Association between renin–angiotensin–aldosterone system blockade and future osteoporotic fracture risk in hypertensive population

A population-based cohort study in Taiwan

Chang-I. Chen, MD, PhD, Jong-Shiuan Yeh, MD, Nai-Wen Tsao, MD, Fen-Yen Lin, PhD, Chun-Ming Shih, MD, PhD, Kuang-Hsing Chiang, MD, MS, Yung-Ta Kao, MD, Yu-Ann Fang, MS, Lung-Wen Tsai, PhD, Wen-Chi Liu, MS, Hironori Nakagami, MD, PhD, Ryuichi Morishita, MD, PhD, Yi-Jie Kuo, MD, PhD, Chun-Yao Huang, MD, PhD

Abstract

Tissue renin–angiotensin–aldosterone system (RAAS) activation in sites of osteoporosis had been demonstrated in animal studies; however, the possibility of RAAS blockade to prevent future osteoporotic fracture had rarely been verified in clinical studies. We used the Taiwan Longitudinal Health insurance database 2000 to 2008, the cohort study comprised patients age over 40 with a recorded new diagnosis of hypertension between January 1, 2000 to December 31, 2008, in addition, patients who had diagnosis of osteoporosis before the date of cohort enter were excluded. After the definite diagnosis of hypertension, each patient was followed until osteoporotic fracture happened or the end of 2008. The occurrence of osteoporotic fracture was evaluated in patients who either were or without taking RAAS blockade agents. Cox proportional hazard regressions were used to evaluate the osteoporotic fracture incidence after adjusting for known confounding factors. In total, 57,132 hypertensive patients comprised the study cohort. Our study results showed that the incidence of osteoporosis fracture in the whole cohort was significantly higher in the RAAS blockade non-user group than the user group. This phenomenon was observed in both sex and all age categories. Sensitivity analysis further showed the concordant lower osteoporosis fracture risk in patients with various RAAS blockers usage durations; the risk of osteoporosis fracture was the lowest in those drug use >365 days when compared with the non-user cohort. In conclusion, our study result demonstrated the lower future osteoporotic fracture risk in hypertensive subjects who received long term RAAS blocker treatment.

Abbreviations: ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin II receptor blockers, AT1R = angiotensin II type 1 receptor, BMD = bone mineral density, CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, ICD-9 = International Classification of Disease, 9th Revision, MRA = mineralocorticoid receptor antagonist, RAAS = renin–angiotensin–aldosterone system, RANKL = receptor activator of NF-kB ligand.

Keywords: hypertension, osteoporotic fracture, renin–angiotensin–aldosterone system

1. Introduction

Osteoporosis is described as low bone mass and corrosion of the micro-architectural of bone tissue, which may result in bone fragility and susceptibility to fractures. Osteoporosis has strong physical and psychosocial consequences, especially those who also suffered from fracture.1 With the increasing longevity, the prevalence of osteoporosis and related complications are growing...
higher; the chance of a 50-year-old subject to have a hip fracture during his or her life-time is 14% to 17% for white women and 5% to 6% for white men in the United States.[2,3] The worldwide annual increase risks of hip fracture for people age 50 years older were 1% to 3% in men and 0.5% to 3.3% in women.[4] The prevalence of vertebral fracture in women worldwide was even higher, with the risk of 0% to 14.6% in their fifties and 26.3% to 50.8% in their 80s.[5] The lifetime estimated prevalence of any fracture was 15.8% for male and 23.4% for female Taiwanese aged over 85 years.[7] Low bone mass in patients with osteoporosis may due to failure to build up optimal peak bone mass or excessive bone loss. According to the aware pathophysiology of osteoporosis, several treatment modalities have been developed to prevent osteoporosis and fracture complications, which may include increase physical activity and prevent long-term bed-rest[8]; increase calcium and vitamin D intake[9]; bisphosphonates treatment[10]; hormone replacement therapy[11]; selective estrogen-receptor modulators therapy[12]; natural estrogens therapy, especially plant-derived phytoestrogens[13]; and also nasal calcitonin.[14] In addition, on top of the aforementioned treatment modalities, multifactorial approaches to prevent falls may well avoid future osteoporotic fracture.[2]

Renin–angiotensin–aldosterone system (RAAS) plays an important role on blood pressure homeostasis, as well as water and sodium regulation. Activation of RAAS may result in hypertension, cardiovascular disease,[15] renal disease,[16] and metabolic syndrome.[17] Previously, the main effect of RAAS was thought to be systemic; however, growing evidences on animal and cell studies had demonstrated the local RAAS activation in bone tissue, could also result in osteoporosis.[18,19] Whether RAAS antagonist can prevent future osteoporotic fracture in human remains unknown. Because RAAS blockers had already been widely used in hypertension subjects and hypertension is also a risk of low bone mass, we designed a cohort study base on the Taiwan insurance data bank trying to demonstrate the possible potential of osteoporotic fracture prevention by RAAS inhibition in hypertensive patients.

2. Materials and methods

2.1. Study design

We showed a nationwide cohort study by retrieving all patients receiving hypertension medications, including RAAS blockade from Taiwan’s National Health Insurance Research Database (NHIRD). The NHIRD has been described in detail in previous studies.[20-22] In brief, it consists of detailed health care data from >23 million enrollees, representing >99% of Taiwan’s entire population. For the purpose of patient privacy protection, our data sources were de-link and de-identify data; however, this study also has been approved by the ethical review board of the Taipei Medical University, Taiwan (certificate no.: N201704037).

2.2. Study cohorts

From the longitudinal health database (n = 1,000,000), patients who were newly diagnosed as hypertension (International Classification of Disease, 9th Revision; ICD-9 Codes 401 or 402) were selected initially (n = 206,077) (Fig. 1). Within these patients, those who fulfilled 2 criteria below will be eligible for further study (n = 169,294): First, hypertension was diagnosed in at least 2 outpatient clinic records or at least 1 inpatient clinic record; second, patients who had received at least 2 times for prescription of anti-hypertension medication. Among these patients, those who were >40 years old and newly diagnosed to have hypertension between January 1, 2000 and December 31, 2008 were enrolled into the study cohort (n = 71,001). We further excluded subjects already had any RAAS blockade prescriptions

Figure 1. Study cohort creation. Using the Taiwan Health Insurance Database (from 2000 to 2008), we assessed the occurrence of osteoporotic fractures in patients who either were or were not taking RAAS blockade agents. A Cox proportional hazards regression model was used to evaluate the incidence of osteoporotic fractures after adjusting for known confounding factors. RAAS = renin–angiotensin–aldosterone system.
within 6 months before the date of cohort enter, and also subjects with any inpatient or outpatient diagnosis related to osteoporosis before the date of cohort enter. RAAS blockers include all kinds of angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), and mineralocorticoid receptor antagonist (MRA) that could be prescribed in Taiwan. The final controlled cohort (n = 57,132) would be further divided into 2 subgroups according to the usage of RAAS blockade medications. Patients who use RAAS blockers for $< 0.56$ days were defined as RAAS blocker non-user. Information regarding patients’ medications was retrieved from the pharmacy prescription database. Reliability of the retrieved information was verified independently by statistician. For each drugs of prescription, the number of days of drug use was calculated. Then, the numbers of days of drug use for each prescription were added together to determine the total number of days of drug use.

### 2.3. Main outcome measurements

The main outcome of our study includes patients who had osteoporosis fracture. In clinical practice, events of osteoporotic fracture was usually defined by: First, diagnosis of osteoporosis (ICD-9 733.0) with the dual-energy x-ray absorptiometry T score $< -2.5$, and also second, at least 1 fracture site recorded. In addition, according to the regulations of Taiwan, the osteoporosis medications would not be reimbursed by health insurance bureau of Taiwan until the diagnosis of osteoporosis fracture was made (National Health insurance administration; http://www.nhi.gov.tw). Thus in our study cohort, subjects with osteoporosis fracture was selected by both osteoporosis diagnosis (ICD-9 733.0) and usage of osteoporosis medications, which may include alendronate, estrogen receptor modular, parathyroid hormone, bisphosphate, selenium, monoclonal antibody for receptor activator of NF-$k$B ligand (RANKL).

We used the incident user design with follow-up for each patient beginning on the date of first prescription of RAAS blockers in the treated cohort. The follow-up for the untreated cohort began on the first day after the index diagnosis of hypertension. All cohorts were followed up until the date of the diagnosis of osteoporosis fracture, or the end of 2008. For subjects who had dropped out from the insurance would become the censored data.

### 2.4. Covariate assessment

Propensity score was calculated using logistic regression as proposed by Rosenbaum and Rubin\(^{[2,3]}\) to estimate the probabilities of assigning a patient to the treated cohort given the background variables including age, sex between groups taking, or not taking RAAS blockers. The adjusted comorbidities included chronic obstructive pulmonary disease (COPD), asthma, received sphingo-oophrectomy, malignancy, medications including steroid drugs, hormone replacement, diuretic, $\beta$-blocking agents, calcium channel blockers, and other classes of hypertension medications were listed in Table 1. The mean and

| Table 1: Characteristic of the sample population. |
|------------------------------------------------|
| **Whole cohort** (n = 57,132) | **RAAS blocker non-user** (< 0.56 days, n = 28,740) | **RAAS blocker user** ($\geq$ 0.56 days, n = 28,392) |
|---------------------------------|-----------------|-----------------|
| Age, y (mean ± SD) | 59.71 (10.42) | 59.71 (10.62) | 59.71 (10.22) |
| Gender | | | |
| Female | 25,440 (44.53) | 13,322 (46.35) | 12,118 (42.68) |
| Male | 31,692 (55.47) | 15,418 (53.65) | 16,274 (57.32) |
| Comorbidities | | | |
| COPD | 18,112 (31.70) | 8585 (29.87) | 9527 (33.56) |
| Asthma | 11,439 (20.02) | 5572 (19.39) | 5867 (20.66) |
| Received sphingo-oophrectomy | 10,132 (17.73) | 5426 (18.88) | 4706 (16.58) |
| Malignancy | 7648 (13.39) | 3844 (13.38) | 3804 (13.40) |
| Steroid drug | | | |
| Never use | 34,401 (60.21) | 18,102 (62.99) | 16,299 (57.41) |
| < 0.56 days | 18,522 (32.42) | 8825 (30.71) | 9697 (33.15) |
| $\geq$ 0.56 days | 4209 (7.37) | 1813 (6.31) | 2396 (8.44) |
| Hormone replacement drug | | | |
| Never use | 50,389 (88.20) | 25,382 (88.32) | 25,007 (88.08) |
| < 0.56 days | 2818 (4.93) | 1460 (5.08) | 1358 (4.78) |
| $\geq$ 0.56 days | 3925 (6.87) | 1898 (6.60) | 2027 (7.14) |
| Diuretics | 21,995 (38.50) | 6736 (23.44) | 15259 (53.74) |
| $\beta$-Blockers | 25,666 (44.32) | 10,915 (37.98) | 14751 (51.95) |
| Calcium channel blockers | 34,666 (61.20) | 14,711 (51.19) | 20255 (71.34) |
| Other-hypertension medications | 7609 (13.32) | 2934 (10.21) | 4675 (16.47) |
| Level of urbanization | | | |
| Urban | 41,307 (72.30) | 20,523 (71.41) | 20,784 (73.20) |
| Suburban | 11,089 (19.41) | 5661 (19.70) | 5428 (19.12) |
| Rural | 25,001 (43.80) | 12,598 (43.69) | 12,403 (43.51) |
| Monthly income (NT$) | | | |
| 0 | 4574 (8.01) | 2259 (7.86) | 2315 (8.15) |
| 1–20,100 | 14,539 (25.45) | 7083 (24.65) | 7456 (26.26) |
| 20,101–30,000 | 20,121 (35.22) | 10,595 (36.86) | 9526 (33.55) |
| $\geq$ 30,001 | 17,898 (31.33) | 8803 (30.63) | 9095 (32.03) |

RAAS = renin-angiotensin-aldosterone system.

*Comparison between RAAS non-users and RAAS users.
2.5. Statistical analysis

To determine the independent risk factors for osteoporosis fracture, multivariable analysis based on age and gender using hazard ratios (HRs) were carried out with modified Cox proportional hazards models after adjusting for propensity score. To assess the dose-dependent effect of RAAS blockers on future osteoporosis fracture, we further conducted the multivariable analysis and use the duration of RAAS blockers prescription as a continuous variable. On multivariable stratified analyses, the association between the duration of RAAS blockers use and the risk of future osteoporosis fracture was examined in patients with hypertension. All subgroup comparisons of comorbidity and related medications were to control for potential confounding factors reported in previous studies. All data management was performed using SAS9.2 software (SAS Institute Inc.). Calculations of cumulative incidences and Cox models in the competing risk analysis were calculated and results were expressed as the estimated number together with the 95% confidence interval (CI).

3. Results

3.1. Demographic characteristics of the hypertension cohort

Table 1 lists the demographic characteristics, including age, gender, comorbid illness, and concurrent medications. In total, 57,132 eligible hypertension patients were included in the study cohort. Among the cohort, we excluded 10,059 patients who had inpatient or outpatient diagnosis related to osteoporosis before the date of cohort enrollment. In addition, 3810 patients who received any RAAS prescription within 6 months before the date of cohort enter were also excluded. A total of 28,740 RAAS blocker non-users and 28,392 RAAS blocker users were identified for the participation of the tested cohort. In our cohort, the RAAS blocker user group had significant higher incidence of older subjects, taking various kinds of hypertensive drugs, including diuretics, β-blockers, and calcium channel blockers, and prevalence of COPD and asthma, taking steroid or hormone replacement therapy (P < 0.001), but significant lower incidence of female gender (P < 0.001). In addition, significantly, more subjects with higher income and resided in urban area were in the user group (P < 0.001).

3.2. Risk of osteoporosis fracture among RAAS blockers user and non-user

Osteoporosis fracture events in study cohort (n=57,132) from January 1, 2001 to December 31, 2008, in Taiwan was showed as Fig. 2. Those who using RAAS blockers >56 days before osteoporosis fracture in comparison with RAAS blocker non-users were examined for risk of osteoporosis fracture (Table 3). After confounding for age, gender, comorbid illness and comedication; the future incidence of osteoporosis fracture in the whole cohort was significantly higher in the RAAS blockers non-user group than the user group (adjusted HR 0.66, 95% CI 0.59–0.75, P < 0.001). Female had higher risk for osteoporotic fracture than male in our cohort, and the usage of RAAS blockers had significantly lower future fracture incidence in both sex (adjusted HR 0.56, 95% CI 0.43–0.72, P < 0.001 for male; adjusted HR 0.68, 95% CI 0.59–0.78, P < 0.001 for female). When taking age into consideration, all the age categories (45–54, 55–64, 65–74, ≥75) showed the concordant reduction of future osteoporotic fracture in RAAS user group (45–54, adjusted HR 0.48, 95% CI 0.30–0.79, P < 0.001; 55–64, adjusted HR 0.70, 95% CI 0.54–0.91, P < 0.001; 65–74, adjusted HR 0.64, 95% CI 0.53–0.77, P < 0.001; ≥75, adjusted HR 0.62, 95% CI 0.50–0.78, P < 0.001). In addition, in the relative younger patents, the magnitude of reduction in future osteoporosis fracture seems even greater in RAAS blocker user (adjusted HR 0.48, 95% CI 0.3–0.79, P < 0.05).

3.3. Sensitivity analysis

When adjusted by the incidence of osteoporosis fracture in RAAS blocker non-user cohort, sensitivity analysis demonstrated the concordant lower incidence of future osteoporosis fracture in RAAS blockers user groups with different drug usage durations.
Whole cohort 835 657.9 (613.3, 702.5) 442 285.5 (258.9, 312.1) 0.66 (0.59, 0.75)

Blockers, male seem to improve disease prognosis.[24] Other than the more well-known RAAS blockers had been demonstrated their effects in patients undergoing pathological consequence in different tissues,[18] including bone which could mediate important physiological stimuli and result in osteoporosis fracture risk may also be observed: the relative risk for future osteoporosis came from several cell and animal studies; in aging mice, elevated local RAAS activation was proved by the highly expressed mRNA of renin, angiotensinogen, and peptides of angiotensin II in their tibia and femur tissue.[26] Shimizu et al[19] in their study showed that the expression of angiotensin II receptors was observed in cultured osteoblasts. By activating AT1R, angiotensin II induced the expression of the RANKL in osteoblasts in cell culture system and in ovariectomized mice, which might lead to the activation of osteoclasts and bone resorption. In other studies, angiotensin II acts through AT1R to inhibit osteoblast differentiation and bone formation in rat calvarial osteoblastic cells.[27–29]

By far, there was still limited clinical evidence addressed on the possible benefit of RAAS blockade to prevent osteoporosis and its related complications, and some of the results are not concordant and even controversy, which may due to study design and ethnic groups involved. A cross-sectional clinical study had shown that use of ACEI was associated with higher bone mineral density (BMD) in Chinese hypertensive subjects aged 65 years above.[30] Another case–control study showed that ACEI treatment was associated with a small but significant reduced risk of fracture by 7%.[31] However, Kwok et al[32] in a US study showed that using ACEI correlated with a small but significant increase bone loss at hip; however, ARB will not result in bone loss. Our study, based on the national cohort data bank of Taiwan, showed the association between RAAS blockade usage and future osteoporosis fracture in hypertensive patients.

One may also ask whether ACEI, ARB, and MRA, which all belong to the RAAS blockade family, should share the same association with future osteoporotic fracture risk reduction in hypertensive subjects. Unfortunately, our current study is not able to examine the fracture risks for ACEI, ARB, and MRA users, respectively. Because of the high exchange frequency of these drugs in a same person, it is hard to tell the ratio of contribution between ACEI, ARB, and MRA on RAAS blockade in our study. Some other previous western study may provide us some clues. Solomon et al[33] using the Medicare beneficiaries data bank showed that, when compared with CCB, ARBs usage but not ACEI had the lower risk of fracture in patients older than 65 years old. Ruths et al in their large cohort study in Norway
Main model is adjusted for age, sex, COPD, asthma, syndrome or sphingo-oophrectomy, malignancy, steroid drug, hormone replacement drug, diuretics, **∗∗∗ P < 0.001.

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4.1. Limitations and weaknesses

Although our study has demonstrated the association between RAAS blockade and future osteoporotic fracture risk in the hypertension population, there are still limitations: first, this is a data-bank based cohort study, to examine the actual potentials of RAAS blockade for osteoporotic fracture prevention, further randomized control trial should be designed to prove this point-of-view; second, we did not examine the individual association between ACEI, ARB, MRA, and risk of further fracture, future specified studies could be designed aimed to answer this issue; third, due to the restriction of the data-bank resource, we were not able to further analysis the site of osteoporotic fracture; and fourth, due to the restriction of the data-bank resource, we were not able to disclose the prevalence of calcium channel blockers or β-blockers treatment could still have the potential to prevent further osteoporotic fracture.

Although early detection and treatment of osteoporosis and related complications are reasonable and important, still a lot percentage of eligible population remain untreated. Even after the release of evidence-based guidelines in women and experience consensus of experts in men for osteoporosis, the rate of evaluation and treatment for osteoporosis in older individuals with fracture still far lag behind guideline recommendations. One study raised by Feldstein et al showed that in women with fractures, only 8.4% had received BMD measurement and 42.4% received any treatment during the first 2 years, and the rate BMD measurement decline significantly with age in women. In men with fracture, only 1.5% had BMD measurement and only 2.8% received any treatment. Reasons that result in the low penetration rate for osteoporosis detection and related complication treatment are multiple, which might involve the combination issues between patent, clinician, health care system, expense and also medical accessibility. RAAS blockers have been widely used in patients with hypertension and cardiovascular disease not only due to their protective effects on renal and cardiovascular system, but also because of their wide safety profiles. RAAS blockers are also relatively cheaper than the current medications for osteoporosis treatment. If RAAS blocker could be one of the drug of choice for osteoporosis, the penetration rate for osteoporosis treatment in the fracture potential groups should be much higher.

5. Conclusions

Our data bank cohort study demonstrated that RAAS antagonist treatment in hypertensive group is associated with significant lower future osteoporotic fractures risk. We need further placebo-controlled study to investigate the osteoporosis fracture prevention potential of RAAS blockers.

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