolites of vitamin D (calcifediol, 1-alpha-calcidiol, calcitriol) there are still no adequate comparative dose-equivalent evaluations with respect to vitamin D or documentation of anti-fracture efficacy analogous to those available for cholecalciferol's ability to provide rationale-based indications under specific conditions.

Calcifediol may be indicated in the case of 25-hydroxylation deficits (e.g., severe liver failure, male hypogonadism, inactivating mutations of the gene encoding enzyme 25-hydroxylase), obesity, intestinal malabsorption;

Calcitriol is indicated in conditions of 1-alphahydroxylase deficiency (i.e., moderate to severe renal insufficiency, hypoparathyroidism, and mutations of the gene encoding enzyme 1-alpha-hydroxylase) and intestinal malabsorption.

Other Nutrients

Increases in protein consumption in patients with inadequate intake reduce the risk of hip fracture in both sexes. Adequate protein intake is necessary to maintain the functions of the musculoskeletal system, but also to reduce the risk of complications after an osteoporotic fracture.

In fact, an adequate protein intake (1.0-1.2 g/kg/day with at least 20-25 grams of proteins per meal) associated with physical resistance exercises (muscle strengthening exercises) increase mass and muscle strength. Even other micro-nutrients such as zinc, silicon, vitamin K, vitamin E, vitamin B6,vitamin B12, magnesium seem to have a protective role with regards to bone and muscle.

5.2 Physical Activity

It is a well-known fact that even short periods of immobilisation adversely affect bone mass and it is, therefore, important to maintain an appropriate level of physical activity, keeping in mind, however, that competitive physical activity in young women may lead to exaggerated hormonal and nutritional abnormalities that can be detrimental to bone.

Types of physical activity divided into two basic categories:

1) low or high impact aerobic activity (e.g., jogging, soccer, basketball, volleyball, baseball, racket sports, gymnastics).
2) muscle-strengthening activities (weight lifting, body building, swimming, cycling or exercise bikes, use of weights for static exercises).

One of the most common forms of aerobic exercise is walking which is very well accepted by older people because it is bland, can be self-managed and easily practised. Meta-analyses, however, have highlighted the absence of significant effects of walking on lumbar and femoral BMD. In postmenopausal women, aerobic training, and, in particular, high-intensity and speed walking, interspersed with jogging, climbing stairs and stepping, can limit reductions in bone density.

5.3 Prevention of Falls

Most fractures, especially of the hip, are caused by falls, and the risk factors for these (physical disabilities, balance disorders, neuromuscular disorders, visual impairment, cardiovascular disease, past medical history of falls, drug treatment and cognitive deficits) are often modifiable in a context of multidisciplinary intervention.

Physical activity, in particular personalized muscle strengthening exercises, balance and gait rehabilitation, are able to reduce the risk of falls related to trauma in the elderly. Individual evaluation of fall risks and associated prevention recommendations such as a reduction in the use of psychotropic drugs has a positive impact on falls. A fall-prevention strategy for the elderly, including adequate intake of vitamin D, physical exercise and education regarding risks within the home, is highly recommendable.

5.4 Integrated Approaches for Secondary Prevention of Fractures

The secondary prevention of fragility fractures, aimed at preventing re-fracture, is very complex and all the strategies adopted over the years have yielded disappointing results. In fact, OSMED data, recently published in Italy by AIFA, indicate that approximately 80% of patients with fragility fractures (femoral or vertebral), or chronic treatment with glucocorticoids, do not receive either a correct diagnosis or adequate medical treatment and that after one year, only about 50% of patients continue to follow their therapy correctly.

It is therefore necessary to develop new integrated and multidisciplinary models, such as Orthopaedic and Geriatric Co-Management ('Cogestioni Ortogeriatriche'), Fracture Unit and Fracture Liaison Services. These are flexible models based on improved communication between the various specialists and the general practioners involved in the management of patients with fragility fractures. The strength of these multidisciplinary models is their ability to be implemented in the context of very different clinical and organisational systems. The role of nurses with specific expertise in the field of osteoporosis and fragility fractures (Nurse Case Manager or Bone Care Nurses) is essential for them to function properly.

3.1 Overall Assessment of Fracture Risk

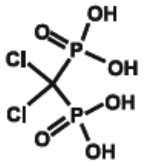
Using specific algorithms, it is possible to perform an integrated assessment of BMD including the most important risk factors, partially or wholly independent of BMD, so as to arrive at amore accurate estimate of middling-term (5-10 years) risk of fragility fractures and, therefore, identification of subjects in whom drug treatment is the most appropriate therapeutic solution.

Currently, in order to evaluate multiple risk-factor combinations, it is possible to use mathematical algorithms that quantify risk in terms of "10-year fracture risk." One of the algorithms most commonly used today is FRAX® (http: www.shef.ac.uk/FRAX/), which, however, has inherent limitations, due mainly to the use of dichotomous variables only. In Italy, to improve the accuracy of FRAX® it was converted into a version known as "Derived Fracture Risk Assessment" or DeFRA (http://defra-osteoporosi.it).

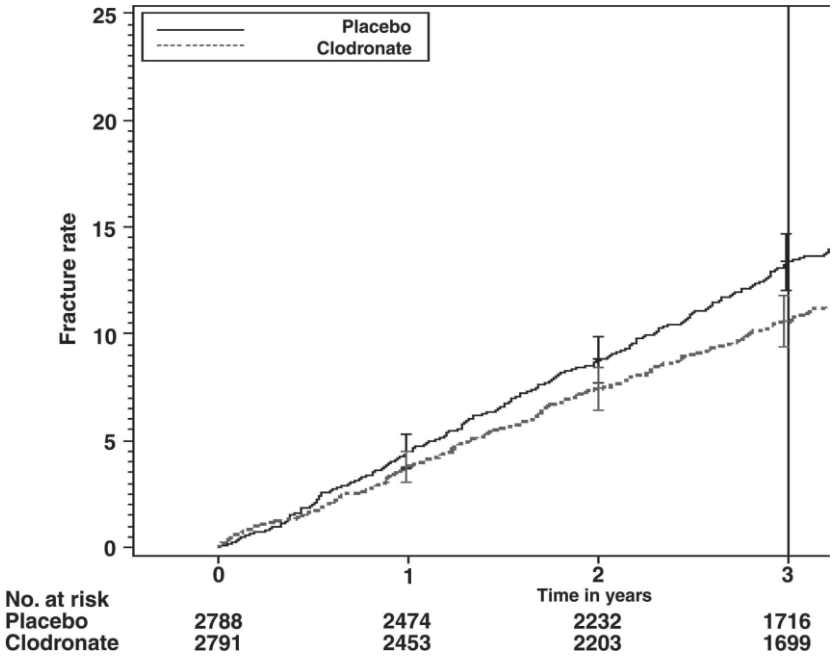
6.2 ANTI-OSTEOPOROTIC DRUGS

6.2.1 Anti-catabolic Drugs

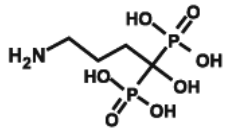
Etidronate is not indicated in osteoporotic patients and clodronate was effective in reducing clinical fractures at a dose of 800 mg/day orally. The anti-fracture efficacy of intramuscular clodronate therapy at the most commonly used dosage in Italy (100 mg/week or 200 mg every 2 weeks) has not been definitively demonstrated and accordingly it must be regarded as a second-choice drug for the treatment of osteoporosis.



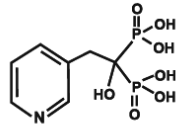
Clodronate



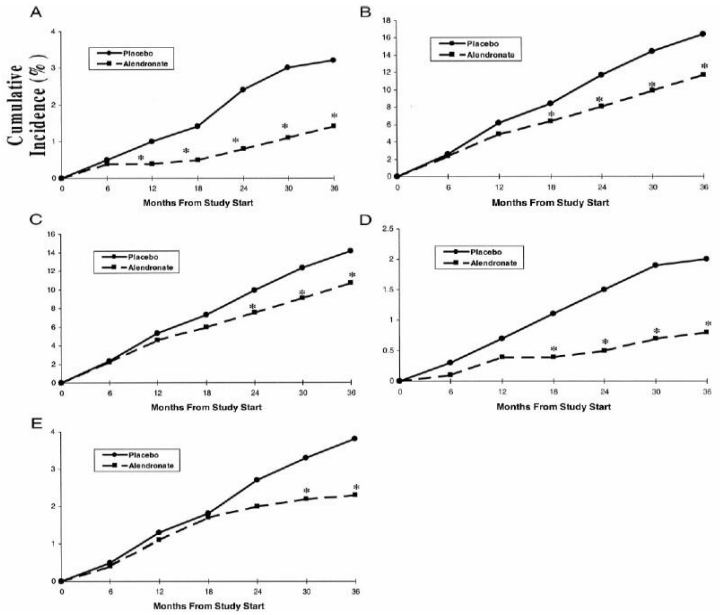
The efficacy of alendronate and risedronate for the prevention of vertebral and non-vertebral fractures (including hip) are extensively documented. Their anti-fracture efficacy has been demonstrated with the daily administration of the two drugs and can be used in weekly administrations (70 mg/week of alendronate and 35 mg/week or 75 mg 2 days/month for risedronate) on the basis of the equivalence of different formulations in determining increases in BMD. Recently in Italy formulations of alendronate in a liquid form have also become available.

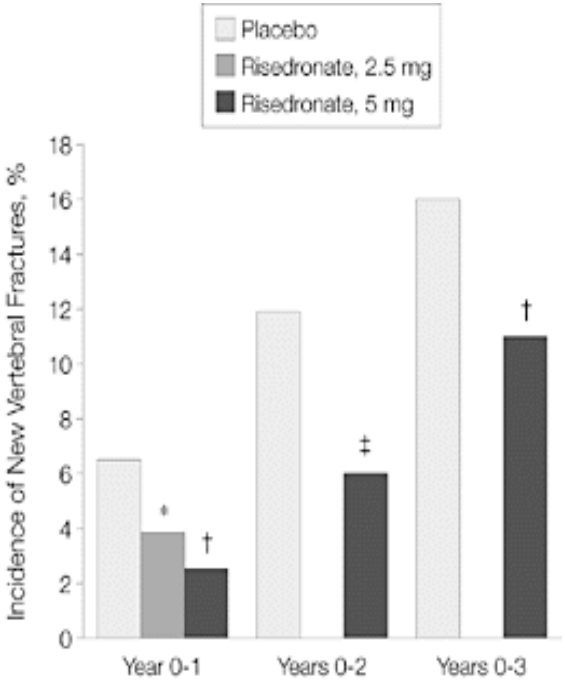


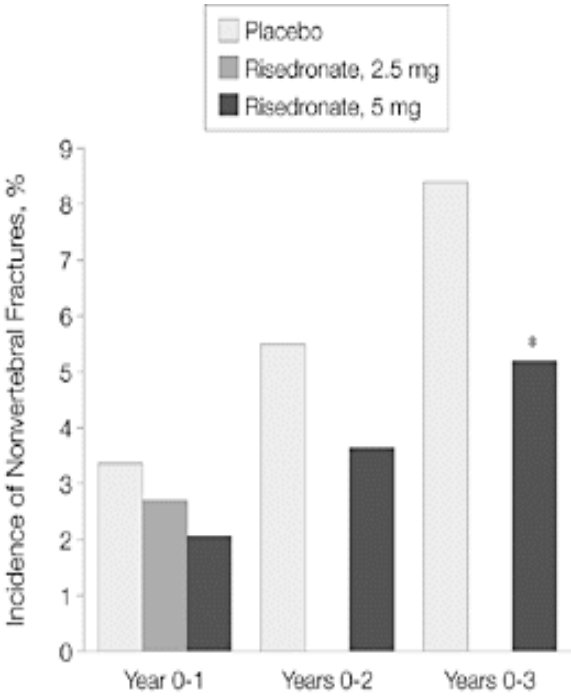
Alendronate



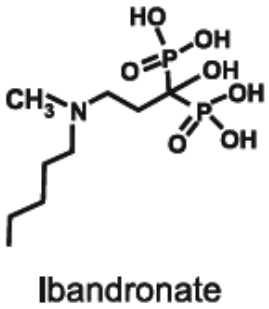
Risedronate



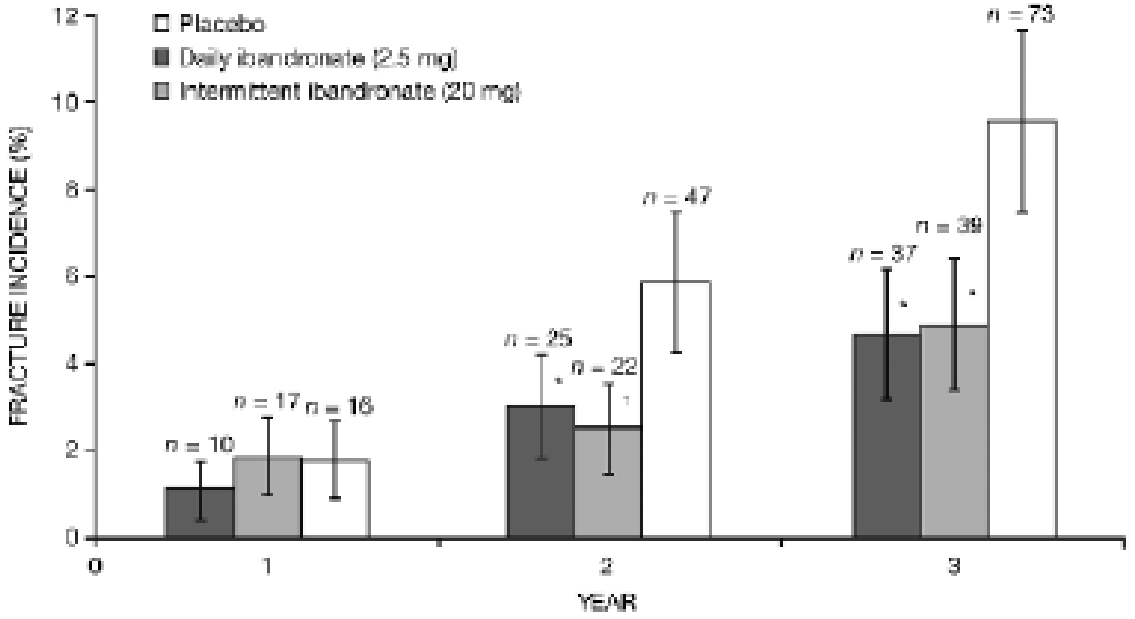




Ibandronate was registered based on studies using a dosage of 2.5 mg/day. At this dose, it has proven effective in reducing only the risk of vertebral fractures and has been subsequently marketed at a dosage of 150 mg/month or 3 mg iv/3 months, or cumulative-bioavailable double doses to those used in the pivotal studies.



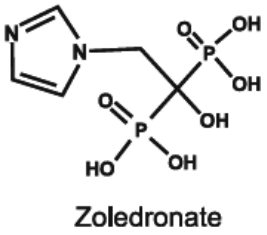
Ibandronate

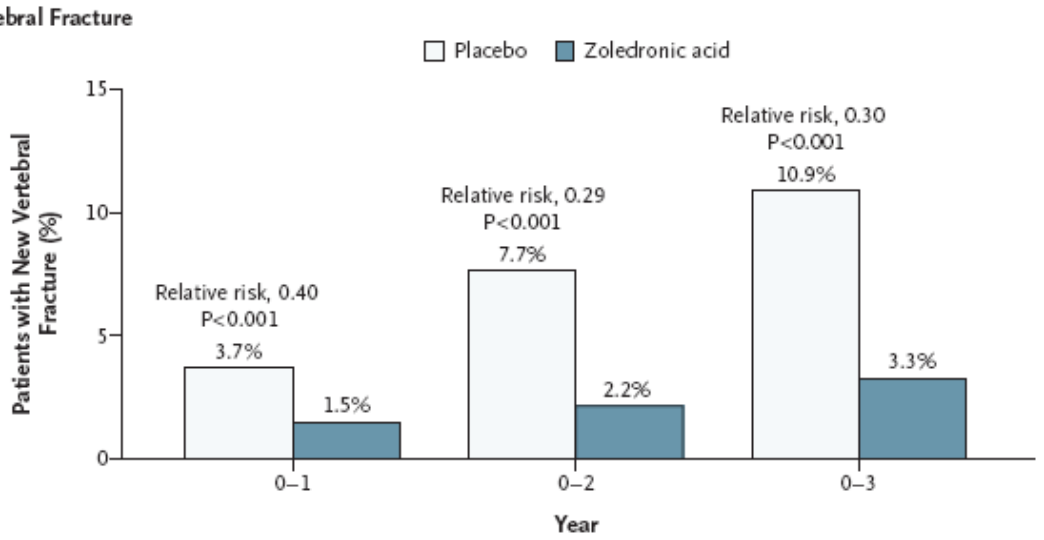


* $p < 0.001$ versus placebo

† $p < 0.0017$ versus placebo

Zoledronic acid (5 mg/iv/year) was registered for the treatment of osteoporosis based on a study that documents clearly reduced risk of vertebral, non-vertebral and hip fractures after three years of treatment. In one ancillary study, a reduction in overall mortality was also demonstrated.





Alendronate, risedronate and zoledronate have also been registered for the treatment of male and corticosteroid-induced osteoporosis.

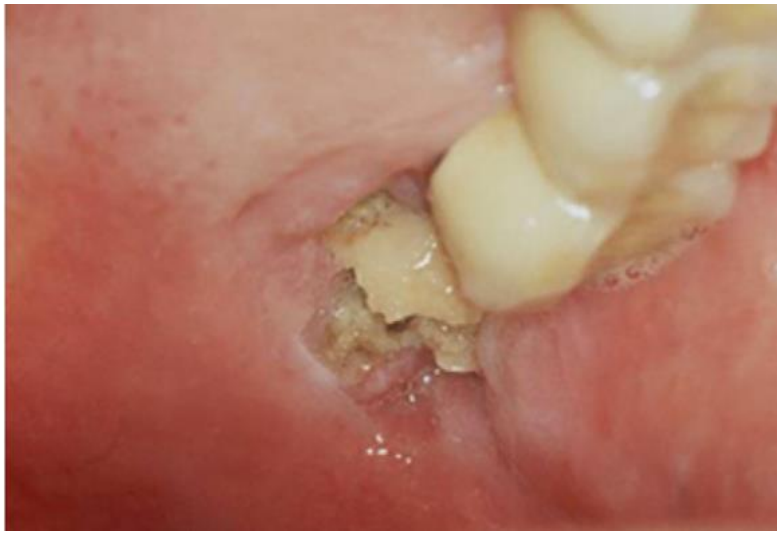
Neridronate is the only BP indicated for the treatment of osteogenesis imperfecta and in Italy, it is currently indicated for the treatment of algodystrophy (complex regional pain syndrome type I) on the basis of data obtained in a randomised controlled trial.

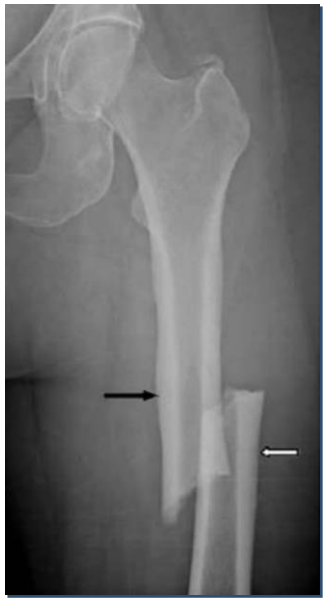
As for adverse events due to BP, these can be classified as follows:

a) Acute Phase Reaction.

b) Atypical sub-trochanteric fractures: these are transverse stress fractures whose diagnosis requires compliance with precise classification criteria.

c) ONJ (OsteoNecrosis of the Jaw) or osteomyelitis of the jaw.





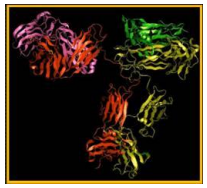
Duration of bisphosphonate therapy.

In view of the adverse events associated with long-term therapy with BP, the need for continued treatment should be reviewed at regular intervals. Based on available data, risk reassessment should be carried out after 5 years of treatment with alendronate, ibandronate and risedronate and after 3 years for treatment with zoledronate.

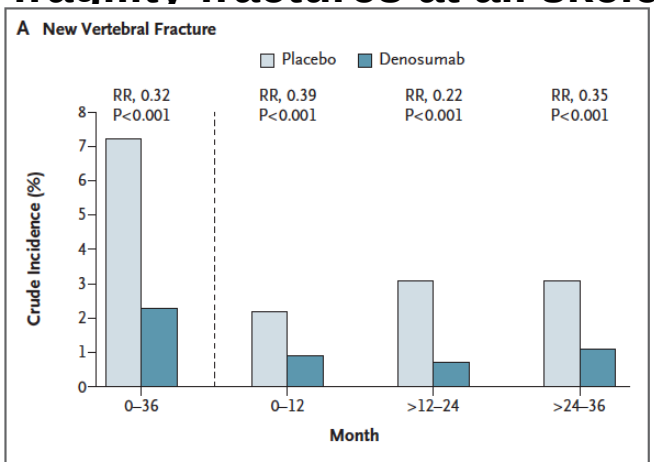
Suspending treatment for 12-24 months in patients who have received oral BP for over 5 years and are at low risk of fracture is advisable. However, continuation of treatment up to 10 years (maximum duration of treatment hitherto investigated) in patients at high risk of fracture, such as those with femoral T-score <-2.5 or with prior vertebral fractures and T-score femur less than -2.0, is recommended.

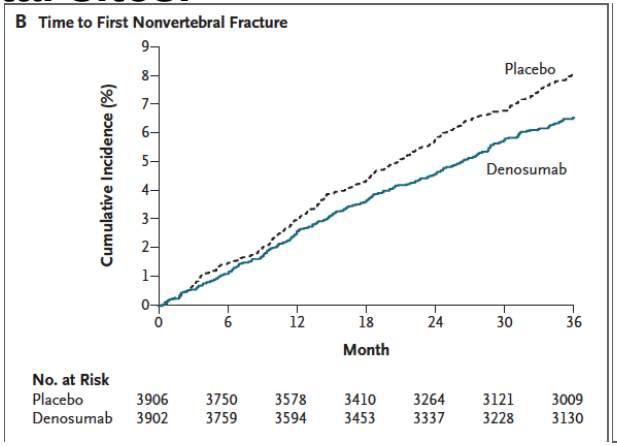
In high-risk patients treated with zoledronate, continued treatment with zoledronate for other 3 years is indicated.

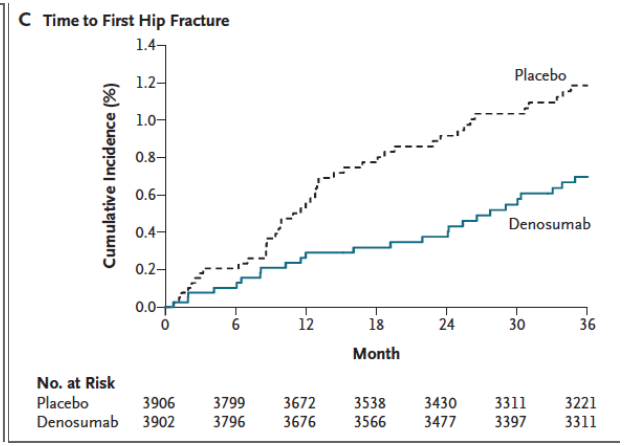
Denosumab



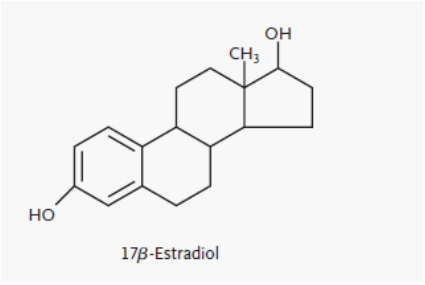
Denosumab is a human monoclonal antibody capable of neutralising RANKL. Pivotal studies were conducted using 60 mg of subcutaneous denosumab every six months. This dose determines an increase in BMD higher than that obtainable with BP both in trabecular and cortical bone with a consequent reduction of fragility fractures at all skeletal sites.







Denosumab was effective in reducing the risk of fractures in women with breast cancer treated with aromatas inhibitors and in men with prostate cancer being treated with anti-androgens. In very bad cases of severe osteoporosis, the combination denosumab/teriparatide therapy has resulted in a marked increase in BMD. Similar advantages in terms of increase in BMD were obtained with sequential teriparatide-denosumab therapy.



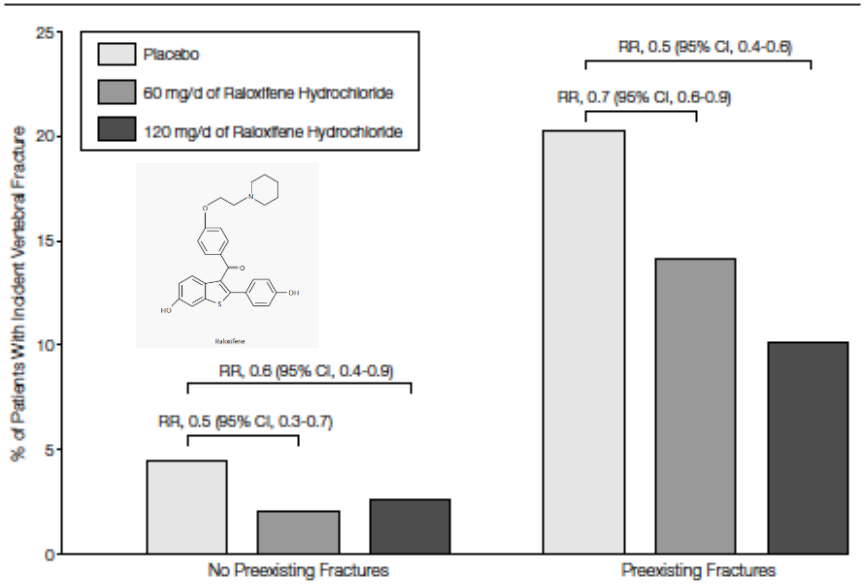
17β-Estradiol

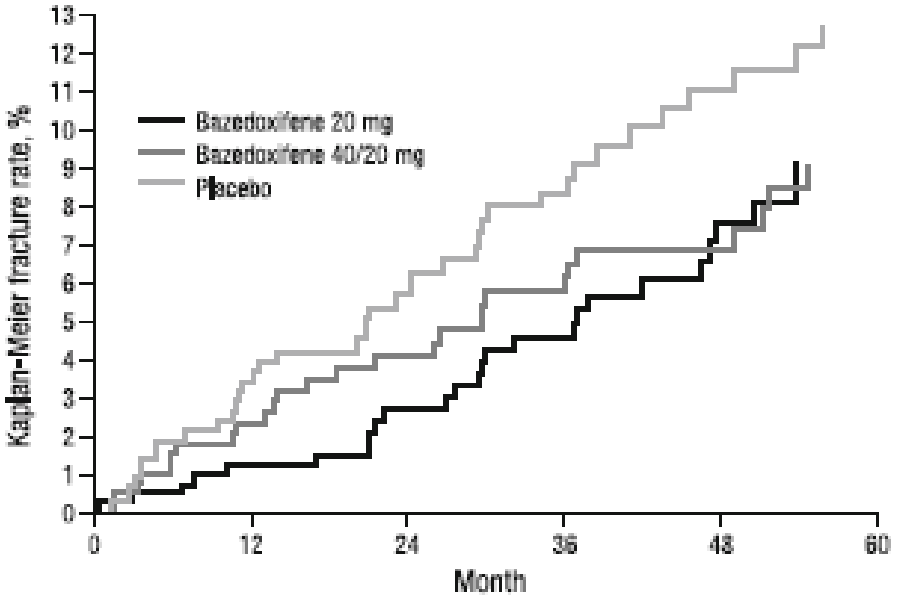
Hormone Replacement Therapy (HRT)

Menopausal women undergoing oestrogen treatment, on its own or in combination with progestin, and with tibolone, are able to reduce bone turnover and increase bone mass. Oestrogen anti-fracture efficacy has been confirmed by several randomised trials and major observational studies (especially the WHI study). Despite the positive effect on fractures, to which may be added a reduction in the risk of colorectal cancer, these drugs entail an increased risk of breast cancer, stroke and thromboembolic events. Therefore, HRT is no longer indicated for the treatment or prevention of osteoporosis.

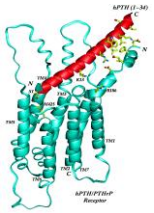
Selective Oestrogen Receptor Modulators (SERMs)

The SERMs currently approved in Italy for the prevention and treatment of osteoporosis, are raloxifene and bazedoxifene. During the pivotal trial MORE raloxifene (60 mg/day) reduced the ncidence of new vertebral fractures (but not those of non-vertebral and femoral fractures) andinvasive breast cancer, accentuating vasomotor phenomena in some patients.
Bazedoxifene (20 mg/day) significantly reduced the risk of vertebral and non-vertebral fractures (but not hip fractures) in high-risk of fracture women treated for 3-5 years.





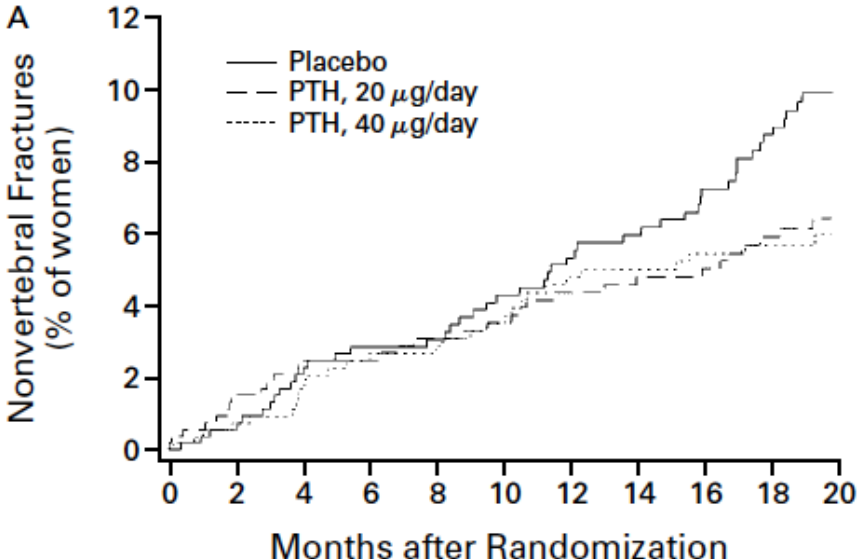
6.2.2 Anabolic Drugs

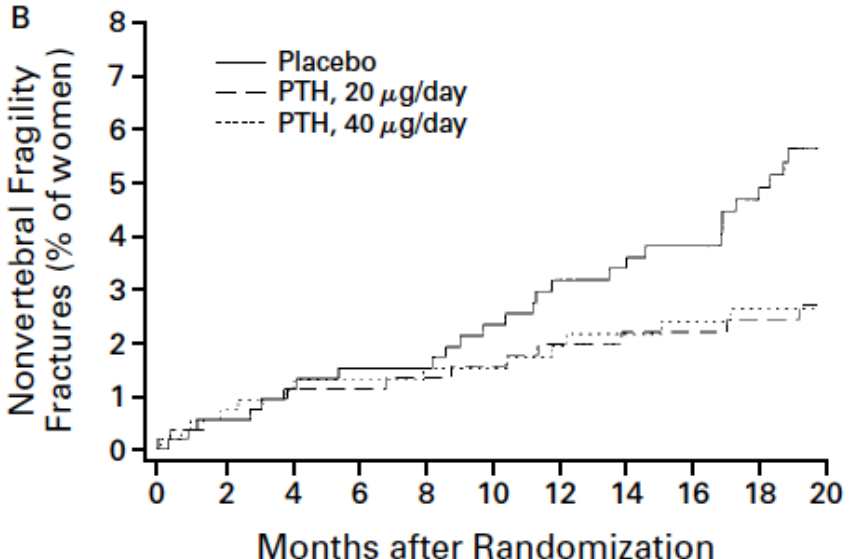


Teriparatide

The administration of parathyroid hormone and in particular of its active fragment 1-34 (teriparatide) stimulates both neoformation and bone resorption, with a predominant effect on neoformation (anabolic window) which is evident especially during the first 12 months of treatment.

Teriparatide (20 µg/day sc), has proved capable of reducing vertebral and non-vertebral fractures in post-menopausal women, and currently its administration cannot exceed a total of 24 months.. Due to its high cost, it is reimbursed by the National Health Service for secondary prevention in patients with osteoporosis at high risk of fracture or "non-responsive" to anti-resorptive medications.





6.2.3 Double Action Drugs

Strontium Ranelate

Treatment with strontium ranelate is effective to reduce risks of vertebral, nonvertebral and hip fractures in postmenopausal women with osteoporosis. This drug increased bone formation markers and decreased those for resorption modestly.

Since treatment with strontium ranelate has also been associated with an increased risk of myocardial infarction and thromboembolic events, it is contraindicated in patients with ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease, or a history of, or uncontrolled high blood pressure.

7.0 KYPHOPLASTY AND VERTEBROPLASTY

The methods currently proposed to stabilise or reduce-stabilise vertebral fractures are vertebroplasty, in which cement under high pressure is injected with greater risk of leakage and pulmonary embolism, and kyphoplasty, in which the cement is introduced at low pressure with lower risk of leakage after the introduction of a balloon which is then inflated within the vertebral body often enabling a partial reduction of the deformity

Vertebroplasty or kyphoplasty can only be recommended for patients with intractable pain for weeks, with due consideration of the potential risks associated with the procedures and the uncertain benefits in the long term. The use of these procedures is therefore not indicated in patients with few or no symptoms.

However, it is essential that all patients with vertebral fragility fractures treated with vertebroplasty and/or kyphoplasty are prescribed a suitable pharmacological treatment in so that the presence of cement within the vertebral body, when there are systemic conditions for bone fragility, does not expose adjacent vertebrae to an increased risk of fracture.