Beneficial effects of statins on outcomes in pneumonia: a systematic review and meta-analysis

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Abstract. – OBJECTIVES: There exist reports that statin treatment has beneficial effects for patients with pneumonia. The objective of this study was to evaluate whether the available published data support that statins as adjunctive therapy could reduce mortality associated with pneumonia and, thus, help to assess whether a randomized controlled study is warranted.

MATERIALS AND METHODS: A meta-analysis of observational studies such as cohort studies and case-control studies identified in Pubmed, Scopus, EMBASE, the Cochrane Central Register of Controlled Trials and Clinicaltrials.gov. Eligible patients were adults with pneumonia. Studies that reported mortality of pneumonia grouped by statins usage were included. Data was analyzed and pooled using Revman 5.1.

RESULTS: Fourteen studies with 269,739 participants were included in this study. Pooled analysis showed that statin treatment was associated with lower 30-day mortality, with an OR of 0.44 (95% CI, 0.29-0.67), and an adjusted OR of 0.59 (95% CI 0.48-0.73, NNT30d = 19). Statin therapy was also associated with lower long-term (> 30 days) mortality, with an OR of 0.49 (95% CI, 0.29-0.84) and an adjusted OR of 0.65 (95% CI, 0.51-0.82, NNTlong-term = 15). For pneumonia inpatients, the raw data demonstrated no significant benefit from statin therapy (OR = 0.86, 95% CI, 0.56-1.34). Adjusted data showed a marginal benefit (adjusted OR = 0.89, 95% CI, 0.81-0.97, NNTinpatient = 230). Subgroup analysis revealed that current statin users might have better outcomes than recent or past statins users.

CONCLUSIONS: This meta-analysis supports that patients who happen to be receiving statin therapy have less mortality from pneumonia. However, it remains unclear whether initiation of statins at time of diagnosis is beneficial. There is only modest evidence to support the value of a well-designed randomized controlled clinical trial.

Introduction

Pneumonia remains a major cause of mortality even when antibiotics are provided timely. In America, community-acquired pneumonia (CAP) leads to 500,000 hospitalizations and 45,000 deaths every year[1]. The average cost to patients older than 65 years is estimated to be 7000 US dollars, and the total medical costs for pneumonia patients are over 1 billion US dollars per year[2].

The mortality of pneumonia is ascribed to the virulence and invasiveness of the infecting microorganisms and damage to lung tissue that results from the host responses. Modulation of the release of inflammatory mediators with glucocorticoids, macrolides, aspirin, and Toll-like receptor antagonists is a component of some treatment strategies. The application of these drugs has been limited by their adverse effects and limited supporting evidence.

Statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors] are extensively used as lipid-lowering agents and atherosclerotic plaque stabilizers. Experimental studies have indicated that statins may also have the ability to modulate both innate and adaptive immune responses and to reduce the level of pro-inflammatory mediators and thrombosis[3,4]. Several clin-

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ical studies have shown that statins as adjunctive therapy provide survival benefit in patients with bacteremia and sepsis[5,6]. These findings suggest statins might be beneficial in the treatment of patients with pneumonia. No randomized controlled trials have evaluated this possibility but there are observational studies in the published literature. We performed a systematic review and meta-analysis of the available data to provide an assessment of the potential effect size of statins as adjunctive therapy in the management of pneumonia.

Materials and Methods

Eligibility Criteria

We selected cohort studies (prospective/retrospective) and case-controlled studies that reported patient mortality with pneumonia grouped by statin usage. Included studies: (1) enrolled adult patients (≥ 18 years old) with a diagnosis of pneumonia; (2) reported the mortality of both the treatment group (statin users) and a control group; (3) reported an adjusted effect for one or more potential confounders.

Search Sources and Strategy

The literature search was conducted in PubMed, Scopus, EMBASE, the Cochrane central register of controlled trials and Clinicaltrials.gov. The search was conducted using terms for statins ("Hydroxymethylglutaryl-CoA Reductase Inhibitors", "HMG CoA reductase inhibitors", "simvastatin", "lovastatin", "pravastatin", "fluvastatin", "atorvastatin", "rosuvastatin", "pitavastatin" and "statins") and combined with the term pneumonia ("pneumonia", and "low-respiratory-tract-infection") as a MeSH or text word. The searches were limited to studies in the English language. There were no restrictions on publication date or pneumonia status. Search results were saved as EndNote files (Version: Endnote X5).

Screening and Data Extraction

Two reviewers independently assessed publication eligibility and excluded any articles that failed to meet the inclusion criteria. Disagreement was resolved by consensus. The following data were abstracted from each study: study characteristics (publication year, country, study design, sample size), participant characteristics (gender, mean age, types of pneumonia), type and dose of statins, clinical outcome, and confounder adjustments. Two authors separately qualified the enrolled cohort studies and case-controlled studies using the Newcastle-Ottawa Quality Assessment Scale.

Data Analysis

Raw data of all-cause mortality and its adjusted odds ratio (OR) were pooled for the meta-analysis according to the statistical methods of Mantel-Haenszel and Generic Inverse Variance. Heterogeneity between studies was explored using the Cochran's Q test and I^2. An I^2 value of 25%, 50% and 75% was considered low, moderate and high level heterogeneity, respectively[7]. When substantial heterogeneity was confirmed (p value of Cochran's Q test < 0.1 or I^2 value > 50%) a random-effects model was used to conduct the meta-analyses. Otherwise a fixed-effect model was used.

3 clinical outcomes were evaluated using a pooled analysis: (1) in-hospital mortality; (2) 30-day mortality; and (3) long-term (> 30 days) mortality. If a study reported two or more clinical outcomes, results were abstracted simultaneously and separate pooled analyses were performed. Results of "current users" were extracted rather than "recent" or "past" if both were provided. The number needed to treat (NNT) was estimated when the pooled results favored statin treatments. Publication bias was assessed intuitively using a funnel plot. A Begg/Egger's test was used in the case of an asymmetric funnel plot or inconclusive findings. Subgroup analyses were conducted to explore whether continuation of statin treatment, dosage of statin or severity of pneumonia had implications for the effect size of the statin therapy.

Statistical analyses were performed using Revman version 5.1 (Nordic Cochrane Centre, Kobenhavn, Denmark).

Results

Identification and Characteristics of Included Studies

The initial search strategy yielded 1381 studies, of which 50 articles were chosen for full review (Figure 1). A total of 14 studies[8-21] addressing the roles of statins in the treatment of pneumonia were finally included.

There were 2 case-controlled studies[11,20], 3 prospective cohort studies[8,12,19] and 9 retrospective
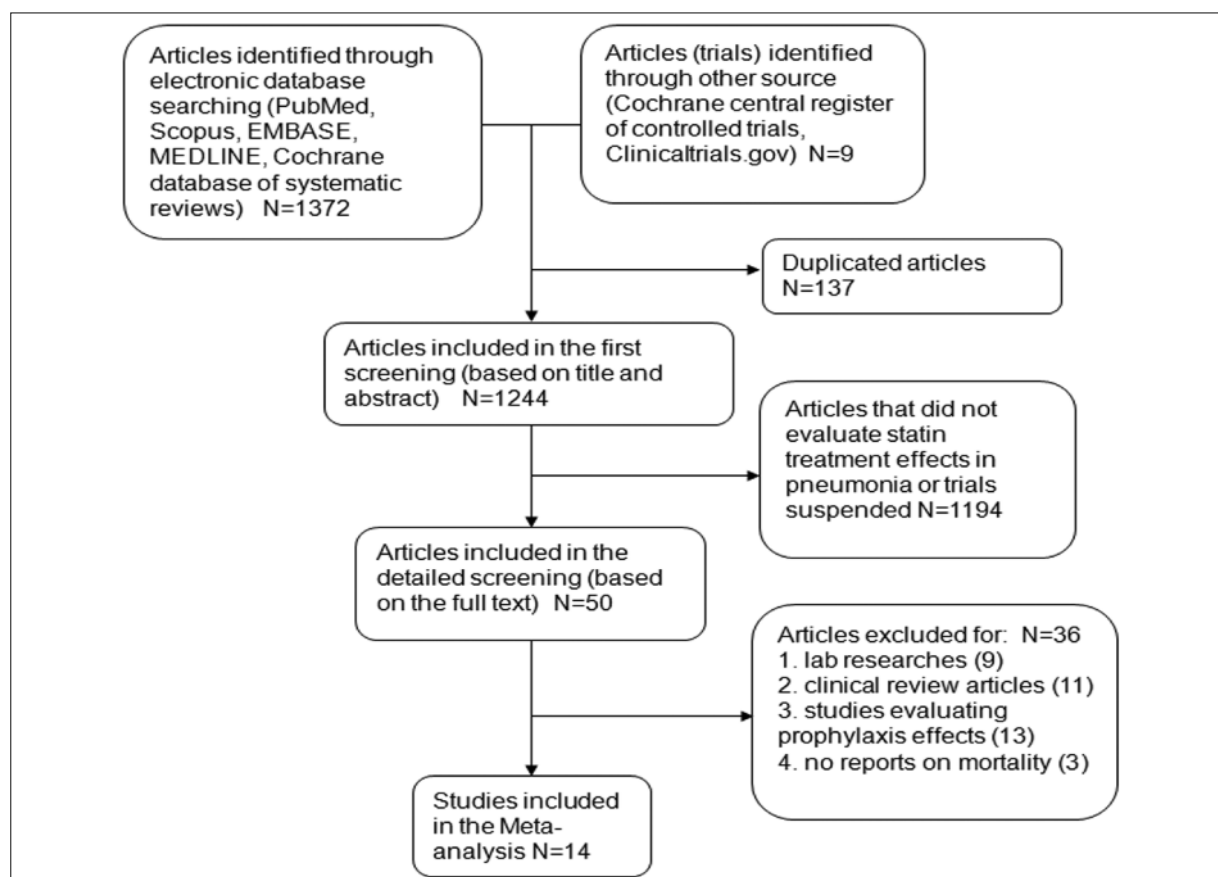
Figure 1. Flow diagram of the process of article selection for the meta-analysis.

cohort studies that fulfilled the inclusion criteria. The findings of 269,739 patients were reported, with the largest study having almost 98,000 patients. The studies were geographically diverse. The majority were from Europe (4 British studies and 1 from Denmark) and North America (7 from the USA and 2 from Canada). Patient information was abstracted from the health databases of local governments or hospitals. The patients were mainly Caucasian (78%-91%), with ages from 60 to 75 years. Patients from 6 studies were diagnosed with community-acquired pneumonia. The classification of pneumonia was not stated in the other studies. Since the incidence of hospital-acquired pneumonia globally is about 0.5%-5.0%, the unspecified pneumonia was considered to be CAP. Smoking status was reported in 8 studies and vaccination status was stated in five. All the studies adjusted potential confounders using a propensity score analysis or multivariable logistic regression models.

Among the 14 included studies, 2 studies[16,18] reported both 30-day mortality and long-term

mortality. Results were abstracted and analyzed separately. All of the included studies were of high quality. The average Newcastle-Ottawa Scale (NOS) score was 6.6. Characteristics and results of each study were extracted and summarized in Table I.

Meta-Analysis

Meta-analysis of unadjusted data from 3 studies[11,12,17] showed no benefit for statin users for in-hospital pneumonia mortality (OR = 0.86, 95% CI 0.56-1.34). However, pooled analysis of adjusted data revealed an association between statin therapy and lower hospital pneumonia mortality (adjusted OR = 0.89, 95% CI 0.81-0.97), with a number needed to treat of 230 patients (Figure 2).

Of the 9 studies[8,9,13-16,18,20,21] reporting 30-day mortality, only five provided raw data for unadjusted pooling. One study (Kwong, et al) reported unadjusted ORs (OR = 0.84, 95% CI 0.77-0.91) without raw data. Combined analyses of both unadjusted and adjusted data revealed that statin therapy was associated with a lower 30-day

Table I. General characteristics and results of included studies.

Study	Study design	Mean age (yrs) M ±SD	Type of pneumonia	Sample size (statins/total)	Statin types; doses	Outcome	Results (%) Statin Event/total	Results (%) Control Event/total	Adjusted odds ratio (95% CI)	Confounders adjustments	Quality score
Floyd J. Frost[11]; USA; 2007	(RC) CC	NAD	Pneumonia	19058 match (57174 RC); 397/54136 (CC)	No type; moderate daily dose (≥ 4 mg/d)	In-hospital mortality	30/3340	336/50955	0.62 (0.43-0.91)	Sex, birth year, duration	6
Sumit R. Majumdar[12]; Canada; 2006	PC	75	CAP	325/3415	Simvastatin, pravastatin, atorvastatin	In-hospital mortality	25/325	574/3090	1.03 (0.64 -1.68)*	Age, sex, nursing home care, comorbidities (IHD, HF, COPD, NI), number of drugs prescribed, PSI, immunizations up to date, functional status, former smoke, propensity score.	6
Michael B. Rothberg[17]; USA; 2012	RC	70.2 ± 15.9	Pneumonia	23285/121254	Simvastatin, atorvastatin, pravastatin	In-hospital mortality	901/ 23285	5617/ 97969	0.90 (0.82-0.99)	Demographic variables, comorbidities, medications associated with statin use; non-pneumonia treatments, interaction terms, severity of pneumonia.	6
James D. Chalmers[8]; British; 2008	PC	66 (50-78)	CAP	257/1007	Simvastatin, atorvastatin, pravastatin,	30-day mortality	NAD	NAD	0.46 (0.25-0.85)	Age, PSI score, comorbidity (HF, CVD, CRF, COPD, DM), and smoking status.	7
Simit M. Doshi[9]; USA; 2012	RC	Statin users 68.6 ± 10 Nonusers 63.6 ± 12	Pneumonia	90/347	NAD	30-day mortality	7/90	38/257	HR (95% CI) 0.39 (0.16-0.92)	Age, race, comorbidities, bacteremic status, alcohol use, length of stay and disease severity determined by PORT score.	6
Eric M. Mortensen[15]; USA; 2005	RC	60 ± 16	CAP	110/787	NAD mortality	30-day	5/110	67/677 (0.14-0.92)	0.36	Propensity score, use of statin at presentation, and process of care measures	7

Table I (Continued). General characteristics and results of included studies.

Study	Study design	Mean age (yrs) M ±SD	Type of pneumonia	Sample size (statins/total)	Statin types; doses	Outcome	Results (%) Statin Event/total	Results (%) Control Event/total	Adjusted odds ratio (95% CI)	Confounders adjustments	Quality score
Eric M Mortensen[14]; USA; 2008	RC	75.2 ± 6.1	CAP	1567/8652	Atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin;	30-day mortality	NAD	NAD	0.54 (0.42 -0.70)	Age, sex, race, being married, VA means test, classes of medications and the Charlson composite score (without age)	5
Eric M. Mortensen[13]; USA; 2012	RC	74.8 ± 6.7	Pneumonia	7763/22996	Atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin	30-day mortality	NAD	NAD	0.68 (0.59-0.78)	Sociodemographic variables, receipt of guideline concordant antibiotics, comorbid conditions, other medications	7
†Puja R. Myles[16]; British; 2009	RC	NAD	Pneumonia (majority) of CAP	357/3681	No mention	30-day mortality / Follow-up mortality (2.8y)	12/177 95/357	860/3324 1406/3324	HR (95% CI) 0.33 (0.19-0.58) 0.45 (0.32-0.62)	Age, sex, current smoking status; socio-economic status; comorbidities (Charlson Index)	8
Jeffrey C. Kwong21; Canada; 2009	RC	74.34 ± 5.78	Pneumonia	NAD/13027	Atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin	30-day mortality	NAD**	NAD**	0.90 (0.82-0.98)	Age, sex, chronic institutionalization, number of hospitalizations in the prior three years, number of medications prescribed in the prior year, and risk factors for influenza-related complications	7
Raymond G. Schlienger[20]; British; 2007	CC	NAD but age distribution was provided instead	Pneumonia	150/1181	NAD	30-day mortality	19/150	229/1031	0.47 (0.25-0.88)	Matched on age, sex, the general practitioner's practice, the index date. Adjusted confounders: moking status, BMI, svaccination, other lipid-lowering agents, corticosteroids, antiviraltherapy, chronic comorbid conditions	6

Table Continued

Table I *(Continued)*. General characteristics and results of included studies.

Study	Study design	Mean age (yrs) M ±SD	Type of pneumonia	Sample size (statins/total)	Statin types; doses	Outcome	Results (%)			Confounders adjustments	Quality score
							Statin Event/total	Control Event/total	Adjusted odds ratio (95% CI)		
‡Reimar W. Thomsen[18], Denmark; 2008	RC	73 (60-81)	CAP	1372/29900	Simvastatin 61%, pravastatin 15%, Atorvastatin 15%, others 9%	30-day mortality 90-day mortality	141/1372 230/1372	4489/28528 6381/28528	RR (95% CI) 0.69 (0.58-0.82) 0.75 (0.65-0.86)	Age, sex, comorbidity, marital status, calendar period, alcoholism-related disorders, level of urbanization of place of residence, type of hospital, preadmission of drugs***	8
Ian Douglas[10], British; 2011	RC	NAD but age distribution was provided instead.	Pneumonia	956/4461 (for mortality analysis)	NAD	6-month mortality	109/847	578/2927	HR (99% CI) 0.67 (0.49 to 0.91)	Age; sex; observation time in THIN; BMI; smoking status; socioeconomic status; consultation rate; prescribing rate; drinking habits; DM; CHD; CVD; AF; HF; cancer; dementia; hepatic, renal, thyroid disease; steroids; antipsychotics, antidepressants, cardiovascular drugs	7
Sachin Yende[19]; 2011	PC	72.15 ± 11.5	CAP	354/1895	Atorvastatin 47.7% simvastatin 39.4% pravastatin 7.7% lovastatin 3.5%, fluvastatin 1	90-day mortality	28/354	186/1541	0.73 (0.47-1.13)	Demographics and comorbidities; severity of illness; treatments received; healthy user indicators	7

CC: case-controlled studies; PC: prospective cohort studies; RC: retrospective cohort studies; CAP: community-acquired pneumonia; HAP: hospital-acquired pneumonia; PSI: pulmonary severity index; BMI: body mass index; HMO: health maintenance organization; NAD: No available data; IHD: ischaemic heart disease; HF: heart failure; AF: atrial fibrillation; CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease; NI: neuropsychiatric illnesses; CVD: cerebrovascular/cardiovascular disease; CRF: chronic renal failure; DM: diabetes mellitus; ACEI: angiotensin-converting enzyme inhibitor; *Adjusted OR of in-hospital mortality was not reported in the original article, the results was extracted from article by Chopra V.32 **There was no raw data available in the original article, but unadjusted odds ratio was reported OR = 0.84 (0.77-0.91). ***Preadmission of drugs: antibiotics, low-dose aspirin, β-blockers, ACEI, immunosuppressive drug. †The authors provided 30-day mortality and long-term mortality (2.8y) simultaneously. ‡The authors provided 30-day mortality and 90-d mortality simultaneously.
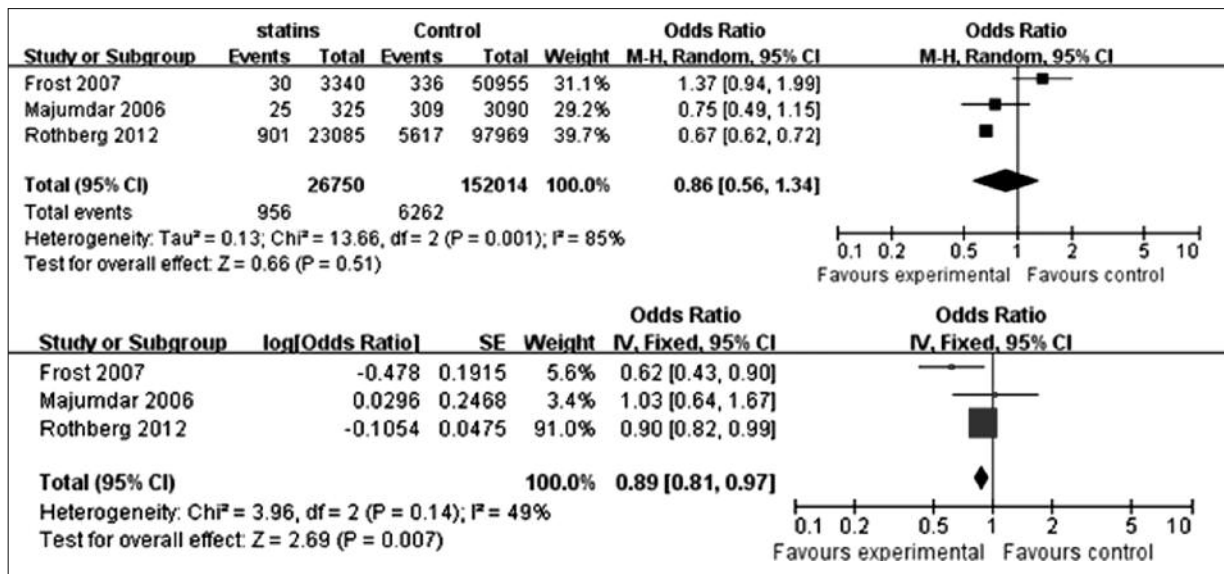
Figure 2. Forest plots of unadjusted and adjusted odds ratios for pneumonia mortality in statin users and non-statin users. A study of In-hospital mortality.

mortality (OR = 0.44, 95% CI 0.29-0.67, I^2 = 68%; adjusted OR = 0.59, 95% CI 0.48-0.73, I^2 = 81%) and a number needed to treat of 19 patients (Figure 3).

2 studies reported 90-day mortality[18,19], one reported 6-month mortality[10], and one reported mortality with an average of 2.8 years follow-up[16]. Pooled analyses of both unadjusted and ad-
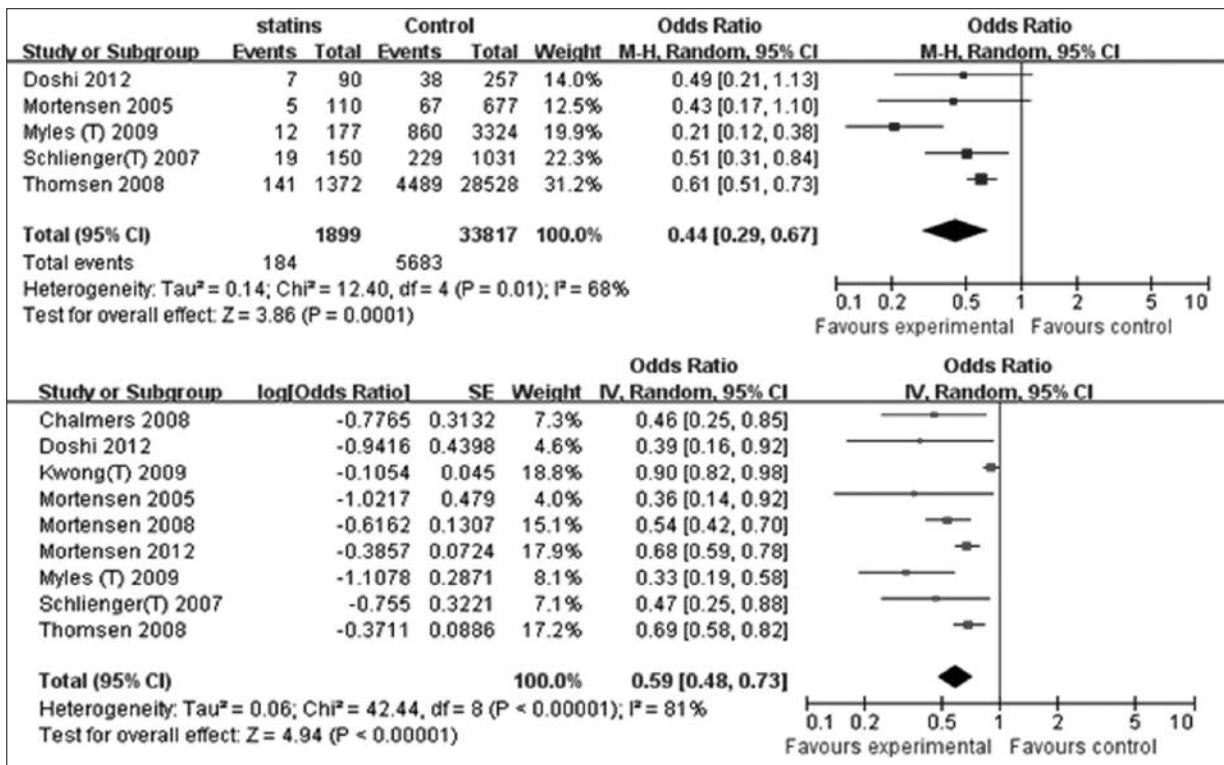

Figure 3. Forest plots of unadjusted and adjusted odds ratios for pneumonia mortality in statin users and non-statin users. A study of 30-day mortality.

justed data indicated that statin users were associated with a decreased long-term mortality (OR = 0.49, 95% CI 0.29-0.84; adjusted OR = 0.65, 95% CI 0.51-0.82) and a number needed to treat of 15 patients (Figure 4).

Risk of Bias and Sensitivity Analyses

Funnel plot of 30-day mortality showed an asymmetric diagram. The *p*-value for the Egger's test was 0.004, indicating publication bias in these studies. The Begg/Egger test was performed in the other 2 subgroups and no publication bias was demonstrated (for in-hospital mortality: Pr = 1.000, *p* = 0.717; for long-term mortality: Pr = 0.734, *p* = 0.412). A sensitivity analysis was performed to address the source of bias, but failed to identify a single study that contributed most of the heterogeneity. The sensitivity analysis of 30-day mortality is shown in Table II.

Subgroup Analyses

Of the 14 studies included, 4 studies[13,16,18,19] reported the risk of death after pneumonia grouped by "current/continued users", "recent users" and "past users" (Table III). A trend was found between current statin use and decreased pneumonia mortality.

Three studies[8,19,12] conducted a census of statin types. 90% of the statins prescribed were simvastatin, atorvastatin or pravastatin. Thomsen et al[18]

reported that only simvastatin was associated with a reduced mortality (simvastatin: OR 0.60, 95% CI 0.48-0.75; atorvastatin: OR 0.96, 95% CI 0.66-1.40; pravastatin: OR 0.81, 95% CI 0.53-1.23).

Only one study (Frost et al[11]) explored the relationship between statin dose and pneumonia mortality. A moderate dose (adjusted OR 0.62, 95% CI 0.43-0.91) and not a low dose (adjusted OR 0.26, 95% CI 0.04-2.13) was associated with lower pneumonia-related mortality.

Chalmers et al[8] reported that 30-day mortality of severe pneumonia (PSI ≥ IV) was significantly lower among patients receiving statin adjunctive therapy (OR 0.46, 95% CI 0.25-0.85). The mortality of patients with PSI I-III was not reported.

Adverse Reports

Adverse effects were not reported in any of the included studies.

Discussion

This meta-analysis suggests a relationship between statin therapy and decreased 30-day/long-term mortality of pneumonia patients. However, our analysis can not determine causality. Based on our analysis, the association of statin therapy with reductions in in-hospital mortality is substantially lower.
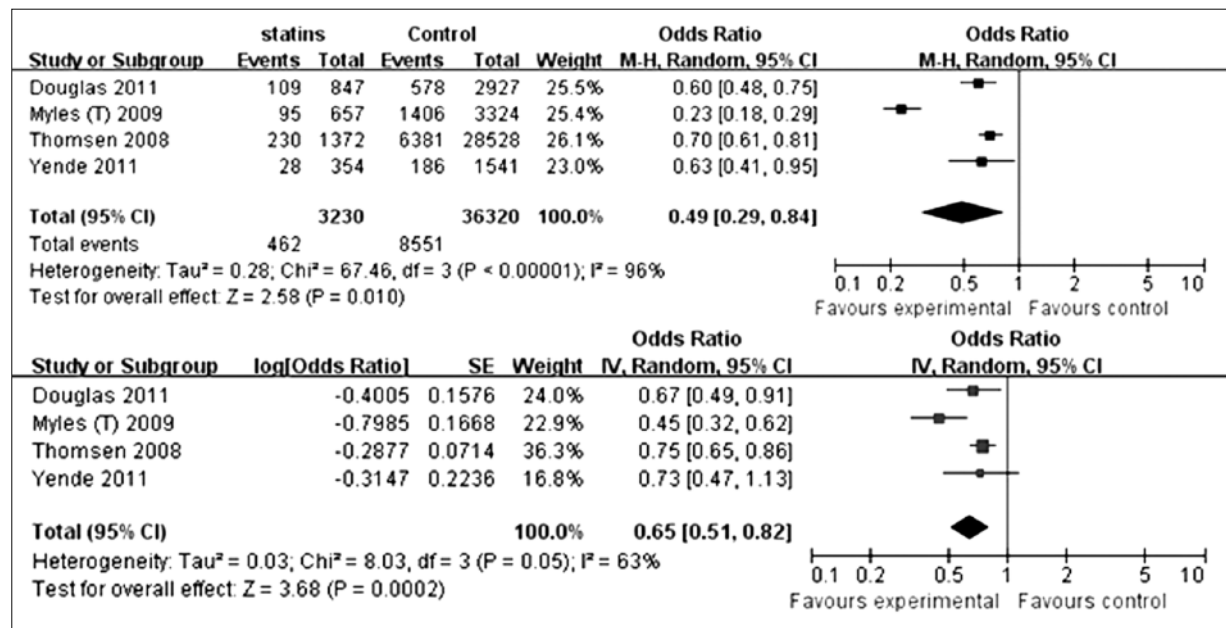
Figure 4. Forest plots of unadjusted and adjusted odds ratios for pneumonia mortality in statin users and non-statin users. A study of long-term mortality.

Table II. Sensitivity analyses of 30-day mortality.

Scenario	Sensitivity analysis outcomes, (OR, 95% CI), I²
Subgroup by study design	
Case-controlled study[20]	0.47 (0.25, 0.88)
Perspective cohort study[8]	0.46 (0.25, 0.85)
Retrospective cohort studies[9,13-16,18,21]	0.77 (0.72, 0.82), I² = 84%
Subgroup by geography region	
North America[9,13-15,21]	0.64 (0.49-0.84), I² = 85%
Europe[8,16,18,20]	0.50 (0.34-0.73), I² = 62%
Excluding studies with sample size[8,13,14,16,18,20,21]	0.62 (0.50-0.76), I² = 84%
Excluding studies with NOS score < mean[8,13,15,16,18,21]	0.64 (0.50-0.80), I² = 83%

Frost et al[11] reported an in-hospital mortality rate of less than 1%, much lower than that reported by Majumdar et al[12] (9.8%) and Rothberg et al[17] (5.4%). Heterogeneity displayed in the subgroup may be caused by differences in the general characteristics of the 3 studies (e.g., overall mortality), as the I² value fell to an acceptable level after adjustment. Furthermore, the $NNT_{inpatient}$ indicated that 230 pneumonia patients needed to be treated to prevent one additional hospital death, a weak preventive effect of statins against pneumonia.

The meta-analysis of both unadjusted and adjusted 30-day mortality and long-term mortality revealed that statin therapy was associated with lower risk of death in pneumonia patients. 19 and 15 patients, respectively, needed to be treated to prevent one additional death during 30 days or long-term follow-up after diagnosis of pneumo-

nia. Although a larger percentage of deaths occurred during hospitalization, the 30-day interval is a time point which has been invoked as being most correlated with mortality from pneumonia[22].

Mortensen et al[13], Myles et al[16] and Thomsen et al[18] reported that 30-day mortality was significantly reduced among statin users who took the last prescription within 90 days (Thomsen et al: 125 days) of admission. Previous users that took statins more than 90 days before admission (Thomsen et al: 125 days) received no benefit. Similar results were reported by Myles et al and Thomsen et al regarding long-term mortality. Yende et al[19] found that decreased mortality was only found in patients taking statins within 1 week of admission. Subgroup analysis revealed that statins may be more effective if taken before and during treatment. A study of patients undergoing aortic reconstructive surgery

Table III. Mortality of current users and prior users of statins (OR, 95% CI).

Studies	Current/continued users	Recent users	Past/prior users
30-day mortality			
Mrotensen (2012)	0.68 (0.59-0.78) – in-hospital use	0.74 (0.68-0.82) – in-hospital use	NAD
Myles	0.33 (0.19-0.58) – using within 30 days before admission	0.58 (0.34-0.99) – last prescription within 31-90 days before admission	0.36 (0.86-2.16) – last prescription dating over 90 days before admission
Thomsen	0.69 (0.58-0.82) – using within 125 days before admission	NAD	0.97 (0.64-1.48) – last prescription dating over 125 days before admission
Long-term mortality			
Myles	0.45 (0.32-0.62) – using within 30 days before admission	0.62 (0.43-0.89) – last prescriptionwithin 31-90 days before admission	1.13 (0.77-1.65) – last prescription dating before 90 days before admission
Thomsen	0.75 (0.65-0.86) – using within 125 days before admission	NAD	NAD
Yende	0.73 (0.47-1.13) – using before and after admission	0.90 (0.63-1.29) – last prescription with 1 week before admission	NAD

found that patients that discontinued statin therapy had a higher mortality from cardiovascular events than patients that took statins[23]. It is not clear whether the mechanism of statin action in pneumonia patients is similar to that in patients with cardiovascular diseases.

There is not enough evidence to confirm the relationship between statin dose and treatment effects, although the study by Frost et al[11] supported a dose-dependent effect. The relationship between pneumonia severity and statin treatment effect needs further study.

Statins in Severe Infections

Statins were first reported to be effective in patients with bacteremia in 2001 by Liappis et al[24]. In their cohort study, statin users had a lower all-cause mortality and attributable mortality after infections with aerobic gram-negative bacilli and *Staphylococcus aureus*. This study prompted additional studies to evaluate the role of statins in patients with severe infectious diseases[6]. A meta-analysis of 41 studies demonstrated the protective effect of statins in patients with sepsis, bacteremia, pneumonia and mixed infections. These findings were weakened by the cohort design of most of the reported studies and variable definition of statin exposure[25]. There are not enough randomized controlled trials to establish a clear relationship between statin use and improved survival in patients with severe infections.

Other Adjunctive Agents in Pneumonia

Glucocorticosteroids (GCs) have been used as adjunctive therapy in infectious diseases since the 1950s. Clinical evidence supports the anti-inflammatory, immunosuppressive and hemodynamic properties of GCs as improving oxygenation in patients with septic shock and ARDS. A meta-analysis suggested low-dose corticosteroids could improve the survival of patients with ARDS[26]. Another meta-analysis from the Cochrane database included 6 RCTs and 437 participants. There was a trend toward a more rapid recovery of patients with pneumonia. However, the small number of patients and methodological limitations did not allow any conclusive findings[27]. GCs may have more activity than statins, but they are also associated with more risks. These risks include secondary infections, glucose intolerance, neuromyopathy and aseptic bone necrosis. GCs are not recommended for the treatment of community-acquired pneumonia patients without septic shock or ARDS[28].

Macrolides are another adjunctive agent used in pneumonia therapy that possesses a myriad of immunomodulatory effects unrelated to killing of the bacterial pathogen. These benefits have been demonstrated in clinical practice with the successful treatment of diffuse panbronchiolitis, cystic fibrosis and asthma. Several, but not all, studies have demonstrated an improved survival of CAP patients treated with both cephalosporins/quinolones and macrolides, compared to cephalosporins/quinolones alone[29,30]. Macrolide therapy is thought to benefit patients with severe pneumonia[31].

Strengths and Limitations of this Meta-analysis

There are several strengths of our systematic review and meta-analysis. First, we enrolled 14 studies and had a large sample size with 269,739 participants. This is much larger than the 2 previous meta-analyses of this topic[32,33]. Second, 2 studies reporting pneumonia mortality and pneumonia prophylaxis[20,21] were included. Third, both unadjusted and adjusted data were pooled. We found different effects with statin adjunctive therapy used in different severities of pneumonia, a finding that has not been previously reported. Fourth, we conducted subgroup analyses to evaluate the relationship between the continued use of statin therapy, statin dose, pneumonia severity and patient survival. The evidence we found supporting the association of statin use with decreased hospital pneumonia mortality was weaker than that of the previous two studies. Our inferences were weakened by individual study design. It is possible that the effects of statins in pneumonia were confounded by factors such as age, underlying diseases, and life style including smoking, alcohol abuse and vaccination[12]. Publication bias and heterogeneity among the studies could not be ruled out by our sensitivity analyses. Several randomized controlled trials are in progress to address the efficacy of adjunctive statin use[34,35].

Of course, there is no realistic expectation that statins can or should be started population-wide in anticipation of the small potential for an individual to develop pneumonia. The NNT with prophylactic statin therapy would be enormous. Therefore the only relevant question for clinical decision-making purposes is whether statin therapy should be *initiated* or *discontinued* upon diagnosis of pneumonia. Although a recent cohort study in Taiwan reported favourable outcomes of pneumonia in previous statin users[36], the current-

ly available data from RCT in regard to this specific question remain limited. Papazian et al[37] reported a multicenter randomized blinded placebo-controlled clinical trial in which simvastatin therapy or placebo was initiated in suspected Ventilator-Associated Pneumonia (VAP), but the study was stopped at the first check point for futility. Indeed, there appeared at this early point an adverse effect of simvastatin with a nearly statistically significant increase in 28-day mortality. This was a study of VAP, not a study of CAP, but it decreases enthusiasm for the potential value of initiating statins for treatment of CAP.

The positive effects on 30 day mortality evident in our meta-analysis may result from beneficial effects of statins in pneumonia, or from the multiple confounders that remain uncontrolled in the cohort studies available to analyze. From our data, we cannot say whether initiation of statin therapy at diagnosis of pneumonia is potentially beneficial.

Conclusions

This meta-analysis supports that patients on statin therapy have less mortality from pneumonia. However, the key clinically-relevant question is whether initiation of statins at the time of pneumonia diagnosis is beneficial or not. A meta-analysis of the available cohort data can not provide useful information to clinicians for their determination of therapy for pneumonia, but rather can only provide evidence to support or refute the potential utility of investing in a carefully designed clinical trial of initiation of statins upon diagnosis of CAP. The attention already given to this issue of statins in the literature may cause clinicians to "try" statin therapy acutely in pneumonia, and such use may in the future lead to data sufficient for a retrospective cohort study capable of beginning to address the question. Optimally, if there is to be further study of this question, the effort should be made only with a carefully designed randomized controlled clinical trial. The evidence to support the utility of such a trial remains marginal at this time.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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