

Statins and outcomes in patients admitted to hospital with community acquired pneumonia: population based prospective cohort study

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Abstract

Objectives To determine whether statins reduce mortality or need for admission to intensive care in patients admitted to hospital with community acquired pneumonia; and to assess whether previously reported improvements in sepsis related outcomes were a result of the healthy user effect.

Design Population based prospective cohort study.

Setting Six hospitals in Capital Health, Edmonton, Alberta, Canada.

Participants Adults admitted to hospital with pneumonia and categorised according to use of statins for at least one week before admission and during hospital stay.

Main outcome measures Composite of in-hospital mortality or admission to an intensive care unit.

Results Of 3415 patients with pneumonia admitted to hospital, 624 (18%) died or were admitted to an intensive care unit. Statin users were less likely to die or be admitted to an intensive care unit than non-users (50/325 (15%) *v* 574/3090 (19%), odds ratio 0.80, *P* = 0.15). After more complete adjustment for confounding, however, the odds ratios changed from potential benefit (0.78, adjusted for age and sex) to potential harm (1.10, fully adjusted including propensity scores, 95% confidence interval 0.76 to 1.60).

Conclusions Statins are not associated with reduced mortality or need for admission to an intensive care unit in patients with pneumonia; reports of benefit in the setting of sepsis may be a result of confounding.

Introduction

Observational studies have reported that patients taking statins at the time they develop serious infections such as pneumonia are less likely to have or die from sepsis or be admitted to an intensive care unit.¹⁻³ Benefits from statins are ascribed to pleiotropic effects (for example, antioxidative and anti-inflammatory properties).¹⁻³ These effects are also used to explain other beneficial findings from observational studies, for example, that statins prevent cancer,⁴ reduce osteoporotic fractures,⁵ and prevent dementia.⁶ Given that these benefits and others are not apparent in randomised trials of statins,^{7,8} another explanation might be that of selection bias and residual confounding. Specifically, that statins are preferentially prescribed to relatively healthy or health seeking patients ("healthy users").⁹ That is not to say that healthy users do not have comorbidities but that coding of diseases in administrative databases might omit important information that suggests a patient is a healthy user and therefore might intrinsically be expected to have better health related outcomes.

We hypothesised that the benefits of statins in relation to sepsis and community acquired pneumonia are more likely to be a manifestation of the healthy user effect than to pleiotropic statin effects. We carried out a large, prospective, population based study of patients admitted to hospital with pneumonia.

Methods

Details of our study are reported elsewhere.¹⁰⁻¹² Briefly, from 2000-2 a clinical pathway for community acquired pneumonia¹³ was implemented for adults admitted to the six hospitals in Capital Health, Canada.¹⁰ Over two years 3415 patients were admitted with pneumonia by 318 doctors (see bmj.com for exclusions).

Six nurses assisted with implementation of the pathway and prospectively collected data on clinical and laboratory findings and information not routinely available in administrative databases, such as functional status, immunisations, advanced directives, and drugs used in hospital. We recorded drugs according to class and defined use as drugs taken for one week before admission and continued during hospital stay. We calculated the pneumonia severity index for each patient.¹⁴ The explanatory variable of interest was the use of statins.

The primary outcome was the composite of in-hospital mortality or admission to an intensive care unit. This was chosen as the best measure to reflect the severity of pneumonia related sepsis. If a patient was admitted to an intensive care unit and died, only the death contributed to the composite outcome. Outcomes (hospital based events) were collected prospectively and ascertained by research nurses blinded to hypotheses regarding statins, healthy user effects, and outcomes.

Statistical analyses

We carried out a series of multivariate analyses using logistic regression to determine the association between statin use and adverse outcomes. Firstly, we adjusted for age and sex. Secondly, we analysed a "typical" administrative database and adjusted for age, sex, admission from a nursing home, four comorbidities (ischaemic heart disease, heart failure, chronic obstructive pulmonary disease, neuropsychiatric illnesses), and number of drugs prescribed. Thirdly, we incorporated clinical and laboratory data as well as data not routinely available in most administrative databases that might reflect healthy user status.

Finally, we used multivariate logistic regression to construct a propensity score that reflected a patient's

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likelihood of being prescribed a statin.^{1 2 10 15 16} We calculated rates of our composite outcome across fifths of increasing propensity and tested for trend using χ^2 tests. We then entered the score, as a continuous variable,^{1 10 15 16} into the models. Finally, we built the best fitting multivariate model of in-hospital mortality or admission to an intensive care unit possible, after forcing in age, propensity score, and statin use and then including only variables that achieved an adjusted P value of less than 0.10. We report odds ratios, 95% confidence intervals, and P values. We used the C-statistic to compare models (values >0.8 are considered excellent).¹⁷ Analyses were carried out using SPSS version 14.

Results

In total, 3415 patients (median age 75 years) were admitted to hospital with community acquired pneumonia; 53% were men, 10% (n=325) used a statin, and 62% (n=2128) were categorised as high risk according to the pneumonia severity index (see [bmj.com](#)).

Statin users were older and more likely to have atherosclerosis related comorbidities. They were, however, more likely to be admitted from their homes, have independent mobility, be former smokers, have up to date vaccinations, and have less need for an advanced directive (see [bmj.com](#)). These findings were confirmed by the propensity score analysis (C-statistic 0.91). Rates of statin use increased across fifths of increasing propensity score (1%, 3%, 5%, 12%, and 27%, P<0.001 for trend) whereas rates of in-hospital mortality or admission to an intensive care unit progressively decreased (21%, 21%, 18%, 18%, and 14%, P=0.003 for trend).

Overall, 334 (10%) patients died in hospital, 351 (10%) were admitted to an intensive care unit, and 624 (18%) achieved the composite end point of death or admission to an intensive care unit. In univariate analyses, patients who used statins were less likely to die than non-users (25/325 (8%) v 309/3090 (10%), odds ratio 0.75, P=0.18), to be admitted to an intensive care unit (29/325 (9%) v 322/3090 (10%), odds ratio 0.84, P=0.39), and to achieve the composite outcome of death or admission to an intensive care unit (50/325 (15%) v 574/3090 (19%), odds ratio 0.80, P=0.15). All three analyses suggest a clinically important benefit, and the composite outcome reached marginal statistical significance.

By constructing multivariate models with incrementally greater discriminatory power, the adjusted odds ratio for statin use and adverse outcomes increased from 0.78 (adjusted for age and sex, 95% confidence interval 0.57 to 1.07) to 0.88 (typical adjustments in databases including age, sex, nursing home resident, comorbidities, and number of drugs, 0.63 to 1.22) and to 1.07 (previous variables plus clinical data, including former smoker, independent mobility, immunisations, and pneumonia severity, 0.75 to 1.52; see [bmj.com](#)). Inclusion of the propensity score as a continuous variable in this last model further moved the estimates in the direction of harm (adjusted odds ratio 1.12, 95% confidence interval 0.77 to 1.64). A model including only the propensity score produced an estimate of statin effect of 1.01 (0.72 to 1.41).

Multivariate logistic regression analysis of correlates for mortality or admission to an intensive care unit in 3415 patients admitted to hospital with community acquired pneumonia

Variables	Adjusted odds ratio (95% CI)	P value
Statin use	1.10 (0.76 to 1.60)	0.61
Propensity score (continuous)	0.65 (0.22 to 1.88)	0.42
Administrative data commonly used for adjustment		
Age ≥65years	0.70 (0.54 to 0.91)	0.008
Previous condition:		
Ischaemic heart disease	0.70 (0.55 to 0.90)	0.006
Heart failure	1.26 (0.99 to 1.61)	0.056
Chronic obstructive pulmonary disease	1.22 (0.98 to 1.53)	0.077
Neuropsychiatric illness	1.49 (1.19 to 1.87)	<0.001
Clinically important data rarely available for adjustment		
Former smoker	0.73 (0.57 to 0.93)	0.010
Pneumococcal vaccine	0.61 (0.40 to 0.92)	0.018
Influenza vaccine	0.43 (0.29 to 0.63)	<0.001
Independent mobility	0.38 (0.24 to 0.58)	<0.001
Pneumonia specific data rarely available for adjustment		
Pneumonia severity index*:		
Class I or II	1.00	
Class III	2.45 (1.61 to 3.80)	
Class IV	5.13 (3.45 to 7.62)	<0.001
Class V	14.40 (9.43 to 22.00)	<0.001
Levofloxacin not first antibiotic	2.08 (1.69 to 2.56)	<0.001
Aspiration pneumonia	3.89 (2.74 to 5.53)	<0.001
Documented bacteraemia	1.86 (1.29 to 2.67)	0.001

*Based on three personal variables, five comorbidities, five physical findings, and seven laboratory tests.¹⁴

Finally, we constructed the best multivariate model of adverse pneumonia related outcomes possible, in which only age, propensity score, and statin use was forced (C-statistic 0.84, table); the estimate of statin effect was 1.10 (95% confidence interval 0.76 to 1.60). Models that considered in-hospital mortality only or admission to an intensive care unit only were virtually identical, with two notable exceptions: older age and heart disease significantly increased risk of mortality (adjusted odds ratio 2.10 and 1.11) but significantly “protected” against admission to an intensive care unit (0.44 and 0.21). When these end points were pooled, older age and heart disease seemed to reduce the risk of adverse events related to community acquired pneumonia (table). In no adjusted models, however, did statin use have a statistically significant effect or point estimate consistent with benefit.

Discussion

We found no association between use of statins and mortality or admission to an intensive care unit in more than 3000 patients admitted to hospital for pneumonia. Although our unadjusted data suggested a 20% reduction in adverse outcomes among statin users (P=0.15), with more complete adjustment for confounding our data were more consistent with a 10% relative increase in adverse outcomes (P=0.61). Furthermore, our propensity score analyses, which included clinical information not usually available in administrative databases, shows selection bias for those prescribed a statin in the community and probably reflects the healthy user effect.^{9 18}

In a retrospective cohort study of pneumonia related outcomes, Mortensen et al observed a significant 64% reduction in mortality at 30 days

among statin users.¹ Although that study was carefully carried out, and included a propensity score, it was small, included mainly men, was retrospective, was not population based, and did not include the types of clinical data we used.¹ Conversely, the most rigorous population based study of statins and sepsis reported no significant association between statin use and 28 day mortality ($P=0.66$, adjusted).¹⁸

It seems likely that the prescription of statins is a robust proxy for the healthy user effect rather than a measure of the many beneficial pleiotropic effects of these drugs.^{9 18 19} Our propensity score analyses support this assertion, as do our observations that statin users were more likely to be former smokers and have current immunisations for pneumococcus and influenza and less likely to need advanced directives or be admitted from a nursing home. It has been suggested that many of the benefits seen in observational studies of hormone therapy in postmenopausal women were also a result of this healthy user effect.¹⁹ The same gradients in socioeconomic and health status associated with hormone therapy¹⁹ have also been described for statins.²⁰ Although the confounded relation between statin use and healthy user status has implications for those studying the effectiveness of statins on atherosclerosis related outcomes, the impact of the healthy user effect might be more problematic for those searching administrative databases for non-lipid related benefits of statins.⁴⁻⁶

Several limitations merit consideration. Firstly, we examined patients with only pneumonia and not other serious infections. However, community acquired pneumonia is common and contributes to many of the patients with sepsis included in previous studies. Secondly, we did not have data on indications, duration of use, doses, or statin types. Thirdly, we defined use as taking statins for one week before admission and during hospital stay. Fourthly, our results lack some precision despite our sample size, and 95% confidence intervals are consistent with a 24% decrease or a 60% increase in adverse outcomes. Lastly, we examined only admissions to an intensive care unit and mortality during hospital stay; one study suggested no early benefit from statin use but better late outcomes for those who survived the index episode.¹⁸

In our study, patients with pneumonia who used statins did not have better outcomes than non-users. Our analyses raise concerns that previous observational studies that show the benefits of statins in patients with sepsis (and other conditions not related to atherosclerosis) might have been consistently measuring and reporting the healthy user effect.

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What is already known on this topic

Statins have been reported to prevent sepsis and reduce complications from serious infections such as pneumonia, as well as preventing cancer, fractures, diabetes, and dementia

One explanation for such disparate findings is selection bias and confounding, namely the healthy user effect

What this study adds

Use of statins in patients admitted for pneumonia did not reduce mortality or need for admission to an intensive care unit

Patients prescribed statins were relatively healthy users

Observational studies showing the putative benefits of statins in patients with sepsis (and perhaps other conditions) were probably reporting confounding by the healthy user effect

Competing interests: None declared.

Ethical approval: This study was approved by the ethics board of the University of Alberta.

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