

Effect of the Post-Fracture Use of Anti-osteoporotic treatment in Cardiovascular Mortality

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Introduction

Osteoporosis is a prevalent disease worldwide, and the clinical outcome of osteoporosis is osteoporotic fracture. Compared with all other osteoporotic fractures, hip fractures lead to remain a significant source of morbidity and mortality for the elderly population. In a recent large scale study involving 122808 participants from eight cohorts in Europe and the USA, hip fracture was associated with increased mortality in the first year, and the greater risk of mortality remained significant 8-year post-fracture [1]. Approximately 10-25% of formerly community dwelling patients require long term nursing care after sustaining a hip fracture [2-4]. Although recent studies show that the incidence of hip fracture is decreasing in many areas, the life-time risk of hip fracture is unchanged [5], and the absolute number of fracture and number of comorbidity after fracture [6] are indeed rising, due to prolonged life

expectancy. Therefore, hip fracture will remain a key public health issue.

One of the consequence of hip fracture is increased risk of cardiovascular mortality [7, 8]. The underlying mechanism between hip fracture and cardiovascular mortality is largely unknown, and alteration of mineral metabolism may play an important role in it. Altered mineral metabolism has been known to be a risk factor of cardiovascular event and mortality, especially hypercalcemia. Epidemiological studies have well demonstrated the relationship between elevated calcium levels and cardiovascular mortality in general population [9-12] or patients with CKD [13, 14]. Acute rise in serum calcium or hypercalcemia is commonly observed in patients sustaining a hip fracture [15], but not in patients with osteoporosis, due to acute immobilization and increased bone resorption; while the use of bisphosphonate in immobilized hip fracture patients reduces serum calcium levels [16]. Anti-osteoporotic agents are generally used to treat osteoporosis by regulating bone and mineral metabolism, the use of these agents in patient sustaining a hip fracture is known to reduce all-cause mortality, however it remains largely unknown if it is also beneficial in reducing cardiovascular mortality. Therefore, we hypothesize that the use of anti-osteoporotic treatment after fracture reduces risk of cardiovascular mortality in patient sustaining a hip fracture. To test this hypothesis, we conducted a population-based cohort study to

determine the risk of cardiovascular mortality in patients sustaining a hip fracture with and without anti-osteoporotic treatment using the data from a large territory-wide healthcare database.

Materials and methods

The study protocol was approved by the institutional review boards of the University of Hong Kong and Hospital Authority Hong Kong.

Data source

Data were collected from the Clinical Data Analysis and Reporting System (CDARS), an electronic medical databased managed by the Hong Kong Hospital Authority (HA). HA is a public healthcare provider which manages 42 hospitals and institutions, and 120 out-patient clinics, serving over 80% of admission in Hong Kong[17]. CDARS is a centralized database developed for research and audit purpose. It includes records of demographics, admission, prescription, diagnosis, procedure, laboratory test, and death information. All records are anonymized to protect patients' identity. The database has been widely used for conducting high quality population-based studies[18, 19].

Study cohort

This is a retrospective cohort study. We identified patients aged 50 and above who were admitted via emergency rooms, between January 1 2005 and December 31 2013, with a new diagnosis of hip fracture (International Classification of Diseases codes, Ninth-Revision, Clinical Modification, ICD-9, 820.XX) and discharged to home. To reduce bias, we excluded patients who met ≥ 1 of the following criteria: i) had previous exposure of anti-osteoporosis medications in two years before admission; ii) had length of stay (LOS) in hospital longer than 60 days (as the average LOS of hip fracture in Hong Kong was reported to be 24-53 days[20]); and iii) had concurrent or history of cancer in 5 years before admission, since patients with cancer has a high risk of mortality and receive bisphosphonate treatment that may introduce bias in the analysis.

Definition of exposures

The exposure of interest was the treatment of anti-osteoporotic medications after hip fracture. Patients who had at least one prescription record of any anti-osteoporosis medications in one year after admission were assigned as “treated” group. Otherwise, patients were assigned as “untreated” group. Anti-osteoporotic medications included alendronate, ibandronate, risedronate, zoledronate, denosumab, raloxifene, salcatonin,

teriparatide, strontium ranelate, and hormone replacement therapy. The medications were categorized into “bisphosphonates” (including alendronate, ibandronate, risedronate, zoledronate) and “non-bisphosphonates” (including all the other drugs). Primary analysis studied treatment effect of any anti-osteoporotic medications while secondary analysis evaluated the effect stratified by individual drug and drug classes.

Definition of outcomes

The outcome of interests were all-cause mortality and cardiovascular mortality during follow-up period. The date and cause of death in CDARS were linked to the death certificate of the patients. The cause of death was coded with ICD-10, in which cardiovascular mortality was coded with I00-I99 [21].

Follow-up

Index date in treated group was defined as the date of first prescription record of anti-osteoporotic medication after hip fracture. For untreated group, index date was assigned using the prescription time distribution matching (PTDM) approach to control immortal time bias. Immortal time bias is introduced when the patient had a delay or waiting period of receiving treatment and the results will be in favour of the treatment group. Such bias has been discussed in literatures [22, 23]. To perform

PTDM, the prescription time in treated group, which defined as the number of days from admission to first treatment, was calculated. The prescription time in untreated group was selected randomly from the pool of prescription time in treated group and the index date was assigned based on the selected prescription time. Patients in the untreated group were excluded if death was occurred before the assigned index date [23]. Follow-up period started from index date until death, switch of anti-osteoporosis treatment, or one year after treatment, whichever occurred first. In addition, follow-up until the date of data retrieval (November 11 2016) were also studied to investigate the long-term mortality.

Propensity score matching

Propensity score (PS) matching was used to control potential bias due to treatment allocation [24]. The likelihood of patient receiving anti-osteoporotic treatment was calculated using logistic regression. Covariates which associated with treatment allocation and the risk of outcome were included in the model. These included sex, age on admission, year of hip fracture, length of stay in hospital, medical history of cardiovascular diseases (including congestive heart failure, ischemic stroke/transient ischemic attack, ischemic heart attack, atrial fibrillation, systemic embolism), chronic obstructive pulmonary disease (COPD), diabetes mellitus, dementia, liver disease,

chronic renal disease, rheumatic/collagen disorders, osteoporosis, Paget's disease of bone, fall, other major fractures (including fracture at spine, wrist, and humerus). The ICD9 codes for the medical conditions were listed in supplementary table 1. Treated and untreated patients were matched by PS at 1:2 ratio using a greedy matching algorithm. The performance of matching was accessed by the standardized difference between treatment groups for of all covariates.

Statistical analysis

Continuous variables were presented as mean±standard deviation (SD) and categorical variables as percentages. Time-to-event analysis was used to evaluate the association of anti-osteoporotic medication and mortality after hip fracture. Survival time was the number of days of the follow-up period. Hazard ratios (HR), and 95% confident intervals (CIs) were calculated using cox proportional hazard regression model. The proportional hazards assumption was evaluated using the Schoenfeld residuals method and the result showed no violation in the model. Analysis was performed in both unmatched and PS-matched cohorts.

As cardiovascular mortality was the major outcome of interest, we conducted a subgroup analysis to investigate the risk of cardiovascular mortality in patients with

and without history of cardiovascular diseases. In addition, we conducted a sensitivity analysis by excluding patients with treatment status contrary to prediction to investigate any residual and unmeasured confounding [25]. Treatment status contrary to prediction was defined as 5% trimming of PS i.e. treated patients with PS below 5% of that in treated group or untreated patients with PS above 95% of that in untreated group. HRs with p-value less than 0.05 was considered significant.

Results

There were 35,746 patients newly diagnosed with hip fracture identified in CDARS from January 1 2005 and December 31 2013 included in the current study, with 3,900 (10.9%, treated group) of them received prescription of anti-osteoporotic medication during the first year after fracture. After propensity score-matching, 7,800 patients without prescription were successfully matched as untreated group. All baseline characteristics were balanced between treated and untreated groups after propensity score-matching as indicated by the standardized differences of <0.026 (Table 1). The mean age of the cohort was $79.4 \pm X$ years and X patients (X%) were female. The mean follow-up was $X \pm X$ days.

In one-year follow up study (short-term), 1027 (8.8%; incidence rate: 9.2 per 100

patient-year) out of 11,700 patients died from all-cause, while 215 (20.9%; incidence rate: 9.2 per 100 patient-year) of them died due to cardiovascular-cause.

Discussion

In this large territory-wide healthcare database study of hip fracture patient, the use of anti-osteoporotic medication is low despite guideline suggested initiation of anti-osteoporotic treatment in patients sustained a hip fracture, only 10.9% of them received anti-osteoporotic medication within one-year after hip fracture. Patients receiving anti-osteoporotic treatment, particularly bisphosphonates, had a significant reduced risk of cardiovascular mortality, in addition to its known beneficial effect on all-cause mortality, and the effect could last for 4 years after fracture. On the other hand, the use of salcalcitonin was associated with increased risk of cardiovascular mortality. This was the first population-based study that determines the risk of cardiovascular mortality in hip fracture patients with and without anti-osteoporotic treatment using a large electronic clinical patient record database in Hong Kong. Our study suggests that initiation of bisphosphonate treatment is clinically important to reduce the cardiovascular event in hip fracture patients.

Hip fracture is highly prevalent and associated with loss of independence, immobility,

reduced quality of life, increased morbidity, and mortality. Although the incidence rate of hip fracture is declining in many areas of the world, the absolute number of hip fracture remain stable or even increase due to prolonged life expectancy, posing a huge burden to individual and society. Since the risk of subsequent fracture in patient sustaining hip fracture is high, clinical guidelines [26-29] have recommended the initiation of anti-osteoporotic treatment in hip fracture patients. However, osteoporosis is often under-treated. For example, in our recent study conducted using patient surveys and medical charts of postmenopausal women discharged after hip fractures from treatment centres in China, Hong Kong, Singapore, South Korea, Malaysia, Taiwan, and Thailand, the use of anti-osteoporotic medication in hip fracture in the 6 months after discharge was only 33% [30]. In the current study, we observed that only X% of hip fracture patients received anti-osteoporotic medication in 1 year after discharge. We here showed that, the use of anti-osteoporotic medication in the first three and twelve months after discharge reduced all-cause mortality by X% and Y%, which agrees with those reported in literatures XXX. This highlighted the importance to initiate anti-osteoporotic treatment after hip fracture.

Positive association between osteoporosis and cardiovascular has been reported in literatures [31], partially due to the shared risk factors and the mechanisms underlying

these two diseases. For example, osteocalcin, a bone-derived hormone, affects whole body energy metabolism [32] and cardiovascular events [33, 34]; atrial-fibrillation associated gene, GREM2 [35], was also shown to be a susceptibility gene of osteoporosis [36, 37]; whereas bone-specific alkaline phosphatase, but not total alkaline phosphate, was associated with parameters of metabolic syndrome [38]. Among all these factors, mineral metabolism underlies both aetiology of osteoporosis and cardiovascular disease [39]. Although an increased risk in cardiovascular mortality is observed in hip fracture patients, whether anti-osteoporotic treatment can reduce cardiovascular mortality after hip fracture remain largely unknown. A meta-analysis of participants enrolled in three clinical trials of risedronate (a bone mass study; a vertebral fracture study; and a hip fracture study) showed a trend toward lower cardiovascular mortality (RR=0.77; 95% CI:0.57-1.03) [40]. Since the participants in the bone mass study had no prior fracture, whether use of risedronate reduced cardiovascular mortality in fracture patients is unknown. Another retrospective analysis of a randomized controlled trial of zoledronate in hip fracture patients showed that zoledronate reduced arrhythmias-cause mortality [8]. Here we showed that the use of bisphosphonate is associated with X% reduction in cardiovascular mortality in the first year, and the effect was last for at least 4 years. The exact underlying mechanism is unclear, but it has been proposed that

bisphosphonate can modulate ion channel in cardiac myocytes [41, 42], and has an anti-inflammatory effect [43]. Moreover, bisphosphonate is used to treat hypercalcemia and hence potentially reduce risk of cardiovascular mortality. After hip fracture, there is an acutely increase in serum calcium. Abnormal cardiac change, such as QT interval shortening and arrhythmias, are commonly seen in patients with severe hypercalcemia. This postulation is in line with the previous study showed that cardiac arrhythmias is the leading cause of death (HR: 14.3) in hip fracture patients, while zoledronate reduced arrhythmias-cause mortality in these patient [8]. Therefore, the effect of acute rise in calcium on cardiovascular event warrants further investigation.

Strontium ranelate and Salcalcitonin are associated with increased risk of cardiovascular mortality. The effect of strontium ranelate on cardiovascular event has been reported previously. In a large pooled analysis in 7,572 postmenopausal women showed that strontium ranelate increased risk of myocardial infarction, with estimated annual incidences of 5.7 and 3.6 cases per 1,000 patient-years of myocardial infarction for strontium ranelate and placebo, respectively. Similar incidence rates of cardiovascular mortality are observed in the current study (X and Y cases per 1,000 patient-years for strontium ranelate and untreated group, respectively). Nowadays,

strontium ranelate is not recommended in patients with history of ischaemic heart disease. In the current study, we performed subgroup analysis to evaluate if the use of anti-osteoporotic medication in hip fracture patients with and without history of CVD, and found that none of the anti-osteoporotic medication, including strontium ranelate, increased risk of cardiovascular mortality in hip fracture patients with history of CVD. However, the increased risk of cardiovascular mortality was still observed with strontium ranelate and salcatonin in hip fracture patients without history of CVD. This is unclear why strontium ranelate and salcatonin did not increase risk of cardiovascular mortality in hip fracture patients with history of CVD, it could be due to small sample size or the protective effect of CVD treatment ameliorate the adverse effect of these drugs. Nevertheless, further study is required in this area and bisphosphonates should be used in hip fracture patients regardless to the history of CVD.

Our study has several strengths. To our best knowledge, this is the first population-based study to compare the risk of cardiovascular mortality among hip fracture patients with and without anti-osteoporotic treatment in the real-life practice. The large electronic patient record database is a powerful platform to conduct large-scale, post-marketing, drug surveillance studies, as indicated in our previous

studies [44, 45]. The database we used, CDARS, is an electronic medical record for clinical management purpose, all records were validated with high accuracy. For example, we recently showed that the positive predictive value of hip fracture coding in CDARS is 100%. The study is also carefully designed. For example, previous exposure of anti-osteoporotic agents was excluded to avoid residual effect of treatment. Similarly, patients with history of hip fracture and cancer were also excluded. Using a propensity-score matching design with multiple comorbidities, the potential confounding factors between treated and untreated groups should be minimized. The PTDM approach was used to control immortal time bias. Multiple sensitivity analyses were also conducted and consistent result was obtained.

Nevertheless, there are limitations. First, although we excluded patients with prescription record 2 years prior hip fracture, the effect of anti-osteoporotic medication, especially bisphosphonates, may last more for than 2 years, but the effect should be minimal. Second, like other healthcare databases, over-the-counter prescription records are not captured by the CDARS, therefore these prescriptions cannot be controlled in the analysis. However, patients with chronic diseases requiring long-term treatment care commonly use the service of HA because the medication cost is highly subsidized (85-98%) by the government [46]. Therefore, the impact of

uncaptured medications on our results is anticipated to be minimal. Third, there may be unmeasured residual confounding effect. Fourth, the effect of bone mineral density (BMD) in cardiovascular mortality is unknown, since BMD is not routinely measured. One would expect that patients with lower BMD may have a high chance of receiving anti-osteoporotic treatment. However, it is known that low BMD is associated with higher cardiovascular mortality, whereas lower cardiovascular mortality was indeed observed in patients receiving treatment. Therefore, even if BMD affects treatment decision, it will lead to under-estimation, instead of over-estimation, of the treatment effect.

In conclusion, osteoporosis is under-treated among patients with hip fracture. The use of bisphosphonate was associated with reduced risk of cardiovascular mortality, and the protective effect was observed in both patients with and without history of CVD, and may last for at least 4 years. On the other hand, the use of strontium ranelate and calcitonin were associated with increased risk of cardiovascular mortality. Therefore, the initiation of bisphosphonate treatment in patients sustaining a hip fracture is clinically important for reducing cardiovascular mortality.

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