Comparative Effectiveness of Oral Bisphosphonates in Reducing Hip Fracture Risk in Older Men and Women

Suzanne M. Cadarette, PhD[1,2]; Linda Lévesque, BScPhm, PhD[2,3]; Muhammad Mamdani, PharmD, MS, MPH[1,2,4,5]; Sylvie Perreault, BScPhm, PhD[6]; David N. Juurlink, BPhm, MD, PhD[7;] J. Michael Paterson, MSc[2,5,9,10]; Greg Carney, BSc[8]; Nadia Gunraj, MPH[2]; Gillian A. Hawker, MD, MSc[2,5,11]; Mina Tadrous, PharmD, MS[1]; Lindsay Wong[1]; Colin R. Dormuth, ScD[8]

1. Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto ON
2. Institute for Clinical Evaluative Sciences, Toronto ON
3. Department of Community Health and Epidemiology, Queen's University, Kingston ON
4. Applied Health Research Centre, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto ON
5. Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto ON
6. Faculty of Pharmacy, University of Montreal, Montreal QC
7. Sunnybrook Research Institute, Toronto ON
8. Therapeutics Initiative, University of British Columbia, Victoria BC
9. Department of Family Medicine, McMaster University, Hamilton ON
10. Centre for Evaluation of Medicines, St. Joseph's Healthcare, Hamilton ON
11. Women's College Research Institute, Women's College Hospital, Toronto ON

Correspondence to: Suzanne M. Cadarette, Leslie Dan Faculty of Pharmacy, University of Toronto, 144 College Street, Toronto, Ontario, M5S 3M2 Canada. Tel: 416-978-2993, Fax: 416-978-8511, E-mail: s.cadarette@utoronto.ca

Running Title: Comparative effectiveness of oral bisphosphonates

Manuscript word count: 1795

Number of Figures: 2, Number of Tables: 1

Appendices: 1 Figure

Number of References: 22

Keywords (MeSH): Bisphosphonates, Drug Policy, Fractures, Osteoporosis,

Pharmacoepidemiology

Abstract

Background: Oral bisphosphonates (alendronate, etidronate, risedronate) are effective in reducing vertebral fracture risk, however, only alendronate and risedronate have proven efficacy in reducing hip fracture risk. Little head-to-head comparative data exist, particularly among men.

Methods: We examined the comparative effectiveness of oral bisphosphonates in reducing hip fracture risk among new users in British Columbia (BC) and Ontario between 2001 and 2008 (N=321,755). We used province and sex-specific propensity score matching strategies to maximize comparability between exposure groups. Cox-proportional hazards models were used to compare time-to-hip fracture within one year of treatment between exposures by sex in each province. Secondary analysis considered hip fracture rates to 2-years and 3-years. Alendronate was the reference for all comparisons. Provincial estimates were pooled using random effects, variance weighted meta-analysis.

Results: We identified little difference in fracture rates between risedronate and alendronate among men (HR_{pooled}=0.94; 95%CI=0.74-1.14) or women (HR_{pooled}=1.15; 95%CI=0.73-1.56). We similarly identified little difference in fracture rates between etidronate and alendronate among women (HR_{pooled}=1.00; 95%CI=0.82-1.18). However, we identified lower hip fracture rates among men treated with etidronate relative to alendronate (HR_{pooled}=0.77; 95%CI=0.60-0.94). Results extended to 2- and 3-years of follow-up were similar. However, with 3-years of follow-up, hip fracture rates were lower among BC women treated with alendronate.

Interpretations: We identified little overall difference between alendronate and risedronate in reducing hip fracture risk in men or women. Our finding that etidronate is associated with lower fracture risk among men likely results from selection bias. The long-term comparative effects of oral bisphosphonates warrants further study.

INTRODUCTION

Osteoporosis is characterized by low bone mineral density and reduced bone quality, and results in substantial fracture-related morbidity and premature death.[1-4] Hip fractures are the most devastating consequence of osteoporosis, with an estimated annual $282 million in direct attributable healthcare costs in Ontario, and $1.1 billion in Canada.[4] In addition, approximately 19% of men and 24% of women living in the community at the time of hip fracture enter a long term care facility, and 22% of women and 33% of men die within the first year following hip fracture.[4] Oral bisphosphonates (alendronate, etidronate, risedronate) are the most commonly prescribed drugs for osteoporosis in Canada.[5] Each drug is effective in reducing vertebral fracture risk, however, only selected bisphosphonates (alendronate, risedronate), have demonstrated significant reductions in hip fracture risk compared to placebo.[6,7] Consequently, Canadian osteoporosis practice guidelines recommend alendronate and risedronate as first line therapy, and etidronate in a list of second-line options.[8] In contrast to practice guidelines, many publicly funded drug plans across Canada limit coverage for first-line therapies, yet provide unrestricted coverage for etidronate—a second-line therapy.[9] For example, the province of British Columbia (BC) only covers etidronate without restriction, and the public drug plan in Ontario had restrictive coverage for alendronate and risedronate until 2007.[5]

The discrepancy in listing status is related to the price differential between these agents, with etidronate being the least expensive. For example, the annual drug cost (before dispensing fees) for generic medications paid through the Ontario Drug Benefit Program is approximately $80 for cyclical etidronate, and $130 for weekly generic alendronate or risedronate.[10] The difference in costs between agents may be justifiable if one agent is more effective at reducing fracture risk. Indeed, the mean attributable cost in the first year after hip fracture is estimated to

be $36,929 (95%CI: $36,380-37,466) among women and $39,479 (95%CI: $38,311-$40,677) among men,[4] and thus a $50 annual difference in preventive pharmacotherapy costs could be cost-effective. However, little "head-to-head" data are available to support the superiority of any of the oral bisphosphonates in reducing hip fracture risk, particularly among men. We used data from BC and Ontario to compare the effectiveness of etidronate and risedronate to alendronate in reducing hip fracture risk separately among men and women.

METHODS

We completed a population-based cohort study using healthcare utilization data from BC and Ontario to examine the comparative effectiveness of oral bisphosphonates in reducing hip fracture risk. BC data included all drugs dispensed in community pharmacies. Ontario data included drugs covered through the public Ontario Drug Benefit Program that restricted alendronate and risedronate coverage to those at higher fracture risk between 2001 and 2007.[5] Since 2007, all three oral bisphosphonates have been open listed in Ontario. We previously identified the first date (index date) of any osteoporosis medication prescription among residents aged 66 or more years in BC and Ontario from 1995 to 2009.[5] In the current study, we restricted inclusion to new users of an oral bisphosphonate from April 1, 2001 to March 31, 2008. We therefore restricted inclusion to oral bisphosphonates as first line therapy with no evidence of prior osteoporosis treatment. We selected April 2001 as the earliest exposure period to restrict analyses to when all three oral bisphosphonates were available. We also excluded patients with conditions that may impact bone integrity or bisphosphonate effectiveness: celiac disease, Cushing's syndrome, hypercalcemia, hyperparathyroidism, malignant neoplasm, osteomalacia, osteopetrosis, Paget's disease, organ transplant, and renal impairment or dialysis. Finally,

patients receiving clodronate or pamidronate, men receiving estrogen therapy, and patients receiving alendronate or risedronate through the restrictive PharmaCare program in BC were excluded.

Pharmacy data were linked within each province to medical care data (outpatient, inpatient, emergency department services) to identify baseline covariates and outcomes of interest. Our primary outcome was hip fracture within 1-year (365 days) after treatment initiation. Secondary outcomes were hip fracture within 2- and 3-years after treatment initiation.

Statistical Analysis

Within each province, we summarized covariate information into a single score by developing sex-specific propensity scores for etidronate and risedronate with alendronate as the referent drug.[11] We did this by first defining two sex-specific contrast cohorts within each province: 1) etidronate and alendronate users, and 2) risedronate and alendronate users. Second, we used logistic regression to create province-specific propensity scores within the contrast cohorts separately for men and women. The main benefit of using the separate logistic regression model approach with two contrast cohorts, versus a single multinomial logistic regression approach, is that it is then simpler to restrict analyses to propensity score overlap.[11] Covariates included in the propensity scores are listed in Table 1, and in brief included factors that may impact fracture risk: age at index date, health services use in the past year, fracture history, osteoporosis management (bone mineral density test, osteoporosis diagnosis), and comorbidities. We also included quintiles of: number of outpatient visits and number of medications; and calendar time (month and year) of index prescription to adjust for potential secular trends in prescribing.

We used province and sex-specific propensity score matching, restricted to propensity score overlap, to maximize comparability between exposure groups. Cox-proportional hazards models were then used to compare hip fracture rates within one year of treatment initiation between exposures for each province separately for men and women. Alendronate was the reference in all analyses. In our primary analysis, we considered a patient exposed to drug throughout the length of follow-up by censoring only at date of death, switch between agents, or end of follow-up (one year after treatment initiation). We used this analytic strategy for two reasons: 1) bisphosphonates persist in bone and thus the benefit-window of opportunity extends beyond time on therapy,[12,13] and 2) given that etidronate is dispensed as a 90-day supply (includes 14 days of active drug plus 76 days of calcium), but alendronate and risedronate are typically dispensed as a 28- or 30-day supply, it may be difficult to determine when to censor follow-up among etidronate users due to drug stoppage. A secondary analysis censored only on death date or administrative end of follow-up. Hazard ratios were pooled between regions using a random-effects model weighted by variance.

RESULTS

We identified 58,406 (11,402 from BC) eligible men and 263,349 (51,863 from BC) eligible women, **Appendix Figure.** Comparison of baseline covariates by sex between new users of each agent in BC identified that alendronate users were at higher fracture risk (e.g., more had a prior fracture) compared to etidronate or risedronate, **Table 1**. Comparing baseline covariates between new users of each agent in Ontario identified that alendronate and risedronate users were similar in terms of background risk for fracture; however, etidronate users had lower baseline fracture risk based on measured variables. All characteristics were well-balanced after matching on

propensity scores. Propensity-score matched results identified little difference in fracture rates between risedronate and alendronate among men (HR_{pooled}=0.94; 95%CI=0.74-1.14) or women (HR_{pooled}=1.15; 95%CI=0.73-1.56), **Figure 1**. We similarly identified little difference in fracture rates between etidronate and alendronate among women (HR_{pooled}=1.00; 95%CI=0.82-1.18). However, we identified lower hip fracture rates among men treated with etidronate relative to alendronate (HR_{pooled}=0.77; 95%CI=0.60-0.94). Results that did not censor on switch date were similar. Results extended to 2- and 3-years of follow-up were also similar (Figures 1 and 2), however, women in BC taking etidronate or risedronate were noted to have higher hip fracture risk compared to alendronate users.

INTERPRETATION

We identified little difference in the effectiveness of alendronate or risedronate in reducing 1-year hip fracture risk among men or women. These results among older Canadians residing within two different provinces corroborate prior findings of comparable fracture rates within 1-year of treatment among women,[14,15] and provide evidence for the first time about the comparable effectiveness of risedronate and alendronate in reducing fracture risk among men. To our knowledge, only a single prior study has directly compared the effectiveness of etidronate to alendronate or risedronate in reducing fracture risk.[16] By studying a cohort of female fracture patients in Ontario who initiated oral bisphosphonates between 1998 and 2002, authors found little difference in hip fracture rates within two years between etidronate and alendronate or risedronate (HR=1.0, 95%CI=0.6-1.6).[16] These results may seem puzzling in light of placebo-controlled trial evidence that identifies hip fracture protection versus placebo with alendronate and risedronate, but not with etidronate. However, clinical trials establish drug efficacy within

defined patient populations, often not representative of those who may benefit from pharmacotherapy, or how the agents are used in practice.[17] Indeed, part of the lack of difference in observed effectiveness of alendronate and risedronate compared to etidronate may relate to poor adherence and thus reduced drug effectiveness.[18-22] However, given the known drug-induced policy restrictions in Ontario that initially limited alendronate therapy to men and women at higher risk for fracture,[5] we postulate that the lack of clinical difference could at least partially result from policy-induced selection bias (confounding by indication). In fact, we identified significantly lower hip fracture rates among men treated with etidronate compared to men treated with alendronate in Ontario. Although we were able to adjust for bone mineral density (BMD) testing and "claims-based" diagnosis of osteoporosis, we could not adjust for BMD. In particular, from 2003-2007, alendronate and risedronate coverage was restricted to patients with two of the following criteria: 1) BMD T<-3.0, 2) aged 75 or more years, and 3) prior osteoporosis-related fracture.[5] Further research that is able to adjust for baseline BMD is important to clarify our findings. Of interest, extending follow-up among women in BC to 3-years identified higher fracture rates among female etidronate versus alendronate users (HR=1.22, 95%CI=1.04-1.43). Although BC data were not subject to drug-policy restrictions, the public plan effectively only covered etidronate and thus there may be some residual differences in unmeasured characteristics between exposure groups in BC. Again, further evidence adjusting for baseline BMD is important to clarify our findings.

Overall, we identified little difference in hip fracture risk between risedronate and alendronate. However, in the secondary analysis that followed BC patients for up to 3 years, female risedronate users had higher hip fracture rates compared to alendronate users (HR=1.50; 95%CI=1.15-1.96). Given that alendronate persists in bone longer than risedronate, this finding

warrants further study. Indeed, a prior paper identified a trend towards higher hip fracture rates among risedronate (HR=1.77; 95%CI=1.15-2.74) compared to alendronate users when followed for up to three years.[15] Given that we only identified a possible difference among women in one province, this finding is hypothesis generating and deserves further attention.

Better evidence regarding the comparative effectiveness of oral bisphosphonates are needed to inform drug policy decision making in Canada. At this time, we identify comparable effectiveness of alendronate and risedronate among women and men. However, due to possible residual confounding, we cannot comment on the relative benefits of etidronate compared to alendronate. Further research that considers the long-term comparative effects of oral bisphosphonates is of interest.

ACKNOWLEDGEMENTS

This research was supported by research grants to Dr Cadarette from the Canadian Institutes of Health Research (CIHR, DSA-10353) and Ontario Ministry of Research and Innovation Early Researcher Award (ER09-06-043). Drs Cadarette (Aging and Osteoporosis, MSH-95364) and Dormuth (Knowledge Translation) hold CIHR New Investigator Awards. Authors acknowledge Milica Nikitovic for project coordination in 2010 and 2011, and Brogan Inc. for providing access to drug identification numbers used to identify eligible drugs. The Institute for Clinical Evaluative Sciences (ICES) is a non-profit research corporation funded by the Ontario Ministry of Health and Long-Term Care. The opinions, results and conclusions are those of the authors and are independent from the funding sources. No endorsement by CIHR, ICES or the Ontario Ministry of Health and Long-Term Care is intended or should be inferred.

REFERENCES

1. Cadarette SM, Burden AM. The burden of osteoporosis in Canada. *Can Pharm J* 2011;144:S3.

2. Papaioannou A, Kennedy CC, Ioannidis G, et al. The impact of incident fractures on health-related quality of life: 5 years of data from the Canadian Multicentre Osteoporosis Study. *Osteoporos Int* 2009;20:703-714.

3. Haentjens P, Magaziner J, Colon-Emeric CS, et al. Meta-analysis: excess mortality after hip fracture among older women and men. *Ann Intern Med* 2010;152:380-390.

4. Nikitovic M, Wodchis WP, Krahn MD, Cadarette SM. Direct health-care costs attributed to hip fractures among seniors: a matched cohort study. *Osteoporos Int* 2012:in press.

5. Cadarette SM, Carney G, Baek D, Gunraj N, Paterson JM, Dormuth CR. Osteoporosis medication prescribing in British Columbia and Ontario: impact of public drug coverage. *Osteoporos Int* 2012;23:1475-1480.

6. MacLean C, Newberry S, Maglione M, et al. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann Intern Med* 2008;148:197-213.

7. Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C. IX: Summary of meta-analyses of therapies for postmenopausal osteoporosis. *Endocr Rev* 2002;23:570-578.

8. Papaioannou A, Morin S, Cheung AM, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. *CMAJ* 2010;182:1864-1873.

9. Osteoporosis Canada. Provincial Drug Coverage Chart. http://www.osteoporosis.ca/index.php/ci_id/9046/la_id.htm; accessed: September 17, 2012.

10. Ontario Ministry of Health and Long-Term Care. Formulary Search: Ontario Drug Benefit Formulary/Comparative Drug Index. https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp; accessed: September 17, 2012.

11. Cadarette SM, Gagne JJ, Solomon DH, Katz JN, Sturmer T. Confounder summary scores when comparing the effects of multiple drug exposures. *Pharmacoepidemiol Drug Saf* 2010;19:2-9.

12. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment. The Fracture Intervention Trial Long-Term Extension (FLEX): a randomized trial. *JAMA* 2006;296:2927-2938.

13. Watts NB, Chines A, Olszynski WP, et al. Fracture risk remains reduced one year after discontinuation of risedronate. *Osteoporos Int* 2008;19:365-372.

14. Cadarette SM, Katz JN, Brookhart MA, Stürmer T, Stedman MR, Solomon DH. Relative effectiveness of osteoporosis drugs for preventing nonvertebral fracture. *Ann Intern Med* 2008;148:637-646.

15. Curtis JR, Westfall AO, Cheng H, Saag KG, Delzell E. RisedronatE and ALendronate Intervention over Three Years (REALITY): minimal differences in fracture risk reduction. *Osteoporos Int* 2009;20:973-978.

16. Mamdani M, Kopp A, Hawker G. Hip fractures in users of first- vs. second-generation bisphosphonates. *Osteoporos Int* 2007;18:1595-1600.

17. Lindsay R. Beyond clinical trials: the importance of large databases in evaluating differences in the effectiveness of bisphosphonate therapy in postmenopausal osteoporosis. *Bone* 2007;40:S32-S35.

18. Kothawala P, Badamgarav E, Ryu S, Miller RM, Halbert RJ. Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis. *Mayo Clinic Proceedings* 2007;82:1493-1501.

19. Cramer JA, Gold DT, Silverman SL, Lewiecki EM. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. *Osteoporos Int* 2007;18:1023-1031.

20. Wilkes MM, Navickis RJ, Chan WW, Lewiecki EM. Bisphosphonates and osteoporotic fractures: a cross-design synthesis of results among compliant/persistent postmenopausal women in clinical practice versus randomized controlled trials. *Osteoporos Int* 2010;21:1943-1951.

21. Imaz I, Zegarra P, Gonzalez-Enriquez J, Rubio B, Alcazar R, Amate JM. Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis. *Osteoporos Int* 2010;21:1943-1951.

22. Siris ES, Selby PL, Saag KG, Borgstrom F, Herings RMC, Silverman SL. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. *Am J Med* 2009;122:S3-S13.

Table 1. Baseline characteristics* of new users of oral bisphosphonates, by province, sex and drug, 04/2001-03/2008

	British Columbia						Ontario					
	Men			Women			Men			Women		
Characteristic	**ALD**	**ETD**	**RSD**	**ALD**	**ETD**	**RSD**	**ALD**	**ETD**	**RSD**	**ALD**	**ETD**	**RSD**
sample size:	**2,816**	**7,514**	**1,072**	**12,262**	**34,350**	**5,251**	**11,173**	**26,608**	**9,223**	**48,010**	**122,852**	**40,624**
Demographics and health services												
Age [mean, SD]	77.6 (6.9)	77.1 (6.7)	77.2 (6.8)	76.5 (7.0)	76.9 (7.0)	76.3 (6.9)	76.9 (6.9)	75.6 (6.5)	77.1 (7.0)	75.7 (7.3)	75.1 (6.8)	76.4 (7.6)
Health services use in the year prior to index												
Hospitalization, %	42.2	34.4	31.7	31.0	26.8	26.2	25.4	19	24.4	18.1	13.1	18.3
Nursing home resident, %	4.9	4.3	1.8	3.5	4.3	1.7	6.6	3.9	7.6	6	4	7.8
Fracture history and osteoporosis-related												
1-year fracture history, %												
Hip	5.5	2.4	2.3	4.6	2.4	2.7	5.5	1.9	5	4.1	1.7	4.2
Humerus / radius / ulna	2.1	1.5	1.6	4.2	3.9	4.0	2.7	1.5	2.8	4	2.9	4.4
Vertebra	5.1	3.4	4.9	2.9	2.3	2.2	3.1	2	3.1	1.6	1	1.8
Other OP-related fracture	6.8	4.2	4.1	5.6	3.4	3.0	9.2	4.3	8.7	7.3	3.5	7.4
>1-5-year fracture history, %												
Hip	2.3	1.7	1.9	1.8	1.9	1.5	1.9	1.4	2	2	1.4	2.2
Humerus / radius / ulna	1.6	1.5	1.6	3.6	3.2	3.3	3	2.2	2.9	5.2	4.2	5.1
Vertebra	1.1	0.8	1.4	0.6	0.6	0.6	1.1	0.7	1.2	0.8	0.6	0.8
Other OP-related fracture	4.3	3.2	3.0	2.7	2.5	2.3	5	3.7	4.9	4.8	3.6	5
Number of prior fractures, %												
0	81.9	88.3	85.5	82.8	86.3	86.3	80.7	88.3	80.7	81	87	80.2
1	5.1	4.4	5.1	3.8	3.9	3.2	9.6	7.1	10.1	10.7	8.5	11.4
≥ 2	13.1	7.3	9.3	13.5	9.8	10.5	9.7	4.6	9.2	8.3	4.5	8.4
DXA test, %	44.1	34.1	53.4	55.5	46.1	62.3	55.8	61.7	59.6	57.6	69.7	61.7
Osteoporosis diagnosis, %	25.6	19.6	29.3	33.1	25.1	37.3	36.2	35.4	38.5	37.3	38.9	39.7
Comorbidities and drug use												
Comorbidities, %												
Alzheimer's / other dementia	7.8	4.2	3.6	5.5	3.9	2.9	11.1	6.5	11.8	8.4	5.6	9.9
Asthma / COPD / emphysema	11.7	12.2	8.7	6.4	6.2	4.6	13.7	14.9	13.5	6.5	6.2	6.5
Depression	3.6	1.8	1.5	2.9	1.6	1.3	18.3	17.3	18.2	19.9	19.4	20.3
Diabetes	13.1	12.8	10.3	7.4	8.2	7.0	12.5	12.7	13.6	8.9	9.5	9
Falls / syncope / neurological / gait abnormalities / hypotension	10.0	5.1	4.9	9.4	5.8	6.1	9.3	3.1	8.7	7.5	2.6	7.6

Characteristic	British Columbia						Ontario					
	Men			Women			Men			Women		
	ALD	ETD	RSD	ALD	ETD	RSD	ALD	ETD	RSD	ALD	ETD	RSD
sample size:	2,816	7,514	1,072	12,262	34,350	5,251	11,173	26,608	9,223	48,010	122,852	40,624
Hyperthyroidism	0.4	0.3	0.4	0.5	0.6	0.6	0.6	0.6	0.5	0.9	0.9	0.9
Inflammatory arthritis	1.0	0.9	0.7	0.6	0.6	0.2	6.5	7.3	7.1	4.7	4.6	5.1
Inflammatory bowel	0.8	0.8	1.2	0.4	0.6	0.6	0.6	0.7	0.7	0.4	0.5	0.4
Liver disease	0.1	0.1	0.0	0.1	0.1	0.0	0.2	0.1	0.1	0.1	0.1	0.1
Parkinson's disease	4.3	3.0	3.5	1.8	1.5	1.0	4.1	2.8	4.3	1.5	1.3	1.6
Stroke / TIA	3.5	3.4	3.3	2.5	2.3	1.7	6.7	5.5	6.3	4.3	3.7	4.5
Drug use, %												
Angiotensin-II receptor blockers (ARB)	8.2	7.5	8.4	10.1	10.0	12.3	5.5	4.2	5.8	5.7	4.3	6.7
Anticonvulsants	3.4	3.0	2.3	2.0	2.0	1.9	3.4	2.9	3.4	1.9	1.9	2.1
Antiandrogens (men only)	7.0	3.9	6.3	-	-	-	6.2	3.4	5.9	-	-	-
Aromatase inhibitors (women only)	-	-	-	0.0	0.0	0.0	-	-	-	1	0.5	1.1
Benzodiazepienes	26.4	23.7	21.3	28.6	29.0	26.6	19.5	19.8	20.4	23.6	24.6	24.9
Beta-blockers	21.1	20.1	19.9	18.5	19.0	18.5	9.2	9.1	9	8.8	9.8	8.7
Corticosteroids (oral)	0.0	0.0	0.0	0.0	0.0	0.0						
None	75.9	71.9	77.8	89.0	87.2	89.7	84.5	83	84.7	92.7	92.7	92.1
0 mg < total prednisone < 675 mg	12.7	16.4	12.2	7.2	8.2	6.5	4.3	5.1	4.3	3	3.1	3.2
Prednisone Equivalent ≥ 675 mg	11.4	11.8	10.0	3.8	4.6	3.8	11.2	11.9	11	4.3	4.2	4.8
Gastroprotective	29.6	29.5	27.3	23.5	26.6	23.4	33.1	33.4	34.3	28	29.2	31.4
Glitazones	1.5	0.9	0.9	0.8	0.6	1.0	1.1	0.6	1.6	0.8	0.5	0.9
Other antidiabetic medications	10.7	11.8	9.9	6.8	9.3	5.8	12	12.8	12.8	8.6	9.8	9
Hormone therapy (women only)	-	-	-	12.0	11.3	10.2	-	-	-	5.6	9.4	4.9
Nitrates	9.7	11.7	10.0	7.3	8.5	5.8	11.7	12.5	11.9	8.3	9.1	9
Narcotics: opioid agonists	0.1	9.8	11.7	8.9	8.1	0.8	34.6	33	34.6	26.8	26.2	28.6
NSAIDs	0.3	29.2	23.5	23.1	25.6	20.2	30.2	38.3	29.5	26.5	33.1	26.1
SERMs (women only)	-	-	-	0.0	0.0	0.0	-	-	-	1	0.9	1
SSRIs	11.5	8.9	7.6	12.3	12.1	9.8	11	8.3	11.1	12.2	10.7	13
Non-SSRI antidepressants / antimanics / antipsychotics	11.6	11.4	10.4	12.5	13.6	11.3	11.6	9.7	12.5	12	11.7	13.6
Statins	28.4	25.0	29.9	21.5	21.6	23.4	38.7	33.3	40.4	30.6	28.3	31.1
Thiazide diuretics	16.9	14.5	14.5	21.1	20.2	20.6	20.4	17.5	20.9	27.4	26.7	27.9
Thyroid therapy	9.1	7.8	6.5	19.2	18.9	19.0	7.9	7.1	8.2	19	17.4	19.6

*Age at date of treatment initiation and unless otherwise indicated, other covariates were determined based on the year prior to treatment initiation

	Sex	Province	ALD No. Events	RSD No. Events	ALD Event Rate	RSD Event Rate	HR (95% CI)	Weight (%)
1 Year	F	BC	41	61	0.89	0.13	1.48 (1.00, 2.20)	29
		ON	762	773	2.04	2.06	1.01 (0.92, 1.12)	71
		pooled					1.15 (0.73, 1.56)	
	M	BC	9	9	1.00	0.99	0.99 (0.39, 2.49)	4
		ON	171	161	2.13	1.96	0.94 (0.76, 1.16)	96
		pooled					0.94 (0.74, 1.14)	
2 Years	F	BC	76	102	0.95	1.26	1.33 (0.99, 1.79)	25
		ON	1222	1275	1.79	1.87	1.05 (0.97, 1.13)	75
		pooled					1.12 (0.88, 1.36)	
	M	BC	15	14	0.99	0.90	0.91 (0.44, 1.89)	5
		ON	249	227	1.77	1.59	0.91 (0.76, 1.09)	95
		pooled					0.91 (0.74, 1.07)	
3 Years	F	BC	89	135	0.86	1.28	1.50 (1.15, 1.96)	40
		ON	1224	1276	1.34	1.42	1.05 (0.97, 1.13)	60
		pooled					1.23 (0.79, 1.67)	
	M	BC	19	18	1.00	0.92	0.92 (0.48, 1.75)	6
		ON	250	228	1.41	1.27	0.91 (0.76, 1.09)	93
		pooled					0.91 (0.75, 1.07)	

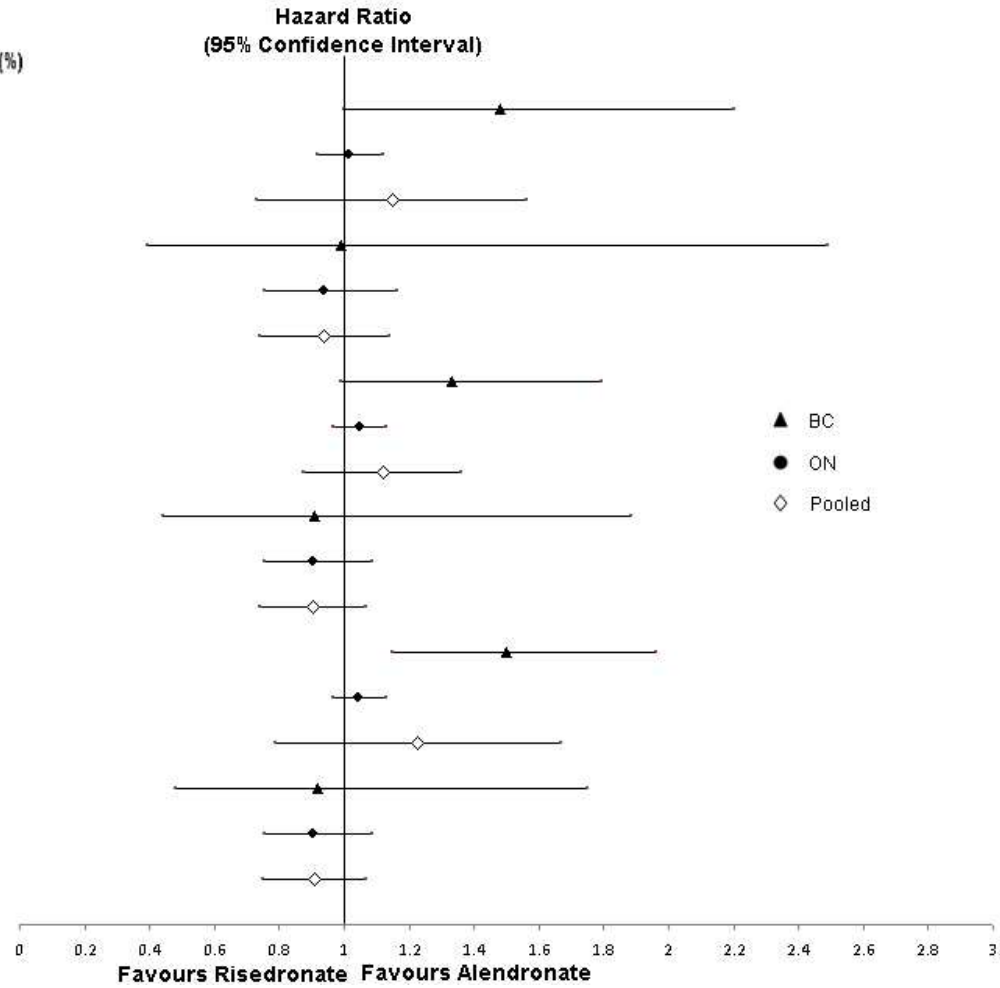


Figure 1. Forest plot comparing the effectiveness of risedronate to alendronate in reducing hip fracture risk, propensity score matched. Results pooled using a random effects variance weighted model. Propensity scores used for matching included all characteristics presented in Table 1, as well as index date and quintiles of: number of outpatient visit and number of generic drugs.

	Sex	Province	ALD No. Events	ETD No. Events	ALD Event Rate	ETD Event Rate	HR (95% CI)	Weight (%)
1 Year	F	BC	116	134	1.05	1.21	1.15 (0.89, 1.47)	28
		ON	742	677	1.92	1.74	0.94 (0.85, 1.04)	72
		pooled					1.00 (0.82, 1.18)	
	M	BC	25	26	1.02	1.06	1.04 (0.60, 1.81)	9
		ON	166	112	2.01	1.42	0.75 (0.59, 0.95)	92
		pooled					0.77 (0.60, 0.94)	
2 Years	F	BC	202	231	1.03	1.17	1.13 (0.94, 1.37)	22
		ON	1224	1204	1.67	1.62	1.00 (0.92, 1.08)	78
		pooled					1.03 (0.92, 1.14)	
	M	BC	48	47	1.13	1.11	0.98 (0.66, 1.47)	13
		ON	254	181	1.68	1.31	0.80 (0.67, 0.97)	87
		pooled					0.83 (0.68, 0.97)	
3 Years	F	BC	258	318	1.00	1.22	1.22 (1.03, 1.43)	41
		ON	1226	1204	1.23	1.17	0.99 (0.92, 1.08)	59
		pooled					1.08 (0.87, 1.30)	
	M	BC	63	55	1.16	1.02	0.88 (0.61, 1.27)	18
		ON	255	181	1.31	1.03	0.80 (0.66, 0.97)	82
		pooled					0.82 (0.68, 0.95)	

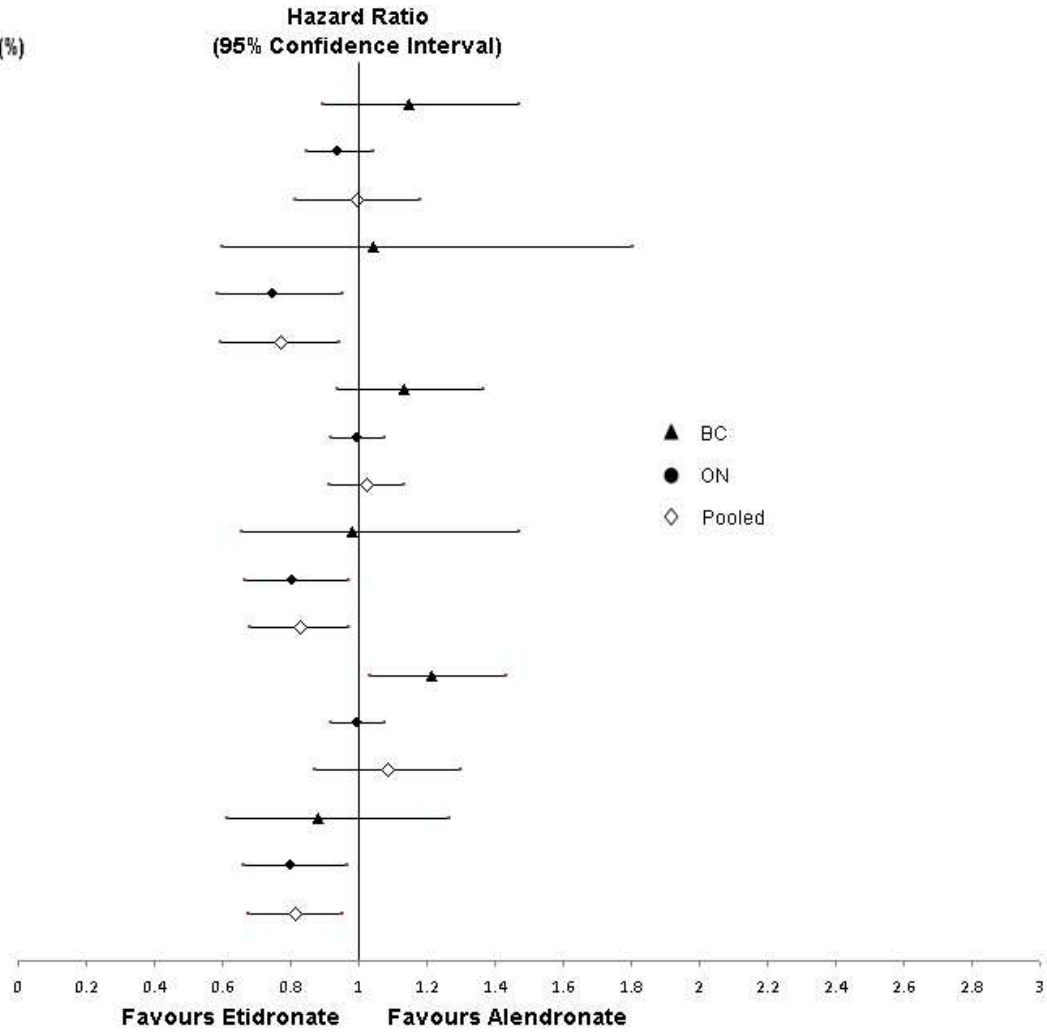
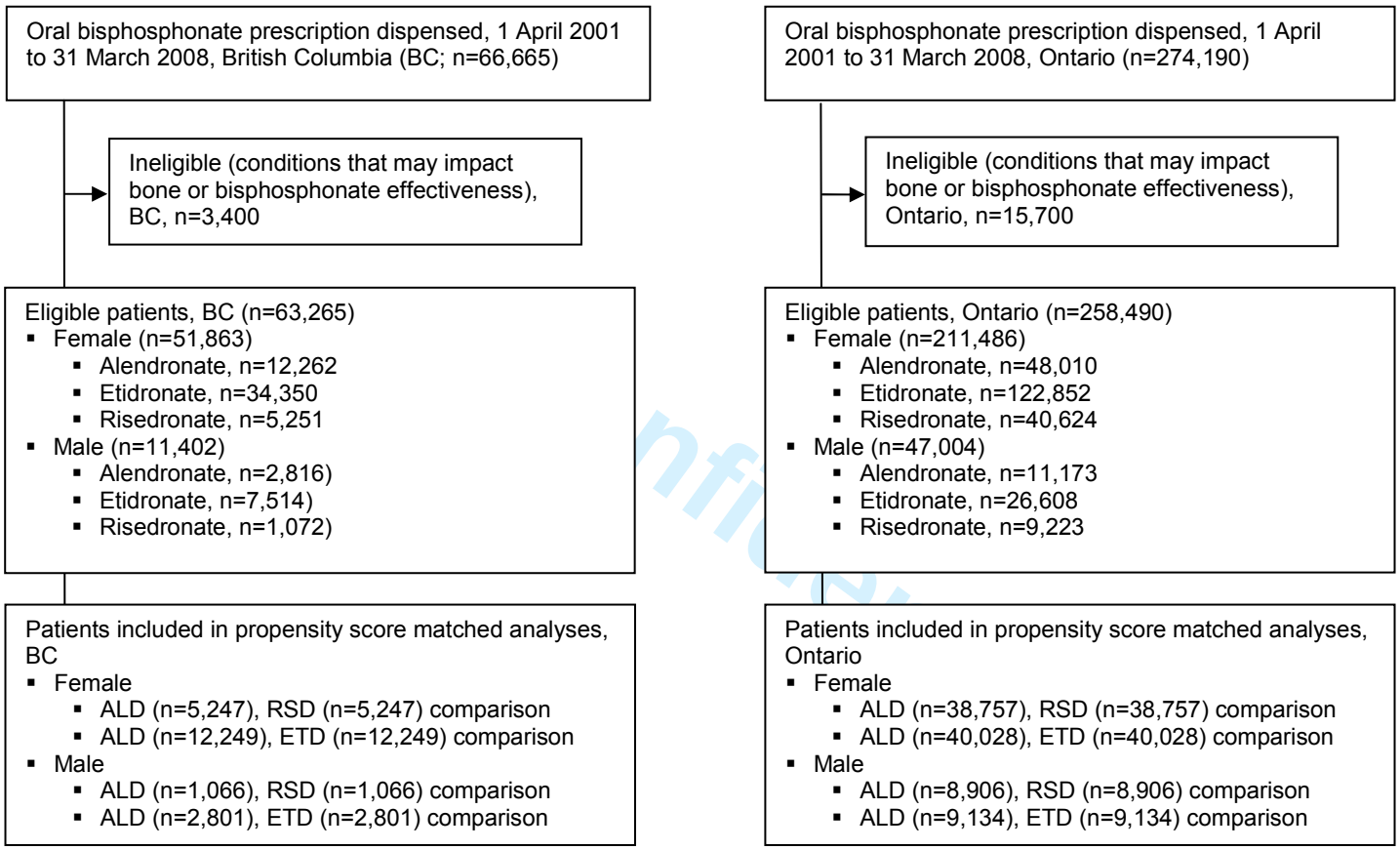


Figure 2. Forest plot comparing the effectiveness of etidronate to alendronate in reducing hip fracture risk, propensity score matched. Results pooled using a random effects variance weighted model. Propensity scores used for matching included all characteristics presented in Table 1, as well as index date and quintiles of: number of outpatient visit and number of generic drugs.



Appendix Figure. Study flow diagram. Oral bisphosphonates included 10 mg or 70 mg alendronate, cyclical etidronate and 5 mg or 35 mg risedronate. Inclusion period restricted to when all three oral bisphosphonates were available. Ineligibility criteria: celiac disease, Cushing's syndrome, hypercalcemia, hyperparathyroidism, malignant neoplasm, osteomalacia, osteopetrosis, Paget's disease, organ transplant, and renal impairment or dialysis, as well as patients receiving clodronate or pamidronate, men receiving estrogen therapy, and BC patients receiving alendronate or risedronate through PharmaCare.