# Simvastatin in critically ill patients with Covid-19

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**Abstract**

[286/250 words]

*Background*:

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

*Methods*:

In an ongoing international, randomized, multifactorial, adaptive platform trial, we evaluated simvastatin 80mg daily compared to 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, an ordinal scale combining in-hospital death (assigned a label of −1) and days free of organ support through day 21 in survivors, analyzed using a Bayesian hierarchical ordinal model. The adaptive design prespecified statistical stopping criteria for treatment superiority (>99% posterior probability the odds ratio was >1) and futility (>95% posterior probability the odds ratio was <1.2).

*Results*:

Enrollment began on October 28, 2020. On January 8, 2023, enrollment closed based on low anticipated likelihood of reaching prespecified stopping criteria as Covid-19 cases reduced. The final analysis included 2684 critically ill participants. 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, 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. Secondary analyses were consistent

with the primary analysis. Serious Adverse Events, such as elevated liver enzymes and creatinine kinase levels, were reported more frequently with simvastatin treatment.

*Conclusions*:

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

## Main text

[3024/2700 words]

## Introduction

There have been over 760 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 in 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, on the World Health Organization's list of essential medicines, predominantly used for its lipid lowering and cardioprotective properties.[4] Simvastatin also has anti-inflammatory 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 in Acute Respiratory Distress Syndrome (ARDS) found no benefit, subsequent post-hoc analyses support the hypothesis that simvastatin treatment may be beneficial in patients with a hyperinflammatory phenotype of ARDS.[10,11] Meta-analyses of observational studies in Covid-19 have demonstrated an association between prior statin use and improved clinical outcomes, including reduced mortality.[12,13]

We investigated the effect of commencing 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

that was closed due to operational futility as cases of Covid-19 reduced, resulting in a low anticipated likelihood of reaching prespecified stopping criteria.

## Methods

*Trial Design and Oversight*

REMAP-CAP is an ongoing international platform trial (NCT02735707) designed to evaluate treatments for patients with severe pneumonia in both pandemic and non-pandemic settings.[14–23] Its design has previously been reported.[24] This report includes patients enrolled in the Covid-19 pandemic stratum and randomized in the domain comparing simvastatin to no statin (control); all 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 a blinded International Trial Steering Committee (ITSC) and an unblinded independent Data and Safety Monitoring Board (DSMB). The trial has multiple international funders and sponsors. The funders had no role in designing the trial, analyzing data, writing the manuscript, or the decision to submit for publication. The relevant research ethics committee in each jurisdiction approved the trial protocol. Informed consent was obtained before randomization from all 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. All authors vouch for the data and analyses, as well as for the fidelity of this report to the trial protocol and statistical analysis plan. There are no confidentiality agreements that preclude the investigators publishing the trial findings.

*Patients*

Adult patients, 18 years of age or older, with either clinically suspected or microbiologically confirmed Covid-19 who were admitted to hospital were enrolled. Patients were stratified by disease severity state into critically ill ('severe state') and noncritically ill ('moderate state') groups at enrolment. Patients receiving respiratory (high-flow nasal oxygen with flow rate ≥30 L/min and FiO2 ≥0.4, or non-invasive or invasive mechanical ventilation) or cardiovascular (vasopressor/ inotrope) organ support in an intensive care unit (ICU) were classified as critically ill. All other hospitalized patients were considered noncritically ill. It was pre-specified that critically ill and noncritically ill adults would be analyzed and reported separately, with Bayesian dynamic borrowing used to share information based on the concordance of treatment effects in the two populations. As only 184 noncritically ill patients were recruited, their results are presented in the supplementary appendix. Exclusion criteria included recent or ongoing receipt of statin therapy or another medication that could not be co-administered with simvastatin, severe liver disease, creatinine >2.26mg/dL (unless receiving renal replacement therapy) and greater than 48 hours since commencement of organ support in an ICU. Detailed domain and platform exclusion criteria are listed in the Supplementary Appendix.

*Randomization*

Participants were randomly assigned by 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 using allocation probabilities derived from the probability each intervention was most favorable based on the accumulating evidence within the trial.

Simvastatin 80mg was administered daily by the enteral route. This high dose was informed by preclinical[7] and observational studies.[25] Simvastatin 80mg was safe[10] and improved both pulmonary inflammation and 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 receiving assignments in this domain, participants could be randomly assigned to other interventions within other domains, depending on domains active at the site, patient eligibility, and consent (see the protocol and www.remapcap.org). The simvastatin domain was open label. Participants, treating clinicians, and outcome assessors were aware of treatment 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 accruing patient outcomes.

*Outcome measures*

The primary outcome was organ support-free days, up to day 21. In this composite ordinal outcome, all deaths within 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 pre-specified in the statistical

analysis plan (appendix) and included survival to day 90, days free of vasopressors/inotropes, days free of respiratory support, duration of ICU and hospital stay, and modified World Health Organization ordinal score at day 14. Site investigators reported serious adverse events (SAEs) considered at least possibly related to a trial procedure/intervention and SAEs of specific interest to the respective trial coordinating center and subsequently to the DSMB 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 the primary outcome on the basis of evidence accumulated in the trial and prior probability distributions. The primary model used to estimate the effect of simvastatin versus controls randomized 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 compared to 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 on the log odds ratio (inducing a prior median (95% CrI) of 1.0 (0.14 to 7.10) on the odds ratio). The posterior distributions for these effects were shrunk towards the overall effect to an extent reflective of their similarity (dynamic borrowing).

The primary analysis was conducted by the Statistical Analysis Committee in all Covid-19 patients in the platform with complete follow-up, entered up to 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 for simvastatin were concurrently randomized. Patients were analyzed according to group assignment. Missing outcomes were not imputed and were excluded from the analysis..

The model was fit using a Markov Chain Monte Carlo algorithm that drew iteratively (20,000 draws) from the joint posterior distribution. Posterior odds ratios with 95% credible intervals (CrI) were calculated, along with the posterior probability that simvastatin was superior to control (odds ratio >1), harmful (odds ratio <1), and futile (odds ratio <1.2). For the primary outcome, an ordinal scale with 23 categories (worst category, death, and best category, alive with 21 days free of organ support), the odds ratio denotes the relative odds of being in the category >i vs. <=i, for i= – 1 to 21.

The predefined statistical criteria for ceasing enrolment and reporting a treatment effect were superiority (>99% posterior probability, odds ratio >1) and futility (>95% posterior probability, odds ratio <1.2).

Sensitivity and secondary analyses were undertaken using only data from the simvastatin domain and other completed domains. Additional sensitivity analyses that

used different analysis populations, and pre-specified subgroup analyses, are detailed in the statistical analysis plan (appendix). Data management and summaries were created using R version 4.1.2, the primary analysis was computed in R version 4.3.1 (2023-06-16), using the rstan package version 2.21.0.

**Results**

Enrollment began on October 28, 2020. On January 8, 2023, enrollment was closed by the ITSC based on low anticipated likelihood of reaching one of the prespecified stopping criteria due to low recruitment, as the number of Covid-19 cases dropped. This decision was made prior to unblinding and was based on simulations (Supplementary Protocol Documents) which considered the amount of time needed to complete enrolment, based on recent recruitment rates, in order to reach a prespecified threshold assuming a range of plausible treatment effects.

2739 critically ill patients and 187 noncritically ill patients were enrolled in the Simvastatin domain at 141 sites across 13 countries (Figure 1). 54 patients subsequently withdrew consent and four patients had missing primary outcomes. The population for this analysis consists of 2,684 critically ill patients. 184 noncritically ill patients are reported in the supplementary appendix only as numbers are too small to provide meaningful interpretation. Accrual summaries and response-adaptive randomization proportions over time are provided in Figure S1 and Table S1. Covariate effects were estimated from 8,220 critically ill patients enrolled across all REMAP-CAP domains.

*Patients*

Baseline characteristics were balanced across intervention groups (Table 1). All but two patients were receiving respiratory support at the time of randomization, including high flow nasal oxygen (31%), non-invasive (34%) and invasive (35%) mechanical ventilation. The use of concomitant therapies at enrollment or within the following 48 hours occurred in 97.2% (glucocorticoids) and 52.4% (tocilizumab/sarilumab) and was balanced across both groups.

*Primary Outcome*

Median organ support-free days were 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 for simvastatin compared with control (Table 2 and Figure 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).

*Secondary outcomes*

The secondary outcomes are listed in Table 2. Survival to hospital discharge occurred in 1,352/1,843 (73.4%) in the simvastatin group and 589/841 (70.0%) in the control group yielding an adjusted odd ratio of 1.04 (95% credible interval, 0.85, 1.27) with a 64.4% posterior probability of superiority of simvastatin compared with control. Death within 90-days occurred in 504/1835 in the simvastatin group and 257/837 in the control group excluding 8 and 4 censored patients, respectively. 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 compared with control (Figure 3). The findings were similar for other secondary outcomes (Table 2, Figures 3 and S2).

The pre-specified subgroup analyses are presented in Figure S3. It was not possible to undertake the planned subgroup analysis by the two pre-specified ARDS inflammatory phenotypes[11,27] as the vast majority of patients in the study population (98.8%) were categorized as one phenotype. The findings were consistent both in patients receiving and not receiving interleukin-6 receptor antagonist therapy (Table S4).

There were 62 SAEs (n = 1846, 3.4%) reported in the simvastatin group and 17 SAEs (n = 842, 2.0%) in the control group (Table S5a). There were 13 (0.7%) patients reported to have raised transaminases, of which 9 were assessed as related to simvastatin and in 8 of these cases treatment was either temporarily or permanently discontinued. There were 13 (0.7%) patients reported to have significantly raised CK, all of which were assessed as related to simvastatin and in 12 of these cases treatment was either temporarily or permanently discontinued. One additional SAE, an episode of acute pancreatitis, was assessed as related to simvastatin and treatment was discontinued. All other SAEs were assessed as not related to simvastatin (Table S5).

**Discussion**

In this domain of an adaptive platform trial, we observed a 95.9% probability that commencing simvastatin improved the primary outcome, a composite of organ support-free days and death, as compared with standard of care 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 that antecedent statin use is associated with improved Covid-19 outcomes.[12] A meta-analysis of published randomized controlled trials (RCTs) of statins commenced as treatment for Covid-19 reported a risk ratio for all-cause mortality of statins compared with controls of 0.92 (95% confidence interval 0.75-1.13), the point estimate of which is similar to the effect size seen in REMAP-CAP.[28] Our trial is larger than the seven previous RCTs of statin therapy in Covid-19 combined, which recruited 1,830 participants in total. It is plausible that smaller trials were underpowered to detect a modest beneficial effect.

The incidence of SAEs, particularly elevated creatine kinase and liver transaminases, was higher in the simvastatin group. This may in part be due to selective reporting of adverse events in the simvastatin group in an open label design, as SAEs were reported to be similar to placebo in previous blinded trials investigating statins in the critically ill.[10,29] Regardless, this underlines the importance of regular creatine kinase and liver function monitoring in critically ill patients treated with simvastatin, and discontinuation of treatment in the setting of significantly elevated creatine kinase and liver transaminases.

A subgroup analysis suggested a larger association of simvastatin with the primary outcome in critically ill patients who were not receiving mechanical ventilation at randomization. In this group of patients, 37.0% of patients in the simvastatin group and

42.5% of patients in the control group progressed to require intubation, extra-corporeal membrane oxygenation, or died.

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

The lower prevalence of the hyperinflammatory phenotypes may relate to the increased use of glucocorticoids and immunomodulatory agents in Covid-19 and also methodological factors, such as phenotype categorization using the worst variable in a 24-hour period, contrasting with using data from a fixed daily timepoint in our trial. Interestingly, systemic inflammation, as measured by CRP and ferritin, was increased in our study and subgroup analyses suggested a larger association of simvastatin with the primary outcome in those with higher CRP and ferritin. It is recognized that CRP is a poor discriminator of inflammatory phenotype in ARDS with similarly high CRP values observed in both the hypoinflammatory and hyperinflammatory phenotypes.[34] This suggests that the mechanisms causing increased CRP and ferritin are different from the mechanisms that drive the hyperinflammatory phenotype in Covid-19 patients. More work will be required to assess potential heterogeneity of treatment effect to

optimize simvastatin treatment based on disease severity and inflammatory biomarkers.[35]

Strengths of our trial include the study of a repurposed inexpensive intervention which is widely available, as well as recruitment of a population receiving contemporary standard of care which included glucocorticoids in 97.2% and interleukin-6 receptor antagonists in 52.4% of patients, 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 including 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 there may be a chance that clinicians were concerned that enteral absorption of drugs might be reduced which could have introduced bias in patient selection, even though failure of enteral absorption was not an exclusion criterion to randomisation in this domain. Our sensitivity analyses do exclude other patients not randomised in the simvastatin domain from the analytical model and the results were consistent. While the 95.9% posterior probability of efficacy is high, the trial was stopped for operational futility prior to reaching a pre-specified stopping trigger. In response to falling Covid-19 infection rates and fewer critical care admissions, and informed by simulations conducted by blinded investigators, the blinded ITSC chose to close recruitment and report results to inform clinicians rather than continue and possibly never reach the pre-specified 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 (RAR) allowed blinded randomization probabilities to be modified as evidence about treatment effects was accrued throughout the trial. RAR allocated more patients to simvastatin but this may have reduced the ability to reach a statistical trigger because of low numbers enrolled to the control arm. This highlights potential simultaneous advantages and disadvantages of allowing RAR proportions to deviate too far from balanced randomization in two arm trials; more patients in the trial receive the favourable intervention but this may lengthen trial duration.

**Conclusions**

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

**Statement of Support**

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**Legends**

**Figure 1: Screening, Enrollment, Randomization, and Inclusion in Analysis.**

a = Patients could meet more than one ineligibility criterion. Full details are provided in the supplement.
b = Full details regarding noncritically ill patients are provided in the supplement.
c = The primary analysis of interventions within the Simvastatin Domain is estimated from 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 patients enrolled in the critically ill COVID-19 cohort (for whom there is consent and follow-up) are included in the analytical model but only concurrent controls for simvastatin are used to estimate simvastatin's effectiveness relative to control.
^ Contraindications are hypersensitivity, severe liver disease, creatinine more than 200 μmol/L (2.26 mg/dL) and not receiving renal replacement therapy, current treatment with a medicine that cannot be co-administered with simvastatin, and current or planned treatment with any statin.
*Commencement of organ support in ICU was used instead of date and time of ICU admission for patients who had already received an allocation in the Moderate illness state.
ICU denotes intensive care unit, and REMAP-CAP Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia. A domain describes a specific set of competing interventions which, for the purposes of the platform, are mutually exclusive and exhaustive.

**Figure 2: Distribution of Organ Support–free Days**
Panel A) the cumulative proportion (y-axis) for each intervention group by day (x-axis), with death listed first. Curves that rise more slowly indicate a more favorable distribution in the number of days alive and free of organ support. The height of each curve at the point labelled "Death" indicates the in-hospital mortality rate for each intervention. The height of each curve at any point, for example, at day = 10, indicates the proportion of patients with organ support-free days (OSFD) of 10 or lower (i.e. 10 or worse). The difference in height of the two curves at any point represents the difference in the percentile in the distribution of OSFDs associated with that number of days alive and free of organ support. Panel B) Organ support–free days as horizontally stacked proportions by intervention group. Red represents worse outcomes and blue represents better outcomes. The median adjusted odds ratio from the primary analysis, using a Bayesian cumulative logistic model, was 1.15 (95% credible interval, 0.98 to 1.34) for simvastatin compared with control, yielding a 95.9% posterior probability of superiority.

**Figure 3: Distributions of selected secondary clinical outcomes**
Shown are the Kaplan-Meier survival curves (Panel A). Median follow-up time was 90 days in both treatment groups; there were 8 (0.4%) and 4 (0.5%) patients censored prior to day 90 in the simvastatin and control groups, respectively. There were 504/1835 deaths (27.5%) in the simvastatin group and 257/837 deaths (30.7%) in the control group. Denominators exclude censored patients. This resulted in a hazard ratio of 1.12 (95% credible interval, 0.95 to 1.32), yielding a 91.9% posterior probability of superiority of simvastatin to control. The blue line represents simvastatin and the red

line represents control. Patients known to be alive at 90-days are censored at 90-days. Patients with unknown 90-day mortality status are censored at the date of last follow-up (the date of discharge if discharged from hospital or the date last known alive for those in hospital). Also shown is the distribution of the modified World Health Organization 8-point scale, measured at day 14, for simvastatin and control (Panel B). 0-2= No longer hospitalized, 3= Hospitalized without oxygen, 4=Hospitalized with oxygen by mask or nasal cannula, 5=requires non-invasive ventilation or high flow oxygen, 6= requires intubation and mechanical ventilation, 7= requires mechanical ventilation and additional vasopressor, renal replacement therapy, or extracorporeal membrane oxygenation support, 8= death. The distributions of days free of respiratory support through 28 days are shown as horizontally stacked proportions by intervention group (Panel C). The distributions of days free of vasopressor/inotropes support through 28 days are also shown as horizontally stacked proportions by intervention group (Panel D).

**Table 1: Baseline Characteristics of the Patients in the Simvastatin Domain**
Percentages may not sum to 100 because of rounding. SD denotes standard deviation.
[a] Data collection was not approved in Canada and continental Europe. 'Other' includes 'declined' and 'other ethnic group'. Participants (or their surrogates) self-reported their race/ ethnicity via 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.
[b] Body-mass index is the weight in kilograms divided by the square of the height in meters.
[c] Acute Physiology and Chronic Health Evaluation II scores range 0 to 71, with higher scores indicating greater severity of illness.
[d] 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.
[e] SARS-CoV2 infection was confirmed by respiratory tract polymerase chain reaction test.
[f] Kidney disease was determined from the most recent serum creatinine level prior to this hospital admission, except in patients who were receiving dialysis. Abnormal kidney function was defined as a creatinine level of 130 μmol/L or greater (1.5mg/dL) for males or 100 μmol/L or greater (1.1mg/dL) for females 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, high-dose or long-term steroid treatment, or presence of immunosuppressive disease.
[g] Extended Cardiovascular SOFA Score reflects criteria for blood pressure and inotropic or vasoactive support, with higher scores indicating worse cardiovascular organ failure.
[h] Laboratory results available when captured for clinical care.
[i] Within 48hr of randomization.

**Table 2: Primary and Secondary Outcomes**
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 SAE analysis, are structured such that a higher odds/hazard ratio is favorable. Odds/hazard ratios are summarized with the posterior median and 95% credible interval.

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

| | Simvastatin (n = 1846) | Control (n = 842) |
|---|---|---|
| Age in years, median (IQR) | 56.0 (45.0-65.0) | 57.0 (48.0-64.0) |
| Female sex, n (%) | 617 (33.4) | 290 (34.4) |
| Race / Ethnicity [a], n / N (%) | | |
| 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) |
| Body-mass index [b], median (IQR) | 31.0 (26.6-37.1) (n=1622) | 31.6 (26.8-37.6) (n=724) |
| APACHE II score [c], median (IQR) | 11.0 (7.0-17.0) (n=1833) | 12.0 (8.0-18.0) (n=832) |
| Clinical Frailty Score [d], median (IQR) | 2.0 (2.0-3.0) (n=1837) | 2.0 (2.0-3.0) (n=838) |
| Confirmed SARS-CoV-2 infection [e], n / N (%) | 1636/1674 (97.7) | 749/774 (96.8) |
| Preexisting condition [f], n / N (%) | | |
| 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) |
| Time to enrollment, median (IQR) | | |
| From hospital admission, days | 1.8 (0.9-3.7) | 1.9 (1.0-3.7) |
| From ICU admission, hours | 17.5 (9.0-23.8) | 17.1 (10.1-22.7) |
| Acute respiratory support, n (%) | | |
| 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 / supplemental oxygen | 2/1841 (0.1) | 0/840 (0.0) |
| $PaO_2$ / $FiO_2$, median (IQR) | 120.0 (90.0-162.0) (n=1708) | 115.0 (88.0-153.0) (n=789) |
| Systolic blood pressure, mmHg | 124.0 (110.0-140.0) (n=1805) | 125.0 (110.0-142.0) (n=816) |
| Vasopressor support, n (%) | 332/1841 (18.0) | 171/840 (20.4) |
| Median laboratory values (IQR) [h] | | |
| C-reactive protein, µg/mL | 101.0 (50.8-171.1) (n=1557) | 112.6 (60.0-184.0) (n=741) |
| Lactate, mmol/L | 1.3 (1.0-1.7) (n=1675) | 1.3 (1.0-1.7) (n=774) |
| Creatinine, mg/dL | 0.8 (0.6-1.0) (n=1822) | 0.8 (0.6-1.0) (n=833) |
| eGFR, ml/min/1.73m$^2$ | 101.5 (82.0-112.6) (n=1822) | 100.8 (81.8-110.2) (n=833) |
| Concomitant therapies, n / N (%) [i] | | |
| Remdesivir | 385/1837 (21.0) | 218/840 (26.0) |
| Corticosteroids | 1778/1839 (96.7) | 827/840 (98.5) |
| Tocilizumab or sarilumab | 977/1838 (53.2) | 426/840 (50.7) |
| Continent, n (%) | | |
| 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) |

**Table 2. Primary and Secondary Outcomes**

| Outcome or Analysis | Simvastatin (N=1846) | Control (N=842) |
|---|---|---|
| **Organ support-free days** | | |
| Median (IQR), no. of patients | 11 (–1 to 17) n = 1843 | 7 (–1 to 16) n = 841 |
| Adjusted odds ratio | 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) | 589/841 (70) |
| Adjusted odds ratio | 1.04 (0.85 to 1.27) | 1 |
| Probability of superiority to control – % | 64.4 | - |
| **90-day survival** | | |
| Adjusted hazard ratio | 1.12 (0.95 to 1.32) | 1 |
| Probability of superiority to control – % | 91.9 | - |
| **Progression to invasive mechanical ventilation, ECMO or death, restricted to those not intubated at baseline** | | |
| Free of invasive mechanical ventilation at baseline | 1218 | 539 |
| Progression to intubation, ECMO or death, n (%) | 451 (37) | 229 (42) |
| No progression to intubation, ECMO or death, n (%) | 767 (63) | 310 (58) |
| Adjusted odds ratio | 1.23 (0.98, 1.55) | 1 |
| Probability of superiority to control – % | 96.4 | - |
| **Respiratory support-free days** | | |
| Median (IQR), no. of patients | 18 (–1 to 24) n = 1845 | 14 (–1 to 23) n = 842 |
| Adjusted odds ratio | 1.16 (1.00 to 1.35) | 1 |
| Probability of superiority to control – % | 97.4 | - |
| **Vasopressor/inotropes support-free days** | | |
| Median (IQR), no. of patients | 27 (–1 to 28) n = 1846 | 26 (–1 to 28) n = 842 |
| Adjusted odds ratio | 1.13 (0.96 to 1.34) | 1 |
| Probability of superiority to control – % | 93.1 | - |
| **WHO Scale at 14 days** | | |
| Median (IQR), no. of patients | 4 (2 to 7) n = 1846 | 5 (2 to 7) n = 842 |
| Adjusted odds ratio | 1.23 (1.06 to 1.43) | 1 |
| Probability of superiority to control – % | 99.6 | - |
| **ICU length of stay** | | |
| Median duration in days | 11 | 14 |
| Adjusted hazard ratio | 1.08 (0.97, 1.20) | 1 |
| Probability of superiority to control – % | 93.0 | - |
| **Hospital length of stay** | | |
| Median duration in days | 22 | 28 |
| Adjusted hazard ratio | 1.10 (0.99, 1.22) | 1 |
| Probability of superiority to control – % | 95.7 | - |
| **Serious Adverse Events** | | |
| no. of patients (%) | 57 (3.1) | 17 (2.0) |
| Adjusted odds ratio | 1.56 (1.13, 2.14) | 1 |
| Probability of inferiority to control – % | 99.6 | - |