Osteoporosis: risk factors and diagnostic approach

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Chapter 6

Adherence and persistence of patients after case-finding for osteoporosis: 3 years of follow-up.

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Submitted

ABSTRACT

Objective Fracture and osteoporosis (FO) clinics are important in the identification of patients with osteoporosis and making treatment recommendations. Patient adherence to advice and persistence in taking medication are crucial for a successful treatment, as well as concordance of general practitioners (GPs) with a treatment advice.

Design In total, 554 patients of 50 years and older with a recent fracture who participated in a case-finding program for osteoporosis, received a recommendation letter with a treatment advice, based on absolute 10-years fracture risk and BMD results. One, two and three years later, patients received follow-up questionnaires to collect information on their adherence to advice and persistence to therapy, concordance of GPs with advice, and new incident fractures. Based on this information, initial advice was adjusted, if needed.

Results Follow-up was completed by 504 (91%) patients at the 1st year, 458 (83%) at the 2nd year, and 355 (64%) at the 3rd year. At the 1st year, adherence of patients to new treatment advice was 89% (203 of 229), concordance of their GPs to our advice was 72% (146 of 203), persistence of those who started medication due to our advice, was 87% (123 from 146).

Overall, this resulted in 58% of patients on antiresorptive treatment due to our advice at the end of the 1st year of follow-up. Due to reminders, this percentage increased to 69% at the 2nd year, and remained 67% at the 3rd year of follow-up. Overall, 51 patient (10%) reported 61 fractures: 20 (4%), 22 (4.8%), and 19 (5.4%) in the 1st, 2nd and 3rd years of follow-up, respectively. The incidence of new fractures in those who were at high 10-years risk for fracture at baseline, was higher from the 1st year of follow-up than in those at low risk: 8.2% versus 2.4% (p=0.003).

Conclusions Patients showed high adherence to advice and high persistence to therapy at the 1st year of follow-up. Reminders in this period increased both adherence and persistence of patients, as the concordance of their GPs. Patients who suffered a new fracture during 3 years after case-finding, had high absolute 10-years fracture risk at baseline.

INTRODUCTION

In the last years, many fracture and osteoporosis (FO) clinics have emerged to improve the identification of patients with osteoporosis and to make recommendations for treatment (1-4).
These programs for assessment for osteoporosis proved to be very successful. In a coordinated post-fracture osteoporosis education and treatment program in Canada, >95% of patients were appropriately diagnosed, treated, or referred for osteoporosis care (5). In Glasgow, the general practitioner received recommendations for treatment with bisphosphonates or raloxifene for up to 31 % of the patients (6).
However, these programs can only be successful if the adherence of patients to the treatment advice is sufficient. Unfortunately, in real life, the opposite is true. Patient compliance to long-term therapeutic regimens is poor, averaging 50% in developed countries, and contributes to an increase in the burden of the disease, death, and increased health care costs (7-9). The term “adherence” is now preferred over the earlier term “compliance” because it recognizes patient choice as opposed to passive obedience to the physician (10,11). Adherence to a medication regimen is defined as the extent to which the patient’s behaviour matches agreed recommendations from the prescriber. An even better term is “concordance”, which implies a negotiated agreement between the patient and the physician or other healthcare professional and therefore implies patient involvement in the treatment process. In our study, we used “concordance” to describe the acceptance of our advice by GPs. We used terms “persistence” (or continuation rate), to describe the percentage of patients still on treatment at the end of the period of interest (11,12), and “adherence” (or the range of behaviors shown by an individual in response to medical advice or any health advice) (11), to describe whether patients followed our advice or not. It has been stated that by increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments (13).
We performed this study to investigate the adherence of patients, as well as evaluation of persistence in using medication in those who started medication. We also tried to get an insight in the policy of GPs after receiving our advice, and in the reasons of GPs for being non-concordant with our advice, i.e. not prescribing the advised medication to their patients. Furthermore, we followed patients for three years to investigate the impact of the risk factors and of our intervention on the incidence of new fractures.

MATERIALS AND METHODS

Subjects

All patients of 50 years and older who came to the Department of Trauma Surgery of the VU University Medical Center (VUmc) or Emergency Department of Slotervaart Hospital (SH) with a fracture were invited to participate. Polytrauma patients, patients with more than two fractures, and patients with skull fractures were excluded. From January 2003 till July 2004, 1435 patients were invited for the assessment. Of those, 554 successfully completed the assessment including a questionnaire on risk factors and BMD measurement (n=554) and Vertebral Fracture Assessment (VFA) in a subgroup (n=149).

Informed consent was obtained from all participants and the study was approved by the Ethical Review Board of the VU University Medical Center (VUmc).

Recommendation

The absolute 10-years hip, wrist or vertebral fracture risk was estimated according to sex and age of the patient, using five risk factors from the Dutch Guidelines for Osteoporosis (recent fracture, low body weight (< 60 kg), prevalent vertebral fracture, serious immobility, and use of corticosteroids >7.5 mg per day) (14,15). It was predefined that if the absolute 10-years risk for hip, wrist and vertebral fracture was < 10%, patient was at a low risk of fracture. If the absolute 10-years risk for hip, wrist or vertebral fracture was > 10%, patient was at high risk of fracture. The results of the case-finding (estimated absolute 10-years hip, wrist or vertebral fracture risk and BMD) were used to make the treatment recommendations for the general practitioner (GP). The four possible treatment recommendations included lifestyle advice (with sufficient dietary calcium intake and vitamin D when sunlight exposure was insufficient), antiresorptive treatment (bisphosphonates or raloxifene), referral to a specialist, or continuation of treatment in patients already on antiresorptive medication. All patients with a T-score of -2.5 SD or lower were advised an antiresorptive treatment. In patients with a T-score being normal (T-score > -1) or representing osteopenia (-2.5 < T-score < -1), an intervention threshold (IT) to advice antiresorptive treatment was chosen at a 10-years hip, wrist, or vertebral fracture risk of 10%. All patients with the recommendations “lifestyle advice” or “continue treatment” received a letter with the diagnosis based on BMD (and VFA if applicable), and advice for sufficient dietary calcium intake and sunlight exposure and/or vitamin D. All patients with recommendations “antiresorptive treatment” or “referral to a specialist” received a letter with the diagnosis in which they were asked to make an appointment with

their GP for further management. At the same time, the GPs of all patients received a copy of the BMD (and VFA if applicable) results, a risk score overview, and estimation of the absolute 10-years risk for a hip, wrist or vertebral fracture, including a recommendation whether to treat the patient, refer him or her to the specialist, or to wait and see.

Follow-up

A follow-up questionnaire with a return envelope was mailed at 1 year to all patients who had completed an assessment and received a recommendation letter. The purpose of the follow-up questionnaire was to collect information on [1] adherence of patients to advice; [2] concordance of GPs to advice (i.e. acceptance of advice by GPs); [3] persistence of patients with prescribed therapy; [4] new fractures or other risk factors; [5] adjustment of advice, if needed.

If patients were non-adherent to our advice, a reminder was sent to them and to their GP. If GPs were non-concordant with our advice, we sent them a short reminder and questioned them to explain their policy and a reason for not following our recommendation. We evaluated the reasons for non-adherence of the patients and non-concordance of GPs. At the end of the 1st year follow-up, all patients received a new recommendation letter. For the 2nd and the 3rd year follow-up, a similar procedure was followed.

Statistical analyses

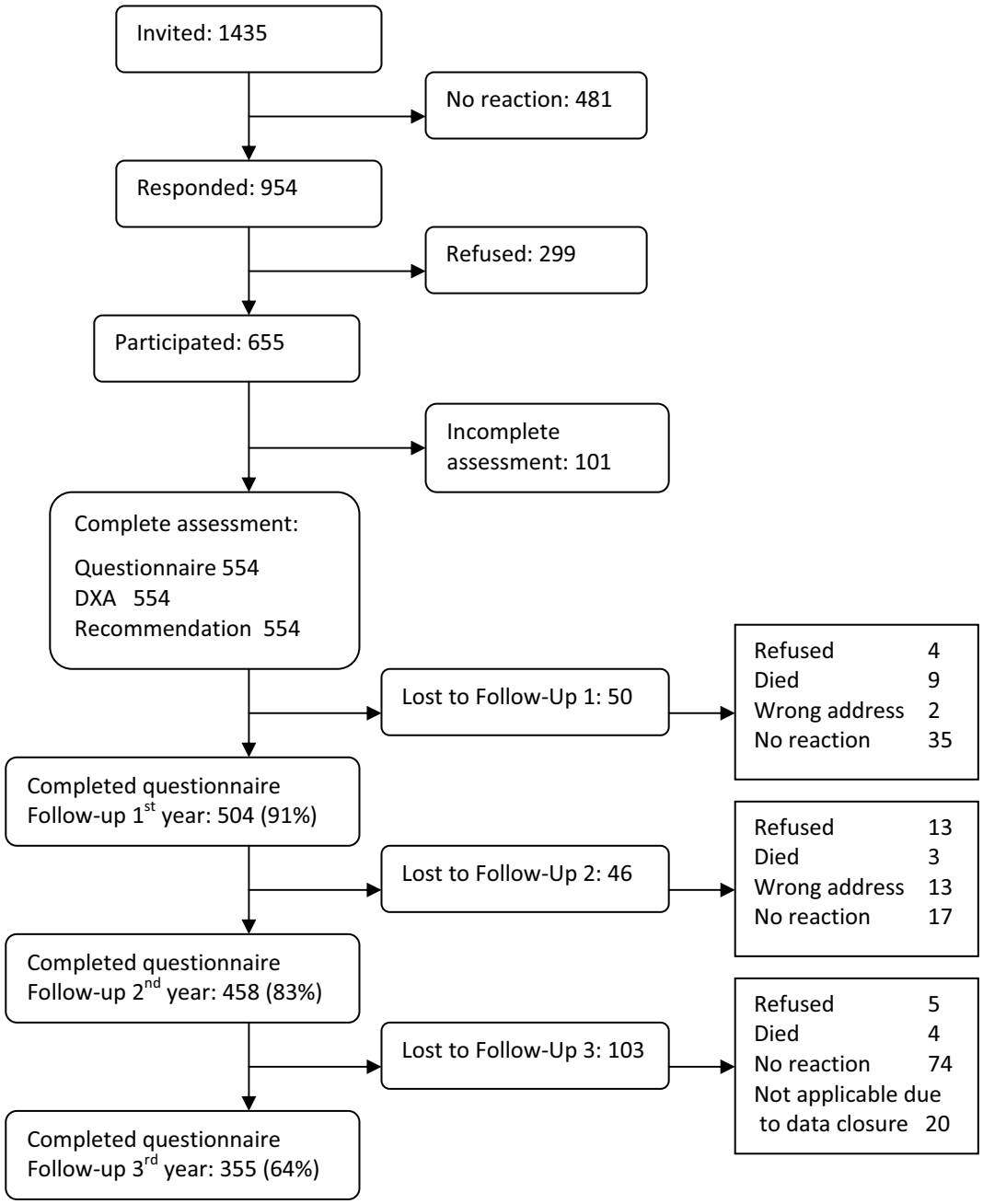
The data were analyzed using SPSS 15.0 Software. In this study we used descriptive statistics to describe the study population. The analysis of adherence of patients was performed in men and women together, after testing for the differences in compliance according to sex. Differences between groups with and without new fracture were tested using Chi-Square analysis.

RESULTS

At 1st year follow-up, we sent a questionnaire to 554 patients (n=121 men and n=433 women) who completed the diagnostic procedure and received a recommendation letter (Fig.1). From those, 504 (91%) completed the questionnaire (88% of men, n=106; and 92% of women, n=398).

No differences between men and women were observed in this group and in 50 patients (9%) who were lost to follow-up due to refusal, death, moving to other address, or for unknown reasons. Therefore, follow-up was evaluated in men and women together.

Figure 1. Flow-diagram for the case-finding for osteoporosis, treatment advice and 3 years of follow-up.



The responding patients represented two different groups: 229 patients who were advised to visit their GP (the GPs of these patients were advised to prescribe an antiresorptive treatment, to refer their patients to a specialist, or to stop antiresorptive treatment) and 275 who were not (from these patients, 250 received only a lifestyle advice, 24 were recommended to continue antiresorptive treatment which they already received prior to the study, and 1 was advised to stop treatment). Table 1 shows that from those 229 patients who were advised to contact their GP, 203 patients (89%) were adherent to this advice. General practitioners of those 203 patients prescribed antiresorptives to 146 patients, and were therefore for 72% concordant with our advice. From 146 patients who received antiresorptive drugs, 142 started to use them, and 123 were using them at the end of the 1st year follow-up, representing the persistence of 87%. These 123 patients represent 54% of those 229 who were expected to start and to use antiresorptive drugs at the end of the 1st year follow up. Those who already received antiresorptive treatment prior to the study and were advised to continue treatment, were usually still using it at the 1st year follow up (23 from 24 patients, 96%, data not shown). Therefore, from 253 patients who were advised antiresorptives at baseline (229 were advised to start and 24 were advised to continue), 146 patients were using antiresorptives at the 1st year of follow-up (persistence of 58%). One woman who was advised to stop antiresorptive treatment, contacted her GP and stopped bisphosphonates.

The remaining 106 patients represent 46% of those who were not using antiresorptive drugs at the 1st year of follow-up, despite our recommendation. The reasons for this were either “never started” (“did not contact GP”, “advised by us but not prescribed by GP” or “prescribed by GP but never used”); or “stopped” (“adverse events”, “end of treatment”, or “other reasons”). We sent reminders to all patients who did not visit their GP, and we sent reminders to all GPs (n=68) who gave their patients other advices than recommended by us. GPs were questioned to explain their policy (the reason for non-concordance with our advice), and 52 questionnaires (76%) were returned (Table 2). Of 250 patients who received a lifestyle advice, 71 (28%) still contacted their GP and 6 of them (8%) even were prescribed bisphosphonates and were still using them at the 1st year follow up (data not shown). These six patients had osteopenia at baseline.

Table 1. Adherence to advice and persistence to prescribed medication at 1st year of follow-up in 229 patients who were recommended antiresorptives or a referral to a specialist.

	N, count	%
Total	229	100
Contacted GP	203	89
Antiresorptives prescribed	146	64
Start to use antiresorptives	142	62
Using antiresorptives at 1st year	123	54
Not using antiresorptives at 1st year	106	46
Never started:	87	
- did not contact GP	26	
- advised but not prescribed	57	
- prescribed but never used	4	
Stopped at 1st year:	19	
- adverse events	13	
- end of treatment	2	
- other reason	4	

Adherence of patients to advice: 203/229=89%; concordance of GPs with our advice: 146/203=72%; persistence of patients to therapy: 123/142=87%.

Table 2. Reasons for non-concordance of general practitioners

		Reminders sent back	
		Count	%
Reason for not following advice	According to GP Guidelines	5	9.6%
	Patient refused medication	13	25.0%
	Patient did not attend GP	2	3.8%
	Medical condition of patient	11	21.2%
	Advice was followed	15	28.8%
	Advice was followed after reminder	4	7.7%
	GP changed, no information	2	3.8%
Total		52	100.0%

Due to reminders at the 1st year of follow-up, overall persistence of patients who were using antiresorptives at the 2nd and 3rd year, increased. At the 2nd year, 155 from 226 patients (68.6%) were using antiresorptives, and at the 3rd year, 117 from 175 patients (67.0%), data not shown.

Furthermore, we asked patients what advices they received from their GPs if they visited the GP after receiving our recommendation letter. Almost 75% of the patients who were recommended to use antiresorptive drugs or to be referred to a specialist, actually received these advices from their GP. Other common advices include “no specific advice” (17%), “extra calcium” (15%), and physical exercise (4%), according to patients (data not shown). At the baseline, 33.6% of patients used calcium or vitamin D tablets, while at the 1st year of follow-up, 50.8% used calcium and/or vitamin D.

During 3 years of follow-up, 51 patients (10%) reported 61 fractures: 20 (4%) in the 1st year, 22 (4.8%) in the 2nd, and 19 (5.4%) in the 3rd year of follow-up. Fractures of feet and toes (n=16, 26%), wrist (n=13, 21%), shoulder (n=6, 10%), hip (n=5, 8%) and ribs (n=5, 8%) were the most common. Table 3 shows the incidence of reported new fractures in patient groups and the incidence based on the absolute 10-years hip, wrist or vertebral fracture risk, as estimated at baseline. The predicted 10-years fracture risk for hip, wrist or vertebral fracture was similar to the incidence of any new fracture already in 3 years of follow-up (Table 3A). The incidence of new fractures in those who were at high 10-years risk for hip, wrist or vertebral fracture at baseline, was already higher in the 1st year of follow-up, and stayed higher after 3 years of follow-up (Table3B). Those who reported a hip fracture, had high 10-year risk of hip fracture at baseline, while those who did not report a hip fracture were at low 10-year risk for hip fracture at baseline (14.0±9.0% and 6.1±6.1%, respectively, $p<0.01$, data not shown).

Table 3A. Incidence of new reported fractures according to estimated absolute 10-years hip, wrist or vertebral fracture risk

Risk group[a]	Any new fracture in the 1st year of follow-up[b]		Any new fracture in 3 years of follow-up[c]		Total, % (n)
	Yes, % (n)	No, % (n)	Yes, % (n)	No, % (n)	
<10%	2.4 (9)	97.6 (361)	8.4 (31)	91.6 (339)	100 (370)
10-20%	7.8 (8)	92.2 (94)	13.7 (14)	86.3 (88)	100 (102)
20-30%	11.5 (3)	88.5 (23)	23.1 (6)	76.9 (20)	100 (26)
>30%	0	100.0 (6)	0	100.0 (6)	100 (6)
Total	4.0 (20)	96.0 (484)	10.1 (51)	89.9 (453)	100 (504)

[a] *Absolute 10 years hip, wrist or vertebral fracture risk*
[b] *p=0.015, by Chi-square test*
[c] *p=0.043, by Chi-square test*

Table 3B. Incidence of new reported fractures according to estimated absolute 10-years hip, wrist or vertebral fracture risk

Risk group[a]	Any new fracture in the 1st year of follow-up[b]		Any new fracture in 3 years of follow-up[c]		Total, % (n)
	Yes, % (n)	No, % (n)	Yes, % (n)	No, % (n)	
<10%	2.4 (9)	97.6 (361)	8.4 (31)	91.6 (339)	100 (370)
>10%	8.2 (11)	91.8 (123)	14.9 (20)	85.1 (114)	100 (102)
Total	4.0 (20)	96.0 (484)	10.1 (51)	89.9 (453)	100 (504)

[a] *Estimated absolute 10 years hip, wrist or vertebral fracture risk*
[b] *p=0.003, by Pearson Chi-square test*
[c] *p=0.031, by Pearson Chi-square test*

DISCUSSION

This study, in which we investigated the adherence of patients and a concordance of their GPs with the treatment advice, and evaluated the persistence in using medication in those patients who were adherent to advice, showed high adherence of patients to advice and high persistence to therapy at the 1st year of follow-up. Reminders in this period increased both adherence and persistence of patients, as the concordance of their GPs. In our study, we used self-reported data in the follow-up questionnaires. We did not check the data about the medication with the pharmacist or GP. We did not investigate adherence as a percentage of

prescribed drugs taken, but as a dichotomous state. If a patient reported the visit to GP according to our advice, the patient was adherent to our advice. Persistence was assessed as the percentage of patients who reported using antiresorptives at the 1st, 2nd and 3rd years of follow-up.

Access to medication is necessary but insufficient in itself for the successful treatment of a disease (8). It is also well known that medication use is complex. A recent study showed that long unexplained interruptions in treatment are common among users of osteoporosis medications (16), and that adherence behaviour can change abruptly. Younger patients, women, patients with a recent hip fracture or history of fracture, those discharged from nursing homes, were more likely to return to treatment. In that study, an estimated 30% of patients who stopped therapy for at least 60 days, restarted treatment within 6 months, and 50% restarted within 2 years. If a patient in our study reported that he or she did not visit GP despite of our advice, or did not use any antiresorptives despite receiving a prescription from GP, or stopped antiresorptives without giving a good reason, we sent a follow-up recommendation letter with a reminder to start , or restart treatment.

So we tried to increase both the adherence to advice and persistence with treatment of all patients. Furthermore, at the 1st year of follow-up, we sent a reminder to all patients who were non-adherent to, and all GPs who were non-concordant with our advice. As a result, at the 2nd year of follow-up, the percentage of persistent patients increased from 58% to 68.6%, confirming the hypothesis that monitoring or attention by a health care professional is better than no monitoring (12). In our study, 87% (123 from 142) of those who started to use prescribed antiresorptives, were still using them at the 1st year of follow-up, which represents good persistence. This is in contrast to another study, where after 1 year, only 52 % of weekly alendronate users and 30% to 42% of daily bisphosphonate users were persistent (17). In a study where adherence was assessed as mean medication possession ratio (MPR), it ranged from 0.59 to 0.81, while the percentage of patients persisting with therapy for one year ranged from 17.9% to 78.0% (18). In our study, we used a questionnaire with self-reported medication use, and although this method is relatively easy to use, questioning the patient can be susceptible to misinterpretation and tends to result in overestimation of patient adherence by the health care provider (9).

We found that the concordance of GPs with our advice is as important for successful treatment after a diagnosis of osteoporosis, as the adherence and persistence of patients. A patient who was advised to visit his/her GP to initiate antiresorptive treatment, was four steps away from successful treatment. A

patient had to visit a GP (adherence to advice 89%), receive a prescription (concordance of GP with advice 72%), start to use it (97%), and continue to use it at the end of the 1st year (persistence 87%). Although each of these percentages appears quite high, the result is that from every 100 patients, only 54 (100x0.89 x 0.72 x 0.97 x 0.87=54) will end up using antiresorptives at the end of the 1st year of follow-up, which is a somewhat disappointing result. So, all the factors which influence each of this steps, need to be addressed in order to improve the overall percentage of patients who are treated as a result of case-finding.

Adherence and persistence of those who are treated for osteoporosis, is often inadequate what limits the effectiveness of treatment (12,19). The relatively low rate of patient adherence and persistence with osteoporosis therapy means that only a small percentage of patients is receiving adequate therapy. In a managed care cohort of 38,120 women with a diagnosis of osteoporosis, adherence to treatment was very low: a rapid decline was observed during the first 2 years, after which the adherence level stabilized around 60%. Low adherence was associated with a higher risk of fractures regardless of other known and important risk factors; and with a 37% increase in the risk of all-cause hospitalization (20).

In a retrospective analysis of a large population of new users of alendronate with diagnosed osteoporosis, less than half of the women were found to be adherent to bisphosphonate therapy (Medication Possession Rate [MPR] ≥ 80%) and approximately 40% of women persisted with treatment for 12 months without a substantial gap in therapy (19). In that study, the adjusted risk of hip fracture increased by 0.4% for each decrease of the MPR by one percent, while the relative risk reduction for hip fracture was 60% for persistent compared to non-persistent patients. Non-adherent bisphosphonate use was associated with a 45% increased fracture risk compared to adherent use (MPR ≥80%) in another study (21), where fracture risk gradually increased with poorer adherence. This emphasizes that adherence and persistence to therapy is a crucial factor for optimizing the treatment goals of osteoporosis, which is fracture reduction.

Many reasons exist for non-adherence to medical regimens, including problems with the regimen (such as adverse effects), poor instructions, poor provider-patient relationship, poor memory, and patients' disagreement with the need for treatment or inability to pay for it (7). Other explanations of non-adherence are: medicines are artificial, lack of trust in medications, doubts about general practitioners competence, lack of understanding of how multiple medications work (22). It is also interesting, that the use of calcium and vitamin D increased from 33% at a baseline to over 50% at 1st, 2nd and 3rd follow-up. Calcium treatment is seen, in the literature, as a cost-effective treatment compared with

other alternatives. Because calcium is cheap, and has little side effects, it is favored by many patients. Patients believe that 25% protection with no side effect is better than the 50% with side effects (22).

A survey with collected retrospective data relating to patients' decisions to take or to stop taking bisphosphonate medication, showed that patients' decisions to stop taking bisphosphonates were based on more than simply the experience of side effects. Concerns about medication, dissatisfaction with treatment, and practical difficulties taking the medication, including too frequent dosing and management of co-medications, were associated with non-persistence in taking daily and weekly bisphosphonates (23).

In a study where up to 41% of the patients who started medication did not continue the initial medication (24), the main reasons for discontinuation were side effects and cost, but the correct understanding of DXA results resulted in higher treatment rates and better adherence to treatment among patients with low BMD. In the Netherlands, the costs of the bisphosphonates are reimbursed by the medical insurance. All our patients received a letter with the DXA results and, if applicable, VFA results on presence of a vertebral fracture, and an advice. In this letter, the telephone number was mentioned for patients to call if they had questions, and some of them called us for additional explanation. Some patients made an appointment with their GP to discuss their results even if they were not advised to contact their GP for medication. So, the awareness of DXA results and the fact that our patients already had a fracture and were at high risk of suffering a new fracture, may explain their high persistence. Patients who remain on therapy i.e. are persistent, have a substantially lower risk of fracture; improved adherence is associated with less functional impairment, better quality of life, and reduced morbidity (25), so the value of both adherence and persistence with osteoporosis therapy is evident.

The major weakness of our study is in the self-reported data in the follow-up questionnaires. Sub-optimal adherence, possible fractures in those who were lost to follow-up, were not assessed. We confirmed the importance of the clinical risk score in decision-making for antiresorptive treatment. Those who reported a hip fracture, had high 10-year risk of hip fracture at baseline, while those who did not report a hip fracture, were at low 10-year risk for hip fracture at baseline, confirming an intervention threshold for the absolute 10-years hip fracture risk to be around 10%. We are convinced that the case-finding in FO clinics or fracture liaison services (4) is an effective way of secondary prevention of fractures, allowing patients who are at high absolute risk for fracture to be investigated and appropriately treated. The strength of our study is mainly in its realistic approach,

long follow-up of 3 years after case-finding, and in assessment of both adherence of patients and concordance of GPs with our advice. Addressing these issues in clinical practice may improve adherence and persistence and result in better disease outcomes for patients.

Given the magnitude and importance of poor adherence to medication regimens, the World Health Organization has published an evidence-based guide for clinicians, health care managers, and policymakers to improve strategies of medication adherence (8).

However, a recent review on the interventions for enhancing medication adherence stated that almost all interventions that were effective for long-term care were very complex (7). They included combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counseling, family therapy, psychological therapy, crisis intervention, manual telephone follow-up, and supportive care. Unfortunately, even these complex interventions did not lead to large improvements in adherence and treatment outcomes.

Nevertheless, every effort should be done to continuously stimulate the patients who attend FO clinics, explaining the importance of good adherence and persistence. We believe that the first year of follow-up is most important in the monitoring of patients and should be a part of the service provided by a FO clinics.

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