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Research

Comparison of orally administered bisphosphonate drugs in reducing the risk of hip fracture in older adults: a population-based cohort study

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Abstract

Background: Orally administered bisphosphonate drugs (i.e., alendronate, etidronate, risedronate) can reduce the risk of vertebral fracture. However, only alendronate and risedronate have proven efficacy in reducing the risk of hip fracture. We sought to examine the comparative effectiveness of orally administered bisphosphonate drugs in reducing hip fractures among older adults.

Methods: We identified new users of orally administered bisphosphonate drugs in British Columbia and Ontario between 2001 and 2008. We used province- and sex-specific propensity score–matching strategies to maximize comparability between exposure groups. We used Cox proportional hazards models to compare time-to-hip fracture within 1 year of treatment between exposures by sex in each province. Our secondary analyses considered hip fracture rates within 2 and 3 years' follow-up. We used alendronate as the reference for all comparisons and pooled provincial estimates using random effects variance-weighted meta-analysis.

Results: We identified 321 755 patients who were eligible for inclusion in the study. We found little difference in fracture rates between men (pooled hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.74–1.14) or women (pooled HR 1.15, 95% CI 0.73–1.56) taking risedronate and those taking alendronate. We similarly identified little difference in fracture rates between women taking etidronate and those taking alendronate (pooled HR 1.00, 95% CI 0.82–1.18). However, we identified lower rates of hip fracture among men taking etidronate relative to alendronate (pooled HR 0.77, 95% CI 0.60–0.94). Results extended to 2 and 3 years' follow-up were similar. However, with 3 years' follow-up, rates of hip fracture were lower among women in British Columbia who had taken alendronate.

Interpretation: We identified little overall difference between alendronate and risedronate in reducing the risk of hip fracture in men or women. Our finding that etidronate is associated with lower fracture risk among men is likely due to selection bias. The long-term comparative effects of orally administered bisphosphonate drugs warrant further study.

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 $282 million in attributable health care costs in Ontario annually ($1.1 billion in Canada).[4] In addition, about 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 after a hip fracture.[4] Orally administered bisphosphonate drugs (i.e., alendronate, etidronate, risedronate) are the most commonly prescribed drugs for osteoporosis in Canada.[5] Each drug is efficacious in reducing vertebral fracture risk; however, only the use of selected bisphosphonates (alendronate and risedronate) has shown significant reductions in hip fracture risk compared with placebo.[6,7] Consequently, Canadian osteoporosis practice guidelines recommend alendronate and risedronate as first-line therapy, with etidronate in a list of second-line options.[8] In contrast to practice guidelines, many publicly

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funded drug plans across Canada limit coverage for first-line therapies, but provide unrestricted coverage for etidronate — a second-line therapy.[9] For example, British Columbia's drug plan 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. The annual drug cost (before dispensing fees) for generic medications paid through the Ontario Drug Benefit Program is about $80 for cyclical etidronate and $130 for weekly alendronate or risedronate.[10] The difference in costs between agents may be justifiable if one of them is more effective at reducing fracture risk. The mean attributable cost in the first year after hip fracture is estimated to be $36 929 (95% confidence interval [CI] $36 380–$37 466) among women and $39 479 (95% CI $38 311–$40 677) among men;[4] thus, a $50 annual difference in preventive pharmacotherapy could be cost-effective. However, little "head-to-head" data are available to support the superiority of any of these drugs in reducing hip fracture risk, particularly among men. Thus, we sought to compare the effectiveness of etidronate and risedronate to alendronate in reducing hip fracture risk separately for men and women. Although the intravenously administered bisphosphonate zoledronic acid is available in Canada, we previously identified fewer than 210 people using zoledronic acid in British Columbia and Ontario combined;[5] thus, we could not consider the comparative effects of zoledronic acid in our study.

Methods

We completed a population-based cohort study using administrative claims data from British Columbia and Ontario. British Columbia PharmaNet data are comprehensive and include all drugs dispensed in community pharmacies. These data therefore include drugs covered by the public system, as well as drugs paid for through private insurance or out of pocket. In contrast, Ontario data available for analysis included only drugs covered through the public Ontario Drug Benefit Program, which restricted coverage for alendronate and risedronate to patients at higher fracture risk between 2001 and 2007.[5] Since 2007, all 3 orally administered bisphosphonate drugs have been open listed in Ontario. Including data from 2 provinces permits us to compare results in the context of differential access to medication through provincial drug policies, and thus allows us to examine the consistency of our findings. The study was approved by the University of British Columbia Clinical Research Ethics Board (Vancouver, British Columbia) and the Sunnybrook Health Sciences Centre Research Ethics Board (Toronto, Ontario).

We identified the first date of dispensing (i.e., the index date) of any osteoporosis medication among residents aged 66 years or older in British Columbia and Ontario from Apr. 1, 1995, to Mar. 31, 2009, in a previous study.[5] In the current study, we restricted inclusion to new users of an orally administered bisphosphonate from Apr. 1, 2001, to Mar. 31, 2008; we therefore restricted inclusion to patients using orally administered bisphosphonate drugs as first-line therapy. We selected April 2001 as the earliest exposure period to restrict analyses to the period when all 3 drugs were available on the market. We excluded patients with conditions that may impact bone integrity or the effectiveness of bisphosphonates (celiac disease, Cushing syndrome, hypercalcemia, hyperparathyroidism, malignant neoplasm, osteomalacia, osteopetrosis, Paget disease, organ transplant, and renal impairment or dialysis). We also excluded patients receiving clodronate or pamidronate, men receiving estrogen therapy and patients receiving alendronate or risedronate through the restrictive PharmaCare program in British Columbia (the public drug plan).

We linked pharmacy data 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 d) after the start of treatment. Our secondary outcomes were hip fracture within 2 and 3 years after the start of treatment.

Statistical analyses

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.[11] We did so by first defining 2 sex-specific contrast cohorts within each province: etidronate and alendronate users, and risedronate and alendronate users. We then used logistic regression to create province-specific propensity scores within the contrast cohorts separately for men and women. The main benefit of using this approach with 2 contrast cohorts instead of a single multinomial logistic regression approach is the simplicity of restricting analyses to propensity score overlap.[11] Covariates included in the propensity scores included factors that could affect fracture risk, such as age at index date, use of health services in the past year, fracture history, osteoporosis management (bone mineral density test, osteoporosis diagnosis) and comorbidities (Table 1). In addition, we included quintiles of number of outpatient visits and number of medications, as well as date (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. We then used Cox proportional hazards models to compare hip fracture rates within 1 year of the start of treatment between exposures for each province separately for men and women. We used alendronate as the reference in all analyses.

In our primary analysis, we considered a patient exposed to a drug throughout the length of follow-up by censoring only at date of death, a switch between agents, or end of follow-up (1 yr after the start of treatment). We used this analytic strategy because bisphosphonates persist in bone and thus the benefit-window of opportunity extends beyond time on treatment[12,13] and, given that etidronate is dispensed as a 90-day supply (includes 14 d of active drug plus 76 d of calcium), but alendronate and risedronate are typically dispensed as a 28- or

Table 1 (part 1 of 3): Baseline characteristics* of new users of oral bisphosphonates, by province, sex and drug, April 2001 to March 2008

Characteristic	British Columbia						Ontario					
	Men			Women			Men			Women		
	ALD *n* = 2 816	ETD *n* = 7 514	RSD *n* = 1 072	ALD *n* = 12 262	ETD *n* = 34 350	RSD *n* = 5 251	ALD *n* = 11 173	ETD *n* = 26 608	RSD *n* = 9 223	ALD *n* = 48 010	ETD *n* = 122 852	RSD *n* = 40 624
Age, yr, 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 before index												
Admission to hospital, %	42.2	34.4	31.7	31.0	26.8	26.2	25.4	19.0	24.4	18.1	13.1	18.3
Resident of long-term care facility, %	4.9	4.3	1.8	3.5	4.3	1.7	6.6	3.9	7.6	6.0	4.0	7.8
1-year fracture history, %												
Hip	5.5	2.4	2.3	4.6	2.4	2.7	5.5	1.9	5.0	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	4.0	2.9	4.4
Vertebra	5.1	3.4	4.9	2.9	2.3	2.2	3.1	2.0	3.1	1.6	1.0	1.8
Other osteoporosis-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- to 5-year fracture history, %												
Hip	2.3	1.7	1.9	1.8	1.9	1.5	1.9	1.4	2.0	2.0	1.4	2.2
Humerus/radius/ulna	1.6	1.5	1.6	3.6	3.2	3.3	3.0	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	5.0	3.7	4.9	4.8	3.6	5.0
No. of previous fractures, %												
0	81.9	88.3	85.5	82.8	86.3	86.3	80.7	88.3	80.7	81.0	87.0	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

Continued.

Table 1 (part 2 of 3): Baseline characteristics* of new users of oral bisphosphonates, by province, sex and drug, April 2001 to March 2008

	British Columbia						Ontario					
	Men			Women			Men			Women		
Characteristic	ALD *n* = 2 816	ETD *n* = 7 514	RSD *n* = 1 072	ALD *n* = 12 262	ETD *n* = 34 350	RSD *n* = 5 251	ALD *n* = 11 173	ETD *n* = 26 608	RSD *n* = 9 223	ALD *n* = 48 010	ETD *n* = 122 852	RSD *n* = 40 624
Comorbidities, %												
Alzheimer/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	9.0
Falls/syncope/neurologic/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
Hyperthyroidism	0.4	0.3	S†	0.5	0.6	0.6	0.6	0.6	0.5	0.9	0.9	0.9
Inflammatory arthritis	1.0	0.9	S†	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	S†	S†	S†	0.1	0.1	S†	0.2	0.1	S†	0.1	0.1	0.1
Parkinson 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	8.2	7.5	8.4	10.1	10.0	12.3	5.5	4.2	5.8	5.7	4.3	6.7
Anticonvulsant agents	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)	7.0	3.9	6.3	–	–	–	6.2	3.4	5.9	–	–	–
Aromatase inhibitors (women)	–	–	–	S†	S†	S†	–	–	–	1.0	0.5	1.1
Benzodiazepines	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	9.0	8.8	9.8	8.7

Continued.

Table 1 (part 3 of 3): Baseline characteristics* of new users of oral bisphosphonates, by province, sex and drug, April 2001 to March 2008

	British Columbia						Ontario					
	Men			Women			Men			Women		
Characteristic	ALD *n* = 2 816	ETD *n* = 7 514	RSD *n* = 1 072	ALD *n* = 12 262	ETD *n* = 34 350	RSD *n* = 5 251	ALD *n* = 11 173	ETD *n* = 26 608	RSD *n* = 9 223	ALD *n* = 48 010	ETD *n* = 122 852	RSD *n* = 40 624
Corticosteroids (orally)												
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	3.0	3.1	3.2
Prednisone equivalent ≥ 675 mg	11.4	11.8	10.0	3.8	4.6	3.8	11.2	11.9	11.0	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	S†	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	9.0
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	9.0
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	S†	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)	–	–	–	S†	S†	S†	–	–	–	1.0	0.9	1.0
SSRIs	11.5	8.9	7.6	12.3	12.1	9.8	11.0	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	12.0	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	19.0	17.4	19.6

Note: ALD = alendronate, COPD = chronic obstructive pulmonary disease, DXA = dual-energy X-ray absorptiometry, ETD = etidronate, NSAID = nonsteroidal anti-inflammatory drug, OP = osteoporosis, RSD = risedronate, SERM = selective estrogen-receptor modulator, SD = standard deviation, SSRI = selective serotonin reuptake inhibitor, TIA = transient ischemic attack.
*Age at start of treatment; unless otherwise indicated, other covariates were determined based on the year before the start of treatment.
†Denotes data suppression for fewer than 10 patients.

30-day supply, it may be difficult to determine when to censor follow-up among patients taking etidronate because of drug stoppage. A secondary analysis censored only on date of death or administrative end of follow-up. Hazard ratios (HRs) were pooled between regions using random-effects, variance-weighted meta-analysis.

Results

We identified 58 406 (11 402 from British Columbia) eligible men and 263 349 (51 863 from British Columbia) eligible women (Figure 1). Comparison of baseline covariates by sex between new users of each agent in British Columbia identified patients taking alendronate as being at higher fracture risk (e.g., more of these patients had a previous fracture) compared with patients taking etidronate or risedronate (Table 1). Comparing baseline covariates between new users of each agent in Ontario showed that patients taking alendronate and those taking risedronate were similar in terms of background risk for fracture; however, patients taking etidronate 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 men or women taking risedronate and those taking alendronate (pooled HR for men 0.94, 95% CI 0.74–1.14; pooled HR for women 1.15, 95% CI 0.73–1.56) (Figure 2). We similarly identified little difference in fracture rates between women taking etidronate and those taking alendronate (pooled HR 1.00, 95% CI 0.82–1.18 (Figure 3). However, we identified lower rates of hip fracture among men taking etidronate relative to alendronate (pooled HR 0.77, 95% CI 0.60–0.94) (Figure 3). Results were similar when we did not censor on switch date (data not shown). When we

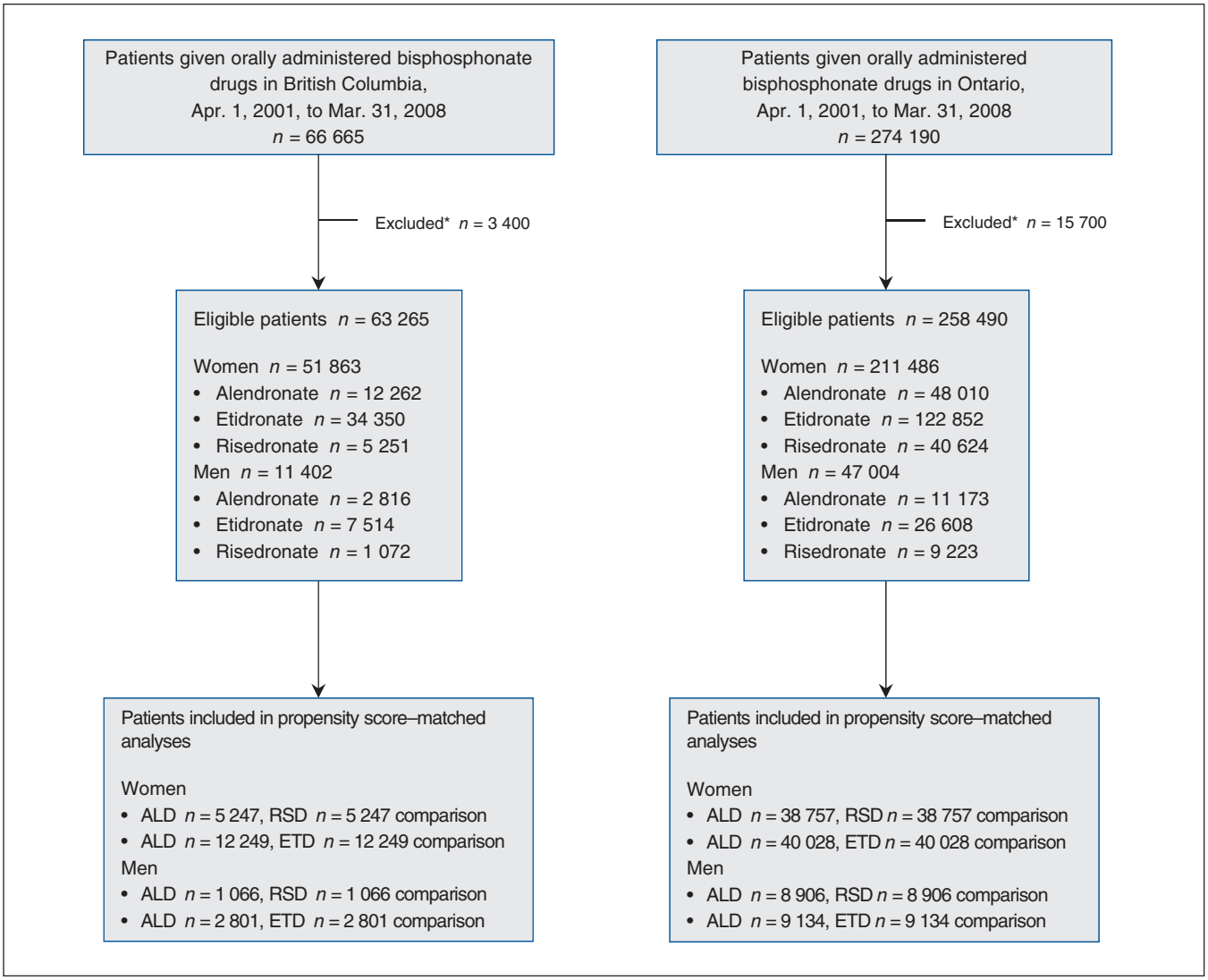

Figure 1: Flow of patients through the study. ALD = alendronate, ETD = etidronate, RSD = risedronate. *Exclusion criteria included celiac disease, Cushing syndrome, hypercalcemia, hyperparathyroidism, malignant neoplasm, osteomalacia, osteopetrosis, Paget disease, organ transplant, renal impairment or dialysis, receiving clodronate or pamidronate, men receiving estrogen therapy, and receipt of alendronate or risedronate in British Columbia through PharmaCare.

extended follow-up to 3 years (Figures 2 and 3), however, women in British Columbia taking etidronate or risedronate were noted to have higher risk of hip fracture compared with women taking alendronate when followed for up to 3 years.

In our secondary analysis that followed patients in British Columbia for up to 3 years, we found that women taking risedronate had higher rates of hip fracture than those taking alendronate (HR 1.50, 95% CI 1.15–1.96). Furthermore, women taking etidronate had higher rates of hip fracture than those taking alendronate (HR = 1.22, 95% CI = 1.03–1.43).

Follow-up, yr	Sex	Province	Event rate (no.) ALD	Event rate (no.) RSD	HR (95% CI)
1	F	BC	0.89 (41)	0.13 (61)	1.48 (1.00–2.20)
		ON	2.04 (762)	2.06 (773)	1.01 (0.92–1.12)
		Pooled			1.15 (0.73–1.56)
	M	BC	1.00 (S)	0.99 (S)	0.99 (0.39–2.49)
		ON	2.13 (171)	1.96 (161)	0.94 (0.76–1.16)
		Pooled			0.94 (0.74–1.14)
2	F	BC	0.95 (76)	1.26 (102)	1.33 (0.99–1.79)
		ON	1.79 (1222)	1.87 (1275)	1.05 (0.97–1.13)
		Pooled			1.12 (0.88–1.36)
	M	BC	0.99 (15)	0.90 (14)	0.91 (0.44–1.89)
		ON	1.77 (249)	1.59 (227)	0.91 (0.76–1.09)
		Pooled			0.91 (0.74–1.07)
3	F	BC	0.86 (89)	1.28 (135)	1.50 (1.15–1.96)
		ON	1.34 (1224)	1.42 (1276)	1.05 (0.97–1.13)
		Pooled			1.23 (0.79–1.67)
	M	BC	1.00 (19)	0.92 (18)	0.92 (0.48–1.75)
		ON	1.41 (250)	1.27 (228)	0.91 (0.76–1.09)
		Pooled			0.91 (0.75–1.07)

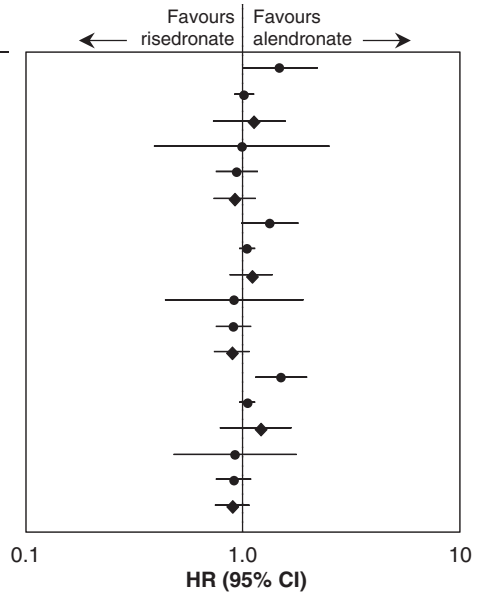

Figure 2: Comparison of risedronate and alendronate in reducing risk of hip fracture using propensity score matched analysis. Results were pooled using a random effects variance-weighted model. Propensity scores used for matching included all characteristics presented in Table 1, as well as index date and quintiles of number of outpatient visits and number of generic drugs. ALD = alendronate, CI = confidence interval, HR = hazard ratio, RSD = risedronate, S = data suppressed for fewer than 10 patients.

Follow-up, yr	Sex	Province	Event rate (no.) ALD	Event rate (no.) ETD	HR (95% CI)
1	F	BC	1.05 (116)	1.21 (134)	1.15 (0.89–1.47)
		ON	1.92 (742)	1.74 (677)	0.94 (0.85–1.04)
		Pooled			1.00 (0.82–1.18)
	M	BC	1.02 (25)	1.06 (26)	1.04 (0.60–1.81)
		ON	2.01 (166)	1.42 (112)	0.75 (0.59–0.95)
		Pooled			0.77 (0.60–0.94)
2	F	BC	1.03 (202)	1.17 (231)	1.13 (0.94–1.37)
		ON	1.67 (1224)	1.62 (1204)	1.00 (0.92–1.08)
		Pooled			1.03 (0.92–1.14)
	M	BC	1.13 (48)	1.11 (47)	0.98 (0.66–1.47)
		ON	1.68 (254)	1.31 (181)	0.80 (0.67–0.97)
		Pooled			0.83 (0.68–0.97)
3	F	BC	1.00 (258)	1.22 (318)	1.22 (1.03–1.43)
		ON	1.23 (1226)	1.17 (1204)	0.99 (0.92–1.08)
		Pooled			1.08 (0.87–1.30)
	M	BC	1.16 (63)	1.02 (55)	0.88 (0.61–1.27)
		ON	1.31 (255)	1.03 (181)	0.80 (0.66–0.97)
		Pooled			0.82 (0.68–0.95)

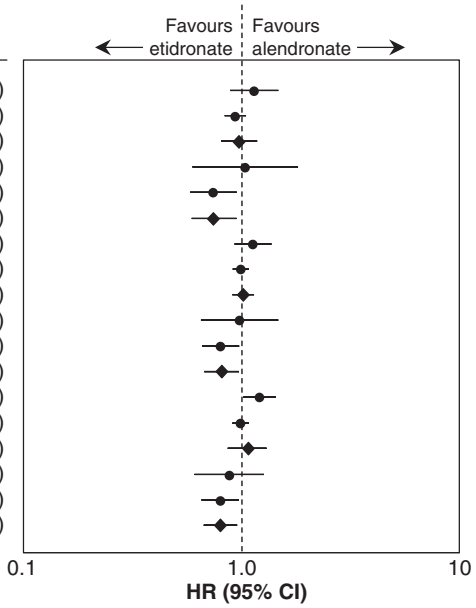

Figure 3: Comparison of etidronate and alendronate in reducing risk of hip fracture using propensity score matched analysis. Results were pooled using a random effects variance-weighted model. Propensity scores used for matching included all characteristics presented in Table 1, as well as index date and quintiles of number of outpatient visits and number of generic drugs. ALD = alendronate, CI = confidence interval, HR = hazard ratio, ETD = etidronate.

Interpretation

We identified little difference in the effectiveness of alendronate or risedronate in reducing 1-year risk of hip fracture among men or women. We found inconsistent results when comparing etidronate and alendronate. With alendronate and risedronate showing similar effectiveness, physicians may feel comfortable prescribing their first-line bisphosphonate of choice to patients. More evidence with better clinical data is needed to understand the relative benefits of etidronate compared with alendronate or risedronate.

Our results among older adult Canadians residing within 2 different provinces corroborate previous findings of comparable fracture rates within 1-year of treatment among women[14,15] and provide evidence about the comparable effectiveness of risedronate and alendronate in reducing fracture risk among men. Given that alendronate persists in bone longer than risedronate does, and that the results of our secondary analysis extended to 3 years' follow-up identified higher hip fracture rates among women in British Columbia who were taking risedronate compared with alendronate, the long-term comparative effectiveness of alendronate and risedronate warrant further study. Indeed, a previous paper identified a trend toward higher rates of hip fracture among people taking risedronate (HR 1.77, 95% CI = 1.15–2.74) than among those taking alendronate when followed for up to 3 years.[15] Given that we identified a possible difference among women in only 1 province, this finding is hypothesis-generating and deserves further attention.

In our primary analysis, we identified little difference in 1-year hip fracture rates between men or women taking etidronate and those taking alendronate in British Columbia, but we saw higher fracture rates among men in Ontario taking alendronate. To our knowledge, only a single previous study has directly compared the effectiveness of etidronate to alendronate or risedronate in reducing fracture risk.[16] In a cohort study involving female patients in Ontario who started taking bisphosphonates between 1998 and 2002, authors found little difference in rates of hip fracture within 2 years between those using etidronate and those using 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 with alendronate and risedronate, but not etidronate. However, clinical trials establish drug efficacy within defined patient populations, which are often not representative of patients who may benefit from pharmacotherapy or how the agents are used in practice.[17] Part of the lack of difference in observed effectiveness of alendronate and risedronate compared with 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 among women in the previous study and in our study, as well as the higher fracture rates among men taking alendronate in our study, could at least partially result from policy-induced selection bias (i.e., confounding by indication).

Limitations

Similar to all studies that rely on administrative claims data, the data available for our analysis were limited in clinical detail. For example, although we were able to adjust for bone mineral density testing and "claims-based" diagnosis of osteoporosis, we could not adjust for bone mineral density. In particular, from 2003 to 2007, insurance coverage for alendronate and risedronate in Ontario was restricted to patients who met 2 of the following criteria: bone mineral density T-score less than –3.0, age 75 years or older, and previous osteoporosis-related fracture.[5] Further research that is able to adjust for baseline bone mineral density is important to clarify our results that compare etidronate and alendronate. Of interest, extending follow-up among women in British Columbia to 3 years identified higher fracture rates among women using etidronate versus alendronate.

Although data from British Columbia were not subject to drug-policy restrictions, the public plan effectively only covered etidronate; thus, there may be some residual differences in unmeasured characteristics between exposure groups in British Columbia, given that the Canadian guidelines recommend etidronate as second-line therapy. Given that clinical practice guidelines recommend alendronate and risedronate as first-line therapy, and that drug policy restrictions were similar for alendronate and risedronate, selection bias and residual confounding is less likely in our comparisons of risedronate and alendronate.

Conclusion

Our results among older adult Canadians residing within 2 different provinces identify comparable 1-year effectiveness of alendronate and risedronate for women and men. Physicians may therefore feel comfortable prescribing their first-line agent of choice to patients (alendronate or risedronate). However, a possible difference in effectiveness between alendronate and risedronate with 3 years' follow-up deserves further attention. In addition, owing to possible residual confounding, we cannot comment on the relative benefits of etidronate compared with alendronate. Further research that considers the comparative effects of etidronate and alendronate or risedronate, as well as the long-term comparative effects of orally administered bisphosphonates, is needed.

In addition to clinical implications, our results support the critical importance of considering prescribing practices and formulary listing status changes over time when designing and interpreting postmarketing drug safety and effectiveness studies. Canada now supports a National Drug Safety and Effectiveness Network that provides rapid safety and effectiveness data to drug policy decision-makers.[23] We identified policy-induced selection bias in Ontario that relates to restricted access to selective drugs based on risk for fracture, including bone mineral density that we cannot adjust for using administrative claims data. The inclusion of data from British Columbia that identified little difference in risk of hip fracture between men taking etidronate and those taking alendronate strengthens our hypothesis that policy-induced selection bias exists when comparing these agents using

Ontario data. The inclusion and separate analysis of data from several provinces permits the comparison of results between datasets that may have different drug restriction policies, and thus may help to mitigate the misinterpretation of results in the context of policy-induced selection bias.

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