

# Increase in prophylaxis of glucocorticoid-induced osteoporosis by pharmacist feedback: a randomised controlled trial

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Received: 27 June 2013 / Accepted: 16 October 2013 / Published online: 13 November 2013  
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## Abstract

**Summary** The aim of this study was to determine whether feedback by pharmacists to prescribers of patients eligible for glucocorticoid-induced osteoporosis prophylaxis would stimulate the prescribing of osteoporosis prophylaxis. The

intervention did not significantly increase the prescribing of bisphosphonates in the total study population, but a significant increase was seen in men and in the elderly. However, the proportion of bisphosphonate-treated patients remained low.

**Introduction** The aim of this study was to determine whether feedback by pharmacists to prescribers of patients eligible for glucocorticoid-induced osteoporosis prophylaxis (GIOP) would stimulate the implementation of the Dutch GIOP guideline.

**Methods** This randomised controlled trial included 695 patients who were dispensed  $\geq 675$  mg prednisone equivalents without a concomitant bisphosphonate prescription within 6 months before baseline. Pharmacists were asked to contact the physicians of GIOP-eligible patients in the intervention group to suggest osteoporosis prophylaxis. The primary endpoint was a bisphosphonate prescription. Secondary endpoints were a prescription of calcium supplements, vitamin D or any prophylactic osteoporosis drug (bisphosphonate, calcium supplements, vitamin D).

**Results** The group assigned to the intervention was slightly younger than the control group ( $68.7 \pm 15.4$  vs.  $65.9 \pm 16.9$  years,  $p=0.02$ ) and used hydrocortisone more often (7.0 % vs. 3.1 %,  $p=0.02$ ). Within 6 months, the intervention did not significantly increase the prescribing of bisphosphonates (11.4 % after intervention vs. 8.0 % for controls; hazard ratio [HR] 1.47, 95 % confidence interval [CI] 0.91–2.39). However, subgroup analyses showed a significant increase for the primary endpoint in men (12.8 % vs. 5.1 %, HR 2.53, 95 % CI 1.11–5.74) and patients  $\geq 70$  years (13.4 % vs. 4.9 %, HR 2.88, 95 % CI 1.33–6.23). The prescribing of calcium and vitamin D was not significantly altered.

**Conclusion** This study showed that active identification of patients eligible for GIOP by pharmacists did not significantly

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increase the prescribing of bisphosphonates in the total study population, but there was an increase in men and the elderly. However, the proportion of GIOP-treated patients remained low.

**Keywords** Glucocorticoid-induced osteoporosis · Intervention · Pharmacist · Physician

## Introduction

The use of glucocorticoids, even in low doses, is associated with rapid bone loss and an increased risk of fractures [1–4]. Bisphosphonates have been shown to be the most effective drugs for glucocorticoid-induced osteoporosis prophylaxis (GIOP) [5, 6] and are therefore recommended in (inter)national guidelines for management of GIOP [7–9]. The most important recommendation in the Dutch guideline is to consider starting bisphosphonates in post-menopausal women and men over 70 years who are expected to be treated with >7.5 mg prednisone (equivalents) per day for at least 3 months. In addition, all other patients who are expected to use >15 mg prednisone (equivalents) for more than 3 months should be treated with bisphosphonates. Although the awareness of the importance of osteoporosis prophylaxis seems to have increased [10], the widespread implementation of guidelines remains difficult. Audits have shown that only 10–60 % of patients who are eligible for GIOP receive appropriate treatment [11–14]. Previous intervention trials that aimed to increase GIOP were mostly conducted by training of physicians (general practitioners and rheumatologists) and frequently included education of patients at risk of GIOP [15–18]. Unfortunately, these attempts have yielded limited success.

Until now, a limited number of studies have determined the impact of pharmacy-based interventions with regard to GIOP [15, 19]. In the Dutch health care system, pharmacists share a responsibility with prescribers to properly inform patients on the advantages and disadvantages of pharmacotherapy and to assist physicians in this respect. Therefore, pharmacists could play an important role in the implementation of guidelines for management of GIOP. The previously conducted studies that used a pharmacy-based approach for the improvement of GIOP have shown a significant increase in the prescribing rates of prophylactic osteoporosis drugs. However, these studies were limited by a lack of randomisation [15] and a lack of power [19]. Therefore, the aim of this randomised controlled trial was to determine whether feedback by community pharmacists to physicians of patients eligible for GIOP would stimulate the implementation of the Dutch GIOP guideline.

## Materials and methods

### Study participants and setting

This randomised controlled trial was conducted at 29 pharmacies from different parts in the Netherlands. Pharmacists were invited to participate in the study by a short announcement in the Dutch Pharmacy Journal. The pharmacies were located all over the Netherlands. There was no particular chain of pharmacies involved.

At each participating pharmacy, drug dispensing data from all patients were collected at baseline (date of first data extraction, January 2005 to May 2005). We selected all patients who were dispensed  $\geq 675$  mg prednisone equivalents ( $\geq 67.5$  defined daily dosages [DDDs] [7, 8]) without a concomitant bisphosphonate prescription within the 180 days before baseline and with at least one prescription for a glucocorticoid within the 90 days before baseline. In the Netherlands, the vast majority of the population obtains their medication from only one community pharmacy, enabling the collection of longitudinal medication histories [20]. Medication records of patients were pseudonymised and were sent to the researchers. We have excluded patients who had less than 6 months of medication records before baseline.

### Intervention

Block randomisation (using the survey select procedure of SAS, version 8.2) was performed. After the randomisation, the pharmacists received feedback on patients who were assigned to the intervention group. They received a letter with the Dutch GIOP guideline [8] and a list on paper with all the eligible patients. Pharmacists were expected to forward the patients on this list to their own general practitioners and to suggest the start of osteoporosis prophylaxis (a bisphosphonate). It was left at the disposal of the individual pharmacist how to communicate with the general practitioner.

At the end of 6 months of follow-up, additional pharmacy dispensing records of all patients in the intervention and control group (usual care) were retrieved. These medication records were reviewed for the dispensing of bisphosphonates, calcium supplements and vitamin D during the follow-up period. After the study period, pharmacists received comparable information on patients who were originally assigned to the control group.

This study was not covered by the Medical Research Involving Human Subjects Act (WMO) since the patients were not directly exposed to the intervention, and approval by an ethical committee was not required.

### Outcome measurements

All patients were followed up from baseline until the start of osteoporosis prophylaxis or the end of the study period (the

date of second data extraction), whichever came first. The primary endpoint was a dispensing of a bisphosphonate. Secondary endpoints were the dispensing of other prophylactic osteoporosis drugs (calcium supplements or vitamin D) and a dispensing of any prophylactic osteoporosis drug as a composite endpoint (bisphosphonate, calcium supplements or vitamin D, only the first event was counted).

### Statistical analyses

We assumed an event rate of 10 % in the control group over 6 months and an increase to 20 % in the intervention group [18, 21]. With a two-sided alpha of 0.05 and 90 % power, a total sample size of 584 patients was estimated which was increased to 695 patients.

Chi-square tests or Fisher's exact tests were used to determine baseline differences between the comparison groups for categorical variables and independent sample *t* tests for continuous variables ( $p < 0.05$ ). Cox proportional hazard models were used to estimate hazard ratios (HRs) for the start of osteoporosis prophylaxis during the follow-up period by comparing the intervention group to the control group. Hazard ratios were adjusted for covariates that were unevenly distributed between the intervention group and control group ( $p < 0.05$ ). Patients who did not receive any

prescription of glucocorticoids during the follow-up period were censored at 1 day after baseline.

In subgroup analyses, results were stratified by gender, the number of prednisone equivalents (DDDs) received in the 6 months before baseline (67.5–134, 135–270, >270) and age categories ( $\leq 70$ , >70 years) for the primary and composite endpoint.

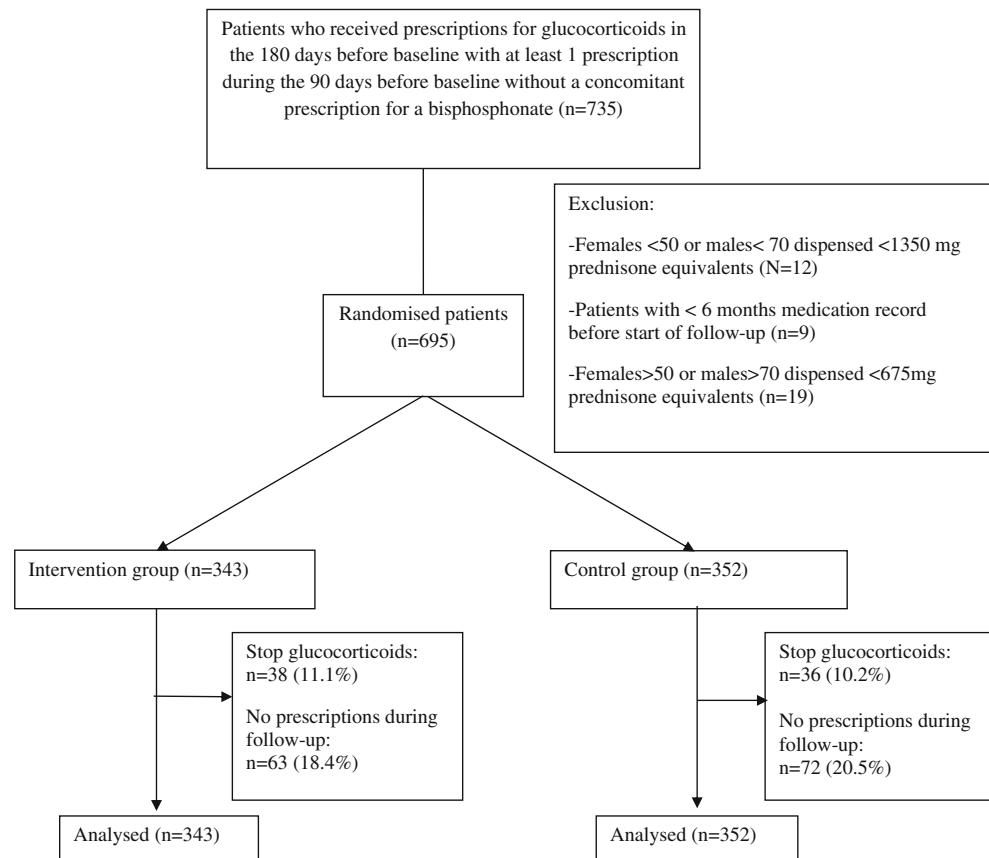
Finally, a Kaplan–Meier plot was used to visualize the time to start of bisphosphonate use after baseline and the proportion of patients being newly treated for GIOP during the study period. This plot was stratified by the randomised intervention.

All analyses were performed using SAS, version 9.1.

### Results

During the first data extraction period, 735 patients were selected from the participating pharmacies. Of these patients, 31 (4.2 %) were not eligible for bisphosphonate prophylaxis according to the Dutch guideline. These patients were either females younger than 50 years or males younger than 70 years using less than 1,350 mg (135 DDDs) prednisone equivalents, or females older than 50 or males older than 70 using less than 675 mg (67.5 DDDs) prednisone equivalents. Moreover, nine

**Fig. 1** Flow chart of the study procedure



patients (1.2 %) were excluded as they had medication records available for less than 6 months prior to the first extraction date. Overall, 695 patients could be randomised, with 343 allocated to the intervention group and 352 to the control group. During the follow-up period, 38 (11.1 %) patients who were allocated to the intervention group and 36 (10.2 %) patients in the control group did not receive any new glucocorticoid prescription but did collect prescriptions for other drugs. Furthermore, 63 (18.4 %) patients in the intervention group and 72 (20.5 %) patients in the control group did not collect any prescription during follow-up (Fig. 1).

The group assigned to the intervention was slightly younger than the control group ( $65.9 \pm 16.9$  vs.  $68.7 \pm 15.4$  years,  $p = 0.02$ ) and used hydrocortisone more often in the 6 months before baseline (7.0 % vs. 3.1 %,  $p = 0.02$ ). All other baseline characteristics and mean follow-up time were similar between the intervention and the control group (Table 1).

During a mean follow-up period of 6.2 months, the primary endpoint (a prescription for a bisphosphonate during follow-up) was achieved by 39 patients (11.4 %) in the intervention group and by 28 patients (8.0 %) in the control group. Figure 2 shows the time to initiation of a bisphosphonate for both study groups. The intervention did not significantly increase the prescribing rate of bisphosphonates when compared to the control group (unadjusted HR 1.47, 95 % confidence interval [CI] 0.91–2.39). This effect changed marginally after adjustment for age and use of hydrocortisone in the 6 months before baseline (Table 2). However, subgroup analyses showed that the prescribing rate of bisphosphonates was significantly increased in the intervention group for male patients (12.8 % vs. 5.1 %; unadjusted HR 2.53, 95 % CI 1.11–5.74; adjusted HR 2.55, 95 % CI 1.12–5.80) and for patients older than 70 years (13.4 % vs. 4.9 %; unadjusted HR 2.88, 95 % CI 1.33–6.23; adjusted HR 2.99, 95 % CI 1.38–6.47). The received cumulative number of DDD prednisone equivalents in the 6 months before baseline did not change the effect of the intervention. Similar results were seen for the composite endpoint of any prophylactic osteoporosis drug (Table 3).

## Discussion

This randomised controlled trial showed that active identification of GIOP-eligible patients by community pharmacists did not significantly increase the prescribing rate of bisphosphonates in the total study population. However, subgroup analyses showed that there was a significant increase in the primary endpoint in males and in the elderly (>70 years). Similar results were seen for the composite

endpoint of any prophylactic osteoporosis drug (bisphosphonate, calcium, or vitamin D).

To the best of our knowledge, this is the first randomised controlled trial where pharmacists identified GIOP-eligible patients and subsequently contacted the prescriber, without further training of the patient or the physician [22]. The only previously conducted pharmacy-based randomised controlled

**Table 1** Baseline characteristics of patients in the intervention group and control group

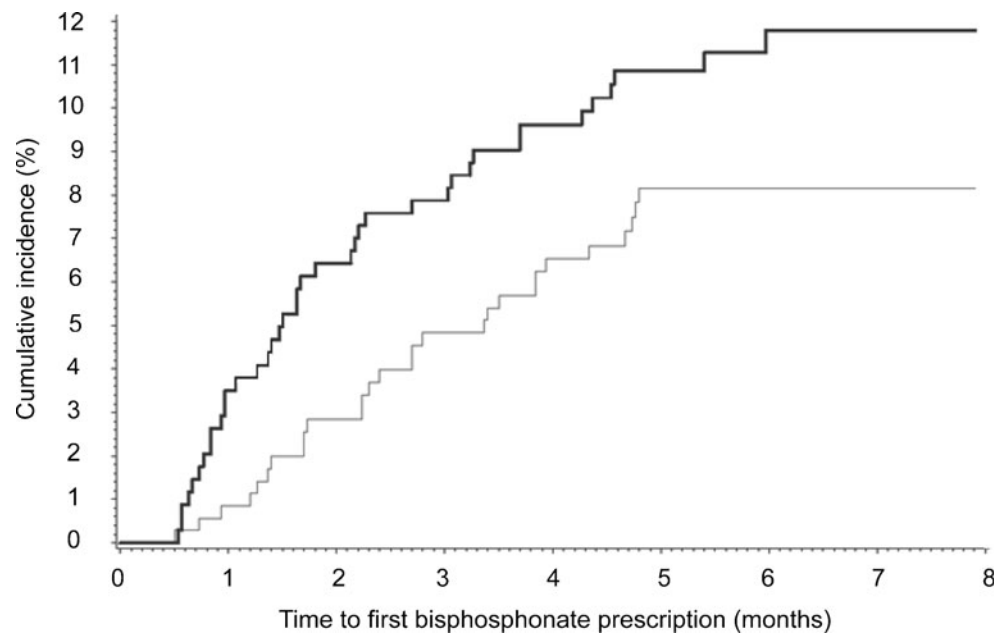
	Control group <i>N</i> =352	Intervention group <i>N</i> =343	<i>p</i> value
Follow-up (mean±SD months)	6.2±1.1	6.2±1.1	NS
Female	55.4 %	54.5 %	NS
Age (mean±SD years)	68.7±15.4	65.9±16.9	0.02
Age categories			
<50 years	11.6 %	18.4 %	0.01
50–70 years	36.1 %	31.5 %	NS
>70 years	52.3 %	50.1 %	NS
Type of glucocorticoid in the 6 months before baseline <sup>a</sup>			
Betamethasone	1.4 %	0.3 %	NS
Cortisone acetate	3.1 %	4.4 %	NS
Dexamethasone	7.9 %	6.1 %	NS
Fludrocortisone	2.0 %	2.9 %	NS
Hydrocortisone	3.1 %	7.0 %	0.02
Methylprednisolone	0.3 %	0.3 %	NS
Prednisolone	17.2 %	17.2 %	NS
Prednisone	79.3 %	75.5 %	NS
Triamcinolone	1.7 %	1.5 %	NS
Cumulative DDDs of prednisone equivalents in the 6 months prior to baseline (mean±SD)	183.3±161.4	185.0±172.3	NS
Cumulative DDD categories			
<135 DDDs	41.2 %	37.9 %	NS
135–270 DDDs	44.6 %	50.7 %	NS
>270 DDDs	14.2 %	11.4 %	NS
Co-medication in the 6 months prior to baseline			
Opioid analgesics	6.2 %	7.0 %	NS
Cytostatic drugs	5.7 %	3.8 %	NS
Anti-emetic drugs	4.5 %	2.9 %	NS
Calcium	16.7 %	16.6 %	NS
Vitamin D	6.0 %	7.0 %	NS
HRT or SERMs	0.9 %	2.0 %	NS
Anti-ulcer drugs	43.6 %	44.3 %	NS
Bisphosphonate use >6 months prior to baseline	12.2 %	10.8 %	NS

Comparison of baseline characteristics between groups was significant at  $p < 0.05$

HRT hormone replacement therapy, SERM selective estrogen receptor modulator, SD standard deviation, DDD defined daily dosage.

<sup>a</sup> Use of more than one type of glucocorticoids per patient is possible

**Fig. 2** Incident bisphosphonate use in the intervention group (black line) and control group (grey line)



trial that aimed to increase GIOP found an increased prescribing rate of calcium but not of bisphosphonates [19]. This trial was conducted at 15 community pharmacies (intervention 70 patients, control 26 patients). The pharmacists received training for GIOP, identified eligible patients, gave them education for GIOP and contacted the prescriber when necessary. However, pharmacists in both the intervention and control groups received training about GIOP and the importance of bone mineral density (BMD) testing which may have diluted the results. Another randomised controlled trial has shown a twofold increase (28 patients (22 %) intervention group vs. 14 patients (11 %) control group; relative risk 2.1, 95 % CI 1.1–3.7) in the composite endpoint of BMD testing or incident osteoporosis treatment with a community pharmacist screening programme [21]. In contrast to the present study, all patients and pharmacists received education about osteoporosis. Other attempts to increase GIOP mostly included educational interventions directed at physicians (general practitioners or rheumatologists) but were often without or with modest results [16–18].

The lack of an overall intervention effect was accompanied by a low number of bisphosphonate-treated patients [14, 17]. It should be noted that the study population did not include patients who already received a prescription for a bisphosphonate in the 6 months prior to baseline. Chitre et al. (2008) similarly excluded these patients and found comparable incident treatment rates for osteoporosis prophylaxis. In addition, our study population included patients who received a bisphosphonate more than 6 months before baseline (10.8 % in the intervention group, 12.2 % in the control group). These patients could have had earlier adverse effects for bisphosphonates or had other reasons for discontinuing these drugs. Moreover, not all patients still used glucocorticoids during follow-up or tapered off the dose, and as a result, GIOP prophylaxis was no longer required.

In the control group, the proportion of GIOP-treated males was twofold lower as compared to females. The neglecting of osteoporosis prophylaxis in males is in line with other studies [11, 14, 23]. The difference in the intervention effect between males and females may be explained by this phenomenon; prescribers may have been more likely to have previously

**Table 2** Start of osteoporosis prophylaxis drugs after intervention, as compared to usual care

Treatment	Start OP intervention (%)	Start OP control (%)	Unadjusted HR (95 % CI)	Adjusted HR (95 % CI) <sup>a</sup>
Bisphosphonate	11.4	8.0	1.47 (0.91–2.39)	1.54 (0.95–2.50)
Calcium	5.3	2.6	2.06 (0.93–4.59)	2.12 (0.95–4.72)
Vitamin D	3.5	1.7	2.05 (0.77–5.47)	2.08 (0.78–5.55)
Bisphosphonate, calcium or vitamin D	13.4	9.4	1.48 (0.94–2.31)	1.53 (0.98–2.39)

OP osteoporosis prophylaxis drugs, HR hazard ratio, CI confidence interval

<sup>a</sup> Adjusted for age categories ( $\leq 70$ ,  $>70$ ) and use of hydrocortisone in the 6 months before baseline

considered osteoporosis prophylaxis in females. The low prescribing rate in the elderly may be explained by the initial belief of physicians that extra treatment with bisphosphonates would be inappropriate due to the presence of multiple comorbidities or a large number of medicines. On the other hand, elderly patients do have a higher absolute fracture risk and the consequences of fractures (especially for those of the hip) can be tremendous [24]. The increased prescribing of bisphosphonates for elderly in the intervention group may be explained by an increased awareness for this fact. It should, however, be noted that the power of this study was not calculated specifically for these subgroup analyses.

Strengths of this study include its size and the simple set-up of the intervention. In contrast to previous trials, patients and physicians were not educated for GIOP and pharmacists only received the recent guideline without further training [19, 21]. This study is therefore a better reflection of the real-life situation. The identification of patients at risk for GIOP can easily be integrated in the tasks of the pharmacists and is not

labour intensive or costly when compared to interventions involving education of physicians and/or patients [25]. However, the lack of an overall significant increase in the number of bisphosphonate-treated patients calls for additional measures. The intervention in its present form can be combined with interdisciplinary meetings between pharmacists and general practitioners beforehand and after follow-up, which include feedback about current prescribing and differences between practices. This approach is not very costly and is achievable in daily practice. In addition, clinical rules are currently implemented, and this would make it even easier to extract GIOP-eligible patients from pharmacy information systems. Indeed, a large randomised controlled trial (RCT) showed the significant benefit of a more intensive, pharmacist-led intervention in reducing the number of prescribing errors [26]. Pharmacists did not only give feedback to physicians about medication errors during meetings, but also reviewed medical records and invited the patients.

**Table 3** Start of osteoporosis prophylaxis drugs after intervention, as compared to usual care, stratified by gender, cumulative dosage prednisone equivalents and age categories

	Start OP intervention (%)	Start OP control (%)	Unadjusted HR (95 % CI)	Adjusted HR (95 % CI) <sup>a</sup>
<b>Bisphosphonate</b>				
Overall	11.4	8.0	1.47 (0.91–2.39)	1.54 (0.95–2.50)
Stratified by gender				
Men	12.8	5.1	2.53 (1.11–5.74)	2.55 (1.12–5.80)
Women	10.2	10.3	1.03 (0.55–1.93)	1.10 (0.58–2.06)
Stratified by cumulative dosage prednisone equivalents within 6 months before baseline				
67.5–134 DDDs	10.8	7.6	1.52 (0.69–3.36)	1.54 (0.70–3.38)
135–270 DDDs	10.9	6.4	1.65 (0.77–3.56)	1.67 (0.77–3.59)
>270 DDDs	15.4	14.0	1.48 (0.50–4.41)	1.47 (0.49–4.38)
Stratified by age category <sup>b</sup>				
≤70 years	9.4	11.3	0.84 (0.43–1.63)	0.89 (0.46–1.73)
>70 years	13.4	4.9	2.88 (1.33–6.23)	2.99 (1.38–6.47)
<b>Bisphosphonate, calcium or vitamin D</b>				
Overall	13.4	9.4	1.48 (0.94–2.31)	1.53 (0.98–2.39)
Stratified by gender				
Men	14.7	6.4	2.33 (1.11–4.89)	2.32 (1.10–4.88)
Women	12.3	11.8	1.09 (0.61–1.93)	1.14 (0.64–2.04)
Stratified by cumulative dosage prednisone equivalents within 6 months before baseline				
67.5–134 DDDs	11.5	9.0	1.38 (0.66–2.89)	1.39 (0.66–2.93)
135–270 DDDs	13.8	8.3	1.61 (0.82–3.15)	1.60 (0.81–3.15)
>270 DDDs	17.9	14.0	1.77 (0.62–5.05)	1.74 (0.61–4.99)
Stratified by age category <sup>b</sup>				
≤70 years	13.5	12.5	1.10 (0.61–1.98)	1.16 (0.64–2.09)
>70 years	13.4	6.5	2.14 (1.07–4.30)	2.22 (1.11–4.47)

OP osteoporosis prophylaxis drugs, HR hazard ratio, CI confidence interval, DDDs defined daily dosage prednisone equivalents

<sup>a</sup> Adjusted for age categories (≤70, >70) and use of hydrocortisone in the 6 months before baseline

<sup>b</sup> Adjusted for hydrocortisone use in the 6 months before baseline

The major limitation of this study is that we do not know how motivated the pharmacists were to perform the intervention. It is likely that pharmacists did not notify all GPs, but this has not been systematically registered. In addition, we do not know if discussions between prescribers and their patients about the start of GIOP took place. Possibly, a number of approached patients refused to start osteoporosis prophylaxis. Therefore, the actual effect of the pharmacist intervention on the physician's behaviour may have been greater than the reported effect. In addition, we had no clinical data available such as (prior) BMD testing or the occurrence of fractures (history). Guidelines recommend that premenopausal women who use 7.5–15 mg of prednisone equivalents for  $\geq 3$  months should receive a BMD measurement. However, this study presumably included post-menopausal women ( $\geq 50$  years). Furthermore, we also have included patients who were dispensed less than 135 DDD prednisone equivalents in the 6 months before baseline (41.2 % in the control group, 37.9 % in the intervention group), who were possibly not eligible for GIOP according to the Dutch guideline. However, in the Netherlands, patients are frequently dispensed medication for 3 months, and we would have missed these patients if the inclusion period was only 3 months before baseline. Moreover, all patients were required to receive a dispensing for glucocorticoids within 3 months before baseline, and our results show that the cumulative number of DDD prednisone equivalents did not modify the intervention effect. Another limitation of this study was that we were unable to exclude patients where osteoporosis prophylaxis would have been contraindicated or inappropriate (e.g. patients with serious cognitive or renal impairment). Finally, this was a non-blinded RCT with a lack of clinical equipoise between the pharmacists in the intervention group [27]. In other words, it is very likely that all included pharmacists saw the importance of the intervention. As a result, pharmacists could have been motivated to self-identify patients other than those in the intervention group who would also benefit from GIOP. This may have masked the effect of the intervention.

The present study showed that simple feedback by community pharmacists to physicians about patients eligible for GIOP did not manage to significantly increase the prescribing of bisphosphonates in the overall study population. Subgroup analyses showed a significant increase in males and in patients older than 70 years. However, the absolute number of GIOP-treated patients remained low which calls for more intensive pharmacy-based interventions.

**Acknowledgments** This study was supported by The Netherlands Organization for Health Research and Development (ZonMw; grant number 113101007). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Conflicts of interest** The Division of Pharmacoepidemiology & Clinical Pharmacology (employing CK, FV, MK, TvS, TE and MB) has received unrestricted funding from the Netherlands Organisation for Health Research and Development (ZonMw), the Dutch Health Care Insurance Board (CVZ), the Royal Dutch Pharmacists Association (KNMP), the private–public funded Top Institute Pharma ([www.tipharma.nl](http://www.tipharma.nl); including co-funding from universities, government, and industry), the EU Innovative Medicines Initiative (IMI), the EU 7th Framework Program (FP7) and the Dutch Ministry of Health and industry (including GlaxoSmithKline, Pfizer and others). The authors TV and JB have no competing interests.

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