ESTABLISHED STATIN USE REDUCES MORTALITY FROM COMMUNITY-ACQUIRED PNEUMONIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Disclosure: The authors have declared no conflicts of interest.
Received: 24.11.14 **Accepted:** 27.02.15
Citation: EMJ Respir. 2015;3[1]:46-55.

ABSTRACT

Background: Statin therapy (ST) has been associated with improved outcomes from sepsis. Our objective was to systematically review the association between established ST and outcomes of patients with community-acquired pneumonia (CAP) that is severe enough to require hospitalisation.
Methods: Two meta-analyses were conducted following a search of articles published before 31st January 2013. After exclusions, seven studies were included to assess the effects of statins on 30-day mortality from CAP, and eight studies were included to assess the effects of statins on the development of CAP. Endpoints were a reduction in the risk of 30-day mortality or risk of developing CAP.
Results: A reduction in the risk of 30-day mortality from CAP was identified in patients established on ST (pooled odds ratio [OR]: 0.70, 95% confidence interval [CI]: 0.65-0.76; adjusted OR: 0.58, 95% CI: 0.47-0.69). The pooled OR for risk of developing CAP in patients with and without established ST was 1.01 (95% CI: 0.98-1.04).
Conclusion: There appears to be weak evidence to suggest a potential benefit of established ST. It is associated with a reduced risk of 30-day mortality in patients subsequently hospitalised with CAP. Further evidence is required, but ST could be considered as a means of reducing the risk of mortality from pneumonia.

Keywords: Statin, pneumonia, respiratory tract infection, bacterial infection, bacterial pneumonia.

BACKGROUND

Community-acquired pneumonia (CAP) is the most common infectious disease requiring hospitalisation in developed countries. CAP is associated with an in-hospital mortality of approximately 10% and a significant risk of intensive care unit (ICU) admission (estimated to be 5.9%, with a subsequent in-hospital mortality of approximately 50%).[1] It represents a major public health threat in the developed and developing world.[2] Therefore, any beneficial adjuncts to traditional anti-microbiological therapy would be of great value in reducing its impact on both patient mortality and healthcare resources.

There has been much scientific interest in novel adjunctive therapy in the prevention and treatment of sepsis. Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) have been postulated to have pleiotropic effects that can modulate immune function.[3-5] Since their introduction and initial approval for lowering cholesterol in 1987,[6] the beneficial effects of statins on cholesterol have been demonstrated in many high-quality, landmark studies[7-9] and they are now an integral part of many international guidelines for prevention and treatment of cardiovascular disease.[10] If statins can be shown to be a useful adjunctive therapy in CAP, their introduction would hold significant benefits for drug development, as compared with the introduction of novel therapies.

Statins are already a widely used group of drugs, with over 60 million prescriptions each year in the UK alone.[11] They are inexpensive, readily available, easy to administer, display a well-established safety profile, and confer additional health benefits.

The mechanism(s) by which statins exert their beneficial effects in sepsis is not understood, but animal and *in vitro* experiments have provided some evidence that they reduce the levels of inflammatory cytokines, deactivate immune cells, and cause a reduction in the production of nitric oxide by cells. Statin therapy (ST) has been shown to reduce high sensitivity C-reactive protein, a clinical marker of inflammation and an acute-phase reactant produced in response to pro-inflammatory cytokines. These potential, adjunctive benefits in sepsis have been suggested in both animal models[12,13] and humans.[14-18] There is some evidence to suggest that such effects are mediated by an inhibitory effect of statins on isoprenoid synthesis.[3] This may be relevant in sepsis, where anti-inflammatory actions could reduce tissue damage and organ failure, thereby leading to improved clinical outcomes. It has been proposed that statins affect immune function in many ways, rather than via a particular mediator.[4]

Another theory relates to the effect of statins on low-density lipoprotein (LDL) receptors. There are some data to suggest a lower incidence of pneumonia in obese patients who have reduced levels of circulating pro-inflammatory cytokines (e.g. interleukin-6), i.e. a suppressed inflammatory response.[19] It has been postulated that this is because lipopolysaccharides (endotoxin) may be cleared more effectively if there are more adipose tissue stores. Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors increase cell-surface LDL and very low-density lipoprotein (VLDL) receptors, thereby improving the clearance of LDL, VLDL, and endotoxin. Experiments using PCSK9 knockout mice or PCSK9 antibody have shown a reduced inflammatory response, reduced endotoxin levels, and a lower incidence of sepsis. Perhaps more importantly, it has been suggested that polymorphisms in the *PCSK9* gene in humans are associated with a mortality benefit in patients with septic shock.[20] This could mean that by increasing cell-surface LDL receptors, statins will reduce circulating LDL levels and consequently dampen the inflammatory response. This could explain why starting a statin in the acute phase is unhelpful, whereas established statin use could be beneficial.

The clinical studies of statins in patients with a broad diagnosis of sepsis are very heterogeneous, largely observational and retrospective, and use very different endpoints (e.g. mortality, development of sepsis) and patterns of statin use. Some studies show no benefit of adjunctive ST in certain cohorts of patients.[21-24] This review includes studies in a less heterogeneous group of patients (CAP requiring hospitalisation) in order to investigate the potential adjunctive effects of established ST on two different but important outcomes.

METHODS

Data Source and Study Selection

The database search was limited to English language articles and those including human adults. Both MEDLINE and EMBASE databases were searched (before January 31st 2013) using the following terms:

- (ANTICHOLESTERAEMIC AGENTS) or LOVASTATIN or (HYDROXY-METHYLGLUTARYL-CO A REDUCTASE INHIBITORS) and each of:
- (PNEUMONIA: BACTERIAL or PNEUMOCOCCAL or RESPIRATORY TRACT INFECTIONS);
- (BACTERIAL INFECTIONS or BACTERAEMIA/ VIRUS DISEASES);
- (SEPSIS; SYSTEMIC INFLAMMATORY RESPONSE SYNDROME);
- (RESPIRATORY TRACT [DISEASES OR INFECTIONS] or RESPIRATORY SYSTEM)

Pertinent references from identified articles were retrieved.

Exclusion Criteria

Studies primarily including patients with:

i) Immunocompromise (e.g. transplant recipients) due to the potential influence on the proposed immunomodulatory effects of statins and a higher risk of atypical infections

ii) Post-operative infections

iii) Chronic obstructive pulmonary disease due to potential immunomodulatory effects

iv) Multi-organ failure and acute lung injury due to non-infectious causes

v) Sepsis with no respiratory cause

Inclusion Criteria

i) Studies in which ST was established prior to hospital admission (within 90 days)

ii) Primary studies with an endpoint of 30-day mortality from CAP or development of CAP requiring hospitalisation

Statistical Methods

The data from all of the eligible studies were pooled and used in two meta-analyses:

i) Established ST and 30-day mortality from CAP

Only studies with 30-day mortality data were included. Many studies used different endpoints that could not be pooled, e.g. 90-day or in-hospital mortality. Where possible the 30-day data were obtained from authors. The pooled data were analysed using a nonlinear mixed model (SAS Proc NLMIXED) to obtain an unadjusted and an adjusted odds ratio (OR), so as to account for any confounding variables. This models the log odds of death comparing statin and non-statin patients reported in the studies using 30-day mortality as an endpoint. It has been reported to be superior to a DerSimonian and Laird model as it specifically models the inter-study heterogeneity.[25] Each study was treated as a random variable. The overall adjusted OR included age, sex, and smoking status.

ii) Established ST and development of CAP

Data from eligible studies were pooled (number of patients hospitalised with CAP and prior established statin use). The statistical analysis used a random-effects meta-regression model (SAS Proc NLMIXED) to assess the effects of study-level covariates on the overall OR. Models not improved with the addition of covariates were estimated without covariates using a more simplified random effects model (DerSimonian and Laird).

We used the mixed model estimates of inter-study variance in order to assess study heterogeneity. The grades of recommendation, assessment, development, and evaluation (GRADE) system was used to establish the quality of the individual studies. This is important since it influences the interpretation of the results of the meta-analysis. The GRADE system helps to guide recommendation for clinical application of the use of statins in the circumstances studied.[26]

RESULTS

A total of 146 articles were identified using our search criteria, of which 116 were selected for further review. After excluding reviews, abstracts, comments, and letters, 23 studies were specific to pneumonia.[27-40] Of these, seven relevant studies reported the effects of statins on 30-day mortality from pneumonia[27-31,39,40] and eight studies reported the effects of statins on development of CAP.[32-38] These studies were included in the meta-analyses.

It is important to note that many of these studies did not provide data about the severity of CAP (e.g. those requiring ICU admission), the pneumonia itself (e.g. lobar, bilateral), or the micro-organism(s) responsible. The diagnosis of CAP in the individual studies was largely obtained from coding and the comorbidity scores varied between studies. A number of other studies were excluded from the meta-analysis because, despite their methodologies being similar, many lacked sufficient data for univariate and multivariate analyses.[39-42] Some studies lacked the correct endpoint (they used 90-day or in-hospital mortality), others lacked any breakdown of comorbidities or used very different and incomparable methodology. For some of these studies additional unpublished data were provided by the authors, which enabled these studies to be included.[28-31,39,40]

Established ST and 30-Day Mortality from CAP

Eleven observational studies were identified (Table 1) but, even after seeking additional data from authors, only five were suitable for inclusion in the meta-analysis to give an adjusted OR,[27-31] and a further two were suitable to contribute to an unadjusted OR. These two studies contained insufficient data to calculate an adjusted OR, the published adjusted OR used a different combination of covariates.[39,40] The remaining studies were excluded either because of insufficient published data,[41] a different mortality endpoint,[42,43] or an unusual study design.[44] The total number of patients included was 87,909 in the pooled adjusted OR and 126,461 in the unadjusted OR. The total number of patients who died was 19,885 (14,379 in the five studies included in the adjusted OR).

The unadjusted OR from the seven studies was 0.70 (95% confidence interval [CI]: 0.65-0.76) (Figure 1A). Nine different covariates were

considered in the adjusted analysis (age, sex, smoking status, ischaemic heart disease [IHD], heart failure [HF], hypertension, dementia, malignancy), but the overall adjusted OR only included age and sex. Of note, IHD was associated with a higher risk of mortality (OR: 2.5, 95% CI: 0.7-4.3) while diabetes and HF were associated with a lower risk of mortality (OR: 0.31, 95% CI: 0.03-0.59; and OR: 0.31, 95% CI: 0.12-0.49, respectively). The meta-analysis shows that in the five included studies the adjusted OR was 0.58 (95% CI: 0.47-0.69) (Figure 1B). The difference between the ORs in Table 2 and Figure 1 can be accounted for by the weighting of studies.

Table 1: Studies showing the effect of statin therapy on mortality due to pneumonia.

Study	Population studied	Design	n	Primary outcome	Results	30-day mortality rate	Evidence GRADE	Reason for exclusion from adjusted analysis
Included in adjusted and unadjusted meta-analysis:								
Mortensen et al.[27]	USA 1999-2002 Adults with CAP	Mc R C	787	30-day mortality	AOR=0.36 (0.14-0.92)	Statin 4.5% No statin 10.3% Overall 9.5%	Low	-
Majumdar et al.[28]	Canada 2000-2002 Adults hospitalised with CAP	Mc P C	3,415	In-hospital mortality (30-day data obtained)	AOR=1.10 (0.76-1.60)	Statin 8.6% No statin 10.0% Overall 9.9%	Very low	-
Myles et al.[29]	UK 2001-2002 Adults with discharge diagnosis of pneumonia	R C	3,709	30-day mortality	OR=0.25 (0.14-0.44) AOR=0.33 (0.19-0.58)	Statin 9.9% No statin 26.6% Overall 25.3%	Low	-
Douglas et al.[30]	UK 1995-2006 Adults in contact with GP in last 6 months	R C	9,073	6-month mortality (30-day data obtained)	OR=0.62 (0.47-0.81) AOR=0.67 (0.49-0.91)	Statin 5.9% No statin 10.0% Overall 9.1%	Low	-
Nielsen et al.[31]	Denmark 1997-2009 Adults hospitalised with CAP	R C CC	71,746	30-day mortality	AOR=0.73 (0.67-0.79)	Statin 11.3% No statin 13.3% Overall 13.1%	Low	-
Included in unadjusted meta-analysis:								
Thomsen et al.[39]	Denmark 1997-2004 Adults hospitalised with CAP	R C CC	C: 29,900 CC: 2,692	30-day and 90-day mortality	Cohort: OR=0.63 (0.54-0.75) Case control: OR=0.63 (0.51-0.78) AOR=0.64 (0.52-0.8)	Statin 10.3% No statin 15.7% Overall 15.5%	Low	Insufficient data available to use covariants
Mortensen et al.[40]	USA 1999-2000 Adults hospitalised with CAP/influenza	R C	8,652	30-day mortality	OR=0.54 (0.42-0.7) AOR=0.57 (0.45-0.73)	Statin 5.0% No statin 11.0% Overall 9.9%	Very low	Insufficient data available to use covariants
Excluded studies								
Chalmers et al.[41]	UK 2005-2007 Adults hospitalised with CAP	P C	1,007	30-day mortality	AOR=0.46 (0.25-0.85)	-	Low	Insufficient data available

Table 1 Continued.

Study	Population studied	Design	n	Primary outcome	Results	30-day mortality rate	Evidence GRADE	Reason for exclusion from adjusted analysis
Yende et al.[42]	USA 2001-2003 Adults hospitalised with CAP	Mt P C	1,895	90-day mortality/risk of severe sepsis	AOR=0.74 (0.48-1.24)	-	Low	Endpoint is not at 30 days
Rothberg et al.[43]	USA 2003-2005 Adult. Discharge diagnosis of pneumonia	R C	121,254	In-hospital mortality	AOR=0.86 (0.79-93)	-	Low	Endpoint is not at 30 days
Sever et al.[44]	UK cohort of ASCOT RCT Adults assigned statin after closure of ASCOT-LLA	R (RCT data)	2,434	Mortality due to infection or respiratory illness	RRR=36%; p=0.04	-	Very low	Cross over design; endpoint is not at 30 days

Mc: multi-centred; R: retrospective; P: prospective; CC: case control; C: cohort; OR: odds ratio; AOR: adjusted odds ratio; RRR: relative risk reduction; RCT: randomised controlled trials; CAP: community-acquired pneumonia; LLA: lipid-lowering arm; GP: general practitioner.

Table 2: Studies showing the effect of statin therapy on development of community-acquired pneumonia.

Study	Population studied	Design	Primary outcome	n	Cases	Results	Evidence GRADE
van de Garde et al.[32]	UK 1987-2001 Adult diabetics. Controls and CAP	R CC	Development of CAP	142,175	4,719	OR=0.51 (0.37-0.68) AOR=0.49 (0.35-0.69)	Very low
Schlienger et al.[33]	UK 1995-2002 Adults: Controls and CAP	R CC	Development of fatal pneumonia	134,262	1,253	AOR=0.71 (0.56-0.89)	Low
Smeeth et al.[34]	USA 1995-2006 Adults started on statins	P CC	Development of CAP	600,241	8,837	AOR=0.84 (0.74-0.95)	Low
Dublin et al.[35]	USA 2000-2002 Adults: Controls and CAP	R CC	Development of CAP	46,824	1,125	AOR=1.26 (1.01-1.56)	Low
Fleming et al.[36]	UK 1998-2006 Adults: Controls and CAP	R CC	Occurrence of acute respiratory infection	329,881	707	AOR=0.91 (0.73-1.13)	Low
Vinogradova et al.[37]	UK 1996-2005 Adults: Controls and CAP	R CC	Development of CAP	98,239	17,755	OR=0.78 (0.74-0.87)	Low
Nielsen et al.[31]	Denmark 1997-2009 Adults hospitalised with CAP	R CC	Development of CAP	780,054	70,914	AOR=0.80 (0.77-0.83)	Low
Novack et al.[38]	International 2003-2006 Healthy Adults	P RCT	Incidence of infections (pneumonia)	17,802	8,901	OR=0.80 (0.67-0.97)	Low

CAP: community-acquired pneumonia; R: retrospective; P: prospective; CC: case control; RCT: randomised controlled trial; OR: odds ratio; AOR: adjusted odds ratio.

Established ST and Development of CAP

Eight studies were identified (Table 2), all of which were included in the analysis.[31-38] These represent 114,211 cases of pneumonia in 2,149,478 patients. Models were not improved with the addition of covariates and so the final overall OR was estimated without covariates. The overall OR was 1.01 (95% CI: 0.98-1.04) (Figure 1C). Inter-study variance was estimated for all final models and in all cases estimates were not statistically significant (p>0.09).

Figure 1A: Effect of established statin therapy on risk of 30-day mortality from community-acquired pneumonia (unadjusted OR, 95% CI).

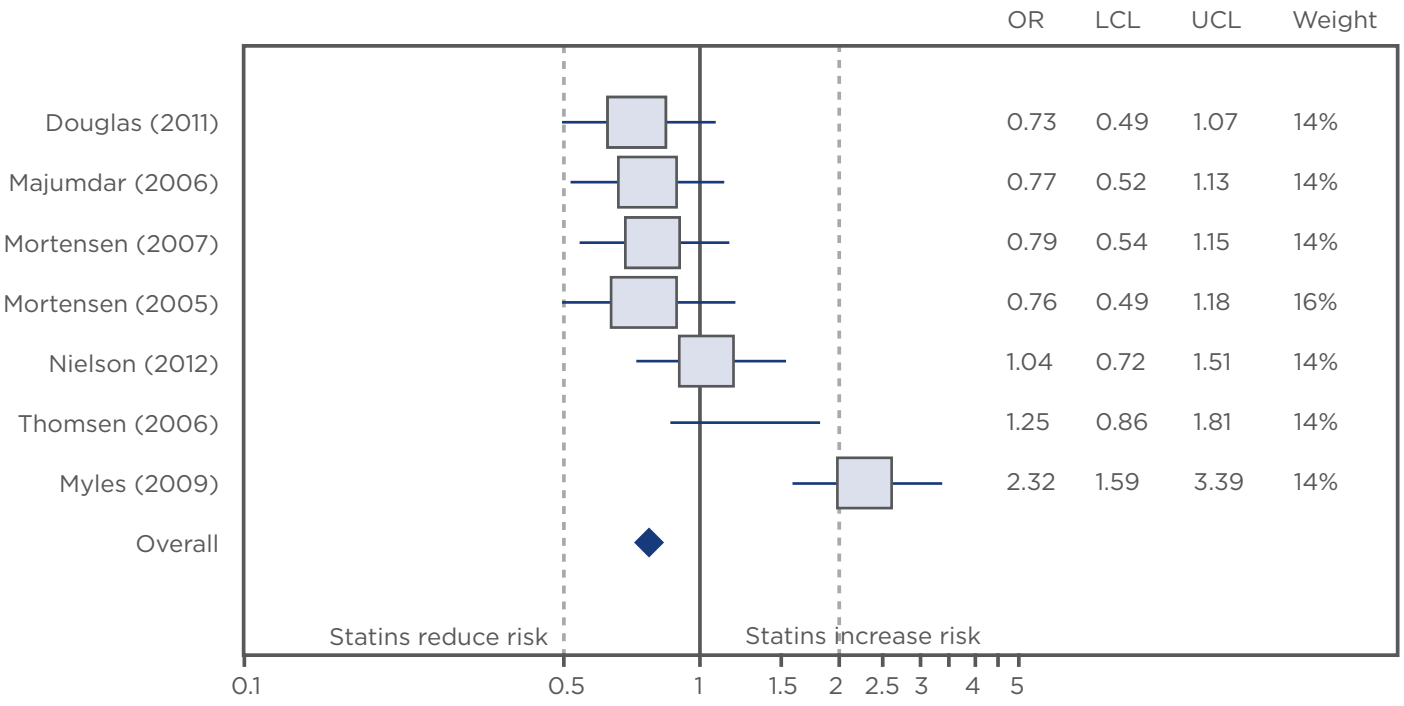

Figure 1B: Effect of established statin therapy on risk of 30-day mortality from community-acquired pneumonia (adjusted [sex and age] OR, 95% CI).

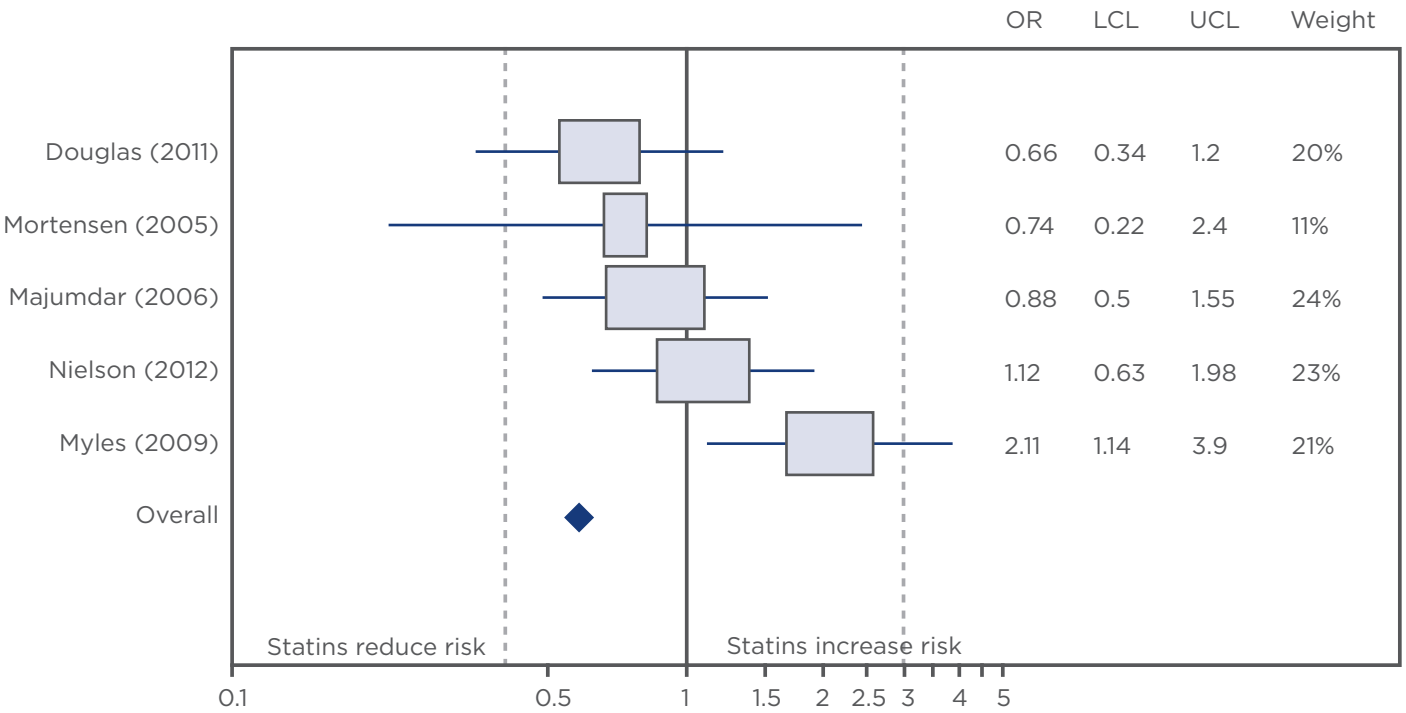

Figure 1C: Effect of established statin therapy on risk of developing community-acquired pneumonia (unadjusted OR, 95% CI).

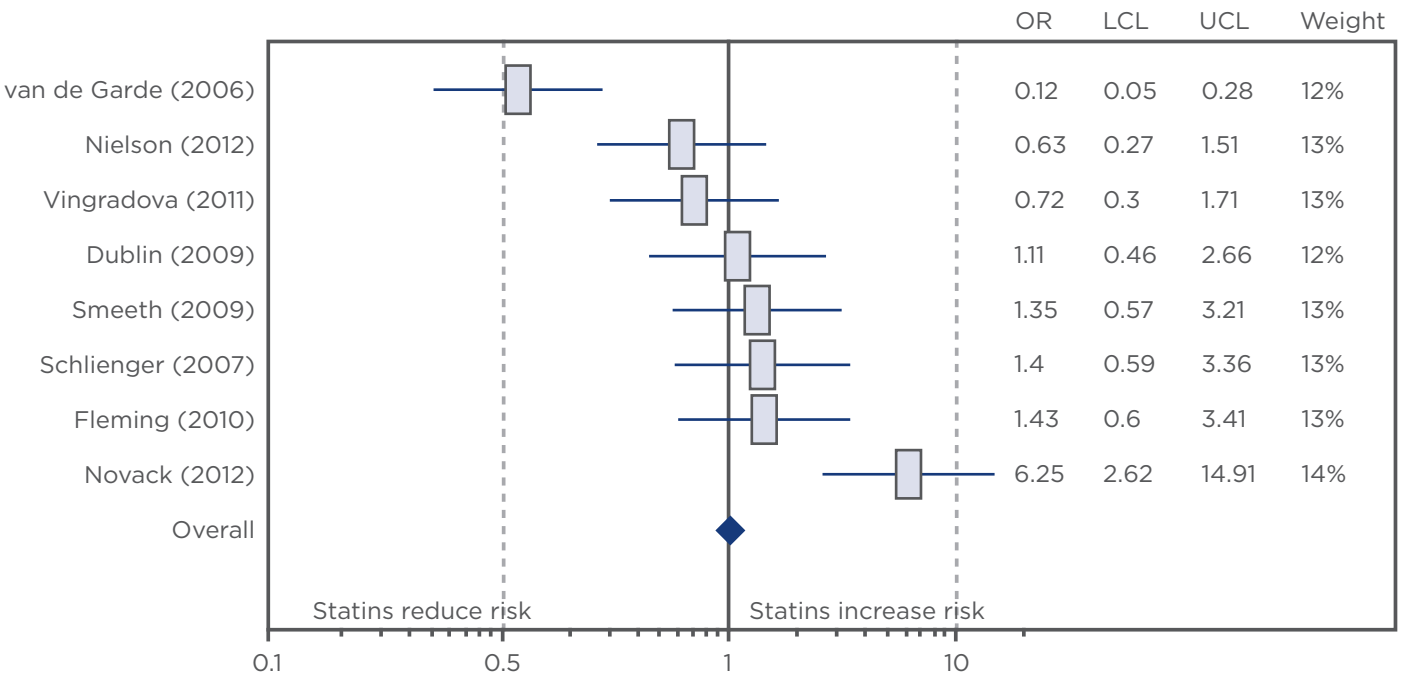

Figure 1: Forest plots to illustrate pooled odds ratios.
CI: confidence interval; LCL: lower control limit; OR: odds ratio; UCL: upper control limit.

DISCUSSION

There is an association between established ST and lower risk of 30-day mortality from CAP. The overall GRADE recommendation is weak because the quality of evidence is low or very low. However, the intervention (ST) does not influence or prevent the use of other treatments (except that certain drug–drug interactions may need to be avoided, e.g. clarithromycin). There is also an apparent lack of undesirable effects with the suggestion of some beneficial effects, i.e. there is at least reasonable scientific evidence to suggest that the benefits outweigh any potential risks. The usefulness of a meta-analysis of these heterogeneous studies is arguably questionable, although it does provide an estimate that is more precise due to its large number of patients, but it is prone to bias due to underlying differences in the constituent studies. The evidence from the individual studies does, however, support the trend that the meta-analysis suggests (Figure 1).

The studies excluded from the meta-analysis[41-44] report results are consistent with a mortality benefit from established statin use in patients hospitalised with CAP (Table 1). Only one study gave an adjusted OR, but this was of a similar magnitude to that obtained from our meta-analysis.[41] The two studies that used in-hospital mortality as an endpoint showed a lower adjusted OR, but this may have included patients with a variable length of stay.[42,43] The interpretation of the randomised controlled trials (RCTs) is very difficult due to large differences in study design and the lack of a pre-determined endpoint.[44]

Paradoxically, the OR is elevated (non-significantly) when IHD is included, which perhaps is in keeping with the idea that statins provide beneficial effects through a mechanism other than an effect on the cardiovascular system. The OR is reduced when HF is included, but with very wide confidence intervals around the ORs, suggesting that these could be confounding variables that lead to model instability. Since our aim is not to evaluate the individual predictors of the OR but instead to improve the overall predictive power of the model, we chose a simplified model including only age and sex as covariates, which were both important on their own and make sense from a biological perspective.

With regards to the second hypothesis, there is no evidence to suggest that established statin use is associated with a reduction in the risk of developing CAP that requires hospitalisation. The

pooled analysis shows that this is not significant and the quality of evidence was generally poor. There is no evidence from this analysis to suggest a recommendation for the use of statins as an adjunct for reducing the risk of developing CAP that requires hospitalisation.

There is little evidence available that addresses the concept of initiating ST in an already unwell patient. Critically ill patients with sepsis were randomised to receive either atorvastatin or placebo in a recent RCT.[45] The research group concluded that there was no statistically significant reduction in mortality with initiation of *de novo* statin treatment, but that continued use of atorvastatin therapy in established users was associated with a reduction in 28-day mortality. This is consistent with the results that we have found and could indicate that statins need time in order to exert any beneficial effects, and that established therapy utilises a mechanism of action that *de novo* therapy does not.

The concept of harm from statin use was not specifically addressed by any of the trials identified in this search. There was no declaration of adverse effects (AEs) secondary to statin use in any of the studies. This would be consistent with the known, very well-established side-effect profile that comes from their widespread use, and the fact that they are generally well tolerated. Their serious AEs appear to be minimal.

The studies exhibit some selection bias. Some include low numbers of patients with liver disease, a low rate of statin use in older patients, and a higher number of comorbidities in statin users.[28-30] The 'healthy user effect' is a potential source of bias and has been used as a reason to explain the positive impact of statins in studies that dispute these effects.[28] Some studies suggest that the universal access to healthcare and/or low-to-no cost prescriptions removed this effect.[39-41] However, if this were true, one would expect to see a similar decrease in mortality with other prescription drugs, but this is not consistently seen.

Importance of Statin Types

One would expect lipophilic statins (e.g. simvastatin, atorvastatin) to penetrate cell membranes more readily than hydrophilic statins (e.g. rosuvastatin) and consequently to elicit more pleiotropic effects,[3] thus supporting a theory that some of the cholesterol-independent effects of statins may be mediated by a reduction in circulating isoprenoid levels. The type of statin used varied between and within studies. One study claimed that simvastatin lowered mortality more than other statins,[39] while another did not disclose the drug used.[33] Doses were often not disclosed and when they were, they varied enormously.

LIMITATIONS

This review does have some limitations despite looking at a less heterogeneous patient population. The studies are largely observational, mostly retrospective, and have inherent weaknesses relating to data collection and identification of associations and not causality. There are some important inter-study variations that must be considered, e.g. exclusion criteria and country of study, which varied immensely (and have potential for huge variations in practice and criteria for prescription of statins).

There were also variations in data sources and quality and standards of care (e.g. in one study, only 50% of patients received antibiotics within 8 hours of arrival in hospital).[27] Many studies used general practice (GP) databases but even these varied, with some data originating from GPs completing once-weekly returns.[36] Two studies used the same data sources.[28,32]

The diagnostic criteria for CAP were similar, with many identifying their participants using coding data rather than a bacteriological diagnosis, potentially allowing misclassification. This is demonstrated by an abstract (excluded) that showed, on reviewing the data, only 108 of 200 had the correct diagnosis.[46] Escalation of care to ICU is not mentioned by the majority of studies and is therefore a major limitation in comparing mortality outcomes. Duration of pre-admission statin treatment was also extremely variable. This analysis has tried to compensate for this by defining statin use as within the previous 90 days.

Evidence from RCTs is lacking in this subject area. The JUPITER trial[38] looked at the effects of ST in previously well adults and suggested a benefit by reducing the risk of developing pneumonia. However, it was not designed to study this and relies on reports of respiratory infections by trial investigators. These may be incomplete, and therefore are graded as low quality. There have only been four other RCTs conducted, none of which look specifically at pneumonia.[47-50] Historically, it has been difficult

to recruit to RCTs, many have terminated early and consequently there are only a few registered - these are mostly inactive.

CONCLUSION

The evidence available seems to suggest that established statin use is beneficial as an adjunctive therapy to reduce the risk of 30-day mortality from CAP (weak recommendation), but that established statin use does not reduce the risk of developing CAP requiring hospitalisation. It would seem from the current evidence that long-term statin use could be beneficial. The questions that we really wish to know the answers to are yet to be accurately addressed in the literature: i) Are statins useful generic adjuvants in pneumonia, and ii) will giving statins to patients not ordinarily requiring them improve their chances of avoiding or surviving pneumonia?

One could propose that a long-term, placebo-controlled, prospective trial should be conducted that includes patients not previously prescribed statins and looks specifically at development of CAP and outcomes from CAP (e.g. hospitalisation, critical-care admissions, and mortality). However, a study would need to be very large to gain adequate power, as the incidence of CAP is approximately 5 cases per 1,000 individuals per year and the estimated reduction in incidence from observational studies is only 13%. Overall, there is potential for a reduction in risk of mortality from CAP in established statin users, but this is not consistently demonstrated in the studies. Ideally, more evidence is required, but it is difficult to conduct studies when there are so many confounding variables.

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