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SYSTEMATIC REVIEW

Statin therapy for acute respiratory distress syndrome: an individual patient data meta-analysis of randomised clinical trials

Myura Nagendran[1], Daniel F. McAuley[2], Peter S. Kruger[3,8], Laurent Papazian[4], Jonathon D. Truwit[5], John G. Laffey[6], B. Taylor Thompson[7], Mike Clarke[2] and Anthony C. Gordon[1*]

Abstract

Purpose: We performed an individual patient data meta-analysis to assess the possible benefits and harms of statin therapy in adults with acute respiratory distress syndrome (ARDS) and to investigate effects in specific ARDS subgroups.

Methods: We identified randomised clinical trials up to 31 October 2016 that had investigated statin therapy versus placebo in patients with ARDS. Individual patient data from each trial were compiled. Conventional two-stage meta-analyses were performed for primary and secondary outcomes, and one-stage regression models with single treatment–covariate interactions for subgroup analyses. Risk of bias was assessed using the Cochrane Risk of Bias Tool.

Results: Six trials with a total of 1755 patients were included. For the primary outcomes, there was no significant effect of statin therapy on 28-day mortality [relative risk (RR) 1.03, 95% CI 0.86–1.23], ventilator-free days (mean difference 0.34 days, 95% CI −0.68 to 1.36) or serious adverse events (RR 1.14, 95% CI 0.84–1.53). There was a significantly increased incidence of raised serum creatine kinase or transaminase levels with statin therapy (106/879; 12.1%) versus control (78/876; 8.9%) (RR 1.40, 95% CI 1.07–1.83, $p = 0.015$). There were no significant treatment–covariate interactions in the predefined subgroups investigated.

Conclusions: We found no clinical benefit from initiation of statin therapy in adult patients with ARDS, either overall or in predefined subgroups. While there was an increased incidence of raised serum creatine kinase and transaminase levels, there was no difference in serious adverse events among groups. Therefore, we do not recommend initiation of statin therapy for the treatment of ARDS.

Keywords: Statin, ARDS, ALI, Meta-analysis

Introduction

Acute respiratory distress syndrome (ARDS) describes a clinical syndrome consisting of acute hypoxaemic respiratory failure in the absence of cardiogenic causes of pulmonary oedema [1, 2]. ARDS is common and associated mortality can be as high as 40% [3, 4]. The severity of the condition means that protracted intensive care unit (ICU) and hospital stays are common and the financial and resource implications of caring for such patients are correspondingly high [4–6]. Many survivors require prolonged post-discharge rehabilitation, with a large proportion unable to return to employment 1 year after leaving hospital [7]. The substantial health and economic burden of ARDS therefore provides a pressing need to identify

*Correspondence: anthony.gordon@imperial.ac.uk
[1] Section of Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Imperial College London and Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK
Full author information is available at the end of the article

Take-home message: There was no clinical benefit from statin therapy in patients with ARDS, either overall or in predefined subgroups and no increase in serious adverse events. We do not recommend statin therapy for the treatment of ARDS.

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novel, effective treatments that can improve the clinical course of patients.

Hydroxymethylglutaryl coenzyme A (CoA) reductase inhibition with statin therapy forms the mainstay of long-term lipid reduction in patients with high cardiovascular risk. Their pleiotropic effects are increasingly being explored as a new therapeutic strategy in many other areas of medicine, including ARDS [8, 9]. Evidence from animal studies has suggested that the immunomodulatory properties of statins may improve outcomes in acute lung injury (ALI) patients [9]. Such effects typically occur at the transcriptional level and include reduced production of chemokines, cytokines and C-reactive protein (CRP) [10, 11]. However, the results of large randomised trials of statin therapy have been less promising than anticipated. The SAILS trial showed no significant difference in 60-day mortality or ventilator-free days (VFDs) in a cohort of 745 patients treated with either rosuvastatin or placebo, while the HARP-2 trial (540 patients) also showed no significant difference in VFDs or 28-day mortality [12, 13].

While statin therapy does not appear to be associated with harm, the precise clinical benefits for patients with ARDS remain unclear [14, 15]. This has led to disagreement among clinicians as to the role for statin therapy in ARDS patients [16–18]. Specifically, questions remain regarding which specific groups of patients may benefit (sepsis versus non-sepsis, those with shock, statin-naïve versus previous user), when statin therapy would be ideally delivered (pretreatment or during acute episode) and the optimal dose and type of statin. For example, in another randomised trial, 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 [19].

Individual patient data meta-analyses are considered the gold standard for synthesising information from randomised trials [20]. They provide a means to answer some of the aforementioned uncertainties around the possibility of different effects for different types of patient or statin, and to standardise the analysis of outcomes. The provision of the individual patient data reduces the need for imputation and estimation of non-published data, as well as providing increased statistical power for investigating differential treatment effects [21]. Therefore, the aim of this review was to use individual patient data meta-analyses to quantify the safety and efficacy of statin therapy within randomised trials for ARDS, both overall and in predefined subgroups. We hypothesised that any beneficial anti-inflammatory effects of statin therapy may be greater in subgroups of patients with more inflammation (high CRP, sepsis, shock), in those patients already receiving statins, and that a higher dose of statins may be more efficacious but may lead to more adverse events.

Methods

The protocol for this study was published in the PROSPERO database (CRD42014015389) prior to the analysis. The protocol is available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014015389. This manuscript has been prepared in line with the guidelines by the PRISMA-IPD group and a checklist is available within the Supplementary Appendix.

Trial identification, selection and acquisition of data

We performed a comprehensive search using MeSH and free-text terms for various forms of the terms 'acute lung injury', 'respiratory distress syndrome', 'sepsis' and 'statin', including specific drug names. We included sepsis-related terms in the search as some trials investigating the use of statins in sepsis might contain patients with ARDS whose data could be included. The search strategy is listed in Appendix 1 of the study protocol. The following electronic databases were searched from 1990 to October 2016: MEDLINE, Embase, Science Citation Index Expanded, Cochrane Central Register of Controlled Trials, Clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) search portal. Additional articles or abstracts were retrieved by manually scrutinising the reference list of relevant publications [22]. There were no restrictions on language. We also searched conference abstracts from major critical care conferences for the last 3 years (full details in study protocol).

Publications were selected for review if they satisfied the following inclusion criteria: non-crossover randomised trial, ventilated human adults with ARDS (as defined by the American-European Consensus Conference criteria or the Berlin ARDS definition), ratio of partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) (P/F ratio) of less than 300 mmHg, intervention (statin) versus placebo or no statin with minimum duration for statin therapy (2 weeks and/or until ICU discharge). To fully satisfy the definition for ARDS, such patients would also require a chest radiograph demonstrating bilateral pulmonary infiltrates in the absence of a cardiogenic cause. However, we recognised that this final criterion might not have been recorded in sepsis trials. Thus, data satisfying the ventilation and P/F ratio criteria were accepted into the data set with a sensitivity analysis to assess the impact of including such data.

After removal of clearly irrelevant records, two authors independently screened abstracts for potentially eligible studies. Full-text reports were then assessed for eligibility.

Where there was not enough information to make a decision on inclusion from published information, study authors were contacted for further details. Authors of eligible studies were invited to supply anonymised data. The variables requested of authors are detailed in Appendix 2 of our study protocol. Risk of bias was assessed by applying the Cochrane Risk of Bias Tool [23]. 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 was rated as low, uncertain or high risk of bias as per the definitions of the Cochrane Collaboration. A trial was rated to be at low risk of bias if all the domains were rated as low. Any unclear or missing information was sought from the original trial investigators.

Our co-primary efficacy outcome measures were VFDs to day 28 and mortality at day 28. Our primary safety outcome was the number of serious adverse events. Secondary outcomes included duration of ventilation in survivors, requirement for renal replacement therapy (RRT), ICU-free days to day 28, long-term mortality (maximum follow-up day 60–180), ICU length of stay, hospital length of stay, non-serious adverse events, defined as creatine kinase (CK) at ten times the upper limit of normal or alanine transaminase (ALT)/aspartate transaminase (AST) at eight times the upper limit of normal. We assessed the following a priori defined subgroups: shock, sepsis, prior statin use, high versus low CRP, statin type, statin dose, P/F ratio and trial risk of bias. These variables were operationalised as detailed in the study protocol (see Supplementary Appendix methods).

Statistical analysis

We estimated the overall intervention effects and generated forest plots using a conventional two-stage approach (trial summary measures that are then combined by standard meta-analytical methods) [24]. For dichotomous outcomes, such as proportion dead at day 28, we used the number of events and patients to calculate the Mantel–Haenszel odds ratio. For continuous outcomes such as length of stay, we used the mean and standard deviation to calculate the mean difference. These estimates were then combined in a fixed-effect model that stratified the analyses by trial. Fixed and random-effects models were compared to assess for model robustness.

To explore the effect of patient characteristics on outcomes, we fitted one-stage regression models with single treatment covariate interactions. We opted not to use two-stage models for treatment covariate interactions as many subgroups were defined partially or totally by the trial (e.g. presence of sepsis and type of statin) [25]. Three specifications of model were assessed: (a) the standard model, (b) a model allowing for independent effects of the covariate across trials and (c) a model accounting for aggregation bias by separation of within- and across-trial information [25]. Model fit was compared using the Akaike information criterion (AIC). All analyses were performed using Stata SE version 12.1 (College Station, TX).

Trial sequential analysis was added to the analysis for primary outcomes upon request during the peer review process. For dichotomous outcome analysis, settings were alpha (α) of 0.05 (two-sided), beta (β) of 0.20 (power of 80%), an anticipated relative risk reduction of 20% and a control event proportion as per the control arm. For the only continuous outcome (VFDs), settings were α of 0.05 (two-sided), β of 0.20 (power of 80%), an anticipated mean difference of 1.5 days and a variance as per the included trials. Analyses were performed using trial sequential analysis (Copenhagen Trials Unit, Denmark).

Results

The electronic search yielded 4584 records up to October 2016 for further assessment (see Fig. S1, Supplementary Appendix). There were no extra records identified by conference abstract searching that were not already selected in the electronic search. Our screening identified 15 articles that were potentially eligible, of which six were excluded immediately on inspection of their full text. Reasons for exclusion of full-text records are detailed in Fig. S1. Authors for three studies were contacted to determine eligibility because the limited information in the publication did not allow for definitive assessment [26–28]. Unfortunately, no replies were received from these authors and the studies were therefore excluded. This left six studies for inclusion in the analysis [12, 13, 19, 29–31].

The general characteristics of the six included studies are listed in Supplementary Appendix Table S1. Risk of bias was rated as low for all six studies (see Table S2 in the Supplementary Appendix) and individual patient data were provided for all six studies. As per our protocol, publication bias was not assessed as there were less than 10 included trials. There were no important issues identified with integrity of individual patient data. Baseline patient characteristics of the combined dataset are displayed in Table 1. There were a total of 1755 eligible ventilated patients. In the majority of cases (87%) sepsis was the cause of ARDS (as opposed to, for example, trauma, aspiration or transfusion). Just over half of the patients (55%) had a vasopressor requirement and three quarters (75%) had a P/F ratio of less than 200 mmHg.

Table 1 Patient demographics

Characteristic	Statin ($n = 879$)	Placebo ($n = 876$)	Total ($n = 1755$)
Age, years	55.1 ± 16.7	55.4 ± 16.5	55.2 ± 16.6
Male	485 (55.2)	525 (59.9)	1010 (57.6)
Sepsis	757 (86.1)	768 (87.7)	1525 (86.9)
Shock	482 (54.8)	485 (55.4)	967 (55.1)
APACHE II	20.7 ± 7.3	20.2 ± 7.2	20.5 ± 7.3
APACHE III	92.1 ± 28.4	94.8 ± 27.9	93.4 ± 28.2
SOFA	8.4 ± 3.4	8.4 ± 3.1	8.4 ± 3.2
P/F ratio (mmHg)	156.8 ± 67.9	158.0 ± 64.7	157.4 ± 66.3
Creatinine (μmol/l)	123.5 ± 103.3	118.1 ± 90.3	120.8 ± 97.1
CRP (mg/l)	237.5 ± 282.4	224.7 ± 190.0	231.1 ± 240.9
Previous statin use, *n* (%)[a]	93 of 577 (16.1)	92 of 556 (16.6)	185 of 1133 (16.3)
ARDS severity (PaO_2/FiO_2 in mmHg)			
Mild (200–299)	211 (24.2)	207 (23.8)	418 (24.0)
Moderate (100–199)	448 (51.4)	474 (54.4)	922 (52.9)
Severe (<100)	198 (22.7)	181 (20.8)	379 (21.7)
Trial, *n* (%)			
SAILS	379 (43.1)	366 (41.8)	745 (42.5)
HARP-2	259 (29.5)	280 (32.0)	539 (30.7)
STATIN-VAP	134 (15.2)	122 (13.9)	256 (14.6)
STATInS	69 (7.9)	74 (8.5)	143 (8.2)
HARP-1	30 (3.4)	30 (3.4)	60 (3.4)
Kruger 2011	8 (0.9)	4 (0.5)	12 (0.7)

Continuous data are mean ± SD, categorical variables are *n* (%)

APACHE acute physiology and chronic health evaluation, *SOFA* sequential organ failure assessment, *CRP* C-reactive protein, *ARDS* acute respiratory distress syndrome, PaO_2 arterial partial pressure of oxygen, FiO_2 fraction of inspired oxygen

[a] Data for previous statin use was only available for 1133 patients (64.6% of the overall cohort)

Crude outcome data is shown in Table 2. Only trials which measured the outcome of interest and had at least one event were included for each analysis (for example, the 2011 trial by Kruger et al. [30] did not provide data on mortality or VFDs and there were no SAEs in either arm). For the primary outcomes, there was no detectable effect of statin therapy with two-stage fixed-effect analyses on 28-day mortality (five of six trials; relative risk [RR] 1.03, 95% CI 0.86–1.23, Fig. 1a), VFDs [four of six trials; mean difference (MD) 0.34 days, 95% CI −0.68 to 1.36, Fig. 1b] or serious adverse events (five of six trials; RR 1.14, 95% CI 0.84–1.53, Fig. 1c). There was no evidence of statistical heterogeneity (I^2 of 0%) in these three analyses and there was no material difference in results with a random-effects specification (full results in Tables S3 and S4 in the Supplementary Appendix). A two-stage fixed-effect sensitivity analysis of the primary outcomes with only the three trials that explicitly used established ARDS criteria for inclusion of patients (i.e. chest radiograph with bilateral pulmonary infiltrates in the absence of a cardiogenic cause) did not demonstrate any change in results (Table S5 in the Supplementary Appendix).

For the secondary outcomes, there was no detectable effect of statin therapy with two-stage fixed-effect analyses on ventilation duration (two of six trials; MD −1.04 days, 95% CI −6.02 to 3.93), requirement for renal replacement therapy (three of six trials; RR 0.97, 95% CI 0.80–1.19), ICU-free days to day 28 (five of six trials; MD 0.09 days, 95% CI −0.75 to 0.94), mortality to day 90 (three of six trials; RR 0.97, 95% CI 0.82–1.15), ICU length of stay (five of six trials; MD −0.58 days, 95% CI −1.81 to 0.64) or hospital length of stay (four of six trials; MD −0.63 days, 95% CI −2.59 to 1.32). There was no material difference in results with a random-effects specification (full results appear in Tables S3 and S4 in the Supplementary Appendix).

There was, however, a significantly increased incidence of non-serious adverse events with statin therapy (106/879; 12.1%) versus control (78/876; 8.9%) (five of six trials; RR 1.40, 95% CI 1.07–1.83, $p = 0.015$). This estimate was statistically insensitive to specification (random-effects RR 1.36, 95% CI 1.04–1.77, $p = 0.024$). One-stage models under both fixed- and random-effects specifications also suggested an increased incidence of non-serious adverse events with statin therapy (odds ratio (OR) 1.49, 95% CI 1.08–2.05, $p = 0.014$).

There were no significant treatment covariate interactions in the predefined subgroups that we investigated. These results were insensitive to various model specifications that accounted for aggregation bias where applicable (full results appear in Tables S6–S8 in the Supplementary Appendix). Forest plots for the three primary outcomes stratified by subgroup are shown in Fig. 2a–c. The required information sizes calculated during trial sequential analyses were samples of 4137 for 28-day mortality, 3019 for VFDs and 7979 for SAEs. For VFDs, the cumulative Z curve reached the adjusted boundary for futility. For 28-day mortality and SAEs, the cumulative Z curves did not reach adjusted boundaries (for either significance or futility). Analyses appear in Figs. S2–S4 in the Supplementary Appendix. A summary of the evidence according the Grading of Recommendations Assessment, Development and Evaluation (GRADE) recommendations is included in Table 3 and Table S9 in the Supplementary Appendix.

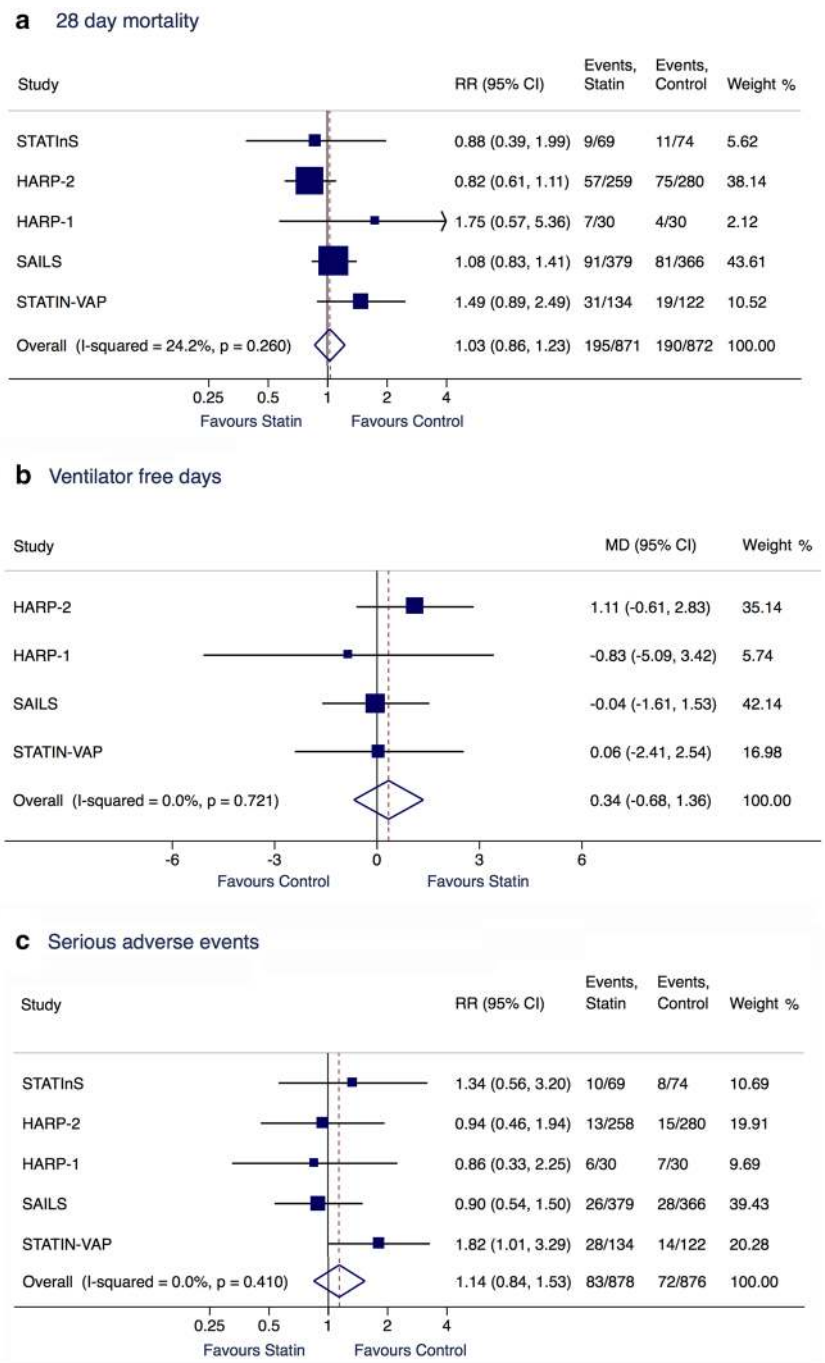

Fig. 1 Forest plot of efficacy outcomes: **a** 28-day mortality, **b** ventilator-free days, **c** serious adverse events

Discussion

There are three main findings in this individual patient data meta-analysis of trials assessing statin therapy for adult patients with ARDS. First, there was no evidence to suggest statin superiority in any of the primary or secondary efficacy outcomes. Second, from a safety perspective, there was no significant increase in our primary safety outcome of serious adverse events with statin therapy. However, statins did lead to an increased incidence of raised serum CK and ALT/AST levels. Third, we found no evidence to suggest statin superiority in any of the predefined subgroups that we investigated.

Table 2 Primary and secondary outcomes

Outcome	Statin	Placebo	Total
Primary			
28-day mortality, *n* (%)	195/871 (22.4)	190/872 (21.8)	385/1743 (22.1)
VFDs, mean ± SD	13.1 (10.5)	12.8 (10.8)	12.9 (10.7)
SAEs, *n* (%)	83/878 (9.5)	72/876 (8.2%)	155/1754 (8.8%)
Secondary			
Ventilation duration, days, mean ± SD	21.9 (27.2)	23.1 (29.7)	22.5 (28.4)
Requirement for RRT, *n* (%)	145/706 (20.5)	153/720 (21.3)	298/1426 (20.9)
ICU-free days to day 28, mean ± SD	12.9 (9.6)	13.0 (9.7)	12.9 (9.6)
90-day mortality, *n* (%)	194/707 (27.4)	203/719 (28.2)	397/1426 (27.8)
ICU length of stay, days mean ± SD	14.9 (15.3)	16.0 (20.2)	15.4 (17.9)
Hospital length of stay, days mean ± SD	25.9 ± 39.1	25.3 ± 25.7	25.6 ± 33.0
Non-serious adverse events, *n* (%)	106/879 (12.1)	78/876 (8.9)	184/1755 (10.5)

ICU intensive care unit, *RRT* renal replacement therapy, *SAEs* serious adverse events, *SD* standard deviation, *VFDs* ventilator-free days

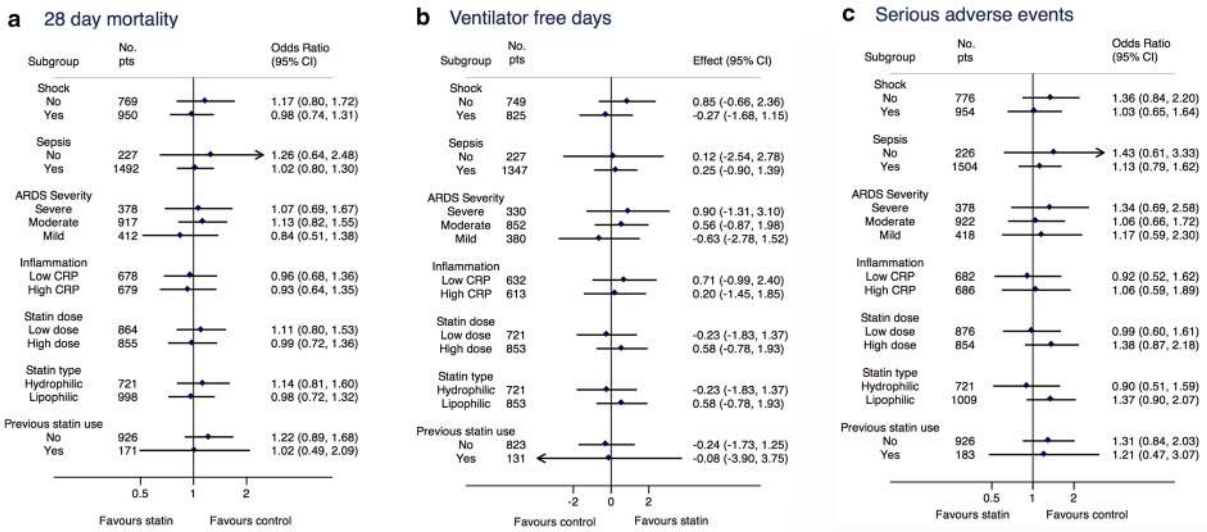

Fig. 2 Efficacy outcomes by subgroup: **a** 28-day mortality, **b** ventilator-free days, **c** serious adverse events

Our findings suggesting no role for statin therapy in established ARDS are broadly in line with recent meta-analyses published in patients with severe sepsis [32, 33]. This is perhaps unsurprising given the degree of overlap between the studies included in these meta-analyses and our ARDS cohort. However, there remain several recent observational studies suggesting a benefit for statin therapy in previous statin users [34–36]. We did not find evidence to support this assertion in the 65% of our cohort that had available information on prior statin use.

Our study results contrast with the reported potential benefits of statins in observational studies [37–40]. This is most likely due to the intrinsic limitations of non-randomised trial evidence, e.g. correlation of statin use with a confounder such as prior access to healthcare, rather than a direct benefit of statin therapy in ARDS, or an overestimate of treatment effect when using propensity score analysis in septic patients [41]. The other subgroups we investigated assessed a range of previously proposed plausible populations that might benefit from statin therapy [12, 13]. We also assessed the effect of the dose and type of statin and found no difference in effect between lipophilic or hydrophilic statins, or between high or low doses. Given these findings, further trials investigating statin therapy in established ARDS cannot be recommended. However, it is important to highlight that the definition of ARDS includes clinical subphenotypes with

Table 3 GRADE summary of findings table: primary outcomes

Primary outcomes	№ of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with statin therapy
Mortality to day 28	1743 (5 RCTs)	⊕⊕⊕◯ Moderate[a,b]	RR 1.03 (0.86 to 1.23)	218 per 1000	7 more per 1000 (31 fewer to 50 more)
Ventilator-free days	1600 (4 RCTs)	⊕⊕⊕◯ Moderate[b]	–	The mean ventilator-free days was 11.33 days	MD 0.34 days higher (0.68 lower to 1.36 higher)
Serious adverse events	1754 (5 RCTs)	⊕⊕⊕◯ Moderate[a,b]	RR 1.14 (0.84 to 1.53)	82 per 1000	12 more per 1000 (13 fewer to 44 more)

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

CI confidence interval, *RR* risk ratio, *MD* mean difference

[a] Rated moderate due to potential for imprecision given that required information size not met in trial sequential analysis

[b] Rated moderate due to potential for imprecision given that confidence intervals may include a clinically significant effect in both directions

distinct biological characteristics that may respond differently to treatment and it is unclear if any of these subphenotypes may be statin-responsive [42].

The potential role of statins in the prevention of ARDS in patients at high risk of developing ARDS has also not yet been evaluated. Data that pretreatment with simvastatin reduced pulmonary inflammatory responses to endotoxin in healthy human subjects supports this hypothesis [43]. Future studies could focus on randomising patients at high risk of ARDS, such as patients undergoing high-risk surgery.

The increased incidence of adverse events with statins in our study (defined as CK at ten times the upper limit of normal or ALT/AST at eight times the upper limit of normal) has important implications for the investigation of statins in other critical care settings. Importantly there was no increased requirement for renal replacement therapy and no increase in serious adverse events. Therefore, there is no clear contraindication to statin therapy during ARDS if there is another compelling indication for statin therapy.

The main strengths of our study are a systematic and comprehensive search (with pre-published analysis plan), the explicit inclusion of only randomised trial data (with regard to estimation of statin therapy benefits), collection of individual patient data with which to facilitate standardised subgroup analyses and the use of models that accounted for aggregation bias where applicable. Our findings must also be considered in light of several limitations. First, in more than 85% of patients in our cohort, the cause of ARDS was sepsis and so the generalisability of our findings to other causes such as trauma, aspiration and transfusion is limited. However, given that sepsis is the most common cause of ARDS, this is a high priority group for study. Second, not all trials reported data on all of the outcomes of interest. For example, the duration of ventilation was only reported in two trials and some other secondary outcomes only in three trials. In such cases, it is likely that the results were dominated by the larger trials (SAILS, HARP-2 and STATIN-VAP). Where data were available, heterogeneity in recording of outcomes restricted some planned analyses. For example, we had initially planned to assess prior statin use separately by any prior use, as well as immediate versus non-immediate use. Unfortunately, the data was not exclusively recorded in this way, thereby limiting our analysis of statin exposure to any prior use only. This highlights the need for core outcome sets in studies of patients receiving mechanical ventilation [44].

Furthermore, only three of the six included trials explicitly used established ARDS criteria for inclusion of patients. For the other trials, we assumed that septic ventilated patients with a P/F ratio of less than 300 mmHg were likely to have ARDS though there was no chest radiograph data collected to support this diagnosis. Nonetheless, sensitivity analyses excluding these trials did not materially affect our results. Fourth, we cannot exclude the possibility that some studies investigating statin therapy were not captured by our search. We mitigated against this by conducting a comprehensive search

of both electronic and non-electronic-based repositories. Nonetheless, there were three trials that may potentially have provided additional data but that we were forced to exclude because of lack of further information from study authors, although given that the sample sizes in these studies were small it is unlikely to have materially affected the results [26–28].

Other limitations include the use of co-primary outcomes, to assess both efficacy and safety, but without the use of more stringent statistical significance threshold testing (i.e. $p < 0.05$). However, we found no significant effect of statins even with a less stringent threshold. Finally, the inclusion of surrogate outcomes such as enzyme rises could be considered a limitation, as they are usually a proxy for harder clinical outcomes. However, although such outcomes are not directly patient-centred, they still have value as clinicians may base management decisions on absolute levels or trends in these variables during routine clinical care and most importantly they form part of a safety assessment.

Conclusions

We found no clinical benefit to the initiation of statin therapy in adult patients with ARDS, either overall or in predefined subgroups. While there was a significant increase in non-serious adverse events (raised serum CK and transaminase levels), there was no difference in serious adverse events between groups, thereby suggesting a reasonable safety profile of statins in ARDS patients. On the basis of our findings, we do not recommend initiation of statin therapy for treatment of ARDS, although it appears safe to continue statins with caution in such patients if specific clinical indications exist.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-016-4649-0) contains supplementary material, which is available to authorized users.

Author details

[1] Section of Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Imperial College London and Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK. [2] School of Medicine, Dentistry and Biomedical Sciences, Queen's University of Belfast, Belfast, UK. [3] Princess Alexandra Hospital, Metro South Health, Woolloongabba, QLD, Australia. [4] Medical Intensive Care Unit, North Hospital, Aix-Marseille University, Marseille, France. [5] Pulmonary and Critical Care Medicine, Froedtert and Medical College of Wisconsin, Milwaukee, WI, USA. [6] Departments of Anesthesia and Critical Care Medicine, St Michael's Hospital, University of Toronto, Toronto, Canada. [7] Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA. [8] School of Medicine, University of Queensland, Brisbane, Australia.

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Compliance with ethical standards

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Conflicts of interest

DMcA reports Grants from the National Institute for Health Research, Efficacy and Mechanism Evaluation, the Health Research Board, Health and Social Care Research & Development office, the Intensive Care Society Ireland, and REVIVE to support the conduct of HARP-2. Outside the submitted work, DMcA reports personal fees from consultancy for GlaxoSmithKline (GSK), SOBI, Bayer, Boehringer Ingelheim and Peptinnovate. His institution has received grants from the NIHR and others, as well as funds from GSK for DMcA undertaking bronchoscopy as part of a clinical trial. In addition, DMcA also holds a patent for the use of a pharmacotherapy (not a statin) for treatment of ARDS awarded to Queen's University Belfast. BTT reports Grants from the National Heart, Lung, and Blood Institute of the National Institute of Health. Outside the submitted work, BTT reports personal fees from consultancy for Alexion, Asahi Kasei, Boehringer Ingelheim, GlaxoSmithKline, and Regeneron. ACG reports, outside the submitted work, grants from the National Institute for Health Research that he has received speaker fees from Orion Corporation Orion Pharma and Amomed. He has consulted for Ferring Pharmaceuticals, Tenax Therapeutics and received Grant support from Orion Corporation Orion Pharma, Tenax Therapeutics and HCA International with funds paid to his institution. Other authors declare that they have no conflicts of interest.

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