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ORIGINAL ARTICLE

Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women

V. Rabenda · R. Mertens · V. Fabri · J. Vanoverloop · F. Sumkay · C. Vannecke · A. Deswaef · G. A. Verpooten · J.-Y. Reginster

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Abstract
Summary Adherence is now one of the major issues in the management of osteoporosis and several papers have suggested that vertebral fractures might be increased in patients who do not follow appropriately their prescriptions. This paper relates the strong relationship existing between adherence to anti-osteoporosis treatment and the risk of subsequent hip fracture.

Introduction A study was performed to investigate adherence to bisphosphonate (BP) therapy and the impact of adherence on the risk of hip fracture (Fx).
Methods An exhaustive search of the Belgian national social security database was conducted. Patients enrolled in the study were postmenopausal women, naïve to BP, who received a first prescription of alendronate. Compliance at 12 months was quantified using the medication possession ratio (MPR). Persistence was calculated as the number of days from the initial prescription to a gap of more than 5 weeks after completion of the previous refill. A logistic regression model was used to estimate the impact of compliance on the risk of hip fracture. The impact of persistence on hip fracture risk was analysed using the Cox proportional hazards model.
Results The mean MPR at 12 months was significantly higher among patients receiving weekly (n=15.021) compared to daily alendronate (n=14,136) (daily=58.6%; weekly=70.5%; $p<0.001$). At 12 months, the rate of persistence was 39.45%. For each decrease of the MPR by 1%, the risk of hip Fx increased by 0.4% (OR: 0.996; CI95%:0.994–0.998; $p<0.001$). The relative risk reduction for hip Fx was 60% (HR: 0.404;CI95%:0.357–0.457; $p<0.0001$) for persistent compared to non-persistent patients.
Conclusion These results confirm that adherence to current therapeutic regimens remains suboptimal.

Keywords Adherence · Bisphosphonates · Hip fracture · Osteoporosis

V. Rabenda · J.-Y. Reginster
WHO Collaborating Center for Public Health Aspects of Osteoarticular Disorders, University of Liège,
Liège, Belgium

V. Rabenda (✉) · J.-Y. Reginster
Department of Public Health,
Epidemiology and Health Economics, University of Liège,
CHU–Bât. B23,
4000 Liège, Belgium
e-mail: veronique.rabenda@ulg.ac.be

R. Mertens · F. Sumkay
Alliance Nationale des Mutualités Chrétiennes,
Brussels, Belgium

R. Mertens · V. Fabri · J. Vanoverloop
Agence Intermutualiste,
Brussels, Belgium

V. Fabri · J. Vanoverloop
Union nationale des Mutualités Socialistes,
Brussels, Belgium

C. Vannecke · A. Deswaef
Institut National d'Assurances Maladie Invalidité,
Brussels, Belgium

G. A. Verpooten
Department of Nephrology-Hypertension,
Antwerp University Hospitals,
Antwerp, Belgium

Introduction

Poor adherence to medications, particularly those used to treat chronic diseases, such as osteoporosis, is a widespread

medical problem, associated with a significant burden both on patients and on health service resources.

The treatment of osteoporosis among postmenopausal women represents a major public health challenge because long-term therapy is needed to prevent fractures and chronic disability. Bisphosphonates are usually the first-line treatment option for postmenopausal osteoporosis because of their ability to provide substantial increases in bone mineral density at the lumbar spine and hip, and to decrease significantly bone turnover [1–7], and this translates into a reduction in the risk of vertebral fracture of up to 65% and of non-vertebral fracture of up to 53% [3–5, 8–11]. However, long-term adherence to therapy is required for optimal therapeutic benefit for patients with osteoporosis.

Poor adherence is considered to be one primary reason for suboptimal clinical benefit. In the case of osteoporosis, poor compliance with dosing recommendations and premature discontinuation of treatment adversely affects the rate of bone turnover and bone mineral density gains and, consequently, leads to an increased risk of fracture [12–16]. Aside from having a detrimental effect on the patient's health, poor adherence to treatment also has a major impact on healthcare systems and resources. Therefore, addressing poor adherence could potentially benefit both patients and society. However, few data are available on the rate of adherence to this treatment in clinical practice, where compliance and persistence are likely to be different than in clinical trials. Findings of experimental research are of limited value in assessing the appropriateness of antiosteoporotic drug used in clinical practice. Furthermore, few studies have investigated the relationship between poor adherence and the likelihood of incurred fractures in actual practice. Although hip fracture is unanimously considered as the most dramatic consequence of osteoporosis, no study in Europe has, to our knowledge, specifically investigated the impact of poor adherence on the incidence of hip fracture.

The aim of this study was to investigate patient compliance and persistence with alendronate, in real-world treatment settings, using the extensive Belgian national social security database. We also assessed the impact of poor adherence to alendronate on the risk of hip fracture.

Material and methods

Data source

Data for this analysis were gathered from health insurance companies collected by AIM (Agence Intermutualiste) for the Belgian national social security institute (INAMI). This database includes all prescriptions of bisphosphonates for the whole Belgian population. In this paper, the term "prescription" should be understood as a prescribed drug that has actually been delivered and reimbursed by social security. The data available in each prescription include the anatomical-therapeutic-chemical (ATC) code of the drug purchased, number of packs, and number of units per pack, dosage and prescription date. It is important to note that, for the purposes of this analysis, we only considered alendronate treatment because risedronate treatment was only available on the market during the last months of the study follow-up, so that few prescriptions for this drug were recorded. 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 directly identified as being linked to a fracture of the proximal femur.

Study design and population

This study is a retrospective cohort analysis that included only the records of patients who received bisphosphonates for the first time during the study period. Patients enrolled in the study were postmenopausal women aged>45 years, and were new users, who had received a first prescription for bisphosphonates between April 2001 and June 2004. New users were defined as patients who had not been prescribed any bisphosphonate or raloxifene in the 3 months preceding the enrolment date. Patients were women with a BMD T-score of below −2.5 and/or with previous vertebral fractures, i.e., the mandatory conditions for obtaining bisphosphonate reimbursement in Belgium.

Patients were categorized according to their alendronate formulation use (daily group, weekly group and daily followed by weekly [switch] group). In Belgium, at the time of the study, the daily alendronate treatment was only available in monthly (28 defined daily dose) packaging and the weekly alendronate treatment was available in monthly (28 DDD) or quarterly packaging (84 DDD). 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.

Outcome measures

We investigated two aspects of adherence to bisphosphonates by investigating persistence (treatment period as defined below) and compliance (how often the treatment was correctly taken). For the analysis of persistence, all naïve women initiating alendronate treatment and belonging to one of the three predefined groups (daily, weekly or switch) at the time of a break or of the stopping of the treatment were included. The women's follow-up started at the time of the first alendronate prescription and ended at one of the following points: time of patient death, a break in the treatment, the stopping of the treatment, or at the end of

the study period (June 2004). Duration of therapy was measured by the count of days of therapy without an interruption of drug purchases greater than 5 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 5 weeks was greater than or equal to the number of days between the refill prescription's purchase date and the enrolment date for the treatment episode. If the cumulative days supply plus 5 weeks was less than the total days between the purchase date of the refill prescription and the enrolment date, the count of continuous days of therapy was terminated. Patients who discontinued treatment were considered as "non-persistent".

For the assessment of compliance, all naïve women who initiated alendronate treatment and who could be followed up during at least one year were considered. Patients who may have switched to another BPs or regimens during the first year of therapy were excluded from the analysis. Compliance to the treatment was quantified using the medical possession ratio (MPR) by dividing the number of DDD delivered during the first year of therapy by 365. The total DDD were capped at 365 DDD to prevent situations in which MPR could be greater than 100%. Patients who had a 12-month MPR ≥80% were considered as "greater compliant".

In order to investigate the impact of compliance on the risk of hip fracture, a case-control study was performed. For each woman who incurred a hip fracture during the follow-up, five matched subjects were randomly selected to constitute the control group. The two matched criteria were age and the duration of follow-up. The follow-up of cases started at the time of the first alendronate prescription and ended at the time of the first hip fracture (censure date). The date of admission into hospital was taken as the time of fracture occurrence. Recurrent fractures were not considered. For the controls, their follow-up started at the time of the first alendronate prescription and was stopped at the censure date in order that they be followed and exposed to treatment for the same duration as the cases. Patients who switched to another BP or regimen before the censure date were excluded from the analysis. In other words, only women who had taken daily or weekly alendronate until the censure date were considered. For each subject (cases and controls), the MPR was calculated as the cumulative number of DDD prescribed divided by the theoretical number of DDD (i.e., the number of DDD that would be delivered between the first prescription and the censure date).

The impact of persistence on the risk fracture was also evaluated. For this analysis, all naïve patients who started alendronate treatment and who belonged to one of the three groups (daily, weekly, switch) at the time of the first fracture, or at a break or the stopping of the treatment were included. The follow-up of subjects started at the time of the first alendronate prescription and ended at the time of the first fracture, death, or at a break in or at the stopping of the treatment, or at the end of the study period (June 2004).

Statistical analysis

The comparison of the mean MPR at 12 months between the daily and the weekly group was made using the unpaired student's t test. We estimated the cumulative treatment persistence rate using Kaplan–Meier survival curves, in which data were censored for women at the end of observation if they were still receiving treatment. A forward stepwise selection procedure based on the logistic regression model was used in order to select the determinants of incurring a hip fracture. The following independent variables were considered: the MPR (included as a continuous variable), dose frequency (daily or weekly), age and preferential coverage (i.e., patients with low income receiving increased reimbursement by national social security) (yes or no). We also estimated the probability of hip fracture as a function of the full range of MPR values (0% to 100%), using logistic regression model.

As persistence can change over time, assessment of its effect requires a proper accounting for the cumulative and varying nature of the measure. This was done by fitting a Cox proportional hazards model that included a persistence indicator defined as a time-dependent factor. Two additional covariates included in this model were age category (70–79 years or >79 years compared with <70 years) and preferential coverage (yes or no). All results were considered to be statistically significant if the corresponding p value was below 0.05.

Results

We initially identified 142,302 women aged 45 years or older who were prescribed osteoporosis drugs (bisphosphonates or raloxifene) between January 2001 and June 2004. We excluded 42,378 women who had prior use of any osteoporosis drugs, resulting in a final cohort of 99,924 women.

A total of 29,157 naïve women were included for the analysis of compliance (daily group n=14,136; weekly group n=15,021) (Fig. 1). The mean MPR at 12 months was 64.7%. A statistically significant difference was observed between the two formulations (daily and weekly) (Table 1). The mean MPR at 12 months was significantly higher for patients who received weekly alendronate compared to those who received daily alendronate during the first year of therapy (daily group MPR=58.6%; weekly group MPR=70.5%; p<0.001). This difference of compliance between the two alendronate formulations (daily or

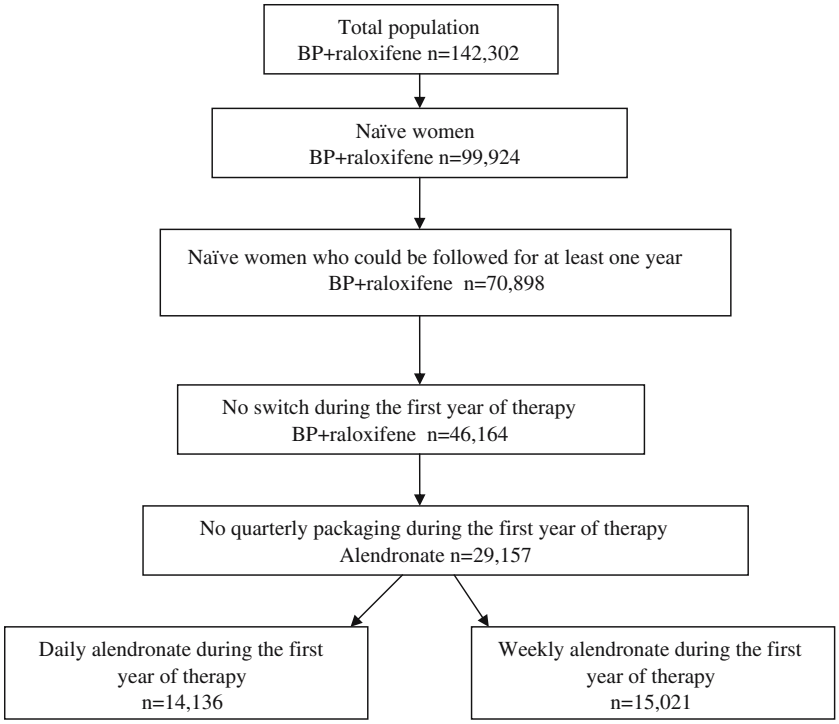

Fig. 1 Study population for the analysis of compliance

weekly) was also observed when the population was subdivided into age groups (Table 1). 48.1% of patients had a 12-month MPR ≥80%. 40.4% of women receiving daily therapy and 57% of women receiving weekly therapy achieved an MPR of 80% or higher.

For the analysis of persistence, we excluded 8,710 naive women treated by alendronate weekly quarterly packaging (84 DDD) because this formulation was marketed in Belgium during the last months of the study period. A total of 54,807 women were included (daily group n=16.156; weekly group n=16,189; switch group=22,462) (Fig. 2). The probability of persistence with alendronate over time is shown in Fig. 3. At 6 months, 58% of women persisted with their therapies. At the end of the first year of therapy, only 40% of women continued to take their alendronate treatment, without a gap of more of 5 weeks in treatment. The median duration of persistence was 35.7 weeks. In the sensitivity analysis, persistence was analyzed with refill gaps of different lengths (2, 4, 6, 8 weeks or 3 months). The persistence rate at one year was 16% with a 2-week gap, 32% with a 4-week gap, 43% with a 6-week gap, 52% with an 8-week gap and 60% with a 3-month-gap.

Table 2 summarizes the characteristics of the population included in the case-control study. We identified 901 naïve women who incurred a hip fracture during the study period and who received daily or weekly alendronate from the first prescription until the incurrence of the hip fracture. Four thousand five hundred and five matched controls were randomly selected. The MPR was a significant predictor of incurring a hip fracture. The logistic regression model estimated that for each decrease of the MPR by one percent, the adjusted risk of hip fracture increased by 0.4%

Table 1 Mean MPR (%) at 12 months for daily and weekly alendronate, for the total population and by age group

	Daily alendronate	Weekly alendronate	p-value
Total population	58.61	70.5	<0.001
Age group			
<70 years	57.38	70.46	<0.001
70–79 years	60.19	72.74	<0.001
>79 years	58.61	65.29	<0.001

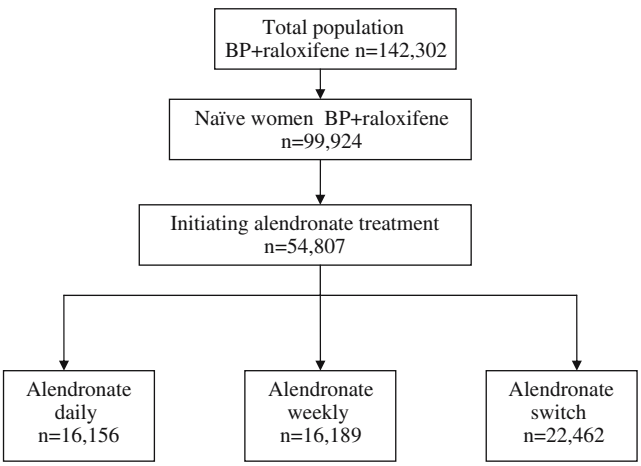

Fig. 2 Study population for the analysis of persistence

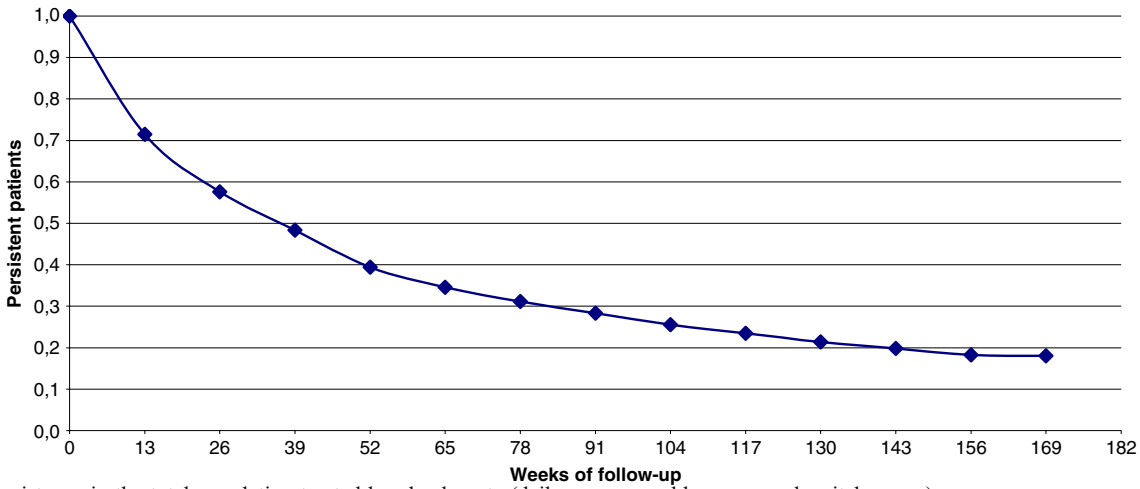

Fig. 3 Persistence in the total population treated by alendronate (daily group, weekly group and switch group)

(OR: 0.996; CI95%:0.994–0.998; $p<0.001$) (Table 3). As shown in Fig. 4, there was a negative linear estimated relationship between the probability of hip fracture and the value of the MPR. Treatment regimen was also an important determinant of incurring hip fracture. Women who received daily alendronate were more likely to incur a hip fracture than women taking the weekly regimen (OR: 0.836; CI95%:0.724–0.964; $p<0.05$). The preferential coverage was not associated with the likelihood of incurring a hip fracture. The relationship between compliance and fracture risk persist after adjustment for age in the multivariate model.

For the analysis of the impact of persistence on the risk of hip fracture, a total of 47 868 naïve women were included (hip fracture $n=1,280$; no hip fracture $n=46,588$). Persistence to alendronate treatment was a significant predictor of incurring a fracture. The relative risk reduction for hip fracture was 60% for persistent patients compared to non-persistent patients (HR: 0.404;CI95%:0.357–0.457;$p<0.0001$) (Table 4). Age was also a significant determinant in incurring a hip fracture. Women aged between 70 and 79 years and women aged more than 79 years had a higher risk of incurring a hip fracture than younger women (HR:2.88; CI95%:2.49–3.34; $p<0.0001$; HR:5.64; CI95%:4.82–6.6; $p<0.0001$). Once again, the preferential coverage was not associated with the risk of hip fracture.

Table 2 Characteristics of the case-control study sample

	Cases ($n=901$)	Controls ($n=4.505$)
Age group (%)		
<70 years	19.4	19.4
70–79 years	46.9	46.9
79 years	33.6	33.6
Preferential coverage (%)	41.95	40.78
Daily alendronate (%)	51.3	46.5
Mean MPR (%)	69.35	73.98
Mean duration of follow-up (weeks)	40.3	40.3

Discussion

This retrospective analysis of a large population of new users of alendronate with diagnosed osteoporosis confirms that both compliance and persistence, in actual practice, is low and inadequate. Less than half of the women were found to be compliant with bisphosphonate therapy (MPR≥ 80%) and approximately 40% of women persisted with treatment for 12 months without a substantial gap in therapy.

Results of previous studies were not directly comparable to ours because of methodological differences in terms of the population selected, the parameterization of compliance and persistence, the duration of follow-up, the analytical techniques used, and differences in populations, practices and health care systems. Moreover, it is important to note that, the Belgian system of conditional reimbursement (only for patients presenting with a prevalent vertebral fracture or low BMD) targets the population to be treated and allows treatment to be given to patients really osteoporotic. It is likely that, in excluding from treatment the patients who do

Table 3 Logistic regression analysis (forward stepwise selection procedure): impact of compliance and other factors on the risk of hip fracture

Factors	Odds ratio	CI 95%	*p*-value
Daily vs. weekly	0.836	0.724–0.964	<0.05
Compliance	0.996	0.994–0.998	<0.001

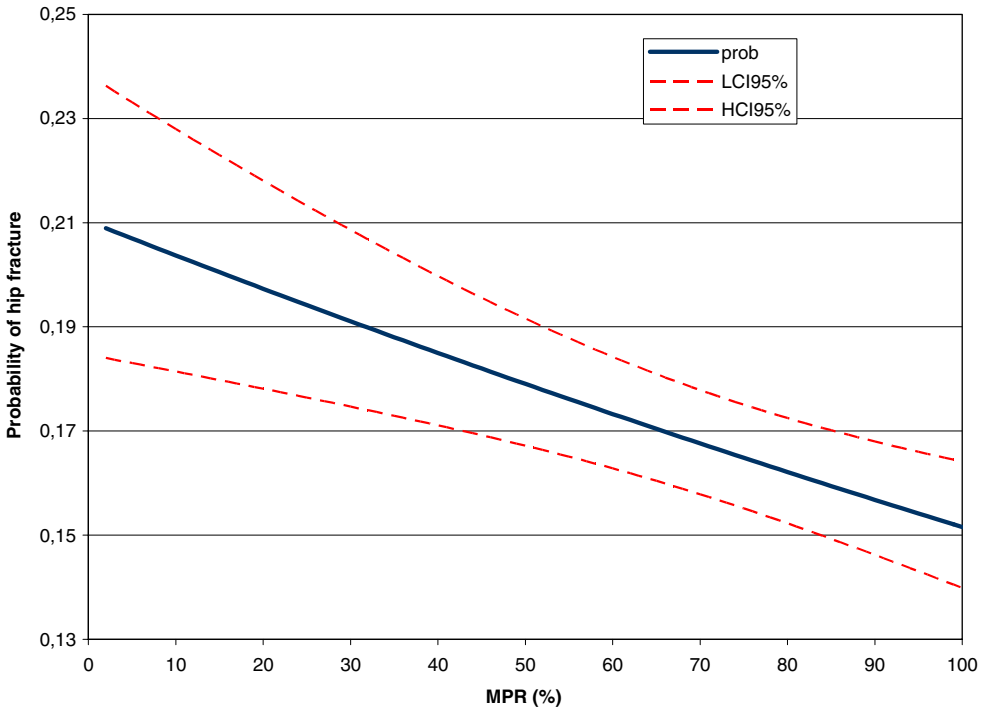

Fig. 4 Probability of hip fracture according to the full range of MPR

not present with osteoporosis, more severely affected patients are targeted and better adherence can be expected. Despite these methodological differences, in general, our results are consistent with previous studies often conducted in smaller, more homogenous populations, which have reported suboptimal compliance and persistence associated with osteoporosis therapies.

It has been shown that treatment adherence improves as the number of daily doses decreases [17], and with weekly versus daily regimens [18, 19, 20, 21]. Our results provide further evidence that, in comparison with daily dosing, weekly dosing does improve compliance to treatment, not only during controlled clinical trials but also in routine clinical practice. A recent study by Cramer et al. used nationwide administrative claims data to follow the compliance and persistence of 2,741 women with osteoporosis who had been newly prescribed weekly alendronate or daily alendronate or risedronate [19]. The MPR reported in that study were 57.6% for daily oral bisphosphonates and 69.2% for weekly alendronate, which is very similar to the rates observed in our study. The treatment persistence during the 12-month follow-up period was 196 days, very close to ours. In our study, there appears to be a steep decline in persistence during the first year of therapy. The largest drop in alendronate continuation was evident after the first six months of therapy (42% non-persistent); this pattern of early discontinuation has been corroborated by numerous other studies [18, 19]. The rate of persistence begins to stabilize approximately one year after the start of the treatment. Our choice of 5 weeks for refill gaps period, while somewhat arbitrary, was based on the typical length of refill gaps used in previous studies [19, 22, 23]. Indeed, several studies used a refill gap of 30 days to determine treatment persistence. We conducted a sensitivity analysis in which the refill gaps period was increased to 6 weeks, 8 weeks or 3 months and reduced to 2 weeks. As expected, and according with previous studies [24], the proportion deemed that have discontinued was sensitive to the refill gap length and still suboptimal whatever the length of the refill gap period.

The overall strength of our analysis is that we had access to all bisphosphonates prescriptions delivered in Belgium between January 2001 and June 2004, allowing us to study the behaviour of a very large number of osteoporotic women in real life. However, as mentioned above, only alendronate prescriptions were analysed because, in Belgium, risedronate was marketed only during the last months of the study period. Compared with clinical practice, adherence to treatment in a clinical trial setting may be enhanced and may result in falsely elevated persistence treatment rates. Results of this study were obtained without

Table 4 Cox regression analysis: impact of persistence and other factors on the risk of hip fracture

Factors	Hazard ratio	CI 95%	*p*-value
70–79 years	2.881	2.486–3.339	<0.0001
>79 years	5.641	4.819–6.604	<0.0001
Preferential coverage	1.100	0.981–1.232	0.1022
Persistence	0.404	0.357–0.457	<0.0001

the artificial constraints of randomized controlled studies, which are designed generally to minimize the occurrence of 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 to other indirect measures of adherence, such as the use of questionnaires, where data are often self-reported and therefore subjective, and consequently may be overestimated.

To our knowledge, this study is the first large scale study in Europe, investigating the impact of adherence, both in terms of compliance and persistence, specifically, on the risk of hip fracture. Despite limitations inherent in using claims data in analyses like these [25, 26], the results indicate that both high compliance and persistence with prescribed osteoporosis medication are significantly associated with reduced hip fracture risk. Moreover, we found differences in fracture outcomes between the two regimens (daily or weekly), in favour of the weekly therapy. The importance of osteoporosis drug (particularly bisphosphonates) adherence has been demonstrated in several studies. Women who have better adherence show a greater BMD response [14, 27] and a lower fracture risk [16, 23, 28, 29]. In an analysis of a US claims database, it was demonstrated that compliant patients (defined as having one year of uninterrupted therapy) to various osteoporosis medications had a significantly lower risk of fractures of the spine (OR= 0.6; $p<0.05$) and hip (OR=0.38; $p<0.01$), compared to non-adherent patients [29]. Similar findings from a Canadian database including 11,252 women showed that highly compliant patients (MPR>80%) had a 16% lower fracture rate (hazard ratio=0.84; $p<0.005$) than low compliant patients [16]. Most recently, Siris et al. estimated the probability of fracture along a gradient of adherence to bisphosphonates [23]. At an MPR from 0% to 50%, the probability of fracture during a period of 24 months remained consistent at about 11% and declined progressively once a threshold value of 50% was achieved. In our analysis, we showed that there was a linear decrease in the probability of hip fracture as the MPR increased. The range of probability of hip fracture observed in our 3-year follow-up was between 0.15 and 0.21, which is close to that observed by Siris et al. over a period of 24 months (0.08–0.11). However, our results were not directly comparable because of reasons already mentioned above but also because Siris et al. estimated the probability of incurring all types of fracture, whereas we focused our analysis only on fractures of the hip.

Administrative claims data are a commonly used method to estimate compliance and persistence. However, certain limitations exist with these types of data. Administrative claims are only an indirect measure of medication-taking behaviour and the presence of a prescription claim does not necessarily imply that the medication was effectively ingested [30, 31]. We could not exclude the possibility that patients had retrieved their prescriptions, but that they did not take them properly, according the strict guidelines of intake. Nonetheless, claims databases have been found to be a reliable estimate of patient use of medications [32]. Some important information is not available in the database. Demographic data are limited to age, and no individual patient information is available on other risk factors for osteoporosis or fractures (such as premature menopause, history of fracture, low dietary intake of calcium,etc.). Also, other potential confounders that might relate to good compliance and reduced fracture risk, were, unfortunately, not available in the database (such as co-morbidities, smoking, body mass index, etc.). Whether these would modify the impact of adherence on fracture risk is unclear. However, given clinical trials results, it is extremely unlikely that the impact of low adherence on fracture risk would be due primarily to confounding factors. Another limitation is the fact that drugs dispensed at the hospital are not recorded in the database. Consequently, patients could be misclassified as non-adherent (non-persistent and low compliance) during their hospital stay. This may be a source of overestimation of global non-adherence. Lastly, it is important to note that our analysis is conservative, as we only included patients who submitted their prescriptions. We cannot exclude the fact that many patients may actually receive a prescription but that they never have it filled.

Despite these limitations, the results of our study demonstrate that the objective of keeping patients on treatment is not achieved adequately in clinical practice. Perhaps the advent of medications with more convenient dosing schedules will improve this situation. Newer antiresorptive drugs with longer intervals between doses are becoming available. While these new agents may not show superior fracture reduction efficacy in clinical trials compared with daily or weekly oral bisphosphonates, they can offer greater convenience and potentially higher adherence in the real world compared with daily or weekly bisphosphonate therapy [22].

Conclusions

In conclusion, these results confirm that, in actual practice, adherence to current therapeutic regimens remains poor and is associated with an increased risk of hip fracture. Pursuing interventions that could improve adherence is worthwhile. The development of new medications with extended dosing intervals and interventions to involve patients in the treatment of their diseases may promote compliance, enhance patient satisfaction and outcomes, and decrease the social and economic burden of this debilitating condition.

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