Characterization of patients with an inadequate clinical outcome from osteoporosis therapy: the Observational Study of Severe Osteoporosis (OSSO)


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Summary

Background: Osteoporotic fractures remain a major public health problem. Currently available osteoporosis therapies significantly reduce the risk of fractures, but up to 50% of patients have an inadequate clinical outcome to therapy.

Aim: To describe the clinical and quality of life (QOL) of a study population meeting a proposed definition of inadequate clinical outcome to osteoporosis therapy, recruited for the Observational Study of Severe Osteoporosis (OSSO).

Design: Cross-sectional, observational study.

Methods: Post-menopausal women with osteoporosis (n = 2314) were divided into Group 1 (those who had previously experienced a fragility fracture despite osteoporosis drug therapy for at least 12 months) (n = 1309, 57%), or Group 2 (those who had previously discontinued osteoporosis drug therapy due to non-compliance or side-effects) (n = 1005; 43%). Baseline clinical characteristics, quality of life (QOL) and osteoporosis/falls risk factors were analysed.

Results: The overall population had low BMD (mean ± SD T-score at lumbar spine −3.1 ± 1.1), and risk factors for fracture such as previous fractures (67.8%), family history (15.1%), and prolonged glucocorticoid use (17.5%). QOL was poor: total QUALEFFO and EQ-5D scores were 46.8 ± 18.7, and 0.50 ± 0.33, respectively. Patients in Group 1 had higher age and body mass index, fewer hours of exercise, more previous fragility fractures and falls, and poorer QOL scores.

Discussion: Our definition of inadequate clinical outcome from osteoporosis drug therapy identifies a severe osteoporosis cohort with poor QOL and increased fracture risk. Using such a definition may lead to earlier recognition of inadequate clinical outcome to osteoporosis therapy, and improved interventions and results.
Introduction

Osteoporosis is a skeletal disorder characterized by decreased bone mass and deterioration of bone micro-architecture, leading to increased bone fragility and susceptibility to fracture. Osteoporosis-related fractures are associated with significant morbidity and mortality. Their non-fatal consequences include pain, physical impairment and loss of functional ability, which can have significant adverse effects on patient quality of life. There are also substantial costs to society in terms of diminished activity, hospitalization and lengthy stays in nursing homes.

The primary aims of therapeutic intervention in osteoporosis are to prevent the first fragility fracture from occurring, and to prevent subsequent fractures in those who already have an existing fracture. There is strong evidence from large randomized controlled trials for the efficacy of currently available therapies in reducing the risk of fracture in patients with osteoporosis, with the efficacy data being generally stronger for vertebral than for non-vertebral fractures. However, none of the currently available medications completely abolishes the risk of fracture, and clinical trials have demonstrated that a significant proportion of patients with existing fractures will sustain new fractures in a relatively short period while they are on osteoporosis therapy. Moreover, non-compliance with osteoporosis drug therapy and drug discontinuation is unacceptably high, especially in clinical practice. A major reason for discontinuation of osteoporosis therapy is the occurrence of adverse side-effects.

This concept of inadequate response to, or failure of, osteoporosis therapy has been raised in recent therapeutic guidelines for osteoporosis drugs, where various bodies have sought to define appropriate roles for new and existing therapies. However, there is no consensus on what constitutes an inadequate clinical response to osteoporosis therapy. Moreover, non-compliance with osteoporosis drug therapy and drug discontinuation is unacceptably high, especially in clinical practice. A major reason for discontinuation of osteoporosis therapy is the occurrence of adverse side-effects.

However, therapy-associated changes in BMD vary considerably between individuals, and between drugs registered for osteoporosis therapy, and there is only a weak correlation between changes in BMD and fracture rate. Thus, the use of bone densitometry to monitor treatment response is controversial, and the lack of a significant increase in BMD is not generally accepted as an inadequate response to therapy. Other methods for measuring responsiveness to therapy, such as monitoring biochemical markers of bone metabolism, are not well established in clinical practice.

The Observational Study of Severe Osteoporosis (OSSO) is the first prospective study designed to analyse the impact of an inadequate clinical outcome to osteoporosis drug therapy in the observational setting. The primary objective is to evaluate changes in health-related quality of life in postmenopausal women with osteoporosis who have an inadequate response to anti-resorptive medications. The OSSO study will also determine resource utilization and identify risk factors associated with fracture in patients with an inadequate response to osteoporosis drug therapy.

We present the baseline clinical and quality of life characteristics of our study population, and the risk factor differences between the two subgroup categories of inadequate clinical outcome to osteoporosis drugs.

Methods

Study design

OSSO is a multinational, 12-month prospective observational study in the out-patient setting at 469 sites in six European countries: France, Germany, Greece, Portugal, Spain and the UK. Recruitment commenced in April 2003 and was completed in June 2004. The study was approved by local ethics committees or review boards, depending on the local requirements for each participating country. All patients gave informed consent for the provision and collection of data regarding care and outcomes for a period of at least one year. Investigators were recruited from a variety of specialties, and included rheumatologists, internists, endocrinologists and orthopaedists.

Investigators were asked to consecutively screen all postmenopausal women with a naturally occurring visit for study eligibility. They offered enrolment to all postmenopausal women with diagnosed osteoporosis and a well-documented inadequate clinical response to osteoporosis medications. Diagnosis of osteoporosis was based...
on axial or peripheral dual X-ray absorptiometry (DXA) bone mineral density measurements, or conventional X-ray, and was confirmed by physician review of medical reports or radiographs. Inadequate clinical outcome to osteoporosis drug therapy was defined as: (i) a past history of fragility fracture sustained despite prescription of any approved osteoporosis treatment for at least 12 months prior to this fracture (index fracture group); and/or (ii) a past history of discontinuation of any approved osteoporosis drug therapy due to compliance problems and/or side-effects. Patients were excluded from the study if they were currently being treated with an investigational drug or procedure.

**Data collection**

At the baseline visit, the following data were collected: patient demographics, medical and osteoporosis history, risk factors for osteoporosis and falls, medication use, disease status, health-related quality of life and medical resource use. Subsequent data collections at 6 and 12 months will include medical history, medication use, quality of life, medical resource use and data on new incident fractures.

The patients’ demographic and reproductive characteristics recorded at baseline were: age, race, weight, height, age at menarche, age at menopause, type of menopause and parity. Details about the following clinical and lifestyle risk factors were collected: history of fragility fractures after age 40 years, history of fragility hip fracture in the mother, number of falls in the last year, problems with sense organs, smoking status, alcohol consumption, regular exercise and mobility status. The presence of concurrent diseases, or previous and current use of certain drugs that may increase the risk of osteoporosis or falls was recorded. Details of the date and method of diagnosis of osteoporosis (DXA or conventional X-ray) were collected, together with the BMD T- and Z-score values (i.e. the number of standard deviations below the peak bone mass of young adults, and of age-matched subjects of the same sex, respectively). Details of previous osteoporosis drugs that were being taken at the time of the index fracture or discontinued due to adverse events or non-compliance, were recorded, together with the start and stop dates, dose and reasons for discontinuation.

Health-related quality of life was assessed by patients using two self-administered questionnaires: the osteoporosis disease-specific QUALEFFO questionnaire developed by the Working Party for Quality of Life of the European Foundation for Osteoporosis; and the generic health-related quality of life instrument EuroQoL.

**Analysis**

Patients eligible for analysis were included in either Group 1 (index fracture) or Group 2 (compliance/side-effects), based on the entry criteria. Those satisfying the criteria for both groups were assigned a group according to the event that occurred first. In cases where both events occurred in the same month and year, or where the order of events could not be determined, patients were included in Group 1, due to fracture being the most clinically relevant event. Patients were excluded from the analysis if only vitamin D and/or calcium was recorded as their osteoporosis medication at the time of index fracture or discontinuation due to non-compliance or side-effects.

Data management and analysis were centralized, and analyses were conducted according to a pre-specified plan. Descriptive summary statistics such as frequencies, percentages, means and standard deviations (SD) were used to describe the study population at baseline. Comparisons between Groups 1 and 2 were generally made using t-tests for continuous data; however, when the normality assumption was violated, data were either transformed prior to analysis or non-parametric tests were used. χ² tests were used for categorical data. After applying a Bonferroni correction, p values less than 0.003 were considered statistically significant, giving an overall significance level of 0.10 across all tests. Analyses were carried out using SAS software version 8.

**Results**

A total of 2314 patients were included in the analysis of the baseline characteristics. The number of patients in each participating country by eligibility group (1 vs. 2) is summarized in Table 1. Initially, 1085 patients (46.9%) were eligible solely because of an index fracture, 856 (37.0%) solely because of discontinuation of osteoporosis drug therapy (for reasons of non-compliance and/or side-effects), and 373 (16.1%) satisfied both these criteria. Of these 373 satisfying both criteria, 224 (60.1%) patients were placed in Group 1 and the remaining 149 (39.9%) in Group 2 (see Methods for explanation).

Thus Group 1 included 1309 patients (56.6%) and Group 2, 1005 patients (43.4%). This means that 17.1% of patients in Group 1 had also discontinued an osteoporosis therapy and 14.8% of those in Group 2 had also experienced an index fracture.
Table 1 shows baseline demographic and reproductive characteristics of the women taking part in the OSSO study. All patients were Caucasian, had a mean SD age of 70.2 ± 9.0 years (range 35.3–93.8 years), were a mean SD 23.2 ± 9.8 years post-menopausal, and had a mean SD body mass index (BMI) of 25.8 ± 4.4 kg/m². Overall, the two groups showed similar demographic characteristics (Table 2), except that patients in Group 1 were older (mean SD age 71.2 ± 8.9 vs. 69.0 ± 9.0 years, p < 0.001), had a higher BMI (mean 26.1 vs. 25.4 kg/m², p < 0.001) and had been post-menopausal for longer (mean 23.7 vs. 22.4 years, p = 0.002) than those in Group 2.

**Risk factors for fracture**

Clinical and lifestyle risk factors for osteoporotic fracture at baseline are summarized in Table 3. The two groups were similar in terms of the main risk factors for fracture at baseline, except that significantly more patients in Group 1 than in Group 2 reported previous historical fractures (excluding the index fracture) (73.8% vs. 59.9%, p < 0.001), and they had a longer time since the diagnosis of osteoporosis (Table 3). In Group 1, 34.4% of patients had a single previous fracture and 39.4% of patients had two or more previous fractures, whereas in Group 2, 30.1% of patients had a single previous fracture and 29.8% of patients had two or more previous fractures (all values exclude index fractures). Women in Group 2 had a higher frequency of alcoholic drink intake (Table 3).

The majority of patients (80.1%) had their osteoporosis diagnosed by DXA. The mean latest lumbar spine and femoral neck BMD T- and Z-scores were similar in both groups (Table 3).

Baseline fall-related risk factors for fracture are summarized in Table 4. The number of patients who...
reported one or more falls during the last year was significantly higher in Group 1 (50.5% vs. 38.4%, \( p < 0.001 \)), and a significantly higher proportion of women in Group 1 vs. Group 2 needed to use their arms to stand up from a chair (57.6% vs. 50.3%, \( p < 0.001 \)). Levels of physical activity were low (mean 3.0 h exercise per week for the total study population) and were similar between groups, but there was high variability (Table 4).

### Medications and concurrent diseases related to the risk of osteoporosis and falls

At baseline, 57.3% of all patients for whom data was available were currently taking medications related to the risk of osteoporosis and falls (Table 5). Antihypertensives were the most commonly used medication in the total population (31.5%), and their use was similar in both groups. Glucocorticoids, antidepressants and thyroid hormones were the next most commonly used medications in the total study population (used by 12.3%, 11.5% and 11.3% of patients, respectively; there were no significant differences between groups in terms of glucocorticoid and antidepressant use, but thyroid hormones were used by significantly more patients in Group 2 than in Group 1 (13.7% vs. 9.4%, \( p = 0.001 \)).

Twenty-seven percent of all patients had concurrent diseases related to the risk of osteoporosis and falls at baseline, most commonly rheumatoid arthritis (10.4%) and chronic obstructive pulmonary disease (6.7%) (Table 6). Each of the other specified diseases occurred in <5% of the total population. There were no significant differences between the two groups in the overall prevalence of concurrent diseases or in the prevalence of specific concurrent diseases (Table 6).

### Quality of life

The baseline mean EQ-5D Health State Value (HSV) for the total OSSO population was 0.50 ± 0.33. The baseline HSV was significantly lower (i.e. worse quality of life) for patients in Group 1 (0.47 ± 0.34) vs Group 2 (0.53 ± 0.32) \( (p < 0.001) \). The baseline
mean EQ-5D patient scored visual analogue scale (VAS) for the total OSSO population was 54.0 ± 19.3. The baseline VAS was also significantly lower (i.e., worse quality of life) for patients in Group 1 (52.1 ± 19.2) vs. Group 2 (56.3 ± 19.1) (p < 0.001). Overall, 21.9% of patients reported extreme problems in pain or discomfort (25.0% in Group 1, 18.1% in Group 2).

Baseline mean Total QUALEFFO score for the total OSSO population was 46.8 ± 18.7. Women in Group 1 had higher total QUALEFFO score (i.e., worse quality of life) than those in Group 2 (49.0 ± 18.4 vs. 44.0 ± 18.6; p < 0.001). Similar results were found for each QUALEFFO sub-domain (data not shown).

**Index fractures**

An index fracture was defined as a past clinical or radiographic fragility fracture sustained despite osteoporosis drug therapy for at least 12 months before the fracture. At study baseline, the median time since index fracture was 5.0 months (range 0–206 months). Overall, there were data on 1446 index fracture locations; Figure 1 shows their distribution. The most common locations were: vertebra (61.3%), forearm/wrist (12.0%) and hip (6.4%). All other types of fractures occurred at a rate of <5% each.

Of the 1298 patients with data on osteoporosis medications at the time of index fracture, 389 (30%) were taking more than one osteoporosis drug. Alendronate was taken by 46.8%, followed by risedronate (23.1%), calcitonin (19.5%), etidronate (16.4%) and raloxifene (12.2%). The antiresorptive therapy duration before the index fracture occurred were 24, 42, 18, 22 and 26 months, respectively.

**Compliance/side-effects**

Sixty percent of the women in Group 2 (the compliance/side-effects group) reported a history of previous fragility fracture (Table 3). Of the 1005

### Table 5 Current use of medications related to the risk of osteoporosis and falls (%)

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 2287)</th>
<th>Group 1 (n = 1296)</th>
<th>Group 2 (n = 991)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensives</td>
<td>31.5</td>
<td>33.7</td>
<td>28.6</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>12.3</td>
<td>12.4</td>
<td>12.2</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>11.5</td>
<td>12</td>
<td>10.7</td>
</tr>
<tr>
<td>Thyroid hormones*</td>
<td>11.3</td>
<td>9.4</td>
<td>13.7</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>9.5</td>
<td>10.3</td>
<td>8.5</td>
</tr>
<tr>
<td>Anti-arrhythmics</td>
<td>6.2</td>
<td>6.5</td>
<td>5.9</td>
</tr>
<tr>
<td>Oral anticoagulants/heparin</td>
<td>5.2</td>
<td>5.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Insulins/oral hypoglycaemics</td>
<td>4.5</td>
<td>4.6</td>
<td>4.4</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>2.0</td>
<td>2.1</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Data represent number of women taking the specified medication relative to the number for whom data was available. *p < 0.003.

### Table 6 Concurrent disease status

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 2174)</th>
<th>Group 1 (n = 1233)</th>
<th>Group 2 (n = 951)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>10.4</td>
<td>11.1</td>
<td>9.5</td>
</tr>
<tr>
<td>Chronic pulmonary obstructive disease</td>
<td>6.7</td>
<td>5.6</td>
<td>8.0</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>2.6</td>
<td>2.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Chronic inflammatory intestinal disease</td>
<td>2.4</td>
<td>1.7</td>
<td>3.4</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>2.1</td>
<td>1.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Parkinson’s disease and other movement disorders</td>
<td>1.7</td>
<td>2.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Urolithiasis</td>
<td>1.7</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1.6</td>
<td>1.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.2</td>
<td>1.1</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*Data (all percentages) are relative to the number of patients who responded to the question. Disorders reported in <1% of the study population are not included.*
women in this group, 855 (85.3%) patients were included because they experienced side-effects during osteoporosis therapy. At the time of discontinuation due to non-compliance or side-effects, 349 (34.7%) were taking more than one osteoporosis medication.

The reasons for discontinuation are summarized by osteoporosis medication in Table 7. Non-compliance as the reason for discontinuation was more frequently observed in calcitonin (27.4%) and hormone therapy (HT) (oestrogens plus gestagens) (24.1%) users, while it was observed in approximately 15% of patients receiving oral bisphosphonates and 11% in raloxifene users (Table 7). Discontinuation due to osteoporosis medication-related side effects was more frequently observed with oral nitrogen-containing bisphosphonates (72.7% and 75.6% for alendronate and risedronate, respectively), and raloxifene (68.1%). Gastrointestinal problems were the main reason for discontinuing alendronate (62.7%), risedronate (62.2%) and etidronate (48.5%), but were the reason for drug discontinuation in <21% of the patients treated with other anti-resorptives (Table 7). Rhinitis was the cause of 17.7% of calcitonin discontinuations, and breast symptoms were the
Table 7  Reasons for drug discontinuation, by anti-resorptive medication

<table>
<thead>
<tr>
<th>Anti-resorptive medication</th>
<th>Non-compliance</th>
<th>Side-effects</th>
<th></th>
<th></th>
<th>Thromboembolic events</th>
<th>Uterine bleeding</th>
<th>Breast symptoms</th>
<th>Rhinitis</th>
<th>Virilizing effects</th>
<th>Other adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GI symptoms</td>
<td>Hot flushes</td>
<td>Leg cramps</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate (n=517)</td>
<td>14.9</td>
<td>62.7</td>
<td>0.6</td>
<td>0.8</td>
<td>–</td>
<td>–</td>
<td>1.2</td>
<td>–</td>
<td>–</td>
<td>7.5</td>
</tr>
<tr>
<td>Risedronate (n=254)</td>
<td>11.4</td>
<td>62.2</td>
<td>0.4</td>
<td>1.2</td>
<td>0.4</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>11.4</td>
</tr>
<tr>
<td>Etidronate (n=171)</td>
<td>11.1</td>
<td>48.5</td>
<td>0.6</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.6</td>
<td>–</td>
<td>–</td>
<td>7.6</td>
</tr>
<tr>
<td>Raloxifene (n=160)</td>
<td>11.3</td>
<td>20.6</td>
<td>15.6</td>
<td>11.9</td>
<td>5.0</td>
<td>3.1</td>
<td>3.1</td>
<td>–</td>
<td>–</td>
<td>8.8</td>
</tr>
<tr>
<td>Calcitonin (n=124)</td>
<td>27.4</td>
<td>12.1</td>
<td>11.3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.6</td>
<td>17.7</td>
<td>–</td>
<td>9.7</td>
</tr>
<tr>
<td>HT (n=83)</td>
<td>24.1</td>
<td>–</td>
<td>1.2</td>
<td>–</td>
<td>7.2</td>
<td>7.2</td>
<td>14.5</td>
<td>–</td>
<td>2.4</td>
<td>15.7</td>
</tr>
<tr>
<td>Pamidronate (n=32)</td>
<td>3.1</td>
<td>9.4</td>
<td>–</td>
<td>–</td>
<td>3.1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>28.1</td>
</tr>
<tr>
<td>ET (n=27)</td>
<td>18.5</td>
<td>3.7</td>
<td>3.7</td>
<td>–</td>
<td>3.7</td>
<td>3.7</td>
<td>18.5</td>
<td>–</td>
<td>–</td>
<td>18.5</td>
</tr>
<tr>
<td>Fluoride (n=16)</td>
<td>6.3</td>
<td>12.5</td>
<td>–</td>
<td>6.3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>37.5</td>
</tr>
<tr>
<td>Tibolone (n=6)</td>
<td>16.7</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>16.7</td>
<td>16.7</td>
<td>–</td>
<td>–</td>
<td>50.0</td>
</tr>
</tbody>
</table>

Data are percentages of discontinuations for each anti-resorptive medication, where n is the number of discontinuations of each anti-resorptive medication. GI, gastrointestinal; HT, hormone therapy; ET, oestrogen therapy.
cause of 18.5% and 14.5% of oestrogen therapy (ET) and HT discontinuations, respectively. Raloxifene was discontinued for a variety of reasons, including gastrointestinal symptoms (20.6%), other reasons (20.6%), hot flushes (15.6%) and leg cramps (11.9%).

Median treatment durations before discontinuation were 6, 7, 8, 17 and 21 months for risedronate, alendronate, raloxifene, calcitonin and etidronate, respectively (Figure 3).

Discussion

Prevention of fragility fracture is an important public health concern, and is the goal of pharmacotherapy of post-menopausal osteoporosis. At present, no osteoporosis drug therapy completely abolishes the risk of fracture, and osteoporosis guidelines seeking to define the roles of new and existing therapies include the concept of treatment ‘failure’. Better understanding of the characteristics of patients who have an inadequate outcome to osteoporosis therapy may lead to improved management and a reduced fracture risk. Improved outcomes may be achieved by enhancing patient compliance with therapy, reinforcing lifestyle habits, or by changing to an alternative therapy or combination of therapies, especially drugs that have a different mode of action.

OSSO is the first observational study to focus on post-menopausal women with an inadequate outcome for osteoporosis drug therapy in routine clinical practice. Little attention has been paid in the literature to what constitutes an inadequate clinical response to osteoporosis treatment, and there is no consensus on its definition. It has been suggested that serial measurement of BMD or biochemical markers of bone turnover should be used to assess response to treatment. However, BMD changes correlate poorly with the reduction in fracture risk induced by osteoporosis drug therapy, and the inter-individual variability in markers of bone turnover limit their usefulness, and there are no convincing data on their prognostic value for fracture outcomes at the individual level. While factors such as incorrect administration, poor compliance, low intestinal absorption, co-morbidity, calcium or vitamin deficiency, metabolic factors or (in some cases) a low rate of turnover of bone components, may contribute to a poor treatment response, further data on the magnitude and underlying causes and impact of an inadequate outcome to osteoporosis therapy are needed.

We defined an inadequate clinical outcome to osteoporosis drug therapy as a new fracture despite receiving osteoporosis treatment for a minimum of 12 months, and/or drug discontinuation due to non-compliance or side-effects. Similar criteria have been proposed by others. In the UK, the National Institute of Health and Clinical Excellence (NICE) defined ‘unsatisfactory response’ as another fragility fracture despite adhering fully to treatment for 1 year, together with evidence of a decline in BMD below pre-treatment baseline. Fracture while on therapy is obviously a key endpoint indicating poor response to treatment, but may not be indicative of treatment failure, because no osteoporosis drug therapy completely abolishes the risk of fracture. In the active treatment arms of the
pivotal osteoporosis drug trials, between 8% and 18% of patients sustained a new fracture after 3–5 years while on therapy.\textsuperscript{8–13} It is thus important to consider other potential risk factors and causes of inadequate response to osteoporosis therapy, such as poor compliance with the treatment regimen, inadequate dietary calcium or vitamin D intake, or secondary causes of osteoporosis.\textsuperscript{37} In clinical practice, rates of non-compliance with osteoporosis therapy can be as high as 50% among women with osteoporosis, limiting the effectiveness of treatment.\textsuperscript{16,18} In a study of 11,248 women with osteoporosis in clinical practice, 51% were poorly compliant with osteoporosis medication, and had a 16% greater risk of fracture than women who were compliant with therapy.\textsuperscript{38} Side-effects are often given as a reason for non-compliance with osteoporosis therapy, although not all patients who report side-effects discontinue therapy.

In the OSSO study, we combined patients who discontinued treatment due to non-compliance and those who discontinued treatment due to side-effects into one group (Group 2) and taken together, they accounted for 43% of the study population. Non-compliance as a reason for drug discontinuation varied with anti-resorptive medication, ranging from 3.1% for pamidronate to 27.4% for calcitonin and, among the bisphosphonates, was highest for alendronate (14.9%). Gastrointestinal side-effects were the major cause of discontinuation of alendronate (62.7%) and risedronate (62.2%). These findings support post-marketing surveillance data that aminobisphosphonates such as alendronate can be associated with upper gastrointestinal side-effects, including oesophageal ulceration.\textsuperscript{22,39} In one study, half of the patients who discontinued alendronate treatment within 10 months did so due to upper gastrointestinal side-effects.\textsuperscript{16} In a recent 12-month observational study, drug discontinuation was significantly higher with alendronate than raloxifene (25.8% vs. 16.4%), and the main reason for discontinuation was adverse events (11.0% vs. 4.8%; \(p<0.001\)), especially gastrointestinal adverse events (9.9% vs. 3.4%; \(p<0.001\)).\textsuperscript{19}

In this study, comparing the two groups (index fracture vs. non-compliance/side effects) did not show a clear pattern of clinical risk factors that differentiated the two. Although the patients who fulfilled the index fracture criteria of the inadequate clinical response definition were older and had a higher BMI, the clinical significance of the absolute difference is limited, given the large sample size and/or the high within- and between-group variability. As expected, more patients in the index fracture cohort had a previous history of fractures (73.8% vs. 59.9%), reported a higher frequency of falling, and more frequent need to use their arms to stand up from a chair, all of which are well-known risk factors for fragility fractures. We may however conclude that age, time since diagnosis of osteoporosis, previous fractures, falls and neuro-muscular deficits continue to be active as risk factors for subsequent fractures, even in patients on active therapy. Thus, patients with one or a combination of these risk factors are at higher risk for subsequent fractures, even when compared to a group that is non-compliant with medical therapy. Intensive patient monitoring and intervention in terms of falls prevention and exercise could be possible countermeasures for this subset of patients.

Interestingly, more patients in Group 2 reported concomitant therapy with thyroid hormones, while the use of other common chronic medications associated with falling or osteoporosis was not significantly different between the two groups; the reason for this difference is unclear.

The post-menopausal women taking part in OSSO were similar to patients in other osteoporosis epidemiological surveys, in that they had numerous risk factors for fracture (especially age), a history of previous fractures, and low BMD. A history of previous fracture is one of the strongest predictors for subsequent fracture.\textsuperscript{41,42} Two-thirds of the participants in OSSO had a history of previous fracture (mostly vertebral), and the majority of index fractures were vertebral fractures, suggesting that the women taking part in OSSO, particularly those in the index fracture cohort, are at very high risk of subsequent fracture. In contrast, the quality of life scores (measured by a general health questionnaire, as well as by a targeted disease-specific tool) suggest that our patients have a worse quality of life than previously reported. The mean baseline total QUALLEFFO scores for the whole OSSO population (46.8), Group 1 (49.0) or Group 2 (44.0), were greater than those reported by Oleksik et al.\textsuperscript{43} for osteoporotic women in the Multiple Outcomes of Raloxifene Evaluation (MORE) study without fracture (21.3), with a single vertebral fracture (27.0) or with multiple vertebral fractures (range 29.5 for two fractures to 37.6 for \(\geq 4\) fractures).

The mean HSV scores for Group 1 (0.47) and Group 2 (0.53) were lower than the UK norm HSV score for 70–79 year old women (0.74)\textsuperscript{44} and the utility values used in the NICE assessment report,\textsuperscript{23} which were adjusted for the impact of vertebral or hip fractures to give values of 0.62 in the year of fracture and 0.69 in subsequent years. Although the OSSO patient scores include the effects of comorbidities such as rheumatoid arthritis, the possibility remains that the NICE assessment
underestimated the value of all interventions that prevent vertebral and non-vertebral fractures in this population.

The strengths of the OSSO study include the large and diverse study population, with no eligibility restrictions on concomitant diseases or medications. Consequently, its findings should be applicable to a large proportion of older women with post-menopausal osteoporosis in clinical practice. Important features of OSSO include the use of a standardized design, conduct and a priori analyses, which reduce the likelihood of methodological differences among participating centres. Moreover, index fracture data were not based on patient self-report, but required confirmation by X-ray, and all fracture sites were considered.

The OSSO study has some important limitations. Firstly, the findings may not apply to younger or non-Caucasian women, or men with osteoporosis. Secondly, the use of non-restrictive eligibility criteria could lead to within- and between-group heterogeneity at baseline. All between-group comparisons were univariate tests and are therefore unadjusted for any confounding factors; although the tests serve as a useful standardized indicator of the magnitude of the observed differences, causality of an observed difference cannot necessarily be established. Thirdly, recall bias due to self-reported risk factor information and history of previous fractures cannot be excluded, despite indications that self-report has a high level of accuracy. Another limitation is that we may be masking potentially important differences between countries by presenting pooled data from the six participating European countries. Indeed, several population-based studies have shown geographic variations in the incidence of fractures both between and within European countries. Country-specific analyses of the data from OSSO are planned.

In summary, the baseline clinical characteristics and risk factor profile of the OSSO study population have been described. The relatively straightforward definition of inadequate clinical outcome used in OSSO has enabled us to identify a group of patients with poor quality of life and high risk of further fracture. This is a population whose management should be carefully monitored. The patients’ quality of life, resource use and fracture rate in actual clinical practice in Europe will be prospectively examined over a 12-month follow-up. Better understanding of the characteristics of post-menopausal women with osteoporosis and an inadequate clinical response could lead to improved interventions and a reduced fracture rate.

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