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Angiotensin-converting enzyme inhibitor use and pneumonia risk in a general population

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ABSTRACT: The aim of the present study was to assess whether the use of angiotensin-converting enzyme (ACE) inhibitors is associated with a decreased risk of hospitalisation for community-acquired pneumonia (CAP) in a general, essentially white population.

Data were obtained from the Dutch PHARMO Record Linkage System. Cases were defined as patients with a first hospital admission for CAP. For each case, up to four population controls were matched by age and sex.

The study population comprised 1,108 patients with a first hospital admission for CAP and 3,817 matched controls. After adjusting for several confounders, ACE inhibitor use was not associated with a decreased incidence of pneumonia (adjusted odds ratio (OR) 1.12; 95% confidence interval (CI) 0.88–1.43). Additionally, no significant association was observed in patients with diabetes, respiratory diseases, heart failure, or patients with both of the last two conditions. Furthermore, adjustment of treatment effects on pneumonia risk using stratification on balancing score also showed no significant association between ACE inhibitor use and pneumonia risk within the different strata (overall adjusted OR 1.09; 95% CI 0.87–1.36).

In contrast with previous findings in Asian populations, the current authors were not able to confirm the beneficial effect of angiotensin-converting enzyme inhibitors on pneumonia risk in a general, essentially white population.

KEYWORDS: Angiotensin-converting enzyme inhibitor, angiotensin-converting enzyme insertion/deletion polymorphism, pneumonia

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Community-acquired pneumonia (CAP) is a major direct cause of death in the elderly, with mortality rates ranging 5–20% [1, 2]. The increased incidence of CAP in the elderly is thought to be caused first by silent or manifest aspiration of oropharyngeal flora into the lungs and, secondly, by decreased function of the immune system [3, 4]. Angiotensin-converting enzyme (ACE) has a number of functions in the inflammatory/immune system. Along with its effect that cleaves angiotensin I to angiotensin II, ACE also metabolises the protussive peptides, substance P and bradykinin [5]. The decreased metabolism of these peptides by ACE inhibition could enhance the cough reflex and prevent aspiration. Besides this, ACE inhibition prevents the angiotensin II-induced transcription of the pro-inflammatory nuclear factor-κβ [6, 7]. Recent studies have demonstrated that ACE inhibitor use is associated with a reduced incidence of pneumonia, particularly in the elderly [8–12]. These studies were performed in subjects of Asian ethnicity with a history of stroke. Although these studies add to the body of evidence about the possible effects of these drugs on pneumonia risk, little is known about the extent of the protective effect and whether or not it is present in the general population. The aim of the present study was to assess whether use of ACE inhibitors is associated with a decreased risk of hospitalisation for CAP in a general, essentially white population.

METHODS

Data source

The PHARMO record linkage system (www.pharmo.nl) was used to provide data for the study. PHARMO includes pharmacy dispensing records from community pharmacies, and is linked to the hospital discharge records of >2,000,000 community-dwelling residents of >40 population-defined areas in the Netherlands from 1985 onwards [13]. Since virtually all patients in the Netherlands are registered with a single

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community pharmacy, independent of prescriber, pharmacy records are virtually complete with regard to receipt of prescription drugs.

The computerised drug dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen, and the estimated duration of use. The duration of use of each dispensed drug is estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. The hospital discharge records are obtained from PRISMANT, previously known as the Dutch Centre for Healthcare Information (LMR database), an institute that collates nationwide all hospital discharge records in the Netherlands since the 1960s into a standardised format. These records include detailed information concerning the primary and secondary discharge diagnoses, as well as diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM).

Patients

The study period consisted of a 6-yr period between January 1, 1995 and December 31, 2000. Cases were selected according to the following criteria: adult (aged >18 yrs) hospitalised with a primary discharge diagnosis of CAP and pneumococcal pneumonia (ICD-9-CM code 481), other bacterial pneumonia (ICD-9-CM code 482), bronchopneumonia, organism unspecified (ICD-9-CM code 485) or pneumonia, organism unspecified (ICD-9-CM code 486). Besides this, patients with a signature of bacterial pneumonia (secondary discharge diagnosis) coupled with a primary pulmonary diagnosis (ICD-9-CM codes 491–493 or 496) were selected. Deaths that were recorded during hospitalisation were also selected as cases. For each case, up to four population controls were matched by age and sex. Controls were patients who were present in the PHARMO database without a hospitalisation for CAP. The date of admission was the index date. For all subjects, pharmacy dispensing data were collected. Patients with no pharmacy dispensing history for the period minus 365 days until the index date were excluded.

Study design

The current study was a population-based case–control study.

Exposure assessment

For each patient, all prescriptions for ACE inhibitors and angiotensin-II antagonists (ATC code C09A–C09D) were identified between entry into the cohort and the index date. The exposure time of ACE inhibitor and angiotensin-II antagonist use was determined by calculation of the legend duration of treatment episodes. Treatment episodes were defined as a series of subsequent prescriptions refills for these drugs. A new episode was assumed if an interval of $\geqslant$30 occurred between the theoretical end date of a prescription and the dispensing date of the next prescription for the same patient. Patients were classified as current users if the index date was between the start date and end date of a treatment episode. Patients were classified as past users if they were not using at the index date, but had a history of use in the year before the index date. Patients were classified as new users if they received a first dispensing <14 days prior to the index date.

Assessment of potential confounders

Potential confounders in this study were drugs and ''medical signatures'' as measured by the receipt of prescriptions drugs that have been associated with an increased or decreased risk of CAP [14–17]. Cardiovascular drugs (cardiac glycosides and diuretics) were used as a marker for heart failure. Respiratory morbidity was measured by assessing the use of inhaled glucocorticoids, β-agonists or anticholinergic drugs. Furthermore, diabetes was assessed through the use of oral antidiabetic agents and/or insulin [18]. Identified confounding drugs were systemic glucocorticoids [19] and gastric acid-suppressing drugs [20]. For all these drugs, a patient was considered exposed if more than one dispensing took place within a 1-yr period prior to the index date.

Analysis

The data analysis was approached in two ways. First, as a measure of the association between ACE inhibitor use and the occurrence of hospitalisation for CAP, estimations of the relative risk through odds ratios (OR) were used. These were calculated using multivariable conditional logistic regression. Statistical interaction terms were used to determine potential modification of the association by comorbidities (heart failure, respiratory diseases or diabetes). Secondly, the balancing score method was applied to further determine potential modification of the effect of ACE inhibition by overall pneumonia risk [21, 22]. This technique enabled assessment of the association of ACE inhibitor use with pneumonia occurrence in patients who had an equal probability of being a case. Logistic regression analysis was used to model for being a case. Variables considered for inclusion in this model included all prescription drugs (except ACE inhibitors and angiotensin-II antagonists) evaluated as potential confounders in the current study. The model was used to calculate the probability of being a case for each individual patient in the full data set (1,108 cases and 3,817 controls). Patients were stratified by quintiles of the distribution of their balancing score. The goodness of fit of the balancing score was evaluated using its ability to balance the covariates within each quintile group, using the logistic regression. Subsequently, the effect of ACE inhibitor use on pneumonia risk was assessed within each quintile group. An overall effect was calculated using the Mantel–Haenszel statistic.

RESULTS

A total of 1,108 patients with a primary diagnosis of CAP were identified and matched to 3,817 controls. Baseline characteristics are shown in table 1. Both cases and controls had a mean$\pm$SEM age of 67$\pm$0.51 yrs and ~55% of the patients were male. The use of prescription drugs for both cases and controls is shown in table 2. The prevalence of using ACE inhibitors (current use) was higher among the cases (15.2%) than among controls (9.7%), yielding a crude OR of 1.65 (95% confidence interval (CI) 1.36–1.99). As only a very small number of patients (2.1%) were using angiotensin-II antagonists, this was

TABLE 1 Patient characteristics of cases and controls

Characteristics	Cases	Controls
Subjects n	1108	3817
Age yrs		
<40	99 (8.9)	396 (10.3
40–49	91 (8.2)	352 (9.2)
50–59	116 (10.5)	461 (12.1)
60–69	190 (17.1)	637 (16.7)
70–79	353 (31.9)	1048 (27.5)
80–89	218 (19.7)	798 (20.9)
⩾90	41 (3.7)	125 (3.3)
Sex		
Male	650 (58.7)	1998 (52.3)
Female	458 (41.3)	1819 (47.7)
CAP discharge diagnosis		
Primary diagnosis of CAP	1100 (99.3)	
Pneumococcal pneumonia	84 (7.6)	
Other bacterial pneumonia	90 (8.1)	
Bronchopneumonia, organism unspecified	140 (12.6)	
Pneumonia, organism unspecified	794 (71.7)	
Comorbidities		
Heart failure	126 (11.4)	108 (2.8)
Respiratory diseases	454 (41.0)	333 (8.7)
Diabetes	134 (12.1)	259 (6.8)

Data are presented as n and n (%). CAP: community-acquired pneumonia.

not analysed further. None of the patients could be classified as new users of ACE inhibitors or angiotensin-II antagonists. After adjusting for respiratory diseases, heart failure, diabetes, the use of systemic corticosteroids and gastric acid-suppressing drugs, the OR decreased to 1.12 (95% CI 0.88–1.43). Considering different comorbidities, as shown in table 3, no significant association was observed in patients with diabetes (adjusted OR 1.02; 95% CI 0.59–1.77), respiratory diseases (adjusted OR 0.97; 95% CI 0.59–1.60), heart failure (adjusted OR 0.69; 95% CI 0.30–1.60) or patients with both of the last two conditions (adjusted OR 1.06; 95% CI 0.40–2.87).

TABLE 2 Univariate odds ratios (OR) of hospitalisation for community-acquired pneumonia and use of medication in the year before the index date

Characteristics	Cases	Controls	Crude OR (95% CI)
Subjects n	1108	3817	
Cardiac glycosides	124 (11.2)	156 (4.1)	2.92 (2.26–3.77)
ACE inhibitors	168 (15.2)	370 (9.7)	1.65 (1.36–1.99)
Ca-channel blockers	179 (16.2)	346 (9.1)	1.82 (1.49–2.24)
β-blockers	155 (14.0)	575 (15.1)	0.87 (0.72–1.06)
Diuretics	392 (35.4)	638 (16.7)	3.16 (2.66–3.75)
Oral corticosteroids	176 (15.9)	58 (1.5)	11.41 (8.27–15.76)
Anticholinergic inhalation	258 (23.3)	134 (3.5)	8.43 (6.58–10.80)
β-agonist inhalation	324 (29.2)	183 (4.8)	7.69 (6.21–9.53)
Inhaled corticosteroids	347 (31.3)	196 (5.1)	8.07 (6.52–9.98)
H2 antagonists	93 (8.4)	172 (4.5)	1.95 (1.49–2.55)
Proton pump inhibitor	144 (13.0)	226 (5.9)	2.33 (1.85–2.92)
Influenza vaccination	244 (22.0)	560 (14.7)	2.52 (1.94–3.28)

Data are presented as n, n (%) or OR (95% confidence interval (CI)). ACE: angiotensin-converting enzyme.

The balancing score derivation model, which included the variables use of cardiac glycosides, diuretics, calcium channel blockers, oral corticosteroids, anticholinergic inhalation, β-agonists, inhaled corticosteroids, gastric acid-suppressing drugs, cancer medication and influenza vaccination, was reliable since the OR for component variables were all between 0.90 and 1.10. None of the variables reached a significance level of 0.05 in any of the strata. In none of the balancing score strata was ACE inhibitor use significantly associated with pneumonia risk (table 4; overall adjusted OR 1.09; 95% CI 0.87–1.36).

TABLE 3 Associations between hospitalisation for community-acquired pneumonia and the use of angiotensin-converting enzyme inhibitors in all patients and different subgroups

Characteristics	Crude OR (95% CI)	Adjusted OR (95% CI)
All patients		
Current use	1.65 (1.36–1.99)	1.12 (0.88–1.43)#
Past use	2.09 (1.39–3.13)	1.43 (0.89–2.31)#
Patients with diabetes		
Current use	1.10 (0.69–1.75)	1.02 (0.59–1.77)¶
Patients with respiratory diseases		
Current use	0.98 (0.61–1.52)	0.97 (0.59–1.60)¶
Patients with heart failure		
Current use	0.81 (0.39–1.80)	0.69 (0.30–1.60)¶
Patients with both respiratory diseases and heart failure		
Current use	1.05 (0.40–2.75)	1.06 (0.40–2.87)¶

OR: odds ratio; CI: confidence interval. #: adjusted for diabetes, respiratory diseases, heart failure, use of systemic corticosteroids and gastric acid-suppressing drugs; ¶: adjusted for the use of systemic corticosteroids and gastric acid-suppressing drugs.

TABLE 4 Adjusted treatment effects on pneumonia risk using stratification on balancing score

	Subjects n	OR (95% CI)
Total sample	4925	1.09 (0.87–1.36)#
1st quintile group	982	1.48 (0.68–3.22)
2nd quintile group	986	1.22 (0.63–2.39)
3rd quintile group	694	1.66 (0.82–3.37)
4th quintile group	1278	0.90 (0.56–1.45)
5th quintile group	985	1.03 (0.75–1.42)

OR: odds ratio; CI: confidence interval. #: calculated using the Mantel–Haenszel statistic. Strata vary in size because a large group of patients with similar balancing scores near the 3rd quintile cut-off were entirely allocated to the 4th quintile group.

DISCUSSION

In the present study, no significant association between the use of ACE inhibitors and reduced risk of hospitalisation for CAP could be observed in a general, essentially white population. The initially observed overall higher use of ACE inhibitors for the cases compared with controls could, in the current authors' opinion, be explained by cardiovascular morbidity as a risk factor and indication for in-patient treatment of CAP [1, 16]. The fact that many of the patients used an ACE inhibitor in combination with a diuretic and cardiac glycosides could indicate that they were suffering from congestive heart failure as well. Additionally, the use of respiratory drugs was also higher for the cases, confirming chronic pulmonary diseases as risk factors for CAP [17]. The striking lower use of β-blockers for the cases could, in the current authors' opinion, be explained as confounding by contraindication. In the observed study period, the use of β-blockers was contraindicated for both heart failure and patients with asthma or chronic obstructive pulmonary disease (COPD; nonselective β-blockers) [23].

When considering the reduction of CAP risk using ACE inhibitors, there are several reasons to explain the difference between the present findings and those of the previously mentioned Asian studies [8, 10, 11]. One major difference with the study of OKAISHI *et al.* [11] is that the current study included patients with CAP admitted to a hospital, instead of nosocomial pneumonia in an in-patient ward. In addition, OKAISHI *et al.* [11] only included 55 cases and almost 80% of all cases (47% for controls) in this study were suffering from dementia and were in a bedridden state. It is unclear in what way pneumonia risk could be affected by these underlying chronic conditions. Previous studies have shown an increased pneumonia risk among patients in a bedridden state. It is presumed that ACE inhibitors can be protective in this specified patient group, but that their protective effect is absent in a larger general population. In contrast with the present study, OHKUBO *et al.* [10] only included patients with a history of stroke or transient ischaemic attack. In this randomised trial, a subject was considered as a case if pneumonia was reported by the patient during a routine follow-up with the researcher. The high percentage of fatal pneumonia in the study by OHKUBO *et al.* [10] (115 fatal and 155 nonfatal) is remarkable. In the current study, only 7.4% of all pneumonias was fatal, which corresponds well with literature reporting mortality rates ranging 5–20% [1, 2]. Given this information, this could mean an underestimation of nonfatal pneumonias in their study population. Another difference that was previously mentioned is the ethnicity. OKAISHI *et al.* [11] used Asian subjects exclusively and OHKUBO *et al.* [10] had a high percentage (39%) of Asian subjects as well. Although OHKUBO *et al.* [10] studied a more ambulatory population of patients with a history of stroke, they were not able to associate ACE inhibitor use with reduced pneumonia risk in their non-Asian participants, which is something that seems to be confirmed in the present study. One possible explanation for this is the higher prevalence of the I allele and II genotype in Asian participants. The ACE insertion/deletion polymorphism accounts for 47% of the total variance of serum ACE, with lowest ACE levels in the II genotype [24].

As mentioned previously, induction of the cough reflex is one possible explanation for the protective effect of ACE inhibitors on pneumonia risk. The mechanisms by which ACE inhibitors induce cough are thought to be inhibition of ACE and, with this, the metabolism of bradykinin and substance P, both inflammatory peptides that sensitise airway sensory nerves and enhance the cough reflex [5]. Considering that patients with the II genotype already have the lowest ACE activity, administration of an ACE inhibitor in these patients could increase bradykinin levels possibly above a cough threshold. This is something that seems to be confirmed by the study of YE *et al.* [25], which showed that the cough induced by ACE inhibitors was related to the I allele and II genotype and that ACE levels were significantly lower in patients with ACE inhibitor-induced cough. In addition, ACE inhibitor-related cough has been reported to be more prevalent in individuals of Asian ethnicity [26]. As the prevalence of the II genotype in white and African populations is low compared with the Asian population (18 *versus* 39%) [24], this provides a possible explanation why the current authors were not able to associate ACE inhibitor use with a reduced pneumonia risk in a general, essentially white population. However, in the recent study by OHKUBO *et al.* [10], this hypothesis could not be confirmed, possibly indicating that other unknown factors are involved.

The strength of the present study is that a large number of patients were included, it was population based and there was good data quality regarding exposure assessment. Furthermore, different methods were used to adjust for potential confounding. In both models, no association between ACE inhibitor use and pneumonia risk was observed. The application of the balancing score method to stratify patients in the present case–control study provided additional information that ACE inhibitor use was not associated with hospitalisation for CAP in both low- and high-risk patients.

A limitation of the current study is that only cases of hospitalised CAP were selected. Considering that not all CAP is treated as in-patient and that only the cases at risk of a worse outcome are hospitalised means it cannot be concluded whether ACE inhibitors are protective in low-risk patients. Another limitation is that pneumonia based on ICD-9 codes was included [27]. In the present study, >70% of the patients had a diagnosis of pneumonia of unspecified

organism recorded. It has been found that the aetiology of the infectious agent in many pneumonia cases remains unknown [28]. This could imply that, for example, some nonpneumonic exacerbations of COPD could be incorrectly recorded as pneumonia. However, other studies using advanced analytical techniques report percentages with known aetiology of up to 87% [29, 30], indicating that the fact no organism was specified using conventional techniques does not imply any pathogen was involved. Concerning adjusting for confounding in the current study, as many confounders as possible were corrected for. However, the current authors realise that there are additional risk factors that could not be controlled for [15–17]. In the present study, ''medical signatures'' by the receipt of prescription drugs were used to adjust for confounding through comorbidities. For this reason, the present authors were not able to adjust for other additional risk factors (*e.g.* current smoking, low body mass index, excessive use of alcohol, hypertension or stroke) as these medical conditions do not share a specific pharmacological treatment that could be uniquely measured. An additional limitation is that patients with no pharmacy dispensing history for the period minus 365 days until the index date were excluded. This could imply selection bias through exclusion of CAP patients without antecedent pharmological treatment. However, due to the high age of patients with pneumonia and the fact that many patients at least receive antibiotics for their pneumonia, the number of patients hospitalised for CAP without ever using prescription drugs is expected to be negligible.

In conclusion, angiotensin-converting enzyme inhibitor use does not reduce risk of hospitalisation for community-acquired pneumonia in a general, essentially white population. Further steps to elucidate the possible effects of angiotensin-converting enzyme inhibitors on community-acquired pneumonia may include more detailed information of angiotensin-converting enzyme genotype, angiotensin-converting enzyme gene expression profiles and (inflammatory) biomarkers to ascertain community-acquired pneumonia disease severity.

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