Greater first year effectiveness drives favorable cost-effectiveness of brand risedronate versus generic or brand alendronate: modeled Canadian analysis

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Abstract

Summary—The RisedronatE and ALendronate (REAL) study provided a unique opportunity to conduct cost-effectiveness analyses based on effectiveness data from real-world clinical practice. Using a published osteoporosis model, the researchers found risedronate to be cost-effective compared to generic or brand alendronate for the treatment of Canadian postmenopausal osteoporosis in patients aged 65 years or older.

Introduction—The REAL study provides robust data on the real-world performance of risedronate and alendronate. The study used these data to assess the cost-effectiveness of brand

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Disclosures of interest Daniel Grima is a paid employee of and shareholder in Cornerstone Research Group, Inc. Cornerstone received funding to conduct the cost-effectiveness analysis and develop the manuscript. Cornerstone conducts other consulting activities for the Alliance for Better Bone Health and other pharmaceutical companies that market osteoporosis therapies. Alexandra Papaioannou is or has been a consultant to the following companies: Amgen, Eli Lilly, Merck Frosst, Procter & Gamble, Sanofi-Aventis. Dr Papaioannou has conducted clinical trials for: Eli Lilly, Merck Frosst, Procter & Gamble, and Sanofi-Aventis. Melissa Thompson is a paid employee of Cornerstone Research Group, Inc. Cornerstone received funding to conduct the cost-effectiveness analysis and develop the manuscript. Cornerstone conducts other consulting activities for the Alliance for Better Bone Health and other pharmaceutical companies that market osteoporosis therapies. Margaret Pasquale is a paid employee of P&G Pharmaceuticals Inc., which is a member of the Alliance for Better Bone Health. Jonathan D. Adachi is/has been a consultant/speaker for Amgen, Astra Zeneca, Eli Lilly, GSK, Merck, Novartis, Pfizer, Procter & Gamble, Roche, Sanofi-Aventis, and Servier. He has participated in clinical trials for Amgen, Eli Lilly, GSK, Merck, Novartis, Pfizer, Procter & Gamble, and Roche.

risedronate versus generic or brand alendronate for treatment of Canadian postmenopausal osteoporosis patients aged 65 years or older.

Methods—A previously published osteoporosis model was populated with Canadian cost and epidemiological data, and the estimated fracture risk was validated. Effectiveness data were derived from REAL and utility data from published sources. The incremental cost per quality-adjusted life-year (QALY) gained was estimated from a Canadian public payer perspective, and comprehensive sensitivity analyses were conducted.

Results—The base case analysis found fewer fractures and more QALYs in the risedronate cohort, providing an incremental cost per QALY gained of \$3,877 for risedronate compared to generic alendronate. The results were most sensitive to treatment duration and effectiveness.

Conclusions—The REAL study provided a unique opportunity to conduct cost-effectiveness analyses based on effectiveness data taken from real-world clinical practice. The analysis supports the cost-effectiveness of risedronate compared to generic or brand alendronate and the use of risedronate for the treatment of osteoporotic Canadian women aged 65 years or older with a BMD T-score ≥ -2.5 .

Keywords

Bisphosphonates; Cost-effectiveness; Hip fracture; Model; Postmenopausal osteoporosis

Introduction

The most commonly prescribed therapies for osteoporosis in Canada are the oral bisphosphonates: risedronate and alendronate. Large head-to-head randomized clinical trials comparing fracture outcomes between risedronate and alendronate treatment are not available; as such, cost-effectiveness analyses have relied on linking data from clinical trials through placebo arms. However, this method has had two main weaknesses as a basis for policy decision-making. It often required comparing different at-risk populations and efficacy data derived from different methodologies. In addition, it did not consider how real-world effectiveness of the product may differ from the efficacy observed in clinical trials [1]. While efficacy is concerned with whether a drug produces an intended effect among highly selected patients in a closely controlled environment, effectiveness is concerned with whether the drug is efficacious in patients who are prescribed the drug in a real world setting. The differences in effectiveness versus efficacy are a function of a number of factors that are more heterogeneous in actual practice than in clinical trials. Prescribing is conducted by a large group of physicians with varied backgrounds, training, experience, and therapeutic preferences. These physicians prescribe the drug to a more heterogeneous group of patients who undergo less frequent and intensive management compared to a trial population [2, 3]. Due to such differences between real-life prescribing and clinical trials, guidelines from agencies such as the Canadian Agency for Drugs and Technologies in Health (CADTH) often state a preference for effectiveness data over efficacy data [2].

Recent data from a retrospective cohort study of once-a-week bisphosphonates provide robust information on real-world performance of risedronate and alendronate. The RisedronatE and ALendronate (REAL) cohort study was conducted to assess the incidence

of hip and nonvertebral fractures in the first 6 and 12 months following the initiation of bisphosphonate therapy [4]. The study included over 35,000 women from the Ingenix and Medstat health plans, aged 65 years or older and receiving once-a-week brand risedronate or brand alendronate over a sampling period, spanning July 2002 to September 2004. Cox proportional hazard modeling was used to adjust for potential differences in measurable risk factors in the treatment groups at baseline. It was noted that the two treatment cohorts had similar fracture incidence in the 6-month period prior to therapy initiation and during the first 3 months of observation, indicating a similar risk of fracture in the baseline populations. The study found significantly fewer hip fractures in the risedronate cohort; a 46% (95% CI 0.09–0.68) lower incidence at 6 months and a 43% (95% CI 0.13–0.63) lower incidence at 12 months (incidence of 0.37% and 0.58% for risedronate and alendronate, respectively at 12 months). Nonvertebral fracture incidence in the risedronate cohort compared to the alendronate cohort was 19% lower (95% CI 0.00–0.35) at 6 months and 18% lower (95% CI 0.02–0.32) at 12 months (incidence of 1.99% and 2.30% for risedronate and alendronate, respectively at 12 months).

The REAL study provides a new opportunity to conduct head-to-head cost-effectiveness analyses based on effectiveness data taken from real-world clinical practice. This study examines the impact of such data on the cost-effectiveness of risedronate compared to generic alendronate, when treating Canadian postmenopausal osteoporosis patients aged 65 years or older.

Methods

The study examined the use of risedronate or alendronate in the treatment of all postmenopausal osteoporosis women aged 65 years or older with a bone mineral density (BMD) T-score of -2.5 with or without a previous vertebral fracture. Pricing for generic alendronate was used due to the availability of a lower cost generic alendronate and the common practice of generic substitution in Canada. It was assumed that the effectiveness of brand alendronate from the REAL study was applicable to generic alendronate. Pricing for brand risedronate was used as a generic version is not currently available in Canada. The patient population was selected to reflect the broad range of patients indicated in osteoporosis guidelines [5] and funded under provincial drug plans [6]. The age limit of 65 years was chosen to reflect the age criteria commonly used to govern eligibility for public reimbursement of medications by provinces in Canada [6].

The analysis was conducted from a provincial Ministry of Health perspective. This perspective includes the costs of physician assessments, tests and procedures, emergency room visits, hospitalizations (ward costs, procedures, assessments, and medications), long-term care costs, home care costs, and drug formulary costs (medications). Societal costs such as loss of productivity were not included.

Treatment with either risedronate or alendronate was assumed to occur for 1 year. Treatment duration was based upon 12 months of observation in the REAL study from which the fracture reduction measure was derived. An assumption of no discontinuation within the 1-

year treatment period was adopted. Alternative treatment durations and discontinuation patterns were explored in the sensitivity analyses.

Patients were followed in the model for an additional 4 years after treatment to capture the ongoing impact of fracture prevention on costs, life years, and quality-adjusted life-years (QALYs). Guidelines for economic evaluations recommend a lifetime time horizon when the disease or therapy has a chronic impact. Nevertheless, a shorter time horizon was considered more clinically meaningful given the 1-year time horizon of the REAL study.

Incremental cost-effectiveness ratios (ICERs) were reported as incremental cost per hip fracture avoided and incremental cost per QALY gained, calculated by dividing the difference in costs by the difference in outcomes. Lower ratios indicate the outcome comes at a lower total cost and therefore indicates more value for money. Both costs and outcomes were discounted by 5% in the base-case analysis.

Osteoporosis model

A previously developed and published model of osteoporosis [7] was used. The model is consistent with an osteoporosis reference model proposed by Zethraeus et al. in 2007 [8] and has been used over the past 7 years for analyses in Canada, the US, and other countries [9–13]. During development, the predictive validity and technical accuracy of the model were assessed in terms of its ability to accurately estimate life expectancy, fracture risk, and age at first hip fracture in comparison to reported population data. Tosteson et al. [7] provides details on the model and validation. Subsequently, the model has been validated against a model by Borgstorm et al. [14].

The REAL study included data on the rate of several nonvertebral fractures (hip, wrist, humerus, clavicle, pelvis, and leg); however, it was decided that the analysis would focus on hip fracture for two reasons: 1) hip fractures have the largest clinical (morbidity and mortality) and economic consequences (costs) of all osteoporotic fractures; and 2) there is a large amount of Canadian data available on the mortality, morbidity, and costs associated with hip fractures [15–17].

The state-transition cohort model [18] uses a fracture incidence-based approach to simulate the occurrence of fractures and the impact of therapy. At the start of the model, a cohort of patients entered the well state; each year, patients could move between health states according to state- and age-dependent transition probabilities (see Fig. 1). Patients who fractured entered the 1st hip fracture state for the remainder of the year. At the end of that year, patients entered the post-1st hip fracture state or the dead state. From the Post-1st hip fracture state, patients could remain in that state, experience a 2nd hip fracture, or die of other causes. Patients experiencing a second hip fracture and surviving, entered the post-2nd hip fracture state where they could remain or die to other (non-fracture) causes.

Each state was associated with an economic cost and a quality-of-life value (i.e., health utility weight¹), which were used to estimate lifetime costs and QALYs. The post-hip fracture states were used to capture the long-term cost and quality-of-life impacts of chronic

morbidity associated with hip fractures. Annual cost and QALY data for each year in the model were summed to estimate the total outcomes for the cohort.

Population analysis

The analysis considered treatment of all women with osteoporosis aged 65 years or older with a BMD T-score of -2.5 , with or without previous vertebral fractures. In order to consider all women aged 65 years or older, simulations included a number of cohorts. Each cohort was defined based on age and the presence or absence of a previous vertebral fracture, as both of these factors are known to have a strong impact on fracture risk. In total, eight cohorts were analyzed; ages 65–69, 70–74, 75–79, and 80+, with or without an existing vertebral fracture.

The costs, fractures, and QALYs calculated for each cohort were weighted based on the prevalence of each subpopulation (Table 1). The prevalence was based on the Ontario Drug Benefit Formulary data for bisphosphonate use by age (31%, 65–69; 27%, 70–74; 25%, 75–79; 16%, 80+); this was assumed to approximate the distribution of osteoporotic patients by age. This was combined with data on the age-specific prevalence of existing vertebral fractures in a population with a BMD T-score of -2.5 from the Canadian Multicentre Osteoporosis Study (CaMos) database (35%, 65–69; 50%, 70–74; 62%, 75–79; 64%, 80+) [19].

Annual mortality

The age-specific probabilities of death in the general population were derived from the World Health Organization (WHO) Life Tables, 2002. Excess mortality in the year after hip fracture was taken from Kanis et al. [20]. Canadian sources reporting similar data were not available. The study also found that only 24% of deaths associated with hip fracture were causally related to the fracture and thus preventable. Therefore, excess mortality in the year after hip fracture was reduced by 76% to avoid an overestimation of the effects of fracture prevention on associated mortality (Table 2).

Hip fracture incidence

Canadian age-specific hip fracture incidence rates based on 1993–1994 data were used [21]. The reported rates were adjusted down by 10% to reflect declining hip fracture rates in Ontario women aged 50 years or older from 1997 onward compared to 1992–1996 (Table 2). The reason for the decline is unknown but may be related to increased screening and treatment [22].

The general population fracture incidence rates were then further adjusted to reflect the increased risk of fracture in the target population, which had reduced BMD and in some cases previous fractures. The relative risk (RR) of fracture in the target population compared to the general population was calculated using the methodology and data from Black et al. [23]. The methodology employed is supported by a similar independent study by Kanis et al.

¹Health utility is a quantitative measure of health-related quality of life that expresses the quality of life associated with a health state on a scale from 0 (dead) to 1 (perfect health).

[24]. In brief, the risk of fracture in the target population (tp) was calculated by multiplying the fracture incidence rate of the general population (gp) by a RR indicative of the risk in the target population versus the risk in the general population ($RR_{tp/gp}$). The overall $RR_{tp/gp}$ is the product of the RR associated with previous vertebral fracture and BMD, adjusted for the prevalence of each risk factor in the general population. For BMD, the methodology considered RR for all patients in the target population at or below a T-score of -2.5 as opposed to RR for patients at -2.5 . Consideration of the RR at the threshold is known to underestimate fracture risk when considering patients at or below a threshold [23]. It should be noted that RR values used in the Black et al. [23] study were adjusted for confounding effects; therefore, they were not treated as independent variables.

The RR values used in the analyses are provided in Table 2. These RR values are similar to those reported in an independent study by Kanis et al. [24] (see Table 3). The 10-year absolute risks of hip fracture predicted by the current model were compared to estimates from another independent study (Table 4) [25]. The similarity of the magnitude of these results supports the validity for the fracture risks used in this analysis.

Treatment effectiveness

Effectiveness data were derived from the REAL study [4]. The REAL study also included an analysis of 3,060 minimal treatment patients [26]. Minimal treatment patients were defined as those that received only one prescription for either brand risedronate or brand alendronate. These data were used to derive effectiveness of risedronate and alendronate versus ‘no therapy’, which is the format required by the model. These analyses found a RR of hip fracture for risedronate compared to no therapy of 0.493 (p-value=0.01) and for alendronate compared to no therapy of 0.882 (p-value=0.59) over a 12-month period. These results were based on a Cox regression model adjusted for treatment, age, estrogen use, concomitant medications, rheumatoid arthritis, nonvertebral fracture history, and vertebral fracture history. The RR values versus no therapy provide the same RR of hip fracture for risedronate versus alendronate as reported in the REAL study publication [4]. The adjusted age-specific fracture rates were multiplied by these RR values to estimate fracture rates in the treated cohorts. For purposes of this study, it was assumed that generic alendronate was equivalent in efficacy to brand alendronate.

Health utilities and costs inputs

Utility weights were applied to each health state to allow for the calculation of QALYs. Utilities reflect how quality of life in a health state is valued on a scale from 0 (death) to 1 (perfect health). A utility decrement of 0.18 (95% CI 0.04–0.31) [17] in the year of hip fracture was applied to the age-specific health utility values for women [27] experiencing a fracture. To reflect long-term morbidity, an assumed utility decrement of 0.09 was applied to each year subsequent to the year of hip fracture (Table 2).

All costs were reported in 2006 Canadian dollars (Table 2). Drug costs were obtained from the Ontario Drug Benefit Formulary and do not include dispensing fees or mark-ups. In the base-case analysis, the cost of generic alendronate was used given the availability of a lower cost generic alendronate and the common practice of generic substitution. Brand risedronate

cost was used given the lack of a generic version. The first-year costs following a hip fracture were derived from a published Canadian study of direct health care costs of hip fracture [28]. The published data were adjusted to exclude the cost of long-term care (LTC) for patients already residing in a LTC facility at the time of fracture. As well, cost for informal care and the patient co-pays for LTC were excluded. All costs were updated to the year 2006, using the medical care component of the consumer price index [29].

There are currently no published Canadian studies reporting the cost of hip fracture beyond the first year. The primary driver for cost of hip fracture in subsequent years is residency in LTC facilities due to hip fracture morbidity. Approximately 22% of patients living in the community at the time of hip fracture transfer to a LTC facility within 12 months [28]. Based on an annual cost of approximately \$20,000 for LTC and the additional costs of physician visits and BMD testing, the weighted average cost of a hip fracture in subsequent years was estimated (Table 2). Over time, it is assumed that a proportion of patients entering LTC after a hip fracture would have been admitted to LTC for other causes; as such, the subsequent year costs related to LTC may not be applicable for all years after a hip fracture. Based on Canadian rates of LTC admission for all causes, the age-specific costs of LTC following a hip fracture were estimated [30]. These estimates assume that as patients age, the LTC costs attributable to the hip fracture decline.

Sensitivity analysis

A probabilistic sensitivity analysis was conducted using the 95% confidence intervals for the RR of fracture for risedronate (range 0.28 to 0.86, log normal distribution) and alendronate (range 0.56 to 1.40, triangular distribution) relative to no therapy. A log normal distribution could not be used for alendronate as the relative risk reduction in the model would cross 0.² Crystal Ball Pro software (2000) (Decisioneering Inc., Denver, OH) was used to simulate 1,000 trials. For each trial, the program selected a random number for each distribution, assuming independence of the distributions. Based on those numbers, a RR value from the distributions was selected for each therapy. The model was then run using those RR values and a cost-effectiveness ratio was calculated based on the costs and outcomes for each therapy. This process was repeated for each of the 1,000 simulations. The cost-effectiveness results for the 1,000 trials were then combined to determine: 1) the proportion of runs where risedronate was dominant (lower costs and better outcomes), 2) the proportion of times generic alendronate was dominant, 3) the proportion of times that risedronate was more effective and more costly, and 4) the proportion of times that risedronate was less effective but less costly. For the last two options, the cost-effectiveness ratios of risedronate versus alendronate were calculated and summarized as the proportion of runs in which cost per fracture averted or per QALY gained were below \$5,000, \$10,000, \$15,000, \$20,000, \$25,000 and \$30,000. This process was repeated for each of the eight cohorts that were used in the base-case population analysis. The results were then used to calculate the proportion of runs where risedronate was dominant or within the cost-effectiveness ratio thresholds

²Once results were obtained, we found that applying the triangular distribution rather than the log normal distribution to risedronate changed each of the values specified in points 1) to 4) of this paragraph by less than one percentage point.

described above. This analysis allows a decision maker to determine the likelihood that the cost-effectiveness of a therapy is below a threshold, given uncertainty in the input parameter.

Deterministic sensitivity analyses were performed to determine the impact on the study results of the uncertainty in key model inputs. The base case analysis focused on the impact of 12 months of treatment due to a lack of long-term data from the REAL study. A sensitivity analysis assuming 2 years of treatment was conducted, assuming that the effectiveness advantage of risedronate over alendronate remained the same in year 2 (i.e., RR for risedronate versus alendronate of 0.56) or that it diminished by 25%. In the later case, it was assumed that the RR of risedronate versus no therapy remained constant and that the RR of alendronate versus no therapy improved, such that the RR for risedronate versus alendronate was approximately 67% in year 2.

Many studies utilize residual therapy effects after discontinuation to reflect that patients experience continued reductions in the risk of fracture after stopping therapy [31]. A sensitivity analysis assumed a clinical benefit of risedronate and generic alendronate in year 2, after discontinuation at the end of year 1. A linear decline to zero in effectiveness over year 2 was assumed. The base case assumed no discontinuation during the first year. Three sensitivity analyses were conducted over the range of 10%, 30%, and 50% discontinuation within 12 months, with equal proportions dropping off in months 0–3 and months 4–12. The proportion dropping off by month 3 was assumed to incur drug costs but no fracture protection. Suitable alternative values for utility and costs were not readily available.

Sensitivity analyses were also conducted for the following: 1) utility in the year of fracture using the confidence interval for the published utility decrements, 2) utility in subsequent years using 25% and 75% of the first year utility decrement instead of 50%, 3) fracture costs increased and decreased by 15%, 4) alternative hip fracture mortality data [21], 5) a 10-year time horizon: 1 year of treatment and 9 years of additional follow-up, and 6) cost of brand alendronate.

Results

The base case analysis used the effectiveness data from the REAL study, which found substantially lower hip fracture rates in patients treated with risedronate compared to alendronate over a 1-year period. The lower fracture rate resulted in approximately seven fewer hip fractures in the 1,000-patient risedronate cohort, and an associated benefit of an additional 3.43 QALYs, due to less hip-fracture related mortality and morbidity. Total fracture-related costs were lower in the risedronate arm compared to the generic alendronate arm; however, drug acquisition costs were higher. This resulted in an incremental total cost of \$13,305 per 1,000 patients for risedronate compared to generic alendronate when drug acquisition costs were included (Table 5). If the cost of brand alendronate was used, fewer fractures, greater QALYs and lower total costs were found with risedronate. This was due to the higher cost and lower reduction in fractures with brand alendronate.

The analysis found an incremental cost per hip fracture avoided of \$1,867 and an incremental cost per QALY gained of \$3,877 for risedronate compared to generic

alendronate (Table 5). The results could also be summarized as 140.3 patients would need to switch from generic alendronate to brand risedronate to avoid one hip fracture, at a total cost of \$1,867. These results reflect treatment of all women 65 years or older with a BMD -2.5 , with or without a previous vertebral fracture. It considers that some women will be at higher risk of fracture due to older age, lower BMD T-score, or the presence of prevalent vertebral fracture.

The probabilistic sensitivity included 1,000 simulations with sampling from the 95% confidence interval for the effectiveness of risedronate and alendronate. If both therapies had a similar range for the 95% confidence interval; 50% of runs would have been below the base case ratios. In over 54% of the simulations the ratios were well below the base case with risedronate being the dominant therapy; that is, it was less costly and more effective than generic alendronate. This was due in part to the wider 95% confidence interval for alendronate, where the relative risk reduction spanned zero, such that in some simulations the number of fractures was higher than with no therapy. In 84% of the simulations, the cost per fracture averted for risedronate compared to generic alendronate was below \$10,000. In 61% of the simulations, the cost per QALY gained for risedronate compared to generic alendronate was below \$10,000 (Fig. 2). The proportions increased to 94% and 68%, respectively, at a threshold of \$20,000, and to 98% and 72% at a threshold of \$30,000.

The base case assumed a 1-year treatment duration within a 5-year time horizon. When the treatment duration was increased to 2 years and when the effectiveness of risedronate compared to generic alendronate remained the same as year 1, the cost per QALY gained and the cost per hip fracture averted were both decreased to less than \$200. This is due to an increase in the total fractures avoided, the QALYs gained, and a reduction in the difference in the total costs. When the treatment duration was increased to 2 years but the difference in effectiveness of risedronate compared to generic alendronate was assumed to decline by 25% from year 1 to year 2, the cost per fracture averted and cost per QALY gained rose to \$7,725 and \$14,985, respectively (Table 6).

The base case also assumed no residual effects of therapy after stopping. When 1 year of treatment and a linearly declining residual effect of therapy in year 2 were assumed, risedronate became dominant (less costly and more effective) over generic alendronate. In this scenario the additional fractures in the generic alendronate arm compared to risedronate weighed heavily on the lower acquisition costs of generic alendronate, resulting in higher total medical costs for patients treated with generic alendronate. Risedronate was also dominant when the treatment duration was held constant and the time horizon was increased to include 9 years of post-treatment follow-up. The longer time horizon captures more of the downstream costs related to permanent hip fracture morbidity. Given that the generic alendronate group had more hip fractures with a longer time horizon the cost savings related to lower acquisition costs of generic alendronate were no longer able to offset the greater costs of fracture (Table 6).

The base case did not consider discontinuation. When discontinuation was introduced in sensitivity analyses, the cost per QALY increased from \$4,861 at 10% discontinuation to \$10,108 at 50% discontinuation. The results are sensitive since, in each case, half of the

population discontinuing were assumed to discontinue by 3 months and receive no fracture protection while incurring 3 months of drug costs.

Several factors caused minor changes in the cost-effectiveness ratio. These included lower hip fracture mortality based on Canadian inpatient data, health utility in the first year, health utility in subsequent years and 3% discounting. In no cases did either ratio increase to above \$5,500.

Discussion

The analysis explored the cost-effectiveness of risedronate and alendronate using fracture outcomes from real-world clinical practice (i.e., effectiveness data), as observed in the REAL study. The base case analysis considered all women typically treated in Canada for osteoporosis, by including multiple cohorts aged 65 years or older, with a BMD T-score -2.5 , with or without a previous vertebral fracture. The analysis supports the cost-effectiveness of brand risedronate compared to alendronate, even in the case of generic alendronate that has a substantially lower cost. The results are driven by the larger 12-month fracture reduction for risedronate compared to alendronate observed in the REAL study [4]. The lower fracture rate produced savings related to fracture treatment costs that partially offset the difference in price between risedronate and generic alendronate. When the uncertainty around the effectiveness results from the REAL study was considered, risedronate was less costly and more effective than generic alendronate in 54% of cases, with strong cost-effectiveness ratios in another 20% of cases.

The analysis is unique in its use of effectiveness data from the REAL study rather than efficacy data from controlled trials. Previous economic evaluations have relied on linking clinical data from separate trials. Indirect comparisons of efficacy are suggestive, but these must be viewed cautiously due to differences between RCTs. For example, the alendronate and risedronate trials were different in terms of patient inclusion/exclusion criteria, baseline demographics, methodology to assess fracture outcomes, and statistical approach. On the other hand, the REAL study was a head-to-head comparison of fracture outcomes that adjusted for potential differences in measurable risk factors for fractures using a Cox proportional hazard model. The REAL study was subject to limitations common to all observational studies. Two common systematic errors are selection bias and measurement misclassification. It is possible that selection bias may have resulted from differences in fracture risk between the two cohorts of patients at initiation of therapy. Fracture risk was assessed based on commonly recorded known risk factors (e.g. bone mineral density, family history, and smoking history), however unrecorded or unknown fracture risk characteristics may have varied between cohorts. In addition, measurement misclassification of fracture events are inevitable. Potential study limitations were addressed in detail in the original publication and tested through the following sensitivity analyses: 1) intent to treat analysis that observed all subjects for 12 months regardless of therapy adherence; 2) a proportional hazard model using the propensity score to adjust for differences in baseline fracture risk between cohorts; 3) several changes in inclusion criteria for the study population (such as: (a) exclude patients with historical use of steroids, (b) exclude patients with historical use of estrogen, calcitonin or raloxifene, (c) include patients with less than 6 months of history, (d)

exclude patients using alendronate 35 mg, which was 8% of the population, and (e) exclude patients with clinical diagnosis of hip, nonvertebral, or vertebral fracture bisphosphonate therapy during the 6 month period before); and 4) a change in the inclusion criteria for the study outcome (analysis with no exclusion of any medical claims for a fracture). In addition, the REAL analysis was reproduced through independent analysis by every author and their organizations to ensure credibility of the results [4].

The findings from REAL are consistent with data from randomized controlled trial findings thereby giving credence to these findings. A comparison of results from the randomized clinical trials of each bisphosphonate, though limited by methodological variation between trials, suggests potential differences in the rate of fracture reduction between risedronate and alendronate, especially in the first 6 to 12 months of therapy. The alendronate and risedronate trials were not adequately powered to detect differences in hip fracture rates at 6 or 12 months, as such a comparison to the 12-month REAL data cannot be made. However, in the primary analyses of trials that followed patients for at least 3 years, risedronate significantly reduced the incidence of nonvertebral fractures by up to 39% [32, 33], and alendronate reduced the incidence of nonvertebral fracture by up to 21% [34–36]. Post hoc analyses of these trial data suggest that there are differences in the onset of fracture reduction. In those analyses, reduction of nonvertebral fractures began at 6 months of risedronate therapy and at 12 months of alendronate therapy. At 12 months, reductions in nonvertebral fractures were 74% with risedronate [37] and 47% with alendronate [38]. Risedronate has also been shown to decrease clinical vertebral fractures by 69% [39] compared to 59% [40] with alendronate at 12 months.

Effectiveness data have the advantage of reflecting real-world clinical practice that include much greater heterogeneity in terms of prescribing practice, disease severity, co-morbidities, other patient characteristics, and compliance when compared to controlled trials. As such, effectiveness data have greater relevance to the general treatment population. The greater relevance of effectiveness outcomes is one reason why the CADTH guidelines state a preference for effectiveness data over efficacy data [2].

The base case analysis was limited to 12 months to reflect the REAL study. When conducting a sensitivity analysis on extending treatment beyond the 12 months in the REAL study, the results were sensitive to assumptions regarding duration and magnitude of benefit. If the difference in effectiveness between risedronate and alendronate was maintained in a second year of treatment, risedronate approached dominance over generic alendronate. If the difference in effectiveness diminished over time the ratios rose; however, in the sensitivity analyses they remained below \$15,000 per QALY gained. As more long-term data become available, head-to-head comparisons of longer duration to address this uncertainty may be feasible.

The current analysis is based on Canadian fracture rates and practice patterns. The Canadian analysis population was at higher risk of hip fracture compared to the REAL population at baseline due to the analysis requirement for a confirmed BMD -2.5 . In contrast, the REAL population reflected current clinical practice that includes treatment of patients at higher BMD levels. For example, the guidelines from the National Osteoporosis Foundation

recommend treatment of postmenopausal Caucasian women with a T-score < -1.5 if other risk factors are present and a T-score < -2.0 without other risk factors [41]. After use of Canadian fracture rates adjustment for risk factors, the analysis found seven fewer hip fractures in the risedronate cohort compared to the alendronate cohort, which is a greater difference than observed in the REAL study (2.5 per 1,000 patients). Approximately 0.4% of risedronate treated patients in the REAL study experienced a hip fracture [4]. The model does not track women individually, but assumes one hip fracture per woman; 0.9% of women in the risedronate cohort experienced a fracture. The analysis population was therefore at approximately 2.3 times the risk of hip fracture compared to the REAL population. The findings of the analysis may not be applicable to lower risk populations.

The applicability of the results to other countries is also limited by the use of Canadian cost and mortality data that may differ from that of other countries. However, it is likely that, in countries with similar osteoporosis epidemiology and patterns of treatment, similar cost-effectiveness would be found for treatment of women with established osteoporosis.

As with all simulation models assumptions have been made. Uncertainty in these assumptions has been addressed, where possible, through sensitivity analyses. In addition, conservative assumptions were made in the base case analysis such that it biased against risedronate and may understate the true cost-effectiveness. First, the time horizon was restricted to 5 years, with 1 year of treatment and 4 years of follow-up. When the time horizon was increased to 10 years in a sensitivity analysis, risedronate became dominant over generic alendronate, having lower costs and better outcomes. Second, the study did not consider residual effect of therapy after stopping treatment. Evidence shows that patients experience continued reductions in the risk of fracture after stopping therapy and this assumption has been used in a number of analyses [8, 24]. When a linearly declining residual effect for 1 year was included in a sensitivity analysis, risedronate became dominant over generic alendronate. Third, the analysis did not include other fracture sites in the skeleton due to the weakness of published cost, utility, and incidence data. Their exclusion results in a greater bias against risedronate since the anti-fracture benefit for nonvertebral fracture was greater in risedronate patients. Inclusion of these fractures would have provided additional cost and quality-of-life benefits for risedronate compared to generic alendronate. Finally, the base-case analysis used the effectiveness for brand alendronate from the REAL study and the costs for generic alendronate, which are approximately half of the costs for brand alendronate. This assumes equivalent efficacy for brand and generic alendronate, which has not been demonstrated. Concerns over the impact of differences in the disintegration profile of brand and generic alendronate have been raised, as they may cause differences in the efficacy of the products [42].

Conclusions

The REAL study offered an opportunity to consider real-world, head-to-head effectiveness comparing two commonly used bisphosphonates within a cost-effectiveness analysis. The analysis supports the cost-effectiveness of brand risedronate compared to generic or brand alendronate and the use of risedronate for the treatment of osteoporotic Canadian women aged 65 years or older with a BMD T-score ≥ -2.5 .

Acknowledgments

Funding for the study was provided by the Alliance for Better Bone Health.

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Fig. 1.
Model states and allowed state transitions

Fig. 2.

Probabilistic sensitivity analysis based on confidence intervals of relative risk reductions for hip fractures for risedronate versus no therapy and alendronate versus no therapy. CE = cost-effectiveness; QALY = quality-adjusted life-year

Table 1

Distribution of women among the eight cohorts defined by age and previous vertebral fracture

Age (years)	Previous vertebral fracture (%)	Without previous vertebral fracture (%)	Total (%)
65–69	11.0	20.4	31.4
70–74	13.6	13.6	27.2
75–79	15.7	9.6	25.3
80+	10.3	5.8	16.1
Total	50.6	49.4	100.0

Table 2

Model input data

Parameter	Value	
All-cause annual mortality rates	Canadian life tables	
Mortality rate in the year following a hip fracture (per 1,000 patients)	All	Attributable
65–69 years	39.94	9.56
70–74 years	55.66	13.36
75–79 years	77.52	18.60
80–84 years	112.94	27.11
85–89 years	172.44	41.38
Hip fracture incidence rates in the general female population (per 1,000 patients)	Unadjusted	Adjusted
65–69 years	3.59	3.24
70–74 years	5.81	5.24
75–79 years	7.74	6.98
80–84 years	15.16	13.67
85–89 years	24.50	22.10
Relative risk of hip fracture in target population (Age ≥ 65, BMD ≤ -2.5)	Without previous fracture	With previous fracture
65–69 years	4.18	6.41
70–74 years	2.73	4.04
75–79 years	2.73	3.91
80–84 years	1.83	2.53
Health utility decrements		
Year of hip fracture	0.18	
All subsequent years	0.09	
Drug costs		
Risedronate (35 mg, once a week)	486.72	
Generic alendronate (70 mg, once a week)	230.10	
Brand alendronate (70 mg, once a week)	492.96	
Hip fracture costs (CDN\$)	Year of fracture	Each subsequent year
65–74 years	24,772	5,308
75–84 years	24,772	2,790
85+ years	24,772	0

Table 3

Relative risk of fracture compared to the general population risk

Age (years)	Kanis et al. 2004 [24]	Current model
Women with a T-score of -2.5		
50	6.30	6.00
55	5.16	6.00
60	4.21	4.18
65	3.51	4.18
70	2.95	2.73
75	2.43	2.73
80	2.09	1.83
85	1.60	1.83
90	1.40	1.33
Women 70 years of age		
-2.5 No Previous Vertebral Fracture	2.95	2.73
-2.5 with Previous Vertebral Fracture	6.31	4.03

Table 4

10-year risk of hip fracture in model populations by age and BMD T-score

Age (years)	10-year risk of hip fracture (%)	(BMD T-score -2.5)
	Kanis et al. 2001 [25]	Current analysis
65	10.9	8.3
75	21.5	19.5
85	21.9	24

Table 5

Results (per 1,000 patients) for patients aged 65 years or older with BMD -2.5 (with and without a prevalent vertebral fracture) treated for 1 year with a follow-up period of 4 additional years

	Total costs (CDN\$)	Total hip fractures	Total QALYs
Generic alendronate	2,931,773	92.91	3,521.94
Risedronate	2,945,078	85.78	3,525.37
Incremental difference (risedronate compared to generic alendronate)	13,305	-7.13	3.43
Incremental cost per hip fracture avoided (CDN\$)	1,867		
Incremental cost per QALY gained (CDN\$)	3,877		

QALY = quality-adjusted life-year.

Values rounded for display.

Table 6

Sensitivity analysis results

Variable	Cost per hip fracture avoided (CDN\$)	Cost per QALY gained (CDN\$)
Base case	1,867	3,877
Fracture reduction from treatment in year 2:		
a). RRR of 44% for risedronate compared to alendronate in year 1 and year 2	a) 68	a) 133
b.) RRR of 33% for risedronate compared to alendronate in year 2	b) 7,725	b) 14,985
Residual effect of therapy after discontinuation based on linear decline of effectiveness to 0% over year 2 for both therapies	Risedronate dominant	Risedronate dominant
Mortality post hip fracture: Canadian inpatient data	1,807	3,857
Discontinuation of therapy		
a) 10%	a) 2,341	a) 4,861
b) 30%	b) 3,456	b) 7,176
c) 50%	c) 4,869	c) 10,108
Utility (year of fracture)		
a) Upper 95% confidence interval	Utility has no impact on	a) 3,053
b) Lower 95% confidence interval	this outcome	b) 5,466
Utility (subsequent years)		
a) 75% of first year utility decrement	Utility has no impact on this outcome	a) 3,007
b) 25% of first year utility decrement		b) 5,456
All fracture costs		
a) Increase 15%	a) Risedronate dominant	a) Risedronate dominant
b) Decrease 15%	b) 6,989	b) 14,511
Cost of brand risedronate	Risedronate dominant	Risedronate dominant
Time horizon: 9 years follow-up	Risedronate dominant	Risedronate dominant
Discounting (3%)	1,470	2,964

QALY = quality-adjusted life-year; RRR = relative risk reduction.

Dominant indicates lower total costs and superior clinical outcomes.