Journal of Internal Medicine 2003; **254**: 548–554

Use of α-blockers and the risk of hip/femur fractures

P. C. SOUVEREIN[1], T. P. VAN STAA[1,2], A. C. G. EGBERTS[1], J. J. M. C. H. DE LA ROSETTE[3], C. COOPER[2] & H. G. M. LEUFKENS[1]

From the [1]Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht, The Netherlands, [2]Medical Research Council, Environmental Epidemiology Unit, Southampton University Hospital, Southampton, UK; and [3]Department of Urology, Academic Medical Center, Amsterdam, The Netherlands

Abstract. Souverein PC, Van Staa TP, Egberts ACG, De la Rosette JJMCH, Cooper C, Leufkens HGM. (Utrecht Institute for Pharmaceutical Sciences, Utrecht, The Netherlands; Southampton University Hospital, Southampton, UK; and Academic Medical Centre, Amsterdam, The Netherlands). Use of α-blockers and the risk of hip/femur fractures. *J Intern Med* 2003; **254:** 548–554.

Objective. To study the association between use of α-blockers and risk of hip/femur fractures.
Design. Population-based case–control study.
Setting. General Practice Research Database.
Subjects. Cases were defined as men, aged 40 years and older with a first diagnosis for hip/femur fracture. Controls were matched 1 : 1 on gender, year of birth and general practitioner-practice.
Results. In all, 4571 cases and an equal number of controls were identified. Current use of α-blockers (prazosin, doxazosin, indoramin, terazosin, alfuzosin and tamsulosin) was compared with non-use of α-blockers. Current use of α-blockers on the index date was associated with an increased risk of hip/femur fracture [adjusted odds ratio (OR) 1.9, 95% confidence interval (CI): 1.1–3.0] in the overall analysis. The effect was particularly strong for first prescriptions within a treatment episode (adjusted OR 5.1, 95% CI: 1.0–31.7) and during the first month of treatment (adjusted OR 4.1, 95% CI: 0.7–23.9). Stratification according to indication of use showed that current use of α-blockers was not associated with hip/femur fracture in men with a diagnosis of benign prostatic hyperplasia (adjusted OR 1.0, 95% CI: 0.4–2.5), but was associated in men who used α-blockers for cardiovascular disease (adjusted OR 2.8, 95% CI: 1.4–5.4).
Conclusion. Current use of α-blockers was associated with an increased risk of hip/femur fracture and with the start of a new treatment episode. The effect seemed to be confined to patients who used α-blockers for cardiovascular disease. Caution with respect to first-dose effects related to the initiation of a new episode of α-blocker treatment is advised.

Keywords: adrenergic alpha-antagonists, case–control studies, hip fractures, pharmacoepidemiology.

Introduction

α-blockers were originally developed for the treatment of hypertension, but have become increasingly popular in the treatment of the benign prostatic hyperplasia (BPH) in the last decade. The hemodynamical activity of such drugs is a potential source of concern. Elderly patients are more vulnerable to vasodilatory side-effects associated with α-blockers, because of the age-dependent reduction of cardiac output, baroreceptor sensitivity, plasma renin level and renal function [1]. Adverse events that have been reported in clinical trials of α-blockers include dizziness, weakness, headache, postural hypotension and syncope [1, 2]. Such vasodilatory effects of α-blockers are a source of concern, as these adverse effects are well-known risk factors for falling. Falls and their consequences are a major source of morbidity, disability, hospitalization and mortality. One of the most serious fractures resulting from accidental falls are hip/femur fractures [3, 4]. In this case–control study, we studied the association between the use of α-blockers and risk of hip/femur fracture using data from the General Practice Research Database (GPRD).

Methods

General practitioners (GPs) play a key role in the health care system in the UK, as they are responsible for primary health care and specialist referrals. Patients are semi-permanently affiliated to a practice, which centralizes the medical information not only from the GPs themselves, but also from specialist referrals and hospitalizations. The current study includes 683 practices from different geographical areas in the UK, registered within the GPRD. The data recorded in the GPRD include demographical information, prescription data, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes [5]. Clinical data are stored and retrieved by means of OXMIS and Read codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9). Each entry in the GPRD is internally validated by cross-checking within the practice and by comparisons with external statistics [5]. Only data from practices that pass this quality control are compiled and are part of the GPRD database. Several independent validation studies have confirmed a high level of completeness and validity of the GPRD, which is owned by the Department of Health and managed by the Medicines Control Agency in the UK [6].

Study population

Within the GPRD, a case–control study was conducted. Cases were defined as permanently registered men (i.e. with residence in the practice neighborhood) aged 40 years or older with a first record for a fracture of the hip or femur recorded in their medical records between the enrollment date of their practice in the GPRD and the end of data collection (July 1999). Data collection for the GPRD started in 1987. The classification of fractures was based on ICD-9 codes 820 and 821. Previous studies of GPRD data have reported a high level of validity of the GPRD with respect to fractures (>90% of fractures were confirmed) [6, 7]. Each case was matched to one control patient by year of birth (within 1 year), sex and medical practice. The index date of the control patient was that of their matched case. However, for control patients who had transferred to another practice or had died prior to this date, an index date between registration and transfer dates was randomly assigned. Further details on the study population can be found elsewhere [8].

Exposure assessment

α-blockers that were evaluated were tamsulosin, alfuzosin, terazosin, doxazosin and prazosin and indoramin. In the UK, tamsulosin and alfuzosin are indicated for the treatment of BPH only, whilst the other α-blockers listed are indicated for both the treatment of BPH and hypertension. We considered tamsulosin and alfuzosin as selective α-blockers, as these drugs are indicated for BPH only. In addition, we evaluated the use of finasteride, a 5-alpha-reductase inhibitor that is indicated for the treatment of BPH.

The duration of α-blocker use (and finasteride use) was determined by calculation of the length of treatment episodes. Treatment episodes were defined as series of subsequent prescription refills for an α-blocker, independent of switching to another type of drug or changes in dose regimen. A new episode was assumed if an interval of 30 days or more occurred between the theoretical end date of a prescription and the dispensing date of the next prescription for the same patient. Patients were classified as current users when the index date fell between the start and end date of a treatment episode. Former users were defined as patients who were not current users at the index date, but had a history of α-blocker (or finasteride) use before the index date.

Assessment of potential confounders

Potential confounders in this study were clinical variables and medications that are known to be associated with fractures, and included diabetes mellitus, rheumatoid arthritis (RA), hyperthyroidism, congestive heart failure, hypertension, anaemia, depression, Parkinson's disease, psychotic disorder, dementia, cerebrovascular accidents, chronic obstructive pulmonary disease and seizures. We also assessed whether patients had a diagnosis of BPH or lower urinary tract symptoms (LUTS) in their medical records before the index date. Further, the use of prescription drugs was evaluated in a 6-month period prior to the index date. Medications that were assessed included the use of anticonvulsants, non-steroidal anti-inflammatory

drugs (NSAIDs), methotrexate, hormone replacement therapy, diuretics, anxiolytics/hypnotics, antipsychotics, antidepressants, antiparkinsonian drugs, systemic and inhaled corticosteroids, bronchodilators, opiates, antiepileptics, nitrates and antihypertensive drugs. In addition, the latest data on smoking status (history or no history of smoking, or unknown) and body mass index (BMI; <20, 20–24, 25–29 and ≥30 kg m^{-2}, or unknown) were used.

Data analysis

The strength of the association between use of α-blockers and the occurrence of hip/femur fractures was estimated using conditional logistic regression analysis and expressed as crude and adjusted odds ratios (OR) and 95% confidence intervals (CI). Covariates were included in the regression model if they were either independently and significantly associated with the outcome, or induced a 10% change or more in the crude matched OR for use of α-blockers.

Possible effect-modification between α-blockers and covariates was assessed by including first-order interaction terms to the bivariate model containing α-blocker use and the covariate. The effect of timing of use (current and former) and duration of use was evaluated. Further, we evaluated whether the effect was different between new starters of α-blockers (current use, first treatment episode) and current users who had filled prescriptions for α-blockers previously (current use, multiple treatment episodes). As patients with concomitant diseases and prescription drug use, that are associated with falling (and resulting risk of fractures), might not have been prescribed α-blockers, we stratified according to whether patients were prone to falling or not. Because the exposure prevalence of α-blocker use was lower within the stratum of patients who had a history of anaemia, RA, cerebrovascular disease, depression, history of falls, use of nitrates, antiepileptics or thiazide diuretics, a summary variable 'fall-prone' was created.

Furthermore, we assessed whether the use of finasteride was associated with an increased risk of hip/femur fracture. This analysis was used as a reference analysis, as this type of BPH drug is not associated with cardiovascular effects and an increased risk of fractures was therefore not expected in patients using this drug.

Results

The study population consisted of 4571 men aged 40 years and older with a first record of hip/femur fracture and an equal number of matched controls. The characteristics of the study population are shown in Table 1. The majority of men were aged between 70 and 90 years. In general, cases had a higher prevalence of diagnoses of medical conditions and used more prescription drugs frequently. The most prevalent medical conditions amongst cases and controls were cerebrovascular disease (17.4 vs. 9.4%), heart failure (14.8 vs. 9.1%) and diabetes (7.4 vs. 6.2%). The largest difference between cases and controls was for history of falls. The most frequently prescribed drugs amongst cases and controls in the 6-month time window before the index date were NSAIDS (19.1 vs. 12.8%) and hypnotic/anxiolytics (16.3 vs. 8.4%). The prevalence of BPH amongst cases and controls was 7.6 and 5.4%, respectively.

Table 2 shows the overall association between use of α-blockers and risk of hip/femur fracture. The frequency of current use of α-blockers was higher amongst cases ($n = 53$, 1.2%) compared with controls ($n = 28$, 0.6%), yielding a crude OR of 1.9 (95% CI: 1.2–3.0). Adjustment for confounders did not affect the OR: adjusted OR 1.9 (95% CI: 1.1–3.4). Former use of α-blockers was not associated with an increased risk of hip/femur fracture: adjusted OR 1.3 (95% CI: 0.9–2.0). The start of a new treatment episode (first prescription within an episode) was associated with a significantly increased risk of hip/femur fracture: adjusted OR 5.6 (95% CI: 1.0–31.7). There was no difference with respect to whether the exposure was the initial treatment episode or a later episode: adjusted OR 1.8 (95% CI: 0.9–3.6) and 2.2 (95% CI: 0.9–5.5), respectively. Evaluation of the effect of the duration of the treatment episode prior to the index date showed that the point estimate of the adjusted OR was the highest, but not significantly increased in the first 30 days of treatment: adjusted OR 4.1 (95% CI: 0.7–23.9). Use of finasteride was not associated with an increased risk of hip/femur fractures.

We stratified according to the diagnosis of BPH in order to assess whether the observed association was consistent for patients having BPH and patients not having BPH (Table 3). Amongst patients who did not have a diagnosis of BPH and used α-blockers for

Table 1 Characteristics of cases and matched control patients in relation to risk of hip/femur fracture in univariate analyses

Characteristic	Cases ($n = 4571$) (%)	Controls ($n = 4571$) (%)	Crude OR (95% CI)
Age (years)			
40–49	253 (5.5)	260 (5.7)	NA
50–59	350 (7.7)	360 (7.9)	NA
60–69	628 (13.7)	675 (14.8)	NA
70–79	1410 (30.8)	1493 (32.7)	NA
80–89	1569 (34.3)	1522 (33.3)	NA
≥90	361 (7.9)	261 (5.7)	NA
Body mass index			
20–24	993 (21.7)	968 (21.2)	1.0 (reference)
<20	252 (5.5)	126 (2.8)	2.0 (1.6–2.5)
25–29	655 (14.3)	960 (21.0)	0.7 (0.6–0.8)
≥30	192 (4.2)	275 (6.0)	0.7 (0.6–0.8)
Unknown	2479 (54.2)	2242 (49.0)	1.2 (1.0–1.3)
Smoking status			
Yes	1001 (21.9)	905 (19.8)	1.2 (1.1–1.4)
Unknown	1899 (41.5)	1841 (40.3)	1.1 (1.0–1.3)
Prescription drug use in 6-month period before the index date			
Antipsychotics	326 (7.1)	117 (2.6)	3.0 (2.4–3.8)
Antidepressants	460 (10.1)	171 (3.7)	2.9 (2.4–3.5)
NSAIDs	875 (19.1)	585 (12.8)	1.6 (1.4–1.8)
Antiepileptics	254 (5.6)	68 (1.5)	4.0 (3.0–5.2)
Antiparkinsonian drugs	309 (6.8)	79 (1.7)	4.2 (3.2–5.4)
Hypnotics/anxiolytics	744 (16.3)	385 (8.4)	2.2 (1.9–2.5)
Cardiovascular drugs	1718 (37.6)	1312 (28.7)	1.5 (1.4–1.7)
Diagnosis of medical conditions in the year before the index date			
Heart failure	678 (14.8)	418 (9.1)	1.8 (1.6–2.1)
Anaemia	202 (4.4)	75 (1.6)	2.9 (2.2–3.9)
Rheumatoid arthritis	106 (2.3)	48 (1.1)	2.2 (1.6–3.1)
Cerebrovascular disease	797 (17.4)	430 (9.4)	2.1 (1.8–2.4)
Osteoporosis	114 (2.5)	41 (0.9)	2.8 (2.0–4.0)
Psychotic disorder	327 (7.2)	118 (2.6)	3.0 (2.4–3.8)
Depression	237 (5.2)	77 (1.7)	3.3 (2.5–4.3)
Falls	662 (14.5)	85 (1.9)	9.7 (7.6–12.6)
Diagnosis of lower urinary tract disease in year before the index date			
LUTS	262 (5.7)	142 (3.1)	1.9 (1.6–2.4)
BPH	348 (7.6)	248 (5.4)	1.5 (1.2–1.7)
Prostate cancer	204 (4.5)	88 (1.9)	2.4 (1.9–3.1)

OR, odds ratio; CI, confidence interval; NA, not applicable; NSAID, non-steroidal anti-inflammatory drug; LUTS, lower urinary tract symptoms; BPH, benign prostatic hyperplasia.

the treatment of cardiovascular disease, the adjusted OR for current use of α-blockers was 2.8 (95% CI: 1.4–5.4), compared with 1.0 (95% CI: 0.4–2.5) for patients with a diagnosis of BPH. Furthermore, stratification on potential confounders showed that the exposure prevalence of α-blocker use was lower amongst cases compared with controls for patients having diagnoses of anaemia, RA, cerebrovascular disease, depression, history of falls, as well as patients using nitrates, antiepileptics and thiazide diuretics (data not shown). In all the mentioned patient groups, ORs for current use of α-blockers versus non-use were below unity. These findings suggest selective prescribing of α-blockers and confounding by contra-indication: patients with underlying diseases and/or use of prescription drugs that are associated with a high risk of falling were not prescribed α-blockers. A summary variable to indicate whether the patients were 'fall-prone' was created to increase statistical power (Table 3). In the stratum of patients who did not have a diagnosis of BPH and did not have a condition that was associated with selective prescribing of α-blockers, the adjusted OR was 3.8 (95% CI: 1.6–9.0). Amongst patients who were fall-prone, but did not have diagnosis of BPH, the adjusted OR was 1.7 (95% CI: 0.8–3.8). In the stratum of patients

Table 2 Association between use of α-blockers and risk of all hip/femur fractures

Exposure characteristic	Cases ($n = 4571$) (%)	Controls ($n = 4571$) (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Any use before the index date				
α-blockers	158 (3.5)	91 (2.0)	1.8 (1.4–2.3)	1.5 (1.1–2.1)
Finasteride	35 (0.8)	19 (0.4)	1.8 (1.1–3.2)	1.2 (0.6–2.4)
Current use on the index date				
α-blockers	53 (1.2)	28 (0.6)	1.9 (1.2–3.0)	1.9 (1.1–3.4)
First treatment episode	35 (0.8)	17 (0.4)	2.1 (1.2–3.7)	1.8 (0.9–3.6)
Later treatment episode	18 (0.4)	11 (0.2)	1.6 (0.8–3.5)	2.2 (0.9–5.5)
First prescription within episode	11 (0.2)	2 (0.0)	5.5 (1.2–24.8)	5.6 (1.0–31.7)
Later prescription within episode	42 (0.9)	26 (0.6)	1.6 (1.0–2.7)	1.6 (0.9–3.0)
Duration of current use <30 days	9 (0.2)	2 (0.0)	4.5 (1.0–20.8)	4.1 (0.7–23.9)
Duration of current use <60 days	13 (0.3)	3 (0.1)	4.3 (1.2–15.2)	3.4 (0.8–13.7)
Duration of current use <90 days	16 (0.4)	6 (0.1)	2.7 (1.0–6.8)	2.4 (0.8–7.1)
Non-selective α-blocker	47 (1.0)	26 (0.6)	1.8 (1.1–2.9)	1.9 (1.1–3.3)
Selective α-blocker	6 (0.2)	2 (0.0)	3.0 (0.6–14.9)	2.6 (0.3–20.0)
Finasteride	20 (0.4)	10 (0.2)	2.0 (0.9–4.3)	1.4 (0.6–3.6)
Former use				
α-blockers	105 (2.3)	63 (1.4)	1.7 (1.3–2.4)	1.3 (0.9–2.0)
Finasteride	15 (0.3)	9 (0.2)	1.8 (0.8–4.0)	1.1 (0.4–3.1)

OR, odds ratio; CI, confidence interval.
[a]Adjusted for use of non-steroidal anti-inflammatory drugs, hyponotics/anxiolytics, antipsychotics, antiparkinsonian drugs, glucocorticoids, bronchodilators, heart failure, diabetes mellitus, osteoporosis, prostate cancer and benign prostatic hyperplasia/lower urinary tract symptoms.

Table 3 Stratum specific OR (95% CI) for current use of α-blockers and risk of hip/femur fracture: stratification on diagnosis of BPH and medical conditions/drug use associated with an increased risk of falling (fall-prone)

Exposure characteristic	Cases ($n = 4571$) (%)	Controls ($n = 4571$) (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
No diagnosis of BPH				
Current use of α-blockers	36 (0.8)	17 (0.4)	2.2 (1.2–3.9)	2.8 (1.4–5.4)
Not fall-prone	17 (0.7)	6 (0.2)	3.5 (1.5–7.9)	3.8 (1.6–9.0)
Fall-prone	19 (1.0)	11 (1.0)	1.2 (0.6–2.4)	1.7 (0.8–3.8)
Diagnosis of BPH				
Current use of α-blockers	17 (5.5)	11 (5.0)	1.1 (0.5–2.3)	1.0 (0.4–2.5)
Not fall-prone	7 (4.8)	5 (3.8)	1.9 (0.7–5.1)	1.8 (0.6–5.2)
Fall-prone	10 (6.1)	6 (6.6)	0.7 (0.3–1.6)	0.9 (0.3–2.3)

OR, odds ratio; CI, confidence interval.
[a]Adjusted for use of non-steroidal anti-inflammatory drugs, hyponotics/anxiolytics, antipsychotics, antiparkinsonian drugs, glucocorticoids, bronchodilators, heart failure, diabetes mellitus, osteoporosis, prostate cancer and other lower urinary tract symptoms.

with BPH, the point estimate of the adjusted OR for current use of α-blockers amongst patients who were not fall-prone was nonsignificantly increased (OR 1.8, 95% CI: 0.6–5.2), whilst for patients with a diagnosis of BPH who were considered fall-prone, the adjusted OR was below unity: adjusted OR 0.9 (95% CI: 0.3–2.3).

Discussion

In this study, we found an increased risk of hip/femur fracture amongst men, aged 50 years and older, who were newly starting a treatment episode with α-blockers. The effect was particularly strong for first prescription within a treatment episode and during the first month of treatment.

α-blockers were originally developed as antihypertensive drugs, but are increasingly used in the treatment of BPH. The haemodynamical activity of such drugs might pose problems as elderly patients, usually the target population, are more vulnerable to vasodilatory side-effects associated with α-blockers, because of an age-dependent reduction of cardiac output, baroreceptor sensitivity,

plasma renin level and renal function [1]. To our knowledge, two other studies investigated the association between the use of α-blockers and fractures. Chrischilles *et al.* found in a retrospective cohort study in the US that use of α-blockers in a 4-month window around the index date was associated with an increased risk of clinical events, including fractures [9]. Farmer *et al.* conducted a nested case–control study in the GPRD within a cohort of men with BPH/LUTS and found no association between fractures and use of α-blockers [10]. This finding seems in line with our findings, as there seemed to be no increased risk associated with α-blocker use in the stratum of patients with BPH in our study.

We found that BPH and LUTS were independent risk factors for hip/femur fracture. Stratification on a diagnosis of BPH was performed to assess whether the observed effect of α-blockers in the overall analysis was consistent for patients using α-blockers for BPH and patients using them for hypertension. Within the stratum of patients who had a diagnosis of BPH, there was no significant association between α-blocker use and hip/femur fractures, suggesting that the underlying medical condition, in particular irritative symptoms (frequency, nocturia) are important risk factors associated with hip/femur fracture. Use of other antihypertensive agents, like β-blockers, diuretics, calcium channel blockers and acetylcholine esterase (ACE)-inhibitors was not associated with an increased risk of hip/femur fractures, supporting a direct effect of α-blockers and not an intrinsic effect of high blood pressure.

However, we also found that the prevalence of α-blocker use was lower amongst patients who had medical conditions that were associated with an increased risk of falling. The data suggested that confounding by contra-indication might have been an issue in prescribing α-blockers. ORs for current use of α-blockers were <1.0 amongst patients who had medical conditions that made them prone to falling. It seems likely that patients with such conditions were preferentially not prescribed α-blockers. Alternatively, patients with a history of falls in the year before the index date might have experienced side-effects of α-blocker use earlier. Amongst patients with a history of falls, we found that the prevalence of exposure to α-blockers amongst former users was higher amongst patients with a history of falls. Stratification on whether patients with BPH were fall-prone showed that the OR for patients who were not fall-prone was non-significantly increased: OR 1.8 (95% CI: 0.6–5.2) and that patients who were fall-prone had an OR of 0.9 (95% CI: 0.3–2.3).

The risk estimates were high for new starters of a treatment episode and in the first month of a treatment episode. Because of the small number of patients, the results for the duration of α-blocker use did not reach statistical significance, although the point estimates of the OR indicated an association with duration of use. This finding indicated adaptation of the patient to the hypotensive effect of α-blockers. The exposure prevalence to α-blockers was low. Therefore, it was not possible to conduct stratified analyses regarding timing of use and duration of use. The results of the overall analysis show that there was a consistent association between current use of α-blockers and risk of hip/femur fracture. We explored the sensitivity of our definition of fall-prone patients by expanding the definition to all comorbidities that are associated with an increased risk of falling. However, the results were not substantially different.

Hip/femur fractures occur through an acute trigger, usually a fall. It has been estimated that 90% of hip/femur fractures are associated with falls [11]. Risk factors for fractures can be classified in two categories: those that pertain to falling and those regarding the propensity to fracture after a fall. Risk factors involved in falling are physical impairments (vision, muscular weakness and problems with vestibular functioning), cognitive impairment and use of medication [12–14]. In our analyses, we adjusted for a range of medical conditions and medications that are associated with falling or have an effect on bone mass density. Therefore, history of falls and osteoporosis might be considered as intermediate variables in the causal path, rather than actual confounders. Running the analyses without these variables did not yield large differences in the results.

The cases in our study were identified through ICD-9 codes 820 and 821. The GPRD holds limited information on the exact fracture location. Consequently, a concern might be that fractures caused by high-impact accidents were included, rather than low-energy impact fractures caused by falls. However, Van Staa *et al.* found after reviewing medical records that over 90% of the fractures recorded as femur fractures were actually proximal femur fractures,

which are more associated with low-energy trauma [15]. Therefore, inclusion of high-impact trauma patients amongst our cases seems to be of low concern.

Drug treatment in observational studies is not randomized and is vulnerable for bias and confounding. In the analysis, we controlled for a range of medical conditions and prescription drugs that are associated with an increased risk of hip/femur fracture. However, we cannot rule out the possibility that residual confounding occurred or that an alternative causes for our findings exists. The data were obtained from the patients' GP records. It is unknown to what extent history of falls was recorded by the GP. It is possible that prior history of falling was recorded more frequently in the group of patients with hip/femur fractures when compared with control patients. This bias would have overestimated the association between falls and fractures. However, as indicated above, this would not have influenced the results in the overall analyses. For the stratified analysis, the proportion of patients that was considered fall-prone would have been underestimated in the control group.

Patients using α-blockers without a diagnosis of BPH or another urological condition were classified as users of α-blockers for cardiovascular indications. Misclassification with respect to the recording of diagnosis of urological disease can not be excluded, but it seems unlikely that misclassification was differential between cases and controls. In this study, the exposure prevalence of alfuzosin and tamsulosin, α-blockers specifically indicated for the treatment of BPH, was low. As hypertension and BPH are more likely to be the concomitant conditions amongst ageing males, it could be that non-selective α-blockers were prescribed to treat both conditions at the same time.

In conclusion, we found a statistically significant increased risk of hip/femur fractures in men aged 40 years and older, especially amongst those who were starting a new α-blocker treatment episode. The effect seemed to be confined to patients who used α-blockers for cardiovascular disease. Caution with respect to initiating α-blocker therapy is warranted.

Conflict of interest statement

No conflict of interest was declared.

References

1 Man in't Veld AJ. Symptomatic BPH and hypertension: does comorbidity affect quality of life? *Eur Urol* 1998; **34** (Suppl. 2): 29–36.
2 Clifford GM, Farmer RD. Medical therapy for benign prostatic hyperplasia: a review of the literature. *Eur Urol* 2000; **38**: 2–19.
3 Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2002; **359**: 1761–7.
4 Cummings SR, Nevitt MC. Falls. *N Engl J Med* 1994; **331**: 872–3.
5 Walley T, Mantgani A. The UK General Practice Research Database. *Lancet* 1997; **350**: 1097–9.
6 Van Staa TP, Abenhaim L. The quality of information recorded on a UK database of primary care records: a study of hospitalization due to hypoglycemia and other conditions. *Pharmacoepidemiol Drug Saf* 1994; **3**: 32–4.
7 Van Staa TP, Abenhaim L, Cooper C, Zhang B, Leufkens HGM. The use of a large pharmacoepidemiologic database to study exposure to oral corticosteroids and risk of fractures: validation of study population and results. *Pharmacoepidemiol Drug Saf* 2000; **9**: 359–66.
8 Van Staa TP, Wegman S, De Vries F, Leufkens B, Cooper C. Use of statins and risk of fractures. *JAMA* 2001; **285**: 1850–5.
9 Chrischilles E, Rubenstein L, Chao J, Kreder KJ, Gilden D, Shah H. Initiation of nonselective alpha 1-antagonist therapy and occurrence of hypotension-related adverse events among men with benign prostatic hyperplasia: a retrospective cohort study. *Clin Ther* 2001; **23**: 727–43.
10 Farmer RDT, Logie JW, Christie N. A study of the incidence of fractures in men receiving medical therapy for lower urinary tract symptoms (LUTS). *Pharmacoepidemiol Drug Saf* 2002; **11**: S170.
11 Youm T, Koval KJ, Kummer FJ, Zuckerman JD. Do all hip fractures result from a fall? *Am J Orthop* 1999; **28**: 190–4.
12 Herings RM, Stricker BH, De Boer A, Bakker A, Sturmans F. Benzodiazepines and the risk of falling leading to femur fractures. Dosage more important than elimination half-life. *Arch Intern Med* 1995; **155**: 1801–7.
13 Herings RM, Stricker BH, De Boer A, Bakker A, Sturmans F, Stergachis A. Current use of thiazide diuretics and prevention of femur fractures. *J Clin Epidemiol* 1996; **49**: 115–9.
14 Cumming RG, Nevitt MC, Cummings SR. Epidemiology of hip fractures. *Epidemiol Rev* 1997; **19**: 244–57.
15 Van Staa TP, Dennison EM. Leufkens HG, Cooper C. Epidemiology of fractures in England and Wales. *Bone* 2001; **29**: 517–22.

Received 20 March 2003; revision received 2 June 2003; accepted 26 June 2003.

Correspondence: P.C. Souverein, Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, PO Box 80082, 3508 TB Utrecht, The Netherlands (fax: +31 30 253 9166; e-mail: p.c.souverein@pharm.uu.nl).