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## Osteoporosis in older adults

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**Abstract**

The incidence of fragility fractures increases progressively with advance in age after 50 years, and the phenomenon of population ageing will lead to an increased proportion of the world population having osteoporosis and fractures. The consequences of fractures are more serious in older adults: all low-trauma fractures were associated with increased mortality risk and the risk of a second major osteoporotic fracture after a first one also increased with advance in age. Along with the decrease in bone mineral density, falls play an essential role in the occurrence of fragility fractures in older adults, and the assessment of the risk of falling is part of the fracture risk assessment. Despite advances in the diagnosis of osteoporosis, the assessment of fracture risk, and a wide range of effective anti-osteoporosis medications, with parenteral route which can improve observance, many data indicate that the therapeutic care gap is particularly wide in the elderly in whom the importance and impact of a treatment are high and even more in those living in institutions.

Keywords: osteoporosis; fracture; older adult; fall

## **1. Introduction**

The thresholds used to define older people vary according to authors and periods. Life expectancy is increasing, and the income level, consumption behaviour and health status of young retirees make the 65-year threshold initially used less relevant. Age is only a partial indicator to define an older person. Quite often nowadays, we use the term older adult to refer to an adult over 75 years of age because it is around this age that health deteriorates durably and that more or less important vulnerabilities appear. Beyond the age of 85 ("very old age"), the risk of loss of autonomy for the activities of daily living increases sharply. Population ageing is a global phenomenon: almost every country in the world is facing an increase in its elderly population. The phenomenon of population ageing will lead to an increased proportion of the world population having age-associated chronic diseases, including osteoporosis, fractures and their consequences.

Even if there is substantial variability in fracture incidence worldwide and fracture risk according to geography, ethnicity and socioeconomic status, ageing remains one of the principal risk factors for fractures and osteoporosis is a disease most common in older adults [1]. Very few fragility fractures occur before the age of 50 years, and the incidence of these fractures increases progressively with advance in age after 50 years. About 10% of women aged 60 years, 20% of women aged 70, 40% of women aged 80 and two-thirds of women aged 90 years have osteoporosis, and half of the fractures occur after 75 years [2].

## **2. Epidemiology of fragility fracture**

In a recent study on the epidemiology of osteoporosis in the European Union [2], the prevalence of densitometric osteoporosis, defined by a T-score  $\leq -2.5$  at the femoral neck was estimated at 6% in European women aged 50-55 years and 47% in women  $\geq 80$  years, for European men the prevalence was estimated at 2.5% and 16% respectively. Fragility fracture incidence increases with advance in age both in men and women, very rapidly from the age of 70 years in women and 80 years in men. In women, all major osteoporotic fractures sites showed age-related increases, whereas, in men, only hip fracture was clearly age-related. The distribution of the site of fracture after 80 years old differs from the fracture site at 50 years old. Thus, fracture of the distal forearm represents about 40% of fractures due to bone fragility in women between 50 and 55 years of age and 10% of fractures in women between 80 and 89 years of age. Conversely, hip fracture represents 4% of fractures in women between 50 and 55 years of age and almost 40% of fractures in older women. In women, the median age of hip fracture is 80 years. The 10-year fracture risk at any site in women increases from 9.8% at age 50 to 21.7% at age 80, with a specific risk of hip fracture increasing from 0.3% to 8.7%. In men, the risk of fracture for all sites increases slightly from 7.1% at age 50 to 8.0% at age 80, but the risk of hip fracture increases from 0.2% to 2.9% at age 50 to 80.

Because of the ageing of the population, the absolute number of fractures and particularly of hip fractures increases, both in men and women and above all  $> 85$  years. Briot et al. analyzed changes in the number and incidence of hip fracture from 2002 to 2013 based on hospitalizations for hip fracture in metropolitan France of subjects  $\geq 60$  years old [3]. During this period, the incidence of hip fracture in women decreased in the 60-74y, 75-84y and  $>84y$  age groups, the absolute number of hip fractures decreased in the 60-74y and 75-84y age groups but increased in the  $>84y$  age group (+12%) due to the rise in the number of very old subjects. Hip fractures among women  $>84y$  accounted for 49% of the total of hip fractures of women over 60y in 2002 and 57% in 2013. Among men, the number of hospitalizations for hip fractures increased by 35% from 2002 to 2013.

## **3. Consequences of fragility fracture**

The consequences of fractures are more serious in older adults. In older women and men, all low-trauma fractures were associated with increased mortality risk. Predictors of mortality after any fragility fracture for both men and women included age, quadriceps weakness, subsequent fracture and low bone mineral density (BMD) [4, 5].

In France, in 2008-2009, all causes combined, 23.5% of patients aged 55y and over died within one year of a hip fracture. This rate was higher in men (32.9%) than in women (20.6%). Mortality at one year increased with advance in age: less than 15% before the age of 65y in men, and more than 30% after the age of 75y. In women, it was less than 10% before the age of 70y and did not exceed 30% until the age of 90y.

The determinants of this excess of mortality and weight of them remain debated, encompassing the decompensation of underlying diseases (cardiac, respiratory or renal insufficiency, cognitive disorders), hospitalization and surgery complications (bedsores, infection,

venous thrombosis, arterial accident). The influence of surgical delay on the mortality and morbidity of hip fracture patients has been the subject of numerous studies with controversial results; however, it has been shown that surgery performed after the 48th hour is a predictor of mortality at one year [6]. This threshold sometimes comes up against the benefit/risk ratio of postponing an operation to obtain optimal patient stabilization or better exploration of intercurrent pathologies.

It is well-established that fragility fractures increase the risk of a further fracture. The relative risk of having a hip fracture or a vertebral fracture was approximately 2-fold higher for most types of prior fracture [7]. The increase in relative risk may not be constant with time or age; thus, a recent occurrence of fracture is a higher risk factor for subsequent fracture than a history of earlier fracture, demonstrated for vertebral fracture, hip, humeral and forearm fractures and all fractures combined, this is what is called imminent fracture risk [8]. In the study of Johannson et al., one year after the first major osteoporotic fracture (vertebral fractures, humeral fractures, distal forearm fracture, and hip fractures), the risk of a second fracture was 2.7 (2.4-3.0) fold higher than the population risk. After ten years, this risk ratio was 1.4 (1.2-1.6) and remained above unity for the subsequent 15 years. In individuals with an incident fracture that were examined over a 10-year time, 20% of cases re-fractured within one year and 34% within two years. The high risk in the immediate post-fracture interval was age-dependent in that the marked transient increase in risk was not found at the age of 60 years and became progressively evident with advancing age. The risk of a second major osteoporotic fracture after a first one increased by 5% for each year of age and was 25% more likely for women than men [9].

In older adults, hip fractures are associated with a four-time increase in the likelihood of requiring long-term institutionalization within the following year. The risk of institutionalization after fractures of the spine and pelvis was similar to the risk after hip fracture. These fracture sites seem to be associated with a significant decline in physical function [10]. The factors that predicted new institutionalization are age, living alone, and length of hospital stay [11]. The percentage of patients moving into long-term care following a hip fracture increased significantly with age, from 4% at ages 70–79 years to 14% at ages 80-89 and to 35.3% at ages 90–100 years [2].

#### **4. Determinants of fractures in the older adults**

Although decreased BMD is a major determinant of fracture risk [12], it does not fully explain the increase in hip fractures with advancing age. For a given level of BMD, the risk of hip fracture beyond age 65y is approximately doubled for every ten years of age increase. Thus, other factors play an essential role in the occurrence of non vertebral fractures in older adults, most notably, falls. Ninety per cent of hip fractures are preceded by a fall. It is

estimated that one-third of subjects over 65 years of age and half of those over 85 years of age have one or more falls per year. The incidence of falls is twice as high among women as among men. Falls have become one of the main causes of admission to emergency departments, acute geriatric care units and institutions for dependent older people and about eight per cent of falls are responsible for fractures. Contrary to hip fractures, for which the fall is almost always the precipitating event, in women aged 85 years old, a vertebral fracture is the consequence of a fall in only ¼ of cases. In contrast, they occur in half the cases after a fall before the age of 85y [13].

The etiology of falls is multifactorial based on complex combinations of more than 400 risk factors, including gait and balance disorders, muscle weakness, vision disorders, sedative and/or hypotensive medication, cognitive disorders, and vitamin D deficiency. All these factors are also predictive of the risk of hip fracture. They influence not only the risk of falling but also the ability to protect oneself in the event of a fall.

Vitamin D deficiency is associated with an increased risk of falling due to changes in neuromuscular motor control [14]. The role of vitamin D on muscle is supported by the finding of proximal muscle weakness in vitamin D deficiency, expression of the vitamin D receptor by muscle fibers, observational studies suggesting a positive association between vitamin D concentration and muscle strength [15], and several randomized controlled trials showing that vitamin D supplementation improves muscle strength [16], balance and decreases the risk of falling particularly in institutionalized frail older individuals. In parallel, the discovery of the neurosteroid properties of vitamin D in animal and cell experiments and in humans suggests that the risk of falling due to vitamin D deficiency is also explained by a decline in cognitive performance, particularly in executive performance, directly influencing high-level control of walking.

Some treatments such as hypnotics, benzodiazepines and antipsychotics are associated with an increased risk of falls and hip fractures. The risk of fractures associated with antihypertensive drugs varies according to therapeutic class, being greater with loop diuretics via orthostatic hypotension and ionic disorders such as hyponatremia. Some studies have also suggested that beyond the effect of fall-risk-increasing drugs (FRIDs), the mere number of prescribed medications may also increase the risk of falls in older people. This association between polypharmacy and the risk of falls could stem from the physiologically detrimental effects of multiple drug use on older adults' physical and cognitive functioning. Still, this association may also be due to confounding-by-indication bias since polypharmacy is most often the consequence of chronic multimorbidity [17].

The fall is often part of general frailty. Frailty, which concerns half of those aged 85 years and over, has no consensual definition but is generally considered as a state of vulnerability and poor adaptability to aggression (medical, psychological, social or iatrogenic) [18]. Frailty is responsible for negative health events, including disability, institutionalization and death, but also falls and fractures [19]. On the one hand, frailty is a natural consequence of advancing age; on the other hand, frailty also signifies an abnormal condition with an earlier onset and a higher rate in the accumulation of these age-related changes. Some researchers suggest that elderly individuals with osteoporosis-related fractures should not be considered as “average elderly” but rather, as frail. Frailty is higher among individuals who have suffered a fracture. The change in frailty status over 1 and 2 years was significantly greater among women who had sustained a major osteoporotic fracture than among those who had not. Emerging studies suggest that frailty may be an effective predictor of osteoporotic fracture since individuals with severe frailty have an increased likelihood of prevalent and incident fractures [20, 21]. Previous studies have reported that measures of frailty can predict the risk and occurrence of falls and fall-related fractures [22]. There is also an overlap between the characteristics of

individuals with frailty and fragility fracture [23], and an association between FRAX and frailty [24].

As an older person reaches their sixth decade of life, there is a progressive decline in bone mineral density (~1-1,5% per year) and muscle mass (~1% per year) and strength (~2,5-3% per year), which predispose to the risk of osteoporosis and sarcopenia. Numerous studies have demonstrated a relationship between muscle mass and strength and the decline in bone density and microarchitecture, which is called osteosarcopenia. Genetic, mechanical, endocrine, localized and systemic factors can explain the age-related association between muscle and bone loss. This syndrome has gained clinical interest due to its association with falls, fragility fractures and mortality [25]. It may occur in 5-37% of community-dwelling adults over the age of 65 years and increases with age in men and women [26]. This wide range is driven by variation in populations, settings, and definitions applied.

## **5. Evaluation of the risk of fracture**

Regardless of age, BMD is an important risk factor for fracture, but for a given T-score, the risk of fracture increases with age [12]. Thus, among the FRAX® criteria, age is the factor that most increases the risk of fracture.

Evaluation of the risk of fracture in older adults is the same as in the general population, but even more so in older adults, the assessment of the risk of falling is part of the fracture risk assessment.

## **6. Treatment**

Despite advances in the diagnosis of osteoporosis, the assessment of fracture risk, the development of interventions that reduce the risk of fractures, many data indicate that a minority of men and women at high fracture risk receive treatment. In patients who sustain a fragility fracture, fewer than 20% of individuals receive therapies to reduce the risk of a future fracture within the year following the fracture. Paradoxically, the therapeutic care gap may be particularly wide in the elderly in whom the importance and impact of a treatment are high and even more in those living in institutions [27].

There are many obstacles to the implementation of treatment in older adults: the fracture is often considered as a 'normal' medical event at this age, treatment is considered unnecessary because life expectancy is short, medical treatment takes second place to non-pharmacological management, compliance by oldest-old subjects is questioned, and it may be considered unnecessary to add a drug to an already substantial list. Impaired renal function can also restrain drug introduction.

### **6.1. Prevention of falls**

The prevention of falls is of paramount importance, and it has been shown that the implementation of appropriate measures in older adults at risk of falling reduce falls both in those still living at home and also in the hospitalized ones. Prevention is all the more effective as it is based on a multifactorial strategy to correct the various identified risk factors for falls [28]. Fall prevention starts with asking patients about falls. Patients with a fall or fear of falling should undergo gait and balance assessments. A comprehensive assessment of falls risk factors should include testing and treatment for visual impairment, treatment of vitamin D deficiency, reduction of environmental risks of falls at home (removal of carpets from the living room, installation of a grab bar in the bathroom, installation of a non-slip mat inside the shower and outside, installation of a shower stool...), adaptation of footwear, practice of physical activities involving walking and balance exercises [29], and the progressive reduction or deprescribing of fall-risk-increasing drugs, in particular psychotropic drugs, benzodiazepines, and drugs that induce orthostatic hypotension. It is essential to reassess the

indication of all the medicines taken by older adults and to remove treatments whose benefit/risk balance is harmful. Exposure to prescription drugs associated with fracture risk is infrequently reduced following fragility fracture occurrence. While some patients eliminate their exposure to drugs associated with fracture, an equal number initiate new high-risk drugs [30].

The benefit of wearing a hip protector is still under discussion; it could reduce the risk of hip fracture in institutionalized subjects, but compliance with this device is too poor [31].

## **6.2. Vitamin D and calcium intake**

The muscle and bone-specific effect of vitamin D supplementation remains debated [32, 33]. Vitamin D reduces fall risk in institutionalized people at risk of fracture [33] but not in ambulatory people [34]. The recommended vitamin D intake for falls prevention is 800 to 1200 units/day. The effectiveness of higher doses has not been demonstrated, and high-dose intake (monthly bolus of 60,000 IU or mega-dose of 500,000 IU of vitamin D) may increase the risk of falling [35, 36], particularly in people who already have an adequate status.

Vitamin D supplements do not improve bone density in clinical trials except in analyses of subgroups with baseline levels of 25-hydroxyvitamin D <30 nmol/L [37, 38]; when baseline circulating concentrations of 25-hydroxyvitamin D (25(OH)D) are < 30 nmol/L, increases in BMD of 1%–2% result from vitamin D supplementation. A meta-analysis of trials supplementing with vitamin D alone shows no effect on total fracture risk.

The optimal concentration of 25(OH)D to be obtained in older adults is 75 nmol/L. In the event of vitamin D insufficiency or deficiency, it is recommended that "loading" therapy be prescribed to achieve a 25(OH)D concentration above the target value of 75 nmol/L, followed by a "maintenance" dose to maintain this optimal concentration over time [39]. A measurement of circulating 25(OH)D may be useful after nine months to adjust the frequency or dosage of supplements if necessary.

In older adults, the amount of calcium ingested is decreased, as is the capacity for intestinal absorption. Low calcium intake associated with vitamin D deficiency leads to secondary hyperparathyroidism. Calcium supplements produce a 1% increase in bone density in the first year of use, without further increases subsequently. Most observational studies do not show a relationship between calcium intake and fracture risk. The recommended daily calcium intake for the elderly is 1000 mg. It is preferable to favor dietary intake because excess calcium intake without calcium supplements may be responsible for digestive, renal, and cardiovascular complications [40].

Thus, the International Osteoporosis Foundation recommends that "supplementation with calcium alone for fracture reduction is not supported by the literature" but that "calcium supplementation, with concomitant vitamin D supplementation, is supported for patients at high risk of calcium and vitamin D insufficiency" [41]. Correction of severe vitamin D deficiency (<25 nmol/L) is also necessary before the use of potent anti-resorptive drugs to avoid hypocalcemia.

## **6.3. Protein dietary intake**

Malnutrition and undernutrition are common in the elderly and are potential causes of sarcopenia and falls. In hip fracture elderly patients, poor nutritional status strongly predicts one-year mortality, independently of demographic, functional, cognitive and clinical risk factors [42]. No randomized controlled trial has examined the effect of dietary protein on fracture risk, irrespective of the fracture site [43]. In older adults, a daily protein intake higher than 1.0 g/kg/day has been proposed for preserving muscle function, up to 1.5 g/kg/day in case of acute or chronic disease (except in case of severe renal failure).

#### **6.4. Pharmacological management**

As it is more difficult to include very old people in randomized controlled trials, little data are available for this specific population. However, except for raloxifene, which is used preferably in women aged under 70 years, data show the densitometric and anti-fracture efficacy of anti-osteoporotic treatments in people > 70 years of age with early efficacy and a positive benefit/risk ratio, provided that the contraindications are respected, particularly renal insufficiency.

Thus, pharmacological management of older adults is based on the recommendations for the management of osteoporosis in the general population.

The use of parenteral route in older adults should be preferred as they already have a variety of comorbidities with many treatments, and memory disorders reducing compliance.

##### **6.4.1. Teriparatide**

From the pivotal Fracture Prevention Trial, Boonen S et al. compared the effect of teriparatide vs. placebo in women over 75 years of age (mean age 78.3 years). At 19 months, 5.2% of women in the teriparatide group had a new vertebral fracture vs. 15.1% in the placebo group (RR = 0.35,  $p < 0.05$ ) [44]. In the 2-year, randomized, double-blind, active-controlled fracture endpoint VERO study included postmenopausal women with established osteoporosis, patients were treated with either s.c. daily teriparatide 20 $\mu$ g or oral weekly risedronate 35 mg. Mean age was 72.1 years, 31.9% were <68.7 years, and 36.8% were aged  $\geq 76.8$  years. The risk of new vertebral fractures and clinical fractures was statistically significantly reduced with teriparatide compared with risedronate and consistently observed across all age subgroups [45].

##### **6.4.2. Bisphosphonates**

\* Alendronate

A post-hoc FIT analysis evaluated the anti-fracture effect of alendronate in postmenopausal women at high risk of fracture. The analysis included a subgroup of women  $\geq 75$  years of age (ages 75-82). After 3 years of treatment with alendronate the risk of vertebral fractures was reduced by 38% (RR = 0.62; 95% CI 0.41-0.94) in women  $\geq 75$  years vs. 51% in the younger group (RR = 0.49; 95% CI 0.35-0.68) [46]. In another analysis that calculated fracture rates by age (55 - <65 years, 65 - <70 years, 70 - <75 years, and 75 - 85 years), the relative risk reduction for hip fracture (RR = 0.47; 95% CI 0.27-0.81) and vertebral fracture (RR = 0.55; 95% CI 0.37-0.83) was consistent across all age groups with a higher absolute risk with increasing age given the increased risk of fracture in the placebo group with increasing age [47]. In another study, in patients over 80 years of age with a previous fracture, treatment with alendronate was associated with a reduced risk of hip fracture (HR = 0.66; 95% CI 0.5-0.86)[48].

\*Risedronate

In the Hip study, assessing the efficacy of risedronate in the prevention of hip fracture, one group consisted of 5445 women 70 to 79 years old who had osteoporosis, indicated by either a T-score at the femoral neck < -4 or a femoral-neck T-score < -3 plus at least one risk factor for hip fracture. Another group consisted of 3886 women 80 years of age or older who had at least one non skeletal risk factor for hip fracture. The women were randomly assigned to receive treatment with oral risedronate (2.5 or 5.0 mg daily) or placebo for three years.

In the group of women with osteoporosis (those 70 to 79 years old), the incidence of hip fracture among those assigned to risedronate was 1.9%, as compared with 3.2% among those assigned to placebo (RR= 0.6; 95CI 0.4 to 0.9; P=0.009). In the group of women selected primarily on the basis of non skeletal risk factors (those at least 80 years of age), the incidence of hip fracture was 4.2% among those assigned to risedronate and 5.1% among those assigned

to placebo ( $P=0.35$ ) [49]. A second analysis pooling the VERT and HIP studies involving 1392 osteoporotic women aged  $\geq 80$  years found a 44% decreased risk of vertebral fractures (HR = 0.56; 95% CI 0.39-0.81) after three years of treatment with risedronate, but the incidence of non-vertebral fractures was not significantly different [50].

#### \* Zoledronic acid

In 2010, a post-hoc analysis of the HORIZON Pivotal Fracture Trial and HORIZON Recurrent Fracture Trial studies focused on osteoporotic women (T-score  $\leq 2.5$  femoral neck or  $\geq$  one prevalent vertebral fracture or recent hip fracture) aged  $\geq 75$  years (mean age 79.4 years). After three years of treatment, the incidence of vertebral fractures was significantly decreased by 66% in the zoledronic acid group compared with placebo and the incidence of non-vertebral fractures was significantly decreased by 27% (HR = 0.34; 95% CI 0.21-0.55 and HR = 0.73; 95% CI 0.6-0.9) [51]. The decreased risk of fracture with zoledronic acid was comparable to that of women  $< 75$  years of age. However, the decrease in the risk of hip fracture was not significant. In the ZEST study (The Zoledronic acid in frail Elders to STrengthen bone study), a randomized controlled trial vs. placebo, women with an average age of 85 years, non-autonomous and some with upper function disorders or polyopathy were included. They all had osteoporosis that had never been previously treated with bisphosphonates. After a single infusion of zoledronic acid 5 mg, bone density increased significantly in the spine and hip at 1 and 2 years compared to the placebo group. However, there was no difference in the incidence of vertebral and non-vertebral fractures or mortality. There were significantly more patients in this study who had fallen in the previous year in the zoledronic acid group compared to the placebo group [52].

Another study showed that, in patients with a hip fracture, the reduction in future fracture rates by zoledronic acid was similar in those with and without cognitive impairment even with large differences in mortality rate [53].

#### **6.4.3. Denosumab**

In an initial post-hoc analysis of the FREEDOM study, the reduction in the risk of hip fracture in women aged  $\geq 75$  years treated with denosumab was 62% compared to women of the same age on placebo (2.3% placebo vs. 0.9% denosumab). In another FREEDOM post-hoc study, women aged at  $\geq 75$  years treated with denosumab had a significant 64% (3.1% vs. 8.6%) decrease in the risk of a new vertebral fracture, but no difference in the risk of a non-vertebral fracture (7.9% vs. 9%) compared to women receiving placebo after three years of treatment [54].

#### **6.4.4. Romosozumab**

In the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH), comparing the effectiveness of a treatment regimen starting with romosozumab and transitioning to alendronate with alendronate treatment alone in reducing the risk of fracture among postmenopausal women with osteoporosis and a previous fracture, romosozumab treatment for 12 months followed by alendronate resulted in a significantly lower risk of fracture than alendronate alone. In this study, there is no aged-subgroup analysis but 52% of the women were  $\geq 75$  years old [55].

### **7. Care facilities adapted to older adults**

The management of osteoporotic patients can be facilitated by fracture liaison services (FLS) which aim to identify fractured patients, investigate risk factors, initiate treatment and prevention of falls, and ensure compliance with treatment. The ultimate goal is to decrease the risk of further fracture. Some studies show a  $\sim 30\%$  reduction in any re-fractures at the FLS

hospital compared with a similar non-FLS hospital [56]. The age at which a FLS no longer offers significant benefit is unknown, and FLS services need to be tested in the oldest-old population [57]. An orthogeriatric organization which concerns perioperative care can also improve the management of older adults hospitalized for fracture [58]. Older adults with hip fractures admitted early to a dedicated geriatric unit and cared for by a multidisciplinary team have a decrease in mortality and better resumption of walking [58]. Low-quality evidence suggests that orthogeriatric care is associated with higher rates of diagnosing osteoporosis, initiation of calcium and vitamin D supplements and anti-osteoporosis medication. Whether orthogeriatric care prevents subsequent falls and fractures in older hip fracture patients remains unclear [59].

## **8. Conclusions**

Osteoporosis and consequent fractures are common in older adults. Despite a wide range of effective anti-osteoporosis medications, the proportion of patients receiving adequate treatment remains too low. With the ageing of the world's population, it is of paramount importance to develop the management of osteoporotic patients, to limit the number of severe fractures and thus to limit hospitalization and death after a fracture. In addition to drug treatment, multidisciplinary management will make it possible to reduce the co-morbidities and falls associated with the increased risk of fracture.

## **Disclosure of interest**

None

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