Long-term Effects of Antihypertensive Drug Use and New-onset Osteoporotic Fracture in Elderly Patients: A Population-based Longitudinal Cohort Study

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Abstract

Background: Antihypertensive drugs have been linked to new-onset osteoporotic fracture (NOF), and different classes of antihypertensive drugs may alter the risk for the development of NOF; however, the classic effect of different antihypertensive drugs on the development of NOF in the elderly has not been well studied during long-term follow-up.

Methods: In this study, we investigated the association between different classic antihypertensives and the development of NOF in the elderly. This was a longitudinal cohort study performed using data from claim forms submitted to the Taiwan Bureau of National Health Insurance in Central Taiwan, China including case patients with NOF aged 65–80 years from January 2002 to December 2012 and non-NOF controls. Prescriptions for antihypertensives before the index date were retrieved from a prescription database. We estimated the hazard ratios (*HR*s) of NOF associated with antihypertensive use. Non-NOF controls served as the reference group.

Results: A total of 128 patients with NOF were identified from among 1144 patients with hypertension during the study period. The risk of NOF after adjusting age, sex, comorbidities, and concurrent medications was higher among the users of angiotensin-converting enzyme (ACE) inhibitors (*HR*, 1.64; 95% confidence interval [*CI*], 1.01–2.66) than among nonusers. Patients who took calcium channel blockers (CCBs) (*HR*, 0.70; 95% *CI*, 0.49–0.99) were at a lower risk of developing NOF than nonusers. Loop diuretics, thiazide diuretics, angiotensin receptor blocker, beta-blocker, and alpha-blocker were not associated with the risk of NOF.

Conclusions: Elderly with hypertension who take CCBs are at a lower risk of NOF and that the use of ACE inhibitors was associated with a significantly increased risk of developing NOF during the 11-year follow-up.

Key words: Antihypertensive Drugs; Elderly; New-onset Osteoporosis Fracture

Introduction

Aging of the world's population is inevitable. Concerns about the health care of the elderly, particularly in terms of age-related diseases, have gradually increased worldwide.[1,2] Osteoporotic fracture, which is more common in older than in younger individuals, is considered an age-related disease. Osteoporotic fractures result in significant health-care costs because they have been shown to adversely affect the health-related quality of life and have become a major public health problem.[3,4]

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Hypertension is a risk factor for osteoporotic fracture and significantly contributes to morbidity and mortality both in men and women.[4-6] Recently, several prospective trials led to a debate on whether the use of antihypertensive drugs is associated with new-onset osteoporotic fracture (NOF) in hypertensive patients undergoing treatment.[7-10] However, the results of these studies are inconsistent, partly because of a head-to-head comparison of antihypertensive agents and short follow-up periods.[10-12] It is also unclear whether certain antihypertensive drug classes are associated with a higher risk of NOF when compared with other antihypertensive drug classes in the elderly population during long-term follow-up. Therefore, this study aimed to investigate the effect of classic antihypertensive drugs (diuretics, beta-blockers, calcium channel blockers [CCBs], alpha-blockers, angiotensin-converting enzyme [ACE] inhibitors, and angiotensin receptor blockers [ARBs]) on NOF among elderly hypertensive patients by conducting a retrospective cohort study in Taiwan, China.

METHODS

Study population

Data were collected from claim forms of the Taiwan National Health Insurance (NHI) that had been submitted to the Taiwan Bureau of National Health Insurance in Central Taiwan, China, from January 2002 to December 2012. The Taiwan NHI program has been operating since 1995 and represents approximately 99% of population in Taiwan, China. The claim forms contain inpatient and outpatient records. The information from the claim forms is stored in two tables: a visit table and a prescription table. Visit tables contain patient identification numbers, sex, age, three diagnostic codes, medical expenditures, and hospital and physician information. Prescription tables contain the quantity and expenditure of all drugs, surgeries, and treatments. Patients were included in the study if they had been diagnosed with hypertension without osteoporotic fracture at baseline (January 1, 2002). We summarized the claim records of each patient into one record.

Study design

Participants were included in the study if they had been diagnosed with hypertension (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 401–405) from January 1, 2002 to June 30, 2002. At least one of the following enrollment criteria had to be met for inclusion in the study: (1) two or more outpatient visits within a 6-month period; (2) all prescriptions of antihypertensive drugs continuously administered to the patients for more than 6 months within an 11-year follow-up period; or (3) one or more inpatient admissions with a diagnosis of hypertension. The primary end point was the development of NOF, which was defined by the time an osteoporotic fracture (ICD-9-CM codes 733.11 and 805–829) or fracture-related surgery (ICD-9-CM codes 78.1, 78.4, 78.5, 78.9, 79, and 81) first appeared in the inpatient or outpatient claim records. Comorbidities related to osteoporotic fracture were defined according to the ICD-9-CM code

and included coronary artery disease (ICD-9-CM code 410–415), hyperlipidemia (ICD-9-CM code 272), diabetes mellitus (ICD-9-CM code 250), and chronic kidney disease (ICD-9-CM code 585). Antihypertensive drugs are available only by prescription in Taiwan, China. Patients using only one type of antihypertensive drug before the development of NOF were categorized as single users based on the antihypertensive drug class prescribed, including loop or thiazide diuretics, alpha-blockers, beta-blockers, CCBs, ACE inhibitors, and ARBs. Patients using more than one type of antihypertensive drug before the development of NOF were categorized as combined users. Patients who fulfilled any of the following criteria were excluded from the study: (1) had a prior history of osteoporotic fracture or fracture-related surgery; (2) patients taking calcium supplements, biphosphates, selective serotonin-specific reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, estrogen, or calcitonin; and (3) patients suffering from other major medical problems, leaving the patient with a life expectancy of <6 months. Initially, 1567 outpatients fulfilled the inclusion criteria; however, 291 patients were excluded from the study based on the diagnosis of osteoporotic fracture before January 1, 2002. Therefore, a total of 1276 patients were enrolled in the study at baseline [Figure 1]. Furthermore, 118 patients who were lost at follow-up and 17 patients who died without the diagnosis of NOF or NOF-related death were excluded from the study. Finally, a total of 1144 outpatients were included in this study. This study was approved by the Ethics Committee of China Medical University Hospital (DMR101-IRB2-194). The Ethics Committee waived the need for patient consent for this study.
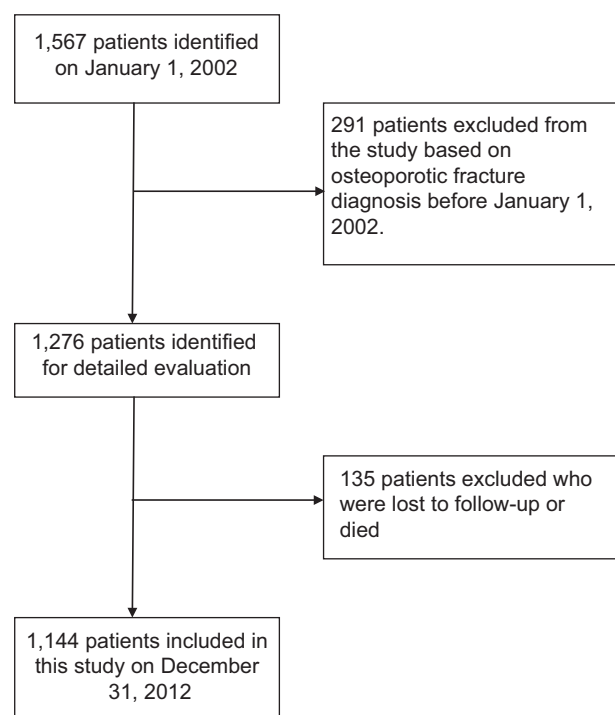

Figure 1: Flowchart of selection of patients for the inclusion in this study.

Statistical analysis

Data were presented as valid percentages and mean values with standard deviations. Chi-square test and *t*-test were used for univariate analyses. This study aimed to examine the association between the use of certain antihypertensive drug classes and NOF. The Cox proportional hazard regression model was used to compare the NOF development between antihypertensive drug users and nonusers. Adjusted hazard ratios (*HR*s) and 95% confidence intervals (*CI*) were calculated, adjusting for important factors, including age, sex, comorbidities, and concurrent medication. *P* < 0.05 was considered statistically significant. All statistical calculations were performed using Statistical Analysis software, version 9.3 (SAS institute, Inc., Cary, NC, USA).

RESULTS

Baseline characteristics of patients

Baseline characteristics, comorbidities, and concurrent medication use among the overall study population are shown in Table 1. Among 1144 eligible patients with defined hypertension, 128 (11.4%) developed NOF from January 2002 to December 2012. The mean age for NOF patients was 78.9 years and that of non-NOF patients was 75.6 years. There were statistically significant differences in age between these two groups of patients (*P* < 0.001).

In total, 264 (23.1%) patients took a drug of only one class, 423 (37.0%) took drugs from two classes, 344 (30.1%) took drugs from three classes, and 112 (9.8%) took drugs from four classes. Over 50% of the patients took CCBs (788, 68.8%) or ARBs (593, 51.8%). Only 9.8% (86) of the patients took an alpha-blocker. The distributions of prescription loop (10.7%) or thiazide diuretics (35.1%), beta-blockers (40.6%), and ACE inhibitors (12.6%) used are shown in Table 1.

Relative risk of new-onset osteoporotic fracture

The crude *HR* of NOF was lower for alpha-blockers users [*HR*, 0.37; 95% *CI*, 0.11–1.00, Table 2]. After adjusting for age, sex, comorbidities, and concurrent medication, the risk of NOF development was not associated with the use of alpha-blockers [*HR*, 0.42; 95% *CI*, 0.15–1.18, Table 2]. Initially, the crude *HR* of NOF development was not statistically significantly different for CCBs or ACE inhibitor users. However, the risk estimate of NOF after adjusting for age, comorbidities, and concurrent medication for ACE inhibitors users (*HR*, 1.64; 95% *CI*, 1.01–2.64) was significantly higher (*P* < 0.05) than that for nonusers. Patients who took CCBs (*HR*, 0.70; 95% *CI*, 0.49–0.99) were at a lower risk of developing NOF than nonusers. Loop diuretics (*HR*, 1.05; 95% *CI*, 0.61–1.80; and adjusted *HR*, 1.11; 95% *CI*, 0.64–1.93), thiazide diuretics (*HR*, 0.94; 95%

Table 1: Baseline characteristics of all eligible patients with defined hypertension

Characteristics	NOF (*n* = 128)	non-NOF (*n* = 1016)	Total (*N* = 1144)	*P**
Age (years)	78.9 ± 7.0	75.6 ± 6.3	75.9 ± 6.4	<0.001
Male	33 (25.8)	466 (45.9)	499 (43.6)	<0.001
Female	95 (74.2)	550 (54.1)	645 (56.4)	<0.001
Number of prescription				
1	44 (34.4)	220 (21.7)	264 (23.1)	0.002
2	45 (35.2)	378 (37.2)	423 (37.0)	
3	35 (27.3)	309 (30.4)	344 (30.1)	
4	4 (3.1)	108 (10.6)	112 (9.8)	
Comorbidities				
Coronary artery diseases	10 (7.8)	89 (8.8)	99 (8.7)	0.674
Hyperlipidemia	33 (25.8)	382 (37.6)	415 (36.3)	<0.001
Diabetes mellitus	38 (29.7)	370 (36.4)	408 (35.7)	0.134
Chronic kidney disease	10 (7.8)	90 (8.9)	100 (8.7)	0.693
Drug class				
Loop diuretics	15 (11.7)	107 (10.5)	122 (10.7)	0.685
Thiazide diuretics	37 (28.9)	365 (35.9)	402 (35.1)	<0.001
Beta-blockers	43 (33.6)	422 (41.5)	465 (40.6)	<0.001
CCBs	80 (62.5)	708 (69.7)	788 (68.8)	<0.001
Alpha-blockers	4 (3.1)	94 (9.3)	98 (8.6)	<0.001
ACE inhibitors	20 (15.6)	124 (12.2)	144 (12.6)	0.001
ARBs	57 (44.5)	536 (52.8)	593 (51.8)	<0.001
Concurrent medications				
Aspirin	110 (85.9)	854 (84.1)	964 (84.3)	
Statins	45 (35.2)	354 (34.8)	399 (34.9)	
PPIs/H$_2$ blockers	6 (4.7)	82 (8.1)	88 (7.7)	0.176
Non-BZD hypnotics	34 (26.6)	271 (26.7)	305 (26.7)	0.979
Inhaled corticosteroids	4 (3.1)	25 (2.5)	29 (2.5)	0.652

Data were presented as mean ± SD or *n* (%).*P value between NOF and non-NOF. NOF: New-onset osteoporotic fracture; CCBs: Calcium channel blockers; ACE: Angiotensin-converting enzyme; ARBs: Angiotensin receptor blockers; PPIs: Proton pump inhibitors; BZD: Benzodiazepine; SD: Standard deviation.

Table 2: Incidence of *HR*s with 95% *CI* for new-onset osteoporotic fracture according to prescriptions for antihypertensive drugs compared with nonusers

Drugs	*HR* (95% *CI*)	*P*	Adjusted *HR** (95% *CI*)	*P*
Loop diuretics	1.05 (0.61–1.80)	0.864	1.11 (0.64–1.93)	0.822
Thiazide diuretics	0.94 (0.63–1.38)	0.737	0.97 (0.65–1.44)	0.723
Beta-blockers	0.70 (0.49–1.01)	0.059	0.77 (0.52–1.12)	0.064
CCBs	0.77 (0.54–1.10)	0.147	0.70 (0.49–0.99)	0.048
Alpha-blockers	0.37 (0.14–1.00)	0.043	0.42 (0.15–1.18)	0.065
ACE inhibitors	1.58 (0.98–2.55)	0.051	1.64 (1.01–2.66)	0.043
ARBs	0.89 (0.63–1.26)	0.506	0.89 (0.63–1.27)	0.508

*HR was adjusted for age, sex, comorbidities, and concurrent medication. CCBs: Calcium channel blockers; ACE: Angiotensin-converting enzyme; ARBs: Angiotensin receptor blockers; *HR*s: Hazard ratios; *CI*: Confidence intervals.

CI, 0.63–1.38; and adjusted *HR*, 0.97; 95% *CI*, 0.65–1.44), beta-blockers (*HR*, 0.70; 95% *CI*, 0.49–1.01; and adjusted *HR*, 0.77; 95% *CI*, 0.52–1.12), and ARBs (*HR*, 0.89; 95% *CI*, 0.63–1.26; and adjusted *HR*, 0.89; 95% *CI*, 0.63–1.27) were not associated with the risk of NOF development from crude *HR* to adjusted *HR* [*P* > 0.05, Table 2].

DISCUSSION

In this study, the use of ACE inhibitors was independently associated with an increased risk of NOF development in elderly hypertensive patients. The use of CCBs was also independently associated with a decreased risk of NOF in elderly hypertensive patients. Loop diuretics, thiazide diuretics, beta-blockers, ARBs, and alpha-blockers were not associated with the risk of NOF development in elderly hypertensive patients.

Loop diuretics have been shown to accelerate NOF in hypertensive patients who use them continuously for more than three years.[13] Our results contradicted this study but were comparable with the results reported by Solomon *et al*.,[14] who studied the risk of NOF in 376,061 elderly hypertensive patients using loop diuretics or CCBs. Solomon *et al*. observed no difference in the relative risk of hip fractures (*HR*, 1.03; 95% *CI*, 0.90–1.16), wrist fractures (*HR*, 0.98; 95% *CI*, 0.83–1.16), or femur fractures (*HR*, 0.98; 95% *CI*, 0.83–1.16) in individuals using a loop diuretic compared with those using CCB.

An observational study showed that patients using thiazide diuretics for more than one year had a decreased risk of developing hip fractures compared with those who did not use these drugs (*HR*, 0.46; 95% *CI*, 0.21–0.96);[15] the authors concluded that the long-term use of thiazide diuretic decreased the incidence of NOF. However, our study, which included an 11-year follow-up period, revealed no association between NOF and the use of thiazide diuretics. In addition, many observational studies have demonstrated findings similar to those of our study.[16,17] For example, LaCroix *et al*.[17] evaluated 9518 hypertensive patients and reported that the relative risk of NOF for patients using thiazide diuretics was 0.88 (95% *CI*, 0.52–1.74) in East Boston, 0.53 (95% *CI*, 0.27–1.05) in New Haven, and 0.67 (95% *CI*, 0.39–1.14) in Iowa.

In vitro data show that the sympathetic nervous system has a catabolic effect on bones.[18,19] Therefore, beta-blockers are generally considered to decrease the risk of NOF.[20-22] Many studies have indicated that beta-blockers are associated with a decreased risk of NOF compared with thiazide diuretics.[20,21] For example, Schlienger *et al*.[21] evaluated 30,601 patients and reported that the relative risk of NOF in patients who used beta-blockers was 0.77 (95% *CI*, 0.72–0.83) compared with those not using beta-blockers or using a thiazide diuretic. However, our results showed a neutral effect on the risk of developing NOF, similar to the two studies by Rein *et al*.[23] and Levasseur *et al*.[24] In the study by Rein *et al*.,[23] the adjusted relative risk of NOF in individuals using a beta-blocker was 0.92 (95% *CI*, 0.81–1.05) compared with those not using beta-blocker in a cohort of elderly women. Similarly, Levasseur *et al*.[24] reported that beta-blockers were not associated with an increased risk of NOF in female hypertensive patients.

In the present study, we found that the use of ACE inhibitors increased the risk of NOF development at a similar level as that found in a previous study, in which 301,591 elderly hypertensive patients were evaluated. The relative risk of developing NOF when using ACE inhibitors was found to be 1.53 (95% *CI*, 1.12–2.10) in that study.[25] However, many studies have reported that ACE inhibitors decrease the risk of NOF development in hypertensive patients because they block the renin–angiotensin system, thus shifting the balance toward bone formation.[9,26] In the study by Rejnmark *et al*.,[26] in which 124,655 patients were evaluated, the use of ACE inhibitors was found to decrease the risk of NOF development compared with the use of CCBs (odds ratio, 0.93; 95 % *CI*, 0.90–0.96).

In this study, ARBs were not associated with a decrease in the risk of NOF development. This result is consistent with the results observed in the report by Butt *et al*.,[25] which showed a nonstatistically significant increase in NOF of the hip (incidence rate ratio, 1.41; 95% *CI*, 0.65–3.05). However, some studies found that ARB use was associated with a statistically significant decrease in the risk of NOF development.[14] For example, Solomon *et al*.[14] evaluated 376,061 hypertensive patients and found that the risk of NOF development decreased in those who used ARBs (*HR*, 0.76; 95% *CI*, 0.68–0.86).

This study shows that the use of ACE inhibitors was independently associated with an increased risk of NOF development. On the other hand, the use of ARB was not independently associated with an increased risk of NOF development in elderly hypertensive patients. The mechanism driving this difference is currently not known. However, in a rat ovariectomy model, they found that hypertensive rats treated with ARB experienced less decrease in bone marrow density because of ARB, which can increase the activity of tartrate-resistant acid and bone resorption.[14]

Our results show that the use of CCBs is associated with a statistically significant decrease in the risk of NOF. Previous studies have consistently demonstrated that CCB class of antihypertensive drugs has protective effects on bone metabolism in experimental and human studies.[26-29] A study, which is similar to our study, reported that the use of CCBs was associated with a 6% (95% *CI*, 4–9%) decrease in the risk of NOF.[26] In contrast, there has also been a study that reported no protective effect on NOF risk for the users of CCBs.[29]

This study is the long-term longitudinal epidemiological investigation of the association between the use of alpha-blockers and developing osteoporotic fractures, with a follow-up period of 11 years.[10] We found that alpha-blockers were not associated with NOF in elderly hypertensive patients. This study also suggest that alpha-blockers have a neutral effect against NOF. There have been many studies reporting a negative protection relationship of alpha-blockers with NOF.[10,12,30] The statistically significant increase in the risk of NOF among the groups of alpha-blocker users observed in previous studies may be explained by the current use and short-term follow-up.[10]

Some limitations of this study need to be emphasized. First, this was a descriptive retrospective study conducted in Taiwan, China over a period of 11 years. Moreover, we excluded irregularly treated hypertensive patients from the analyses. Therefore, caution must be exercised in interpreting our data. Second, all cases in this study were collected from claimed datasets of the Taiwan NHI that were submitted from the China Medical University Hospital, and the diagnoses were based on physician reports only; therefore, it is unclear how our findings can be generalized to patients in different areas of the world. Third, the process of osteoporosis in patients who developed NOF in this study would have started many years before the diagnoses, and NOF may have coexisted with the process of hypertension for which antihypertensive drugs were used. Thus, the cause and effect relationships between NOF and the antihypertensive drugs cannot be determined in this study. Fourth, the data on genetic evaluation for hypertension, such as *CaMK4*, *PLA2*, and *GRKs*,[5] were not available from the secondary data used for this study. Fifth, the risk factors for osteoporotic fractures, such as obesity, body mass index, smoking status, alcohol consumption, physical activity, family history, and treatment adherence, were also not available from these datasets of Taiwan NHI.

In conclusion, our results show that elderly hypertensive patients who use ACE inhibitors are at a higher risk of developing NOF than patients who are nonusers. The use of CCBs was also independently associated with a decreased risk of NOF in elderly hypertensive patients. Our findings may provide some support for the hypothesis that there are differences in the risk of developing NOF with the use of different classes of antihypertensive drugs in elderly hypertensive patients.

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Conflicts of interest

There are no conflicts of interest.

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