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Osteoporosis management: a perspective based on bisphosphonate data from randomised clinical trials and observational databases

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Abstract

Aims: The efficacy of treatments for osteoporosis can be evaluated using a variety of <u>study</u> designs. This article aims to comprehensively review the evidence for bisphosphonate antifracture efficacy in postmenopausal women, discussing the strengths and limitations associated with each study <u>method</u>.

Methods: Literature analysis included English-language publications reporting results of randomised controlled trials (RCTs), post hoc analyses, meta-analyses and observational studies evaluating the efficacy of alendronate (ALN), ibandronate (IBN), risedronate (RIS) and zoledronate (ZOL), with an initial sample size \geq 100 patients, and follow-up data for at least 1 year.

Results: Primary and secondary analyses of RCT data suggest differences among bisphosphonates with regard to site-specific anti-fracture efficacy and onset of fracture risk reduction. While some observational studies indicate differences in clinical outcomes among these agents, others report similar effectiveness. ALN and RIS data demonstrate sustained fracture protection for up to 10 and 7 years of treatment, respectively. The efficacy of IBN and ZOL has been evaluated for up to 3 and 5 years, respectively.

Conclusions: Understanding of the benefits of bisphosphonate treatment can be maximised

by evaluating complementary data from RCTs and observational database studies. Fracture

risk reduction with bisphosphonates is shown in RCTs and in real-world clinical settings.

Word count: <u>200</u> (max 250)

Keywords: bisphosphonates; observational; osteoporosis; placebo-controlled; randomised clinical trial

Review criteria

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Deleted: design.

Deleted: The relative effectiveness of bisphosphonate therapies needs further evaluation using standardised methodologies across studies. Deleted: 214

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The US National Library of Medicine (PubMed) was used to search and collect osteoporosis studies published in the English language from 1995 through to 2009. Studies were included in this report if they focused on treatment rather than prevention of osteoporosis, used a primary outcome measure related to fracture risk or bone mineral density, included an initial sample size of \geq 100 patients and had follow-up data for at least 1 year.

Message for the clinic

Our knowledge of the potential benefits and limitations of bisphosphonate treatments for osteoporosis can be extended by evaluating data from randomised controlled trials (RCTs) and observational database studies. Both types of studies indicate fracture risk reduction with bisphosphonates. RCTs suggest differences among bisphosphonates with regards to site-specific anti-fracture efficacy and onset of fracture risk reduction. Potential differences in effectiveness between bisphosphonates in real-world clinical settings needs further investigation.

Introduction

As the worldwide population ages, the prevalence of osteoporosis is increasing. In the USA and Europe, it has been estimated that > 40% of postmenopausal women will suffer 1 or more fragility fracture during their lifetime (1,2), with other regions of the world also affected (3–5). As expected from the relatively high prevalence of osteoporosis, resulting fractures contribute substantially to overall medical costs (6). US costs for osteoporotic fractures during 2005 were estimated at > \$19 billion, with projections indicating an increase of > 48% in fractures and costs by 2025 (7).

Health-related quality of life and survival are substantially reduced after experiencing an osteoporotic fracture (1,8,9). Only 15% of European patients experiencing a hip fracture are able to return to unassisted ambulation after 6 months, and 24% die within the first year after fracture (1). Likewise, another study has reported that 1-year mortality after hip fracture was 17% in the USA and 23–30% in Latin America (3). Using worldwide osteoporosis prevalence data, disability adjusted-life-years due to osteoporotic fracture can be calculated as 5.8 million, with 64% attributed to fractures in women (10). Nearly 1% of the global burden from non-communicable diseases can be attributed to osteoporosis (10).

Effective therapies for osteoporosis include calcium and vitamin D supplementation, oestrogen or selective oestrogen-receptor modulators (e.g., raloxifene), bisphosphonates (e.g., alendronate [ALN], ibandronate [IBN], risedronate [RIS] and zoledronate [ZOL]), teriparatide and strontium ranelate. <u>ALN, IBN, RIS and ZOL are all approved in Europe and</u> the USA for treatment of postmenopausal osteoporosis.

Due to the infrequent occurrence of new fractures during short-term clinical trials, surrogate markers of fracture risk are sometimes selected as primary efficacy end-points. As lower bone mineral density (BMD) scores in untreated patients are associated with increased fracture risk, clinical trials have often evaluated improvements in BMD as a possible marker of reduced fracture risk (11–17). Changes in bone turnover markers are also used as surrogate markers of bone health to predict risk for fracture (18,19). The relationship between improvements in surrogate markers of fracture risk and actual fracture risk reduction, is discussed further in the results section.

In order to fulfil regulatory requirements as set by the Committee for Medicinal Products for Human Use (CHMP) (20), randomised controlled trials (RCTs) use standardised methods for the selection of patients and the determination of outcome measures. RCTs are designed to minimise internal bias, ensuring that differences in clinical outcomes can be attributed to treatment effects. Homogeneous populations are selected and randomly assigned to each study group, and compliance with treatment is maximised through close follow-up.

Although RCTs are considered the gold standard in clinical research, the clinical relevance of the data is limited by the strict selection of study participants and by the tightly controlled design, which is difficult to apply in clinical practice. Patients with comorbid illnesses such as thyroid disease, gastrointestinal disease, active cardiovascular disease, bilateral hip replacement, rheumatoid arthritis and iron-deficiency anaemia are typically excluded from RCTs (11,12). Recent use of osteoporosis therapy is another common exclusion criterion (11,21–23). The impact of strict exclusion criteria has been highlighted in a study evaluating 120 women with osteoporosis who were newly considered for osteoporosis therapy (24). This study showed a marked discordance between actual patient samples and those utilised for

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clinical trials (24). Although all of the patients were deemed candidates for osteoporosis treatment, only 3%, 4%, 7% and 21% were eligible to participate in each of 4 RCTs (24). Patients were most commonly excluded due to comorbid illness (60%), concomitant medications (60%), disease severity (19%) and age (36%) (24).

Secondary analyses of RCTs may be used to identify changes in study subpopulations or alternative outcome measures. Unfortunately, post hoc analyses typically use smaller sample sizes and/or alternative outcome measures for which the original study was neither designed nor powered. Meta-analyses process data from patients who did not participate in the same study pool, increasing the power of single RCTs to ascertain drug efficacy using less frequent outcomes. Meta-analyses can also investigate specific effects within subpopulations. Although pooling data in this way helps increase sample size and may provide a broader and more diverse study sample, differences in patient selection criteria, treatment and follow-up assessments reduce the validity of data interpretation.

Long-term efficacy can be evaluated using extensions of previously conducted RCTs. Extension studies utilise the same patient population selection as the original RCT, although patients elected to continue treatment are often those achieving good efficacy and tolerability during the original RCT (25).

Additional information on the effects of a treatment in actual patient settings can be collected from observational studies based on large national or international databases, which are commonly used in Europe and the USA, with outcome measures incorporating treatment efficacy, adherence and tolerability (26,27). The high level of treatment adherence seen in RCTs is often not reproduced in actual clinical practice. For example, in the 4-year Fracture

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Intervention Trial (FIT), about 82% of patients were still taking the study drug (ALN or placebo) at study completion (22). Conversely, a survey of women in the Australian Longitudinal Study on Women's Health reported a median time to discontinuation of a new bisphosphonate of 170 days (28). Observational database analyses provide readily accessible data on large, unselected patient cohorts representing real-world treatment conditions. Conclusions drawn from these studies have, however, important limitations, including possible selection bias due to the lack of randomisation and the restricted availability of information. Robust statistical planning, including clear primary and secondary end-points and well-defined sensitivity analysis to adjust for possible confounders, will reduce the possibility of selection bias and increase data robustness.

This article reviews the evidence available for bisphosphonate efficacy in the treatment of postmenopausal osteoporosis. Data from a wide range of study designs are discussed and the strengths and limitations associated with each study and each study design are highlighted.

Methods

The US National Library of Medicine (PubMed) was used as a source of data. Englishlanguage publications reporting results of RCTs, post hoc analyses, meta-analyses, extension studies and observational studies evaluating the efficacy of second-generation bisphosphonates (ALN, IBN, RIS and ZOL) in postmenopausal women were selected. Studies were included if they focused on treatment rather than prevention of osteoporosis, used a primary outcome measure of fracture risk or BMD, included an initial sample size of ≥ 100 patients and had follow-up data for at least 1 year. Studies were excluded if they represented duplicate reports of previously published data, contained only unique patient subpopulations, reported preliminary or incomplete data sets or presented major

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methodological problems (e.g., excluding fractures that occurred during the first 6 months of treatment). Studies reporting outcomes of combination or sequential therapy or treatment switch were excluded, as were active comparator trials evaluating different dosing regimens of the same bisphosphonate.

Results

An initial literature search identified 136 studies which included efficacy evaluations of at least one of the second-generation bisphosphonates (ALN, IBN, RIS and ZOL) for postmenopausal osteoporosis, with fracture or BMD as an evaluation measure. Detailed analysis of each of these using the full inclusion and exclusion criteria, rendered a total of 16 RCTs , 3 head-to-head studies, 25 post-hoc/meta-analyses, 9 long-term extensions and 11 observational studies for inclusion in the current analysis. An additional 6 post-hoc/metaanalyses publications were included, which discussed the relationship between improvements in surrogate markers of fracture risk and actual fracture risk reduction. **Deleted:** ALN, IBN, RIS and ZOL are approved in the USA and Europe for the treatment of postmenopausal osteoporosis. All of these agents are associated with increases in BMD, decreases in levels of markers of bone resorption and reductions in the risk of osteoporotic fractures.

Deleted: Due to the infrequent occurrence of new fractures during shortterm clinical trials, surrogate markers of fracture risk are sometimes selected as primary efficacy end-points. As lower BMD scores in untreated patients are associated with increased fracture risk, clinical trials have often evaluated improvements in BMD as a possible marker of reduced fracture risk (12,13,22–26).

RCTs

In clinical trials of bisphosphonates, BMD increases have been consistently demonstrated for bisphosphonate-treated patients compared with placebo patients (11–17). In RCTs with fracture end-points, ALN, RIS and ZOL treatment have been shown to reduce the risk of vertebral and nonvertebral fractures, including those of the hip (12,22,29–34). IBN has demonstrated anti-fracture efficacy at vertebral sites, but nonvertebral and hip fracture risk reduction was not shown in the overall study population of the phase III fracture trial (35).

The anti-fracture efficacy data of bisphosphonates reported in placebo-controlled studies are summarised in Figure 1. This figure illustrates the relative risk (RR) of incident vertebral

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(Figure 1A), nonvertebral (Figure 1B) and hip (Figure 1C) fracture for each bisphosphonate study (12,13,22,29–35). Fracture risk was reduced in these trials over a range of 30–70%. Table 1 summarizes information regarding treatment regimens, patient numbers, treatment duration, treatment completers and BMD changes for all the studies reported in Figure 1 (12,13,22,29–35).

Alendronate (ALN)

The Alendronate Phase III Osteoporosis Treatment Study reported a 48% reduction (p = 0.03) in the risk of vertebral fractures in women with low BMD after 3 years of ALN (5-20 mg daily) treatment (13). The subsequent Fracture Intervention Trial (FIT) reported that ALN Deleted: (5–10 mg daily) treatment in women with previous vertebral fractures, significantly decreased the risk of Deleted: (N = 1022 for ALN 5-10 mg daily; N = 1005 for placebo) vertebral and hip fractures by 47% (p < 0.001) and 51% (p = 0.047), respectively (29). The 4-Deleted: (N = 2214 for ALN 5-10 mg daily; N = 2218 for placebo) year FIT study in women with postmenopausal osteoporosis but no vertebral fracture likewise showed a 44% (p = 0.002) reduction in the risk of vertebral fracture with ALN (22). The FOSamax International Trial (FOSIT) reported a 47% (p = 0.021) reduction in the risk of **Deleted:** (*N* = 950 for ALN 10 mg daily; N = 958 for placebo) (13). nonvertebral fractures in postmenopausal women with low BMD treated for 1 year with ALN. (12).

Ibandronate (IBN)

The iBandronate Osteoporosis vertebral fracture trial in North America and Europe (BONE) in postmenopausal women with a BMD T-score ≤ -2.0 and 1–4 prevalent vertebral fractures showed that 3 years of IBN treatment significantly reduced vertebral fracture risk (35). IBN 2.5 mg daily and IBN 20 mg intermittently, were associated with a 62% (p = 0.0001) and 50% (p = 0.0006), respectively, reduction in the risk of vertebral fracture compared with placebo (35). Overall there was no significant reduction in the incidence of nonvertebral fractures in

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IBN patients compared with placebo patients (35). A subgroup analysis of patients with femoral neck BMD T-score < -3.0 was associated with a decrease of 69% (p = 0.012) in the risk of nonvertebral fractures (35).

Risedronate (RIS)

Data from the North American arm of the Vertebral Efficacy with Risedronate Therapy (VERT-NA) trial showed that after 3 years of RIS treatment in women with previous vertebral fracture, vertebral and nonvertebral fracture risks were reduced by 41% (p = 0.003) and 40% (p = 0.02), respectively (30). In the multinational arm of the VERT trial, vertebral fracture risk was reduced by 49% (p < 0.001) in women with at least 2 prevalent vertebral fractures treated with RIS over a 3-year period (31). Reduction in nonvertebral fractures did not reach significance (33%, p = 0.06) (31). In the Hip Intervention Program (HIP), 3 years of RIS treatment was associated with an overall reduction in hip and nonvertebral fracture risks of 30% (p = 0.02) and 20% (p = 0.03), respectively (32).

Deleted: (N = 813 for RIS 5 mg daily; N = 815 for placebo),

Deleted: (N = 407 for RIS 5 mg daily; N = 407 for placebo),

Deleted: (*N* = 3093 for RIS 2.5 mg daily; *N* = 3104 for RIS 5 mg daily; *N* = 3134 for placebo)

Zoledronate (ZOL)

The 3-year Health Outcomes and Reduced Incidence with Zoledronic acid Once yearly (HORIZON) Pivotal Fracture Trial demonstrated that ZOL treatment in postmenopausal women with a BMD T-score ≤ -2.5 , or a BMD T-score ≤ -1.5 and prevalent vertebral fracture(s), decreased the risks of incident vertebral, nonvertebral and hip fractures by 70% (p < 0.001), 25% (p < 0.01) and 41% (p = 0.002), respectively (33). Reductions in vertebral fracture risk were observed as early as 12 months after treatment initiation (60%; p < 0.001) (33). Hip and nonvertebral fracture risk reductions were observed at 24 months (33). The HORIZON Recurrent Fracture Trial showed that ZOL treatment for 2 years in patients with a recent hip fracture decreased clinical vertebral and nonvertebral fracture incidence by 46% (p

= 0.02) and 27% (p = 0.03), respectively (34). A reduction of 28% (p = 0.01) in deaths from any cause was observed in the treatment group compared with placebo patients (34).

Data from RCTs can be used to calculate the number needed to treat (NNT) to achieve prevention of a single fracture (Table 2) (12,13,29–33,35). In general, fewer patients require treatment for prevention of vertebral compared with nonvertebral fractures. NNT data should not be used to compare clinical efficacy between drugs because the different study populations included in each RCT are likely to present differences in fracture risk.

Head-to-head trials

Direct efficacy comparisons between bisphosphonates in randomised trials have only used surrogate efficacy markers such as BMD and markers of bone turnover. The Fosamax Actonel Comparison Trial (FACT) was a 12-month head-to-head trial of once-weekly ALN (70 mg) and once-weekly RIS (35 mg) (21,36). In both the North American (21) and international (36) arms of the FACT trial, ALN produced greater gains in BMD and greater reductions in markers of bone turnover than RIS. The 1-year, head-to-head MOTION study compared clinical outcomes of once-monthly IBN 150 mg and once-weekly ALN 70 mg (37). Increases in BMD from baseline were similar in both treatment groups, as were vertebral fracture incidences (0.6% in both groups) (37). The incidences of nonvertebral fractures with ALN and IBN were 1.4% and 1.6%, respectively (37).

BMD, bone turnover markers and actual fracture risk reduction

Data from the BONE trial indicate corresponding changes between improvements in surrogate markers and actual reduction in clinical fracture risk (38). However, there is increasing evidence that the BMD-fracture risk relationship is not a linear one, and that it is

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affected differentially by different bisphosphonates (39–41). For example, it has been reported that BMD changes account for < 30% of the reduction in vertebral fractures in women treated with osteoporosis therapy, including bisphosphonates (39). A post hoc analysis of data from 3 RIS trials has demonstrated that although treated patients showing an increase in spine BMD had a lower vertebral fracture risk than treated patients showing a decrease in BMD, greater increases in BMD did not provide greater decreases in vertebral fracture risk (40). A subsequent analysis of the same trials also indicated that in RIS-treated patients, the incidence of nonvertebral fractures was similar between patients whose BMD increased from baseline and those whose BMD decreased (41). In a recent meta-analysis of 4 IBN trials, an inverse linear relationship was observed between percentage change in lumbar spine BMD and the rate of clinical fractures, while the same type of relationship could not be established between increases in total hip BMD and nonvertebral fracture rate (42).

Regarding other possible surrogate markers of bone health, bone resorption markers have been reported to account for half of the reduction in clinical fractures with RIS (43), while a post hoc analysis of the HORIZON Pivotal Fracture Trial failed to correlate low levels of bone formation markers with an increased risk of fracture (44).

Post hoc and meta-analyses of RCTs

Alendronate (ALN)

Post hoc and meta-analyses of ALN trials have consistently reported anti-fracture efficacy at the spine (45–51), nonvertebral sites (47–54) and hip (48,53–56). Treatment with ALN has also been shown to reduce the risk of clinical vertebral fractures after 12 months of treatment, while the onset of hip protection was reported at Month 18 (48). A Cochrane Review of 11 ALN trials (N = 12,068; ALN 10 mg daily) showed a significant 45% reduction in the risk of

vertebral fractures (RR 0.55; 95% confidence interval [CI]: 0.45–0.67) for both primary and secondary fractures (57). Reduction in the risk of nonvertebral fractures was not significant for primary fracture, but was significant at 23% for secondary fractures (RR 0.77; 95% CI: 0.64–0.92), including a 53% reduction in hip fractures (RR 0.47; 95% CI: 0.26–0.85) and a 50% reduction in wrist fractures (RR 0.50; 95% CI: 0.34–0.73) (57).

Ibandronate (IBN)

A post hoc analysis of the BONE trial indicated that oral IBN 2.5 mg daily has a pronounced effect on the more severe vertebral fractures, reporting at 1 year a reduction of 59% in the RR of combined new moderate and severe vertebral fractures (p = 0.0164) (58). Data from the BONE trial (35) and a meta-analysis by Liberman et al. (54) indicated a lack of nonvertebral fracture protection with daily or intermittent IBN dosing. In a recent meta-analysis of 4 separate RCTs including daily, intermittent and monthly dosing regimens of IBN (N = 8710), results were compared by annual cumulative dosage of IBN (59). High dosage was defined as 150 mg/month orally, 2 mg intravenously every 2 months, or 3 mg intravenously every 3 months (59). Fracture risk compared with placebo was significantly reduced among women treated with high-dose IBN for all nonvertebral fractures (30% reduction; p = 0.04) and clinical fractures (29% reduction; p = 0.01) (59).

Risedronate (RIS)

A post hoc analysis of the VERT trial in postmenopausal women with prevalent vertebral fractures (N = 2442) indicated that 5 mg daily RIS treatment is associated with a reduced risk of clinical vertebral fractures within 6 months of treatment initiation (60). Meta-analyses of RIS trials have consistently shown reduction in the risk of vertebral (47,51,54,61–66), nonvertebral (47,51,52,54,61,67) and hip (52,54,55) fractures. In a meta-analysis of 4 RIS

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trials, it was further demonstrated that 5 mg RIS treatment significantly reduced the incidence of nonvertebral fractures within 6 months of treatment (67). A Cochrane Review of 7 RIS trials (N = 14,049; RIS 5 mg daily) reported no significant reduction in primary fracture risk (68). For secondary prevention, a 39% reduction in the risk vertebral fractures (RR 0.61; 95% CI: 0.50–0.76) was demonstrated, as well as a 20% reduction for nonvertebral fractures (RR 0.80; 95% CI: 0.72–0.90) and a 26% reduction for hip fractures (RR 0.74; 95% CI: 0.59– 0.94) (68). Wrist fractures were not significantly reduced with RIS (68). When primary and secondary prevention studies were combined, the reduction in fractures remained significant for both vertebral (RR 0.63, 95% CI: 0.51–0.77) and nonvertebral fractures (RR 0.80, 95% CI: 0.72–0.90) (68).

Zoledronate (ZOL)

No post hoc or meta-analyses regarding fracture outcomes have been conducted to date with ZOL trials.

Head-to-head studies

A post hoc analysis of the FACT trial reported that more ALN- than RIS-treated patients achieved predefined increases in BMD at 12 months and reductions in biochemical markers of bone turnover at 3 months of treatment (69). Also, more RIS- than ALN-treated patients were classified as apparent 'non-responders' (i.e. experienced any bone loss) after 12 months of therapy (69).

Long-term extension analyses

Long-term treatment can be evaluated using extensions of previously conducted RCTs. ALN, RIS and ZOL treatment have been assessed for up to 10, 7 and 5 years of treatment, respectively.

Alendronate (ALN)

Extensions of the Alendronate Phase III Osteoporosis Treatment Study reported that the therapeutic effects of ALN were sustained over a 10-year period, as assessed by mean increases in BMD compared with baseline values (70,71). Discontinuation of ALN, although it did not lead to accelerated bone loss, resulted in a gradual loss of the effects of the treatment (70,71). Long-term treatment with ALN was also evaluated in the Fracture intervention Long-term EXtension (FLEX) trial (25,72). Patients assigned to ALN in the FIT trial (N = 1099) were re-randomised to ALN or placebo for an additional 5 years of study (25). Patients who were switched to placebo after 5 years of ALN treatment had no increase in the risk of morphometric vertebral or nonvertebral fractures over the next 5 years compared with patients who continued ALN for up to 10 years (25). However, the risk of clinically diagnosed vertebral fractures was significantly lower (55%) among those who continued therapy compared with those who discontinued ALN after 5 years of treatment (25).

Ibandronate (IBN)

The efficacy of IBN has not been evaluated beyond 3 years of treatment.

Risedronate (RIS)

To evaluate the long-term efficacy of RIS, the multinational VERT trial was extended for an additional 2 years, during which patients continued double-blind treatment according to the original randomisation (73). During extension Years 4 to 5, vertebral fracture incidence was reduced by 59% (p = 0.01) with RIS compared with placebo, while in the first 3 years of

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treatment, vertebral fracture risk was reduced by 49% (73). At the end of the 5-year study period, RIS and placebo patients were offered open-label RIS therapy for 2 additional years (74). In patients continuously treated with RIS, the incidence of vertebral and nonvertebral fractures during Years 6 to 7 was similar to what was observed during the first 3 years, indicating that RIS treatment up to 7 years is associated with sustained fracture protection (74).

In the VERT-NA study, RIS and placebo patients stopped therapy at the end of year 3 and were given the possibility of remaining in the study for an additional year, during which active treatment and placebo were discontinued (75). Vertebral fracture incidence during the fourth year was 46% lower in the prior-RIS group than in the prior-placebo group, indicating that fracture risk remains reduced 1 year after RIS discontinuation (75).

Zoledronate (ZOL)

The long-term efficacy of ZOL was evaluated in a randomised, double-blind, placebocontrolled trial (N = 119) of 1 year duration, followed by 2 consecutive, open-label, 2-year extension studies (76). Anti-fracture efficacy was not evaluated, but treatment with ZOL was associated with sustained BMD increases and bone turnover reductions (76). The BMD gains achieved by month 36 were well-maintained for a further 2 years in all patients (76).

Head-to-head studies

A 12-month extension to the FACT study (N = 403 for ALN 70 mg; N = 395 for RIS 35mg) reported that the greater increases in BMD seen with ALN compared with RIS during the original trial were maintained in the additional extension year (77). Over the 2-year

treatment, fractures occurred in 5.7% of ALN-treated patients and in 6.3% of RIS-treated patients (77).

Observational database studies

Results from the Incidence and ChAracterization of inadequate clinical Responders in Osteoporosis (ICARO) trials indicated that during treatment with ALN, RIS or raloxifene for > 1 year, fracture incidence in postmenopausal women with established osteoporosis is considerably higher than that observed in RCTs (78,79). Apparent drug effectiveness obtained from observational databases is primarily dependent on the baseline risk of that particular population and the adherence to treatment.

Several studies have demonstrated the importance of adherence to treatment for fracture risk reduction (80–83). Data from a large health insurer were used to identify 58,109 osteoporosis patients who initiated drug therapy for osteoporosis (hormone replacement therapy, bisphosphonates and raloxifene) (80). Results indicated that 1-year compliance rates were < 25% for all osteoporosis therapies and that vertebral and hip fracture incidences were reduced in compliant patients, who also used fewer physician's and hospital-care services (80). A study including 35,537 women who received a new ALN or RIS prescription reported that 43% of the patients were compliant, and 20% persisted with bisphosphonate therapy during the 24-month study period (81). Total, vertebral, nonvertebral and hip fractures were significantly lower in compliant and persistent patients, with relative risk reductions of 20–45% (81). Using pharmacy and hospital-claims records from patient databases, 1- and 2-year treatment persistence was evaluated in postmenopausal women (N = 14,760) treated with bisphosphonates for osteoporosis in the Netherlands (82). Persistence rates were 44% after 1 year and 27% after 2 years (82). Persistent bisphosphonate use reduced fracture risk by 26%

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after 1 year and 32% after 2 years (82). Likewise, another observational database study including 4769 women revealed that patients persistent with ALN therapy were 26% less likely to have a fracture diagnosed during the 2-year study period than non-persistent patients (83).

Relative effectiveness of bisphosphonates

An observational study by Watts and colleagues used a proprietary administrative-claims database to identify managed-care members who received a new prescription for RIS, ALN or nasal calcitonin (84). The incidence of nonvertebral fractures was evaluated in the first 6 and 12 months following treatment initiation (84). In the 6-month analysis (N = 774 for calcitonin; N = 5307 for ALN; N = 1000 for RIS), the risk of nonvertebral fractures was reduced by 69% for RIS users compared with calcitonin users (p = 0.02) (84). A non-significant reduction in the risk of nonvertebral fractures was observed for RIS users compared with ALN users (54%, p = 0.07) and for ALN users compared with calcitonin patients (26%; p = 0.28) (84). Twelve-month results (N = 656 for calcitonir; N = 3716 for ALN; N = 652 for RIS) indicated nonvertebral fracture risk reductions of 75% for RIS versus calcitonin users (p < 0.01) and 59% for RIS compared with ALN users (p = 0.04) (84). A non-significant 25% decrease in nonvertebral fractures was demonstrated for ALN versus calcitonin patients (p = 0.27) (84).

Data from the large RisedronatE ALendronate (REAL) study were collected from > 100 health plans in 34 US states, providing a broad sample of patients (N = 12,215 for RIS; N = 21,615 for ALN) and clinician practice patterns (85). Fracture incidence was similar between RIS and ALN patients during the first 3 months of treatment, supporting the comparable riskprofile at baseline of the 2 treatment groups (85). Nonvertebral fracture incidence with RIS

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treatment was 19% lower (p = 0.05) after 6 months and 18% (p = 0.03) lower after 12 months compared with ALN treatment (85). Hip fracture incidence was reduced by 46% (p = 0.03) after 6 months and by 43% (p = 0.01) after 12 months of RIS treatment as compared with ALN therapy (85). Differences at 6 and 12 months persisted after adjusting analyses for adherence, baseline fracture, and demographics (85). The strength of the conclusions that might be drawn from this study, however, are limited because 80% of patients were lost to follow-up at 12 months, with reasons not catalogued, and information on switching between bisphosphonates was unknown (85).

Subsequent to REAL, another observational study enrolling 43,135 new recipients of ALN, RIS, calcitonin or raloxifene compared the relative effectiveness of these treatments to reduce nonvertebral fracture risk (86). No significant differences in fracture risk were found between RIS and ALN or between raloxifene and ALN (86).Patients who received calcitonin experienced more nonvertebral fractures than those who received ALN (86). Results were similar in sensitivity analyses restricted to hip fracture and at different lengths of follow-up (6 and 24 months) (86). Nevertheless, it should be noted that the confidence bounds of some comparisons were too wide to rule out potential clinical differences between agents (86).

The recently reported RisedronatE and ALendronate Investigation over Three Years (REALITY) observational study showed no significant differences in fracture rates between ALN (N = 12,956) and RIS users (N = 6107) at 1 year and beyond (87). Adjusted hazard ratios (HR) were not significant for clinical vertebral or overall nonvertebral fractures, with significance shown favouring ALN for hip fractures (HR 117, 95% CI: 1.15–2.74) (87).

The eValuation of IBandronate Efficacy (VIBE) study compared fracture rates between

patients newly treated with monthly IBN and weekly oral ALN or RIS (88). The primary analysis population included 7345 monthly-IBN and 56,837 weekly-ALN or -RIS patients, who were adherent to treatment during the first 90 days after the index date (88). After the 12-month observational period, fracture risk was similar between patients receiving monthly IBN or weekly bisphosphonates for hip, nonvertebral or any clinical fracture (88). IBN patients had a 64% lower risk of vertebral fracture than weekly-bisphosphonates patients (p = 0.006) (88). In the intent-to-treat analysis, which included all patients who received at least 1 bisphosphonate prescription, RRs for fracture were not significantly different between treatment groups for all fracture types (88).

Discussion

A positive change in BMD has been demonstrated for each of the bisphosphonates evaluated in RCTs. Although BMD and bone turnover markers are probably reasonable surrogates for comparing different dosing schedules of a given bisphosphonate (e.g., daily vs. weekly) or its effects in different populations (e.g., women vs. men), comparing anti-fracture efficacy between bisphosphonates using these surrogate markers may not be valid. Surrogate endpoint trials cannot substitute for fracture end-point trials and do not allow a formal comparison of the magnitude of the treatment effects between bisphosphonates. Likewise, the CHMP has clearly indicated that change in BMD is inappropriate for confirmatory evidence to be established in clinical trials, and has proposed the use of fracture incidence as the appropriate primary end-point (20).

Selection of the site used for determining BMD is also controversial. RCTs typically select the lumbar spine as the primary evaluation site for determining change in BMD. A recent study compared the discriminative ability of BMD measurements in typically selected sites

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for identifying patients with osteoporotic fractures (89). In this sample of 432 adults aged 65– 85 years, BMD in the hip more effectively predicted vertebral fractures than measurements in the lumbar spine (89). RCTs utilising elderly patients can improve the value of their results by incorporating femur BMD and incident fractures as primary efficacy outcomes rather than lumbar spine BMD (32,34,89).

Evidence of anti-fracture efficacy in original RCTs has been shown for the vertebrae with ALN (22,29), IBN (35), RIS (30,31) and ZOL (33,34). Protection against nonvertebral fractures was demonstrated for ALN (12), RIS (30,32) and ZOL (33,34), with specific reduction in hip fractures evidenced with ALN (29), RIS (32) and ZOL (33,34). Although similar criteria have generally been utilised across RCTs for selecting study candidates and outcome measures, important differences do exist among study designs and among study populations, limiting direct comparisons of results.

Post hoc and meta-analyses of RCTs provided additional data regarding efficacy and onset of action. These studies generally confirmed the vertebral and nonvertebral fracture protection associated with ALN (45–56) and RIS (47,51,52,54,55,61–67). Nonvertebral fracture protection was not shown for IBN in the overall population of the phase III fracture trial (35). Nevertheless, a recent meta-analysis including placebo- and non-placebo-controlled trials and different dosing regimens reported anti-fracture efficacy at nonvertebral sites for the high IBN doses (59). This discrepancy in results clearly demonstrates that caution should be taken when pooling data from studies that use different patient populations or dosing regimens. In general, meta-analyses may be particularly difficult to interpret, as baseline patient characteristics are often not reported, there might be differential loss to follow-up in the included studies, and the criteria for excluding some trials and/or patients sometimes remain

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obscure and/or may be subject to bias (47,61). To identify possible publication bias, metaanalyses should evaluate for each outcome the relationship between a measure of study size and magnitude of treatment effect. Assuming that there is no publication bias, one would anticipate less random error, and thus more consistent results, among larger trials. Smaller trials are subject to greater random error and thus would demonstrate greater variability in results. These errors should be symmetrical about the true value, and thus the data should resemble a funnel (funnel plot). Asymmetry in the distribution of results might indicate publication bias (90).

Long-term efficacy data are available for up to 10, 7 and 5 years for ALN, RIS and ZOL, respectively. Possible bias may be introduced into such studies, due to selective drop-outs, and a lack of control over the long-term use of vitamin D and calcium supplementation. Despite these limitations, extension studies provide an opportunity to investigate the long-term efficacy and safety among those patients responding to the initial treatment, which is clinically meaningful.

Observational database analyses can complement findings from RCTs and meta-analyses, with direct insights into day-to-day clinical practice. While some observational studies report differences in clinical effectiveness among bisphosphonates (84,85), others show modest differences or similar effectiveness among these agents (86–88). Methodological differences in study designs, such as bisphosphonate dose and the nonvertebral sites considered in the analyses, might partially explain discrepancies in the data. <u>Given the extensive use of bisphosphonates in clinical practice, the number of observational studies identified through our search was relatively small and likely did not include all published studies. Unpublished observational data were not discussed in this review.</u>

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Analysing the strengths and limitations associated with each particular study and study design will help to interpret outcomes and their validity. The primary understanding of treatment outcomes occurs by evaluating data from RCTs, whereas observational studies can mainly be used to help support the evidence for effectiveness of a therapy in the real world.

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Author contributions

S. Boonen, R. Kay, C. Cooper and S. Ferrari were responsible for the concept and design of this work and the interpretation of the data presented. Every author made substantial contributions to article drafting and the manuscript was critically revised by all authors, and subsequently approved.

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Figure legend

Figure 1 Efficacy outcomes of bisphosphonates in randomised controlled trials (RCTs): relative risk (RR) of incident fractures after bisphosphonate treatment (ALN = alendronate, IBN = ibandronate, RIS = risedronate, ZOL = zoledronate) with 95% confidence intervals (CI). (A) Vertebral fractures (13,22,29–31,33–35); (B) nonvertebral fractures (12,30,32–34); (C) hip fractures (29,32–34).

Table 1 Randomised controlled trials of bisphosphonates

<u>Study</u>	Treatment regimen (N)	Duration,	Treatment completers, N (%)	Change in BMD, % (p-value)
		<u>years</u>		
<u>Alendronate (ALN)</u>				
Liberman et al., 1995	ALN 5-20 mg daily (597);	<u>3</u>	<u>ALN 500 (84);</u>	ALN 10 mg vs. placebo:
<u>(13)</u>	<u>placebo (397)</u>		<u>placebo 365 (84)</u>	LS 8.8; FN 5.9; hip 2.5 (all <0.001)
Black et al., 1996 (29)	ALN 5-10 mg daily (1022);	<u>3</u>	<u>ALN 981 (96);</u>	ALN vs. placebo:
	<u>placebo (1005)</u>		<u>placebo 965 (96)</u>	LS 6.2; FN 4.1; hip 4.7 (all <0.001)
Cummings et al., 1998	ALN 5-10 mg daily (2214);	4	<u>ALN 2057 (93);</u>	ALN vs. placebo:
<u>(22)</u>	<u>placebo (2218)</u>		<u>placebo 2077 (94)</u>	LS 6.6; FN 4.6; hip 5.0 (all <0.001)
Pols et al., 1999 (12)	ALN 10 mg daily (950);	<u>1</u>	<u>ALN 832 (88);</u>	ALN vs. placebo:
	<u>placebo (958)</u>		<u>placebo 865 (90)</u>	LS 4.9; FN 2.5; hip 3.0 (all <0.001)
Ibandronate (IBN)			61.	
Chestnut III et al., 2004	<u>IBN 2.5 mg daily (982);</u>	<u>3</u>	<u>IBN daily 648 (66)</u>	IBN daily/intermittent vs. placebo:
<u>(35)</u>	IBN 20 mg intermittent		IBN intermittent 662 (67);	LS 5.2/4.4; FN 3.4/3.0; hip 4.1/3.6
	<u>(982);</u>		<u>placebo 628 (64)</u>	(all <0.0001)
	<u>placebo (982)</u>			
<u>Risedronate (RIS)</u>				<u></u>
Harris et al., 1999 (30)	<u>RIS 5 mg daily (813);</u>	<u>3</u>	<u>RIS 489 (60);</u>	RIS 5 mg vs. placebo:
	placebo (815)		<u>placebo 450 (55)</u>	LS 4.3; FN 2.8; hip 4.0 (all <0.05)
Reginster et al., 2000	<u>RIS 5 mg daily (407);</u>	<u>3</u>	<u>RIS 251 (62);</u>	RIS 5 mg vs. placebo:

		D		
Study	<u>Treatment regimen (N)</u>	Duration,	<u>Treatment completers, N (%)</u>	<u>Change in BMD, % (p-value)</u>
		<u>years</u>		
(31)	<u>placebo (407)</u>		placebo 221 (54)	LS 5.9; FN 2.1; hip 6.4 (all <0.001)
McClung et al., 2001	RIS 2.5 mg daily (3093);	<u>3</u>	<u>RIS both doses 3093 (50);</u>	RIS 2.5/5 mg vs. placebo:
(32)	<u>RIS 5 mg daily (3104);</u>		<u>placebo 1584 (50)</u>	<u>FN 2.1/3.4; hip 3.8/4.8 (NR)</u>
	<u>placebo (3134)</u>			
Zoledronate (ZOL)				
Black et al., 2007 (33)	ZOL 5 mg yearly (3889);	<u>3</u>	ZOL 5 mg 3248 (84); placebo	ZOL vs. placebo:
	<u>placebo (3876)</u>		<u>3269 (92)</u>	LS 6.7; FN 5.1; hip 6.0 (all <0.001)
Lyles et al., 2007 (34)	ZOL 5 mg yearly (1065);	3	<u>ZOL 770 (72);</u>	FN at years 1, 2 and 3 with ZOL vs.
	<u>placebo (1062)</u>		<u>placebo 746 (70)</u>	placebo, respectively:
			R	<u>0.8 vs1.7, 2.2 vs2.1 and 3.6 vs0.7</u>
				Hip at years 1, 2 and 3 with ZOL vs.
				placebo, respectively:
				<u>2.6 vs1.0, 4.7 vs0.7 and 5.5 vs0.9</u>
				<u>(all <0.001)</u>
BMD = bone mineral	density, \overline{FN} = femoral neck, LS	= lumbar spine,	NR = not reported.	

Table 2 Number needed to treat (NNT) over 1 or 3 years to prevent a fracture

A. 1-year data

Drug	Study	Fracture type	NNT <u>(95% CI)*</u>
ALN	Pols et al., 1999 (12)	Nonvertebral	50 <u>.0 (32.5–</u>
			<u>227.3)</u>
RIS	Harris et al., 1999 (30)	Vertebral (morphometric)	25 <u>.0 (19.3–41.2)</u>
			1 <u>3.5 (9.9–24.0)</u>
ZOL	Black et al., 2007 (33)	Vertebral (morphometric)	45.5^{\dagger}

B. 3-year data

Drug	Study	Fracture type	NNT <u>(95% CI)*</u>
ALN	Black et al., 1996 (29)	Vertebral (morphometric)	14.3 (11.3–20.8)
		Нір	9 <u>0.9 (59.2–</u>
			<u>5000.0)</u>
	Liberman et al., 1995 (13)	Vertebral (morphometric)	3 <u>3.3 (22.4–</u>
			<u>322.6)</u>
IBN	Chesnut et al., 2004 (35)	Vertebral (morphometric)	2 <u>0.4 (14.5–29.4)</u>
RIS	Harris et al., 1999 (30)	Vertebral (morphometric)	20.0 (10.8–34.1)
		Nonvertebral	3 <u>1.3 (19.5–74.6)</u>
	Reginster et al., 2000 (31)	Vertebral (morphometric)	9.2 (5.4–12.8)
	McClung et al., 2001 (32)	Hip	90.9 (64.1-
			<u>256.4)</u>
ZOL	Black et al., 2007 (33)	Vertebral (morphometric)	13.2 (12.1–14.8)
		Nonvertebral	37 <u>.0 (26.0–71.9)</u>
		Hip	9 <u>0.9 (69.0–</u>

Deleted: ¶ Hip

			40)
			232.6)	
*CIs for the NI	T were calculated using	g the CIs reported in each	study for the absolute risk	
eductions.				
CI for the relat	ive or absolute risk redu	ictions were not reported i	n the manuscript.	
ALN = alendro	nate, CI = confidence in	terval, IBN = ibandronate	, RIS = risedronate, ZOL =	
zoledronate,				Deleted: "T-score ≤ -4.0 or ≤ -3.0 an ≥ 1 risk factor [] ^b T-score ≤ -4.0 and ≥ 1 risk factor or T.
				score ≤ -3.0 and hip-axis length ≥ 11.1 cm¶ ¶

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	Incident Vertebral Fractures, RR (95% CI)
ZOL 5 mg yearly, intravenous [Lyles et al., 2007 (34)]	
ZOL 5 mg yearly, intravenous [Black et al., 2007 (33)]	-
RIS 5 mg daily, oral [Reginster et al., 2000 (31)]	•
RIS 5 mg daily, oral [Harris et al., 199	99 (30)]
IBN 20 mg intermittent, oral [Chesnut et al., 2004 (35)]	•
IBN 2.5 mg daily, oral [Chesnut et al., 2004 (35)]	•
ALN 5–10 mg daily, oral [Cummings e al., 1998 (22)]	et
ALN 5–10 mg daily, oral [Black et al., 1996 (29)]	+
ALN 5-20 mg daily, oral [Liberman et al., 1995 (13)]	•
	0.5 1
Nonvertebral fractures	
Ir	Incident Nonvertebral Fractures, RR (95% CI)
ZOL 5 mg yearly, intravenous [Lyles et al., 2007 (34)]	•
ZOL 5 mg yearly, intravenous [Black et al., 2007 (33)]	•
RIS 2.5–5 mg daily, oral [McClung et al., 2001 (32)]	
RIS 5 mg daily, oral [Harris et al., 1999 (30)]	•
ALN 10 mg daily, oral	•
[Pols et al., 1999 (12)]	
	0.5 1
Hip fracture	Incident Hip Fractures, RR (95% CI)
ZOL 5 mg yearly, intravenous	•
ZOL 5 mg yearly, intravenous [Lyles et al., 2007 (34)]	•
ZOL 5 mg yearly, intravenous [Lyles et al., 2007 (34)] ZOL 5 mg yearly, intravenous	•
ZOL 5 mg yearly, intravenous [Lyles et al., 2007 (34)] ZOL 5 mg yearly, intravenous [Black et al., 2007 (33)]	• · · · · · · · · · · · · · · · · · · ·
ZOL 5 mg yearly, intravenous [Lyles et al., 2007 (34)] ZOL 5 mg yearly, intravenous [Black et al., 2007 (33)]	• · · · · · · · · · · · · · · · · · · ·
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ZOL 5 mg yearly, intravenous [Lytes et al., 2007 (34)] ZOL 5 mg yearly, intravenous [Black et al., 2007 (33)] RIS 2.5-10 mg daily, oral [McClung et al., 2001 (32)]	• • • • • • • • • • • • • • • • • • •
ZOL 5 mg yearly, intravenous [Lyles et al., 2007 (34)] ZOL 5 mg yearly, intravenous [Black et al., 2007 (33)] RIS 2,5-10 mg daily, oral [McClung et al., 2001 (32)]	• • • • • • • • • • • • • • • • • • •
ZOL 5 mg yearly, intravenous [Lyles et al., 2007 (34)] ZOL 5 mg yearly, intravenous [Black et al., 2007 (33)] RIS 2.5-10 mg daily, oral [McClung et al., 2001 (32)] ALN 5-10 mg daily, oral [Black et al., 1996 (29)]	• • • • • • • • • • • • • • • • • • •
ZOL 5 mg yearly, intravenous [Lyles et al., 2007 (34)] ZOL 5 mg yearly, intravenous [Black et al., 2007 (33)] RIS 2.5–10 mg daily, oral [McClung et al., 2001 (32)] ALN 5–10 mg daily, oral [Black et al., 1996 (29)]	• • • • • • • • • • • • • • • • • • •

Efficacy outcomes of bisphosphonates in randomised controlled trials (RCTs): relative risk (RR) of incident fractures after bisphosphonate treatment (ALN = alendronate, IBN = ibandronate, RIS = risedronate, ZOL = zoledronate) with 95% confidence intervals (CI). (A) Vertebral fractures (13,22,29–31,33–35); (B) nonvertebral fractures (12,30,32–34); (C) hip fractures (29,32–34). 209x299mm (300 x 300 DPI)