Angiotensin-converting enzyme inhibitor use and protection against pneumonia in patients with diabetes

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Objectives **Because of the high risk of pneumonia in patients with diabetes, we aimed to assess the effect of angiotensin-converting enzyme (ACE) inhibitor use on the occurrence of pneumonia in a general population of patients with diabetes.**

Methods **The study population comprised all patients in the UK General Practice Research Database who had a diagnosis of diabetes (both type 1 and type 2) between 1987 and 2001. Cases were defined as patients with a first diagnosis of pneumonia. For each case, up to four controls were matched by age, gender, practice, and index date. Patients were classified as current ACE inhibitor user when the index date was between the start and end date of ACE inhibitor therapy. Conditional logistic regression analysis was used to estimate the strength of the association between ACE inhibitor use and pneumonia risk.**

Results **ACE inhibitors were used in 12.7% of 4719 cases and in 13.7% of 15 322 matched controls [crude odds ratio (OR) = 0.92, 95% confidence interval (CI) = 0.82–1.01]. After adjusting for confounding, ACE inhibitor therapy was associated with a significant reduction in pneumonia risk (adjusted OR = 0.72, 95% CI = 0.64–0.80). The protective association was consistent across different relevant subgroups with the strongest association in patients with a history of stroke. There was a significant dose–effect relationship (*P* for trend <0.001).**

Conclusions **The use of ACE inhibitors is associated with a significant reduction in pneumonia risk and, apart from blood pressure-lowering properties, may be useful in the prevention of pneumonia in patients with diabetes.**
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Introduction

Community-acquired pneumonia is a major direct cause of death in the elderly with overall mortality rates varying from 5–20% [1,2]. Elderly patients and patients with comorbidities, such as diabetes, are at increased risk for pneumonia [1,3]. In the literature, there is evidence that angiotensin-converting enzyme (ACE) inhibitors, apart from their blood pressure-lowering properties, could protect against pneumonia [4–6]. To date, these studies were all conducted in patients with a history of stroke because induction of the cough reflex and prevention of aspiration was noted as the mechanism behind this protective effect [7,8]. Currently, there is accumulating evidence that ACE inhibitors also have different anti-inflammatory and immunomodulatory effects [9–11], providing an additional explanation for a protective effect, which could also be present in patients without a history of stroke. Therefore, we assessed the effects of ACE inhibitor use on the risk of acquiring pneumonia in an unselected high-risk population of diabetic patients.

Patients and methods

Data setting

Data for this study were obtained from the General Practice Research Database (GPRD), which contains the computerized medical records of approximately 650 general practices. The GPRD is owned by the UK Department of Health and managed by the Medicines Control Agency. Approximately 6.5% of the total population of England and Wales is represented in the database. The computer records contain patient demographics, characteristics (i.e. height, weight), symptoms and diagnosis [using the Oxford Medical Information System and Read codes, which are mapped onto International Classification of Disease codes], referrals to specialist care, hospital admissions and their major outcomes, and all drug prescriptions in chronological order. The computerized recording of patient information was started by many general practitioners in the late 1980s, and replaced the handwritten records used previously. Several independent validation studies have shown that

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the GPRD database has a high level of completeness and validity [12,13]. The study was approved by the Scientific and Ethical Advisory Group of the GPRD.

Study design and population

A population-based retrospective case–control study among diabetic patients (both type 1 and type 2) was conducted using data from 1 June 1987 to 21 January 2001. Cases were defined as patients aged 18 years and older who had a first diagnosis of pneumonia (for selected codes, see Appendix 1). The date of the pneumonia diagnosis recorded was the index date. For each case, up to four controls were matched on sex, age (± 2 years), general practice and index date. Controls were selected from patients also present in the GPRD database without a record for pneumonia. Both cases and controls were eligible when they had a medical history in the database for at least 365 days before the index date.

Drug exposure

For each patient, we identified all prescriptions for ACE inhibitors prior to the index date (cilazapril, captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril and trandolapril). The timing of ACE inhibitor use was determined by calculation of the legend duration of treatment episodes. Treatment episodes were defined as series of subsequent prescriptions for these drugs. A new episode was assumed if an interval of 14 days or more occurred between the theoretical end date of a prescription and the date of the next prescription for the same patient. Patients were classified as current users when the index date was between the start and the end date of a treatment episode. Patients were classified as past users when they were not a current user, but had a history of use in the year before the index date. Prescribed daily doses were expressed as the number of defined daily doses (DDDs) per day. This unit corresponds to the average daily dose of a drug for its main indication in adults and is recommended by the World Health Organization [14].

Potential confounders

For each patient, we identified co-morbidities and the receipt of prescriptions for drugs that have been associated with an increased or decreased risk of pneumonia. We evaluated the presence or absence of the following frequently occurring co-morbidities as potential confounders: congestive heart failure, history of stroke, evident alcohol abuse and pulmonary diseases (asthma and chronic obstructive pulmonary disease) [15–18]. Potential confounding drugs were pneumococcal vaccination, statins, oral glucocorticoids, gastric acid suppressing drugs and influenza vaccination [19–23]. A patient was considered to have been exposed to a prescription drug if more than one prescription was issued within a 1-year period prior to the index date, except for vaccination drugs that required only one prescription. In addition, diuretics (thiazides and loop diuretics) were examined as control drug because diuretics share the same indication as ACE inhibitors but are not expected to protect against pneumonia. Furthermore, smoking status was evaluated as a potential confounder. We calculated the number of general practitioner (GP) visits in the year before the index date as a proxy for general health status and health consumption.

Statistical analysis

Univariate analysis by the chi-squared test and Student's *t*-test was applied to test for statistically significant differences in baseline characteristics between cases and controls. Conditional logistic regression analysis was used to estimate the strength of the association between ACE inhibitor use and pneumonia and was expressed as odds ratios (OR) and 95% confidence intervals (CI). Potential confounders were included in the multivariate model when they were retained after backward stepwise elimination ($P < 0.10$). To assess a potential dose–response relationship, ACE inhibitor exposure was categorized into three categories of less than 1 DDD per day, 1–1.5 DDD per day and more than 1.5 DDD per day, respectively.

Results

The study population comprised 4719 patients with a diagnosis of pneumonia and 15 322 controls. Among the cases, 271 had a diagnosis of pneumococcal pneumonia, 46 had other bacterial pneumonia, 2050 had a diagnosis of bronchopneumonia with unspecified organism and 2291 had pneumonia with unspecified organism. Approximately 28% of all cases were referred to a hospital. Approximately 48% of the patients were male and both cases and controls had a mean $\pm$ SD age of 73 ± 11 years but, in cases, the proportion of very old was higher than in controls (Table 1). The prevalence of stroke, congestive heart failure, pulmonary diseases, alcohol abuse and smoking was higher in cases than controls, as was the use of diuretics, gastric acid suppressing drugs and oral glucocorticoids. Pneumococcal vaccination was more frequent among controls. Cases visited the GP more often than controls (15 versus nine visits per year, respectively; $P < 0.01$).

Among the 4719 cases, 600 patients (12.7%) were current users of ACE inhibitors compared to 13.7% for the control group (crude OR = 0.92, 95% CI = 0.89–1.01). After adjusting for confounders, current use of ACE inhibitors (OR = 0.72, 95% CI = 0.64–0.80) was significantly associated with a decreased risk of pneumonia. Covariates used for adjustment were age, congestive heart failure, history of stroke, pulmonary diseases, smoking, number of GP visits/year, oral glucocorticoid use, statin use, pneumococcal vaccination and use of gastric acid suppressing drugs. The decrease of the odds ratio was primarily caused by adding congestive heart failure to the model. The association was similar for all type of ACE inhibitors

Table 1 Characteristics of both cases and controls

Characteristic	Cases ($n=4719$), *n* (%)	Controls ($n=15322$), *n* (%)	Crude OR (95% CI)
Age (years)			
<60	525 (11.1)	1776 (11.6)	NA
60–69	785 (16.6)	3066 (20.0)	NA
70–79	1533 (32.5)	5665 (37.0)	NA
80–89	1622 (34.4)	4431 (28.9)	NA
≥ 90	254 (5.4)	384 (2.5)	NA
Gender			
Male	2275 (48.2)	7336 (47.9)	NA
Female	2444 (51.8)	7986 (52.1)	NA
Comorbid conditions			
History of stroke	1186 (25.1)	1901 (12.4)	2.37 (2.19–2.57)
Congestive heart failure	1421 (30.1)	2158 (14.1)	2.63 (2.43–2.84)
Pulmonary diseases	949 (20.1)	1592 (10.4)	2.17 (1.99–2.37)
Alcohol abuse	17 (0.4)	34 (0.2)	1.62 (0.91–2.91)
Prescription drugs			
Diuretic	831 (17.6)	1990 (13.0)	1.43 (1.31–1.56)
Pneumococcal vaccination	144 (3.1)	569 (3.7)	0.82 (0.68–0.98)
Influenza vaccination	1955 (41.4)	6114 (39.9)	1.07 (1.00–1.14)
Gastric acid suppressing drugs	967 (20.5)	1988 (13.0)	1.73 (1.59–1.88)
Oral glucocorticoids	311 (6.6)	329 (2.1)	3.22 (2.74–3.77)
Statins	63 (1.3)	365 (2.4)	0.55 (0.42–0.73)
Behavioural habits			
Current smoking[a]	407 (12.7)	1169 (9.2)	1.48 (1.31–1.67)

CI, Confidence interval; OR, odds ratio; NA, not applicable. [a]Percentage for current smoking calculated in subjects with information on smoking history recorded in the General Practice Research Database.

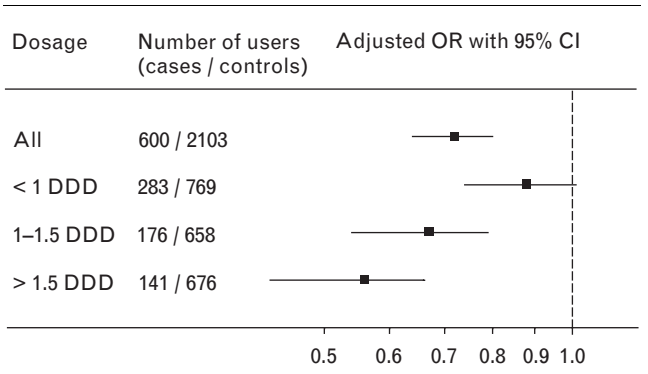
and consistent across all seasons (data not shown). Furthermore, a protective effect was present in all comorbidity related subgroups with the strongest association in patients with a history of stroke (adjusted OR = 0.54, 95% CI = 0.43–0.69; no history of stroke: adjusted OR = 0.77, 95% CI 0.68–0.88). For patients with heart failure and/or pulmonary diseases the adjusted OR was 0.72 (95% CI = 0.63–0.80) and 0.83 (95% CI = 0.62–1.09), respectively. The protective effect of current ACE inhibitor use could only be established for pneumonia treated in primary care (adjusted OR = 0.61, 95% CI = 0.53–0.70). We could not demonstrate such an association between ACE inhibitor use and risk of pneumonia requiring hospitalization (adjusted OR = 1.00, 95% CI = 0.82–1.24). In the analyses regarding a potential dose–response, dosages of ACE inhibitors of more than 1.5 DDD per day showed a stronger inverse association with pneumonia risk (OR = 0.54; 95% CI = 0.44–0.67) than lower daily dosages of ACE inhibitors with a significant dose–response relationship (Fig. 1, *P* for trend <0.001). Past use of ACE inhibitors was not associated with a decreased pneumonia risk (OR = 1.83, 95% CI = 1.50–2.23). Furthermore, current use of diuretics was not associated with a decreased pneumonia risk (OR = 0.96, 95% CI = 0.86–1.07) when adjusted for age, congestive heart failure, history of stroke, pulmonary diseases, smoking, number of GP visits/year, oral glucocorticoid use, ACE inhibitor use, statin use, pneumococcal vaccination and use of gastric acid suppressing drugs.

Discussion

The present study demonstrates that use of ACE inhibitors is associated with a reduction in the risk of pneumonia in diabetic patients and that the effect is consistent across several relevant subgroups with the strongest effect in patients with a history of stroke. Furthermore, a significant dose–response relationship is present. The study has several strengths, including the use of a large representative and valid database, the inclusion of a high-risk population of diabetic patients and the possibility to adjust for important potential confounders.

Experimental studies have suggested two potential mechanisms along which ACE inhibitors may reduce the occurrence of pneumonia: (i) decreased metabolism of the protussive peptides bradykinin and substance P by ACE

Fig. 1



Current use of different dosages of angiotensin-converting enzyme inhibitors and association with pneumonia. *Adusted for age, congestive heart failure, history of stroke, pulmonary diseases, smoking, number of general practitioner visits/year, oral glucocorticoid use, statin use, pneumococcal vaccination, and use of gastric acid suppressing drugs. OR, Odds ratio; CI, confidence interval; DDD, daily defined dose.

inhibition could enhance the cough reflex and prevent aspiration [7], and (ii) ACE inhibition could influence the inflammatory response to pathogens in the lung. For example, ACE inhibitors have been linked to lower tumour necrosis factor-α and interleukin-6 levels in humans and reduced lipopolysaccharide-induced pulmonary neutrophil influx [11]. Furthermore, angiotensin II is believed to play an important role in tissue repair and remodelling [24] and inhibition of ACE has revealed an important role in acute lung injury-related endothelial cell damage and acute respiratory distress syndrome [10]. One possible mechanism behind this is the prevention of angiotensin II-induced transcription of the proinflammatory nuclear factor-κB [25]. Nuclear factor-κB regulates the transcription of several genes that encode proteins (such as cytokines, chemokines, adhesion molecules and enzymes) involved in mediator synthesis and the further amplification and perpetuation of the inflammatory response [26]. The findings from the present study indicating that the protective effect was also present for patients without a history of stroke and that there was an evident dose–effect relationship suggest that the protection against pneumonia could, in addition, be explained by the proposed immunomodulatory effect of ACE inhibitors. Further research is necessary to explore the anti-inflammatory properties of ACE inhibitors in community-acquired pneumonia.

Furthermore, to our knowledge, the present study is the first to associate the use of ACE inhibitors with reduced pneumonia risk in a predominantly white population. Previous studies with similar results were solely conducted in elderly Asian populations [4–6], except for the study by Ohkubo *et al.* [5] who included non-Asian participants as well but was unable to confirm a beneficial effect in their non-Asian participants. The finding of a null effect was explained by potential genetic differences in the ACE gene between Asian and non-Asian populations [27,28]. In addition, this is also the first study to indicate a possible role for ACE inhibition in preventing pneumonia in outpatients. Approximately 80% of all pneumonia is treated in an outpatient setting [29,30]. In the present study, the protective effect of ACE inhibition was primarily present for outpatient-treated pneumonia. The fact that no association was observed for hospitalized pneumonia could possibly be explained by selection bias through comorbidities treated by ACE inhibitors serving as indication for inpatient treatment [31]. In particular, heart failure is a strong reason for inpatient treatment in different prediction rule models and, subsequently, this could lead to an overestimation of ACE inhibitor use in identified admitted pneumonia cases versus population controls. This might explain why, in two previous case–control studies, no protective association between ACE inhibitor use and pneumonia was observed [32,33].

Our observational study also has some potential limitations. First, our study was based on computerized databases and subject to the limitations of such studies. Second, the identification of cases with pneumonia has a potential for misclassification due to inaccurate diagnostic assessment or incorrect coding. For example, acute exacerbations of chronic obstructive pulmonary diseases could be inaccurately classified as pneumonia. However, most variables that were considered to be risk factors for pneumonia appeared to be associated with pneumonia in our study [15,16,19–21], reducing the plausibility of misclassification, unless the misclassified diseases share comparable risk factors. Also, the incidence of pneumonia during the year showed an expected pattern, with most cases occurring during the winter season. Finally, if anything, misclassification of pneumonia would have been random, which will always lead to the finding of a null effect.

Another concern could be that people on ACE inhibitors take more comfort out of good health support, which can also lower pneumonia risk. However, we believe that this healthy user effect, if present, is small in the UK because ACE inhibitors are prescribed for numerous indications associated with an increased pneumonia risk (e.g. hypertension, heart failure). The fact that the use of ACE inhibitors in the present study is still associated with a decreased risk of pneumonia provides good evidence for ACE inhibitors being beneficial, as well as because diuretics did not show a protective effect (adjusted OR = 0.96; 95% CI = 0.86–1.08). Another limitation of this study is the lack of information on certain prognostic factors, such as socio-economic status (SES) which has been proposed as a potential confounder [34]. We tried to minimize such confounding through matching subjects on practice, and thereby on geographical region and city area. However, the use of postcodes as a proxy for SES is debated in literature [35,36]. We cannot rule out confounding due to unknown or unmeasured factors in this observational study.

Furthermore, misclassification of exposure to ACE inhibitor therapy is a concern because we used prescription data. Patients using ACE inhibitors could have been non-compliant with their therapy and therefore could have used less ACE inhibitors than prescribed. However, this would have led to an underestimation of the association between ACE inhibitor use and pneumonia occurrence.

To our knowledge, the mechanism of ACE inhibition is no different between patients with and without diabetes, indicating that the association found in the present study may be applicable for the general population at large. However, the association in the general population could be less pronounced due to the lower probability of pneumonia compared to diabetic patients [3]. Further studies are required to elucidate a possible protective effect in non-diabetic patients.

In conclusion, the use of ACE-inhibitors is associated with a significant dose-dependent reduction in risk of pneumonia in diabetic patients and with a strong dose–effect relationship. These findings could provide additional support for using ACE-inhibitors in the treatment of hypertension and heart failure in patients with diabetes.

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Appendix

Description of the Oxford Medical Information System and the Read codes used with case selection

Codes	Description
H28.00	Atypical pneumonia
H261.0	Basal pneumonia due to unspecified organism
485	Bronchopneumonia
H25.00	Bronchopneumonia due to unspecified organism
H21.00	Lobar (pneumococcal) pneumonia
481 B	Lobar pneumonia
H260.0	Lobar pneumonia due to unspecified organism
H22.00	Other bacterial pneumonia
486	Pneumonia
H2. . .0	Pneumonia and influenza
486 AP	Pneumonia aspiration
483 AT	Pneumonia atypical
481 BA	Pneumonia basal
H26.00	Pneumonia due to unspecified organism
483 M	Pneumonia mycoplasal
H2z.00	Pneumonia or influenza NOS
481 A	Pneumonia pneumococcal
4823	Pneumonia staphycoccal
486 T	Pneumonitis