The association of renin–angiotensin system blockades and pneumonia requiring admission in patients with COPD

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Background: The hallmark of COPD is chronic airway inflammation, which may be mediated by renin–angiotensin system. The renin–angiotensin system blockers such as angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) have exhibited anti-inflammatory and immunomodulatory effects in patients with various diseases. We explored the effects of ACEi and ARBs on the risk of pneumonia in patients with COPD.

Methods: A nested case–control study was performed on COPD patients recruited from January 2010 to August 2013 in two referral hospitals in Korea. A total of 130 COPD patients admitted with pneumonia were included, and 245 COPD patients without pneumonia were selected as controls from a total of 1,646 such patients. Controls were matched with test patients by age, sex, and severity of airflow limitation. The effects of ACEi/ARBs use on the odds ratio (OR) for the development of pneumonia were tested through conditional logistic regression.

Results: Elderly patients (over 70 years of age) constituted ~30% of each group; most of the patients were male (85%). Of the COPD patients with pneumonia, 21.5% had taken ACEi/ARBs for a mean of 9.8 months (standard deviation ±3.5 months). The proportions of ACEi/ARBs users and the mean duration of such use did not differ when compared to those of the control patients (26.9%, P=0.25; 9.6 ±3.6 months, P=0.83). Univariate analyses indicated that the use of ACEi/ARBs was not associated with a decreased risk of pneumonia (OR=0.70, 95% confidence interval 0.41–1.23, P=0.21), whereas both a history of pulmonary tuberculosis (OR=1.85, 95% confidence interval 1.12–3.06, P=0.02) and exposure to systemic steroids (OR=2.33, 95% confidence interval 1.28–4.23, P=0.005) did show an association. After adjustment for a history of tuberculosis, comorbid chronic renal disease, and exposure to corticosteroids, ACEi/ARBs reduced the risk of pneumonia in COPD patients (OR=0.51, 95% confidence interval 0.27–0.98, P=0.04).

Conclusion: This study revealed that the use of ACEi/ARBs was associated with reducing the risk of pneumonia in patients with COPD. Further prospective studies are necessary to confirm the protective effect of ACEi/ARBs and elucidate the underlying mechanisms in COPD patients.

Keywords: angiotensin-converting enzyme inhibitors, angiotensin receptor antagonist, COPD, pneumonia

Introduction
COPD is an increasing cause of chronic morbidity and mortality worldwide. As the general populations age, the incidence and prevalence of COPD increase. Recently, the incidence of COPD in adults ≥40 years of age was estimated to be...
admission. Totally, 130 cases were confirmed of pneumonia patient with pneumonia (ICD-10 code) who required hospital treatment in two referral hospitals in Korea (Seoul National University Hospital and Seoul Metropolitan Government-Seoul National University Boramae Medical Center) from January 2010 to August 2013. A case was defined as a COPD patient with pneumonia (AECOPDs) are common. In AECOPD, airway inflammation and the systemic response to COPD are accentuated; infections (including pneumonia) are common and debilitating.

Angiotensin-converting enzyme (ACE) is present at high levels in lungs and is activated by hypoxia. Thus, RAS blockers would be expected to have anti-inflammatory actions both in lungs and in extra-pulmonary sites in patients with chronic lung diseases including COPD. Some RAS blockers have been used to make an effort to attenuate the chronic inflammation of COPD.

In terms of pneumonia, the effects of RAS and its blockers have been extensively studied. ACE inhibitors (ACEi) increase the levels of substance P and bradykinin and improve asymptomatic dysphagia and cough reflex. Angiotensin receptor blockers (ARBs) have anti-inflammatory effects and alleviate acute lung injury. Several clinical studies have shown that RAS blockers reduce the risk of pneumonia or have a generally protective effect in specific populations (including the elderly, neurologically ill, and the Asians). The mechanism has been described elsewhere. However, the results of RAS blockade are not consistent, and well-designed studies on large populations are rare.

As RAS blockers have anti-inflammatory effects and protect against pneumonia in some populations, roles of RAS blockades should be explored in COPD patients focusing the impact on the risk of pneumonia. However, no study to date has explored the possible association between RAS blockade and infections including pneumonia in COPD patients. Therefore, we evaluated the effects of RAS blockade on the incidence of pneumonia in such patients.

Materials and methods
Study design and population
This was a nested case–control study on COPD populations treated in two referral hospitals in Korea (Seoul National University Hospital and Seoul Metropolitan Government-Seoul National University Boramae Medical Center) from January 2010 to August 2013. A case was defined as a COPD patient with pneumonia (ICD-10 code) who required hospital admission. Totally, 130 cases were confirmed of pneumonia during that period among 1,646 cohort population. Control patients with no history of admission to treat pneumonia over the same period were also enrolled. To ensure appropriate matching in a nested case–control study, the duration of observation must be fixed and index dates for both the cases and controls must be defined. The duration of observation must be comparable in cases and controls. The first date on which a case was admitted during the study period was defined as the index date. The index date of each control (possible date of entry for control patients) was permitted if they had visited these hospitals before or after 6 months of index date of the matched cases.

All the control patients were required to attend at least three outpatient visits or to have a record of at least 1 year at either hospital. For each case, two controls were precisely matched by sex, age (within 5-year age group), and airflow limitation (forced expiratory volume for 1 second predicted; defined by the Global Initiative for Chronic Obstructive Lung Disease [GOLD] grade) within the index date. If we could not match a patient appropriately, we widened the GOLD grade, but only by a single grading unit. Even then, we could not find controls for some cases. Of the 1,516 possible controls, we excluded those with any history of asthma, a pulmonary operation (pneumonectomy or pulmonary lobectomy), rheumatoid arthritis, inflammatory bowel disease, a connective tissue disorder, a vascular disease, or malignancy within the prior 5 years. Finally, 245 controls were enrolled (two each for 115 cases and one each for 15 cases). The study design and methods were approved by the Institutional Review Board of both Seoul National University Hospital (IRB No H-1402-070-557) and Seoul Metropolitan Government-Seoul National University Boramae Medical Center (IRB No B-16-2015-122). The Institutional Review Boards permitted the exemption of consent from study participants derived from the nature of the study design (a retrospective nested case–control study conducted by an electronic medical record chart review), in which it was not possible for receiving consents (paper or verbal) from the study population. For this, we removed all the personal IDs (ie, hospital ID), which distinguish participants individually before building up the database. We used newly created numbers that were unique only for the database and that could not identify the participants in the database instead of personal IDs.

Definition and measurement of exposure to ACEi/ARBs
The principal variable was prescription of ACEi/ARBs. As we expected that such drugs would have relatively long-term effects, an ACEi/ARB user was defined as a subject to whom...
ACEi/ARBs were prescribed for more than 30 days within the year before the index date. Each dose of inhaled corticosteroid (ICS) was calculated as the fluticasone equivalent.

**Covariates**

We considered the following comorbidities as potential covariates: heart disease (ischemic and congestive), a history of pulmonary tuberculosis (TB), cerebrovascular disease, liver disease, renal disease, and solid organ malignancy. We adjusted for the use of drugs that might affect the risk of pneumonia development. For example, ICSs and statins were considered to be covariate drugs because both have anti-inflammatory effects and may influence the development of pneumonia. Statins have recently been studied within COPD patients for relatively high incidence of pneumonia assumed by their anti-inflammatory action.29,30 A covariate drug user was defined as a patient taking an ACEi/ARB who was prescribed that covariate drug for more than 30 days during the year before the index date. However, systemic steroids were considered to be covariates whenever prescribed, thus regardless of the duration of medication. The daily doses of ICSs were classified as low (<250 µg/day of the fluticasone equivalent), medium (250 to <500 µg/day), and high (≥500 µg/day).31,32

**Statistical analysis**

The Mann–Whitney U-test and Student’s t-test were used to perform between-group comparisons of continuous variables, and the chi-squared test was used to compare the categorical variables. Conditional logistic regression was employed to explore the association between ACEi/ARB use and the risk of pneumonia in COPD patients. In univariate analyses, the crude odds ratios (ORs) with 95% confidence intervals (CIs) were employed to describe associations between pneumonia and each variable. The risk estimation with a two-tailed P-value <0.05 was considered significant. Univariate logistic regression was performed to identify factors that were significantly associated with pneumonia. In multivariate analysis, prominent factors (P<0.20) in the univariate analyses and factors with clinical significance were included in multivariate models. All the results are reported as adjusted ORs with 95% CIs and P-values. Subgroup analysis of patients using ACEi and ARBs was not possible; the number of patients taking ARBs was relatively small.

**Results**

Finally, a total of 130 COPD patients with pneumonia, who required hospital admission, were enrolled, and 245 matched controls were selected from 1,646 COPD patients. The clinical characteristics of the cases and controls are listed in Table 1. Elderly patients (over 70 years of age) constituted more than 30% of the study population, and most of the patients were male. There were no significant differences in smoking habits or comorbidities (except for a history of pulmonary TB; 40.8% of cases vs 27.8% for controls, P=0.03) between cases and controls (Table 1).

In initial frequency analyses, the number of ACEi/ARBs users did not significantly differ between cases and controls (21.5% vs 26.9%, P=0.25). The mean duration of ACEi/ARBs therapy was also similar in the two groups (9.8 vs 9.6 months, P=0.83). We found no difference in the number of ICS users, the types of ICS used, or the equivalent ICS dose, in COPD patients with and without pneumonia. However, the level of exposure to systemic steroids and their cumulative doses were higher in COPD patients with pneumonia than those without pneumonia. The numbers of statin users were similar in both the groups (Table 2).

In univariate analyses, a history of pulmonary TB (OR =1.85, 95% CI 1.12–3.06, P=0.02) and use of systemic steroids (OR =2.33, 95% CI 1.28–4.23, P=0.005) were independently associated with the risk of pneumonia, but ACEi/ARB use was not (OR =0.70, 95% CI 0.41–1.23, P=0.21). Neither statin nor ICS use increased the risk of pneumonia (Table 3).

After the adjustment of statistically and clinically prominent risk factors that were revealed by univariate analysis (a past history of pulmonary TB, chronic renal disease, and use of systemic steroids and ICS), ACEi/ARBs were found to protect against the development of pneumonia (OR =0.51, 95% CI 0.27–0.98, P=0.04). The use of systemic steroids (OR =2.83, 95% CI 1.47–5.46, P=0.002), a history of pulmonary TB (OR =2.16, 95% CI 1.27–3.69, P=0.005), and renal disease (OR =2.94, 95% CI 1.18–7.31, P=0.02) were consistently associated with an increased risk of pneumonia (Table 4). ICS use was not a significant risk factor for the development of pneumonia, irrespective of the frequency of use or the cumulative dose.

**Discussion**

We defined the risk factors for the development of pneumonia in COPD patients taking RAS blockers including ACEi/ARBs; use of these drugs reduced the risk of pneumonia after adjustment for covariates including age, sex, severity of airflow limitation, comorbid disease, and the use of immunomodulatory drugs. To the best of our knowledge, this is the first study to show that ACEi/ARBs protect against the risk of pneumonia development in COPD patients.

Many drugs have been tried to find the association with pneumonia in COPD. The data are inconsistent; however,
Table 1  Clinical characteristics of study population

| Characteristics                      | COPD patients with pneumonia (n=130) | COPD patients without pneumonia (n=245)* | P-valueb |
|--------------------------------------|--------------------------------------|------------------------------------------|----------|
| Age, years (%)                       |                                      |                                          |          |
| 40–49                                | 11 (8.5)                             | 15 (6.1)                                 | 0.74     |
| 50–59                                | 21 (16.2)                            | 45 (18.4)                                |          |
| 60–69                                | 58 (44.6)                            | 116 (47.4)                               |          |
| ≥70                                  | 40 (30.7)                            | 69 (28.1)                                |          |
| Sex                                  |                                      |                                          |          |
| Male/female (ratio)                  | 110/20 (5.5)                         | 210/35 (6.0)                             | 0.77     |
| FEV₁, % predicted (%)                |                                      |                                          |          |
| <30                                  | 8 (6.1)                              | 7 (2.9)                                  | 0.28     |
| 30–50                                | 50 (38.5)                            | 85 (34.7)                                |          |
| 50–80                                | 66 (50.8)                            | 144 (58.8)                               |          |
| >80                                  | 6 (4.6)                              | 9 (3.7)                                  |          |
| Smoking habits (%)                   |                                      |                                          |          |
| Never                                | 7/90 (7.8)                           | 14/144 (9.7)                             | 0.11     |
| Ex-smoker                            | 62/90 (68.9)                         | 86/144 (59.7)                            |          |
| Current smoker                       | 21/90 (23.3)                         | 44/144 (30.6)                            |          |
| Comorbidities (%)                    |                                      |                                          |          |
| Pulmonary tuberculosis               | 53 (40.8)                            | 68 (27.8)                                | 0.03     |
| Diabetes mellitus                    | 27 (20.8)                            | 39 (15.9)                                | 0.35     |
| Hypertension                         | 45 (34.6)                            | 72 (29.4)                                | 0.42     |
| Ischemic heart disease               | 12 (9.2)                             | 17 (6.9)                                 | 0.50     |
| Congestive heart failure             | 11 (8.5)                             | 11 (4.5)                                 | 0.20     |
| Other heart diseases                 | 17 (13.1)                            | 21 (8.6)                                 | 0.27     |
| Cerebrovascular disease              | 10 (7.7)                             | 20 (8.2)                                 | 0.63     |
| Liver disease                        | 5 (3.9)                              | 14 (5.7)                                 | 0.37     |
| Renal disease                        | 12 (9.2)                             | 11 (4.5)                                 | 0.13     |
| Malignant disease                    | 9 (6.9)                              | 30 (12.2)                                | 0.17     |

Notes: *Controls matched with age, sex, and category of post-FEV₁ spirometry results within proper index date of matched patients; two matched controls for 115 cases and one matched control for 15 cases. +Chi-square test for categorical variables and Student’s t-test for continuous variables.

Abbreviation: FEV₁, forced expiratory volume for 1 second.

Table 2  Distribution of therapeutic medication in study population

| Therapeutic medication          | COPD patients with pneumonia (n=130) | COPD patients without pneumonia (n=245) | P-valuec |
|--------------------------------|--------------------------------------|------------------------------------------|----------|
| ACEI/ARBs                       |                                      |                                          |          |
| Ever use (%)                    | 28 (21.5)                            | 66 (26.9)                                | 0.25     |
| Months, mean (SD)               | 9.8 (3.5)                            | 9.6 (3.6)                                | 0.83     |
| Inhaled corticosteroids         |                                      |                                          |          |
| Ever use (%)                    | 77 (59.2)                            | 144 (58.8)                               | 0.32     |
| Types (%)                       |                                      |                                          |          |
| Fluticasone                     | 56 (72.7)                            | 102 (70.8)                               | 0.77c    |
| Budesonide                      | 20 (26.0)                            | 38 (26.4)                                |          |
| Beclomethasone                  | 1 (1.3)                              | 4 (2.8)                                  |          |
| Daily dose, µg/day (%)          |                                      |                                          |          |
| Low (<250)                      | 32 (42.6)                            | 49 (34.0)                                | 0.33     |
| Medium (250 ≤ <500)             | 14 (18.2)                            | 38 (26.4)                                |          |
| High (≥ 500)                    | 31 (40.2)                            | 57 (39.6)                                |          |
| Equivalent dose, median (IQR)   | 333.3 (125.0–625.0)                   | 354.2 (200.0–500.0)                      | 0.93d    |
| Systemic steroids               |                                      |                                          |          |
| Ever use (%)                    | 30 (23.1)                            | 27 (11.0)                                | 0.005    |
| Cumulative dose, median (IQR)   | 359.5 (176.0–811.0)                   | 172.0 (128.0–336.0)                      | 0.03e    |
| Statins                         |                                      |                                          |          |
| Ever use (%)                    | 9 (6.9)                              | 37 (15.1)                                | 0.52     |

Notes: +Chi-square test for categorical variables and Student’s t-test for continuous variables. Fisher’s exact test. Wilcoxon rank sum test. *Equivalent dose of fluticasone.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; IQR, interquartile range; SD, standard deviation.
ACEi/ARB use is widespread and increasing and will rise further as the incidences of chronic diseases requiring ACEi/ARBs such as cardiovascular, endocrine, and renal diseases increase. Such conditions are common comorbidities in COPD patients. The RAS plays a role in cardiovascular disease, renal disease, and hypertension. Moreover, targeting the RAS of other organs (eg, the lung) might be of benefit.15,17,37 RAS is also potentially implicated in the pathogenesis of COPD through its involvement in inducing proinflammatory mediators in the lung.6,7 Thus, RAS is a potential therapeutic target in COPD patients.15

The protective effect of a RAS blockade on pneumonia may be explained as follows. The blockade is anti-inflammatory in nature and immunomodulatory and has antioxidative effects in the lung.15 Angiotensin II stimulates the release of cytokines including interleukin-6, tumor necrosis factor-α, and monocyte chemotactic protein-1. Pneumonia patients with COPD exhibit various inflammatory patterns and have more pneumonia events than do patients with pneumonia alone.7,38 An anti-inflammatory effect achieved via RAS blockade may affect not only the outcomes but also the incidence of pneumonia in COPD patients. A RAS blockade is anti-inflammatory in nature and also immunomodulates the T-cell responses mediating the lung tissue injuries associated with COPD.39 Reactive oxygen species can be generated by the RAS via the angiotensin II type 1 receptor; these contribute to the oxidative stress and impaired redox signaling observed in COPD patients.40,41 In addition, an ACE inhibitor-associated mechanism improving asymptomatic dysphagia and the cough reflex may contribute to effective protection.18,19

In this study, the use of systemic steroids, a history of pulmonary TB, and the presence of renal disease were associated with increased risks of pneumonia. The use of systemic steroids reflects the occurrence of (at least moderate) exacerbation events. Whether the use of systemic steroids increased the incidence of pneumonia or whether systemic steroids were used more frequently for managing AECOPD cannot

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**Table 3** Risk of pneumonia (cOR) according to each variable in univariate analysis

| Variable                        | cOR  | 95% CI | P-value |
|---------------------------------|------|--------|---------|
| Comorbidities                   |      |        |         |
| Pulmonary tuberculosis          | 1.85 | 1.12–3.06 | 0.02   |
| Congestive heart failure        | 1.84 | 0.79–4.31 | 0.16   |
| Renal disease                   | 2.18 | 0.96–4.95 | 0.06   |
| Malignant disease               | 0.56 | 0.26–1.20 | 0.15   |
| ACEi/ARB                        |      |        |         |
| No use                          | 1.00 |        | 0.21    |
| Ever use                        | 0.70 | 0.41–1.23 |        |
| Inhaled corticosteroids         |      |        |         |
| No use                          | 1.00 |        | 0.74    |
| Ever use                        | 0.92 | 0.58–1.47 |        |
| Inhaled corticosteroids,        |      |        |         |
| equivalent dose (µg/day)        |      |        |         |
| No use                          | 1.00 |        | 0.34a   |
| Low (<250)                      | 1.09 | 0.61–1.94 |        |
| Medium (≥250, <500)             | 0.63 | 0.31–1.30 |        |
| High (≥500)                     | 0.96 | 0.54–1.69 |        |
| Systemic steroids               |      |        |         |
| No use                          | 1.00 |        | 0.005   |
| Ever use                        | 2.33 | 1.28–4.23 |        |
| Statins                         |      |        |         |
| No use                          | 1.00 |        | 0.48    |
| Ever use                        | 0.72 | 0.28–1.83 |        |

Notes: Conditional logistic regression analysis for the incidence of pneumonia by each variable. P-value for trend.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; CI, confidence interval; cOR, crude odds ratio.

statins have been reported to reduce pneumonia risk.9,16,33 ICSs actually increase the risk in COPD patients.44,45 Therefore, we considered such drug use and created all covariates necessary to allow us to determine the true association between ACEi/ARB use and the pneumonia risk. Multivariate analysis then revealed that ACEi/ARBs protected against pneumonia development.

Associations between ACEi/ARBs use and pneumonia risk have been inconsistent in previous studies on general populations and stroke patients, even in meta-analyses.23,24,26–28 However, ACEi/ARB use has been reported to lower the risk of pneumonia or to have a protective effect in specific populations including the elderly, neurologically ill, and the Asians.21–26 It could be inferred that these drugs affect differently on selective populations. COPD patients are vulnerable to pneumonia in old age, to concomitant drugs, and to deterioration of COPD per se. Several studies on COPD patients have been published.9,33 Mortensen et al33 found that the use of statins and ACEi prior to admission reduced the mortality of patients hospitalized with COPD exacerbations. Nevertheless, few reports have evaluated the associations between ACEi/ARB use and pneumonia in susceptible populations or the risk of hospitalization to treat pneumonia in COPD patients. Thus, our data are of clinical significance.

It is more important to reduce the risk of pneumonia in COPD patients than the risk in general populations. Such risk minimization would reduce the incidence of AECOPD, a well-known cause of which is pneumonia.9–11,33 AECOPD has negative effects on the quality of life, lung function, and mortality.9–11,33 Therefore, ACEi/ARBs could be expected to protect any risk of event explained by pneumonia similar to exacerbation attack and maintain proper health status in patients with COPD.

ACEi/ARB use is widespread and increasing and will rise further as the incidences of chronic diseases requiring ACEi/ARBs such as cardiovascular, endocrine, and renal diseases increase. Such conditions are common comorbidities in COPD patients. The RAS plays a role in cardiovascular disease, renal disease, and hypertension. Moreover, targeting the RAS of other organs (eg, the lung) may be of benefit.15,17,37 RAS is also potentially implicated in the pathogenesis of COPD through its involvement in inducing proinflammatory mediators in the lung.6,7 Thus, RAS is a potential therapeutic target in COPD patients.15

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In this study, the use of systemic steroids, a history of pulmonary TB, and the presence of renal disease were associated with increased risks of pneumonia. The use of systemic steroids reflects the occurrence of (at least moderate) exacerbation events. Whether the use of systemic steroids increased the incidence of pneumonia or whether systemic steroids were used more frequently for managing AECOPD cannot
be assessed. Frequent exacerbation is a well-known COPD phenotype, regardless of baseline lung functional values.\textsuperscript{10,42} Several mechanisms of exacerbation exist but remain poorly defined. An increased susceptibility to viral infection has been suggested to trigger more frequent exacerbation; bacterial infection and colonization may also be in play.\textsuperscript{9,12–14} Patients with histories of frequent exacerbation are most likely to be admitted to hospitals.\textsuperscript{10,13} These patients need more systemic steroids, and it might make the patients more susceptible to pneumonia. Despite ambiguity in the temporal relationships between systemic steroid use and pneumonia, steroid use was closely associated with the prevalence of pneumonia in our study.

Notably, a history of pulmonary TB was associated with pneumonia in COPD patients. Such a history was defined when radiological data indicated prior TB or a history of anti-TB medication was noted. Although all reviews were retrospective, all the patients had been followed up in the Pulmonary Divisions of the Departments of Internal Medicine of our two hospitals, and any history of pulmonary TB was thus reliably taken. Pulmonary TB is associated with chronic airflow obstruction that continues for several years after TB treatment; the obstruction is similar to that of COPD.\textsuperscript{10,43} Previous studies\textsuperscript{16,44,45} also found that a history of pulmonary TB increased the risk of COPD; the prevalence of COPD was higher in such patients. Patients with COPD are at higher risk of community-acquired pneumonia, in particular those who are elderly, who have comorbidities, and who have severe COPD.\textsuperscript{46} This TB–COPD–pneumonia interrelationship explains the increased risk of pneumonia in COPD patients with histories of TB.

Renal disease is a well-known risk of hospitalization with and death from pneumonia; the risk is greater for patients with lower glomerular filtration rates.\textsuperscript{14,38,47} One study found that the cumulative 5-year probability of hospitalization to treat pneumonia was 36% in hemodialysis patients.\textsuperscript{31} In addition, renal diseases, such as chronic kidney disease and conditions necessitating dialysis, were associated with an increased risk of pneumonia requiring hospital admission.

A nested case–control study retrospectively compares cases with controls treated during a certain period. In this study, drug use for at least 1 month was required to define a user. We employed the concept of the index date, which was the date of admission to treat pneumonia for cases, and the day (within 6 months before or after the case index date) when a control COPD patient visited the hospital. We ensured comparability by thorough individual matching that was preserved throughout the entire analytical process. Our principal finding is that ACEi/ARBs significantly lower the risk of pneumonia development.

Despite the interesting findings of this study, there are still limitations. First, the use of drugs (ICSs, steroids, and ACEi/ARBs) was estimated only with reference to prescription records; we had no data on adherence to medication regimes. This may have biased our analysis of drug efficacies.
However, most patients were regularly prescribed drugs to treat comorbid renal or heart diseases in the appropriate department of our hospitals. In addition, we excluded patients who took ACEi/ARBs for less than 30 days in the year prior to the index date. Additionally, ACEi/ARB is known to be a drug of high adherence. Therefore, there is much less possibility of missed estimation for the tested drugs in this study. Second, our study population was relatively small and our review was retrospective. However, we utilized a nested case–control design; this is appropriate when drug utility is to be evaluated. We also defined appropriate index dates and exposure times, allowing risks to be compared between the two groups. Third, unknown confounding factors may have affected our results. However, we evaluated common drugs used for COPD patients as well as comorbidities related to COPD, which were enough for covariates in statistical analysis.

**Conclusion**

This study showed that the exposure to ACEi/ARBs was associated with the reduction in the risk of pneumonia development in patients with COPD. Considering the anti-inflammatory effects of ACEi/ARB and their protective impact on pneumonia in this study, further prospective studies are necessary to confirm our results and elucidate the underlying mechanisms of ACEi/ARB in protecting pneumonia in COPD patients.

**Author contributions**

DKK planned this study, had access to the data, and took responsibility for the integrity of the data and data analysis. JK and DKK contributed to study concept and design, analysis, and preparation of the manuscript. JL contributed to study concept, data collection, and preparation of manuscript. EYH contributed to study concept, data collection, and preparation of manuscript. HSC contributed to study concept, data collection, and preparation of manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

**Disclosure**

The authors report no conflicts of interest in this work.

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