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Compound Risk of High Mortality Following Osteoporotic Fracture and Refracture in Elderly Women and Men

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ABSTRACT

After fracture there is increased risk of refracture and premature mortality. These outcomes, particularly premature mortality following refracture, have not previously been studied together to understand overall mortality risk. This study examined the long-term cumulative incidence of subsequent fracture and total mortality with mortality calculated as a compound risk and separated according to initial and refracture. Community-dwelling participants aged 60+ years from Dubbo Osteoporosis Epidemiology Study with incident fractures, followed prospectively for further fractures and deaths from 1989 to 2010. Subsequent fracture and mortality ascertained using cumulative incidence competing risk models allowing four possible outcomes: death without refracture; death following refracture; refracture but alive, and event-free. There were 952 women and 343 men with incident fracture. Within 5 years following initial fracture, 24% women and 20% men refractured; and 26% women and 37% men died without refracture. Of those who refractured, a further 50% of women and 75% of men died, so that total 5-year mortality was 39% in women and 51% in men. Excess mortality was 24% in women and 27% in men. Although mortality following refracture occurred predominantly in the first 5 years post–initial fracture, total mortality (post-initial and refracture) was elevated for 10 years. Most of the 5-year to 10-year excess mortality was associated with refracture. The long-term (>10 years) refracture rate was reduced, particularly in the elderly as a result of their high mortality rate. The 30% alive beyond 10 years postfracture were at low risk of further adverse outcomes. Refractures contribute substantially to overall mortality associated with fracture. The majority of the mortality and refractures occurred in the first 5 years following the initial fracture. However, excess mortality was observed for up to 10 years postfracture, predominantly related to that after refracture. © 2013 American Society for Bone and Mineral Research.

KEY WORDS: FRACTURE; REFRACTURE; MORTALITY; OSTEOPOROSIS; COMPETING RISKS; EPIDEMIOLOGY

Introduction

Osteoporotic fractures represent a major public health problem as a result of their high prevalence and the associated clinical consequences. There is substantial evidence that an osteoporotic fracture increases the risk of future fractures.[1–5] Premature mortality following fracture is also well recognized, particularly for hip and vertebral fractures,[6–9] and there is accumulating evidence of increased mortality risk following other types of osteoporotic fractures,[7,10–13] although increased mortality following minor fractures, such as those of the forearm, has not been demonstrated in all studies.[8,14] However, whereas the separate, short-term risks of refracture and mortality have been documented, the relationship between them, in particular the excess mortality following a refracture compared with the excess mortality following the initial fracture, is unknown. Previous analyses, including our own, have generally assessed refracture or mortality outcomes separately because of inherent difficulties in assessing both endpoints together.

The difficulty in assessing the long-term risk of an outcome such as refracture stems from its dependency upon survival. The most widely used method to analyze time-to-event outcomes is the Kaplan-Meier method. This method was

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initially designed to analyze the time to a single event. With this method, any other outcome, such as death, which may prevent the outcome of interest, such as refracture, is censored. This is not a problem if the other events are independent of the event of interest; eg, loss to follow-up. However, if a competing event is related to the event of interest and particularly if it is a high-frequency event, censoring of the competing risk can lead to an overestimate of the event of interest. This is exactly the case following fracture, when both refracture and associated mortality are high and refracture is itself associated with increased mortality. Moreover, it is axiomatic that in the event of a patient dying, there is no possibility of a subsequent fracture.

The use of a competing risk model, in which both these outcomes are considered as separate time-to-event occurrences, and which does not make any assumptions about dependency, overcomes the shortcomings of the Kaplan-Meier analysis. Although competing risk or cumulative incidence competing risk (CICR) analyses have been mainly used in the cancer literature, they are now also appearing in other medical fields.

In order to present a realistic picture of all the outcomes of interest following an event such as fracture, the most accurate way of describing the separate incidences of these outcomes is to use a competing risk model. In such a design, all separate outcomes are modeled and censoring is reserved for those whose time of follow-up is limited by their time of entry into the study or by their loss from the study. Importantly, a competing risk analysis in this situation should simultaneously describe all the possible outcomes following fracture, including refracture, mortality, and mortality following refracture. The simpler competing risk model in which refracture is considered as an endpoint itself, without following up its consequences, will underestimate the overall mortality.

Knowing the true risk of refracture, mortality following fracture and mortality following refracture is important from a clinical point of view for a number of reasons. First, it is well established that, at least for those with osteoporosis and a low bone density, up to 50% of refractures can be prevented with treatment. Second, there is increasing evidence that premature mortality is related to fracture.[7,10] Third, there has been recent evidence that treatment may reduce postfracture mortality risk.[15–19] Thus, accurate reporting of all fracture outcomes is essential.

The aim of this study, therefore, is to determine, in one model, the cumulative incidences of subsequent fracture and total mortality, the latter separated according to that following both the initial and subsequent fracture, in a cohort of women and men over the age of 60 years using a competing risk model. This study differs from those previously reported in which either mortality[10] or refracture[4] were considered as single endpoints using Kaplan-Meier methodology. Here, the four outcomes: death following initial fracture; refracture and alive; refracture followed by death; and alive and free of refractures are considered simultaneously. This gives a comprehensive overview as well as graphical representation of the absolute outcomes postfracture not possible with traditional Kaplan-Meier analyses.

Subjects and Methods

Study population

The study cohort consisted of a subset of women and men over the age of 60 years with incident fractures, participating in the Dubbo Osteoporosis Epidemiology Study. The study is an ongoing prospective observational population-based study that started in 1989 in Dubbo, a semi-urban city with a population of 32,000 people. Dubbo has a stable population with the same age- and gender-distribution as the general Australian population. These characteristics, together with its relative isolation and centralized health services, make the site optimal for epidemiological research. The study methodology and general goals have been published.[20]

This study was approved by the St Vincent's Hospital Human Research Ethics Committee.

Data collection

Fracture ascertainment

The fracture cohort for this study was the same as that previously reported for mortality as a single outcome,[10] but followed for an additional 3.5 years, thus with more complete data on refracture and mortality. Fracture collection started in April 1989 and subjects were followed until December 2010. Fractures were identified through the only two (and for some time three) radiological services in Dubbo, as previously reported.[4] Only fractures occurring during the study period and after enrolment into the study were included in this analysis. Any person who sustained a fracture before the beginning of the study was excluded from this analysis

The circumstance of the fracture was obtained through direct interview. Only minimal trauma fractures, defined as a fracture occurring following a fall from standing height or less were included in this analysis. High-trauma fractures, and pathological fractures (eg, cancer, or Paget's disease) as well as fractures of the head, fingers, and toes were excluded.

Mortality status

Mortality status was ascertained regularly for all study participants through systematic searches of funeral directors lists, local newspapers, and Dubbo media reports. Mortality for the Dubbo population was obtained from the Australian Bureau of Statistics for each year of the study.

Statistical analysis

Two competing risk models were created to demonstrate the difference in results depending on the analysis. The first, simple one, had refracture or death as the competing risk events. In this model a subject could either have refractured, died without refracture, or remained alive and fracture free. When a subject has refractured, this model does not distinguish whether the subject subsequently died or remains alive. Time to event was calculated from the initial low-trauma fracture until refracture, or death, or the end of the analysis time frame (December 31, 2010). Thus death following a refracture was not considered as a separate event.

The second competing risk model was constructed with four possible outcomes: death following refracture, refracture but remaining alive, death without refracture, and event-free. Time to event was calculated from the date of initial fracture until the date of death for the first two outcomes, until the date of refracture for the third outcome or until the end of the analysis time frame for the fourth outcome.[21]

The aim of these two models was to highlight the different interpretations arising from the analysis of partial and full exploration of all potential linked fracture outcomes, with particular emphasis on the difference in mortality after taking into account the deaths related to refracture.

Data for cumulative incidences of refracture and mortality risk following initial low-trauma fracture and following refracture were analyzed. On the one hand, this permitted the evaluation of the sum of all these events postfracture at particular time points, whereas on the other hand, it allowed the estimate of those left free of any adverse events.[21] Mortality of the fracture population (following initial and refracture) was compared with the mortality of an age- and sex-matched general population using a life-table analysis. Excess deaths were calculated as the difference between the observed and expected number of deaths.

The effect of time to subsequent fracture on mortality risk was then analyzed in a univariable and multiple-variable adjusted Cox proportional hazards model. The variables included in this model were age (two categories: 60–74 years, and 75+ years), fracture type (three dummy variables corresponding to hip, vertebral, and non-hip non-vertebral fractures), and refracture as a time-dependent variable. The assumption of proportionality was satisfied on the collective variable test. However, in simple Kaplan-Meier survival curves assumption of proportionality was not met, suggesting a time interaction.

Standardized mortality ratios (SMRs) were calculated for the 5-year mortality following both initial and the subsequent fractures based on the Dubbo population mortality. Mortality rates were calculated for the whole Dubbo population, in 5-year age groups for each year of follow-up based on the actual number of deaths and mid-year population, separately for women and men. These rates were then used to estimate the survival for the general population age-matched to the fracture cohort.

All statistical analyses were performed using SAS version 9 (SAS Institute, Inc., Cary, NC, USA).

Results

As previously described, 2245 women (952 with an initial fracture) and 1760 men (343 with an initial fracture) were followed over 29,660 and 20,717 person-years in women and men, respectively from April 1989 (Fig. 1). Individuals who experienced a low-trauma fracture were followed until December 2010 (7670 person-years for women and 2263 person-years for men). The median and interquartile follow-up ranges were 7.2 years (IQR, 3.4–12.0) for women and 5.4 years (IQR, 1.4–9.8) for men. During this period, 358 women and 90 men experienced a subsequent fracture, and 318 women and 144 men died without refracture. An additional 169 women and 62 men died following a subsequent fracture, leaving 276 women and 109 men alive and free of fracture at the end of follow-up (Fig. 1).

Women and men had a similar age at initial fracture (women: 78.5 ± 7.7 years versus men 77.8 ± 7.7 years; $p = 0.14$) and a similar fracture type distribution (hip: n = 183 [19.2%] and n = 63 [18.3%] for women and men, respectively; vertebral: n = 283 [29.7%] and n = 107 (31.2%) for women and men, respectively; and non-hip non-vertebral: n = 486 [51%] and n = 173 (50.4%) for women and men, respectively).

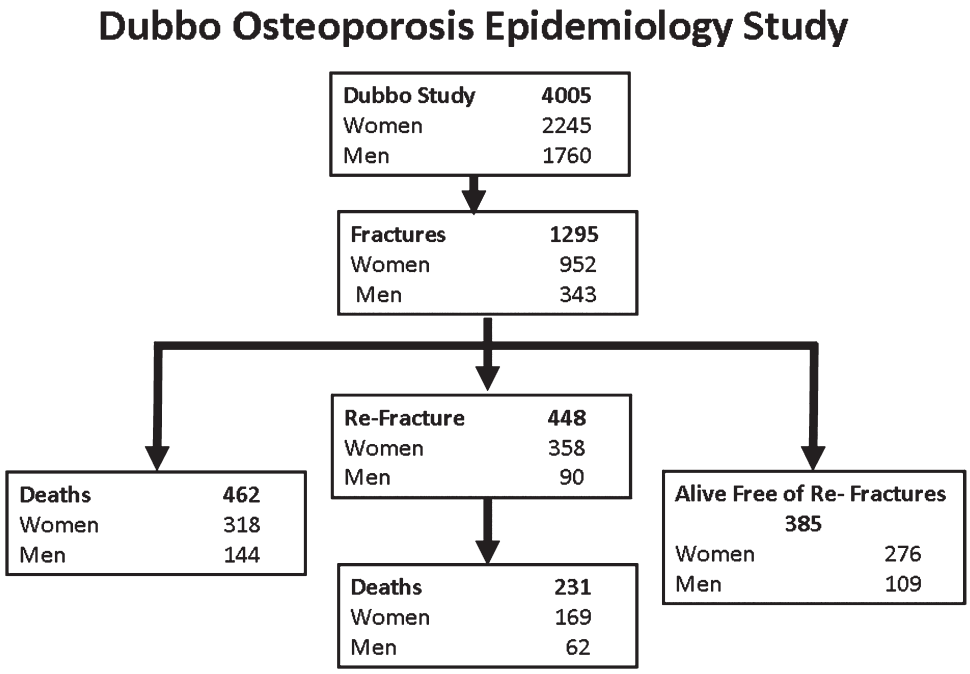

Fig. 1. Flowchart for the participants in the Dubbo Osteoporosis Epidemiology Study.

Model 1: Refracture or mortality as final outcomes following the initial low trauma fracture

Following an initial low-trauma fracture, both mortality risk as well as refracture risk in survivors had a similar pattern, with the highest incidence in the first 5 years postfracture for both women and men (Fig. 2), which declined thereafter.

In the first 5 years postfracture approximately 26% of women died and 24% experienced a refracture. Both mortality risk and refracture decreased significantly over the next 5 years (refracture to 1.8% per year and mortality to 1.4% per year). After 10 years, fracture and mortality rates were less than 1% per year.

Men had a similar refracture risk, but higher mortality risk in the first 5 years postfracture; 37% of men died and 20% experienced a refracture. As with women after that 5 year period, the rate of both events dropped to 1% or less per year for the remaining period of follow-up.

Although the 5-year absolute risk of refracture was similar for men and women, this model highlights the reduced long-term cumulative incidence of refracture in both women and men by the competing risk of death. This was particularly evident in the older age-groups with the higher mortality rates. After 10 years of follow-up for those older than 75 years, there were no refracture events in men and very few in women, in part because the number of individuals alive and at risk of refracture was significantly reduced by high mortality rates (Table 1). However, in the younger age-groups (60–74 years), refracture events continued to occur, albeit at a lower rate. In this analysis the higher death rate in men also impacted the long-term refracture risk.

Model 2: Combined risk of all outcomes risk postfracture

The combined risk of all four outcomes following the initial low trauma fracture: refracture and remaining alive, death following refracture, death without refracture, and alive and event free, is best appreciated as a stacked graph (Fig. 3). Each shaded area represents the proportion of the population with that specific outcome and the height of each area is the cumulative incidence of that outcome at a given time point. Thus the black panel represents mortality following initial fracture. The combination of the light gray and dark gray areas represent the total proportion of the population with refracture with the height of the combined light and dark gray areas being the cumulative incidence of refracture at any given time point. The dark gray area alone represents those people with refractures who have died. The upper curve corresponds to the sum of all the three cause-specific outcomes, so the fourth outcome of remaining alive and refracture-free is represented by the nonshaded area above.

At 5 years following the initial low-trauma fracture, 26% of women died without refracture, 24% suffered a subsequent fracture, and a further 50% of those with subsequent fracture died, bringing the total 5-year mortality rate to 39%. For men these numbers were slightly higher; 37% died without refracture, 20% had a subsequent fracture, and 75% of those with a subsequent fracture died, bringing the total 5-year mortality rate to 51%. Compared with the Model 1, the total mortality was higher because mortality associated with subsequent fracture had not previously been counted. Whereas the majority of events occurred in the first 5 years, they continued to accumulate.

By 10 years post–initial fracture, for both women and men, less than a third was alive and free of further fractures (Fig. 3).

Mortality risk following initial and subsequent fracture

The cumulative mortality risk post–first fracture and post–subsequent fracture was considered together with population mortality. Following the initial fracture, mortality risk was increased for up to 5 years in both women and men, but then declined so that the excess mortality was no longer greater than

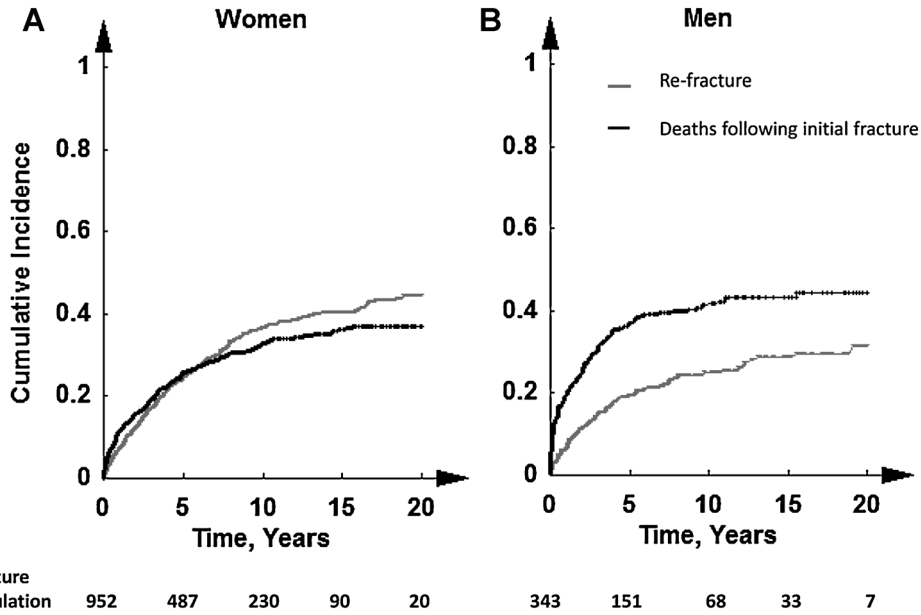

Fig. 2. Cumulative incidences of refracture and mortality following initial osteoporotic fracture: (*A*) women; (*B*) men.

Table 1. Cumulative Incidences of Refracture and Mortality Risk Without Refracture According to Age

Time from first fracture, years	Cumulative incidence of refracture (%)		Cumulative incidence of death (%)	
	60–74 years old[a]	75+ years old[a]	60–74 years old[a]	75+ years old[a]
Women				
0–5	20	26	16	30
>5–10	34	38	23	38
>10	46	43	28	42
Men				
0–5	22	18	19	45
>5–10	26	24	27	48
>10+	37	24	31	50

[a]Age at initial fracture.

that of the population by 10 years (Fig. 4, excess mortality related to initial fracture is represented by the dark gray shaded area). However, once mortality following refracture was considered, the total mortality risk was elevated for ≥10 years post–initial low-trauma fracture. The excess mortality again occurred predominantly in the first 5 years post-fracture, with most of the excess mortality between 5 and 10 years a result of that following refracture (Fig. 4, excess mortality related to refracture is represented by the light gray shaded area).

Of the 39% mortality observed in women and the 51% mortality in men at 5 years, the excess mortality attributed to fracture above that of an age- and sex-matched population was 24% in women and 27% in men. This corresponded to 3 excess deaths per 100 fracture person-years for women and 7 for men for the first 5 years postfracture but declined somewhat to 1.5 excess deaths per 100 fracture person-years in women and 1.8 in men for the 5 to 10 years following initial fracture.

In a Cox proportional hazard model, consistent with these competing risk analyses, time to refracture, was an independent mortality risk predictor along with older age and fracture type. Refracture within 5 years was associated with a higher mortality than refracture after 5 years (hazard ratio [HR] 3.23; 95% confidence interval [CI], 2.08–5.02 for women; and HR 2.50; 95% CI, 1.21–5.18 for men).

Discussion

This study is the first study to our knowledge that examines four outcomes following a low-trauma fracture in one model (death following the initial fracture, refracture and remaining alive, death following refracture, and those free of any adverse outcome). Using a multi-outcome competing risk model, we have been able to estimate the extent of mortality associated with the first fracture, the percentage of refractures and the extent the mortality associated with those refractures. This study shows that the risk of mortality associated with an initial fracture is compounded by the combined risks of refracture post–initial fracture and mortality associated with refracture. It shows that refractures contribute substantially to the overall mortality associated with fracture. The long-term refracture risk is reduced especially in the elderly due to the high mortality in this group.

The majority of the refractures and mortality, including the deaths following refracture, occurred in the first 5 years post–

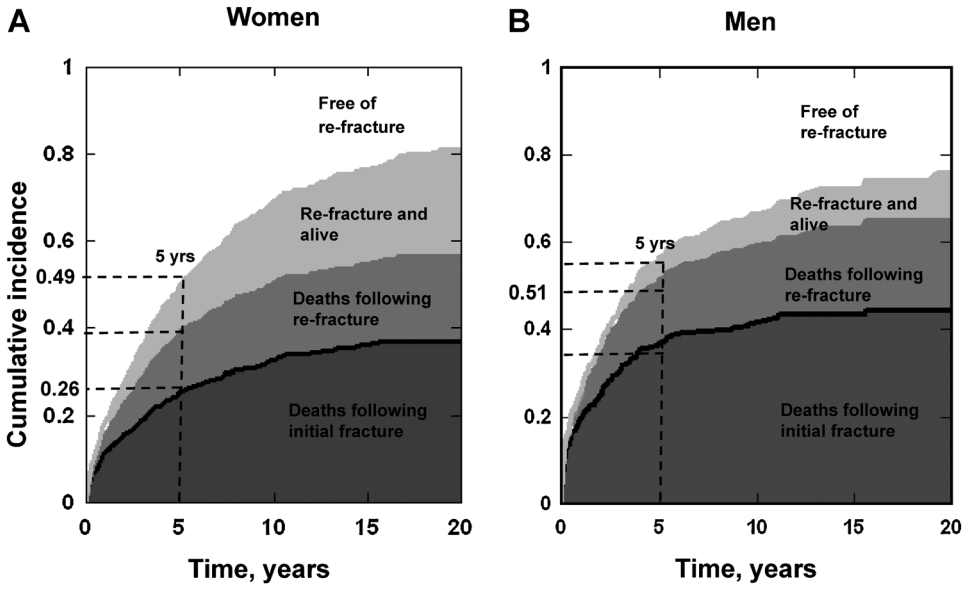

Fig. 3. Stacked graph of cumulative incidences of refracture, mortality following initial osteoporotic fracture, and mortality following refracture: (*A*) women; (*B*) men. The height of each shaded area represents the cumulative incidence of that specific outcome. The area below the bottom line in black represents the population who died following the initial fracture. The area between the bottom and top lines; ie, the light and dark gray areas combined, represents the population who had a refracture. The height of the light and dark shaded area represents the cumulative incidence of refracture at a given time. The dark gray area alone represents the proportion of those with refracture who died. The area above the light gray shading represents the proportion of the population alive with no refractures.

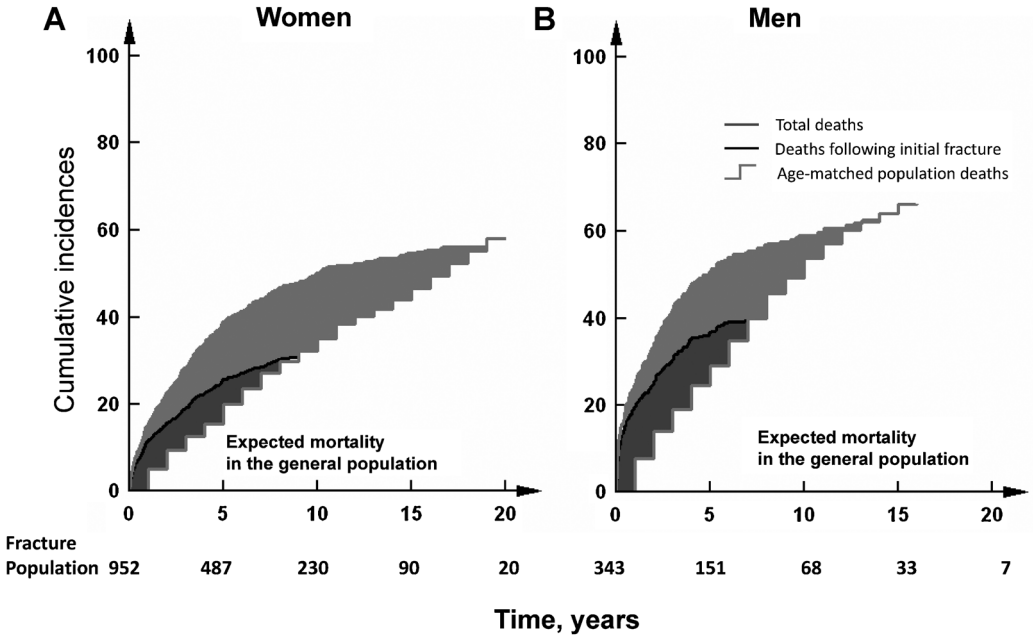

Fig. 4. Stacked graph of cumulative incidences of mortality following initial osteoporotic fracture in black and following refracture in gray compared to an age-matched general population in green: (*A*) women; (*B*) men. The dark gray area represents the excess mortality (ie, above population mortality) related to the initial fracture. The light gray area represents the excess mortality related to the refracture. The height of the green, black, and gray line represents the cumulative incidence of mortality in general population, mortality following initial fracture and total mortality at a given time.

initial low trauma fracture; ie, both mortality and refracture occurred within the first few years postfracture. However, these events continued to occur, so that by the end of 10 years of follow-up, only approximately 30% of women and men were alive and free of fracture. By 5 years post–initial fracture, 51% of men and 39% of women had died following the initial or subsequent fracture. The majority of this mortality, 27% in men and 24% in women, was in excess of an expected age- and sex-adjusted mortality. Moreover, close to one-third of this total mortality followed a refracture.

This fracture cohort had a higher mortality risk than that of an age-adjusted general population for up to 10 years following the initial low trauma fracture. The increased mortality risk beyond 5 years postfracture has been previously reported in the Dubbo Osteoporosis Epidemiology Study[10] and other studies[11,22,23] However, this study demonstrates that the mortality beyond 5 years post–initial fracture was due primarily to that following refracture.

Refracture[2–4,9,24] and mortality risk postfracture[8,10,11,22,23,25] have been reported previously, but only in separate studies. Traditional Kaplan-Meier analysis of a single outcome, such as refracture risk, has been criticized in this situation when there is a high competing risk such as a high risk of mortality. The competing risk of mortality is not appropriately accounted for in the Kaplan-Meier analysis, resulting in an overestimate of the outcome of interest; ie, refracture.[26] In more recent times researchers have turned to competing risk models to overcome this shortcoming. However, a simple competing risk analysis that considers only refracture and mortality as outcomes, such as Model 1 in this study, is misleading. It appropriately reduces the refracture risk in those with high mortality rates (compared with a Kaplan-Meier analysis) but underestimates the overall total mortality because it does not take into account the mortality associated with refracture. In this instance of related outcomes in which refracture itself is associated with a high mortality risk, the cumulative incidence of all outcomes must be considered for a complete understanding of the consequences of fracture. This is all the more important when refracture itself is associated with a comparable mortality risk to that of the initial fracture. We have previously reported an increased mortality associated with fracture, but have not previously contrasted mortality related to an initial fracture with mortality related to a refracture.

In this study, both refracture and mortality postfracture displayed a similar pattern of increased risk for the first 5 years postfracture, followed by a pattern of reducing risk. These findings suggest that refracture and mortality following fracture events are related and potentially triggered by common risk factors. This study was not designed to examine predictors for the joint risk of these outcomes. However, factors such as accelerated bone loss and weight loss as well as decreased muscle strength have been found to be independently related to both fracture risk and nontraumatic mortality,[10,27–30] and may play a role in the risk of both refracture and mortality risk postfracture.

The cause of the excess mortality postfracture is vexed with some studies, suggesting it is related to the fracture event, at least in the short-term, whereas others suggest a stronger relationship with comorbidities and other frailty factors, particularly in the longer term. However, in this analysis, by combining the risk of refracture and mortality, including that following refracture, it appeared that the excess mortality risk beyond 5 years postfracture was observed entirely in individuals

who refractured, suggesting the refracture event plays an important role in this deleterious outcome.

There is much randomized controlled trial (RCT) data demonstrating efficacy of antiresorptive therapy for reducing fracture risk in the setting of osteoporosis and some in the setting of osteopenia.[31,32] Moreover, there has been one RCT of zoledronic acid, given post–hip fracture that also demonstrated a 28% reduction in mortality, although only 8% of this mortality reduction was attributable to the reduction in subsequent hip fracture.[15] Thus it is interesting to speculate on what effect antiresorptive therapy would have on the totality of these outcomes following any low-trauma fracture, the majority of which are not hip fractures and occur in those with osteopenia. Definitive clinical trials, although expensive, are needed for this large group of patients. However, it is clear from the present study that these adverse consequences appeared to occur with greatest frequency in the first 5 years postfracture. Thus it is likely that the maximal benefit would occur with early intervention in appropriate fracture subjects. Importantly, it was also notable that those who survived and were refracture free 10 years post–initial fracture appeared to do well and so may provide a rationale for a review of the need for treatment in this population.

This study has a number of major strengths. The long follow-up of 20 years has allowed a long-term accumulation of postfracture outcomes, essential for the aims of this study. The relatively isolated location has also meant that the collection of fracture and mortality data is highly reliable. There was also a low 10% loss to follow-up in this study.

However, there are some limitations. Although the competing risk models give unbiased refracture and mortality estimates, they are associated with some limitations. First, the implementation of this technique is limited to only a few software applications, and requires a certain knowledge of programming. Second, and most importantly, the available choices for competing risk modeling does not allow for multiple variable adjustments. Other minor limitations include a population almost entirely white, so these findings may not be able to be generalized to other ethnic populations. Nevertheless, fracture rates in the Australian population are fairly comparable with those in the United Kingdom. For women under the age of 75 years they were lower than that in the Unite States but for older women and men, fracture rates were comparable between all countries.[33] In addition, deaths following fracture were obtained from local death and funeral listings and thus these may have been underestimated but this would only have led to an underestimation of the high mortality risk.

In summary, this study has demonstrated high cumulative incidence of adverse outcomes following all low-trauma fractures with 51% men and 39% women dead within 5 years postfracture with a large proportion of this premature mortality related to a refracture. The majority of this mortality (27% in men and 24% in women) was above that expected for an age- and sex-matched population. Refracture and mortality risk were highest immediately after the initial fracture; however, excess mortality was observed up to 10 years postfracture due primarily to the increased mortality of those who refractured. The long-term refracture rate was reduced in this competing risk analysis, particularly in the elderly due to their high mortality. Interestingly, those who survived and were free of refracture 10 years following the initial fracture had a low risk of further adverse outcomes.

This study has important clinical implications: it supports the need for early aggressive treatment intervention after a first low-trauma fracture, at least in those with low bone density, to reduce refracture, and possibly the associated premature mortality, with perhaps a less aggressive clinical approach to the survivors of those 10 years postfracture.

Disclosures

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Authors' roles: Study funding: TVN, JAE, JRC. Study design: DB, NDN, TVN, JAE, JRC. Data analysis: DB, JRC. Data interpretation: DB, JAE, JRC. Manuscript drafting: DB, JRC. Revision of the manuscript: DB, NDN, TVN, JAE, JRC.

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