International Journal of COPD

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ORIGINAL RESEARCH

Comparative effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on the risk of pneumonia and severe exacerbations in patients with COPD

This article was published in the following Dove Press journal:
International Journal of COPD

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Objectives: This study aimed to compare the effects of angiotensin-converting-enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) on the risk of pneumonia and severe exacerbations in patients with COPD.

Patients and methods: All patients with COPD who used ACEis and ARBs for >90 days between 2000 and 2005 were recruited. Pairwise matching (1:1) of the ACEi and ARB groups resulted in two similar subgroups, with 6,226 patients in each. The primary outcomes were pneumonia and COPD exacerbations, and the secondary outcome was death.

Results: During the follow-up period, the incidence of pneumonia was 7.20 per 100 person-years in the ACEi group and 5.89 per 100 person-years in the ARB group. The ACEi group had a higher risk of pneumonia (adjusted hazard ratio [aHR], 1.22; 95% CI, 1.15–1.29) than the ARB group. The incidence of severe exacerbations was 0.65 per person-year for the patients receiving ACEis and 0.52 per person-year for those receiving ARBs. The patients receiving ACEis had a higher risk of severe exacerbations (aHR, 1.19; 95% CI, 1.16–1.21) than those receiving ARBs. Similar trends were noted in terms of severe exacerbations requiring hospitalization (aHR, 1.24; 95% CI, 1.21–1.28) or emergency department visits (aHR, 1.16; 95% CI, 1.13–1.18), pneumonia requiring mechanical ventilation (aHR, 1.35; 95% CI, 1.24–1.47), and mortality (aHR, 1.33; 95% CI, 1.26–1.42).

Conclusion: ARBs were associated with lower rates of pneumonia, severe pneumonia, and mortality than ACEis in patients with COPD.

Keywords: angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, COPD, severe exacerbation, pneumonia, mortality

Introduction

The prevalence of COPD is increasing globally, and COPD has become a major cause of mortality.[1,2] In patients with COPD, respiratory tract infections such as pneumonia are a common cause of COPD exacerbations, and frequent exacerbations can result in a greater decline in health status. In addition, patients with COPD are at a higher risk of pulmonary infection than the general population.[3,4] Moreover, many studies[5–7] have shown that inhaled and systemic corticosteroid therapy, which is frequently used to control COPD and manage COPD exacerbations, can further increase the risk of pneumonia. Therefore, preventing pneumonia in patients with COPD has become an important issue. In addition to vaccination which is recommended by the Global initiative for chronic Obstructive Lung Disease guidelines,[8] a nested case–control

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http://dx.doi.org/10.2147/COPD.S158634

study reported that the use of angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) was associated with a lower risk of pneumonia in patients with COPD.[9]

Although some studies[9–12] have investigated the effect of ACEis and ARBs on the risk of pneumonia, the issue remains controversial due to differences in the study population and effects. One recent meta-analysis[10] reported that ACEis exhibited a preventive effect equating to a relative risk ranging from 0.32 to 0.81 compared with controls, and that the overall relative risk of ACEi-treated patients versus controls was 0.61 (95% CI, 0.51–0.75; $P<0.001$). Another population-based case–control study[11] found that a current prescription for ACEis was associated with a reduction in the risk of pneumonia (adjusted odds ratio, 0.75; 95% CI, 0.65–0.86). In contrast, a case-crossover study using the Taiwan Longitudinal Health Insurance Database found that neither the use of nor the cumulative dose of ACEis or ARBs was associated with the risk of pneumonia among the general population in Taiwan. Moreover, it is not known which renin–angiotensin system blocker (an ACEi or ARB) is more effective in preventing pneumonia.[13–16] To date, no study has compared the effect of ACEi and ARB treatment on the risk of pneumonia in patients with COPD. Therefore, we used a national database to investigate the effect of ACEis and ARBs on the risk of pneumonia in patients with COPD. In addition, we compared the effects of ACEis and ARBs on the risk of severe exacerbations of COPD.

Patients and methods

Study design and patient selection

The Taiwan National Health Insurance Research Database (NHIRD) is a database constructed by the National Health Research Institutes, and includes the comprehensive medical care records of >97% of the hospitals and clinics in Taiwan. We retrieved all claims data of ambulatory care records, outpatient visits, prescriptions, inpatient care records, registration files, and disease and vital status data from the NHIRD. The patient records and information were anonymized and de-identified prior to analysis. The study protocol was approved by the Institutional Review Board of Cardinal Tien Hospital (CTH-104-3-5-030).

This study used a subset of the NHIRD comprising information on individuals with COPD.[5,7] There were 62,505 eligible COPD patients who were aged older than 40 years between 2000 and 2005. We excluded 40,026 patients who did not meet the following criteria: 1) patients without prescription of ACEi or ARB before COPD index date; 2) patients who received ACEi or ARB <90 days after COPD index date; 3) patients with ACEi and ARB combined treatment; and 4) patients who died or were diagnosed with pneumonia or severe pneumonia prior to being indexed (Figure 1). Eligible patients who received prescriptions for an ACEi or ARB within 90 days after diagnosis of COPD were allocated to the ACEi and ARB cohorts. After 1:1 propensity score matching, the remaining 12,452 patients were included for further analysis (Figure 1).

Exposure measures and potential confounders

We included patients who received ACEis or ARBs for >90 days. Therefore, the index date was defined as the date of the 91st day of the prescription of ACEis or ARBs after a diagnosis of COPD. The patients were followed from the index date to 31 December 2011, the end of drug treatment, emigration, or death, whichever occurred first. The patients who changed from an ACEi to an ARB or from an ARB to an ACEi were censored.

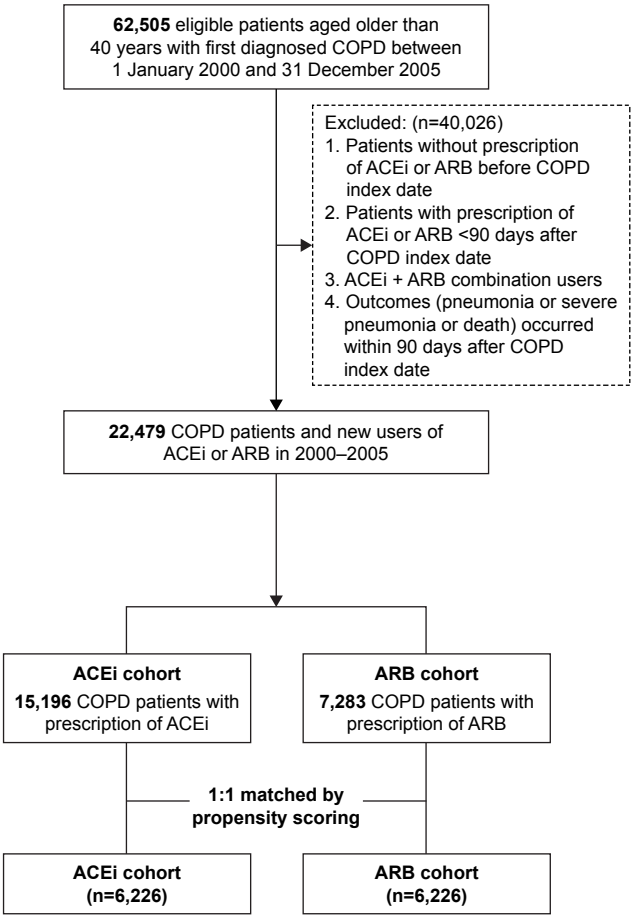

Figure 1 Flowchart of selection of study subjects.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Outcome measurements

The primary outcomes were pneumonia and severe exacerbations. The patients with pneumonia were identified according to the International Classification of Diseases, Ninth Revision, Clinical Modification codes as previously described.[5,17] For patients with more than one episode of pneumonia, only the first episode was included. A severe exacerbation was defined as a COPD-related hospitalization or emergency department visit.[5] The first episode of a severe exacerbation and the frequency of severe sepsis (every year) were recorded. The secondary outcome was mortality.

Demographic characteristics and comorbidities

The demographic characteristics of the patients, including age, gender, monthly income (<NT$ 19,100, NT$ 19,100–NT$ 41,999, and >NT$ 42,000), hospital level at admission (medical center, regional, district, and others), and severe exacerbations of COPD in the 1 year prior to the index date (never, 1, or ≥2 times/year), were extracted. Underlying comorbid conditions were identified according to the International Classification of Diseases, Ninth Revision, Clinical Modification codes and grouped as follows: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, rheumatologic disease, peptic ulcer disease, hemiplegia or paraplegia, renal disease, diabetes, moderate/severe liver disease, and tumor. The Charlson Comorbidity Index was used to determine the severity of comorbidities for each patient. Important medications including aspirin, clopidogrel, ticlopidine, dipyridamole, nitrates, statins, nonsteroidal anti-inflammatory drugs, anti-hyperglycemic drugs, proton-pump inhibitors, medications for hypertension (including alpha-blockers, beta-blockers, calcium channel blockers, and diuretics), and medications for COPD including long-acting beta agonists, short-acting beta agonists, long-acting muscarinic antagonists, and inhaled corticosteroids were recorded.

Statistical analysis

Data analysis was performed using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA). The baseline characteristics were presented as descriptive statistics (means, SDs, counts, and percentages). Categorical baseline variables were compared using Pearson's chi-square test, and the independent *t*-test was used to compare continuous baseline variables. To minimize the imbalance of baseline characteristics between the ACEi and ARB groups, we performed 1:1 propensity score matching. Covariates that may have caused interference or bias in the association between exposure and outcomes of interest such as demographic characteristics, comorbidities, and severe exacerbations of COPD in the 1 year prior to the index date (never, 1, or ≥2 times/year) were included in the propensity matching.

Intention-to-treat analysis was used as the primary analysis in this study because of the more reliable real-world estimates of comparative treatment effectiveness. Both cohorts were followed until the study end according to the original treatment allocation, regardless of adherence to or subsequent withdrawal or deviation from the inclusion criteria. In the as-treated analysis, the patients were censored when they switched from an ACEi to an ARB or from an ARB to an ACEi and when they left the study because of death or emigration. We used the last time point that they were known to be alive to censor those without an event. Cumulative incidence curves were constructed using the Kaplan–Meier method, and differences between the two treatment groups were tested using the log-rank test.

The crude incidence rates of individual outcomes were calculated as the total number of events during the follow-up period divided by person-years. Cox proportional regression models were used to calculate crude hazard ratios (HRs) and adjusted hazard ratios (aHRs), which were adjusted for propensity score, of different outcomes between the ACEi and ARB groups. Annual severe exacerbation event rates (emergency department visits or admissions to hospital) were compared between the two groups using Poisson regression, with events as the dependent variable and time on a specific fixed combination treatment as an offset variable. A two-sided *P*-value <0.05 was considered to indicate statistical significance in all analyses.

Results

Characteristics of the study population

Initially, 22,479 patients with COPD who used ACEis (n=15,196) or ARBs (n=7,283) between 2000 and 2005 were included. There were significant differences between the two groups in some demographic characteristics including index year; age; gender; monthly income; hospital level; episodes of prior severe exacerbations; underlying comorbidities such as myocardial infarction, congestive heart failure, peptic ulcer disease, hemiplegia or paraplegia, and diabetes mellitus; and the use of medications including beta-blockers, calcium channel blockers, diuretics, clopidogrel, ticlopidine, dipyridamole, statins, nonsteroidal anti-inflammatory drugs, and inhalation therapy for COPD (Table 1). Therefore, we used

Table 1 Demographic characteristics of the study subjects

Variables	Before matching					After matching				
	ACEi cohort		ARB cohort		*P*-value	ACEi cohort		ARB cohort		*P*-value
Number of patients	15,196		7,283			6,226		6,226		
Index year										
2000	3,763	24.76%	768	10.55%	<0.0001	736	11.82%	768	12.34%	0.9693
2001	2,985	19.64%	884	12.14%		883	14.18%	880	14.13%	
2002	2,552	16.79%	1,109	15.23%		1,068	17.15%	1,047	16.82%	
2003	2,017	13.27%	1,336	18.34%		1,132	18.18%	1,130	18.15%	
2004	2,002	13.17%	1,695	23.27%		1,264	20.30%	1,264	20.30%	
2005	1,877	12.35%	1,491	20.47%		1,143	18.36%	1,137	18.26%	
Age (years, SD)	68.15±9.77		66.75±9.95		<0.0001	67.43±10.01		67.24±9.82		0.2919
Male gender	11,071	72.85%	4,983	68.42%	<0.0001	4,405	70.75%	4,359	70.01%	0.3666
Monthly income NT$, n (%)										
<19,100	6,597	43.41%	2,973	40.82%	<0.0001	2,658	42.69%	2,625	42.16%	0.8336
19,100–41,999	7,050	46.39%	3,262	44.79%		2,784	44.72%	2,807	45.09%	
≥42,000	1,549	10.19%	1,048	14.39%		784	12.59%	794	12.75%	
Hospital level, n (%)										
Level 1	3,360	22.11%	3,095	42.50%	<0.0001	2,374	38.13%	2,366	38.00%	0.593
Level 2	3,625	23.85%	2,254	30.95%		1,959	31.46%	1,994	32.03%	
Level 3	3,088	20.32%	1,335	18.33%		1,319	21.19%	1,267	20.35%	
Level 4	5,123	33.71%	599	8.22%		574	9.22%	599	9.62%	
Severe AE (count 1 year before index date)										
0	10,277	67.63%	5,354	73.51%	<0.0001	4,466	71.73%	4,446	71.41%	0.9181
1	2,190	14.41%	918	12.60%		827	13.28%	833	13.38%	
2+	2,729	17.96%	1,011	13.88%		933	14.99%	947	15.21%	
Baseline comorbidities										
Charlson score	1.82±1.06		1.80±1.05		0.4771	1.84±1.07		1.82±1.05		0.3405
Myocardial infarction	391	2.57%	131	1.80%	0.0003	142	2.28%	128	2.06%	0.389
Congestive heart failure	2,164	14.24%	849	11.66%	<0.0001	824	13.23%	796	12.79%	0.4557
Peripheral vascular disease	156	1.03%	71	0.97%	0.7167	70	1.12%	59	0.95%	0.3303
Cerebrovascular disease	1,675	11.02%	786	10.79%	0.6047	687	11.03%	679	10.91%	0.8186
Dementia	181	1.19%	87	1.19%	0.9822	81	1.30%	75	1.20%	0.6288
Rheumatologic disease	141	0.93%	74	1.02%	0.5249	60	0.96%	66	1.06%	0.5911
Peptic ulcer disease	2,830	18.62%	1,187	16.30%	<0.0001	1,087	17.46%	1,068	17.15%	0.6526
Hemiplegia or paraplegia	23	0.15%	15	0.21%	0.3510	9	0.14%	10	0.16%	0.8184
Renal disease	458	3.01%	275	3.78%	0.0026	216	3.47%	228	3.66%	0.562
Diabetes	1,650	10.86%	933	12.81%	<0.0001	799	12.83%	787	12.64%	0.747
Moderate or severe liver disease	682	4.49%	337	4.63%	0.6387	281	4.51%	299	4.80%	0.444
Tumor	410	2.70%	223	3.06%	0.1228	202	3.24%	191	3.07%	0.5729
Medication for hypertension										
Alpha-blocker	2,056	13.53%	936	12.85%	0.1613	846	13.59%	831	13.35%	0.6938
Beta-blocker	6,354	41.81%	3,156	43.33%	0.0309	2,671	42.90%	2,671	42.90%	1
Calcium channel blocker	9,748	64.15%	5,128	70.41%	<0.0001	4,299	69.05%	4,306	69.16%	0.892
Diuretic	7,825	51.49%	3,474	47.70%	<0.0001	3,095	49.71%	3,042	48.86%	0.3421
Other medication										
Aspirin	2,220	14.61%	1,115	15.31%	0.1667	953	15.31%	927	14.89%	0.5152
Clopidogrel	356	2.34%	340	4.67%	<0.0001	265	4.26%	267	4.29%	0.9294

(*Continued*)

Table 1 (*Continued*)

Variables	Before matching					After matching				
	ACEi cohort		ARB cohort		*P*-value	ACEi cohort		ARB cohort		*P*-value
Ticlopidine	591	3.89%	237	3.25%	0.0180	219	3.52%	220	3.53%	0.9612
Dipyridamole	4,415	29.05%	1,563	21.46%	<0.0001	1,444	23.19%	1,432	23.00%	0.7986
Nitrate	46	0.30%	23	0.32%	0.8681	21	0.34%	22	0.35%	0.8786
Statin	1,167	7.68%	1,031	14.16%	<0.0001	725	11.64%	733	11.77%	0.8236
NSAID	12,905	84.92%	5,929	81.41%	<0.0001	5,073	81.48%	5,111	82.09%	0.3776
Anti-hyperglycemic drugs	2,560	16.85%	1,275	17.51%	0.2183	1,127	18.10%	1,102	17.70%	0.5589
Proton-pump inhibitor	1,211	7.97%	611	8.39%	0.2800	547	8.79%	533	8.56%	0.6558
COPD drug										
Long-acting beta-agonist	670	4.41%	396	5.44%	0.0007	317	5.09%	327	5.25%	0.6857
Short-acting beta-agonist	3,171	20.87%	1,432	19.66%	0.0361	1,253	20.13%	1,236	19.85%	0.7032
Long-acting muscarinic antagonist	85	0.56%	80	1.10%	<0.0001	59	0.95%	60	0.96%	0.9266
Inhaled corticosteroid	2,323	15.29%	1,479	20.31%	<0.0001	1,147	18.42%	1,196	19.21%	0.2612

Abbreviations: AE, acute exacerbation; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NSAID, nonsteroidal anti-inflammatory drug.

pairwise matching (1:1) of the ACEi and ARB groups, which resulted in two similar subgroups with 6,226 patients in each. There were no significant differences in index year, age, sex, monthly income, hospital level, inhaled medications, anti-hypertension medications, or commonly used medications including aspirin, clopidogrel, ticlopidine, dipyridamole, anti-hyperglycemic agents, and proton-pump inhibitors (Table 1).

Effect on the risk of severe exacerbations

Following matching, the post-index all severe exacerbation rates were 0.6521 and 0.5198 per person-year in the ACEi and ARB groups, respectively (adjusted rate ratio [RR], 1.19; 95% CI, 1.16–1.21), as shown in Table 2. The patients treated with ACEis had significantly higher rates of COPD exacerbations requiring hospitalization (adjusted RR, 1.24; 95% CI, 1.21–1.28) or emergency department visit (adjusted RR, 1.16; 95% CI, 1.13–1.18), as shown in Table 2. The results before matching were the same as after matching.

Effect on the risk of pneumonia and death

During the follow-up period, the incidence of pneumonia was 7.39 per 100 person-years for the patients receiving ACEis and 5.66 per 100 person-years for those receiving ARBs. Moreover, the ACEi group had a higher risk of pneumonia (aHR, 1.20; 95% CI, 1.14–1.26) than the ARB group. Furthermore, the incidence of pneumonia requiring mechanical ventilation was 2.90 per 100 person-years in the ACEi group and 1.97 per 100 person-years in the ARB group, and the ACEi group had a higher risk of pneumonia requiring mechanical ventilation (aHR, 1.34; 95% CI, 1.24–1.45) than the ARB group. Finally, the mortality rate was 5.82 per 100 person-years in the ACEi group and 3.90 per 100 person-years in the ARB group. Overall, the patients

Table 2 Annual incidence and RR of severe exacerbation of COPD

Variables	ACEi cohort	ARB cohort	Crude RR (95% CI)	Adjusted RR[a] (95% CI)
	Annual incidence (per person-year)	Annual incidence (per person-year)		
Before propensity score matching				
Severe exacerbation	0.6873	0.5109	1.32 (1.30–1.34)	1.19 (1.17–1.21)
Hospitalization for COPD exacerbation	0.3573	0.23579	1.49 (1.46–1.52)	1.27 (1.25–1.30)
Emergency department visits for COPD exacerbation	0.4639	0.3765	1.21 (1.19–1.23)	1.14 (1.12–1.16)
After propensity score matching				
Severe exacerbation	0.6521	0.5198	1.19 (1.17–1.21)	1.19 (1.16–1.21)
Hospitalization for COPD exacerbation	0.3213	0.2438	1.25 (1.21–1.28)	1.24 (1.21–1.28)
Emergency department visits for COPD exacerbation	0.4620	0.3778	1.16 (1.13–1.18)	1.16 (1.13–1.18)

Note: [a]Adjusted for propensity score.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; RR, rate ratio.

Table 3 Annual IR and risk of pneumonia among COPD patients

Variables	ACEi cohort			ARB cohort			Crude	Adjusted[b]	Competing risk
	Event	Person-year	IR[a]	Event	Person-year	IR[a]	HR (95% CI)	HR (95% CI)	subHR (95% CI)
Before propensity score matching									
Mortality	6,277	107,841.55	5.82	2,057	52,759.75	3.90	1.50 (1.42–1.57)	1.29 (1.22–1.37)	–
Pneumonia	6,516	88,135.31	7.39	2,564	45,316.88	5.66	1.30 (1.24–1.36)	1.20 (1.14–1.26)	1.15 (1.09–1.20)
Pneumonia requiring MV	3,005	103,492.68	2.90	1,010	51,298.54	1.97	1.47 (1.37–1.58)	1.34 (1.24–1.45)	1.15 (1.09–1.20)
After propensity score matching									
Mortality	2,326	42,503.29	5.47	1,864	45,472.26	4.10	1.33 (1.25–1.42)	1.33 (1.26–1.42)	–
Pneumonia	2,536	35,204.12	7.20	2,281	38,750.59	5.89	1.22 (1.15–1.29)	1.22 (1.15–1.29)	1.19 (1.13–1.26)
Pneumonia requiring MV	1,122	40,864.53	2.75	899	44,158.63	2.04	1.35 (1.23–1.47)	1.35 (1.24–1.47)	1.19 (1.13–1.25)

Notes: [a]Per 100 person-years. [b]Adjusted for propensity score.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HR, hazard ratio; IR, incidence rate; MV, mechanical ventilation; subHR, subdistribution hazard ratio.

receiving ACEis had a higher risk of death (aHR, 1.29; 95% CI, 1.22–1.37) than those receiving ARBs. When we treated death as a competing risk, the ACEi group had a higher risk of pneumonia and pneumonia requiring mechanical ventilation than the ARB group. Similar trends were noted after using propensity score matching, and the ACEi group had a higher risk of pneumonia and pneumonia requiring mechanical ventilation than the ARB group, even when treating death as a competing risk (Table 3).

Sensitivity analysis

Table 4 shows the sensitivity analysis of the risk of pneumonia and death among the patients with COPD receiving ACEis compared to the matched patients receiving ARBs. When we treated death as a competing risk in the intention-to-treat analysis, the patients receiving ACEis had a higher risk of pneumonia and pneumonia requiring mechanical ventilation compared to the matched patients receiving ARBs (aHR, 1.19; 95% CI, 1.13–1.26 for pneumonia; aHR, 1.19; 95% CI, 1.13–1.25 for pneumonia requiring mechanical ventilation). In the as-treated analysis, the patients receiving ACEis had a higher risk of pneumonia and pneumonia requiring mechanical ventilation compared to the matched patients receiving ARBs. When death was treated as a competing risk in the as-treated analysis, the patients receiving ACEis had a higher risk of pneumonia than those receiving ARBs (aHR, 1.08; 95% CI, 1.01–1.15). The results of analysis conducted before propensity score matching were consistent with those after propensity score matching.

Discussion

In this large national study, we compared the effect of the prior use of ACEis and ARBs on the risk of pneumonia and severe exacerbations in patients with COPD. After adjusting

Table 4 Sensitivity analysis

Variables	Before matching		After matching	
	Crude	Adjusted[a]	Crude	Adjusted[a]
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Primary analysis				
Mortality	1.5 (1.42–1.57)	1.29 (1.22–1.37)	1.33 (1.25–1.42)	1.33 (1.26–1.42)
Pneumonia	1.3 (1.24–1.36)	1.2 (1.14–1.26)	1.22 (1.15–1.29)	1.22 (1.15–1.29)
Pneumonia requiring MV	1.47 (1.37–1.58)	1.34 (1.24–1.45)	1.35 (1.23–1.47)	1.35 (1.24–1.47)
ITT analysis + competing risk				
Mortality				
Pneumonia	1.04 (1–1.09)	1.15 (1.09–1.2)	1.19 (1.13–1.26)	1.19 (1.13–1.26)
Pneumonia requiring MV	0.96 (0.92–1)	1.15 (1.09–1.2)	1.19 (1.12–1.25)	1.19 (1.13–1.25)
As-treated analysis				
Mortality	1.5 (1.4–1.61)	1.28 (1.19–1.38)	1.29 (1.19–1.4)	1.3 (1.2–1.41)
Pneumonia	1.28 (1.21–1.36)	1.17 (1.1–1.26)	1.16 (1.08–1.25)	1.17 (1.09–1.26)
Pneumonia requiring MV	1.38 (1.25–1.52)	1.25 (1.13–1.39)	1.21 (1.07–1.36)	1.21 (1.08–1.37)
As-treated analysis + competing risk				
Mortality				
Pneumonia	1.07 (1.01–1.13)	1.06 (1–1.12)	1.07 (1–1.15)	1.08 (1.01–1.15)
Pneumonia requiring MV	1.01 (0.96–1.07)	1.03 (0.97–1.1)	1.04 (0.98–1.12)	1.04 (0.97–1.12)

Note: [a]Adjusted for propensity score.
Abbreviations: HR, hazard ratio; ITT, intention-to-treat; MV, mechanical ventilation.

for possible confounding factors and using different methods of analysis, the risks of pneumonia and severe exacerbations were significantly higher in the patients who received ACEis than in those who received ARBs. In addition, the patients with COPD who used ACEis had a significantly higher mortality rate than those who used ARBs. Taken together, these findings suggest that ARBs are associated with fewer COPD complications, including severe exacerbations, pneumonia, and mortality, than ACEis, and this may further suggest that ARBs are more appropriate for patients with COPD, in terms of the risk of severe exacerbations and pneumonia, than ACEis.

A previous study investigating the effects of ACEis and ARBs on the risk of pneumonia did not find any obvious differences between ACEis and ARBs in the general population.[12] In contrast, another study enrolling patients with hypertension found that ARB users, but not ACEi users had lower rates of hospitalization for sepsis, compared with untreated hypertensive patients.[13] In this study, we found significant differences between ACEi and ARB treatments in terms of COPD exacerbations and the risk of pneumonia. The difference between this study and previous reports[12,13] may be due to different study populations, and further studies are warranted to investigate differences in the effects between ACEis and ARBs in specific populations. Regarding the effect on mortality between the ACEi and ARB groups, our findings are consistent with a time-matched nested case–control study in which ARB users seemed to have a lower mortality rate than ACEi users.[6]

The significant difference in complications of COPD between users of ARBs and ACEis may be explained by their different mechanisms of action on the renin–angiotensin system in pulmonary diseases.[10,11,18] In an animal model, valsartan was shown to be protective against bleomycin-induced pulmonary injuries via the suppression of total and active transforming growth factor-beta 1.[11] Another investigation[18] demonstrated that candesartan can reduce bleomycin-induced lung fibrosis. In addition, ARBs have been reported to be able to use the ACE2/AT2R/Mas axis to ameliorate inflammation.[19,20] These additional effects of ARBs may result in the differences with ACEis with regards to the risk and outcomes of severe exacerbations and pneumonia in patients with COPD.

The strength of this study is that we enrolled a large cohort of patients with COPD and various cardiovascular risk profiles with a long follow-up period, which represents the general condition in real-word practice. Based on the data from the NHIRD, we were able to analyze many known confounding factors including comorbidities, drug usage, and the frequency of severe exacerbations, which allowed us to minimize the effects of confounders.

This study also has several limitations. First, as with all studies based on claims databases, some confounders such as pulmonary function and clinical symptoms and signs were not available for analysis. Therefore, we could not evaluate the severity of COPD. However, we used episodes of severe exacerbations to partly represent the severity of COPD. Second, only data on all-cause mortality are contained in the NHIRD, so we could not analyze specific causes of death. Therefore, we could not analyze whether the difference in mortality rates between the ACEi and ARB groups was due to cardiovascular event-related death or another etiology.

Conclusion

ARB treatment was associated with lower rates of severe exacerbations, pneumonia, and mortality than ACEi treatment in patients with COPD.

Acknowledgments

This work was supported by grants from the National Science Council (NSC 104-2314-B-002-185-MY2, 101-2325-B-002-064, 102-2325-B-002-087, 103-2325-B-002-027, 104-2325-B-002-035, 105-2325-B-002-030, 104-2314-B-567-002, and 105-2314-B-567-001) and from the National Health Research Institutes (intramural funding).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2095–2128.
2. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med*. 2006;3(11):e442.
3. Lange P. Chronic obstructive pulmonary disease and risk of infection. *Pneumonol Alergol Pol*. 2009;77(3):284–288.
4. Lv Y, Lv Q, Lv Q, Lai T. Pulmonary infection control window as a switching point for sequential ventilation in the treatment of COPD patients: a meta-analysis. *Int J Chron Obstruct Pulmon Dis*. 2017;12:1255–1267.
5. Yang HH, Lai CC, Wang YH, et al. Severe exacerbation and pneumonia in COPD patients treated with fixed combinations of inhaled corticosteroid and long-acting beta2 agonist. *Int J Chron Obstruct Pulmon Dis*. 2017;12:2477–2485.
6. Mancini GB, Etminan M, Zhang B, Levesque LE, FitzGerald JM, Brophy JM. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. *J Am Coll Cardiol*. 2006;47(12):2554–2560.
7. Wang CY, Lai CC, Yang WC, et al. The association between inhaled corticosteroid and pneumonia in COPD patients: the improvement of patients' life quality with COPD in Taiwan (IMPACT) study. *Int J Chron Obstruct Pulmon Dis*. 2016;11:2775–2783.

8. Cimen P, Unlu M, Kirakli C, et al. Should patients with COPD be vaccinated? *Respir Care*. 2015;60(2):239–243.
9. Kim J, Lee JK, Heo EY, Chung HS, Kim DK. The association of renin-angiotensin system blockades and pneumonia requiring admission in patients with COPD. *Int J Chron Obstruct Pulmon Dis*. 2016;11:2159–2166.
10. Papp M, Li X, Zhuang J, Wang R, Uhal BD. Angiotensin receptor subtype AT(1) mediates alveolar epithelial cell apoptosis in response to ANG II. *Am J Physiol Lung Cell Mol Physiol*. 2002;282(4):L713–L718.
11. Mancini GB, Khalil N. Angiotensin II type 1 receptor blocker inhibits pulmonary injury. *Clin Invest Med*. 2005;28(3):118–126.
12. Liu CL, Shau WY, Chang CH, Wu CS, Lai MS. Pneumonia risk and use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. *J Epidemiol*. 2013;23(5):344–350.
13. Dial S, Nessim SJ, Kezouh A, Benisty J, Suissa S. Antihypertensive agents acting on the renin-angiotensin system and the risk of sepsis. *Br J Clin Pharmacol*. 2014;78(5):1151–1158.
14. Suberviola B, Rodrigo E, Gonzalez-Castro A, Serrano M, Heras M, Castellanos-Ortega Á. Association between exposure to angiotensin-converting enzyme inhibitors and angiotensin receptor blockers prior to septic shock and acute kidney injury. *Med Intensiva*. 2017;41(1):21–27.
15. Mortensen EM, Nakashima B, Cornell J, et al. Population-based study of statins, angiotensin II receptor blockers, and angiotensin-converting enzyme inhibitors on pneumonia-related outcomes. *Clin Infect Dis*. 2012;55(11):1466–1473.
16. Wu A, Good C, Downs JR, et al. The association of cardioprotective medications with pneumonia-related outcomes. *PLoS One*. 2014;9(1):e85797.
17. Hsu WT, Lai CC, Wang YH, et al. Risk of pneumonia in patients with gastroesophageal reflux disease: a population-based cohort study. *PLoS One*. 2017;12(8):e0183808.
18. Otsuka M, Takahashi H, Shiratori M, Chiba H, Abe S. Reduction of bleomycin induced lung fibrosis by candesartan cilexetil, an angiotensin II type 1 receptor antagonist. *Thorax*. 2004;59(1):31–38.
19. Callera GE, Antunes TT, Correa JW, et al. Differential renal effects of candesartan at high and ultra-high doses in diabetic mice-potential role of the ACE2/AT2R/Mas axis. *Biosci Rep*. 2016;36(5):e00398.
20. Clancy P, Koblar SA, Golledge J. Angiotensin receptor 1 blockade reduces secretion of inflammation associated cytokines from cultured human carotid atheroma and vascular cells in association with reduced extracellular signal regulated kinase expression and activation. *Atherosclerosis*. 2014;236(1):108–115.