FAST TRACK

Atorvastatin versus placebo in patients with covid-19 in intensive care: randomized controlled trial

INSPIRATION-S Investigators

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ABSTRACT

OBJECTIVE
To assess the effect of statin treatment versus placebo on clinical outcomes in patients with covid-19 admitted to the intensive care unit (ICU).

DESIGN
INSPIRATION/INSPIRATION-S was a multicenter, randomized controlled trial with a 2×2 factorial design. Results for the anticoagulation randomization have been reported previously. Results for the double blind randomization to atorvastatin versus placebo are reported here.

SETTING
11 hospitals in Iran.

PARTICIPANTS
Adults aged ≥18 years with covid-19 admitted to the ICU.

INTERVENTION
Atorvastatin 20 mg orally once daily versus placebo, to be continued for 30 days from randomization irrespective of hospital discharge status.

MAIN OUTCOME MEASURES
The primary efficacy outcome was a composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or all cause mortality within 30 days from randomization. Prespecified safety outcomes included increase in liver enzyme levels more than three times the upper limit of normal and clinically diagnosed myopathy. A clinical events committee blinded to treatment assignment adjudicated the efficacy and safety outcomes.

RESULTS
Of 605 patients randomized between 29 July 2020 and 4 April 2021 for statin randomization in the INSPIRATION-S trial, 343 were co-randomized to intermediate dose versus standard dose prophylactic anticoagulation with heparin based regimens, whereas 262 were randomized after completion of the anticoagulation study. 587 of the 605 participants were included in the primary analysis of INSPIRATION-S, reported here: 290 were assigned to atorvastatin and 297 to placebo (median age 57 years (interquartile range 45-68 years); 256 (44%) women). The primary outcome occurred in 95 (33%) patients assigned to atorvastatin and 108 (36%) assigned to placebo (odds ratio 0.84, 95% confidence interval 0.58 to 1.21). Death occurred in 90 (31%) patients in the atorvastatin group and 103 (35%) in the placebo group (odds ratio 0.84, 95% confidence interval 0.58 to 1.22). Rates for venous thromboembolism were 2% (n=6) in the atorvastatin group and 3% (n=9) in the placebo group (odds ratio 0.71, 95% confidence interval 0.24 to 2.06). Myopathy was not clinically diagnosed in either group. Liver enzyme levels were increased in five (2%) patients assigned to atorvastatin and six (2%) assigned to placebo (odds ratio 0.85, 95% confidence interval 0.25 to 2.81).

CONCLUSIONS
In adults with covid-19 admitted to the ICU, atorvastatin was not associated with a significant reduction in the composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or all cause mortality compared with placebo. Treatment was, however, found to be safe. As the overall event rates were lower than expected, a clinically important treatment effect cannot be excluded.

TRIAL REGISTRATION
ClinicalTrials.gov NCT04486508.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Studies have shown that statins might have anti-inflammatory, antithrombotic, and antifibrotic properties

Some clinical studies before covid-19 indicated that statin treatment might be associated with reduced mortality in patients with hyperinflammatory acute respiratory distress syndrome

Some observational studies have suggested an association between a history of statin use or continued use of statins during hospital admission and improved outcomes in patients with covid-19

WHAT THIS STUDY ADDS

In this randomized trial, atorvastatin compared with placebo was not associated with a significant reduction in the primary outcome, a composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or all cause mortality

Because the event rates were lower than expected, a smaller treatment effect cannot be excluded

Results within subgroups, including patients who presented within seven days of symptom onset, are hypothesis generating and require additional confirmation in the ongoing studies

Introduction

Covid-19 can result in multiorgan manifestations.[1 2] The overactive immune response can lead to pulmonary and extrapulmonary injury.[3] Pulmonary parenchymal injury, which can progress to acute respiratory distress syndrome, is the most common and sinister feature of severe covid-19. Vascular endothelial activation, a hypercoagulable state, and immobility because of severe illness or medical instrumentation might increase the risk of microthrombosis and macrothrombosis, particularly venous thrombo-embolism in patients with covid-19.[4-8] The rates of thrombosis and mortality are highest among patients with covid-19 who are admitted to the intensive care unit (ICU).[9-13]

Hydroxymethylglutaryl coenzyme A reductase inhibitors, or statins, have anti-inflammatory and

antithrombotic properties.[14 15] Statins inhibit the nuclear factor kappa light chain enhancer of activated B cells (NF-kB) pathway and reduce inflammation.[16 17] Statins might also exert antioxidant and anti-apoptotic effects.[18] In the Hydroxymethylglutaryl-CoA Reductase Inhibition with Simvastatin in Acute Lung Injury to Reduce Pulmonary Dysfunction–2 Study (HARP-2), simvastatin compared with placebo was not associated with a reduced mortality in the overall population.[19] In the subset of patients with a hyperinflammatory phenotype, however, simvastatin was shown to reduce all cause mortality.[20] In addition to reducing inflammation, statins might exert endothelial stabilizing properties, such as increased nitric oxide production.[17] Moreover, statins are known to have antithrombotic and modest profibrinolytic activities. In pre-covid-19 studies, statins have been shown to reduce plasminogen activator inhibitor-1, platelet aggregation,[21] and the risk of vascular events[22] such as venous thromboembolism.[23 24] Statins might also interfere with viral entry through the disruption of the membrane lipid rafts.[17 25] Therefore, we hypothesized that statin treatment might be of benefit to adults with covid-19[26] admitted to the ICU by reducing the risk of thrombotic events or death related to worsening inflammation or respiratory status.

The Intermediate vs Standard-Dose Prophylactic Anticoagulation in Critically-ill Patients With COVID-19: An Open Label Randomised Controlled Trial (INSPIRATION) and INSPIRATION-statin (INSPIRATION-S) studies were part of a randomized clinical trial with a 2×2 factorial design in patients with covid-19 admitted to the ICU. The first randomization tested the effect of intermediate dose versus standard dose prophylactic anticoagulation with heparin based regimens. The results are reported elsewhere.[27 28] The second randomization tested the effect of atorvastatin 20 mg orally once daily versus placebo in patients with covid-19 admitted to the ICU. This manuscript reports the results of this second randomization (INSPIRATION-S).

Methods

INSPIRATION/INSPIRATION-S were part of a multicenter, randomized controlled trial with a 2×2 factorial design created by an international committee and conducted in 11 Iranian hospitals in Tehran, Tabriz, and Karaj. The rationale and design of the trial have been described previously.[27 29] Patients or their healthcare proxies provided written informed consent for participation. An independent data and safety monitoring committee, not part of the authorship team, monitored the trial results.

Participants

We recruited adults aged ≥18 years with reverse transcription polymerase chain reaction confirmed covid-19 who were admitted to an ICU and had no definite indication for therapeutic anticoagulation or baseline statin use. Adults were excluded if their estimated survival was less than 24 hours, they weighed <40 kg, they had major bleeding or serious bleeding diathesis within 30 days from enrollment, their liver enzyme test results were greater than five times the upper limit of normal, they had active liver disease (liver function test results greater than three times the upper limit of normal with histological evidence of cirrhosis, inflammation, or necrosis), and their creatine kinase concentration was >500 U/L. Supplementary appendix 3 provides a full list of the inclusion and exclusion criteria.

Site clinicians at the enrolling centers screened patients in the ICU for eligibility. Eligible patients who agreed to participate were randomized and followed-up for 30 days from the time of randomization. While the patients were in hospital, their follow-up was performed by the site clinicians who enrolled them. Site clinicians were responsible for collecting the baseline clinical information and clinical outcomes. Follow-up on hospital discharge was done through weekly telephone calls, either by the same site clinicians, or, if needed, by the trial coordinating center.

Randomization and blinding

Eligible adults were randomly assigned to atorvastatin or matching placebo in a 1:1 ratio. A centralized computer based system with a block size of 4 was used for randomization. The site clinicians who enrolled patients received a unique trial registration number for each randomized patient. Access to the allocation sequence was concealed from the site clinicians. The study drug and placebo were identical in appearance and given to treatment teams (in the hospital) or the patients or their caregivers on hospital discharge. The boxes of drugs contained three 10-pill blister packs and had distinct codes for the randomization sequence and study drug. The study investigators and participants remained blinded to assigned treatments until completion of the analyses.

Intervention

The study intervention was atorvastatin 20 mg orally once daily compared with placebo. For patients who were mechanically ventilated, atorvastatin was delivered through a nasogastric or orogastric tube. The plan was for the study drug to be continued for 30 days from randomization or until the primary outcome was reached within the first 30 days post-randomization.

Outcomes

The primary efficacy outcome was a composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or all cause mortality within 30 days from randomization. Secondary efficacy outcomes included the individual components of the primary outcome (venous thromboembolism, arterial thrombosis, and all cause mortality) and ventilator-free days (the difference between total number of days alive post-enrollment and total number of days receiving invasive mechanical ventilation). Exploratory outcomes included objectively clinically diagnosed type I acute myocardial infarction, stroke, and acute peripheral

arterial thrombosis, the proportion of patients discharged alive from the ICU, length of hospital stay in the ICU, incident atrial fibrillation, and new renal replacement therapy. Venous or arterial thrombotic events were diagnosed based on treating clinicians' suspicion and subsequent confirmation by appropriate imaging tests. The supplementary appendix provides details about the confirmatory tests required for ascertainment of thrombotic events. For example, deep vein thrombosis was diagnosed in the presence of confirmatory findings on vascular ultrasonography, contrast enhanced computed tomography, magnetic resonance imaging, or invasive venography, or at autopsy. Routine screening for thrombotic events was not dictated in the study protocol. The treating clinicians performed the diagnostic tests according to their clinical judgment.

Prespecified safety outcomes included an increase in liver enzyme levels (defined as more than three times the upper limit of normal) and new clinically diagnosed myopathy, as identified by treating clinicians. Another safety outcome, major bleeding, was assessed according to the Bleeding Academic Research Consortium criteria (BARC type 3 or 5). A clinical events committee blinded to treatment assignment adjudicated all clinical efficacy and safety outcomes. The supplementary appendix provides additional details about the definitions of the outcomes (also see table 2). Patients who were discharged alive from the hospital received regular weekly telephone follow-up.

Statistical analysis

To avoid type I error inflation, it was prespecified to not conduct interim analyses to test the superior efficacy of atorvastatin versus placebo.[29 30] The data and safety monitoring board had independent access to the study data and conducted prespecified interim safety analyses at 25%, 50%, and 75% of recruitment.

Patients enrolled between 29 July 2020 and 19 November 2020 were considered for eligibility to be randomized to anticoagulation, followed by randomization to statin treatment.[29] At trial design phase, considering a two sided type I error rate of 0.05 and a 25% relative risk reduction for the primary outcome with statin treatment compared with placebo, the investigators estimated a priori that the study would be underpowered to detect a significant difference between the groups (supplementary fig S1). Therefore, the study protocol prespecified that if resources allowed and the study investigators agreed to collaborate, enrollment for the statin randomization could be continued after completion of enrollment for the anticoagulation hypothesis (ie, randomization to intermediate dose prophylactic anticoagulation versus standard dose prophylactic anticoagulation). To maintain harmony with eligibility criteria, the steering committee used the same eligibility criteria (including the anticoagulation hypothesis eligibility criteria) for patients who would be considered only for the statin randomization. By the time randomization of 600 patients was completed for the anticoagulation study, 364 were assigned to atorvastatin or to placebo. Based on an estimated event rate of 55% from the pre-randomization period at enrolling sites, this sample size would have provided a 63% power to detect a significant difference for the primary outcome between the two groups for the statin randomization. Considering an actual pooled event rate of 44.8% for the primary outcome in the INSPIRATION (anticoagulation) study, a sample of 596 patients was estimated to provide 80% power to detect a significant difference for the primary outcome between statin treatment and placebo. The target sample size for INSPIRATION-S was increased to 626 patients (313 in each group) to account for an exclusion rate of 5% owing to duplicate or incorrect entries. Therefore, enrollment for only the statin randomization was planned to continue from 20 November 2021. On 4 April 2021 the steering committee terminated enrollment owing to the lack of additional funding and the excessive burden of new enrollment to site investigators. By that time, 605 patients were randomized to receive atorvastatin or placebo.

The primary analysis population consisted of randomized patients who received at least one dose of the study drug (atorvastatin or placebo), were not excluded, and did not withdraw consent. Additional analyses were performed among all randomized patients and in the per protocol efficacy cohort that included only those patients who completed the treatment as originally allocated until reaching the primary endpoint or the end of 30 day follow-up, whichever occurred first.

Assessment of the primary outcome was performed through generalized linear mixed models accounting for the enrolling site as a random effect, the assigned treatment as the exposure variable, and odds ratio as the main effect measure. The conditional distribution of the primary endpoint given the random effects was assumed to be Bernoulli, with success probability determined by the logistic cumulative distribution function. Risk difference was also reported for descriptive purposes, by subtracting the cumulative incidence in the placebo group from the cumulative incidence in the statin group, with the respective 95% confidence interval through the Clopper-Pearson interval. In a supplementary analysis, results were assessed in generalized linear mixed models accounting for the enrolling site as a random effect, the assigned treatment as the exposure variable, and hazard ratio as the effect measure. The proportionality assumption was tested by the Schoenfeld residuals, which did not indicate violation of the assumption. Time to event was shown with Kaplan-Meier curves.

Subgroup analyses were performed based on age, sex, history of smoking (current or former *v* non-smoker), history of hypertension, diabetes mellitus, obstructive airway disease, history of renin-angiotensin-aldosterone system inhibitor use, symptom onset (≤7 days *v* >7 days), cotreatment with corticosteroids, body mass index (BMI ≥30 or <30), aspirin use at baseline, type of assigned anticoagulation regimen during the

statin treatment (standard dose, intermediate dose, and therapeutic dose prophylactic anticoagulation), and duration of assigned regimen (≥80% of study period *v* <80%). Sensitivity analyses were performed with inclusion of all randomized patients meeting the eligibility criteria, and also in the per protocol cohort, consisting of patients who received the assigned treatment until completion of 30 day follow-up or who met the primary efficacy outcome.

All clinical outcomes were available for assessment in all patients and no outcome values were missing. For baseline characteristics, the study protocol allowed for multiple imputations if missing values occurred for >5% but <20% of values. Since none of the baseline characteristics met these criteria, multiple imputations were not used for the study variables. No adjustment was planned for the P value thresholds for multiplicity of comparisons. Therefore, owing to the potential for type 1 error, results from analyses other than the primary efficacy outcome should be considered exploratory. Statistical analyses were performed using R statistical package, version 4.0.3 (R Core Team).

Patient and public involvement

In the context of the pandemic and the need to design the study in a short period, no patients were involved in setting the research questions or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. The study results and the manuscript were shown to a few members of the public after submission of the manuscript.

Results

A total of 2868 patients were screened for eligibility between 29 July 2020 and 4 April 2021, of whom 605 were enrolled and randomized: 303 assigned to atorvastatin and 302 assigned to placebo. After the exclusion of 14 patients who did not meet the eligibility criteria and four who did not receive at least one dose of the study drugs, 587 entered the prespecified primary analysis population: 290 assigned to atorvastatin and 297 assigned to placebo (fig 1). No losses to follow-up occurred and no values were missing for clinical outcomes.

Table 1 summarizes the baseline characteristics of the two groups. Median age of the study participants was 57 years (interquartile range 45-68 years) and 256 (44%) were women. The two groups were balanced for baseline characteristics, except for history of smoking, which was more common in patients assigned to atorvastatin than to placebo (31 (11%) *v* 10 (3%) patients), and median white blood cell count, which was lower in patients assigned to atorvastatin than to placebo (8.6×10^9/L (interquartile range $6.1\text{-}11.7\times10^9$/L) *v* 9.5×10^9/L ($7.0\text{-}12.5\times10^9$/L)).

Among patients in the prespecified primary analysis population, the median duration of use of the assigned treatment was 21 days (interquartile range 7-30 days) for atorvastatin and 19 (7-30) days for placebo (P=0.79). Supplementary table S3 summarizes the reasons for post-randomization changes to the assigned treatments.

Efficacy

Because no interactions occurred between the two interventions (ie, anticoagulation intensity and use of atorvastatin) for the primary efficacy outcome based on Mantel Haenszel χ^2 test (P=0.97 for interaction), the results for statin randomization are reported independently. By 30 day follow-up, the primary efficacy outcome occurred in 95 (33%) patients assigned to atorvastatin and 108 (36%) assigned to placebo (odds ratio 0.84, 95% confidence interval 0.58 to 1.21, P=0.35, fig 2). This translated to a risk difference of −3.6% (95% confidence interval −11.2% to 4.0%). Results for the primary outcome were largely driven by all cause mortality: 90 (31%) deaths occurred in the atorvastatin group and 103 (35%) in the placebo group (odds ratio 0.84, 95% confidence interval 0.58 to 1.22). No patient was treated with extracorporeal membrane oxygenation.

The use of imaging tests for the diagnosis of venous thromboembolism was similar between the study groups 57 (20%) in the atorvastatin group and 58 (20%) in the placebo group; P=0.64). These tests included 17 computed tomography pulmonary angiograms in each group, and 40 venous doppler studies in the atorvastatin group and 41 in the placebo group (supplementary table S4). Venous thromboembolism was diagnosed in six (2%) patients assigned to atorvastatin and nine (3%) assigned to placebo (odds ratio 0.71, 95% confidence interval 0.24 to 2.06). The rate of arterial thrombosis did not differ significantly between the two groups (0% *v* 0.3%, risk difference −0.3%, 95% confidence interval −0.9% to 0.3%; P=0.32). Adjudicated type I myocardial infarction was not clinically diagnosed in either group.

The median length of ICU stay was 5 days (interquartile range 3-9 days) in the atorvastatin group and 5 (2-10) days in the placebo group. The median duration of ventilator-free days was 30 (interquartile range 10-30) days in the atorvastatin group and 30 (4-30) days in the placebo group (P=0.08).

No significant differences were found between patients assigned to atorvastatin or to placebo for 30 day incident atrial fibrillation (two (1%) *v* four (1%) patients; odds ratio 0.51, 95% confidence interval 0.09 to 2.87) or new renal replacement therapy (10 (3%) *v* 8 (3%) patients; 1.30, 0.50 to 3.38). Table 2 summarizes the results of efficacy and safety outcomes in the two groups.

Safety

An increase in liver enzyme levels more than three times the upper limit of normal occurred in five (2%) patients assigned to atorvastatin and six (2%) assigned to placebo (odds ratio 0.85, 95% confidence interval 0.25 to 2.81; P=0.79). Myopathy was not clinically diagnosed in either group.

Major bleeding was adjudicated in 11 (4%) patients assigned to atorvastatin and five (2%) assigned to

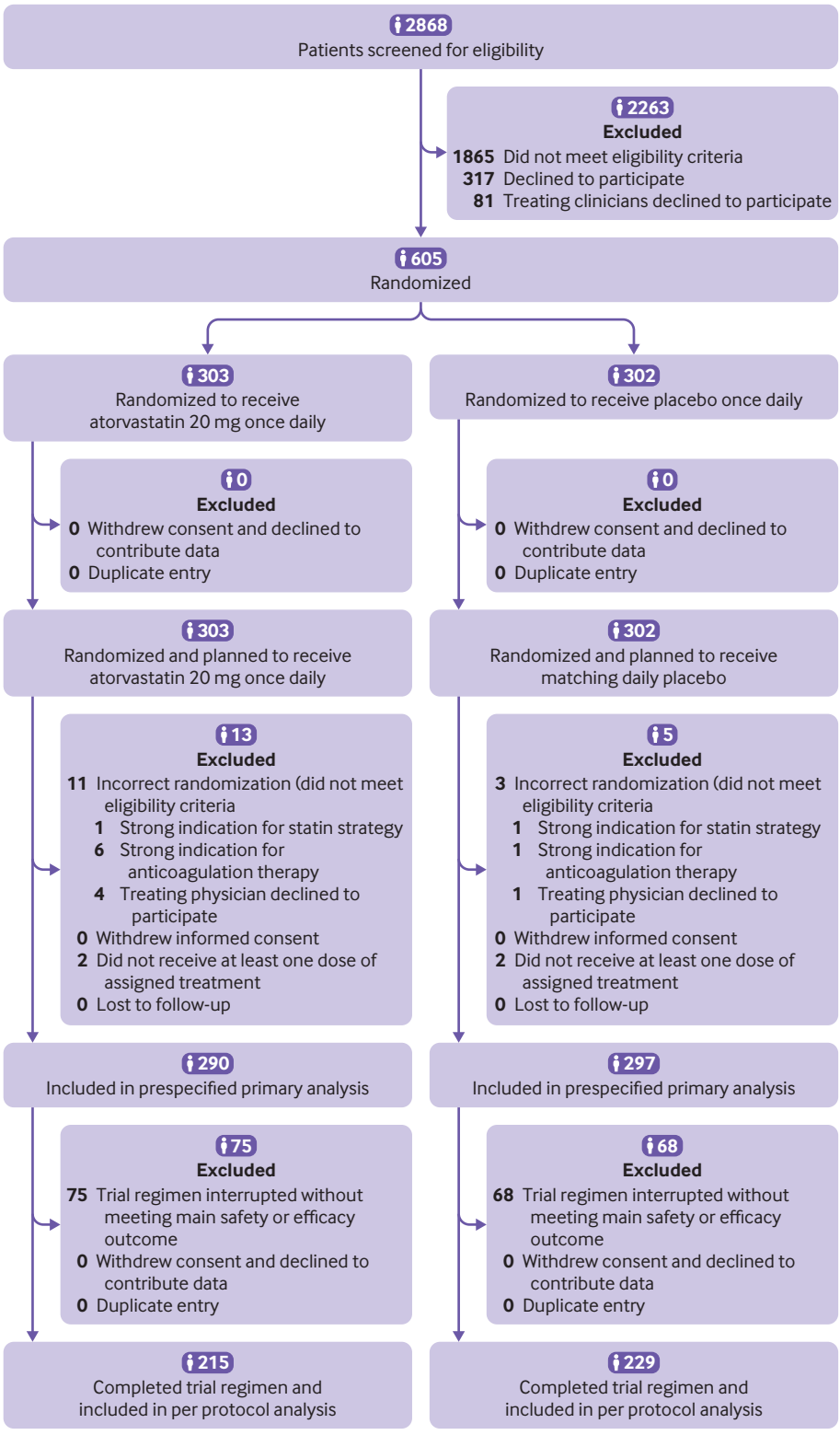


Fig 1 | Study flow diagram. Of 605 randomized patients, 587 met the criteria to be considered in the prespecified primary analysis

placebo (odds ratio 2.30, 95% confidence interval 0.78 to 6.73; P=0.12). The rate of fatal bleeding was not significantly different between the atorvastatin group and placebo group (two (1%) *v* two (1%); 1.02, 0.14 to 7.32; P=0.98). Table 2 reports additional safety outcomes.

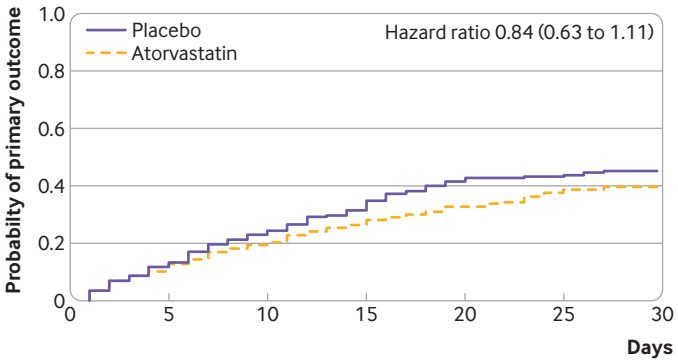
Subgroup and sensitivity analysis

Findings were consistent in most of the prespecified subgroups, including in women and men, those with or without obesity, and those with or without diabetes (fig 3). In a prespecified subgroup analysis, use of atorvastatin compared with placebo was associated

Table 1 | Baseline characteristics of participants assigned to atorvastatin or to placebo in prespecified primary analysis population.* Values are medians (interquartile ranges) unless stated otherwise

Characteristics	Atorvastatin group (n=290)	Placebo group (n=297)
Age (years)	57 (45-67)	57 (45-68)
No (%) of women	125 (43)	131 (44)
No (%) of men	165 (57)	166 (56)
Body mass index	27 (24-29)	27 (24-30)
No (%) of current smokers	31 (11)	10 (3)
Comorbidities (No (%)):		
Diabetes	49 (17)	49 (16)
Hypertension	89 (31)	96 (32)
Hyperlipidemia	11 (4)	8 (3)
Coronary artery disease	0	0
Obstructive airway disease	24 (8)	23 (8)
Heart failure	0	0
Ischemic cerebrovascular event	0	0
Hemorrhagic stroke	0	0
Venous thromboembolism	0	0
Duration of symptoms before hospital admission (days)	7 (4-9)	7 (4.5-9)
Duration of hospital admission pre-randomization (days)	3 (2-5)	4 (2-5)
Baseline indicators of illness severity:		
No (%) with systolic blood pressure <100 mm Hg at time of randomization	29 (10.0)	27 (9.0)
No (%) requiring vasopressor agent support <72 hours of enrollment	35 (12.0)	49 (16.4)
Acute Physiology and Chronic Health Evaluation† II at time of randomization	6 (4-10)	7 (4-10)
No (%) with fraction of inspired oxygen >50% at time of randomization	125 (43)	133 (45)
Acute respiratory support at time of enrollment (No (%)):		
Nasal cannula	28 (10)	30 (10)
Face mask	28 (10)	31 (10)
Reservoir mask	103 (35.5)	91 (31)
High flow nasal cannula	10 (3)	9 (3)
Non-invasive positive pressure ventilation	87 (30)	91 (31)
Invasive positive pressure ventilation (endotracheal intubation)	34 (12)	45 (15)
Invasive positive pressure ventilation within 48 hours of enrollment	57 (20)	76 (25.5)
Drug history‡ (No (%))		
Baseline drug:		
Aspirin	72 (25)	85 (29)
P2Y12 inhibitors	4 (1)	11 (4)
Co-treatment:		
Any antiviral therapy	233 (80)	237 (80)
Remdesivir	195 (67)	194 (65)
Favipiravir	50 (17)	47 (16)
Lopinavir-ritonavir	1 (0.3)	3 (1)
Atazanavir-ritonavir	14 (5)	17 (6)
Corticosteroids	268 (92)	280 (94)
Colchicine	7 (2)	9 (3)
Chloroquine or hydroxychloroquine	22 (7.5)	22 (7)
Renin–angiotensin–aldosterone system inhibitors	51 (17.5)	48 (16)
Tocilizumab	43 (15)	42 (14)
Laboratory values at baseline§:		
Plasma creatinine (µmol/L)	88.4 (70.7-106.1)	88.4 (79.6-106.1)
White blood cells count ($\times 10^9$/L)	8.6 (6.1-11.7)	9.5 (7.0-12.5)
Hemoglobin level (g/L)	135 (118-147)	134 (120-147)
Platelet count ($\times 10^9$/L)	227 (170-289)	240 (180-304)
D dimer¶ (ng/mL)	800 (401-1565)	1000 (520-1943)
Aspartate transaminase (U/L)	43 (33.2-57)	44 (33-60)
Alanine transaminase (U/L)	40 (26-56)	39 (27-58)
Total bilirubin ((µmol/L)	6.8 (3.4-10.2)	6.8 (3.4-11.9)
Direct bilirubin (µmol/L)	5.1 (3.4-6.8))	5.1 (3.4-6.8)
Creatine phosphokinase (U/L)	105 (65-204)	115 (67-215)
Erythrocyte sedimentation rate (mm/h)	58 (32-78)	50 (29.5-70)
C reactive protein** (µg/L)	625(310-942)	560 (340-800)
Ferritin†† (µg/L)	528 (327-898)	459 (210-908)

*Imbalance between the two groups was significant (P<0.05) for current smokers and white blood cells count and a potentially important imbalance (P<0.15) for D dimer level. These hypothesis tests were not adjusted for multiplicity of comparisons.
†Index for severity of disease (range 0-71), composed of three components: acute physiology score, age, and chronic health status. Higher scores indicate poorer outcomes.
‡No patients received convalescent plasma.
§Normal ranges of measured laboratory tests defined as: 53.5-123.7 µmol/L for plasma creatinine, 4.5-11.0×10^9/L for white blood cells count, 135-175 g/L for men, and 120-156 g/L for women for hemoglobin level, 150-450×10^9/L for platelet count, <500 ng/mL for D dimer level, 10-40 U/L for men and 9-32 U/L for women for aspartate transaminase level, 4-36 U/L for alanine transaminase, 5.1-17 µmol/L for total bilirubin level and 3.4-12.0 µmol/L for direct bilirubin level, 200-395 U/L (upper limit of normal) for creatine phosphokinase level, <30 µg/L for C reactive protein level, and 24-336 µg/L for men and 11-307 µg/L for women for ferritin. Normal range for erythrocyte sedimentation rate varies with age and sex.
¶D dimer level at baseline was available for 199 patients (100 in atorvastatin arm, 99 in placebo arm).
**Checked in 385 patients (183 in atorvastatin arm, 202 in placebo arm) through quantitative assay, which have been included in the present analysis and performed with qualitative and semiquantitative assays in five and seven patients, respectively, which have not been included in the present analysis
††Checked in 290 patients (139 in atorvastatin arm, 151 in placebo arms) with quantitative assay (included in resent analysis) and seven patients with semiquantitative assay (not included in present analysis).



Intermediate dose

Patients at risk						
290	262	239	223	209	199	195
Primary outcome						
0	28	23	16	14	10	4
All cause mortality						
0	25	23	15	13	10	4
Venous thromboembolism						
0	3	1*	1	1	0	0
Ischemic stroke						
0	0	0	0	0	0	0

Standard dose

Patients at risk						
297	264	236	217	196	193	189
Primary outcome						
0	33	28	19	21	3	4
All cause mortality						
0	28	27	19	22	3	4
Venous thromboembolism						
0	4*	3*	1	1*	0	1*
Ischemic stroke						
0	1†	0	0	0	0	0

Fig 2 | Time to event for the primary outcome, a composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or all cause mortality during 30 days from randomization, in the prespecified primary cohort, consisting of patients who received at least one dose of the study drug, were not excluded, and did not withdraw consent. *All cause mortality events were censored by precedent venous thromboembolism events. †Venous thromboembolism event was censored by a precedent ischemic stroke event

with lower odds of the primary efficacy outcome among patients with symptom onset within seven days of hospital admission (0.60, 95% confidence interval 0.37 to 0.99) but not among patients with symptom onset more than seven days before hospital admission (1.27, 0.73 to 2.21) (P=0.05 for interaction).

Results from sensitivity analyses including all randomized patients and all randomized patients who met the eligibility criteria yielded similar results to those of the primary analysis (supplementary tables S8 and S9). Findings were similar when hazard ratio was used as the effect measure.

Discussion

In this study of adults with covid-19 admitted to the ICU, use of atorvastatin 20 mg once daily compared with placebo was not associated with a significantly reduced odds of the primary outcome, a composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or all cause mortality. Findings were consistent for several additional outcomes, including mortality and venous thromboembolism, and in study subgroups and sensitivity analyses. The current trial does not support a large 30 day benefit from statin treatment in patients with covid-19 admitted to the ICU. Despite adjustments for sample size estimates midway during the trial, the event rates were ultimately lower than expected and we cannot exclude a smaller treatment effect.

Potential explanations for the observed findings

These findings can be explained in several ways. First, it is possible that statin treatment in this study had a small protective role, which was not detected. Despite our re-estimation of the sample size, the primary efficacy outcome event rate was lower than expected. This issue might have been multifactorial, including more frequent use of corticosteroids,[31] better general care in the ICU, and lower acuity of illness in some patients. Second, it is possible that statin treatment is beneficial in early covid-19 before the inflammatory response leads to irreversible damage.[32] This is in line with the prespecified subgroup analysis that suggested a potential treatment effect in patients who were enrolled within the first seven days of hospital admission. However, as this finding was not adjusted for multiplicity, the results should be considered exploratory. Third, it is possible that the effect of statins on venous or arterial thrombosis or mortality become apparent beyond the 30 days of follow-up. Assessment of outcomes at 90 days is still ongoing and will be reported in the future.

The rate of thrombotic events in the current study was lower than in several other studies.[4 9 33] In INSPIRATION-S, routine imaging screening for thrombotic disease was not part of the study protocol. Imaging tests were performed only in cases of clinical suspicion. Although underdiagnosis is possible, many more patients were tested with imaging than those with an ultimate diagnosis of thrombosis. Among patients who had diagnostic imaging tests for venous thromboembolism, the proportion with confirmed venous thromboembolism was 13% (supplementary table S2). Some studies suggest that most thrombotic events in patients admitted to the ICU with covid-19 include subsegmental pulmonary embolism, distal deep vein thrombosis, and catheter associated thrombosis, which are less severe forms of venous thromboembolism. Furthermore, recent large multicenter observational studies[34 35] suggest lower event rates for venous thromboembolism in covid-19 than initially estimated in smaller studies; a finding that was confirmed in a recent systematic review and meta-analysis.[10] This finding could be partly related to more frequent use of prophylactic anticoagulation and anti-inflammatory treatments in more recent studies, compared with those that were conducted early during the covid-19 pandemic.

Table 2 | Thirty day outcomes in prespecified primary analysis population. Values are numbers (percentages) unless stated otherwise

Outcomes	No (%)		Risk difference (95% CI) (%)	Odds ratio (95% CI)	P value
	Atorvastatin group (n=290)	Placebo group (n=297)			
Primary outcome					
Composite of acute venous thrombosis, arterial thrombosis, treatment with ECMO, or all cause mortality*	95 (32)	108 (36)	−3.6 (−11.2 to 4.0)	0.84 (0.58 to 1.21)	0.35
Secondary outcomes					
All cause mortality	90 (31)	103 (35)	−3.3 (−10.8 to 4.2)	0.84 (0.58 to 1.22)	0.39
Venous thromboembolism	6 (2)	9 (3)	−0.9 (−3.5 to 1.5)	0.71 (0.24 to 2.06)	0.53
Median (IQR) ventilator-free days†	30 (10-30)	30 (4-30)			0.08
Exploratory outcomes					
Clinically diagnosed type I acute myocardial infarction‡	0	0			
Clinically diagnosed stroke§	0	1 (0.3)	−0.3 (−0.9 to 0.3)		0.32
Clinically diagnosed acute peripheral arterial thrombosis	0	0			
Median (IQR) ICU length of stay	5 (3-9)	5 (2-10)			0.31
Patients discharged from ICU (either home or ward)	201 (69)	199 (67)	2.0 (−5.4 to 9.6)	1.11 (0.76 to 1.61)	0.58
Incident atrial fibrillation	2 (1)	4 (1)	−0.6 (−2.2 to 0.9)	0.51 (0.09 to 2.87)	0.45
Undergoing new in-hospital renal replacement therapy	10 (3)	8 (3)	0.7 (−2.0 to 3.5)	1.30 (0.50 to 3.38)	0.57
Safety outcomes					
Fatal bleeding (BARC type 5)	2 (1)	2 (1)	0 (−1.3 to 1.3)	1.02 (0.14 to 7.32)	0.98
Major bleeding BARC type 3 or 5)¶	11 (4)	5 (2)	2.1 (−0.5 to 4.7)	2.30 (0.78 to 6.73)	0.12
Clinically relevant non-major bleeding** (BARC type 2)	6 (2)	8 (3)	−0.6 (−3.0 to 1.8)	0.77 (0.26 to 2.27)	0.64
Severe thrombocytopenia††	4 (1)	3 (1)	0.3 (−1.3 to 2.1)	1.30 (0.28 to 5.94)	0.73
Clinically diagnosed myopathy‡‡	0	0			
Increase in liver enzyme levels§§	5 (2)	6 (2)	−0.2 (−2.4 to 1.8)	0.85 (0.25 to 2.81)	0.79

ECMO=extracorporeal membrane oxygenation; IQR=interquartile range; ICU=intensive care unit; BARC=Bleeding Academic Research Consortium.
Participants in INSPIRATION and INSPIRATION-S were not completely identical. From 29 July 2020 to 19 November 2020, patients were being screened for the anticoagulation randomization, some of whom did not qualify for the statin randomization (primarily owing to an existing indication for statin treatment). Once the anticoagulation randomization completed enrollment, as prespecified in the study protocol, patient enrollment for the statin randomization continued. (See supplementary figure S1 for details).
*All venous thromboembolism events were adjudicated by the online clinical event committee. Each event was only confirmed by presenting a guideline recommended imaging test (see supplementary appendix). Acute arterial thrombosis was defined as type I acute myocardial infarction, ischemic stroke, and acute peripheral arterial thrombosis. No patients received ECMO.
†Difference between total number of days alive post-enrollment and total number of days receiving invasive mechanical ventilation.
‡Type I myocardial infarction was defined as increase or decrease, or both in cardiac troponin values with at least one value above the 99th centile upper limit of normal with at least one of the followings: symptoms of ischemia, or new or presumed new ischemic electrocardiographic (ECG) change, or development of pathologic Q waves on the ECG, or imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality in a pattern consistent with an ischemic cause; confirmed by coronary angiography, intravascular imaging, or autopsy. Myocardial injury was noted in six patients with a combination of increase in cardiac biomarker and ECG changes. Coronary angiography was only pursued in one patient (with normal coronary vasculature) and thus type I myocardial infarction was not adjudicated in any participants.
§For events with zero incidence in one group, only absolute risk difference was reported.
¶Consisted of BARC type 3 or 5, which is defined as type 3a for overt bleeding plus hemoglobin decrease of 30 to 50 g/L or any transfusion with overt bleeding; type 3b for overt bleeding plus hemoglobin decrease of 50 g/L, cardiac tamponade or bleeding requiring surgical intervention for control; type 3c for intracranial hemorrhage; and type 5 for fatal bleeding.[17]
**Clinically important bleeding that warranted attention from medical staff, but not fulfilling criteria for major bleeding.
††Platelet count <20×10^9/L.
‡‡New myopathy diagnosed by treating clinicians based on clinical and laboratory results.
§§Acute increase in liver enzyme levels >3 times the upper limit of normal.

Other ongoing and completed studies

It is conceivable that lipid modulating agents might affect the risk of thrombosis or inflammation in patients with covid-19.[36] Several ongoing randomized controlled trials are assessing the effects of lipid modulating agents, including statins, omega 3 fatty acids, fibrates, and niacin across the spectrum of illness severity in covid-19.[17] Specifically, for patients admitted to the ICU, three additional trials are ongoing (NCT04813471, NCT04359095, and NCT04631536) and the results will be informative about whether statins do have a benefit in the treatment of acute severe covid-19. In the adaptive Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia (REMAP-CAP) trial (NCT02735707), simvastatin (80 mg orally once daily for up to 28 days) is being compared with no treatment. The main study outcomes include days alive not receiving organ support in the ICU by day 21, and 90 day all cause death.

A distinct treatment effect for statins based on the underlying inflammatory biomarkers is possible.[20 37] INSPIRATION-S, however, did not have a prespecified biomarker study. Results from other randomized controlled trials, assessing the results based on background and interval changes in biomarkers and use of other anti-inflammatory drugs (such as corticosteroids) should elucidate this issue.

The daily dose of statin used in the current study (atorvastatin 20 mg once daily) was relatively similar to that used in HARP-2 (simvastatin 80 mg once daily).[20] This dose was chosen in INSPIRATION-S to minimize the risk of statin associated adverse effects, especially by coadministration of antiviral agents. The rates of statin associated adverse events (increased liver enzyme levels and myopathy) were, however, low in the current study. This observation is in part explained by the brief period of study intervention, compared with cardiovascular trials in which patients receive statin treatment for months or years.[38] In this regard, atorvastatin 40 mg once daily or rosuvastatin 20 mg once daily might have been more effective without compromising safety.

Since INSPIRATION-S focused on patients with covid-19 admitted to the ICU, the findings are not generalizable to other patient subgroups, including

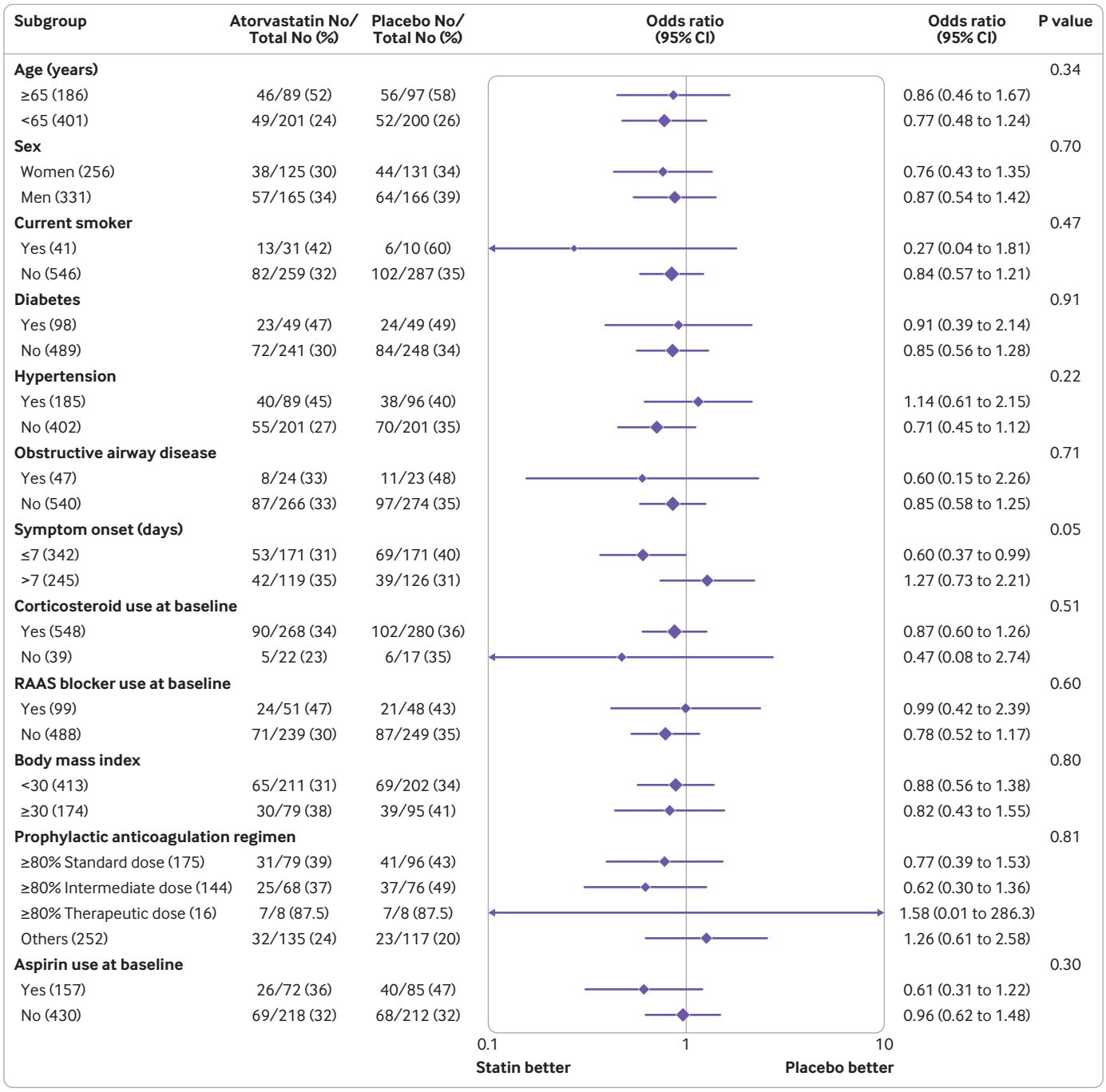


Fig 3 | Effect of atorvastatin in prespecified subgroups. RAAS=renin–angiotensin–aldosterone system. The x axis is on a log scale. Whiskers represent 95% confidence intervals

those admitted to medical wards or outpatients with covid-19. Other randomized controlled trials are investigating the effects of statins in these subgroups.[17] Most recently, results from a randomized controlled trial of 40 patients admitted to hospital with reverse transcription polymerase chain reaction confirmed covid-19 who were randomized to atorvastatin 40 mg once daily (in addition to combined lopinavir and ritonavir) compared with lopinavir-ritonavir alone, was published, suggesting reductions in C reactive protein levels (P=0.01) and hospital length of stay (8.0 *v* 9.8 days, P=0.01). The study was small, however, and open label and did not identify a significant difference between the two groups for the clinical outcomes.[39]

Strengths and limitations of this study

The strengths of this study include the multicenter enrollment of more than 500 patients from the ICU. Also, the double blind design reduced the risk of performance bias. A committee blinded to treatment assignment adjudicated all clinical outcomes, which enhances the reliability of reported outcomes.

This study has several limitations. First, type II error remains possible. Enrollment was stopped before the

target sample size was reached. Although the study included 98% of the planned sample size based on re-estimations in 2020, the final primary outcome event rate was lower than expected. This situation might have been because of improved care for patients with covid-19 in the latter months of enrollment compared with the early months of the pandemic. Therefore, the trial was underpowered for the original hypothesis. Findings from the other ongoing statin trials in patients admitted to the ICU are awaited.[17] Second, the acuity of illness in this study was lower than in ICU cohorts in some other studies, which might impact generalizability to extremely sick patients in the ICU. This challenge is likely multifactorial. The enrollment criteria required a minimum estimated survival of 24 hours and excluded patients already treated with extracorporeal membrane oxygenation to be able to discern a treatment effect if one were to exist. Such factors could have led to the exclusion of the sickest patients, such as those with unstable respiratory status on invasive mechanical ventilation or those receiving multiple vasopressors from enrollment. Nevertheless, the study population was very ill, as evidenced by the need for cardiopulmonary support and high mortality rates at 30 day follow-up. Several of the baseline treatments and presenting features are similar to those of other randomized controlled trials of patients in the ICU with covid-19.[40]

Finally, the treatments and care for patients with covid-19 have improved over time and could have affected the results. However, we did not identify a significant interaction between the assigned treatment and season of enrollment for the primary outcome (supplementary table S11).

Conclusions

In patients with covid-19 admitted to the ICU, atorvastatin 20 mg daily compared with placebo was not associated with a significant reduction in the composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or all cause mortality. The effects of a more potent statin regimen or the impact on a more targeted population of patients with covid-19 require additional investigation.

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See Appendix for trial committees and subcommittees.

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The study coordinating centres were the Rajaie Cardiovascular Medical and Research Center and the Tehran Heart Center. The trial protocol (see supplementary appendix 1) was approved by the Rajaie Cardiovascular Medical and Research Center ethics committee and accepted by all enrolling sites.

Contributors: PS and HB take responsibility for the integrity of the data and the accuracy of the analyses in this manuscript. They are the guarantors. BB, PS, and AHT designed the trial. FR, PPM, HB, DJ, AG, MVM, SAP, MM, GP, AJK, BVT, GWS, GYL, SZG, and HK contributed to the trial design. PS, AHT, BS, FR, MTB, KG, SR, AD, SHS, MF, AA, RA, TR, MY, SL, PR, SM, OT, KM, EZ, HR, SHS, SMS, HA, PS, MS, MA, VE, PP, HK, HT, TT, SS, SF, ST, HK, AK, and SS were responsible for collection and acquisition of the data. BB, PS, AHT, and HB drafted the manuscript, which was critically revised by all INSPIRATION-S investigators. BB and PS controlled the analysis plan and the decision to submit. HB conducted the analyses with help from PS and BB. PS an HB had full access to all the study data an vouch for the accuracy of the analyses. All authors take the responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: The trial protocol was approved by the Rajaie Cardiovascular Medical and Research Center ethics committee and accepted by all enrolling sites (IR.RHC.REC.1399.045). Patients or their healthcare proxies provided written informed consent for participation.

Data sharing: Data will become available to interested investigators upon submitting a reasonable research request by email and approved by the steering committee of the trial to B Bikdeli (bbikdeli@bwh.harvard.edu) or P Sadeghipour (psadeghipour@hotmail.com).

BB and PS affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The study was designed during the second wave of the covid-19 pandemic at a rapid pace, and consequently no specific plan was made for dissemination of the trial's results to patients and public communities. Upon publication of the manuscript, appropriate communications will be made with the press, and an excerpt of the findings will be shared on social media, with appropriate citations to the work.

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Appendix 1: trial protocol
Appendix 2: statistical analysis plan
Appendix 3: additional figures, tables, and other information
Supplementary information: Full list of author affiliations