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ORIGINAL ARTICLE

Predictors of re-fracture amongst patients managed within a secondary fracture prevention program: a 7-year prospective study

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Abstract
Summary This 7-year prospective observational study determined the predictors of re-fracture amongst 234 patients managed within a Secondary Fracture Prevention programme. Poor compliance, multiple co-morbidities, corticosteroid therapy, low hip bone mineral density (BMD) or low body weight were all significantly associated with re-fracture in patients commenced on long-term anti-resorptive therapy.
Introduction Risk factors for osteoporotic fracture amongst treatment-naïve patients are well established. In contrast, predictors of re-fracture in patients optimally managed within a Secondary Fracture Prevention (SFP) programme are ill-defined.
Methods This prospective observational study included 234 subjects with incident osteoporotic fractures managed long-term by the Concord SFP programme. Using Cox proportional hazards models, predictors of re-fracture were analysed separately for patients commenced on specific pharmacotherapy (group 1, N=171) and subjects receiving calcium and/or vitamin D supplements only (group 2, N=63). Relevant anthropometric, clinical and technical data were documented at each visit. Compliance and persistence were analysed as time-varying covariates.
Results During a mean follow-up of 5.2 (range 3.5–7.3) years, 20.9 % of all subjects re-fractured (26.3 % in group 1, 6.3 % in group 2). Multivariate predictors of re-fracture in group 1 were significant co-morbidity (HR 2.04 if >3, 95 % CI 1.10–3.79, p=0.024), corticosteroid use (HR 1.75, 95 % CI 1.12–2.73, p=0.013) and total hip BMD (HR 1.36 per 0.1 g/cm^2 decrease, 95 % CI 1.08–1.70, p=0.008). In contrast, gender, prevalent fractures and lumbar spine BMD were not associated with re-fracture. Amongst patients with complete compliance data, a medication possession ratio of ≤ 50 % (HR 3.36, 95 % CI 1.32–8.53, p=0.011) and low body weight (HR 1.04 per 1-kg decrease, 95 % CI 1.003–1.08, p=0.032) were significantly associated with re-fracture.
Conclusions Amongst patients managed within a dedicated SFP programme, poor compliance, multiple co-morbidities, corticosteroid therapy, low hip BMD or low body weight are all associated with increased risk of re-fracture. This subgroup of patients therefore require intensive management including strategies to improve compliance.

Keywords Anti-resorptive · Compliance · Osteoporosis · Persistence · Re-fracture predictors · Secondary fracture prevention programme

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Introduction

Fractures following inadequate trauma are the hallmark of osteoporosis [1]. More than 50 % of post-menopausal women and 30 % of men over the age of 60 years will suffer at least one minimal trauma fracture during their remaining lifetime [2, 3]. Any osteoporotic fracture predisposes to further fractures, significant morbidity and premature death [4, 5]. Importantly, following a first minimal trauma fracture, both men and women have a two- to threefold increased risk of subsequent fracture [6–8]. Not surprisingly, timely diagnosis

and optimal treatment of osteoporosis prevent further fractures.

In recent years, a number of systematic interventions have been designed and locally implemented to improve the management of patients with osteoporotic fracture. A recent systematic review evaluating models of care for the secondary prevention of osteoporotic fractures demonstrated that intensive, co-ordinated programmes ("type A models") are more effective in increasing treatment initiation rates than interventions based solely on patient or doctor education ("type C, D models") [9, 10]. Whilst predictors of fracture amongst treatment-naïve patients have been well characterised (e.g. older age, previous fractures, falls, low bone mineral density, female gender), the factors associated with re-fracture in patients treated and managed within a Secondary Fracture Prevention (SFP) programme have not been determined. As early identification of patients who might re-fracture despite optimal therapy would justify additional, targeted interventions to lower the re-fracture risk, we aimed to determine the predictors of re-fracture amongst patients managed long-term for osteoporosis within the Concord SFP programme, an ongoing prospective observational study based at Sydney, Australia.

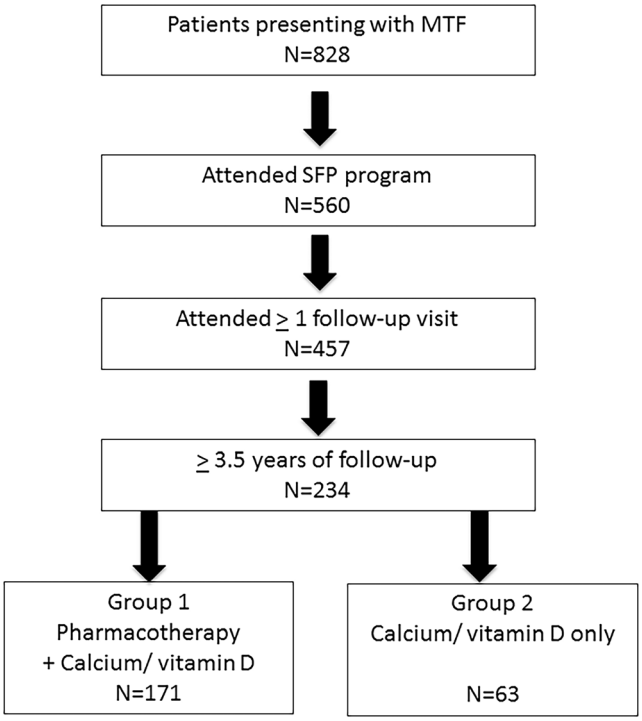

Fig. 1 Study flow diagram. *MTF* minimal trauma fracture, *SFP* secondary fracture prevention

Materials and methods

Study population and design

The current analysis includes 234 patients who, following an incident osteoporotic fracture, were managed by the Concord Hospital SFP programme for a minimum of 3.5 years (Fig. 1). Relevant anthropometric, clinical and technical data were documented annually during a comprehensive clinical review. The first patient was recruited on 23 May 2005, and the last follow-up visit for the population in the current analysis was on 30 August 2012.

The study population consisted of men and women aged 45 years and over who had sustained a symptomatic fracture due to minimal trauma (defined as a fall from a standing height or lesser impact). Patients were excluded from the trial if they were unable to provide informed consent, resided in a nursing home or hostel at the time of the index fracture or were diagnosed with malignant or metabolic bone disease. The study was approved by the Sydney Local Health District Human Research Ethics Committee (CH62/6/2009-021). All patients provided written consent to take part in the study, including consent for extraction of pharmaceutical claims data.

Patients identified by and/or referred to the Concord SFP programme were clinically assessed as described previously [9, 11, 12]. The following socio-demographic and clinical measures were obtained using a standardised questionnaire for each patient at baseline: date of birth, gender, smoking status (current smoker, former smoker, never smoked), alcohol intake, dietary calcium intake (in serves/week), index fracture site, family history of osteoporosis, maternal history of hip fracture, co-morbidities, past or current corticosteroid use, previous minimal trauma fracture (prior to index fracture) and ethnicity (Caucasian vs. non-Caucasian). Age was recorded at the time of the index fracture. Weight was measured in clothing without shoes, and height was measured using a Harpenden stadiometer (Dyfed, UK). All minimal trauma fractures apart from the face and skull were included. Hip, pelvis, wrist, humerus, vertebral, tibia and fibula fractures were classified as major fractures, whilst all other fracture sites were considered minor.

Total hip (TH), femoral neck (FN) and lumbar spine (L2–4) areal bone mineral density (BMD) (g/cm^2) were measured at baseline and annually thereafter by dual X-ray absorptiometry using a GE/Lunar Prodigy (Lunar Corp. Madison, WI, USA; Software version 13.6) or a QDR4500-W Acclaim scanner (Hologic Inc., Bedford, Mass., USA; Software version 3.2). Osteoporosis was defined based on WHO diagnostic criteria [13]. For the Lunar densitometer, the coefficient of variation (%) and least significant change (g/cm^2) were 0.8 % and 0.019 g/cm^2 for the total hip, 0.5 % and 0.013 g/cm^2 for the femoral neck and 1.5 % and 0.044 g/cm^2 for the lumbar spine, respectively. For the Hologic densitometer, the corresponding numbers were 1.5 % and 0.034 g/cm^2 for the total hip, 3.6 % and 0.069 g/cm^2 for the femoral neck and 1.4 % and 0.033 g/cm^2 for the lumbar spine, respectively. The standardised BMD

was calculated using previously published equations [14, 15], and annual percent change in BMD from baseline was analysed for each individual at each site.

Urinary deoxypyridinoline (uDPD) concentrations were measured in a second morning void sample, using an enzyme-labelled chemiluminescent immunoassay (Pyrilinks-D, Siemens Healthcare Diagnostics, UK). The intra-assay coefficient of variation at a mean uDPD level of 30 and 100 nmol/L was 15 and 10 %, respectively. The inter-assay coefficient of variation was 7.1 % at uDPD concentrations between 11.6 and 110.3 nmol/L. Results were corrected for urinary creatinine levels and expressed as the ratio of uDPD to urinary creatinine (uDPD/cr).

The decision to treat was based on individual risk factors, co-morbid conditions and patient preference, as described previously [12, 16]. Patient management followed the current Australian osteoporosis guidelines as approved by the National Health and Medical Research Council and the Royal Australasian College of Physicians [17]. All patients were recommended non-pharmacological measures regarding bone health and falls prevention, including physical activity (e.g. weight-bearing and muscle strengthening exercises) and balance training (e.g. Tai Chi), as well as lifestyle changes such as sensible sunlight exposure and dietary calcium intake, as appropriate.

Patients deemed at high risk of re-fracture (group 1) were initiated on specific pharmacotherapy and were supplemented with calcium (600–1,200 mg/day) and vitamin D (1,000 IU/day) if and as required. Pharmacotherapy mainly consisted of oral bisphosphonates, while a smaller number of patients received intravenous bisphosphonates, strontium ranelate, denosumab, teriparatide and raloxifene. Pharmacotherapy was subsidised in all patients by the Australian Pharmaceutical Benefits Scheme (PBS). Patients considered at low risk of re-fracture (group 2) were advised to optimise their calcium intake and given instructions to help maintain sufficient vitamin D levels (Fig. 1).

Compliance and persistence with osteoporosis medication were calculated from pharmaceutical dispensing data obtained through Medicare Australia, as described previously [16]. The term compliance was defined as the extent to which patients act in accordance with the prescribed interval and dose of a treatment regimen [18]. In the present study, compliance was measured by calculating the medication possession ratio (MPR), i.e. the ratio of the number of days a patient is in possession of a medication over the observation period, with a maximum possible value of 1. A patient was considered persistent during the study period if there were no gaps in therapy of more than 30, 60 or 90 days over a 12-month observation period. Compliance and persistence were measured starting from the date that the patient was advised to commence therapy, which in the majority of cases was the baseline visit.

The primary outcome measure was a further minimal trauma fracture while being managed within the SFP programme. All new fractures were radiographically confirmed. Re-fractures sustained in the first 6 months after treatment initiation were excluded due to the known delay in the anti-fracture effect of most osteoporosis medications [19–21]. Traumatic fractures and fractures of the toes, fingers and skull were also excluded from the analysis. There were no pathological fractures observed during the study period.

Statistical analyses

Demographic characteristics and osteoporosis risk factors at baseline were described using means and standard deviations for normally distributed continuous variables and percentages for categorical variables. In order to obtain an accurate measure of how compliance (MPR) and persistence changed over time, each individual's MPR and persistence were measured as a moving average over the previous 12 months, recalculated every 30 days. These measures of MPR and persistence were used as time-varying covariates to predict re-fracture amongst those with complete PBS data over the period from baseline to end of follow-up or re-fracture (i.e. time to event).

Employing Cox proportional hazards models, predictors of time to re-fracture were analysed separately for patients who were commenced on specific osteoporosis pharmacotherapy (group 1) and those maintained on calcium and vitamin D (group 2). Patients were censored on the date of the first fracture following the index fracture. In patients who did not suffer a further fracture during the follow-up period, data was censored on the date of the last clinic visit or the end of the study (30 August 12). Univariate (unadjusted) and multivariate (adjusted) analyses using clinical and socio-demographic variables (described above) were used to determine predictors of further fracture in both group 1 and group 2. Three multivariate analyses using a forward sequential method were conducted utilising variables with a p value <0.05 on univariate analysis:

1. All patients in group 1.
2. Patients in group 1 with complete PBS data (N=69), using MPR and persistence as time-varying covariates.
3. All patients in group 2.

An additional sensitivity analysis included only patients treated with oral bisphosphonates. This analysis was performed to evaluate potential differences in anti-fracture efficacy between oral bisphosphonates and other osteoporosis therapies [19–25]. A second sensitivity analysis included re-fractures sustained within the first 6 months following treatment initiation.

Data were analysed using SPSS Statistics version 21 and SAS version 9.3.

Results

Baseline characteristics

The study population (n=234; mean age 65 years) was mostly female (80 %), with 39 % having sustained a minimal trauma fracture prior to the index fracture. Approximately, 70 % of index fractures were classified as major. Over one third of patients in groups 1 and 2 sustained an index fracture of the wrist. Mean follow-up time was 5.2 years with a range of 3.5 to 7.3 years.

Individuals deemed at high risk of fracture and hence commenced on specific pharmacotherapy (group 1, N=171) represented 73 % of the total study population. As expected, these patients were older, had more co-morbidities and prior fragility fractures, a lower body weight and lower lumbar spine and hip bone mineral density, and a higher urinary DPD/creatinine ratio than subjects in group 2 (Tables 1 and 2). Patients with incomplete (n=102) or complete (n=69) pharmaceutical claims data were similar at baseline for all variables listed in Tables 1 and 2, except that subjects with complete claims data had fewer falls (10.8 vs. 40.4 %, p<0.001) and a higher frequency of oral steroid use (14.5 vs. 4.9 %, p=0.030) and maternal history of hip fracture (5.8 vs. 0 %, p=0.014). Within group 1, baseline characteristics of patients treated with oral bisphosphonates (N=143, 84 %) were not different from those treated with other osteoporosis agents (N=28, 16 %), except for a higher frequency of peptic ulcer disease in the latter group.

Re-fractures

Over a mean follow-up time of 5.2 years (range 3.5–7.3 years), 20.9 % of all subjects had sustained a further fracture, with an incidence of 44.4 per 1,000 person-years. In group 1, 26.3 % of patients sustained at least one further fracture, with an incidence of 57.1 fractures per 1,000 person-years (6.4 % had 2 further fractures and 5.3 % had 3 or more fractures). In contrast, 6.3 % of patients in group 2 sustained at least one further fracture, with an incidence of 12.7 fractures per 1,000 person-years (1.6 % sustained 2 further fractures). In group 1, the majority (60 %) of re-fractures occurred within the first 3 years from baseline (Fig. 2).

Amongst the 69 patients in group 1 with complete PBS data, 26.1 % of subjects had sustained a further fracture over a mean (SD) follow-up of 5.0 (0.8) years. In comparison, 26.5 % of subjects in group 1 with incomplete PBS data sustained a further fracture.

Predictors of re-fracture

Univariate predictors of re-fracture in patients considered at high risk of fracture (group 1) are listed in Table 3. Of note, age, gender, a minimal trauma fracture prior to the incident fracture, current smoking, a maternal history of hip fracture or lumbar spine bone mineral density were *not* associated with re-fracture in this high-risk group. In multivariate analyses, more than three co-morbidities, oral corticosteroid use (past or current) and lower total hip BMD remained significantly associated with re-fracture in group 1 (Table 4).

Amongst patients with complete PBS data, a MPR ≤0.5 and lower body weight were significantly associated with re-fracture (Table 5). In contrast, a MPR ≤0.8 (vs. >0.8) was not a predictor of re-fracture (HR 1.10, 95 % CI 0.44–2.77, p=0.842). Non-persistence, defined as a gap in therapy of either more than 30 days (HR 0.54, 95 % CI 0.21–1.40, p=0.205), 60 days (HR 0.62, 95 % CI 0.23–1.69, p=0.353) or 90 days (HR 0.69, 95 % CI 0.24–1.99, p=0.490), was not a predictor of re-fracture. Proton pump inhibitor use was not a predictor of re-fracture (HR 1.31, 95 % CI 0.52–3.30, p=0.566).

Results were similar when the analysis was limited to patients treated with oral bisphosphonates only, with the exception that the number of co-morbidities was no longer associated with re-fracture. Results were also similar when re-fractures sustained in the first 6 months following treatment initiation were included in the analysis.

In patients considered at low risk of fracture (group 2), re-fractures were only associated with a higher baseline uDPD/cr (HR per unit increase 1.66, 95 % CI 1.02–2.70, p=0.042).

Discussion

Secondary fracture prevention programmes significantly reduce the risk of further fragility fractures in patients with osteoporosis [9, 12, 26, 27]. However, even with the optimised treatment offered within a SFP programme, a proportion of patients will fracture again. The present long-term prospective, observational study identified poor compliance with osteoporosis therapy, significant co-morbidity, low hip BMD, low body weight and therapy with corticosteroids as major predictors of re-fracture amongst patients receiving high-intensity interventions within a SFP programme. Of note, risk factors known to be associated with the risk of fracture in treatment-naïve individuals, such as age, gender, prevalent fractures, previous falls, smoking, family history of hip fracture and lumbar spine bone mineral density [28–30], did not predict further fractures in our population. Although

Table 1 Baseline characteristics—clinical and anthropometric data

Variable	*N*	Group 1	*N*	Group 2
Years follow-up, mean (SD)	171	5.22 (0.95)	63	5.17 (0.97)
Age (years), mean (SD)	171	67.3 (10.2)	63	58.8 (8.0)
Female gender, *N* (%)	171	148 (86.5)	63	39 (61.9)
Caucasian ethnicity, *N* (%)	163	139 (85.3)	57	45 (78.9)
Time to 1st visit (days), median (IQR)	169	56 (31–85)	63	53 (33–84)
Major MTF (Index Fracture), *N* (%)	171	127 (74.3)	63	37 (58.7)
Weight (kg), mean (SD)	170	68.4 (13.9)	63	83.2 (15.7)
BMI (kg/m^2), mean (SD)	170	27.3 (5.1)	62	30.2 (5.4)
Calcium intake (serves/week), mean (SD)	166	12.7 (7.5)	61	12.9 (7.0)
Current smoking, *N* (%)	168	20 (11.9)	60	5 (8.3)
Alcohol ≥30 g/day, *N* (%)	73	16 (21.9)	39	10 (25.6)
Anti-convulsant use, *N* (%)	171	6 (3.5)	63	1 (1.6)
COPD, *N* (%)	171	11 (6.4)	63	1 (1.6)
Malabsorption, *N* (%)	171	5 (2.9)	63	0 (0)
Previous HRT, *N* (%)	148	27 (18.2)	42	8 (19.0)
MTF prior to incident fracture, *N* (%)	171	81 (47.4)	63	14 (22.2)
Falls in the last 12 months (prior to last visit), *N* (%)	164	47 (28.7)	63	11 (17.5)
Inflammatory arthritis, *N* (%)	171	1 (0.6)	63	0 (0)
Maternal history of hip fracture, *N* (%)	171	4 (2.3)	63	1 (1.6)
Premature menopause, *N* (%)	161	73 (45.3)	33	7 (21.2)
Oral steroid use (past or present), *N* (%)	171	15 (8.8)	63	1 (1.6)
Chronic renal failure, *N* (%)	171	10 (5.8)	63	1 (1.6)
Hyperthyroidism, *N* (%)	171	5 (2.9)	63	1 (1.6)
Co-morbidity count, mean (SD)	171	2.7 (1.6)	63	2.0 (1.5)
Co-morbidity count >3, *N* (%)	171	49 (28.7)	63	10 (15.9)
Osteoarthritis, *N* (%)	170	59 (34.7)	63	9 (14.3)
Cardiovascular disease, *N* (%)	169	99 (58.6)	63	28 (44.4)
Diabetes mellitus, *N* (%)	169	22 (13.0)	63	9 (14.3)
Gout, *N* (%)	169	6 (3.6)	63	3 (4.8)
Gastro-oesophageal reflux disease, *N* (%)	169	67 (39.6)	63	17 (27.0)
Infectious disease, *N* (%)	169	1 (0.6)	63	1 (1.6)
Mental disorder, *N* (%)	169	11 (6.5)	63	7 (11.1)
Neurological disease, *N* (%)	170	19 (11.2)	63	9 (14.3)
Peptic ulcer disease, *N* (%)	169	19 (11.2)	62	6 (9.7)
Peripheral vascular disease, *N* (%)	169	6 (3.6)	63	0 (0)

BMI body mass index, *COPD* chronic obstructive lung disease, *HRT* hormone replacement therapy, *MTF* minimal trauma fracture

the sample size in our study was limited, it appears that the factors determining the risk of re-fracture differ significantly between treated and treatment-naïve populations.

These results contrast with those of a recent observational cohort study into the predictors of multiple (i.e. two or more) re-fractures in post-menopausal women treated for osteoporosis by their primary care physician [31]. Over 3 years of follow-up, prior fractures, two or more falls in the last 12 months and a worse score on a physical functioning/vitality questionnaire, were associated with further fractures. However, only 1.3 % of patients sustained multiple fractures while on treatment, incident fractures and adherence to therapy were self-reported and no data on baseline BMD, bone turnover or vitamin D status were available. Moreover, data were analysed using logistic regression rather than incorporating time-to-event information.

The current study demonstrates that even in the optimised setting of a SFP programme, low compliance to osteoporosis pharmacotherapy remains one of the most important predictors of re-fracture. Using MPR as a measure of compliance, previous reports found an increased risk of fracture at a MPR of less than 0.8 [32–35] or 0.5 [36]. However, in these studies,

Table 2 Baseline characteristics—investigational results

Variable	*N*	Group 1	*N*	Group 2
25-OH vitamin D (nmol/L), mean (SD)	170	55.3 (21.0)	62	60.3 (27.3)
Creatinine (umol/L), mean (SD)	171	71 (26)	63	70 (18)
Calcium (mmol/L), mean (SD)	168	2.35 (0.10)	61	2.32 (0.10)
Phosphate (mmol/L), mean (SD)	165	1.26 (0.18)	60	1.22 (0.21)
uDPD/cr (nmol/mmol cr), median (IQR)	157	7.3 (5.5–9.4)	54	5.5 (4.6–7.1)
% change/year uDPD/cr, median (IQR)	132	−8.1 (−12.7to −2.5)	18	−5.7 (−9.9 to 2.2)
PTH (pmol/L), median (IQR)	169	4.5 (3.3–6.6)	61	4.1 (3.2–5.4)
TSH (mU/L), median (IQR)	163	1.4 (1.0–2.2)	60	1.6 (1.0–2.3)
Bone-specific ALP (ug/L), median (IQR)	149	15.0 (10.8–19.3)	56	14.0 (10.5–16.5)
Abnormal coeliac screen, *N* (%)	162	7 (4.3)	59	2 (3.4)
Abnormal myeloma screen, *N* (%)	160	9 (5.6)	59	3 (5.1)
L2–4 sBMD (g/cm^2), mean (SD)	166	0.997 (0.170)	63	1.236 (0.146)
L2–4 T-score (g/cm^2), mean (SD)	166	−1.7 (1.4)	63	0.2 (1.2)
FN sBMD (g/cm^2), mean (SD)	166	0.768 (0.115)	63	0.919 (0.097)
FN T-score (SD), mean (SD)	166	−1.9 (0.9)	63	−0.7 (0.8)
TH sBMD (g/cm^2), mean (SD)	163	0.814 (0.133)	62	0.998 (0.104)
TH T-score (SD), mean (SD)	163	−1.6 (1.1)	62	−0.3 (0.8)
% change/year L2–4 sBMD, mean (SD)	143	1.53 (2.03)	30	−0.07 (1.39)
% change/year FN sBMD, mean (SD)	146	0.38 (1.54)	30	−0.16 (0.92)
% change/year TH sBMD, mean (SD)	144	0.55 (1.26)	30	−0.21 (0.72)

sBMD standardised bone mineral density, *L2–4* lumbar spine 2 to 4, *FN* femoral neck, *TH* total hip, *uDPD/cr* urinary deoxypyridinoline to creatinine ratio, *PTH* parathyroid hormone, *TSH* thyroid-stimulating hormone, *ALP* alkaline phosphatase

only 4 to 5 % of patients had sustained previous fractures; hence, the majority of events were not re-fractures per se [34–36]. Only one report has analysed MPR as a predictor of re-fracture in patients receiving oral bisphosphonate treatment [37]. In this study, a MPR of less than 0.5 was a significant predictor of re-fracture.

Reporting on the outcomes of a 2-year RCT within the setting of the Concord SFP programme, we recently demonstrated that compliance and persistence remained high once patients were initiated on treatment within the programme, independent of whether follow-up occurred with their primary care physician or a specialist within the SFP clinic [16]. Of note, one of the strengths of the latter and the present study is that MPRs were obtained from a claims database (rather than self-reported compliance) and analysed as a time-varying covariate to take into account the variation in MPR over time. Given the long duration of follow-up and inter-individual variation in time to event, a single measure of MPR (e.g. over the first 12 months) would not have accurately reflected compliance. Thus, our findings highlight the fact that encouraging patient compliance with therapy remains one of the major goals of physician follow-up.

The only predictor of re-fracture for group 2 was a higher urinary DPD/creatinine ratio, indicative of accelerated bone resorption. Both population-based and clinical studies have demonstrated that the rate of bone resorption (as measured by bone markers) is associated with the risk of hip and non-hip fractures in treatment-naïve post-menopausal women [38–40]

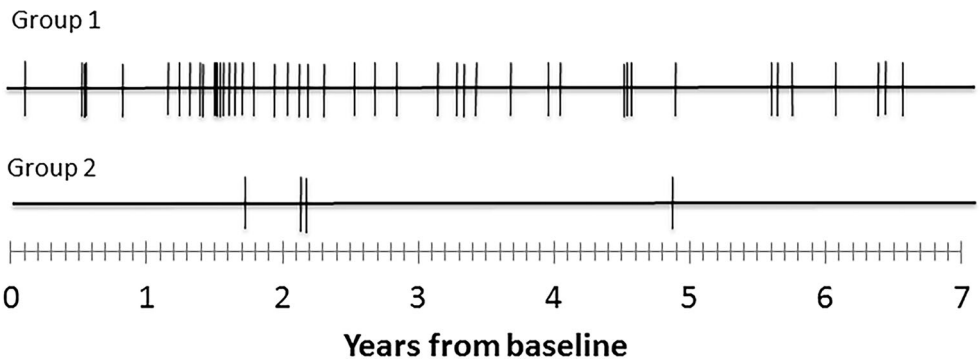

Fig. 2 Re-fractures over 7 years of follow-up for groups 1 and 2. Each *vertical line* represents an incident fracture

Table 3 Univariate predictors of re-fracture, group 1 (N=171)

Variable	HR	95 % CI	p value
Weight (per unit decrease)	1.03	1.01–1.06	<0.001
BMI (per unit decrease)	1.07	1.01–1.14	0.023
Oral steroid use—past or present (yes/no)	2.92	1.29–6.58	0.010
Hyperthyroidism (yes/no)	1.92	1.06–3.46	0.030
Falls in the 12 months prior to last clinic visit (yes/no)	2.10	1.14–3.85	0.017
Neurological disease (yes/no)	1.57	1.10–2.24	0.013
Co-morbidity count >3	1.86	1.02–3.38	0.043
sBMD FN (per 0.1 g/cm^2 decrease)	1.34	1.02–1.75	0.038
sBMD TH (per 0.1 g/cm^2 decrease)	1.35	1.08–1.69	0.008
TH BMD (per 1 % change per year)	1.35	1.03–1.77	0.030
MPR (≤0.5 vs. >0.5)	3.27	1.29–8.31	0.013

sBMD standardised bone mineral density, *FN* femoral neck, *TH* total hip, *BMI* body mass index, *MPR* medication possession ratio

and men [41], independent of BMD [38, 39]. Moreover, the degree of suppression of bone turnover during treatment with anti-resorptive agents appears to be associated with fracture risk reduction [42, 43]. Thus, in patients perceived as "low risk", high bone turnover may still indicate the need for more intensive intervention.

The re-fracture rate in our total cohort was 20.9 % over a mean follow-up time of approximately 5 years. This number is significantly lower than the re-fracture rates reported in untreated/unmanaged populations. For example, in a state-wide analysis of hospital admission data from New South Wales, Australia, 35 % of patients with incident osteoporotic fractures suffered another fracture within 6 years [44]. The latter figure is likely to be an underestimate, as the current coding system in New South Wales fails to capture all osteoporotic fractures. In comparison, the incidence of re-fracture reported in the Dubbo Osteoporosis Epidemiology Study (DOES) was 69 per 1,000 person-years in women and 71 per 1,000 person-years in men again significantly higher than in our population (44.4 per 1,000 person-years) [45]. This is consistent with the fact that the majority of patients in the current study received specific pharmacotherapy for osteoporosis whereas the DOES population remained largely untreated with 14 % of women and 4 % of men treated with anti-resorptive therapy.

Table 4 Multivariate predictors of re-fracture, group 1 (MPR and persistence data excluded, n=171)

Variable (N=163)	HR	95 % CI	p value
Co-morbidity count (>3 vs. ≤3)	2.04	1.10–3.79	0.024
Oral steroid use (past/present vs. never used)	1.75	1.12–2.73	0.013
sBMD TH (per 0.1 g/cm^2 decrease)	1.36	1.08–1.70	0.008

Abbreviations as per Table 3

Table 5 Multivariate predictors of re-fracture, group 1 (patients with complete MPR data only, n=68)

Variable	HR	95 % CI	p value
MPR (≤0.5 vs. >0.5)	3.36	1.32–8.53	0.011
Weight (per unit decrease)	1.04	1.003–1.08	0.032

Abbreviations as per Table 3

Our study has several strengths. Apart from the large range of clinical and technical variables assessed during direct patient contact, the long follow-up of up to 7 years and the availability of PBS claims data in a subgroup of subjects, all re-fractures were confirmed radiologically and the fracture mechanism was ascertained by the study physician to exclude traumatic fractures. Furthermore, the cohort of patients in this study is highly representative of the populations managed by most SFP programmes; our results are therefore clinically relevant and widely applicable.

There are also several limitations of this study. Firstly, our sample size was relatively small and only 40 % of patients in group 1 had complete PBS data, limiting the power of our compliance analysis. However, baseline characteristics of those with and without complete PBS data were similar, indicating that the results of the compliance analysis may be valid for the entire group. Secondly, the study design is observational rather than a randomised controlled trial, which amongst a population at high risk of re-fracture would have been non-ethical. Thirdly, patients in the Concord SFP programme were prescribed different medications approved for the treatment of osteoporosis in Australia. As we cannot exclude that some of these agents may differ in terms of their anti-fracture efficacy, we performed a sensitivity analysis including only patients treated with *oral* bisphosphonates. This subgroup comprised 84 % of the total population and results did not differ significantly from the initial analysis. However, similar studies with other agents may have resulted in different outcomes. Furthermore, the majority of patients in this study were of Caucasian ethnicity and results may not be transferrable to other ethnicities. Lastly, pharmaceutical claims data provide no information whether the medication was actually taken by the patient and whether it was taken with the correct technique.

Overall, this study provides clinically applicable evidence of the predictors of re-fracture amongst patients with incident osteoporotic fractures managed within the setting of a SFP programme. While significant co-morbidity, low bone mineral density or body weight, and corticosteroid use may identify patients at high risk of re-fracture despite optimised post-fracture follow-up, poor compliance to therapy is the major driver of re-fracture in this population. Hence, improving and encouraging compliance to therapy remains the predominant task in any clinical setting.

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Ethics approval All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Conflicts of interest None.

References

1. World Health Organisation (2001) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Report of a WHO Study Group. Geneva: WHO, 1994 (Technical Report Series 843). J Am Med Assoc 285:785–795
2. Kanis JA, Johnell O, Oden A (2000) Long-term risk of osteoporotic fracture in Malmo. Osteoporos Int 11:669–674
3. Nguyen ND, Ahlborg HG, Center JR, Eisman JA, Nguyen TV (2007) Residual lifetime risk of fractures in women and men. J Bone Miner Res 22:781–788
4. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Centre JR (2009) Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. J Am Med Assoc 301:513–521
5. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA (1999) Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet 353:878–882
6. Center J, Bliuc D, Nguyen TV, Eisman J (2007) Risk of subsequent fracture after low-trauma fracture in men and women. J Am Med Assoc 297:387–394
7. Langsetmo L, Goltzman D, Kovacs CS, Adachi JD, Hanley DA, Kreiger N, Josse R, Papaioannou A, Olszynski WP, Jamal SA (2009) Repeat low-trauma fractures occur frequently among men and women who have osteopenic BMD. J Bone Miner Res 24:1515–1522
8. van Geel TA, van Helden S, Geusens PP, Winkens B, Dinant GJ (2009) Clinical subsequent fractures cluster in time after first fractures. Ann Rheum Dis 68:99–102
9. Ganda K, Schaffer A, Pearson S, Seibel MJ (2014) Compliance and persistence to oral bisphosphonate therapy following initiation within a secondary fracture prevention program: a randomised controlled trial of specialist vs. non-specialist management. Osteoporos Int 25:1345–1355
10. Sale JEM, Beaton D, Posen J, Elliot-Gibson V, Bogoch E (2011) Systematic review on interventions to improve osteoporosis investigation and treatment in fragility fracture patients. Osteoporos Int 22: 2067–2082
11. Cooper MS, Palmer AJ, Seibel MJ (2012) Cost-effectiveness of the Concord Minimal Trauma Fracture Liaison service, a prospective, controlled fracture prevention study. Osteoporos Int 23:97–107
12. Lih A, Nandapalan H, Kim M, Yap C, Lee P, Ganda K, Seibel MJ (2011) Targeted intervention reduces refracture rates in patients with incident non-vertebral osteoporotic fractures: a 4-year prospective controlled study. Osteoporos Int 22:849–858
13. Kanis JA (2002) Diagnosis of osteoporosis and assessment of fracture risk. Lancet 359:1929–1936
14. Genant HK, Grampp S, Gluer CC, Faulkner KG, Jergas M, Engelke K, Hagiwara S, Van Kuijk C (1994) Universal standardization for dual x-ray absorptiometry: patient and phantom cross-calibration results. J Bone Miner Res 9:1503–1514
15. Lu Y, Fuerst T, Hui S, Genant HK (2001) Standardization of bone mineral density at femoral neck, trochanter and Ward's triangle. Osteoporos Int 12:438–444
16. Ganda K, Puech M, Chen JS, Speerin R, Bleasel J, Center JR, Eisman JA, March L, Seibel MJ (2013) Models of care for the secondary prevention of osteoporotic fractures: a systematic review and meta-analysis. Osteoporos Int 24:393–406
17. (2010) Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men. The Royal Australian College of General Practitioners, South Melbourne
18. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, Wong PK (2008) Medication compliance and persistence: terminology and definitions. Value Health 11:44–47
19. Black DM, Delmas PD, Eastell R et al (2007) Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 356:1809–1822
20. Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC, Nevitt MC, Suryawanshi S, Cummings SR (2000) Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. J Clin Endocrinol Metab 85:4118–4124
21. Harrington JT, Ste-Marie LG, Brandi ML, Civitelli R, Fardellone P, Grauer A, Barton I, Boonen S (2004) Risedronate rapidly reduces the risk for nonvertebral fractures in women with postmenopausal osteoporosis. Calcif Tissue Int 74:129–135
22. Cranney A, Papaioannou A, Zytaruk N, Hanley D, Adachi J, Goltzman D, Murray T, Hodsman A (2006) Parathyroid hormone for the treatment of osteoporosis: a systematic review. CMAJ 175: 52–59
23. Cummings SR, San Martin J, McClung MR et al (2009) Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 361:756–765
24. Guyatt GH, Cranney A, Griffith L, Walter S, Krolicki N, Favus M, Rosen C (2002) Summary of meta-analyses of therapies for postmenopausal osteoporosis and the relationship between bone density and fractures. Endocrinol Metab Clin N Am 31:659–679
25. Stevenson M, Davis S, Lloyd-Jones M, Beverley C (2007) The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women. Health Technol Assess 11:1–134
26. Dell R, Greene D, Schelkun SR, Williams K (2008) Osteoporosis disease management: the role of the orthopaedic surgeon. J Bone Joint Surg Am 90(Suppl 4):188–194
27. Dell RM, Greene D, Anderson D, Williams K (2009) Osteoporosis disease management: what every orthopaedic surgeon should know. J Bone Joint Surg Am 91(Suppl 6):79–86
28. Diez-Perez A, Olmos JM, Nogues X et al (2012) Risk factors for prediction of inadequate response to antiresorptives. J Bone Miner Res 27:817–824
29. Abrahamsen B, Rubin KH, Eiken PA, Eastell R (2013) Characteristics of patients who suffer major osteoporotic fractures despite adhering to alendronate treatment: a National Prescription registry study. Osteoporos Int 24:321–328
30. Prieto-Alhambra D, Pages-Castella A, Wallace G, Javaid MK, Judge A, Nogues X, Arden NK, Cooper C, Diez-Perez A (2014) Predictors of fracture while on treatment with oral bisphosphonates: a population-based cohort study. J Bone Miner Res 29:268–274
31. Diez-Perez A, Adachi JD, Adami S et al (2014) Risk factors for treatment failure with antiosteoporosis medication: the global longitudinal study of osteoporosis in women (GLOW). J Bone Miner Res 29:260–267
32. Adachi J, Lynch N, Middelhoven H, Hunjan M, Cowell W (2007) The association between compliance and persistence with bisphosphonate therapy and fracture risk: a review. BMC Musculoskelet Disord 8:97
33. Imaz I, Zegarra P, Gonzalez-Enriquez J, Rubio B, Alcazar R, Amate JM (2010) Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis. Osteoporos Int 21:1943–1951

34. Patrick AR, Brookhart MA, Losina E, Schousboe JT, Cadarette SM, Mogun H, Solomon DH (2010) The complex relation between bisphosphonate adherence and fracture reduction. J Clin Endocrinol Metab 95:3251–3259
35. Sampalis JS, Adachi JD, Rampakakis E, Vaillancourt J, Karellis A, Kindundu C (2011) Long-term impact of adherence to oral bisphosphonates on osteoporotic fracture incidence. J Bone Miner Res
36. Siris SE, Harris ST, Rosen C, Barr CE, Arvesen JN, Abbott TA, Silverman S (2006) Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clin Proc 81:1013–1022
37. Cadarette SM, Solomon DH, Katz JN, Patrick AR, Brookhart MA (2011) Adherence to osteoporosis drugs and fracture prevention: no evidence of healthy adherer bias in a frail cohort of seniors. Osteoporos Int 22:943–954
38. Garnero P, Hausherr E, Chapuy MC, Marcelli C, Grandjean H, Muller C, Cormier C, Breart G, Meunier PJ, Delmas PD (1996) Markers of bone resorption predict hip fracture in elderly women: the EPIDOS Prospective Study. J Bone Miner Res 11:1531–1538
39. Garnero P, Sornay-Rendu E, Claustrat B, Delmas PD (2000) Biochemical markers of bone turnover, endogenous hormones and the risk of fractures in postmenopausal women: the OFELY study. J Bone Miner Res 15:1526–1536
40. van Daele PL, Seibel MJ, Burger H, Hofman A, Grobbee DE, van Leeuwen JP, Birkenhager JC, Pols H (1996) Case-control analysis of bone resorption markers, disability, and hip fracture risk: the Rotterdam study. Br Med J 312:482–483
41. Meier C, Nguyen TV, Center JR, Seibel MJ, Eisman JA (2005) Bone resorption and osteoporotic fractures in elderly men: the dubbo osteoporosis epidemiology study. J Bone Miner Res 20:579–587
42. Bauer DC, Black DM, Garnero P, Hochberg M, Ott S, Orloff J, Thompson DE, Ewing SK, Delmas PD, Fracture Intervention Trial Study G (2004) Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: the fracture intervention trial. J Bone Miner Res 19:1250–1258
43. Sarkar S, Reginster JY, Crans GG, Diez-Perez A, Pinette KV, Delmas PD (2004) Relationship between changes in biochemical markers of bone turnover and BMD to predict vertebral fracture risk. J Bone Miner Res 19:394–401
44. (2009) NSW re-fracture admission data 2002–2008 analysis discussion. Greater Metropolitan Clinical Taskforce Sydney