Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial

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Summary

Background **Precision medicine approaches that target patients on the basis of disease subtype have transformed treatment approaches to cancer, asthma, and other heterogeneous syndromes. Two distinct subphenotypes of acute respiratory distress syndrome (ARDS) have been identified in three US-based clinical trials, and these subphenotypes respond differently to positive end-expiratory pressure and fluid management. We aimed to investigate whether these subphenotypes exist in non-US patient populations and respond differently to pharmacotherapies.**

Methods **HARP-2 was a multicentre, randomised controlled trial of simvastatin (80 mg) versus placebo done in general intensive care units (ICUs) at 40 hospitals in the UK and Ireland within 48 h of onset of ARDS. The primary outcome was ventilator-free days, and secondary outcomes included non-pulmonary organ failure-free days and mortality. In a secondary analysis of HARP-2, we applied latent class analysis to baseline data without consideration of outcomes to identify subphenotypes, and we compared clinical outcomes across subphenotypes and treatment groups.**

Findings **540 patients were recruited to HARP-2. One patient withdrew consent for the use of their data, so data from 539 patients were analysed. In our secondary analysis, a two-class (two subphenotype) model was an improvement over a one-class model (p<0·0001), with 353 (65%) patients in the hypoinflammatory subphenotype group and 186 (35%) in the hyperinflammatory subphenotype group. Additional classes did not improve model fit. Clinical and biological characteristics of the two subphenotypes were similar to previous studies. Patients with the hyperinflammatory subphenotype had fewer ventilator-free days (median 2 days [IQR 0–17] *vs* 18 [IQR 0–23]; p<0·0001), fewer non-pulmonary organ failure-free days (15 [0–25] *vs* 27 [21–28]; p<0·0001), and higher 28-day mortality (73 [39%] *vs* 59 [17%]; p<0·0001) than did those with the hypoinflammatory subphenotype. Although HARP-2 found no difference in 28-day survival between placebo and simvastatin, significantly different survival was identified across patients stratified by treatment and subphenotype (p<0·0001). Specifically, within the hyperinflammatory subphenotype, patients treated with simvastatin had significantly higher 28-day survival than did those given placebo (p=0·008). A similar pattern was observed for 90-day survival.**

Interpretation **Two subphenotypes of ARDS were identified in the HARP-2 cohort, with distinct clinical and biological features and disparate clinical outcomes. The hyperinflammatory subphenotype had improved survival with simvastatin compared with placebo. These findings support further pursuit of predictive enrichment strategies in critical care clinical trials.**

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Introduction

Acute respiratory distress syndrome (ARDS) is a common and frequently fatal cause of respiratory failure among patients who are critically ill, with an incidence of nearly 200 000 cases per year in the USA alone, an estimated prevalence of 10% among critically ill patients worldwide, and a mortality of 30–40%.[1,2] ARDS is defined by clinical criteria including acute onset of hypoxaemia (ratio of the partial pressure of arterial oxygen [PaO_2] to the fraction of inspired oxygen [FiO_2] <300 mm Hg), bilateral chest radiographic opacities, and exclusion of cardiac failure as the sole cause of the syndrome.[3] Since the first consensus definition of ARDS in 1988, experts have debated whether patients should be subdivided by natural history, clinical features, biology, or a combination of all three.[4] During the ensuing three decades, positive trials of several supportive care interventions, including most notably lung protective ventilation, have led to decreases in ARDS mortality.[5] However, over the same period, dozens of pharmacotherapies that seemed to show great promise in preclinical studies have failed in clinical trials.[6,7] An often-cited reason for this discouraging failure rate has been the considerable clinical and biological heterogeneity within ARDS, but objective data to guide a more precise approach to clinical trials have been lacking.

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Research in context

Evidence before this study

Previous studies of patients with acute respiratory distress syndrome (ARDS), using data from US-based randomised controlled trials, have identified two distinct subphenotypes with differential responses to mechanical ventilation and fluid therapy. Whether these subphenotypes can be identified in non-US patient populations by use of different datasets and, more importantly, whether these subphenotypes respond differently to pharmacotherapies is unknown. We searched PubMed for any study reporting differential responses to pharmacotherapy by ARDS subphenotype published from database inception to March 7, 2018, using the terms ("ARDS" or "acute lung injury") AND (subtype OR subphenotype OR endotype) and no language restrictions. We identified no previous studies.

Added value of this study

Our study reports the identification of two distinct ARDS subphenotypes in a secondary analysis of a UK-based randomised controlled trial of simvastatin for ARDS treatment. The hyperinflammatory subphenotype of ARDS had a survival benefit from simvastatin. To our knowledge, our study is the first to report a differential response to pharmacotherapy by molecular subphenotype in ARDS.

Implications of all the available evidence

Although other areas of medicine (eg, cancer and asthma) have made substantial progress through identification of biologically distinct subtypes of disease with differential treatment responses, critical care medicine has lagged behind. Our findings suggest that targeting specific biological subtypes of critical illness syndromes in clinical trials might yield progress after decades of negative pharmacotherapy trials in the intensive care unit.

Latent class analysis is a well validated statistical method that uses objective criteria to identify subgroups within a broader population. We previously applied latent class analysis in independent analyses of three cohorts of patients derived from National Heart, Lung, and Blood Institute ARDS Network randomised controlled trials. We observed strong evidence for two distinct and consistent subphenotypes of ARDS in all three cohorts, which included more than 2000 patients in total.[8,9] In all three cohorts, one subphenotype (hyperinflammatory) representing roughly 30% of patients with ARDS was consistently characterised by increased inflammatory biomarkers, more profound shock and acidosis, and significantly worse clinical outcomes. This subphenotype had a significantly different response to randomly assigned positive end-expiratory pressure and fluid management strategy, compared with the other subphenotype (hypoinflammatory).[8,9] These findings suggest that improved understanding of these subphenotypes could be crucial to future success in ARDS clinical trials.[7] However, it is not known whether these ARDS subphenotypes are generalisable to non-US populations, whether they can be identified with less extensive datasets, and most importantly, whether they might respond differently to pharmacotherapies.

To test these questions, we designed a secondary analysis of a phase 2b randomised trial of simvastatin for treatment of ARDS (the HARP-2 study).[10] On the basis of our previous research, we hypothesised a priori that latent class analysis of the HARP-2 cohort would identify two distinct subphenotypes of ARDS, with similar clinical and biological characteristics to those we had previously identified. We also hypothesised, on the basis of the anti-inflammatory effects of statins in laboratory and preclinical models of ARDS,[11] that patients with the hyperinflammatory subphenotype would preferentially respond to simvastatin.

Methods

Study design and participants of HARP-2

We present secondary analysis of data from the previously reported HARP-2 trial. HARP-2 was a multicentre, randomised controlled trial done in general intensive care units (ICUs) at 40 hospitals in the UK and Ireland.[10] Patients were eligible if they were intubated and mechanically ventilated and were within 48 h of the onset of ARDS, as defined by a ratio of PaO_2 to FiO_2 of 300 mm Hg or less, if bilateral pulmonary infiltrates consistent with pulmonary oedema were present on chest radiography and if there was no evidence of left atrial hypertension. Patients were randomly assigned (1:1) to receive daily simvastatin or placebo and stratified according to study site and vasopressor requirement (yes *vs* no).[10]

Procedures in HARP-2

Patients were enrolled within 48 h of meeting ARDS criteria and received once-daily enteral simvastatin 80 mg or identical placebo tablets. The first dose was given as soon as possible, ideally within 4 h after randomisation, and subsequent doses were administered each morning, beginning the following day. Study drug was continued until day 28, discharge from ICU, death, or development of a contraindication to continued statin therapy.

Outcomes of HARP-2

The original primary outcome of HARP-2 was ventilator-free days. Secondary outcomes included non-pulmonary organ failure-free days and mortality (see original publication[10] for all secondary outcomes); there were no

significant differences in any of these outcomes by treatment allocation, as assessed in the original publication.[10]

Assay procedures for secondary analysis

For our new analysis, we measured interleukin 6 and soluble tumour necrosis factor receptor 1 (sTNFr1) using plasma drawn before randomisation and stored at –80°C. Biomarkers were measured in duplicate with commercially available ELISAs (R&D Systems, Minneapolis, MN, USA).

Latent class analysis

For our secondary analysis, to estimate the optimal number of classes in the data, we fitted latent class models in Mplus v8[12] using baseline demographics (age and sex), available baseline clinical data (direct and indirect ARDS risk factors, bilirubin, creatinine, platelet count, PaO_2 to FiO_2 ratio, plateau pressure, tidal volume, and use of vasopressors), and baseline interleukin 6 and sTNFr1 as class-defining variables (appendix). Fewer clinical and biomarker variables were available for these analyses than in our previous studies.[8,9] We did not include outcome variables in the modelling. We estimated models ranging from one to four classes to identify the optimal number of classes. From these four models, we evaluated best fit using Bayesian Information Criteria, the Vuong-Lo-Mendell-Rubin likelihood ratio test (which compares fit of model k classes to k–1 classes), class size, and entropy.[13,14] Before beginning this modelling, we examined variables for their distribution, and continuous variables with substantially skewed distributions were log transformed. To estimate model parameters, we placed continuous variables on a z scale with a mean of 0 and SD of 1, as in our previous work.[8,9] As a sensitivity analysis, we repeated these models including C-reactive protein concentrations. For additional details on the latent class analysis modelling, see the appendix.

Once we established the optimal number of classes, we assigned study participants to their most likely class, and compared their baseline characteristics using t tests, Pearson's χ^2, or Wilcoxon rank-sum test depending on the nature of the variable. We tested associations between class assignment and clinical outcomes using χ^2 for mortality (ie, the proportion who died) and Wilcoxon rank-sum for ventilator-free days. To test for interactions between treatment and class assignment, we used logistic regression for mortality and zero-inflated Poisson regression for ventilator-free days. We compared count-based models of ventilator-free days for best fit and tested for overdispersion to inform model selection. Model diagnostics were satisfactory (appendix). To test for differential response to treatment by class for survival (time to death), we compared time-to-event Kaplan-Meier curves using the log-rank test. For modelling time to unassisted breathing, a competing risks model was estimated with death before day 28 as the competing risk.[15] We did analyses other than latent class analysis using SAS (version 9.4). Some results were previously reported in an abstract.[16]

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 21, 2010, and March 13, 2014, 540 patients were recruited to HARP-2 and randomly assigned to receive simvastatin or placebo. One patient withdrew consent for the use of their data, so data from 539 patients were analysed. Baseline characteristics of patients enrolled in the HARP-2 trial have been fully described elsewhere (appendix).[10] Pneumonia was the most common contributing risk factor for ARDS (appendix). Overall, median number of ventilator-free days was 13 (IQR 0–22), and 28-day mortality was 25% (appendix).

See Online for appendix

Analysis of the four latent class analysis models showed that a two-class model was a better fit for the population than a one-class model, and additional classes did not improve model fit (appendix). Entropy in all models was 0·75 or greater, indicating adequate class separation. The Bayesian Information Criteria decreased as the number of classes in the model increased, indicating improved model fit with additional classes. The two-class model had a significantly improved fit compared with the one-class model (Vuong-Lo-Mendell-Rubin likelihood ratio p<0·0001). These findings, along with the small number of patients in the additional class in a three-class model (n=40), led us to proceed using a two-class model. In the two-class model, 353 (65%) patients were assigned to

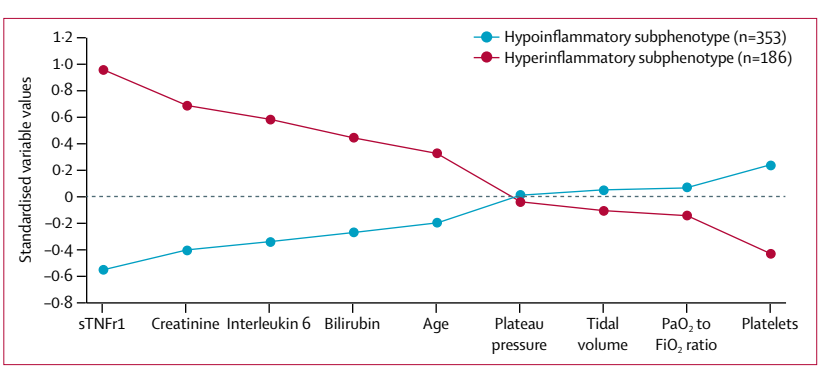

Figure 1: **Differences in standardised values of each continuous variable by subphenotype in the HARP-2 trial**
Variables are sorted on the basis of the degree of separation between the subphenotypes, from maximum positive separation on the left (ie, hyperinflammatory subphenotype higher than hypoinflammatory subphenotype) to maximum negative separation on the right (ie, hyperinflammatory subphenotype lower than hypoinflammatory subphenotype). The y-axis represents standardised variable values, in which all means are scaled to 0 and SDs to 1. A value of +1 for the standardised variable signifies that the mean value for a given subphenotype was 1 SD higher than the mean value in the cohort as a whole. Mean values are joined by lines to facilitate display of subphenotype profiles. sTNFr1=soluble tumour necrosis factor receptor-1. PaO_2=partial pressure of arterial oxygen. FiO_2=fraction of inspired oxygen.

	Hypoinflammatory subphenotype (n=353)	Hyperinflammatory subphenotype (n=186)	p value
Age (years)	51 (16)	60 (15)	<0·0001
Female sex	158 (45%)	74 (40%)	0·32
Direct ARDS risk factors			<0·0001
Aspiration	36 (10%)	13 (7%)	..
Pneumonia	215 (61%)	80 (43%)	..
Trauma	26 (7%)	5 (3%)	..
Other	24 (7%)	4 (2%)	..
None	52 (15%)	84 (45%)	..
Indirect ARDS risk factors			<0·0001
Sepsis	116 (33%)	108 (58%)	..
Pancreatitis	4 (1%)	14 (8%)	..
Other	19 (5%)	14 (8%)	..
None	214 (61%)	50 (27%)	..
Vasopressor use	205 (58%)	151 (81%)	<0·0001
PaO_2 to FiO_2 ratio, kPa	17·6 (8)	16·1 (7)	0·02
Plateau pressure, cm H_2O*	24 (6)	24 (6)	0·87
Tidal volume, mL/kg	8·3 (2·6)	7·9 (2·6)	0·099
Platelet count, thousands	216 (119)	148 (114)	<0·0001
Bilirubin, µmol/L	9 (6–16)	19·5 (11–36)	<0·0001
Creatinine, µmol/L	76 (42)	156 (91)	<0·0001
C-reactive protein, mg/L	174 (109)	208 (110)	0·0008
Interleukin 6, pg/mL	79 (35–197)	348 (133–1355)	<0·0001
sTNFr1, pg/mL	3511 (2382–5008)	11 202 (7810–16 703)	<0·0001
Randomised to simvastatin	175 (50%)	84 (45%)	0·38

Data are mean (SD), n (%), or median (IQR). Statistical comparison was done by Pearson's χ^2, *t* test, or Wilcoxon rank-sum as appropriate. ARDS=acute respiratory distress syndrome. PaO_2=partial pressure of arterial oxygen. FiO_2=fraction of inspired oxygen. sTNFr1=soluble tumour necrosis factor receptor 1. *Plateau pressure was missing for 245 (45%) patients.

Table 1: **Key subphenotype-defining variables at baseline**

	Hypoinflammatory subphenotype (n=353)	Hyperinflammatory subphenotype (n=186)	p value
28-day mortality	59 (17%)	73 (39%)	<0·0001
90-day mortality	78 (22%)	87 (47%)	<0·0001
Ventilator-free days	18 (0–23)	2 (0–17)	<0·0001
Non-pulmonary organ failure-free days	27 (21–28)	15 (0–25)	<0·0001

Data are n (%) or median (IQR). Ventilator-free days and non-pulmonary organ failure-free days were measured to day 28.

Table 2: **Clinical outcomes by subphenotype**

class one and 186 (35%) patients to class two. These proportions are consistent with our previous latent class analyses,[8,9] despite the HARP-2 analyses using far fewer clinical and biomarker variables (n=14) as inputs than our previous work (n=35–37). Inclusion of C-reactive protein in the latent class analysis models as a sensitivity analysis did not affect the results (data not shown). Average latent class probabilities were 0·93 for class one and 0·92 for class 2. These findings are also consistent with previous studies and indicative of robust class assignment.

Class 2 had clinical and biological features similar to those found in previous studies[8,9] and consistent with a hyperinflammatory phenotype. Specifically, patients in class 2 had higher values of sTNFr-1 and interleukin 6, lower platelet counts (figure 1; table 1), and more vasopressor use (table 1) than did those in class 1. For simplicity, we will refer to the classes as the hypoinflammatory subphenotype (class 1) and the hyperinflammatory subphenotype (class 2). Although the distribution of direct and indirect ARDS risk factors was significantly different across the two subphenotypes (table 1; p<0·0001), the most common ARDS risk factors of sepsis, pneumonia, and aspiration were highly prevalent among both groups, as in previous studies.[8,9] Furthermore, as in previous studies, patients with the hyperinflammatory subphenotype had fewer ventilator-free days, fewer non-pulmonary organ failure-free days, and higher 28-day mortality than did those with the hypoinflammatory subphenotype (table 2).

The original HARP-2 trial found no difference in 28-day survival curves between placebo and simvastatin (p=0·20).[10] By contrast, we observed significantly different survival curves across patients stratified by treatment and subphenotype (figure 2; p<0·0001). Specifically, within the hyperinflammatory subphenotype, patients treated with simvastatin had significantly higher 28-day survival than did patients treated with placebo (p=0·008). This effect was not observed in patients with the hypoinflammatory subphenotype. A similar pattern was observed for 90-day survival (figure 2; p<0·0001 for overall comparison; p=0·03 for hyperinflammatory subphenotype simvastatin *vs* placebo).

In contrast to the curves stratified by subphenotype and treatment, survival curves stratified by ARDS severity (PaO_2 to FiO_2 ratio) and treatment were not significantly different (p=0·12). Survival curves stratified by APACHE II score (dichotomised at the mean) and treatment revealed no differential effect of treatment in either the high or low APACHE groups (appendix).

28-day mortality was 32% (27 of 84 patients) in patients with the hyperinflammatory subphenotype treated with simvastatin, in comparison to 45% (46 of 102 patients) in patients with the hyperinflammatory subphenotype treated with placebo. By contrast, 28-day mortality was similar in patients with the hypoinflammatory subphenotype regardless of treatment assignment (16% [29 of 178 patients] on placebo *vs* 17% [30 of 175 patients] on simvastatin). The interaction between treatment and subphenotype for mortality was not significant (p=0·14).

In the original HARP-2 trial, time to unassisted breathing did not differ significantly between patients assigned to simvastatin or placebo. When stratified by subphenotype and treatment, time to unassisted breathing differed significantly (figure 3; p<0·0001). However, the difference between patients with the hyperinflammatory subphenotype treated with simvastatin and placebo was

not significant (p=0·10). In the hyperinflammatory subphenotype, median ventilator-free days were numerically higher in patients assigned to simvastatin than in those assigned to placebo (7 days [IQR 0–18] *vs* 0 [0–17]), in contrast to patients with the hypoinflammatory subphenotype, for whom the median number of ventilator-free days was the same in both groups regardless of treatment (18 [2–22] for the simvastatin group *vs* 18 [0–23] for the placebo group). However, the interaction between treatment and subphenotype in regression models was not significant (p=0·15).

Discussion

Our analyses have two novel findings with important implications for future clinical trials in ARDS. First, two distinct ARDS subphenotypes with features similar to those we have previously reported were identified for the first time in a non-US patient population, using a different and much smaller set of clinical and biomarker data than in previous studies. These findings indicate that these subphenotypes are consistent across geographical sites and are robust to variations in specific data collected, enhancing the generalisability of previous studies. Second, patients with these two subphenotypes of ARDS responded differently to randomly assigned simvastatin, with evidence of improved survival at both 28 and 90 days uniquely among those with the hyperinflammatory subphenotype of ARDS. These findings suggest that identification of ARDS subphenotypes might be fundamentally important in future ARDS clinical trials and, more broadly, that targeting distinct subphenotypes of critical illness syndromes could finally yield progress after decades of negative pharmacotherapy trials in the ICU.

The heterogeneous, clinically defined syndromes of sepsis and ARDS are thought of as dead ends for novel pharmacotherapies, despite their high prevalence and mortality, and critical care has lagged behind other fields in its development of precision biomarker-guided treatments.[17] The concept of targeting specific biomarker-defined subgroups of heterogeneous syndromes, a variant of precision medicine, has fundamentally changed approaches to patient care in oncology, with examples ranging from oestrogen receptor status in breast cancer to *BRAF* mutation status in melanoma and other malignancies.[18] In other fields, such as asthma, recognition of the importance of distinct subphenotypes is crucial to the design of new clinical trials and is beginning to affect patient care.[19] Over the past few years, increasing evidence has been found of the biological and clinical heterogeneity in sepsis and ARDS, including our previous work showing subphenotype specific responses to positive end-expiratory pressure and fluid management strategy,[8,9] but until now, to our knowledge there has been no reported evidence that biologically distinct subphenotypes have differential responses to pharmacotherapy in ARDS.

That patients with the hyperinflammatory ARDS subphenotype preferentially responded to randomly assigned simvastatin has biological plausibility based on the presumed mechanism of action of statins in ARDS. Statins reduce lung inflammation and injury in both animal models of ARDS and preclinical human experimental studies[11] and have endothelial stabilising properties. Thus, patients with more systemic inflammation, such as those with the hyperinflammatory subphenotype, could be most likely to respond to this therapy.

In this analysis, as in our previous studies on the same topic, we noted that extrapulmonary factors (such as creatinine, bilirubin, and platelet concentrations) seemed to contribute more to subphenotype identification than did pulmonary-specific variables, such as PaO_2 to FiO_2 ratio and ventilator parameters. A potential explanation for these findings is that patients were enrolled into this trial (as in all ARDS clinical trials) on the basis of specific

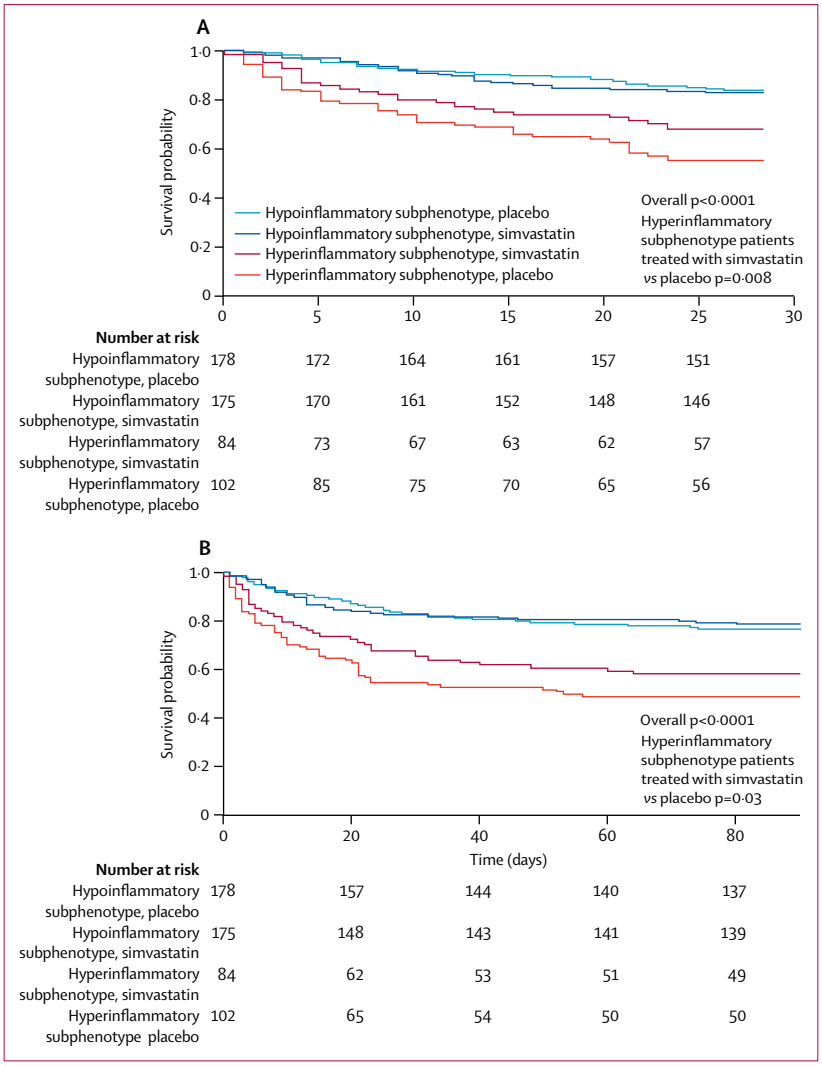

Figure 2: **Kaplan-Meier survival curves**
(A) 28-day and (B) 90-day patient survival in HARP-2, stratified by acute respiratory distress syndrome subphenotype and treatment (simvastatin *vs* placebo).

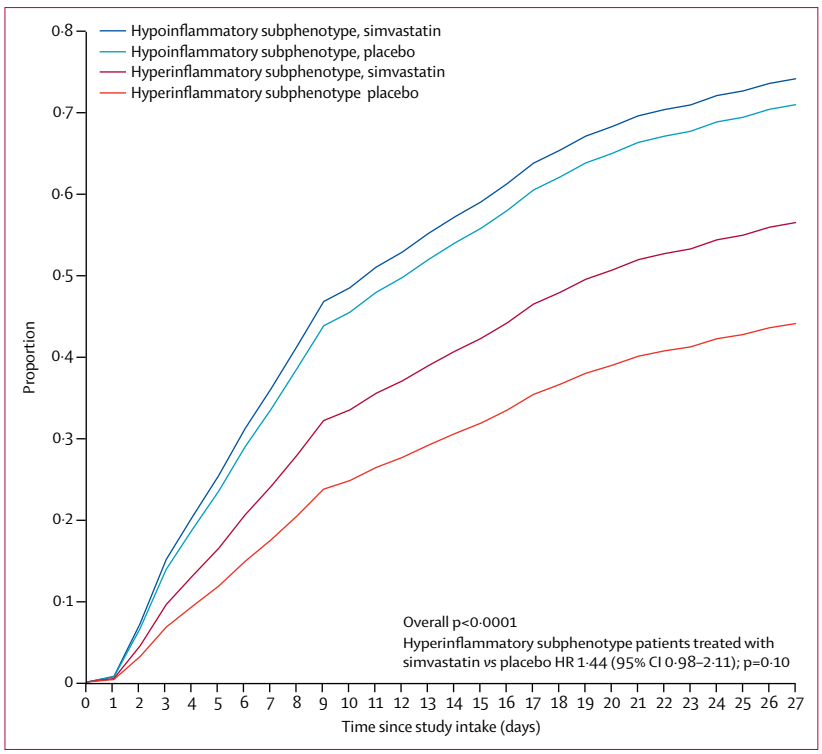

Figure 3: **Time to unassisted breathing over 28 days**
Data are stratified by subphenotype and treatment condition, from Fine-Gray competing risks model. HR=hazard ratio.

pulmonary criteria (eg, PaO_2 to FiO_2 ratio), and other pulmonary criteria (eg, tidal volume and plateau pressure) are determined at least in part by protocols designed for patients with ARDS. Thus, it is not entirely surprising that these pulmonary criteria converge and contribute less to identifying subgroups of patients than do non-pulmonary criteria. Also, biological differences between subphenotypes could either drive or be driven by multisystem organ failure, which then contributes to poorer outcomes.

We observed a clinically significant but not statistically significant difference in median ventilator-free days for patients with the hyperinflammatory subphenotype treated with simvastatin (7 days) versus placebo (0 days). These data contrast with the findings of our survival analysis, in which survival was significantly better with simvastatin in the hyperinflammatory subphenotype. Our interpretation of these results is that the ventilator-free days analyses might be underpowered and reflect a pattern of preferential benefit to simvastatin in the hyperinflammatory subphenotype similar to that identified in the survival analysis, although other interpretations are also possible. Nevertheless, these findings highlight some of the challenges in using ventilator-free days as an outcome for clinical trials of ARDS.

When results of any subgroup analysis in a clinical trial are examined, several important issues (in addition to biological plausibility) should be considered, including multiple hypothesis testing, post-hoc analyses, and statistical power and methodology.[20] In our analyses, only one subgroup analysis was done—specifically, latent classes were sought by use of an unbiased, data-driven approach that has identified distinct ARDS subphenotypes in three previous studies.[8,9] Thus, multiple hypothesis testing (aside from the hypothesis of the original clinical trial) should not be an issue. This analysis was not planned as part of the original trial design because the trial was designed before our group's first description of ARDS subphenotypes.[21] However, given our previous findings that ARDS subphenotypes respond differently to randomly assigned interventions (eg, positive end-expiratory pressure and fluid conservative therapy) in two previous large clinical trials,[8,9] we thought this was an important hypothesis to test in our analysis. As with many subgroup analyses, the original HARP-2 trial was not powered for this analysis; we also note that, despite a 13% absolute risk reduction for mortality in the hyperinflammatory subphenotype with simvastatin compared with placebo, the statistical test for interaction in the analyses of 28-day mortality did not give a statistically significant result (p=0·14). In this case, given the biological plausibility of a preferential response to statins in the hyperinflammatory subphenotype and our previous findings of differential treatment responses to other interventions, we thought it appropriate to directly compare the survival curves for patients with the hyperinflammatory subphenotype treated with simvastatin versus placebo. However, a prospective clinical trial of simvastatin targeting patients with the hyperinflammatory subtype should be done before making any treatment recommendations for this group.

Our study has several strengths, including the consistency of the latent class analysis results compared with previous studies, the data-driven and unbiased nature of latent class analysis for subgroup identification, the biological plausibility of the results, and the setting within a randomised controlled trial, which allows stronger causal inference regarding treatment effects compared with observational studies. Our study also has some limitations, most of which derive from its origin as a subgroup analysis and are detailed above. As in some other previous ARDS clinical trials,[5,22] plateau pressure was missing in a substantial proportion of patients (45%). Although latent class models can include patients with missing data, more complete data on this variable might have been useful. Furthermore, because of the nature of latent class models, it is not possible to prove that the two subphenotypes identified in this cohort are the same as the two subphenotypes identified in our previous studies, although the similarity of the clinical and biological variables distinguishing the two groups in this work and previous studies provides strong supportive evidence. As in nearly all randomised controlled trials of ARDS, mortality was lower in the HARP-2 cohort than in contemporary observational ARDS cohorts.[2] Additional studies of ARDS subphenotypes in less carefully selected

patient populations are needed. Finally, patients in the original trial were not randomised on the basis of their ARDS subphenotype, so in addition to the aforementioned caveats regarding subgroup analyses, unmeasured confounders could have contributed to our findings. Prospective confirmation of simvastatin benefit in the hyperinflammatory subphenotype in a randomised controlled trial is needed.

Moving forward, how might these findings be translated to future clinical trials in ARDS? As reported in previous studies, the hyperinflammatory ARDS subphenotype can be accurately identified using as few as three variables (eg, interleukin 8, sTNFr1, and bicarbonate).[8,9] Development of the capability to measure these biomarkers in real time will be crucial for precision clinical trials in this setting. More broadly, our results suggest that predictive enrichment approaches to critical care clinical trials should be strongly considered. Investigators studying sepsis have identified distinct subtypes within that heterogeneous syndrome, defined by differences in whole blood gene expression, although testing for differential responses to randomly assigned treatment has not yet been done.[23–25] If similar patterns are identified in sepsis, clinical trials in syndromes known to encompass substantial biological heterogeneity could consider targeting patients on the basis of their underlying biology rather than on a less specific syndromic diagnosis.

In conclusion, this secondary analysis of the HARP-2 trial of simvastatin for ARDS treatment identified two distinct subphenotypes of ARDS, one of which had significantly improved survival with simvastatin therapy compared with placebo. Two distinct subphenotypes of ARDS have now been identified in four different randomised controlled trial cohorts, with differential responses to mechanical ventilation, fluid management strategy, and now pharmacotherapy. These findings support further pursuit of predictive enrichment strategies in critical care clinical trials.

Contributors

CSC, KLD, and DFM conceived and designed the study. JH, MS-H, CM, JGL, CMO, and DFM collected the data. CSC, KLD, PS, MAM, CMO, and DFM contributed to data analysis and interpretation. CSC, KLD, PS, and DFM drafted the manuscript. All authors contributed to revision of the manuscript and approved the final version.

Declaration of interests

CSC reports grants from the National Institutes of Health during the conduct of the study, grants and personal fees from GlaxoSmithKline and Bayer, and personal fees from Boehringer Ingelheim, Roche/Genentech, CSL Behring, and Prometic outside the submitted work. DFM reports grants from the UK National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) Programme, Health Research Board Ireland, Northern Ireland Public Health Agency Research and Development, Intensive Care Society of Ireland, and REVIVE for the conduct of the study. DFM reports personal fees for consultancy for GlaxoSmithKline, Swedish Orphan Biovitrium, Peptinnovate, Boehringer Ingelheim, and Bayer, all outside the submitted work. DFM's institution has received grants from the NIHR and others and GlaxoSmithKline for DFM undertaking bronchoscopy as part of a clinical trial outside the submitted work. DFM has a patent issued to his institution for a treatment for ARDS. CMO reports grants from NIHR EME and Health and Social Care Research and Development during the conduct of the study. CMO's spouse has received consultancy fees from GlaxoSmithKline, Bayer, Boehringer Ingelheim, Peptinnovate, and Swedish Orphan Biovitrium. MAM reports grants from the National Heart, Lung, and Blood Institute, the Department of Defense, the Food and Drug Association, Bayer Pharmaceuticals, and GlaxoSmithKline, and personal fees from CSL Behring, Boehringer Ingelheim, Cerus Therapeutics, Roche/Genentech, Quark Pharmaceuticals, and Thesan Pharmaceuticals, all outside the submitted work. JGL reports grants from Health Research Board Ireland during the conduct of the study. All other authors declare no competing interests.

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