Osteoporos Int (2013) 24:1–6
DOI 10.1007/s00198-012-2176-6

REVIEW

# The effect of treatments for osteoporosis on mortality

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Received: 30 July 2012 / Accepted: 26 September 2012 / Published online: 18 October 2012


**Abstract** The incidence of osteoporotic fractures increases exponentially in later life, in parallel with the progression of frailty and the risk of dying. Several pharmacologic therapies are now available that reduce the risk of fragility fractures. Data from observational studies report that osteoporotic fractures are associated with an increased risk of dying, particularly in the first few years after an event, and that, in osteoporotic populations, bisphosphonate therapy is associated with a reduced risk of death. Data emerging from randomised controlled trials suggest that drugs which significantly reduce fracture risk might also prolong survival in osteoporotic populations. Further research into the nature, magnitude and mechanisms of the effects of osteoporosis treatments on mortality is required, but in the interim, clinicians and their patients should consider the available data in their deliberations about the use of these medications.

**Keywords** Fracture · Mortality · Osteoporosis · Treatment

## Introduction

Osteoporosis, being impaired bone strength leading to an increased risk of fragility fracture, is most often a consequence of ageing, with contributions of variable magnitude from behavioural, genetic and medical factors. Fracture rates increase substantially in later life [1], in parallel with the incidence of comorbidities affecting other tissues and with the risk of dying. Unsurprisingly therefore, it is consistently reported in observational studies that adverse skeletal outcomes are associated with an increased risk of dying. Such analyses beg the question as to whether there is a causal relationship between osteoporosis and/or osteoporotic fractures and mortality. There is little doubt that hip fracture confers an increased risk of dying in the short and medium term [2], but such fractures are a minority of total fractures [3, 4].

The conduct of randomised, placebo-controlled trials of pharmacological agents for fracture risk reduction provides a means by which it is possible to test the hypothesis that treating osteoporosis influences risk of dying. The finding from one such trial that the intravenous bisphosphonate zoledronate reduced the risk of all-cause mortality in participants who had suffered a hip fracture [3] provoked renewed interest in this question. If treatment of osteoporosis impacts favourably on mortality, there would be several important potential implications for management of skeletal health specifically and for health care of the elderly in general. In this review, we examine the evidence that osteoporosis treatments affect mortality in older people.

## Associations between skeletal health and mortality

Several prospective cohort studies have reported positive associations between indices of skeletal fragility (low bone mineral density (BMD) and incident fractures) and increased mortality [5–13] (Table 1). In an analysis of national data in France, 2 % of death certificates included fracture as a cause, of which half were hip fractures [14]. The relationship between fractures and risk of dying applies across a wide age range and to both men and women. In three studies which reported data according to participant age, each found that the relative risk of dying was higher in younger people who sustained an incident fracture than in older people [8, 12, 15]. This finding might be explained by the greater competing risk of dying from other comorbidities in the elderly population. Thus, in frail elderly people in whom risk of mortality from several conditions is already high, a

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**Table 1** Observational studies reporting the relationship between osteoporosis and mortality

| Study | Population | Follow-up | Skeletal variable | Mortality risk estimate |
|---|---|---|---|---|
| SOF [5, 6] | 9,704 White women, >65 years | 2.8 years | BMD forearm | 1.2/1 SD decrease |
| | | | | 1.1/1 SD decrease$_{adj}$ |
| | | 5.9 years | Non-spine fracture | 1.7 |
| | | | Hip/pelvis fracture | 2.4 |
| Dubbo [7, 8] | 2,413 women, >60 years; 1,898 men, >60 years | 5 years | Proximal femur fracture | 2.2 women |
| | | | | 3.2 men |
| | | | Vertebral fracture | 1.7 women |
| | | | | 2.4 men |
| | | | Other major fracture | 1.9 women |
| | | | | 2.2 men |
| | | 10–13 years | Hip fracture | 2.4 women |
| | | | | 3.5 men |
| | | | Vertebral fracture | 1.8 women |
| | | | | 2.1 men |
| | | | Other major | 1.7 women |
| | | | | 1.7 men |
| EPIDOS [9] | 7,512 women, >75 years | 3.9 years | Hip fracture | 2.1 |
| CaMos [10] | 5,506 women, >50 years; 2,187 men, >50 years | 4 years | Hip fracture | 3.0 women |
| | | | | 3.1 men |
| | | | Vertebral fracture | 3.7 women |
| | | | | 1.0 men |
| EPOS [11] | 3,353 women, 50–79 years; 3127 men 50–79 years | 2.3 years | Vertebral deformity | 1.6 women |
| | | | | 1.2 men |
| Malmo [12] | 2,847 older men and women | 5 years | Hip fracture | 1.6, 5.4 women[a] |
| | | | | 2.2, 5.8 men[a] |
| | | | Vertebral fracture | 1.0, 4.3 women[a] |
| | | | | 1.3, 4.3 men[a] |
| | | | Shoulder fracture | 0.9, 1.4 women[a] |
| | | | | 1.8, 2.1 men[a] |
| | | | Forearm fracture | 1.2, 1.9 women[a] |
| | | | | 1.0, 1.2 men[a] |
| FIT [13] | 6,549 women, 55–81 years with low BMD | 3.8 years | Hip fracture | 6.7 |
| | | | Vertebral fracture | 8.6 |
| | | | Any clinical | 2.2 |

[a] Risk estimates provided for ages 60 and 80 years; in each case, the lower estimate applies to older participants

hip fracture might produce a relatively small impact on risk of death compared to that produced in a younger person, whose range of comorbid diseases, and consequent risk of dying, will be smaller. In addition, an osteoporotic fracture in a person aged 60–80 years might reflect the presence of premature frailty, with corresponding risk of death. Some [8], but not all [10], studies suggest a stronger association between fractures and mortality in men than women. In the Fracture Intervention Trial, which enrolled participants with low BMD, risk estimates for mortality associated with fractures seemed to be higher than those generated in studies performed in non-osteoporotic populations [13]. Although there has rightly been considerable emphasis on the high risk of death in the short-term following hip fracture [2], several studies suggest that incident vertebral fracture is associated with a similarly high risk of dying [8, 10, 13].

Some studies have evaluated the effect of time since the incident fracture on the risk of mortality. Collectively, they demonstrate that the risk of death is highest in the 1–2 years immediately following the fracture [9, 10, 12, 13, 15]. Subsequently, there is diminution of the increased risk, although it remains above that of non-fracture controls at 5 years follow-up [8, 12]. In one study with prolonged follow-up, incident hip fracture, but not fractures at other

sites, was associated with higher mortality at 10 years [8]. A second study also found increased mortality following hip fracture after 10 years of observation [15]. In the Dubbo study, the investigators assessed risk of mortality after a *second* incident fracture and found that it was higher than expected for at least 5 years after the event. Mortality risk was also higher in the 5 years after the second fracture than in the corresponding time period after the first fracture, implying a cumulative effect of skeletal fragility on risk of dying [8].

However, although most observational studies have reported a positive relationship between fractures and risk of death, they also report that only a minority of the deaths in the fracture cases were clearly attributable to a fracture. It was estimated that 23 % of the mortality following hip fracture in Sweden was attributable, either directly or indirectly, to the fracture [16]. In the Study of Osteoporotic Fractures, only 14 % of the deaths following hip and pelvic fractures were considered attributable to the fracture itself [6]. The Dubbo investigators estimated that fractures were responsible for 13–14 % of the population-attributable risk of death [8].

Ultimately, observational studies, no matter how carefully they are conducted and analysed, cannot prove or disprove whether osteoporosis *causes* an increased risk of dying. In cohort studies, fracture cases are older, thinner, more frail and have more comorbidities than non-fracture controls [9, 15], and the ability to adjust for differences in baseline health status is limited. The hypothesis that there is a causal link is supported by the finding in several observational studies that the risk of dying is the greatest shortly after a fracture event, then declines but does not disappear [8–10], and the observation that risk of death is increased, at least in the short-term, after hip fracture in elderly people without significant comorbidities [15].

## Effect of treating osteoporosis on mortality

If osteoporosis is causally associated with a higher risk of death, it would be expected that effective treatments for osteoporosis might reduce the risk of dying. Observational studies are necessarily limited in their ability to determine whether interventions to treat osteoporosis confer a survival benefit because of the potential for confounding, in particular by indication. That said, several cohort studies have reported results consistent with that possibility [17–21] (Table 2). Almost exclusively, these studies have assessed the effects of therapy with oral bisphosphonates on risk of death. In each study, participants receiving bisphosphonate therapy had lower risk of dying, by 24–66 %, during follow-up than those who were not treated, a finding that did not change appreciably after adjustment for measured confounders. In some studies, those who received bisphosphonates had worse baseline health status than those who did not [19]; in others, the group receiving no treatment had more comorbidities [20]. A Danish study reported a protective effect of bisphosphonate treatment initiated prior to hip fracture on mortality in the 3-month period immediately after an incident hip fracture [20], raising the possibility that such treatment increases resilience in older people.

Some studies recorded information on cause of death. In the study by Sambrook et al., conducted in a frail elderly population, mortality from cardiovascular and infectious diseases was non-significantly lower (risk reductions 25–36 %) in the participants taking a bisphosphonate. Data from the Dubbo study suggest that mortality from cardiovascular diseases may be lower in those prescribed a bisphosphonate, but the number of deaths was too few to permit firm conclusions to be drawn [17].

**Table 2** Observational studies reporting the relationship between osteoporosis treatment and mortality

| | Study design | Participants | Duration of follow-up | Treatment | Mortality risk estimate | Adjusted mortality risk estimate[a] |
|---|---|---|---|---|---|---|
| Cree [21] | Prospective cohort | 449 hip fracture patients, >65 years | <5 years | Any[b] | NR | 0.34 (0.17, 0.70) |
| Center [17] | Prospective cohort | 1,223 women, >60 years; 819 men, >60 years | 15 years | BP | 0.8 (0.4,1.4) | 0.3 (0.2, 0.5) |
| Beaupre [18] | Prospective cohort | 209 hip fracture patients, >50 years | 3 years | BP | 0.94 (0.90, 0.98) | 0.37 (0.28, 0.51) |
| Sambrook [19] | Prospective cohort | 2,005 institutionalised people, >65 years | 3.4 years | BP | 0.74 (0.56, 0.98) | 0.73 (0.56, 0.94) |
| Bondo [20] | Registry-based cohort | 42,076 people, >55 years with a hip fracture | 3.8 years | BP[c] | 0.84 (0.75, 0.94) | 0.76 (0.68, 0.85) |
| | | | <3 month of hip fracture | BP[d] | 0.76 (0.66, 0.87) | 0.68 (0.59, 0.77) |

*NR* not reported, *BP* bisphosphonate

[a] Adjusted for measured confounders

[b] >75 % bisphosphonates

[c] Bisphosphonate commenced <1 year of hip fracture

[d] Bisphosphonate commenced prior to hip fracture

Randomised controlled trials provide a much more rigorous means by which to assess treatment effects. A signal that osteoporosis treatment might reduce the risk of dying came from a randomised, placebo-controlled trial of annual intravenous zoledronate in participants with an average age of 75 years who had suffered a hip fracture within the preceding 90 days and had a life expectancy of at least 6 months [3]. Mortality was a pre-specified safety outcome. Over a median follow-up of 1.9 years, the risk of death in the participants allocated to zoledronate was significantly lower, by 28 %, than that in the placebo group. The time-to-event analysis for mortality demonstrated similar incidence in the treatment groups for the first year, then steady separation in years 2 and 3. The differences between the groups appeared to be due to a lowered mortality rate in the zoledronate group in the second half of the study, whereas the mortality rate in the placebo group remained constant.

This finding provided the first convincing evidence that a treatment for osteoporosis might prolong survival. To further address this possibility, our group conducted a trial-level meta-analysis of the effects on mortality of effective osteoporosis treatments [22]. Randomised trials were eligible for inclusion if they were studied drugs with proven efficacy against both vertebral and non-vertebral fractures administered at the registration dose for treatment of osteoporosis, were longer than 1 year in duration, studied participants >50 years with osteoporosis, and included >10 deaths. Trials conducted in participants with glucocorticoid osteoporosis or of agents with multi-system effects, such as estrogenic drugs, were excluded. Data were extracted from the primary trial publication or the Food and Drug Administration website. In the resulting analysis, which included 1,295 deaths in >33,000 participants over a median follow-up of 3 years, the risk of dying was reduced by 11 % in the participants allocated to active therapy (Fig. 1). In only one of the individual contributing trials was there a significant reduction in mortality [3], although none was powered to investigate a survival benefit. Most of the contributing trials were of bisphosphonates, but the risk estimates for mortality in trials of strontium and denosumab were both <1 (0.94 and 0.78, respectively) in the groups receiving active therapy. Sensitivity analyses that included trials of alendronate, in which the dose of drug was less than that approved for clinical use during part of the trial, and of ibandronate, for which evidence of treatment efficacy at non-vertebral sites is arguable, did not affect the results.

A point of note is that the two zoledronate trials generated quite different estimates of mortality risk, with the trial conducted in osteoporotic women reporting a relative risk for dying of 1.16 [4]. The reason(s) for this discrepancy is not apparent, but possible explanations include the play of chance and baseline differences in the trial populations.

A limitation of trial-level meta-analysis is the inability to perform time-to-event analyses or to rigorously examine the effects of potentially important co-variables. However, in meta-regression analyses using trial summary data for covariates of interest, no relationship was found between mortality risk reduction and age, the achieved magnitude of fracture risk reduction or fracture risk in the placebo groups. An inverse relationship was apparent between mortality risk reduction and mortality rate in the placebo groups of contributing trials (Fig. 2). This finding implies that osteoporosis treatments impact on mortality to a greater extent in the frailest populations, in which intervention would be predicted to produce an absolute reduction in death of ~7/1,000 patient-years of treatment. It is noteworthy that mortality rates in participants in the clinical trials included in the meta-analysis are relatively low, reflecting both the healthiness of those who enrol in such studies and the restrictions imposed by inclusion and exclusion criteria. In the zoledronate post-hip fracture trial, for example, mortality in the placebo group was only 13.3 % during 23 months of follow-up [3], compared with approximately 30 % mortality during 12 months of follow-up in an overview of observational studies [2].

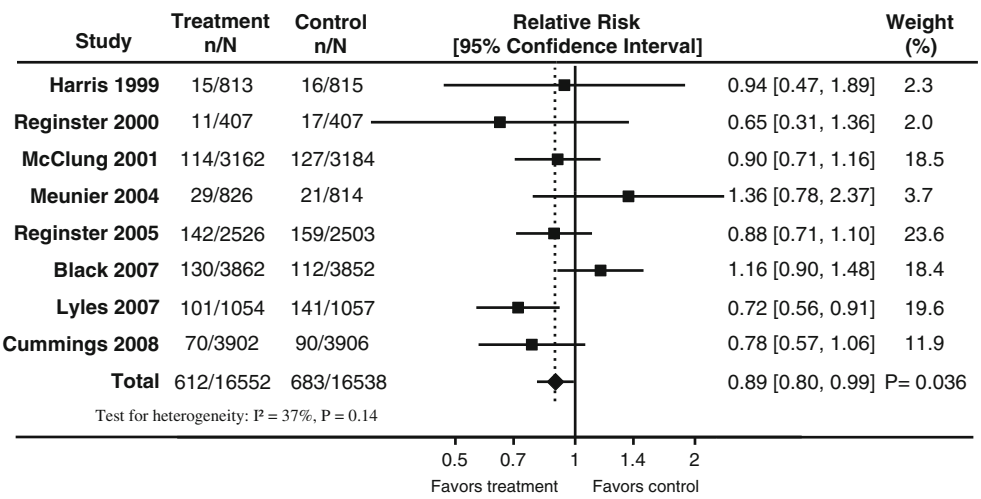


**Fig. 1** Meta-analysis of trial-level mortality data from randomised controlled trials of osteoporosis treatments. Reproduced with permission from Bolland et al. [22], copyright 2010, The Endocrine Society

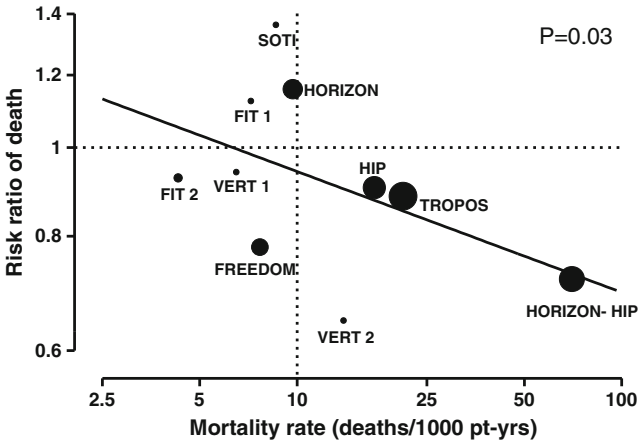


**Fig. 2** Meta-regression of mortality risk reduction against trial population mortality in randomised controlled trials of osteoporosis treatments. Copyright M Bolland, reproduced with permission

The data from randomised controlled trials, therefore, suggests that currently available treatments for osteoporosis probably impact favourably on survival, particularly in frail populations. It is possible that the greater mortality risk reduction reported in observational studies than in randomised trials reflects the greater frailty of participants in the former studies, as evidenced by the higher mortality rates.

## Mechanism of effects of osteoporosis treatments on mortality

Only limited analyses have been conducted to investigate how treatments for osteoporosis might impact on survival. Because mortality was not a primary endpoint of any of the randomised trials of osteoporosis treatment, information on causes of death is limited. In the zoledronate post-hip fracture trial, a post hoc analysis of causes of death was limited by reliance in a significant proportion of cases on death certificates completed by the participants' physicians. This analysis suggested that the survival benefit was consistent across various trial population subgroups, including those defined by age [23]. However, there was no evidence of survival benefit from zoledronate treatment in subgroups of very frail participants, such as those with cognitive impairment or those residing in nursing facilities. In contrast to the anti-fracture effect, which was apparent by 6 months [3], the zoledronate effect on mortality was not apparent until 16 months of follow-up had elapsed. Further analyses suggested that only 2 % of the 25 % reduction in risk of death (that is, 8 % of the survival benefit) could be directly attributed to fracture prevention by zoledronate. Importantly, the *incidence* of several comorbidities, including cardiac, vascular, infectious and neoplastic disease, was not altered by allocation to zoledronate, but the risk of dying from some of the same causes, notably arrhythmias and pneumonia, was lower in the zoledronate group. Although no formal evaluation of cause of death has been conducted in the phase III denosumab trial, which reported a 22 % reduction in mortality in the group randomised to active therapy, there were no between-groups differences in the incidence of investigator-reported cardiac, infectious or neoplastic events [24]. These results raise the possibility that effective treatments for osteoporosis may improve survival by improving physiological resilience and/or preventing frailty.

Other mechanisms of action have been suggested to explain the survival benefit conferred by bisphosphonates. They include beneficial effects on endothelial function [25], immune function [26] and systemic inflammation [27]. It remains speculative as to whether any of these actions are clinically significant. More importantly, if any were relevant in vivo, one might expect to observe a reduction in the incidence of vascular and/or infective events in clinical trials of bisphosphonates. Further, the survival benefit apparent in response to osteoporosis treatment does not appear to be limited to bisphosphonates, although there are fewer data from trials of non-bisphosphonate therapies.

## Clinical implications

The evidence that zoledronate reduces the risk of dying after hip fracture should make it the treatment of choice for patients who have experienced this serious fracture. In other osteoporotic populations, clinicians and their patients might reasonably consider the probable modest reduction in risk of dying in their discussions about initiation of treatment for fracture risk reduction. The absolute benefit of such an effect will be greatest in those at highest mortality risk, namely the frail elderly with other comorbidities. Such individuals are likely to also be at high absolute risk of fracture and to receive significant treatment benefits within a short time of starting anti-resorptive therapy. It therefore makes sense to estimate fracture risk in elderly patients over a time frame (3–5 years) that reflects onset of treatment efficacy and duration of therapy, rather than relying on algorithms that predict risk over a long time interval and incorporate the competing risk of mortality.

## Conclusions and future research

A growing body of evidence, from both observational studies and randomised trials, suggests that effective treatments for osteoporosis prolong survival. Observational studies, which can generate but not test the hypotheses of causation, consistently report positive relationships between incident fractures and risk of dying, and inverse relationships between bisphosphonate therapy and risk of dying. Data from randomised controlled trials, which permit inference of causation, indicate that

zoledronate prolongs survival in people who have had a hip fracture and suggest that effective osteoporosis treatments, being those which prevent both vertebral and non-vertebral fractures, reduce risk of dying by about 10 % over 3 years in osteoporotic populations. The mechanism(s) by which this effect is conferred is unclear but may include delaying the progression of frailty.

The impact of osteoporosis treatments on mortality is an important issue that has the potential to influence clinical practice. There is potential for additional observational studies in this area, but in the absence of randomization, even the most carefully performed pharmacoepidemiologic cohort studies will not be definitive. Inclusion of mortality as a secondary endpoint, and careful collection and adjudication of cause of death data should be undertaken in ongoing and planned randomised trials of treatments for osteoporosis. As more anabolic agents come into clinical trials, it will be very important to assess their effects on mortality—currently, the effect of the only clinically available anabolic agent, teriparatide, on the risk of dying is unknown. Meta-analysis of individual patient data from existing randomised trials of osteoporosis treatments would be helpful in permitting examination of the time course of the mortality risk reduction, allowing a more rigorous interrogation of covariates of interest, and providing insight into the mechanisms by which the treatments affect survival. Such an analysis would require the cooperation of several pharmaceutical companies in making individual patient data from registration trials available.

**Acknowledgments** Grant support from the Health Research Council of New Zealand. Dr Bolland is the recipient of a Hercus Fellowship from the Health Research Council of New Zealand.

**Conflicts of interest** None.

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