ORIGINAL ARTICLE

Simvastatin in the Acute Respiratory Distress Syndrome

Daniel F. McAuley, M.D., John G. Laffey, M.D., Cecilia M. O'Kane, Ph.D., Gavin D. Perkins, M.D., Brian Mullan, M.B., T. John Trinder, M.D., Paul Johnston, M.B., Philip A. Hopkins, Ph.D., Andrew J. Johnston, M.D., Cliona McDowell, M.Sc., Christine McNally, B.A., and the HARP-2 Investigators, for the Irish Critical Care Trials Group*

ABSTRACT

BACKGROUND

Studies in animals and in vitro and phase 2 studies in humans suggest that statins may be beneficial in the treatment of the acute respiratory distress syndrome (ARDS). This study tested the hypothesis that treatment with simvastatin would improve clinical outcomes in patients with ARDS.

METHODS

In this multicenter, double-blind clinical trial, we randomly assigned (in a 1:1 ratio) patients with an onset of ARDS within the previous 48 hours to receive enteral simvastatin at a dose of 80 mg or placebo once daily for a maximum of 28 days. The primary outcome was the number of ventilator-free days to day 28. Secondary outcomes included the number of days free of nonpulmonary organ failure to day 28, mortality at 28 days, and safety.

RESULTS

The study recruited 540 patients, with 259 patients assigned to simvastatin and 281 to placebo. The groups were well matched with respect to demographic and baseline physiological variables. There was no significant difference between the study groups in the mean (±SD) number of ventilator-free days (12.6±9.9 with simvastatin and 11.5±10.4 with placebo, P=0.21) or days free of nonpulmonary organ failure (19.4±11.1 and 17.8±11.7, respectively; P=0.11) or in mortality at 28 days (22.0% and 26.8%, respectively; P=0.23). There was no significant difference between the two groups in the incidence of serious adverse events related to the study drug.

CONCLUSIONS

Simvastatin therapy, although safe and associated with minimal adverse effects, did not improve clinical outcomes in patients with ARDS. (Funded by the U.K. National Institute for Health Research Efficacy and Mechanism Evaluation Programme and others; HARP-2 Current Controlled Trials number, ISRCTN88244364.)

From the Centre for Infection and Immunity, Queen's University of Belfast (D.F.M., C.M.O.), the Regional Intensive Care Unit (D.F.M., B.M.) and Northern Ireland Clinical Trials Unit (D.F.M., C. McDowell, C. McNally), Royal Victoria Hospital, and the Intensive Care Unit, Ulster Hospital (T.J.T.), Belfast, the Heart of England National Health Service (NHS) Foundation Trust, Birmingham (G.D.P.), Warwick Medical School Clinical Trials Unit, University of Warwick, Warwick (G.D.P.), the Intensive Care Unit, Antrim Area Hospital, Antrim (P.J.), the Critical Care Units, King's Health Partners (King's College Hospital), London (P.A.H.), and the John Farman Intensive Care Unit, Cambridge University Hospitals NHS Foundation Trust, Cambridge (A.J.J.) — all in the United Kingdom; the Department of Anaesthesia, School of Medicine, Health Research Board Galway Clinical Research Facility, Clinical Sciences Institute, National University of Ireland, Galway, Ireland (J.G.L.); and the Department of Anesthesia, Centre for Critical Care Research, Keenan Research Centre for Biomedical Science, St. Michael's Hospital, University of Toronto, Toronto (J.G.L.). Address reprint requests to Dr. McAuley at the Centre for Infection and Immunity, Queen's University of Belfast, Health Sciences Bldg., 97 Lisburn Rd., Belfast BT9 7AE, United Kingdom, or at d.f.mcauley@qub.ac.uk.

*A complete list of investigators in the Hydroxymethylglutaryl-CoA Reductase Inhibition with Simvastatin in Acute Lung Injury to Reduce Pulmonary Dysfunction–2 Study (HARP-2) is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 30, 2014, at NEJM.org.

DOI: 10.1056/NEJMoa1403285

The acute respiratory distress syndrome (ARDS) is a common, devastating clinical syndrome characterized by life-threatening respiratory failure requiring mechanical ventilation and by multiple organ failure. In ARDS there is an uncontrolled inflammatory response that results in alveolar damage, with the exudation of protein-rich pulmonary-edema fluid in the alveolar space that results in respiratory failure.[1]

The inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase with statins has been shown to modify a number of the underlying mechanisms implicated in the development of ARDS.[2] Statins decrease inflammation and histologic evidence of lung injury in murine models of ARDS.[3] Simvastatin reduced pulmonary and systemic inflammatory responses in a human model of ARDS induced by lipopolysaccharide inhalation.[4] In addition, in a small, single-center, randomized, placebo-controlled study involving patients with acute lung injury, simvastatin ameliorated nonpulmonary organ dysfunction and was safe.[5] That phase 2 study was not designed or powered to show an effect of simvastatin on clinical outcomes. The aim of this trial was to test the hypothesis that treatment with enteral simvastatin at a dose of 80 mg daily would improve clinical outcomes in patients with ARDS, regardless of the cause.

METHODS

STUDY DESIGN

Patients were adults recruited from general intensive care units (ICUs) in 40 hospitals in the United Kingdom and Ireland (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The study was approved by a national research ethics committee and by the research governance department at each study site in the United Kingdom and by the institutional research ethics committee at each study site in Ireland. The Northern Ireland Clinical Trials Unit coordinated the overall trial, with support from the Health Research Board Galway Clinical Research Facility for centers in Ireland. All the patients or their representatives provided written informed consent. Simvastatin was purchased for use in the study. The funders had no role in the study design, data acquisition, data analysis, or manuscript preparation.

The study design has been published previously,[6] and the study protocol, including the statistical analysis plan, is available at NEJM.org. The first three authors designed the study, and all the authors made a substantial contribution to the development of the study protocol. The first author wrote the first draft of the manuscript, and all the authors critically reviewed it for important intellectual content. All the authors approved the manuscript and made the decision to submit it for publication. The first and second authors vouch for the integrity, accuracy, and completeness of the data and analyses and for the fidelity of the study to the protocol.

PATIENTS

Patients were eligible if they were intubated and mechanically ventilated and were within 48 hours after the onset of ARDS as defined by a ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FIO_2) of 300 mm Hg or less, if bilateral pulmonary infiltrates consistent with pulmonary edema were present on chest radiography, and if there was no evidence of left atrial hypertension.[7] The main exclusion criteria are listed in Figure 1, and the full list is provided in the study protocol. The study protocol was amended to permit the enrollment of patients receiving macrolides 9 months into the study and to increase the eligibility criterion regarding the level of alanine aminotransferase or aspartate aminotransferase from more than 5 times the upper limit of the normal range to 8 times the upper limit of the normal range 15 months into the study.

STUDY MEDICATION

Randomization was performed with an automated, centralized, 24-hour randomization service. Patients were randomly assigned to the study groups in a 1:1 ratio with the use of permuted blocks and stratification according to study site and vasopressor requirement (yes vs. no).

Patients received once-daily simvastatin (at a dose of 80 mg) or identical placebo tablets enterally for up to 28 days. The first dose of the study drug was administered as soon as possible, ideally within 4 hours after randomization, and subsequent doses were given each morning starting on the following calendar day.

The study drug was continued until day 28, discharge from critical care (ICU or high-depen-

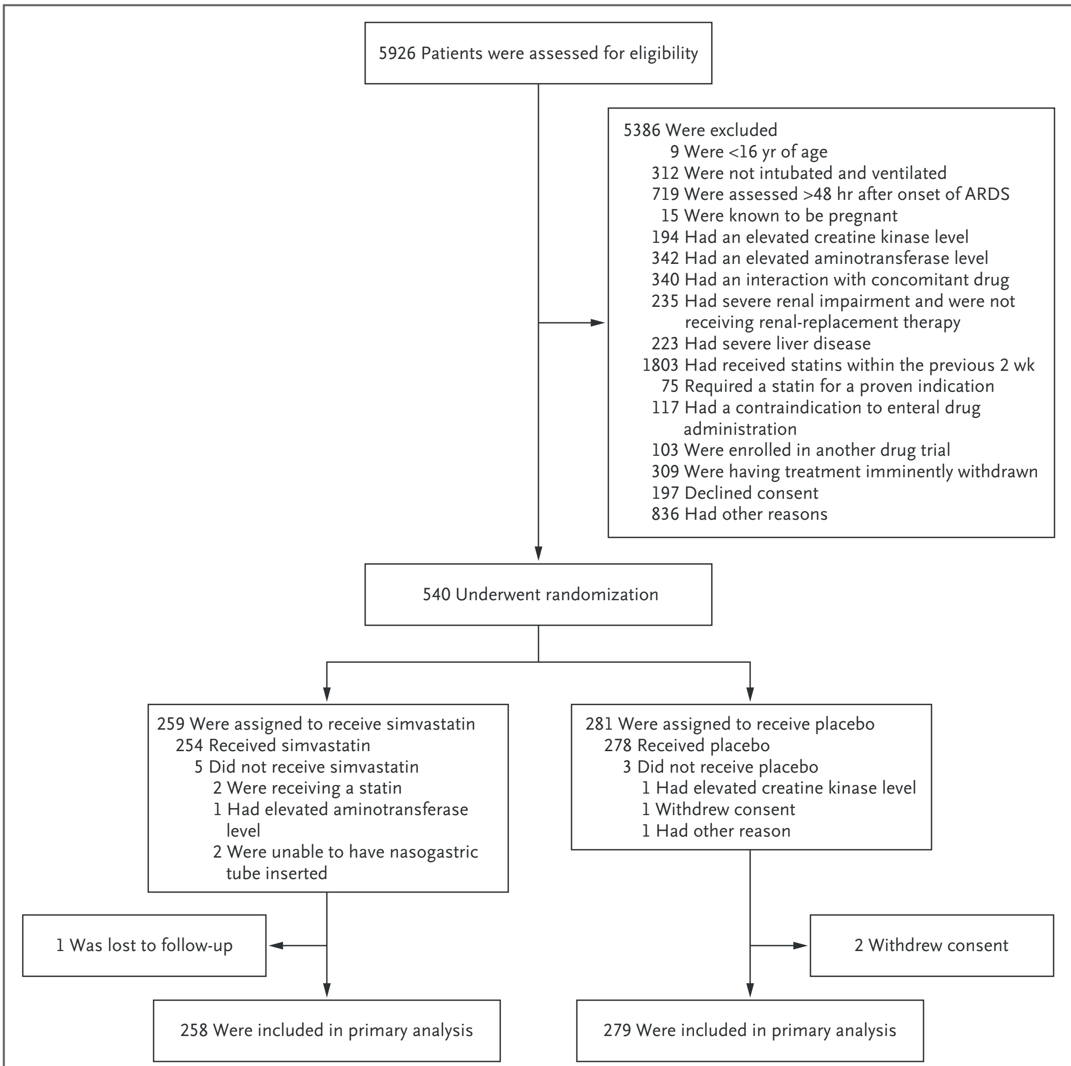

Figure 1. Screening, Randomization, and Follow-up of the Study Participants.
There may have been more than one reason for exclusion of a patient from the study. Severe liver disease was defined as a Child–Pugh score of more than 12 (on a scale from 5 to 15, with higher scores indicating more severe liver disease).

dency unit, in which patients requiring organ support but not intensive care or invasive mechanical ventilation are treated), death, discontinuation of active medical treatment, development of a clinical condition requiring immediate treatment with a statin, or withdrawal of the patient from the study. The study drug was stopped on safety grounds if the attending clinician determined that this was required, if the level of creatine kinase was more than 10 times the upper limit of the normal range, or if the level of alanine aminotransferase or aspartate aminotransferase was more than 8 times the upper limit of the normal range.

DATA COLLECTION AND PROCEDURES

At enrollment, each patient's demographic characteristics, ventilatory and physiological variables, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score at the time of admission were recorded. The cause of ARDS was identified by the treating clinician. For each day in the ICU, ventilatory and physiological variables as well as data regarding organ support, which were based on the Critical Care Minimum Data Set of the United Kingdom,[8] were recorded. Vital status at 28 days was recorded, but for patients who died, the cause of death was not recorded.

Participating ICUs were encouraged to use low-tidal-volume ventilation at 6 to 8 ml per kilogram of predicted body weight and to maintain a plateau pressure of less than 30 cm of water,[9] but no specific ventilator-management scheme was promulgated. All other treatment decisions were made by the patients' physicians.

OUTCOME MEASURES

The primary outcome measure was the number of ventilator-free days to day 28, which was defined as the number of days from the time of initiating unassisted breathing to day 28 after randomization.[6] A detailed definition of ventilator-free days is provided in the study protocol. Secondary outcomes included the change in the oxygenation index and the Sequential Organ Failure Assessment (SOFA) score[10] up to day 28, the number of days free of nonpulmonary organ failure to day 28, death from any cause within 28 days after randomization, death before discharge from critical care or the hospital, and safety. Scores on the SOFA range from 0 to 24, with higher scores indicating more severe disease. The score is calculated from the sum of six individual organ scores (each on a scale from 0 to 4), for the respiratory, cardiovascular, hepatic, coagulation, renal, and neurologic systems. Individual organ scores of less than 2 were used to indicate the absence of clinically significant organ dysfunction.

Additional secondary outcomes are listed in the study protocol. The plasma C-reactive protein level was measured by means of an immunoturbidimetric assay (Randox Testing Services) in blood obtained at baseline and on days 3 and 7.

STATISTICAL ANALYSIS

Sample-size assumptions were based on previously published data.[5,9] Assuming a mean (±SD) number of ventilator-free days of 12.7±10.6, we estimated that a sample of 524 patients would need to be enrolled in order for the study to have 80% power, at a two-tailed significance level of 0.05, to detect a mean between-group difference of 2.6 ventilator-free days. On the basis of data from the Pulmonary Artery Catheters in Management of Patients in Intensive Care (PAC-Man) trial, we estimated that the study-withdrawal rate would be 3%,[11] and we therefore calculated that the study required a total of 540 patients.

Analyses were performed on an intention-to-treat basis. Because ventilator-free days and days free of nonpulmonary organ failure are known to have a bimodal distribution, the data were initially analyzed by means of Student's t-test, with between-group differences presented as means and 95% confidence intervals. A secondary analysis of these outcome measures involving a bootstrapped t-test was also conducted to support the results of the primary analysis, as detailed in the statistical analysis plan (see the study protocol). For binary outcome measures, risk ratios and associated 95% confidence intervals were calculated. Time-to-event data are presented as Kaplan–Meier plots. The hazard ratios were calculated and the log-rank chi-square test was used to compare survival in the two study groups. All hazard ratios are presented with a two-sided 95% confidence interval. All reported P values are two-sided. Prespecified subgroup analyses were performed to determine whether the treatment effect was modified by age, vasopressor requirement, presence or absence of sepsis, or baseline C-reactive protein level. We used a statistical test of interaction for the subgroup analyses, and the results are reported with 99% confidence intervals.

RESULTS

PARTICIPANTS

Patients were recruited from December 21, 2010, until March 13, 2014. Of the 5926 patients who were assessed for eligibility, 540 (9%) underwent randomization. A total of 8 patients who did not fulfill the eligibility criteria underwent randomization in error, with 4 assigned to each group; these patients were included in the analysis. A total of 5 patients in the simvastatin group and 3 in the placebo group did not receive the assigned study drug. One patient, in the simvastatin group, was lost to follow-up. No data on the primary outcome were available for this patient in the simvastatin group and for 2 patients in the placebo group (Fig. 1).

The baseline characteristics of the patients at randomization were similar in the two study groups, except for a small but significant difference in the PaO_2:FIO_2 ratio, which was lower in the simvastatin group than in the placebo group

(Table 1). The main causes of ARDS were pneumonia and sepsis. At day 3, the tidal volume in the simvastatin group did not differ significantly from that in the placebo group; the mean difference was 0.05 ml per kilogram of predicted body weight (95% confidence interval [CI], −0.61 to 0.71; P=0.89).

Patients received the study drug for a mean of 10.2±7.1 days in the simvastatin group and 11.0±7.9 days in the placebo group (P=0.23). The most common reasons for discontinuation of the study drug were discharge from critical care, death, and an adverse event that was considered to be related to the study drug. A total of 5 patients assigned to simvastatin and 3 assigned to placebo received treatment with nontrial statins (Table S1 in the Supplementary Appendix).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Simvastatin (N=259)	Placebo (N=280)
Age — yr	53.2±16.1	54.4±16.7
Male sex — no. (%)	137 (52.9)	170 (60.7)
Sepsis — no. (%)	189 (73.0)	218 (77.9)
Cause of ARDS — no. (%)†		
Smoke or toxin inhalation	1 (0.4)	2 (0.7)
Gastric-content aspiration	21 (8.1)	29 (10.4)
Thoracic trauma	22 (8.5)	10 (3.6)
Pneumonia	161 (62.2)	154 (55.0)
Sepsis	106 (40.9)	118 (42.1)
Pancreatitis	5 (1.9)	17 (6.1)
Nonthoracic trauma	4 (1.5)	8 (2.9)
Other	30 (11.6)	36 (12.9)
APACHE II score‡	19.4±6.9	18.3±6.2
SOFA score§	8.5±3.2	8.8±2.9
Vasopressor-dependent — no. (%)	169 (65.3)	187 (66.8)
Lowest mean arterial pressure — mm Hg	65.4±9.3	64.9±8.4
Inspiratory plateau pressure — cm of water	23.6±6.07	23.6±6.03
Tidal volume — ml/kg of predicted body weight¶	8.1±2.8	8.1±2.6
Pa_{O_2}:F_{IO_2} — mm Hg	123.0±54.8	132.4±55.4
Oxygenation index — cm of water/mm Hg	15.0±11.6	14.9±11.9
Alanine aminotransferase — U/liter	45.5±47.1	45.8±43.2
Aspartate aminotransferase — U/liter	59.9±49.4	65.3±63.9
Creatine kinase — U/liter	327.2±499.3	298.3±487.7

* Plus–minus values are means ±SD. There were no significant differences in baseline characteristics between the study groups except for the ratio of partial pressure of arterial oxygen (Pa_{O_2}) to the fraction of inspired oxygen (F_{IO_2}) (P=0.049). For one patient who had been randomly assigned to the placebo group, baseline data were not available because consent was withdrawn, including permission to use the data collected to the point of study withdrawal. ARDS denotes acute respiratory distress syndrome.

† Patients may have had more than one cause of ARDS identified.

‡ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II scale range from 0 to 71, with higher scores indicating more severe disease.

§ Scores on the Sequential Organ Failure Assessment (SOFA) scale range from 0 to 24, with higher scores indicating more severe disease.[10]

¶ The predicted body weight was calculated as 2.3 kg for each inch of height above 60 in. (152 cm) added to a base weight of 50.0 kg for men or 45.5 kg for women.

OUTCOMES

The number of ventilator-free days did not differ significantly between the two study groups (12.6±9.9 days with simvastatin and 11.5±10.4 days with placebo; mean difference, 1.1 days [95% CI, −0.6 to 2.8]; P=0.21). There was also no significant between-group difference in the number of ventilator-free days after adjustment for the baseline Pa_{O_2}:F_{IO_2} ratio (mean difference, 1.4 days [95% CI, −0.3 to 3.2]; P=0.10).

The change from baseline to day 28 in the oxygenation index did not differ significantly between the two groups (Tables S2 and S3 in the Supplementary Appendix), nor did the SOFA score (Table S2 in the Supplementary Appendix). There were no significant differences in the number of days free of nonpulmonary organ failure or in mortality at 28 days. Mortality at ICU discharge or hospital discharge was also not significantly different between the two groups (Table 2). Among survivors, the mean duration of the ICU stay was 13.9±14.4 days in the simvastatin group and 14.4±13.3 days in the placebo group (mean difference, −0.5 days [95% CI, −3.2 to 2.2]; P=0.71); the mean duration of the hospital stay was 37.7±64.5 days and 35.4±31.1 days, respectively (mean difference, 2.3 days [95% CI, −8.0 to 12.6]; P=0.66). From randomization to day 28, there were no significant differences between the two groups in the probability of breathing without assistance or the probability of survival (Fig. 2).

Subgroup analyses did not suggest that the effects of simvastatin were modified by any of the variables investigated. There was no significant interaction between treatment and age (P=0.62), vasopressor requirement (P=0.17), presence or absence of sepsis (P=0.50), or baseline C-reactive protein level (P=0.77) (Table S4 in the Supplementary Appendix).

Table 2. Main Clinical Outcomes.*

Variable	Simvastatin	Placebo	Student's t-Test		Bootstrapped t-Test	
			Difference or Risk Ratio (95% CI)	P Value	Difference (95% CI)	P Value
Ventilator-free days, randomization to day 28†						
No. of patients in analysis	258	279				
No. of days (95% CI)	12.6±9.9 (11.3 to 13.8)	11.5±10.4 (10.2 to 12.7)	1.1 (−0.6 to 2.8)‡	0.21	1.1 (−0.7 to 2.8)	0.22
Days free of nonpulmonary organ failure, randomization to day 28§						
No. of patients in analysis	257	279				
No. of days (95% CI)	19.4±11.1 (18.0 to 20.8)	17.8±11.7 (16.4 to 19.2)	1.6 (−0.4 to 3.5)‡	0.11	1.6 (−0.3 to 3.5)	0.10
Death from any cause						
No. of patients in analysis	259	280				
Randomization to day 28 — no. (% [95% CI])	57 (22.0 [17.0 to 27.1])	75 (26.8 [(21.6 to 32.0])	0.8 (0.6 to 1.1)¶	0.23	—	—
Before discharge from critical care — no. (% [95% CI])‖	56 (21.6 [16.6 to 26.6])	70 (25.0 [19.9 to 30.0])	0.9 (0.6 to 1.2)¶	0.36	—	—
Before discharge from hospital — no. (% [95% CI])	67 (25.9 [20.5 to 31.2])	90 (32.1 [26.7 to 37.6])	0.8 (0.6 to 1.1)¶	0.13	—	—

* Plus–minus values are means ±SD.
† Ventilator-free days were defined as the number of days from the time of initiating unassisted breathing to day 28 after randomization (see the study protocol). Patients who died before day 28 were assigned 0 ventilator-free days.
‡ The data show the difference in the number of days.
§ The definition of days free of nonpulmonary organ failure is provided in the study protocol. Patients who died before day 28 were assigned 0 days free of nonpulmonary organ failure. Organs were considered to be failure-free after patients were discharged from the intensive care unit (ICU).
¶ The data show the risk ratio.
‖ Critical care was defined as care in the ICU or the high-dependency unit, in which patients requiring organ support but not intensive care or invasive mechanical ventilation are treated.

There were no significant differences between the simvastatin and placebo groups in the plasma C-reactive protein level at baseline, at day 3, or at day 7 (Table S6 in the Supplementary Appendix). There was also no significant between-group difference in the change in the C-reactive protein level from baseline to day 7 (Table S5 in the Supplementary Appendix).

SAFETY

Overall, adverse events related to the study drug were significantly more common in the simvastatin group than in the placebo group. The majority of the adverse events were related to elevated creatine kinase and hepatic aminotransferase levels. The numbers of serious adverse events (other than those reported as trial outcomes, such as death) were similar in the two groups (Table S7 in the Supplementary Appendix). There was no significant between-group difference in the proportion of patients with nonpulmonary organ dysfunction, as measured by a SOFA score of less than 2 for each organ (Table S8 in the Supplementary Appendix).

DISCUSSION

In this large, multicenter, double-blind, randomized, placebo-controlled clinical trial involving patients with ARDS, simvastatin, as compared with placebo, did not improve clinical outcomes. Simvastatin was associated with an increase in adverse events; however, there was no increase in serious adverse events. The recent Statins for Acutely Injured Lungs from Sepsis (SAILS) study, which involved patients with sepsis-associated ARDS, showed that rosuvastatin did not improve clinical outcomes, as compared with placebo, and was associated with fewer days free of renal and hepatic failure.[12] The population in our study was not limited to patients with sepsis-associated ARDS, and therefore, taken together, these data show little value in the routine use of statins in ARDS, regardless of the cause.

We used simvastatin at a dose of 80 mg on the basis of our previous data from clinical studies,[4,5] in which simvastatin improved surrogate outcomes and biologic mechanisms implicated in ARDS. The data from our current study and the SAILS trial show that neither a lipophilic statin (simvastatin) nor a hydrophilic statin (rosuvastatin) is effective in the treatment of ARDS. The high dose of simvastatin (80 mg) used in this trial was selected on the basis of our pilot data[5] as well as preclinical data[3] and observational studies.[13,14] Although we did not measure simvastatin concentrations, it is likely that an adequate simvastatin concentration was achieved, for several reasons. A prior study involving critically ill patients showed that simvastatin at a daily dose of 80 mg produced systemic drug concentrations that were in the high therapeutic range.[15] Furthermore, patients received simvastatin for a mean of 10 days. Finally, the increased incidence of expected statin-related adverse events suggests that sufficient simvastatin concentrations were achieved. The lack of an effect on the plasma C-reactive protein level suggests that statins cannot modulate inflammation sufficiently to provide a beneficial clinical effect in ARDS. It is possible that HMG-CoA reductase is already substantially inhibited, as reflected by the low cholesterol levels seen in critically ill patients.[16]

Although the incidence of treatment-related adverse events was higher in the simvastatin group than in the placebo group, the number of serious adverse events was similar in the two groups. The finding that the proportion of patients with no organ dysfunction, as measured by the SOFA score, was similar in the two groups over the course of the study is reassuring. The absence of serious harm with simvastatin in this

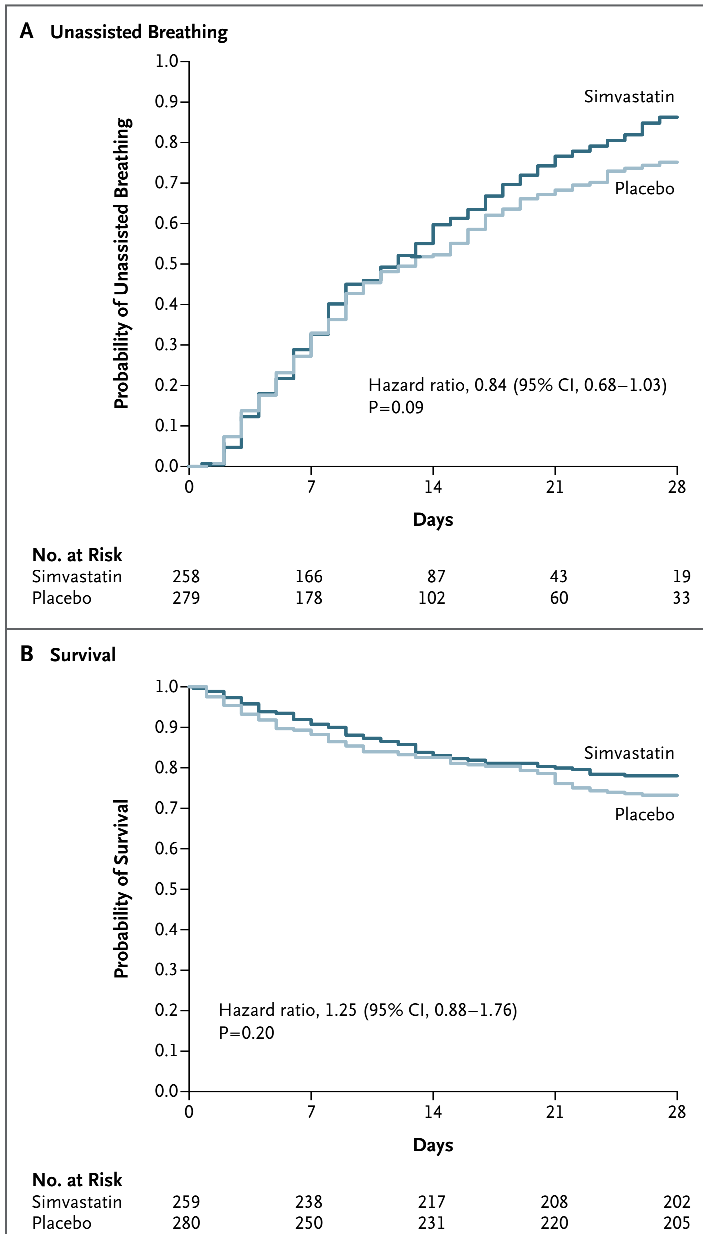

Figure 2. Probabilities of Survival and Breathing without Assistance from Randomization to Day 28, According to Whether Patients Received Simvastatin or Placebo.

Data regarding the primary outcome of unassisted breathing to day 28 were available for 258 patients in the simvastatin group and for 279 in the placebo group (Panel A). Data regarding survival at 28 days were available for 1 additional patient in each study group (Panel B): in the simvastatin group, we were able to determine survival status for 1 patient although we did not have primary-outcome data; and in the placebo group, 1 patient who withdrew from the study allowed the use of limited additional data including survival to be collected and used.

population provides reassurance with regard to the safety of statins being used for other proven indications in patients with ARDS.

We recruited a heterogeneous cohort of patients with ARDS due to any cause to ensure that our findings would be generalizable. Recent data have suggested that it may be possible to identify specific phenotypes within ARDS.[17] Future studies may identify a subpopulation of patients with ARDS who might have a greater response to simvastatin than was observed in our study.

Although we recommended best practice for the treatment of ARDS, including lung-protective ventilation, we did not record, in detail, all the aspects of clinical management. At randomization, the mean tidal volume was 8.1 ml per kilogram of predicted body weight, and it is possible that this level of tidal volume confounded the potential effects of simvastatin. However, this situation is unlikely, given the similar absence of benefit with rosuvastatin in the SAILS study, in which the mean tidal volumes were 6.6 and 6.8 ml per kilogram of predicted body weight in the two study groups.[12] Our data on tidal volume and plateau pressure are consistent with those observed in other clinical trials in critical care in which ventilation was not strictly defined in the protocol.[18]

Despite promising findings in early-phase clinical trials of statins for the treatment of ARDS, these findings have not been translated into improvements in patient-centered outcomes in large clinical trials. A recent randomized, controlled trial involving patients with ventilator-associated pneumonia showed that simvastatin did not improve clinical outcomes.[19] Data on efficacy that are based on surrogate outcomes must be considered with caution, given the absence of a clear correlation between surrogate and patient-centered outcomes. Surrogate outcomes that more closely track patient outcomes need to be identified.

In conclusion, our study showed that simvastatin, as compared with placebo, did not increase the number of ventilator-free days or improve other clinical outcomes in patients with ARDS, although it had an acceptable safety profile. These results do not support the use of simvastatin in the management of ARDS.

The views expressed in this article are those of the authors and not necessarily those of the Medical Research Council (MRC), National Health Service, National Institute for Health Research (NIHR), or Department of Health.

Supported by the U.K. Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership (08/99/08). The EME Programme is funded by the MRC and NIHR, with contributions from the Chief Scientist Office in Scotland, the National Institute for Social Care and Health Research in Wales, and the Health and Social Care (HSC) Research and Development Division, Public Health Agency for Northern Ireland; by a Health Research Award (HRA_POR-2010-131) from the Health Research Board (HRB), Dublin; and by additional funding from the HSC Research and Development Division, Public Health Agency for Northern Ireland, the Intensive Care Society of Ireland, and Revive.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank all the patients and their legal representatives who participated in the trial, all the research nurses and the pharmacists in all the participating centers, and the medical and nursing staff in participating centers who cared for patients and collected data; Rejina Verghis, Evie Gardner, and all the staff of the Northern Ireland Clinical Trials Unit for support in conducting the trial; Michael Faherty, Emma Deenihan, Veronica McInerney, and Lisa Daly from the HRB Galway Clinical Research Facility, Galway, Ireland, for help in conducting the study in Ireland; Margaret McFarland and the staff at Victoria Pharmaceuticals (Belfast, United Kingdom) for management of the study drugs; the staff of the Intensive Care National Audit and Research Centre (ICNARC) for providing APACHE II data for study sites that participate in the ICNARC Case Mix Programme; the staff of the Northern Ireland Clinical Research Network and the NIHR Clinical Research Network for help with patient recruitment and data acquisition; and the members of the U.K. Intensive Care Foundation for their overall assistance with the study.

REFERENCES

1. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med 2000;342:1334-49.
2. Terblanche M, Almog Y, Rosenson RS, Smith TS, Hackam DG. Statins: panacea for sepsis? Lancet Infect Dis 2006;6:242-8.
3. Jacobson JR, Barnard JW, Grigoryev DN, Ma S-F, Tuder RM, Garcia JGN. Simvastatin attenuates vascular leak and inflammation in murine inflammatory lung injury. Am J Physiol Lung Cell Mol Physiol 2005;288:L1026-L1032.
4. Shyamsundar M, McKeown ST, O'Kane CM, et al. Simvastatin decreases lipopolysaccharide-induced pulmonary inflammation in healthy volunteers. Am J Respir Crit Care Med 2009;179:1107-14.
5. Craig TR, Duffy MJ, Shyamsundar M, et al. A randomized clinical trial of hydroxymethylglutaryl- coenzyme A reductase inhibition for acute lung injury (The HARP Study). Am J Respir Crit Care Med 2011;183:620-6.
6. McAuley DF, Laffey JG, O'Kane CM, et al. Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in acute lung injury to reduce pulmonary dysfunction (HARP-2) trial: study protocol for a randomized controlled trial. Trials 2012;13:170.
7. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149:818-24.
8. Felton TW, Sander R, Al-Aloul M, Dark P, Bentley AM. Can a score derived from the Critical Care Minimum Data Set be used as a marker of organ dysfunction? — a pilot study. BMC Res Notes 2009;2:77.
9. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury

and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
10. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996; 22:707-10.
11. Harvey S, Harrison DA, Singer M, et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. Lancet 2005;366:472-7.
12. The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. N Engl J Med 2014;370:2191-200.
13. Al Harbi SA, Tamim HM, Arabi YM. Association between statin therapy and outcomes in critically ill patients: a nested cohort study. BMC Clin Pharmacol 2011; 11:12.
14. Shah AI, Sobnosky S, Shen AY, Jorgensen MB. High dose statins are associated with a reduced all cause mortality in patients hospitalized with sepsis and severe sepsis. Crit Care Med 2008; 36:A15. abstract.
15. Drage SM, Simpkin AL, Neuvonen PJ, Watkinson PJ, Barber VS, Young JD. Plasma simvastatin concentrations in critically ill septic patients. J Intensive Care Soc 2009;10:61.
16. Chiarla C, Giovannini I, Giuliante F, et al. Severe hypocholesterolemia in surgical patients, sepsis, and critical illness. J Crit Care 2010;25(2):361.e7-361.e12.
17. Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. Lancet Respir Med 2014;2:611-20.
18. Jaswal DS, Leung JM, Sun J, et al. Tidal volume and plateau pressure use for acute lung injury from 2000 to present: a systematic literature review. Crit Care Med 2014 August 5 (Epub ahead of print).
19. Papazian L, Roch A, Charles PE, et al. Effect of statin therapy on mortality in patients with ventilator-associated pneumonia: a randomized clinical trial. JAMA 2013;310:1692-700.