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Renin-angiotensin system antagonists and mortality due to pneumonia, influenza, and chronic lower respiratory disease in patients with hypertension

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ABSTRACT

BACKGROUND It is controversial whether angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEI/ARB) have a potentially beneficial role in the respiratory system. This study investigated the association between ACEI/ARB medications and respiratory-related mortality in hypertensive patients in a real-world nationally representative cohort.

METHODS This was a retrospective analysis based on a prospective cohort study. A total of 10,530 patients with hypertension aged ≥ 20 years were included. The data was extracted from the US National Health and Nutrition Examination Survey during 1988–1994 and 1999–2006. The study was approved by the Institutional Review Boards. Moreover, inform concent was taken form all the participants.

RESULTS Overall, 27.7% (n = 2920) patients took ACEI/ARB agents. During a median follow-up of 12.4 years, 278 individuals died of respiratory disease, including chronic lower respiratory disease (n = 155) and influenza or pneumonia (n = 123). Compared with the patients without ACEI/ARB use, those taking ACEI/ARB were not associated with respiratory-specific mortality in a multivariable-adjusted Cox model. After 1: 1 matching, taking ACEI/ARB was also not related to respiratory mortality (Hazard ratio (HR) = 1.07, 95% CI: 0.79–1.43), influenza- or pneumonia-related (HR = 1.00, 95% CI: 0.65–1.54) and chronic pulmonary mortality (HR = 1.13, 95% CI: 0.75–1.69). After separating ACEI and ARB from anti-hypertensive medications, those associations remained unchanged.

CONCLUSIONS We discovered no significant link between ACEI or ARB medication and pulmonary-related mortality in hypertensive patients. In hypertensive patients, standard ACEI/ARB administration may have little effect on the respiratory system.

The renin-angiotensin system (RAS) has established a vital role in maintaining blood pressure and fluid homeostasis.[1] Angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor blockers (ARB), targeting RAS, have been used in clinical practice as first-line therapy for anti-hypertension and improving cardiac remodeling.[2] Moreover, local RAS in lung tissue is implicated in regulating inflammation, fibrosis, and proliferation in various pulmonary diseases, such as pneumonia, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), and idiopathic pulmonary disease.[1,3] Particularly, Angiotensin-converting enzyme (ACEII), a distinctive homolog of ACE, acts as a natural brake for the classic RAS pathway to relax vessels and protect the respiratory system.[4] ACEI/ARB medications may increase ACEII expression.[5] Furthermore, bradykinin and substance P stimulate the cough reflex and sensitize the sensory nerves of the tracheobronchial airways, possibly protecting against pulmonary infection.[6] These links indicate

that ACEI/ARB medications may have additional benefits for the respiratory system.

Clinical trials and clinical practice have now confirmed the cardiovascular benefits of RAS inhibitors. Some studies have evaluated the associations between risk of respiratory disease or death and use of ACEI/ARBs, whereas inconsistent results were mixed. Several large-scale retrospective studies supported the potentially beneficial role of ACEI/ARBs in the reduced risk of incident sepsis and all-cause mortality in patients with chronic obstructive pulmonary disease (COPD), as well as the reduced mortality in patients with sepsis.[7,8] By contrast, several observational studies noted a neutral relationship between ACEI/ARB therapy and pneumonia risk in general populations of older adults.[9–12] According to experimental research, RAS blocker treatment consistently reduced systemic inflammation but did not mitigate lung inflammation in the COPD mice model.[13] Unexpectedly, a recent placebo-controlled, double-blind, randomized trial firstly demonstrated that ACEI administration decreased, but didn't improve, the exercise capacity in patients with COPD.[14] Coronavirus disease 2019 (COVID-19) and influenza spreaded across the world. Individuals on ACEI/ARB therapy were thought to be more susceptible to coronavirus and influenza virus infection.[4] However, recent cross-sectional studies demonstrated no robust relationship between ACEI/ARB administration and risks of COVID-19 infection or mortality during hospitalization.[2,5,15,16] Therefore, it remains necessary to investigate whether ACEI/ARBs therapy has an additional protective effect on the respiratory system when administrated in cardiovascular practice. RAS blockers are frequently prescribed to hypertensive patients. In this study, we aim to evaluate whether the use of ACEI/ARBs is associated with the risk of mortality caused by pneumonia, influenza, and chronic lower respiratory disease in hypertensive patients.

METHODS

Data Source and Study Population

This was a retrospective analysis based on a prospective cohort study, the US National Health and Nutrition Examination Survey (NHANES) linked to the National Death Index (NDI) was conducted. As described in our previous reports,[17,18] the NHANES survey was a stratified, multi-stage probability sampling to represent the non-institutionalized civilians of all ages in the US. Data from two parts of the NHANES surveys were used: NHANES III (1986–1994) and continuous NHANES (1999 to 2006). Among the 75,468 participants aged ≥ 20 years, 11,828 adults were diagnosed with preexisting hypertension. In this study, individuals with lung cancer (n = 41), emphysema (n = 387), congestive heart failure (n = 866), and loss of follow-up for mortality status (n = 4) were excluded. Finally, 10,530 individuals were available for analysis (Figure 1). The National Center for Health Statistics' Institutional Review Boards approved the study's protocol.[19] All participants provided informed consent, and information in detail was available at http://www.cdc.gov/nchs/nhanes/irba98.htm.

Antihypertensive Medications

At baseline, during personal interviews, NHANES participants were asked about prescription medicines they had taken in the previous 30 days. Names of prescription drugs were recorded according to the medication container label. Each medication was linked to a generic prescription medication name that was standardized.[19] Antihypertensive drugs were classified as ACEIs, ARBs, beta-blockers, calcium-channel blockers, diuretics, and others. Vascular smooth muscle relaxants, central and peripheral antiadrenergic agents, and renin inhibitors were among the other blood pressure-lowering medications. Table S1 contains a list of ACEI and ARB medications.

Covariates

General information on age, sex, race/ethnicity, smoking status, and drink was recorded using standardized questionnaires during the interview.[18] Alcohol consumption (g/day) was estimated via a frequency questionnaire of alcoholic drinks over the past year. One drink that is equal to 12-oz beer, 4-oz wine, or 1 ounce of liquor covers approximately 10 g of alcohol.[17] The Mobile Examination Center (MCE) used standardized procedures to conduct physical examinations and collect biospecimens. Blood pressure was calculated as the mean of three

eligible readings. Body mass index (BMI) was calculated from weight (in kilograms) divided by height (in meters) squared. Blood tests were carried out in specialized laboratories using standard procedures. High-density lipoprotein cholesterol (HDL-C), glycosylated hemoglobin (HbA1c), and creatinine were available. The estimated glomerular filtration rate (eGFR) was estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Diabetes mellitus was identified by anti-hyperglycemic medication or HbA1c ≥ 6.5%. Prior cardiovascular diseases consisted of self-reported coronary heart disease, myocardial infarction, and stroke. Asthma, chronic bronchitis, and cancer were defined based on the self-reported preceding diagnosis. Lifestyle modification was defined as controlling weight, reducing salt/sodium, exercising more, and reducing alcohol consumption for lowering blood pressure. Inhalant glucocorticoids and bronchodilators were used as chronic respiratory agents (such as methylxanthines, adrenergic agonists, and anticholinergic agents). Non-local glucocorticoids, monoclonal antibodies, calcineurin inhibitors, alkylating agents, antiproliferative agents, and other antitumor cytotoxic drugs were all included in the immunosuppressive agent's category.[2]

Outcomes

In this study, respiratory-related mortality was considered the primary endpoint. All participants were linked to the National Death Index through December 31, 2015, with unique sequence numbers at the National Center for Health Statistics. The follow-up period was defined from baseline until the date of death or the end of follow-up, whichever came first. The underlying cause of death was defined as mortality caused by chronic lower respiratory diseases (J40-J47), Influenza, and pneumonia (J09-J18) by the International Classification of Diseases 10th Revision (ICD-10).

Propensity Score Matching

A propensity score–matching approach was used to balance the baseline differences in patients with hypertension between ACEI/ARB and non-ACEI/ARB groups, including age, sex, race/ethnicity, smoking, alcohol consumption, BMI, systolic and diastolic blood pressure, plasma C reactive protein, high-density lipoprotein-cholesterol, eGFR, diabetes, chronic bronchitis, asthma, cardiovascular disease, cancer, lifestyle modified for lowering blood pressure, β-blockers, calcium-channel blockers, diuretics, other antihypertensive agents, bronchodilators, inhaled glucocorticoids, and immunosuppressive medications. Each individual's propensity score was calculated using logistic regression. Paired patients were selected using the nearest neighbor matching algorithm and non-replacement method with a caliper size of 0.2 standard deviations of the logit of the propensity score.[20] Furthermore, the standardized difference was used to assess the covariate balance between the two groups after matching; covariates with a standardized difference less than 0.01 were considered well-balanced.

Statistical Analysis

Statistical analyses were performed based on the analytic guidelines for the NHANES dataset. All weighted parameters were estimated by the masked variance of the primary sampling unit, pseudo-strata, and appropriate sampling weights.[17] Participants' baseline characteristics were summarised using descriptive analyses based on their ACEI/ARBs use status. The chi-square test and the *t*-test were used to compare categorical and continuous data. Nonparametric imputation was applied to account for missing values based on a random forest model using the R package "mice".[21] Weighted Cox proportional hazards regression was used to estimating the link between the use of ACEI/ARB medications and respiratory-related mortality. The multivariable model was adjusted for those covariates that propensity score matching included. We further analyzed the associations between ACEI or ARB use and mortality separately. Additional analyses were limited to high-risk patients with asthma, bronchitis, or immunosuppressive conditions who were 65 years or older. Excluding the hypertensive patients without lowering blood pressure medication and blood pressure >140/90 mmHg, repeated matching, and analysis were carried out. A 2-sided *P*-value less than 0.05 was regarded as statistical significance. All analyses were conducted using Stata (version 15.0) and R (version 4.0).

RESULTS

Participant Characteristics at Baseline

This study cohort included 10,530 individuals who were diagnosed with preexisting hypertension at baseline during 1986–1994 and 1999–2006. Overall, 27.7% of patients (n = 2920) had ACEI/ARB medications at baseline. Among these patients, ACEI were used by 2284 patients, while ARB medications were used by 677 patients. The baseline characteristics of hypertensive participants with and without the use of ACEI/ARB are presented in Table 1. Patients taking ACEI/ARB were more likely to be older, had a higher body mass index, and had less alcohol or tobacco use. The ACEI/ARB group had a

Table 1 Baseline characteristics of hypertensive patients.

	Non-use (n = 7610)	ACEI/ARB (n = 2920)	P-value
Age, yrs	60.5 ± 12.5	52.7 ± 16.1	0.000
Male, %	44.4	44.5	0.938
Race/ethnicity, %			0.011
Non-Hispanic White	73.9	76.9	
Non-Hispanic Black	14.3	13.4	
Hispanic-Mexican	4.5	3.3	
Other Ethnicity	7.3	6.4	
Smoking status, %			0.000
Never smoking	47.8	49.6	
Former smoker	28.5	36.4	
Current smoker	23.7	14.0	
Alcohol consumption, g/day	5.3 ± 30.5	3.8 ± 9.0	0.016
BMI, kg/m^2	29.7 ± 6.5	31.2 ± 6.7	0.000
Modified lifestyle, %	52.5	59.5	0.000
Systolic BP, mmHg	134.7 ± 19.2	136.5 ± 19.6	0.004
Diastolic BP, mmHg	76.8 ± 12.7	73.1 ± 15.2	0.000
HDL-C, mmol/L	1.3 ± 0.4	1.3 ± 0.4	0.013
C-reactive protein, mg/dL	0.5 ± 0.8	0.6 ± 0.7	0.054
eGFR, mL/min per 1.73 m^2	81.3 ± 22.6	77.7 ± 20.6	0.000
Asthma, %	10.5	12.7	0.027
Chronic bronchitis, %	8.2	8.8	0.410
Cardiovascular diseases, %	9.8	19.8	0.000
Diabetes, %	10.9	24.6	0.000
Cancer, %	11.2	14.0	0.009
Beta-blockers, %	19.5	22.9	0.014
Calcium-channel blockers, %	15.1	25.9	0.000
Diuretics, %	22.6	43.9	0.000
Other antihypertensive drugs, %	6.5	6.6	0.927
Bronchodilators, %	3.1	5.7	0.000
Inhaled glucocorticoids, %	1.0	3.0	0.000
Immunosuppressive agents, %	2.3	3.5	0.018

Data are presented as means ± SD or percent. Missing values: diabetes (n = 5), bronchitis (n = 16), asthma (n = 11), alcohol consumption (n = 1492), BMI (n = 1154), C-reactive protein (n = 1670), HDL-C (n = 1692), and eGFR (n = 1737). ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blockers; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate calculated by CKD-EPI formula; HDL-C: high-density lipoprotein cholesterol.

higher prevalence of chronic diseases, such as diabetes, cardiovascular disease, and cancer, as well as a higher proportion of people taking other antihypertensive medications. After imputation for missing values, the whole characteristics were similar to non-imputation data.

Further analysis of 2881 pairs of hypertension patients who did or did not take ACEI/ARB was undertaken after a 1: 1 ratio matching on the propensity score to explain any confounding factors that might cover the link between using RAS inhibitors and respiratory disease mortality. The difference between each covariate was negligible with standardized differences < 0.1, suggesting that the baseline characteristics between both groups were well-balanced (Table 2). Individually, we matched ACEI and non-ACEI users, as well as ARB users and non-ARB users (Table S2 and S3).

ACEI/ARB Use and Respiratory-Related Mortality

Over a median follow-up of 12.4 years (interquartile range, 9.2–16.7 years), 4789 individuals died. Respiratory diseases (n = 278) claimed the lives of 155 and 123 people, respectively, and included chronic lower respiratory infections, influenza, and pneumonia (unweight). The weighted mortality per 1000 person-years was 1.50 (95% CI: 1.27–1.78) for respiratory-related mortality, 0.91 for chronic pulmonary disease deaths, and 0.59 for respiratory infection mortality (Table 3).

In crude Cox proportional hazards analysis, taking ACEI but not ARB was associated with a higher risk of influenza and pneumonia mortality (HR = 2.19; 95% CI: 1.44–3.34; P < 0.001). However, after adjusting for age, gender, race, lifestyle, comorbidities, an inflammatory biomarker, other antihypertensive agents, respiratory medications, and immunosuppressant drugs, taking ACEI or ARB agents were not significantly associated with increased or decreased respiratory-related mortality among patients with hypertension in Table 3 (HR = 1.29; 95% CI: 0.85–1.96, P = 0.232). Furthermore, after imputation, those associations did not change much. In propensity score-matched analysis, compared with the patients without taking ACEIs/ARBs, the use of RAS blockers exhibited a non-significant association with the death risk of acute and chronic pulmonary diseases (HR = 1.07; 95% CI: 0.79–1.43, P = 0.673). Furthermore, we looked into whether taking an ACEI or an ARB was linked to death from respiratory disease. The relationships with mortality caused by influenza, pneumonia, or chronic lower respiratory disease were also negligible when both ACEI and ARB were included in one model at the same time, independent of imputation.

Additional Analysis

Similar results were found in sensitivity analyses in older patients (Table S4), as well as those with a high risk of respiratory disease mortality, such as asthma, chronic bronchitis, and immunosuppressive drugs (Table S5). Hypertensive patients with medication for decreasing blood pressure had less heterogeneity across the groups with or without ACEI/ARB use; those patients with blood pressure ≤ 140/90 mmHg might have favorable medication compliance. A consistent trend was noted in those participants (Table S6 and S7).

DISCUSSION

In this nationally representative cohort of 10,530 patients with previously diagnosed hypertension, 2920 (22%) participants had ACEI/ARBs treatments. We found no link between renin-angiotensin-system inhibitor use and death from pneumonia, influenza, or chronic lower respiratory diseases. High-dimensional propensity score matching was consistent with the unmatched multivariable analysis. Thus, our results might suggest a minor effect of ACEI/ARBs on the risk of respiratory-specific mortality in hypertensive patients of the real world.

The respiratory system's alveolar macrophages, bronchiolar epithelial cells, endothelial cells, and fibroblasts all expressed AngII and AT1 receptors.[1] Numerous experimental studies reported that the AngII/AT1 axis was involved in cytokine production, inflammatory cell migration, epithelial cell apoptosis, oxidative stress, and fibroblast activation in lung tissue.[1,3] Specifically, ACEII cut an amino acid from AngII and produced the heptapeptide Ang 1–7 to play a favorable effect against AngII/AT1 pathway activation.[1,4] Most deaths due to influenza and pneumonia attacks were associated with induced acute lung injury (ALI) or acute respiratory distress syndrome (ARDS).[1] The previous ex-

Table 2 Characteristics of hypertensive patients with ACEI/ARB use or nonuse before and after matching.

	Before matching			After matching*		
	Non-use (*n* = 7610)	ACEI/ARB (*n* = 2920)	Standardized Difference	Non-use (*n* = 2881)	ACEI/ARB (*n* = 2881)	Standardized difference
Age, yrs	57.5 ± 17.9	64.5 ± 13.5	0.443	65.3 ± 15	64.4 ± 13.6	0.061
Male, %	42.7	44.4	0.033	44.3	44.4	0.002
Race/ethnicity, %						
Non-Hispanic White	47.6	54.0	0.128	55.4	53.8	0.031
Non-Hispanic Black	29.4	25.8	0.080	25.3	25.9	0.013
Hispanic-Mexican	18.2	15.4	0.074	14.8	15.5	0.021
Other Ethnicity	4.9	4.8	0.004	4.6	4.8	0.010
Smoking status, %						
Never smoking	50.6	49.5	0.021	50.8	49.7	0.022
Former smoker	28.4	36.7	0.178	36.5	36.3	0.002
Current smoker	21.0	13.8	0.193	12.7	13.9	0.035
Alcohol intakes, g/day	4 ± 19.7	2.9 ± 8.6	0.071	3.4 ± 28	2.9 ± 8.6	0.021
BMI, kg/m^2	29.4 ± 6.6	30.4 ± 6.8	0.146	30.1 ± 6.9	30.3 ± 6.8	0.033
Systolic BP, mmHg	138.4 ± 21.4	140.5 ± 22.6	0.096	141.4 ± 20.9	140.6 ± 22.6	0.040
Diastolic BP, mmHg	76.4 ± 14	72.2 ± 17.6	0.269	73.1 ± 15	72.4 ± 17.4	0.047
C-reactive protein, mg/dL	0.5 ± 0.9	0.6 ± 0.8	0.010	0.6 ± 0.7	0.6 ± 0.8	0.003
HDL-C, mmol/L	1.3 ± 0.4	1.3 ± 0.4	0.010	1.3 ± 0.4	1.3 ± 0.4	0.008
eGFR, mL/min per 1.73 m^2	77.3 ± 25.1	73.8 ± 23	0.148	72.5 ± 24	73.8 ± 23	0.056
Asthma, %	8.9	11.3	0.082	9.9	11.0	0.038
Chronic bronchitis, %	6.8	7.8	0.041	7.7	7.7	0.003
Diabetes, %	15.0	29.9	0.363	27.8	29.3	0.033
Cardiovascular diseases, %	12.3	22.1	0.259	21.1	21.5	0.011
Cancer, %	11.1	14.8	0.111	15.3	14.6	0.019
Bronchodilators, %	3.0	4.8	0.091	3.8	4.6	0.038
Inhaled glucocorticoids, %	0.8	2.3	0.118	1.5	2.2	0.049
Immunosuppressive agents, %	2.2	3.2	0.060	3.1	3.1	0.002
Anti-hypertension, %						
Lifestyle modified, %,	57.6	62.8	0.108	64.6	62.7	0.040
Beta-blockers, %	17.5	22.2	0.118	22.5	22.0	0.012
Calcium-channel blockers, %	18.7	27.9	0.218	28.5	27.5	0.022
Diuretics, %	26.0	44.1	0.388	43.5	43.6	0.003
Other antihypertensive drugs, %	9.5	8.1	0.050	8.3	8.2	0.006

Data are presented as percent or means ± SD. Variable with standardized difference less than 0.1 was well balanced. *Propensity score matching with a caliper of 0.2 SD of the estimated propensity score. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blockers; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate calculated by CKD-EPI formula; HDL-C: high-density lipoprotein cholesterol.

perimental studies indicated that ACEII ameliorated the progression of ALI/ARDS induced by pathogens, acid aspiration, endotoxin, and sepsis *in vivo* and *in vitro*.[1,3,22] The loss of function experiment supported that ACEII inhibition worsened lung function and increased mortality in ALI/ARDS mice.[23] These biological mechanisms support RAS blockers protective role in the respiratory tract.

However, that association in clinical studies significantly varied. According to a pooled analysis, taking ACEI instead of ARB might be related to a lower incidence of pneumonia and pneumonia-re-

Table 3 The associations between ACEI/ARB use and respiratory related mortality in patients with hypertension.

Cause of death	Crude	*P*-value	Adjusted*	*P*-value	Adjusted#	*P*-value	After matching**	*P*-value
Respiratory related								
ACEI	1.74 (1.22–2.49)	0.003	1.25 (0.82–1.92)	0.297	1.26 (0.86–1.86)	0.237	1.08 (0.78–1.51)	0.637
ARB	1.14 (0.67–1.94)	0.630	1.28 (0.75–2.19)	0.363	0.95 (0.54–1.67)	0.852	1.43 (0.70-2.93)	0.327
ACEI or ARB	1.71 (1.16–2.50)	0.007	1.29 (0.85–1.96)	0.232	1.21 (0.81–1.81)	0.338	1.07 (0.79–1.43)	0.673
Influenza and pneumonia								
ACEI	2.19 (1.44–3.34)	0.000	1.77 (0.95–3.31)	0.072	1.76 (1.11–2.79)	0.016	1.26 (0.77–2.07)	0.355
ARB	0.56 (0.21–1.47)	0.233	0.77 (0.24–2.44)	0.655	0.59 (0.21–1.67)	0.313	1.02 (0.29–3.54)	0.975
ACEI or ARB	1.83 (1.22–2.76)	0.005	1.61 (0.86–3.01)	0.135	1.52 (0.96–2.42)	0.075	1.00 (0.65–1.54)	0.997
Chronic pulmonary disease								
ACEI	1.50 (0.92–2.44)	0.104	1.01 (0.55–1.85)	0.980	1.04 (0.59–1.85)	0.886	0.95 (0.60-1.50)	0.827
ARB	1.52 (0.83–2.78)	0.175	1.49 (0.76–2.90)	0.241	1.11 (0.57–2.19)	0.749	1.69 (0.70-4.09)	0.245
ACEI or ARB	1.63 (0.95–2.81)	0.076	1.13 (0.63–2.03)	0.679	1.07 (0.60-1.90)	0.807	1.13 (0.75–1.69)	0.562

*Multivariable weighted cox regression without imputation (n = 8356); #Multivariable weighted cox regression after imputation for missing value (n = 10,530); **Propensity score matching with 1: 1 ratio for use or nonuse of ACEI/ARB (2881: 2881), ACEI (2282: 2282), and ARB (671: 671). Adjusted model: adjustment for age, sex, race/ethnicity, smoking, alcohol consumption, body mass index, systolic and diastolic blood pressure, plasma C reactive protein, high density lipoprotein- cholesterol, eGFR, diabetes, chronic bronchitis, asthma, cardiovascular disease, cancer, lifestyle modified for lowering blood pressure, β-blockers, calcium-channel blockers, diuretics, other antihypertensive agents, bronchodilators, inhaled glucocorticoids, and immunosuppressive medications. ACEI and ARB use was adjusted for each other. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blockers; eGFR: estimated glomerular filtration rate.

lated mortality in patients with cardiovascular disease or chronic nephropathy, but obvious heterogenicity might limit its extrapolation.[6] Several observational studies noted a neutral relationship between pneumonia risk and ACEI/ARB therapy or its cumulative dose in general populations of older adults.[9–12] By contrast, analysis from Taiwan's National Health Insurance Research Database noted that treatment with ARBs was associated with lower all-cause mortality than ACEIs in patients with COPD. However, this was primarily due to CVD death. In the real-world hypertensive population, we found a non-significant link between ACEI/ARB treatments and pneumonia and influenza-related mortality. As a result, RAS blockers may have a less noticeable effect on the respiratory system than cardiovascular targets.

ACEII is a direct gateway to invade cells for influenza viruses and coronaviruses and theoretically increases the incidence of infection. However, ACEII knockout mice could still be infected with coronavirus and even have worse outcomes compared with infected wild-type mice.[23,24] Interestingly, the treatment with recombinant human ACEII ameliorated the lung injury of the mouse model caused by the avian influenza H5N1 virus.[22] According to a recent observational study, RAS inhibitors were more commonly used by hospitalized survivors with COVID-19 than non-survivors. However, no robust relationship between survival rate and taking ARBs was noted.[2,5,15,16] Despite one multi-center study of China observing 188 hypertensive individuals with COVID-19 taking ACEI/ARB medications having a decreased mortality rate compared with that nonuse of ACEI/ARBs, the sample size may limit its robustness.[21] Because unstable blood pressure and acute renal failure are more likely to cause death during hospitalization, ACEI/ARBs were used less frequently in critical patients. In addition, several large cross-sectional studies from Lombardy, New York, and Cleveland regions, as well as Madrid, showed that taking ACE/ARB agents had no effect on the risk of COVID-19 positivity or severity.[2,5,16,25] Our results support that ACEI/ARB medications were not associated with pneumonia- or influenza-related mortality in patients with hypertension during a long-term follow-up. According to a recent systematic review, the impact of administration of ACEI/ARBs on ACEII expression in most animal studies was small or insignificant. Nearly all studies that observed an increase in ACEII had greater doses of ACEI/ARBs used than equivalent doses

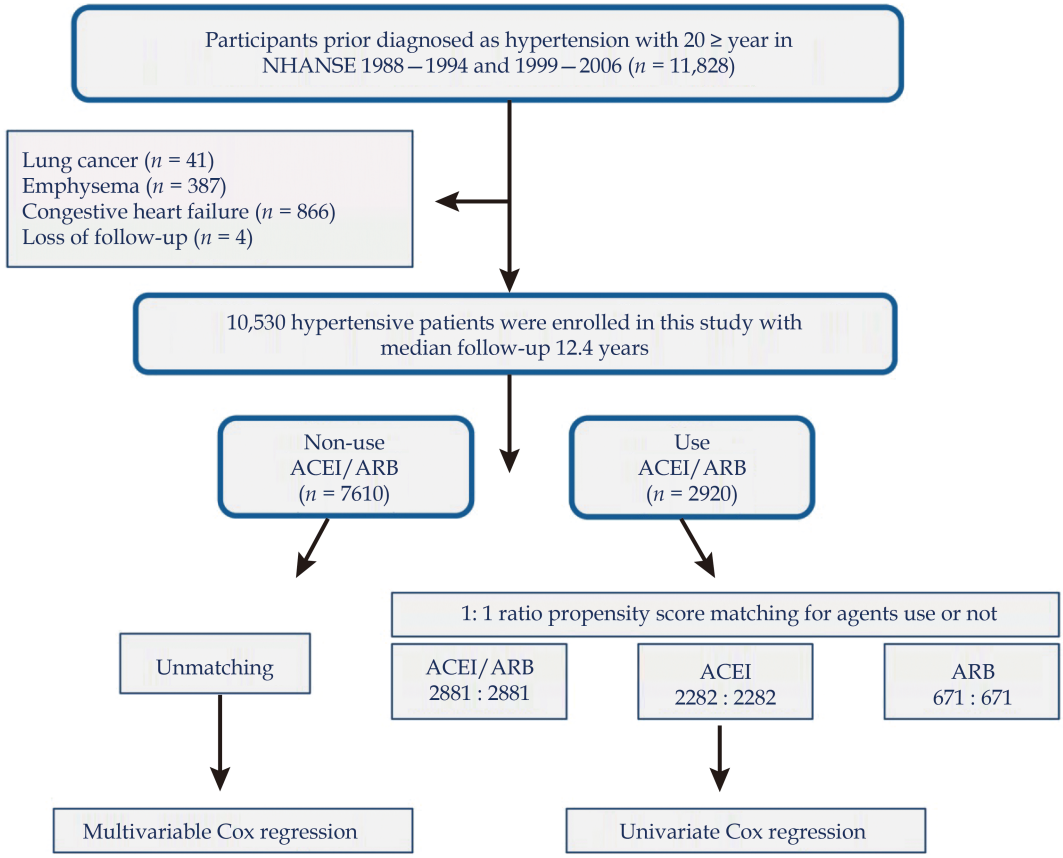

Figure 1 Flow diagram of study. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blockers.

administered to patients.[26] Despite being inferior to the evidence of interventional trials, other and our observational reports suggested that there is no strongly protective effect of conventional dose of ACEI/ARBs on acute infectious lung injury in patients with hypertension.

In patients with COPD acute exacerbations, treatment with ACEI/ARBs was linked to a lower risk of in-hospital mortality.[8,27] Similarly, RAS inhibition, in particular the ACEIs, may reduce the risk of pneumonia within high-risk patients, and decrease the risk of short- and long-term mortality among patients with lower respiratory tract infections or community-acquired pneumonia.[6,28] In contrast, the propensity score method was rarely used to correct for significant disparities in baseline parameters. Another possible explanation was that the reduced mortality risk might be attributed to cardiovascular benefits because cardiovascular death remained the leading cause.[26] Currently, respiratory diseases have not been listed in the indications of ACEI/ARB use that need rigorous evaluation through well-designed randomized controlled trials.[29] Our results could not rule out the beneficial effect of ACEI/ARB on the lung following severe acute pulmonary infection, because comorbidities highly susceptible to respiratory-related mortality were excluded in this study, including emphysema, lung cancer, and congestive heart failure. However, our findings suggest that the routine use of ACEI/ARBs for blood pressure control may not provide additional respiratory benefits in the general hypertensive population.

The ACE activity and AT1R expression in the lung of patients with the chronic pulmonary disease were significantly increased.[30] Besides, circulating ACEII in patients with heart failure and COPD was also lower than those without COPD.[31] Paradoxically, the recent pathological study observed that smokers and patients with COPD have increased ACEII in airway tissue.[32] Smoking mice also had elevated higher levels of both ACE and ACEII in their lungs.[33] As a result, the interaction of ACEII

and RAS signals in the respiratory system could be tricky. Furthermore, administration of ACEI/ARBs has been shown to increase ACEII gene expression in the heart of the post-infarction rat model.[34,35] However, previous human studies reported an inconsistent relationship between the administration of ACEI/ARBs and ACEII protein levels of heart, lung, kidney, and circulation.[26] Acute injury models and excessive dosage in animals are common factors in the increase of ACEII expression in response to ACEI/ARB treatment. BIOSTAT-CHF study discovered that ACEI/ARBs had a weak effect on plasma ACEII levels in patients with chronic heart failure.[31] Thus, data from human studies did not strongly support the hypothesis that ACEI/ARB use increases ACEII expression. Possibly, ACEII had a higher expression in renal and cardiovascular tissues than that in the lung.[36] Thus, the additional benefits of the conventional dose of RAS blockers outside the cardiovascular system through ACEII may be minor.

LIMITATIONS

The strengths of this study include national representative data of sampling, fully adjusted for relative prescription drug use, and long-term follow-up of cause-specific mortality. There are a few drawbacks to consider. For starters, patients with hypertension did not know the difference between primary and secondary hypertension. Second, pneumonia or influenza-related mortality was not quantified individually. As a result, more large-scale cohort studies are needed to distinguish the mortality rates of bacterial and viral infections. Third, the differences in medication compliance and specific RAS drugs are not considered. Finally, even though potential confounders were adjusted or matched to the greatest extent possible, residual confounding obscured those associations and could not be completely ruled out.

CONCLUSION

Our findings refute the notion that standard ACEI/ARB therapy provides additional pulmonary protection in patients with hypertension. The long-term use of ACEI/ARB does not increase the risk of mortality due to acute lung infection and chronic respiratory disease in patients with hypertension. ACEI/ARB medication and ACEII may have minor effects on the respiratory system, according to recent studies on RAS and COVID-19.

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CONFLICT OF INTEREST

None.

AVAILABILITY OF DATA AND MATERIALS

The raw datasets are available to all researchers to reproduce the results (https://www.cdc.gov/nchs/index.htm).

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