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A. Delbar, Arnaud Pflimlin, I. Delabrière, Camille Ternynck, Christophe Chantelot, Francois Puisieux, Bernard Cortet, Julien Paccou

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Delbar Anthony[1], Pflimlin Arnaud[1], Delabrière Isabelle[2], Ternynck Camille[3], Chantelot Christophe[4], Puisieux François[2], Cortet Bernard[5], Paccou Julien[5]

Affiliations:

[1] Univ. Lille, CHU Lille, Department of Rheumatology, 59000 Lille, France

[2] Univ. Lille, CHU Lille, Department of Gerontology, 59000 Lille, France

[3] Univ. Lille, CHU Lille, ULR 2694 - METRICS: Évaluation des technologies de santé et des pratiques médicales, F-59000 Lille, France

[4] Univ. Lille, CHU Lille, Department of Traumatology, 59000 Lille, France

[5] Univ. Lille, CHU Lille, MABlab ULR 4490, Department of Rheumatology, 59000 Lille, France

Corresponding author:

Julien Paccou, MD, PhD

Department of Rheumatology, Lille University Hospital, Lille, France

Email: julien.paccou@chru-lille.fr

Email addresses of all authors:

Delbar A: anthony.DELBAR.etu@univ-lille.fr

Pfimlin A: Arnaud.PFLIMLIN@CHRU-LILLE.FR

Delabrière I: Isabelle.DELABRIERE@CHRU-LILLE.FR

Ternynck C: camille.ternynck@chru-lille.fr

Chantelot C: Christophe.CHANTELOT@CHRU-LILLE.FR

Puisieux F: Francois.PUISIEUX@CHRU-LILLE.FR

Cortet B: Bernard.CORTET@CHRU-LILLE.FR

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ABSTRACT

Purpose/Introduction: A Fracture Liaison Service (FLS) was set up at Lille University Hospital in 2016. The purpose of this study was to assess persistence with osteoporosis treatment in patients from the FLS over a period of 1 year, and to determine predictors of discontinuation.

Methods: The study population comprised adults of both genders, aged 50 or over, admitted to Lille University Hospital between January 2016 and January 2019 for a low-trauma fracture and managed in our FLS. Outcomes included (1) persistence rate at 1 year after treatment initiation, (2) persistence rate at 2 years after treatment initiation, (3) persistence rate at 1 and 2 years after treatment initiation according to type of treatment, (4) predictors of non-persistence, and (5) reasons for discontinuing treatment over 1 year after initiation. Persistence was determined using the Kaplan–Meier method.

Results: In all, 1,224 patients (≥ 50 years old) with a recent history of low-trauma fracture (≤ 12 months) were identified. Of these, 380 patients – 79.2% female; mean (SD) age 76 (11) years – were seen at the FLS. In those 380 patients, 410 fractures were found and 360 of them (87.8%) were major fractures, breaking down as follows: vertebra (44%), hip (19%), proximal humerus (10%), and pelvis (8%). Osteoporosis treatment was prescribed for 367 (96.6%) patients and 275 of them began the prescribed treatment. The following anti-osteoporosis drugs were prescribed: zoledronic acid (n=150, 54.5%), teriparatide (n=63, 22.9%), and denosumab (n=39, 14.2%). Oral bisphosphonates were prescribed for a few patients (n=23, 8.4%). Persistence with osteoporosis medication (any class) was estimated at 84.1% (95% CI: 79.1% to 88.1%) at 12-month follow-up, and dropped to 70.3% (95% CI: 63.7% to 75.9%) at 24 months. When drug-specific analyses were performed using the Kaplan–Meier method, persistence rates at 12 and 24 months were found to be higher with denosumab than with any other treatment. Independent predictors of non-persistence at 12 months were 'follow-up performed by a general practitioner (GP)' – Odds Ratio (OR) for GP *vs.* FLS = 3.68; 95% CI, 1.52 to 8.90, p=0.004 – and 'treatment with zoledronic acid' – OR for zoledronic acid *vs.* denosumab = 3.39; 95% CI, 1.21 to 9.50, p=0.019; OR for zoledronic acid *vs.* teriparatide = 8.86; 95% CI, 1.15 to 68.10, p=0.035.

Conclusions: This study provides evidence of the success of our FLS in terms of long-term persistence with osteoporosis treatments. However, osteoporosis treatment initiation still needs to be improved.

INTRODUCTION

Osteoporotic fractures are common in individuals over the age of 50: one in three women and one in five men sustain a fragility fracture **[1,2]**. Osteoporosis-related fractures may lead to diminished quality of life, disability, and even death **[3-7]**. Studies have found that currently available treatments can reduce vertebral fracture risk by 40 to 70% and hip fracture risk by 30 to 50% **[8-12]**. However, despite their effectiveness, there has been a gradual decline in the number of prescriptions over the last 10 years, and in the year following hospitalization for fracture, less than 15% of patients actually start treatment **[13]**. In response to this global phenomenon **[14,15]**, fracture liaison services have been set up around the world with the aim of filling this treatment gap **[16-18]**. Their implementation has been supported by the International Osteoporosis Foundation (IOF) through its secondary prevention programme, Capture the Fracture (CTF) **[19]**. Several studies have reported the benefits of such organisations, particularly in reducing the risk of fractures, the risk of mortality and health-care costs **[20-22]**.

Persistence with osteoporosis treatment is known to be poor among osteoporosis patients, and persistence rates have been reported to decline to less than 50% over a 12-month period **[23-25]**. In a recent systematic review, persistence with oral bisphosphonates was reported to be between 16 and 60% at one year, and the risk of subsequent fracture was found to increase by 30 to 40% in non-persistent patients compared to persistent patients **[26]**. Several studies have sought to evaluate the impact of FLSs on persistence, and the results are unequivocal: FLSs are associated with a marked improvement in persistence **[17,18,27]**. For example, in a French study involving 182 patients who had been given a prescription for osteoporosis treatment – mainly oral bisphosphonates –, the authors reported a 1-year persistence rate of 74.1% **[18]**. However, oral bisphosphonates are the main treatment prescribed in most FLSs and data are lacking on long-term persistence with injectable osteoporosis treatments (zoledronic acid, teriparatide and denosumab).

An FLS was opened at Lille University Hospital in 2016 and, since then, our practice has been evaluated using IOF criteria **[28]**. However, data on persistence with osteoporosis medication were not available. Moreover, as our patients are elderly, polymedicated and have mainly major fractures and several comorbidities, injectable drugs are preferred (~95%) to improve persistence **[28]**. In this article, we present the results of a survey conducted over a 3-year period among patients in our FLS program. This is the first large-scale study on persistence with injectable osteoporosis treatments (zoledronic acid, teriparatide and

denosumab). We measured 1-year persistence in patients in whom osteoporosis treatment was initiated and determined predictors of discontinuation.

PATIENT AND METHODS

Fracture Liaison Service and selection of patients

The study population comprised adults of both genders, aged 50 or over, admitted to Lille University Hospital between January 2016 and January 2019 for a low-trauma fracture and managed in our FLS. Patients were identified by an FLS clinical research assistant. The patient selection pathway has been previously described **[28]**.

First visit

For all patients seen at the FLS unit, the following data were collected: daily dietary calcium intake, laboratory workup, and hip and lumbar spine BMD (measured by DXA with calculation of the FRAX® score) **[29]**. WHO criteria were used to define osteoporosis (T-score ≤ -2.5) and osteopenia (T-score between -1.0 and -2.5). In line with the French guidelines on the management of postmenopausal osteoporosis **[30]**, vertebral fracture assessment (VFA) and/or X-rays were performed when indicated. VFA is indicated in postmenopausal women with spinal pain or when any of the following criteria are met: loss of height ≥4 cm compared to historical height (at 20 years of age); loss of height ≥2 cm as established prospectively during follow-up; previous vertebral fracture; chronic comorbidities; and treatments associated with a high risk of vertebral fracture (e.g., glucocorticoids and aromatase inhibitors).

Risk factors for osteoporosis were collected, and included: low body mass index (<19 kg/m²); current smoking; current alcohol abuse (≥3 units of alcohol per day for men, and ≥2 units for women); history of rheumatoid arthritis; use of oral corticosteroids (exposed to ≥5 mg/day of prednisolone for ≥3 months); previous low-trauma fracture; secondary osteoporosis; and family history of osteoporosis (hip fracture in mother or father). Data on prior use of menopausal hormone therapy were also collected. Finally, we collected comorbidity data (using the Charlson Comorbidity Index (CCI) **[31]**) and medication data for all patients. We also analysed what kind of osteoporosis treatments had been previously prescribed for each patient. After medical evaluation by the FLS, if osteoporosis treatment was found to be necessary, the initial prescription was made up either by the FLS or the patient's general practitioner (GP). Letters were systematically exchanged between the FLS and GPs at first visit. We also recorded whether follow-up was performed by the FLS or the patient's GP. As

our patients were elderly, polymedicated and had several comorbidities, injectable drugs (zoledronic acid, teriparatide and denosumab) were preferred when the initial prescription was made up by the FLS. The initial prescription was made up and/or follow-up was performed by the patient's GP, rather than by the FLS, only if patients had clearly expressed their preference for that/those option(s). Once patients had started follow-up with their GPs, the FLS did not contact them again. In short, follow-up was performed either by GPs or by the FLS, but never by both.

Follow-up

When follow-up was performed by the FLS, a follow-up appointment was automatically scheduled every 6 or 12 months (6 months for teriparatide and 12 months for zoledronic acid, denosumab and oral bisphosphonates), along with an FLS visit during which the following data were collected: risk factors for osteoporosis; current medications, including calcium and vitamin D supplementation; height and weight; new falls and fractures; and persistence with and tolerance of osteoporosis treatment. Denosumab injections were given once every 6 months, but at each yearly visit, prescriptions were made up for 2 injections. For oral bisphosphonates, prescriptions were made for 1 year. Moreover, VFA and/or X-rays and DXA scans (to determine BMD) were performed when indicated. Letters were systematically exchanged between the FLS and GPs at first visit. Patients' appointments were confirmed by automated text message 1 day before each appointment. For cancelled appointments and no-shows, patients were promptly called to schedule a new follow-up appointment.

Patients

Between January 2016 and January 2019, 969 of the 1224 patients identified by the FLS were eligible for inclusion and 255 patients (20.8%) were excluded. The reasons for exclusion were: severe cognitive disorders (n=207, 16.9%); osteoporosis already being treated (n=35, 2.9%); language barrier (n=7, 0.6%); and living too far away from Lille (n=6, 0.5%). Of the 969 eligible patients, 566 (58.4%) failed to attend appointments at the FLS unit for the following reasons: refusal, or agreed but subsequently failed to attend (n=485, 50.0%); died before being seen (n=22, 2.3%); and still waiting to be seen (n=59, 6.1%) **(Figure 1)**. Of the remaining 403 patients referred to our FLS unit, 23 were excluded from analysis after medical assessment, BMD, and laboratory workup: 9 of the patients had primary hyperparathyroidism, 1 had idiopathic phosphate diabetes, 3 had chronic kidney disease-mineral and bone disorder, and osteoporosis medication was not indicated in 10 patients in line with French guidelines on

the management of postmenopausal osteoporosis **[30]**. After the first visit, 380 patients with an indication for osteoporosis treatment were included.

Study procedure

During the first visit, data were collected in a database that was populated in real time whenever a patient was seen at the FLS. The patients' characteristics were then analysed. Using the collected data we were also able to determine the proportion of patients identified for a non-vertebral fracture who had been assessed for vertebral fractures. In that group of patients, we were able to identify those who actually had one or more unknown vertebral fracture(s). For fall risk, we determined the proportion of patients reporting at least two falls in the year preceding the fracture. ***During the follow-up visits*** to the FLS, data were collected in the same database, which was also populated in real time whenever a patient was seen.

For the purposes of this study, we investigated patients included in the FLS cohort between January 2016 and January 2019 with a minimum follow-up of 12 months. Between February 2020 and April 2020, data were collected when available by reviewing the FLS database and individual patient records, or by contacting and interviewing patients by phone to complete an evaluation questionnaire. When patients were unable to answer the questions, a family member or the patient's GP was interviewed instead. The questionnaire included closed-ended questions on the following topics: (i) actual initiation of treatment or failure to initiate treatment, treatment prescribed, and initial coprescription of calcium and/or vitamin D supplementation; (ii) persistence with treatment – which only concerned patients who had actually initiated treatment – or the reasons for stopping or switching treatment.

Study outcomes

Outcomes included (1) persistence rate at 1 year after treatment initiation, (2) persistence rate at 2 years after treatment initiation, (3) persistence rate at 1 and 2 years after treatment initiation according to type of treatment, (4) predictors of discontinuation, and (5) reasons for discontinuing treatment at 1 year after treatment initiation.

Definition of persistence and predictors of discontinuation

Persistence was quantified using the "estimated level of persistence with therapy" (ELPT) method **[32]**, which determines the percentage of individuals remaining on therapy (i.e., persistent) at a given time. It was calculated as the number of days from initiating osteoporosis treatment (i.e., index date) to the end of treatment, and was estimated as the

proportion of patients refilling each subsequent prescription within the permissible 90-day window. Patients who failed to refill their prescriptions within the permissible window were considered non-persistent. This definition was used for all osteoporosis treatments, including zoledronic acid, teriparatide, denosumab and oral bisphosphonates. Moreover, patients who had switched to another osteoporosis treatment were considered non-persistent. The sole exception to this was for patients who switched from teriparatide at 18 months since teriparatide is used and reimbursed for no more than 18 months.

The variables included as potential predictors of discontinuation were age, gender, BMI, prior osteoporosis treatment, prior fractures, CCI, polymedication (≥5 medications), multiple falls (at least two fall in the last year), type of treatment, type of fracture (vertebral *vs.* non-vertebral), type of follow-up (FLS *vs.* GP), and BMD osteoporosis (T-scores ≤ 2.5 at any site) at initiation of treatment.

Statistical analysis

Continuous variables were expressed as means (standard deviation, SD) in the case of normal distributions, or medians (interquartile range) otherwise. Categorical variables were expressed as numbers (percentage). Normality of distributions was assessed using histograms and the Shapiro-Wilk test. 'Overall treatment duration' and 'treatment duration according to type of treatment' were estimated using the Kaplan-Meier method, with 'discontinuation of treatment' as the event of interest. Estimates for 'treatment duration according to type of treatment' is a non-adjusted method. Death and loss to follow-up were treated as censored events.

In patients who completed the one-year follow-up, we compared the baseline characteristics of those who were persistent and those who were not at one year. Continuous variables were compared using a Mann-Whitney U-test, and categorical variables were compared using a Chi-square test. To assess independent predictors of treatment discontinuation, variables associated with discontinuation at 1 year in univariate analyses (p value < 0.10) were included in a multivariable logistic regression model, with backward step-wise selection using a value of $p<0.10$ as the cut-off for retention in the model. Absence of collinearity between the candidate variables was checked by calculating the variance inflation factors.

Statistical testing was done at the two-tailed α-level of 0.05. Data were analysed using SAS software (version 9.4; SAS Institute Inc., Cary, NC).

RESULTS

Population characteristics

Table 1 shows the baseline characteristics of all 380 patients included in the study. Most of the patients (79.2%) were female. The median age of the study population was 76 years. Of the 380 patients included in the study, 65 (17.1%) had a BMI ≥30 kg/m², 201 (53.0%) had a history of osteoporotic fracture, 81 (21.3%) had prior osteoporosis treatment, 47 (17.6%) had premature menopause (below the age of 45), 36 (9.7%) had a family history of first-degree hip fracture, and 32 (8.4%) had prolonged exposure to corticosteroids. Of the 377 patients analysed, 79 (21.0%) reported having had at least two falls in the previous year. Comorbidities and medication use are shown in **Supplementary Table 1**. For comorbidities, we found 207 patients with a history of or current hypertension (54.5%), 65 with diabetes mellitus (17.1%) and 64 with a history of any cancer (16.8%). The median Charlson (CCI) score was 4.0 (range: 3.0-5.0). Medication use was as follows: oral anticoagulant drugs (78 patients, 20.5%), anxiolytics (64 patients, 16.8%), and diuretics (53 patients, 13.9%).

When the data were examined to assess recent history of fragility fracture (≤12 months), 410 fractures were found in 380 patients **(Figure 2)**. Some patients had several fractures. We found 178 patients with at least one X-ray diagnosed vertebral fracture (43.4%), 78 hip fractures (19.0%), 40 proximal humerus fractures (9.8%), 34 pelvis fractures (8.3%), and 21 distal forearm or wrist fractures (5.1%). There were 360 major fractures (87.8%) (hip, vertebra, distal femur, proximal humerus, pelvis, proximal tibia) according to the definition proposed by Bliuc *et al.* **[5]**, and 317 (77.3%) according to FRAX® (hip, vertebra, proximal humerus and distal forearm/wrist). Of the 202 patients seen for non-vertebral fractures, 140 (69.3%) had undergone a morphological assessment of the spine. An unknown vertebral fracture was diagnosed in 51/140 patients (36.4%).

Treatment prescriptions

Osteoporosis treatment was prescribed in 367/380 patients (96.6%) in line with French guidelines **[30]**. Seven (1.8%) refused the prescription, and no data were found in 6 patients (1.6%). The main osteoporosis drug prescribed was zoledronic acid (n=217, 59.1%), followed by teriparatide (n=70, 19.1%) and denosumab (n=51, 13.9%). Oral bisphosphonates were

prescribed for a few patients (n=29, 7.9%). Calcium and vitamin D supplementation were prescribed in 145 (38.2%) and 312 patients (82.1%) respectively.

Among the 367 patients analysed, 275 actually began the prescribed treatment (see **Table 1** for baseline characteristics and **Supplementary Table 1** for comorbidities and medication use). In 75 patients, osteoporosis medication was prescribed but not initiated for the following reasons: patient refusal (n=30); the GP forgot to make up the prescription (n=10); fear of adverse effects (n=8); prescription lost (n=8); GP refusal (n=7); polymedication (n=5); another health problem (n=5); felt the treatment was irrelevant (n=2). Moreover, no data on treatment initiation were available for 17 patients due to loss to follow-up. As such, osteoporosis treatment was prescribed and initiated in 275 patients (i.e., 367-75-17 = 275). A comparison between the patients who did/did not start treatment revealed no significant differences in demographic characteristics, osteoporosis risk factors, comorbidities and bone mineral density testing (**Supplementary Table 2**). The most frequently prescribed drug was zoledronic acid (n=150, 54.5%), followed by teriparatide (n=63, 22.9%) and denosumab (n=39, 14.2%). Oral bisphosphonates were prescribed for a few patients (n=23, 8.4%). A comparison between the four groups of patients revealed no significant differences in demographic characteristics, osteoporosis risk factors, and bone mineral density testing (**Supplementary Table 3**). However, significant differences were found for 'fragility fracture' ($p<0.001$) and 'prior osteoporosis medications' ($p<0.001$), both of which were often more frequent in patients treated with denosumab.

Persistence with treatment

Kaplan–Meier analyses showed that the rate of persistence with osteoporosis treatment (any class) was 84.1% (95% CI: 79.1% to 88.1%) at 12-month follow-up, and 70.3% (95% CI: 63.7% to 75.9%) at 24 months **(Figure 3)**.

Drug-specific analyses using the Kaplan–Meier method (a non-adjusted method) showed that persistence rates at 12 and 24 months were higher with denosumab than with any other therapy: persistence rates were 97.1% (95% CI: 81.4% to 99.6%] and 91.1% (95% CI: 74.8% to 97.0%) for denosumab at 12 and 24 months, respectively, compared with 73.7% (95% CI: 50.5% to 87.2%) and 67.5% (95% CI: 43.1% to 83.3%) for oral bisphosphonates, 78.7% (95% CI: 71.0% to 84.6%) and 70.9% (95% CI: 62.0% to 77.9%) for zoledronic acid, and 89.9% (95% CI: 78.8% to 95.3%) and 71.8% (95% CI: 57.2% to 82.1%) for teriparatide **(Figure 4)**.

Predictors of discontinuation

As shown in **Table 2**, discontinuation at 12 months was associated with prior osteoporosis treatment (p=0.03), follow-up performed by patient's GP (p=0.002) and class of current osteoporosis treatment (p=0.01). In multivariate analysis, independent predictors of discontinuation were follow-up performed by GP (Odds Ratio (OR) for GP *vs.* FLS = 3.68; 95% CI: 1.52 to 8.90, p=0.004) and treatment with zoledronic acid (OR for zoledronic acid *vs.* denosumab = 3.39; 95% CI: 1.21 to 9.50, p=0.019 and OR for zoledronic acid *vs.* teriparatide = 8.86; 95% CI: 1.15 to 68.10, p=0.035).

Reasons for discontinuation

Exploratory analyses following extensive chart review and patient interviews revealed the major reasons for discontinuing therapy at 12 months. Nineteen (19) patients were censored due to death and 4 patients were lost to follow-up. Of the 41 non-persistent patients, reasons for discontinuation were: forgetfulness or neglect (18 patients); switched to another osteoporosis treatment (15 patients); development of concomitant illnesses (4 patients); fear of anticipated side effects (2 patients); and individual decisions or belief systems (2 patients).

DISCUSSION

The importance of persistence with osteoporosis treatment in achieving fracture prevention is well-known and highlighted in several publications **[33,34]**. In our study, persistence rates with osteoporosis treatment (any class) at 12 and 24 months were 84.1% (95% CI: 79.1% to 88.1%) and 70.3% (95% CI: 63.7% to 75.9%), respectively. At 12 months, we found that the rate of persistence among patients receiving denosumab was 97.1%, compared with 73.7% for oral bisphosphonates, 78.7% for zoledronic acid, and 89.9% for teriparatide. Independent predictors of discontinuation at 12 months were: follow-up performed by GP (*vs.* FLS) (OR=3.68, p=0.004); zoledronic acid *vs.* denosumab (OR=3.39, p=0.019); and zoledronic acid *vs.* teriparatide (OR=8.86, p=0.035).

In this study, the mean age of the patients was 74.9 years, as opposed to 63.3 to 72.9 years in other FLS studies, but the proportion of women in our population (79.2%) did not differ from that reported in other FLS studies **[16-18]**. However, when compared with other FLS populations or even populations in primary care studies, our population differs in 2 key respects. Firstly, most of the patients included in our study had a recent history of *major*

osteoporotic fracture (87.8%). The main types of fractures found were vertebral fractures (43.4%) and hip fractures (19.0%). The predominance of vertebral fractures is probably due to the fact that many of the patients were recruited from Lille University Hospital's Department of Rheumatology, while the low number of other fractures – such as wrist or forearm fracture (5.1%) – can be explained by the low level of recruitment among Emergency Department patients **[28]**. In a population of 279 patients, Boudou *et al.* found that 36% of all fractures were wrist fractures **[17]**. Similarly, Dehamchia-Rehailia *et al.* reported that wrist fractures and ankle fractures – another type of minor fracture – accounted for 26% and 11.7% of all fractures respectively **[18]**. Moreover, in most FLSs, vertebral fractures are either not represented or under-represented **[16-18,27]**. Secondly, in our population, injectable anti-osteoporosis drugs were prescribed for the vast majority of patients (91.6%). Zoledronic acid was prescribed for most patients (54.5%), followed by denosumab and teriparatide. This is in contrast with the current practice in primary care centres, where oral bisphosphonates are the main treatment prescribed **[23-25]**, as is also the case in most FLSs **[16-18,35]**. For example, 73% of the patients from the Amiens University Hospital FLS were treated with oral bisphosphonates **[18]**. The route of administration of these treatments (injection) is considered more suitable for frail patients and this is one of the reasons why those treatments were used in our FLS **[30]**. Since our population was elderly, polymedicated and had several comorbidities, injectable drugs were prescribed preferentially in order to improve both adherence and persistence **[26]**. Furthermore, persistence with zoledronic acid seems to be better than with oral bisphosphonates **[23,24]**, and the relatively high prescription rate of denosumab is related to the prevalence of patients previously treated with (oral or intravenous) bisphosphonates (~22%) as denosumab is reimbursed in France only after bisphosphonate treatment. Additionally, teriparatide was used as the first choice of treatment in patients with at least 2 vertebral fractures, which is the criterion for the reimbursement of this drug in France. Moreover, since parenteral administration may minimize some side effects (e.g., gastrointestinal upset) and spares patients the burden of having to adhere to the complex instructions required for taking oral bisphosphonates properly, this route of administration may improve persistence **[26]**.

In this study, persistence with osteoporosis medication (any class) was 84.1% at 12-month follow-up and dropped to 70.3% at 24 months. Persistence rates for patients seen in an FLS setting are generally higher than those in other populations. When compared with findings in primary care studies, patients from our FLS seem to exhibit better persistence with

osteoporosis medication. Indeed, in recent primary care studies, persistence is less than 50% at 12 months, and between 26% and 31% at 24 months **[23-25]**. However, in primary care settings, oral bisphosphonates are the most common medication (between 68% and 95%) and are prescribed in patients with a lower rate of fragility fractures (up to 36%) in comparison with FLSs **[23-25]**. As regards persistence with osteoporosis treatment, our findings are quite similar to those reported in other FLS studies and fall within the upper range of previously published results **[16-18,27,35]**. In a *prospective* study conducted by Eekman *et al.*, 337 patients receiving mainly oral bisphosphonates (~90%) were followed up *every three months* and the authors reported a persistence rate of 88% at 12 months **[27]**. In a French *retrospective* study involving 155 patients, 88% of whom were under treatment with oral bisphosphonates, the authors reported a persistence rate of 80% at 12 months **[17]**. Finally, the authors of a Canadian study involving 260 patients who had started treatment (79% under treatment with oral bisphosphonates) reported persistence rates of 66.4% and 55.6% at 12 and 24 months, respectively **[35]**.

Studies have generally found that patients are more persistent with injectable osteoporosis therapies – including denosumab, teriparatide, and zoledronic acid – than with oral bisphosphonates **[26]**. Similarly, in a large US study, Cheng *et al.* found that the 12-month persistence rate among patients receiving denosumab was 68%, compared with 29–35% for oral bisphosphonates, and 59% for teriparatide **[36]**. Findings on persistence with yearly intravenous injections of zoledronic acid are also not convincing, as suggested in a study that showed that only one-third of patients agreed to a second administration after 1 year **[37]**.
In our study, we also found better persistence rates at 12 and 24 months with injectable osteoporosis therapies (denosumab, teriparatide, and zoledronic acid) than with oral bisphosphonates. Robust persistence rates with denosumab were found at 12 and 24 months, but few patients received a prescription for this treatment (n=39, 14.2%), and it was mainly prescribed in cases of previous osteoporosis treatment with bisphosphonates. High persistence rates with teriparatide at 12 months (89.9%) and 24 months (71.8%) were also found and could be partly explained by the systematic visit at 6 months. But again, few patients were treated with teriparatide (n=63, 22.9%) and these results should be interpreted with caution. No data are available on teriparatide prescription rates in other FLSs, but "real-world" data show that persistence rates with teriparatide are usually below 80% at 12 months **[38,39]**. Likewise, no data are available on prescription rates for zoledronic acid, especially in FLSs. In our study, patients under treatment with zoledronic acid were more often followed up in

our FLS and systematically had a scheduled visit one year later, which limited the risk of non-renewal and improved persistence.

The factors determining persistence with osteoporosis treatment are not fully understood, but it is likely that several factors are involved, including, but not limited to age, polymedication, comorbidities, socio-economic-related factors and history of prior vertebral fractures **[26,40,41]**.

The literature is scant on the impact on persistence of follow-up by GP versus secondary fracture prevention program (i.e., FLS). This could be explained by the fact that very few FLSs perform longitudinal follow-ups on a systematic basis, and even fewer make use of a combined approach, i.e. with follow-up performed either by GPs or in their FLS. For example, in most Spanish FLSs (75%), patient follow-up is perform in the hospital setting through a face-to-face visit with a specialist (with a combined approach in one third), while in 25% of FLSs, follow-up is performed exclusively by GP **[42]**. To the best of our knowledge, only one study has addressed the difference in persistence depending on whether follow-up is actively performed in the FLS setting or not **[43]**. The aim of this randomized controlled trial (n=102 patients) was to determine whether management in the FLS setting results in better persistence with oral bisphosphonate therapy than follow-up by GP, after initiation in an FLS. Persistence at 24 months was similar in both groups (64% vs. 61%; p=0.75) **[43]**. However, definitive conclusions cannot be drawn from this trial due to the limited number of patients. Our study was not designed to answer this question, and further studies are needed to determine whether follow-up in the FLS setting is the better option.

Another independent predictor of non-persistence was type of treatment, with a significantly higher risk in patients under treatment with zoledronic acid than in those under treatment with teriparatide or denosumab. However, our analysis only partially reflects reality since, in our study, adjustments were made only for a small number of factors, and the low numbers obtained for certain treatments (mainly teriparatide and denosumab) explain the width of the confidence intervals. As such, despite their significance, our results should be considered preliminary and interpreted with caution.

However, several studies have shown that persistence rates are low in patients treated with bisphosphonates compared to denosumab **[44-47]**. In a retrospective, non-interventional observational study providing real-world data on long-term persistence with denosumab over a 36-month time period, extended treatment with denosumab yielded considerably higher persistence rates (n=743, 64.2% after 36 months) than those observed with oral bisphosphonates **[41]**. In the prospective, randomized Denosumab Adherence Preference

Satisfaction (DAPS) study, 250 postmenopausal osteoporosis patients under treatment with open-label denosumab or weekly alendronate for 24 months were assessed using a 12-month crossover comparative design, and 90% of the patients reported that they preferred injectable denosumab. Persistence with denosumab was also found to be statistically higher **[44]**. Moreover, the recent finding that denosumab discontinuation results in rapid bone loss, and in some individuals may lead to multiple vertebral fractures, is one of the reasons why patients and physicians are particularly attentive to long-term persistence with denosumab **[48,49]**. Further studies are needed to determine whether persistent rates vary across injectable treatments.

One of the strengths of our study is the low proportion of missing data, owing to the fact that our patient information was collected systematically and in a standardised manner during dedicated medical visits and phone calls. Another strength of our study is that we used persistence rates at 12 and 24 months as standardized criteria, which allowed us to compare our results with data from the literature. Of course, we acknowledge that there are some limitations to our study. Our evaluation rate was low (41.6%), but this is probably due to the fact that our FLS only sees patients who agree to be seen, whereas in most FLS units patients are seen systematically once identified. A better evaluation rate could probably be obtained through more active involvement by GPs. Our population of fracture patients was also skewed towards those with major osteoporotic fractures. Another limitation is that we did not evaluate adherence, but measuring adherence is challenging in a real-world setting. Lastly, we did not perform a sensitivity analysis, adjusting the permissible window to 30 or 60 days instead of 90 days. Given the difficulties and divergent methods in defining persistence for several type of treatments, we decided to use the same permissible window for each treatment, regardless of the mode of administration. It should be noted that a certain number of patients who had discontinued their treatment and were considered non-persistent, subsequently switched to another treatment (~36% of the 41 non-persistent patients).

In conclusion, our study provides compelling evidence of the success of a secondary fracture prevention program in improving long-term persistence with injectable osteoporosis treatments. Despite somewhat better persistence with parenteral osteoporosis treatments compared to persistence with oral bisphosphonates in the primary care setting, as reported in the literature, less frequent administration of parenteral zoledronic acid has not fully resolved the issue of low persistence to osteoporosis treatments. As our results show, ~20% of patients

treated with zoledronic acid did not receive a second dose during the follow-up period. Interventions continue to be warranted to improve initiation (less than 80% of the patients actually began the treatment prescribed) and long-term persistence with osteoporosis treatments **[26]**. Active participation of GPs in secondary prevention programs is needed, as are systematic follow-ups during the first 6 months, in order to improve both initiation of and persistence with osteoporosis treatments. The lessons learned from this study will enable us to develop a revised and more effective program in the near future.

TABLES AND FIGURES

Table 1 Demographic data and relevant baseline characteristics of all included patients and of patients who initiated treatment

Table 2 Univariate predictors of osteoporosis treatment discontinuation at 12 months in the 252 patients who completed the 12-month follow-up

Figure 1 Study population flow chart

Figure 2 Distribution of the 410 fractures across the 380 patients that were analysed

Figure 3 Kaplan–Meier survival analysis of persistence with osteoporosis medication (any class)

Figure 4 Kaplan–Meier survival analysis of persistence with osteoporosis medication (drug-specific; 1: zoledronic acid; 2: teriparatide; 3: denosumab; 4: oral bisphosphonates) (Kaplan–Meier method is a non-adjusted method)

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Figure 1: Study population flow chart

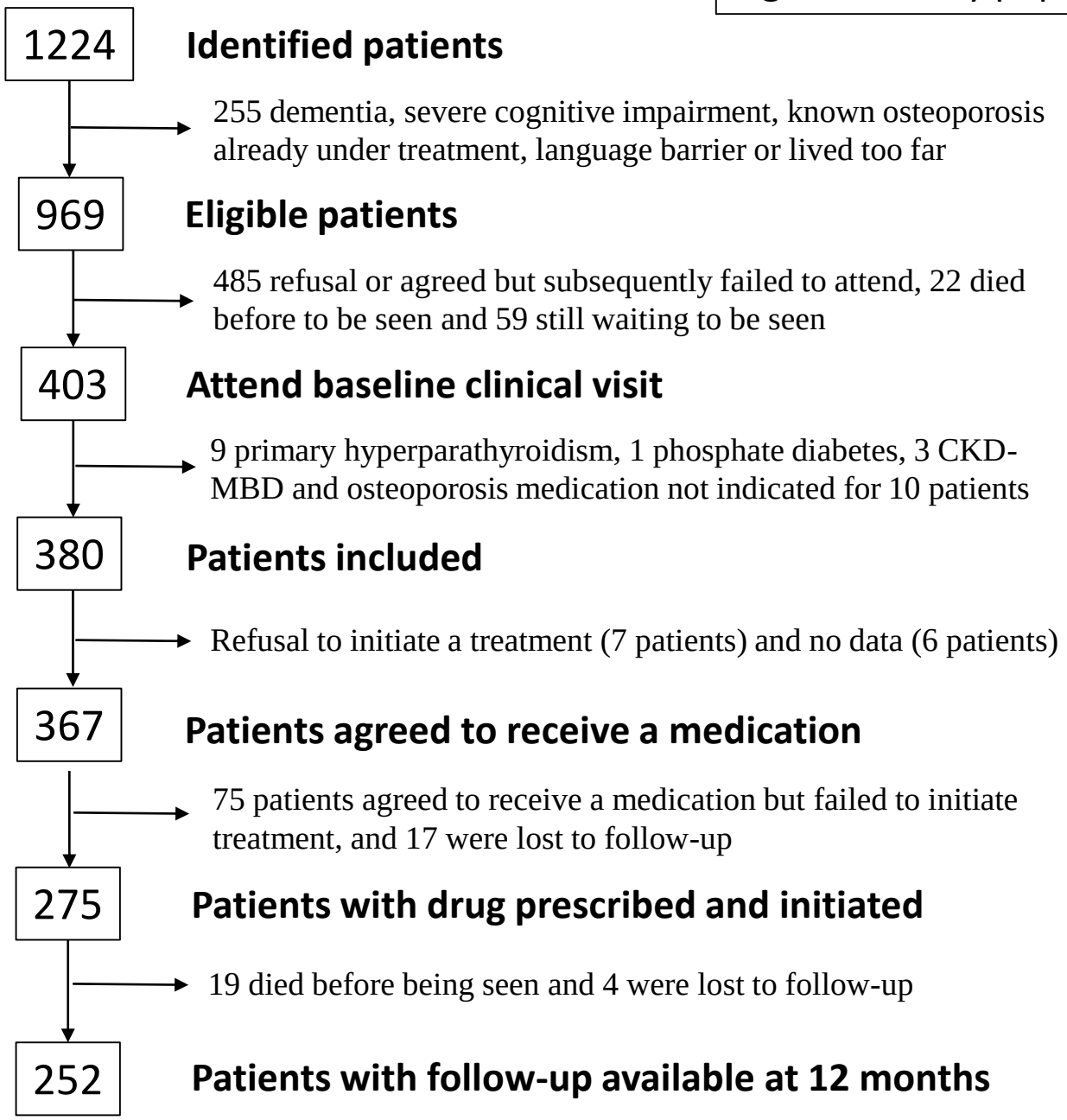
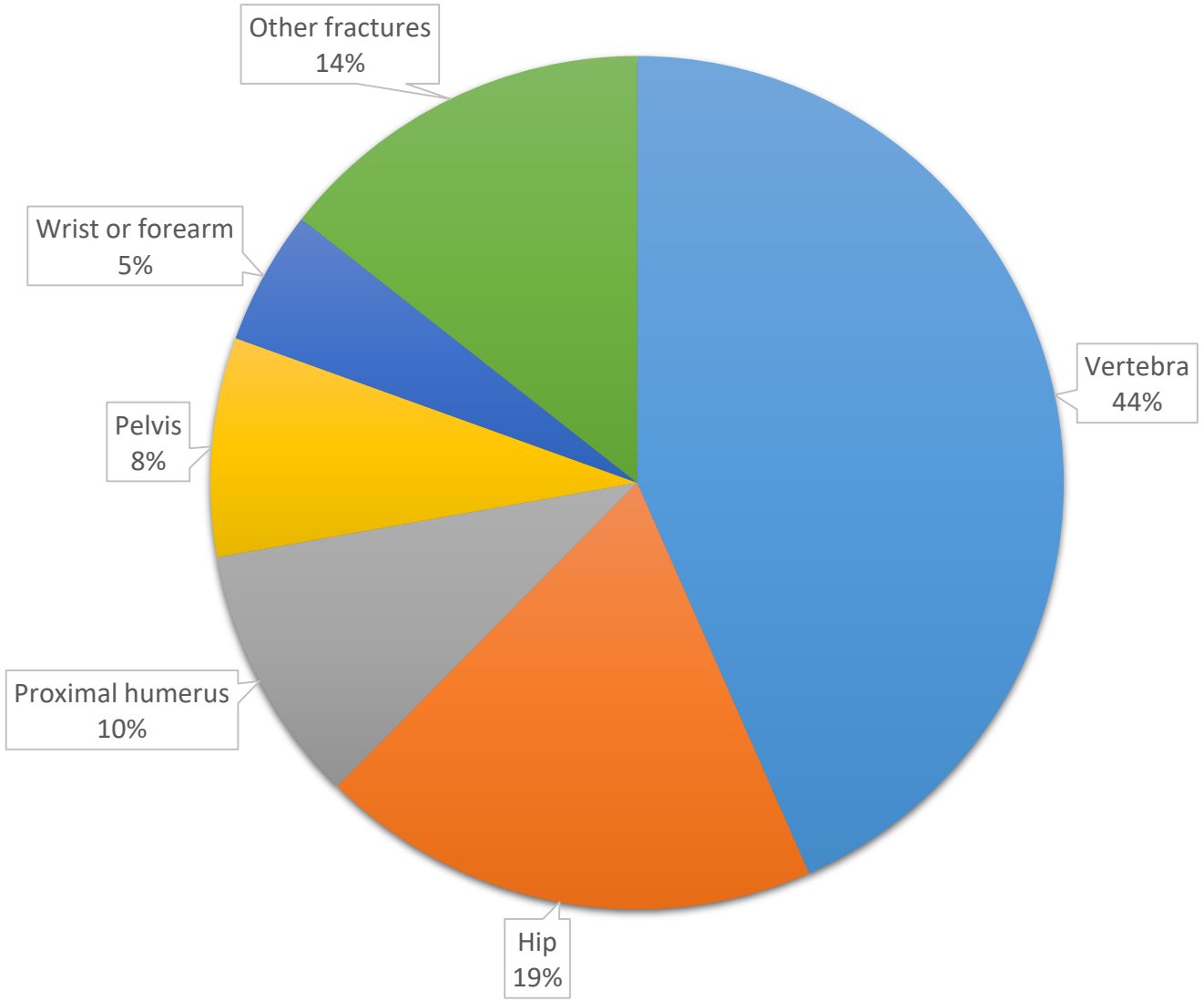


Figure 2: Distribution of the 410 fractures across the 380 patients that were analysed



Survival curve

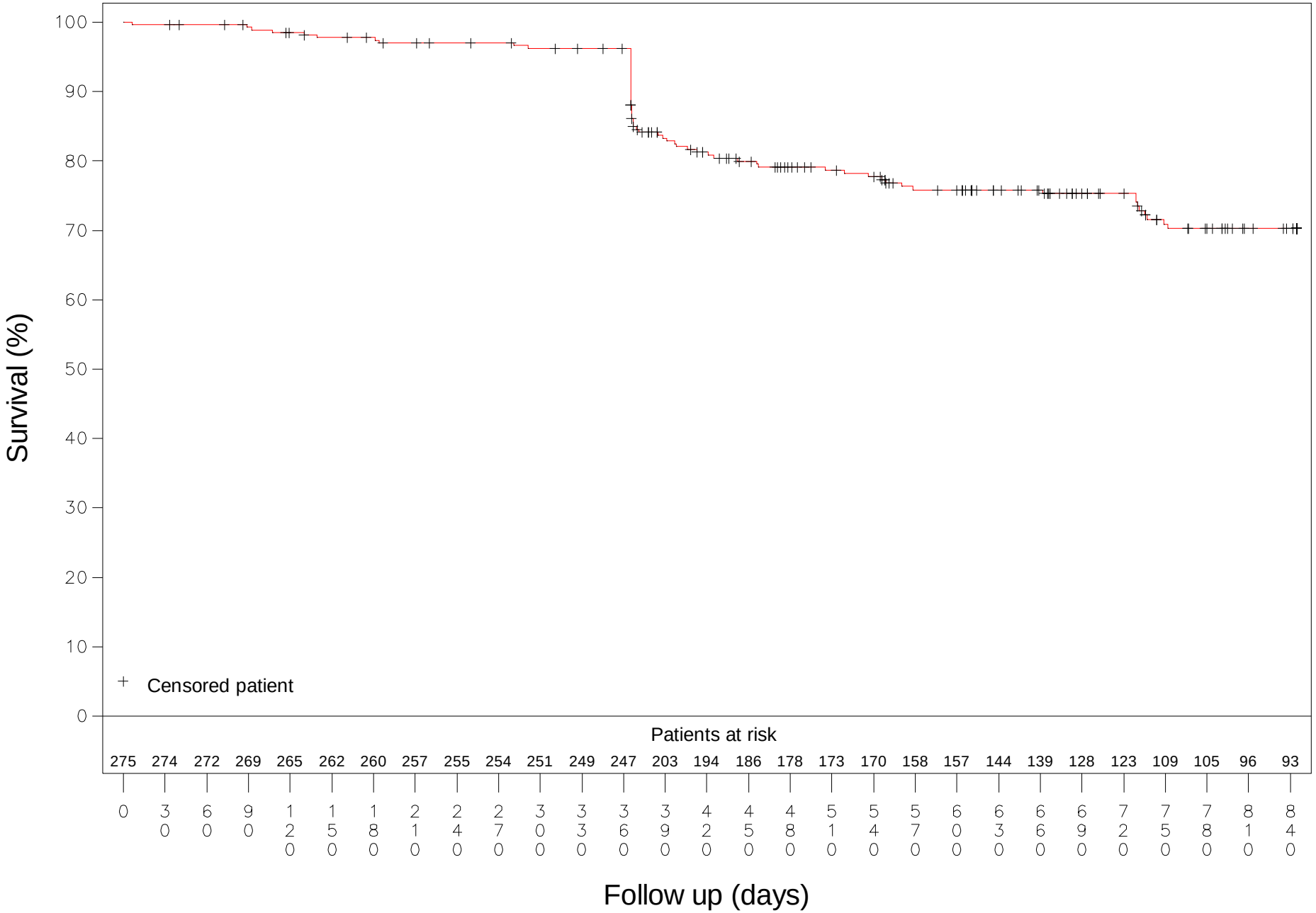
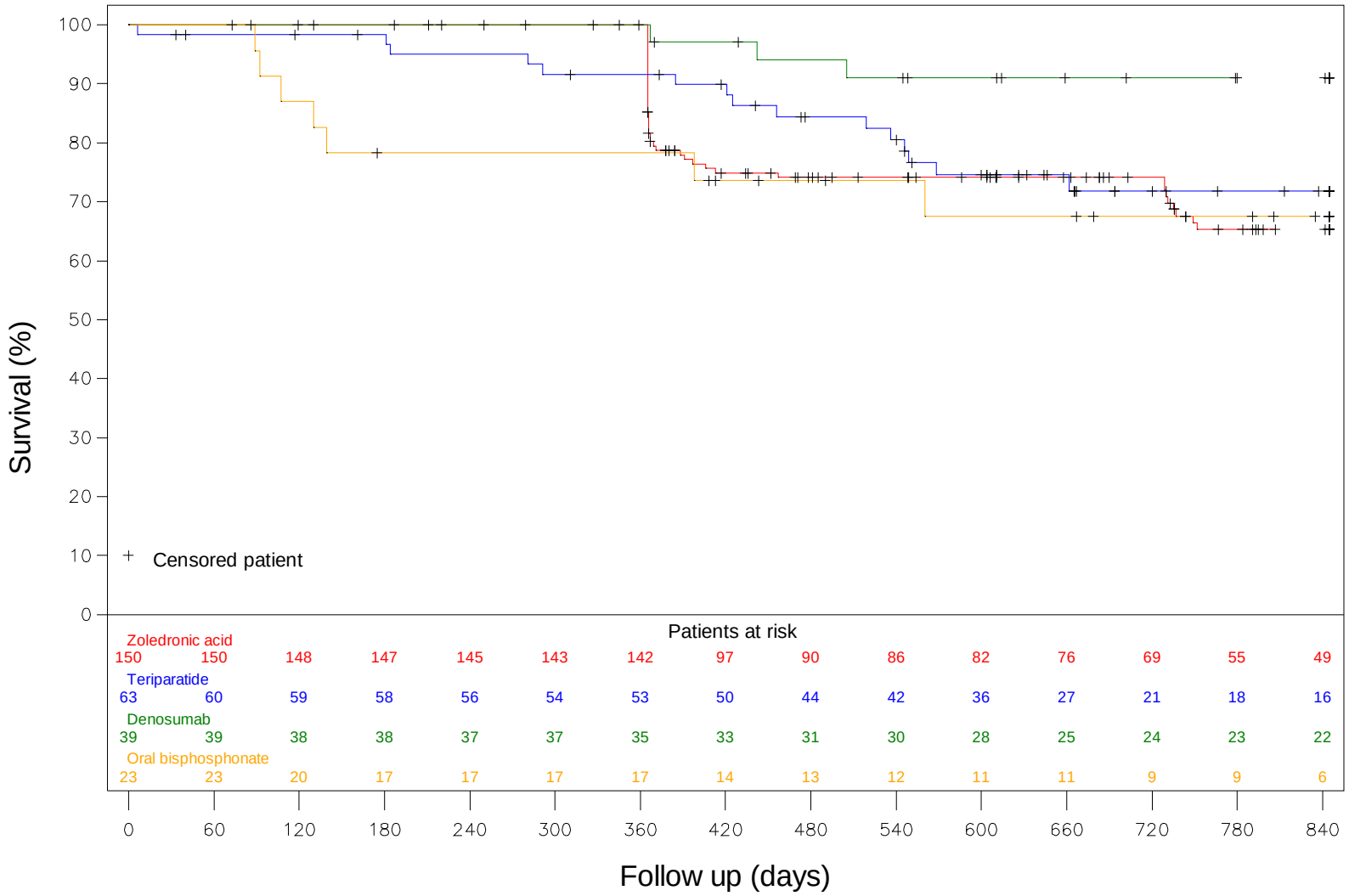


Figure 4 Kaplan–Meier survival analysis of persistence with osteoporosis medication (drug-specific)



1 zoledronic acid **2** teriparatide **3** denosumab 4 oral bisphosphonates

Table 1: Demographic data and relevant baseline characteristics of all included patients and of patients who initiated treatment

Characteristics	**All included patients** **N = 380**	**Patients who initiated treatment** **N = 275**
Female gender	301 / 380 (79.2)	220 / 275 (80.0)
Age, years	76.0 [67.0; 84.0]	76.0 [67.0; 84.0]
Body mass index* (kg/m²)	24.7 [22.1; 28.4]	24.8 [22.4; 28.6]
BMI < 19 kg/m²	18 / 366 (4.9)	14 / 263 (5.3)
19 ≤ BMI < 25 kg/m²	172 / 366 (47.0)	121 / 263 (46.0)
25 ≤ BMI < 30 kg/m²	114 / 366 (31.1)	81 / 263 (30.8)
BMI ≥ 30 kg/m²	62 / 366 (16.9)	47 / 263 (17.9)
Osteoporosis risk factors		
Active smokers	22 / 377 (5.8)	16 / 273 (5.9)
Alcohol abuse	21 / 377 (5.6)	17 / 274 (6.2)
Premature menopause (<45 years)	47 / 267 (17.6)	36 / 197 (18.3)
Family history of hip fracture	36 / 371 (9.7)	26 / 270 (9.6)
Corticosteroids exposure	32 / 379 (8.4)	25 / 274 (9.1)
Multiple falls**	79 / 377 (21.0)	57 / 272 (21.0)
Previous fragility fracture	201 / 379 (53.0)	147 / 274 (53.6)
- Vertebra	82 / 379 (21.6)	67 / 274 (24.5)
- Wrist	60 / 379 (15.8)	42 / 274 (15.3)
- Shoulder	36 / 379 (9.5)	23 / 274 (8.4)
- Hip	31 / 379 (8.2)	19 / 274 (6.9)
- Ribs	24 / 379 (6.3)	17 / 274 (6.2)
- Ankle	16 / 379 (4.2)	14 / 274 (5.1)
- Elbow	12 / 379 (3.2)	11 / 274 (4.0)
- Pelvis	11 / 379 (2.9)	8 / 274 (2.9)
- Other	11 / 379 (2.9)	8 / 274 (2.9)
- Leg	11 / 379 (2.9)	7 / 274 (2.6)
- Foot	7 / 379 (1.8)	6 / 274 (2.2)
Prior osteoporosis medications	81 / 380 (21.3)	64 / 275 (23.3)
Oral bisphosphonate	68 / 380 (17.9)	55 / 275 (20.0)
Zoledronic acid	15 / 380 (3.9)	13 / 275 (4.7)
Teriparatide	10 / 380 (2.6)	10 / 275 (3.6)
Strontium ranelate	5 / 380 (1.3)	4 / 275 (1.5)
Denosumab	3 / 380 (0.8)	1 / 275 (0.4)
Raloxifene	3 / 380 (0.8)	2 / 275 (0.7)
Prior menopausal hormone therapy	48 / 265 (18.1)	40 / 194 (20.6)
BMD testing		
- Osteoporosis	144 / 318 (45.3)	112 / 242 (46.3)
- Osteopenia	144 / 318 (45.3)	108 / 242 (44.6)
- Normal	30 / 318 (9.4)	22 / 242 (9.1)

* n = 366

**at least two falls in the last year

Values are expressed in no. /Total no. (%) or median (IQR)
IQR: interquartile range; BMI: Body mass index

Table 2: Univariate predictors of osteoporosis treatment discontinuation at 12 months in the 252 patients who completed the 12-month follow-up

Characteristics	**Discontinuation**		**P-value**
	No (n = 211)	**Yes (n = 41)**	
Female gender	171 / 211 (81.0)	32 / 41 (78.0)	0.66
Age (years)	76.0 [66.0; 84.0]	75.0 [67.0; 82.0]	0.90
Body mass index (kg/m²)	24.8 [22.4; 29.0]*	25.7 [23.8; 28.0]**	0.32
Multiple falls (≥ 2 falls/year)	48 / 209 (23.0)	5 / 41 (12.2)	0.12
Previous fragility fracture	111 / 210 (52.9)	21 / 41 (51.2)	0.85
Prior osteoporosis medications	53 / 211 (25.1)	4 / 41 (9.8)	**0.031**
Charlson Comorbidity Index	4.0 [3.0; 5.0]	4.0 [3.0; 6.0]	0.32
Type of fracture (vertebral vs. nonvertebral fracture)	108 / 211 (51.2)	20 / 41 (48.8)	0.78
Follow-up by GP	191 / 211 (90.5)	30 / 41 (73.2)	**0.002**
Polymedication (≥ 5 medications)	46 / 211 (21.8)	8 / 41 (19.5)	0.74
BMD Osteoporosis	87 / 191 (45.5)	20 / 39 (51.3)	0.51
Class of current osteoporosis medication:			**0.014**
- **Zoledronic acid (n=138)**	108 / 211 (78.3)	30 / 41 (21.7)	Reference
- **Teriparatide (n=58)**	53 / 211 (91.4)	5 / 41 (8.6)	0.09*
- **Denosumab (n=34)**	33 / 211 (97.1)	1 / 41 (2.9)	**0.03***
- **Oral BisP (n=22)**	17 / 211 (77.3)	5 / 41 (22.7)	1.00*

Values expressed as no. / total no. (%) or median [IQR]

*n = 204; **n=40

P-values obtained using a Chi-square test for qualitative parameters (or Fisher's exact test if the frequency of cells was < 5) or using a Mann-Whitney U-test for quantitative parameters

* P-values from post-hoc analysis performed with zoledronic acid as reference, applying Bonferroni correction

Statistically significant results are indicated in bold type

GP: General Practitioner; BMD: bone mineral density; BisP: bisphosphonates