

Low Incidence of Anti-Osteoporosis Treatment After Hip Fracture

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Background: Following hip fracture, pharmacologic treatment can reduce the rate of subsequent fragility fractures. The objective of the present study was to assess the proportion of patients who are managed with bisphosphonates or selective estrogen-receptor modulators after hip fracture and to evaluate, among those managed with alendronate, the twelve-month compliance and persistence with treatment.

Methods: Data were gathered from health insurance companies and were collected by AIM (Agence Intermutualiste) for the Belgian National Social Security Institute (INAMI). We selected all postmenopausal women who had been hospitalized for a hip fracture between April 2001 and June 2004 and had not been previously managed with bisphosphonates. Patients who had received alendronate treatment after the hip fracture were categorized according to their formulation use during the follow-up study (daily, weekly, daily followed by weekly, or weekly followed by weekly). Compliance at twelve months was quantified with use of the medication possession ratio (i.e., the number of days of alendronate supplied during the first year of treatment, divided by 365). Persistence with prescribed treatment was calculated as the number of days from the initial prescription to a lapse of more than five weeks after completion of the previous prescription refill. The cumulative treatment persistence rate was determined with use of Kaplan-Meier survival curves.

Results: A total of 23,146 patients who had sustained a hip fracture were identified. Of these patients, 6% received treatment during the study period: 4.6% received alendronate, 0.7% received risedronate, and 0.7% received raloxifene. Bisphosphonate treatment was dispensed to 2.6% and 3.6% of the patients within six months and one year after the occurrence of the hip fracture, respectively. Among women who received alendronate daily ($n = 124$) or weekly ($n = 182$) and were followed for at least one year after the hip fracture, the twelve-month mean medication possession ratio was 67% (65.9% in the daily group and 67.7% in the weekly group). The analysis of persistence with treatment included a total of 726 patients (142 in the daily group, 261 in the weekly group, and 323 in the switch group). At twelve months, the rate of persistence was 41% and the median duration of persistence was 40.3 weeks.

Conclusions: The vast majority of patients who experience a hip fracture do not take anti-osteoporotic therapy after the fracture. Furthermore, among patients who begin alendronate treatment after the fracture, the adherence to treatment decreases over time and remains suboptimal.

From a public health perspective, hip fractures are consistently considered to be the most important type of osteoporosis-related fracture^{1,3}. In Europe in 2000, the number of osteoporotic fractures was estimated to be 3.79 million (0.89 million of which were hip fractures), and it has been estimated that 179,000 men and 611,000 women will experience a hip fracture in Europe each year^{6,7}. In Canada, almost 30,000 hip fractures occur each year, and it has been estimated that one

Canadian sustains an osteoporosis-related hip fracture every eighteen minutes^{8,9}. By the year 2030, the number of hip fractures is expected to quadruple. Americans experience more than 1.5 million osteoporotic fractures each year, 300,000 of which are hip fractures¹⁰, and it has been estimated that the number of hip fractures in the United States may double or triple by 2040¹¹. By 2050, the worldwide incidence of hip fracture is projected to increase by 310% in men and 240% in women¹¹. The short-term

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TABLE I Cumulative Number of Patients with Hip Fracture According to Type of Treatment at Progressive Time Periods*

	Month 3	Month 6	Month 9	Month 12	After Month 12
Alendronate	311 (1.34%)	534 (2.3%)	655 (2.83%)	735 (3.18%)	1053 (4.5%)
Risedronate	42 (0.18%)	64 (0.28%)	79 (0.34%)	94 (0.41%)	163 (0.7%)
Raloxifene	30 (0.13%)	68 (0.29%)	88 (0.38%)	106 (0.46%)	160 (0.7%)
Total	383 (1.65%)	666 (2.88%)	822 (3.55%)	935 (4.04%)	1376 (6%)

*The percentages are based on a total of 23,146 patients.

mortality rate associated with hip fracture ranges from 10% to 20%¹². Among survivors, half require assistance walking and one-quarter require long-term nursing home care¹³. Furthermore, hip fractures account for most of the medical costs related to osteoporosis¹⁴.

Several studies have demonstrated that the occurrence of one osteoporotic fracture increases the probability of a second fracture¹⁵⁻¹⁹, and it has been reported that patients with a history of hip fracture have a greater risk of having another hip fracture²⁰. Following the first hip fracture, the rate of a second hip fracture in women increases sixfold, from 3.6 to twenty-two per 1000 person-years. Furthermore, the risk of recurrent fracture begins to increase within the first months and year after the index fracture²¹. Therefore, focusing attention on patients with a hip fracture may be an important step toward a significant reduction in the burden of osteoporosis and subsequent fractures in society²².

A number of pharmaceutical treatments that are now available have been shown in randomized trials to prevent fragility fractures. Recently, antiresorptive agents such as bisphosphonates and raloxifene have been extensively studied and have been indicated as effective options for medical treatment²³⁻²⁹. However, it is unanimously recognized that these agents are underutilized in clinical practice. Several studies in different countries have demonstrated that a significant proportion of patients did not receive any treatment for osteoporosis even after a fracture³⁰⁻³³. Moreover, as is the case with many chronic diseases, the problem of adherence to therapy has emerged as a major challenge to the successful treatment of osteoporosis.

Although long-term adherence to therapy is required for optimal therapeutic benefit for patients with osteoporosis, recent analyses have indicated that adherence to anti-osteoporotic drug therapy is suboptimal, with more than half of the new patients receiving treatment stopping therapy within the first year³⁴⁻³⁶.

The purpose of the present study was to assess the proportion of female patients for whom bisphosphonates or selective estrogen-receptor modulators were prescribed in the year after a hip fracture as reflected in the exhaustive Belgian National Social Security database. We also assessed the twelve-month rates of treatment compliance and persistence among women for whom alendronate treatment was initiated after a hip fracture.

Materials and Methods

Data Source

Data were gathered from health insurance companies and were collected by AIM (Agence Inter mutualiste) for the Belgian National Social Security Institute (INAMI). This database included all prescriptions of bisphosphonates and raloxifene for the entire Belgian population. In the present report, the term "prescription" should be understood as a prescribed drug that has actually been delivered and for which payment has been reimbursed by the Social Security Institute. The data available in each prescription include the anatomical-therapeutic-chemical (ATC) code of the drug purchased, the number of packs, the number of units per pack, the dosage, and the prescription date. Any records of hospitalizations were also available. The Belgian national database of hospital bills is coded according to the nature of the procedure performed. Four codes are related to surgical procedures that are directly identified as being linked to a fracture of the proximal part of the femur.

The present study was a retrospective cohort analysis that included only the records of patients who received bisphosphonates or selective estrogen-receptor modulators for the first time during the study period. These were the only anti-osteoporosis medications for which payments were reimbursed in Belgium at the time of our study. The patients who were enrolled in the study were postmenopausal women, with an age of forty-five years or more, who were new users and who had been hospitalized for a hip fracture between April 2001 and June 2004. New users were defined as patients who had not received a prescription for any bisphosphonate or raloxifene before the occurrence of the hip fracture. All of the patients in the study had a bone mineral density T score of below -2.5 and/or a history of a previous vertebral fracture, which constitute the mandatory conditions that must be met in order to obtain reimbursement in Belgium for these two medications.

Outcome Measures

We investigated two aspects of adherence to alendronate by investigating treatment persistence (according to the treatment period as defined below) and treatment compliance (according to how often the treatment was correctly taken). It is important to note that, for these analyses, we only considered alendronate treatment because risedronate treatment was only available on

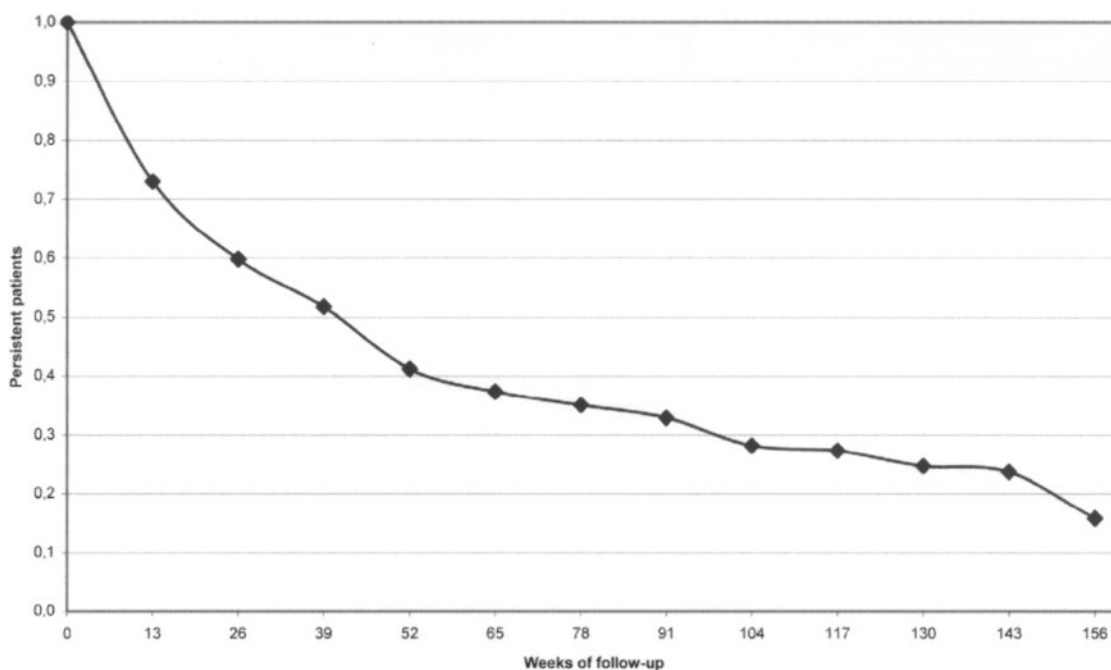


Fig. 1

Persistence with treatment in the total population of patients who began alendronate treatment (including the daily group, weekly group, and switch group) after the occurrence of a hip fracture.

the market during the last months of the study follow-up period and therefore few prescriptions for this drug were recorded. Furthermore, raloxifene was not assessed in this particular trial because of the lack of current evidence with regard to the anti-fracture efficacy of selective estrogen-receptor modulators at the level of the hip³⁷.

Patients were categorized according to their alendronate formulation use (daily group, weekly group, or switch group). In Belgium at the time of the study, the daily alendronate treatment was only available in monthly packaging (twenty-eight defined daily doses) and the weekly alendronate treatment was available in monthly packaging (twenty-eight defined daily doses) or quarterly packaging (eighty-four defined daily doses). The switch group included patients who changed from daily to weekly alendronate and those who changed from the weekly monthly to the weekly quarterly packaging.

For the analysis of persistence, all women who began alendronate treatment for the first time and who belonged to one of the three predefined groups (daily, weekly, or switch) at the time of interruption or discontinuation of treatment were included. The follow-up period started at the time of the first alendronate prescription and ended at the time of death, interruption or discontinuation of treatment, or the end of the study period (June 2004). The duration of therapy was measured as the number of days of therapy without an interruption of drug purchases of more than five weeks. Specifically, a refill prescription was considered to have been purchased without a break in therapy if the cumulative days' supply for all previous

prescriptions plus five weeks was greater than or equal to the number of days between the refill prescription's purchase date and the enrollment date for the treatment episode. If the cumulative days' supply plus five weeks was less than the total number of days between the purchase date of the refill prescription and the enrollment date, the count of continuous days of therapy was terminated. Patients who discontinued treatment were considered to be "nonpersistent."

For the assessment of compliance, all women who began alendronate treatment for the first time and who could be followed for at least one year were considered. Patients who may have switched to another bisphosphonate or to another bisphosphonate regimen during the first year of therapy were excluded from the analysis. Compliance with the treatment was quantified with use of the medication possession ratio by dividing the number of defined daily doses delivered during the first year of therapy by 365. The total number of defined daily doses was capped at 365 to prevent situations in which medication possession ratio could be >100%. Patients who had a twelve-month medication possession ratio of $\geq 80\%$ were considered as having "good compliance."

Statistical Analysis

The comparison of the mean medication possession ratio at twelve months between the daily and weekly groups was performed with use of the unpaired Student t test. The comparison of the mortality rate between treated patients and patients not using anti-osteoporotic drugs was performed with use of

the chi-square test. We estimated the cumulative treatment persistence rate with use of Kaplan-Meier survival curves, in which data were censored for women at the end of observation if they were still receiving treatment.

Results

A total of 23,146 postmenopausal women who had not previously received anti-osteoporotic drugs were hospitalized for a hip fracture between April 2001 and June 2004. Table I shows the distribution of patients receiving each type of anti-osteoporotic treatment at three, six, nine, and twelve months after the hip fracture. Only 1376 patients (6%) received anti-osteoporotic treatment after the hip fracture during the study period. Bisphosphonate treatment was dispensed to 2.6% and 3.6% of the patients within six months and one year after the occurrence of the hip fracture, respectively. We observed a decreased mortality rate for the treated patients as compared with the untreated patients (11.05% compared with 37.11%; $p < 0.0001$).

A total of 306 patients (including 124 in the daily group and 182 in the weekly group) were assessed with regard to compliance at twelve months. The mean medication possession ratio at twelve months was 67%, and no significant difference was observed between the daily group and the weekly group (65.9% compared with 67.7%). At twelve months, 48.7% of the patients had a medication possession ratio of $\geq 80\%$.

A total of 726 women (including 142 in the daily group, 261 in the weekly group, and 323 in the switch group) were assessed with regard to persistence with treatment. The probability of persistence with alendronate treatment over time is shown in Figure 1. At six months, 60% of the women persisted with therapy. At the end of the first year, only 41% of the women continued to take alendronate without a gap of more than five weeks in treatment. The median duration of persistence was 40.3 weeks.

Discussion

Previous studies of osteoporosis treatment patterns have documented undertreatment, but none, to our knowledge, have investigated the adherence to treatment, both in terms of compliance and persistence, among women who initiated treatment for the first time following a hip fracture. During the period from 2001 to 2004, 6% of patients forty-five years and older who had been hospitalized for hip fracture received a prescription, for the first time, for an anti-osteoporotic drug, primarily a bisphosphonate, during the year following the fracture. These findings suggest that only a very small proportion of patients with hip fractures are being treated, leaving the vast majority untreated and at high risk for subsequent fracture. Moreover, compliance and persistence, in actual practice, were low and inadequate. Of the women who were treated, only 41% continued to take their treatment at the end of the first year of therapy and fewer than half were found to be compliant with bisphosphonate therapy (as defined as a medication possession ratio of $\geq 80\%$).

Hip fracture is a major event in a patient's life and is associated with substantial morbidity and mortality. Prevention of the first hip fracture is the ideal strategy, but at least after the first fracture the awareness of the physician should be heightened to prevent future fracture by modifying the risks, which must include optimal management of other medical diagnoses as well as fall prevention³⁸. The relative risk of hip fracture increases with age, with the risk of a second hip fracture being as much as six times greater after the first hip fracture and with the risk of a non-hip fracture being nine to fifty times greater³⁹. Thus, these patients are an important target for anti-osteoporotic therapy¹⁹. Moreover, the results of the present study showed a decreased mortality rate for the patients who were managed with anti-osteoporotic drugs as compared with those who were not. These results highlight the mortality prevention aspect of anti-osteoporotic drug use.

Theoretically, effective prevention and treatment strategies should be implemented once a high-risk patient is identified. It is essential that evidence-based recommendations be incorporated into clinical practice. The guidelines of the National Osteoporosis Foundation state that, following a fragility hip fracture, active anti-osteoporotic medication should be initiated³⁹. Recent advances in the medical treatment of established osteoporosis, including the use of antiresorptive medication, can increase bone mineral density and decrease the incidence of osteoporotic fractures⁴⁰. However, most of the relevant studies have indicated that the rate of treatment with antiresorptive drugs following fracture is very low, ranging from 5% to 44%³⁰⁻³³. Gardner et al. reported that 19.3% of the patients in their study were managed with anti-osteoporotic drugs following hip fracture³⁰. Panneman et al. stated that 15% of the patients with osteoporotic fractures received a prescription for anti-osteoporotic drugs within one year after discharge³². A recent study of patients who had experienced a hip fracture revealed that only 13% received treatment for osteoporosis during the year after the fracture, although baseline bone mineral density results and a copy of guidelines from the National Osteoporosis Foundation were sent to the patients and their primary care physicians⁴¹. In our study, although the medications were reimbursed by the Belgian National Social Security system, the proportion of patients who received a prescription for anti-osteoporotic medication after the hip fracture was even lower, at 6%. It is important to keep in mind that in our study, in contrast with the others, only hip fractures were considered. Furthermore, we did not have information regarding the use of over-the-counter vitamin-D and calcium supplementation or estrogen therapy.

The reasons for the gap between evidence-based treatment guidelines and treatment rates remain unclear, although several barriers have been suggested and explored. It is possible that many health-care providers believe that once an osteoporotic fracture has occurred, it is too late to alter the progression of the disease with drug therapy. Another potential barrier has been confusion regarding which physician is responsible for treating osteoporosis after a hip fracture. A limited survey of twenty-three primary care physicians and eight orthopaedic surgeons in a Midwestern managed-care organization in the United States

revealed possible barriers to the identification and treatment of osteoporosis after hospitalization for a low-trauma fracture⁴². Both the orthopaedic surgeons and the primary care physicians agreed that treatment falls under the domain of the primary care physician because of the medical nature of the disease and the greater likelihood of long-term follow-up by the primary care physician. Moreover, evidence suggests that patients who receive a diagnosis of osteoporosis are more likely to receive therapy for osteoporosis than undiagnosed patients are^{43,44}. Therefore, it appears that the lack of treatment may be related to the lack of diagnosis. Other potential barriers to treatment are the side effects of medications, the costs of prescription drugs, and a lack of awareness by patients and physicians regarding the treatment guidelines and the efficacy of medications for osteoporosis following hip fracture⁴⁵⁻⁴⁷. Failure to comply with therapy also may be due to the asymptomatic nature of osteoporosis and a lack of appreciation of the benefits of therapy.

An important factor influencing adherence is the cost of medication. On the basis of an evaluation of claims data, Caro et al. suggested that adherence and persistence may be strongly influenced by the cost and availability of insurance coverage³⁴. A study conducted in Israel showed that the number of women receiving osteoporosis medication and the persistence with therapy both increased when copayments for osteoporosis medications were eliminated⁴⁸. In Belgium, a great part of the costs for bisphosphonate therapy is paid by the National Social Security system. Costs incurred by patients for bisphosphonate treatment are, on the average, approximately 10€/month (\$15.55/month). However, as revealed by our study, even good insurance prescription coverage does not necessarily guarantee that patients with a chronic, asymptomatic disease will take their medications over the long term.

While less frequent dosing and monitoring of adherence are both associated with better adherence and lower fracture rates, the benefits are still below the high levels considered to be necessary in order to achieve optimal anti-fracture efficacy. Close monitoring of adherence with osteoporosis therapies should be an obligatory duty in clinical care.

The overall strength of our analysis is that we had access to all bisphosphonate prescriptions delivered in Belgium between January 2001 and June 2004, allowing us to study the behavior of a very large number of osteoporotic women in real life. Administrative claims data are commonly used to estimate compliance and persistence. Compared with clinical practice, adherence to treatment in a clinical trial setting may be enhanced and may result in falsely elevated persistence of treatment rates. The results of the present study were obtained without the artificial structure of randomized controlled studies, which are designed generally to minimize premature withdrawal and discontinuation of therapy. The use of an exhaustive database has the advantage of providing accurate adherence data in a real-life setting, compared with other indirect measures of adherence, such as the use of questionnaires,

in which the data are often self-reported and consequently may be overestimated. However, certain limitations exist in association with this type of data. Administrative claims are only an indirect measure of medication-taking behavior, and the presence of a prescription claim does not necessarily imply that the medication was effectively ingested^{49,50}. Nonetheless, claims databases have been found to be a reliable estimate of patient use of medications⁵¹. Last, it is important to note that our analysis is conservative as we only included patients who submitted their prescriptions. We cannot address the fact that many patients may actually receive a prescription but never have it filled.

On the basis of the present study, we conclude that the vast majority of patients who have a hip fracture do not take anti-osteoporosis therapy after the fracture. Furthermore, among patients who initiate alendronate treatment after the fracture, the adherence to treatment decreases over time and remains suboptimal. Strategies need to be developed to ensure that these patients receive and adhere to an osteoporosis drug therapy regimen following recovery from the hip fracture. ■

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