Pharmacological prevention of fragility fractures in Belgium

KCE reports 159C

Belgian Health Care Knowledge Centre
Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
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FOREWORD

Elderly women are at high risk of hip fracture, due to bone decalcification. This is well known by the public, and almost considered a fatality. Less well known is that the risk of vertebral fractures is even higher and that humerus fractures also often are due to osteoporosis. To a certain extent, adaptations in lifestyle can curb the risk, but in addition, there are a number of drugs for the treatment of osteoporosis.

Should each elderly woman take these drugs to prevent a fracture, though? And what about men? Who will, eventually, benefit most from it? Or will only the drug manufacturers benefit, as is suggested by some opponents? By all means, the stakes are high, including for health insurance : in an ageing population, and with this type of long-term treatments, we are readily confronted with astronomical amounts. Hence, more than enough reasons to take a closer look at the way these drugs are used… or should be.

It brought us into an exciting study domain, full of controversies, and in constant evolution. Many have contributed to this endeavour, with a special mention for the panel of high-level experts and validators, who challenged us in a critical but constructive way to explore this complex subject to the root. We thank them sincerely for their much appreciated contribution to this work.

Jean Pierre CLOSON
Vice Director General

Raf MERTENS
Director General

Executive summary

INTRODUCTION

WHAT IS OSTEOPOROSIS?

Osteoporosis is a systemic skeletal condition characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture, mainly of the wrist, humerus, vertebra and hip. The World Health Organisation (WHO) has defined osteoporosis in terms of bone mass density (BMD; g/cm^2) usually measured by dual-energy x-ray absorptiometry (DXA). An individual is considered osteoporotic when his/her BMD measurement (at the spine or hip) presents a T-score below -2.5, i.e. when his/her BMD is more than 2.5 standard deviations below the mean BMD observed in young adults of the reference population. The term severe or established osteoporosis corresponds to a T-score below -2.5 in the presence of one or more fragility fractures.

DOES IT MATTER?

Fragility fractures, particularly of the hip, are an important contributor to the morbidity and mortality of the elderly population. Moreover, their management generates high costs in health services, and this share is likely to increase due to an ageing population. Preventing such fractures could therefore, in theory, be a sound intervention for public health. Such prevention can apply only if individuals at risk of fragility fractures can be identified and if effective means of prevention can be offered to them.

OBJECTIVES OF THE REPORT

This report assesses the validity of the strategies for fragility fracture screening as well as the efficacy of preventive medicines currently at our disposal, in order to draw recommendations for Belgium, if appropriate. The report focuses on the prevention of fragility fractures. Secondary and primary prevention in this context refer to fracture prevention in individuals with and without a prior fragility fracture. Although non pharmacological prevention of fragility fractures is also an important strategy, its assessment was beyond the scope of this report.

METHODS

We carried out a systematic literature review on the efficacy of medicine used for preventing fragility fractures. Routine data collected by sickness funds were used to assess the epidemiology of fragility fractures in Belgium (hip, wrist, femur) and the utilization of preventive medicines. Finally, we reviewed the evidence on screening strategies and we made a comparative appraisal of various national guidelines for osteoporosis management.

All fractures occurring in individuals ≥ 40 years were considered fragility fractures as information on associated high-energy trauma was not accessible. This might have overestimated incidence rates, particularly in the age group 40-60 years. However a minority of overall recorded fractures occurred in that age group and the overestimation is likely low. Incidence rates stratified by age range are presented in the report.

MAIN RESULTS

EFFICACY OF PREVENTIVE MEDICINES

Pharmacotherapy for preventing fragility fractures can be divided in two main drug families, anti resorptive and anabolic agents. The former increase bone strength by reducing bone resorption. This drug family includes the bisphosphonates (in Belgium, these are mainly alendronate, alone or in combination with colecalciferol, risedronate, ibandronate and zoledronate); selective estrogen modulators (raloxifene); calcitonin; and denosumab. Calcitonin is mainly used in Belgium for pain relief after a fragility fracture and rarely for the prevention of further fractures. Denosumab will be reimbursed from July 2011 onwards. The anabolic agents increase bone strength by increasing bone mass due to an increase in the number of bone multicellular units, such as teriparatide. Strontium ranelate is considered both anti-resorptive and anabolic.

All trials with a demonstrated anti-fracture effect had low BMD and/or prevalent vertebral fracture as inclusion criterion. The proportion of patients with a prior vertebral fracture was often high and results were generally not stratified for this factor. The efficacy of osteoporosis drugs in primary prevention is thus grossly undetermined to date. The optimal duration of therapy also remains uncertain.

Relative risks and numbers needed to treat (NNT) are presented by drugs and fracture sites in table 1 and table 2. All the accepted osteoporosis treatment reduced the risk of vertebral fractures. This risk reduction was not significantly different between treatments, except for annual intravenous injection of zoledronate or biannual subcutaneous injection of denosumab which both reduced the risk by around 70% over a 3-year treatment period. In contrast, the prevention of nonvertebral fractures was demonstrated only for alendronate, risedronate, zoledronate, strontium ranelate, and denosumab, and this effect was consistently smaller than for vertebral fractures. Here again, a greater risk reduction of nonvertebral fracture was apparent for zoledronate (2 studies) and denosumab (1 study) in comparison to the other drugs. Studies on alendronate, risedronate, zoledronate, and denosumab reported a protective effect on hip fracture. However, the absolute risk reduction for this fracture site was very small and the confidence interval around the NNT included huge numbers of patients.

PHARMACOLOGICAL SAFETY

The safety profile of osteoporosis drugs has been considered satisfactory up to now, although they are associated with a few rare serious adverse reactions.

An increase of 0.23 per 100 person-years in the incidence of gastroduodenal perforation, ulcers, and bleeding has been reported for alendronate, and a possible increase in the risk of oesaphageal cancer (0.1% over 5 years of bisphosphonate use) has been suggested. Osteonecrosis of the jaw is a serious adverse event observed with bisphosphonates and denosumab. This rare adverse event occurs principally in cancerous patients, particularly when receiving zoledronate. Subtrochanteric or shaft fractures of the femur are serious but rare adverse events associated with bisphosphonate use (0.13%). A increased risk of serious atrial fibrillation has been reported for bisphosphonates, particularly zoledronate. Denosumab has numerous adverse effects. In placebo-controlled trials, this monoclonal antibody was associated with a higher incidence of deep-seated infections such as endocarditis, cancer, and skin rash.

Adverse events associated with long-term therapy are still poorly known.

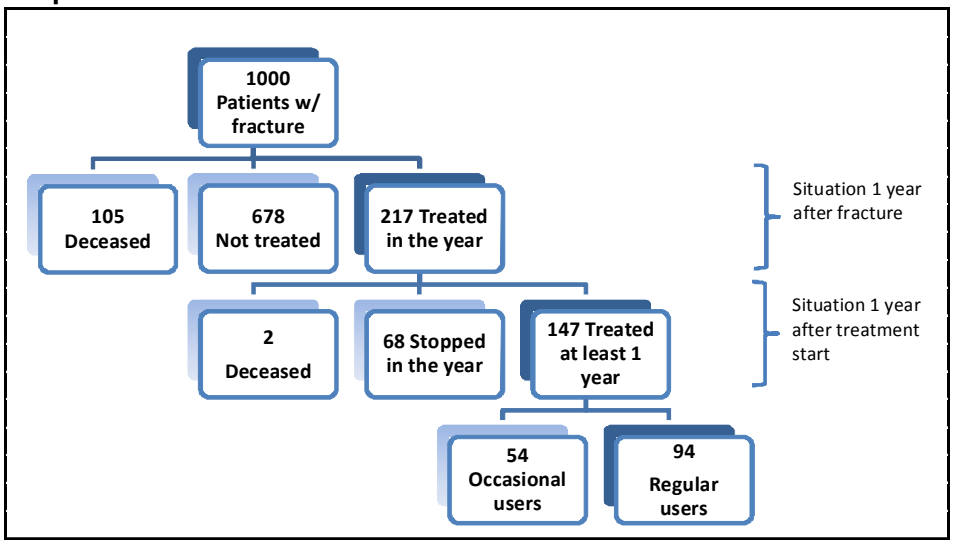
INCIDENCE OF FRAGILITY FRACTURES IN BELGIUM

The burden of disease is important. In 2008, 14 720 hip fractures, 9 680 humerus fractures and 18 040 wrist fractures were recorded in the Belgian population ≥ 40 years. The corresponding annual incidence rates in females were 3.66 (95%CI: 3.59, 3.73), 2.57 (95%CI: 2.51, 2.63) and 4.94 per 1000 person-years (95%CI: 4.85, 5.02), respectively. The low incidence rate observed for vertebral fractures (0.79 per 1000 person-years) results from under-detection and under-reporting, the majority of these fractures being clinically silent. The overall number of fractures increased by 5% between 2002 and 2008. However, standardized incidence rates remained constant over time, except for hip fracture which showed a limited albeit significant reduction in incidence rate over this time period. For all fracture sites, the incidence rate was consistently higher in females than in males. The incidence rate of hip fractures increased exponentially with age. On average, humerus and wrist fractures occurred 10 years earlier than hip fractures.

UTILIZATION OF PREVENTIVE MEDICINES IN BELGIUM

In 2009, more than 230 000 patients used osteoporosis drugs. The number of Defined Daily Doses (DDDs) increased by 45% between 2004 and 2009, for 61 754 266 DDDs purchased in 2009, and an annual INAMI/RIZIV budget close to 53 millions €. The bisphosphonates were the drug class the most widely used, and in particular alendronate alone or in combination (65.2% of the DDDs used in 2009). The combination of alendronate and colecalciferol which was introduced in 2006 already accounted for 33.5% of all DDDs in 2009, although firm evidence on the clinical interest of such combination is inexistent.

Figure: Treatment path per 1000 patients ≥40 years with fragility fracture in the period 2002-2008



Rates of prevention after a fracture were remarkably low: 67.8% of patients suffering a fragility fracture didn't receive any anti-osteoporotic treatment in the following 12 months (treatment rate at 1 year: 16.1 per 1000 person-months; 95%CI: 15.1; 17.2). Adherence and persistence to treatment were also sub-optimal (see figure). Around 20% of patients bought only one drug package. A year after a fragility fracture, only 10.5% (94/893) of living patients was still receiving an appropriate treatment on a regular basis.

SCREENING FOR FRAGILITY FRACTURES

Because of the BMD-based definition of osteoporosis, detecting patients at high risk of fractures has been relying heavily on measuring that parameter. This measure presents a relatively good specificity but a poor sensitivity. BMD at the femoral neck (the reference site) is a strong predictor of hip fractures (gradient of risk ≅ 3.00) and of fractures at other sites (gradient of risk ≅1.40) both in men and women. However, the relatively low predictive value of the test and the large proportion of false negatives preclude the utilization of only BMD for screening patients at risk of fractures.

Other risk factors for fragility fractures have been identified, including current cigarette smoking, alcohol intake ≥ 3 unit per day, age, being a female, corticosteroid exposure, a family history of hip fracture, a prior fragility fracture, a low body mass index, and suffering from rheumatoid arthritis or other conditions causing secondary osteoporosis. The use of such risk factors enhances the performance of BMD in the prediction of osteoporotic fractures. The individual absolute risk of fractures can be computed with various algorithms, among which the FRAX® promoted by WHO and available on line (http://www.shef.ac.uk/FRAX/). The FRAX®, also calibrated for Belgium, gives a 10-year probability of hip fracture or of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture) for each combination of the above mentioned factors, with or without BMD.

Clinical practice guidelines have thus quite recently evolved from the use of BMD thresholds to a more complex consideration of the patient's 10-year absolute fracture risk. This shift was retrieved in most of the national guidelines we reviewed (USA, Canada, UK, Australia, The Netherlands). However, no risk threshold above which initiating a treatment would be recommended has been validated in prospective studies to date. Most guidelines used the risk factors of fragility fractures as a pre-screening tool to define who should undergo a DXA, and the BMD results remained the most important criterion to recommend an osteoporosis treatment. Only in 2 guidelines was the FRAX® proposed for treatment decision and this was with conflicting strategies: the National Osteoporosis Guideline Group in the UK recommended a threshold varying with age whereas the National Osteoporosis Foundation in the USA proposed a fixed cut-off of 20% 10-year risk of major osteoporotic fractures.

Worth mentioning, a prior fragility vertebral fracture was generally considered a sufficient criterion on its own to start a treatment. No clinical practice guidelines existed in Belgium.

There is to date no sufficient evidence to support the use of other medical imaging or biochemical markers in the individual assessment of the absolute fracture risk. Finally, direct evidence of the effectiveness and cost-effectiveness of screening for osteoporosis or for high-risk individuals was scarce (only 2 studies with inappropriate design and low-quality evidence). No studies evaluating potential harms were retrieved.

Table 1: Meta-analyses of osteoporosis treatments (relative risk reduction)

DRUGS		FRACTURES				
		Vertebral	Nonvertebral	Hip	Wrist	Humerus
Alendronic acid 5 or 10 mg/day	**RR (95%CI)**	**0.55 (0.46, 0.66)**	**0.83 (0.74, 0.93)**	**0.62 (0.40, 0.96)**	**0.85 (0.67,1.09)**	
1 to 4 years	GRADE quality	high/moderate	high/moderate	high/moderate	low/very low	
6 to 70% PF	Trials (patients)	9 trials (8074)	8 trials (10429)	3 trials (7453)	3 trials (7453)	
Etidronate 400 mg/day	**RR (95%CI)**	**0.51 (0.31, 0.83)**	**0.72 (0.29, 1.80)**	**1.02 (0.21, 4.94)**	**4.95 (0.24, 101.93)**	
1 to 5 years	GRADE quality	moderate	low	very low	very low	
0 to 100% PF	Trials (patients)	8 trials (1039)	4 trials (472)	2 trials (246)	1 trial (209)	
Risedronate 5mg/day	**RR (95%CI)**	**0.61 (0.50, 0.74)**	**0.81 (0.72, 0.90)**	**0.73 (0.58, 0.92)**	**0.68 (0.43, 1.07)**	**0.46 (0.23, 0.93)**
1 to 5 years	GRADE quality	moderate/low	moderate/low	moderate/low	moderate/low	moderate/low
100% PF	Trials (patients)	7 trials (2845)	7 trials (12658)	4 trials (11923)	2 trials (2439)	2 trials (2439)
Ibandronic acid 2.5mg/day	**RR (95%CI)**	**0.51 (0.34, 0.74)**	**1.11 (0.83,1.48)**			
1 to 3 years	GRADE quality	low/very low	low/very low			
43 to 94% PF	Trials (patients)	1 trial (1952)	1 trial (1952)			
Zoledronate 5mg/year (IV)	**RR (95%CI)**	**0.30 (0.24, 0.38)**	**0.75 (0.66, 0.85)**	**0.62 (0.47, 0.83)**		
1.9 to 3 years	GRADE quality	high/moderate	high/moderate	high/moderate		
63 to 100% PF	Trials (patients)	2 trials (7802)	2 trials (9863)	2 trials (9863)		
Strontium ranelate 2 g /day	**RR (95%CI)**	**0.62 (0.55, 0.71)**	**0.86 (0.74, 0.99)**	**0.85 (0.61, 1.19)**	**1.00 (0.74, 1.36)**	**0.53 (0.29, 0.94)**
2 to 3 years	GRADE quality	moderate/low	moderate/low	moderate/low	moderate/low	moderate/low
54% to 100% PF	Trials (patients)	3 trials (5254)	2 trials (6374)	1 trial (4932)	1 trial (4932)	1 trial (4932)
Teriparatide 20µg/day (subcutan.)	**RR (95%CI)**	**0.36 (0.23, 0.57)**	**0.49 (0.27, 0.87)**	**0.25 (0.03, 2.24)**	**0.29 (0.06, 1.38)**	**1.01 (0.14 to 7.11)**
11 to 18 months	GRADE quality	moderate	moderate	very low	very low	very low
29% to 100% PF	Trials (patients)	2 trials (910)	2 trials (1383)	1 trial (1085)	1 trial (1085)	1 trial (1085)
Raloxifene 60mg/day	**RR (95%CI)**	**0.64 (0.54, 0.78)**	**0.91 (0.78, 1.05)**	**1.12 (0.64, 1.94)**	**0.88 (0.68, 1.14)**	
1 to 3 years	GRADE quality	moderate/low	low	low	very low	
10% to 100% PF	Trials (patients)	2 trials (4639)	2 trials (7793)	2 trials (7793)	1 trial (7705)	
Denosumab 60mg/6months (subcut.)	**RR (95%CI)**	**0.32 (0.26, 0.41)**	**0.80 (0.67, 0.95)**	**0.60 (0.37, 0.97)**		
3 years	GRADE quality	high/moderate	high/moderate	high/moderate		
23.5% PF	Trials (patients)	1 trial (7868)	1 trial (7868)	1 trial (7868)		

PF: Prior Fracture; RR: Relative Risk

Table 2: Meta-analyses of osteoporosis treatments (NNT)

DRUGS		FRACTURES				
		Vertebral	Nonvertebral	Hip	Wrist	Humerus
Alendronic acid 5 or 10 mg/day	**NNT (95%CI)**	**33 (25, 50)**	**50 (33, 100)**	**200 (100, >1000)**		
1 to 4 years	Rate in controls	0.04 to 0.35	0.02 to 0.18	0.013 to 0.08		
Etidronate 400 mg/day	**NNT (95%CI)**	**25 (13, 100)**				
1 to 5 years	Rate in controls	0.03 to 0.16				
Risedronate 5mg/day	**NNT (95%CI)**	**17 (21, 25)**	**50 (33, 100)**	**125 (100, >1000)**		**100 (50, >1000)**
1 to 5 years	Rate in controls	0.00 to 0.26	0.04 to 0.13	0.02 to 0.08		0.01 to 0.03
Ibandronic acid 2.5mg/day	**NNT (95%CI)**	**25 (17, 50)**				
1 to 3 years	Rate in controls	0.07				
Zoledronate 5mg/year (IV)	**NNT (95%CI)**	**13 (12, 17)**	**50 (25, 100)**	**100 (70, >200)**		
1.9 to 3 years	Rate in controls	0.11	0.10	0.02 to 0.03		
Strontium ranelate 2 g /day	**NNT (95%CI)**	**NR**	**NR**			**160 (110, >1000)**
2 to 3 years	Rate in controls	NR	NR			0.013
Teriparatide 20µg/day (subcutan.)	**NNT (95%CI)**	**11 (8, 20)**	**50 (25, 100)**			
11 to 18 months	Rate in controls	0.14 to 0.17	0.02 to 0.04			
Raloxifene 60mg/day	**NNT (95%CI)**	**25 (20, 50)**				
1 to 3 years	Rate in controls	0.04 to 0.29				
Denosumab 60mg/6months (subcut.)	**NNT (95%CI)**	**21 (19-24)**	**67 (37, 250)**	**208 (130, >1000)**		
3 years	Rate in controls	0.07	0.08	0.012		

PF: Prior Treatment; NNT: Number Needed to Treat

DISCUSSION AND CONCLUSION

It can be expected that patients with the highest risk of fragility fracture will draw the greatest benefit from a pharmacological prevention and that targeting such high risk patients would result in better cost-effectiveness. However, the evidence in support of such case-finding and treatment strategy is still weak at 3 levels.

First, in spite of the prediction improvement they provide in comparison to BMD alone, all the risk assessment tools, including FRAX®, were limited in their ability to predict fractures, especially non-hip fractures. The absence of important risk factors in the assessment tools (e.g. a history of falls) and not accounting for the dose-dependence effect of some risk factors (e.g. alcohol consumption or prior fractures) might be explanatory elements.

Second, all the clinical trials carried out for assessing the efficacy of osteoporosis treatment selected patients on the basis of low BMD and/or prior vertebral fracture, not on absolute risk of fracture. It is thus unknown how far their results can be extrapolated to patient populations identified on a different basis. There is to date contradictory evidence regarding the modifying effect of baseline risk on therapeutic efficacy. Another important area of uncertainty concerns how various combinations of risk factors, for a given fracture risk, could modify the treatment effect.

Third, treatment efficacy has been well demonstrated for preventing vertebral fractures in secondary prevention. However, results for prevention of fragility fractures at other sites, and in particular at the hip, indicated considerable NNTs. Moreover, the efficacy of treatment in primary prevention was lower than in secondary prevention and was demonstrated only for vertebral fractures.

The only straightforward indication for osteoporosis treatment is the presence of a prior fragility fracture. Paradoxically, treatment is initiated in a minority of such cases in our country. An important step forward for improving osteoporosis management would be to treat appropriately patients with fragility fractures. This step can be achieved without waiting for more refined diagnosis tools.

Very low patients' persistence and adherence to treatment were observed in Belgium, as in many other countries. These factors undermine the prevention of fragility fractures. Injectable drugs with long-lasting action, such as zoledronate and denosumab, might represent an important advance to address this issue. However, these are recent drugs and their risk-benefit balance on the long term must still be assessed.

RECOMMENDATIONS[a]

RECOMMENDATIONS FOR CLINICIANS

- **The pharmacological prevention of fragility fractures should be targeted to high-risk patients, i.e. patients who will benefit the most from the treatment.**
- **The individual fracture risk is assessed with clinical algorithms. BMD should be measured only in individuals presenting risk factors of fragility fractures.**
- **All patients presenting a fragility fractures should be proposed a pharmacological prevention of further fractures. Worth mentioning, such prevention is more effective on vertebral fractures than on fractures at other sites. NNT for preventing 1 hip fracture is high.**
- **In the absence of prior fragility fractures, a strategy based on the individual absolute risk of fracture must be implemented. There is today no consensus on the definition of what a high 10-year fracture risk is, i.e. there is no consensus on a risk threshold above which a prevention should be implemented. The following treatment strategy is therefore recommended:**
  - **If the 10-year fracture risk is high with a low BMD, a treatment is recommended. However, it should be acknowledged that the protective effect of pharmacological treatment in such patients has been demonstrated only on vertebral fractures, which are in majority clinically silent.**
  - **If the 10-year fracture risk is high with a BMD in the normal range, a treatment is generally not recommended as evidence allowing the translation of existing trial results to such patient population is currently limited. However, this does not preclude clinicians from considering a treatment on an individual basis (the predictive value of a negative test in such population is decreased).**
  - **If the 10-year fracture risk is low, a treatment is not recommended.**
- **Considerations, such as patient preferences or adherence, should also intervene in the treatment decision. Absolute risk of fracture, risk reduction expected from treatment, and risk of serious adverse events should be discussed with the patients.**
- **The pharmacological prevention of fragility fractures should be viewed as a component of a comprehensive management plan. Such management plan should primarily identify risk factors amenable to non-pharmacological interventions such as: low dietary intake of calcium; environmental risk factors for falls; lack of physical activity; consumption of alcohol and/or psychotropic drugs; etc… Causes of secondary osteoporosis, such as hypogonadism or hyperparathyroidism, should also be duly identified and treated.**
- **Monitoring treatment with repeated DXA is not recommended. There is currently not enough evidence to recommend other types of treatment monitoring.**

a The KCE is the only responsible for the recommendations given to the public authorities

RECOMMENDATIONS FOR POLICY-MAKERS

- **The utilization of clinical algorithms for assessing the absolute 10-year risk of fragility fracture should be promoted in all individuals presenting one or more risk factors, particularly during consultations in general medicine. It could be part of the Global Medical File. The dissemination of screen-and-treat algorithm for individuals at high risk of fragility fractures in Belgium would be an asset.**
- **The health services should be encouraged to consider treatment in every patient presenting a fragility fracture, e.g. by an information campaign.**
- **Expensive molecules which clinical benefit is not supported by firm evidence (such as calcitonin and combination of bisphosphonates with colecalciferol) should not be reimbursed except for very specific indications.**

RECOMMENDATIONS FOR RESEARCHERS

- **There is an urgent need to assess the effectiveness of treatments according to different levels of 10-year risk of fractures and different combinations of risk factors.**
- **There is a need to design and assess operational strategies aimed at improving the adherence and persistence of treatment in patients at high risk of fragility fractures in Belgium.**

Scientific summary

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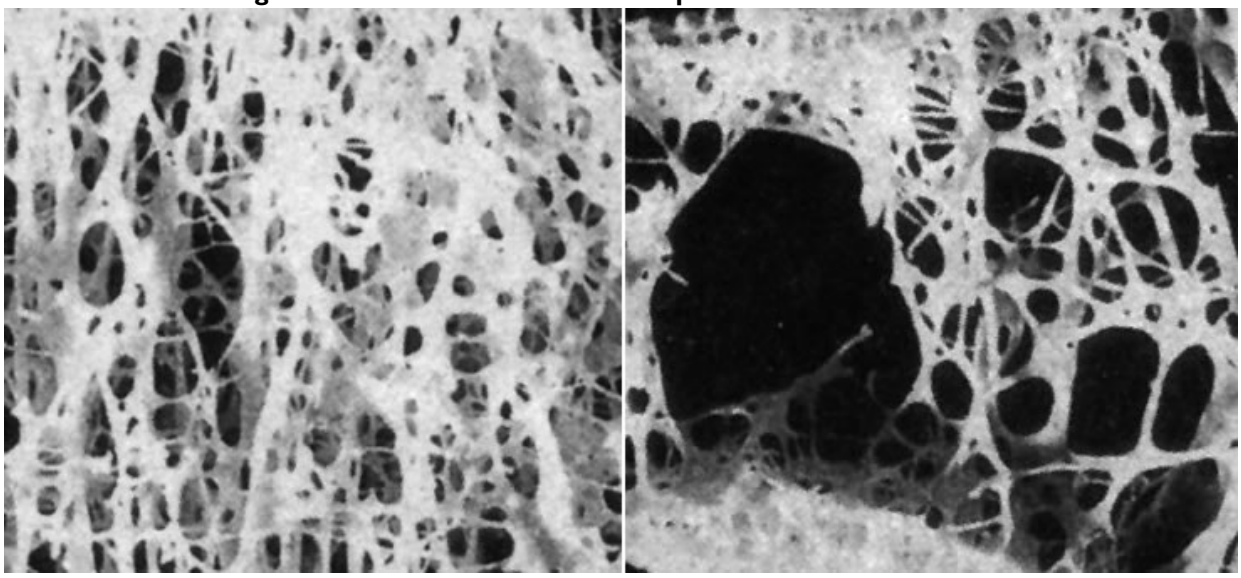
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1 INTRODUCTION

Osteoporosis is a systemic skeletal condition characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [1]. Osteoporosis may occur without a known cause or secondary to another condition, such as hyperthyroidism, hyperparathyroidism, rheumatoid arthritis and the utilization of glucocorticoid or hormonal ablative therapies

Figure 1: Normal bone versus osteoporotic bone



WHO defined operationally osteoporosis on the basis of the bone mineral density (BMD), the reference method to measure BMD being the central dual-energy X-ray absorptiometry (DXA) [1]. An individual is considered osteoporotic when his/her BMD measurement (spine or hip) presents a T-score below -2.5, i.e. when his/her BMD is more than 2.5 standard deviations below the mean BMD observed in young female adults (20-29 years) of the reference population [2]. The term "severe or established osteoporosis" habitually denotes a T-score below -2.5 in the presence of one or more fragility fractures. Osteopenia is defined as a BMD T-score between -1 and -2.5. Although no WHO definition for osteoporosis exists for men, in clinical practice the same cut-off for the diagnosis of osteoporosis is applied for women and men, i.e. a BMD below -2.5 standard deviations of the female reference range. Epidemiological studies have shown a similar relationship between BMD and fracture risk in men and in postmenopausal women, i.e. the predictive value of BMD for the occurrence of fractures is similar in men and in women [3].

Early osteoporosis is not usually diagnosed and remains asymptomatic. It does not become clinically evident until fractures occur. In the vast majority of cases, vertebral fractures are not recognized by the patients and go undetected [4]. The incidence of osteoporotic fractures rises with age [5]. Adults who sustain a low trauma fracture are at substantially greater risk of sustaining other fragility fractures [6-8].

Besides BMD and prior fractures, other independent risk factors of fragility fractures have been identified: age, a family history of hip fractures, high bone turnover, low body mass index, tobacco use, and alcohol abuse, are the most important factors to be considered. Genetic and nutritional factors (e.g. calcium intake and vitamin D repletion) play significant roles.

Osteoporotic fractures are an important contributor to the morbidity and mortality in elderly population. Moreover, their management generates high costs in health services, and this share is likely to increase within an ageing population. It was estimated that osteoporotic fractures account for 2.7 million fractures in men and women in Europe at a direct cost of 36 billion Euros [1]. In Belgium, more than 14 000 hip fractures occur every year. Therefore, the prevention of osteoporotic fractures appears to be a sound intervention of public health. Such prevention can apply only if individuals at risk of fragility fractures can be identified and if effective means of prevention can be proposed to them. This report aimed at assessing the validity of the tools available for osteoporosis screening as well as the efficacy of pharmacological treatments currently at our disposal, in order to draw recommendations for Belgium, if appropriate. Non pharmacological prevention of fragility fractures is also important but was beyond the scope of our report.

Our report includes four chapters:

- Analysis of the Belgian situation: epidemiology of fragility fractures and utilization of osteoporosis drugs
- Screening for patients at high-risk of fractures: validity of the screening tools and effectiveness of screening programmes
- Efficacy of anti-osteoporotic drugs in primary and secondary prevention
- Comparative appraisal of national guidelines for managing osteoporosis

Only pharmaceutical prevention of fragility fractures will be examined here. However, it should be kept in mind that physical activity (walking, aerobic and weight-bearing exercises), quitting smoking, preventing falls (by Tai Chi exercices, muscle and balance training, and reducing psychopharmacological treatments), and hip protectors, are also means of prevention [9]. This non-pharmacological management of osteoporosis has been recently synthesized in a consensus paper for Belgium [10].

2 BELGIAN SITUATION ANALYSIS

This section aims at describing the epidemiology of fragility fractures in Belgium, as well as the utilization of pharmacological treatments of osteoporosis.

2.1 METHODS

2.1.1 Data sources

We utilized two data sources:

1. a random sample of claim data collected between years 2002-2008 by sickness funds (the permanent sample/échantillon permanent/permanente steekproef – EPS, from the IMA-AIM database). The Permanent Sample (EPS) is a representative random sample of 2.5% of all persons covered by the compulsory health insurance, stratified by age and gender (with a supplementary sampling of another 2.5% for people ≥65 years). The EPS contains all reimbursement data and some demographic and socio-economic characteristics of individuals (on a maximum period of 10 years).
2. We extracted from the EPS all individuals ≥ 40 years who during the period 2002-2008 suffered a bone fracture at the hip, wrist, humerus or vertebral level AND/OR who utilized osteoporosis drugs (the authorization granted by the Sectoral Committee can be found in appendix).
3. This dataset was used for assessing the epidemiology of fragility fractures under the assumption that the vast majority of bone fractures occurring at age ≥40 years are associated with osteoporosis. The dataset also allowed analysing individual patterns of osteoporosis drugs.
4. the Pharmanet dataset which aggregates sales data of drugs in the ambulatory sector only. This dataset served for documenting trends in the use of osteoporosis drugs over time at the level of the whole population between 1997 and 2009 (the number of patients has been available from 2004 onwards).

2.1.2 Epidemiology of fragility fractures

We considered four types of fractures in the present study: hip, humerus, wrist and vertebral fractures. We acknowledge that an important proportion of vertebral fractures is undetected and that estimates of fracture incidence based on claim data are likely biased downwards. However, it remains relevant to document the management of the subset of diagnosed vertebral fractures. For humerus and wrist, we first considered nomenclature codes with high specificity, i.e. fracture of the head/neck of the radius or of the humerus (see Table 23 in appendix). Preliminary analyses showed that age and gender distributions were very similar for other groups of codes, i.e. fracture of the wrist, fracture of the shoulder and fracture of the humeral diaphysis (see Figure 8, Figure 9 and Figure 11 in appendix). Therefore we pooled the corresponding codes (i.e. codes for a fracture of the forearm distal extremity were pooled with the codes specific to a fracture of the radius head or neck codes, both types being considered as wrist fractures; similarly, the humerus fractures included humerus head or neck fractures and diaphysis fractures).

For hip fracture, specific nomenclature codes were available (see Table 23 in appendix). In the particular case of a total hip replacement, an additional filter was used for differentiating cases of osteo-arthrosis from fractures. In such cases, we used an algorithm already validated in a previous study [11]. Codes of total hip replacement were considered related to a hip fracture if the following conditions were met: the procedure was performed in the week-end and/or during the night and/or a traction was performed in the last 30 days, AND, in any case, there was no X-ray taken between 182 days (6 months) and 15 days before the surgery.

Worth mentioning, we considered all fractures occurring above age 40 years as fragility fracture. Traumatic and osteoporotic fractures cannot be disentangled in the IMA dataset. This might have overestimated the incidence rate of fragility fractures, particularly in the younger age-range (40-59 years). To account for this potential bias, results were also stratified by age range. When 2 codes for fractures were separated by less than 30 days, the 2 codes were considered to correspond to the same event. We also acknowledge that an important proportion of vertebral fractures is undetected and that estimates of fracture incidence based on claim data are likely biased downwards. Vertebral fracture rates are thus unreliable. However, we kept considering vertebral fractures in our report to assess treatment rates in the subset of diagnosed vertebral fractures. Annual incidence rates were computed for each year and fracture type. Analysis were weighted to account for the oversampling (≥ 65 years).The 95% confidence interval was calculated with the following formula:

$$95\%\ CI = \frac{\sum events}{\sum observation\ months} \pm 1.96 * \left(\frac{\sqrt{\sum events}}{\sum observation\ months} \right)$$

Annual standardized rates were calculated by direct standardization. The reference population was the Belgian population on January 1st 2005. The annual standardized rate (ASR) and the 95% confidence interval were calculated with the following formulas:

$$ASR = \frac{\sum_{i=a;j=z}^{kl} number\ of\ expected\ fractures}{\sum_{i=a;j=z}^{kl} Belgian\ Population} \times 1000 \qquad (where\ i = gender, j = age\ category)$$

$$95\%CI = ASR \pm 1.96 * \frac{\sqrt{\left(\sum_{i=1;j=1}^{kl} Belgian\ Pop.\right)^2 * \frac{ASR}{\sum_{i=1;j=1}^{kl} EPS\ patient - years}}}{\sum_{i=1;j=1}^{kl} \mathbf{Belgian\ Pop.}}$$

Death rates following a fracture were also computed. Cox regression models were used for multivariate analysis. However, preliminary analysis showed that the proportionality of hazards were not respected for most of the covariates. It was therefore decided to describe the mortality rate (per 1000 person-years) after fracture overall and at 1-year after fracture by fracture site, stratified by gender and age category. The analysis was performed on the patients with fractures within the period 2002 – 2007 for reaching a minimum follow-up of 12 months for all the years considered.

All analysis were carried out in SAS 9.2 and Stata 9.0.

2.1.3 Osteoporosis drugs consumption

Utilization of bisphosphonates, strontium ranelate, raloxifene, teriparatide, and calcitonin was analysed (Table 24 in the appendix).

2.1.3.1 Global trends

Data from Pharmanet (ambulatory sector only) were aggregated per year by INAMI/RIZIV and plotted in Excel by KCE. We assessed the evolution of the following parameters:

- Number of patients per year (from 2004 to 2009)
- Number of DDDs per year (from 1999 to 2009)
- RIZIV/INAMI cost per year (from 1999 to 2009)
- Patient Part cost per year (from 1999 to 2009)
- Total cost per year (from 1999 to 2009)

For each parameter, there was an overall description by ATC level 4 (chemical subgroup level) and a specific description by ATC level 5 (chemical substance level).

2.1.3.2 *Individual utilization*

The EPS allows following up individual patients over the years. The different periods of time when a patient was covered by a treatment were reconstructed based on the daily doses delivered. Parameters used to characterize patient profiles are presented in Table 1.

Table 1: Definition of parameters of drug utilization

Term	Definition
User	Individual with at least one purchase of osteoporosis drug during the observation period
Medication Possession Ratio (MPR)	The Medication Possession Ratio is the number of DDDs purchased divided by the number of days during the period of use defined as: ((date last delivery-date first delivery)+number of medication days covered by the last delivery)
One-shot user	Individuals with only one purchase (MPR can not be calculated)
Regular user	User with a Medication Possession Ratio (MPR) ≥80%.
Occasional user	User with a MPR < 80% (excluding the one-shot users)
Defaulter	User stopping definitively his/her treatment (no further prescriptions until the end of the observation period)
Secondary prevention	Start of any osteoporosis drug within the year following a fragility fracture (can be established only from year 2003 onwards[1])
Primary prevention	Start of any osteoporosis drug in individuals with no history of fragility fracture in the preceding year (can be established only from year 2003 onwards[2])

The number of DDDs were computed by ATC5 level. When two ATC5 classes were delivered on the same day as first treatment, the ATC5 class associated with the highest number of DDDs was considered as the first ATC5 delivered[3]. A similar rule was applied to determine the most delivered ATC5 class on the whole treatment.

No Medication Possession Ratio (MPR) was calculated for the users who received only 1 delivery (one-shot users) because two deliveries are needed to do the calculation. We defined persistence as the rates of users still on treatment 12 months after the start of the treatment.

Treatment rates after a fracture and defaulting rates were also computed. Cox regression models were to be used for multivariate analysis. However, preliminary analysis showed that the proportionality of hazards were not respected for most of the covariates. It was therefore decided to report the rates (per 1000 person-months) after 3 and 12 months with stratification by covariates (age, sex, type of treatment, year of treatment start).

Treatment/defaulting rates after 12 months were based on events (fractures or new treatment) occurred between 1st January 2002 and 31st December 2007 allowing a 1-year follow-up. Treatment/defaulting rates after 3 months were based on events (fractures or new treatment) occurred between 1st January 2002 and 30th September 2008.

Determinants of regular use of osteoporosis drugs were analyzed with a logistic regression.

Data analysis was carried out in SAS version 9.2 and Stata 9.0.

---

1 Start of treatment: no treatment documented in at least the 12 preceding months

2 A small proportion of treatments classified as "primary prevention" might be misclassified. This could occur when a treatment was started after the diagnosis of a prior fragility fractures which occurred more than 1 year before treatment initiation. However this misclassification is likely limited as the vast majority of the treatment are indeed begun in the first 3 months after a fragility fracture, and very little additional treatments are started after that time window.

3 The number of patients with two same doses delivered for two different ATC5 on the same date was marginal (2 patients)

2.1.3.3 Reimbursement rules

The legal texts and recommendations by INAMI/RIZIV were reviewed.

2.2 RESULTS

2.2.1 Epidemiology of hip, humerus, vertebral and wrist fractures

2.2.1.1 Incidence rates

In 2008, the annual incidence rate of wrist and hip fractures in females was 4.94 per1000 person-years (95%CI: 4.85, 5.02) and 3.66 per 1000 person-years (95%CI: 3.59, 3.73) in males. For all fracture sites, the incidence rate was consistently higher in females than in males and increased with age (Table 2). Higher rates of vertebral fractures in men at younger age suggest the contribution of traumatic fractures. For instance, in the age range 80-89 years, the incidence rate of hip fracture was 19.03 per 1000 person-years (95%CI: 18.54, 19.53) in females and 10.54 per 1000 person-years in males (95%: 10.06, 11.03). Expectedly, the incidence rate of vertebral fractures was much lower than at other sites. There are 2 reasons for this observation: a substantial proportion of vertebral fractures goes undetected and from those detected only a fraction will be registered by the present methodology. On average, humerus and wrist fractures occurred 10 years earlier than hip fractures (Table 2; Figure 10 in the appendix). The burden of disease is important. In 2008, 46 020 fragility fractures were recorded, among which 14 720 hip fractures (Table 3).

Table 2: Incidence rate per type of fracture, gender and patient age (number of fractures per 1000 persons-years ≥40 years) - EPS 2008

	HIP			HUMERUS		
Age	**Female**	**Male**	**Total**	**Female**	**Male**	**Total**
40-59	0.24 (0.22 - 0.27)	0.32 (0.29 - 0.35)	**0.28 (0.26 - 0.30)**	1.05 (1.00 - 1.10)	0.48 (0.44 - 0.51)	**0.76 (0.73 - 0.79)**
60-69	1.10 (1.01 - 1.18)	0.72 (0.65 - 0.80)	**0.91 (0.86 - 0.97)**	2.82 (2.68 - 2.96)	0.92 (0.83 - 1.00)	**1.89 (1.80 - 1.97)**
70-79	4.64 (4.45 - 4.83)	2.90 (2.73 - 3.07)	**3.87 (3.74 - 4.00)**	3.70 (3.52 - 3.87)	1.29 (1.18 - 1.41)	**2.63 (2.52 - 2.74)**
80-89	19.03 (18.54 - 19.53)	10.54 (10.06 - 11.03)	**15.92 (15.56 - 16.28)**	7.45 (7.14 - 7.75)	3.34 (3.07 - 3.61)	**5.95 (5.73 - 6.17)**
90+	34.84 (33.13 - 36.55)	30.71 (27.84 - 33.58)	**33.86 (32.39 - 35.33)**	4.57 (3.96 - 5.17)	2.74 (1.89 - 3.60)	**4.14 (3.64 - 4.65)**
Total rate	**3.66 (3.59 - 3.73)**	**1.62 (1.57 - 1.67)**	**2.69 (2.64 - 2.73)**	**2.57 (2.51 - 2.63)**	**0.89 (0.85 - 0.92)**	**1.77 (1.73 - 1.8)**
Mean age (SD)	81.79 (41.75)	77.17 (57.12)	**80.46 (47.47)**	71.26 (62.72)	67.98 (68.86)	**70.47 (64.45)**
	VERTEBRA			**WRIST**		
Age	**Female**	**Male**	**Total**	**Female**	**Male**	**Total**
40-59	0.27 (0.24 - 0.29)	0.45 (0.42 - 0.48)	**0.36 (0.34 - 0.38)**	2.54 (2.46 - 2.62)	1.27 (1.21 - 1.33)	**1.90 (1.85 - 1.95)**
60-69	0.33 (0.28 - 0.38)	0.15 (0.12 - 0.19)	**0.24 (0.21 - 0.27)**	4.69 (4.50 - 4.87)	1.68 (1.57 - 1.79)	**3.21 (3.10 - 3.32)**
70-79	1.65 (1.53 - 1.76)	0.36 (0.30 - 0.42)	**1.08 (1.01 - 1.15)**	8.33 (8.07 - 8.59)	1.82 (1.68 - 1.95)	**5.41 (5.26 - 5.57)**
80-89	2.41 (2.24 - 2.59)	1.95 (1.75 - 2.16)	**2.25 (2.11 - 2.38)**	11.20 (10.82 - 11.58)	2.19 (1.97 - 2.41)	**7.88 (7.63 - 8.14)**
90+	2.88 (2.40 - 3.35)	5.47 (4.27 - 6.66)	**3.48 (3.02 - 3.94)**	9.24 (8.38 - 10.10)	8.26 (6.78 - 9.73)	**9.01 (8.26 - 9.76)**
Total rate	**0.79 (0.75 - 0.82)**	**0.50 (0.48 - 0.53)**	**0.65 (0.63 - 0.67)**	**4.94 (4.85 - 5.02)**	**1.53 (1.49 - 1.58)**	**3.31 (3.26 - 3.36)**
Mean age (SD)	74.17 (59.54)	64.38 (93.69)	**70.56 (75.65)**	69.39 (67.48)	61.18 (79.8)	**67.57 (72.01)**

Table 3: Number of fractures per year (extrapolated to the whole population aged ≥40 years) – EPS 2002-2008

	2002	2003	2004	2005	2006	2007	2008	Total
HIP	15080	14060	14320	14000	13600	13960	14720	99740
HUMERUS	9300	8440	8240	8600	7940	9420	9680	61620
VERTEBRA	3180	3100	3260	3360	3320	3400	3580	23200
WRIST	16300	17100	16420	17620	16520	16100	18040	118100
Total	43860	42700	42240	43580	41380	42880	46020	302660

The overall absolute number of fractures increased by 5% (2160/43860) between 2002 and 2008. However, standardized incidence rates remained constant over time, except for hip fracture which showed a limited albeit significant reduction in incidence rate over time (Table 4;Figure 12 in appendix). In individuals ≥ 65 years, the rate of hip fractures went down from 7.62 per 1000 person-year to 6.54 per 1000 person-year between 2002 and 2008 (Table 26 in appendix; Figure 13 in appendix).

Table 4: Age and gender standardized incidence rates per type of fracture (per 1000 persons-years ≥40 years) – EPS 2002-2008

	HIP	HUMERUS	VERTEBRA	WRIST
year	**Std rate (95%CI)**	**Std rate (95%CI)**	**Std rate (95%CI)**	**Std rate (95%CI)**
2002	2.95 (2.73 - 3.17)	1.82 (1.62 - 2.01)	0.61 (0.51 - 0.72)	3.23 (2.97 - 3.49)
2003	2.73 (2.52 - 2.94)	1.62 (1.45 - 1.80)	0.59 (0.49 - 0.69)	3.34 (3.07 - 3.60)
2004	2.74 (2.53 - 2.94)	1.57 (1.39 - 1.74)	0.62 (0.51 - 0.73)	3.17 (2.91 - 3.42)
2005	2.59 (2.39 - 2.80)	1.60 (1.43 - 1.78)	0.62 (0.51 - 0.73)	3.36 (3.09 - 3.63)
2006	2.44 (2.25 - 2.63)	1.47 (1.31 - 1.64)	0.60 (0.49 - 0.70)	3.12 (2.87 - 3.37)
2007	2.39 (2.21 - 2.58)	1.73 (1.54 - 1.91)	0.61 (0.51 - 0.72)	2.99 (2.75 - 3.24)
2008	2.45 (2.27 - 2.64)	1.74 (1.56 - 1.92)	0.62 (0.52 - 0.73)	3.31 (3.05 - 3.57)

2.2.1.2 Death rates

Death rates by sex, age ranges and fracture sites are presented in Table 5. Death rate after a fracture did not differ significantly between males and females, excepted for hip fractures where the death rate was consistently higher in males than in females. The highest death rate was observed for hip fracture which was associated with a 255.7 per 1000 person-year rate. Death rates associated with a fragility fracture increased with age, although the risk attributable to concomitant morbidities could not be assessed in the frame of our project.

Table 5: Death rates (per 1000 person-years) after fractures – EPS (individuals ≥40 years)

		Individuals of 40+		60-79		80+	
Characteristics	Class	Overall period	1st year rate	Overall period	1st year rate	All period	1st year
All	All	82.9 [78.9 - 87.1]	116.2 [107.4 - 125.8]	56.0 [51.2 - 61.2]	68.9 [58.9 - 80.4]	188.4 [177.0 - 200.5]	247.0 [224.6 - 271.6]
Type of fracture							
Hip	Female	164.6 [152.2 - 178.0]	230.5 [204.6 - 259.7]	108.4 [92.2 - 127.5]	123.2 [92.0 - 165.0]	210.7 [192.5 - 230.7]	292.2 [255.9 - 333.7]
	Male	229.0 [202.6 - 258.9]	331.3 [278.8 - 393.7]	170.7 [138.2 - 210.9]	262.0 [193.6 - 354.5]	391.7 [334.7 - 458.5]	488.3 [393.3 - 606.3]
	total	179.2 [167.8 - 191.4]	255.7 [231.8 - 282.0]	125.4 [110.2 - 142.6]	165.5 [134.2 - 204.2]	238.1 [220.1 - 257.5]	328.3 [293.1 - 367.6]
Humerus	Female	63.7 [55.1 - 73.7]	73.7 [57.0 - 95.4]	45.2 [35.6 - 57.4]	56.2 [37.4 - 84.6]	137.0 [112.8 - 166.3]	144.5 [102.2 - 204.4]
	Male	59.3 [46.3 - 75.9]	112.3 [79.8 - 157.9]	71.9 [50.0 - 103.5]	119.1 [70.6 - 201.2]	253.9 [168.7 - 382.1]	408.4 [237.1 - 703.3]
	total	62.5 [55.1 - 70.8]	84.2 [68.6 - 103.4]	50.9 [41.7 - 62.2]	70.3 [50.9 - 97.0]	149.6 [125.6 - 178.3]	177.7 [132.7 - 238.0]
Vertebra	Female	71.1 [55.9 - 90.3]	85.7 [57.0 - 129.0]	46.2 [30.7 - 69.5]	38.6 [16.1 - 92.7]	142.3 [104.8 - 193.2]	194.2 [122.4 - 308.3]
	Male	99.1 [74.7 - 131.5]	109.3 [66.9 - 178.4]	117.9 [79.0 - 175.9]	147.7 [76.9 - 283.9]	280.3 [182.8 - 429.9]	264.2 [125.9 - 554.1]
	total	80.6 [67.1 - 96.7]	94.1 [68.7 - 128.7]	67.0 [50.4 - 89.2]	73.5 [43.5 - 124.1]	170.8 [133.1 - 219.0]	209.8 [141.8 - 310.5]
Wrist	Female	37.5 [33.1 - 42.4]	40.3 [32.0 - 50.8]	22.7 [18.2 - 28.2]	18.9 [11.7 - 30.3]	119.4 [102.5 - 139.1]	120.6 [91.4 - 159.1]
	Male	32.6 [24.9 - 42.7]	27.7 [15.7 - 48.8]	43.7 [30.0 - 63.8]	24.2 [9.1 - 64.5]	263.7 [156.2 - 445.3]	256.2 [115.1 - 570.3]
	total	36.5 [32.7 - 40.9]	37.9 [30.6 - 46.9]	25.8 [21.4 - 31.1]	19.7 [12.8 - 30.2]	124.8 [107.8 - 144.5]	127.8 [98.4 - 166.1]
Gender							
	Female	78.4 [74.0 - 83.2]	230.5 [204.6 - 259.7]	46.0 [41.2 - 51.3]	49.9 [40.6 - 61.3]	167.4 [156.0 - 179.6]	215.6 [193.2 - 240.7]
	Male	97.9 [89.0 - 107.7]	150.4 [130.5 - 173.4]	96.1 [82.5 - 111.8]	136.9 [108.1 - 173.3]	346.8 [303.2 - 396.6]	432.6 [358.2 - 522.4]

2.2.2 Utilization of osteoporosis drugs

2.2.2.1 Global evolution over time

In 2009, more than 230 000 patients used osteoporosis drugs (Table 6). The number of DDDs increased by 45% between 2004 and 2009, for 61 754 266 DDDs purchased in 2009 (Table 7), and an INAMI/RIZIV budget close to 53 millions Euros (Table 8). The bisphosphonates were the drug class the most widely used, and in particular alendronate alone or in combination (65.2% of the DDDs (40 265 936/61 754 266) used in 2009). The combination of alendronate and colecalciferol which was introduced in 2006 already accounted for 33.5% of all DDDs in 2009. Clodronic acid and tiludronic acid are generally not used for the treatment of osteoporosis in Belgium. The number of users of raloxifene and calcitonin decreased steadily over the years. Teriparatide was used marginally (Figure 2).

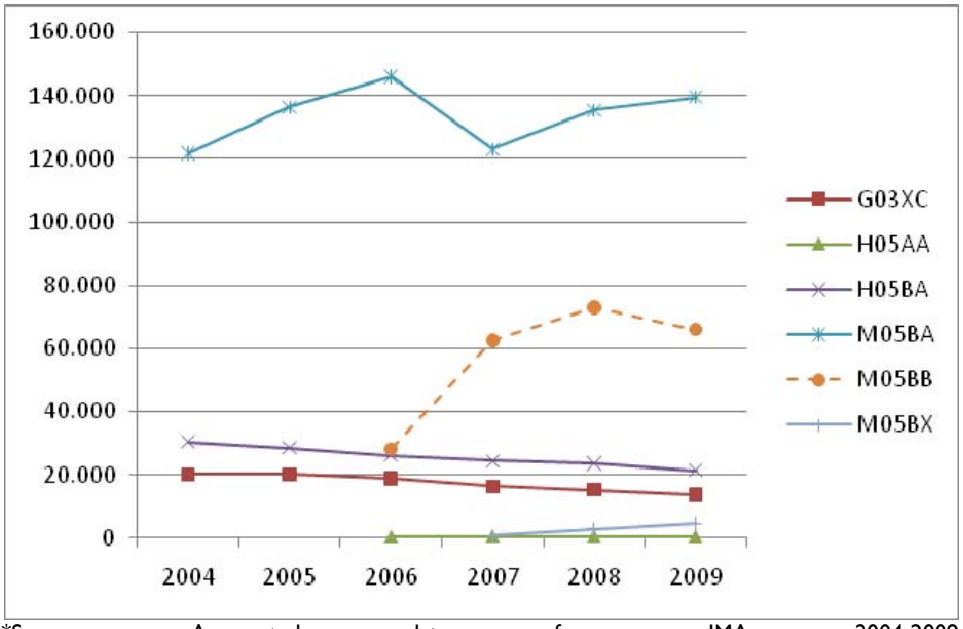
More details on utilization of osteoporosis drugs can be found in appendix (from Figure 14 to Figure 23 and Table 27).

Table 6: Number of Patients per Year by Chemical group (ATC level 4) and Chemical substance group (ATC level 5)

ATC level 4 / ATC level 5	Year 2004	2005	2006	2007	2008	2009
G03XC: Selective estrogen receptor modulators						
G03XC01: RALOXIFENE	20.136	20.127	18.982	16.439	15.285	13.697
H05AA: Parathyroid hormones and analogues						
H05AA02: TERIPARATIDE			305	497	471	405
H05BA:Calcitonin preparation						
H05BA01: CALCITONIN (SALMON SYNTHETIC)	30.440	28.540	26.115	24.516	23.678	21.511
M05BA: Biphosphonates	121.841	136.407	146.014	123.019	135.380	139.544
M05BA01: ETIDRONIC ACID	787	539	394	303	245	184
M05BA02: CLODRONIC ACID	1.043	847	694	419	356	283
M05BA04: ALENDRONIC ACID	101.499	108.353	109.318	75.203	77.412	78.443
M05BA05: TILUDRONIC ACID	147	123	69	30	26	16
M05BA06: IBANDRONIC ACID		284	3.025	12.317	19.793	22.214
M05BA07: RISEDRONIC ACID	18.365	26.261	32.472	34.715	36.094	32.282
M05BA08: ZOLEDRONIC ACID			42	32	1.454	6.122
M05BB: Biphosphonates, combinations			28.210	62.514	72.903	66.054
M05BB01: ALENDRONIC ACID AND COLECALCIFEROL			28.210	62.514	72.903	63.336
M05BB02 : RISEDRONIC ACID, CALCIUM AND COLECALCIFEROL, SEQUENTIAL						2.718
M05BX: Other drugs affecting bone structure and mineralisation						
M05BX03: STRONTIUM RANELATE				743	2.989	4.614
Total (extrapolated from EPS 2002-2008) Unique patient	**160.920**	**175.080**	**187.040**	**200.480**	**229.220**	**-**

*Source: Aggregated data from IMA 2004-2009 & extrapolation from EPS for Total (unique patient)

Figure 2: Number of Patients per year – ATC level 4



*Source: Aggregated data from IMA 2004-2009
GO3XC: Raloxifen; H05HA: Teriparatide; H05BA: Calcitonin; M05BA01: Etidronate; M0502: Clodronate; M05BA04: Alendronate; M05BA05: Tiludronate; M05BA06: Ibandronate; M05BA07: Risedronate; M05BA08: Zoledronate; M05BB03: Alendronate+colecalciferol; M05BB04: risedronate+colecalciferol; M05BX: Strontium ranelate

Table 7: Number of DDDs per Year (ATC level 4 & ATC level5)

ATC level	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
G03XC											
G03XC01			76.656	4.005.543	5.539.684	5.838.544	5.760.515	5.581.821	4.961.441	4.581.132	4.128.432
H05AA											
H05AA02								50.590	106.623	89.451	76.488
H05BA											
H05BA01	2.133.412	1.940.237	1.914.572	1.725.051	1.500.828	1.356.624	1.188.803	1.087.438	1.000.647	956.255	866.481
M05BA	**9.455.679**	**14.079.055**	**16.504.484**	**17.376.425**	**28.424.072**	**35.365.840**	**38.886.124**	**39.566.161**	**31.794.510**	**33.904.368**	**35.013.096**
M05BA01	2.111.424	1.966.087	1.911.959	228.440	60.105	37.183	24.300	19.276	14.675	11.434	8.081
M05BA02	162.921	150.270	132.652	118.549	112.755	107.312	93.525	78.259	55.997	47.675	37.529
M05BA04	7.138.147	11.918.542	14.422.125	16.673.491	26.061.410	30.500.356	31.198.858	29.089.119	18.007.745	17.457.035	19.555.595
M05BA05	43.187	44.155	37.747	23.164	13.591	9.795	8.681	4.966	2.315	1.796	1.361
M05BA06							562.972	1.236.972	3.711.142	5.681.479	6.000.652
M05BA07				332.781	2.176.212	4.711.194	6.997.789	9.137.517	10.002.597	10.703.113	9.402.167
M05BA08								51	39	1.836	7.711
M05BB								**3.332.544**	**15.984.425**	**19.889.536**	**20.732.128**
M05BB03								3.332.544	15.984.425	19.889.536	20.710.341
M05BB04											21.788
M05BX											
M05BX03									87.880	543.695	937.641
Total	**11.589.091**	**16.019.292**	**18.495.712**	**23.107.019**	**35.464.584**	**42.561.008**	**45.835.441**	**49.618.554**	**53.935.527**	**59.964.439**	**61.754.266**

*Source: Aggregated data from IMA 1999-2009

GO3XC01: Raloxifen; H05HAA02: Teriparatide; H05BA01: Calcitonin; M05BA01: Etidronic acid; M05BA02: Clodronic acid; M05BA04: Alendronic acid; M05BA05: Tiludronic acid; M05BA06: Ibandronic acid; M05BA07: Risedronic acid; M05BA08: Zoledronate; M05BB03: Alendronic acid and colecalciferol; M05BB04: Risedronic acid, calcium and colecalciferol, sequential; M05BX: Strontium ranelate

Table 8: Third Party Payer expenditure in € (ATC level 4 & level 5)

ATC level 4 / ATC level 5	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
G03XC											
G03XC01			78.340	4.074.182	5.341.348	5.610.153	5.518.206	5.337.514	4.835.452	4.487.419	4.042.370
H05AA											
H05AA02								685.685	1.445.059	1.211.753	1.036.012
H05BA											
H05BA01	9.588.065	8.352.101	8.118.437	7.331.020	6.348.544	5.502.204	4.573.408	3.967.624	3.453.224	3.284.626	2.880.038
M05BA	13.089.098	17.678.886	20.131.397	19.706.501	31.075.212	37.929.041	41.170.944	40.198.408	31.619.015	30.354.666	28.292.900
M05BA01	3.869.436	3.389.910	3.296.455	391.981	101.781	63.657	42.531	31.533	22.135	17.170	12.005
M05BA02	1.156.318	1.054.728	954.034	860.010	812.761	772.054	668.456	546.981	391.932	289.617	230.878
M05BA04	7.713.853	12.876.866	15.570.990	17.913.907	27.819.269	32.087.562	32.469.311	29.101.893	17.293.540	11.953.342	8.561.759
M05BA05	349.491	357.383	309.917	191.319	112.316	80.819	70.921	39.320	18.343	14.316	10.750
M05BA06							671.907	1.419.521	4.004.327	6.674.581	7.531.163
M05BA07				349.285	2.229.086	4.924.950	7.247.818	9.040.169	9.874.387	10.833.687	9.597.285
M05BA08								18.990	14.351	571.953	2.349.060
M05BB								3.367.194	16.112.615	19.852.726	15.520.437
M05BB03								3.367.194	16.112.615	19.852.726	15.262.828
M05BB04											257.608
M05BX											
M05BX03									111.668	691.018	1.174.407
Total	**22.677.163**	**26.030.987**	**28.328.175**	**31.111.704**	**42.765.105**	**49.041.398**	**51.262.558**	**53.556.425**	**57.577.034**	**59.882.208**	**52.946.164**

*Source: Aggregated data from IMA 1999-2009

GO3XC01: Raloxifen; H05HAA02: Teriparatide; H05BA01: Calcitonin; M05BA01: Etidronic acid; M05BA02: Clodronic acid; M05BA04: Alendronic acid; M05BA05: Tiludronic acid; M05BA06: Ibandronic acid; M05BA07: Risedronic acid; M05BA08: Zoledronate; M05BB03: Alendronic acid and colecalciferol; M05BB04: Risedronic acid, calcium and colecalciferol, sequential; M05BX: Strontium ranelate

2.2.2.2 *Treatment rates after a fragility fracture*

The vast majority of treatments (≅93%) were initiated in patients without an history of fragility fracture in the 12 months preceding the treatment[d](Table 9). However, the proportion of treatments started after a vertebral fracture undetected by our methodology is unknown and might be substantial[e]. Therefore, the relative proportion of patients in primary prevention is unknown and figures must be considered cautiously. There were no obvious differences between patients beginning a primary vs. a secondary prevention, excepted that individuals in primary prevention were younger (Table 10).

Table 9: Type of prevention and type of users (patients aged ≥40 years)– EPS 2003-2007

	2003	2004	2005	2006	2007
Type of prevention					
Primary prevention	93.17% (92.10 - 94.24)	91.70% (90.47 - 92.94)	92.11% (90.84 - 93.38)	92.56% (91.26 - 93.86)	93.09% (91.87 - 94.31)
Secondary prevention	6.83% (5.76 - 7.90)	8.30% (7.06 - 9.53)	7.89% (6.62 - 9.16)	7.44% (6.14 - 8.74)	6.91% (5.69 - 8.13)
Type of users					
One-shot users	18.93% (17.20 - 20.66)	19.00% (17.19 - 20.82)	21.35% (19.32 - 23.38)	21.49% (19.38 - 23.60)	20.54% (18.46 - 22.61)
Other users	81.07% (79.34 - 82.80)	81.00% (79.18 - 82.81)	78.65% (76.62 - 80.68)	78.51% (76.40 - 80.62)	79.46% (77.39 - 81.54)

The treatment rates after a fragility fracture were strikingly low (Table 11). They were a little bit higher in the 60-79 years, but even in that age range only 51.1 per 1000 person-months (95%CI: 46.1, 56.5) begun a treatment in the 3 month period following the fracture. Treatment rates presented in Table 11 included calcitonin which in our country is mainly used for alleviating pain in the short-term after a fragility fracture, i.e. not for reducing the risk of further fractures. Calcitonin was used in 18% to 32% of fragility fractures, depending upon the fracture sites considered. When removing calcitonin from the computation, the general treatment rates fell to 27.3 per 1000 person-months (95%CI: 24.9, 29.8). Treatment rates were higher in the 3 first months after fracture and decreased afterwards (Figure 3). Males were consistently less treated than females. The treatment rates also varied with fracture site. The highest rates were observed for vertebral fractures (149.2; 95%CI: 117.2;189.9). However, there were not significant differences in treatment rates for fractures of the hip, the humerus or the wrist. The treatment rates improved in 2008, although not significantly.

[d] For a small proportion of patients starting a treatment in 2003, a fragility fracture might have occurred before 2002 and thus be undetected by us. This would lead to a misclassification of patients in primary instead of secondary prevention. However, such situation is exceptional as the majority of patients with a fragility fracture who begin a treatment does so within the first 3 months after the fracture.

[e] This may occur when the fracture was diagnosed incidentally and the corresponding nomenclature codes were not used.

Table 10: Characteristics of patient starting an osteoporosis treatment (patients ≥40 years)- EPS 2003-2007

		Prevention	
		Primary prevention	Secondary prevention
N patients	N	211800	17100
Age at first drug delivery	Mean	68.17	71.82
	Std	12.05	12.12
	Median	69.00	74.00
Gender	% male	17.80%	16.84%
Major treatment			
G03X	%	5.85	3.16
H05A	%	0.04	.
H05B		27.91	44.33
M05B	%	66.19	52.51
Medication Possession ratio	Mean	0.93	0.92
	Std	0.53	0.45
	Median	0.95	0.94
Compliance			
One-shot users	%	19.89	23.51
Regular users (MPR>=80%)	%	56.88	52.98
Occasional users (MPR<80%)	%	23.23	23.51

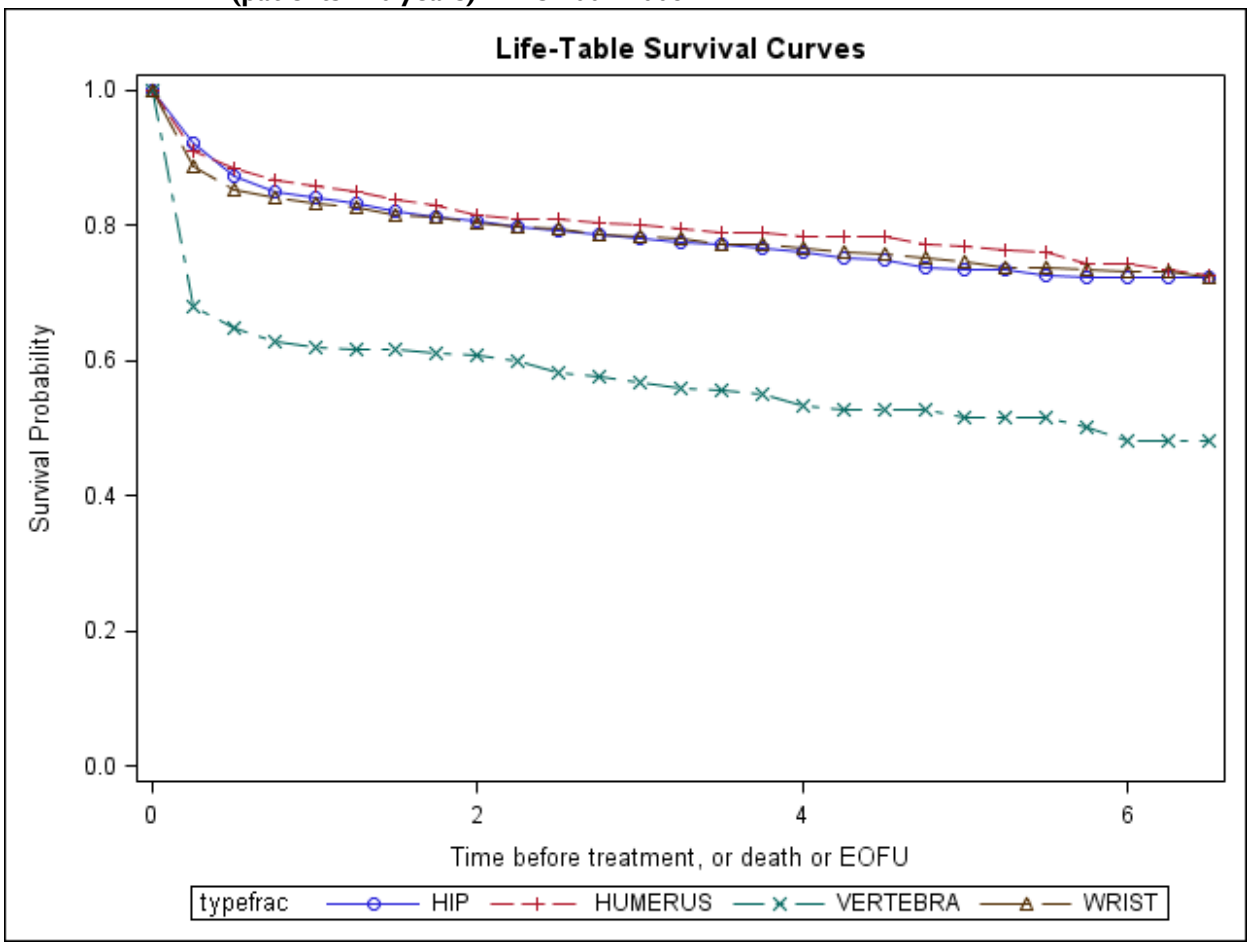
GO3XC: Selective Estrogen receptor modulators (Raloxifene); H05A: Parathyroid hormones and analogues (Teriparatide); H05BA: Calcitonin preparations (Calcitonin (Salmon synthetic)); M05BA01: Etidronic acid; M0502: Clodronic acid; M05BA04: Alendronic acid; M05BA05: Tiludronic acid; M05BA06: Ibandronic acid; M05BA07: Risedronic acid; M05BA08: Zoledronate; M05BB03: Alendronic acid and colecalciferol; M05BB04: risedronic acid, calcium and colecalciferol, sequential; M05BX: Other drugs affecting bone structure and mineralisation (Strontium ranelate)

Table 11: Osteoporosis treatment rates after a fracture per 1000 person-months (patients aged 40 or more) - EPS 2002-2008*

		Individuals of 40+		60-79		80+	
Characteristics	**Class**	**1st year rate**	**first 3-months rate**	**1st year rate**	**first 3-months rate**	**1st year rate**	**first 3-months rate**
All	All	16.1 [15.1 - 17.2]	40.4 [36.0 - 45.4]	19.8 [18.1 - 21.8]	51.1 [46.1 - 56.5]	17.1 [15.3 - 19.1]	40.1 [35.3 - 45.5]
Type of fractures							
Hip	Female	18.3 [16.0 - 20.8]	33.9 [28.7 - 40.0]	25.2 [20.6 - 31.0]	41.5 [31.5 - 54.8]	15.3 [12.8 - 18.2]	31.0 [25.1 - 38.3]
	Male	5.6 [3.8 - 8.3]	11.0 [6.7 - 18.0]	7.8 [4.6 - 13.1]	17.1 [9.2 - 31.9]	5.1 [2.8 - 9.5]	7.4 [3.1 - 17.7]
	total	14.9 [13.2 - 16.9]	27.9 [23.9 - 32.7]	19.4 [16.1 - 23.5]	33.6 [26.1 - 43.2]	13.3 [11.2 - 15.7]	26.4 [21.5 - 32.4]
Humerus	Female	16.1 [13.5 - 19.1]	42.3 [35.0 - 51.2]	20.2 [16.3 - 25.2]	55.9 [44.3 - 70.5]	15.3 [11.0 - 21.3]	34.7 [23.7 - 51.0]
	Male	4.9 [3.0 - 8.1]	11.3 [6.2 - 20.3]	5.2 [2.5 - 11.0]	9.9 [3.7 - 26.4]	14.3 [6.0 - 34.5]	32.1 [12.1 - 85.7]
	total	12.8 [10.9 - 15.1]	33.6 [28.0 - 40.3]	16.5 [13.4 - 20.3]	44.8 [35.7 - 56.2]	15.1 [11.1 - 20.7]	34.4 [24.0 - 49.2]
Vertebra	Female	64.4 [53.9 - 77.1]	180.8 [150.7 - 216.9]	66.2 [51.1 - 85.6]	192.8 [148.0 - 251.1]	81.2 [61.9 - 106.5]	212.6 [161.6 - 279.8]
	Male	19.0 [13.0 - 27.7]	69.2 [48.4 - 99.0]	20.1 [11.1 - 36.3]	70.1 [38.8 - 126.5]	36.4 [18.2 - 72.8]	122.1 [63.5 - 234.7]
	total	44.8 [38.1 - 52.6]	135.8 [115.5 - 159.7]	48.5 [38.3 - 61.4]	149.2 [117.2 - 189.9]	69.8 [54.2 - 89.8]	191.4 [148.6 - 246.5]
Wrist	Female	16.7 [14.9 - 18.7]	47.2 [41.8 - 53.2]	20.2 [17.4 - 23.3]	57.8 [49.5 - 67.5]	17.0 [13.5 - 21.5]	46.4 [36.1 - 59.6]
	Male	6.7 [4.7 - 9.4]	15.8 [10.6 - 23.6]	7.4 [4.4 - 12.5]	17.0 [9.1 - 31.5]	9.8 [3.2 - 30.5]	9.3 [1.3 - 66.3]
	total	14.6 [13.1 - 16.2]	40.4 [36.0 - 45.4]	17.9 [15.6 - 20.7]	50.6 [43.5 - 58.8]	16.6 [13.2 - 20.8]	43.6 [34.0 - 55.9]
Gender	Females	19.3 [18.0 - 20.7]	48.6 [45.0 - 52.6]	23.6 [21.4 - 26.0]	60.8 [54.6 - 67.6]	18.5 [16.5 - 20.8]	44.1 [38.7 - 50.3]
	Males	7.2 [5.9 - 8.7]	18.5 [14.9 - 23.0]	8.3 [6.2 - 11.0]	20.2 [14.5 - 28.1]	9.2 [6.3 - 13.5]	19.3 [12.3 - 30.2]
Year of Fracture	2002	14.4 [12.1 - 17.1]	37.7 [30.8 - 46.1]	21.9 [17.8 - 26.9]	55.2 [43.2 - 70.7]	11.0 [7.7 - 15.6]	28.7 [19.1 - 43.2]
	2003	17.9 [15.3 - 21.0]	44.4 [36.7 - 53.7]	15.4 [12.0 - 19.8]	44.8 [33.8 - 59.2]	26.4 [21.0 - 33.2]	56.4 [42.4 - 75.1]
	2004	15.8 [13.3 - 18.7]	37.6 [30.5 - 46.3]	22.4 [18.0 - 28.0]	58.2 [45.0 - 75.3]	12.3 [8.8 - 17.2]	24.6 [15.9 - 38.2]
	2005	16.3 [13.9 - 19.1]	36.2 [29.6 - 44.3]	18.3 [14.5 - 23.2]	40.2 [29.7 - 54.4]	19.3 [14.9 - 24.9]	38.9 [28.1 - 54.0]
	2006	16.0 [13.5 - 18.9]	38.1 [31.1 - 46.8]	21.9 [17.5 - 27.3]	51.2 [39.0 - 67.2]	14.4 [10.7 - 19.3]	30.8 [21.1 - 44.9]
	2007	16.8 [14.4 - 19.6]	40.8 [33.8 - 49.2]	19.3 [15.3 - 24.2]	47.0 [35.5 - 62.1]	19.8 [15.6 - 25.2]	46.1 [34.6 - 61.3]
	2008	-	53.3 [44.6 - 63.8]	-	62.6 [48.3 - 81.1]	-	54.1 [40.1 - 72.9]

* treatment rates at 1-year (3-months) were calculated based on individuals with fractures between 2002 and 2007 included (2002 and Sept 2008 included), in order to have a 1-year (3-months) follow-up.

Figure 3: Time to treatment after a fracture per 1000 person-months (patients ≥40 years) - EPS 2002-2008



2.2.2.3 *Compliance*

An important proportion (≅21%) of users were one-shot users, i.e. they purchased only one drug conditioning (Table 9). This was principally due to the utilization of calcitonin which is used in the short-tem in our country. Still, the proportion of one-shot users was as high as 10% for the other drugs. This proportion was not different in primary and secondary prevention (Table 10), and remained constant over the years. When one-shot users were discarded, the proportion of regular users was around 70% with a significant improvement over the years. In 2008, nearly 77% of the users were regular. Being a female was a factor associated to a better compliance (Table 12).

Table 12: Factors influencing a regular use in users 2003-2007 (patients ≥40 years)– EPS 2002-2008 (logistic regression)

Parameters	% regular users (95%CI)	Odds ratios			
		OR	95% confidence limits		p-value
Gender					
Female	72.30 (71.15 - 73.45)	1.371	1.333	1.411	<.0001
Male	62.65 (59.55 - 65.75)	1.00			
Year of starting drug treatment					
2003	64.82 (62.50 - 67.13)	0.523	0.506	0.541	<.0001
2004	68.77 (66.40 - 71.14)	0.641	0.619	0.663	<.0001
2005	72.51 (70.10 - 74.95)	0.779	0.752	0.807	<.0001
2006	73.95 (71.45 - 76.46)	0.834	0.805	0.865	<.0001
2007	76.85 (74.44 - 79.26)	1.00			
Type of prevention					
Primary prevention	71.01 (69.89 - 72.14)	0.993	0.954	1.033	0.7150
Secondary prevention	69.27 (65.28 - 73.25)	1.00			
Major treatment drug:					
G03X	76.68 (72.63 - 80.74)	1.289	1.232	1.349	<.0001
H05B	59.92 (57.14 - 62.70)	0.595	0.579	0.610	<.0001
M05B	73.17 (71.96 - 74.38)	1.00			
Age class:					
40-59 years	67.53 (64.68 - 70.38)	0.865	0.804	0.930	<.0001
60-69 years	72.37 (70.32 - 74.43)	1.013	0.942	1.090	0.7274
70-79 years	72.86 (71.20 - 74.52)	1.062	0.988	1.142	0.1026
80-89 years	69.56 (67.27 - 71.85)	0.891	0.827	0.959	0.0022
90+ years	70.10 (63.60 - 76.60)	1.00			

GO3XC: Selective Estrogen receptor modulators (Raloxifene); H05BA: Calcitonin preparations (Calcitonin (Salmon synthetic)); M05B: Drugs affecting bone structure and mineralisation (M05BA01: Etidronate; M0502: Clodronate; M05BA04: Alendronate; M05BA05: Tiludronate; M05BA06: Ibandronate; M05BA07: Risedronate; M05BA08: Zoledronate; M05BB03: Alendronate+colecalciferol; M05BB04: risedronate+colecalciferol; M05BX: Strontium ranelate)

2.2.2.4 Persistence of treatment

Defaulting rates were high, particularly in the immediate period after the start of the treatment: the overall rate was 112.8 per 1000 person-months in the first 3 months (Table 13 and Figure 4). The rates were strikingly high for calcitonin (H05B). This is because calcitonin is mainly used temporary for fractures with pain. When removing calcitonin from the computations, the defaulting rates were still at 32.8 per 1000 person-months in the first 3 months (95%CI: 29.9, 36.0) (see Table 14). The defaulting rates remained constant between 2003 and 2007. Males defaulted consistently more than females. Defaulting rates in secondary prevention (138.2 per 1000 person-months at month 3) were as high as those observed in primary prevention (110.9 per 1000 person-months at month 3). This was a counter-intuitive finding as one would expect a better persistence in patients who had suffered recently a fragility fracture.

Table 13: Defaulting rates per 1000 person-months (patients ≥40 years) - EPS 2003-2008*

		Individuals of 40+		60-79		80+	
Characteristics	Class	1-year	3-month	1-year	3-month	1-year	3-month
Total	total	47.8 [45.9 - 49.9]	112.8 [107.8 - 118.1]	38.7 [36.4 - 41.2]	93.3 [87.2 - 99.8]	52.1 [47.6 - 57.0]	113.2 [102.5 - 125.1]
G03X	Female	17.7 [13.7 - 22.9]	27.6 [18.9 - 40.3]	17.8 [12.8 - 24.8]	27.7 [17.0 - 45.2]	27.9 [15.5 - 50.4]	57.7 [27.5 - 121.0]
H05B	Female	307.9 [289.4 - 327.5]	449.1 [421.7 - 478.3]	320.6 [291.8 - 352.2]	461.1 [419.0 - 507.5]	242.8 [213.1 - 276.6]	389.4 [339.9 - 446.0]
	Male	336.1 [307.2 - 367.6]	459.6 [419.0 - 504.1]	329.7 [288.4 - 376.8]	465.3 [405.0 - 534.7]	304.1 [236.6 - 390.8]	409.0 [316.2 - 529.1]
	total	316.4 [300.7 - 332.9]	452.4 [429.4 - 476.5]	323.5 [299.6 - 349.4]	462.5 [427.4 - 500.4]	253.7 [226.0 - 284.8]	393.5 [348.9 - 443.7]
M05B	Female	15.0 [13.8 - 16.4]	28.2 [25.2 - 31.6]	12.8 [11.3 - 14.5]	24.8 [21.2 - 29.1]	20.4 [17.2 - 24.0]	37.2 [30.2 - 45.9]
	Male	32.3 [27.4 - 38.2]	69.4 [57.3 - 84.1]	29.4 [23.5 - 36.8]	62.2 [47.8 - 81.0]	51.3 [36.7 - 71.8]	100.9 [68.7 - 148.2]
	total	17.0 [15.7 - 18.4]	33.2 [30.1 - 36.6]	14.8 [13.2 - 16.4]	29.5 [25.7 - 33.7]	23.1 [19.9 - 26.8]	43.5 [36.2 - 52.3]
Gender	Female	39.2 [37.3 - 41.2]	93.2 [88.3 - 98.4]	31.5 [29.3 - 33.9]	76.3 [70.4 - 82.7]	46.0 [41.5 - 50.8]	100.4 [89.7 - 112.3]
	Male	108.0 [99.8 - 116.9]	223.4 [205.6 - 242.8]	89.8 [80.1 - 100.8]	193.7 [171.2 - 219.0]	110.1 [90.0 - 134.6]	210.3 [169.8 - 260.4]
Type of prevention	Primary	46.6 [44.6 - 48.7]	110.9 [105.7 - 116.3]	37.3 [35.0 - 39.8]	89.7 [83.6 - 96.3]	52.3 [47.6 - 57.6]	115.3 [103.8 - 128.1]
	Secondary	65.0 [56.5 - 74.8]	138.2 [118.5 - 161.3]	61.3 [50.1 - 75.0]	147.9 [119.3 - 183.5]	50.0 [38.1 - 65.6]	97.1 [70.6 - 133.4]
Year of Start	2003	42.5 [38.9 - 46.5]	108.1 [97.5 - 119.8]	32.7 [28.8 - 37.2]	82.6 [71.0 - 96.1]	61.5 [51.0 - 74.0]	141.4 [114.0 - 175.3]
	2004	43.8 [39.8 - 48.1]	105.4 [94.4 - 117.7]	34.5 [30.1 - 39.6]	81.7 [69.2 - 96.4]	55.3 [45.3 - 67.5]	133.1 [106.0 - 167.1]
	2005	50.4 [45.9 - 55.4]	120.0 [107.7 - 133.8]	43.2 [37.6 - 49.6]	109.0 [93.1 - 127.8]	43.0 [34.8 - 53.2]	86.2 [65.7 - 113.2]
	2006	52.7 [47.8 - 58.1]	128.7 [115.1 - 144.0]	45.3 [39.3 - 52.3]	117.7 [100.2 - 138.2]	48.7 [39.3 - 60.4]	103.1 [79.2 - 134.3]
	2007	52.7 [48.0 - 58.0]	111.9 [99.6 - 125.6]	43.0 [37.3 - 49.7]	92.0 [77.1 - 109.9]	52.6 [43.1 - 64.2]	104.9 [81.8 - 134.6]
	2008		106.0 [93.9 - 119.5]		86.0 [71.5 - 103.6]		111.3 [86.6 - 143.1]

* defaulting rates at 1-year (3-months) were calculated based on individuals with start of treatment between 2003 and 2007 included (2003 and Sept 2008 included), in order to have a 1-year (3-months) follow-up.

Figure 4: Time to defaulting after treatment start per 1000 person-years (patients ≥40 years) - EPS 2002-2008

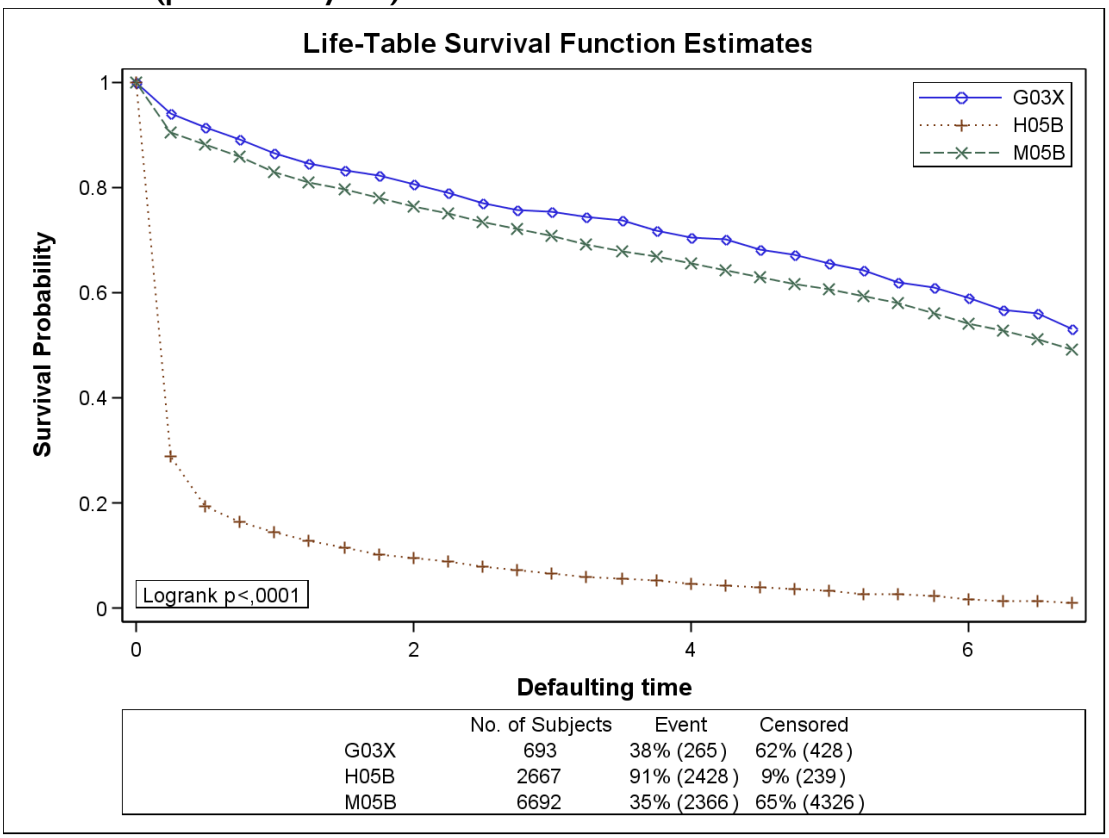


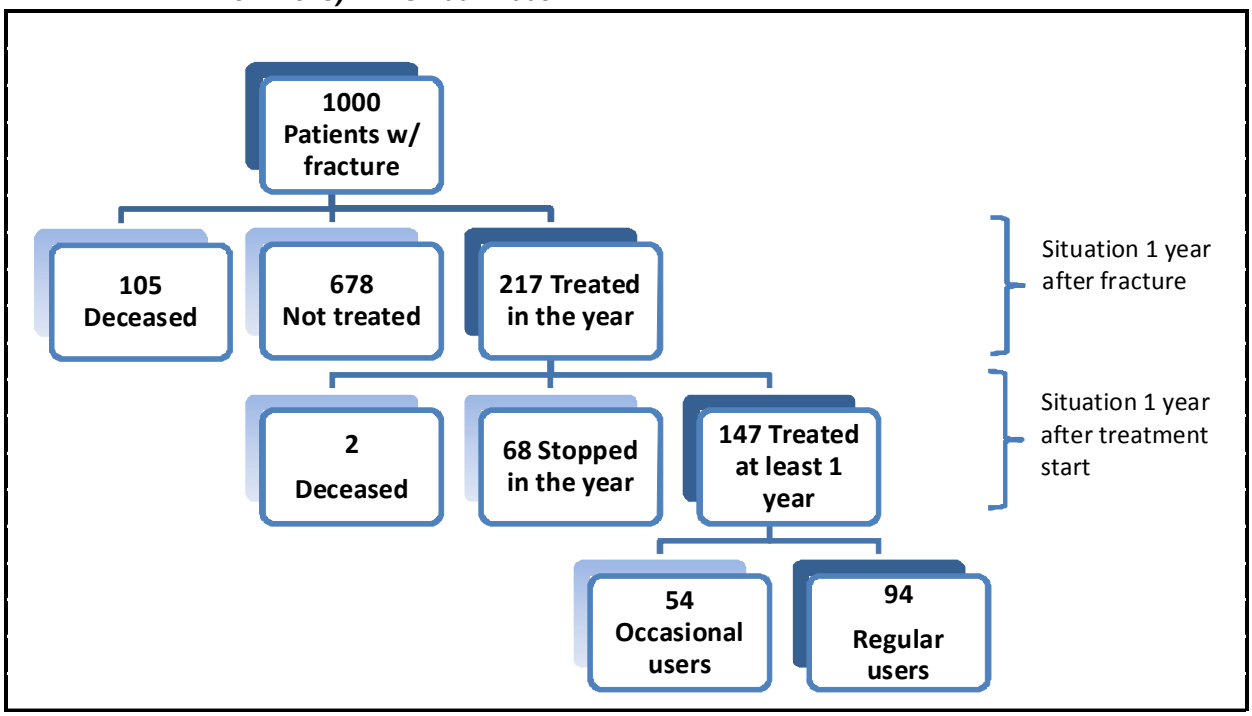
Table 14: Defaulting rates per 1000 person-months (patients ≥40 years) - EPS 2003-2008* (without Calcitonin users)

Characterstics	Class	Individuals of 40+ 1-year	3-month
Total	total	17.1 [15.8 - 18.4]	32.8 [29.9 - 36.0]
G03X	Female	17.7 [13.7 - 22.9]	27.6 [18.9 - 40.3]
	Male		
	total	17.7 [13.7 - 22.9]	27.6 [18.9 - 40.3]
M05B	Female	15.0 [13.8 - 16.4]	28.2 [25.2 - 31.6]
	Male	32.3 [27.4 - 38.2]	69.4 [57.3 - 84.1]
	total	17.0 [15.7 - 18.4]	33.2 [30.1 - 36.6]
Gender	Female	15.3 [14.1 - 16.6]	28.2 [25.3 - 31.4]
	Male	32.3 [27.4 - 38.2]	69.4 [57.3 - 84.1]
Type of prevention	Primary prevention	17.1 [15.8 - 18.5]	33.4 [30.4 - 36.8]
	Secondary prevention	16.4 [12.0 - 22.2]	23.1 [14.7 - 36.2]
Year of Start			
	2003	15.3 [13.1 - 17.9]	32.1 [26.0 - 39.6]
	2004	14.3 [12.0 - 17.1]	23.5 [18.1 - 30.5]
	2005	17.1 [14.4 - 20.3]	29.0 [22.6 - 37.2]
	2006	18.3 [15.4 - 21.8]	33.3 [26.1 - 42.6]
	2007	21.5 [18.4 - 25.1]	36.1 [28.8 - 45.3]
	2008		44.4 [36.3 - 54.5]

* defaulting rates at 1-year (3-months) were calculated based on individuals with start of treatment between 2003 and 2007 included (2003 and Sept 2008 included), in order to have a 1-year (3-months) follow-up.

In Figure 5, we present the resulting combination of compliance and persistence in secondary prevention. We voluntarily adopted a simplified approach based on proportions (instead of rates) to make the result presentation more straightforward. Only 217 over 1000 patients suffering a fragility fracture will be treated in the year following their fracture (even if we assume that all the deaths would have been treated the treatment probability would amount to 32.2%). This proportion is 159 per 1000 if calcitonin is discarded. Among patients beginning a treatment, 67.7% (147/217) will still be under treatment one year later, 63.9% (94/147) of whom were regular users. Finally, only 10.5% of living patients (94/893) was still receiving an appropriate treatment on a regular basis one year after the index fragility fracture. This last proportion is not modified if calcitonin is discarded from the computation.

Figure 5: Treatment path per 1000 patients with fracture (patients aged 40 or more) - EPS 2002-2008



2.2.3 Reimbursement rules

Most of the anti-osteoporotic drugs are in the Chapter IV of drug legislation, i.e. their reimbursement is conditional and must be submitted to the approval of advisors from sickness funds. An approval is valid for a 12 month period. The approval may be renewed for new periods of 12 months upon request.

2.2.3.1 Drugs with a priori control in postmenopausal women

For reimbursement in postmenopausal women, at least one of the 2 following conditions must be fulfilled:

- A BMD with a T-score<-2.5 as measured by DEXA at the lumbar spine (L1-L4 or L2-L4) or at the hip (total or neck)
- A prior vertebral fracture. Such fracture is defined as a minimum 25% reduction (4mm in absolute value) in front, centre or back height of the vertebra considered, as assessed by a X-ray exam.

These conditions apply to Fosamax (alendronate), Fosavance (alendronate+colecalciferol), Bonviva (ibandronate), Aclasta (Zoledronate), Actonel (risedronate), Actonel Combi D (risedronate+calcium+colecalciferol), Evista (raloxifene), and Prolia (denosumab[f]).

Protelos (strontium ranelate) is reimbursed if one of the 2 above conditions is fulfilled in women ≥ 80 years

Osteodidronel (etidronate) is reimbursed if the two above conditions are met simultaneously.

Aclasta (Zoledronate), in addition to the 2 above conditions, is also reimbursed for postmenopausal women with a prior hip fracture.

[f] Denosumab will be reimbursed since July 1 2011 onwards.

Forsteo (teriperatide) is reimbursed in postmenopausal women fulfilling the following conditions:

- Being granted the reimbursement of a bisphosphonate or a SERM for a 12 month period AND
- A BMD with a T-score<-2.5 as measured by DEXA at the lumbar spine (L1-L4 or L2-L4) or at the hip (total or neck) measured 6 months before the prescription at the later AND
- Two prior vertebral fractures. Such fracture is defined as a minimum 25% reduction (4mm in absolute value) in front, centre or back height of the vertebra considered, as assessed by a X-ray exam. One the fractures must have occurred after at least 12 months of treatment by a bisphosphonate or a SERM

Actonel (risedronate) is reimbursed in case of osteoporosis induced by long-term (>3 months) glucorticoid treatment with a daily dose of at least 7.5 mg prednisone (or equivalent) for an indication scientifically sound in postmenopausal women without hormonal substitution. The first approval is valid for 6 months and may be renewed for further 12-month period.

2.2.3.2 Drugs with a priori control in men

Aclasta (Zoledronate) is also reimbursed in men with a prior hip fracture or with at least 2 of the following conditions:

- A BMD with a T-score<-2.5 as measured by DEXA at the lumbar spine (L1-L4 or L2-L4) (male population reference)
- A BMD with a T-score<-1 as measured by DEXA at the hip (total or neck) (male population reference)
- A prior vertebral fracture. Such fracture is defined as a minimum 25% reduction (4mm in absolute value) in front, centre or back height of the vertebra considered, as assessed by a X-ray exam.

Prolia (denosumab) is reimbursed in men receiving hormonal-ablative treatments in the frame of a prostate cancer or receiving gonadotrophinereleasing-hormone (GnRH) analogues or antagonists, and fulfilling at least 1 of the following conditions:

- A BMD with a T-score<-2.5 as measured by DEXA at the lumbar spine (L1-L4 or L2-L4) (male population reference)
- A BMD with a T-score<-1 as measured by DEXA at the hip (total or neck) (male population reference)
- A prior vertebral fracture. Such fracture is defined as a minimum 25% reduction (4mm in absolute value) in front, centre or back height of the vertebra considered, as assessed by a X-ray exam.

2.2.3.3 Drugs with indications other than osteoporosis

Some of the drugs are indicated for other conditions than osteoporosis.

Actonel (risedronate), Skelid (tiludronate) and Aclasta (zoledronate) are reimbursed for Paget disease.

Bondronat (ibandronate) per os or IV is reimbursed in women with breast cancer complicated by bone metastasis. Bondronat IV is also reimbursed in women with neoplastic hypercalcemia.

Zometa (zoledronate) is reimbursed in patients with bone metastasis and receiving only palliative care. An injection is allowed every 3 weeks under the supervision of a medical doctor.

2.2.3.4 *Drugs without a priori control*

Drugs in Chapter I can be prescribed without a priori control. This administrative simplification applies to products which price is at least 39.5% lower than the price ex-factory (for alendronate: MB/BS [C − 2007/22181], 16th February 2007)g. This applies to:

- generic alendronate
- some generic formulations of risedronate
- Calcitonin for intramuscular, intravascular or subcutaneous administration (calcitonin in nasal spray is not reimbursed in Belgium)
- Ibandronate: a demand to transfer generic formulations in Chapter I is currently being considered by the Belgian regulatory authorities.
- Clodronate

2.2.3.5 *Reimbursement of densitometry*

The osteodensitometry by DEXA can be reimbursed since 1st August 2010 (A.R. 2.6.2010 MB/BS 28.6.2010) if one of the following conditions is fulfilled:

1. women ≥65 years with an history of hip fracture in parents or grand-parents
2. individuals with at least one of the following risk factors:
   a. history of low impact vertebral fracture not associated with cancer
   b. history of a low impact non-vertebral fracture, excepted fracture of the fingers, toes, skull, face or cervix vertebra
   c. patients with a corticoids treatment >3 months with a daily dose>7.5 mg of prednisone (or equivalent)
   d. cancer patients with anti-hormonal therapy
   e. patients with at least one of the following disease :
   - 1° rheumatoid arthritis;
   - 2° progressing hyperthyroidism with no treatment;
   - 3° hyperprolactinemia;
   - 4° long-lasting hypogonadism (including orchiectomy or long-term treatment with gonadotrophinereleasing-hormone (GnRH) analogue;
   - 5° renal hypercalciuria;
   - 6° primary hyperparathyreoïdea;
   - 7° osteogenesis imperfecta;
   - 8° Cushing disease;
   - 9° anorexia nervosa with Body Mass Index < 19 kg/m^2;
   - 10° early menopause (< 45 years).

The DEXA exam can be re-done after 5 years at the same conditions as described above.

g Fosamax, the brandname of alendronate produced by MSD, is still in chapter IV.

2.3 DISCUSSION

The incidence rates of hip fracture decreased over the recent years. This trend has also been observed in other countries [12,13,14, 15]. Such a trend could be explained by a more widespread prevention, pharmacological or not, of fragility fractures at the population level. Other factors, i.e. global health improvement, prevention of falls, non-smoking campaigns, increased prevalence of obesity, may also play a role. However, these changes should logically also affect the incidence of other fragility fractures, an assumption not confirmed by our analysis. This discrepancy in the incidence trend of fragility fractures at different sites might be due to an improved prevention of fragility fracture focused towards the population ≥80 years, an age group where hip fracture is the most prevalent. This hypothesis is consistent with the results of a study similar to ours which was recently carried out in France and reported indeed a higher incidence reduction of hip fractures in women ≥85 years as compared to younger individuals [12].

The treatment rates after a fracture were low. This is consistent to observations from other countries, although such phenomenon had been mainly reported for hip fractures. In particular in Belgium, Rabenda et al. reported that in the period 2001-2004, only 6% of patients ≥45 years with a hip fracture received an anti-osteoporotic drug during the year following the fracture [16,17]. However, analysis on treatment rates after a hip fracture might be confounded by age, hip fracture peaking in patients ≥80 years and treatment rates being particularly low in that age range. In our study, we showed that the treatment rates are equally low in younger patients (60-79 years) and for fragility at other sites such as the wrist or the humerus. Only for vertebral fractures were the treatment rates higher, but the external validity of our sample for that particular fracture site is unknown. Concomitantly with a low treatment rate post-fracture, most of the users were in primary prevention, i.e. they begun an anti-osteoporotic drug with no history of a fracture in the preceding 12 months. Worth mentioning, the proportion of primary prevention was likely biased upwards because of the high rate of vertebral fractures which are not registered in claim data.

Bisphosphonates, alone or in combination, were the most utilized drug class. The increase of alendronate+colecalciferol was particularly sharp since its marketing in 2006, although firm evidence on the clinical interest of such combination is scarce [18] and there are no general accepted strategies for combined drug treatments in osteoporosis. Only 1 RCT comparing alendronate+alfacalcidol against alendronate alone was retrieved [19]. This trial suggested that alendronate+alfacalcidol was superior to increase BMD and prevent fractures. However, that quality of that trial was low/very low (see section 4.2.1.1). Whether this combination is preferentially used by patients deficient in vitamin D (e.g. patients in nursing home) could not be assessed with the data at our disposal. Marketing might have played a plausible role. Alendronate+colecalciferol was licensed when generic copies of alendronate alone became available and prices decreased (12 week treatment costs 29.6€, 50.70€ and 69.8 € for generic alendronate, branded alendronate and branded alendronate+colecalciferol, respectively). Moreover, patients buying separately vitamin D supplements and alendronate must pay the full price for vitamin D, whereas the combination of alendronate+colecalciferol is reimbursed in category B. Users of raloxifene decreased importantly between 2004 and 2009, either because of safety concerns, i.e. an increased risk of venous thromboembolism and fatal stroke [20], or because other osteoporosis drugs were considered more efficient, particularly in the older patients. The use of calcitonin has also decreased over the same period, but in 2009 still more than 20 000 patients (≅9% of all patients using anti-osteoporotic drugs) received it. This is a surprising observation for a drug which efficacy is based on poor quality evidence and has only been demonstrated for vertebral fractures. Moreover, it is much more expensive than any other first-line therapy. Use of calcitonin undoudtedly pertains for a substantial part to a variety of uses for poorly defined situations with bone pains; this is no longer to be considered a specific osteoporosis treatment, certainly not the injectable form (personal communication Prof. Kaufman, Gent University).

Actually, calcitonin is mainly used as pain killer mostly after a vertebral fracture and not for fracture prevention.

Compliance and persistence were both low, and not better in secondary than in primary prevention. This is consistent with utilization patterns observed in other countries [21]. An important proportion of patients stopped very early their treatment. In particular, we showed that the number of one-shot users was around 20%. The reason of such important early defaulting should be investigated in depth. A recent review reported that although less frequent dosing was preferred (e.g. weekly over daily alendronate), other factors such as perceived efficacy, side effects, medication cost, availability of patient support programmes and route of delivery were equally important [21]. New molecules (e.g. acid zoledronic administered yearly) might help improve the compliance and persistence. However, these molecules were introduced recently and not enough data was available for analysis. Non-adherence with anti-osteoporotic drugs result in reduced effectiveness and cost-effectiveness[22-24].

3 SCREENING FOR PATIENTS AT HIGH RISK OF FRACTURES

3.1 METHODS

We searched the databases Medline, Embase, The Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effectiveness *(DARE*), and the websites of HTA agencies (SBU, NICE, DACEHTA, MSAC, MAS, HAS, AHRQ, BCBS, AETSA, AATRM, CCOHTA, ECRI, DIMDI, IQWIG) for:

1. Relevant systematic reviews on screening for osteoporosis with the following search strategy: Mass Screening[Mesh] AND "Osteoporosis"[Mesh] AND systematic[sb]. Our inclusion criteria were: systematic review on screening tools or strategies for osteoporosis in women or men; our exclusion criteria were: systematic review on diagnosis tools for osteoporosis in specific patient sub-populations, e.g. patients with cancer; systematic review on risk factors for low bone mass.
2. Studies on the efficiency of screening for osteoporosis with the following search strategy: (fracture, bone[Mesh] OR mortality[Mesh] OR morbidity[Mesh]) AND (osteoporosis[Mesh]) AND ("Mass Screening"[Mesh] OR screen* OR case-finding OR "case finding") AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw]))) NOT ((animal[mh] NOT human[mh]) OR case report [ti] OR editorial [ti] OR editorial [pt] OR letter [pt] OR newspaper article [pt])

Inclusion criteria were: studies reporting on incidence of fragility fractures, morbidity AND/OR mortality in screened population (individuals or communities) versus unscreened population; randomized or quasi-randomized design.

The search strategies were modified for use in other databases where appropriate. The search was updated in March 2011.

3.2 RESULTS

The search for systematic reviews on screening for osteoporosis yielded 39 hits, 2 of which fulfilled our inclusion criteria. These were high-quality and recent systematic reviews on screening for osteoporosis in men and women [25, 26].

The search for studies on the effectiveness of osteoporosis screening yielded 94 hits, 11 of which were selected on title and/or abstract. Eventually, only 2 studies were included. Studies excluded and reasons for exclusion are presented in Table 15.

Table 15: Excluded studies on screening effectiveness

Studies	Reason for exclusion
[27] [28] [29] [30]	no fracture outcome
[31] [32] [33]	No screening programme, testing the validity of screening tools or strategies for improving management of patients at risk of osteoporosis
[34]	Cohort study
[35]	Comparison of participants (35%) and non-participants (65%) in a screening programme. No randomization

3.2.1 Measuring BMD

Historically, the diagnosis of osteoporosis has been defined in relation to BMD levels (see point 1). Therefore, screening for osteoporosis has been relying heavily on measuring bone density. Ultrasound in the heels, finger, wrist and knee or quantitative computed tomography (QCT) for measurement of the vertebrae and wrist are alternative techniques [9].

3.2.1.1 DXA

BMD (g/cm^2) is usually measured by dual-energy x-ray absorptiometry (DXA). It is noteworthy that DXA measures only BMD and yields no information on the bone architecture which is also an important determinant of bone strength. To date, no technique allows such measurement in routine[h]. The ability to predict fractures is expressed as the increase in relative risk of fracture per standard deviation unit decrease in bone mineral measurement, i.e. the gradient of risk. The risk of any fracture increases 1.60-fold for each SD decrease in hip BMD (2.60-fold for hip fracture)[37]. Thus an individual with a T-score of -3 SD will have a 4-fold (1.60^3) higher risk of fracture than a reference individual. These figures were confirmed in further good-quality, prospective cohort studies evaluating the performance of DEXA in predicting fractures. For instance, in the Rotterdam study, the gradient of risk for each SD decrease in femoral neck BMD was 1.4 (95% CI: 1.2, 1.6) and 1.5 (95%CI: 1.4, 1.6) in men and women, respectively, for all nonvertebral fractures. The hazard ratio for vertebral fracture was 1.8 (95%CI: 1.3, 2.4) for men and 1.9 (95%CI: 1.6, 2.4) for women [38, 39].

A meta-analysis of data from 12 cohort studies including 168,366 person-years confirmed that BMD measurement at the femoral neck with DXA was a strong predictor of hip fractures both in men and women [40]. At the age of 65 years, the risk gradient was 2.94 (95% CI: 2.02–4.27) in men and 2.88 (95% CI: 2.31–3.59) in women for each SD decrease in BMD [40]. So the association is largely independent of sex. However, the effect was dependent on age, with a significantly higher gradient of risk at age 50 years than at age 80 years. The reason of this reverse gradient is not well explained, but could be due to the adverse effect of age on the structural or material properties of the femur. Although the gradient of hip fracture risk decreased with age, the absolute risk still rose markedly with age. For any osteoporotic fracture, the gradient of risk was lower than for hip fractures. At the age of 65 years, the risk of osteoporotic fractures increased in men by 1.41 per SD decrease in BMD (95% CI: 1.33–1.51) and in women by 1.38 per SD (95% CI: 1.28–1.48). In contrast with hip fracture risk, the gradient of risk increased with age. For the prediction of any osteoporotic fracture (and any fracture), there was a higher gradient of risk the lower the BMD. At a z score of –4 SD, the risk gradient was 2.10 per SD (95% CI: 1.63–2.71) and at a z score of –1 SD, the risk was 1.73 per SD (95% CI: 1.59–1.89) in men and women combined. A similar but less pronounced and non-significant effect was observed for hip fractures. The underlying mechanisms of this phenomenon are unknown, but might be related to lower BMI, muscle weakness, co-morbidities and structural changes in bone associated to lower values of BMD. The prediction power of the BMD was quite stable through the 10 years following the baseline examination, although a slight attenuation was observed in the case of hip fractures [40].

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h recent developments in magnetic resonance (MR) techniques, including the availability of clinical 3T scanners, and advances in computed tomography (CT) technology makes in-vivo imaging of the trabecular bone architecture more feasible [36]).

Figure 6: Case study. Sensitivity, specificity and likelihoods of BMD (T-score<-2.5) in the Rotterdam study [38]

Population :	3357 women ≥ 55 years followed up during 6.8 years
Prevalence of osteoporosis:	29.1%
Incidence of nonvertebral fracture:	14.9% (499/3357)
Sensitivity:	44% (220/479)
Specificity:	74% (2101/2858)
LR+:	1.66 (95%CI: 1.50, 1.83)
LR -:	0.76 (95%CI: 0.70, 0.82)
Posterior Probability Odds + :	23% (95%CI : 21%, 25%)
Posterior Probability Odds - :	12% (95%CI: 11%, 13%)

All the computations done by us.

Of note, significant differences in the performance of different techniques at different skeletal sites were found, and the performance depended on the type of fracture to be predicted [37]. These considerations have led to the adoption of a reference site, i.e. the hip. This does not preclude the use of other sites, but the prediction of fracture is not improved by the use of multiple sites [41].

DXA presents a relatively good specificity but a poor sensitivity. The majority of the fractures at the spine, hip, forearm or proximal humerus occur in women without osteoporosis [38, 42-45 i]. The important numbers of false negative tests preclude the utilization of DXA alone for screening patients at risk of fractures [46]. The false positives are also a matter of concern.

For instance, on the basis of the results reported in the Rotterdam Study [38], we computed that 66% of all nonvertebral fractures occurred in women without osteoporosis and that 77% of women assessed as osteoporotic, and thus eligible nowadays for a treatment, didn't suffer an incident fractures during the 6.8 years follow-up (see Figure 6). The sensitivity and specificity vary in different studies, partly due to measurement accuracy, but the positive predictive value (PPV) of BMD with the WHO cut-off for osteoporosis is always low. For instance, in the Study of Osteoporosis Fracture (SOF), the PPV was 47%, a value very close to the one observed in the Rotterdam study, although the specificity/sensitivity pattern was quite different (sensitivity=20%; specificity=90%) [47]. Similar results were reported in the NORA study[45]. Such test characteristics preclude the utilization of BMD alone in screening for individuals with high fracture risk.

Fracture risk is also driven by parameters including bone size and shape, bone turnover, micro-architecture, damage accumulation (micro cracks), and degree of mineralisation or collagen structure, all playing a role in bone strength, and hence in the risk of osteoporotic fractures.

Lastly, a number of points need to be acknowledged regarding DXA [1]:

- Diagnostic thresholds differ from intervention thresholds. For a same diagnosis threshold, the fracture risk will vary according to other parameters such as age, the presence of other risk factors and the intensity of bone turnover.
- The accuracy of the exam will vary with the presence of a number of factors, such as osteoarthritis (more density but no more bone strength), osteomalacia (underestimation of bone mass), bone size (overestimation of BMD in individuals with larger bones).

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i From 59.7% to 67.8% of osteoporotic fractures occurred in women presenting a normal BMD in the study by Cranney et al. [43]. In the Rotterdam study, Only 44% of all non-vertebral fractures occurred in women with a T-score below _2.5; in men, this percentage was even lower (21%) [38]. 82% of the 2259 women who reported fractures at 1 year had peripheral T scores greater than −2.5, and 67% had T scores greater than −2.0 in the NORA study [45].

3.2.1.2 Other medical imaging

Other potential screening tests include calcaneal quantitative ultrasound (QUS) and quantitative computer tomography (QCT) radiography. There is increased interest in osteoporosis screening using QUS because it is portable, does not expose patients to radiation, and is relatively inexpensive. Sound waves are passed through the calcaneus, and the speed of sound and absorption patterns of various sound wavelengths are measured, which is known as broadband ultrasound attenuation. A meta-analysis of 25 studies compared the accuracy of QUS against the reference standard of a T-score <–2.5 obtained by DXA, in identifying people with osteoporosis [48]. At a T –score threshold of –2.5, the sensitivity and specificity of QUS were 21%–45% and 88%–96%, respectively. The authors concluded that additional research was needed before use of this test could be recommended in evidence-based screening programs for osteoporosis. Data for ultrasound and peripheral measurements were available from three cohorts. The predictive ability of these devices was somewhat less than that of DXA measurements at the femoral neck by age, sex, and BMD value [40].

It is also possible to use QCT to measure BMD. An advantage of QCT is that it can analyze cortical and trabecular bone, so it is less influenced by the changes caused by degenerative disease, which can interfere with DXA accuracy. However, it is more expensive than DXA, and QCT exposes patients to a marked increase in radiation. The use of QCT as a screening tool for osteoporosis has not yet been extensively researched, and it has not yet been validated in relation to T–scores that predict fracture risk.

One crucial issue when comparing the value of alternative techniques to DXA is that in all RCTs that documented antifracture efficacy of validated treatments BMD criteria for inclusion of subjects has been based on DXA. The treatment efficacy of patients identified with other means than DXA has not been assessed.

3.2.2 Prediction models

3.2.2.1 FRAX

At all ages, low BMD explained a minority of the total risk, a proportion that decreased with age [49]. In addition to low BMD many other independent risk factors for fractures, in particular hip fracture, have been identified. These factors, including smoking, corticosteroid exposure, a family history of fracture, secondary osteoporosis, are presented in details in appendix. Recent efforts by the World Health Organization Metabolic Bone Disease Group have resulted in a risk assessment tool (FRAX) using clinical risk factors with and without femoral neck BMD to enhance fracture prediction [50], particularly for hip fracture prediction at younger ages. For instance, at the age of 50 years, the gradient of risk for a hip fracture with BMD alone was 3.7/SD, but with the addition of clinical risk factors (BMI, family history, prior fracture, smoking, alcohol, glucocorticoids, rheumatoid arthritis) it was 4.2/SD [51]. The WHO determined that for many secondary causes of osteoporosis, fracture risk was mediated primarily through impact on BMD. For this reason, when T-scores are inserted into FRAX®, the secondary osteoporosis button is automatically inactivated. To develop the FRAX, Kanis and colleagues used data from 9 epidemiologic cohorts on baseline BMD and common clinical risk factors easily determined by primary care clinicians that were identified from previous meta-analyses. The performance characteristics of the FRAX tool were then validated in 11 independent population-based cohorts [51]. Country specific FRAX algorithm (including Belgium [52]) is now available online and allows computing individual patient's 10-year probability of hip fracture and 10-year probability of major osteoporotic (hip, clinical vertebral, wrist, or humerus) fracture (http://www.shef.ac.uk/FRAX/). FRAX is now recommended by WHO for screening patients at high risk of fracture.

Clinical practice guidelines regarding when to initiate osteoporosis treatment have thus evolved from the use of BMD thresholds to a more complex consideration of the patient's 10-year absolute fracture risk, although this is not yet the case in Belgium[j].

The FRAX also present limitations:

- A dose-response present in some risk factors (e.g. dose of glucocorticoids, level of alcohol consumption, number and sites of prior fractures) is not acknowledged in the evaluation of the global fracture risk [l]. For such risk factors, only a Yes/No answer is possible in FRAX.
- Only femoral neck BMD is taken into account by FRAX[k]. As BMD measures vary according to the technology used and the site measured, results from other sites and technologies cannot be used.
- A number of risk factors for fractures are not accounted for, such as an history of falls or physical activity. A reason put forward by the initiatiors of the FRAX for not including such risk factors was the lack of extensive validation data and that these risk factors were not amenable to pharmacological treatment. Two important objections can be opposed to the latter argument. First, in the current FRAX other non amenable risk factors are included (e.g. a prior fracture). Secondly, and more importantly, the focus should be put on appropriate management of the fracture risk not only on drug treatment. In this perspective, a tendency to fall is an extremely important parameter to investigate.
- The calibration for each specific country accounts for mortality rates and prevalence of hip fractures. It is assumed that the ratio hip fracture/non hip fracture observed is constant over countries. The validity of this assumption has not been formally assessed (personal communication Prof. JJ Body).

These limitations should be accounted for when making any clinical judgement.

3.2.2.2 The WHI Hip Fracture Risk Calculator

Different authors have combined different risk factors to predict risk fractures, notably the researchers of the Women Health Initiative and the Osteoporosis Society of Canada and Canadian Association of Radiologists Working Group. The former have proposed a tool similar to the FRAX on the basis of a dataset including 93 676 postmenopausal women and validated among 60 000 women [57], the WHI Hip Fracture Risk Calculator (http://hipcalculator.fhcrc.org/).

3.2.2.3 The QFractureScores

The algorithms have been specifically developed for use in the UK in order to predict risk of fracture in primary care populations in the UK [58]. One specificity of the QFractureScores is the absence of DXA assessment. Also, the scores have been built up in a population without prior fractures (http://www.qfracture.org/)

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j Validated questionnaires may also be used to identify patients at risk of osteoporosis. Such questionnaires include the Osteoporosis Self-assessment Tool (OST), the Osteoporosis Index of Risk (OSIRIS), the Simple Calculated Osteoporosis Risk Estimation (SCORE), the Osteoporosis Risk Assessment Instrument (ORAI), the Age, Body Size, No Estrogen (ABONE) decision rules 9. The DOEScore, the FOSTA, the SOFSURF, the OPERA and the National Osteoporosis Foundation (NOF) guideline also exist. It should be noted that those questionnaires allow estimating the risk of osteoporosis but not of fractures 31 53. Thus, they will not be further reviewed in this report. However, although not specific, such pre-screening tests are highly sensitive, i.e. they indicate who should not receive a DXA 54. This was also verified in Belgium (for the OST, SCORE, ORAI and OSIRIS scales) 55. As such, they could be cost-effective in mass-screening programmes 56.

k The femoral neck was the only site for which BMD was available for all the study cohorts.

3.2.2.4 *Other risk assessment tools*

Other risk assessment tools are available such as Australian nomograms http://www.fractureriskcalculator.com, or the risk-assessment tool proposed by the Osteoporosis Society of Canada [59]. It includes age, sex, BMD, fragility fracture history, and glucocorticoid use, and also allows computing a 10-year absolute fracture risk. However, patients are classified in 3 broad categories: low (less than 10%), moderate (10 to 20%), and high (over 20%). Other indexes to predict fractures were defined [60 61]. However, those were created within specific study population, and generally with a relatively limited amount of data. They will not be further reviewed here.

3.2.2.5 *Comparing the algorithms*

The FRAX allows a number of additional functionalities in comparison to other risk assessment tools. It can be adapted to the country area, it can compute risk for men, and up to 90 years, and it can integrate the results of the BMD and the corresponding predictive value. It also allows computing probabilities for major osteoporotic fractures (i.e. not only hip fracture). In comparison the WHI Hip Fracture Risk Calculator is limited to predicting risk of hip fracture only in American women under age 79 years.

We simulated the individual risk fracture as assessed by the 2 algorithms using risk factors common to both FRAX and WHI calculator (Table 16). From Table 16, it is apparent that the results derived from the 2 algorithms are strikingly similar. Some differences are apparent for the risk factors "previous fracture" and "smoking", but the absolute differences are small and of no interest for prediction of hip fracture at the individual level.

Table 16: 5-years probabilities of hip fracture predicted by the FRAX or the WHI algorithms for Caucasian American women with different configurations of risk factors

	1	2	3	4	5	6	7	8	9	10	11
Age (years)	65	65	65	65	65	65	65	65	65	79	79
Weight (kg)	68	68	68	68	68	68	68	68	82	82	82
Height (cm)	165	165	165	165	165	165	165	165	165	165	165
Previous fracture	No	Yes	No	No	No	Yes	No	Yes	No	No	Yes
Parent fractured hip	No	No	Yes	No	No	Yes	No	Yes	No	No	Yes
Current smoking	No	No	No	Yes	No	No	Yes	Yes	No	No	Yes
Glucocorticoids	No	No	No	No	Yes	No	Yes	Yes	No	No	Yes
FRAX	0.8%	2.0%	1.1%	1.2%	1.7%	2.7%	2.5%	8.0%	0.4%	2.9%	26%
WHI	0.7%	1.1%	1.0%	1.6%	1.5%	1.5%	3.4%	7.6%	<0.5%	2.4%	22.6%

Only parameters common to the 2 algorithms were utilized. In the FRAX, we answered no to "presence of rheumatoid arthritis", "secondary osteoporosis", "alcohol consumption of more than 3 units or more per day", "femoral neck BMD" and "sex". In the WHI, we rated "self-rated health" as good, considered that all women were under 12 MET per week for "Physical activity" and answered no to "Diabetes treatment".
The FRAX provides a 10-years probability, and the WHI a 5-years probability. Assuming that the risk of fracture is constant over the 10 years in the FRAX, we divided the risk by a factor 2 and reported 5-years probabilities for both algorithms.
All simulations concerned Caucasian American women.

The performance of the various risk-assessment instruments were recently compared in a systematic literature review [25]. That review included 11 studies evaluating 11 externally validated clinical risk-assessment instruments and reported performance estimates of the area under the curve (AUC) for the receiver-operating characteristic curve predicting fractures. Instruments included from 1 to more than 15 variables, although most include age, weight or body mass index, and previous fracture. Family history of fractures, smoking status, and estrogen use were also commonly included. Important methodological limitations of studies included non representative samples, cross-sectional rather than prospective data collection, inconsistent performance of the reference standard, and differences in performance measures across studies. The studies reported AUC estimates from 0.48 to 0.89. The AUC estimates for FRAX ranged from 0.54 to 0.78 for osteoporotic fractures and 0.65 to 0.81 for hip fractures. Three studies compared FRAX with simple models, such as age and BMD or age and fracture history, and found that simple models did as well as FRAX in predicting hip and other clinical fractures [62,63] and vertebral fractures [64]. A very recent study reported consistent results [65].

3.2.3 Biochemical markers

Other potential screening tests include serum and urine tests for markers of bone formation and resorption. Markers of bone formation include bone-specific alkaline phosphatase, osteocalcin, and procollagen I carboxy and N-terminal extension peptides. Markers of bone resorption include urinary levels of pyridinolines and deoxypyridinolines, and serum and urine levels of type I collagen telopeptides. The level of these markers may identify changes in bone remodeling within a relatively short time interval (several days to months) before changes in BMD can be detected. These biochemical markers of bone turnover are often used in the research setting but have limited clinical utility. They do not predict bone mass or reliably estimate fracture risk, but they may be helpful in monitoring response to anti-resorption therapies in patients with osteoporosis 66.

3.2.4 Effectiveness of screening for osteoporosis

Only two original researches assessing the value of osteoporosis screening were retrieved [33, 67, 68]. However, although their authors argued about the need for assessing whether bone density prevents hip and other osteoporotic fractures, those studies were not powered to evidence such an effect. The details of the studies are presented in Table 17.

In the study by Lacroix et al., age adjusted rates of total fracture were lowest in the universal testing group (74.11/1000), highest in the SCORE testing group (99.44/1000; p= 0.009) and intermediate in the SOF-based testing group (91.77/1000; p=0.02). Hip fracture rates were also lowest in the universal group (8.54/1000), intermediate in the SCORE testing group (9.04/1000), and highest in the SOF-based testing group (13.31/1000; Table 2) but these differences were not statistically significant. Rates of initiation of osteoporosis therapy did not differ significantly among all women contacted. Because of the limitations reported in the Table 17 and acknowledged by the authors, caution is required in analyzing fracture data. In study by Barr et al., 35% of women were screened (life-style questionnaire, quality of life questionnaires (Short Form-36 and EuroQol), and had their height, weight and blood pressure measured. The QUSparameters, broadband ultrasound attenuation (BUA), and velocity of sound (VOS) were measured in the left calcaneus by using a CUBA Clinical scanner (McCue, Winchester, UK), and 65% acted as a non screened control population [68]. Increased risk of hip fracture was defined arbitrarily as those with the QUS parameter, BUA in the lowest quartile of the manufacturer provide normal range, and/or the presence of two or more clinical risk factors for hip fracture (low body weight, smoker, previous fracture, maternal hip fracture). As soon as possible after screening, the GPs of women who were found at screening to be at increased risk of hip fracture were asked to prescribe a calcium and vitamin D supplement. The GPs of women considered not to be at increased risk of fracture were also sent the QUS result but no treatment was suggested. The annual rate of falls was significantly higher in the control group than in the entire active group at follow-up (0.55 ± 11.17 vs. 0.43 ± 0.95 falls per year).

Compared with the control group, the active group had a 43% lower risk of fracture (OR, 0.54; 95% CI, 0.33–0.87 unadjusted). This was increased to 51% following adjustment for age and weight (OR, 0.49; 95% CI, 0.30–0.81) and further increased to 56% when also adjusted for calcium and vitamin D treatment status at follow-up (OR, 0.44; 95% CI, 0.24–0.81). In conclusion, direct evidence of the benefits of screening for osteoporosis on relevant outcomes is scarce.

No studies evaluating potential harms were retrieved. Potential harms associated with osteoporosis screening and treatment have been previously identified. These include anxiety from perceived vulnerability to fracture when osteoporosis is identified. False negative results can occur from bone density screening, leading to missed opportunities for treatment. Studies are lacking on the harms related to repeated DXA scans and harms pertaining to osteoporosis screening in men. Harms associated with osteoporosis screening may also occur from the adverse effects related to treatment of osteopenia or osteoporosis.

Table 17: Results of studies on osteoporosis screening

Ref	Year	Population	Intervention	Results	Comments
[33, 67]	2005	3167 women aged 60-80 with no hormone replacement or osteoporosis medication for at least 12 months	Random allocation in 3 groups: 1. BMD for all 2.BMD if SCORE questionnaire ≥7 3. BMD if SOF score ≥5 Every participant received an information brochure and pesonalized feedback on BMD results. Criteria for referral to GP was (T-score <-2.5 AND SOF≥5) AND/OR fracture after 50 y.	TF=74.11/1000 HF=8.54/1000 TF=99.44/1000 HF=9.04/1000 TF=91.77/1000 HP=13.31/1000	- Random allocation process not explained -Adequacy of data analysis unclear (Cox regression used?) -Possible selection bias: response rates were around 40%; - Fracture rates evaluated during a 2-year period and based on ICD9. No validation of the procedure. - No blinded ascertainment of other parameters
[68]	2005	5,306 women aged ≥70 in 11 GP practices	Random allocation in 2 groups: 1. calcaneus ultrasound + questionnaire 2. No screening	- Annual rate of falls=0.43±0.95 vs 0.55±11.17 -OR for HF=0.44 (95%CI: 0.24-0.81)	- The follow-up was longer in controls - Active non-attendees were older, poorer and had more falls in previous year than active attendees resulting in a plausible selection bias -Combination of parameters to define risk has not been validated

TF= Total fracture rate; HF=Hip fracture rate

3.3 DISCUSSION

BMD, the parameter used to define osteoporosis, is not sensitive enough to serve for screening individuals at high risk of fragility fractures. An important proportion of patients suffering such fractures have a BMD in the normal range. In the recent years, there has been a shift from assessing fracture risk on BMD alone to an approach based on the absolute risk of fracture due to the presence of various risk factors. Among those risk assessment tools, FRAX presents a number of advantages: it has been extensively validated; it applies to both men and women in the United States, Europe, Australia and Asia; it takes into account country-specific fracture and death rates. On this basis, WHO recommends using FRAX for identifying patients at high risk of fractures and initiating osteoporosis treatment.

However, important issues are still pending concerning that recommendation.

First, FRAX, in comparison to BMD alone, improves hip fracture prediction but not that much [62]. In the FRAX development study, the predictive power for hip fracture of a model combining FRAX and BMD resulted in a small increment in the gradient of risk per 1SD change in risk score compared to BMD alone (5% to 19% increase) [50, 51]. The increment was also small for fractures at other sites. Moreover, the AUC with FRAX was not significantly higher than the one obtained with more parsimonious models [25].

Second, all the risk assessment tools, including FRAX, are limited in their ability to predict fracture, especially non-hip fractures. The AUC of FRAX for hip fracture is between 0.65 and 0.81, and for all osteoporotic fractures between 0.54 and 0.78. Thus, risk prediction remains challenging.

Third, the shift towards basing clinical management of osteoporosis on absolute risk of fracture might have major implications for the proportion of patients requiring osteoporosis treatment. A risk threshold triggering osteoporosis treatment must be defined, and to date it is not clear. For instance, the National Osteoporosis Foundation (NOF) in the United States recommends drug treatment for adults ≥50 years with osteopenia and level of 10-year absolute probability ≥3% for hip fracture or ≥20% for major osteoporotic fractures as assessed by FRAX. In Belgium, every woman ≥68 years, even in the absence of other risk factors and without osteoporosis (BMD T-score=-2.2), have a 3% 10-year risk of hip fracture. Every woman ≥84 years, even in the absence of other risk factors, present a 20% 10-year risk of major osteoporotic fractures. So, a single universal threshold is unlikely to be appropriate. The threshold should take into account patient age and sex and possibly specific risk combination. A proposal for intervention thresholds for the UK is particularly demonstrative of the way different parameters can be combined to target treatment [69]. A similar proposal has been made for Belgium, extrapolating the level of risk due to a prior fragility fracture to other combinations of risk factors in function of age [52].

A final important issue concerns the ability of risk assessment tools to identify fracture risk which would be amenable to an osteoporosis treatment. All the clinical trials carried out for assessing the efficacy of osteoporosis treatment selected patients on the basis of low BMD and/or prior fracture, not on absolute risk of fracture. It is thus unknown how far their results can be extrapolated to patient populations identified on a different basis. It might be that a proportion of patients identified as being at high-risk of fractures by FRAX (>10-years major osteoporosis fracture risk ≥20%) also present a BMD in the osteoporosis range, as reported by a study in Canada [70]. However, that study raised also further questions. First, 30% of patients had a DXA at the femoral neck ≥-2.5. Second, how the cross-classification was modified by different FRAX risk profile was not reported. Lastly, the study was performed in a population where 14% had a femoral neck T-score≤-2.5.

The issue of translating trial results to patients identified on absoluter risk fracture is discussed in more length in section 4.3.2.

4 EFFICACY OF PHARMACOLOGICAL TREATMENT

Pharmacotherapy for prevention and treatment of osteoporosis includes two primary types of drugs, anti resorptive and anabolic agents. Anti resorptive agents increase bone strength by decreasing the number of bone multicellular units. This reduces resorption and prevents further structural damage of trabecular bone and by reducing cortical porosity. In contrast, anabolic agents increase bone strength by increasing bone mass due to an increase in the number of bone multicellular units. As a result, the magnitude of the formation phase is greater than the resorption phase. The majority of the agents currently available for the treatment of osteoporosis are anti resorptive (e.g. bisphosphonates, selective estrogen modulators, calcitonin and denosumab) and there are a few anabolic agents (e.g. intermittent recombinant human parathyroid hormone and fluoride). Strontium ranelate simultaneously decreases bone resorption and stimulate bone formation.

4.1 METHODS

We searched the databases Medline, Embase, The Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effectiveness *(DARE*). The Medline search strategy is presented here below. This was modified for use in other databases where appropriate. Standard search filters for systematic reviews and RCTs were used. We also search the website of other HTA agencies. The search was updated in March 2011.

SBU http://www.sbu.se/en/

NICE http://www.nice.org.uk/

DACEHTA http://www.sst.dk/english/

MSAC http://www.msac.gov.au/

MAS http://www.health.gov.on.ca/

HAS http://www.has-sante.fr/portail/jcms/j_5/accueil

AHRQ http://www.ahrq.gov/

BCBS http://www.bcbs.com/

AETSA http://www.juntadeandalucia.es/

AATRM http://www.gencat.cat/

CCOHTA http://www.cadth.ca/index.php/en/home

ECRI https://www.ecri.org/Pages/default.aspx

DIMDI http://www.dimdi.de/static/de/index.html

IQWIG http://www.iqwig.de/index.2.en.html

For each single drug, our strategy was set in 2 steps:

Step 1: identifying the most recent high-quality review on the use of the specific drug in the prevention/treatment of osteoporosis.

The following search strategy was applied: *Name of the substance* AND ("Fractures, Bone"[Mesh]) AND ("systematic review*" OR "systematic literature review*" OR meta-analysis [pt] OR meta-analysis [ti] OR metaanalysis [ti] OR meta-analyses [ti] OR evidence-based medicine OR (evidence-based AND (guideline* [tw] OR recommendations*[tw])) OR health technol* assess*) NOT ((animal[mh] NOT human[mh]) OR case report [ti] OR editorial [ti] OR editorial [pt] OR letter [pt] OR newspaper article [pt]).

High quality was defined according to the evaluation check-list provided by SIGN (http://www.sign.ac.uk/guidelines/fulltext/50/checklist1.html). The retained review served as the reference data source for the specific drug under consideration.

Step 2: reviewing the evidence published since the issue of the systematic literature review identified at step 1. For this step, the following search strategy was applied: *Name of the substance* AND ("Fractures, Bone"[Mesh]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw]))) NOT ((animal[mh] NOT human[mh]) OR case report [ti] OR editorial [ti] OR editorial [pt] OR letter [pt] OR newspaper article [pt])

We reviewed the evidence for drugs commonly used in Belgium, i.e. used by at least 500 patients in 2009. Althouhg Denosumab is not yet reimbursed in Belgium, evidence was also reviewed because it is a new class drug.

Name of the substance= raloxifene OR strontium ranelate OR denosumab OR alendronate OR risedronate OR ibandronate OR (zoledronic OR zoledronate) OR calcitonin

Our inclusion criteria were as follows:

- Patients: postmenopausal women or older men suffering from osteoporosis.
- Intervention: any drug treatment for primary or secondary prevention of bone fractures[1]
- Comparison: placebo or vitamin D +/- calcium (provided that the intervention group also received vitamin D +/- calcium), i.e. studies comparing the effect of different active substances were not considered
- Outcomes: 1) fragility fractures as primary or secondary outcomes, i.e. studies reporting only on BMD results were not considered; 2) any safety issues
- Study design: systematic reviews & randomized controlled trials

Exclusion criteria: study population presenting a very specific morbidity pattern:

- individuals receiving prolonged (more than 3 months) oral corticosteroid therapy
- individuals with secondary causes of osteoporosis, including but not limited to, celiac disease, chronic liver disease, chronic renal failure, hyperparathyroidism, hypercortisolism, hyperthyroidism, and transplant recipients
- individuals with compromised physical function resulting from factors such as rheumatoid arthritis, neurological conditions, or spinal paralysis from various causes
- women with untreated hypogonadism, including postmenopause, primary hypogonadism, premature menopause, secondary amenorrhea (eg. following anorexia nervosa or associated with extreme levels of exercise or certain forms of oral contraceptives) and early hysterectomy
- men with primary or secondary hypogonadism.

These patient populations are recognised as important. However, they were not specifically addressed in this document focusing on screening for osteoporosis in the general population.

[1] BMD is not a an appropriate surrogate for fracture reduction [71] However EMA guidelines recommend bridging studies based on BMD for male osteoporosis.

The quality of evidence for each drug and each outcome was graded following the methodology proposed by the GRADE working group (http://www.gradeworkinggroup.org/index.htm). According to the GRADE scheme, evidence is classified as high, moderate, low or very low:

- high – further research is very unlikely to change our confidence in the estimate of effect
- moderate – further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- low – further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- very low – any estimate of effect is very uncertain.

The following procedure was adopted when using the GRADE scheme.

1. A quality rating was assigned, based on the study design, for example, RCTs start as high and observational studies as low.
2. This rating was up or downgraded according to specified criteria: study quality[m], consistency[n], directness[o], preciseness[p] and reporting bias. Criteria were given a downgrade mark of −1 or −2, depending on the severity of the limitations.
3. The downgrade/upgrade marks were then summed and the quality rating revised. For example, a decrease of −2 points for an RCT would result in a rating of 'low'.
4. Wherever possible, reasoning was explained for the downgrade marks.

The GRADE-pro software was used to produce tables of evidence.

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[m] For randomised trials, the following factors were taken into account: the adequacy of allocation concealment; blinding of participants for comparisons and outcomes susceptible to bias; attrition (missing data); and baseline comparability. A downgrade mark of −1 was given for inadequate allocation concealment and for a loss to follow-up of more than 20% in any one group or overall. A loss to follow-up of 50% or more was given a downgrade of −2.

[n] When several RCTs had widely differing estimates of treatment effect (heterogeneity or variability in results) the results were regarded as inconsistent. This was defined as a p-value for heterogeneity less than 0.1 and/or an I2 value greater than 50%. In such cases, a downgrade mark of −1 was given. If the p-value was less than 0.1 and the I2 value was greater than 80%, a downgrade mark of −2 was given. Generally, single trials (especially smaller ones) were not considered as having inconsistency unless there were a priori defined subgroups showing widely different effects.

[o] Directness refers to the extent to which the population, interventions, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is only relevant if there is a compelling reason to expect important differences in the size of the effect. For example, many interventions have more or less the same relative effects across patient groups, so extrapolation is possible and reasonable.

[p] Evidence is considered to be imprecise in the following cases:
-The sample size is small. This is a subjective measure and is more important in a single study. If there is a power calculation for that outcome and comparison, it is used to decide if a study is 'small'; otherwise, the rule of thumb was used that, if the study has less than 25 patients in any one arm, this is too small. The rationale for this is that, below 25 patients, assumptions about normal distributions become much less valid. However, if these small studies are combined in a meta-analysis, this would be more acceptable.
-There are sparse data (only a few events and they are uninformative).
If CIs are sufficiently wide that the effect estimate is consistent with both important harms and important benefits, and would lead to conflicting recommendations. If CIs are very wide, a downgrade mark of −2 is given.

4.2 RESULTS

4.2.1 Bisphosphonates

Bisphosphonates are stable analogues of naturally occurring pyrophosphates. The mechanism of action of these drugs is to inhibit bone resorption through their effects on osteoclast function. Bisphosphonates are poorly absorbed and avidly taken up by bone on active sites of resorption.

Our review focuses on the bisphosphonates most often used in Belgium, i.e. alendronate (alone or combined with colecalciferol and/or calcium), ibandronate, risedronate, and zoledronate. Results on efficacy are presented in Table 18 & Table 19

A review on side-effects of drugs is available inTable 40 (in appendix).

4.2.1.1 Alendronate

Alendronate is a second generation nitrogen containing bisphosphonate which is administered daily or once weekly (depending on formulation) and does not impair bone mineralization at doses that maximally inhibit bone resorption. The recommended doses for the prevention and treatment of osteoporosis in postmenopausal women are 5 mg/day (35 mg/week) or 10 mg/day (70 mg/week).

The search for systematic review returned 15 hits. Two recent high-quality systematic reviews (SR) were identified: a Cochrane review by Wells et al. who reviewed RCTs published up to February 2007 [72] and a NICE review which was updated in June 2008 [73]. The NICE review therefore served as the reference document. The update search returned 28 hits (including the Cochrane review itself). Among those, only 1 paper met the inclusion criteria 19 (for papers rejected and reason for rejection, please see Table 31 in appendix 3)

The results of the NICE review are synthesized in Table 18 & Table 19. The results of the Cochrane review are very consistent.

The Cochrane review included 11 trials representing 12,068 post-menopausal women receiving at least one year of alendronate vs. placebo and/or concurrent calcium/vitamin D [72]. In that review, Relative (RRR) and absolute (ARR) risk reductions for the 10 mg dose were as follows. For vertebral fractures, a significant 45% RRR was found (RR 0.55, 95% CI 0.45 to 0.67). This was significant for both primary preventionq, with 45% RRR (RR 0.55, 95% CI 0.38 to 0.80) and 2% ARR, and secondary prevention with 45% RRR (RR 0.55, 95% CI 0.43 to 0.69) and 6% ARR. For non-vertebral fractures, a significant 16% RRR was found (RR 0.84, 95% CI 0.74 to 0.94). This was significant for secondary prevention, with 23% RRR (RR 0.77, 95% CI 0.64 to 0.92) and 2% ARR, but not for primary prevention (RR 0.89, 95% CI 0.76 to 1.04). There was a significant 40% RRR in hip fractures (RR 0.60, 95% CI 0.40 to 0.92), but only secondary prevention was significant with 53% RRR (RR 0.47, 95% CI 0.26 to 0.85) and 1% ARR. The only significance found for wrist was in secondary prevention, with a 50% RRR (RR 0.50 95% CI 0.34 to 0.73) and 2% ARR.

[q] In this review, studies of primary prevention were defined as follows: the averageT-score (and SD) was such that it included women whose bone density was within 2 SD of the mean, or the prevalence of vertebral fracture at baseline was less than 20%. Studies on secondary prevention were defined as follows: the inclusion criteria restricted the population to women whose bone density was at least 2 SD values below the peak bone mass, or the inclusion criteria restricted the population to women who had experienced previous vertebral compression fractures. If such inclusion criteria were not provided, the trial was considered as secondary prevention if the average age was above 62 years.

Ringe et al. randomized 30 patients to receive either 1 µg Alfacalcidol daily + 500 mg calcium (A) or 70 mg Alendronate weekly + 1,000 mg Calcium (B) + 1,000 IU vitamin D daily or 1 µg Alfacalcidol daily + 70 mg Alendronate weekly+ 500 mg calcium daily (C) during 24 months [19]. The authors reported a 0.067 (2/30) fractures incidence in the C group, while this amounted to 0.333 (10/30) in group B and to 0.300 (9/30) in the group A. Important methodological problem of this study included an absence of description of the randomization process and of allocation concealment. Assessors of fractures are reported to be blinded but no description of this was provided. The latter is a crucial point as most of the fractures were at the spinal level (although the exact proportion is not reported) and there is thus more room for observation bias than for fractures in other sites, e.g. hip.

Table 18: Meta-analyses of osteoporosis treatments (RR, relative risk)

DRUGS		FRACTURES				
		Vertebral	Nonvertebral	Hip	Wrist	Humerus
Alendronic acid 5 or 10 mg/day	**RR (95%CI)**	**0.55 (0.46, 0.66)**	**0.83 (0.74, 0.93)**	**0.62 (0.40, 0.96)**	**0.85 (0.67,1.09)**	
1 to 4 years	GRADE quality	high/moderate	high/moderate	high/moderate	low/very low	
6 to 70% prior fractures (PF)	Trials (patients)	9 trials (8074)	8 trials (10429)	3 trials (7453)	3 trials (7453)	
Etidronate 400 mg/day	**RR (95%CI)**	**0.51 (0.31, 0.83)**	**0.72 (0.29, 1.80)**	**1.02 (0.21, 4.94)**	**4.95 (0.24, 101.93)**	
1 to 5 years	GRADE quality	moderate	low	very low	very low	
0 to 100% PF	Trials (patients)	8 trials (1039)	4 trials (472)	2 trials (246)	1 trial (209)	
Risedronate 5mg/day	**RR (95%CI)**	**0.61 (0.50, 0.74)**	**0.81 (0.72, 0.90)**	**0.73 (0.58, 0.92)**	**0.68 (0.43, 1.07)**	**0.46 (0.23, 0.93)**
1 to 5 years	GRADE quality	moderate/low	moderate/low	moderate/low	moderate/low	moderate/low
100% PF	Trials (patients)	7 trials (2845)	7 trials (12658)	4 trials (11923)	2 trials (2439)	2 trials (2439)
Ibandronic acid 2.5mg/day	**RR (95%CI)**	**0.51 (0.34, 0.74)**	**1.11 (0.83,1.48)**			
1 to 3 years	GRADE quality	low/very low	low/very low			
43 to 94% PF	Trials (patients)	1 trial (1952)	1 trial (1952)			
Zoledronate 5mg/year (IV)	**RR (95%CI)**	**0.30 (0.24, 0.38)**	**0.75 (0.66, 0.85)**	**0.62 (0.47, 0.83)**		
1.9 to 3 years	GRADE quality	high/moderate	high/moderate	high/moderate		
63 to 100% PF	Trials (patients)	2 trials (7802)	1 trial (5675)	2 studies (9863)		
Strontium ranelate 2 g /day	**RR (95%CI)**	**0.62 (0.55, 0.71)**	**0.86 (0.74, 0.99)**	**0.85 (0.61, 1.19)**	**1.00 (0.74, 1.36)**	**0.53 (0.29, 0.94)**
2 to 3 years	GRADE quality	moderate/low	moderate/low	moderate/low	moderate/low	moderate/low
54% to 100% PF	Trials (patients)	3 trials (5254)	2 trials (6374)	1 trial (4932)	1 trial (4932)	1 trial (4932)
Teriparatide 20µg/day (subcutan.)	**RR (95%CI)**	**0.36 (0.23, 0.57)**	**0.49 (0.27, 0.87)**	**0.25 (0.03, 2.24)**	**0.29 (0.06, 1.38)**	**1.01 (0.14 to 7.11)**
11 to 18 months	GRADE quality	moderate	moderate	very low	very low	very low
29% to 100% PF	Trials (patients)	2 trials (910)	2 trials (1383)	1 trial (1085)	1 trial (1085)	1 trial (1085)
Calcitonin 200 IU/day (nasal)	**RR (95%CI)**	**0.65 (0.48, 0.88)**	**0.22 (0.02, 1.96)**	**0.54 (0.18, 1.59)**		
2 to 5 years	GRADE quality	low	very low	very low		
10% to 75% PF	Trials (patients)	4 trials (753)	2 trials (152)	1 trial (620)		
Raloxifene 60mg/day	**RR (95%CI)**	**0.64 (0.54, 0.78)**	**0.91 (0.78, 1.05)**	**1.12 (0.64, 1.94)**	**0.88 (0.68, 1.14)**	
1 to 3 years	GRADE quality	moderate/low	low	low	very low	
10% to 100% PF	Trials (patients)	2 trials (4639)	2 trials (7793)	2 trials (7793)	1 trial (7705)	
Denosumab 60mg/6months (subcut.)	**RR (95%CI)**	**0.32 (0.26, 0.41)**	**0.80 (0.67, 0.95)**	**0.60 (0.37, 0.97)**		
3 years	GRADE quality	high/moderate	high/moderate	high/moderate		
23.5% PF	Trials (patients)	1 trial (7868)	1 trial (7868)	1 trial (7868)		

Table 19: Meta-analyses of osteoporosis treatments (NNT)

DRUGS		FRACTURES				
		Vertebral	Nonvertebral	Hip	Wrist	Humerus
Alendronic acid 5 or 10 mg/day	**NNT (95%CI)**	**33 (25, 50)**	**50 (33, 100)**	**200 (100, >1000)**		
1 to 4 years	Rate in controls	0.04 to 0.35	0.02 to 0.18	0.013 to 0.08		
Etidronate 400 mg/day	**NNT (95%CI)**	**25 (13, 100)**				
1 to 5 years	Rate in controls	0.03 to 0.16				
Risedronate 5mg/day	**NNT (95%CI)**	**17 (21, 25)**	**50 (33, 100)**	**125 (100, >1000)**		**100 (50, >1000)**
1 to 5 years	Rate in controls	0.00 to 0.26	0.04 to 0.13	0.02 to 0.08		0.01 to 0.03
Ibandronic acid 2.5mg/day	**NNT (95%CI)**	**25 (17, 50)**				
1 to 3 years	Rate in controls	0.07				
Zoledronate 5mg/year (IV)	**NNT (95%CI)**	**13 (12, 17)**	**50 (25, 100)**	**100 (70, >200)**		
1.9 to 3 years	Rate in controls	0.11	0.10	0.02 to 0.03		
Strontium ranelate 2 g /day	**NNT (95%CI)**	**NR**	**NR**			**160 (110, >1000)**
2 to 3 years	Rate in controls	NR	NR			0.013
Teriparatide 20µg/day (subcutan.)	**NNT (95%CI)**	**11 (8, 20)**	**50 (25, 100)**			
11 to 18 months	Rate in controls	0.14 to 0.17	0.02 to 0.04			
Calcitonin 200 IU/day (nasal)	**NNT (95%CI)**	**13 (8, 50)**				
2 to 5 years	Rate in controls	0.07 to 0.26				
Raloxifene 60mg/day	**NNT (95%CI)**	**25 (20, 50)**				
1 to 3 years	Rate in controls	0.04 to 0.29				
Denosumab 60mg/6months (subcut.)	**NNT (95%CI)**	**21 (19-24)**	**67 (37, 250)**	**208 (130, >1000)**		
3 years	Rate in controls	0.07	0.08	0.012		

PF: Prior Fracture; NNT: Number Needed to Treat

4.2.1.2 Risedronate

Risedronate is a nitrogen containing pyridinyl third generation bisphosphonate which

is administered daily or once weekly (depending on formulation). The recommended dose for the prevention and treatment of osteoporosis in postmenopausal women is 5 mg/day (35 mg/week).

The search for systematic review returned 19 hits. We identified two recent high-quality SR: a Cochrane review by Wells et al. who reviewed RCTs published up to February 2007 [74] and a NICE review with an update up to June 2008 73. Other systematic reviews examined specific aspects of the treatment by risedronate such as the interaction with age 75 or the effect in men 76. The NICE review therefore served as the reference review.

The update search returned 54 hits (including the Cochrane review itself), none of which was selected (for papers rejected and reason, please see Table 32 in appendix 3)

The results of the NICE review are synthesized in Table 18 & Table 19.

The results of the Cochrane review are consistent. The Cochrane review by Wells et al. included 7 trials with 14 049 post-menopausal women who received at least one year of risedronate vs. placebo and/or concurrent calcium/vitamin D [74]. Relative (RRR) and absolute (ARR) risk reductions for the 5 mg dose were as follows. Risk estimates for primary prevention were available only for vertebral and non vertebral fractures and showed no statistically significant effect of risedronate on fractures. For secondary prevention, a significant 39%RRR in vertebral fractures (RR 0.61, 95%CI 0.50 to 0.76) with 5%ARR was found. For nonvertebral fractures, a significant 20% RRR (RR 0.80, 95% CI 0.72 to 0.90) with 2% ARR and for hip fractures there was a significant 26% RRR (RR: 0.74, 95% CI 0.59 to 0.94) with a 1% ARR. When primary and secondary prevention studies were combined, the reduction in fractures remained statistically significant for both vertebral (RR 0.63, 0.51 to 0.77) and non vertebral fractures (RR 0.80, 0.72 to 0.90)

4.2.1.3 Zoledronate

Zoledronate is a potent bisphosphonate that can be administered intravenously once yearly.

The only systematic review was produced by NICE in 2008 [73]. Therefore, we used this SR as the basis of the present review. The update search yielded 68 hits. Among those, only 2 studies were eligible and were already included in the NICE review (see Table 33 in appendix 3 for studies rejected and reasons)[77,78].

The results of the NICE review are synthesized in Table 18 & Table 19. The review included only 2 studies, one in postmenopausal women only 78 and the other in both men and women over 50 years [77]. In the Lyles study [77], patients were included in the study only if they had undergone repair of a hip fracture and if they were unwilling or unable to take oral bisphosphonates. This may not have been a representative population. Mean baseline femoral neck T-scores were reported in both studies. In Black's study, the majority (71%) had a T-score measured at the femoral neck of less than −2.5 SD; some women (28%), had a T-score between 2.5 and −1.5 SD, and were included only if there was radiological evidence of at least two mild vertebral fractures or one moderate vertebral fracture [78]. About 63% of the participants had one or more vertebral fractures at baseline. The second study reported that 42% of the patients had femoral neck T-scores of −2.5 SD or below, 34% had T-scores from above −2.5 to −1.5 and 11% had T-scores above −1.5 SD 77. Thus the participants in each study had osteoporosis or osteopenia. Zoledronate 5 mg was given as a 15-min intravenous infusion at baseline, and again at 12 and 24 months in both studies. The duration of the studies was 3 years in Black and a median of 1.9 years in Lyles. In the latter, the study was terminated when efficacy had been established, based on the number of clinical fractures. In both studies, all participants received oral calcium 1000–1500 mg/day and vitamin D 400–1200 IU/day (Black 2007) and 800 IU/day (Lyles 2007). The comparison group received placebo.

The quality of both studies was high. However, in the Black study, 627 people (16%) in the zoledronate group did not complete the trial, and there were 592 (15%) in the placebo group [78]. Efficacy analyses were performed on all participants except for 29 who were discontinued from one of the study sites. The Lyles (2007) study had more than 20% of patients who did not complete the trial (28% and 30% in the zoledronate and placebo groups respectively), and all participants were included in an ITT analysis.

Each study showed there were significantly fewer people with vertebral fractures in the zoledronate group compared with placebo, but there was significant heterogeneity between studies (I^2 = 75%; p = 0.05). A sensitivity analysis in the absence of the Lyles (2007) study, which had a higher potential for bias, and for which the use of concomitant medications may have diluted the vertebral fracture rate, showed significantly fewer people had a fracture in the zoledronate group RR=0.30 (95% CI: 0.24 to 0.38). This corresponds to a NNT of 13 (95%CI: 12 to 17) for a placebo group rate of 11%. The number of patients with clinically assessed vertebral fractures in both strata (7736 patients) RR 0.23 (95% CI 0.14 to 0.37). The NNT was 50 (95% CI 50 to 100) for a placebo group rate of 2%. There were significantly fewer people with nonvertebral fractures in the zoledronate group compared with placebo RR=0.75 (95% CI 0.66 to 0.85), NNT 50 (95% CI 25 to 100), for a control group rate of 10%. There were also fewer people with hip fractures in the zoledronate group compared with placebo RR 0.62 (95% CI 0.47 to 0.83), NNT 100 (95% CI 50 to >1000), for a control group rate of 2–3%.

4.2.1.4 Ibandronate

Ibandronate is a nitrogen-containing bisphosphonate. It can be taken orally (2.5 mg/day or 150 mg/month) or in iv injection (3 mg/3 months). The most recent good-quality SR has been written by NICE which includes an update of the literature up to June 2008 73. Three other meta-analysis were identified and were used for the discussion, although the methods of the SRs are of moderate/low quality [79-81]

The update search yielded 12 references (including studies by Cranney et al., Harris et al. and Sebba et al. [79-81]. None were included in our review (for excluded studies and reasons, please see Table 35 in annex 3)

The NICE SR included 8 studies reporting 5 trials. Only one compared ibandronate to placebo. Results are synthesized in Table 18 & Table 19. One study of low quality in 1952 patients showed that significantly fewer patients had a vertebral fracture when taking 2.5 mg ibandronic acid in comparison to placebo RR= 0.51 (95%CI 0.34 to 0.74) [82]. This corresponds to a number needed to treat of 25 (95%CI 17 to 50) for a control group rate of 7%. The same study showed that there was no significant difference between interventions in the number of patients with non-vertebral clinical osteoporotic fractures RR= 1.11 (95% CI 0.83 to 1.48).

4.2.2 Strontium ranelate

In vitro, strontium ranelate has been suggested to have a dual effect on bone; however, in vivo long term dosing of strontium ranelate in rats and monkeys resulted in increased bone formation but non-significant trends of bone resorption. In human studies (phase III trials), there is some evidence of increases in bone formation markers (serum bone-specific alkaline phosphatase and C-terminal propeptide of type I procollagen) and decreases in markers of bone resorption (serum C-telopeptide and urinary N-telopeptide cross links) from the third month of treatment (2 g of strontium ranelate daily) up to three years. Potential mechanisms of action include activation of calcium-sensing receptor or induction of cellular differentiation [83].

The search for systematic reviews returned 8 hits. One Cochrane review [83], 1 HTA report [84], and 1 NICE systematic review [73] were eligible systematic reviews. However, the formers had reviewed evidence up to March 2005 only. The NICE review was thus selected [73]. The update search yielded 24 papers, two of which were retained [85] [86]. These papers presented the results of the SOTI trial at 4 years [85] and the results of the TROPOS trial at 5 years [86]. For papers rejected and reason for rejection, please see Table 36 in appendix 3)

Results of the NICE review are synthesized in Table 18 & Table 19.

The NICE review included five papers describing three trials: the Treatment of Peripheral Osteoporosis–TROPOS study 87-89; the STRontium Administration. for Treatment of OSteoporosis–STRATOS study 90; the Spinal Osteoporosis Therapeutic Intervention–SOTI study 91. All three studies were in postmenopausal women; the mean time since menopause ranged from 18 to 28 years across the studies. TROPOS included women who had a mean femoral neck T-score of −3.13 (SD 0.6); SOTI reported that the women had a mean T-score of −2.8 (SD 0.8) measured at the femoral neck. In STRATOS the mean lumbar T-score for the strontium ranelate group was −3.86 (SD 1.1) and −3.97 (SD 0.95) for the placebo group.

In TROPOS, 54–55% of the participants had existing fractures at baseline, while all the women in the other two studies (STRATOS and SOTI) had fractures at baseline. Overall, all of the studies had potential for bias because all had missing data greater than 20%, however this was more significant for the STRATOS study: missing data were partly taken into account in the time-to-event analyses for TROPOS and SOTI.

There were significantly fewer people with vertebral fractures in the strontium ranelate group compared with placebo: RR 0.62 (95% CI 0.55 to 0.71). There were also significantly fewer women with nonvertebral fractures for strontium ranelate compared with placebo after 3 years of intervention: RR=0.86 (95% CI 0.74 to 0.99). One study recorded the incidence of hip fracture in all 4932 ITT patients 88. There was no significant difference between interventions after 3 years of intervention; RR 0.85 (95% CI 0.61 to 1.19). The same study reported no significant difference in incidence of wrist fractures between interventions after 3 years of intervention (RR 1.00 (95% CI 0.74 to 1.36), while for humerus fractures, there were significantly fewer women with a fracture in the strontium ranelate group (RR 0.53; 95% CI 0.29 to 0.94).

The 5-year results of the TROPOS study gave a RR for vertebral fractures of 0.76 (95% CI 0.65 to 0.88), which was less efficacious than that reported at 3 years 86. The RR for non vertebral fracture at 5 years was 0.85 (95% CI: 0.77 to 0.99), which was very similar to that reported at 3 years. The RR for hip fracture was 0.57 (95%CI: 0.33 to 0.97), which was not significantly different of that observed at 3 years, although it became marginally significant at 5 years. However, it is worth mentioning that the RR for hip fracture was assessed in a post-hoc analysis on a subset of patients who were at high risk of fractures (age ≥74 years with BMD T-score≤-2.4).

The 4-years follow-up of the individuals in the SOTI trial yielded a RR for vertebral totally similar to what had been observed at 3 years (RR: 0.67; 95%CI: 0.55, 0.81) [85].

4.2.3 Calcitonin

The search for SR returned 10 hits. However, a NICE review was the most recent high-quality SR 73 with an update up to June 2008. The search for more recent RCTs yielded 5 hits, none of which was retained (see Table 37 in appendix 3 for studies rejected and reason for rejection)

Results of the NICE review are synthesised in Table 18 & Table 19.

That meta-analysis including 753 women showed that significantly fewer had a vertebral fracture when taking 200 IU calcitonin nasal spray in comparison to placebo or no treatment: RR=0.65 (95% CI 0.48 to 0.88); this corresponds to a NNT of 13 (95% CI 8 to 50) for a control group rate of 7–26%. There was no heterogeneity between studies (I2 = 0%; p = 0.58). The study by Chesnut 92 had potential for bias because of high levels of missing data. In the absence of this study the CIs were too wide to determine if there was a difference between interventions. There was no significant risk reduction for the other fractures.

4.2.4 Selective Estrogen Receptor Modulators (SERM): Raloxifene

Raloxifene is an oral selective estrogen receptor modulator (SERM) that has estrogenic actions on bone and anti-estrogenic actions on the uterus and breast.

The search for SR yielded 2 relevant hits [73, 93]. However, the former meta-analysis was not based on a genuine SR. Therefore, the NICE review updated up to June 2008 was retained 73. The search for more recent RCTs yielded 18 hits, none of which were included. For studies excluded and exclusion reasons, please Table 38 in appendix 3.

Results of the NICE review are synthesised in Table 18 & Table 19.

Four reports describing four trials were included in the NICE review: the Multiple Outcomes of Raloxifene Evaluation–MORE [94; 95-97]. Participants in all four studies were postmenopausal and their mean age ranged from 61 to 68 years. In Lufkin (1998) all participants had at least one fracture at baseline [96]. Some participants in Ettinger (1999) had one or more fractures at baseline: 10–11% in study group 1 and 88–90% in study group 2 [94]. In Reginster (2003) about 25% of women had fractures at baseline [97], and Michalska (2004) did not report if any women had prior fractures [95]. All four studies were stated to be randomized, although details of the techniques used were provided in none, but one, study [96]. Allocation concealment was reported in none, but one, study [94]. All four studies used double-blind methodology, although it was not made clear which of the investigators were blinded, except for Reginster (2003), which reported that the radiologist assessing the fractures was blinded to treatment allocation [97]. Drop-out rates were high, ranging from 3% [95] to 30% [97]. Significantly fewer patients had vertebral fractures in the raloxifene group compared with placebo RR=0.64 (95% CI 0.54 to 0.78). This corresponds to a NNT of 25 (95% CI 20 to 50) for a control group rate range of 4–29%. There was no significant difference in the number of patients with nonvertebral fractures for raloxifene compared with placebo RR=0.91 (95% CI 0.78 to 1.05), for a control group rate range of 7–9%. There was no significant difference in the number of patients with hip fractures for raloxifene compared with placebo RR=1.12 (95% CI 0.64 to 1.94), for a control group rate of 0.7%.

4.2.5 Denosumab

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density. One systematic review was retrieved [98]. However, it didn't integrate the results of more recent and most important RCT [99]. Therefore we carried out a systematic review of RCTs on denosumab.

The search for RCTs yielded 33 hits, only one of which met the inclusion criteria [99]. Fracture rates were also presented in two other RCTs which were excluded. The first one was a Phase II trial not powered to assess fracture and where fractures where considered side effects [100]. The second one was carried out in patients receiving adjuvant aromatase inhibitors [101]. For other studies excluded and reasons for exclusion, please see Table 39.

The results of the study by Cummings et al. are summarized in Table 18 and Table 19. The effect on new vertebral fracture after 36 months of treatment was important, for both morphometric or clinical fractures. The reduction of nonvertebral fractures was much less important (between 5% and 33%), although the rates of non-vertebral fractures in the control group was similar to the rate of vertebral fracture. Thus the differential effect on vertebral vs. nonvertebral fracture could be a real therapeutic difference. The higher increase of BMD by denosumab at the spine relatively to the hip site is a consistent observation.

Interaction for the presence of a prior fracture was not tested. 18% did not complete the study: if the defaulting was balanced among trial groups was not reported.

4.3 DISCUSSION

4.3.1 Influence of fracture site

All the osteoporosis treatment reduced the risk of vertebral fractures. This risk reduction was not significantly different between treatments, except for zoledronate which reduced the risk by 70% (95%CI: 62%, 76%). In contrast, the prevention of nonvertebral fractures was demonstrated only for alendronate, risedronate, zoledronate, strontium ranelate, and denosumab and this risk reduction was less important than for vertebral fractures. Here again, the zoledronate displayed a greater risk reduction of nonvertebral fracture than other bisphosphonates. The greater effect of zoledronate may be due to its high binding affinity to bone mineral but also to the intravenous route of administration with less problem of absorption and adherence. However, this result was based on only 2 studies including 63% to 100% of patients with a prior fracture. It would be of interest to assess the effect of zoledronate in primary prevention.

What factors could explain a less protective effect in vertebral and in nonvertebral sites? Three hypotheses can be proposed: nonvertebral fractures being less frequent, studies were not powered to detect them with sufficient accuracy; non-clinical vertebral fractures being assessed on the basis of moprhometry, the diagnosis process is more prone to assessment error than for other fracture sites; treatment have truly a different effect on different bone sites. Let's examine how evidence relates to these 3 hypotheses in a recent trial on denosumab [99]. That study enrolled 7868 women between the ages of 60 and 90 years who had a bone mineral density T score of less than −2.5 but not less than −4.0 at the lumbar spine or total hip. The HR in all new vertebral fractures and in clinical new vertebral fractures were similar (0.32 and 0.31, respectively). Thus the hypothesis of a differential diagnosis bias towards morphometric fractures does not hold. The HR for nonvertebral fractures was much different (0.80) although the incidence rate was the same as for new vertebral fractures (8.0 and 7.2, respectively). Subsequently, the statistical power was the same for both nonvertebral and vertebral fractures. Lastly, changes in BMD were measured in a subset of 441 participants. At 36 months, the spine BMD had increased by nearly 10% whereas this amounted to only 5% in hip BMD.

On the basis of this evidence, it can be inferred that denosumab had a different effect on BMD in vertebra and hip, and that difference could explain, at least partly, the difference in the protective effect against incident fractures at different sites. Also falls are not influenced by pharmacological treatments which may explain why fractures related to falls (hip, humerus, wrist) are less reduced by treatments. To review systematically the published studies to assess if these findings are consistent would be extremely interesting. However, this task was beyond the scope of our project.

4.3.2 Influence of baseline risk

As can be seen in Table 18, the eligibility criteria for most clinical trials of osteoporosis therapy have been based upon the presence of a prior fracture and/or reduced BMD. The proportion of patients with prior fracture was high in most trials. The presence of prior fractures might modify treatment efficacy, as suggested by some post-hoc analysis. For instance, in the MORE study, raloxifene decreased the risk of non-vertebral fractures only in patients with moderate or severe vertebral fractures at baseline [94, 102]. It is therefore important to ascertain how anti-osteoporotic drugs are effective in patients without prior fractures (called hereafter primary prevention).

The effort to disentangle the treatment effect in patients with or without previous fragility fractures has been carried out in meta-analyses on alendronate [103], etidronate [104], risedronate [105]. The authors found no statistically significant results for primary prevention of fragility fractures with these 3 drugs, with the exception of vertebral fractures for alendronate. It should be noted that disentangling primary and secondary prevention in existing trials was a difficult process based on a number of assumptions[r], with resulting uncertainty in the comparison of patients with or without previous fractures at baseline. Another meta-analysis focused on treatment efficacy in primary prevention [25]. It confirmed that for postmenopausal women in primary prevention, a protective effect of osteoporotic drugs could be observed only for vertebral fractures. Moreover, results for bisphosphonates were statistically significant only when alternative pooling methods were used, and even then the statistical significance was marginal (Peto OR=0.84 (95% CI: 0.72, 0.98); fixed-effects Mantel-Haenszel with inverse sample size continuity correction RR=0.82 (95%CI: 0.74, 0.99). The authors of the meta-analysis emphasized the paucity of data in primary prevention [25]. To our knowledge, only one study was specifically designed to address the issue of a differential therapeutic effect between patients with or without previous vertebral fractures at baseline [106]. The authors of that study concluded that the effect of alendronate on fracture prevention was similar in both groups of patients. However, the FIT study presented shortcomings as regards that group comparison. First, the 2 groups also differed on parameters other than the presence of a previous vertebral fracture. The patients without vertebral fracture had a significantly lower BMD at the hip and the spine although being significantly younger, i.e. BMD-defined osteoporosis was more prevalent in the group without baseline fracture [107]. These patients also reported more often antecedents of parental fracture. In spite of these elements, the fracture risk in the placebo arm was much higher in the group with baseline fracture. Second, the statistical power to detect significant differences in fracture reductions between the two subgroups (with and without existing vertebral fracture) was limited [107]. Another trial on risedronate reported results stratified by vertebral fracture at baseline [108]. The protective effect of risedronate on hip fracture was observed only in secondary prevention [108].

r A hierarchy was used to define primary versus secondary prevention according to the information available in the Cochrane reviews. If the inclusion criteria restricted the population to women whose bone density was at least 2 SD values below the peak bone mass, or the inclusion criteria restricted the population to women who had experienced previous vertebral compression fractures, then the trial was considered a secondary prevention study. If such inclusion criteria were not provided, then the baseline statistics were considered as follows: (a) the trial was considered as primary prevention if the average T-score (and SD) was such that it included women whose bone density was within 2 SD of the mean, or if the prevalence of vertebral fracture at baseline was less than 20%; and (b) when these data were not available, the trial was considered secondary prevention if the average age was above 62 years.

Other factors than a previous fracture might interact with treatment efficacy. For instance, in the TROPOS study, post-hoc analyses suggested that strontium ranelate significantly decreased the risk of hip fracture only in high-risk subgroup defined on age and BMD (women aged ≥74 years and with femoral neck BMD T score<-2.4 SD) [88s]. Moreover, in clinical practice, computer-based algorithms combining various risk factors, such as FRAX®, are increasingly used to determine the fracture probability of patients. Such algorithms allow identifying high-risk patients. However, it is unclear how treatments which efficacy has been tested in populations with low BMD and/or prior fracture will behave in patients without prior fracture but identified as high-risk with such composite algorithms. Evidence on this point is contradictory. On the one hand, secondary analysis of trials on bazedoxifene [109] and clodronate [110] reported that the treatment efficacy of these 2 drugs increased in patients with 10-year probabilities of a major osteoporotic fracture at baseline ≥16%-20%. In contrast, there was no significant interaction of treatment efficacy with 10-year fracture probability for raloxifene [93] and strontium ranelate [111]. For raloxifene, treatment efficacy even decreased with increasing fracture probability, and at younger ages treatment efficacy surprisingly increased with decreasing fracture probability [93].

Worth mentioning, in both studies on raloxifene and strontium ranelate, the mean baseline 10-years probability of osteoporotic fracture according to FRAX® was high (>20%) and the proportion of patients with a previous fracture of any kind was important (64.4% and 62.7%, respectively). In comparison, in the studies on bazedoxifene and clodronate, 32% and 22% patients had a prior fracture [109, 110]. It can be hypothesized that the presence of prior fracture modifies the importance of other risk factors on treatment outcome. An indication of this can be found in the FIT trial. Among women with existing vertebral fracture, reduction in clinical fracture risk with alendronate did not depend on baseline BMD [106, 112]. However, in the group without prior vertebral fracture, the reduction in risk of clinical fractures with alendronate depended on the level of baseline BMD [113].

There was much less evidence of the antifracture efficacy of the drugs in male and glucocorticoid-induced osteoporosis than in postmenopausal women [114]. RCTs have shown that, only alendronate prevents vertebral fractures in men with osteoporosis, and that alendronate and risedronate can prevent vertebral fractures in patients receiving glucocorticoid treatment [114]. Zoledronate seems to be non-inferior to risedronate in preventing fractures in glucocorticoid-induced osteoporosis but generates more adverse events [115].

In conclusion, there is to date contradictory evidence as regards the modifying effect of baseline risk on therapeutic efficacy. In particular, the treatment efficacy in high-risk patient populations without prior fracture has been poorly investigated, i.e. the efficacy of primary prevention is not clearly demonstrated. Another important area of uncertainty concerns how various combinations of risk factors, at constant fracture risk level, can impact on treatment effect.

4.3.3 Influence of treatment duration

The optimal duration of therapy remains uncertain (see Table 41 in appendix). On the one hand, long-term use could generate side-effects. In the case of bisphosphonates, retrospective studies and case reports suggest that long-term therapy may result in the suppression of bone turnover and confer a predisposition to increase bone fragility, with an increased risk of atypical femur fractures, i.e. sub-trochanteric or diaphyseal femur [116]. The occurrence of this problem is very rare, and the increased risk in long-term users of bisphosphonates has not been confirmed to date according to Black et al.[117]. However, it is worth mentioning that the analysis of these authors was based on only 3 trials, two of which were middle-term (3 years to 4.5 years of daily alendronate in the FIT trial; 3 years of yearly Zoledronate in the HORIZON trial).

s Worth mentioning 62.7% (4000/6374) of patients had a previous fracture in the TROPOS study.

In the FLEX trial (an extension of the FIT trial) assessing the effect of alendronate over 10 years, all the enrolled women had received alendronate during 3 years in the FIT trial. Therefore, side-effects of long-term therapy are still poorly known.

Prospective studies are needed to estimate the long-term risk of side effects associated with anti-osteoporosis drugs [118]. Meanwhile, the prolonged use of bisphosphonates should be balanced against potential risk of harm until long-term robust safety data are available [119].

On the other hand, the therapeutic effect could be long-lasting after drug discontinuation. Pharmacokinetic studies show that bisphosphonates remain in bone matrix for many years. This would allow (temporary) drug holiday providing some relief to patients with likely improvement in cost-effectiveness [120]. According to Watts et al., patients at mild risk might stop treatment after 5 yr and remain off as longas bone mineral density is stable and no fractures occur. Higher risk patients should be treated for 10 yr, have a holiday of no more than a year or two, and perhaps be on a nonbisphosphonate treatment during that time [120].The most prominent data source is the FLEX trial [121]. This RCT assessed the effects of continuing or stopping alendronate after 5 years of treatment. Discontinuation did not increase the risk of nonvertebral fractures or x-ray detected vertebral fractures over the next 5 years, but the risk of clinically diagnosed vertebral fractures was significantly increased among those who discontinued. Although the power for assessing differences in fracture rates was weak in that trial, this was consistent with the observation that in the discontinuation group BMD remained at or above baseline values 10 years earlier and bone turnover was still somewhat reduced [121].

4.3.4 Influence of treatment type

All the accepted osteoporosis treatment reduced the risk of vertebral fractures. This risk reduction was not significantly different between treatments, except for annual intravenous injection of zoledronate or biannual subcutaneous injection of denosumab which both reduced the risk by around 70% over a 3-year treatment period. In contrast, the prevention of nonvertebral fractures was demonstrated only for alendronate, risedronate, zoledronate, strontium ranelate, and denosumab, and this effect was consistently smaller than for vertebral fractures. Here again, a greater risk reduction of nonvertebral fracture was apparent for zoledronate (2 studies) and denosumab (1 study) in comparison to the other drugs. Studies on alendronate, risedronate, zoledronate, and denosumab reported a protective effect on hip fracture. However, the absolute risk reduction for this fracture site was very small and the confidence interval around the NNT included huge numbers of patients. The confidence intervals were overlapping.

Worth mentioning, there was very few head-to-head trials carried out. Therefore, there is no direct evidence so far of a clear higher benefit linked to the utilization of one specific drug in comparison to the others. A network meta-analysis comparing zoledronate (1 study), alendronate (3), ibandronate (1), risedronate (2), and etidronate (1) in terms of fractures with a follow-up of 3 years reported a 79% probability that zoledronate shows the greatest reduction in vertebral fractures of all bisphophonates compared [122]. Whether this is due to a true greater therapeutic effect of zoledronate or to the fact that intravenous injection eliminates the problem of poor compliance observed with oral bisphosphonates is unknown [122].

4.3.5 Safety issues

The safety profile of osteoporosis drugs has been considered satisfactory up to now, although they are associated with a few very rare serious adverse reactions. However, side-effects of long-term therapy are still poorly known.

Bisphosphonates can generate upper gastro-intestinal symptoms which are generally mild. They include acid reflux, esophageal irritation, nausea, vomiting and heartburn. However, serious problems are seen in approximately in 1 of 10,000 alendronate users [123]. Gastroduodenal perforation, ulcers, and bleeding occur in 3.4 per 1000 person-year (95%CI: 1.8-5.7; absolute risk increase: 2.3 per 1000 person-years) [124]. In a nested case-control study of a cohort study (n=1 million) in the UK reported that the incidence of oesophageal cancer was increased in people with one or more previous prescriptions for oral bisphosphonates compared with those with no such prescriptions (relative risk 1.30, 95% confidence interval 1.02 to1.66; P=0.02) [125]. Risk of oesophageal cancer did not differ significantly by bisphosphonate type, and risk in those with 10 or more bisphosphonate prescriptions did not vary by age, sex, smoking, alcohol intake, or body mass index; by diagnosis of osteoporosis, fracture, or upper gastrointestinal disease; or by prescription of acid suppressants, non-steroidal anti-inflammatory drugs, or corticosteroids. Cancers of the stomach and colorectum were not associated with prescription of bisphosphonate [125]. Other researchers, although using the same data source, reported no association between oesophageal cancer and bisphosphonate use [126].

Bisphosphonates can also generate severe musculoskeletal pain. The FDA issued a safety alert on this problem in early 2008. The pain may occur within days, months, or years after drug initiation and require discontinuation of treatment. These symptoms are different from the acute response that may accompany initial exposure to bisphosphonates and which resolve with continued use. Intravenous administration of zoledronate causes acute phase reactions in up to 30% to 40% of patients receiving their first dose. These reactions are characterized by fever and muscle aches lasting several days..

Osteonecrosis of the jaw (ONJ) is a serious adverse event observed with bisphosphonates and denosumab. It is however considered a rare event and age ≥60 years, female sex, and previous invasive dental treatment were the most common characteristics of those who developed ONJ [127]. Another systematic review reported consistent factors [128]. In that review the mean age was 69.4 years, 87.3% were female, and 83.3% were receiving oral, but not intravenous, bisphosphonates; of the 63 patients reporting dental care information, 88.9% had a dental procedure before the onset of osteonecrosis of the jaw. Of all cases providing medical information, 71% were taking at least one medication that affects bone turnover in addition to the bisphosphonate, and 81.3% reported additional underlying health conditions. This adverse event has mainly been observed in patients with cancer. For instance, in a meta-analysis on incidence of bisphosphonates induced jaw osteonecrosis in adjuvant treatment of breast cancer, ONJ occurred in 0.24% patients and mainly in patients receiving zoledronate IV (incidence: 0.33%) [129]. Treatment with zoledronate was significantly associated to the occurrence of osteonecrosis of the jaw (OR = 3.23, 95% CI = 1.7-8) compared with no use. Figures from one cancer centre were however higher: osteonecrosis of the jaw occurred in 1.8% and 1.3% of patients in the denosumab and zoledronate groups during the primary treatment phase of cancerous patients in one centre. The incidence after approximately 4 additional months of denosumab treatment was 2.2% [130].

Subtrochanteric or shaft fractures of the femur are serious but rare adverse events associated with bisphosphonate use. For instance, In a population-based, nested case-control study to explore the association between bisphosphonate use and fractures in a cohort of women aged 68 years or older from Ontario, Canada, including 52,595 women with at least 5 years of bisphosphonate therapy, a subtrochanteric or femoral shaft fracture occurred in 71 (0.13%) during the subsequent year and 117 (0.22%) within 2 years [131]. Another population-based study in Sweden reported that the increase in

absolute risk was 5 cases per 10,000 patient-years (95% CI, 4 to 7) [132]. The duration of use influenced the risk (odds ratio per 100 daily doses, 1.3; 95% CI, 1.1 to 1.6).

After drug withdrawal, the risk diminished by 70% per year since the last use (odds ratio, 0.28; 95% CI, 0.21 to 0.38) [132]. The European Medicine Agency (EMA) issued a safety alert on this problem in April 2011.

Although bisphopshonates are generally considered safe, concerns have been raised about an increase risk of serious atrial fibrillation. This serious adverse event has been detected for the first time for zoledronate [133]. A meta-analysis including 4 RCTs (26126 postmenopausal women) revealed that serious atrial fibrillation occurred more frequently in the bisphosphonate group compared to the placebo group (RR 1.5; 95% CI: 1.17 to 2.0; p=0.002) [133]. That review also included 3 population based case-control studies and found that 2 out of 3 studies indicated a statistically significant increase in the risk of atrial fibrillation with bisphosphonate therapy. Subsequently, the US FDA issued a cautionary advisory and is conducting an ongoing safety review. Other meta-analyses, including RCTs on ibandronate and on risedronate [134] or combining observational studies [135] reported a trend towards an increase risk of atrial fibrillation, although not statistically significant. Worth mentioning, all the meta-analyses included a restricted number of RCTs on bisphosphonates because this adverse event was measured in a minority of studies. None were designed or powered to evaluate arrhythmia endpoints. Heterogeneity of the existing evidence, as well as paucity of information on some of the agents, precludes any definitive conclusions on the exact nature of the risk [135]. There is no enough information to date to determine if the risk of fibrillation is linked to specific drugs, or specific patient characteristics. Until definitive evidence is available, clinicians will continue to have to make clinical judgments based on the available and often inconsistent evidence to date.

Denosumab has numerous adverse effects. In placebo-controlled trials, this monoclonal antibody was associated with a higher incidence of deep-seated infections such as endocarditis, cancer, and skin rash. More data are needed on the risk of pancreatitis, long-term bone disorders (atypical fractures, delayed fracture healing, osteonecrosis of the jaw [136]), hypocalcaemia and cataracts, all of which were reported in clinical trials. On the other hand, there is no evidence that denosumab is more effective than other molecules, e.g. alendronate. Therefore, the risk-benefit balance of denosumab seems to date less favorable than alendronate and should be used with caution until more data on its safety are issued [137].

Given these safety issues, some of which are not yet clarified, osteoporotic drugs should be used in patients with the highest risk of fragility fractures in order to ensure the best possible risk-benefit balance. Such balance should always be clearly explained to the patients and a treatment decision taken after duly informed consent.

For instance, in one pivotal trial on zoledronate during 36 months [78], the absolute risk reductions in hip fractures and clinical vertebral fractures were 1.1% and 1.9%, respectively. However, the absolute risk increase in serious atrial fibrillation was 0.8%, i.e. for nearly each hip fracture prevented the treatment would also generate a case of serious atrial fibrillation.

5 GUIDELINES FOR OSTEOPOROSIS MANAGEMENT

5.1 METHODS

Numerous clinical practice guidelines are available to assist clinicians in the management of osteoporosis. We took a convenient sample of such guidelines to identify strong and consistent recommendations by professional groups involved in osteoporosis management worldwide.

5.2 RESULTS

We reported recommendations for screening by BMD measurement (Table 20), for identification of patients eligible for a pharmaceutical treatment (Table 21), and for treatment monitoring (Table 22). One recommendation quite consistent throughout the guidelines was that a prior fragility fracture, particularly a vertebral fracture, was a strong signal for initiating a treatment. In such case, measuring BMD was not considered necessary, albeit potentially useful to assess severity and as a baseline measure for monitoring treatment. In the absence of a prior fragility fracture, the vast majority of guidelines recommended that BMD measurement should be reserved to patients presenting risk factors for fragility fractures, with the notable exception of the USA where the recommendation to screen all women ≥ 65 years and men ≥70 years, regardless of clinical risk factors, was made. In the UK, the NOGG guideline proposed different thresholds of fracture risk, in function of age, for deciding if a DXA was necessary [138]. For instance, in women aged 60 years with no prior fracture and presenting one risk factor, measuring BMD would be recommended only if her 10-year fracture risk is between 7% and 10 %. Below that limit, no treatment would be recommended, and above 12% a treatment could be started without BMD measurement (see Figure 7 for an illustration).

Despite the recommendation of assessing the risk fracture profile of the patient as a first step, the decision to treat him/her still depended essentially of the results of the BMD measure (treatment recommended if the T-score<-2.5 SD). The algorithms from the Netherlands or Australia were quite illustrative of this. Only the NOGG guideline proposed to start a treatment on the basis of a risk which can be assessed without BMD above a threshold. This threshold is in fact the fracture risk observed in individuals with a prior fracture [138]. For instance, in women aged 60 years with no prior fracture and presenting one risk factor, and in whom the BMD T-score is -3, should be treated (10-year fracture risk=18%). This approach is underpinned by cost-effectiveness analysis with generic alendronate as the intervention.

For treatment monitoring, some guidelines recommended repeating DXA exams every year, or at least after the first year of treatment, but the supportive evidence was generally weak.

5.3 DISCUSSION

The shift towards basing the detection and clinical management of osteoporosis on absolute fracture risk is well reflected in recent clinical guidelines, except in the USA. In the latter, universal bone densitometry combined with alendronate therapy for those diagnosed with osteoporosis is still considered highly cost-effective for women aged ≥65 years and for men aged ≥80 years [139]. In spite of that shift, in most guidelines, risk factors were used as a pre-screening tool to define who should undergo a DXA, and the BMD results remained the most important criterion to recommend an osteoporosis treatment (excepted in the case of a prior fragility fracture which is considered a sufficient criterion on its own to start a treatment). Such strategy is based on the principle that the presence of risk factors improves fracture prediction. Is this a valid strategy? First, we have already discussed that the fracture prediction is not that much increased when risk factors and BMD results are combined [62].

For instance, in a 75 year old Belgian woman with rheumatoid arthritis and no other risk factor (BMI=21.2), the 10-year risk of major osteoporotic fractures is 20% (12% for hip fracture). Even a BMD T-score=-3.0 will have a very limited value on treatment decision: the 10-year risk will be 21% for major osteoporotic fractures (11% for hip fracture). This is also true for the detection of prevalent vertebral fractures [140]. Second, the positive predictive value of a BMD T-score<-2.5 will increase if the test is carried over in a high-risk population, i.e. in a population where the incidence of fragility fracture is higher than in the general population. This is a positive point as treatments will be more given to patients with genuine higher risk of fracture, i.e. in patients who will get a greater benefit from the treatment. However, it should be noted that this improvement is also limited given the low sensitivity of BMD. Even in very high risk patients, the predictive value of a positive test will remain. Moreover, the proportion of false negative cases will also concomitantly increase, i.e. the predictive value of a negative test will decrease. For instance, it can be computed that in the Rotterdam study, if the incidence of new fractures would have been 30% instead of 14.9%, the negative predictive value would have been 75% (instead of 88%). Thus 1 individual over 4 excluded from treatment on the basis of the BMD score would indeed suffer a fracture in the 6.8 years of follow-up of that study. It is therefore surprising that in the algorithms from the Netherlands and from Australia, a BMD T-score>-1.0, even in patients with a prior non-vertebral fractures in the Netherlands, will lead to a decision of no treatment.

NOGG has proposed an alternative approach where the decision for BMD or for treatment is truly based on the absolute 10-years fracture risk. If the absolute risk is already high, there is no need of a BMD, and treatment is recommended. This strategy could be sound under two assumptions. The first one is that for a given level of absolute fracture, whatever the contributing risk factors are, the treatment will provide the same level of fracture protection. There is to date contradictory evidence about the validity of this assumption, as discussed in section 4.3.2. The second one is that a high absolute risk of fracture as assessed by the presence of risk factors also identify individuals with prevalent vertebral fractures [140] and/or low BMD [70]. The evidence supporting this assumption is still scarce, and the limits of this case-finding strategy poorly known.

Regarding treatment monitoring by regular DXA proposed in some guidelines, the supporting evidence is also contradictory. Analyses of clinical trials show an inconsistent relationship between increased spinal BMD and a decreased risk of vertebral fracture. Increased BMD accounts for less than 25% of the overall reduction in fracture risk in most instances [141]. The early increase in BMD is largely determined by the pre-treatment remodelling rates. When the pre-treatment remodelling rate is low, the increase in BMD is small but the fracture risk reduction is not different to that in patients with high baseline remodelling and a greater BMD increase [142]. Another problem for individual follow-up is that the variation in BMD due to treatment effects is much less than the within-person variation on treatment [143]. More evidence is thus needed before deciding whether BMD should be used for monitoring treatment effects at an individual level.

Table 20: Recommendations for screening by BMD measurement

COUNTRY	Reference	SCREENING BY BMD
USA-ACPM 2009 USA-NOF 2010 USA-AACE 2010	[53] [144] [123]	- In all women ≥ 65 years and men ≥70 years, regardless of clinical risk factors - In postmenopausal women and men age 50-69, when there is concern based on their risk factor profile (at least one major or 2 minor risk factors). - In individuals who have had a fracture ≥ 50 years, to determine degree of disease severity.
USA- USPSTF 2011	[145]	- In all women aged ≥ 65 years - In women <65 years whose fracture risk is equal to or greater than that of a 65-year-old white woman who has no additional risk factors
Canada-2010	[146]	- In all individuals ≥ 65 years - In individuals 50-64 years with: -Fragility fracture after age 40 -Prolonged use of glucocorticoids or other high risk medications -Parental hip fracture -Vertebral fracture or osteopenia identified on radiography -High alcohol intake or current smoking -Low body weight (< 60 kg) or major weight loss (> 10% of body weight at age 25) -Other disorders strongly associated with osteoporosis -In individuals <50 years with: -Fragility fractures -Use of high-risk medications -Hypogonadism -Malabsorption syndromes -Chronic inflammatory conditions -Primary hyperparathyroidism -Other disorders strongly associated with rapid bone loss or fractures
European guidance-2008	[1]	-No universally accepted policy for population screening in Europe to identify patients with osteoporosis or those at high risk of fracture. -No widespread population-based screening with BMD recommended -BMD recommended in individuals who have a high fracture probability, provided that it will influence the management decision -Biomarkers of bone turnover: evidence is lacking
Australia-NHMRC2010	[147]	-BMD in the presence of major risk factors -BMD recommended but not essential to start treatment in case of any low trauma fracture
UK-NOGG 2009	[138]	-Women with a prior fragility fracture should be considered for treatment without the need for further risk assessment although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women (see Figure 7)

		- Men and women with probabilities above the lower assessment threshold but below the upper assessment threshold can be tested with BMD using DXA -Men and women with probabilities above the interventions threshold should be considered for treatment without BMD
France-HAS 2006	[148]	-Individuals with a history of fragility fracture -Individuals likely to suffer a secondary osteoporosis -Postmenopausal women with risk factors
The Netherlands-CBO 2011	[149]	-Individuals ≥ 50 years with recent nonvertebral fracture (including hip fracture) -Individuals with suspected secondary osteoporosis -Individuals ≥60 years with 4 risk factors -Not necessary in individuals ≥ 50 years with prior vertebral fractures

NOF: National Osteoporosis Foundation; USPSTF: US Preventive Services Task Force ; NHMRC: National Health and Medical Research Council; NOGG: National Osteoporosis Guideline Group; AACE: American Association of Clinical Endocrinologists; HAS: Haute Autorité de Santé, CBO: Kwaliteitsinstituut voor de gezondheidszorg; BBC: Belgian Bone Club

Table 21: Recommendations for individuals eligible for therapeutical treatment of osteoporosis

COUNTRY	Reference	TREATMENT
USA-ACPM 2009 USA-NOF 2010 USA-AACE 2010	[53] [144] [123]	- Hip or vertebral (clinical or morphometric) fractures. - BMD T-scores ≤ -2.5 at the femoral neck or spine by DXA, after appropriate evaluation. - In postmenopausal women and men age 50 and older with low bone mass (T-score between -1.0 and -2.5, osteopenia) at the femoral neck or spine and a 10-year hip fracture probability ≥ 3% or a 10-year major osteoporosis-related fracture probability ≥ 20% based on the US-adapted FRAX®.[t]
Canada-2010	[146]	- In high risk individuals (10-year fracture risk > 20% or prior fragility fracture of hip or spine or > 1 fragility fracture) - In individuals with moderate risk factor (10-year fracture risk 10%–20%), the following factors may warrant therapy: -Additional vertebral fracture(s) (by vertebral fracture assessment or lateral spine radiograph) -Previous wrist fracture in individuals aged > 65 and those with T-score ≤–2.5 -Lumbar spine T-score << femoral neck T-score -Rapid bone loss -Men undergoing androgen-deprivation therapy for prostate cancer

[t] The therapeutic thresholds proposed in this Guide are for clinical guidance only and are not rules. All treatment decisions require clinical judgment and consideration of individual patient factors, including patient preferences, comorbidities, risk factors not captured in the FRAX model (e.g., frailty, falls), recent decline in bone density and other sources of possible under- or over-estimation of fracture risk by FRAX®. The therapeutic thresholds do not preclude clinicians or patients from considering intervention strategies for those who do not have osteoporosis by BMD (WHO diagnostic criterion of T-score ≤ -2.5), do not meet the cut points after FRAX®, or are not at high enough risk of fracture despite low BMD. Conversely, these recommendations should not mandate treatment, particularly in patients with osteopenia. Decisions to treat must still be made on a case-by-case basis.

		-Women undergoing aromatase inhibitor therapy for breast cancer -Long-term or repeated use of systemic glucocorticoids (oral or parenteral) not meeting conventional criteria for recent prolonged use -Recurrent falls (≥2 in the past 12 mo) -Other disorders strongly associated with osteoporosis, rapid bone loss or fractures
European guidance-2008	[1]	- Prior fragility fracture -Women ≥ 65 years with risk factors -Women <65 years with (secondary causes of osteoporosis OR cigarette smoking OR alcohol>3 units daily) AND T-score<-2.5 -Women <65 years with glucocorticoids AND T-score<-2 -Women <65 years with a parental history of hip fracture AND T-score<-1
Australia-NHMRC2010	[147]	-Individuals with BMD≤-2.5 -Individuals with -2.5<BMD<-1.0 AND low trauma fracture
UK-NICE 2011	[150]	Primary prevention: -Women ≥70 years with an independent clinical risk factor for fracture OR an indicator of low BMD and who are confirmed to have osteoporosis (T-score ≤ −2.5 SD). -Women ≥ 75 years with two or more independent clinical risk factors for fracture or indicators of low BMD, a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible. -Women aged 65–69 years with an independent clinical risk factor for fracture and who are confirmed to have osteoporosis - Postmenopausal women younger than 65 years who have an independent clinical risk factor for fracture and at least one additional indicator of low BMD and who are confirmed to have osteoporosis Secondary prevention: -Post-menopausal women with confirmed osteoporosis (T-score ≤ −2.5 SD)
UK-NOGG 2009	[138]	-Men and women with probabilities above the intervention threshold should be considered for treatment. The intervention threshold, based on the 10-year probability of fracture, varies with age (see Figure 7)
The Netherlands-CBO 2011	[149]	-Individuals with prior vertebral fracture -Individuals ≥50 years with a BMD T-score<-2.5 -Individuals ≥60 years with a BMD T-score between -1.0 and -2.5 without prevalent vertebral fracture but with risk factors (recent fracture and T-score<-2; conditions favouring a secondary osteoporosis; recent and repeated falls) consider treatment

NOF: National Osteoporosis Foundation; USPSTF: US Preventive Services Task Force ; NHMRC: National Health and Medical Research Council; NOGG: National Osteoporosis Guideline Group; AACE: American Association of Clinical Endocrinologists; HAS: Haute Autorité de Santé, CBO: Kwaliteitsinstituut voor de gezondheidszorg; BBC: Belgian Bone Club

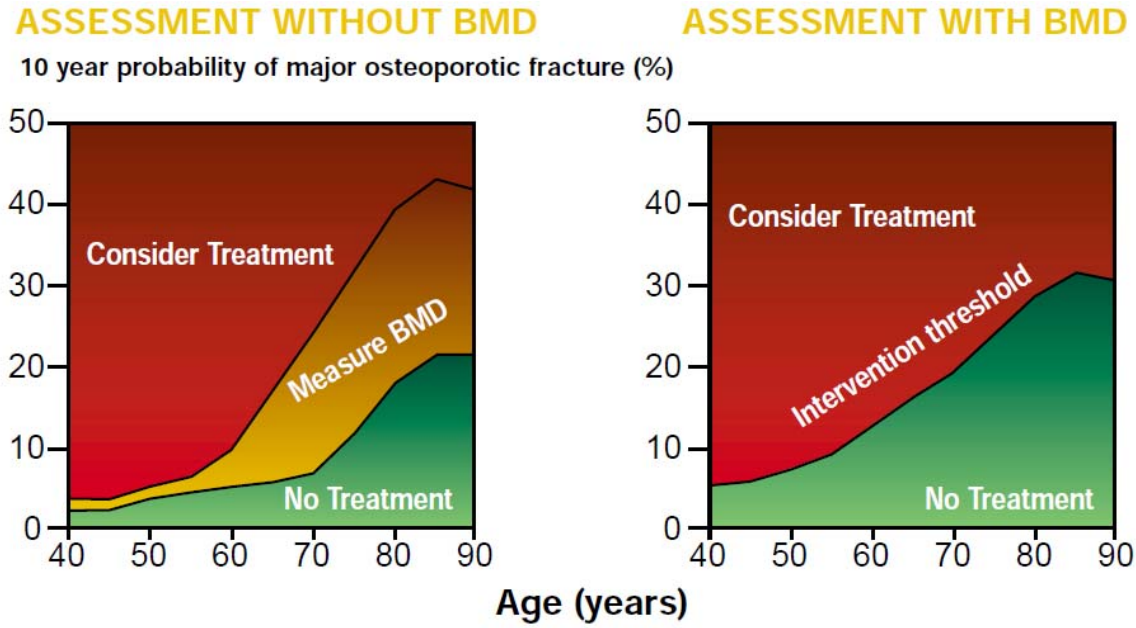
Table 22: Recommendations for treatment monitoring

COUNTRY	Reference	TREATMENT MONITORING
USA-ACPM 2009 USA-NOF 2010 USA-AACE 2010	[53] [144] [123]	For patients on pharmacotherapy, it is typically performed two years after initiating therapy and every two years thereafter; however, more frequent testing may be warranted in certain clinical situations. Obtain a baseline DXA, and repeat DXA every 1 to 2 years until findings are stable. Continue with follow-up DXA every 2 years or at a less frequent interval (AACE)
European guidance-2008	[1]	BMD not recommended for treatment with inhibitors of bone resorption, unclear for bone-forming agents[u] Biochemical markers: no specific recommendation
Australia-NHMRC2010	[147]	BMD considered at 1 year if there is a change in anti-osteoporotic treatment or the patient is on steroids (>7.5 mg/day x 3 months) or has other secondary osteoporosis. Repeat BMD when likely to be approaching T=–2.5. Average decline in T-score is 0.1/year
UK-NOGG 2009	[138]	Further research needed
Belgium-BBC 2010	[157]	-In patients treated with bisphosphonates or strontium ranelate, regular assessment (yearly) of BMD is deemed appropriate -For RAL-treated patients, biochemical markers of bone turnover, brought back to normal values for premenopausal women, may be a better indication of efficacy. - For patients with teriparatide, further research is needed.
The Netherlands-CBO 2011	[149]	-DXA after 2-3 years in case of intolerance, poor compliance, new nonvertebral fracture, suspicion of new vertebral fracture -DXA after 5 years (2 years for teriparatide) for assessing the fracture risk

NOF: National Osteoporosis Foundation; USPSTF: US Preventive Services Task Force ; NHMRC: National Health and Medical Research Council; NOGG: National Osteoporosis Guideline Group; AACE: American Association of Clinical Endocrinologists; HAS: Haute Autorité de Santé, CBO: Kwaliteitsinstituut voor de gezondheidszorg; BBC: Belgian Bone Club

[u] Whereas 16% of vertebral fracture risk reduction after treatment with alendronate was attributed to an increase in BMD at the lumbar spine, larger increases in BMD at both the spine and hip, observed with alendronate were associated with greater reductions in the risk of non-vertebral fractures [151]. However, for patients treated with risedronate or raloxifene, changes in BMD predict even more poorly the degree of reduction in vertebral (raloxifene) or non-vertebral (risedronate) fractures. Twelve percent and 7% of the effects of risedronate to reduce non-vertebral fractures were attributed to changes in the spine and femoral neck BMD respectively. For raloxifene, the percentage changes in BMD accounted for 4% of the observed vertebral fracture risk reduction [152, 153].
For bone-forming agents, increases in BMD account for approximately one-third of the vertebral fracture risk reduction with teriparatide [154]. Preliminary data suggest that a larger proportion (up to 74%) of the anti-fracture efficacy of strontium ranelate might be explained by changes in total hip or femoral neck BMD [155, 156]. Further data are needed on the role of BMD monitoring patients treated with bone-forming agents, but appears to be of greater value than their use with inhibitors of bone resorption.

Figure 7: Assessment and treatment thresholds in the absence of a BMD test (left) and with a BMD test to compute fracture probability (right) for men and women [138]



The intervention thresholds at each age is set at a risk equivalent to that associated with a prior fracture.

6 RECOMMENDATIONS

6.1 RECOMMENDATIONS FOR CLINICIANS

1. The pharmacological prevention of fragility fractures should be targeted to high-risk patients, i.e. patients who will benefit the most from the treatment. The individual fracture risk is assessed by the use of clinical algorithms. BMD should be measured only in individuals presenting risk factors of fragility fractures.

2. The following treatment strategy is recommended:

2.1.All patients presenting a fragility fractures should be proposed a pharmacological prevention of further fractures.

Worth mentioning, such prevention is more effective on vertebral fractures than on fractures at other sites. NNT for preventing 1 hip fracture is high.

2.2. In the absence of prior fragility fractures:

2.2.1. If the 10-year fracture risk is high with a low BMD, a treatment is recommended. However, it should be acknowledged that the protective effect of pharmacological treatment in such patients has been demonstrated only on vertebral fractures, which are in majority clinically silent.

2.2.2.If the 10-year fracture risk is high with a BMD in the normal range, a treatment is generally not recommended as evidence allowing the translation of existing trial results to such patient populations is currently limited. However, this does not preclude clinicians from considering a treatment on an individual basis (the predictive value of a negative test in such population is decreased).

2.2.3. If the 10-year fracture risk is low, a treatment is not recommended.

3. There is today no consensus on the definition of what a high 10-year fracture risk is, i.e. there is no consensus on a risk threshold above which a prevention should be implemented. Considerations, such as patient preferences or adherence, should also intervene in the treatment decision. Absolute risk of fracture, risk reduction expected from treatment, and risk of serious adverse events should be discussed with the patients.

4. The pharmacological prevention of fragility fractures should be viewed as a component of a comprehensive management plan.

Such management plan should primarily identify risk factors amenable to non-pharmacological interventions such as: low dietary intake of calcium; environmental risk factors for falls; lack of physical activity; consumption of alcohol and/or psychotropic drugs; etc… Causes of secondary osteoporosis, such as hypogonadism or hyperparathyroidism, should also be duly identified and treated.

5. Monitoring treatment with repeated DXA is not recommended. There is currently not enough evidence to recommend other types of treatment monitoring.

6.2 RECOMMENDATIONS FOR POLICY-MAKERS

1. The utilization of clinical algorithms for assessing the absolute 10-year risk of fragility fracture should be promoted in all individuals presenting one or more risk factors, particularly during consultations in general medicine. It could be part of the Global Medical File. The dissemination of screen-and-treat algorithm for individuals at high risk of fragility fractures in Belgium would be an asset.

2. The health services should be encouraged to consider treatment in every patient presenting a fragility fracture, e.g. by an information campaign.

3. Expensive molecules which clinical benefit is not supported by firm evidence (such as calcitonin and combination of bisphosphonates with colecalciferol) should not be reimbursed except for very specific indications.

6.3 RECOMMENDATIONS FOR RESEARCHERS

1. There is an urgent need to assess the effectiveness of treatments according to different levels of 10-year risk of fractures and different combinations of risk factors.

2. There is a need to design and assess operational strategies aimed at improving the adherence and persistence of treatment in patients at high risk of fragility fractures in Belgium.

7 APPENDIXES

7.1 APPENDIXES ON BELGIAN SITUATION ANALYSIS

Table 23: INAMI/RIZIV selection codes per type of fractures per year – EPS 2002-2008

Selection	Code	Setting	Label
Femur1	298255	A	Fracture du col du fémur
	298266	H	Fracture du col du fémur
	298270	A	Fracture intertrochantérienne du fémur
	298281	H	Fracture intertrochantérienne du fémur
	298734	A	Fracture du col du fémur
	298745	H	Fracture du col du fémur
	298756	A	Fracture intertrochantérienne du fémur
	298760	H	Fracture intertrochantérienne du fémur
Femur2	289332	A	Traitement sanglant d'une fracture sous-trochantérienne du fémur
	289343	H	Traitement sanglant d'une fracture sous-trochantérienne du fémur
	289354	A	Traitement sanglant d'une fracture per-ou intertrochantérienne du fémur
	289365	H	Traitement sanglant d'une fracture per-ou intertrochantérienne du fémur
	289376	A	Traitement sanglant d'une fracture du col du fémur par synthèse
	289380	H	Traitement sanglant d'une fracture du col du fémur par synthèse
	289391	A	Traitement sanglant d'une fracture du col du fémur par prothèse
	289402	H	Traitement sanglant d'une fracture du col du fémur par prothèse
Femur3	289030	A	Arthroplastie de la hanche avec prothèse fémorale
	289041	H	Arthroplastie de la hanche avec prothèse fémorale
Femur4	289074	A	Arthroplastie de la hanche avec prothèse totale (cotyle et tête fémorale)
	289085	H	Arthroplastie de la hanche avec prothèse totale (cotyle et tête fémorale)
Humer1	283791	A	Traitement sanglant d'une fracture de la tête humérale
	283802	H	Traitement sanglant d'une fracture de la tête humérale
	283813	A	Traitement sanglant d'une fracture du col huméral
	283824	H	Traitement sanglant d'une fracture du col huméral
	283835	A	Traitement sanglant d'une luxation-fracture de la tête humérale
	283846	H	Traitement sanglant d'une luxation-fracture de la tête humérale
Humer2	283850	A	Traitement sanglant d'une fracture de la diaphyse de l'humérus
	283861	H	Traitement sanglant d'une fracture de la diaphyse de l'humérus
Humer3	296236	A	Fracture de la tête ou du col de l'humérus
	296240	H	Fracture de la tête ou du col de l'humérus
	296811	A	Fracture de la tête ou du col de l'humérus
	296822	H	Fracture de la tête ou du col de l'humérus
Humer4	296214	A	Luxation et fracture de l'épaule
	296225	H	Luxation et fracture de l'épaule
Humer5	296251	A	Fracture de la diaphyse de l'humérus
	296262	H	Fracture de la diaphyse de l'humérus
	296833	A	Fracture de la diaphyse de l'humérus
	296844	H	Fracture de la diaphyse de l'humérus
Vertebra	281013	A	Réduction sanglante d'une luxation, fracture ou fracture-luxation de la colonne cervicale sans fixation
	281024	H	Réduction sanglante d'une luxation, fracture ou fracture-luxation de la colonne cervicale sans fixation
	281514	A	Réduction sanglante d'une luxation, fracture ou fracture-luxation de la colonne dorso-lombaire
	281525	H	Réduction sanglante d'une luxation, fracture ou fracture-luxation de la colonne dorso-lombaire
	295013	A	Traitement des fractures, luxations ou luxations-fractures de la colonne vertébrale sans réduction

Selection	Code	Setting	Label
	295024	H	Traitement des fractures, luxations ou luxations-fractures de la colonne vertébrale sans réduction
	295035	A	Traitement des fractures, luxations ou luxations-fractures de la colonne vertébrale avec réduction
	295046	H	Traitement des fractures, luxations ou luxations-fractures de la colonne vertébrale avec réduction
Wrist1	284572	A	Traitement sanglant d'une fracture de l'extrémité distale d'un ou des deux os de l'avant-bras
	284583	H	Traitement sanglant d'une fracture de l'extrémité distale d'un ou des deux os de l'avant-bras
Wrist2	284513	A	Traitement sanglant d'une fracture de la tête ou du col du radius
	284524	H	Traitement sanglant d'une fracture de la tête ou du col du radius
Wrist3	296332	A	Fracture de la tête ou du col du radius
	296343	H	Fracture de la tête ou du col du radius
	296892	A	Fracture de la tête ou du col du radius
	296903	H	Fracture de la tête ou du col du radius
Wrist4	296391	A	Fracture de l'extrémité distale d'un ou des deux os de l'avant-bras
	296402	H	Fracture de l'extrémité distale d'un ou des deux os de l'avant-bras
	296936	A	Fracture de l'extrémité distale d'un ou des deux os de l'avant-bras
	296940	H	Fracture de l'extrémité distale d'un ou des deux os de l'avant-bras

A: Ambulatory H:Hospital

Figure 8: comparison of age distribution of patients selected on EPS: humerus subgroups

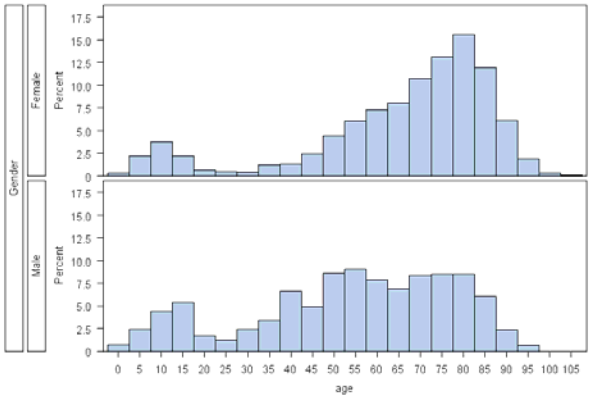
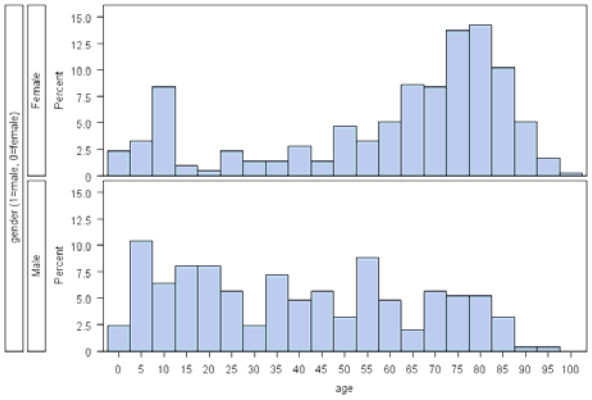
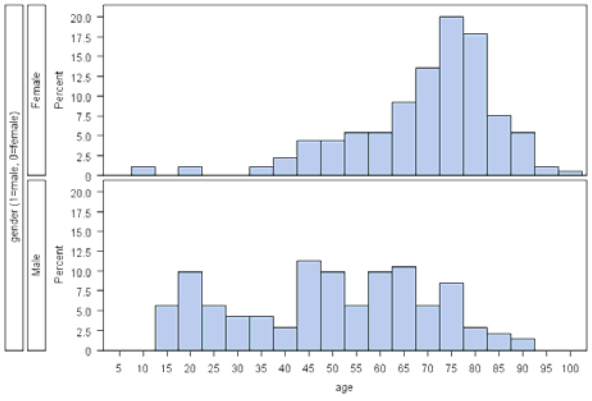
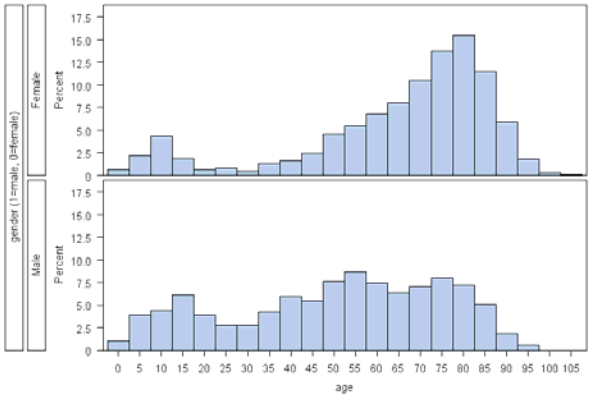
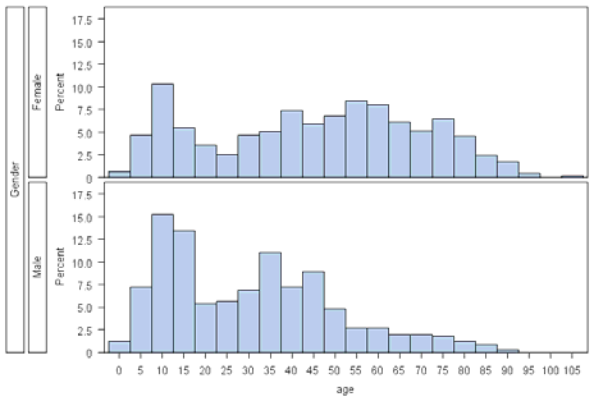
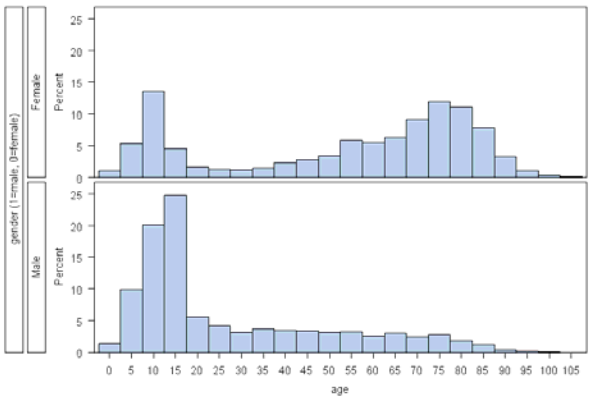
First selection: humer1 or humer3 (col/tête humerus)	Alternative selection: humer2 or humer5 (diaphyse)
	
Selection: humer4 (luxation ou fracture de l'épaule)	**Alternative selection: ALL HUMER (12345)**
	

Figure 9: comparison of age distribution of patients selected on EPS: wrist subgroups

First selection: wrist2 or wrist3 (col/tête radius)



Alternative selection: wrist1 or wrist4 (extr.distale)



Selection: wrist1234 (ALL radius)

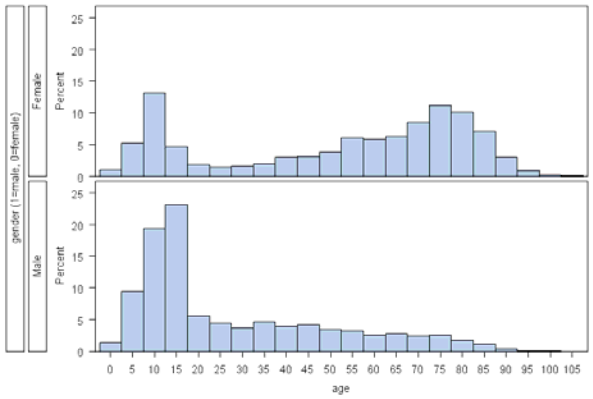
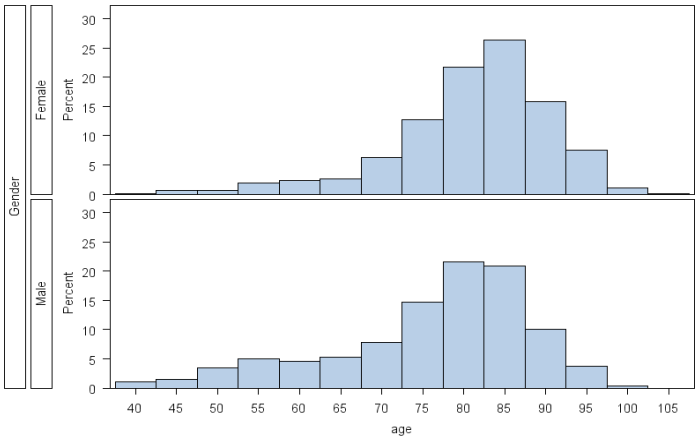


Table 24: ATC level description

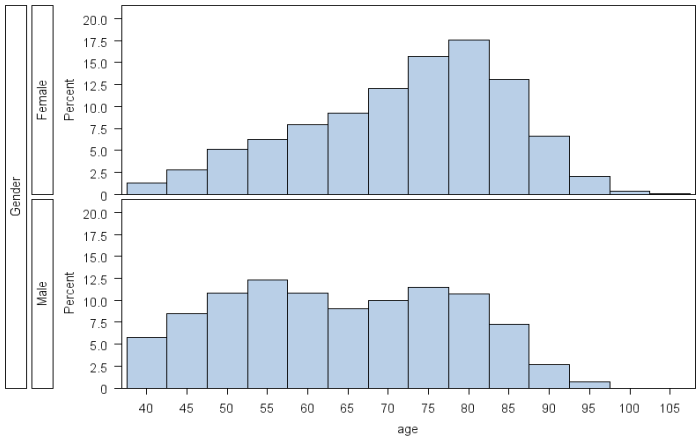
ATC level 4 – Therapeutic/Pharmacological subgroup ATC Level 5 – Chemical subgroup
G03XC: Selective estrogen receptor modulators
G03XC01: RALOXIFENE
H05AA: Parathyroide hormones and analogues
H05AA02: TERIPARATIDE
H05BA:Calcitonin preparation
H05BA01: CALCITONIN (SALMON SYNTHETIC)
M05BA: Biphosphonates
M05BA01: ETIDRONIC ACID
M05BA02: CLODRONIC ACID
M05BA04: ALENDRONIC ACID
M05BA05: TILUDRONIC ACID
M05BA06: IBANDRONIC ACID
M05BA07: RISEDRONIC ACID
M05BA08: ZOLEDRONIC ACID
M05BB: Biphosphonates, combinations
M05BB01: ALENDRONIC ACID AND COLECALCIFEROL
M05BB02 : RISEDRONIC ACID, CALCIUM AND COLECALCIFEROL, SEQUENTIAL
M05BX: Other drugs affecting bone structure and mineralisation
M05BX03: STRONTIUM RANELATE

Figure 10: Age distribution per fracture type (patients aged ≥ 40 years) – EPS 2008

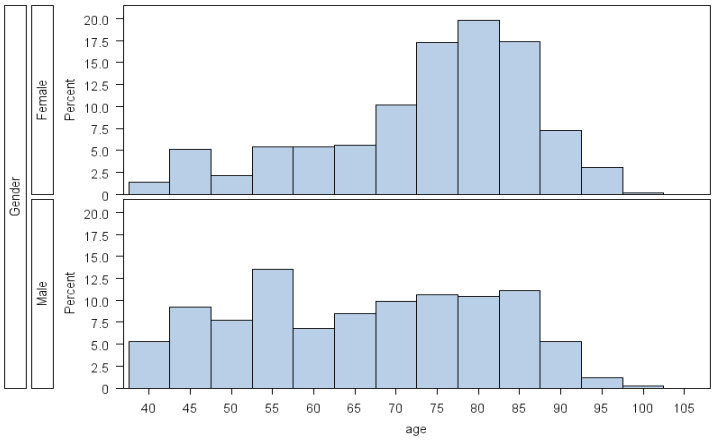
HIP



HUMERUS



VERTEBRA



WRIST

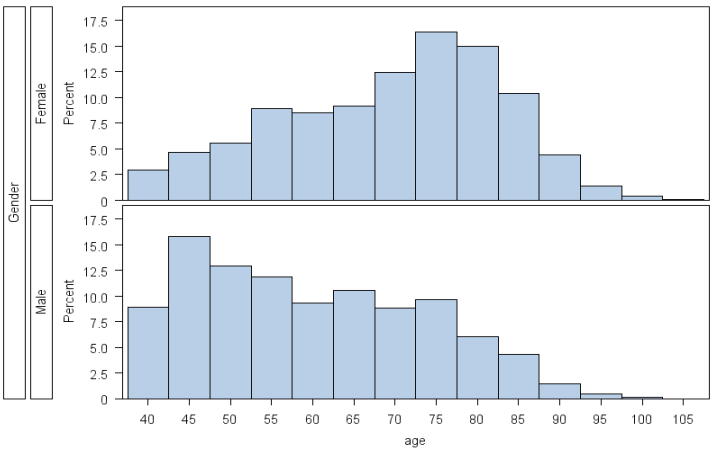


Figure 11: Age distribution per fracture type (extrapolated to the whole population) – EPS 2008

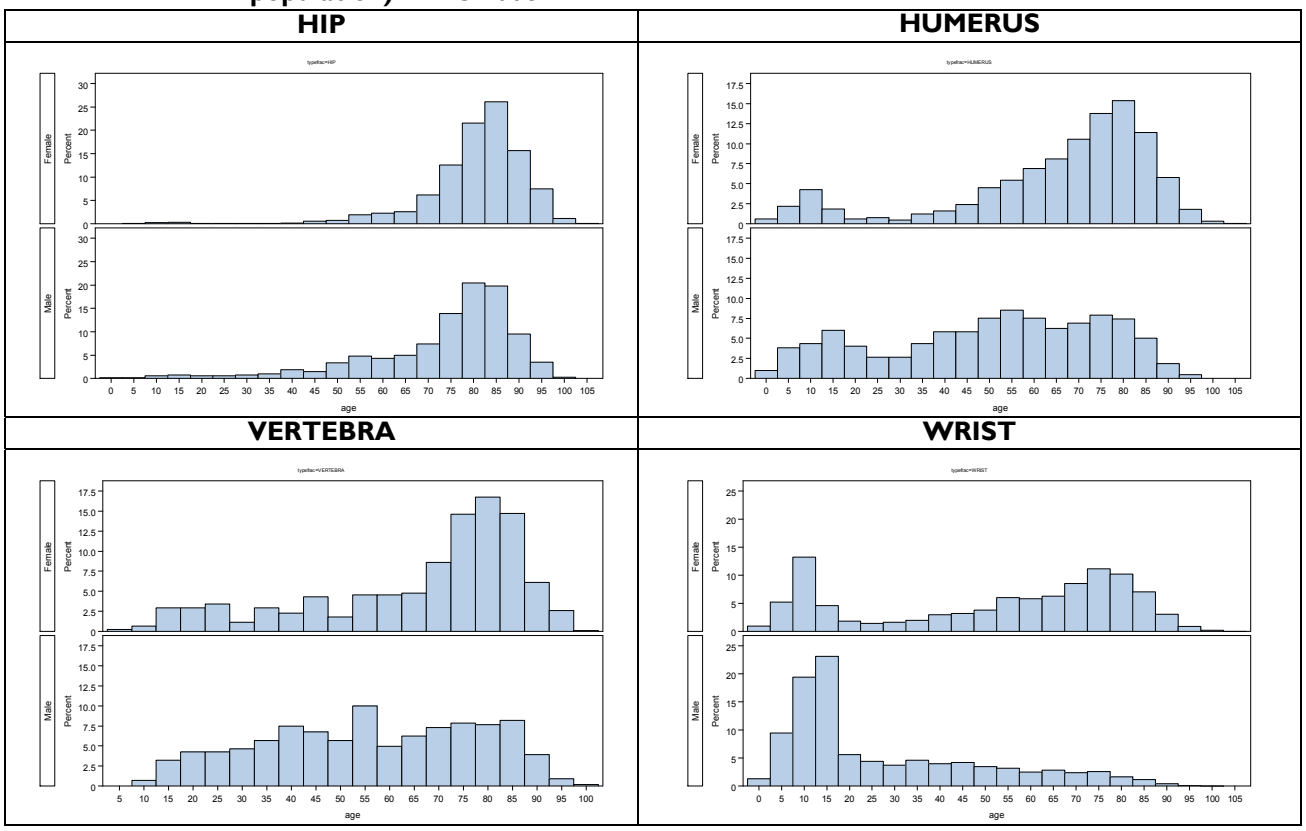


Table 25: Number of fractures per year (extrapolated to the whole population) – EPS 2002-2008

Population	Frequency Col Pct	2002	2003	2004	2005	2006	2007	2008	Total
All	HIP	15560	14420	14600	14120	13920	14480	14920	102020
	HUMERUS	11180	9880	10360	11240	9580	11500	11720	75460
	VERTEBRA	3940	4140	3860	3960	4200	4280	4500	28880
	WRIST	31860	32300	32660	32900	32240	31300	32800	226060
	Total	62540	60740	61480	62220	59940	61560	63940	432420

Figure 12: Age and gender standardized rates per type of fracture (per 1000 persons-years ≥40 years) – EPS 2002-2008

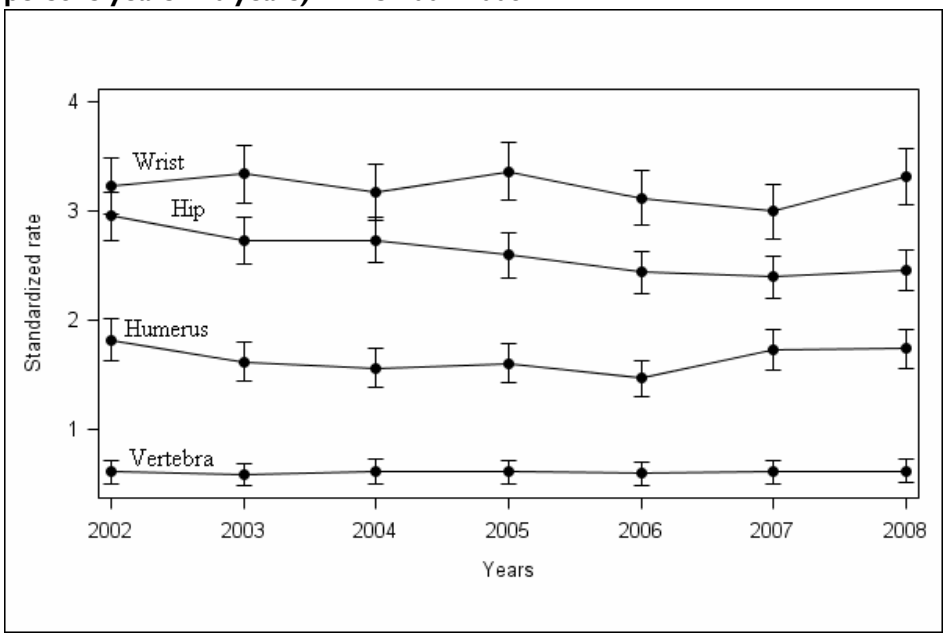


Table 26: Age and gender standardized incidence rates per type of fracture (per 1000 persons-years aged 65 or more) – EPS 2002-2008

	HIP	HUMERUS	VERTEBRA	WRIST
year	**Std rate (95%CI)**	**Std rate (95%CI)**	**Std rate (95%CI)**	**Std rate (95%CI)**
2002	7.62 (7.04 - 8.19)	3.27 (2.89 - 3.64)	1.46 (1.21 - 1.71)	5.76 (5.26 - 6.27)
2003	7.36 (6.80 - 7.93)	3.49 (3.10 - 3.87)	1.33 (1.09 - 1.57)	5.80 (5.30 - 6.30)
2004	7.27 (6.71 - 7.83)	2.94 (2.59 - 3.29)	1.15 (0.93 - 1.36)	5.52 (5.04 - 6.01)
2005	6.71 (6.19 - 7.24)	3.07 (2.72 - 3.43)	1.22 (1.00 - 1.44)	5.46 (4.98 - 5.94)
2006	6.47 (5.96 - 6.98)	2.98 (2.63 - 3.33)	1.15 (0.94 - 1.37)	5.74 (5.24 - 6.23)
2007	6.22 (5.73 - 6.71)	3.08 (2.73 - 3.44)	1.23 (1.01 - 1.45)	5.25 (4.78 - 5.72)
2008	6.54 (6.04 - 7.04)	3.28 (2.92 - 3.65)	1.18 (0.96 - 1.39)	5.72 (5.23 - 6.21)

Figure 13: Age and gender standardized rates per type of fracture (per 1000 persons-years aged 65 or more) – EPS 2002-2008

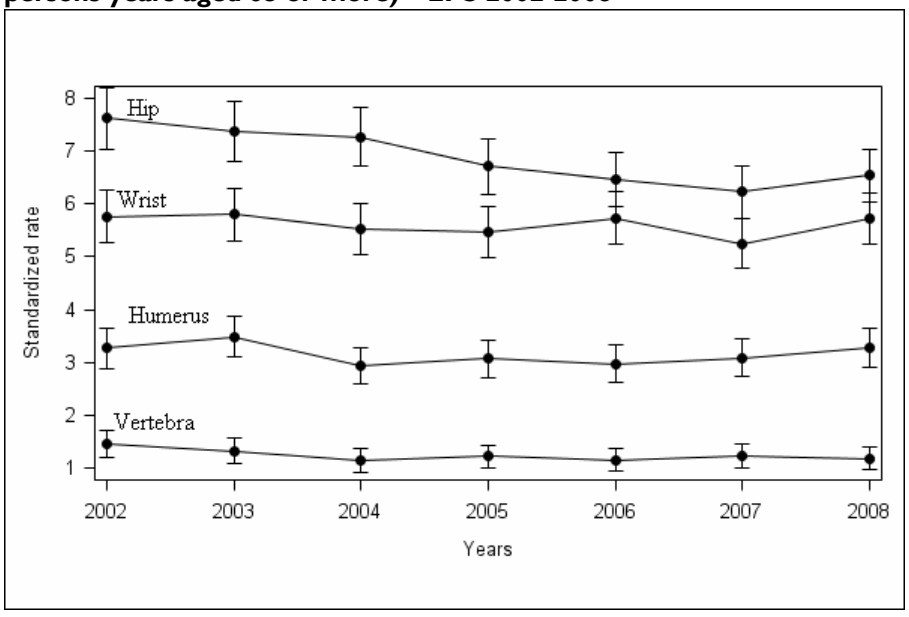


Figure 14: Number of Patients per year (ATC level 5) - M05B class

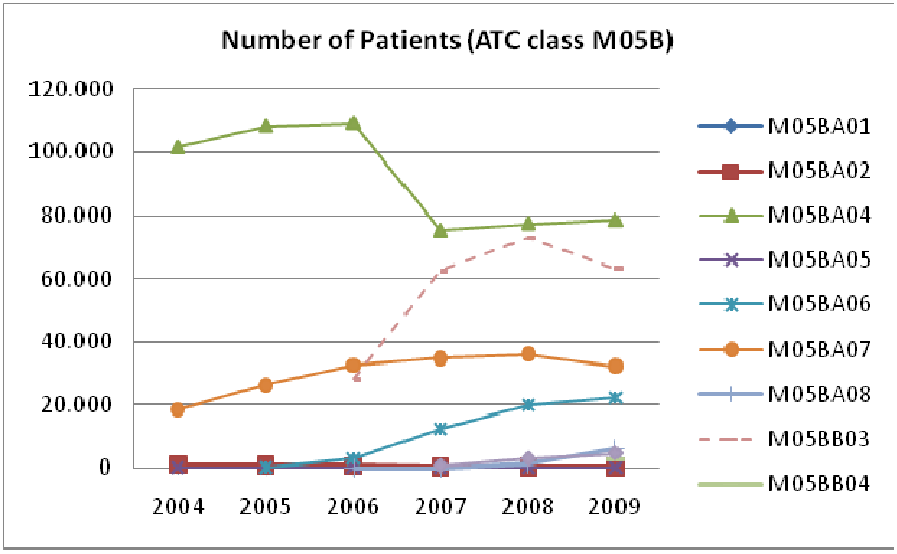


Figure 15: Number of Patients per year (ATC level 5) - Other class

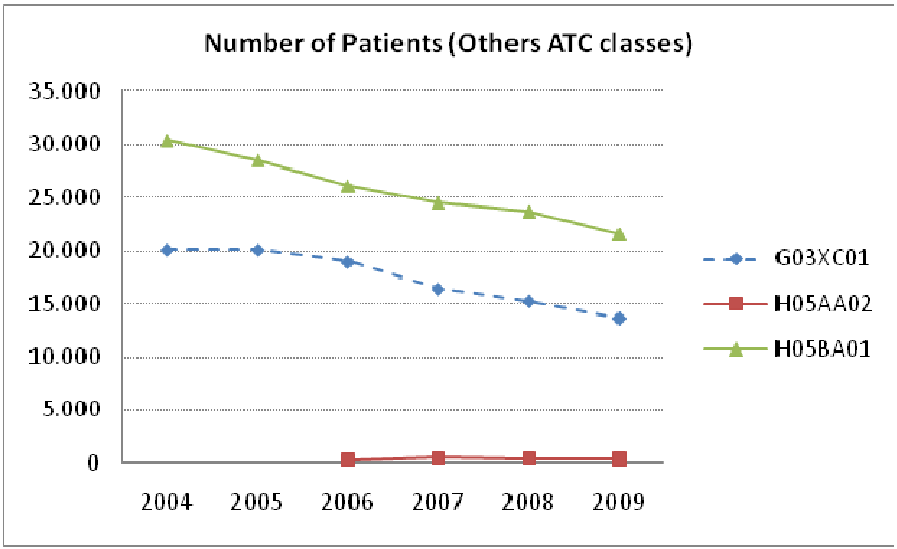
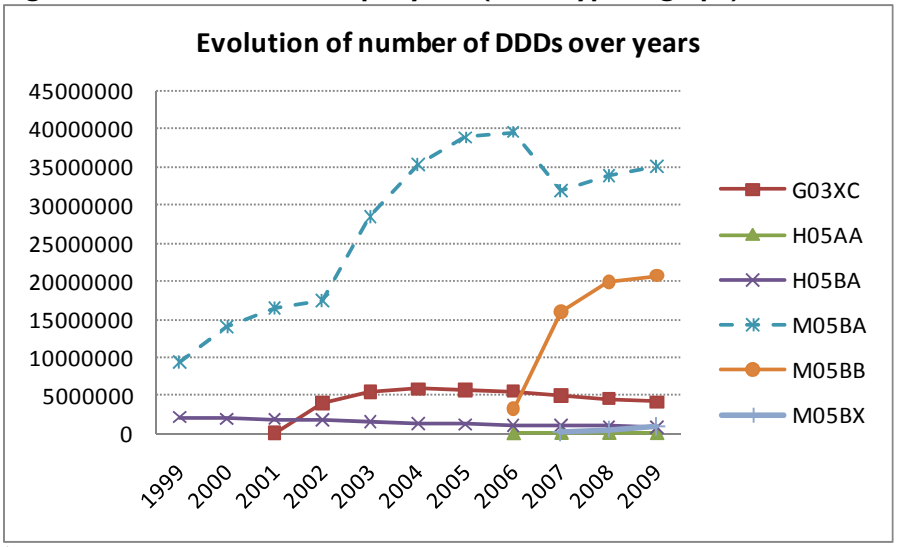
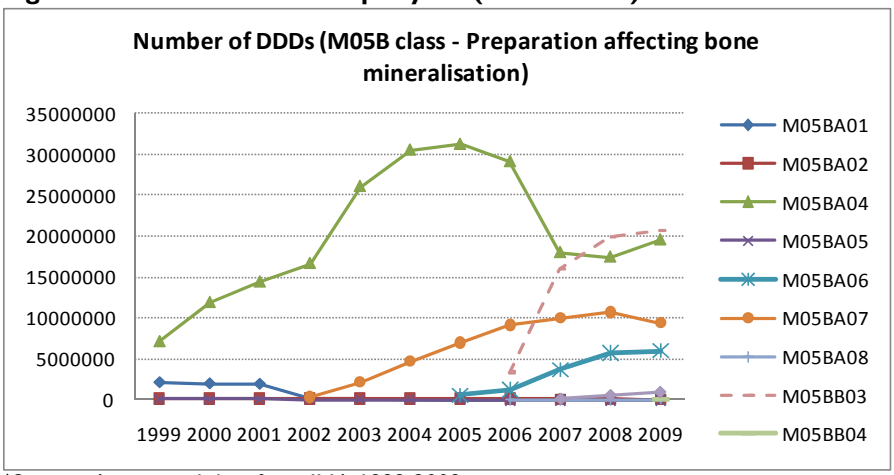


Figure 16: Number of DDDs per year (other type of graph)– ATC level 4



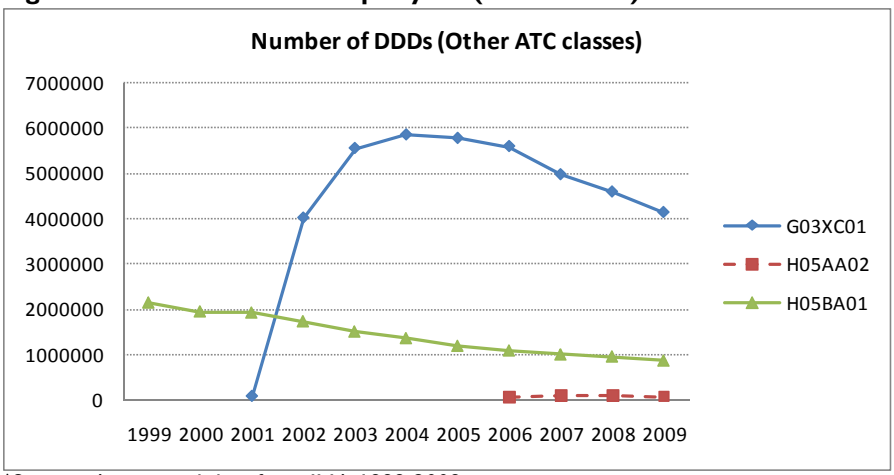
*Source: Aggregated data from IMA 1999-2009

Figure 17: Number of DDDs per year (ATC level 5) – M05B class



*Source: Aggregated data from IMA 1999-2009

Figure 18: Number of DDDs per year (ATC level 5) – Other class



*Source: Aggregated data from IMA 1999-2009

Figure 19: Third Party Payer expenditures (in €) – ATC level 4

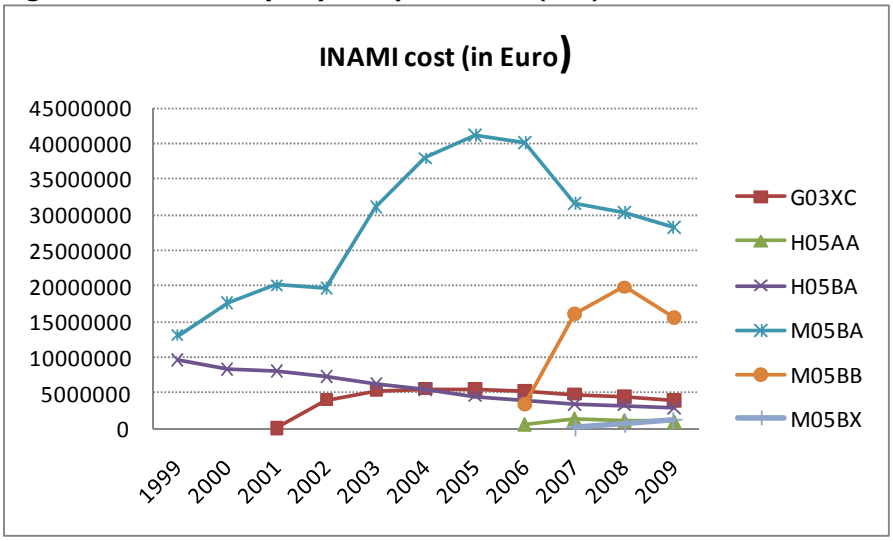


Figure 20: Third Party Payer expenditures (in €) ATC level 5 – M05B class

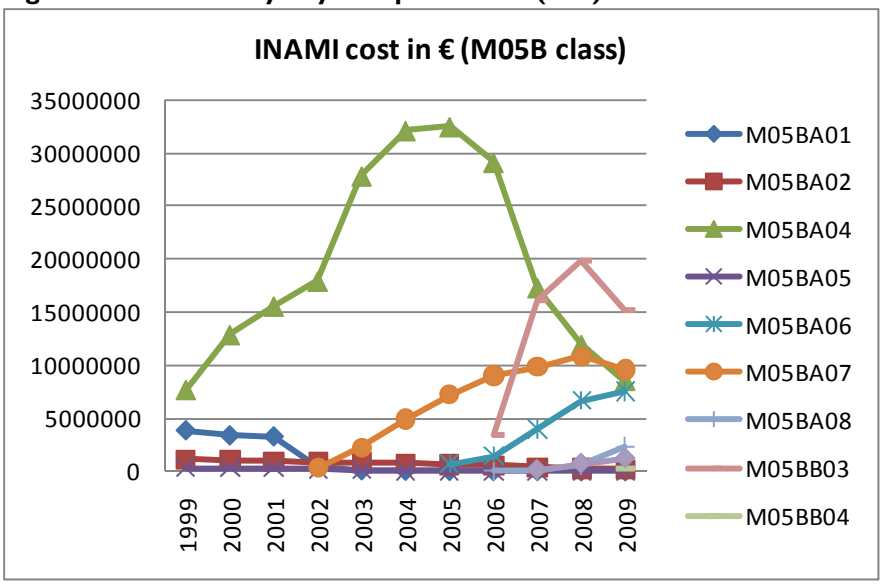


Figure 21: Third Party Payer expenditures (in €) ATC level 5 – Other class

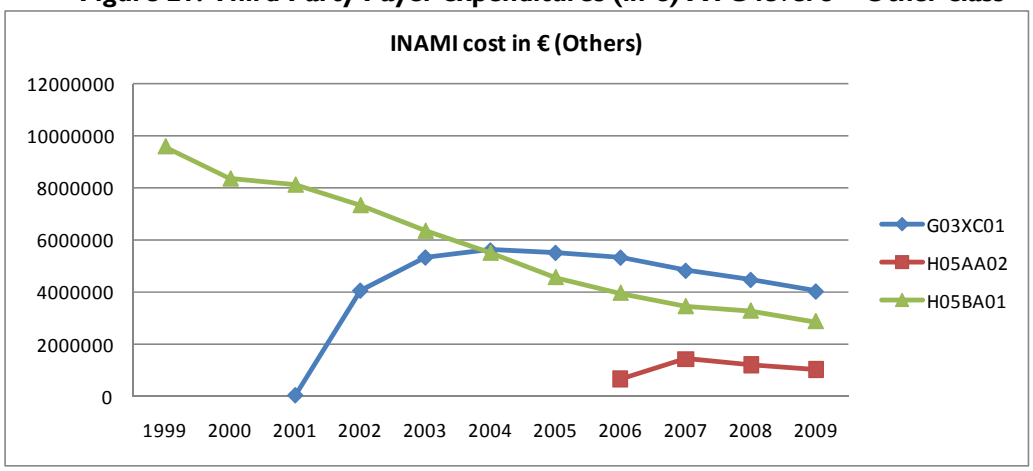


Table 27 Total Expenditure in € (ATC level 4)

ATC level 4 / ATC level 5	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
G03XC											
G03XC01			85.956	4.492.850	6.213.304	6.548.275	6.461.044	6.277.294	5.579.833	5.151.870	4.643.043
H05AA											
H05AA02								702.135	1.479.819	1.241.490	1.061.575
H05BA											
H05BA01	10.583.316	9.224.341	8.939.794	8.096.282	7.017.424	6.112.713	5.084.439	4.436.745	3.895.141	3.712.920	3.266.971
M05BA	**16.312.028**	**22.151.605**	**25.294.238**	**24.869.979**	**38.056.019**	**42.779.418**	**46.378.341**	**47.141.721**	**37.180.870**	**35.542.092**	**32.386.489**
M05BA01	4.929.663	4.323.834	4.209.396	498.975	128.145	80.592	54.204	40.136	28.052	21.847	15.326
M05BA02	1.219.702	1.110.666	1.003.164	905.555	860.215	816.643	710.882	595.826	424.689	313.510	246.788
M05BA04	9.787.271	16.333.345	19.749.275	22.875.271	34.410.074	36.327.674	36.762.287	34.384.933	20.651.025	14.812.296	10.681.160
M05BA05	375.392	383.760	332.403	206.111	120.929	87.153	77.238	44.322	20.658	16.026	11.676
M05BA06							671.907	1.466.805	4.457.120	7.398.974	8.260.697
M05BA07				384.067	2.536.656	5.467.355	8.101.823	10.590.122	11.584.519	12.391.480	10.760.108
M05BA08								19.577	14.808	587.959	2.410.735
M05BB								**3.734.160**	**17.911.802**	**22.119.328**	**17.632.822**
M05BB03								3.734.160	17.911.802	22.119.328	17.345.163
M05BB04											287.659
M05BX											
M05BX03									123.409	763.504	1.299.710
Total	**26.895.344**	**31.375.946**	**34.319.988**	**37.459.111**	**51.286.747**	**55.440.405**	**57.923.824**	**62.292.056**	**66.170.875**	**68.531.203**	**60.290.611**

Figure 22: Total expenditures (in €) ATC level 4

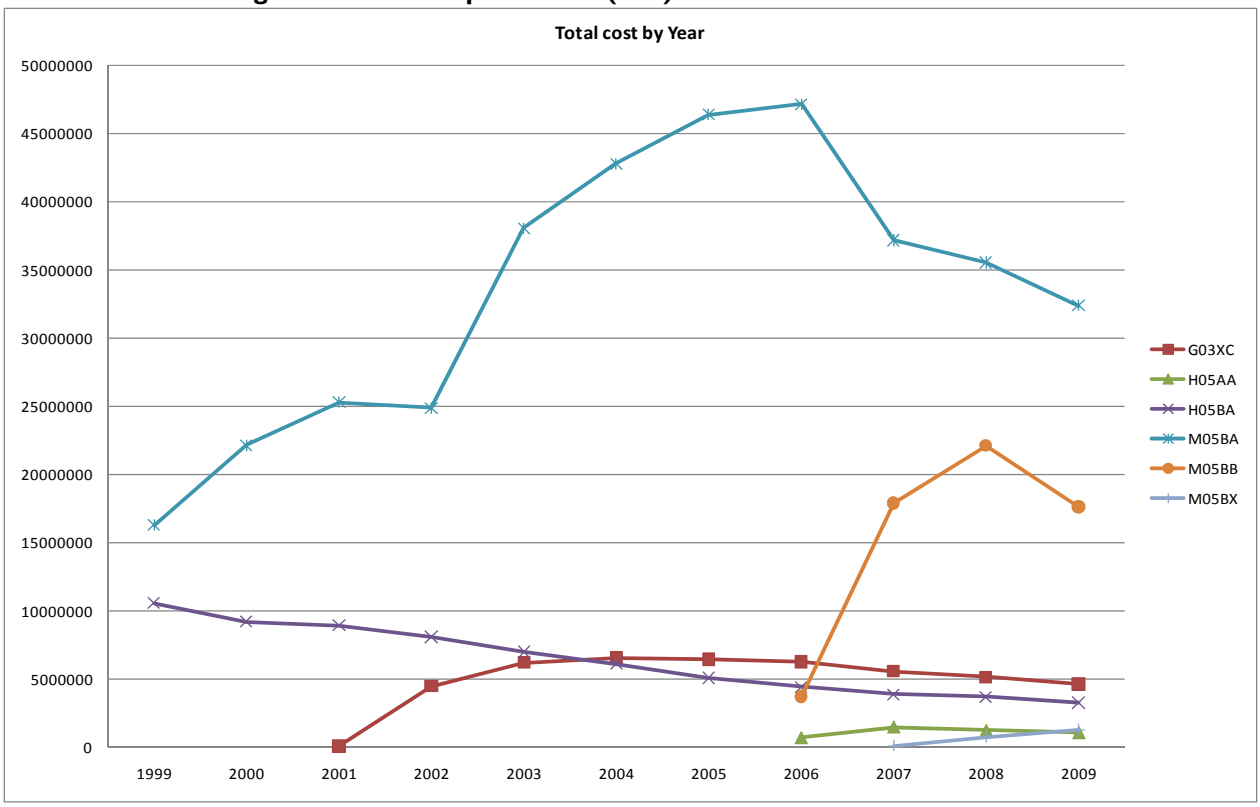


Figure 23: Total expenditures (in €) ATC level 5 – M05B class

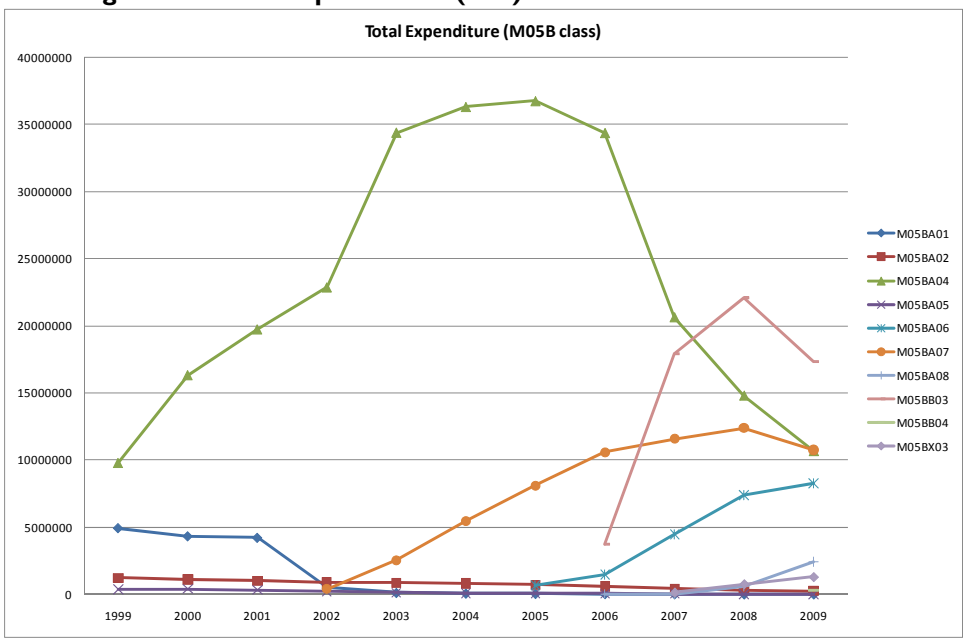


Figure 24: Total expenditures (in €) ATC level 5 – Other class

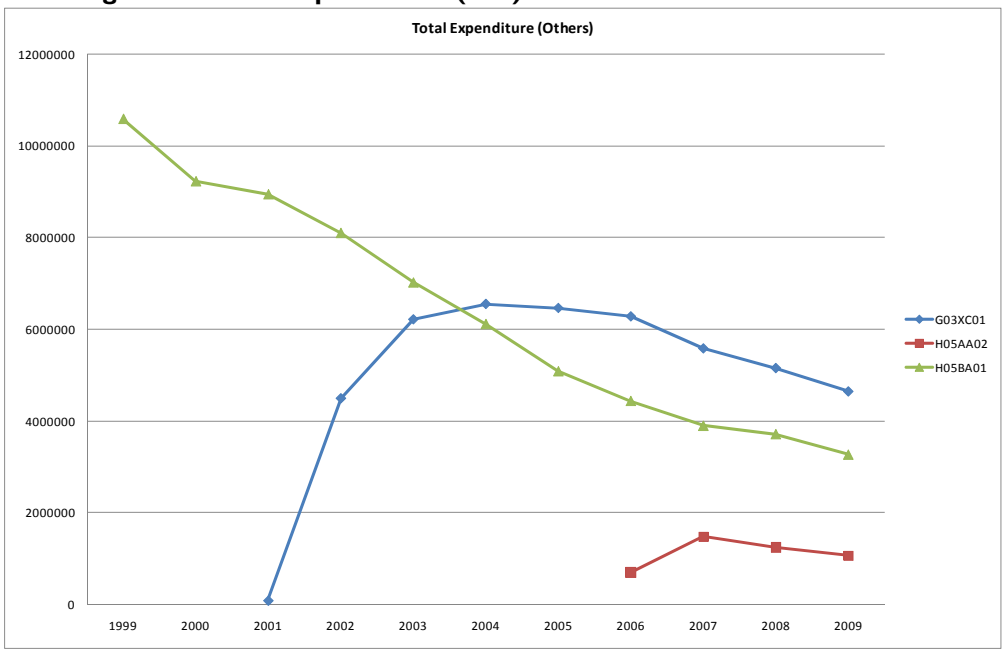


Table 28: Treatment compliance for the regular users and occasional users (patients aged 40 years or more)– EPS 2002-2008

		Year of first drug delivery							ALL
		2002	2003	2004	2005	2006	2007	2008	
N regular or occasional users	N	110300	43680	39640	34700	32080	32660	33820	**326880**
Medication Possession ratio	Mean	0.81	0.85	0.89	0.98	0.95	0.99	1.06	**0.90**
	Std	0.47	0.43	0.39	0.71	0.52	0.56	0.37	**0.50**
	Median	0.89	0.91	0.94	0.95	0.96	0.99	1.01	**0.94**
Compliance									
Regular users (MPR>=80%)	N	68100	28300	27260	25160	23720	25100	29240	**226880**
	(%)	(61.74%)	(64.79%)	(68.77%)	(72.51%)	(73.94%)	(76.85%)	(86.46%)	**(69.41%)**
Occasional users (MPR<80%)	N	42200	15380	12380	9540	8360	7560	4580	**100000**
	(%)	(38.26%)	(35.21%)	(31.23%)	(27.49%)	(26.06%)	(23.15%)	(13.54%)	**(30.59%)**

Table 29: Number (%) of Individuals by Number of different ATC level 3 drug used by Major ATC 3 drug – Belgium (Extrapolated Results from EPS – All users)

Major ATC 3	All N = 410 860		G03XC N = 28 240		H05A N = 120		H05B N = 10 6 200		M05B N = 276 300	
Number of different ATC 3	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
1	353260	86.0	16180	57.3	60	50.0	103400	97.4	233620	84.6
2	54300	13.2	10520	37.3	40	33.3	2720	2.6	41020	14.8
3	3240	0.8	1500	5.3	20	16.7	80	0.1	1640	0.6
4	60	0.0	40	0.1					20	0.0

As described in the methodology section, each user was attributed to the Therapeutical group within which most of their drug consumption came from (in term of number of DDDs). Globally, the majority of users (86.0%) had purchased drugs inside the same therapeutical group (ATC level 3) or inside 2 different therapeutical groups for 13.2% of the users.

The majority of calcitonine users (97.4%) and bisphosphonates users (84.6%) consumed only drugs within the same therapeutical group (calcitonine or bisphosphonates, respectively). In contrast, only fifty-seven percent (57.3%) of raloxifene users never changed for other type of medications and 37.3% used medications from 2 different therapeutical groups.

7.2 APPENDIXES ON SCREENING FOR OSTEOPOROSIS

Risk factors of fractures

1. Prior corticosteroid use

It was clearly demonstrated that previous corticosteroid use was associated with a significantly increased risk of any fracture independently of BMD and prior fracture [158]. The risks were also increased in case of current use of corticosteroids. The relative risk ranged from 1.98 at the age of 50 years to 1.66 at the age of 85 years, and the increase in relative risk was most marked at ages younger than 65 years. There was, however, no statistical difference in relative risk by age or between men and women. The mechanism for the BMD-independent increase in risk could be caused, at least in part, by the nature of the underlying diseases for which corticosteroids were prescribed (e.g. rheumatoid arthritis). Adverse effects of corticosteroids on muscle strength and metabolism may also increase the liability of falling and impaired protective responses to falling, thereby increasing fracture risk. A further possibility is the effects of these agents on skeletal architecture, which seems to differ from the effects of gonadal deficiency at sites of cancellous bone. It is also suggested that glucocorticoids affect osteocyte viability, which might induce alterations in the material properties of bone [158]. Whatsoever, the risk of all fractures is substantially greater in corticosteroid induced osteoporosis than in postmenopausal osteoporosis for the same level of BMD. However, as the prevalence of corticosteroid use is relatively low, the impact of treating such patients with bone active agents on fracture burden in the general community will not be great.

2. A family history of fracture

A parental history of fracture is associated with a modest but significantly increased risk of any fracture independently of BMD [159]. For a family history of any fracture, the increase in risk of an osteoporotic fracture was of borderline significance in the entire cohort but consistently significant up to the age of 75 years (see Table 5). For hip fracture outcome, the association was stronger and, as expected, was significant up to the age of 80 years. A parental history of hip fracture provided a stronger risk indicator, but was significant only in women. The mechanism for the BMD-independent increase in risk may be related to important skeletally related factors such as size and shape of bone or the microarchitecture of trabecular elements in cancellous bone. But it may not be entirely due to skeletal factors, at least as captured by the measurement of BMD. A family history may act, for example, as a surrogate for falls. The frequency of falling is less in black people than amongst white, as is the risk of fracture, which might indicate an important genetic factor related to falls. Height does not affect the relationship between family history and fracture outcome [159].

3. A history of previous fracture

Previous fracture was associated with a significantly increased risk of any subsequent fracture. There was no difference in the risk ratio between men and women. In men and women combined, the independent (i.e. adjusted for BMD) risk ratio ranged from 1.72 to 1.99 depending upon age (mean independent RR at all ages: 1.77 (1.64-1.91) [160]. A prior fracture history was also a significant risk factor for hip fracture at all ages (see table). For all fractures and for osteoporotic fractures, the risk ratios were relatively constant with age. In the case of hip fracture, risk ratios decreased with age. This could be explained by a recall bias. The mechanism for the BMD-independent increase in risk is likely due, in part, to coexisting morbidity that might increase the risk of falls or impair the protective responses to injury. In addition, changes in the microarchitecture of cancellous and cortical bone with rapid bone loss after fracture or immobilization may weaken the resistance to mechanical force out of proportion to any effect on BMD [160].

4. Current smoking

A history of smoking carried a modest but significant risk for future fractures. The risk of subsequent fractures was greater in the case of hip fracture than for all fractures, and intermediate for osteoporotic fractures. Risk ratios for hip fracture tended to decrease with age. In contrast, risk ratios for osteoporotic fractures (which included hip fractures) increased with age. After adjustment for BMD, for any fracture overall or osteoporotic fracture specifically, the associations between smoking and fracture were no longer significant in women. In men, the effect was less marked or not apparent. In men and women together, low BMD accounted for the minority of the risk associated with current smoking. For fractures overall, 45% of the risk was explained by BMD, whereas for osteoporotic fracture alone it was 40% and for hip fracture, only 23% [161].

The strength of the association was lower than for ever-smokers (except for hip fractures), consistent with the view that the effect of smoking appears to wane slowly after a person stops smoking. There was no significant difference in risk ratio between men and women, no difference when adjusted for BMD (results adjusted for BMD were no reported by the authors). No dose-effect was investigated due to differences in data collection between cohorts.

The association between smoking and fractures may result, in part, from lower levels of physical activity or from co-existing morbidity, which might in turn increase the risk of falls or impair protective responses to injury. It is also possible that smoking-induced changes in the microarchitecture of cancellous bone would weaken the resistance to mechanical force out of proportion to any effect on BMD.

5. Alcohol intake

No significant increase in risk was observed at intakes of 2 units or less daily. Above this threshold, alcohol intake was associated with an increased risk of any fracture (risk ratio [RR]=1.23; 95% CI, 1.06–1.43), any osteoporotic fracture (RR=1.38; 95% CI, 1.16–1.65), or hip fracture (RR=1.68; 95% CI, 1.19–2.36) [162]. There was no significant interaction with age, BMD, or time since baseline assessment. Risk ratios were moderately but not significantly higher in men than in women, and there was no evidence for a different threshold for effect by gender. The mechanism for the BMD-independent increase in risk could not be determined from this study, but might be due in part to coexisting morbidity that in turn increases the risk of falls or interferes with the protective response to injury [162]. With regard to BMD there are several mechanisms whereby alcohol might adversely affect fracture risk. Alcohol is shown to have direct effects on osteoblasts including those derived from man. Alcohol also increases the endogenous secretion of calcitonin. In addition, heavy drinkers may have poor nutrition with respect to calcium, vitamin D, or protein [162]. One weakness of the study was the self-reported alcohol intake, i.e. information bias cannot be ruled out.

6. BMI

Almost 250,000 person-years from 12 prospective population-based cohorts were studied [163]. Overall, the risk ratio (RR) per unit higher BMI was 0.98 (95% CI: 0.97–0.99) for any fracture, 0.97 (95% CI: 0.96–0.98) for osteoporotic fracture and 0.93 (95% CI: 0.91–0.94) for hip fracture (all p <0.001). The RR per unit change in BMI was very similar in men and women (p >0.30). The gradient of fracture risk without adjustment for BMD was not linearly distributed across values for BMI. Instead, the contribution to fracture risk was much more marked at low values of BMI than at values above the median. This nonlinear relation of risk with BMI was most evident for hip fracture risk. When compared with a BMI of 25 kg/m2, a BMI of 20 kg/m2 was associated with a nearly twofold increase in risk ratio (RR=1.95; 95% CI: 1.71–2.22) for hip fracture. In contrast, a BMI of 30 kg/m2, when compared with a BMI of 25 kg/m2, was associated with only a 17% reduction in hip fracture risk (RR=0.83; 95% CI: 0.69–0.99). In conclusion, low BMI confers a risk of substantial importance for all fractures that is largely independent of age and sex, but dependent on BMD, and after adjusting for BMD, these RR became 1 for any fracture or osteoporotic fracture and 0.98 for hip fracture (significant in women). This BMD-independent risk was not observed, however, when only cohorts using femoral neck BMD were analyzed.

The association between low BMI and risk fracture could be explained by muscle weakness, nutritional deficiencies of protein or vitamin D, decreased padding over the great trochanter, or a greater liability to fall [163]. Other possible explanations are the weight-bearing effect on bone and the conversion of androgens to estrogens in fatty tissues. Noteworthy, a potential draw-back is that BMI can be influenced by the height loss associated with vertebral deformities.

7. Physical activity

Despite varying populations and diversity in methods of assessing physical activity, evidence from epidemiological studies suggests that the risk of hip fracture can be reduced by 20% to 50% for active compared with sedentary adults. An important prospective cohort study including 61 200 postmenopausal women in good health (aged 40-77 years and 98% white) demonstrated that risk of hip fracture was lowered by6%(95%CI, 4%-9%; *P*<.001) for each increase of 3 metabolic equivalent (MET)–hours per week of activity (equivalent to 1 h/wk of walking at an average pace) [164]. Active women with at least 24 MET-h/wk had a 55% lower risk of hip fracture (relative risk [RR], 0.45; 95% CI, 0.32-0.63) compared with sedentary women with less than 3 MET-h/wk. Even women with a lower risk of hip fracture due to higher body weight experienced a further reduction in risk with higher levels of activity. More time spent standing was also independently associated with lower risks. Noteworthy, activity must be maintained to preserve the benefits [164]. Most of hip fractures result from a fall, and regular activity can reduce fall occurrence through improvements in muscle strength and balance. Physical activity can also reduce fracture risk by increasing the mechanical load on bone, which promotes remodeling.

It would be of interest to have a valid indicator of physical activity at hand for identification of persons with a higher risk of fractures. There are existing frailty indexes. For instance the SOF index (Study of Osteoporotic Fractures), which combines weight loss, inability to rise from a chair 5 times without using arms, and reduced energy level, is associated with an increased risk of recurrent falls, non-spine fractures and hip fractures [165]. However, such indicator presents 2 shortcomings. First, the analysis was usually not adjusted for confounding factors. As a result, the predictive power was limited (AUC 0.63 95% CI: 0.60-0.65, for hip fracture). Secondly, the index included other factors, and the increased risk of fractures attributable to low physical strength was not disentangled.

8. Impaired balance and frailty

Impaired balance and frailty increase the risk of falls, with subsequent risk of osteoporotic fractures [166]. Therefore, measures of impaired balance and/or frailty could by useful to predict falls and subsequent fractures. A recent prospective study in twins reported strong evidence that self-reported impaired balance was associated with an increased risk of hip fracture (OR=2.00, 95%CI: 1.29-3.11)[167]. This estimate was not attenuated when previously recognized clinical risk factors were inserted in the multivariable model. This has led the authors to recommend integrating such parameter into individual risk profile. However, although the Absolute Risk Difference of hip fracture was 7/1000 person-years (10/1000 person-years compared to 3/1000 person-years in twins without a reported impaired balance), it should be noted that the PPV and NPV were 0.05 and 0.97, respectively, thus the predictive value of a reportedly impaired imbalance was very much limited (Karl Wagner, personal communication)

Frailty indexes can also be used to predict falls. For instance, the SOF index (Study of Osteoporotic Fractures) is based on 3 components: weight loss; subject's inability to rise from a chair 5 times without using his/her arms; and reduced energy level, as identified by an answer of "no" to the question "Do you feel full of energy?" on the Geriatric Depression Scale. Frailty is defined by the presence of 2 or more components.

The CHS (Cardiovascular Health Survey) frailty index defined frailty by the presence of 3 or more of 5 components: unintentional weight loss of 5% or more; weakness, as identified by grip strength in the lowest quintile stratified by body mass index quartile; reduced energy level, as identified by an answer of "no" to the question "Do you feel full of energy?" on the Geriatric Depression Scale; slowness, as identified by a walking speed in the lowest quintile stratified by median standing height; and low physical activity level, as identified by a weighted score of kilocalories expended per week in the lowest quintile. Both indexes were similarly associated to a higher age-adjusted risk of recurrent falls (odds ratio, 2.4), disability (odds ratio, 2.2-2.8), nonspine fracture (hazard ratio, 1.4-1.5), hip fracture (hazard ratio, 1.7-1.8), and death (hazard ratio, 2.4-2.7) (*P*<0.001 for all models), in a prospective cohort of 6701 women 69 years or older[165]. This was also the case in men [168].

9. Food intake

Low intake of calcium is a significant risk factor for fractures. However, a simple questionnaire on the low intake of milk is of no value in case-finding strategies [169]. Low serum 25(OH) vitamin D concentrations seem to be associated with a higher risk for hip fracture [170]. However a recent literature review reported that, in spite of fair evidence of a positive association of 25(OH)D with BMD, the evidence for an association with fractures was inconsistent [171].

Tea drinking is associated with small benefits on bone density in older women [172], although the association to fractures is not demonstrated [173]. For the other foods and nutrients, such as chocolate, the evidence of a link between intakes and fracture risk is not sufficiently secure to make firm recommendations [174].

Table 30: Independent (adjusted for BMD) Risk Ratio

Risk factors	Any fracture	Osteoporotic fracture	Hip fracture	Ref
Ever use of corticosteroids	M: 1.67 (1.10-2.51) F: 1.39 (1.18-1.64)	M: 2.16 (1.42-3.27) F: 1.42 (1.18-1.70)	M: 2.62 (0.91-7.51) F: 2.07 (1.38-3.10)	158*
Parental history of fracture	1.18 (1.07-1.31)	1.22 (1.08-1.38)	1.63 (1.24-2.13)	159**
Parental history of hip fracture	1.41 (1.17-1.71)	1.54 (1.25-1.88)	2.28 (1.48-3.51)	159**
History of a previous fracture	M: 2.04 (1.67-2.48) F: 1.73 (1.59-1.88)	M: 1.91 (1.50-2.43) F: 1.74 (1.57-1.92)	M: 1.97 (1.12-3.48) F: 1.56 (1.23-1.98)	160***
Current Smoking	M: 1.49 (1.20-1.84) F: 1.02 (0.90-1.16) All$: 1.12 (1.01-1.25)	M: 1.54 (1.21-1.95) F: 1.01 (0.87-1.17) All$: 1.11 (0.98-1.26)	M: 1.69 (1.16-2.48) F: 1.55 (1.16-2.07) All$: 1.55 (1.23-1.96)	161***
Alcohol intake (>2 unitsμ a day)	1.24 (1.06-1.45)	1.36 (1.13-1.63)	1.70 (1.20-2.42)	162****
BMI (20 vs. 25)	0.98 (0.90-1.08)	1.02 (0.92-1.13)	1.42 (1.23-1.65)	163£

*: Results based on the observation of 176,000 person-years from seven prospective cohort
**: Results based on the observation of 134,374 person-years from seven prospective cohort
***: Results based on the observation of 250,000 person-years from eleven cohorts
****: Results based on the observation of 75,433 person-years from 3 cohorts
$: adjusted for BMI and age (besides BMD)
μ: 1 unit=8.08g
£: Results based on the observation of 250,000 person-years from twelve cohorts

7.3 APPENDIXES ON TREATMENT EFFICACY

Table 31: Rejected studies on Alendronate

Papers	Reason for rejection
[175]	2, 3
[176]	2
[177]	2
[178]	2, 3
[143]	2, 3 (secondary analysis)
[179]	1, 3
[180]	3 (observational open follow-up study of the STOP-trial)
[181]	3
[182]	3
[183]	3 (secondary analysis of a RCT)
[184]	1, 2, 3
[185]	2
[186]	3, 4
[187]	1, 3
[188]	2, 5 (men with prostate cancer)
[189]	2, 5
[190]	4
[191]	1, 3
[192]	1
[193]	1
[194]	4
[195]	3
[196]	3, 5 (secondary analysis of the FIT trial stratified by renal impairment status)
[197]	2, 4
[198]	2, 5 (high dose glucocorticoid therapy)

1: not in English, French, Spanish, Dutch;
2: not reporting on fracture risk or not powered to measure differences in fracture risk
3: not a RCT;
4: comparing the effect of 2 active substances
5: Very specific patient population (prostate cancer, cystic fibrosis,

Table 32: Rejected studies on Risedronate

Papers	Reason for rejection
[199]	1, 6 (on denosumab)
[175]	2, 3 (on acceptance)
[200]	5 (osteogenesis imperfect)
[201]	4
[176]	2, 4
[180]	3 (observational open follow-up study of the STOP-trial)
[117]	6
[202]	3 (review)
[183]	3 (secondary analysis of a RCT)
[179]	1
[181]	3
[203]	3
[190]	2
[178]	2
[143]	6
[182]	3
[204]	1,3
[205]	1

[184]	1, 3
[206]	1, 3
[64]	6 (FRAX)
[207]	4
[208]	3
[209]	3, 6
[210]	1, 3, 6
[211]	1, 3
[198]	2, 5 (high dose glucocorticoid therapy)
[185]	2
[186]	3, 4
[187]	1, 3
[188]	2, 5 (men with prostate cancer
[212]	3
[213]	3
[189]	2, 5
[214]	6 (vitamin D)
[215]	3, 6
[190]	2, 4
[216]	3
[192, 193, 217, 218]	3, 5
[194]	4
[219]	3
[220]	3, 6
[221]	3
[195]	3
[196]	3, 5 (secondary analysis of the FIT trial stratified by renal impairment status)
[19]	6
[222]	2
[197]	2
[223]	3, 4

1: not in English, French, Spanish, Dutch;
2: not reporting on fracture risk or not powered to measure differences in fracture risk
3: not a RCT;
4: comparing the effect of 2 active substances
5: Very specific patient population (prostate cancer, cystic fibrosis,..)
6: others

Table 33: Rejected studies on Zoledronate

Papers	Reason for rejection
[224]	2, 5 (prostate cancer)
[225]	3
[226]	1, 3
[227]	3, 5 (myeloma)
[228]	3, 5 (breast cancer)
[229]	2, 5 (bony metastatic bladder cancer)
[230]	3 (A post hoc subgroup analysis of pooled data from the Health Outcome and Reduced Incidence with Zoledronate One Yearly (HORIZON) Pivotal Fracture Trial and the HORIZON Recurrent Fracture Trial)
[117]	3 (secondary analyses of RCTs including various diphosphonates)
[120]	3 (review)
[231]	3 (cost-effectiveness)
[232]	3, 5
[233]	3
[234]	3, 5 (cystic fibrosis)

[203]	3
[235]	3
[236]	3 (secondary analyses of the (HORIZON-PFT)
[237]	3 (comparison of different diphosphonates)
[238]	1
[239]	5 (pediatric population)
[208]	3
[211]	1, 3
[240]	3
[213]	3 (comparison of diphoshonates)
[241]	1, 3
[242]	3 (review)
[243]	1, 3
[244]	3, 5
[245]	3
[246]	3 (secondary analysis of the pivotal trial)
[247]	1, 3, 5
[248]	3, 5
[249]	3, 5
[250]	3, 5
[251]	3, 5
[219]	3
[252]	3, 5
[253]	3, 5
[254]	3, 5
[255]	3
[256]	2, 3
[257]	5
[258]	2, 5 (prostate cancer)
[259]	3
[260]	3, 5
[261]	3
[262]	5 (prostate cancer)
[263]	3, 5
[264]	3
[265]	3, 5
[266]	3, 5
[267]	3
[268]	3, 5
[269]	3 (Presentation of the HORIZON recurrent fracture trial)
[270]	3, 5
[271]	4, 5
[272]	3
[273]	3,5
[274]	3
[275]	3
[276]	3
[277]	3
[278]	1, 3, 5
[279]	3,5
[280]	3 (secondary analysis of the HORIZON trial)
[281]	2

1: not in English, French, Spanish, Dutch;
2: not reporting on fracture risk or not powered to measure differences in fracture risk
3: not a RCT;
4: comparing the effect of 2 active substances
5: Very specific patient population (prostate cancer, cystic fibrosis,..)
6: others

Etidronate

Etidronate is a first generation non-nitrogen containing bisphosphonate that inhibits osteoclastic resorption and decreases bone turnover. It is considered a weaker anti-resorptive agent than the other bisphosphonates. It is given orally on a cyclical schedule, 400 mg for 2 weeks every 90 days, followed by calcium, to minimize any potential to inhibit bone mineralization and result in osteomalacia.

The search for SR relating to etidronate yielded 16 hits. We retrieved two recent good-quality study specific to etidronate: a Cochrane review published in 2008 by Wells et al. (with search strategy up to February 2007) [104] and a NICE review with an update up to June 2008. The update search returned 2 hits (including the Cochrane review itself), none of which was selected (for papers rejected and reason, please Table 34).

Table 34: Rejected studies on Etidronate

Papers	Reason for rejection
[282]	5 (patients with stroke)
[283]	2, 4 (only 50 patients)

1: not in English, French, Spanish, Dutch;
2: not reporting on fracture risk or not powered to measure differences in fracture risk
3: not a RCT;
4: comparing the effect of 2 active substances
5: Very specific patient population (prostate cancer, cystic fibrosis,..)
6: others

The results of the NICE review are synthesized in Table 18 & Table 19.

The Cochrane review by Wells et al. included eleven studies representing a total of 1248 post-menopausal women [104]. Eight trials included women with established osteoporosis and were classified as secondary prevention trials (Ishida 2004; Lyritis 1997; Montessori 1997; Pacifici 1988; Shiota 2001; Storm 1990; Watts 1990; Wimalawansa 1998) and the remaining three were classified as primary prevention trials (Herd 1997;Meunier 1997; Pouilles 1997). Nine trials (Herd 1997; Lyritis 1997; Meunier 1997;Montessori 1997; Pacifici 1988; Pouilles 1997; Storm1990; Watts 1990; Wimalawansa 1998) administered etidronate cyclically at the standard dose of 400 mg and two trials (Ishida 2004; Shiota 2001) used a 200 mg dose. Follow up for the 11 studies ranged from two to four years and the mean age of the participants was 53 to 72 years. Two studies (Montessori 1997; Watts 1990) excluded women with a history of gastrointestinal (GI) disease and only one trial (Watts 1990) reported fractures as a stated primary outcome. Allocation concealment was unclear for all 11 trials. Seven trials had a loss to follow up from5%to 20%(Herd 1997; Ishida 2004; Meunier 1997; Montessori 1997; Pouilles 1997; Watts 1990; Wimalawansa 1998), for three trials it was over 20%(Lyritis 1997; Pacifici 1988; Storm 1990) and one trial did not report the loss to follow up (Shiota 2001). Five trials (Herd 1997; Meunier 1997; Pouilles 1997; Storm 1990; Watts 1990) were double blind.

A significant 41% relative risk reduction (RRR) in vertebral fractures across eight studies (RR 0.59, 95% CI 0.36 to 0.96) was found. The six secondary prevention trials demonstrated a significant RRR of 47% in vertebral fractures (RR 0.53, 95% CI 0.32 to 0.87) and a 5% absolute risk reduction (ARR); compared with the pooled result for the two primary prevention trials (RR 3.03, 95% CI 0.32 to 28.44), which was not significant. There were no statistically significant risk reductions for non-vertebral (RR 0.98, 95% CI 0.68 to 1.42), hip (RR 1.20, 95% CI 0.37 to 3.88) or wrist fractures (RR 0.87, 95% CI: 0.32 to 2.36).

Table 35: Rejected studies on Ibandronate

Papers	Reason for rejection
[284]	3
[285]	5 (liver transplant)
[286]	3 (post-hoc analysis of the DIVA study)
[287]	5 (cardiac transplant)
[288]	3, 5 (subgroup analysis of the BONE study)
[289]	3
[290]	5
[79]	3 (pooled analysis, methods of the SR poorly described)
[291]	3
[292]	3
[80]	3 (metanalysis)
[81]	3 (metanalysis)

1: not in English, French, Spanish, Dutch;
2: not reporting on fracture risk or not powered to measure differences in fracture risk
3: not a RCT;
4: comparing the effect of 2 active substances
5: Very specific patient population (prostate cancer, cystic fibrosis,..)
6: others

Table 36: Rejected studies on Strontium ranelate

Papers	Reason for rejection
[293]	3
[201]	4
[176]	2, 4
[294]	3
[295]	3
[296]	3
[297]	1,3
[298]	3
[299]	3
[300]	3
[301]	6 (secondary analysis on biomarkers)
[302]	3
[303]	6 (secondary analysis on biomarkers)
[304]	3 (cost-utility)
[305]	2, 3
[306]	3 (on teriperatide)
[307]	3
[308]	3
[309]	6 (sub-group analysis of 1RCT)
[310]	6 (open-label extension of the TROPOS and SOTI trials; no comparison group)
[311]	6 (sub-group analysis of the SOTI & TROPOS trials)

1: not in English, French, Spanish, Dutch;
2: not reporting on fracture risk or not powered to measure differences in fracture risk
3: not a RCT;
4: comparing the effect of 2 active substances
5: Very specific patient population (prostate cancer, cystic fibrosis,..)
6: others

Table 37: Rejected studies calcitonin

Papers	Reason for rejection
[302]	3
[312]	3
[313]	3
[314]	3
[315]	1, 3

1: not in English, French, Spanish, Dutch;
2: not reporting on fracture risk or not powered to measure differences in fracture risk
3: not a RCT;
4: comparing the effect of 2 active substances
5: Very specific patient population (prostate cancer, cystic fibrosis,..)
6: others

Table 38: Rejected studies on raloxifene

Papers	Reason for rejection
[316]	2 (secondary analysis of the Multiple Outcomes of Raloxifene Evaluation trial
[317]	2
[318]	2
[319]	2
[320]	2
[321]	6 (screening programme)
[109]	6 (not on raloxifene)
[322]	2
[313]	3
[323]	2
[324]	3
[214]	6
[325]	2
[326]	2, 6 (secondary analysis of the MORE trial)
[327]	6 (secondary analysis of the MORE trial)
[328]	6 (secondary analysis of the MORE trial)
[329]	4 (compared raloxifene to bazedoxifene)
[216]	3

1: not in English, French, Spanish, Dutch;
2: not reporting on fracture risk or not powered to measure differences in fracture risk
3: not a RCT;
4: comparing the effect of 2 active substances
5: Very specific patient population (prostate cancer, cystic fibrosis,..)
6: others

Table 39: Rejected studies on denosumab

Papers	Reason for rejection
[330]	2
[331]	4, 5 (prostate cancer)
[332]	4, 5
[333]	4, 5 (breast cancer)
[334]	2
[335]	2
[336]	2
[337]	2
[338]	2
[339]	2
[340]	2, 5 (prostate cancer)
[341]	2
[342]	5 (prostate cancer)
[343]	6
[344]	5 (bone metastases)
[345]	2
[346]	5
[347]	2, 5 (breast cancer)
[348]	5
[349, 350]	5
[351]	2, 4
[101]	2, 5
[352]	2
[353]	2
[354]	2, 5 (multiple myeloma)
[355]	2, 5 (rheumatoid arthritis)
[356]	2
[100]	2
[357]	2
[358, 359]	2

1: not in English, French, Spanish, Dutch;
2: not reporting on fracture risk or not powered to measure differences in fracture risk
3: not a RCT;
4: comparing the effect of 2 active substances
5: Very specific patient population (prostate cancer, cystic fibrosis,..)
6: others

Table 40: Side effects of osteoporotic drugs

Drugs	Side effects
Bisphosphonates	Contraindications to bisphosphonate therapy include hypersensitivity or hypocalcemia. Bisphosphonates should be used with caution, if at all, in patients with reduced kidney function (glomerular filtration rate below 30 mL/ min for risedronate and ibandronate or below 35 mL/min for alendronate and zoledronate). There is some evidence that alendronate and risedronate are safe and effective in patients with moderate reduction of renal function. Orally administered bisphosphonates should be used with caution in patients with active upper gastro-interstinal (GI) disease, inability to follow the dosing regimen for oral use (that is, inability to remain upright for 30 to 60 minutes), or presence of anatomic or functional esophageal abnormalities that might delay transit of the tablet (for example, achalasia or stricture). Intravenous administration of nitrogen-containing bisphosphonates, such as ibandronate and zoledronate, causes acute phase reactions in up to 30% to 40% of patients receiving their first dose. These reactions are characterized by fever and muscle aches lasting several days. Acetaminophen given at the time of treatment may reduce the likelihood of these reactions and can also be given to treat the symptoms. Although rapid administration of nitrogen-containing bisphosphonates may interfere with kidney function, this adverse effect has not been observed with intravenously administered ibandronate or zoledronate given to patients with normal renal function in accordance with appropriate dosing instructions. Some patients treated with an orally or intravenously administered bisphosphonate experience bone, joint, or muscle complaints that may be severe but that usually resolve when use of the drug is discontinued. Osteonecrosis of the jaw (ONJ) has been associated rarely with bisphosphonate therapy for osteoporosis; risk factors include dental pathologic conditions, invasive dental procedures, or poor dental hygiene. Another rare event that may be associated with alendronate is a subtrochanteric fracture. Occasionally, such fractures are described as “chalk stick” because of their radiologic appearance. They occur after minimal or no trauma. Sometimes the patient complains of leg pain preceding the event. A sclerotic appearance to the subtrochanteric region may be seen radiologically. It has been claimed that these patients may have very low bone turnover, although this point has not been rigorously substantiated. Whether a direct etiologic relationship exists between ONJ or these femoral fractures and the use Evidence for atypical femoral shaft fractures has recently been reviewed by a task force of the American Society for Bone and Mineral Research. The possible association between orally administered bisphosphonates and esophageal cancer has been explored. One study suggested no increased risk, and one suggested that risk was increased with long-term use but small in absolute terms—from 1 case per 1,000 in untreated subjects to 2 cases per 1,000 with bisphosphonate use of 5 years or more. Atrial fibrillation as a serious adverse event was noted in the zoledronate Pivotal Fracture Trial but was not seen in other trials of zoledronate or other bisphosphonates and is thought by the FDA to be a chance finding.
Alendronate	Upper GI symptoms such as heartburn, indigestion, substernal discomfort, and pain with swallowing may occur, and rare instances of esophageal erosion, ulceration, or bleeding have been described. Most GI side effects are mild, but serious problems are seen in approximately 1 of 10,000 alendronate users.
Risedronate	Studies of up to 9 years’ duration indicate a good safety profile. In clinical trials, adverse events with risedronate did not differ from those with placebo. Side effects are generally mild and primarily affect the upper GI system.
Ibandronate	Studies of up to 3 years’ duration indicate a good safety profile. In clinical trials, adverse events with ibandronate did not differ from those with placebo. Side effects are generally mild and primarily affect the upper GI system. As with the other bisphosphonates, upper GI side effects can occur with use of ibandronate.
Zoledronate	Intravenous administration of zoledronate can cause acute phase reactions in up to

	30% of patients receiving their first dose. Subsequent doses is associated with a much smaller incidence (less than 2%). These reactions are characterized by fever and muscle aches lasting several days. With zoledronate, most of the published literature has associated osteonecrosis of the jaw (ONJ) with the much higher dose that is used in patients with a malignant condition. No published information suggests that ONJ is more common with intravenously administered zoledronate in the dose used to treat osteoporosis in comparison with orally administered bisphosphonates.
Teriparatide	Side effects of teriparatide have been mild and transient and include nausea, orthostatic hypotension, and leg cramps. Hypercalcemia, usually mild, asymptomatic, and transient, has been observed but is not common.
Calcitonin	Studies of up to 5 years' duration indicate a good safety profile. Common side effects of parenterally administered calcitonin include nausea, local inflammatory reactions at the injection site, and vasomotor symptoms including sweating and flushing. The most common side effect of nasally administered calcitonin is nasal discomfort, including rhinitis, irritation of the nasal mucosa, and occasional epistaxis.
Raloxifene	Increase in occurrence of venous thromboembolic diseases (similar to estrogen), although the absolute risk is low . Other side effects include menopausal symptoms (for example, hot flashes and night sweats) and leg cramps.
Denosumab	Studies of up to 6 years' duration indicate a good safety profile. Hypocalcemia must be corrected before initiation of therapy. Serious infections, including skin infections, may occur. Patients should be advised to seek prompt medical attention if signs or symptoms of infection, including cellulitis, develop. Dermatitis, rashes, and eczema have been reported. In patients treated with denosumab, ONJ has been reported. Suppression of bone turnover of uncertain clinical significance has been demonstrated.

Data extracted from the AACE guidelines [123]

Table 41: Duration of treatment of osteoporotic drugs

Drugs	Duration of treatment
Alendronate	Efficacy and safety beyond 10 years have not yet been established, but observational tracking is now up to 13 years. When alendronate is discontinued, no acceleration of bone loss relative to placebo has been noted, although slow but significant bone loss at the hip has been reported. There is some suggestion that, after 4 to 5 years of therapy (and longer for those with severe osteoporosis), a drug holiday of 1 or 2 years could be offered without substantial loss of antifracture efficacy
Risedronate	Efficacy and safety beyond 7 years have not yet been established, although clinical experience now extends to 9 years. When risedronate is discontinued, no acceleration of bone loss relative to placebo has been noted, although slow bone loss may occur. There is some suggestion that, after 3 years of therapy, a drug holiday of up to 1 year can be offered without significant loss of antifracture efficacy. After 1 year of discontinuation, bone turnover markers essentially returned to baseline pretreatment levels. Resuming risedronate therapy after 1 year is generally recommended.
Ibandronate	Ibandronate has been studied in trials of up to 3 years'duration. Efficacy and safety beyond 3 years have not yet been established. No published studies have addressed the discontinuation of ibandronate therapy.
Zoledronate	Studies of efficacy and safety through 6 years have been completed but are not yet published. No published studies have addressed the discontinuation of zoledronate therapy.
Teriparatide	Efficacy and safety of teriparatide have been assessed for a period of 2 years and are currently unknown thereafter. Treatment with teriparatide is not recommended to exceed 2 years. When use of teriparatide is stopped, bone density declines quickly during the following year, although fracture reduction may persist for 1 or 2 years. Use of alendronate after teriparatide therapy prevents this loss and in some cases will be associated with a further increase in BMD.
Calcitonin	The optimal duration of treatment with calcitonin is unknown. Safety and efficacy data are available through 5 years. When use of calcitonin is stopped, the skeletal benefits are lost fairly quickly (during the subsequent 1 or 2 years).
Raloxifene	Efficacy and safety has been determined for up to 8 years. When use of raloxifene is stopped, the skeletal benefits appear to be lost fairly quickly (during the following 1 or 2 years).
Denosumab	Denosumab has been studied in trials of up to 6 years' duration. Efficacy and safety beyond 6 years have not yet been established, but clinical trials are likely to be extended through 10 years. When treatment with denosumab was stopped after 2 years, BMD decreased to baseline values and bone turnover markers increased to values above baseline by 12 months after discontinuation.

Data extracted from the AACE guidelines [123]

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