ORIGINAL ARTICLE

Simvastatin in Critically Ill Patients with Covid-19

The REMAP-CAP Investigators*

ABSTRACT

BACKGROUND

The efficacy of simvastatin in critically ill patients with coronavirus disease 2019 (Covid-19) is unclear.

METHODS

In an ongoing international, multifactorial, adaptive platform, randomized, controlled trial, we evaluated simvastatin (80 mg daily) as compared with no statin (control) in critically ill patients with Covid-19 who were not receiving statins at baseline. The primary outcome was respiratory and cardiovascular organ support–free days, assessed on an ordinal scale combining in-hospital death (assigned a value of –1) and days free of organ support through day 21 in survivors; the analyis used a Bayesian hierarchical ordinal model. The adaptive design included prespecified statistical stopping criteria for superiority (>99% posterior probability that the odds ratio was >1) and futility (>95% posterior probability that the odds ratio was <1.2).

RESULTS

Enrollment began on October 28, 2020. On January 8, 2023, enrollment was closed on the basis of a low anticipated likelihood that prespecified stopping criteria would be met as Covid-19 cases decreased. The final analysis included 2684 critically ill patients. The median number of organ support–free days was 11 (interquartile range, –1 to 17) in the simvastatin group and 7 (interquartile range, –1 to 16) in the control group; the posterior median adjusted odds ratio was 1.15 (95% credible interval, 0.98 to 1.34) for simvastatin as compared with control, yielding a 95.9% posterior probability of superiority. At 90 days, the hazard ratio for survival was 1.12 (95% credible interval, 0.95 to 1.32), yielding a 91.9% posterior probability of superiority of simvastatin. The results of secondary analyses were consistent with those of the primary analysis. Serious adverse events, such as elevated levels of liver enzymes and creatine kinase, were reported more frequently with simvastatin than with control.

CONCLUSIONS

Although recruitment was stopped because cases had decreased, among critically ill patients with Covid-19, simvastatin did not meet the prespecified criteria for superiority to control. (REMAP-CAP ClinicalTrials.gov number, NCT02735707.)

The members of the writing committee assume responsibility for the overall content and integrity of this article. The full names, academic degrees, and affiliations of the members of the writing committee are listed in the Appendix. Dr. McAuley can be contacted at d.f.mcauley@qub.ac.uk or at the Wellcome–Wolfson Institute for Experimental Medicine, Queen's University Belfast, 97 Lisburn Rd., Rm. 02.057, Belfast BT9 7AE, United Kingdom.

*A complete list of the REMAP-CAP investigators, committees, coordinating centers, and working group is provided in the Supplementary Appendix, available at NEJM.org.

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There have been more than 771 million cases and 6.9 million deaths in the coronavirus disease 2019 (Covid-19) pandemic, and the disease is now transitioning to an endemic respiratory infection.[1] Despite the availability of several effective treatments, mortality among severely ill patients hospitalized with Covid-19 remains considerable, and access to effective treatments for Covid-19, other than dexamethasone, is inequitable.[2,3]

Simvastatin is an inexpensive and widely available medication that is on the World Health Organization (WHO) list of essential medicines and is predominantly used for its lipid-lowering and cardioprotective properties.[4] Simvastatin also has antiinflammatory and immunomodulatory effects.[5,6] Simvastatin therapy reduces pulmonary and systemic inflammation in murine and human models of lung injury.[7-9] Although a trial of simvastatin involving patients with acute respiratory distress syndrome (ARDS) showed no benefit, subsequent post hoc analyses supported the hypothesis that simvastatin treatment may be beneficial in patients with a hyperinflammatory phenotype of ARDS.[10,11] Meta-analyses of observational studies involving patients with Covid-19 have shown an association between previous statin use and improved clinical outcomes, including reduced mortality.[12,13]

We investigated the effect of the initiation of simvastatin treatment on survival and organ support in hospitalized patients with Covid-19 not receiving statins at baseline in the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP). We report the results of the simvastatin domain of the trial; this domain was closed owing to operational futility as cases of Covid-19 decreased, which resulted in a low anticipated likelihood that the prespecified stopping criteria would be met.

Methods

Trial Design and Oversight

REMAP-CAP is an ongoing international platform trial designed to evaluate treatments for patients with severe pneumonia in both pandemic and nonpandemic contexts.[14-23] Its design has been reported previously.[24] This analysis includes patients who were enrolled in the Covid-19 pandemic stratum and underwent randomization in the domain comparing simvastatin with no statin (control); all the patients also received usual care. Patients eligible for the platform are assessed for eligibility to potentially undergo randomization to one or multiple interventions across multiple treatment domains.

The trial is managed by an international trial steering committee whose members are unaware of the trial-group assignments and by an independent data and safety monitoring board whose members are aware of the trial-group assignments. The trial has multiple international funders and sponsors. The funders had no role in designing the trial, analyzing the data, writing the manuscript, or making the decision to submit the manuscript for publication. The first draft of the manuscript was written by the first three and the last two members of the writing committee. The relevant research ethics committee in each jurisdiction approved the trial protocol. Informed consent was obtained before randomization from all the patients or their surrogates, or in a deferred fashion, in accordance with local legislation. The trial was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The writing committee vouches for the completeness and accuracy of the data and for the fidelity of the trial to the protocol and statistical analysis plan, which are available with the full text of this article at NEJM.org. There are no confidentiality agreements that preclude the investigators publishing the trial findings.

Patients

Adult patients (≥18 years of age) with either clinically suspected or microbiologically confirmed Covid-19 who were admitted to the hospital were enrolled. Patients were stratified according to disease severity state into critically ill ("severe state") and noncritically ill ("moderate state") groups at enrollment. Patients receiving respiratory organ support (high-flow nasal oxygen with a flow rate of ≥30 liters per minute and a fraction of inspired oxygen of ≥0.4 or noninvasive or invasive mechanical ventilation) or cardiovascular organ support (vasopressors or inotropes) in an intensive care unit (ICU) were classified as being critically ill. All other hospitalized patients were considered to be noncritically ill. It was prespecified that data from critically ill and noncritically ill adults would be analyzed and reported separately,

with Bayesian dynamic borrowing used to share information on the basis of the concordance of treatment effects in the two populations. Because only 184 noncritically ill patients were enrolled, results for these patients are provided in the Supplementary Appendix, available at NEJM.org. Exclusion criteria included recent or ongoing receipt of statin therapy or another medication that could not be coadministered with simvastatin, severe liver disease, a creatinine level of more than 2.26 mg per deciliter (200 μmol per liter) unless the patient was receiving renal-replacement therapy, and a duration of more than 48 hours since the start of organ support in an ICU. Detailed platform and domain-specific exclusion criteria are listed in the Supplementary Appendix.

RANDOMIZATION

Participants were randomly assigned with the use of a centralized algorithm to receive either simvastatin or no statin (control), starting with balanced assignment to simvastatin and control. Response-adaptive randomization was applied in a concealed fashion at each adaptive analysis with the use of allocation probabilities derived from the probability that each intervention was most favorable on the basis of the accumulating evidence within the trial. Simvastatin (80 mg) was administered daily by the enteral route. This high dose was informed by preclinical[7] and observational[25] studies. Simvastatin at a dose of 80 mg daily has been shown to be safe[10] and to reduce pulmonary inflammation and improve surrogate clinical outcomes.[26] Simvastatin was continued until the time of first ICU discharge or day 28, whichever came first. Simvastatin was dispensed by hospital pharmacies, and administration was open label.

PROCEDURES

Other aspects of patient care were provided according to the standard of care at each site. In addition to undergoing randomization in this domain, participants could be randomly assigned to receive other interventions within other domains, depending on the domains active at the site, patient eligibility, and consent (see the protocol and www.remapcap.org). Participants, treating clinicians, and outcome assessors were aware of the intervention assignments. Although clinical staff were aware of the intervention assignment of individual patients, neither they nor the members of the international trial steering committee were provided any information about aggregate patient outcomes.

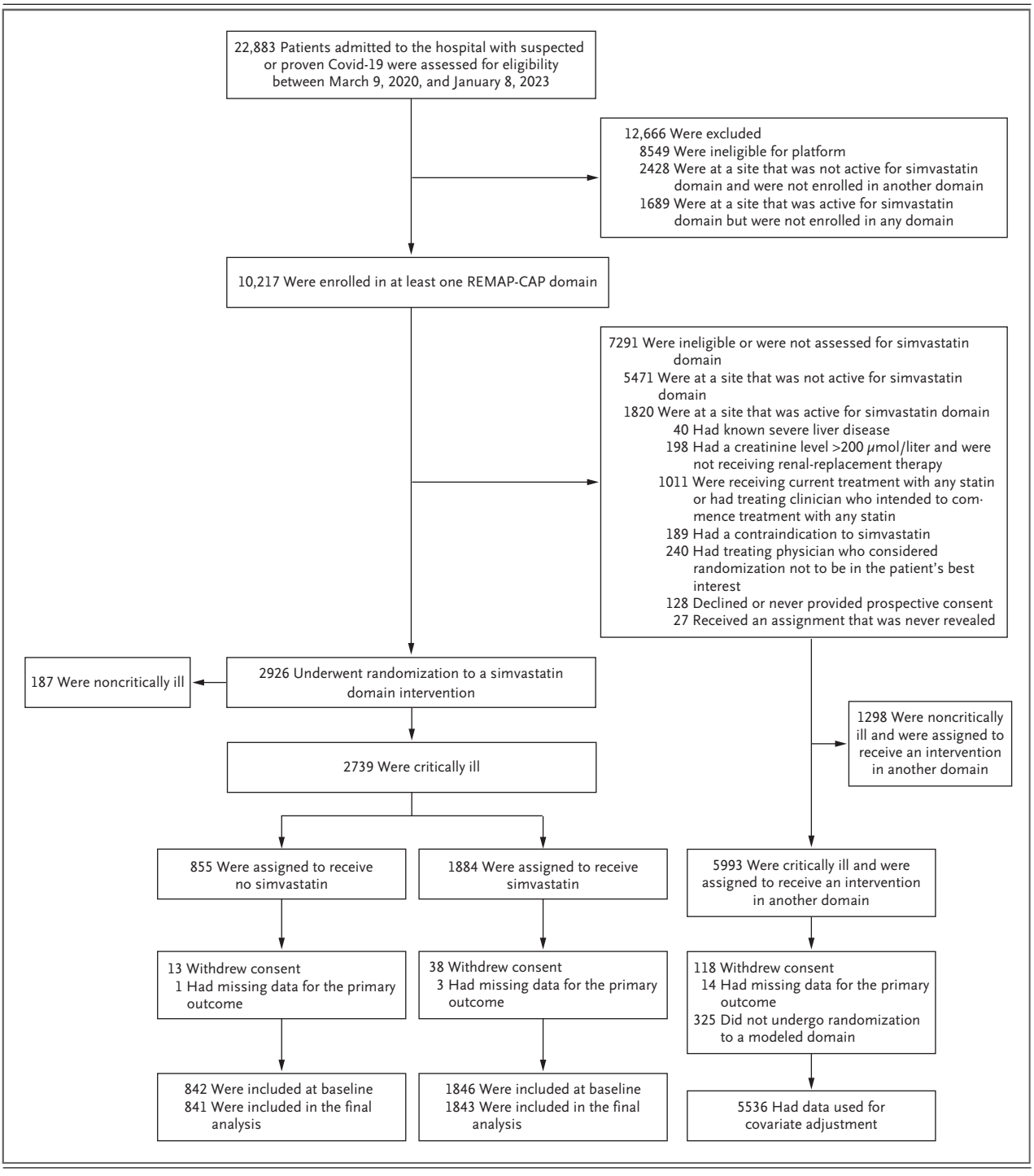
OUTCOME MEASURES

The primary outcome was organ support–free days up to day 21. In this composite ordinal outcome, all deaths within the hospital were assigned the worst outcome (–1). Among survivors, respiratory and cardiovascular organ support–free days were calculated up to day 21, such that a higher number represents faster recovery. Organ support was defined as it was for the inclusion criteria. This hospital-based outcome correlates with longer-term outcomes in REMAP-CAP.[22] Survival to hospital discharge was censored at 90 days. Secondary outcomes were prespecified in the statistical analysis plan and included survival to day 90, days free of vasopressors or inotropes, days free of respiratory support, duration of ICU and hospital stay, and modified WHO ordinal score at day 14. Site investigators reported serious adverse events that were considered to be at least possibly related to a trial procedure or intervention and serious adverse events of specific interest to the respective trial coordinating center and subsequently to the data and safety monitoring board and to national regulatory authorities, as required.

STATISTICAL ANALYSIS

REMAP-CAP uses a Bayesian design with no maximum sample size. Scheduled adaptive analyses are performed, and randomization continues until predefined statistical criteria for domain stopping are met. The primary analysis was generated from a Bayesian cumulative logistic model, which calculated posterior probability distributions of organ support–free days to day 21 (primary outcome) on the basis of evidence accumulated in the trial and prior probability distributions (the assumed previous knowledge). The primary model that was used to estimate the effect of simvastatin as compared with control in the domain was adjusted for location (site, nested within country), age (categorized into six groups), sex, domain eligibility, domain randomization, and time period (2-week calendar epochs) to account for rapid changes in clinical care and outcomes over time during the pandemic.

The model contained treatment effects for each intervention within each domain and prespecified



treatment-by-treatment interactions across domains. The model contained no terms for simvastatin interactions with other treatments. Distinct treatment effects of simvastatin as compared with control were estimated in critically ill and noncritically ill patients by nesting intervention effects in a hierarchical prior distribution, centered on an overall intervention effect estimated with a standard normal prior distribution on the log odds ratio (which induced a prior median on the odds ratio of 1.0 [95% credible interval, 0.14 to 7.10]). The posterior distributions for these effects

Figure 1 (facing page). Screening, Enrollment, Randomization, and Inclusion in Analysis.

A domain describes a specific set of competing interventions which, for the purposes of the platform, are mutually exclusive and exhaustive. Patients could meet more than one ineligibility criterion; full details are provided in the Supplementary Appendix. Contraindications to simvastatin are hypersensitivity, severe liver disease, a creatinine level of more than 2.26 mg per deciliter (200 μmol per liter) unless the patient was receiving renal-replacement therapy, current treatment with a medicine that cannot be coadministered with simvastatin, and current or planned treatment with any statin. Full details regarding noncritically ill patients are provided in the Supplementary Appendix. The primary analysis of interventions within the simvastatin domain is performed with a model that adjusts for patient factors and for assignment to interventions in other domains. To obtain the most reliable estimation of the effect of these patient factors and of other interventions on the primary outcome, all the patients who were enrolled in the critically ill coronavirus disease 2019 (Covid-19) cohort (for whom there is consent and follow-up) are included in the analytic model, but only concurrent controls in the simvastatin domain are used to estimate the effectiveness of simvastatin relative to control. REMAP-CAP denotes Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia.

were shrunk toward the overall effect to an extent reflective of their similarity (dynamic borrowing).

The primary analysis was conducted by the statistical analysis committee and involved all the patients with Covid-19 in the platform who had complete follow-up data on April 15, 2023. The model included additional patients enrolled in other domains of REMAP-CAP to provide robust estimation of covariate effects,[24] but all control participants in the simvastatin domain underwent randomization concurrently. Data were analyzed according to the group to which the patient was assigned. Missing outcomes were not imputed and were excluded from the analysis.

The model was fit with the use of a Markov chain Monte Carlo algorithm that drew iteratively (20,000 draws) from the joint posterior distribution. Posterior odds ratios with 95% credible intervals were calculated, along with the posterior probability that simvastatin was superior to control (odds ratio of >1), harmful (odds ratio of <1), and futile (odds ratio of <1.2). For the primary outcome, an ordinal scale with 23 categories (worst category, death; best category, alive with 21 days free of organ support), the odds ratio denotes the relative odds of being in the category >i as compared with ≤i, for i equals –1 to 21. The predefined statistical criteria for ceasing enrollment and reporting a treatment effect were superiority (>99% posterior probability that the odds ratio was >1) and futility (>95% posterior probability that the odds ratio was <1.2).

Sensitivity and secondary analyses were performed with the use of data only from the simvastatin domain and other completed domains. Details of additional sensitivity analyses that involved different analysis populations, as well as prespecified subgroup analyses, are provided in the statistical analysis plan. Data management was performed and data summaries were created with the use of R software, version 4.1.2; the primary analysis was performed with R software, version 4.3.1 (2023-06-16), with the use of the rstan package, version 2.21.0.

RESULTS

ENROLLMENT AND RANDOMIZATION

Enrollment began on October 28, 2020. On January 8, 2023, enrollment was closed by the international trial steering committee on the basis of a low anticipated likelihood that one of the prespecified stopping criteria would be met owing to low recruitment, because the number of Covid-19 cases had decreased. This decision was made before unblinding and was based on simulations (see the protocol) that considered the amount of time needed to complete enrollment, on the basis of recent recruitment rates, in order to reach a prespecified threshold under the assumption of a range of plausible treatment effects.

A total of 2739 critically ill patients and 187 noncritically ill patients were enrolled in the simvastatin domain at 141 sites across 13 countries (Fig. 1). A total of 51 critically ill patients and 3 noncritically ill patients subsequently withdrew consent, and 4 patients had missing data for the primary outcome. The population for this analysis consists of 2684 critically ill patients. Data for 184 noncritically ill patients are reported in the Supplementary Appendix because numbers are too small to allow for meaningful interpretation. Accrual summaries and response-adaptive randomization proportions over time are provided in Figure S1 and Table S1 in the Supplementary Appendix. Covariate effects were estimated on the basis of data from 8220 critically ill patients enrolled across all REMAP-CAP domains.

Table 1. Baseline Characteristics of the Patients in the Simvastatin Domain.*

Characteristic	Simvastatin (N=1846)	Control (N=842)
Median age (IQR) — yr	56.0 (45.0–65.0)	57.0 (48.0–64.0)
Female sex — no. (%)	617 (33.4)	290 (34.4)
Race or ethnic group — no./total no. (%)†		
Asian	113/1276 (8.9)	67/698 (9.6)
Black	55/1276 (4.3)	29/698 (4.2)
Mixed	20/1276 (1.6)	18/698 (2.6)
White	938/1276 (73.5)	545/698 (78.1)
Other	150/1276 (11.8)	39/698 (5.6)
Median body-mass index (IQR)‡	31.0 (26.6–37.1)	31.6 (26.8–37.6)
Median APACHE II score (IQR)§	11.0 (7.0–17.0)	12.0 (8.0–18.0)
Median Clinical Frailty Score (IQR)¶	2.0 (2.0–3.0)	2.0 (2.0–3.0)
Confirmed SARS-CoV-2 infection — no./total no. (%)‖	1636/1674 (97.7)	749/774 (96.8)
Preexisting condition — no./total no. (%)**		
Diabetes	287/1841 (15.6)	129/840 (15.4)
Respiratory disease	357/1841 (19.4)	170/840 (20.2)
Kidney disease	65/1710 (3.8)	36/776 (4.6)
Severe cardiovascular disease	97/1840 (5.3)	27/840 (3.2)
Any immunosuppressive condition	109/1841 (5.9)	30/840 (3.6)
Median time to enrollment (IQR)		
From hospital admission — days	1.8 (0.9–3.7)	1.9 (1.0–3.7)
From ICU admission — hr	17.5 (9.0–23.8)	17.1 (10.1–22.7)
Acute respiratory support — no./total no. (%)		
Invasive mechanical ventilation	628/1841 (34.1)	303/840 (36.1)
Noninvasive ventilation only	606/1841 (32.9)	301/840 (35.8)
High-flow nasal cannula	605/1841 (32.9)	236/840 (28.1)
None or supplemental oxygen	2/1841 (0.1)	0/840
Median Pao_2:Fio_2 ratio (IQR)††	120.0 (90.0–162.0)	115.0 (88.0–153.0)
Median systolic blood pressure (IQR) — mm Hg‡‡	124.0 (110.0–140.0)	125.0 (110.0–142.0)
Vasopressor support — no./total no. (%)	332/1841 (18.0)	171/840 (20.4)
Median laboratory values (IQR)§§		
C-reactive protein — μg/ml	101.0 (50.8–171.1)	112.6 (60.0–184.0)
Lactate — mmol/liter	1.3 (1.0–1.7)	1.3 (1.0–1.7)
Creatinine — mg/dl	0.8 (0.6–1.0)	0.8 (0.6–1.0)
Estimated GFR — ml/min/1.73 m^2	101.5 (82.0–112.6)	100.8 (81.8–110.2)
Concomitant therapies — no./total no. (%)¶¶		
Remdesivir	385/1837 (21.0)	218/840 (26.0)
Glucocorticoids	1778/1839 (96.7)	827/840 (98.5)
Tocilizumab or sarilumab	977/1838 (53.2)	426/840 (50.7)

Table 1. (Continued.)

Characteristic	Simvastatin (N=1846)	Control (N=842)
Continent — no. (%)		
Asia	60 (3.3)	19 (2.3)
Australia	211 (11.4)	28 (3.3)
Europe	1507 (81.6)	781 (92.8)
North America	68 (3.7)	14 (1.7)

* Percentages may not total 100 because of rounding. FIO_2 denotes the fraction of inspired oxygen, ICU intensive care unit, IQR interquartile range, and PaO_2 the partial pressure of arterial oxygen.
† Data collection was not approved in Canada and continental Europe. "Other" includes "declined" and "other ethnic group." Patients (or their surrogates) reported their race or ethnic group according to fixed categories appropriate to their region. "Declined" does not simply represent missing data. A patient may decline to provide their race at the time of registration, or the person performing the registration may decline to ask the patient to clarify race at the time of registration.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were available for 1622 patients in the simvastatin group and 724 patients in the control group.
§ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating greater severity of illness. Data were available for 1833 patients in the simvastatin group and 832 patients in the control group.
¶ The Clinical Frailty Score is a global measure of fitness and frailty, with increasing scores — ranging from 1 (very fit) to 9 (terminally ill) — reflecting worse fitness and increasing frailty. Data were available for 1837 patients in the simvastatin group and 838 patients in the control group.
‖ Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was confirmed by a respiratory tract polymerase-chain-reaction test.
** Kidney disease was determined from the most recent serum creatinine level before the current hospital admission, except in patients who were receiving dialysis. Abnormal kidney function was defined as a creatinine level of 1.5 mg per deciliter or more (≥130 μmol per liter) for men or 1.1 mg per deciliter or more (≥100 μmol per liter) for women not previously receiving dialysis. Cardiovascular disease was defined as New York Heart Association class IV symptoms. Immunosuppression was defined by the receipt of recent chemotherapy, radiation, or high-dose or long-term glucocorticoid treatment or by the presence of immunosuppressive disease.
†† Data were available for 1708 patients in the simvastatin group and 789 patients in the control group.
‡‡ Data were available for 1805 patients in the simvastatin group and 816 patients in the control group.
§§ Laboratory results were available when captured for clinical care. For C-reactive protein, data were available for 1557 patients in the simvastatin group and 741 patients in the control group. For lactate, data were available for 1675 patients in the simvastatin group and 774 patients in the control group. For creatinine and estimated glomerular filtration rate (GFR), data were available for 1822 patients in the simvastatin group and 833 patients in the control group.
¶¶ These therapies were received before, or within 48 hours after, randomization.

PATIENTS

Baseline characteristics were balanced between the treatment groups (Table 1). At the time of randomization, all but two patients were receiving respiratory support, including high-flow nasal oxygen (31.4%), noninvasive mechanical ventilation (33.8%), and invasive mechanical ventilation (34.7%). At enrollment or within the 48 hours after enrollment, 97.2% of the patients were receiving concomitant glucocorticoids, and 52.4% were receiving concomitant tocilizumab or sarilumab; the use of these therapies was balanced between the treatment groups.

PRIMARY OUTCOME

The median number of organ support–free days was 11 (interquartile range, –1 to 17) in the simvastatin group and 7 (interquartile range, –1 to 16) in the control group. The median adjusted odds ratio (primary outcome) was 1.15 (95% credible interval, 0.98 to 1.34) for simvastatin, yielding a 95.9% posterior probability of superiority of simvastatin to control (Table 2 and Fig. 2). This probability was below the prespecified 99% threshold, and no prespecified statistical criteria were met. The results were generally consistent in sensitivity analyses and across time periods (Tables S2 and S3).

Table 2. Primary and Secondary Outcomes.*

Outcome or Analysis	Simvastatin (N=1846)	Control (N=842)
Organ support–free days		
No. of patients evaluated	1843	841
Median (IQR)	11 (–1 to 17)	7 (–1 to 16)
Median adjusted odds ratio (95% credible interval)	1.15 (0.98 to 1.34)	1
Probability of superiority to control — %	95.9	—
In-hospital survival		
No. of patients/total no. (%)	1352/1843 (73.4)	589/841 (70.0)
Median adjusted odds ratio (95% credible interval)	1.04 (0.85 to 1.27)	1
Probability of superiority to control — %	64.4	—
90-Day survival		
Median adjusted hazard ratio (95% credible interval)	1.12 (0.95 to 1.32)	1
Probability of superiority to control — %	91.9	—
Progression to invasive mechanical ventilation, ECMO, or death		
No. of patients evaluated†	1218	539
Progression — no. (%)	451 (37.0)	229 (42.5)
No progression — no. (%)	767 (63.0)	310 (57.5)
Median adjusted odds ratio (95% credible interval)	1.23 (0.98 to 1.55)	1
Probability of superiority to control — %	96.4	—
Respiratory support–free days		
No. of patients evaluated	1845	842
Median (IQR)	18 (–1 to 24)	14 (–1 to 23)
Median adjusted odds ratio (95% credible interval)	1.16 (1.00 to 1.35)	1
Probability of superiority to control — %	97.4	—
Vasopressor or inotrope support–free days		
Median (IQR)	27 (–1 to 28)	26 (–1 to 28)
Median adjusted odds ratio (95% credible interval)	1.13 (0.96 to 1.34)	1
Probability of superiority to control — %	93.1	—
Score on modified WHO scale at 14 days‡		
Median (IQR)	4 (2 to 7)	5 (2 to 7)
Median adjusted odds ratio (95% credible interval)	1.23 (1.06 to 1.43)	1
Probability of superiority to control — %	99.6	—
ICU length of stay		
Median duration — days	11	14
Median adjusted hazard ratio (95% credible interval)	1.08 (0.97 to 1.20)	1
Probability of superiority to control — %	93.0	—
Hospital length of stay		
Median duration — days	22	28
Median adjusted hazard ratio (95% credible interval)	1.10 (0.99 to 1.22)	1
Probability of superiority to control — %	95.7	—

Table 2. (Continued.)

Outcome or Analysis	Simvastatin (N=1846)	Control (N=842)
Serious adverse events		
No. of patients (%)	57 (3.1)	17 (2.0)
Median adjusted odds ratio (95% credible interval)	1.56 (1.13 to 2.14)	1
Probability of inferiority to control — %	99.6	—

* The primary analysis of organ support–free days and in-hospital death used data from all the patients enrolled in the trial who met coronavirus disease 2019 (Covid-19) severe state criteria and who underwent randomization within at least one domain (8220 patients), with adjustment for age, sex, time period, site, domain eligibility, and domain assignment. Secondary analyses were restricted to 7374 patients, with adjustment for age, sex, time period, site, domain eligibility, and domain assignment. Definitions of outcomes are provided in the trial protocol. All models, except the analysis of serious adverse events, are structured such that a higher odds ratio or hazard ratio is favorable for simvastatin. ECMO denotes extracorporeal membrane oxygenation.

† The analysis was restricted to patients who were free of invasive mechanical ventilation at baseline.

‡ Scores on the modified World Health Organization (WHO) 8-point scale are as follows: 0, 1, or 2 indicates no longer hospitalized, 3 hospitalized without oxygen therapy, 4 hospitalized with oxygen by mask or nasal cannula, 5 receiving noninvasive ventilation or high-flow nasal oxygen, 6 receiving intubation and mechanical ventilation, 7 receiving mechanical ventilation and additional organ support (vasopressor, renal-replacement therapy, or ECMO), and 8 deceased.

SECONDARY OUTCOMES

Results for the secondary outcomes are shown in Table 2. Survival to hospital discharge occurred in 1352 of 1843 patients (73.4%) in the simvastatin group and 589 of 841 patients (70.0%) in the control group, yielding an adjusted odds ratio of 1.04 (95% credible interval, 0.85 to 1.27) with a 64.4% posterior probability of superiority of simvastatin to control. Death within 90 days occurred in 504 of 1835 patients (27.5%) in the simvastatin group and 257 of 837 patients (30.7%) in the control group, excluding 8 and 4 patients, respectively, with censored data. The analysis of 90-day survival yielded an adjusted hazard ratio of 1.12 (95% credible interval, 0.95 to 1.32) with a 91.9% posterior probability of superiority of simvastatin to control (Fig. 3). The findings were similar for other secondary outcomes (Table 2, Fig. 3, and Fig. S2).

Results of the prespecified subgroup analyses are shown in Figure S3. It was not possible to perform the planned subgroup analysis according to the two prespecified ARDS inflammatory phenotypes[11,27] because the vast majority of patients in the trial population (98.8%) were categorized as having one phenotype. The findings were consistent both in patients receiving interleukin-6 receptor antagonist therapy and in patients not receiving such therapy (Table S4).

Serious adverse events were reported in 57 of 1846 patients (3.1%) in the simvastatin group and 17 of 842 patients (2.0%) in the control group (Table 2 and Table S5). A total of 13 patients (0.7%) in the simvastatin group were reported to have elevated aminotransferase levels; in 9 of these patients, the adverse event was assessed as being related to simvastatin, and in 8 patients, treatment was either temporarily or permanently discontinued. A total of 13 patients (0.7%) in the simvastatin group were reported to have clinically significant increases in creatine kinase levels; in all of these patients, the adverse event was assessed as being related to simvastatin, and in 12 patients, treatment was either temporarily or permanently discontinued. One additional serious adverse event, an episode of acute pancreatitis, was assessed as being related to simvastatin, and treatment was discontinued. All other serious adverse events were assessed as being not related to simvastatin (Table S5).

DISCUSSION

In this domain of an adaptive platform trial, we found a 95.9% probability that the initiation of simvastatin therapy was superior to standard care with respect to the primary outcome, a composite of organ support–free days and death, among critically ill patients with Covid-19. This probability did not meet the prespecified 99% threshold. The association of simvastatin with outcomes appeared consistent among secondary and sensitivity analyses.

Our findings align with observational data

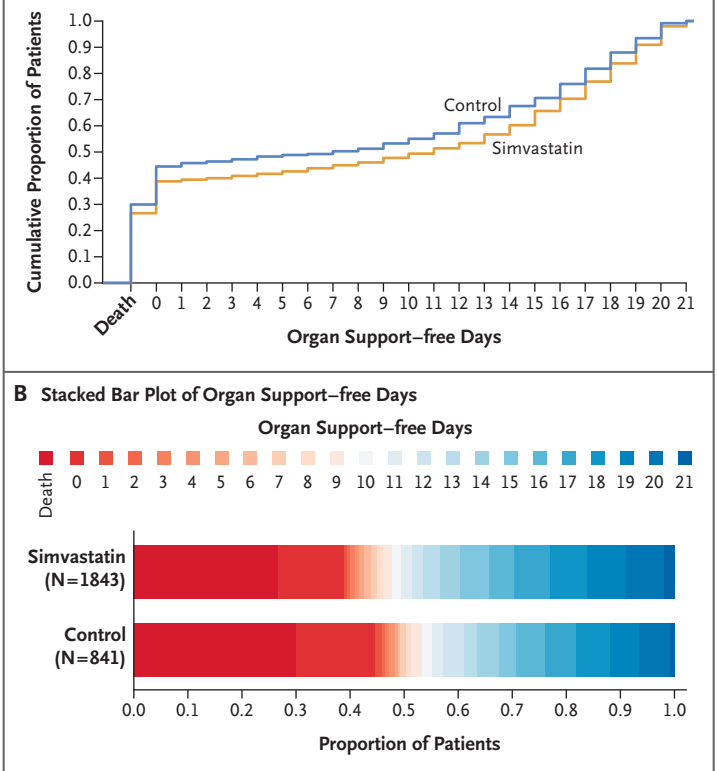


Figure 2. Distribution of Organ Support–free Days.

Panel A shows the cumulative proportion of patients for each intervention group according to day, with death listed first. Curves that rise more gradually indicate a more favorable distribution of the number of days alive and free of organ support. The height of each curve at the point labeled "Death" indicates the in-hospital mortality for each intervention. The height of each curve at any point indicates the proportion of patients who had that number of organ support–free days or fewer (e.g., the height at day 10 indicates the proportion of patients with ≤10 organ support–free days). The difference in height of the two curves at any point represents the difference in the percentile in the distribution of organ support–free days associated with that number of days alive and free of organ support. Panel B shows organ support–free days as horizontally stacked proportions according to intervention group. Red represents worse outcomes, and blue represents better outcomes. The median adjusted odds ratio from the primary analysis, which used a Bayesian cumulative logistic model, was 1.15 (95% credible interval, 0.98 to 1.34) for simvastatin as compared with control, yielding a 95.9% posterior probability of superiority.

that antecedent statin use is associated with improved Covid-19 outcomes.[12] A meta-analysis of published randomized, controlled trials of statins begun as treatment for Covid-19 showed a risk ratio for death from any cause (statins vs. controls) of 0.92 (95% confidence interval, 0.75 to 1.13), the point estimate of which is similar to the effect size seen in REMAP-CAP.[28] Our trial is larger than the seven previous randomized, controlled trials of statin therapy in Covid-19 combined, which enrolled 1830 participants in total. It is plausible that smaller trials were underpowered to detect a modest beneficial effect.

The incidence of serious adverse events, particularly elevated levels of creatine kinase and liver aminotransferases, was higher in the simvastatin group than in the control group. This finding may in part be due to selective reporting of adverse events in the simvastatin group in an open-label design, because serious adverse events were reported to be similar to those associated with placebo in previous blinded trials investigating statins in critically ill patients.[10,29] Regardless, this finding underlines the importance of regular monitoring of creatine kinase levels and liver function in critically ill patients treated with simvastatin and of discontinuation of treatment in the context of clinically significant increases in levels of creatine kinase and liver aminotransferases.

A subgroup analysis suggested a larger association of simvastatin with organ support–free days in critically ill patients who were not receiving mechanical ventilation at randomization. In this subgroup of patients, 37.0% of those in the simvastatin group and 42.5% of those in the control group had progression to invasive mechanical ventilation, extracorporeal membrane oxygenation, or death.

It was not possible to undertake the planned subgroup analysis with respect to the ARDS phenotypes labeled "hyperinflammatory" and "hypoinflammatory."[11] Early data indicated that the hyperinflammatory phenotype could be identified in approximately 20% of patients with Covid-19–related ARDS.[30] However, subsequent studies have shown that the levels of the main circulating biomarkers that are used to classify the hyperinflammatory phenotype are substantially lower in patients with Covid-19–related ARDS than in those with non–Covid-19–related ARDS.[31,32] Furthermore, a recent study, which used serum protein biomarkers to classify the phenotypes, showed that the prevalence of the hyperinflammatory phenotype among patients with Covid-19 was similar to what we observed in our trial.[33]

The low prevalence of the hyperinflammatory phenotype may relate to the increased use of glucocorticoids and immunomodulatory agents to treat Covid-19 as well as to methodologic factors, such as phenotype categorization based

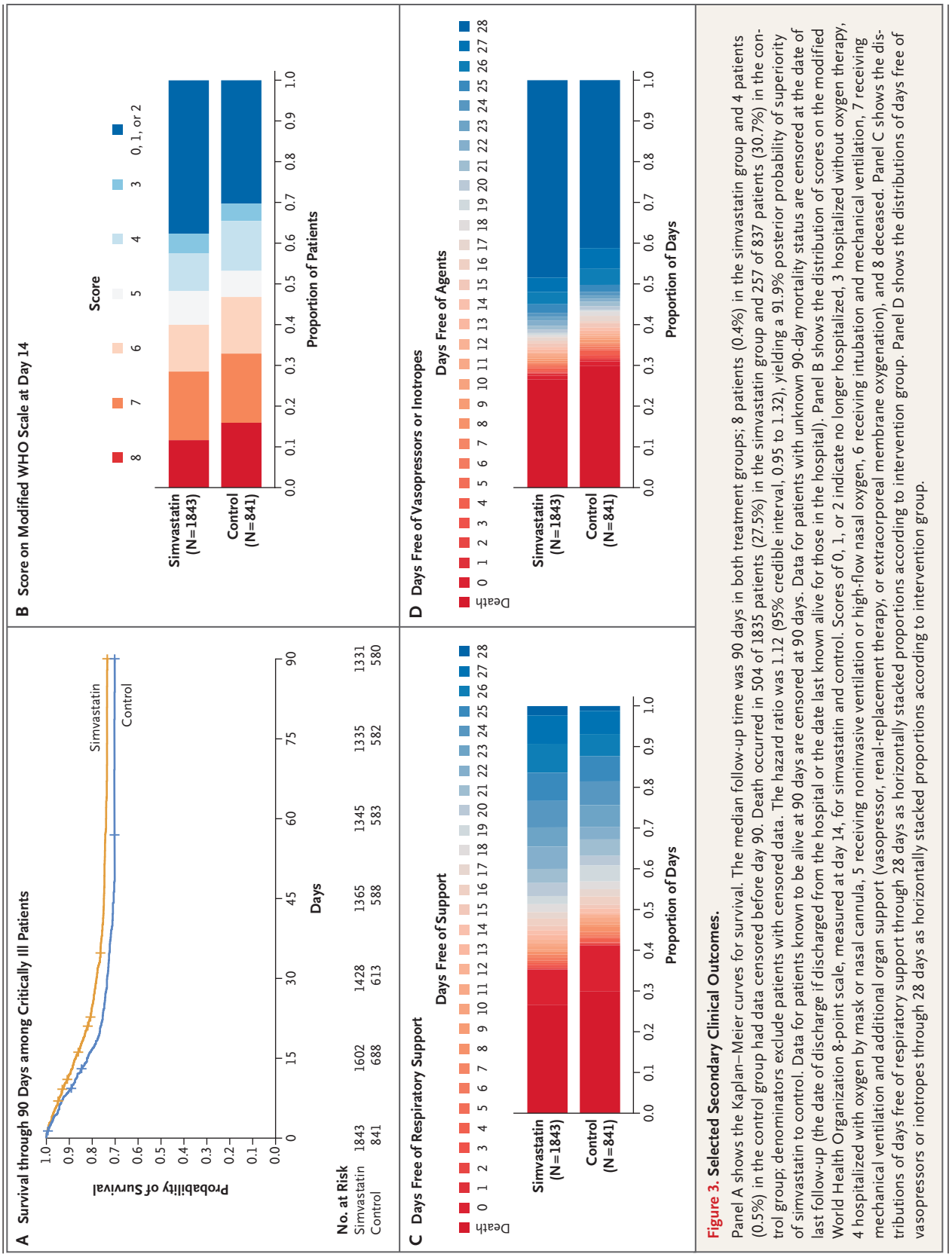


Figure 3. Selected Secondary Clinical Outcomes.

Panel A shows the Kaplan–Meier curves for survival. The median follow-up time was 90 days in both treatment groups; 8 patients (0.4%) in the simvastatin group and 4 patients (0.5%) in the control group had data censored before day 90. Death occurred in 504 of 1835 patients (27.5%) in the simvastatin group and 257 of 837 patients (30.7%) in the control group; denominators exclude patients with censored data. The hazard ratio was 1.12 (95% credible interval, 0.95 to 1.32), yielding a 91.9% posterior probability of superiority of simvastatin to control. Data for patients known to be alive at 90 days are censored at 90 days. Data for patients with unknown 90-day mortality status are censored at the date of last follow-up (the date of discharge if discharged from the hospital or the date last known alive for those in the hospital). Panel B shows the distribution of scores on the modified World Health Organization 8-point scale, measured at day 14, for simvastatin and control. Scores of 0, 1, or 2 indicate no longer hospitalized, 3 hospitalized without oxygen therapy, 4 hospitalized with oxygen by mask or nasal cannula, 5 receiving noninvasive ventilation or high-flow nasal oxygen, 6 receiving intubation and mechanical ventilation, 7 receiving mechanical ventilation and additional organ support (vasopressor, renal-replacement therapy, or extracorporeal membrane oxygenation), and 8 deceased. Panel C shows the distributions of days free of respiratory support through 28 days as horizontally stacked proportions according to intervention group. Panel D shows the distributions of days free of vasopressors or inotropes through 28 days as horizontally stacked proportions according to intervention group.

on the worst variable in a 24-hour period, in contrast with the use of data from a fixed daily time point, as in our trial. Markers of systemic inflammation (C-reactive protein [CRP] and ferritin) were elevated in our trial, and subgroup analyses suggested a larger association of simvastatin with organ support–free days in patients with higher CRP and ferritin levels. It is recognized that CRP levels are a poor discriminator of inflammatory phenotype in ARDS, with similarly high values observed in patients with the hypoinflammatory or hyperinflammatory phenotype.[34] This finding suggests that the mechanisms causing increased CRP and ferritin levels are different from the mechanisms that drive the hyperinflammatory phenotype in patients with Covid-19. More work will be required to assess potential heterogeneity of the treatment effect to guide simvastatin treatment on the basis of disease severity and inflammatory biomarkers.[35]

Strengths of our trial include the study of a repurposed, inexpensive intervention that is widely available, as well as recruitment of a population receiving contemporary standard care that included glucocorticoids in 97.2% of patients and interleukin-6 receptor antagonists in 52.4% of patients, who were recruited in ICUs in a diverse range of health settings across the globe. It is important to note that the treatment effect appeared to be present with or without treatment with interleukin-6 blockade. As a result, these findings are broadly applicable to critically ill patients with severe Covid-19 globally (Table S8).

The open-label design of the trial represents a potential limitation, although the primary outcome, which incorporated survival and receipt of organ support, was selected to minimize bias and to function across a spectrum of illness severity. In patients who were sicker, clinicians may have been concerned that enteral absorption of drugs would be reduced, which could have introduced bias in patient selection, even though failure of enteral absorption was not an exclusion criterion for randomization in this domain. In sensitivity analyses in which other patients who did not undergo randomization in the simvastatin domain were excluded from the analytic model, the results were consistent with those of the primary analysis. Although the 95.9% posterior probability of efficacy is high, the trial was stopped for operational futility before reaching a prespecified stopping trigger. In response to decreasing rates of Covid-19 and fewer critical care admissions, and in light of simulations conducted by investigators who were unaware of the trial-group assignments, the international trial steering committee chose to close recruitment and report results to inform clinicians rather than continue and possibly never reach the prespecified criteria. These criteria were chosen to provide quick answers about large treatment effects during the pandemic and may have been too insensitive to more modest but still important effects. Response-adaptive randomization allowed blinded randomization probabilities to be modified as evidence about treatment effects was accrued throughout the trial. Response-adaptive randomization resulted in more patients being assigned to simvastatin than to control, and this may have reduced the ability to reach a statistical trigger because of low numbers enrolled in the control group. This observation highlights potential simultaneous advantages and disadvantages of allowing response-adaptive randomization ratios to deviate too far from balanced randomization in trials with two groups; more patients in the trial receive the favorable intervention, but this may lengthen trial duration.

Among critically ill patients with Covid-19, simvastatin did not meet the prespecified criteria for superiority to control.

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APPENDIX

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