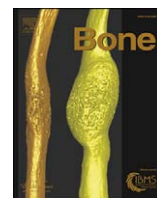


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## Review

## Efficacy and safety of pharmacological agents in managing osteoporosis in the old old: Review of the evidence

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## ABSTRACT

**Introduction:** Osteoporosis and fracture risk increase exponentially in postmenopausal females. This places a significant burden in terms of morbidity, mortality and costs that are likely to increase with an ageing population. Despite this there is very limited data on pharmacological management of osteoporosis in this high risk group.

**Objectives of this review:** To review the published literature on the clinical efficacy and safety of specific anti osteoporosis treatments in the reduction in fracture risk in females  $\geq 75$  years of age. The following major endpoints were used in this review:

1. Vertebral fracture reduction at 1 year and 3 years.
2. Non-vertebral fracture and hip fracture reduction at 1 year and 3 years.
3. Safety data in this group.

**Search methods for identification of studies:** We performed an electronic search of Medline (1970 to June 2007) and the Cochrane Library (1996 to June 2007). Our search strategy included MeSH terms for osteoporosis and treatments. We reviewed the reference list of identified articles for additional relevant published trials.

**Results:** Two hundred and fifty-two potentially relevant abstracts were identified. Only six publications were deemed to meet full eligibility criteria and one met most criteria. There is evidence for significant vertebral fracture relative risk reduction (RR) at 1 year for Risedronate (RR 81%;  $p < 0.001$ ), Teriparatide (RR 65%;  $p < 0.05$ ) and Strontium Ranelate (RR 59%;  $p = 0.002$ ) and 3 years for Risedronate (RR 44%;  $p = 0.003$ ), Alendronate (RR 38%;  $p < 0.05$ ) and Strontium Ranelate (RR 32%;  $p = 0.013$ ). There is evidence for significant non-vertebral fracture relative risk reduction at 1 year for Strontium Ranelate (RR 41%;  $p = 0.027$ ) but not Teriparatide ( $p = 0.66$ ) and 3 years for Strontium Ranelate (RR 31%;  $p = 0.011$ ) but not Risedronate ( $p = 0.66$ ). The only study to report a reduction in hip fracture at 3 years is the TROPOS study with Strontium Ranelate (RR 36%;  $p = 0.046$ ).

**Discussion:** This review reinforces the irony that the least evidence is available for fragility fracture reduction in the group at greatest risk; the old old and those with non vertebral and hip fracture. Although there is good evidence for the benefit of the bisphosphonates (Alendronate and Risedronate), Teriparatide and Strontium Ranelate in vertebral fracture reduction, there are very limited data for non vertebral and hip fracture reduction. Strontium Ranelate is the only agent to date that has demonstrated a reduction in non vertebral and hip fracture events in this high risk elderly female population. Perhaps we need to adopt different strategies in managing older patients with osteoporosis as their fracture risks and treatment strategies may be quite different from younger populations.

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## Introduction

Osteoporosis increases in prevalence with age such that it is common in the elderly [1–3]. For any bone mineral density (BMD) measurement, fracture risk is much higher in the elderly than in the young [4]. Age is one of the most important components of the fracture index derived by Black et al. [5]; and older age groups experience the greatest growth rate of osteoporosis risk in the population [6,7]. So although BMD is a strong risk factor for fragility fracture, its relative importance diminishes if there are other strong risk factors for fracture: advanced age, prior fragility fracture or family history of fragility fracture [4,8].

Older patients are at higher risk of falls [9] due to muscle weakness [10] and more than 90% of fractures occur after a fall [11–13]. Falls result in any fracture in 5% and specifically hip fracture in 1–2% of events [11]. Hence, in an ageing, osteoporotic population, fracture prevention through the optimisation of bone health as well as reducing falls risk should be important goals.

Epidemiological data worldwide have consistently demonstrated that the annual incidence of fragility fracture increases with age [14–19]. Above average fracture rates were described in Australian females residing in Dubbo [20] and Geelong [3] with an exponential increase in risk in the population groups over 74 years of age. The burden of fracture is expected to increase with an ageing population as the oldest old i.e. women  $\geq 80$  years of age comprise approximately 8% of the post-menopausal population but contribute  $>30\%$  of all fragility fractures and 60% of hip fractures because of the high prevalence of osteoporosis and falls in this age group [21,22]. After age 75, hip fracture is the commonest fracture [23–25] with 1/3 of women and 1/6 of men estimated to sustain a hip fracture by the 9th decade [26] and is associated with significant morbidity and mortality [27–29] and financial burden [22,30–33].

Despite the high risk of osteoporotic fracture in older individuals, there is little data regarding treatment of this group. Studies have either included limited numbers or excluded older individuals due to strict entry criteria based on age and related factors. However, economic evaluations have suggested that if current anti osteoporosis agents are as effective in older patients as in younger trial patients, the cost benefit ratios are more favourable given the higher absolute risk in older patients [34–36].

## Objectives of this review

To review the published literature on the clinical efficacy and safety of specific anti osteoporosis treatments in the reduction in

fracture risk in females  $\geq 75$  years of age. The following major endpoints were used:

1. Vertebral fracture reduction at 1 year and 3 years.
2. Non-vertebral fracture and hip fracture reduction at 1 year and 3 years.
3. Safety data in this group.

## Eligibility criteria for inclusion in review

Studies were randomised placebo or active comparator control trials or age comparison trials of at least 1 year duration and included post-menopausal females. Pooled analysis and published sub-group analysis, specifying the sub-groups  $\geq 75$  years were included.

## Analysis

The following outcome and efficacy measures were predetermined:

1. The primary efficacy outcome was the proportion of women with incident vertebral fractures at 1 year and 3 years.
2. The secondary endpoint was non-vertebral and hip fractures at 1 and 3 years.
3. Vertebral fractures and non-vertebral fractures were required to be radiographically proven.
4. Safety measures included the following:
  - a) The proportion with any adverse event reported.
  - b) The proportion that withdrew due to adverse events.
  - c) The proportion with reported serious adverse events.
  - d) The proportion of deaths.
  - e) The proportion with any gastro-intestinal adverse event.

## Search methods for identification of studies

An electronic search of Medline (1970 to June 2007) and the Cochrane Library (1996 to June 2007) using MeSH terms for osteoporosis and treatments was performed. We reviewed the reference list of identified articles for additional relevant published trials. We excluded studies specifically investigating hormone replacement therapy, calcium and vitamin D as a primary treatment measure in this review.

Abstracts of all possibly relevant articles were reviewed independently (AF and ML) for potential eligibility. Those records deemed eligible and those that did not have adequate information to confirm their inclusion underwent a full text review.

All data was summarised in a pre-formulated proforma including inclusion criteria, gender, age, type of study, duration and the main outcome measures. A third reviewer (CI) reviewed all publications meeting the inclusion criteria as well as those deemed to meet some criteria and or included patients from the target age groups and helped resolve difference in interpretation by reviewers AF and ML.

All studies, sub-group analysis or pooled analysis specifically reporting outcomes in the pre-specified age groups were included in the final review. No further or separate sub-group analyses were performed. Authors and industry sponsors were contacted for more information and clarification where sub-group analyses or additional data may be available for the relevant age group being assessed.

## Descriptions of studies

Two hundred and fifty-two potentially relevant abstracts were identified. After excluding studies that did not meet eligibility criteria, 104 studies were fully reviewed for potential inclusion. The number of studies with each anti osteoporosis agent reviewed was as follows:

1. Alendronate 31
2. Clodronate 4
3. Etidronate 7
4. Ibandronate 10
5. Pamidronate 1
6. Parathyroid hormone (PTH 1–34 [Teriparatide]/PTH 1–84) 19
7. Raloxifene 12
8. Risedronate 11
9. Strontium Ranelate 6
10. Zoledronic acid 3

Only six publications were deemed to meet full eligibility criteria [37–42] and one met most criteria [43]. Two publications (Strontium Ranelate [37] and Risedronate [38]) met inclusion criteria based on publication of pooled subgroup analysis from previous studies including patients aged 80 years or older (but did not include patients from the 75–79 year group). Two publications (Teriparatide [39] and Alendronate [40]) met inclusion criteria for publication of subgroup analysis of patients aged 75 years and older from previously published studies. One study (Clodronate [41]) exclusively enrolled women  $\geq 75$  years of age. Where pooled analyses were published, the original studies were also independently reviewed. Although a full review of the original studies was completed, only data from the pooled and/or subgroup publications was considered for inclusion in this review, unless the pooled analysis and or subgroup differed from the subgroups described in the original study [42,43]. The HIP study (Risedronate) [42] met full inclusion criteria and the TROPOS study (Strontium Ranelate) [43] met partial criteria based on these criteria. The TROPOS study included patients from 74 years of age rather than the prespecified 75 years.

## Description of studies including outcomes in patients $\geq 75$ years of age

### Strontium Ranelate study

The Strontium Ranelate study [37] was a pooled analysis of patients from the SOTI [44] and TROPOS [43] studies. The SOTI study assessed the anti vertebral fracture efficacy in 1649 white post menopausal women with osteoporosis and at least one prevalent vertebral fracture and the TROPOS study (5091 patients) assessed the anti non-vertebral fracture efficacy in 1977 white post menopausal women  $\geq 74$  years of age with osteoporosis and femoral neck BMD  $\leq$  cm<sup>2</sup> per cm<sup>2</sup> (measured by Hologic). Subjects were randomised to receive either Strontium Ranelate 2 g/day or placebo powder for three years. They also received supplemental calcium

and vitamin D, if deficient. Of the total 6740 patients enrolled in both studies, 1488 (22%) were in the age range 80–100 years and were included in the pooled analysis [37]. The baseline characteristics of the patients are illustrated in Table 1.

### Risedronate study

The Risedronate study [38] included patients from 3 studies: VERT-NA [45], VERT-MN [46] and HIP Study [42]; all were phase 3 clinical randomised double blind placebo controlled parallel group studies. The VERT studies were designed to determine the effect of Risedronate on vertebral fracture in women with post menopausal osteoporosis and the HIP study was designed to evaluate the effect of Risedronate on hip fracture in elderly women. In all three studies, patients received Risedronate or placebo daily for up to 3 years with supplemental calcium and vitamin D if considered deficient. Patients enrolled in VERT studies were post menopausal with osteoporosis i.e. 2 or more vertebral fracture or one fracture and a lumbar spine BMD of  $<0.83$  g per cm<sup>2</sup> on Hologic BMD measurement. The HIP study included 2 cohorts of patients aged 70–79 years with osteoporosis and at least 1 non skeletal risk factor and patient who were 80 years or greater who had either  $\geq 1$  non-skeletal risk factor for fracture or a BMD showing osteoporosis at the femoral neck with the *T* score of less than  $-4.0$  or a *T* score of  $-3.0$  plus hip axis length of  $\geq 11.1$  cm.

The pooled analysis only included patients who were randomised to 5 mg Risedronate per day and had either femoral neck BMD *T* score  $<-2.5$  or  $>1$  prevalent vertebral fracture(s). Analysis included a total patient cohort of 6126 (Risedronate 5 mg or placebo) of which 1392 (23%) were aged 80 years and older. The baseline characteristics of the patients are illustrated in Table 1.

### Teriparatide study

The Teriparatide subgroup study [39] was a pre-specified sub group analysis of the Fracture Prevention Trial (FPT) [47]. The focus of this analysis was to test whether older women ( $\geq 75$  years) had similar safety and efficacy to that of younger women. The analysis compared whether there was a significant interaction between treatment (Teriparatide 20  $\mu$ g versus placebo) and age ( $<75$  vs  $>75$ ) at a significance level of  $p < 0.10$ . All participants received calcium and vitamin D supplementation. The FPT was terminated early with median treatment duration of 19 months. Of the total 1637 postmenopausal women enrolled in the study, 244 (15%) were aged 75 years or greater with a mean age of 78 and a range of 75 to 86 years. The inclusion criteria were the presence of 1 or more moderate vertebral fracture or 2 mild vertebral fractures. The majority of patients (approximately 89%) had 1 or more fracture at enrollment. Patients who had less than 2 moderate vertebral fractures were required to have a BMD of the hip or lumbar spine *T* score of  $\leq -1.0$ . The baseline characteristics of the 75 years and older age group are illustrated in Table 1.

### Alendronate study

The Alendronate study [40] is a sub group analysis of patients 75 years and older from the FIT study [48]. Subjects received either placebo or Alendronate 5 mg daily for 24 months, followed by 10 mg daily for 12 months plus supplemental calcium and vitamin D. In the original cohort there were 2027 postmenopausal women aged 55 to 82 with low femoral neck bone density and existing vertebral fractures (100%). Subjects were post menopausal females with a femoral neck BMD of  $\leq 0.68$  g/cm<sup>2</sup>, which is equivalent to a *T* score of  $-2.0$  (Hologic measurement) and at least 1 radiographic vertebral fracture. In total there were 539 (27%) subjects, 75 years or older with an age range of 75 to 82 and 100% of subjects had a previous vertebral fracture. The baseline characteristics of the patients are illustrated in Table 1.

**Table 1**  
Baseline characteristics of women  $\geq 75$  years randomised in osteoporosis studies

	Characteristics	Number	Age; mean $\pm$ SD (years) (range)	Weight mean $\pm$ SD (kg)	Lumbar BMD mean $\pm$ SD g/cm <sup>2</sup> T mean $\pm$ SD	Femoral neck BMD mean $\pm$ SD g/cm <sup>2</sup> T mean $\pm$ SD	$\geq 1$ Prevalent vertebral fracture	Inclusion criteria
<b>Alendronate</b>	<b>All</b>	2027	71 $\pm$ 6 (55–82)	65 $\pm$ 11	NA	0.57 $\pm$ 0.07	100%	BMD @ FN $\leq$ 0.68 g/cm (T $-2.0$ ) (hologic) and 1 radiographic VF
	<b>Placebo</b>	275	NA (75–82)	NA	NA	NA	100%	
	<b>Alendronate 5 mg/day <math>\times</math> 24 mths–10 mg/day <math>\times</math> 12 mths</b>	264	NA (75–82)	NA	NA	NA	100%	
<b>Risedronate</b>	<b>All (Pooled 80)</b>	1392	83 $\pm$ 3.0 (80–100)	58.0 $\pm$ 10.8	NA	$-3.1 \pm 0.6$	84	<b>Pooled</b> vert studies: $\geq 2$ VF or fracture and L/S BMD $\leq$ 0.83 g/cm (T $-2.0$ ; hologic) and Hip study SG $>$ 80 with: FN T $< -2.5$ or $> 1$ VF <b>Hip study SG <math>\geq 80</math> years:</b> $\geq 1$ non skeletal risk factor for fracture or FN T $< -4.0$ or $-3.0$ with hip axis length $\geq 11.1$ cm <b>Pooled:</b> SOTI: Osteoporosis (hologic) L/S BMD $\leq$ 0.84 g/cm; $\geq 1$ fracture. TROPOS SG $\geq 80$ FN BMD T, $< -2.5$ (0.600 g/cm <sup>2</sup> ; hologic) *T $-3.3$ (centralised European normative data) corresponds to $-2.7$ (NHANESIII) <b>Tropos SG <math>\geq 74</math> years</b> FN BMD T, $< -3.0$ ( $-2.4$ NHANES III)
	<b>Placebo (Pooled 80)</b>	688	83 $\pm$ 3.0 (80–98)	58.0 $\pm$ 10.4	NA	$-3.1 \pm 0.6$	83	
	<b>Risedronate 5 mg/day (Pooled 80)</b>	704	<b>83 <math>\pm</math> 3.1 (80–100)</b>	<b>58.0 <math>\pm</math> 11.2</b>	<b>NA</b>	<b><math>-3.0 \pm 0.7</math></b>	<b>84</b>	
	<b>Hip study (<math>&gt; 80</math>) Risedronate 2.5 or 5 mg vs placebo</b>	3886	<b>83 <math>\pm</math> 3</b>	<b>60.4 <math>\pm</math> 11.6</b>	<b>NA</b>	<b>NA</b>	<b>NA</b>	
<b>Strontium Ranelate</b>	<b>All (Pooled 80)</b>	1488	83.5 $\pm$ 3.0 (80–100)	57.8 $\pm$ 9.5	( $-2.7 \pm 1.7$ )	( $-3.3 \pm 0.7^*$ )	49	<b>Pooled:</b> SOTI: Osteoporosis (hologic) L/S BMD $\leq$ 0.84 g/cm; $\geq 1$ fracture. TROPOS SG $\geq 80$ FN BMD T, $< -2.5$ (0.600 g/cm <sup>2</sup> ; hologic) *T $-3.3$ (centralised European normative data) corresponds to $-2.7$ (NHANESIII) <b>Tropos SG <math>\geq 74</math> years</b> FN BMD T, $< -3.0$ ( $-2.4$ NHANES III)
	<b>Placebo (Pooled 80)</b>	749	83.5 $\pm$ 2.9	57.5 $\pm$ 9.5	( $-2.8 \pm 1.7$ )	( $-3.3 \pm 0.7^*$ )	51	
	<b>Strontium ranelate 2 g/day (Pooled 80)</b>	739	<b>83.5 <math>\pm</math> 3.0</b>	<b>59.1 <math>\pm</math> 9.6</b>	<b>(<math>-2.7 \pm 1.7</math>)</b>	<b>(<math>-3.3 \pm 0.7^*</math>)</b>	45	
	<b>Tropos (<math>\geq 74</math>) Strontium Ranelate 2 g/day</b>	1977	<b>79.7 <math>\pm</math> 4.6</b>	<b>NA</b>	<b>(<math>-3.6 \pm 1.60</math>)</b>	<b>(<math>-3.5 \pm 0.48</math>)</b>	<b>59 (VF or NVF)</b>	
<b>Teriparatide</b>	<b>All</b>	1637	69 $\pm$ 7 (42–86)	NA	0.82 $\pm$ 0.17	NA	89.0% (approx)	Lumbar fractures $\geq$ one moderate or 2 mild If $> 2$ moderate -BMD (H or L/S T $< -1.0$ )
	<b>Placebo</b>	118	78.2 $\pm$ 2.5 (75–86)	NA	0.83 $\pm$ 0.18 ( $-2.52 \pm 1.50$ )	0.62 $\pm$ 0.11	87.1%	
	<b>Teriparatide 20 <math>\mu</math>g/day</b>	126	<b>78.3 <math>\pm</math> 2.6 (75–86)</b>	<b>NA</b>	<b>0.84 <math>\pm</math> 0.18</b> ( $-2.42 \pm 1.54$ )	<b>0.61 <math>\pm</math> 0.13</b>	<b>90.6%</b>	
<b>Clodronate</b>	<b>All</b>	5592	( $\geq 75$ )	NA	NA	NA (TH 0.75 $\pm$ 0.14 g/cm <sup>2</sup> , FA 0.34 $\pm$ 0.08 g/cm <sup>2</sup> )	NA	Women $\geq 75$ yrs. Community dwelling. General practice registers.
	<b>Placebo</b>	2796	79.6 $\pm$ 4.0 ( $\geq 75$ )	64.7 $\pm$ 12.0	NA	NA	14.7%	
	<b>Clodronate 800 mg/day</b>	2796	79.5 $\pm$ 4.0 ( $\geq 75$ )	65.3 $\pm$ 12.1	NA	NA	14.0%	

NS – Not significant; NA Not available; VF – Vertebral fracture; NVF – Non vertebral fracture; SG – Subgroup; TH – Total Hip; FA – Forearm.

### Clodronate study

The Clodronate study [41] specifically randomised community-dwelling women  $> 75$  years of age who did not need to have proven osteoporosis or any other risk factor. Subjects were randomised to either Clodronate 800 mg daily or placebo for 3 years. Calcium or vitamin D supplements were not given as part of the study. A total of 5592 patients were enrolled equally. The baseline characteristics of the patients are illustrated in Table 1.

### Vertebral fracture risk reduction in patients 75 years of age or older

The results are summarised in Table 2. There are limited published data on vertebral fracture risk reduction in this age group. There are published data at 1 year and 3 years for Risedronate and Strontium Ranelate, 1 year for Teriparatide and 3 years for Alendronate. There are no published data for Clodronate. There is evidence for significant vertebral fracture relative risk reduction at 1 year for Risedronate (RR 81%;  $p < 0.001$ ), Teriparatide (RR 65%;  $p < 0.05$ ) and Strontium Ranelate (RR 59%;  $p = 0.002$ ) and 3 years for Risedronate (RR 44%;  $p = 0.003$ ), Alendronate (RR 38%;  $p < 0.05$ ) and Strontium Ranelate (RR 32%;  $p = 0.013$ ). The Teriparatide study compared patients younger than 75 with those 75 or older and found no age-treatment interaction ( $p = 0.42$ ).

The Risedronate and Strontium Ranelate data only includes patients 80 years or older, making comparisons with the limited evidence available for the other treatment modalities unreliable. Limited comparisons are possible between these 2 groups which enrolled patients of similar age and body weight. However,

Risedronate treatment group had a higher prevalence of vertebral fracture compared to placebo and the Strontium Ranelate group had lower femoral neck BMD at baseline compared to placebo. The Risedronate treated group appeared to have a greater proportional reduction in vertebral fracture risk at 1 year (81% vs 59%). However, the difference in risk reduction, although persistent for both groups was not as marked at 3 years (44% vs 32%).

### Non-vertebral fracture risk reduction in patients 75 years of age and older

The results are summarised in Table 2. There are 1 year data for Strontium Ranelate ( $\geq 80$  years) and Teriparatide ( $\geq 75$  years) and 3 year data in the over 80 age group for Strontium Ranelate and Risedronate. Risedronate was demonstrated to reduce non vertebral fracture in a combined analysis of subjects in the HIP study (70–79 years and 80 years and over groups); relative risk 0.8 (95% CI = 0.7–1.0;  $p = 0.03$ ); no benefit was demonstrated in the older cohort selected primarily on the basis of nonskeletal risk factors ( $p = 0.43$ ). There was no significant reduction in non vertebral fracture risk in the pooled analysis [38] which included subjects with either proven osteoporosis or a prevalent vertebral fracture ( $p = 0.66$ ); although benefit was demonstrated in subjects younger than 80 years; relative risk 0.61 (95% CI = 0.51–0.74;  $p < 0.001$ ). There are no published data for Alendronate and Clodronate.

There is evidence for significant non-vertebral fracture relative risk reduction at 1 year for Strontium Ranelate (RR 41%;  $p = 0.027$ ) but not Teriparatide ( $p = 0.66$ ) and 3 years for Strontium Ranelate (RR 31%;  $p = 0.011$ ) but not Risedronate ( $p = 0.66$ ).

## Hip fracture risk reduction in patients 75 years of age and older

The results are summarised in Table 2. There are only 2 studies specifically designed to look at hip fracture as the primary outcome – the HIP study (Risedronate) and the Clodronate Study. A third study, TROPOS (Strontium Ranelate) reported hip fracture outcome as a secondary outcome in the subgroup  $\geq 74$  years, with more severe osteoporosis. The 80+ subgroup from the latter was also included in the pooled analysis by Seeman et al. [37] which reported hip fracture outcome as a secondary endpoint in patients 80 years or older.

The Clodronate study, with unselected community-dwelling women, reported no significant benefit at 1 year (HR 1.31; 95% CI=0.82–2.03) and 3 years (HR 1.02; 95% CI=0.71–1.47). The HIP study (Risedronate), which enrolled patients at least 80 years old with at least 1 nonskeletal risk factor for hip fracture or low femoral neck BMD, showed no significant benefit in hip fracture reduction at 3 years ( $p=0.35$ ) although hip fracture reduction was demonstrated in the osteoporotic 70–79 year age group (RR 40%;  $p=0.009$ ). The pooled Risedronate study [38] did not report hip fracture outcomes. The pooled Strontium Ranelate data demonstrated non-significant reduction in hip fracture at 3 years in patients at least 80 years of age (32%;  $p=0.112$ ). The only study to report a reduction in hip fracture at 3 years is the TROPOS study (Strontium Ranelate). However, it included the subgroup of patients from 74 years of age rather than our prespecified 75 years. The authors reported hip fracture RRR of 36% ( $p=0.046$ ) in a high risk subgroup aged at least 74 years of age with osteoporosis of the femoral neck on BMD.

## Other studies with significant proportion of patients 75 years or older

### Zoledronic acid

A double-blind, placebo controlled study by Black et al. [49] randomised 3889 postmenopausal, osteoporotic women, mean age  $73 \pm 5$  (range 65–89) years, to either an annual infusion of zoledronic acid 5 mg or placebo at baseline with 12, 24 and 36 months of follow up. In this study 1452 (37.6%) of the placebo group and 1497 (38.6%) of the zoledronic acid group were  $>75$  years of age. However, there

are no published data on this subgroup to date and permission for access was declined by the authors and sponsor of the study.

A double-blind, placebo controlled study of zoledronic acid by Lyles et al. [50] assigned 1065 patients (75% female), mean age  $75 \pm 9$  years following hip fracture to annual zoledronic acid 5 mg and 1062 patients to placebo starting within 90 days of a hip fracture. A total of 601 (56%) in the placebo group and 586 (55%) in the zoledronic acid group were  $\geq 75$  years of age. Significant benefit was shown in the whole group in terms of clinical fracture, clinical vertebral fracture, new non vertebral fracture and mortality. However, there are no published data on the older subgroup to date and permission for access was declined by the authors and sponsor of the study.

### Alendronate (additional data)

A study by Greenspan et al. [51] which included 327 older female patients with osteoporosis (pre-existing fracture and low BMD) in a long term care facility (mean age 78.5; range 65–91 years), randomised patients to Alendronate or placebo for 2 years. Alendronate, produced greater increases in BMD of the spine and femoral neck, and greater suppression of bone turnover markers than placebo. However, there are no published fracture endpoint data.

## Adverse events reported in patients 75 years of age or older

There are limited published data on adverse outcomes in older patient subgroups. The most comprehensive data is published for Risedronate [38] and Strontium Ranelate [37] in the over 80 age group pooled analyses. Table 3 summarises the published adverse events. Neither Risedronate nor Strontium Ranelate resulted in more adverse events than placebo for the following categories: any adverse event, withdrawal due to adverse events, serious adverse events or deaths.

Strontium Ranelate pooled analysis suggested trends towards increased reporting of gastrointestinal (GIT) side-effects i.e. nausea and diarrhoea although the statistical significance of this is not published. The adverse outcomes reported in the older groups were similar to the original study cohorts published. With the Risedronate trials there appeared to be no significant increase in adverse events involving the GIT in the treated group versus the placebo group.

**Table 2**  
Fracture efficacy in women  $\geq 75$  years randomised in osteoporosis studies

	Fracture risk	Vertebral fracture		Non vertebral fracture		Hip fracture	
		1 year	3 years	1 year	3 years	1 year	3 years
Alendronate studies	Placebo	NA	19.4%	NA	NA	NA	NA
	Alendronate	NA	12%	NA	NA	NA	NA
	Relative risk reduction <sup>a</sup> (p value)	NA	38% ( $p<0.05$ )	NA	NA	NA	NA
Risedronate studies	Placebo	10.9%	24.6%	NA	16.2%	NA	5.1%
	Risedronate	2.5%	18.2%	NA	14.0%	NA	4.2%
	Relative risk reduction (p value): Pooled 80 RRR: hip	81% ( $p<0.001$ )	44% ( $p=0.003$ )	NA	NS ( $p=0.66$ )	NA	NA
Strontium Ranelate studies	Placebo	8.3%	26.5%	NA	NS <sup>b</sup>	NA	NS <sup>b</sup> ( $p=0.35$ )
	Strontium Ranelate	3.5%	19.1%	4.0%	14.2%	NA	5.2%
	Relative risk reduction <sup>c</sup> (p value): Pooled 80 RRR: TROPOS $\geq 74$	59% <sup>a</sup> ( $p=0.002$ )	32% ( $p=0.013$ )	41% ( $p=0.027$ )	31% ( $p=0.011$ )	NA	41% (NS $p=0.112$ )
Teriparatide studies	Placebo	NA	NA	NA	NA	NA	36% ( $p=0.046$ )
	Teriparatide	15.1%	NA	4.2%	NA	NA	NA
	Relative risk reduction <sup>d</sup> (p value)	5.2%	NA	3.2%	NA	NA	NA
Clodronate	Placebo	65% ( $p<0.05$ )	NA	25% (NS $p=0.661$ )	NA	NA	NA
	Placebo	NA	NA	NA	NA	0.61%	2.1%
	Clodronate	NA	NA	NA	NA	0.86%	2.0%
	Relative risk reduction <sup>e</sup> (p value)	NA	NA	NA	NA	NS $p>0.05$	NS $p=0.918$

NS – Not significant; NA – Not available.

<sup>a</sup> Any clinical fracture at 3 years HR, 0.80 (95% CI, 0.54–1.17); no treatment age interaction for any clinical fracture ( $p>0.59$ ) or vertebral fracture ( $p>0.48$ ).

<sup>b</sup> Includes Hip study patients only – selected on the basis of non-skeletal risk factors for hip fractures rather than established osteoporosis.

<sup>c</sup> Any clinical fracture RRR at 1 year, 37% ( $p=0.012$ ); 3 years 22% ( $p=0.040$ ).

<sup>d</sup> No treatment age interaction for new vertebral fracture ( $p=0.99$ ) or non vertebral fracture ( $p=0.42$ ).

<sup>e</sup> Any clinical fracture at 3 years HR, 0.80 (95% CI, 0.68–0.94); RRR=20% ( $p<0.05$ ); non-hip osteoporotic fracture RRR=29% ( $p=0.001$ ).

**Table 3**  
Adverse events from antiosteoporosis agents reported in patients 80–100 years old

Adverse event	Strontium Ranelate studies			Risedronate studies		
	Placebo	Strontium ranelate	<i>p</i> value	Placebo	Risedronate	<i>p</i> value
Patient with any adverse event	89.2%	86.8%	NS	89.7%	90.9%	0.469
Withdrawals due to adverse event	23.5%	23.7%	NS	20.3%	20.6%	0.947
Serious adverse event	29.8%	30%	NS	NA	NA	NA
Deaths	12.3%	11.1%	NS	7.1%	5.7%	0.276
Gastrointestinal (any)	NA	NA	NA	26.8%	28.8%	0.338
Nausea	4.4%	6.7%	NA	8.3%	9.4%	0.509
Serious gastrointestinal	NA	NA	NA	2.5%	3.3%	0.424
Diarrhoea	5.8%	7.3%	NA	NA	NA	NA
Constipation	8.9%	7.9%	NA	NA	NA	NA
Dyspepsia	NA	NA	NA	6.8%	6.8%	1.000

NS – Not significant, NA – Not available.

The Teriparatide subgroup study [39] did not specifically report the above prespecified adverse outcomes except the number of patients with at least 1 adverse event which was not different compared to placebo or between age groups. The study reported relevant treatment-emergent adverse events (TEAEs) with an incidence >3% in any treatment group and all TEAEs with significant treatment-by-age interaction (TAI) in patients younger than 75 versus those 75 and older. The TAI were similar between the age groups except for cataracts, deafness, pruritis and weight loss (commoner in the younger) and diarrhoea (commoner in the older) (TAI  $p < 0.05$ ). There was no increase in TEAEs compared to placebo in the older age group. Instead, the study reports statistically significant favourable outcomes compared to placebo in back pain (15% vs 25%), cataract (2% vs 10%) and pruritis (0% vs 5%) compared to placebo ( $p < 0.05$ ).

There are no published studies on adverse outcomes in the older age group for Alendronate or Clodronate. The main adverse outcomes described in the original cohort studies were mainly gastrointestinal i. e. nausea and dyspepsia.

## Discussion

### The current evidence

There is a significant paucity of evidence-based literature on randomised controlled trials in older patients with only some studies including patients over 75 years but the numbers are often small and infrequently analysed as subgroups. Hence, reliance on pooled analysis is required. There are published safety data for Strontium Ranelate, Risedronate and Teriparatide which demonstrate relative safety in the older age groups.

There is acceptable evidence to recommend the bisphosphonates (Risedronate and Alendronate), Strontium Ranelate or Teriparatide for vertebral fracture risk reduction. There are demonstrated benefits for Risedronate, Teriparatide and Strontium Ranelate; and data are consistent with randomised controlled trials in all younger age groups which demonstrate a significant early onset of benefit within 12 months with Teriparatide and Risedronate. There are no one year vertebral fracture endpoints for Alendronate or Clodronate. At three years, there is evidence for sustained benefit in vertebral fracture reduction with Risedronate, Strontium Ranelate and Alendronate with all three agents having similar relative risk reduction. There is no evidence for Teriparatide or Clodronate at 3 years in this age group.

Non-vertebral fracture data are limited. Most evidence is available for Strontium Ranelate which demonstrated a significant reduction in non-vertebral fractures in women 80 years or older by

one year with a sustained benefit of 31% at three years. The 1 year study with Teriparatide and the 3 year pooled study with Risedronate demonstrate no benefit in non-vertebral fracture reduction. The main limitations in interpreting the significance of these latter 2 studies are that they are subgroup analyses with secondary endpoints and not powered to assess efficacy. In the Risedronate pooled study [38], the evidence indicates that patients aged 80 and over had an even more severe degree of osteoporosis than younger patients in this study. Despite this finding, only the younger group aged <80 years (mean age  $72 \pm 5.5$ ) demonstrated a reduction in non-vertebral fractures ( $p = 0.025$ ) at 3 years. The findings in the HIP study were similar with no demonstrated benefit in the older cohort, although the inclusion criteria of the older group without the requirement for demonstrated osteoporosis may be a limiting factor. Notwithstanding this, the lack of demonstrated benefit in older compared with younger cohorts raises questions about the difference in risk and effective pharmacological measures required to manage non vertebral fracture risk in older cohorts compared to younger cohorts. There are no published data for Alendronate and Clodronate. Based on the current evidence, Strontium Ranelate is the only agent with demonstrated benefit in non-vertebral fracture reduction in older women (>80 years).

Evidence for hip fracture reduction is also limited. The TROPOS study (Strontium Ranelate) was powered to assess non-vertebral fracture as an endpoint. The subgroup analysis of patients over 74 years of age and at high risk of hip fracture was the only study to demonstrate a reduction in hip fracture in this age group. The HIP study (Risedronate) and Clodronate study specifically enrolled older patients and were powered to assess hip fracture as an outcome. However, there was no demonstrated hip fracture benefit in either study. The main limitation of both of the latter two studies was that enrollment of the older cohort was contingent on risk factors for hip fracture and did not require patients to be osteoporotic based on traditional BMD criteria and fracture history. Strontium Ranelate is the only agent with demonstrated benefit in hip fracture reduction in a high risk older subgroup.

The discrepancy in non vertebral fracture and hip fracture reduction between younger and older individuals may reflect differences in skeletal factors [52] and non-skeletal risk factors e.g. increased risk of falling with increasing age [53,54]. Osteoporosis of old age, “senile osteoporosis” as described by Riggs et al. [52], may need to be distinguished from other types of osteoporosis. Hip fracture is the predominant fracture after the seventh decade of life [23,24] and the strength of the hip neck area is reliant on preserved osteoblastic activity. Bone formation at this site is often impaired by the ageing process. By contrast, the incidence of fractures owing to increasing osteoclastic activity, a typical feature of post-menopausal osteoporosis, decreases in the older population. [55]. This may explain some of the potential difference in benefit of current antiresorptive agents in younger women with predominantly high bone turnover osteoporosis and older women with “senile osteoporosis”. Hence, reducing bone remodelling rates without improving bone formation rates may be inadequate in older populations who sustain predominantly non-vertebral plus hip fractures and less frequent vertebral fractures compared with younger age groups.

Strontium Ranelate has weaker antiresorptive properties compared to bisphosphonates, but similar benefits in fracture reduction. Although the exact mechanism of action of Strontium Ranelate is unknown, it may have some anabolic effects on bone that may explain its unique benefit in fracture reduction in the older age group [46,56,57]. Teriparatide is a potent anabolic agent with demonstrated benefit in improving BMD and reducing vertebral and non vertebral fracture risk in studies [47]. Its main role may be to treat severe osteoporosis with very low BMD or recurrent fragility fractures. Older patients fit this description extremely well

in terms of risk. However, there are very limited and only short term data in this group. The magnitude of benefit demonstrated as early as 1 year i.e. relative risk reduction of 65% which was non-inferior to treatment in younger age groups of patients with prior fragility fracture is promising.

The cost effectiveness of treating older women with currently available agents has been demonstrated in numerous analyses [34–36] but is based on the assumption that this population responds similarly to treatment compared to younger study populations. One study suggested that the age-specific intervention threshold for cost-effectiveness was exceeded in every person 80 years of age or older without any further risk stratification [36]. The National Institute for Clinical Excellence (2007 – Technology Appraisal Guidance 87) recommends that women aged 75 and older with prior fragility fracture should be offered antiresorptive treatment without further risk stratification (secondary prevention). Based on current literature, it is not possible to make this recommendation for bisphosphonates in primary prevention in view of the findings of the study by McClung et al. [42] and McCloskey et al. [41] which suggested that age and risk factors alone in women over 80 years and 75 years respectively, without pre-existing fracture, was not adequate to justify Risedronate or Clodronate treatment. This hypothesis has not been tested for Teriparatide or Strontium Ranelate. It may be more important in the older individual to consider multifactorial intervention strategies to address fracture risk.

Fracture is a consequence of a triad of factors including bone quality, a precipitating event, e.g. fall or trauma and the interphase between the bone and the contact surface. In older individuals, falls is a significant factor in fracture presentation and is probably the strongest single risk factor [58–60] in over 90% of hip fractures. Improving calcium and vitamin D status [61], and the use of hip protectors [62–64] are demonstrated as important adjunctive strategies.

## Conclusions

Teriparatide, Risedronate, Alendronate and Strontium Ranelate demonstrate significant benefit in vertebral fracture reduction but Strontium Ranelate is the only agent to date that demonstrates reduction in non-vertebral and hip fracture events in a high risk elderly female population.

This review reinforces the irony that the least evidence is available for fragility fracture reduction in the group at greatest risk, who are likely to sustain the greatest potential harm in terms of disability and mortality and at the greatest cost to society. Randomised controlled trials to provide more robust evidence for treatment of this patient group, who are likely to place increasing demands on limited per-capita health care resources in future decades, are needed. Older individuals have unique needs and differ quite significantly from younger populations in terms of their fragility fracture risk and new pharmacological strategies need to be explored. It is important that physicians apply a multi-factorial and multi-disciplinary approach to fracture reduction in addressing the triad of osteoporosis, falls risk and reducing the impact of injury.

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