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ABSTRACT

Background: Osteoporosis is a highly prevalent disease and fractures are a major cause of disability and morbidity.

Aim: the purpose of this study was to characterise postmenopausal women attending osteoporosis centres in Italy, to evaluate physician management, and to determine the incidence of first osteoporotic fracture.

Subjects and methods: PROTEO-1 was an observational longitudinal study with a 12-month follow-up. Data were collected from women attending osteoporosis centres. Women without prevalent fracture were eligible to enter the 1-year follow-up phase: the clinical approach to patients according to their fracture risk profile and the incidence of fracture were recorded.

Results: 4269 patients were enrolled in 80 centres in the cross-sectional phase; 34.2% had an osteoporotic fracture at baseline. Patients with prevalent fractures were older and more likely to be treated compared with non-fractured patients. The incidence of vertebral or hip fracture after 1 year was 3.84%, regardless of the calculated risk factor profile, and was significantly higher in patients with back pain at baseline (4.2%) compared with those without back pain (2.2%; $p = 0.023$). Generally, physicians prescribed more blood exams and drugs to patients at higher risk of fracture. Among fractured patients only 24% were properly treated; the rate of non-responders to treatment was about 4%.

Conclusions: in a large, unselected sample of postmenopausal women attending osteoporosis centres, those without previous fracture were at substantial risk of future fracture, regardless of their theoretical low 10-year fracture risk. The presence of back pain in women without previous fracture warrants close attention.

INTRODUCTION

Osteoporosis is a highly prevalent condition and osteoporotic fractures are a major cause of disability and morbidity (1, 2). It has been estimated that, in the year 2000, there were some 9.0 million osteoporotic fractures worldwide, of which 1.6 million were of the hip (3). Hip fractures are probably the most serious clinical consequence of osteoporosis and are associated with a substantial risk of premature death (4, 5), which may persist for several years after the index fracture (6). Osteoporotic fractures impose a major burden on health care resources, and were estimated to have incurred direct costs of 36 billion Euros in Europe during 2000 (7). In Sweden, the cost of fractures represents approximately 3.2% of total annual health care costs (8). In Italy, the incidence of hospitalization following hip fracture is comparable to that of acute myocardial infarction, and incurs higher direct costs (9). The prevalence of osteoporosis, and the economic and social costs of osteoporotic fractures, are increasing and are predicted to increase further in coming decades (10-13).

Effective pharmacological and non-pharmacological interventions are available to reduce osteoporotic fracture risk (2, 14), and effective treatment has recently been shown to reduce mortality (15). However, targeting treatment in the most effective way remains a significant problem (16). Practice guidelines and case-finding procedures differ markedly between countries, but in many cases treatment strategies are based on secondary prevention in patients with previous osteoporotic (fragility) fracture, or are directed at women with osteoporosis, usually defined as a bone mineral density (BMD) T-score ≤-2.5 (16). It is not yet clear whether such approaches are appropriate, particularly in view of recent studies showing that the majority of

fragility fractures occur in women who do not have osteoporosis (17-20). Furthermore, several studies have shown that osteoporosis management in clinical practice currently falls short of guideline standards. Osteoporosis is widely under-diagnosed. In Denmark, for example, the observed incidence of diagnosed osteoporosis was an order of magnitude lower than expected from epidemiological data (21). Vertebral fractures often go unrecognised (22), and most women with diagnosed osteoporotic fractures do not undergo BMD assessment (23, 24). Treatment rates for secondary prevention are also low (25, 26). For example, in the US National Health and Nutrition Examination Survey only 17% of older women with previous fracture received specific anti-osteoporotic medication (27).

Information on the clinical profile and fracture risk of patients in clinical practice is limited, and the geographical variation in osteoporosis prevalence and fracture rates means that results may not transfer between countries. Italy is classed as a high-risk country for hip fracture in recent European guidelines (2). The PROTEO-1 (Primary pRevention Observational sTudy in ostEOporosis) study was designed to obtain data on the clinical characteristics and management of a sample of postmenopausal women attending osteoporosis centres in Italy, and to determine the actual incidence of first osteoporotic fracture in such a population.

SUBJECTS AND METHODS

PROTEO-1 was a multicentre, observational cohort study, performed in post-menopausal osteopenic and osteoporotic women attending specialist osteoporosis centres across Italy. At baseline, post-menopausal women who accessed the

participating specialist osteoporosis centres were enrolled; age and presence of previous fracture were recorded.

In patients without prevalent fracture, risk factors for fractures, exams and drug prescriptions were recorded. Patients were subsequently recalled to the centre for a follow-up visit after 12 months, at which the incidence of fragility fractures was recorded (Fig.1). In this set of patients the relative risk of hip and vertebral fractures after 10 years (10FR) was calculated by means of the algorithms for vertebral and hip fracture from the SIOMMMS (Italian Society of Osteoporosis, Mineral Metabolism and Skeletal Diseases) 2006 guidelines (Table 1).

Patients

The patient cohort was based on a consecutive sample of all post-menopausal women aged >50 and <85 years who accessed the participating specialist osteoporosis centres during the 3-month enrolment period. For inclusion, patients had to be osteopenic or osteoporotic according to the following criteria:

- Dual-energy X-ray absorptiometry (DXA) vertebral T-score <-2.0, or femoral neck or total hip T-score <-2.0;
- Ultrasound densitometry heel stiffness T-score <-2.0, or amplitude-dependent speed-of-sound (AD-SoS) proximal phalange T-score <-3.0.

Baseline

The aim of the baseline evaluation was to determine the prevalence of femoral and/or vertebral fragility fractures in the study sample. Fragility fractures were clinically defined as fractures occurring for minor trauma.

At enrolment, patients were divided into two groups according to the presence or absence of femoral and/or vertebral fragility fracture assessed at X-ray. In non-fractured patients, medical history, risk factors for osteoporosis and calcium intake were recorded. For fractured patients only age and site of fracture were recorded. The following risk factors were evaluated: bone density, age, family history of osteoporotic fracture, age at menopause, body weight, reduced visual acuity, use of steroids, immobility >3 months, disability, use of benzodiazepines, dietary intake of calcium and vitamin D, physical activity, smoking and alcohol abuse. Physical activity was considered present if patients regularly played sports or usually walked for more then 30 minutes outdoors, and smokers were classified as current, past or non-smokers. Alcohol intake was assessed as the number of units (defined as glass of alcoholic beverage) consumed per day, and patients were classified according to the following cut offs: <1, 1-2 , 2-4 and >4 units/day.

Non-fractured patients received appropriate therapy according to their physician's advice; the study protocol made no recommendations and set no requirements. These patients were invited to come back to the centre 12 months after enrolment; in the follow-up visit medical history was recorded, with particular attention to fragility fractures confirmed by X-rays and drugs prescribed. Blood and urinary exams, performed according to physician advice, were also recorded (Fig.1).

Follow up phase

The aims of the follow-up phase were to evaluate the incidence of fragility vertebral or femoral fractures in patients with no fractures at baseline according to their risk

profile, and to evaluate the diagnostic and therapeutic approach utilized by the physician.

The predictive value of the calculated 10FR based on the SIOMMMS algorithm (Table 1) was assessed using the observed osteoporotic spine and hip fracture incidence by means of a logistic regression model using maximum likelihood estimation. Patients were considered evaluable if they satisfied the inclusion and exclusion criteria and had a correct assessment of osteoporotic fracture status.

The first baseline visit was performed in September, 2007 and the study was completed in March, 2009. The study was performed in accordance with the Declaration of Helsinki and Italian and European Union regulations on the conduct of observational studies. All patients gave written, informed consent. The study was funded by an unrestricted grant by Servier Italia S.p.A.

Statistics

In the cross-sectional phase, the prevalence of femoral and/or vertebral fragility fracture was assessed and fractured and non-fractured patients were compared for age by means of an unpaired T test. Fractured and non-fractured subjects were divided into 10-year periods of age and odds ratios were calculated. Baseline characteristics among these periods were also compared by means of ANOVA or chi-squared test.

The 10FR for femoral or clinical vertebral fracture was calculated in non-fractured patients, in order to evaluate the relationship between 10FR and clinical management. The exams and drugs prescribed were evaluated according to 10FR by means of the chi-squared test using a 10FR cut-off of 20%.

In the longitudinal phase the incidence of femoral and/or vertebral fracture at 12 months follow-up was recorded. The incidence of fracture was analysed according to patient's age and 10FR by means of unpaired T tests. Additionally, treatment among fractured and non-fractured patients was compared by means of chi-square tests. In order to evaluate the dependence between 10FR and clinical management, drug prescription was evaluated according to 10FR by means of the Wilcoxon test.

The SAS 9.2 software package was used to process the data, and p-values were considered significant if equal or lower than 0.05.

RESULTS

Baseline

Prevalence of fragility fractures

A total of 4269 patients were enrolled in 80 centres, of which 4173 were eligible. Patients' mean age was 66.4 ± 8.4 (SD) years, and 1427 patients (34.2%) had experienced a previous vertebral or femoral fragility fracture; the most frequent fracture site was the thoracic vertebrae. Approximately 31% of fractured patients had more than 1 fracture, in particular about 20% of patients had multiple vertebral fractures and about 2% of patients with hip fracture had a concomitant vertebral fracture. Patients with osteoporotic fracture were significantly older (69.5 ± 8.0 years) than those without fracture (65.0 ± 8.1 years, $p < 0.001$). The prevalence of fracture was significantly higher after 80 years; the odds ratios related to age are shown in Figure 2. A high proportion (84%) of patients with fracture were treated with anti-osteoporotic drugs, compared with 51.7% of non-fractured patients ($p<0.0001$), confirming the attention paid by physicians to this severe form of osteoporosis.

Osteoporotic fractures were defined as fractures following minimal trauma and were confirmed by X-ray and medical exam.

Clinical features of non-fractured patients

The characteristics of patients without prevalent fractures (N = 2746) were evaluated in more detail. Most (1743 patients, 63.5%) were "self-referred" to the centres, whereas 563 patients (20.5%) were referred by their general practitioner and 310 (11.3%) were referred by a specialist. The most prevalent risk factor for osteoporotic fractures was lack of physical activity, in 60.1% of patients; other frequent risk factors included current or previous smoking (23.3%), and family history of osteoporotic fracture (20.4%). Sixty-four percent of non-fractured patients had experienced clinically significant back pain during the previous 12 months. During the previous 12 months, 2339 patients (85.2%) had undergone a DXA examination and 476 (17.3%) had been examined by ultrasonography. The total hip BMD T-score was -2.13 ± 0.78 (median -2.20), and vertebral BMD T-score was -2.83 ± 0.74 (median -2.80).

Ten-year risk of fracture

A full set of risk factors and BMD data were available for 1726 patients without fracture at baseline to enable calculation of their 10FR according to the algorithms given in the SIOMMMS 2006 guidelines. The distributions of patients' 10FR were markedly non-normal. The mean relative risk was 19.3 ± 30.9% for hip fracture and 16.2 ± 19.6% for clinical vertebral fracture, but the more representative median values were substantially lower, at 6.9% for hip fracture and 6.1% for vertebral fracture. The proportion of patients with 10FR ≥20% was 18.8% for hip fracture and 30.8% for clinical vertebral fracture.

Clinical management of non fractured patients at baseline

In order to evaluate physicians' diagnostic approach to non-fractured patients, data on laboratory tests undergone by patients without osteoporotic fracture were collected. SIOMMMS guidelines classify such tests into first- and second-level tests. Of the first-level tests, the most frequently performed was serum calcium (40.7% of patients), followed by complete blood count (39.7%) (Table 2). Second-level tests were performed less frequently, the most frequent being transaminases and thyroid hormone tests.

In order to evaluate whether the physician had taken into account the patient's risk profile in order to prescribe blood exams, we divided patients into high risk (10FR >20%) and low risk (10FR ≤20%) and analysed blood exams (first or second level) according to this division. Table 3 shows that physicians tended to prescribe exams in patients at higher risk of fractures.

Follow-up

Incidence of fracture and 10-year relative risk

A total of 2082 patients entered the longitudinal phase of the study and were evaluated for the incidence of osteoporotic spine or hip fracture. Of these patients 80.21% were treated with anti-osteoporotic treatment, an increase of about 30% from the baseline enrolment.

At the end of the 1-year longitudinal phase, 71 patients had experienced a first osteoporotic vertebral or hip fracture, with an incidence of 3.41% (95% confidence

interval 2.63% to 4.19%). The incidence of vertebral fracture was much higher (67 patients, 3.22%) than the incidence of hip fracture (4 patients, 0.19%). Sixteen patients experienced a non-hip, non-vertebral fracture (0.86%), involving wrist (8 patients, 0.38%), ribs (5 patients, 0.24%), tibia (2 patients, 0.1%) and humerus (1 patient, 0.05%). The total incidence of all osteoporotic fractures was 4.27% (95% CI 3.41% to 5.14%), and the incidence did not differ significantly with age. The incidence of vertebral or hip fracture was significantly higher among patients with back pain at baseline (56/1336; 4.19%) than among those without back pain (14/644; 2.17%; $p = 0.023$).

A total of 1694 patients had a femoral DXA evaluation and were evaluable for calculation of 10FR according to the SIOMMMS 2006 algorithms and were also evaluable for the actual incidence of hip and vertebral fractures in the longitudinal phase. In this group the mean femoral BMD T-score was -2.11 ± 0.65 (median -2.10), similar to that of the longitudinal phase sample as a whole. The observed 1-year incidence of osteoporotic spine or hip fracture in this group was 65/1694 (3.84%). The femoral and lumbar BMD was not significantly different among fractured and non-fractured patients (data not shown).

The mean 10FR was $15.05 \pm 18.84\%$ for the cohort of patients in the follow-up. Fracture incidence was not markedly different between subgroups of patients with lower and higher calculated baseline 10FR. The observed fracture incidence was 3.64% in patients with 10FR below the sample median of 5.65%, compared with an incidence of 4.03% in those with greater than the median risk. Similarly, the observed fracture incidence was 3.74% in the 1222 patients with baseline 10-year vertebral

relative risk ≤20%, compared with 4.03% in the 472 patients with relative risk >20%. For femoral fractures the observed fracture incidence was 4.01% in patients below the sample median relative risk of 6.24%, compared with 3.66% in those with greater than the median risk. Finally, the observed fracture incidence was 4.17% in the 1391 patients with 10-year relative risk of hip fracture ≤20%, compared with 2.31% in the 303 patients with relative hip fracture risk >20%. Logistic regression modelling indicated that the observed incidence of osteoporotic spine and hip fractures was significantly higher than predicted by the 10FR calculated using the SIOMMMS 2006 algorithms ($p < 0.001$).

Pharmacological treatment of non fractured patients.

Of the whole cohort, 1670 patients (80.2%) were prescribed pharmacological anti-osteoporotic therapy; the most frequently prescribed therapies are shown in Table 4.

In order to evaluate if drug prescription was in line with the calculated relative risk of fracture, the 10FR was compared between treated and non-treated patients. Mean 10FR was 19.48 ± 31.38% in treated patients compared with 13.52 ± 26.85 in non-treated patients ($p<0.0001$), indicating that physicians were more likely to prescribe therapy in patients with higher 10FR.

Among patients with vertebral or hip fracture, 31 (43.7%) were treated with oral bisphosphonates, 19 (26.8%) with bone-forming agents, 13 (18.3%) with intramuscular clodronate, 6 (16.7%) with neridronate, 1 (1.4%) with raloxifene and 1 (1.4%) with 1 alpha o 1-25-dihidroxy vitamin D. Data on the duration and the adherence to treatment are lacking.

DISCUSSION

The PROTEO-1 study consisted of two phases, each providing information on different aspects of osteoporosis and fragility fractures in clinical practice. The first, baseline evaluation provided a snapshot of a sample of 4269 consecutive postmenopausal patients attending specialist osteoporosis centres in Italy. Approximately one third of the sample (34%) had prevalent vertebral or hip fracture, and of these, 31% had two or more such fractures. Several studies have shown that patients with a previous osteoporotic fracture are at substantially elevated risk of further fractures. This is especially true for vertebral fractures, such that women with previous vertebral fracture have approximately four times greater risk of subsequent vertebral fractures than those without previous fractures (28, 29). It is widely accepted that patients with previous osteoporotic fractures should receive comprehensive evaluation and anti-osteoporotic treatment if appropriate. Consistent with this, a high proportion of such patients (84%) were receiving pharmacological anti-osteoporotic treatment.

The group of patients in our sample without previous osteoporotic fracture represents a more complex challenge to treatment decision making, and were studied in greater detail. This group had a mean age of 65 years and mean BMD T-scores of -2.13 for total hip and -2.83 for spine, and the majority would meet the widely accepted definition for osteoporosis of a T-score <-2.5 at either site (2). Their 10FR, calculated using BMD measurements and clinical risk factors using algorithms from SIOMMMS 2006 (in turn based on those in (30)), were quite low, with medians of 6.9% and 6.1% for hip and vertebral fractures, respectively. The management of the group of patients

without previous fracture was consistent with their being perceived as low-risk patients. DXA was the only examination that was widely performed (in 81% of patients). Serum calcium was measured in only a minority of patients (41%), and vitamin D status was only determined by laboratory test in 12% of patients. Generally, physicians tended to prescribe the use of laboratory tests according to the patient's risk of fracture profile, especially as regards to level II exams. At baseline, only about one half of patients without prevalent fractures received pharmacological anti-osteoporotic treatment, and a similar proportion received calcium and vitamin D supplementation, consistent with their low risk profile. At the follow-up visit the percentage of patients treated increased to 80%, and physicians tended to treat patients at higher risk of fracture according to the SIOMMMS algorithm.

Patients without prevalent fractures were eligible for the 1-year prospective longitudinal phase of the study. In this phase, the observed 1-year incidence of hip and spine fracture was 3.41%, and was dominated by spine fractures (3.22%), with a relatively low incidence of hip fractures (0.19%). This overall incidence is high relative to published studies of patients without previous fracture (20, 31-33). In the studies of patients without previous fracture the overall incidence of fractures is lower than the incidence observed in this study and ranges between 1% and 2.6% per year. The incidence of vertebral fractures in this study is comparable to the incidences seen in the placebo groups in recent randomised trials that included patients at higher risk, with previous fractures. For example, in the HORIZON trial of zoledronic acid the 1-year incidence of vertebral fracture was 3.7% in the placebo group (34). Similarly, in the FREEDOM trial of denosumab the 1-year incidence of new vertebral fracture was approximately 2.2% in the placebo group (35).

The low proportion of hip fractures seen in the longitudinal phase (6% hip, 94% vertebral) was also observed in a recent analysis of patients without previous fractures in the MORE trial (32), where hip fractures again comprised only 6% of the combined hip and spine total. This may be related to the relatively young age of patients (approximately 65 years) in both studies; the incidence of hip fractures increases more steeply with age than vertebral fractures, and the median age for hip fracture in women is approximately 83 years (36, 37).

The incidence of fractures was not significantly influenced by age; this finding could be explained by the low number of fractures observed. The majority (64%) of patients without prevalent fracture at baseline had experienced clinically significant back pain, and these patients had a higher incidence of osteoporotic fracture during the longitudinal phase than patients without back pain. Back pain is not generally regarded as a clinical risk factor for future vertebral fracture. For example, back pain was not found to be a significant risk factor for first vertebral fracture in multivariable models in women (mean age 70.8 years) in the Study of Osteoporotic Fractures in the USA (38, 39). However, in a recent cross-sectional and prospective longitudinal study in Japan, back pain was a significant risk factor for future vertebral fracture ($p = 0.005$) after adjustment for traditional risk factors including age, BMD, and previous vertebral fractures (40). Back pain may indicate the presence of micro-fractures, vertebral degeneration or postural abnormalities that may increase fracture risk. Back pain may be especially prevalent in the present study population; many of whom spontaneously visited a specialist centre ("self-referral") and whose visit may have

been prompted by pain. However, in this population it proved to be a symptom deserving careful attention.

It is noteworthy that 80% of women in the PROTEO-1 longitudinal phase were treated with anti-osteoporotic drugs, but despite the treatment a high number of patients experienced a fracture. However, we do not have data on adherence to treatment and on the duration of treatment, and these shortcomings complicate the interpretation of this finding.

In the subpopulation of patients whose 10FR, based on DXA assessment and clinical risk factors, and observed 1-year fracture incidence were evaluated, the incidence of fractures was significantly higher than predicted. It is possible that the SIOMMMS 2006 algorithms underestimate absolute fracture risk in such populations, and that more recent risk prediction instruments might be more accurate. Although testing the accuracy of algorithms was not the main objective of the longitudinal phase of PROTEO-1, the 10FR estimation allowed an assessment of the distribution of fractures among patients with different levels of risk. A potential explanation of the unexpectedly high incidence of fractures in this sample of apparently low-risk patients might have been that a high proportion of fractures occurred in a small proportion of very high-risk patients. However, this does not seem to have been the case. When groups of patients with 10FR above and below 20%, or above and below the sample median, were compared, the incidence of fractures did not differ markedly. This indicates that the observed fractures were not concentrated in a small proportion of exceptionally high-risk patients.

There has been increasing interest in treatment thresholds based on the individual's absolute risk of fracture (41). Various algorithms have been developed, including the FRAX risk assessment tool, which calculates absolute risk based on clinical risk factors with or without BMD measurements (42). Other models, including simple algorithms based on age and BMD, age and fracture history, or clinical risk factors alone have been evaluated and found to perform similarly to FRAX (42). Country-specific versions of FRAX are now being developed (43, 44), but it has not yet been validated in a Mediterranean patient population.

Regarding the attention paid by physicians towards patients' risk profile in clinical decision making, it is interesting to note that physicians were more likely to treat patients at higher risk according to 10FR. In fact, treated patients had higher 10FR scores than non-treated ones, even if the 10FR was below the chosen cut-off of 20%. In this regard it is important to underline that low bone mineral density cannot be the only decision element in order to start a treatment, but a global risk assessment has to be performed.

The main limitations of this study were the lack of data on the incidence of non-clinical vertebral fractures that could explain the higher risk of fractures in patients with back pain at baseline, and the lack of data on adherence to therapy and on correct supplementation with calcium and vitamin D.

The main conclusion of the PROTEO-1 study was that a large, unselected, consecutive sample of postmenopausal women attending osteoporosis centres in Italy represented a group at substantial risk of future fracture who warrant comprehensive

evaluation. Approximately one-third of the sample had one or more prevalent fractures and should be considered for secondary preventive treatment. Perhaps more importantly, the remaining two-thirds of patients without previous fracture, with a mean age of 65 years, were shown to have a high 1-year incidence of osteoporotic fractures, comparable to patients included in recent intervention trials of anti-osteoporotic drugs.

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TABLES

Table 1. Algorithms for calculating 10-year relative risk of vertebral and hip fracture, according to SIOMMMS 2006 guidelines.

Vertebral fracture using hip BMD T-score: 10-year RR = (1.12 × Age) – (0.008 × Age^2) – (2.3 × Hip BMD T-score) – (0.24 × BMI) – 33
Vertebral fracture using amplitude-dependent speed-of-sound (AD-SoS) proximal phalange BMD T-score: 10-year RR = (1.12 × Age) – (0.008 × Age^2) – (0.8 × AD-SoS T-score) – (0.24 × BMI) – 33
Hip fracture using hip BMD T-score: 10-year RR = (0.33 × Age) – (4.31 × Hip BMD T-score) – 0.25 × BMI) – 20.7
In each case, risk is adjusted according to the presence of the following risk factors: Smoking >10 cigarettes/day +12% Family history of vertebral fracture +59% Rheumatoid arthritis +26% Previous wrist fracture +23% Menopause before age 46 years +27%

BMD: bone mineral density; BMI: body mass index (kg/m^2); RR: relative risk

Table 2. Use of first- and second-level laboratory tests in patients without osteoporotic fracture at baseline

Test	**Patients, n (%)** **N = 2746**
First-level tests	
Blood calcium	1117 (40.7)
Complete blood count	1091 (39.7)
Total alkaline phosphatase	939 (34.2)
Erythrocyte sedimentation rate	921 (33.5)
Plasma creatinine	881 (32.1)
Plasma phosphate	876 (31.9)
Fractionated blood protein (protidaemia)	736 (26.8)
24-hour urinary calcium	417 (15.2)
Second-level tests	
Transaminases	686 (25.0)
Thyroid hormones: TSH, FT4, FT3	573 (20.9)
Serum parathyroid hormone	498 (18.1)
Serum 25-OH-vitamin D	324 (11.8)
Specific pathology tests	70 (2.55)
Urine protein electrophoresis	64 (2.3)
Antibody tests: anti-gliadin, anti-endomysium, anti-transglutaminases	34 (1.2)
24-hour urinary cortisol	6 (0.22)

Table 3. Use of laboratory exams (first- and second-level tests) are indicated according to the 10FR for vertebral or femoral fracture. Number of patients and percentage (in brackets) are indicated. p-value lower than 0.05 is indicated by grey cells.

	Clinical vertebral fracture		**Femoral fracture**	
	10FR ≤20%	**10FR >20%**	**10FR ≤20%**	**10FR >20%**
First level tests				
Blood calcium	476 (39.87)	224 (42.11)	564 (40.26)	136 (41.85)
Complete blood count	469 (39.28)	240 (45.11)	559 (39.90)	150 (46.15)
Total alkaline phosphatase	421 (35.26)	202 (37.97)	491 (35.05)	132 (40.62)
Erythrocyte sedimentation rate	469 (32.5)	184 (34.59)	442 (31.55)	130 (40)
Plasma creatinine	393 (32.91)	200 (37.59)	474 (33.83)	119 (36.62)
Plasma phosphate	366 (30.65)	161 (30.26)	424 (30.26)	103 (31.69)
Fractionated blood protein (protidaemia)	302 (25.29)	157 (29.51)	367 (26.20)	92 (28.31)
24-hour urinary calcium	203 (17)	91 (17.11)	231 (16.49)	63 (19.38)
Second level tests				
Transaminases	303 (25.38)	160 (31.08)	361 (25.77)	102 (31.38)
Thyroid hormones: TSH, FT4, FT3	253 (21.19)	121 (22.74)	309 (22.06)	65 (20)
Serum parathyroid hormone	230 (19.26)	112 (21.05)	272 (19.41)	70 (21.54)
Serum 25-OH-vitamin D	153 (12.81)	69 (12.97)	182 (12.99)	40 (12.31)
Bone turnover markers	126 (10.55)	64 (12.03)	160 (11.42)	30 (9.23)
Specific pathology tests	29 (2.43)	23 (4.32)	33 (2.36)	19 (5.85)
Urine protein electrophoresis	33 (2.76)	18 (3.38)	45 (3.21)	6 (1.85)
Antibody tests: anti-gliadin, anti-endomysium, anti-transglutaminases	13 (1.09)	7 (1.32)	13 (0.93)	7 (2.15)
24-hour urinary cortisol	2 (0.17)	2 (0.38)	3 (0.21)	1 (0.31)

Table 4. Most frequently prescribed anti-osteoporotic therapies during the longitudinal phase

Therapy	**Patients (N = 2082)**	
	n	**%**
Strontium ranelate	711	34.2
Bisphosphonates	964	46.30
Raloxifene	42	2.0
1-alpha-o 1-25-OH vitamin D3	20	0.96

FIGURE LEGENDS.

Figure 1. Graph shows the study design.

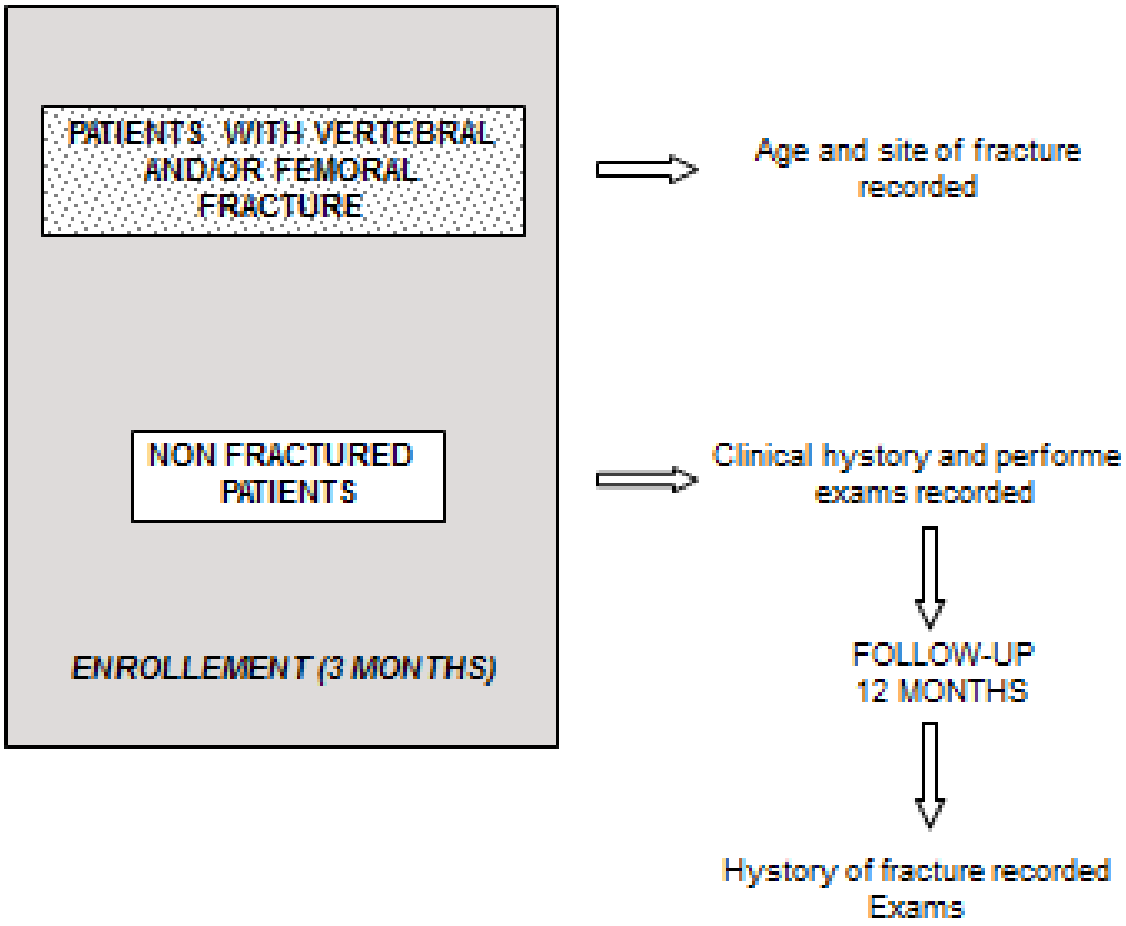

Figure 2. Graph shows the odds ratios (OR) and the corresponding confidence intervals (CI) for fractures between 80-85 years and the indicated years of age periods. OR 1 is indicated by the dotted line.