RESPIRATORY INFECTION

Statin treatment and reduced risk of pneumonia in patients with diabetes

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Background: Recent prognostic studies have shown that previous treatment with statins is associated with a better outcome in patients admitted to hospital with pneumonia. Because of an increased risk of pneumonia in patients with diabetes, we assessed the effects of statin use on the occurrence of pneumonia in adult diabetic patients.

Methods: All patients with a diagnosis of diabetes (types 1 and 2) enlisted in the UK General Practice Research Database between 1 June 1987 and 21 January 2001 were included. A case-control study was performed with cases defined as patients with a first recorded diagnosis of pneumonia. For each case up to four controls were matched by age, sex, practice, and index date. Patients were classified as current users when the index date was between the start and end date of statin treatment. Conditional multiple logistic regression analysis was used to estimate the strength of the association between statin treatment and the occurrence of pneumonia.

Results: Statins were used in 1.1% of 4719 cases and in 2.1% of 15 322 matched controls (crude odds ratio (OR) 0.51, 95% CI 0.37 to 0.68). After adjusting for potential confounders, treatment with statins was associated with a significant reduction in the risk of pneumonia (adjusted OR 0.49, 95% CI 0.35 to 0.69). The association was consistent among relevant subgroups (cardiovascular diseases, pulmonary diseases) and independent of the use of other prescription drugs.

Conclusions: The use of statins is associated with a considerable reduction in the risk of pneumonia in diabetic patients. In addition to lowering the risk of cardiovascular disease, statins may be useful in preventing respiratory infections.

Community acquired pneumonia ranks in the top 10 leading causes of death in the elderly and is a significant and increasing cause of primary care consultations and hospital admissions.[1–3] Individuals with co-morbid conditions such as diabetes types 1 and 2 are at increased risk for lower respiratory tract infections and their complications.[4 5] Furthermore, the impact of diabetes on deaths associated with pneumonia is substantial.[6]

Recent in vitro studies have shown that inhibitors of hydroxy-methylglutaryl coenzyme A reductase (statins) have different immunomodulatory effects and that statins modulate both lipopolysaccharide induced pulmonary inflammation and pulmonary bacterial infection.[7] Clinical prognostic studies have confirmed a potential immune regulatory effect and showed that previous treatment with statins was associated with decreased rates of severe sepsis and mortality in patients admitted to hospital with community acquired bacterial infections such as pneumonia.[8–12] We therefore hypothesised that, if the use of statins can improve the outcome in pneumonia, statin treatment may prevent development of the infection itself. The aim of this study was to assess whether the use of statins is associated with a decreased risk of developing pneumonia in an ambulatory population of diabetic patients.

METHODS

Data source
Data were obtained from the United Kingdom General Practice Research Database (GPRD) which contains the computerised 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 demographic characteristics (height, weight), symptoms and diagnosis (using the Oxford Medical Information System (OXMIS) 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 computerised 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 the GPRD database has a high level of completeness and validity.[13 14] The study was approved by the Scientific and Ethical Advisory Group of the GPRD.

Study design and population
This retrospective case-control study was conducted in a population of 142 175 patients with diabetes (both types 1 and 2) recorded in the GPRD from 1 June 1987 to 21 January 2001 (original data extraction early 2002). This population has been used for previous studies on other topics not related to the present research study.[15 16]

Cases were defined as patients aged 18 years and older with a first medical attendance for an episode of community acquired pneumonia (for selected OXMIS and Read codes see Appendix 1). The date of pneumonia diagnosis was recorded as the index date. For each case up to four controls were matched for sex, age (± 2 years), general practice, and index date of the case. Controls were randomly selected from the baseline cohort of diabetic patients without a record of pneumonia. To be able to control for potential prognostic

differences between comparison groups, both cases and controls were eligible for inclusion in the study if they had a medical history in the database for at least 365 days before the index date.

Exposure to statins

For each patient we identified all prescriptions for statins before the index date (atorvastatin, cerivastatin, fluvastatin, pravastatin, simvastatin). Episodes of statin treatment were defined as a series of subsequent prescription refills for these drugs. We assumed that a new episode of treatment started 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. The theoretical end date was defined as the prescription date plus the duration of use (number of tablets prescribed divided by the prescribed daily dose). Patients were classified as current statin 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.

Potential confounders

To be able to control for potential confounding, medical information was obtained on pneumonia risk factors that could potentially confound the association between statin treatment and outcome. For each patient we evaluated the presence or absence of the following frequently occurring co-morbidities as potential confounders: cardiovascular diseases (congestive heart failure, stroke), pulmonary diseases, and alcoholism.[17–20] In addition, the latest data on smoking status (non-smoking, ex-smoking, current smoking, or unknown) and body mass index (<20, 20–24, 25–30, >30 kg/m^2, or unknown) were assessed. Possible confounding drugs examined were influenza vaccination, pneumococcal vaccination, immunosuppressive drugs (methotrexate, cyclosporin,

tacrolimus, etanercept, infliximab, fludarabin, cladrimycin, rituximab, or alemtuzimab), oral glucocorticoids, and use of gastric acid suppressing drugs.[21–24] A patient was considered to have been exposed to a drug if more than one prescription was issued in the year before the index date, except for vaccination drugs which required only one prescription. The prescription drugs shown above were selected because they have been linked to a decreased or increased risk of pneumonia, and those receiving these drugs may be more likely to receive statins because of their likelihood of attending a physician. We calculated the number of general practitioner (GP) visits in the year before the index date as a proxy for overall health status and healthcare consumption.

Statistical analysis

Univariate analysis by χ^2 tests and Student t tests was used to test for statistically significant differences in baseline characteristics between cases and controls. Conditional logistic regression was used to estimate the strength of the association between statin treatment and the risk of pneumonia and expressed as odds ratios (OR) with 95% confidence intervals (CI). We included all potential confounders and age in the multivariate analysis to adjust for the baseline differences between both groups. Exposure to statins was categorised as current, past, and never (reference). In addition, to elucidate a possible time trend effect, the study population was divided into quartiles based on ranked index dates and analysed separately. Stratified analyses were conducted to detect possible differences in effect between co-morbidity related subgroups.

RESULTS

The study population comprised 4719 patients with a diagnosis of pneumonia and 15 322 matched controls. A diagnosis of pneumococcal pneumonia was recorded for 271 of the cases, 46 had a diagnosis of other bacterial pneumonia,

Table 1 Characteristics of diabetic patients with pneumonia and controls

Characteristic	Cases (n = 4719) n (%)	Controls (n = 15322) n (%)	Crude OR (95% CI)
Age (years)			
<60	525 (11.1%)	1776 (11.6%)	*
60–69	785 (16.6%)	3066 (20.0%)	*
70–79	1533 (32.5%)	5665 (37.0%)	*
80–89	1622 (34.4%)	4431 (28.9%)	*
≥90	254 (5.4%)	384 (2.5%)	*
Sex			
Male	2275 (48.2%)	7336 (47.9%)	*
Female	2444 (51.8%)	7986 (42.1%)	*
Co-morbidities			
Cardiovascular disease	2189 (46.4%)	3611 (23.6%)	2.81 (2.62 to 3.00)
Pulmonary disease	949 (20.1%)	1592 (10.4%)	2.17 (1.99 to 2.37)
Alcoholism	17 (0.4%)	34 (0.2%)	1.62 (0.91 to 2.91)
Body mass index (kg/m^2)			
20–24	689 (14.6%)	2215 (14.5%)	1.00 (reference)
<20	251 (5.3%)	466 (3.0%)	1.73 (1.45 to 2.06)
25–30	1083 (22.9%)	4939 (32.2%)	0.71 (0.63 to 0.79)
>30	485 (10.3%)	2365 (15.4%)	0.66 (0.58 to 0.75)
Unknown	2211 (46.9%)	5337 (34.8%)	1.33 (1.21 to 1.47)
Prescription drugs			
Flu vaccination	1955 (41.4%)	6114 (39.9%)	1.07 (1.00 to 1.14)
Gastric acid suppressing drugs	967 (20.5%)	1988 (13.0%)	1.73 (1.59 to 1.88)
Immunosuppressive drugs	27 (0.6%)	38 (0.2%)	2.32 (1.41 to 3.80)
Oral glucocorticoids	311 (6.6%)	329 (2.1%)	3.22 (2.74 to 3.77)
Pneumococcal vaccination	144 (3.1%)	569 (3.7%)	0.82 (0.68 to 0.98)
Statins (current use)	50 (1.1%)	318 (2.1%)	0.51 (0.37 to 0.68)
Mean (SD) no GP visits/year	14.8 (11.0)	9.1 (7.7)	N/A
Current smoking†	407 (12.7%)	1169 (9.2%)	1.48 (1.31 to 1.67)

*Matching variable.
†Percentage for current smoking was calculated in subjects with information on smoking history recorded in the GPRD.

Table 2 Association between current statin treatment and the occurrence of pneumonia in all patients and in different (co-morbidity) subgroups

(Sub)groups	Crude OR (95% CI)	Adjusted* OR (95% CI)
All patients	0.51 (0.37 to 0.68)	0.49 (0.35 to 0.69)
Men	0.65 (0.42 to 1.02)	0.56 (0.39 to 0.91)
Women	0.51 (0.33 to 0.78)	0.40 (0.25 to 0.62)
No prior cardiovascular diseases	0.63 (0.42 to 0.93)	0.60 (0.40 to 0.91)
Prior cardiovascular diseases	0.35 (0.21 to 0.57)	0.36 (0.22 to 0.62)
No prior pulmonary diseases	0.50 (0.35 to 0.72)	0.41 (0.28 to 0.61)
Prior pulmonary diseases	0.87 (0.47 to 1.58)	0.85 (0.45 to 1.63)

OR, odds ratio; CI, confidence interval.
*Adjusted for age, cardiovascular diseases, pulmonary diseases, smoking, alcoholism, body mass index, gastric acid suppressing drug, flu vaccination, immunosuppressive drugs, pneumococcal vaccination, oral glucocorticoids, and number of GP contacts, with the exception of the grouping variable in the subgroup analysis.

2050 had a diagnosis of bronchopneumonia with unspecified organism recorded, and 2291 had pneumonia with unspecified organism recorded. 28% of cases were referred to hospital because of their pneumonia diagnosis. About 48% of cases and controls were men; the mean age of both cases and controls was 73 years but the proportion of very old was higher among the cases than in the controls (table 1). Matching on age had a median difference in age of 1.00 year with a mean difference of –0.16 years. The median duration of observation in the GPRD was 4.0 years for cases and 4.1 years for controls.

The presence of cardiovascular diseases, pulmonary diseases, smoking, and alcoholism was higher in cases than in controls, as was the use of gastric acid suppressing drugs and oral glucocorticoids. Cases visited the GP more often than controls (15 v 9 visits per year, respectively, p<0.01).

Of the 4719 cases, 50 (1.1%) were on active statin treatment compared with 2.1% for the control group. Univariate analysis showed that current statin treatment was associated with a reduced risk of pneumonia (crude OR 0.51, 95% CI 0.37 to 0.68). After adjusting for age, cardiovascular diseases, pulmonary diseases, body mass

index, alcoholism, smoking, influenza vaccination, pneumococcal vaccination, gastric acid suppressing drugs, immunosuppressive drugs, oral glucocorticoids, and number of GP visits in the year before the index date, the association did not alter substantially, yielding an adjusted OR of 0.49 (95% CI 0.35 to 0.69). The protective effect was similar for all statins and was consistent for both summer and winter seasons. The adjusted ORs for the different statins were 0.57 (95% CI 0.30 to 1.11) for atorvastatin (n = 57), 0.48 (95% CI 0.14 to 1.71) for cerivastatin (n = 17), 0.37 (95% CI 0.10 to 1.31) for fluvastatin (n = 19), 0.36 (95% CI 0.17 to 0.75) for pravastatin (n = 47), and 0.52 (95% CI 0.35 to 0.76) for simvastatin (n = 228). Comparable effects were observed in all co-morbidity related subgroups with a strongest association in patients with a history of cardiovascular disease (table 2).

The effect did not differ substantially between younger (≤70 years; OR 0.56, 95% CI 0.37 to 0.86) and older patients (>70 years; OR 0.35, 95% CI 0.20 to 0.61), and the effect of current statin treatment on the risk of pneumonia was similar for episodes of community acquired pneumonia treated in primary care (OR 0.52, 95% CI 0.36 to 0.77) and those requiring admission to hospital (OR 0.50, 95% CI 0.28 to 0.89). Furthermore, the association was equally present in the more recent years of the study period and in the first years, despite a consistent increase in statin prescriptions with time (fig 1). Past use of statins was not associated with a decreased risk of pneumonia (OR 0.95, 95% CI 0.63 to 1.42).

DISCUSSION
In this study of diabetic patients the use of statins was associated with a considerably reduced risk of pneumonia. These findings add to the accumulating evidence that statins may have immunomodulatory and anti-inflammatory properties in addition to their lipid lowering effects. In vitro studies have indicated that statins have a potentially beneficial effect by normalising the inflammatory response in respiratory bacterial infections.[9][25] This finding seems to have been confirmed by several prognostic clinical studies which found a substantial reduction in severe outcomes among statin users with pneumonia.[7][8][10] Our large case-control study with a long study period and a representative high risk population is the first to extend these findings to examine the possible prophylactic effect of statins on the incidence of pneumonia.

This is important as it suggests that statins not only influence the development of pulmonary infection but could also prevent primary infection. The mechanisms behind this protective effect, however, remain speculative. To our knowledge, the only study addressing the possible effects of statins on primary host defence is the experimental study by Fessler et al[7] which suggested impaired host defence in a murine model. However, there are several limitations in that study which preclude translation to the clinical situation. These include (1) the differences between a murine model and men; (2) the very high doses of lovastatin used (10 times that routinely used in humans); (3) observation of mice for only 48 hours after intratracheal ingestion of bacteria; and (4) lack of correlation between the number of colony forming units and clinical appearance. Furthermore, it is possible that the other anti-inflammatory effects of statins (on macrophages and monocytes) may outweigh any impaired neutrophilic microbicidal capacity.

The prevalence of statin use in our study was relatively low, certainly in comparison with recent years. This is primarily caused by the period under study. We think, however, that this has no impact on the validity of our study. Firstly, no obvious time dependent effect was observed (fig 1). The association was consistently pronounced in the more recent
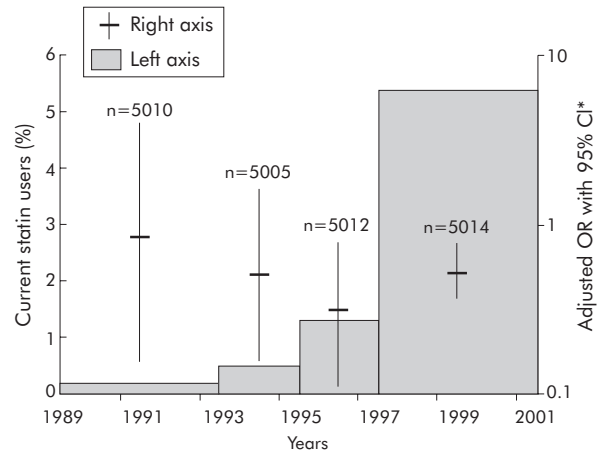

Figure 1 Prevalence of current statin use (left axis) and the association between statin use and the occurrence of pneumonia (right axis) in different time windows based on quartiles of ranked index dates of all subjects. OR, odds ratio; CI, confidence interval. *Adjusted for age, cardiovascular diseases, pulmonary diseases, smoking, alcoholism, body mass index, gastric acid suppressing drug, flu vaccination, immunosuppressive drugs, pneumococcal vaccination, oral glucocorticoids, and number of GP contacts. n = number of subjects in quartile.

years of the study period compared with earlier years, despite a constant increase in the use of statins with time. The large confidence interval in the first quartiles is most likely explained by small numbers. Additionally, although the power to detect differences between individual statins is somewhat limited, all the statins had odds ratios in the same range below 1. This suggests that the effect of statins results from their intrinsic properties and is independent of trends in the prescribing of statins. Furthermore, adjustment of the associations for the presence of many important and frequently occurring co-morbidities and use of other prescription drugs did not substantially change the risk estimates. However, we cannot rule out the possibility of confounding by unknown or unmeasured factors.

This study was conducted in a high risk population of diabetic patients. Although patients with diabetes are more susceptible to infection, to our knowledge the mechanism of action of statins does not differ between diabetic and non-diabetic patients. The protective properties of statins may therefore be applicable to the general population, but further research is needed to establish a possible protective effect in non-diabetic patients.

Our study has some limitations. Firstly, identification of cases of pneumonia has the potential for misclassification due to incorrect coding. It is possible that, because of the broad definitions used for the diagnosis of community acquired pneumonia, GPs could have applied the diagnostic criteria differently—for example, some acute exacerbations of chronic obstructive pulmonary disease could be identified as pneumonia. We believe, however, that such misclassification is independent of statin use and would only lead to an underestimation of the true association between statins and the occurrence of pneumonia. In addition, the overall validity of the GPRD coding has previously been assessed several times and other validation studies on pneumonia coding in different medical databases have also shown positive predictive values ranging from 61% to 85%.[26][27] Assuming that the diagnosis of patients admitted to a hospital is more accurate (better accessibility to chest radiography and sputum and blood cultures), it is reassuring that the association between statin use and pneumonia in admitted hospital was identical to that in patients treated in primary care. In agreement with Laheij et al,[24] our study also showed an association between the use of gastric acid suppressing drugs and pneumonia.

A second possible limitation is misclassification of exposure to statin treatment since we used prescription data. Patients using statins could have been non-compliant with their treatment and therefore could have used fewer statins than were prescribed. However, this would have led to an underestimation of the association between statin use and the occurrence of pneumonia.

Another concern is that people on statins take more comfort out of good health support—the so-called ''healthy user effect''—which can induce confounding. It is possible that statins were preferentially prescribed to patients with higher socioeconomic status and a lower risk of pneumonia. We tried to reduce such confounding by matching subjects on general practice (thereby on geographical region and city area). However, the use of postcodes as a proxy for socioeconomic status has been debated in the literature.[28][29] On the other hand, greater co-morbidity (and therefore a greater risk of pneumonia) could decrease the likelihood that an older person will receive effective treatment for asymptomatic conditions such as raised cholesterol levels. If this was the case, a substantial difference would have been seen between younger and older patients in the protective association between statins and pneumonia and this was not seen in our study.

Finally, we cannot rule out the possibility of confounding by unmeasured factors. However, the finding that the protective effect disappeared after discontinuing statin treatment strongly suggests that it is attributable to the properties of statins.

It must be emphasised that these findings on the preventive potential of statins should not be interpreted as suggesting that statins should be given to all diabetic patients to prevent pneumonia. Further confirmation is needed, particularly from large scale prospective randomised trials. In influenza pandemics statins could possibly provide additional support in the prevention of bacterial super-infections of the lung.

In conclusion, treatment with statins is associated with a considerably decreased risk of pneumonia in diabetic patients and their effects were consistent in all clinically relevant subgroups studied. Evidence is accumulating that treatment with statins may also influence bacterial respiratory infections, which may therefore broaden the indications for these drugs.

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Appendix 1 Medical codes used for case selection

Code	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 staphylococcal
486 T	Pneumonitis

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LUNG ALERT ....

No further tests for PE required in low probability cases with a negative D-dimer test

▲ Kearon C, Ginsberg JS, Douketis J, *et al* for the Canadian Pulmonary Embolism Study Group. An evaluation of D-dimer in the diagnosis of pulmonary embolism. *Ann Intern Med* 2006;**144**:812–21

In patients with suspected pulmonary embolism (PE), further diagnostic testing is often omitted on the basis of a negative D-dimer test result. This study is the first randomised controlled trial to evaluate this approach.

1126 randomised patients with suspected PE were evaluated and classified into low (group A) and high (group B) clinical probability groups; 456 with negative D-dimer test results were randomly allocated to control or experimental interventions. The experimental intervention for both groups was no further testing. The control intervention for group A was a ventilation-perfusion (VQ) scan followed by bilateral leg proximal vein ultrasonography. If the VQ scan was equivocal, ultrasonography was repeated at 7 and 14 days. The control intervention for group B was ultrasonography at 7 and 14 days. All patients in group B had a baseline VQ scan.

The patients were followed up for symptomatic venous thromboembolism (VTE) over a 6 month period. The prevalence of VTE in the 1126 patients enrolled in the study was 15.2%. In group A, six patients were lost to follow up and VTE occurred in 0 of 182 patients in the experimental group and 1 of 185 in the control group (95% CI −3 to 1.6 percentage points). In group B, VTE occurred in 1 of 41 patients in the experimental group and 0 of 41 in the control group.

The authors conclude that, in patients with a low probability of PE and a negative D-dimer test, additional diagnostic testing can be withheld without increasing the frequency of VTE during follow up. However, the study was limited by its use of VQ scanning and lack of double blinding. Computed tomographic pulmonary angiography (CTPA) is now a more widely used diagnostic test for PE.

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