Statin therapy for acute lung injury: an individual patient data meta-analysis

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Study protocol version: 1.0
Date of version: 04 December 2014
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BACKGROUND

Acute lung injury

Acute lung injury (ALI) describes a clinical syndrome consisting of acute hypoxaemic respiratory failure in the absence of cardiogenic causes of pulmonary oedema.\(^1\) Associated mortality can be as high as 40\%, with an estimated annual incidence in the US of almost 200,000 cases.\(^2\) The injury can arise from a wide array of potential insults, both pulmonary and non-pulmonary, of which sepsis is the most common. Such patients are almost exclusively cared for in intensive care units (ICUs) where they can receive mechanical ventilation and other advanced organ support as required.

The severity of the condition means that protracted ICU and hospital stays are common and the financial and resource implications of caring for such patients are correspondingly high.\(^2\)-\(^4\) This is further compounded by the observation that many survivors require prolonged post discharge rehabilitation, with a large proportion unable to return to employment one year after leaving hospital.\(^5\) The substantial health and economic burden of ALI therefore provides a pressing need to identify novel, effective treatments that can improve the clinical course of patients.

Rationale for statin therapy

Hydroxymethylglutaryl coenzyme A (CoA) reductase inhibition with statins forms the mainstay of long-term lipid reduction in patients with high cardiovascular risk. However, their pleiotropic effects are increasingly being explored as a new therapeutic strategy in many areas of medicine including ALI.\(^6\),\(^7\) Evidence from animal studies has suggested that the immunomodulatory properties of statins may improve outcomes in ALI patients.\(^8\) Such effects typically occur at the transcriptional level and include reduced production of chemokines, cytokines and C-reactive protein (CRP).\(^9\),\(^10\) At the human level, several observational studies have demonstrated a benefit for statins in the prevention and treatment of sepsis, although the literature on ALI is less clear cut.\(^11\),\(^12\) The caution required when interpreting observational studies was highlighted by meta-analyses of randomised controlled trials (RCTs) that showed no effect of statins on preventing infection or in reducing mortality from sepsis.\(^13\),\(^14\)
Initial randomised trial evidence for a potential benefit of statins in ALI came from a human model of ALI in 2009. Healthy volunteers were randomised to simvastatin pre-treatment for 4 days or placebo, before exposure to lipopolysaccharide (LPS). Simvastatin was found to have a range of anti-inflammatory effects including reduction in pulmonary neutrophilia, tumour necrosis factor alpha (TNF-α) and CRP. These promising results paved the way for RCTs in patients. A single centre phase 1 RCT (‘Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction’ (HARP-1)) revealed modest improvements in organ dysfunction, a reduction in IL-8 in the lungs and no increase in adverse events in the group treated with 2 weeks of simvastatin. However, the trial included only 60 patients and was not powered to detect differences in hard clinical outcomes.

Results of larger RCTs of statin therapy in ALI are only now beginning to emerge. The ‘Statins for Acutely Injured Lungs from Sepsis’ (SAILS) trial was published earlier this year and showed no significant difference in 60 day mortality or ventilator-free days (VFDs) in a cohort of 745 patients treated with either rosvastatin or placebo. The recent HARP-2 trial (540 patients) also showed no significant difference in 28 day mortality or VFDs.

**Importance of performing this review**

While statin therapy does not appear to be associated with harm, the precise clinical benefits for patients with ALI remain unclear. Questions also remain regarding which specific groups of patients may benefit (sepsis versus non-sepsis, and statin-naïve versus previous user), when statin therapy would be ideally delivered (pre-treatment or during acute episode) and the optimal dose, duration and type of statin. For example, in another RCT, de novo atorvastatin therapy was not associated with improved survival in severe sepsis patients whereas therapy in prior statin users did demonstrate improved 28-day mortality.

Individual patient data (IPD) meta-analyses are considered the gold standard for synthesising information from RCTs. The provision of the IPD reduces the need for imputation and estimation of non-published data, as well as providing increased statistical power for investigating differential treatment effects. Therefore, the aim of this review is to use IPD meta-analyses to quantify the safety and efficacy of statin therapy within RCTs for ALI, both overall and in a priori defined subgroups.
METHODS

Criteria for considering studies for this review

Types of studies
• Non-crossover randomised controlled trials

Types of participants
• Human adults with acute lung injury (as defined by the American-European Consensus Conference criteria or the Berlin Acute Respiratory Distress Syndrome (ARDS) definition)

Types of interventions
• Statin versus placebo or no statin
  o Minimum duration for statin therapy (2 weeks and/or until ICU discharge)

Outcome measures
• Primary:
  o Efficacy – Ventilator free days (VFDs) to day 28
  o Efficacy – Mortality at day 28
  o Safety – Total number of serious adverse events (SAEs)
    ▪ SAEs are defined as any event that is immediately life threatening, is permanently disabling, or severely incapacitating, or requires or prolongs inpatient hospitalisation. The need for renal replacement therapy due to raised CK will be defined as a serious adverse event.
    ▪ As mortality is being assessed in a separate primary outcome, death will not be considered a SAE in the context of this analysis
• Secondary:
  o Duration of ventilation in survivors
  o Requirement for renal replacement therapy
  o ICU free days to day 28
  o Long term mortality (maximum follow up day 60-180)
  o ICU length of stay
  o Hospital length of stay
  o Any adverse events
Search strategy

To identify randomised trials for inclusion we will use MeSH and free-text terms for various forms of the terms ‘acute lung injury’, ‘respiratory distress syndrome’, ‘sepsis’ and ‘statin’, including specific drug names. The ‘Cochrane Highly Sensitive Search Strategies for identifying randomized trials in MEDLINE’ filter will be used to identify only randomised controlled trials.\textsuperscript{24}

We have included sepsis related terms in the search strategy as there are likely to be trials investigating the use of statins in sepsis, which might contain patients with acute lung injury whose data could be included. For data to be used in this meta-analysis, the patients must have been ventilated and have a ratio of partial pressure of oxygen (PaO2) to fraction of inspired oxygen (FiO2) (P/F ratio) of less than 300 kPa. To fully satisfy the definition for ARDS, such patients will also require a chest radiograph demonstrating bilateral pulmonary infiltrates in the absence of a cardiogenic cause. However, it is recognised that this final criterion may not have been assessed in sepsis trials. Thus, data satisfying the ventilation and P/F ratio criteria will be accepted into the individual patient data set with a sensitivity analysis to assess the impact of including such data.

The detailed search strategy for each database is given in appendix 1.

Electronic searches:

- MEDLINE (1990 to date of search)
- EMBASE (1990 to date of search)
- Science Citation Index Expanded (1990 to date of search)
- Cochrane Central Register of Controlled Trials (Latest issue)
- Clinicaltrials.gov (date of search)
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (date of search)

Other searches:

- Abstracts of major congresses (Society of Critical Care Medicine, American Thoracic Society, International Symposium on Intensive Care and Emergency Medicine, and European Society of Intensive Care Medicine) for the previous 3 years from date of search
- Contacting authors of included trials and experts in the field
• Reference searching of included trials to identify further trials

Study selection

Duplicates will be removed from the search results. One author will screen titles and remove any reports that are clearly not eligible. Two authors will then independently screen abstracts for potentially eligible studies. Full text reports will be retrieved for studies identified by at least one of these authors. These will then be assessed for inclusion by two authors independently. There will be no restriction of studies by their sample size or language (non-English articles will be translated to English prior to data extraction, if this is feasible). All disagreements will be resolved by consensus and discussion with a third author.

A preliminary search of all databases revealed a total of approximately 3,500 references. After removal of duplicates, it is anticipated that around 3,000 titles will have to be screened and about 10-25 full texts will have to be obtained, leading to between 5 and 10 eligible trials.

Data procurement

There will be two stages to the analysis. Initially, data will extracted from the publications of eligible trials for an immediate analysis. The original investigators will also be contacted by email and invited to participate in the second stage, an IPD meta-analysis. We define ‘original investigators’ here as the corresponding author listed on the publication (or the lead of the writing committee if authorship is attributed to a collaborative group). If no reply is received, a reminder will be sent after 3 weeks. If the investigators decline the request to participate or no reply is received after reminder, only the aggregate study data will be extracted as far as possible from all publicly available reports of the study. If a trial investigator agrees to participate, they will be sent a written data use agreement confirming that their data:

• Will be used only for the purpose specified in this protocol
• Will remain their property at all times
• Will remain on secure servers at Imperial College London
• Will be accessed only by authorised members of the study team and will not be used for other purposes without the explicit approval of the trial investigator
Electronic transfer of anonymised and encrypted data will be requested after providing investigators with a list of required data. The datasets will then be cleaned with variables recoded as necessary, so as to allow for the construction of a combined dataset with common variables and definitions. Any errors or inconsistencies will be clarified at the data cleaning stage with the original investigators of the trial. A list of the data that will be requested appears in appendix 2.

**Risk of bias assessment**

Risk of bias will be assessed by applying the Cochrane Risk of Bias tool. It includes six domains that could affect the effect estimates due to systematic error. These are: sequence generation, allocation concealment, blinding of participants, healthcare providers and outcome assessors, incomplete outcome data, selective reporting, and other potential sources of bias. Each domain will be rated as low, uncertain or high risk of bias. A trial will be rated to be at low risk of bias if all the domains are rated as low. Any unclear or missing information will be sought from the original investigators of the trial. Initially, these assessments will be done using the trial publications and supplementary information from the original researchers, but further assessments will be possible during the processing of the IPD.

**Statistical analysis**

All analyses will be performed on an intention-to-treat (ITT) basis, where possible. We will follow the initial approach taken by the NSCLC Meta-analyses Collaborative Group. We will begin by estimating the overall intervention effects and generating forest plots using a conventional two-stage approach. This involves generating trial summary measures that are then combined by standard meta-analytical methods. For dichotomous outcomes such as proportion dead at day 28, we will use the numbers of events and patients to calculate the Mantel-Haenszel odds ratio. For continuous outcomes such as length of stay, we will use the mean and standard deviation to calculate the mean difference. These estimates are then combined in a fixed-effect model that stratifies by trial. The results from this analysis will be compared to a random-effects model to assess for model robustness. The fixed-effect model assumes that the treatment effect is the same across studies and that all variation is due to sampling error. In contrast, the random-effects model allows for different effects between the studies with the study means following a normal distribution.
To explore the effect of patient characteristics on outcomes, we will perform regressions with the treatment by subgroup interaction term within trials and the interaction coefficients pooled across trials (for the two-stage analysis). We will then follow the guidance of Stewart and colleagues by fitting one-stage models with single-treatment covariate interactions and comparing these results to the two-stage models. Aggregation bias will be assessed by separation of within and across trial information. If model results are similar between one-stage and two-stage models, we will present the results of the two-stage models.

All analyses will be performed in R for Mac version 3.1.1 (The R Foundation for Statistical Computing) and Stata SE version 12.1 (College Station, TX). We will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Methodological Expectations of Cochrane Intervention Reviews (MECIR standards) for reporting systematic reviews.

**Dealing with missing data**

For trials where IPD are available but incomplete, we will impute missing data on a per trial basis using the chained equation methods described by Buuren and colleagues. For trials where IPD are not available, we will seek as much relevant aggregate information as possible from trial investigators. For continuous outcomes, the missing mean and the standard deviation will be imputed according to the instructions given in the Cochrane Handbook for Systematic Reviews of Intervention. If it is not possible to calculate the standard deviation from the data available from the trial, the standard deviation will be imputed as the highest standard deviation in the other trials included under that outcome, fully recognising that this form of imputation will decrease the weight of the study for calculation of mean differences and will bias the effect estimate to no effect in case of standardised mean difference. The impact of such imputation of either mean or standard deviation or both will be assessed by sensitivity analyses.

**Heterogeneity and reporting bias**

We will explore heterogeneity by chi-squared test with significance set at P value 0.10, as well as by measuring the quantity of heterogeneity using $I^2$. Visual asymmetry in a funnel plot will be used to explore reporting bias if 10 or more trials are identified for a pairwise comparison.
The linear regression approach described by Egger and colleagues will also be performed to determine the funnel plot asymmetry.\textsuperscript{34}

**Subgroup and sensitivity analyses**

**Subgroup analyses**

The following subgroup analyses will be performed:

- Shock versus no shock
  - Shock defined as vasopressor requirement at baseline
- Prior statin use versus no prior use
  - Prior use defined as any statin use preceding randomisation
  - If the information is available we will also analyse “immediate” prior use of statins versus no “immediate” prior use, defined as statin use within the 72 hours prior to randomisation
- Aetiology of acute lung injury (sepsis versus no sepsis)
  - Sepsis defined as per Surviving Sepsis Guidelines 2012
- Low CRP versus high CRP
  - High CRP defined as CRP greater than the median baseline CRP value of the combined individual patient dataset
- Type of statin (lipophilic versus hydrophilic)
  - Hydrophilic include pravastatin and rosuvastatin
  - Lipophilic include simvastatin, atorvastatin, fluvastatin
- Low versus high dose of statin
  - Low dose statin defined as half the maximum dose recommended by the British National Formulary (BNF) or lower
    - Simvastatin low dose: $\leq 40$mg
    - Atorvastatin low dose: $\leq 40$mg
    - Rosuvastatin low dose: $\leq 20$mg
    - Pravastatin low dose: $\leq 20$mg
    - Fluvastatin low dose: $\leq 40$mg
- P/F ratio
  - This will be categorised into three groups based on the Berlin ARDS definition
    - Mild ARDS ($200 < \text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg)
- Moderate ARDS (100<PaO2/FiO2 ≤ 200 mmHg)
- Severe ARDS (PaO2/FiO2 <100 mmHg)

• Low versus high risk of bias trials
  o Low risk trial defined as being at low risk of bias in all assessed domains
  o For this subgroup analysis, high risk is defined as not being at low risk of bias

**Sensitivity analyses**

In addition to the sensitivity analyses described in the statistical analyses methods outline above, we will perform sensitivity analyses to assess:

• The impact of excluding data from sepsis trials in which the criterion of a chest radiograph with bilateral pulmonary infiltrates was not available.
• The impact of imputing the mean, standard deviation or both for aggregate data and of imputing data for individual patients data (in the case of IPD).
REFERENCES


APPENDIX 1 – SEARCH STRATEGY

Medline (OvidSP) 1990 to date of search

1. exp Positive-Pressure Respiration/ or exp Acute Lung Injury/ or exp Respiratory Distress Syndrome, Adult/ or exp Tracheostomy/
2. exp sepsis/ or exp Systemic Inflammatory Response Syndrome/
3. (shock or Sepsis Syndrome* or systemic inflammatory response syndrome or SIRS or Septic Shock or toxic shock or endotoxic shock or septicemia* or septicaemia* or bacteremia* or bacteraemia* or fungemia* or fungaemia* or pyemia* or pyaemia* or pyohemia* or pyohaemia* or blood poisoning* or circulatory failure or circulatory collapse).af.
4. exp Critical Care/
5. (critical care or intensive care or critical therapy or intensive therapy).af.
6. or/1-5
7. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
8. (hydroxymethylglutaryl-coa reductase inhibitor* or HMG-CoA reductase inhibitor* or lipid-lowering agent* or lipid lowering agent* or statin* or fluvastatin or fluindostatin or simvastatin or pravastatin or pitavastatin or lovastatin or cerivastatin or atorvastatin or rosuvastatin or meglutol or mevinolin or monacolin or pravachol or lipex or lipitor or zocor or mevacor or lescol or baycol).af.
9. ((cholesterol or lipid) adj2 (agent or agents or drug or drugs or therapy or lowering)).af.
10. or/7-9
11. 6 and 10
12. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. randomized.ab.
15. placebo.ab.
16. drug therapy.fs.
17. randomly.ab.
18. trial.ab.
19. groups.ab.
20. or/12-19
21. exp animals/ not humans.sh.
22. 20 not 21
23. 11 and 22
Embase (OvidSP) (1990 to date of search)

1. exp Positive-Pressure Respiration/ or exp Acute Lung Injury/ or exp Respiratory Distress Syndrome, Adult/ or exp Tracheostomy/
2. exp sepsis/ or exp Systemic Inflammatory Response Syndrome/
3. (shock or Sepsis Syndrome* or systemic inflammatory response syndrome or SIRS or Septic Shock or toxic shock or endotoxic shock or septicemia* or septicaemia* or bacteremia* or bacteraemia* or fungemia* or fungaemia* or pyemia* or pyaemia* or pyohemia* or pyojaemia* or blood poisoning* or circulatory failure or circulatory collapse).af.
4. exp Critical Care/
5. (critical care or intensive care or critical therapy or intensive therapy).af.
6. or/1-5
7. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
8. (hydroxymethylglutaryl-coa reductase inhibitor* or HMG-CoA reductase inhibitor* or lipid-lowering agent* or lipid lowering agent* or statin* or fluvastatin or fluindostatin or simvastatin or pravastatin or pitavastatin or lovastatin or cerivastatin or atorvastatin or rosuvastatin or meglutol or mevinolin or monacolin or pravachol or lipex or lipitor or zocor or mevacor or lescol or baycol).af.
9. ((cholesterol or lipid) adj2 (agent or agents or drug or drugs or therapy or lowering)).af.
10. or/7-9
11. 6 and 10
12. exp double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/
13. (((((random* or factorial* or placebo* or double*) adj blind*) or single*) adj blind*) or assign* or allocat* or volunteer*).af.
14. 12 or 13
15. 11 and 14
16. limit 15 to yr=1990-2014
Science Citation index (ISI Web of Knowledge) (1990 to present) & Conference Proceedings (ISI Web of Knowledge) (1990 to present)

1. (Positive Pressure Respiration or Positive-Pressure Respirations or Positive-Pressure Ventilation or Positive Pressure Ventilation or Positive End-Expiratory Pressure or Positive End Expiratory Pressure or Acute Lung Injury or Tracheostomy or Adult Respiratory Distress Syndrome or Acute Respiratory Distress Syndrome or ARDS)

2. (shock or Sepsis Syndrome* or systemic inflammatory response syndrome or SIRS or Septic Shock or toxic shock or endotoxic shock or septicemia* or septicaemia* or bacteremia* or bacteraemia* or fungemia* or fungaemia* or pyemia* or pyaemia* or pyohemia* or pyohaemia* or blood poisoning* or circulatory failure or circulatory collapse)

3. ((critical or intensive) AND (care or therapy))

4. #1 OR #2 OR #3

5. (hydroxymethylglutaryl-coa reductase inhibitor* or HMG-CoA reductase inhibitor* or lipid-lowering agent* or lipid lowering agent* or statin* or fluvastatin or fluindostatin or simvastatin or pravastatin or pitavastatin or lovastatin or cerivastatin or atorvastatin or rosuvastatin or meglutol or mevinolin or monacolin or pravachol or lipex or lipitor or zocor or mevacor or lescol or baycol or cholesterol lowering)

6. (random* OR rct* OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*)

7. #4 AND #5 AND #6
Cochrane library (Wiley) (latest issue)

1. MeSH descriptor Positive-Pressure Respiration
2. MeSH descriptor Acute Lung Injury
3. MeSH descriptor Respiratory Distress Syndrome, Adult
4. MeSH descriptor Tracheostomy
5. MeSH descriptor Sepsis
6. MeSH descriptor Systemic Inflammatory Response Syndrome
7. (shock or Sepsis Syndrome* or systemic inflammatory response syndrome or SIRS or Septic Shock or toxic shock or endotoxic shock or septicemia* or septicaemia* or bacteremia* or bacteraemia* or fungemia* or fungaemia* or pyemia* or pyaemia* or pyohemia* or pyohaemia* or blood poisoning* or circulatory failure or circulatory collapse)
8. MeSH descriptor Critical Care
9. ((critical or intensive) near (care or therapy))
10. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
11. MeSH descriptor Hydroxymethylglutaryl-CoA Reductase Inhibitors
12. (hydroxymethylglutaryl-coa reductase inhibitor* or HMG-CoA reductase inhibitor* or lipid-lowering agent* or lipid lowering agent* or statin* or fluvastatin or fluindostatin or simvastatin or pravastatin or pitavastatin or lovastatin or cerivastatin or atorvastatin or rosuvastatin or meglutol or mevinolin or monacolin or pravachol or lipex or lipitor or zocor or mevacor or lescol or baycol)
13. ((cholesterol or lipid) near (agent or agents or drug or drugs or therapy or lowering))
14. #11 or #12 or #13
15. #10 and #14

CTrials.gov (date of search)

(sepsis OR acute lung injury OR acute respiratory distress syndrome OR adult respiratory distress syndrome OR ARDS) AND (statin OR HMG-CoA)

WHO ICTRP (available at http://apps.who.int/trialsearch/) (date of search)

“statin” [note: synonyms automatically produced]
APPENDIX 2 – Data required from original trial investigators

- Investigators are requested to supply anonymised data
- Investigators are permitted to supply data with alternative units but will need to specify this, so that the necessary conversions can be performed centrally
- It is only required that investigators supply data from within their existing trial databases (extraction from other sources is not expected due to logistical constraints)
- Data validation checks will look for improbable and impossible values in each field; and investigators will be contacted to clarify where any issues arise
- The combined final dataset will include a variable to identify the trial for each patient as well as a unique patient ID

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**Trial intervention data**

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