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ORIGINAL ARTICLE

Drug adherence and treatment duration for denosumab and mortality risk among hip fracture patients

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Abstract

Summary This study aimed to assess the impact of drug adherence and treatment duration for denosumab on mortality risk after hip fracture surgery. Lower all-cause mortality risk was associated with drug intervals of 7 months or less and longer treatment duration. The study highlights the importance of proper denosumab administration.

Purpose Prescription of anti-osteoporotic medications (AOMs) after osteoporotic hip fracture may increase bone mineral density (BMD) and decrease mortality risk. However, few studies have been conducted on drug adherence and treatment duration for denosumab, a popular choice among AOMs. This study aimed to assess the impact of denosumab adherence and treatment duration on the mortality risk of hip fracture patients after surgery.

Methods We conducted a cohort study using nationwide population data from National Health Insurance Research Database (NHIRD) in Taiwan. Patients newly diagnosed with osteoporosis and hip fracture between 2008 and 2019 who used denosumab after surgery were included. We assessed drug adherence, treatment duration, and other parameters associated with patient outcomes.

Results A total of 21,316 patients diagnosed with osteoporotic hip fractures were included. Compared with a > 7-month drug interval for denosumab, an interval of ≤ 7 months led to lower all-cause mortality risk (hazard ratio (HR): 0.60, 95% confidence interval (CI): 0.57 ~ 0.64). Patients with denosumab treatment for over 1, 2, and 3 years had lower all-cause mortality risk (HR&CI: 0.68 (0.64 ~ 0.73), 0.48 (0.43 ~ 0.53), 0.29 (0.26 ~ 0.33)) than those with treatment duration < 1 year. Analysis after excluding short-term death yielded similar results. Analysis of causes of death also showed that good adherence and longer duration were associated with reduced mortality due to cancer and cardiovascular disease.

Conclusion Better drug adherence and longer duration of denosumab treatment are associated with lower all-cause mortality risk among hip fracture patients after surgery. Our study highlights the benefits of a proper time interval of denosumab administration. These findings provide important insight into management of osteoporotic hip fractures and may inform clinical practice and development of guidelines.

Keywords Denosumab · Treatment duration · Adherence · All-cause mortality risk

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Abbreviations

AOM	Anti-osteoporosis medication
BMD	Bone mineral density
NHI	National Health Insurance
NHIRD	National Health Insurance Research Database
CCI	Charlson-Deyo comorbidity index
HR	Hazard ratio
CI	Confidence interval

Introduction

Hip fracture is the most serious issue among osteoporotic fractures. It can contribute to functional impairment and increase the mortality rate and is related to many comorbidities, especially those affecting elderly individuals[1–3]. One-year mortality after hip fracture is reported to range from 20 to 40%, and only 30% to 40% of patients return to their baseline functional status[2, 4–6].

Using anti-osteoporotic medications (AOMs) after surgery for osteoporotic hip fracture has been recommended for years. AOMs can increase bone mineral density (BMD), decrease risk of refracture, and even reduce the all-cause mortality rate [7–9]. In addition, some studies have shown that higher adherence to anti-osteoporotic treatment and longer treatment duration may have additional benefits for patients[7, 8, 10].

Denosumab, a monoclonal antibody of receptor activator of nuclear factor-kB ligand, is a popular AOM with an effect of continuously increasing BMD for at least 10 years[11]. In comparison with bisphosphonates, denosumab is associated with better adherence, cost-effectiveness, and patient preference due to its lower frequency of administration[12]. Denosumab might also enhance muscle strength and subsequently decrease falling risk, especially in patients with osteosarcopenia[13]. However, once denosumab use is stopped, bone density may decrease rapidly, increasing risk of multiple vertebral compression fractures. Therefore, when using this medication, the most important consideration is patient drug adherence.

Because stopping the use of denosumab may increase the risk of fractures, we also sought to determine whether poor adherence might be associated with an increase in mortality risk. Therefore, the aim of this nationwide database study was to investigate whether good adherence and longer treatment duration of denosumab reduce all-cause mortality risk for patients after surgery for osteoporotic hip fracture.

Material and methods

Database

Our study was based on National Health Insurance Research Database (NHIRD), which was established by Taiwan's National Health Insurance (NHI) for research use. The NHI was implemented in 1995 and contained more than 99% of the Taiwanese population by 2019. The original claim data and registration files in this database consisted of personal information of the patients, disease diagnoses, drug prescriptions, information of medical personnel and facilities, and details of outpatient and admission orders. The International Classification of Diseases, 9th and 10th Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) was used to encode disease diagnoses. Data from Cause of Death Database were also retrieved from the National Death Registry to analyze death in our target population. Our study received approval from the Institutional Review Board (IRB) of the National Cheng Kung University Hospital (NCKUH).

Subject selection

Inclusion criteria were newly diagnosed patients with osteoporosis and hip fracture between 2008 and 2019. The claim code for osteoporosis is ICD-9-CM code 733 or ICD-10-CM code M81, and hip fracture was defined as ICD-9-CM code 820 or ICD-10-CM code S72 for this study. All subjects received hip fracture surgery. We selected individuals in the above population who received denosumab as postoperative treatment to evaluate outcomes. The index date was the first prescription day of denosumab after hip fracture surgery, and it was administered at 60 mg every 6 months through a subcutaneous route. We excluded patients diagnosed with osteoporosis or osteoporotic hip fracture before 2008. Prescriptions of AOMs other than denosumab were also excluded. The primary endpoint was the all-cause mortality rate. We also investigated \ mortality caused by different major causes of death, including cancer, cardiovascular disease (CVD) and stroke.

Adherence and duration

Adherence to denosumab was measured by the average drug interval, as calculated as the months between the first dose and the last dose divided by the total number of drug intervals (total doses minus 1). A drug interval of $\leqq 7$ months indicated good adherence; a drug interval of > 7 months indicated poor adherence.

In addition, treatment duration was measured by the accumulated years, which was the sum of years that patients were truly exposed to the drug. We then separated treatment duration into four groups: < 1 year, 1 to 2 years, 2 to 3 years and more than 3 years.

Variables

Controlled variables included characteristics of the subjects, including sex, age and Charlson Comorbidity Index (CCI).

The CCI encompasses the number and severity of comorbid conditions to evaluate comorbidity levels. The scoring system contains 17 items of comorbidities: diabetes with diabetic complications, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, liver disease, metastatic tumor, renal disease, hemiplegia, leukemia, lymphoma and acquired immunodeficiency syndrome (AIDS). We calculated the CCI score based on the patient's clinical condition within one year before the hip fracture.

Independent variables were adherence to denosumab and treatment duration. Dependent variables were mortality risks after denosumab treatment according to outpatient and admission files of the NHIRD and National Death Registry Database.

Statistical analysis

Our study used SAS® software, version 9.4 (SAS Institute Inc., Cary, NC, USA) to compute data. First, the difference in all-cause mortality risk was calculated using the $\chi 2$ test for categorical variables and the t test for continuous variables. The variables include sex, age, CCI, the following personal years, drug interval, and accumulated treatment duration. In addition, we used the INTCK system to convert drug intervals into months. Second, Cox proportional hazard regression was performed to estimate all-cause mortality risk associated with drug adherence and treatment duration. Kaplan–Meier analysis was applied to generate a survival curve for each treatment group, and we used the log-rank test to compare the difference between all survival curves. Finally, the results are presented as statistically significant differences according to the Cox proportional hazard model with 95% confidence intervals (CIs). Results were defined as statistically significant based on a two-tailed p value of < 0.05.

Results

After analyzing the NHIRD database, 21,316 participants with osteoporotic hip fractures who received denosumab after surgery were recruited for our study (Fig. 1). There were 9,184 (43.1%) patients with an average interval of denosumab injection over 7 months; only 12,132 (56.9%) patients had good drug adherence (average intervals within 7 months). There were 12,698 (59.6%) patients using denosumab for less than 1 year, 4,366 (20.5%) for 1 to 2 years, 2,149 (10.1%) for 2 to 3 years and 2,103 (9.8%) for more than 3 years. During the follow-up period, 16,091 participants survived, and 5,225 participants died. In terms of baseline characteristics, the nonsurviving group was significantly older (82.12 ± 7.87 versus 77.82 ± 9.31, mean ± standard deviation, SD, $p < 0.0001$) with higher CCI scores (2.77 ± 2.34 versus 2.12 ± 2.02, $p < 0.0001$) than the surviving group (Table 1).

Compared with patients with good drug adherence, patients with a drug interval of more than 7 months had a higher risk of mortality (hazard ratio (HR): 1.66, 95% CI: 1.57–1.76; $p < 0.0001$) after adjusting for age, sex and CCI score (Table 2, Fig. 2A). Patients with denosumab intervals of more than 12 months had a 94% increased mortality risk (HR: 1.94, 95% CI: 1.83–2.05; $p < 0.0001$).

Compared with patients who received treatment for less than 1 year, those with a longer cumulative treatment duration had lower risk of all-cause mortality, with HRs of 0.68 (95% CI: 0.64–0.73; $p < 0.0001$) for patients with 1- to 2-year treatment, 0.48 (95% CI: 0.43–053; $p < 0.0001$) with 2- to 3-year treatment, and 0.29 (95% CI: 0.26–0.33; $p < 0.0001$) with treatment for more than 3 years (Table 3 & Fig. 2B).

Considering that AOMs were less likely to affect short-term mortality after hip fracture, we excluded death events within 2 years after hip fracture and reanalyzed the data. The results were similar, showing that patients with an accumulated treatment duration over 3 years had a lower risk of all-cause mortality than patients with a duration of less than 1 year (HR: 0.58, 95% CI: 0.52–056; $p < 0.0001$) (Table 3).

We further investigate competitive causes of death and found risks of mortality caused by cancer and CVD to be reduced by 30% ($p < 0.001$) and 35% ($p < 0.001$), respectively, for patients with good drug adherence (drug intervals≦7 months). Risk of mortality caused by strokes was also reduced by 16%, but the difference did not reach statistical significance. In addition, patients with duration of denosumab use of more than 3 years had significantly reduced risk of mortality caused by cancer, CVD, and stroke, by 68.7%, 58.5% and 69.6%, respectively. (Table 4).

Discussion

This is the first cohort study evaluating the association between drug adherence, treatment duration and mortality risk of patients receiving denosumab after hip fracture surgery based on a real-world nationwide database. Our study revealed that patients with better drug adherence and longer treatment duration of denosumab had higher overall survival rates and decreased mortality resulting from cancer, CVD, and stroke. These results provide clinical relevance that denosumab injection should be arranged in a timely manner, without delay, for more than 1 month.

Concerning the pharmacodynamics of denosumab, we must consider time intervals when estimating adherence. Denosumab decreases the bone absorption rate by inhibiting activation of osteoclasts. However, the effect is quickly reversed after discontinuing the drug, and the

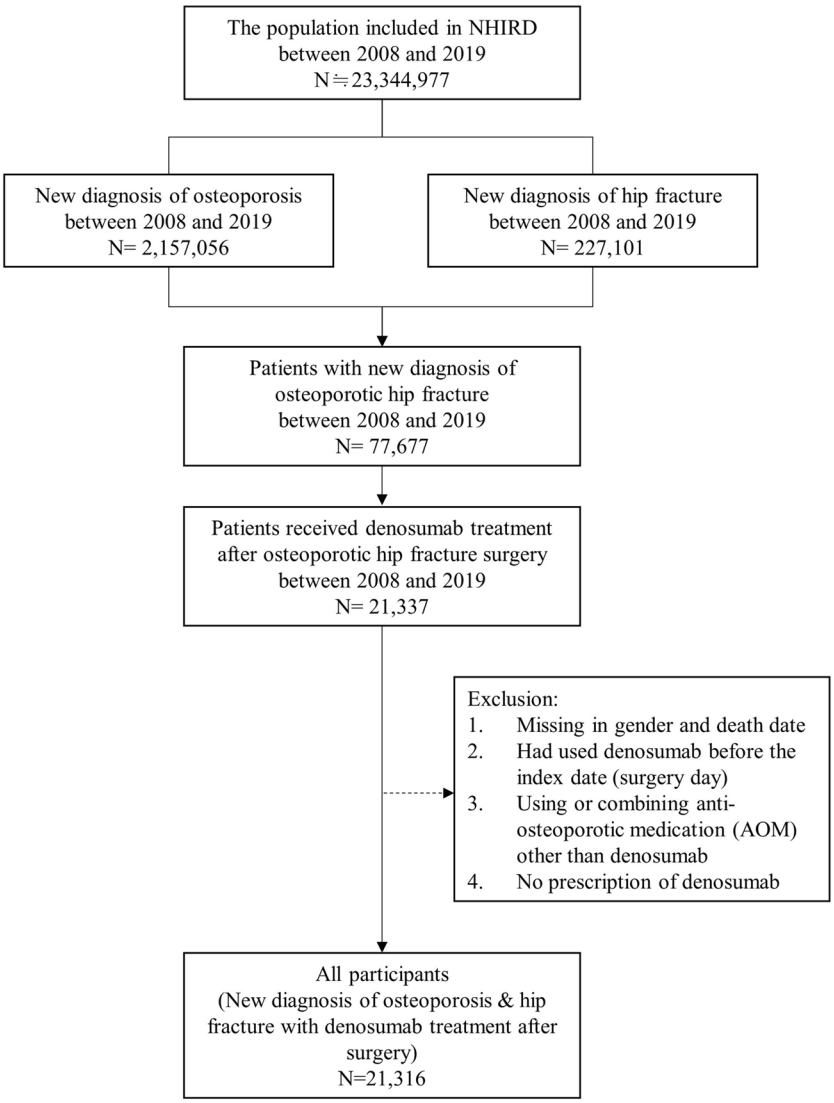

Fig. 1 Flow chart of data collected from National Health Insurance Research Database (NHIRD)

bone turnover rate may subsequently increase even above the baseline level due to osteoclast reactivation, the so-called "rebounding phenomenon" [14–16]. A previous study showed that administration delayed by more than four months contributed to a 2 ~ 4 times higher risk of fracture than on-time administration, especially with major osteoporotic and vertebral fractures. Most of the refracture events occurred between the 8th and 16th months after the last dose [17]. It has been reported that BMD may decrease under administration of denosumab every 7 to 9 months and that the drug effect is diminished within 9 months after the last dose[18].

It is recommended that the subsequent injection should not be delayed by more than 4 weeks because fractures are less likely to occur in patients receiving their subsequent dose within 7 months[19]. In our study, we also defined 7 months as the cutoff point, with a drug interval ≦7 months indicating good adherence. Our results showed a nearly 40% lower all-cause mortality risk in patients with good adherence than in those with suboptimal adherence.

Denosumab is well known for increasing BMD through interaction with osteoclasts, reducing refracture risk[11, 20, 21]. Additionally, denosumab may improve a patient's survival rate and prognosis. Denosumab is thought to bind with RANKL in skeletal muscle cells and regulate calcium storage, enhancing muscle strength[13]. The resulting decreased falling events and improved physical performance would also lead to lower fracture risk and long-term mortality risk after hip fracture[13, 22–24]. According to previous studies, denosumab may also mediate vascular calcification and lower myocardial infarction risk, especially in patients with better drug adherence[25, 26]. In mouse model studies, RANKL was found to be expressed in both skeletal and cardiac muscles, and it was closely related to inflammation and muscle dystrophy. Therefore, use of denosumab may suppress progression of skeletal and cardiac muscle

Table 1 Baseline characteristics of the participants

	Survival (%)	Nonsurvival (%)	χ^2/t	p
Sex			74.8305	< .0001
Male	2756(17.1)	1174(22.5)		
Female	13335(82.9)	4051(77.5)		
Age			-32.72	< .0001
Mean ± SD	77.82 ± 9.31	82.12 ± 7.87		
CCI score			-18.01	< .0001
Mean ± SD	2.12 ± 2.02	2.77 ± 2.34		
Follow-up (person years)			16.33	< .0001
Mean ± SD	3.80 ± 2.68	3.16 ± 2.35		
Drug interval (months)			705.0861	< .0001
Interval > 7 months	6107(38.0)	3077(58.9)		
Interval≦7 months	9984(62.1)	2148(41.1)		
Drug interval (months)			1018.337	< .0001
Interval > 12 months	3975(24.7)	2503(47.9)		
7 < Interval≦12 months	2132(13.3)	574(11.0)		
Interval≦7 months	9984(62.1)	2148(41.1)		
Accumulated treatment duration (years)			307.4368	< .0001
Drug < 1 year	9101(56.6)	3597(68.8)		
1 ≤ Drug < 2 years	3406(21.2)	960(18.4)		
2 ≤ Drug < 3 years	1758(10.9)	391(7.5)		
3 years ≤ Drug	1826(11.4)	277(5.3)		

The CCI score (Charlson Comorbidity Index) includes 17 comorbidity issues to evaluate overall mortality

Drug interval: the average time between every consecutive two doses

Accumulated treatment duration: the duration covered by the drug effect. (Total dose* 6 months)

Table 2 All-cause mortality risk of hip fracture patients with different intervals of denosumab treatment

	HR (95% CI)	*p*	HR (95% CI)	p
Sex				
Male (Ref.)	1.00		1.00	
Female	0.68(0.64–0.73)	< .0001	0.69(0.64–0.73)	< .0001
Age	1.08(1.07–1.08)	< .0001	1.08(1.07–1.08)	< .0001
CCI	1.17(1.15–1.18)	< .0001	1.17(1.15–1.18)	< .0001
Drug interval (months)				
Interval≦7 months (Ref.)	1.00			
Interval > 7 months	1.66(1.57–1.76)	< .0001		
Drug interval (months)				
Interval≦7 months (Ref.)			1.00	
7 < Interval ≦12 months			1.03(0.94–1.12)	0.5974
Interval > 12 months			1.94(1.83–2.05)	< .0001

Multivariable Cox proportional regression

HR: hazard ratio; 95% CI: 95% confidence interval

degeneration[27, 28]. An anticancer effect was also noted: cancer death decreased in patients with good adherence and long duration of denosumab treatment. This is suspected to be related to suppression of tumor-expressed RANK or RANKL and improvement of the effectiveness provided by immune checkpoint inhibitors (ICIs)[29–32].

Some studies have opposite opinions about the survival-promoting effects of denosumab. A meta-analysis published in 2019 showed that AOM treatment can contribute to a reduction in all-cause mortality risk but that it is not likely to be associated with factors other than lower refracture risk[33]. However, this meta-analysis mainly focused on

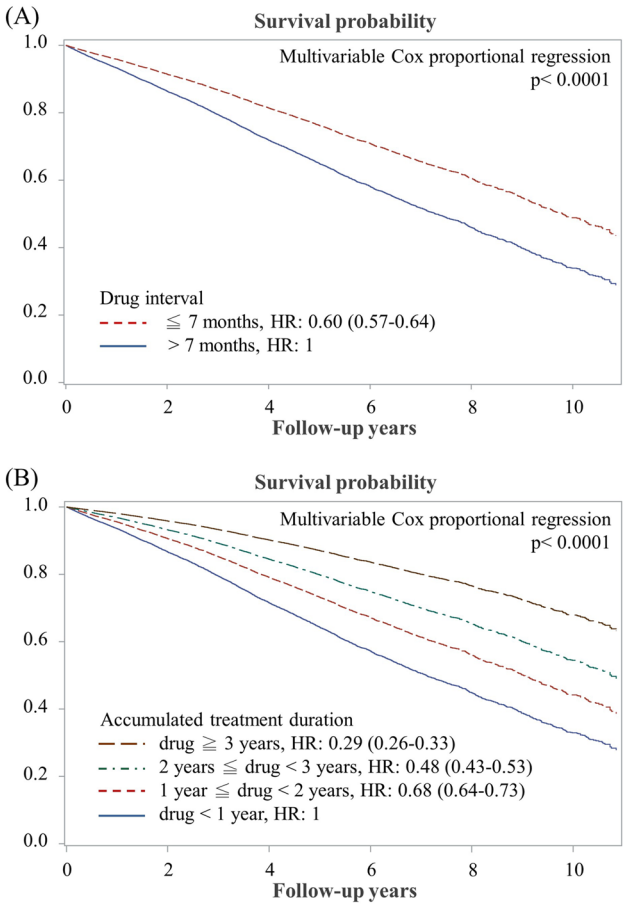

Fig. 2 (A) Mortality of hip fracture patients with different drug intervals of denosumab use. (B) Mortality of hip fracture patients under different treatment durations of denosumab. The analysis was calculated using a multivariable Cox proportional hazard model

Table 3 All-cause mortality risk of hip fracture patients under different treatment durations

	All patients with hip fracture ($n=21,316$)		All patients except deceased patients within 2 years after hip fracture	
	HR (95% CI)	p	HR (95% CI)	*p*
Sex				
Male (ref.)	1.00		1.00	
Female	0.73(0.68–0.78)	< .0001	0.83(0.75–0.92)	0.0004
Age	1.08(1.07–1.08)	< .0001	1.08(1.08–1.09)	< .0001
CCI	1.17(1.15–1.18)	< .0001	1.14(1.12–1.16)	< .0001
Accumulated treatment duration (years)				
Drug < 1 year (Ref.)	1.00		1.00	
1 ≦ Drug < 2 years	0.68(0.64–0.73)	< .0001	1.05(0.95–1.17)	0.3271
2 ≦ Drug < 3 years	0.48(0.43–0.53)	< .0001	0.89(0.79–1.01)	0.0778
3 years ≦ Drug	0.29(0.26–0.33)	< .0001	0.58(0.52–0.65)	< .0001

Multivariable Cox proportional regression

HR: hazard ratio; 95% CI: 95% confidence interval

bisphosphonates and included few articles about denosumab. In addition, a randomized controlled trial based on the database of the FREEDOM trial reported that the administration of denosumab for years does not affect the incidence or progression of CVD[34]. Nevertheless, radiological-based outcome interpretation may not detect slight changes and might miss some possible cardiovascular-protective effects.

Drug adherence plays an important role in the effect of denosumab and other AOMs. In our study, the population receiving denosumab on schedule had lower mortality risk than those with delayed administration, especially when exceeding 7 months. On the other hand, on-time administration enhanced the cardiovascular-protective and anticancer effects of denosumab. A decrease in the mortality risk of cancer, CVD, or stroke was observed among the participants with on-time injections in our study, with 29.9%, 35.0% and 15.9% risk reductions, respectively. In previous studies, patients with good adherence to AOMs (MPR ≥ 80%) had 10 ~ 18% higher short- and long-term survival rates and lower refracture rates than those with poor adherence[35–37]. In comparison to oral bisphosphonates, the intravenous form leads to better treatment compliance due to lower administrative frequency; for the same reason, twice-yearly infusion denosumab has gained patient preference[4, 12, 38, 39]. Tai et al. also mentioned that drug adherence might have a more significant effect on a patient's outcome than the pharmacological mechanisms of different AOMs[4].

Referring to the treatment course, there is still no conclusion about the optimal duration of AOMs. However, our study indicated that a longer treatment duration led to lower all-cause mortality risk, and treatment persistence for at least 3 years reduced mortality risk by 47% compared with a duration of < 1 year. Furthermore, cancer, CVD and stroke mortality were decreased by 68.7%, 58.5% and 69.6%, respectively, when the treatment duration was longer than 3 years. There have been many studies in agreement with our theory. Current clinical guidelines and reviews of osteoporosis treatment found that a longer duration of bisphosphonate use provides higher drug-binding affinity to the bone and that patients with a higher risk of fracture should receive the treatment longer[40–42]. UK clinical guidelines for osteoporosis treatment recommended that patients who had ever experienced hip fracture should receive oral BPs for at least 10 years and intravenous BPs

Table 4 Competitive causes of mortality risk for hip fracture patients between different treatment durations and drug intervals of denosumab

Causes of Death	Cancer		Cardiovascular disease		Stroke	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Sex						
Male (Ref.)	1.00	1.00	1.00	1.00	1.00	1.00
Female	0.77**	0.82*	0.95	1.00	0.69**	0.73*
Age	1.03***	1.03***	1.08***	1.08***	1.05***	1.05***
CCI	1.19***	1.19***	1.08***	1.08***	1.03	1.03
Drug interval (months)						
Drug interval > 7 months (Ref.)	1.00		1.00		1.00	
Drug interval ≦7 months	0.70***		0.65***		0.84	
Accumulated treatment duration (years)						
Drug < 1 year (Ref.)		1.00		1.00		1.00
1 ≦ Drug < 2 years		0.76**		0.75***		0.90
2 ≦ Drug < 3 years		0.58***		0.53***		0.73
3 years ≦ Drug		0.31***		0.42***		0.30***

Multivariate Cox proportional hazard analyses

CVD: cardiovascular disease

*$p < 0.05$ **$p < 0.01$ ***$p < 0.001$

for at least 5 years. According to the 10-year FREEDOM trial, denosumab has the effect of continuously increasing bone mineral density for at least 10 years; concerning the potential immune impact from denosumab, no increased risk of serious adverse events such as severe infection or cancer have been reported[11]. In addition, according to a recent study in Taiwan, longer duration of any type of AOM treatment can lower all-cause mortality risk in patients after fragility hip fracture surgery, and all-cause mortality risk can be reduced by 54% in patients under AOM treatment for more than 3 years[8].

Although there is consensus on the great benefits of AOM, many patients still exhibit poor adherence and persistence to the doctor's prescription. In our study, only 56.9% exhibited good adherence to denosumab and received the treatment on time (within 7 months), and only 20% of the participants persisted with denosumab treatment for over 2 years. In previous studies, adherence to AOM within 1 year varied from 34 to 75%, and furthermore, less than 50% of patients showed compliance to AOM after 2 years[35, 43–45]. An electronic health record-based study published in 2020 showed that almost 50% of the population under denosumab treatment for several years had at least 1 dose delayed by more than 4 months[46]. A low prescription rate of AOM was also reported. Only 15.9% of the patients started their AOM regimen within 6 months after hip fracture[37]. The factors associated with poor adherence included multiple comorbidities, polypharmacy, asymptomatic osteoporosis, decline in memory, health beliefs of the patient and lack of patient education[37, 43, 47, 48].

Our study has some limitations. We used the initial prescription date as the index date, but the time between hip fracture and the first administration of denosumab was not considered in survival in this study. Overall, delay of drug use after hip fracture might vary among patients, though previous studies showed that earlier prescriptions result in better prognosis[1, 38, 49, 50]. This bias was minimal because all included subjects used denosumab and not different kinds of AOMs. The prescription pattern might be similar. Second, the claims database did not contain all the patient's personal or clinical information. We could not retrieve some risk factors associated with mortality and refracture after primary hip fractures, such as BMD, body mass index, patient lifestyle, exercise, smoking and alcohol use. Nevertheless, the prevalence of tobacco and alcohol use was lower in aged group in Taiwan. Third, we could not definitively determine causality between all-cause mortality risk and denosumab treatment based on an observational study; a retrospective cohort study is more appropriate to reveal the clinical condition of the real-world population. Further large-scale prospective studies are required to clarify these issues.

In this nationwide database cohort study, better adherence to denosumab and longer treatment duration were associated with lower all-cause mortality and lower cancer and cardiovascular death after osteoporotic hip fracture. Drug intervals within 7 months and persistence to denosumab over 3 years led to the best clinical outcomes. Therefore, to promote better prognosis for the hip fracture population, adherence and persistence of treatment should be emphasized when prescribing denosumab for osteoporosis treatment after hip fracture.

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Author contributions Conception and design of the study: TWT, CCL, JSH, CHW. Statistical analyses: TWT, CCL, CHW. Research data interpretation: all authors. Acquisition of data: YLT, CCL. Suggestions and discussion: YFC, JSH. Drafting the article: YLT, TWT, CHW. Critical revision of the manuscript: all authors. Final approval of the manuscript: all authors.

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Data Availability NHIRD is only available for on-site analysis after 2016 for the protection of personal information.

Declarations

Conflicts of Interest Ta-Wei Tai: honoraria for lectures and attending meetings from Amgen and Alvogen/Lotus. Jawl-Shan Hwang: honoraria for lectures, attending meetings, and/or travel from Eli Lilly, Roche, Amgen, Merck, Alvogen/Lotus. Chih-Hsing Wu: honoraria for lectures, attending meetings, and/or travel from Eli Lilly, Roche, Amgen, Merck, Servier laboratories, GE Lunar, Harvester, TCM Biotch, Alvogen/Lotus. Jawl-Shan Hwang: honoraria for lectures and attending meetings from Amgen and Alvogen/Lotus. Yi-Lun Tsai, Chia-Chun Li, Chien-An Shih and Yin-Fan Chang declare that they have no conflicts of interest.

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