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Treating osteoporosis in Canada: what clinical efficacy data should be considered by policy decision makers?

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Abstract

Summary—Using a Markov state-transition model, we estimated fractures averted with risedronate using two different types of clinical efficacy data. Summary data, as opposed to individual patient data (IPD), underestimated the number of fractures averted when applied in a specified high risk population. The choice of clinical efficacy data is an important consideration in health economic models evaluating osteoporosis therapies.

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Conflicts of interest Jonathan D. Adachi is a consultant for Amgen; Astra Zeneca, Eli Lilly; GlaxoSmithKline; Merck Frosst; Novartis; Proctor & Gamble; Roche; sanofi-aventis; Servier; and Wyeth (clinical trials: Eli Lilly; GlaxoSmithKline; Merck; Novartis; Pfizer; Proctor & Gamble; sanofi-aventis; Servier; and Wyeth). Alexandra Papaioannou is a consultant and adviser for Amgen, Eli Lilly, Merck Frosst, Novartis, Proctor & Gamble, sanofi-aventis, and Servier (clinical trials: Amgen, Eli Lilly, Merck, Novartis, Proctor & Gamble, and sanofi-aventis). William D. Leslie received speaker fees, research honoraria, and unrestricted research grants from Merck Frosst Canada Ltd; research honoraria and unrestricted educational grants from The Alliance for Better Bone Health: sanofi-aventis and Procter & Gamble Pharmaceuticals Canada, Inc.; unrestricted research grants from Novartis Pharmaceuticals Canada, Inc.; unrestricted educational grants from Genzyme Canada. Valery Walker is a paid consultant for Alliance for Better Bone Health, Procter & Gamble Pharmaceuticals Canada, and sanofi-aventis Canada Inc. Courtney C. Kennedy and George Ioannidis have no disclosures.

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Introduction—This paper contrasts fracture reduction estimates for risedronate utilizing efficacy data from two approaches to meta-analysis: summary data versus individual patient data. We also examined differences in fracture reduction explained by varied cohort selection, especially the inclusion of low- versus high-risk populations.

Methods—Using a Markov state-transition model, we compared fractures averted over 3 years in a hypothetical cohort by inputting fracture risk reduction estimates (risedronate versus placebo) from two data sources (summary data versus IPD). The cohort consisted of 100,000 Canadian women, age ≥65 years with osteoporosis (WHO criteria *T*-score≤−2.5) and prevalent morphometric vertebral fracture.

Results—Non-vertebral fractures averted with risedronate were: 3,571 and 6,584 per 100,000 women for summary data and IPD, respectively. For vertebral fractures, the numbers were 8,552 and 10,127. When IPD versus summary data was used, an additional 3,013 more non-vertebral fractures and 1,575 vertebral fractures were averted.

Discussion—Relative risk estimates from IPD analyses were the best choice for modelling fracture outcomes when applied in a specified high-risk population. In addition to superior statistical methodology, they utilized RCT cohorts that are more representative of higher risk patients requiring treatment (osteoporotic women ≥65 years with a prevalent vertebral fracture).

Keywords

Bisphosphonate; Clinical efficacy; Fracture; Meta-analysis; Osteoporosis; Relative risk

Introduction

Osteoporosis is a chronic disease that affects approximately 26% of Canadian women aged 65 years or older [1]. A 50-year-old Caucasian woman has approximately a 40% chance of sustaining any osteoporotic fracture [2, 3] and a 14–17% chance of sustaining a hip fracture at some point in her remaining lifetime [2, 4]. The individual consequences of osteoporosis can be devastating, often resulting in substantial loss of independence, and sometimes death. Furthermore, the burden on the health care system is also substantial; in Canada alone, it is estimated that the annual cost of hip fractures could rise to $2.4 billion by 2041 [5].

Today, a number of proven interventions are available for the prevention and treatment of osteoporosis, with bisphosphonates considered to be the first line of therapy [6]. With several available treatment options, considerations of cost-effectiveness are of interest to many stakeholders in order to prioritize spending and base policy decisions.

In the absence of head-to-head randomized controlled trials (RCT), meta-analyses can help to inform physicians and policy makers about the effects of individual treatments [7]. By combining the results of multiple smaller placebo controlled trials, meta-analyses may increase the power of the data and provide broader insights into the efficacy of drugs. In the case of osteoporosis treatments, it has also been difficult to examine fracture outcomes through comparative RCTs due to the large sample sizes required for meaningful comparisons, particularly for non-vertebral fractures. A meta-analysis may be conducted

using one of two types of data: published summary statistics (summary data meta-analysis) or primary data (individual patient data, IPD).

A summary data meta-analysis pools proportions or statistics from already published RCT articles. Analyses are performed using these published estimates, which are aggregate numbers from each particular study (i.e., it is not possible to examine each patient's data directly). An IPD meta-analysis, on the other hand, has obtained the primary data from each study to be included and it is possible to perform a new analysis that utilizes individual-level patient data. These alternative approaches to meta-analysis may lead to different conclusions [8–13]. IPD meta-analyses are the "gold standard" [14–17] but are more difficult logistically and require access to the original data from individual clinical trials. On the other hand, they provide more precise and valid estimates of treatment effects and allow control for confounders, adjustments for study effects, common treatment of variables, and survival or time to event analysis.

The primary purpose of this paper is to contrast the fracture reduction estimates for risedronate treatment provided by summary data versus IPD meta-analysis, and to analyze the causes of differences between the estimates. A fracture incidence model is then used to illustrate the impacts of these differences on the numbers of fractures averted in high-risk patients.

Materials and methods

Model overview

A fracture incidence-based model of the natural history of osteoporosis was employed to estimate vertebral and non-vertebral fractures averted using risedronate compared to placebo using the different data types. Risedronate is an oral bisphosphonate indicated for the treatment and prevention of osteoporosis in postmenopausal women. In the studies we included in the model, both risedronate and placebo patients also received either calcium alone (1,000 mg) or calcium (1,000 mg) with vitamin D (500 IU/day if baseline serum 25-hydroxyvitamin D levels <40 nmol/l). The model assumes risk reduction in addition to that offered by calcium and vitamin D.

The model has a treatment period and time horizon of 3 years. This Markov state-transition model permits movement between health states annually according to state-transition probabilities (i.e., age-specific fracture incidence and mortality rates) that were derived from the best available observational data. Long-term health states in the model include healthy, healthy post-vertebral fracture, healthy post-hip fracture, healthy post-second hip fracture, and death. Short-term incident fracture states where patients can enter and leave within a given year include vertebral fracture, hip fracture, second hip fracture, and non-vertebral fracture. All patients start off in the healthy state, which represents the cohort of women who enter the model. Details of the model design, structure, assumptions, and validation have been previously described [18, 19]. Fractures averted was chosen as the primary outcome of interest in our hypothetical cohort, due to the substantial disability [20] and costs associated with fracture [5]. Although the model allows for the calculation of quality-adjusted life years

and costs, the focus of the current paper was fractures averted. Microsoft Excel 2000 was used to perform model calculations.

Model epidemiological data

The hypothetical cohort evaluated in the model consisted of 100,000 Canadian women, 65 years or older with osteoporosis (i.e., bone mineral density of 2.5 or more standard deviations [SD] below young adult mean) and a prevalent vertebral fracture (radiographically determined). This cohort was chosen to reflect the elevated fracture risk in this population [21, 22], and reimbursement policies in Canada. At age 65 and over, BMD testing is recommended for all women and osteoporosis therapies are covered under provincial drug plans.

Several sources of data were used to represent the epidemiological profile of this ‘target’ population. Age-specific general population fracture incidence rates for hip [23], vertebral (defined morphometrically from radiographs of the thoracic and lumbar spine) [24], and non-vertebral [25] fractures were employed within the model, with non-vertebral fracture incidence rates representing the sum of age-specific hip, wrist, clavicle, pelvis, humerus, and leg fracture rates. These fractures were selected as they would be considered ‘osteoporotic’, are commonly considered as ‘non-vertebral’ fractures in clinical trial data, and because incidence rates for these sites were available from updated and comprehensive sources. All fracture incidence rates were adjusted during the analysis based on the risk profile of the target population being modeled. These fracture rate adjustments were derived from the equation developed by Black and colleagues [26]. Mortality experienced by this population was also included in the model using Canadian age-specific mortality rate estimates obtained from the World Health Organization [27]. These data were complemented with mortality rate statistics for the year following the hip fracture (including hip fractures within non-vertebral fractures), which were based on a study by Keene and colleagues [28].

Sources of efficacy data

The sources of clinical efficacy data were as follows:

1. *Summary data*: relative risk reduction estimates for both non-vertebral and vertebral fractures are from the Osteoporosis Research Advisory Group (ORAG), a series of meta-analyses for several osteoporosis agents published in Endocrine Reviews in 2002 [29]. ORAG pooled estimates are based on simple proportions and did not incorporate time-to-event data. Initially, ORAG analyses “chose to pool broadly across doses and treatment durations [29]” and in some instances included doses not available in clinical practice (e.g., some of the risedronate trials included the 2.5 mg dose). Placebo-controlled RCTs were selected for the ORAG risedronate meta-analysis if they examined osteoporosis in post-menopausal women, with at least 1 year of follow-up, and had fracture incidence or BMD data available. Trials classified as either ‘treatment’ or ‘prevention’ studies were eligible for inclusion. Trial characteristics (entry criteria, mean age, and lumbar spine *T*-score) are shown in Tables 1 and 2. The ORAG analysis included all subjects randomized to treatment and placebo arms. The mean

patient age of studies included in ORAG ranged from 51.2 to 78.0 years and mean BMD lumbar spine *T*-scores ranged from −1.0 to −2.9.

2. *Individual patient data*: for non-vertebral fracture, relative risk reduction estimates are based on the Harrington et al. study [13], which incorporated data from the VERT-NA [30], VERT-MN [31], BMD-NA [32], and BMD-MN [33] trials (Table 1). The IPD analysis was restricted to a subset of patients who received risedronate 5 mg per day or placebo and who had a lumbar spine *T*-score of less than −2.5. Patients were required to have all four lumbar spine (L1–L4) vertebrae intact. Osteoporosis-related non-vertebral fractures included in this definition were: hip and pelvis, wrist, humerus, clavicle, and leg. All patients received calcium 1,000 mg/day and patients whose levels of 25 hydroxyvitamin D^3 were less than 40 nmol/L at baseline received up to 500 IU/day of vitamin D. The mean age of patients studied (n=1,172) was 66 years and the mean lumbar spine BMD *T*-score was −3.4. At baseline, 42% of patients studied in the Harrington IPD had no prevalent vertebral fractures; 25% and 33% had one and more than one prevalent vertebral fracture respectively.

For vertebral fracture, relative risk reduction estimates are from the Adachi et al. study [12], which incorporated data from the VERT-NA [30], VERT-MN [31], BMD-NA [32], BMD-MN [33], and ‘Prevention of bone loss in early menopause’ [34] studies (Table 2). The IPD analysis was restricted to a subset of patients who received risedronate 5 mg or placebo with at least one existing vertebral fracture or a femoral neck BMD *T*-score of less than −2.5 at baseline. The mean age of the patients studied in the Adachi et al. analysis was 68 years and the mean lumbar spine *T*-score was −2.74 in the placebo group (n=1,112) and −2.72 in the risedronate 5 mg group (n=1,119). The percentage of patients with a vertebral fracture at baseline was approximately 90% in both the placebo and treatment groups. Patients that were missing baseline data or who had no post-baseline vertebral fracture radiographs were excluded.

Both IPD meta-analyses [12, 13] were based on primary data sources (i.e., authors had access to databases from the original trials including adverse event information).

Results

The relative risk reduction (1-relative risk) associated with risedronate treatment (compared to placebo) for vertebral and non-vertebral fractures for each of the two data types (Table 3) were separately entered into the model to obtain the number of fractures averted over 3 years. The reduction in relative risk associated with treatment for non-vertebral fractures is 0.32 for ORAG (5 mg) and 0.59 for IPD (Table 3). For vertebral fractures, these estimates are 0.38 and 0.45, respectively.

Table 4 presents the total fractures averted with risedronate therapy (versus placebo) per 100,000 women over 3 years for each of the two data types. For comparative purposes (to be consistent with the IPD studies), we present summary data relative risk reduction estimates for the ORAG 5 mg pooled. When the parameters are entered into our model, as illustrated in Table 4, the number of fractures occurring in the risedronate group differed according to

the relative risk estimate used. Based on ORAG (summary data) estimates, the number of non-vertebral fractures averted with risedronate was 3,571 per 100,000 women; based on IPD estimates, this number was 6,584. Correspondingly, the number of vertebral fractures averted per 100,000 women was 8,552 based on ORAG estimates and 10,127 based on IPD. Thus, an additional 3,013 more non-vertebral fractures and 1,575 vertebral fractures were averted per 100,000 women over 3 years when IPD versus summary data are used. Table 4 also provides the number of fractures averted for the ORAG meta-analyses with 2.5+ 5 mg pooled doses.

Discussion

The summary data and IPD meta-analyses lead to different estimates of fracture reduction (Table 3). Our fracture incidence model demonstrates the impact of these differences on the number of vertebral and non-vertebral fractures averted in an important high-risk population of women over 65 years old with osteoporosis and prevalent vertebral fracture (Table 4). IPD meta-analysis estimates 3,013 more non-vertebral and 1,575 more vertebral fractures averted than the ORAG summary data meta-analysis. These differences are explained by varied cohort selection, especially the inclusion of low-risk populations in the ORAG meta-analysis, as well as by methodological differences between these two approaches.

Choosing the IPD-derived estimates for risedronate over those of the ORAG summary data analysis depends first on recognizing that the RCT cohorts included in the former are more representative of patients requiring treatment than the cohorts included in the latter. It is imperative to consider the cohort of interest when considering clinical efficacy data inputs. Tables 1 and 2 present the trials and patient characteristics included in the ORAG summary data and the two IPD analyses.

The ORAG study chose to pool broadly and may have been over-inclusive. It combined prevention and treatment studies, pooled doses, and included a study with a more elderly cohort (80 years or older) and undefined BMD (selected primarily on the basis of non-skeletal risk factors). The Harrington et al. [13] and Adachi et al. [12] IPD analyses included higher risk patients with clearly established osteoporosis (based on a *T*-score or existing vertebral fracture), only studies with a 5 mg dose of risedronate (2.5 mg is not an approved dose), and a more homogenous age group.

It has been well established in the osteoporosis literature that fracture risk varies according to several factors including age, previous fracture history, and severity of BMD *T*-scores [22, 21]. We know from other studies that absolute and relative fracture risk reduction are greater in those with more severely reduced BMD [35]. In an analysis based on summary data, it is not possible to examine subgroups and this may be of particular concern when heterogeneous groups are pooled together because differences between sub-groups may be obscured. This may also occur in an analysis with primary data, if we control for factors that may be related to risk without examining important underlying interactions.

Several methodological differences between the two approaches also contributed to the differences in relative risk estimates and subsequent number of fractures averted. First, in a

summary data meta-analysis it is not possible to control for trial designs or for differences among patient populations (e.g., disease severity and demographic characteristics) in the analysis. There are limits placed on the ability to examine sources of heterogeneity, such as differences in the true treatment effect between studies. Heterogeneity may occur for a number of reasons, such as varied designs and patient characteristics, and if observed, it is important to consider why it exists [15, 16]. In the ORAG series, the authors noted "As is often the case, we were frequently left with heterogeneity of study results that we could not explain with our a priori hypotheses. This may, in part, be due to our having to consider studies as a unit in our analyses [29]." When aggregated patient characteristics are examined to explain heterogeneity, this approach is subject to an aggregation bias (i.e., ecological fallacy [16]), whereby the association observed between variables on an aggregate level is not necessarily the same as the association which exists at the individual level. The true treatment effects in underlying populations may be masked, and may provide different estimates of relative risk reduction from individual trials.

In IPD analysis, with access to the primary data, it is possible to control for covariates such as differences in patient characteristics at an individual level in the analysis. It is also possible to examine potential effect modifiers, or examine patient sub-groups that are most of interest. Simulation studies comparing IPD and summary data indicate clearly that meta-analyses based on summary data have much less power [15, 16, 36] and are generally inadequate at finding a clinically moderate interaction [16].

Secondly, a summary data meta-analysis is limited to comparing simple proportions, in this case the *number* of fracture events reported, without consideration of when the event occurred [29]. Therefore, summary data does not allow patients who dropped out prior to the end of the study to be statistically accounted for [37]. An IPD analysis allows important information regarding *when* the event occurred to be incorporated using a time-to-event analysis, a more powerful and informative presentation of data [38]. One of the chief benefits is that the time-to-event analysis can take into account censored data, and statistical inferences may be drawn regarding the time a patient spent in the study. Patients with censored data contribute valuable information and should not be omitted from the analysis [12, 38]. For example, it is often the sickest patients who drop out or have an outcome of interest.

A large loss to follow-up, particularly for the larger trials, was the major methodological limitation of the risedronate trials cited by the ORAG authors: "loss to follow-up threatens the validity of a trial because the distribution of prognostic factors, and thus the event rate, may be very different in those lost to follow-up than in those who complete the trial [8]." Without access to time-to-event data, the ORAG analysis could only examine simple, end of trial proportions, and likely resulting in an underestimate of the treatment effect for risedronate. As the authors noted, it was "particularly unlikely" that any loss to follow-up favored estimates of risedronate's treatment effect [8], since one of the largest trials included in their meta-analysis (the VERT-NA trial [30]) had a disproportionately large number of high-risk patients in the placebo group lost to follow-up. In the placebo group, 41.4% of patients lost to follow-up were considered high risk for fracture at baseline versus only 37.9% of treatment patients lost to follow-up. Remaining patients were likely healthier as

those that were less healthy had already fractured and, as a consequence, any bias introduced by loss to follow-up favored the placebo group. Large loss to follow-up rates are expected in trials of older patients and for osteoporosis they are often the patients who fracture, discontinue the study and go on treatment.

Methodologically, it is widely accepted that the use of IPD is an 'ideal' approach to meta-analysis, and that summary data offers a second practical alternative when access to primary data is unavailable [14–16, 39]. However few previous reports have examined the degree of discrepancy between the two approaches [39]. Similar to our results, Delmas et al. [40] found that summary data produced different conclusions than IPD analysis. In that study, a comparative analysis was conducted to compare simulated IPD and a summary data meta-analysis of various osteoporosis medications (alendronate, etidronate, raloxifene, HRT, calcitonin, tiludronate) to determine which was more accurate in capturing the true correlation between BMD and fracture risk. IPD was simulated to match the reported summary statistics for each study. Results indicated that the summary data meta-analysis was not sensitive and did not produce the correct correlation between fracture risk reductions and BMD increases, whereas the IPD always provided accurate estimates of the association between BMD and fracture risk reduction.

While the IPD meta-analysis overcomes many of the limitations of a summary data meta-analysis, it does not overcome all of the limitations of meta-analyses. Some of the limitations still present in any type of meta-analysis that do not exist with individual RCTs include: trials with different inclusion/exclusion criteria, different data points collected, differing schedule of events for data points collected, and different study conduct such as following of drop-out patients. Apparent differences may disappear when adjusting for influential confounding variables in both IPD and summary data meta-analyses.

An updated summary data meta-analysis combines primary and secondary prevention risedronate studies [41]. The relative risk reduction was 0.37 (95% CI 0.49, 0.23) for vertebral fractures and 0.20 (95% CI 0.28, 0.10) for non-vertebral fractures. When our analysis was conducted, ORAG was the appropriate comparator and the newer estimates are not widely divergent from the original ORAG analysis.

Conclusions

We believe that the IPD analyses selected for our model [13, 12] are the best choice of relative risk estimates available among meta-analysis approaches. The IPD analyses have the advantage of superior statistical methodology, with the caveat that IPD analyses can be misleading when the adjustment for appropriate covariates is not adequate. Compared with IPD, a summary data meta-analysis has limited ability to examine sources of heterogeneity, has less power, and does not perform as well as IPD when time to event outcomes or particular sub-groups are of interest [15, 16, 36]. The fracture-incidence-based model we used in this study was based on a hypothetical 'higher-risk' cohort of women 65 years or older with osteoporosis and a prevalent vertebral fracture. This cohort would likely benefit most from treatment. The IPD analyses were based on a similar population to our target population. Due to the constraints of summary data methodology, the ORAG analysis was

not able to examine sub-groups based on severity, thus the true treatment effects of higher risk patients may have been masked in that analysis.

Policy makers and health economists should pay careful attention to the choice of clinical efficacy data inputs. Although economic considerations were beyond the scope of this paper, future cost-effectiveness studies should also consider IPD, observational data, and RCTs to examine the economic and societal benefits of treating osteoporosis in a Canadian context. As the population of high-risk patients for osteoporosis (those over age 65) [1] continues to increase, the appropriate management of patients with osteoporosis is an imperative consideration in the decade to come.

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Table 1

RCTs included in individual patient data (IPD) and Osteoporosis Research Advisory Group (ORAG) meta-analyses: non-vertebral fracture

		Harrington et al. [13] (IPD: non- vertebral)[a]			ORAG (non-vertebral analysis) [8]		
Study (duration)	**Entry criteria (skeletal status, duration)**	**N control/Tx (5mg only)**	**Mean age**	**Lumbar spine BMD *T*-score**	**N control/Tx**	**Mean age[b]**	**Lumbar spine BMD *T*-score[b]**
VERT-NA (3 years) [30]	2 or more VF at baseline or 1 VF and a lumbar spine BMD *T*-score of ≤ −2	282/265	68 (7.4)	−3.4 (0.69)	815/812 (5 mg group only, 2.5 mg excluded)	69 (7.3)	−2.4
VERT-MN (3 years) [31]	2 or more VF at baseline	80/69	69 (7.0)	−3.6 (0.72)	406/406 (5 mg group only, 2.5 mg excluded)	71 (7.0)	−2.7
BMD-MN (2 years) [33]	Lumbar spine BMD *T*-score of ≤ −2.0	112/100	65 (7.1)	−3.2 (0.52)	125/172 (includes 2.5 mg and 5 mg)	64.7 (7.2)	−2.9
BMD-NA (1–1.5 years) [32]	Lumbar spine BMD *T*-score of ≤ −2.0	134/130	62 (7.6)	−3.1 (0.50)	220/428 (includes 2.5 mg and 5 mg)	62.5 (0.3)	−2.8
Clemmesen et al. (2 years) [42]	At least one, but not more than four, VF	Not included	–	–	44/88 (2.5 mg only dose in this study)	68.3 (5.7)	−2.4
Mortensen et al. (3 years) [43]	Normal lumbar spine bone mass (>2 SD), 6–60-month post- menopausal (1–2 years treatment + 1 year follow-up)	Not included	–	–	36/75 (5 mg cyclic/or daily only dose in this study)	51.2 (3.8)	−1.0
HIP [44]	Age 70–79: femoral neck *T*-score ≤−4 or femoral neck *T*-score ≤−3 + 1 risk factor) age 80 and over: at least 1 non-skeletal risk factor or low BMD (≤−4 or ≤−3 + risk factor)	Not included[c]	–	–	3,134/6,197 (includes 2.5 mg and 5 mg)	78 (9.7)	−2.8 Femoral neck = −3.7

VF vertebral fracture(s)

[a] Analysis restricted to subset of patients who received risedronate 5 mg per day (or placebo) and who had a lumbar spine *T*-score of less than −2.5. Patients had to have all four lumbar spine (L1–L4) vertebrae intact

[b] From ORAG Table 2 [8] (based on all treatment groups–placebo; 2.5 mg and/or 5 mg groups were applicable)

[c] The HIP study was not included because patients were substantially older (mean age 78 years) than the other study populations that were included (mean age 66 years)

Table 2

RCTs included in individual patient data (IPD) and Osteoporosis Research Advisory Group (ORAG) meta-analyses: vertebral fracture

		Adachi et al. [12] (IPD: vertebral fracture)[a]			ORAG (vertebral analysis) [8]		
	Entry criteria (skeletal status, duration)	***N* control/Tx (5 mg only)**	**Mean age (placebo)**	**Lumbar spine BMD *T*-score (placebo)**	***N* control/Tx**	**Mean age[b]**	**Lumbar spine BMD *T*-score[b]**
VERT-NA [30]	2 or more VF at baseline or 1 VF and a lumbar spine BMD *T*-score of ≤ −2 (3 years)	565/579	69 (6.9)	−2.3	678/696 (5 mg group only, 2.5 mg excluded)	69 (7.3)	−2.4
VERT-MN [31]	2 or more VF (T4–L4) at baseline (3 years)	339/334	71 (6.8)	−2.4	346/344 (5 mg group only, 2.5 mg excluded)	71 (7.0)	−2.7
BMD-MN [33]	Lumbar spine BMD *T*-score (L1–L4) of ≤ −2.0 (2 years)	74/77	66 (7.4)	−2.3	125/172 (includes 2.5 mg and 5 mg)	64.7 (7.2)	−2.9
BMD-NA [32]	Lumbar spine BMD *T*-score of ≤ −2.0 (1–1.5 years)	109/102	64 (7.0)	−2.5	Not included	–	–
Prevention of bone loss in early menopause [34]	Post-menopausal women (6–36 months); 1 VF or a femoral neck BMD of ≤ −2.5 (2 years)	25/26	53 (2.9)	−0.8	Not included	–	–
Clemmesen et al. (1997) [42]	At least one, but not more than four, VF (2 years)	Not included	–	–	44/88(2.5 mg only dose in this study)	68.3 (5.7)	−2.4
Mortensen et al. (1998) [43]	Normal lumbar spine bone mass (>2 SD), 6–60-month post-menopausal (1–2 years treatment + 1 year follow-up)	Not included	–	–	36/75 (5 mg cyclic/or daily only dose in this study)	51.2 (3.8)	−1.0

VF vertebral fracture(s)

[a] IPD analysis restricted to subset of patients who received risedronate 5 mg per day (or placebo) and with at least one existing vertebral fracture or a femoral neck BMD *T*-score of less than −2.5 at baseline

[b] From ORAG Table 2 [8] (based on all treatment groups–placebo; 2.5 mg and/or 5 mg groups were applicable)

Table 3

Reduction in relative risk[a] (95% CI) of fracture for risedronate-treated patients[b]

Data source		Non-vertebral fracture	Vertebral fracture
Osteoporosis Research Advisory Group (ORAG)	2.5 and 5 mg	0.27 (0.13, 0.39) [8]	0.36 (0.23, 0.46) [8]
	5 mg pooled	0.32 (0.13, 0.47)	0.38 (0.24, 0.49)
Individual patient data (IPD)	5 mg	0.59 (0.27, 0.77) [13][c]	0.45 (0.31, 0.57) [12]

CI confidence interval

[a] Reduction in relative risk=1-relative risk

[b] Versus placebo-treated patients

[c] Post hoc analyses of pooled non-vertebral fracture data (collection was prospectively planned in the trials)

Table 4

Number of fractures using 3-year risedronate treatment versus placebo in women 65 years or older with low BMD and prevalent vertebral fracture

Data source		Treatment[a]	Number of fractures per 100,000 women 65years or older with low BMD and prevalent vertebral fracture	
			Non-vertebral	Vertebral
Osteoporosis Research Advisory Group (ORAG)	2.5 mg and 5 mg	Placebo	11,159	22,505
		Risedronate	8,146	14,404
		Fractures averted with risedronate	3,013	8,101
	5 mg pooled	Placebo	11,159	22,505
		Risedronate	7,588	13,953
		Fractures averted with risedronate	3,571	8,552
Individual patient data (IPD)		Placebo	11,159	22,505
		Risedronate	4,575	12,378
		Fractures averted with risedronate	6,584	10,127

[a]Assumes all patients (risedronate or placebo) received calcium only or calcium and vitamin D