Effectiveness of antiresorptives for the prevention of nonvertebral low-trauma fractures in a population-based cohort of women

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Abstract

Summary—Observational studies are needed to quantify real-life effectiveness of antiresorptive therapy in the prevention of clinical fractures. Antiresorptive therapies were associated with an overall 32% reduction in low-trauma non-vertebral fracture risk among women 50 and older. Effectiveness may be lower among older women and those without risk factors.

Introduction—Randomized controlled trials have shown that antiresorptive therapies reduce the risk of fracture in selected populations, but further study is needed to quantify their real-life effectiveness. The study objective was to determine the association between antiresorptive use and low-trauma nonvertebral fracture in women 50 and older.

Methods—The design was a retrospective nested case-control study (density-based sampling) within the Canadian Multicentre Osteoporosis Study. There were 5,979 eligible women with 453 cases and 1,304 matched controls.

Results—The current use of antiresorptives was associated with a decreased risk of fracture with OR=0.68, 95% CI: 0.52–0.91; where OR is the adjusted odds ratio and CI is the confidence interval. Subgroup analysis yielded OR= 0.61, 95% CI: 0.42–0.89 for ages 50–74; OR=0.76, 95% CI: 0.50–1.17 for ages 75+; OR=0.58, 95% CI: 0.40–0.83 for those with a major risk factor; and OR=0.92; 95% CI: 0.59–1.42 for those without a major risk factor. Major risk factors were prevalent low-trauma fracture, vertebral deformity (grade 2+), and BMD T-score ≤ -2.5 .

Conclusions—Antiresorptive therapy is associated with a clinically important reduction in low-trauma nonvertebral fracture risk among community-dwelling women aged 50 and older. Antiresorptive therapy may be less effective for women 75 and older and women without major risk factors.

Keywords

Antiresorptive; Bisphosphonates; Fractures; Hormone replacement therapy; Nested case-control study; Osteoporosis

Introduction

Osteoporosis is a common condition and is the underlying cause of many fractures [1]. For the year 2000, there were an estimated 9 million osteoporosis-related fractures worldwide, of which 1.6 million were of the hip. The lifetime risk of osteoporotic fracture after age 50 is 50% for women and 20% for men [2]. Fractures are associated with morbidity, excess mortality, and staggering costs. About 90% of the direct costs related to fragility fractures are due to non-vertebral fractures [3].

In randomized controlled trials (RCTs), several therapies have been documented to exhibit efficacy in primary and secondary prevention of fractures in postmenopausal women [4]. Antiresorptive therapy, the most commonly used therapeutic class, includes hormone replacement therapy (HRT), bisphosphonates, selective estrogen receptor modulators (SERMs), and calcitonin. Estimates of the anti-fracture efficacy of these agents range between 30 and 65% risk reduction for new and recurrent vertebral fractures and up to 49% for nonvertebral fractures, depending on the agent and the population studied [4–7]. Some

observational studies have documented the effectiveness of antiresorptive agents in reducing fractures among a more general population [8, 9]. However, many clinical variables are unavailable in administrative databases and it is usually unknown whether patients are receiving treatment for primary or secondary prevention of fracture. Using a database with a number of clinical parameters, van Staa et al. documented a 20% reduction in the risk of nonvertebral fractures in patients receiving etidronate compared with those who were untreated [10]. No studies have evaluated the effect of more recent antiresorptive agents in the prevention of nonvertebral fractures in the general population.

Therefore, we sought to determine whether use of antiresorptive therapies among community-dwelling women was associated with a decrease in the risk of nonvertebral fractures using a national study with well-defined data on known risk factors for future fracture.

Materials and methods

Study cohort and study population

The Canadian Multicentre Osteoporosis Study (CaMos) is a prospective cohort study following a randomly selected, population-based cohort of 9,423 men and women aged 25 years and older selected from nine regions across Canada. The methodological details of the longitudinal study have been described elsewhere [11]. Briefly, recruitment for the cohort began in February 1996 and ended in September 1997. At the time of recruitment, and at pre-specified intervals, clinical data were obtained via direct measurement and questionnaires.

The study population for this analysis included all women participants who were at least 50 years old during the first 7 years of follow-up, 5,979 women were eligible.

Study design and study groups

The study design was a retrospective nested case-control study [12] within the study population specified above. Cohort entry for this study was the date of the baseline interview or the participant's 50th birthday, whichever occurred last. Cohort exit for this study was death, loss to follow-up, or 7 years' follow-up, whichever occurred first.

Cases were defined as all those with self-reported incident low-trauma nonvertebral fractures occurring between cohort entry and exit, excluding those of the head, hands, or feet. Low-trauma fractures were events associated with no trauma or a fall of standing height or less [13]. The index time for each case was the time of the first fracture after cohort entry.

Controls were members of the cohort, who at the given time had not had an incident low-trauma nonvertebral fracture after cohort entry, and who were matched with regard to time in study, age in years, baseline clinical diagnosis of osteoporosis or BMD T-score less than or equal to -2.5 , baseline prevalent vertebral deformity (at least grade 2), baseline prevalent low-trauma fracture, and availability of baseline BMD [14]. If available, up to three controls were randomly selected per case. We used a nested case-control design rather than a cohort design in order to use matching to control for confounding. The odds ratio provides an

unbiased estimate of the rate ratio, as controls were selected using density-based sampling [12].

Measurement

All participants were given a standardized interviewer-administered questionnaire (CaMos questionnaire ©1995) at baseline. The questionnaire covered demographics, health, nutrition (including dietary and supplemental calcium and vitamin D intakes), lifestyle, and medication, as well as a medical history that included a detailed history of fracture and major risk factors for fracture. A baseline clinical assessment included height, weight, bone mineral density (BMD), and lateral spine X-ray. Follow-up visits were scheduled at year 3 (for those between 40 and 60 years old) and at year 5 (all) and each visit included an interviewer-administered questionnaire and BMD testing. A self-administered questionnaire was mailed to all participants in all other follow-up years on the anniversary of enrollment. Incident fractures were identified by a yearly postal questionnaire or scheduled interview. Further information concerning the fracture was gathered via special questionnaire and included items on date, fracture site, and circumstances leading to fracture. Finally, medical information from physicians, hospitals, and radiology reports were used to confirm fracture.

Exposure was defined by current use of antiresorptive medication and was updated yearly based on response from postal questionnaire or scheduled interview. For this study, antiresorptive medications included HRT (oral and transdermal preparations containing estrogen) and oral bisphosphonates (etidronate, alendronate, and risedronate). Calcitonin and raloxifene were not included in the exposure as they have not been shown in clinical trials to reduce nonvertebral fracture risk. Participants who used calcitonin or raloxifene were censored at the time of documented initiation of these therapies.

Statistical analysis

Unadjusted and adjusted odds ratios and 95% confidence intervals were computed using conditional logistic regression based on the matched sets of cases and controls. Confounding by indication occurs when exposure occurs because of a higher risk of the outcome, thus resulting in an apparently increased risk among those exposed. A number of potential confounders (known or possible risk factors for fracture) were considered in addition to the variables used in matching; namely BMD of the femoral neck, regional center, level of education, family history of osteoporosis, use of calcium and vitamin D supplementation, use of corticosteroids, prior fall history, Grade 1 vertebral deformities, and co-morbidities (hypertension, diabetes, stroke, heart disease, liver disease, kidney disease, breast cancer, uterine cancer, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, neuromuscular disease, dementia). Adjustment for these potential confounders was made by the following methods. Continuous variables were included directly in the regression model. Inclusion of higher order terms was used to assess possible nonlinearity. The remaining variables were either included directly in the analysis (if they were associated with fracture) or used to create propensity scores, which are estimates of the likelihood of exposure given a certain covariates pattern. Propensity scores may be used to summarize and adjust for confounding when there are too many covariate patterns to make the adjustment directly [15]. Propensity scores for each individual were

created for exposure to the two classes of antiresorptives (HRT and bisphosphonates) using a nonparsimonious logistic regression model. The propensity scores were then included as covariates in the main model.

Studies have shown that the efficacy of anti-osteoporosis medications may vary with age and presence of risk factors [16]. Therefore, we also performed stratified analyses based on two categories for age (50–74 years, 75+years) and baseline risk factors for future fracture (the high risk category was defined by presence of a major risk factor: prevalent low-trauma fracture (any site), vertebral deformity (grade 2+), diagnosis of osteoporosis, femoral neck BMD T-score ≤ -2.5). We also performed analysis according to antiresorptive type (HRT only, bisphosphonates only, HRT and bisphosphonates) and duration (1–2 years, 3–5 years, 6+ years) of antiresorptive exposure.

All analyses were performed using the statistical software Stata 9.2 for Windows.

Ethical considerations and funding

Ethics approval for the study was obtained from the ethics review board at each institution involved in the study. Participants provided written informed consent in accordance with the Helsinki Declaration.

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Results

There were 466 women with incident nonvertebral low-trauma fracture. The most common fracture site was the forearm/wrist (33%), followed by ribs (20%), hip (16%), and shoulder (11%). Controls were randomly selected and matched to cases according to age, time in the study, and risk factors (see Materials and methods). There were 13 cases with no matching control, 19 cases with 1 control, 17 cases with 2 controls, and 417 cases with 3 controls. The mean age of unmatched cases was 84 years (SD=12) and 46% had available baseline BMD, 77% had osteoporosis, 77% had prior low-trauma fracture, 46% had had a vertebral fracture at baseline, and 62% were users of antiresorptive medications at the time of fracture.

The available analysis set included 453 cases with 1,304 matched controls. Baseline characteristics for the cases and controls are shown in Table 1. The mean age of matched cases was 74 years (SD=9); 81% had available baseline BMD, 43% had a diagnosis of osteoporosis, 35% had had a prior low-trauma fracture, and 15% had had a vertebral fracture at baseline. Overall, cases had a lower average BMD, a lower perception of general health and a higher number of co-morbidities compared with the controls. Mean age and prevalence of risk factors (osteoporosis, prior fracture, and vertebral deformity) were similar in cases and controls as a result of matching for these variables.

The type of antiresorptive exposure for cases and controls is shown in Table 2. On the index date, 35% of cases and 39% of controls were users of antiresorptives. Bisphosphonates were used frequently; exclusive bisphosphonate use accounted for 37% of the exposed cases and 45% of the exposed controls. An additional 13% of the exposed cases and 11% of the exposed controls used bisphosphonates and HRT in combination. Exclusive HRT use was also common and accounted for 49% of the exposed cases and 42% of the exposed controls. Propensity scores for use of HRT and use of bisphosphonates predicted exposure well (area under the Receiver Operator Curve 0.73 and 0.79 respectively).

The main analysis compared those who were users of antiresorptive therapies with those who were non-users. In the unadjusted analysis, use of antiresorptive agents was associated with a nonsignificant decreased risk of fracture and the estimated odds ratio was 0.80 (95% CI: 0.63–1.02). Selected variables from the final model are shown in Table 3. The estimated adjusted odds ratio (OR) was 0.68 (95% CI: 0.52–0.91) after controlling for all confounders listed in the Materials and methods section. This estimate corresponds to a 32% reduction in the risk of nonvertebral low-trauma fracture and an associated confidence interval ranging from 9 to 48%. The largest change in point estimate was noted for adjustment for baseline BMD, indicating that this variable was associated with both exposure and outcome. Adjustment for propensity scores alone also changed the point estimate, but the adjustment was minor when BMD was also included in the model.

The results for the stratified analysis are summarized in Fig. 1. There was a stronger association among women with at least one major risk factor for fracture, with estimated OR=0.58 (95% CI: 0.40–0.83). In contrast, among those without these risk factors, there was an estimated OR of 0.92 (95% CI: 0.59–1.42), indicating some uncertainty in the direction of effect.

Based on stratifying the population by age, we noted a stronger association of exposure with reduction of non-vertebral fracture among the women who were between 50 and 74 years old with an estimated OR of 0.61 (95% CI: 0.42–0.89). There was a weaker association among the women aged 75 and older, with an estimated OR of 0.76 (95% CI: 0.50–1.17). It should be noted that assessment of heterogeneity with the usual cut-off ($p=0.05$) would not be definitive in either case. In comparison with younger women, women aged 75 years and older had a higher proportion of falls in the month prior to baseline (8 vs 6%), of baseline diagnosis of osteoporosis (47 vs 36%), and of prevalent fractures (40 vs 30%). Older women also had a lower vitamin D intake (median daily intake 135 IU, interquartile range [IQR] 50–350 vs 150 IU, IQR 50–435), and lower calcium intake (median daily intake 980 mg, IQR 600–1,400 vs 1,020 mg, IQR 630–1,460).

The results for type and duration of antiresorptive therapy are summarized in Fig. 2. The estimate and confidence interval for exclusive HRT use (OR 0.65; 95% CI: 0.45–0.95) was similar to the estimate and confidence interval for exclusive bisphosphonate use (OR 0.71; 95% CI: 0.49–1.03). The confidence interval for combination HRT and bisphosphonate use was too wide for any definitive comparison, but was consistent with the overall results. The estimated effect did vary slightly according to duration of exposure, with the strongest association occurring for exposure of 3–5 years' duration (OR 0.59; 95% CI: 0.38–0.90).

Discussion

We were able to demonstrate that use of antiresorptive osteoporosis therapies was associated with a 32% reduction in the risk of nonvertebral low-trauma fractures in a cohort of randomly selected community-dwelling women. This is the first time that the beneficial effects of antiresorptive therapy for the prevention of nonvertebral fractures have been confirmed in a large, population-based cohort of postmenopausal women. Our results agree with those of published clinical trials, where treatment with antiresorptive agents reduced the risk of incident fractures. Indeed, antiresorptive agents have been shown to reduce the risk of clinical fractures by as much as 45% in individuals with prevalent fractures and in individuals with osteoporosis, as documented by BMD measurement [4]. The larger benefits noted in some clinical trials are consistent with our stratified analysis based on risk and may be attributable to the higher risk profiles of those study populations. Universal calcium and vitamin D supplementation and high adherence to medication in clinical trials could also be contributing factors. In the subgroup of women without risk factors, the results of our analysis were inconclusive. Again, this is consistent with data from previous trials; the anti-fracture efficacy of bisphosphonates in postmenopausal women without risk factors for fractures, such as low BMD or prevalent fractures, has not been clearly demonstrated [17].

Although not definitive, the anti-fracture effectiveness was stronger in women 50–74 years old than in the older group of women (75+ years). The lack of efficacy of antiresorptive therapy in older women has been reported in post-hoc analyses of risedronate trials where, in participants over the age of 80 years, the study medication was not as effective in reducing nonvertebral fractures as it was in those who were younger within the trials [16]. Although we have adjusted for many risk factors associated with age such as fall history, vitamin D and calcium supplementation, baseline BMD, and co-morbidities, our results seem to support a difference of effect between women 50–74 years of age and their older counterparts.

Vitamin D insufficiency is prevalent in the North American adult population and its prevalence increases with age [18]. Indeed, in an earlier study of a subset of the CaMos cohort, in the calendar year 1999, one-third of the study population was found to have inadequate serum levels of vitamin D at least once during the year [19]. Although we did not assess serum vitamin D levels in this study, it is possible that older participants had a more pronounced state of vitamin D insufficiency, potentially resulting in a lower effectiveness of antiresorptive therapy [20]. Further studies directly assessing circulating concentrations of 25-hydroxyvitamin D may assist in resolving this issue.

In our analysis, bisphosphonates and HRT had a similar impact on fracture reduction. Although the study was not designed and is not powered to assess differences between different types of antiresorptive agents, it is reassuring to note that there are no apparent differences in risk reduction between HRT and bisphosphonates. This observation is further supported by an independent meta-analysis [4]. It was unclear whether a combination of antiresorptives provided any advantage over a single antiresorptive.

Most clinical guidelines recommend supplementation if daily calcium intake is below 1,000 mg and daily vitamin D below 400 IU. Similarly, it is recommended that women at high risk of fractures, such as those with advanced age, low BMD, and prevalent fractures, be considered for pharmacological therapy [21]. Despite inappropriate dietary intake, the proportion of women taking calcium and vitamin D supplementation in our study is well below 50%. Close to 60% of women with low-trauma nonvertebral fractures had at least one major risk factor, and yet only one-third of them were on antiresorptive therapy at the time of the fracture. “A care gap refers to a discrepancy between processes of care that have been defined as best practice on the basis of high-quality evidence and the care provided in usual clinical practice” [22]. The presence of a care gap has been documented extensively in the osteoporosis field [23, 24]. Our results confirm, once again, the presence of an osteoporosis care gap in Canadian postmenopausal women.

Although randomized trials are the ideal study design to measure treatment effect, the applicability is often limited due to inclusion criteria and a design aimed at minimizing sample size (and hence cost). Results of observational studies, such as the one we have conducted, complement the body of knowledge collected from previous RCTs and quantify the effectiveness of antiresorptive treatment in real-world practice [25]. It has been reported that careful and rigorous approaches to observational data analyses produce valid inferences [26].

An important strength of our study is the ability to study randomly selected women with data available on the most important clinical variables such as calcium and vitamin D intake, BMD, previous fractures, and previous falls; these variables are unavailable in administrative database studies. We used several methods to control for confounding, and matching was used to control for confounding by the most important risk factors including age and BMD. We were also able to adjust for other important risk factors, either directly or by using propensity scores.

We conducted subgroup analyses to confirm the robustness of the results of the main analysis and showed a positive duration response whereby the estimated fracture reduction was the lowest in women treated for less than 3 years. Further research is necessary to determine whether there is in fact a decline in fracture reduction with exposure duration longer than 5 years, or whether the results observed are due to the adjustment for baseline BMD, which might be an intermediate variable for exposure of longer duration. Black et al. recently noted similar non-vertebral fracture reduction in women continuing alendronate and those stopping therapy after 5 years of treatment [27]. Conversely, others noted that discontinuing HRT had a different impact on BMD than did discontinuing alendronate or combination therapy [28].

Limitations of our study include the inability to confirm the exact level of adherence to antiresorptive therapy and the clinical indication for the initial prescription of medications by their physicians. Furthermore, the associations attributed to a class of agents cannot be attributed to individual members of that class, and should be interpreted within the context of other evidence.

In summary, we have shown that treatment with antiresorptive therapy is associated with a reduced risk of nonvertebral low-trauma fractures in community-dwelling women. We have identified the clinical indications for which antiresorptive agents appear to act optimally, i.e., in women with defined risk factors for osteoporosis (prior low-trauma fracture, prevalent grade 2 vertebral deformity, or prevalent osteoporosis). Optimal therapy for frail elderly patients remains to be defined, as antiresorptive therapy does not address nonskeletal risk factors. Finally, we have shown that risk reduction varies directly with exposure duration, although exposure of more than 5 years' duration may not provide additional benefit. This study therefore provides new evidence supporting and extending results from antiresorptive RCTs to include women seen in clinical practice.

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Fig. 1. Association between antiresorptive use and low-trauma nonvertebral fracture analyzed according to age and risk subgroups

Fig. 2. Association between antiresorptive use and low-trauma nonvertebral fracture analyzed according to type and duration

Table 1

Baseline characteristics of nonvertebral fracture cases and controls

	Cases (N=453)		Controls (N=1,304)	
Age (years)	Mean 74.1	SD 9.3	Mean 74.3	SD 9.1
BMD (T-score) ^a	Mean -1.82	SD 0.85	Mean -1.61	SD 0.96
Short Form-36 general health	Mean 67.3	SD 21.6	Mean 73.1	SD 18.4
With baseline DXA scan	n = 368	81%	n = 1,085	83%
Osteoporosis ^b	n = 193	43%	n = 530	41%
Prior low-trauma fracture ^c	n = 159	35%	n = 446	34%
Vertebral deformity ^d	n = 66	15%	n = 183	14%
Family osteoporosis history ^e	n = 74	16%	n = 188	14%
Prior falls ^f	n = 42	10%	n = 87	7%
Corticosteroid use ^g	n = 75	17%	n = 210	16%
Calcium supplement use (any)	n = 219	48%	n = 611	47%
Vitamin D supplement use (any)	n = 159	35%	n = 451	35%
Co-morbidities ^h				
Hypertension	n = 177	39%	n = 484	37%
Osteoarthritis	n = 164	36%	n = 493	38%
Chronic obstructive pulmonary disease	n = 51	11%	n = 118	9%
Rheumatoid arthritis	n = 48	11%	n = 111	9%
Diabetes	n = 44	10%	n = 84	6%
Stroke	n = 32	7%	n = 72	6%
Myocardial infarction	n = 33	7%	n = 85	7%
Dementia ⁱ	n = 20	4%	n = 32	2%
Breast cancer	n = 20	4%	n = 66	5%
Neurological disease	n = 27	6%	n = 53	4%
Uterine cancer	n = 23	5%	n = 35	3%
Liver disease	n = 16	4%	n = 26	2%
Renal disease	n = 10	2%	n = 19	1%

^aBaseline femoral neck bone mineral density T-score^bBaseline physician-diagnosed osteoporosis or BMD T-score -2.5^cBaseline prevalent fracture incurred after age 50 with no trauma or fall from standing height or less^dVertebral deformity (grade 2 or more) present at baseline^eClinical diagnosis of osteoporosis in immediate family (parents, siblings, children)^fReported falls in month prior to baseline^gSelf-reported use of corticosteroid (oral or intravenous)^hBaseline self-reported physician-diagnosed conditions (except dementia)ⁱBaseline Mini-Mental score (MMSE) less than 24

Table 2

Type of antiresorptive therapy among cases and controls

	<u>Cases (158 users)</u>		<u>Controls (507 users)</u>	
	<i>n</i>	%	<i>n</i>	%
Hormone replacement therapy (HRT) only	59	37	228	45
Bisphosphonates only	78	49	211	42
HRT and bisphosphonates	21	13	58	11

Table 3

Adjusted odds ratios for low-trauma nonvertebral fracture

Variable	OR ^a	95% CI
Antiresorptive (current use)	0.68	0.52–0.91
BMD T-score (unit = 0.121 g/cm ²)	0.59	0.49–0.71
Positive fall history	1.93	1.23–3.02
Grade 1 vertebral deformity	1.60	1.12–2.30

^a Adjustment included all listed variables, propensity scores for hormone replacement therapy and bisphosphonate use, uterine cancer, liver disease, and calcium supplementation