Fracture mortality: associations with epidemiology and osteoporosis treatment

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Abstract | The rates of incident osteoporotic fractures seem to be stabilizing; however, fragility fractures are still associated with considerable disability, costs and an increased risk of mortality, which is particularly the case for fractures of the hip and vertebra. Mortality is usually highest during the first year after fracture; however, a notably increased mortality risk might persist for several years after the event. In addition to its efficacy in the prevention of new and recurrent osteoporotic fractures, medical treatment has been associated with improved survival after osteoporotic fractures. Observational studies and randomized controlled clinical trials have reported increased survival in patients with a fracture who are treated with bisphosphonates. Rates of medical treatment in patients with osteoporosis remain low, and although the rationale for the putative increase in survival is unclear, this emerging evidence might help further justify the use of medical treatment after fracture. However, further work is needed before medical therapy for mortality prevention in patients with osteoporotic fractures is accepted.

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Introduction

A decreased BMD is associated with increased mortality risk in patients with osteoporosis.[1–3] Bone loss might be a marker of underlying inflammatory processes such as cardiovascular disease.[3,4] Incident nontraumatic fractures are another expression of skeletal fragility, which in 2005 represented a total health-care cost of over $19 billion dollars in the USA.[5] In addition to the implications for disability and health-care costs, several prospective studies have documented an increased risk of mortality associated with hip[6–13] and vertebral fractures (radiographic and clinical fractures).[8,13–18] In contrast to the evidence showing excess mortality for hip and vertebral fractures, increased mortality with other major fractures has been seen in some,[8,19,20] but not all,[14,21,22] studies. Increasing age is the key factor associated with increased mortality;[23] however, other factors such as sex, comorbidities and physical activity have an important role in the excess mortality after fracture in patients with osteoporosis.[6,14,24,25] These associations add to the complexity of establishing quality care for these patients.

Since observations of decreased all-cause mortality in a trial of intravenous administration of the bisphosphonate zoledronic acid in patients with hip fracture were published,[26] further evidence has emerged of a possible benefit of this and other bisphosphonates on the risk of mortality. Even though bisphosphonates reduce the rates of re-fracture,[26–28] the low usage of anti-resorptive therapy in patients after a fracture mitigates a population-level benefit.[27,29–31] This emerging evidence of a possible beneficial effect on mortality adds to the rationale for the medical treatment of osteoporosis-related fracture.

In this Review, we summarize the evidence regarding osteoporosis-related fractures and their link with mortality, and we examine data on the effects of treating osteoporosis on mortality in patients with this condition. The postoperative mortality associated with total hip replacement and other available surgical treatments, which is partly related to factors such as surgical technique and complications after surgery, has been reviewed elsewhere in the literature[32–36] and will not be discussed in this Review.

Mortality and hip fractures

Overall risk, incidence and prevalence

A small proportion of all osteoporosis-related fractures are hip fractures; however, they are the most serious of all fractures, leading to a high burden of morbidity, health-care costs and mortality.[5,37] In a systematic review of 22 studies, excess mortality during the first year after a hip fracture ranged from 8.4% to 36.0% and the risk of mortality following hip fracture was estimated to be at least twice as high as that for age-matched control individuals from the general population.[6] The highest risk of death was in the first 6 months after the fracture.[10,38–41] While not supported by all the studies analysed, an increased risk of death was maintained for up to 3 years,[42] 5 years,[25] 10 years[43] and even as long as 20 years after fracture.[44] A meta-analysis found similar results, despite the studies analysed using different inclusion criteria to those in the systematic review.[45] The mortality risk was greatest in the first 3 months after the hip fracture: pooled relative

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Key points

- Hip and vertebral osteoporotic fractures are associated with considerable immediate and long-term increased risk of death
- The fracture event itself is responsible for part of this increased mortality risk; however, other factors such as age, sex, comorbidities and poor prefracture health status are also involved
- The majority of incident osteoporotic fractures are nonhip, nonvertebral fractures
- Evidence of mortality risk in nonhip, nonvertebral fractures is lacking, but evidence of an increased mortality risk with some fractures, such as those in the pelvis and humerus, does exist
- Medical treatment with bisphosphonates has been associated with a decreased risk of mortality in patients with osteoporotic fractures in some observational studies and in one randomized controlled trial
- Decreased cardiovascular-related mortality could be one of the potential mechanisms for the decreased risk of mortality with bisphosphonate therapy; however, further studies are required to clarify this point

hazard (RH) was 5.75 (95% CI 4.94–6.67) for women and 7.95 (95% CI 6.13–10.30) for men. A long-term persistence of the increased mortality risk was not seen in all studies;[11,39] however, an increased RH for all-cause mortality was still present 10 years after hip fracture (RH 1.96 [95% CI 1.30–2.95] for women and RH 1.79 [95% CI 1.14–2.81] for men; Table 1).

The role of hip fractures in this increased mortality risk, and whether the effect is direct or indirect, is still not clear. Even though a 2.4-fold increase in mortality was reported for patients with hip and pelvic fractures in the Study of Osteoporotic Fractures, the authors identified only 14% of the deaths as being caused or hastened by the fracture.[22] A subsequent analysis from the same cohort identified coronary heart disease, cancer and stroke as the leading causes of death in patients with and without fractures.[11] Causally related deaths account for 17–32% of all deaths associated with hip fracture, which represents >1.5% of all deaths in the general population aged ≥50 years.[25] Furthermore, some studies report an increased risk of death after fracture that is attributable to an increased incidence of infections,[11,12,46] cognitive disorders[11] and cardiovascular diseases in patients with hip fractures;[12,47] however, these associations are less consistent in other types of fracture.

Between 1985 and 2005, age and risk-adjusted mortality after hip fracture in women from a US Medicare population declined by 11.9%, 14.9% and 8.8% for 30-day, 180-day and 360-day mortality, respectively.[48] For men in this population, adjusted mortality decreased by 21.8%, 25.4% and 20.0% for the 30-day, 180-day and 360-day mortality, respectively. In their analysis, the authors report that most of this decrease was observed before 1998 and that after this time very little change had been observed in mortality for either sex. Improvements in medical (that is, bisphosphonate treatment and reduction of the number of subsequent fractures) and surgical care (that is, new surgical interventions and devices, improved care after surgery and increased rates of discharge to nonacute health-care settings) might account for the decrease in mortality, but still do not explain the plateau established after 1998.

Death after hip fracture: risk factors

Age

As might be expected, age is the primary independent predictor of mortality, with increasing age associated with increasing fracture-associated mortality (Table 2).[6,49–51] In the USA, a study of Veteran Health Administration Medicare beneficiaries estimated that the risk of mortality following hip fracture increased by ~5% for each additional year of age.[49] However, younger patients (≤70 years old) show a higher excess or relative risk of mortality associated with fractures than do older adults (≥80 years old).[6,8,44,52–54]

Ethnicity and sex

Data on ethnic differences in mortality after hip fracture are scarce. An analysis carried out on three different cohorts of patients with hip fracture found that nonwhite patients, as well as men of any ethnicity, had the lowest survival during the first 6 months after a fracture.[55] This study confirms a previous analysis of Medicare claims data in which black women had a higher risk of mortality than white women during the first 9 months after hip fracture.[56] However, the divergence of these survival curves diminished after 9 months. These observations might relate to ethnic differences in access to health care, such as reduced access to high-intensity rehabilitation[57] or postacute physical therapy after hip fracture in the African American population.[58]

Even though the prevalence of fractures is considerably greater in women, men have a higher risk of death after a hip fracture than women. In a meta-analysis of 24 studies of patients with hip fracture, pooled RHs for mortality 2 years and 6 years after hip fracture were 2.89 (95% CI 2.27–3.68) and 3.83 (95% CI 3.04–4.82), respectively, in women and 3.23 (95% CI 1.95–5.36) and 4.99 (95% CI 3.62–6.89), respectively, in men.[45] Men also have greater mortality associated with hip fracture for up to 20 years after fracture than women.[25,44,53,59–61] Despite men having more comorbidities,[48] more postoperative complications[62] and an increased incidence of infections[46] compared with women, sex-specific differences in fracture mortality have not been observed in all studies.[8,13]

Comorbidities and prefracture health status

The presence of comorbidities (such as hypertension or chronic obstructive pulmonary disease) in patients with hip fractures seems to have an important influence on survival;[49,59,62–67] however, this finding was not consistent in all studies.[19,44] Among Medicare beneficiaries, mortality risk increased during the first 6 months after hip fracture (HR 11.6 [95% CI 8.9–15.1]).[39] However, after adjusting for other variables, including health status before fracture and comorbid conditions, the magnitude of the increased risk was attenuated (HR 6.28, 95% CI 4.82–8.20). This observation, coupled with the loss of a statistically significantly increased mortality risk in the long-term follow-up after adjustment (HR 1.04 [95% CI 0.88–1.23]), led the authors to conclude that comorbidities and health status before fracture have a substantial role in the excess mortality in patients with hip fracture.

Table 1 | Osteoporotic fractures and mortality: summary from observational studies

Study and country	Population			Type of fracture	Cumulative fracture incidence (%)	Follow-up duration (years)	Mortality risk (95% CI)
	n	Sex (% W)	Age range/ mean (years)				
Lee *et al.* (2012)[86] South Korea*	>11 million	~54	>50	Vertebral	1	2	SMR 1.86 (1.83–1.88) W; 2.53 (2.48–2.58) M
Ioannidis *et al.* (2009)[13] Canada*	7,753	70	>50	Hip Vertebral	1.1 1.3	5	1-year HR 4.31 (1.53–12.13) W; 4.13 (0.98–17.39) M 2-year HR 2.65 (1.24–5.63) W
Vestergaard *et al.* (2007)[44] Denmark‡	169,145 cases 524,010 controls	72.4	77	Hip	NA	20	HR 1.95 (1.94–1.97)
Bliuc *et al.* (2009)[19] Australia*	4,005	56	≥60	Hip Vertebral	4.6 W; 1.6 M 7.1 W; 2.7 M	>10	SMR 2.43 (2.02–2.93) W; 3.51 (2.65–4.66) M SMR 1.82 (1.52–2.17) W; 2.12 (1.66–2.72) M
Johnell *et al.* (2004)[8] Sweden‡	2,847 77 75	80.1 78.6	Hip Vertebral	NA	5	RR 5.4 W; 5.8 M§ RR 1.6 W; 2.2 M‖ RR 4.3 W; 4.3 M§ RR 1.0 W; 1.3 M‖	
Empana *et al.* (2004)[10] France*	7,512	100	>75	Hip	4.5	3.9	RR 2.1 (1.6–2.8)
Cauley *et al.* (2000)[14] USA*	6,459	100	55–81	Hip Vertebral	1.2 31.4 prevalent 1.8 incident	3.8	RR 6.68 (3.08–14.52) RR 8.64 (4.45–16.74)
Center *et al.* (1999)[15] Australia*	4,311	56	≥60	Hip Vertebral	1.8 W; 0.6 M 1.8 W; 0.9 M	5	SMR 2.18 (2.03–2.32) W; 3.17 (2.90–3.44) M SMR 1.66 (1.51–1.80) W; 2.38 (2.17–2.59) M

*Prospective cohort. ‡Retrospective cohort. §Risk estimates for population age 60 years. ‖Risk estimates for population aged 80 years. Abbreviations: M, men; NA, not available; SMR, standardized mortality ratio; W, women.

Functional impairments, another variable that was adjusted for in this analysis, were also independently associated with an increased risk of mortality.[59,68]

A meta-analysis published in 2012 that included 64,316 patients with hip fracture who were undergoing surgery identified 12 different preoperative predictors of mortality after fracture. These included nursing home or facility residence, poor preoperative walking capacity, poor ability to carry out the activities of daily living, increased American Society of Anesthesiologists grading, poor mental state, the presence of multiple comorbidities, dementia or cognitive impairment, diabetes mellitus, cancer and cardiac disease.[34] Other comorbidities such as renal disease, congestive heart failure and chronic obstructive pulmonary disease are contributors to increased risk of death following hip fractures.[49,55,63,66] As comorbidities seem to have an important role in the risk of mortality after a hip fracture, a higher prevalence of comorbidities in men than in women might account for the sex differences in mortality.[69]

Other factors

The type of hip fracture can affect the risk of death. For example, higher mortality was observed at 2 months and 6 months after fracture in patients with intertrochanteric fractures compared with patients who had femoral neck fractures.[70] An increased risk of mortality in patients with intertrochanteric fractures has not only been reported by the time of hospital discharge, but also maintained 1 year after fracture (RR 2.5 [95% CI 1.3–5.1])[71] and has even been reported up to 10 years after fracture.[72]

Weak quadriceps strength is another risk factor that is associated with increased mortality risk (HR 1.20 [95% CI 1.00–1.43] for women and 1.21 [95% CI 1.01–1.46] for men). This association, along with an increased mortality risk with subsequent fractures, was reported in the Dubbo Osteoporosis Epidemiology Study (a cohort study from Australia).[19] In addition, residence in a nursing home or another institution before the fracture event has been reported to be associated with increased mortality, independent of the presence of comorbidities.[68,73]

Mortality and vertebral fractures

Overall risk, incidence and prevalence

Vertebral fractures are one of the most frequent complications of osteoporosis;[21,74] however, only one-third to one-quarter of these fractures are clinically diagnosed[75,76] and hospitalization rates are low.[77] The excess mortality 1 year after vertebral fractures varies considerably, ranging from 1.9% to 42.0% (Table 1).[14–18,21,24,78–81] Vertebral fractures

have an increased mortality risk that is lower than that for hip fractures, except for one analysis from the Study of Osteoporotic Fractures, in which mortality risk after a vertebral fracture was greater than that for hip fractures (RR 8.6 and 6.7, respectively).[13,19,20]

An analysis of a population from a South Korean claims database reported an increased standardized mortality ratio (SMR) that peaked 3 months after vertebral fracture at 5.46 (95% CI 5.27–5.65) for men and at 3.25 (95% CI 3.16–3.34) for women.[82] SMRs decreased during follow-up; however, by the end of the 2-year follow-up period the risk of death was still higher than that in the general population. As with hip fractures, mortality rates are highest within the first year following vertebral fracture.[14,15,17,21,80] Analysis from a Medicare claims database reported considerably lower survival for up to 7 years after fracture, when comparing the survival of patients with a vertebral fracture with that of control individuals matched for age, sex, ethnicity and Medicare buy-in status.[83] Increased mortality risk among patients with vertebral fracture has been reported for up to 5 years,[19,21] and even 22 years,[80] after the fracture.

The exact relationship between excess mortality and vertebral fractures is not clear.[84] In a study of the Swedish population, only 28% of the deaths in patients with vertebral fractures were causally related to the fracture event.[17] These results were similar to those reported in a study of hospitalized patients in Spain with vertebral fractures related to osteoporosis, in which 26% of hospital deaths were attributable to the fracture itself. Reduced mortality (1.5%) was observed in a large subgroup of patients with no identifiable comorbidities, which might suggest that vertebral fractures have an intrinsic role in inpatient mortality but also highlights the importance of comorbidities in mortality risk in this population of patients.[78] In light of these observations, specific causes of death, as reported in this population of patients with vertebral fracture, might provide an explanation for the excess mortality. The Study of Osteoporotic Fractures reported that women with vertebral fractures were more likely to die from cancer (HR 1.4 [95% CI 1.1–1.7]), and from pulmonary disease (HR 2.1 [95% CI 1.4–3.0]), than women without vertebral fractures.[85] The risk of death from pulmonary disease was particularly increased in women who had a compromised thoracic spine and presented with severe kyphosis. An increased incidence of cancer and associated mortality in patients with vertebral fracture has also been reported in other studies.[21,80]

Death after vertebral fracture: risk factors

Age

As expected, the incidence of vertebral fracture and the absolute risk of mortality increase with age.[15,17,78] However, compared with age-matched control individuals from the general population, the relative risk of death associated with vertebral fractures is higher in younger individuals (≤70 years old) than in older individuals (≥80 years old).[83,86] This finding is similar to the observations made when analysing trends in the relative risk of mortality associated with hip fracture (Table 2).[6,8,44] In an analysis of a South Korean claims database published in 2012, the authors reported a decrease in SMR with increasing age in women at 3 months, 6 months, 12 months and 24 months after fracture.[86] A similar trend was also observed in men, except for an increased risk of mortality in the group aged 55–59 years compared with other male age groups. These observations are also supported by an analysis of Medicare data.[83] Patients who were 65–69 years old when diagnosed with compression fracture had a higher increased risk of death after vertebral fracture than patients who were ≥85 years at the time of diagnosis (HR 6.88 [95% CI 6.47–7.31] and 1.88 [95% CI 1.84–1.92], respectively). This statistically significant difference in risk was maintained after adjusting for comorbidities. Similar trends have been observed in other studies.[17,19] Data that could conclusively explain the higher excess mortality in the younger population, compared with the older population, are not available. However, a possible explanation is the fact that the excess mortality is higher in young patients with fracture when compared with the low baseline mortality of the aged-matched population.

Sex

Despite the fact that vertebral fractures are more prevalent in women than in men, the increased mortality risk associated with vertebral fractures seems to be higher in men.[8,13,15,16,78,83,85] SMRs for men were notably higher than those for women during the 2 years of follow-up in a South Korean study.[82] This difference was also observed in an analysis of the Dubbo Osteoporosis Epidemiology Study.[19] However, other studies have reported no difference between men and women,[17] or an increased risk in women.[18]

Comorbidities and previous health status

Frailty and comorbidities might explain a major proportion of the excess mortality associated with vertebral fractures.[16,19,79,81,87] Comorbidities such as hypertension and diabetes mellitus have been associated with increased mortality in patients with vertebral fracture (RR 1.37 [95% CI 1.24–1.52] and RR 1.82 [95% CI 1.56–2.12], respectively), and, as mentioned previously, pulmonary comorbidities are also quite frequent, especially in patients with severe kyphosis.[85,87] A study of Spanish patients hospitalized for osteoporosis-related fractures clearly showed an increase in mortality risk following vertebral fracture that was associated with an increasing number of comorbidities measured using the Charlson comorbidity index.[78] Patients with an index of 1–2 had an OR of 2.12 (95% CI 1.53–2.95), whereas those with an index >4 had an OR of 8.50 (95% CI 5.10–14.14). Despite the evidence reported, the importance of comorbidities in the risk of mortality associated with vertebral fractures has not been consistently demonstrated in all studies.[14,15]

Other risk factors

An increased mortality risk after vertebral fracture that was associated with the coexistence of two or more vertebral fractures has been reported,[88] but this finding has

Table 2 | Risk factors associated with increased mortality after osteoporotic fractures (relative risk ratio)

Risk factor	Estimated mortality risk	Comments/observations	References
Hip fractures			
Age For each year increase For 5-year increase >80 years	 1.0–1.1 1.4 1.2–3.5	 Increased risk of mortality increases with age Excess mortality greater in younger population	9,10,34,59,72
Sex (men vs women)	1.3–2.4	Increased mortality risk in men of all age groups in most studies	9,44,52,59,71, 72,117
Ethnicity (black vs white)	1.3 (1.1–1.4)	Black ethnicity negatively associated with survival after hip fracture Risk decreases when adjusting for health status and socioeconomic factors	39,55
Charlson Comorbidity Index 0 1–2 3–4 >4	 Reference 1.8 (1.8–1.8) 2.7 (2.6–2.7) 4.1 (4.0–4.2)	 Not applicable	44
High ASA score (vs low score)*	1.5	High ASA score associated with increased mortality	34,59
Diabetes mellitus	1.3–1.5	Not applicable	39,118
Dementia	1.2–1.5	Not applicable	39,118
COPD	1.0–1.3	Not applicable	39,59,118
Heart failure	1.1–1.9	Not applicable	39,59,72,118
Hospitalization in previous months	1.5–1.7	Not applicable	10,52
Intertrochanteric fracture (vs femoral neck fracture)	1.3–2.5	Increased risk with intertrochanteric fracture compared with femoral neck fracture	52,71,72
Quadriceps strength (weaker)	1.2	Not applicable	19
Residence in nursing home or other institutions	1.7 (1.5–1.9)	Residents of nursing homes or other institutions at baseline had increased mortality risk	39
Vertebral fractures			
Age For 5-year increase >80 years	 1.6 2.0 (1.3–2.8)	 Mortality in patients with vertebral fracture increased with age Excess mortality more pronounced in younger population	78,85,87,88
Sex (men vs women)	1.5–3.0	Not applicable	16,78,88
Tobacco smoking	1.3–2.0	Not applicable	85,87,88
Ethnicity (black vs white)	1.1 (1.0–1.1)	Not applicable	119
Diabetes mellitus	0.9–1.9	Not applicable	85,87,119
COPD	1.2 (1.2–1.2)	Not applicable	119
Hypertension	0.88–1.44	Not applicable	85,119
Charlson Comorbidity Index 0 1–2 3–4 >4	 Reference 1.36–2.10 1.78–5.00 3.08–8.50	 Not applicable	78,119
Multiple vertebral fractures	1.56 (1.01–2.40)	Increased risk with multiple vertebral fractures inconsistent between studies	81,88
Physical activity‡	0.6–1.0	Increased baseline physical activity inversely associated with mortality	85,87,88

*ASA scores 3–4 were categorized as high and compared to low scores (1–2), as reference. ‡Physical activity was defined as +SD kJ per week in both studies by Kado *et al.*[85,87] Trone *et al.* compared physical activity three times per week versus less than three times per week.[88] Abbreviations: ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease.

not been consistently replicated.[81] Other risk factors such as smoking and poor physical function also seem to contribute to the increased risk of mortality following a vertebral fracture.[19,85]

Death in other osteoporotic fractures

Nonhip, nonvertebral osteoporotic fractures make up the largest proportion of all osteoporotic fractures.[5,13,19,37] However, evidence on the mortality risk associated with

these fractures remains scarce, and is still far from conclusive. In the Dubbo Osteoporosis Epidemiology Study, patients with nonhip, nonvertebral major fractures (in the pelvis, distal femur, proximal tibia, multiple ribs and proximal humerus) had an increased mortality risk.[15] The increased risk was noted in both men and women (SMR 1.92 [95% CI 1.70–2.14] and 2.22 [95% CI 1.91–2.52], respectively). Even though the number of deaths was low during follow-up and limits the identification of any patterns, risk was increased during the first year after fracture and decreased during the 5-year follow up. Minor fractures, which included all other osteoporotic fractures, were only associated with an increased mortality risk in men. However, after exclusion of deaths associated with possible pathologic fractures attributable to cancer, the SMR was not statistically significant. An updated analysis of 1,295 fracture events occurring in the same cohort reported that major and minor fractures were responsible for ~50% of all low-trauma fractures; these fractures were associated with >40% of all the deaths reported.[19] In this analysis, the overall SMR for nonhip, nonvertebral fractures was 1.50 (95% CI 1.30–1.73) in women and 1.48 (95% CI 1.18–1.85) in men. Increased risk was reported for major and minor fractures in women, but only for major fractures in men.

Two reports of North American populations have also noted an increased risk of mortality in patients with nonhip, nonvertebral fractures.[20,89] A study using Canadian health-care databases reported an increased mortality risk in women and men with humeral fractures, and an increased risk of mortality during the first year after wrist fracture in men (RR 1.5 [95% CI 1.2–1.9]) but not women.[20] Similar to hip and vertebral fractures, the increased mortality risk associated with humeral fractures persisted for 5 years after the fracture event. A more detailed analysis of other fracture sites in an historical US cohort has shown a statistically significant, although not particularly high, increase in mortality risk associated with these fractures.[89] After adjustment for age, sex and precipitating cause (that is, specific pathology, severe trauma or no more than moderate trauma), increased risk of mortality remained significant for fractures of the axial skeleton, such as the clavicle, scapula or sternum (SMR 1.7, 95% CI 1.2–2.2), ribs (SMR 1.4, 95% CI 1.2–1.7) and pelvis (SMR 1.4, 95% CI 1.1–1.7). Fractures of the proximal humerus were also associated with an increased mortality risk (SMR 1.5, 95% CI 1.1–1.8). However, as seen in other studies,[8,15,22] no associated increased mortality was reported for distal forearm fractures, a finding that is possibly related to the fact that these fractures tend to be most common in middle-aged people.

Despite these studies suggesting an association between mortality and this type of fractures, an increased mortality risk with nonhip, nonvertebral fractures has not been seen in some studies. For example, an analysis of the Fracture Intervention Trial did not identify an increased mortality risk associated with any nonspine, forearm or other fractures (that is, nonhip, wrist or spine fractures) among the 907 women who experienced a fracture during the 3.8 years of follow-up.[14] Another analysis of a Swedish population showed a statistically significant, but slight, increase in risk of mortality in patients with shoulder fractures, which consistently decreased and was similar to that of the general population after 5 years.[8] In this same analysis, forearm fractures were not associated with an increased mortality risk. Finally, an analysis of a Canadian cohort showed no difference in mortality risk when comparing individuals with pelvic, rib and forearm and/or wrist fractures to the general population.[13]

Age and comorbidities seem to increase the risk of mortality associated with some of these fractures, as described by some of the reports available.[19,20] However, a paucity of data and a lack of consistency in the data available are still a considerable limitation for evaluating the true effect of nonhip, nonvertebral osteoporotic fractures on mortality.

Effects of medical treatment

Observations of a possible effect of medical treatment on the risk of mortality related to osteoporotic fracture were initially drawn from a clinical trial in which eligible patients with hip fracture were randomly assigned to receive intravenous annual zoledronic acid or placebo.[26] Patients in the treatment arm had a decreased incidence of further fractures, including hip and nonvertebral fractures. In a secondary analysis, the patients also had reduced all-cause mortality (by 28%). These results, combined with observations from a previous cohort study, renewed interest in the potential importance of medical treatment after fracture events.[29] Further studies, both observational and analysis of randomized controlled trials (RCTs), have provided more information on this issue (Tables 3 and 4). It is important to clarify that, from the RCTs discussed in this Review and in the available literature, only one has clearly established a beneficial effect on the risk of mortality from the use of bisphosphonates in patients after fracture and the rest, although not powered to analyse survival, have only shown trends of this possible effect.

Evidence from RCTs

Data on the reduction in risk of mortality following therapy with bisphosphonates and other osteoporosis medications are growing; however, only one of these studies was initially powered to investigate survival.[26] Available placebo-controlled clinical trials for approved osteoporosis medication treatments that reported mortality rates were included in a meta-analysis.[90] Treatments analysed included alendronic acid,[91,92] risedronic acid,[93–95] strontium ranelate,[96,97] zoledronic acid[26,98] and denosumab. The types of fracture analysed in these studies varied, but most were focused on vertebral fractures.

When excluding the two alendronic acid trials from the analysis (as the doses of alendronic acid used were suboptimal during parts of these studies), an 11% reduction in mortality (RR 0.89, 95% CI 0.80–0.99) was observed.[90] The reduction in the risk of mortality was similar when the two alendronic acid studies were included. An analysis of only the bisphosphonate trials showed a similar reduction in risk of mortality (that was not statistically significant), with a moderate degree of heterogeneity between trials.[90]

Table 3 | Bisphosphonate treatment and mortality risk after osteoporotic fractures: data from RCTs

Study	Population				Follow-up duration (years)	Osteoporosis treatment	Deaths (treatment/ placebo)	Mortality risk (95% CI)
	Sample size	Mean age (years)	Sex (% women)	Fracture event				
Black *et al.* (1996)[91]	Placebo arm *n*=1,005 Treatment arm *n*=1,022	71.0 70.7	100 100	Vertebral	3	Alendronic acid	24/21	1.12 (0.63–2.01)
Cummings *et al.* (1998)[92]	Placebo arm *n*=2,218 Treatment arm *n*=2,214	67.7 67.6	100 100	Clinical	4	Alendronic acid	37/40	0.93 (0.59–1.44)
Harris *et al.* (1999)[93]	Placebo arm *n*=815 Treatment arm *n*=813	NA	100 100	Vertebral	3	Risedronic acid	15/16	0.94 (0.47–1.89)
Reginster *et al.* (2000)[94]	Placebo arm *n*=407 Treatment arm *n*=407	71 (both arms)	100 100	Vertebral	3	Risedronic acid	11/17	0.65 (0.31–1.36)
McClung *et al.* (2001)[95]	Placebo arm *n*=3,134 Treatment arm *n*=3,104	78.5 (both arms)	100 100	Hip	3	Risedronic acid	114/127	0.90 (0.71–1.16)
Black *et al.* (2007)[98]	Placebo arm *n*=3,861 Treatment arm *n*=3,875	73 73.1	100 100	Vertebral	3	Zoledronic acid	130/112	1.16 (0.90–1.48)
Lyles *et al.* (2007)[26]	Placebo arm *n*=1,062 Treatment arm *n*=1,065	74.6 74.4	75.5 76.7	Hip	1.9	Zoledronic acid	101/141	0.72 (0.56–0.93)

Abbreviations: NA, not available; RCT, randomized controlled trial.

Meta-regression analyses carried out in this meta-analysis[90] showed no association between the reduction in risk of mortality and mean age, fractures in the placebo group or the reduction in the risk of fracture with treatment. However, the reduction in risk of mortality was associated with the baseline mortality rates in the placebo group ($P = 0.03$). Populations with a high baseline mortality risk[26,94,96,97] seem to experience a statistically significant reduction in mortality, suggesting that this potential benefit could be most relevant in frail patients. The data from this meta-regression are important, but are far from conclusive owing to low mortality and the individual studies being insufficiently powered to assess survival. However, these meta-regression analyses highlight the need for more RCTs that are sufficiently powered to assess survival among patients who are or are not treated with bisphosphonates.

Evidence from observational studies

Various analyses of Canadian, Australian and Danish cohorts report decreased mortality during the follow-up of patients treated with bisphosphonates. Several differences exist between the populations analysed in these studies, but they consistently reported a reduced mortality risk.

A cohort of patients with hip fracture aged ≥65 years were analysed in relation to treatment initiation and its effects on fracture, hospitalization and mortality rates.[29] Even though no differences in the incidence of subsequent, hip and Colles fractures were seen between the patients who were treated and untreated, patients receiving some osteoporosis treatment (hormone replacement therapy, bisphosphonates, calcitonin, selective estrogen receptor modulators and vitamin D_3) exhibited reduced mortality during follow-up. The effect on mortality was not significant at 1 year after fracture (OR 0.25, 95% CI 0.06–1.12); however, long-term mortality was reduced in this group of patients (OR 0.34, 95% CI 0.17–0.70). Despite the small number of patients and the low use of antiresorptive therapy in this cohort (23%), this study was one of the first to suggest that the risk of mortality was reduced in treated patients with osteoporotic fractures. Similarly, another study carried out in Finnish patients with hip fracture also reported a statistically significant 36–43% adjusted reduction in mortality that was associated with any osteoporosis treatment, but did not report treatment-specific analyses.[99]

Two studies have analysed the effect of bisphosphonate use on mortality in elderly people, independent of fracture occurrence.[27,100] The cohort of the Dubbo Osteoporosis Epidemiology Study, which included men and women aged ≥60 years, reported a 69% reduction in mortality (HR 0.31, 95% CI 0.17–0.59) for women receiving bisphosphonates, even after adjusting for age

Table 4 | Bisphosphonate treatment and mortality risk after osteoporotic fractures: data from observational studies

Study	Population				Follow-up duration (years)	Osteoporosis treatment	Deaths in patients with fracture (%)	Mortality risk (95% CI)	Adjusted mortality risk (95% CI)
	Sample size	Mean age (years)	Sex (% women)	Fracture event					
Cree *et al.* (2003)[29]*	449	>65	66.1	Hip	<5	HRT, bisphosphonate, calcitonin, vitamin D_3	23 (1-year mortality) 44 (long-term mortality)	NA	0.25 (0.06–1.12) 1-year 0.34 (0.17–0.70) long-term
Center *et al.* (2011)[27]*	2,042	70.5	60	All	15.2 for women 13.8 for men	HRT, bisphosphonate, calcium/vitamin D_3	38 women; 49 men	0.8 (0.4–1.4)§	0.31 (0.17–0.59) women 0.48 (0.11–0.98) men§
Sambrook *et al.* (2011)[100]*	2,005	85.7	76.5	All deaths related to fracture events	5	Oral bisphosphonate	80	0.74 (0.56–0.98)	0.73 (0.56–0.94)
Beaupre *et al.* (2011)[28]*	220	>50	76.9	Hip	3	Oral bisphosphonate	11	0.94 (0.90–0.98)	0.37 (0.28–0.51) per year of bisphosphonate exposure
Bondo *et al.* (2013)[101]‡	42,076	80 78.7	73 72.3	Hip	3 months‖ 3.8¶	All bisphosphonates	18# 46#	0.76 (0.66–0.87) 0.84 (0.75–0.94)	0.68 (0.59–0.77) 0.76 (0.68–0.85)

*Prospective cohort. ‡Retrospective cohort. §Only bisphosphonate data shown. ‖Treatment started previous to fracture. ¶Treatment started after fracture. #Calculated from data. Abbreviations: HRT, hormone replacement therapy; NA, not available.

and several frailty markers.[27] In men, a similar but not significant reduction in mortality risk was observed (HR 0.48, 95% CI 0.11–1.98). A prospective cohort study showed a 27% reduction in the risk of death in frail institutionalized older patients who were treated with oral bisphosphonates.[100] The mean age in this cohort was 85 years, and patients in the treatment group had a worse baseline health status than those in the group that did not receive treatment. In both studies, a statistically significant decreased risk of death was noted for all-cause mortality, which was not the case for the specific causes of death analysed. Even though hazard ratios where not statistically significant in any of the independent analyses, reductions in the incidences of cardiovascular and cerebrovascular causes of death were seen,[27,100] as well as in the incidence of infectious diseases, in the group receiving bisphosphonates.[100]

An analysis of a Danish cohort of patients with hip fracture reported a beneficial effect of bisphosphonate use on the risk of mortality after a hip fracture in patients receiving treatment either before or after the fracture event compared with untreated patients.[101] Bisphosphonate treatment prior to the fracture event resulted in a significantly lower 3-month mortality, (adjusted OR 0.68, 95% CI 0.59–0.77) compared with no treatment. Patients who began treatment after the fracture also experienced lower mortality during the follow-up period than untreated patients. This reduction was noted in patients who received multiple medications (adjusted HR 0.73, 95% CI 0.61–0.88) and in those who received a single medication (adjusted HR 0.84, 95% CI 0.73–0.95). In another cohort of 220 patients with hip fracture, 1 year of bisphosphonate exposure was associated with a 63% relative reduction in the risk of death (adjusted HR 0.37, 95% CI 0.28–0.51); a reduction in mortality risk was also observed for each month of treatment.[28]

Potential mechanisms

The available data does not yet explain the reduction in mortality risk observed with medical treatment of osteoporotic fractures; however, several hypotheses have been proposed regarding the possible role of bisphosphonates. A *post hoc* analysis of a zoledronic acid trial in patients with hip fracture analysed specific causes of death.[102] Of the 25% reduction in risk of death observed in patients who received treatment, only 8% of the effect of zoledronic acid was explained by the prevention of subsequent fractures. However, patients in the treatment arm of the trial experienced a decreased risk of death from pneumonia ($P=0.04$) and arrhythmias ($P=0.02$). Trends towards a decreased risk of dying from cardiac events, respiratory failure and neoplasia were also seen in the treatment group, but they were not statistically significant. The occurrence of these complications did not vary between the two arms of the trial, which has resulted in emerging explanations of a possible role of osteoporosis treatment in the recovery from acute illness. Evidence of increased levels of inflammatory markers, such as IL-6, C-reactive protein, tumour necrosis factor and vascular endothelial growth factor have been reported in patients with hip fracture,[103–106] and might explain the increased frailty observed in such patients. The suppression of monocytes and macrophages and alterations in the levels of cytokines has been reported to occur as an acute phase response to bisphosphonates, resulting in 'flu-like' symptoms. This finding suggests bisphosphonates could alter the immune response to stressors and affect the response to acute illnesses such as pneumonia.[107,108]

A link between osteoporosis and cardiovascular disease has been reported,[109] and a study using the Taiwanese Health Insurance Database has reported an association between hip fractures and an increased risk of acute myocardial infarction.[47] Bisphosphonates have affinity

for calcified blood vessels, and might affect the local production of nitric oxide[110] or affect the atherogenic process itself.[111,112] Possible effects of bisphosphonate therapy in reducing the incidence of acute myocardial infarction have been reported in a population-based matched cohort, in which treated individuals had a reduced risk of experiencing an acute myocardial infarction compared with a control population during a 2-year follow-up (HR 0.37, 95% CI 0.16–0.85).[113] The effects of bisphosphonates on cellular ion channels (that is, inhibition or stimulation of epithelial sodium channels and stimulation of non-selective cation conductance)[114,115] could also explain the reduction in death secondary to cardiac arrhythmias.[102] On the basis of these proposed mechanisms of the effects of bisphosphonates on the risk of acute myocardial infarction, a group of investigators from the Mayo Clinic conducted a retrospective analysis in a large cohort of veterans aged ≥65 years.[116] After controlling for atherosclerotic disease risk factors and medications, bisphosphonates were actually associated with an increased risk of acute myocardial infarction (HR 1.38, 95% CI 1.08-1.77). Baseline acute myocardial infarction risk adjustment is limited in this cohort analysis; however, conflicting results like those seen in this cohort emphasize the need for further investigation of these hypotheses.

Irrespective of the mechanism involved, available evidence seems to indicate a potential reduction in the risk of mortality that is associated with bisphosphonate treatment following hip and vertebral osteoporotic fractures. This putative protective effect on mortality seems most notable in frail populations, such as elderly people with various comorbidities. Thus, if this association is confirmed with further studies, an added rationale might exist for use of bisphosphonates in these patients, not only because of the decrease in fracture incidence, but also in light of this new evidence on a possible reduction in the risk of dying.

Conclusions

Osteoporotic hip and vertebral fractures are associated with increased mortality, and this association is part of a multifactorial process that includes many risk factors such as age, sex, ethnicity, comorbidities and functional status. However, for nonhip, nonvertebral fractures, despite the fact they represent the majority of osteoporotic fractures, their true impact, or lack of it, on mortality is still not clear. While still limited, evidence is growing from observational studies and RCTs that medical treatments, especially bisphosphonates, might be associated with a decreased risk of dying following an osteoporotic fracture. Further studies are needed to clarify this association and its possible mechanisms, and particular interest should be directed to outcomes of cardiovascular mortality, in light of recent evidence. Evidence summarized in this Review highlights possible benefits of increased medical treatment in the care of the patients after a fracture, with the aim not only of reducing the incidence of subsequent fractures but also of improving short-term and long-term mortality.

Review criteria

Articles included in this Review were selected after searching the PubMed database for publications up to October 2013. Search entries used included "osteoporosis", "osteoporotic fractures", "fragility fractures", "hip fractures", "vertebral fractures", "mortality", "mortality risk", "osteoporosis treatment", "osteoporotic fracture treatment", "fragility fracture treatment", "bisphosphonates", used alone or in combination. English-language primary research articles and reviews were selected on the basis of relevance. References lists of selected publications were also screened for additional relevant publications.

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Author contributions

S.E.S. researched data for the article, wrote the article and reviewed and edited the manuscript before submission. K.G.S. wrote the article and reviewed and edited the manuscript before submission.