# Preadmission Use of Statins and Outcomes After Hospitalization With Pneumonia

## *Population-Based Cohort Study of 29 900 Patients*

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**Background:** While some experimental and clinical research suggests that statins improve outcomes after severe infections, the evidence for pneumonia is conflicting. We examined whether preadmission statin use decreased risk of death, bacteremia, and pulmonary complications after pneumonia.

**Methods:** We conducted a population-based cohort study of 29 900 adults hospitalized with pneumonia for the first time between January 1, 1997, and December 31, 2004 in northern Denmark. Data on statin and other medication use, comorbidities, socioeconomic markers, laboratory findings, bacteremia, pulmonary complications, and death were obtained from medical databases. We used regression analyses to compute adjusted mortality rate ratios within 90 days and relative risks of bacteremia and pulmonary complications after hospitalization in both statin users and nonusers.

**Results:** Of patients with pneumonia, 1371 (4.6%) were current statin users. Mortality among statin users was lower than among nonusers: 10.3% vs 15.7% after 30 days and 16.8% vs 22.4% after 90 days, corresponding to adjusted 30- and 90-day mortality rate ratios of 0.69 (95% confidence interval, 0.58-0.82) and 0.75 (0.65-0.86). Decreased mortality associated with statin use remained robust in various subanalyses and in a supplementary analysis using propensity score matching. In contrast, former use of statins and current use of other prophylactic cardiovascular drugs were not associated with decreased mortality from pneumonia. In statin users, adjusted relative risk for bacteremia was 1.07 (95% confidence interval, 0.69-1.67) and for pulmonary complications was 0.69 (0.42-1.14).

**Conclusion:** The use of statins is associated with decreased mortality after hospitalization with pneumonia.

*Arch Intern Med. 2008;168(19):2081-2087*

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PNEUMONIA IS A FREQUENT cause of morbidity and mortality in aging Western populations.[1,2] The rate of hospitalization for pneumonia in Europe and the United States has increased 20% to 50% over the past decade, and pneumonia-related mortality remains at 10% to 15%.[1,2]

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A recent review indicated a beneficial effect of statin use on outcomes in patients with sepsis or bacteremia,[3] possibly owing to the antithrombotic, anti-inflammatory, or immunomodulatory properties of statins.[4,5] The 2 studies that addressed outcomes after statin use in patients with pneumonia reached conflicting conclusions.[6,7] Both studies had limitations, including nonrepresentative samples[6] and analytical shortcomings.[7-9] As a result, the role of statin use in pneumonia prognosis, including potential underlying biological mechanisms, remains unclear.

Using Danish health registries,[10] we conducted a population-based cohort study of patients hospitalized with pneumonia. We examined whether prehospitalization statin use affected 30- and 90-day mortality and risk of bacteremia or pulmonary complications.

## METHODS

### STUDY SETTING AND POPULATION

We conducted this study in the Danish counties of Aarhus and North Jutland, with a mixed rural-urban population of approximately 1.15 million. We included all patients aged 15 years or older with a hospital discharge diagnosis of pneumonia between January 1, 1997, and De-

cember 31, 2004. The Danish National Health Service provides free universal, tax-supported health care including reimbursement of most prescription medication costs.[11] Since 1968, all Danish residents have been assigned a unique civil registration number that is used in all health databases and enables unambiguous record linkage.[10]

### PATIENTS HOSPITALIZED DUE TO PNEUMONIA

We identified patients hospitalized due to pneumonia for the first time, including those with legionellosis (*Legionella* pneumonia) and ornithosis (*Chlamydophila psittaci* pneumonia).[2] After excluding 1281 patients who lived in the counties less than 1 year before admission, our cohort comprised 29 900 patients with pneumonia. For the subcohort of patients from North Jutland County (n = 13 262), we assessed pneumonia severity through linkage to a laboratory database that stores records for all specimens sent by hospitals and practitioners.

### STATIN USE

Since 1996, the regional prescription databases have tracked all prescriptions for reimbursable drugs dispensed at all pharmacies, including statins,[10] which are available by prescription only. We defined current statin use as at least 1 filled prescription within 125 days before the hospitalization with pneumonia. Patients who filled at least 1 statin prescription more than 125 days before the hospitalization were classified as former statin users. The 125-day period was chosen to capture most current statin users; with a compliance of 80% to 100%, few statin prescriptions are expected to last beyond 125 days (see http://www.medicine.dk for types of statins and package sizes available in Denmark).

### COVARIATES

We obtained data on comorbidity and other covariates from hospital databases, prescription databases, and the Danish Civil Registration System. From all discharge diagnoses recorded before the hospitalization with pneumonia, we computed the Charlson Comorbidity Index score, defining 3 comorbidity levels: low (score of 0), medium,[1,2] and high (score of ≥3).[10] We also retrieved information on the history of alcoholism-related disorders or disulfiram use, use of immunosuppressant agents within the year before the admission with pneumonia, and use of systemic antibiotic agents within 90 days before admission. To adjust for socioeconomic confounding, we obtained data on patient marital status (married, divorced or widowed, never married, or unknown), population level where they resided (city, ≥100 000 inhabitants; provincial town, 10 000–99 999 inhabitants; and rural area, <10 000 inhabitants), and type of hospital where they were admitted (university, central, or local). We also retrieved data on concurrent use of β-blockers, low-dose aspirin, and angiotensin-converting enzyme (ACE) inhibitors because use of these drugs could potentially confound clinical effects of statins.[12]

### OUTCOME AFTER PNEUMONIA

We defined, a priori, the primary outcome as death from any cause within 30 and 90 days after the admission date, ascertained from the Danish Civil Registration System. Secondary outcomes were bacteremia (ascertained from the Bacteremia Research Database[10] for the North Jutland subcohort) and hospital diagnoses of pulmonary complications (effusion, lung abscess, empyema, or adult respiratory distress syndrome)[13] associated with the index hospitalization or, if discharge occurred before day 30, up to 30 days after the admission date.

### STATISTICAL ANALYSIS

Follow-up extended for 90 days after admission or until death or migration, whichever came first. We constructed survival curves and computed cumulative mortality. We then computed 30- and 90-day mortality rate ratios (MRRs) for current statin users compared with nonusers using Cox regression analysis and controlling for sex, age (15-39, 40-64, 65-79, and ≥80 years), marital status, comorbidity, alcoholism-related disorders, preadmission use of antibiotics and immunosuppressive drugs, level of urbanization of place of residence, type of hospital, calendar period (1997-1999, 2000-2002, and 2003-2004), and preadmission use of β-blockers, low-dose aspirin (fully adjusted model), and ACE inhibitors (fully adjusted model). Stratified analyses were performed by sex, age, comorbidity, and calendar period.

To assess possible confounding by indication or contraindication for statin use, we repeated the analyses restricted to patients between 40 and 80 years of age; those with a known medical indication for statin use (history of stroke, diabetes, atherosclerosis, or ischemic heart disease), and those without a history of malignant neoplasm. Further, we conducted analyses restricted to patients with bacteremia, analyses stratified by type of pneumonia diagnosis (primary or secondary), and recency of onset of statin use before the hospitalization with pneumonia (<1 year [new user] vs >1 year [long-term user]).[14] We then restricted the analyses to former users of statins (last prescription filled >125 days before hospitalization) and to users of other prophylactic cardiovascular drugs. For women, we repeated the analysis replacing statin use with hormone therapy (HT). To estimate the extent of confounding necessary to explain our findings, we conducted a sensitivity analysis using a rule-out approach.[15]

We also conducted a supplementary analysis using propensity score matching.[16] Using logistic regression, we calculated the predicted probability of each patient being a statin user on the basis of his or her covariate profile. This model fitted well (C statistic, 0.87). Then we matched each statin user with 1 nonuser with the closest propensity score and carried out a matched Cox regression analysis with and without adjustment for all covariates in the model. The proportional hazards assumption was assessed graphically and found appropriate.

We used logistic regression to estimate the relative risk (RR) (odds ratio) for bacteremia and pulmonary complications in statin users compared with nonusers while controlling for the covariates. We analyzed data using commercially available software (SAS version 9.1.3 for Windows; SAS Institute, Inc, Cary, North Carolina). The Danish Data Protection Agency and Aarhus University Hospital Registry Board approved the study.

## RESULTS

### DESCRIPTIVE DATA

Of the 29 900 eligible patients hospitalized due to pneumonia during the study period (median age, 73 years; interquartile range, 60-81 years), 1372 (4.6%) were current statin users (**Table 1**). During the 125-day preadmission period, 61% of statin users received simvastatin, 15% received pravastatin, 15% received atorvastatin, and 9% received other statins or more than 1 type of statin. Compared with nonusers, statin users were less likely to be younger than 40 years (0.4% vs 7.9%) or older than 80 years (12.0% vs 31.5%); users were 2 to 5 times more likely than nonusers to have had myocardial in-

**Table 1. Characteristics of 29 900 Patients Hospitalized With Pneumonia for the First Time in Aarhus and North Jutland Counties, Denmark, 1997-2004**

| Characteristics Before Admission (N = 29 900) | Statin Users (n = 1372 [4.6%]) | Statin Nonusers (n = 28 528 [95.4%]) |
|---|---|---|
| Age, No. (%), y | | |
| 15-39 | 5 (0.4) | 2254 (7.9) |
| 40-64 | 422 (30.8) | 6570 (23.0) |
| 65-79 | 781 (56.9) | 10 726 (37.6) |
| ≥80 | 164 (12.0) | 8978 (31.5) |
| Sex, No. (%) | | |
| Female | 551 (40.2) | 13 481 (47.3) |
| Male | 821 (59.8) | 15 047 (52.7) |
| Comorbidity, No. (%) | | |
| Previous myocardial infarction | 598 (43.6) | 2259 (7.9) |
| Congestive heart failure | 318 (23.2) | 2916 (10.2) |
| Peripheral vascular disease | 286 (20.9) | 1968 (6.9) |
| Cerebrovascular disease | 337 (24.6) | 3913 (13.7) |
| Dementia | 15 (1.1) | 601 (2.1) |
| Hemiplegia | 3 (0.2) | 146 (0.5) |
| Chronic pulmonary disease | 326 (23.8) | 5529 (19.4) |
| Connective tissue disease | 66 (4.8) | 1344 (4.7) |
| Peptic ulcer disease | 134 (9.8) | 2491 (8.7) |
| Mild liver disease | 12 (0.9) | 453 (1.6) |
| Moderate to severe liver disease | 1 (0.1) | 113 (0.4) |
| Diabetes without end-stage organ damage | 256 (18.7) | 1856 (6.5) |
| Diabetes with end-stage organ damage | 143 (10.4) | 825 (2.9) |
| Moderate to severe renal disease | 92 (6.7) | 854 (3.0) |
| Solid cancer | 169 (12.3) | 3897 (13.7) |
| Metastatic solid cancer | 25 (1.8) | 587 (2.1) |
| Leukemia | 10 (0.7) | 285 (1.0) |
| Lymphoma | 17 (1.2) | 465 (1.6) |
| AIDS | 1 (0.1) | 22 (0.1) |
| Charlson Comorbidity Index score[a] | | |
| Low, 0 | 187 (13.6) | 11 746 (41.2) |
| Medium, 1-2 | 657 (47.9) | 11 352 (39.8) |
| High, ≥3 | 528 (38.5) | 5430 (19.0) |
| Medical indication for statin use[b] | 1169 (85.2) | 8854 (31.0) |
| Alcoholism-related disorders | 39 (2.8) | 1433 (5.0) |
| Preadmission medication, No. (%) | | |
| Immunosuppressive drugs | 244 (17.8) | 5288 (18.5) |
| Systemic antibiotic therapy | 529 (38.6) | 11 078 (38.8) |
| Angiotensin-converting enzyme inhibitor | 508 (37.0) | 3226 (11.3) |
| β-Blocker | 722 (52.6) | 3952 (13.9) |
| Low-dose aspirin | 600 (43.7) | 4196 (14.7) |
| Marital status, No. (%) | | |
| Married | 817 (59.6) | 12 543 (44.0) |
| Divorced or widowed | 414 (30.2) | 11 197 (39.3) |
| Never married | 71 (5.2) | 3259 (11.4) |
| Unknown | 70 (5.1) | 1529 (5.4) |
| Urbanization of place of residence, No. (%) | | |
| City | 537 (39.1) | 10 426 (36.6) |
| Provincial town | 618 (45.0 | 13 005 (45.6) |
| Rural | 217 (15.8) | 5097 (17.9) |
| Calendar period, No. (%) | | |
| 1997-1999 | 153 (11.2) | 9800 (34.4) |
| 2000-2002 | 465 (33.9) | 11 024 (38.6) |
| 2003-2004 | 754 (55.0) | 7704 (27.0) |
| Characteristics related to pneumonia (n = 13 612)[c] | 624 (4.6) | 12 988 (95.4) |
| Laboratory findings, median (IQR)[d] | | |
| Arterial blood pH (ref: 7.35-7.45) | 7.4 (7.4-7.5) | 7.4 (7.4-7.5) |
| $Pa_{O_2}$, mm Hg (ref: 80-100) | 61 (51-73) | 62 (52-73) |
| Hemoglobin, g/dL (ref: female, 0.74-0.96; male; 0.84-1.08) | 0.81 (0.72-0.87) | 0.8 (0.72-0.88) |
| Glucose concentration, mg/dL (ref: variable) | 113.5 (95.5-142.3) | 111.7 (95.5-136.9) |
| Serum urea nitrogen, mg/dL (ref: 8-23) | 22.4 (15.7-35.6) | 19.9 (13.4-32.5) |
| Creatinine concentration, mg/dL (ref: female, 0.62-1.30; male; 0.68-1.41) | 1.17 (0.95-1.56) | 1.05 (0.84-1.38) |
| Sodium, mEq/L (ref: 136-142) | 138 (134-140) | 138 (134-140) |
| Leukocyte count, /μL (ref: 4500-11 000) | 11 700 (8800-15 300) | 12 100 (8900-16 300) |
| C-reactive protein, mg/L (ref: 0.08-3.1) | 8.08 (2.73-16.9) | 9.34 (3.57-19.0) |
| Total cholesterol, mg/dL (ref: <200) | 173.7 (150.6-208.5) | 193.1 (158.3-227.8) |

Abbreviations: IQR, interquartile range; ref, reference range.

SI conversion factors: To convert $Pa_{O_2}$ to kilopascals, multiply by 0.133; to convert hemoglobin to grams per liter, multiply by 10.0; to convert glucose to millimoles per liter, multiply by 0.0555; to convert serum urea nitrogen to millimoles per liter, multiply by 0.357; to convert creatinine to micromoles per liter, multiply by 88.4; to convert sodium to millimoles per liter, multiply by 1.0; to convert leukocyte count to $\times 10^9$/L, multiply by 0.001; to convert C-reactive protein to nanomoles per liter, multiply by 9.524; to convert total cholesterol to millimoles per liter, multiply by 0.0259.

[a] For an explanation of the Charlson Comorbidity Index score, see the "Covariates" subsection of the "Methods" section.

[b] Previous diagnosis of ischemic or unspecified stroke, ischemic heart disease, atherosclerosis, or diabetes mellitus.

[c] Laboratory findings available only for the North Jutland County subcohort.

[d] First test result on the date of admission (or the day after, if unavailable), except for total cholesterol (closest value recorded within 1 year before and 1 week after admission).

farction, heart failure, peripheral vascular disease, diabetes and/or renal disease but were slightly less likely to have a history of malignant neoplasm, liver disease, or dementia. Medium or high comorbidity index scores were assigned to 86.4% of statin users compared with 58.8% of nonusers. In the North Jutland County subcohort, statin users had higher average admission blood levels of urea nitrogen and serum creatinine but slightly lower levels of C-reactive protein compared with nonusers (Table 1).

## MORTALITY

Throughout the follow-up period, statin users had considerably lower mortality than did statin nonusers. The 30-day mortality was 10.3% in users and 15.7% in nonusers (crude MRR, 0.63; 95% confidence interval [CI], 0.54-0.75) (**Table 2**). Ninety-day mortality was 16.8% in statin users vs 22.4% in nonusers (crude MRR, 0.72; 95% CI, 0.63-0.82). Mortality curves for statin users and nonusers overall are shown in **Figure 1**A and stratified by the Charlson Comorbidity Index score in Figure 1B. Differences in cumulative mortality were independent of comorbidity level.

**Table 2. Association Between Preadmission Statin Use and Death Within 30 and 90 Days After Admission in Patients Hospitalized With Pneumonia**

| Risk Factor | No. of Patients | No. of Deaths | Mortality. % | Mortality Rate Ratio (95% CI) | | *P* Value, Adjusted MRR |
|---|---|---|---|---|---|---|
| | | | | Crude | Adjusted[a] | |
| 0-30 d after admission with pneumonia | | | | | | |
| No statin use | 28 528 | 4489 | 15.7 | 1 [Reference] | 1 [Reference] | |
| Statin use | 1372 | 141 | 10.3 | 0.63 (0.54-0.75) | 0.69 (0.58-0.82) | <.01 |
| 0-90 d after admission with pneumonia | | | | | | |
| No statin use | 28 528 | 6381 | 22.4 | 1 [Reference] | 1 [Reference] | |
| Statin use | 1372 | 230 | 16.8 | 0.72 (0.63-0.82) | 0.75 (0.65-0.86) | <.01 |

Abbreviations: CI, confidence interval; MRR, mortality rate ratio.
[a]Adjusted for age, sex, marital status, type of hospital, calendar period, urbanization of place of residence, comorbidities and alcoholism-related conditions; and preadmission use of β-blockers, low-dose aspirin, antibiotic agents, immunosuppressive drugs, and angiotensin-converting enzyme inhibitors.

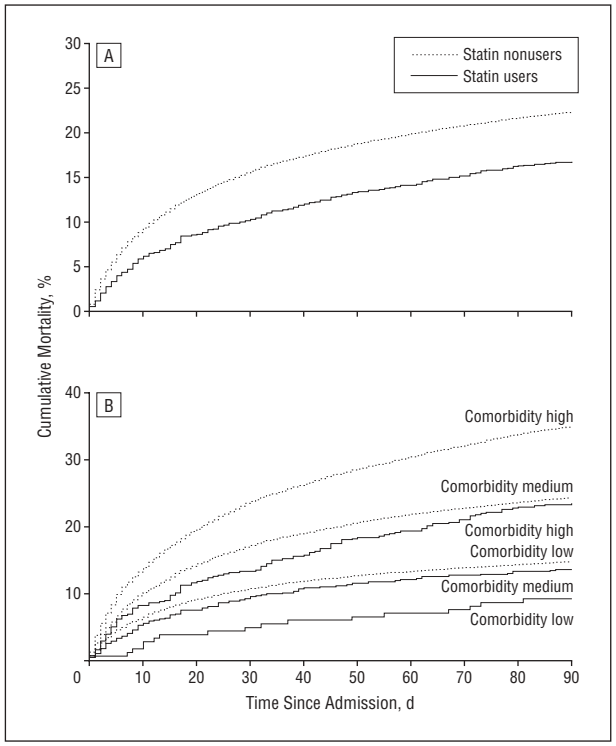


**Figure 1.** Mortality curves for patients with pneumonia who used statins at hospital admission (n=1372) compared with statin nonusers (n=28 528). A, Mortality curves overall. B, Mortality curves stratified according to low, medium, or high Charlson Comorbidity Index score.

Controlling for comorbidity lowered the 30-day MRR from 0.63 to 0.52, and controlling for age raised the 30-day MRR from 0.63 to 0.69, when considering each of these variables singly. After controlling for age, sex, comorbidity, alcoholism, use of immunosuppressive drugs, and use of preadmission antibiotic agents, the adjusted 30- and 90-day MRRs were 0.61 (95% CI, 0.52-0.73) and 0.67 (0.59-0.76), respectively. Further adjustment for calendar period, socioeconomic markers, and other prophylactic cardiovascular drugs increased the respective MRRs to 0.69 (95% CI, 0.58-0.82) and 0.75 (0.65-0.86), respectively (Table 2). Adjustment for individual disease categories in lieu of the Charlson Comorbidity Index score levels yielded slightly higher 30- and 90-day MRRs of 0.73 (95% CI, 0.61-0.87) and 0.79 (0.69-0.91), respectively. The lowest fully adjusted 30-day mortality estimates were observed in users of simvastatin (MRR, 0.60; 95% CI, 0.48-0.75), whereas atorvastatin (0.81; 0.53-1.23) and pravastatin (0.96; 0.66-1.40) conferred less mortality reduction. A sensitivity analysis showed that to fully explain our finding of an adjusted 30-day MRR of 0.69 in current statin users, a confounding protective factor with a prevalence of 20% and the ability to decrease the relative risk of death by 50% would have to be much more common (odds ratio, 12.6) in statin users compared with statin nonusers.

In the propensity score–based analysis, adequate controls were identified for 98.1% of statin users, yielding a cohort of 1346 statin users and 1346 nonusers. This matched analysis yielded MRRs similar to those from the Cox regression. Crude and fully adjusted MRRs in the matched analysis were, respectively, 0.63 (95% CI, 0.51-0.78) and 0.64 (0.52-0.80) after 30 days and 0.69 (0.58-0.82) and 0.71 (0.60-0.84) after 90 days.

The association between statin use and mortality remained robust in subanalyses (**Figure 2**). The lowest relative mortality associated with statin use was found in patients older than 80 years (adjusted 30-day MRR, 0.51; 95% CI, 0.33-0.78) and in patients with bacteremia (0.52; 0.18-1.48). There was no clear association between former statin use (last prescription >125 days preceding hospitalization, n=144) and pneumonia prognosis: the adjusted MRRs were 0.97 (95% CI, 0.64-1.48) over 30 days and 0.84 (0.58-1.22) over 90 days. Discontinuation of statin usage as determined by no filled prescriptions within 90 days after admission was strongly associated with adverse outcome (adjusted 90-day MRR, 1.75; 95% CI, 1.51-2.02); however, this association was likely susceptible to survival bias. There was no clear association between mortality and preadmission use of ACE inhibitors (adjusted 30-day MRR, 0.95; 95% CI, 0.87-1.03) or low-dose aspirin (0.96; 0.89-1.03). Use of β-blockers was associated with slightly decreased mortality (adjusted 30-day MRR, 0.88; 0.81-0.96). Use of HT in women (n=14 032) was associated with a 30-day MRR of 0.77 (95% CI, 0.64-0.92). The adjusted 30-day MRR associated with current statin use in women was 0.73 (95% CI, 0.55-0.96) and was unaltered after simultaneous adjustment for HT use.

### BACTEREMIA AND PULMONARY COMPLICATIONS

In the North Jutland County subcohort, 37 statin users (5.9%) and 744 statin nonusers (5.7%) had bacteremia (adjusted RR for bacteremia, 1.12; 95% CI, 0.78-1.62). However, slightly more statin users (64%) than nonusers (60%) had at least 1 blood culture taken (RR for bacteremia in patients with blood cultures, 1.07; 95% CI, 0.69-1.67). Statin use was associated with decreased risks for all examined pulmonary complications, the cumulative incidence of which was 1.5% in statin users and 2.1% in nonusers (adjusted RR, 0.69; 95% CI, 0.42-1.14). Adjusted RRs for pulmonary complications associated with use of β-blockers, low-dose aspirin, and ACE inhibitors ranged from 1.00 to 1.05.

## COMMENT

In this large population-based cohort study of patients hospitalized with pneumonia, preadmission statin use was associated with decreased mortality that persisted for at least 90 days after the hospital admission. The differences became apparent during the first few weeks of hospitalization, a period associated with a high number of pneumonia-related deaths,[17] and they increased only minimally between 30 and 90 days after admission, which suggests that statin use is beneficial primarily in the early phase of infection. The much weaker reduction in mortality in former compared with current statin users supports the hypothesis of a causal association between statin intake and pneumonia-specific death. At admission, statin users tended to have lower inflammatory markers and fewer pulmonary complications. In contrast, statin use did not affect the risk of concomitant bacteremia.

Because there is universal health coverage in Denmark, we probably identified nearly all pneumonia episodes requiring hospitalization in a well-defined catchment area. The study population was large, yielding robust and consistent estimates in all subanalyses. We used prospectively recorded data from independent medical databases with complete follow-up, thus limiting opportunities for recall, selection, or surveillance bias.

In our cohort, users and nonusers of statins were similar in terms of number of blood cultures performed, prevalence of bacteremia, and preadmission use of antibiotic agents. Thus, differential ascertainment of pneumonia with respect to statin use, though theoretically possible, seems unlikely. However, statins may have reduced pneumonia severity in patients in the community, thereby decreasing the risk of being hospitalized and included in our cohort.

The estimated predictive value of a discharge diagnosis of pneumonia in Denmark is 90% (95% CI, 82%-95%).[2] Only 13% of pneumonia discharge diagnoses in our region represent nosocomial episodes,[2] and enhanced survival associated with statin use in the present study was observed for patients with both primary and secondary pneumonia diagnoses.

Identification of statin use from filled prescriptions may be a reasonable proxy measure of use because compliance with statin therapy in Denmark is high.[18] Long-term adherence may be a marker for unmeasured factors associated with a better prognosis[14]; however, in our study, new and long-term users of statins demonstrated similar survival benefits. Any noncompliance with statin therapy during the hospitalization with pneumonia, for example, in severely ill patients receiving intensive care, would be expected to reduce the magnitude of observed effects of statin use on mortality.

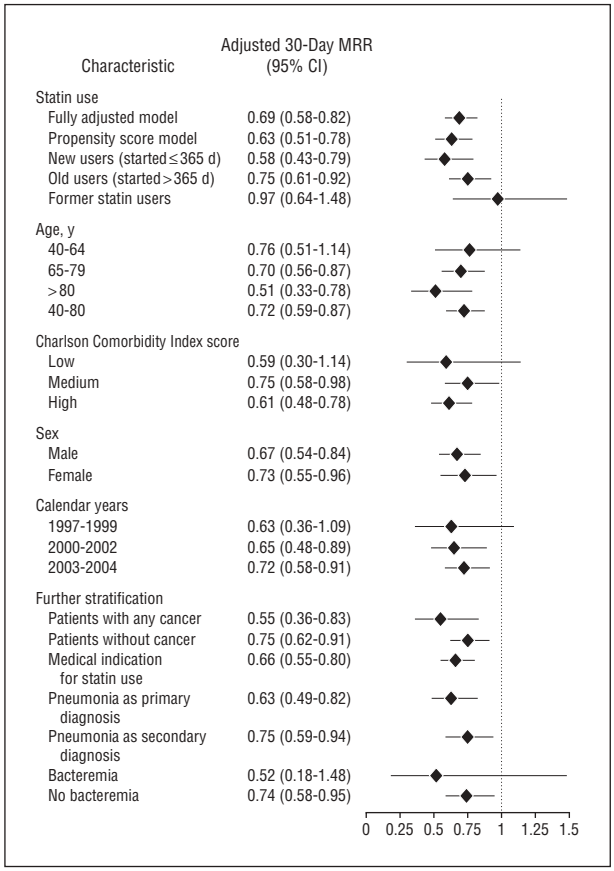


**Figure 2.** Adjusted 30-day mortality rate ratios (MRRs) associated with preadmission statin use overall and within various patient subgroups. CI indicates confidence interval. For an explanation of the Charlson Comorbidity Index score, see the "Covariates" subsection of the "Methods" section.

Despite our study's strengths, the results should be interpreted with caution. As previously discussed,[9] statin users may be "healthy users," that is, younger, healthier, better educated, and socioeconomically privileged, who may be more likely to receive preventive treatments than the frail and less privileged.[12] Severe confounding by socioeconomic differences is unlikely given Denmark's universal health care.[18] In addition, the protective effect with statin use remained robust over the calendar period and after adjustment for a wide range of comorbidities and socioeconomic markers including hospital type, dementia, alcohol abuse, marital status, and urbanization of place of residence. Still, unknown or unmeasured prognostic factors including functional status and immunizations[19] may have caused confounding. Our sensitivity analysis showed that the decrease in mortality associated with statin use could not be explained by even a strong single confounder. To explain our results, several strong, un-

controlled, unmeasured prognostic factors that were imbalanced among statin users and nonusers and at the same time independent of the adjusted confounders would have been necessary.

Unlike investigators in earlier studies,[6,7] we were able to control for use of other preventive cardiovascular medications such as β-blockers, low-dose aspirin, and ACE inhibitors. Use of these drugs, which also may be subject to the healthy user effects, had virtually no effect on pneumonia-related mortality, corroborating findings from a recent study on statin use and risk of fatal infections.[20] In contrast, the use of HT in women showed a protective effect similar to that of statins; whether this finding reflects healthy user or beneficial biological effects of HT[21] should be elucidated in future studies.

Earlier studies of prognosis in statin users with pneumonia yielded conflicting findings.[6,7] Mortensen et al,[6] in a cohort study, found strikingly decreased mortality associated with statin use (adjusted RR, 0.36; 95% CI, 0.14-0.92). However, that study's subjects were few (n=787) and predominantly men, with considerable differences in the distributions of alcoholism and liver disease between statin users and nonusers.[6] More recently, 2 studies that addressed combined pneumonia risk and prognosis found that current statin users had a lower risk of hospitalization with fatal pneumonia than nonusers in the United Kingdom (adjusted odds ratio in a nested case-control design, 0.47; 95% CI, 0.25-0.88)[22] and a decreased risk of inpatient death owing to pneumonia or influenza in the United States (adjusted hazard ratio in a matched cohort design, 0.61; 95% CI, 0.41-0.92).[23] A population-based study of 3415 patients with pneumonia in Canada that controlled for a wide range of healthy user markers found no association between statin use and the combined end point of admission to the intensive care unit and in-hospital death (adjusted RR, 1.10; 95% CI, 0.76-1.60).[7] The effect estimates from these studies might suggest a gradient from early and potentially more confounded studies to the more rigorous and clinically well-populated studies. However, the recent Canadian study may have underestimated the protective statin effect.[9] The unadjusted estimate for statin users in that study paralleled our findings (crude RR, 0.80) despite their older age, comorbidity, and medication use compared with statin nonusers. Disappearance of the apparent protective effect of statin use after adjustment could have been an artifact of using the composite end point of intensive care unit admission or death[8,9] or adjusting for lower pneumonia severity associated with statin use.[9]

Several biological mechanisms may explain our results. Statins modify the humoral immune response; beneficially affect inflammatory gene expression and platelet function, coagulation, and fibrinolysis; and inhibit endothelial cell dysfunction.[24,25] In healthy males receiving lipopolysaccharides, simvastatin suppresses key receptors of innate immunity and the inflammatory response.[25] In our study, C-reactive protein levels at admission tended to be lower in statin users than in nonusers, perhaps because of the anti-inflammatory effects of statins. In patients with pneumonia, early death may be associated with concurrent bacteremia and severe sepsis. In our cohort, the protective effect of statins was most pronounced in the subset of patients with bacteremic pneumonia.

Our study adds to the accumulating evidence that statin use is associated with improved prognosis after severe infections. The decrease in mortality associated with statin use seems to be substantial in patients with pneumonia requiring hospital admission. Randomized trials are needed to examine causality of the associations found in observational studies.[26] Given the availability of statins, with their relatively low cost and mild adverse effects, positive results of statin therapy trials in patients with pneumonia would have substantial clinical and public health implications.

**Accepted for Publication:** January 16, 2008.
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**Author Contributions:** Dr Thomsen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Thomsen, Riis, Kornum, Christensen, and Sørensen. *Acquisition of data:* Thomsen, Riis, and Sørensen. *Analysis and interpretation of data:* Thomsen, Riis, Christensen, Johnsen, and Sørensen. *Drafting of the manuscript:* Thomsen, Riis, and Christensen. *Critical revision of the manuscript for important intellectual content:* Thomsen, Riis, Kornum, Johnsen, and Sørensen. *Statistical analysis:* Thomsen, Riis, and Sørensen. *Obtained funding:* Christensen and Sørensen. *Administrative, technical, and material support:* Sørensen. *Study supervision:* Sørensen.
**Financial Disclosure:** None reported.
**Funding/Support:** This study was supported by the Western Danish Research Forum for Health Sciences and by the Clinical Epidemiological Research Foundation at Aarhus University Hospital, Aarhus, Denmark.
**Role of the Sponsors:** The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.
**Additional Contributions:** Flemming Søndergaard, MSc, Department of Clinical Epidemiology, Aarhus University Hospital, made substantial contributions to the propensity score–based analysis.

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