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

A population-based cohort study in Taiwan

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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-κB 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

Editor: Masanari Kuwabara.

This work was supported by Taipei Medical University (TMU-NTUST-105-03) in Taiwan.

The authors report no conflicts of interest.

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Medicine (2017) 96:46(e8331)

Received: 1 May 2017 / Received in final form: 15 August 2017 / Accepted: 7 September 2017

http://dx.doi.org/10.1097/MD.0000000000008331

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.[5,6] 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

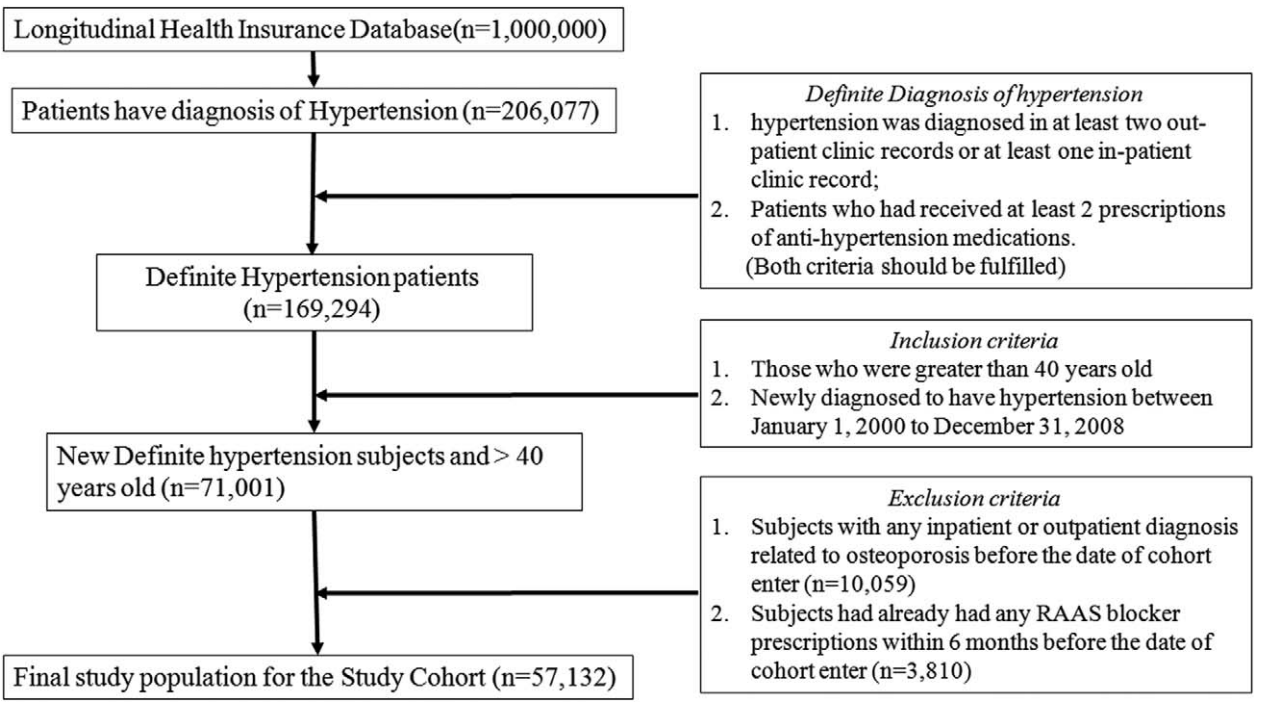

Figure 1. Study cohort creation. Using the Taiwan Health Insurance Database (from 2000 to 2008), we assessed the occurrence of osteoporotic fractures in patients who either were or were not taking RAAS blockade agents. A Cox proportional hazards regression model was used to evaluate the incidence of 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 <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, biphosphnate, selenium, monoclonal antibody for receptor activator of NF-κB 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[23] 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, β-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 (<56 days, n = 28,740)		RAAS blocker user (≥56 days, n = 28,392)		
	n	%	n	%	n	%	P*
Age, y (mean ± SD)	59.71 (10.42)		59.71 (10.62)		59.71 (10.22)		0.988
40–54	23,683	41.45	12,105	42.12	11,578	40.78	<0.001
55–64	15,965	27.94	7859	27.35	8106	28.55	
65–74	11,994	20.99	5839	20.32	6155	21.68	
≥75	5490	9.61	2937	10.22	2553	8.99	
Gender							
Female	25,440	44.53	13,322	46.35	12,118	42.68	<0.001
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	<0.001
Asthma	11,439	20.02	5572	19.39	5867	20.66	<0.001
Received sphingo-oophrectomy	10,132	17.73	5426	18.88	4706	16.58	<0.001
Malignancy	7648	13.39	3844	13.38	3804	13.40	0.936
Comedications							
Steroid drug							
Never use	34,401	60.21	18,102	62.99	16,299	57.41	<0.001
<56 days	18,522	32.42	8825	30.71	9697	34.15	
≥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	0.014
<56 days	2818	4.93	1460	5.08	1358	4.78	
≥56 days	3925	6.87	1898	6.60	2027	7.14	
Diuretics	21,995	38.50	6736	23.44	15,259	53.74	<0.001
β-Blockers	25,666	44.92	10,915	37.98	14,751	51.95	<0.001
Calcium channel blockers	34,966	61.20	14,711	51.19	20,255	71.34	<0.001
Other-hypertension medications	7609	13.32	2934	10.21	4675	16.47	<0.001
Level of urbanization							
Urban	41,307	72.30	20,523	71.41	20,784	73.20	<0.001
Suburban	11,089	19.41	5661	19.70	5428	19.12	
Rural	4736	8.29	2556	8.89	2180	7.68	
Monthly income (NT$)							
0	4574	8.01	2259	7.86	2315	8.15	<0.001
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	
≥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.

Table 2

Two years comparison of fracture incidence of renin–angiotensin–aldosterone system non-user and user.

Groups	First year follow-up			Second year follow-up		
	N at risk	N of event	Incident rate	N at risk	N of event	Incident rate
RAAS blocker non-user	27288.500	284	0.0104	23943.000	159	0.006641
RAAS blocker user	27793.500	35	0.0013	26253.500	71	0.002704

RAAS = renin–angiotensin–aldosterone system.

median propensity scores were compared between RAAS blockers users and non-users. The age group were stratified as 45 to 54, 55 to 64, 65 to 74, and older than 75 of age. In addition, gender was adjusted to differentiate the male from the female population (Table 2).

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 comedications; 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

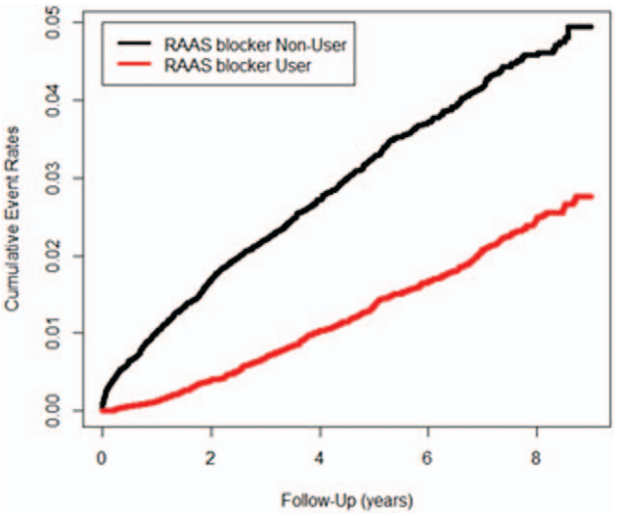

Figure 2. Osteoporosis fracture events in Study Cohort (n = 57132) from January 1, 2001 to December 31, 2008, in Taiwan, stratified by RAA status (log-rank test, $\chi^2=206$; df = 1; $P<0.001$). RAA = renin–angiotensin–aldosterone.

Table 3

Risk of osteoporosis fracture among renin–angiotensin–aldosterone system blocker user and renin–angiotensin–aldosterone system blocker non-user in study cohort.

	RAAS blocker non-user (total follow-up 126914.8 person-years)		RAAS blocker user (total follow-up 154802.2 person-years)		
All Group (n = 105,576)	No. of Patients With Fracture	Incidence Rate (per 10^5 person-years), (95% CI)	No. of Patients With Fracture	Incidence Rate (per 10^5 person-years), (95% CI)	Adjusted HR[#] (95% CI)
Whole cohort	835	657.9 (613.3, 702.5)	442	285.5 (258.9, 312.1)	0.66 (0.59, 0.75)***
Age, y					
45–54[*]	61	115.3 (86.4, 144.2)	25	40.9 (24.8, 56.9)	0.48 (0.30, 0.79)**
55–64[†]	158	445.0 (375.6, 514.4)	106	235.4 (190.6, 280.3)	0.70 (0.54, 0.91)**
65–74[‡]	339	1262.5 (1128.1, 1396.9)	191	540.9 (464.2, 617.6)	0.64 (0.53, 0.77)***
≥75[§]	277	2376.7 (2096.8, 2656.6)	120	902.4 (740.9, 1063.9)	0.62 (0.50, 0.78)***
Gender					
Female[‖]	643	1073.4 (990.4, 1156.4)	345	510.3 (456.4, 564.1)	0.68 (0.59, 0.78)***
Male[¶]	192	286.5 (246.0, 327.0)	97	111.3 (89.1, 133.4)	0.56 (0.43, 0.72)***

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, RAAS = renin–angiotensin–aldosterone system.

[*] Total follow-up 52904.8 person-year for RAAS Non-User and 61170.1 for RAAS User.

[†] Total follow-up 35503.1 person-year for RAAS Non-User and 45020.3 for RAAS User.

[‡] Total follow-up 26852.1 person-year for RAAS Non-User and 35313.9 for RAAS User.

[§] Total follow-up 11654.8 person-year for RAAS Non-User and 13297.9 for RAAS User.

[‖] Total follow-up 59903.6 person-year for RAAS Non-User and 67613.8 for RAAS User.

[¶] Total follow-up 67011.1 person-year for RAAS Non-User and 87188.4 for RAAS User.

[#] Main model is adjusted for age, sex, COPD, asthma, syndrome or sphingo-oophrectomy, malignancy, steroid drug, hormone replacement drug, diuretics, β-blockers, calcium channel blocker, other hypertensive drugs, level of urbanization, monthly income in propensity score.

(56–90 days, adjusted HR 0.77, 95% CI 0.62–0.96, $P < 0.001$; 91–365 days, adjusted HR 0.81, 95% CI 0.69–0.96, $P < 0.001$); and the treated cohort of >365 days had the most significant reduction (adjusted HR 0.44, 95% CI 0.37–0.52, $P < 0.001$) when compared with the non-user cohort (Table 4). Further stratified analysis according to age, gender, comorbid illness and comedication, with the exception of subjects took only few hormone replacement therapy (<56 days), showed that subjects using RAAS blockers >365 days would have the lowest osteoporotic fracture incidence. Some other trends of reduction in osteoporosis fracture risk may also be observed: the relative younger group (45–54) may have lower incidence than the other age groups, and although both gender may benefit from RAAS blockers, male seem to benefit more.

4. Discussion

Our study demonstrates that in hypertensive subjects over 40-year-old, who receive long-term treatment with RAAS blockers >1 year has lower risk of future osteoporotic fracture. The associations between RAAS blockers usage and future osteoporosis fracture reduction were shown in different subgroups, which were stratified by age, gender, different osteoporosis-related comorbid illnesses, or comedications.

In addition to the successful treatment efficacy in hypertension, RAAS blockers had been demonstrated their effects in patients with heart failure, myocardial infarction, coronary artery disease, chronic kidney disease, and high global cardiovascular risk to improve disease prognosis.[24] Other than the more well-known systemic RAAS activations, the local or tissue RAAS activation also plays important roles via the paracrine or endocrine effects, which could mediate important physiological stimuli and result in pathological consequence in different tissues,[18] including bone and osteoporosis.[25] Among the family membranes of tissue RAAS identified, angiotensin II take the most important role and was demonstrated to exert its effect mostly via the angiotensin II receptor type 1 (AT1R).[18]

The possible links between tissue RAAS activations and 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 little 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 lower future osteoporosis fracture in hypertensive population.

One may also ask whether ACEI, ARB, and MRA, which all belongs 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

Table 4

Sensitivity analysis of adjusted hazard ratios of renin–angiotensin–aldosterone system blocker in risk reduction of osteoporosis fracture.

		RAAS blocker user			
	RAAS blocker non-user Adjusted HR (95% CI)	56–90 days Adjusted HR (95% CI)	days Adjusted HR (95% CI)	>365 days Adjusted HR (95% CI)	*P* for trend
Main model†	1.00	0.77 (0.62, 0.96)*	0.81 (0.69, 0.96)*	0.44 (0.37, 0.52)***	<0.001
Subgroup effects					
Age, y					
45–54	1.00	0.70 (0.30, 1.63)	0.67 (0.36, 1.27)	0.24 (0.11, 0.53)***	<0.001
55–64	1.00	1.18 (0.79, 1.78)	0.71 (0.49, 1.03)	0.49 (0.35, 0.69)***	<0.001
65–74	1.00	0.59 (0.40, 0.86)**	0.85 (0.67, 1.08)	0.40 (0.30, 0.52)***	<0.001
≥75	1.00	0.75 (0.50, 1.12)	0.71 (0.52, 0.96)*	0.44 (0.32, 0.62)***	<0.001
Sex					
Female	1.00	0.79 (0.61, 1.01)	0.84 (0.70, 1.01)	0.46 (0.38, 0.56)***	<0.001
Male	1.00	0.68 (0.43, 1.09)	0.68 (0.48, 0.96)*	0.35 (0.25, 0.51)***	<0.001
COPD					
No	1.00	0.72 (0.54, 0.95)*	0.75 (0.61, 0.93)**	0.42 (0.33, 0.52)***	<0.001
Yes	1.00	0.85 (0.60, 1.22)	0.89 (0.69, 1.15)	0.46 (0.45, 0.60)***	<0.001
Asthma					
No	1.00	0.73 (0.57, 0.94)*	0.80 (0.67, 0.96)*	0.45 (0.37, 0.55)***	<0.001
Yes	1.00	0.91 (0.58, 1.43)	0.85 (0.61, 1.18)	0.38 (0.26, 0.56)***	<0.001
Syndrome or sphingo-oophrectomy					
No	1.00	0.81 (0.64, 1.02)	0.77 (0.65, 0.93)**	0.43 (0.35, 0.52)***	<0.001
Yes	1.00	0.58 (0.32, 1.04)	0.97 (0.68, 1.38)	0.45 (0.29, 0.68)***	<0.001
Malignancy					
No	1.00	0.80 (0.63, 1.01)	0.82 (0.68, 0.97)*	0.46 (0.38, 0.55)***	<0.001
Yes	1.00	0.58 (0.30, 1.10)	0.77 (0.52, 1.14)	0.33 (0.21, 0.52)***	<0.001
Steroid drug					
Never use	1.00	0.64 (0.48, 0.86)**	0.76 (0.62, 0.94)*	0.44 (0.35, 0.55)***	<0.001
<56 days	1.00	0.96 (0.65, 1.41)	0.87 (0.65, 1.17)	0.42 (0.31, 0.58)***	<0.001
≥56 days	1.00	1.08 (0.57, 2.05)	0.87 (0.54, 1.42)	0.44 (0.26, 0.75)**	0.005
Hormone replacement drug					
Never use	1.00	0.73 (0.57, 0.93)**	0.82 (0.69, 0.97)*	0.43 (0.36, 0.52)***	<0.001
<56 days	1.00	1.46 (0.68, 3.13)	0.73 (0.35, 1.53)	0.53 (0.25, 1.13)	0.092
≥56 days	1.00	0.77 (0.33, 1.78)	0.75 (0.40, 1.39)	0.36 (0.18, 0.72)**	0.004
Other hypertensive drugs					
No (<56 days)	1.00	0.74 (0.58, 0.93)*	0.82 (0.69, 0.98)*	0.46 (0.38, 0.55)***	<0.001
Yes (≥56 days)	1.00	1.03 (0.54, 1.97)	0.77 (0.47, 1.25)	0.37 (0.23, 0.59)***	<0.001
Diuretics					
No (<56 days)	1.00	0.62 (0.47, 0.83)***	0.83 (0.67, 1.02)	0.43 (0.33, 0.56)***	<0.001
Yes (≥56 days)	1.00	1.11 (0.78, 1.59)	0.77 (0.59, 1.01)	0.40 (0.31, 0.52)***	<0.001
β-Blockers					
No (<56 days)	1.00	0.64 (0.48, 0.84)**	0.79 (0.65, 0.97)*	0.40 (0.31, 0.51)***	<0.001
Yes (≥56 days)	1.00	1.07 (0.74, 1.55)	0.86 (0.66, 1.13)	0.50 (0.38, 0.64)***	<0.001
Calcium channel blockers					
No (<56 days)	1.00	0.71 (0.52, 0.96)*	0.71 (0.55, 0.91)**	0.31 (0.23, 0.43)***	<0.001
Yes (≥56 days)	1.00	0.86 (0.62, 1.18)	0.87 (0.70, 1.08)	0.48 (0.38, 0.59)***	<0.001

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, RAAS = renin–angiotensin–aldosterone system.

* $P<0.05$.

** $P<0.01$.

*** $P<0.001$.

† Main model is adjusted for age, sex, COPD, asthma, syndrome or sphingo-oophrectomy, malignancy, steroid drug, hormone replacement drug, diuretics, β-blockers, calcium channel blocker, other hypertensive drugs, level of urbanization, monthly income in propensity score.

showed that all kinds of hypertension medication may prevent hip fracture except loop diuretics and ACEI in patients older than 80s. And another cohort study in the United States by Kwok et al,[34] on older hypertensive men reported that ARB users had lower risk of fracture than ACEI users.

Several other well-known osteoporosis risk factors or treatment modality may also exert their pro-osteoporosis or anti-osteoporosis effects via the modulations on RAAS activity. Vitamin D could inhibit renin gene transcription and inhibit RAAS activity[35] and the inverse correlation between serum vitamin D level and circulating RAAS activity had also been demonstrated[36,37]. In addition, regular exercise could inhibit tissue RAAS and inhibit future osteoporosis[38–40]. On the contrary, cortisol[41] and obesity may increase tissue RAAS activity. Use of RAAS blockade on patients taking steroid could also prevent further osteoporotic fracture in our studies. Based on our current study results and previous literatures; we may suggest that RAAS activation could possibly play an important role in the pathogenesis of osteoporosis and further fracture complications. Other than the RAAS blockers, several kinds of hypertensive medications had also been demonstrated to prevent osteoporosis and fracture: thiazide diuretics are thought to be protective against bone loss by reducing urinary calcium excretion. Thiazide use in several epidemiology study had been shown to reduce

facture risk.[42,43] In addition, sympathetic nervous system could regulate bone mass[44,45] and osteoblast growth[46,47] mainly via β-2 adrenergic receptors (β2AR) activation.[48] Use of β-blockade may overcome the loss of bone mass in postmenopausal women[49], thereby keeping higher BMD[50] and preventing further osteoporotic fracture.[43,51] The hypertensive cohort we enrolled also included those who take diuretics and β-blockers. Our sensitivity analysis showed that RAAS inhibition on top of diuretics, 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.[52] 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.

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 deigned 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; fourth, we are not able to disclose the prevalence of calcium supplement and vitamin D3 supplements usage in our study cohort, because these drugs belongs to over-the-counter prescription in Taiwan; fifth, we only enrolled subjects with hypertension, the potential osteoporosis fracture prevention benefit of RAAS blockade in normotensive subjects need further study; sixth, physical activity, body mass index, and smoking behavior were not able to be disclosed in the data-bank; and finally, direct renin inhibitors, although also conceptually involved in the RAAS inhibition system, was not enrolled in our study, because it was not until 2009 did physicians in Taiwan started to prescribe direct renin inhibitors.

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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