CLINICAL RESEARCH STUDY

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Is Statin Use Associated with Reduced Mortality After Pneumonia? A Systematic Review and Meta-analysis

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ABSTRACT

OBJECTIVE: The objective of this study was to perform a systematic review and meta-analysis of the effects of statins on mortality following pneumonia.

METHODS: We searched MEDLINE, EMBASE, BIOSIS, Cochrane CENTRAL Register of Controlled Trials, Cambridge Scientific Abstracts, BIOSIS, and Scopus. Studies were included if they involved: participants ≥18 years of age; patients with community-acquired pneumonia; current statin users; and reported overall or adjusted mortality after pneumonia.

RESULTS: Of 491 citations identified, 13 studies involving 254,950 patients met eligibility criteria. Pooled unadjusted data showed that statin use was associated with lower mortality after pneumonia (odds ratio [OR] 0.62, 95% confidence interval [CI], 0.54-0.71). Pooling of adjusted data also showed reduced mortality after pneumonia (OR 0.66, 95% CI, 0.55-0.79). However, this effect was attenuated in subgroup analysis by confounders and in prospective studies.

CONCLUSIONS: Although statin use is associated with decreased mortality after pneumonia, this effect weakens in important subgroups. Only a randomized controlled study can fully explore the link between statins and pneumonia mortality.

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KEYWORDS: Inflammation; Mortality; Outcomes; Pneumonia; Statins

Pneumonia remains a leading global cause of hospitalization and mortality.[1,2] While strategies such as universal vaccination and timely antimicrobial treatment have reduced pneumonia mortality,[3] a growing body of literature suggests that the 3-hydroxy-3-methylglutaryl-coenzyme-A inhibitors (or "statins") also may improve pneumonia outcomes.[4]

Statins possess non-lipid-lowering, pleiotropic properties that mitigate inflammatory pathways.[5] As local and systemic inflammation play critical roles in pneumonia, statin-mediated attenuation of inflammation may improve pneumonia outcomes.[6,7] Indeed, recent meta-analyses suggest that statins improve clinical outcomes in inflammatory states such as sepsis and bacteremia.[8,9] However, the precise effect of statins on pneumonia remains unclear due to differences in study design, concerns about a "healthy-user" effect, and residual confounding by variables that are frequently absent from administrative datasets used by many studies.[10]

Although a recent randomized controlled trial concluded that statins reduce mortality from ventilator-associated pneumonia,[11] there are no randomized clinical trials assessing statin use and outcomes in community-acquired pneumonia. The purpose of this meta-analysis was to provide an evaluation of the available evidence in order to examine the case for undertaking such a study.

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METHODS

Information Sources and Search Strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) recommendations in conducting this meta-analysis.[12,13] With the assistance of a medical research librarian, we performed serial literature searches for English and non-English articles. MEDLINE via PubMed (1950-present), EMBASE (1946-present), BIOSIS (1926-present), the Cochrane CENTRAL Register of Controlled Trials, and the Cochrane Database of Reviews of Effectiveness (1960-present, via Ovid) were searched using Boolean logic for terms including "trial," "statins," "hydroxymethylglutaryl-CoA reductase inhibitors," "pneumonia," "death," and "inflammation." Controlled vocabularies were used to identify synonyms. No publication date, language, or status restrictions were placed on the searches. All human studies published in full-text, abstract, or poster form were eligible for inclusion. We searched for unpublished/ongoing clinical trials through clinicaltrials.gov and the Web portal of the International Federation of Pharmaceutical Manufacturers. Conference abstracts were electronically searched through the Conference Proceedings Index provided by Cambridge Scientific Abstracts, BIOSIS (1926-present), and Scopus (1996-present). Additional studies of interest were identified by hand searches of bibliographies and through content experts (PKL, SAF). A total of 491 articles and conference abstracts were retrieved by our search (last updated January 14, 2012) (**Figure 1**).

Study Eligibility and Selection Criteria

Three authors (VC, SG, and MB) independently determined study eligibility. Any difference in opinion about eligibility was resolved through consensus. Studies were included if they met the following criteria: they were human studies with participants ≥18 years of age; they included patients with community-acquired pneumonia; involved current statin users; and they reported overall or adjusted mortality after an episode of pneumonia. We excluded studies if they did not report mortality after pneumonia; included patients presenting with sepsis where the cause of death could not be directly attributable to pneumonia; included ventilator-associated pneumonia; or involved H1N1 or other strains of influenza.

CLINICAL SIGNIFICANCE

- Statins may mitigate inflammation and lower mortality following pneumonia.
- Observational studies suggest that statin users are less likely to die from pneumonia; however, residual confounding and healthy-user bias limit these conclusions.
- Although statin users appear less likely to die after pneumonia, this effect diminishes when confounding variables are separately pooled.
- A randomized controlled study to investigate the association between statin and pneumonia mortality appears necessary.

Data Abstraction and Validity Assessment

Data were extracted from all included studies independently and in duplicate (SG and MB) on a form adapted from the Cochrane Collaboration data extraction template. We accepted the outcomes reported in each study without independently validating or reviewing their data.

Assessment of Study Quality

Two authors independently assessed quality of the included studies (VC, SG). For the single randomized controlled study included in this analysis,[14] study quality was assessed according to the risk of bias as described by the Cochrane Statistical Methods Group.[15] The study was thus classified as being at low, unclear, or high risk of bias based on the reporting of quality domains. Nonrandomized studies were assessed according to the instrument developed by Downs and Black.[16] This tool encompasses 6 sections that assess reporting (total score of 11), external validity (total score of 3), internal validity/bias (total score of 7), internal validity/confounding (total score of 6), and power (total score of 2). A priori, scores ≥23 were considered high-quality studies.

Definition of Exposure/Treatment Groups

Treatment groups were defined as patients with pneumonia on statin treatment versus those with pneumonia not on such therapy (ie, control). In studies reporting data from patients exposed to statins and other interventions, we excluded patients exposed to multiple interventions.[17,18] In studies reporting prior, recent, or current use of statins, we abstracted only current use of statins. We accepted the definition of statin use as stated in each study.

Definition of Outcomes

The primary outcome of interest was all-cause mortality following an episode of pneumonia. When studies reported death at varying intervals (eg, 30-day and 90-day mortality), we abstracted data from the longest mortality endpoint so as to include the most events. All endpoints were pooled according to the interval at which death was abstracted. Mortality beyond 6 months was not included, as this was clinically difficult to link to the index pneumonia episode. If a study only reported the risk of developing pneumonia, we contacted the corresponding author(s) to determine if mortality data were available. If this information was not available, the study was excluded from our analyses.[19,20]

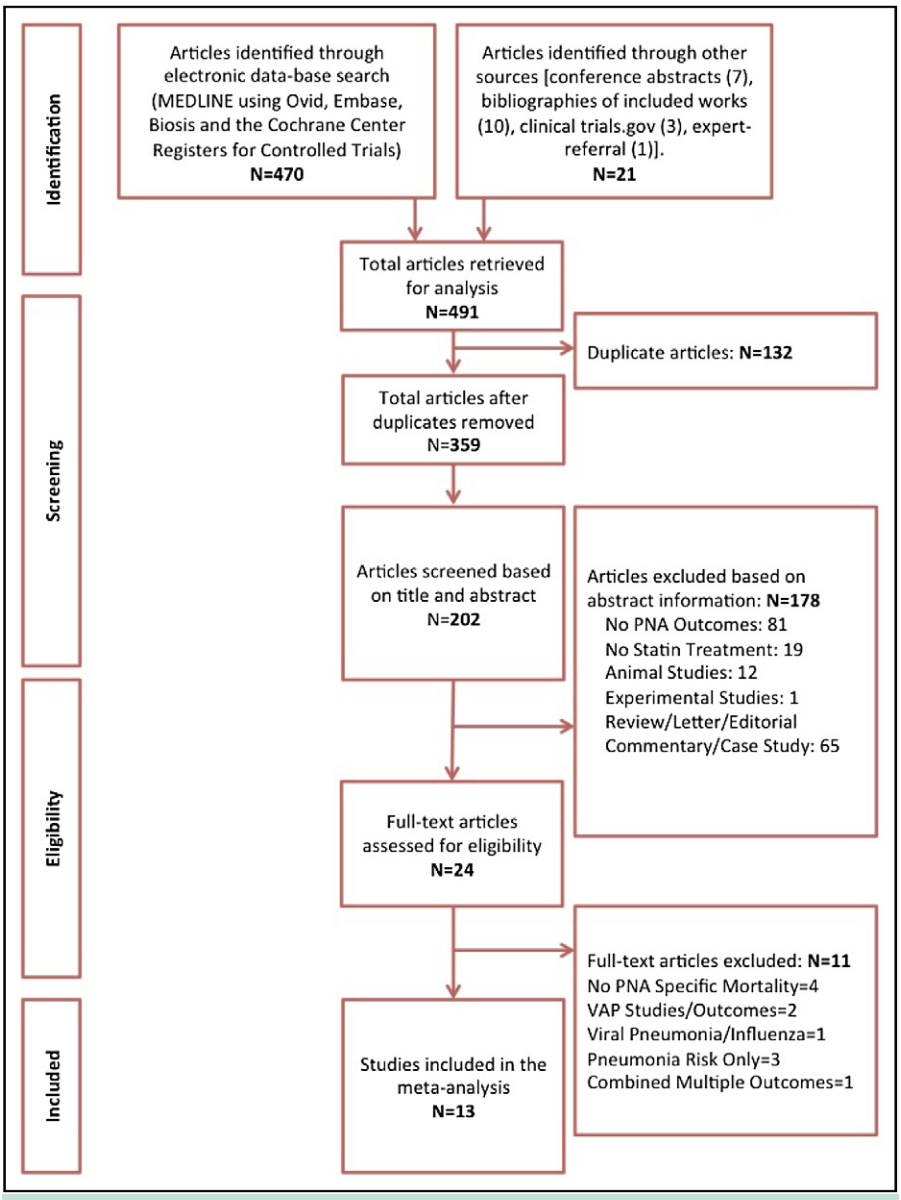

Figure 1 Study flow diagram. Summary of evidence and search selection.

Statistical Analysis

Data were extracted from eligible studies to create 2×2 tables for the calculation of unadjusted odds ratios. Adjusted odds ratios and their corresponding 95% confidence intervals also were abstracted for pooled analyses. Treatment effect estimates were calculated as a weighted average so that an odds ratio <1 favored statin treatment over control. When multiple models of adjustment were presented in a single study, we extracted the adjusted effect size estimates from the final, most complex model. All meta-analyses were conducted using a random-effects model as described by DerSimonian-Laird.[21] We explored heterogeneity between studies using Cochrane's Q test and the I^2 statistic, and classified heterogeneity as low, moderate, or high based on an I^2 statistic of 25%, 50%, and 75%, according to the method suggested by Higgins et al.[22] Publication bias was assessed by Harbord's test (based on the Z-score and its variance) and Peters' test (based on a weighted linear regression of the effect estimates on the reciprocal of sample size), with $P < .05$ indicative of publication bias.

We conducted subgroup analysis to determine whether study design, location of pneumonia treatment (hospital vs. community), adjustment for pneumonia severity (as conducted by each individual study), adjustment for vaccination status, adjustment for smoking, use of propensity scores, or adjustment for uncommon covariates affected the meta-analytic conclusions. Uncommon covariates were defined as clinical parameters that influence pneumonia outcomes, but are rarely available in administrative databases. A priori, these were specified as time to antibiotic delivery, presence of bacteremia, presence of advanced directives, use of home health services, nursing home residence, and

Table 1 General Characteristics of Included Studies

Study (First Author)	Country	Study Design	Mean Age (Y)	% Male	Sample Size (n)			Statin Type(s), Dose	Study Population
					Statin	Nonstatin	Total		
Chalmers[24]	United Kingdom	PC	66	49.7	257	750	1007	Simvastatin (72%), Atorvastatin (21.4%), Pravastatin (6.6%)	Patients admitted with radiographically confirmed pneumonia to Lothian University Hospitals Division in the UK.
Choi[14]	Korea	RCT	67	62.7	33	34	67	Atorvastatin 10 mg daily (100%)	Adults >18 years of age; sepsis due to pneumonia; admitted to an ICU.
Douglas[25]	United Kingdom	RC	NA	NA	847	2927	3774	Not reported	Statin users ≥40 years of age in the THIN (United Kingdom Health Improvement Network) database.
Dublin[26]	United States	CC	NA	50.8	181	944	1125	Simvastatin (76%), Lovastatin (19%), Atorvastatin (3.5%)	Group Health members aged 65 to 94, with: (A) >2 years of continuous membership and (B) ICD-9 based and radiographically confirmed cases of inpatient and outpatient pneumonia.
Frost[27]	United States	RC	NA	NA	19,058	57,174	76,232	Not reported	Patients in the Lovelace Patient Database (LPD), >90 days cumulative statin exposure before death or disenrollment matched to 3 patients on sex, birth year, and HMO enrollment period without a history of statin therapy.
Majumdar[28]	Canada	PC	NA	54.5	325	3090	3415	Simvastatin, Pravastatin, Atorvastatin accounted for 90%	Adults >17 years of age hospitalized for pneumonia in 6 hospitals in Capital Health, Alberta, Canada.
Mortensen 2005[29]	United States	RC	60	79	110	677	787	Not reported	Adults >18 years of age with an admission diagnosis of pneumonia and radiographically confirmed infiltrate, or other finding consistent with pneumonia on radiograph or CT obtained within 24 hours of admission.
Mortensen 2008[17]	United States	RC	75	98.6	798	4924	5722	Not reported	Veterans ≥65 years of age hospitalized with a primary discharge diagnosis of pneumonia or influenza and had received at least one active and filled medication within 90 days of admission.
Myles[18]	United Kingdom	RC	NA	NA	357	3324	3681	Not reported	Adults >40 years of age, general practice pneumonia cases in the THIN (Health Improvement Network) database.
Rothberg[30]	United States	RC	70.2	43.9	23,285	97,969	121,254	Not reported	Adults >18 years of age admitted with a principal diagnosis of pneumonia at 376 acute care facilities that participated in the Premier Perspective database.

Table 1 Continued

Study (First Author)	Country	Study Design	Mean Age (Y)	% Male	Sample Size (n) Statin		Nonstatin	Total	Statin Type(s), Dose	Study Population
Schlienger[31]	United Kingdom	CC	NA	54.4	PNA	314	939	1253	Not reported	Adults >30 years in the United Kingdom-based General Practice Research Database (GPRD) with a pneumonia diagnosis based on Read and Oxford Medical Information Systems coding matched with up to 4 control subjects on the basis of age (± 2 years), sex, general practice attended, and index date of case diagnosis.
Thomsen[32]	Denmark	RC	NA	56.3	Non-PNA 1372	1093	3745 28,528	4838 29,900	Simvastatin (61%) Pravastatin (15%) Atorvastatin (15%) Other (9%)	All individuals >15 years hospitalized with pneumonia for the first time in northern Denmark and Jutland County (Danish National Health Service databases).
Yende[33]	United States	PC	68.8	53.0	426		1469	1895	Atorvastatin (47.7%) Simvastatin (39.4%) Pravastatin (7.7%) Lovastatin (3.5%) Fluvastatin (1.6%)	Adults ≥18 years of age with a clinical and radiological diagnosis of pneumonia. Two different comparison cohorts; prior statin users vs. no prior statin use.

CC = case control; CT = computed tomography; HMO = health maintenance organization; ICD-9 = International Classification of Diseases, 9th Revision; ICU = intensive care unit; PC = prospective cohort; PNA = pneumonia; RC = retrospective cohort; RCT = randomized controlled trial.

measures of frailty other than comorbidity indices. Vaccination status was defined as a dichotomous variable and included vaccination for either pneumococcus or influenza.

Several sensitivity analyses to test the robustness of our findings were performed. We also conducted an influence analysis (the extent to which pooled inferences are affected by a particular study) and an analysis for the *Proteus* phenomenon (the appearance of an early extreme result that is refuted by later research) to ensure the integrity of our conclusions.[23] Data management and analysis were performed using Stata/MP Version 11 (StataCorp, College Station, Tex). Statistical tests were 2-tailed; $P < .05$ considered statistically significant.

RESULTS

Studies Included in the Systematic Review

Thirteen studies involving 254,950 patients published between 2005 and 2011 met inclusion criteria (**Figure 1**).[14,17,18,24-33] The eligible studies varied in design and included 10 cohort studies (3 prospective,[24,28,33] 7 retrospective[17,18,25,27,29,30,32]), 2 case-control studies,[26,31] and one randomized trial[14] available in abstract format only (**Tables 1**, **2**). Sample sizes of the included studies ranged from 67 to 121,254 patients. The studies were geographically diverse and included populations from Europe, Asia, and North America. Most included studies were retrospective and predominantly composed of male patients over the age of 50 years. Only 5 studies reported the types of statins received by the study population.[14,24,28,32,33] Although one study specifically assessed the effect of statin use on mortality during the first few days of hospitalization,[30] none of the included studies reported the specific duration of statin treatment either before or after the pneumonia episode. Most studies included patients hospitalized for treatment of pneumonia;[14,17,24,28-30,32,33] few featured outpatient treatment of pneumonia.[18,25-27,31] Four studies reported in-hospital mortality,[14,27,28,30] 6 reported mortality at 30 days,[17,18,24,26,29,31] 2 reported 90-day mortality,[32,33] and one reported mortality at 6 months.[25]

We successfully contacted 6 study authors to obtain unpublished data for this meta-analysis. Despite direct author queries, no additional information about the cause of death following pneumonia was available other than that included in the published studies. Notably, Dublin et al investigated the risk of developing pneumonia, not mortality after pneumonia.[26] Although we were able to obtain mortality data through author correspondence, adjusted odds ratios for mortality were not available for primary or subgroup meta-analysis.

With respect to the quality of included studies, the average Downs and Black Score for nonrandomized studies

Table 2 Statistical Methods, Outcomes and Quality of Included Studies

Study (First Author)	Comparison Group	Method of Statistical Adjustment	Key Variables Adjusted in Regression Models	Clinical Outcomes Reported	Clinical Outcomes Abstracted	Adjusted Odds Ratio (95% CI)	Quality of Study (Score)
Chalmers[24]	Statin users vs statin nonusers	Multivariable logistic regression	Demographic variables; pneumonia severity score; comorbidity (chronic cardiac failure, cerebrovascular disease, chronic renal failure, chronic obstructive pulmonary disease, diabetes mellitus); smoking; aspirin; β-blockers; ACE-inhibitor use.	30-day mortality	30-day mortality	0.46 (0.25-0.85)	High (24/29)
Choi[14]	Patients randomized to statins vs control	N/A; RCT	N/A; RCT	In-hospital mortality	In-hospital mortality	N/A; RCT	Unclear
Douglas [25]	Statin users vs statin nonusers	Cox regression	Demographic variables (in 5-year bands), sex, propensity score, and year of index date.	6-month mortality	6-month mortality	0.67 (0.49-0.91)	High (26/29)
Dublin[26]	Statin users vs statin nonusers in pneumonia cases and controls	N/A	Did not statistically adjust for mortality	Risk of pneumonia	30-day mortality*	N/A	High (25/29)
Frost [27]	Statin users vs statin nonusers	Multivariable logistic regression	Demographic variables; Days enrolled during phase 1 and phase 2; Charlson comorbidity index score $\geq$2; number of different medications taken; 3 or more influenza vaccinations	In-hospital mortality; survival time	In-hospital mortality	0.73 (0.47-1.13)	Intermediate (21/29)
Majumdar[28]	Statin users vs statin nonusers	Multivariable logistic regression	Demographic variables; nursing home status; comorbidities (ischemic heart disease, heart failure, COPD, etc.); >5 medications taken; vaccination status; smoking status, pneumonia severity score; bacteremia; propensity score.	In-hospital mortality	In-hospital mortality	1.03 (0.64-1.68)	High (26/29)
Mortensen 2005[29]	Statin users vs statin nonusers	Multivariable logistic regression	Demographic variables; propensity score; use of statin at presentation; process of care measures (initial antibiotics within 4 hours, obtaining blood cultures before initial dose of antibiotics, whether antimicrobial therapy was guideline concordant)	30-day mortality	30-day mortality	0.36 (0.14-0.92)	High (24/29)
Mortensen 2008[17]	Cohort of statin users, ACE inhibitor users, combined users, and nonusers	Generalized linear mixed-effects models	Demographic information, comorbid conditions, Charlson comorbidity index; pharmacy data; propensity score	30-day mortality	30-day mortality	0.54 (0.42-0.70)	High (25/29)
Myles[18]	Compared impact of statins, ACE inhibitors, proton pump inhibitors, and H2 receptor antagonist use on pneumonia mortality	Cox regression	Demographic variables; Townsend's deprivation score; current smoking; Charlson comorbidity index score; co-prescription of other exposure drugs.	30-day mortality	30-day mortality	0.33 (0.19-0.58)	Intermediate (21/29)
Rothberg[30]	Statin users vs statin nonusers	Multivariable logistic regression	Demographic variables; comorbidities; additional early non-pneumonia treatments that indicate poor general health; pneumonia type; pneumonia severity indicators; physician specialty; hospital size and teaching status; medications associated with pneumonia use; propensity scores.	In-hospital mortality	In-hospital mortality	0.90 (0.82-0.99)	High (26/29)

Table 2 Continued

Study (First Author)	Comparison Group	Method of Statistical Adjustment	Key Variables Adjusted in Regression Models	Clinical Outcomes Reported	Clinical Outcomes Abstracted	Adjusted Odds Ratio (95% CI)	Quality of Study (Score)
Schlienger[31]	Statin users vs statin nonusers	Conditional logistic regression	Demographic variables; use of fibrates; smoking; BMI; diabetes mellitus; asthma or COPD; stroke; chronic heart failure; ischemic heart disease, epilepsy; alcoholism; current use of corticosteroids; number of visits to general practitioners in the year before the index date.	30-day mortality	30-day mortality	0.47 (0.25-0.88)	Intermediate (22/29)
Thomsen[32]	Statin users vs statin nonusers	Cox regression	Demographic variables; comorbidities; alcohol-related disorders; preadmission use of antibiotics or immunosuppressive drugs; urbanization of place of residence; type of hospital, calendar period (1997-1999, 2000-2002, and 2003-2004); use of β-blockers, low-dose aspirin, or ACE inhibitors.	30-day mortality; 90-day mortality	90-day mortality	0.75 (0.65-0.86)	High (26/29)
Yende[33]	Statin users whose statins were continued in-hospital vs those with either no prior use or no in-hospital use	Multivariate logistic regression	Demographic variables; comorbidities; Charlson comorbidity score; pneumonia severity score; treatments received; healthy user indicators (insured, lives at home, functional status, former smoker, influenza and pneumococcal vaccinations).	90-day mortality; risk of severe sepsis	90-day mortality	0.73 (0.47-1.13)	High (25/29)

ACE = angiotensin-converting enzyme; CI = confidence interval; COPD = chronic obstructive pulmonary disease; N/A = not available; RCT = randomized controlled trial.
*Data obtained through author contact.

was 24.2 (range 21-26), suggesting a high quality of methodology. The only randomized trial in this analysis was of unclear quality, as many details about study design were not available (**Table 2**).[14] Cohen's inter-rater kappa statistic for inclusion agreement, abstraction, and quality assessment were 0.87, 0.90, and 0.89, respectively, indicative of excellent inter-rater agreement.

Pooled Outcomes

Unadjusted Pneumonia Mortality. Of the 13 included studies, 10 studies (2 case control, 7 cohort, and 1 randomized study) involving 171,989 patients reported raw mortality after pneumonia and were pooled for this outcome.[14,18,25,26,28-33] Within the pooled studies, the cumulative incidence of mortality was 9.2% (n = 15,768). The unweighted incidence of mortality among those treated with statins was 5.1% (1358/26,825) versus 10.3% (14,410/140,326) in controls. Pooled meta-analysis revealed that current statin use was associated with decreased overall mortality after pneumonia (odds ratio [OR] 0.62; 95% confidence interval [CI], 0.54-0.71). The size of this protective effect was most pronounced at 30 days (OR 0.42; 95% CI, 0.25-0.71). Although moderate heterogeneity was observed in the overall effect measure ($I^2 = 50.0\%$, Cochrane's Q-test statistic 17.99, $P = .04$), this was largely explained by the time intervals at which mortality was reported within the included studies ($I^2 = 63.4\%$ for the 30-day mortality interval, $I^2 = 0\%$ for all other intervals) (**Figure 2**). Neither Harbords' ($P = .255$) nor Peters' test ($P = .81$) suggested significant publication bias.

Adjusted Pneumonia Mortality

Of the 13 included studies, 11 studies (2 case control, 9 cohort) involving 248,920 patients reported adjusted measures of the effect of statins on mortality after pneumonia.[17,18,24,25,27-33] Adjustments were performed for a diverse range of factors, including social and demographic factors, pneumonia process measures, comorbidity indices, smoking and vaccination status, and propensity to receive statin treatment. Pooling of these data revealed that statin use remained associated with a decrease in the risk of death after pneumonia (OR 0.66; 95% CI, 0.55-0.79). As was the case with the unadjusted analyses, the greatest benefit of statins against mortality was observed at 30 days (OR 0.48; 95% CI, 0.39-0.59). Notably, the overall magnitude of the pooled benefit was virtually identical to that of the unadjusted analyses (**Figure 3**). A high degree of heterogeneity was observed for the pooled adjusted OR of 0.66 ($I^2 = 72.6\%$,

Figure 2 Forest plot (stratified by interval at which mortality was reported), showing the pooled unadjusted association between statin use and pneumonia mortality. At all intervals, unadjusted statin use was associated with reduction in all-cause mortality after pneumonia. The greatest reduction was observed at 30-day mortality, a time-point most associated with pneumonia-related death. Heterogeneity in the pooled effect was explained by the intervals at which mortality was reported.

Cochrane's Q-test statistic 36.6, $P < .001$), which was again explained by the time at which the individual studies reported mortality ($I^2 = 0\%$ for each mortality interval group). Based on this pooled adjusted effect size, we estimated numbers needed to treat to prevent a single death from pneumonia over a range of mortality rates (**Table 3**).

Subgroup Analysis

We performed subgroup analyses to determine whether methodological or clinical factors influenced the meta-analytical estimates of statins on pneumonia mortality (**Table 4**). Although no statistically significant differences were observed, the strength of the association between statin use and mortality substantially diminished when studies were analyzed according to the inclusion of important confounders in their models (**Figure 4**). Further, no effect of statins on mortality after pneumonia was observed in the adjusted pooled OR for prospective cohort studies (0.73; 95% CI, 0.48-1.10]) and for the (underpowered) randomized controlled trial (0.84; 95% CI, 0.32-2.18).

Sensitivity and Influence Analysis

To test the robustness of our meta-analytic conclusions, several sensitivity analyses were performed. These did not produce meaningful differences in the unadjusted or adjusted effect estimates (**Table 5**). An influence analysis determined that no single study significantly influenced the overall conclusions. An analysis for the *Proteus* phenomenon did not suggest this effect ($P = .24$).

DISCUSSION

This meta-analysis of 13 studies finds that current statin users are less likely to die after an episode of bacterial pneumonia compared with nonstatin users. The magnitude of this benefit was similar using both unadjusted and adjusted estimates. In both analyses, the observed mortality benefit was greatest at the 30-day interval, a time-point that has been invoked as being most correlated with mortality from pneumonia.[34] However, this protective effect weakened when subgroups accounting for patient differences

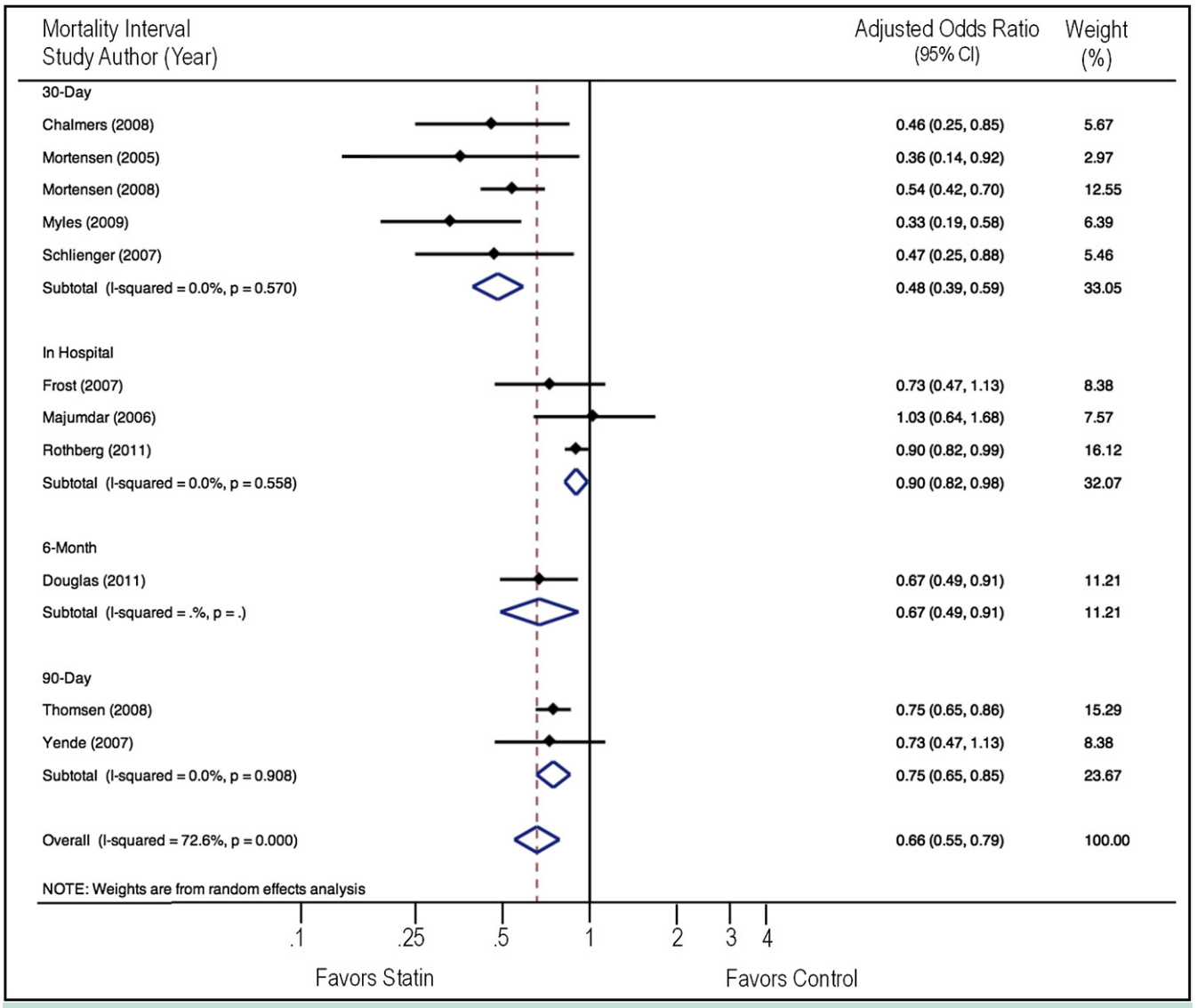

Figure 3 Forest plot (stratified by interval at which mortality was reported), showing the pooled adjusted association between statin use and pneumonia mortality. Statin use was associated with reductions in all-cause mortality after pneumonia in the pooled effect estimates at all time intervals. Heterogeneity in the pooled effect was explained by the intervals at which mortality was reported.

through the use of propensity scores, pneumonia severity indicators, smoking status, vaccination status, and clinically uncommon covariates were constituted. Furthermore, no survival benefit for statin use was found in the 3 prospective studies and in the single randomized controlled study included in this analysis. These findings make the relationship between statin use and pneumonia difficult to discern from the available literature.

How may statins reduce mortality after pneumonia? The evidence suggests that early (in-hospital and 30-day) mortality from pneumonia is directly related to host response and clinical treatment. Thus, timely antibiotic delivery, recognition and goal-directed treatment of severe sepsis, and use of management strategies such as early intensive care unit admission impact early mortality from pneumonia.[35-37]

Table 3 Meta-Analytic Estimates of Reduction In Mortality After Pneumonia By Statin Treatment

Base Scenario (Estimated Mortality from Pneumonia)	Number of Deaths Prevented (Per 1000 Statin Users)*	95% Confidence Interval
1%	3.4	2.1-4.5
5%	16.6	10.3-21.9
10%	32.0	19.7-42.5
15%	46.1	28.2-61.7
20%	58.9	35.8-79.3
25%	70.3	42.4-95.3

Calculations based on pooled adjusted odds ratio = 0.66, 95% confidence interval 0.55-0.79.

Table 4 Subgroup Analysis

Subgroup	Clinical Outcomes OR (95% CI)	
	Unadjusted Data	Adjusted Data
Study design		
Retrospective cohort[18,25,27,29,30,32]	0.60 (0.51-0.71)	0.65 (0.53-0.81)
Prospective cohort[24,28,33]	0.68 (0.51-0.92)	0.73 (0.48-1.10)
Case-control[26,31]	0.57 (0.38-0.83)	0.47 (0.25-0.88)
Randomized controlled trial[14]	0.84 (0.32-2.18)	N/A*
Location of treatment		
Community[18,25-28]	0.51 (0.38-0.68)	0.56 (0.40-0.78)
Hospital[14,24,28-30,32,33]	0.67 (0.63-0.71)	0.71 (0.58-0.87)
Type of statin†		
Simvastatin[24-26,30,32]	0.66 (0.62-0.71)	0.76 (0.63-0.91)
Atorvastatin[14,33]	0.66 (0.45-0.96)	0.73 (0.47-1.13)
Unknown[18,27-29,31]	0.50 (0.34-0.73)	0.56 (0.41-0.77)
Adjustment for pneumonia severity	0.66 (0.62-0.71)[28-30,33]	0.75 (0.56-1.00)[14,24,28-30,33]
Adjustment for vaccination status	0.63 (0.49-0.81)[28,31,33]	0.74 (0.56-0.97)[18,28,31,33]
Adjustment for smoking status‡	0.64 (0.60-0.68)[18,25,28-31,33]	0.63 (0.48-0.83)[18,25,28-31,33]
Use of propensity score	0.66 (0.61-0.70)[25,28,30,33]	0.75 (0.58-0.96)[25,28,30,33]
Adjustment for uncommon covariates	0.67 (0.63-0.71)[28-30,32,33]	0.81 (0.69-0.96)[28-30,32,33]

CI = confidence interval; OR = odds ratio.
All subgroup analyses were performed using random-effects meta-analyses.
*Adjustment for confounding not indicated owing to randomized trial design.
†Based on most frequent statin encountered in study.
‡Former or current smoking.

Theoretically, statins may reduce mortality at this stage via attenuation of pulmonary and systemic inflammation,[7] modification of the sepsis response,[5,38,39] or direct antimicrobial activity.[40] In contrast, mid- and long-term mortality from pneumonia (>30 days) is due to different etiologies.[41,42] For example, cardiac events owing to rupture of vulnerable

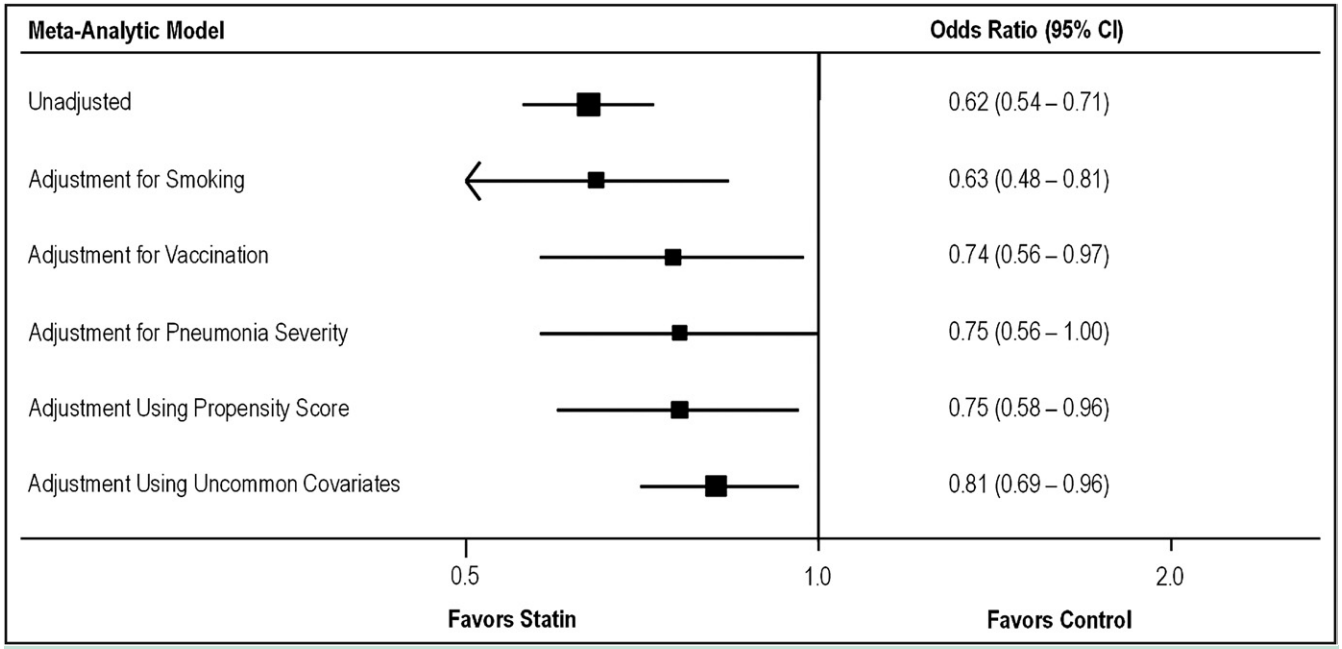

Figure 4 Pooled meta-analytic mortality stratified by specific confounders. Forest plot showing pooled estimates of mortality following pneumonia in statin users when specific confounders were adjusted for in the models. Notably, in studies that adjusted for pneumonia severity and uncommon covariates or those that used propensity scoring to assess the influence of receiving statins, no significant association between statin use and mortality following pneumonia was observed.

Table 5 Sensitivity Analysis

Scenario	Clinical Outcomes OR (95% CI)	
	Unadjusted Data	Adjusted Data
Study effects by region		
North America[17,26-30,33]	0.66 (0.62-0.71)	0.73 (0.56-0.94)
Europe[18,24,25,31,32]	0.51 (0.36-0.72)	0.57 (0.42-0.75)
Asia[14]	0.84 (0.32-2.18)	N/A
Excluding retrospective studies[14,17,24,28,33]	0.70 (0.52-0.92)	0.73 (0.48-1.10)
Excluding studies of intermediate quality[14,24-30,32,33]	0.66 (0.62-0.70)	0.71 (0.59-0.85)
Excluding studies of unclear and intermediate quality[24-30,32,33]	0.66 (0.62-0.70)	0.71 (0.59-0.85)
Excluding study that contained patients without pneumonia[31]	0.63 (0.56-0.71)	0.67 (0.56-0.80)
Excluding studies with sample size >10,000[27,30,32]	0.55 (0.43-0.71)	0.58 (0.46-0.72)

CI = confidence interval; OR = odds ratio.
All sensitivity analyses performed using random effects meta-analyses.
N/A* - Randomized controlled study, no adjustment necessary.

coronary plaque after infection may account for delayed death following pneumonia.[43,44] Heightened cardiac risk following acute infection is pertinent in the context of statin use, as statin users are less likely to suffer acute coronary syndromes and subsequent mortality. Notably, the precise cause of mortality following pneumonia remains elusive in almost all of the included studies in the present analysis.

Some investigators have suggested that any effect of statins on pneumonia represents unresolved confounding.[26,28] We explored this possibility by separately pooling unadjusted and adjusted measures of the effects of statins on mortality after pneumonia, theorizing that differences in these estimates may support these concerns. Although both measures suggest reduction in mortality after pneumonia, subgroup analysis using important confounders weakened this association. While this dissonance may be related to residual confounding or limitations inherent to meta-analysis, it merits further investigation through the lens of a randomized study. As a recently concluded randomized trial found significant decreases in mortality among statin-naïve intensive care unit patients treated with pravastatin,[11] the timing of this study appears opportune.

Our analysis has limitations. First, the studies that present adjusted estimates of effect sizes employed models that varied from one another, leading to potential clinical or statistical heterogeneity. However, we observed that much of the statistical heterogeneity across studies was explained by the time at which mortality was reported, suggesting that model variation did not significantly influence pooled estimates. Second, we restricted inclusion of studies to those specifically reporting outcomes related to community-acquired pneumonia; in doing so, we may have excluded a number of studies in which the pathogenesis of pneumonia was unknown or where the accuracy of coding for pneumonia was poor. This limitation was necessary in view of the need to obtain a "pure" pneumonia cohort. Third, as the prevailing evidence comes almost solely from observational studies, residual confounding and healthy-user bias remains a threat to our conclusions.

However, our analysis has important strengths. First, we separately pooled unadjusted and adjusted measures of the effects of statins on pneumonia mortality, a novel approach that allows for a side-by-side comparison of the 2 data sources that have fueled the debate about the effect of statins on pneumonia. Second, in order to make evident any effects of residual confounding, we created unique subgroups by specifically using covariates associated with the healthy-user phenomenon and clinical process measures that influence pneumonia outcomes. Third, our analysis comprises a large pool of previously unpublished data, inclusion of which provides the most complete and accurate characterization of the effect of statins on pneumonia mortality.

In conclusion, we found that current statin use was associated with decreased mortality after pneumonia. However, the strength of this association weakened in important subgroups and in studies with greater methodological rigor, highlighting why a large randomized controlled trial is necessary to understand this relationship. As pneumonia remains a leading cause of worldwide mortality, exploring this novel intervention may prove valuable in our battle against this old adversary.

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