Atorvastatin versus placebo in ICU patients with COVID-19: ninety-day results of the INSPIRATION-S trial

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Abstract

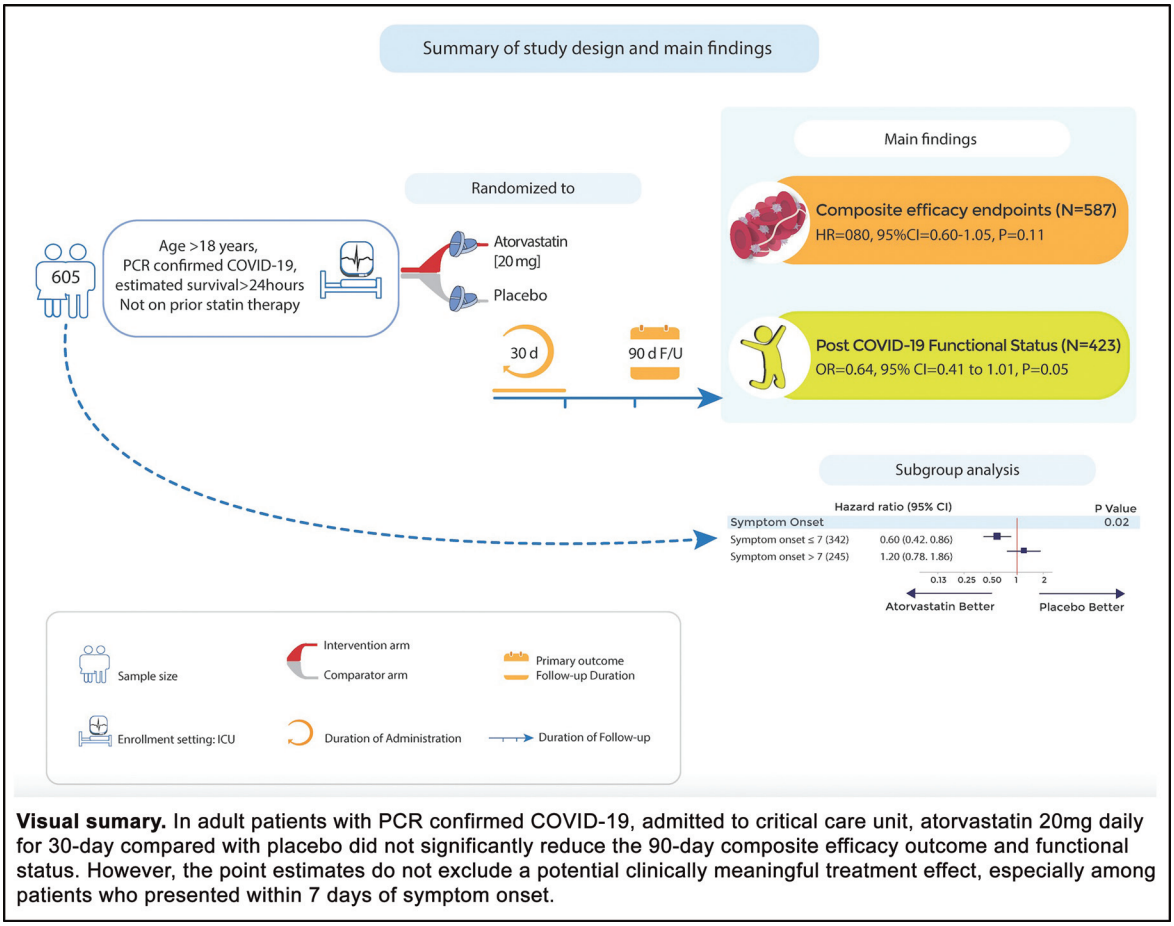
Background In the INSPIRATION-S trial, atorvastatin versus placebo was associated with a nonsignificant 16% reduction in 30-day composite of venous/arterial thrombosis or death in intensive care unit (ICU) patients with COVID-19. Thrombo-inflammatory response in coronavirus disease 2019 (COVID-19) may last beyond the first 30 days.

Methods This article reports the effects of atorvastatin 20 mg daily versus placebo on 90-day clinical and functional outcomes from INSPIRATION-S, a double-blind multicenter randomized trial of adult ICU patients with COVID-19. The main outcome for this prespecified study was a composite of adjudicated venous/arterial thrombosis, treatment with extracorporeal membrane oxygenation (ECMO), or all-cause mortality. Functional status was assessed with the Post-COVID-19 Functional Scale.

Results In the primary analysis, 587 patients were included (age: 57 [Q1–Q3: 45–68] years; 44% women). By 90-day follow-up, the main outcome occurred in 96 (33.1%) patients assigned to atorvastatin and 113 (38.0%) assigned to placebo (hazard ratio [HR]: 0.80, 95% confidence interval [CI]: 0.60–1.05, $p = 0.11$). Atorvastatin in patients who presented within 7 days of symptom onset was associated with reduced 90-day hazard for the main outcome (HR: 0.60, 95% CI: 0.42–0.86, $p_{interaction} = 0.02$). Atorvastatin use was associated with improved 90-day functional status, although the upper bound CI crossed 1.0 ($OR_{ordinal}$: 0.64, 95% CI: 0.41–1.01, $p = 0.05$).

Conclusion Atorvastatin 20 mg compared with placebo did not significantly reduce the 90-day composite of death, treatment with ECMO, or venous/arterial thrombosis. However, the point estimates do not exclude a potential clinically meaningful treatment effect, especially among patients who presented within 7 days of symptom onset (NCT04486508).

Keywords
- statin
- atorvastatin
- lipid
- COVID-19
- functional limitations



Visual sumary. In adult patients with PCR confirmed COVID-19, admitted to critical care unit, atorvastatin 20mg daily for 30-day compared with placebo did not significantly reduce the 90-day composite efficacy outcome and functional status. However, the point estimates do not exclude a potential clinically meaningful treatment effect, especially among patients who presented within 7 days of symptom onset.

Introduction

Coronavirus disease 2019 (COVID-19) disease severity is determined in large part by the intensity of inflammatory response and its potential for organ damage.[1–3] Targeting inflammation and thrombosis in patients with COVID-19 is considered an important strategy for disease management to improve clinical outcomes.[4–6]

Statins have pleiotropic effects which may attenuate the worsening inflammatory process in patients with COVID-19.[7,8] In addition, statins reduce platelet thrombogenicity[9] and modestly inhibit coagulation. Therefore, it has been hypothesized that statin therapy decreases the incidence of thrombotic complications and improves patient outcomes.[10,11]

The effect of statin therapy on clinical outcomes of patients with COVID-19 remains uncertain.[11] In the INSPIRATION-statin (INSPIRATION-S) trial, the effects of atorvastatin 20 mg daily compared with placebo for 30 days on short-term (30-day) clinical outcomes in patients with COVID-19 admitted to the intensive care unit (ICU) were previously reported.[12] The study was terminated prematurely with lower event rates than originally anticipated. In this context, although use of atorvastatin was safe and suggested favorable point estimates for efficacy, it was not shown superior to placebo in reducing the 30-day rate of the composite of adjudicated venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation (ECMO), or all-cause mortality.[12] However, considering the persistent elevation of inflammatory mediators beyond the first 30 days in patients with COVID-19,[13–17] and the reported durable modulatory effect of statins on thromboinflammation beyond the early period of drug use,[18] a longer follow-up might clarify the role of statins in this population. In addition, patients who survived COVID-19 are frequently forced to cope with worse quality-of-life and neuropsychiatric changes.[19] It is unknown if statins can modify such functional outcomes. This manuscript summarizes the prespecified 90-day clinical and functional status outcomes of the INSPIRATION-S trial.

Methods

The trial design has been described previously.[20] Briefly, the Intermediate versus Standard-Dose Prophylactic Anticoagulation in Critically-ill Patients With COVID-19: An Open Label Randomized Controlled Trial (INSPIRATION) and INSPIRATION-statin (INSPIRATION-S) was a trial with a 2×2 factorial design in patients with COVID-19 admitted to the ICU. Details on study sites is mentioned in the ►**Supplementary Material** (available in the online version). Results of the anticoagulation randomization and short-term (i.e., 30-day) findings for atorvastatin randomization have been reported in separate prior publications.[12,21–23]

Study Patients

Adult patients with polymerase chain reaction-confirmed COVID-19 who were admitted to the ICU within 7 days of initial hospitalization and had expected survival of more than 24 hours were considered for inclusion. Major exclusion criteria were strong indication or ongoing use of statins prior to hospitalization, liver enzyme tests >5 times upper normal limit or active liver disease (liver enzyme tests >3 times upper normal limit plus histological findings including cirrhosis, or inflammation, or necrosis), and creatine kinase >500 U/L. We planned to assess the effects of treatment with atorvastatin on acute inflammatory processes due to COVID-19 in a prospective clinical trial. We chose to exclude patients who had a solid indication for statin therapy, since it is unethical to randomize such patients to active treatment versus placebo. The full list of eligibility criteria[20,21] is available in the ►**Supplementary Material** (available in the online version).

Intervention and Control

The study intervention was atorvastatin 20 mg once daily versus placebo. This dose of atorvastatin (instead of 40 or 80 mg per day) was used because of possible interaction with lopinavir/ritonavir, routinely used for COVID-19 treatment during the study period. The study drug was intended to be continued until 30 days from enrollment or reaching the 30-day primary efficacy outcome. Patients, investigators, and study physicians remained blinded to treatment assignment. For those patients discharged before 30 days, a supply of the study drug was provided. Postdischarge adherence was monitored via weekly phone and video interviews by site clinicians or the trial coordinating center. Details regarding the randomization procedure and timing have been reported previously.[12]

Study Outcomes

For this prespecified 90-day follow-up analysis, the main outcome was a composite of objectively confirmed venous thromboembolism (VTE), arterial thrombosis, treatment with ECMO, or all-cause mortality. Additional efficacy outcomes included the 90-day occurrence of individual components of the composite outcome along with the rates of renal replacement therapy and incident atrial fibrillation.

Ninety-day functional outcomes were assessed by the Post-COVID-19 Functional Status (PCFS) scale[24,25] (translated by the authors into Farsi [►**Supplementary Material**, available in the online version]). PCFS is an ordinal outcome scale that grades patients from 0 (no functional limitations) to 4 (severe functional limitations) and 5 (death). Notably, the decision to include functional outcomes in INSIPRATION-S was finalized by the steering committee on August 28, 2020, and thus patients recruited before this time point were not included in this sub-analysis (►**Supplementary Fig. S1**, available in the online version).

The Patient Health Questionnaire-2 (PHQ-2)[26,27] was used to screen for the 90-day depressive symptoms. PHQ-2 is scored from 0 to 6, with scores ≥3 translated to a higher likelihood of major depressive disorder.[28] For completion of PHQ-2, patient direct participation was required and therefore, this analysis was performed in patients who survived and accepted to participate in 90-day follow-up assessment.

Prespecified safety outcomes included rise in liver enzymes (defined as >3 times upper normal limit), clinically diagnosed myopathy, and major bleeding, as assessed according to the Bleeding Academic Research Consortium criteria (BARC type 3 or 5), within 90 days of statin initiation. Efficacy and safety outcomes were adjudicated by a clinical events committee who remained blinded to treatment assignment. Access to the randomization log was restricted and permitted only on an emergency basis, as requested by the Data Safety and Monitoring Board.

Statistical Analysis

Frequency counts (percentages) were used to report categorical variables. Continuous variables were reported as mean and standard error, or median with interquartile ranges (for variables that were not normally distributed).

All randomized patients who met the eligibility criteria, did not withdraw consent, and received at least one dose of the assigned treatment were included in the primary analysis. Assessment of the 90-day composite efficacy outcome was prespecified to be performed via mixed-effects models with hazard ratio (HR) as the effect measure and accounting for the enrolling sites as a random effect. Since INSPIRATION/INSPIRATION-S employed a 2×2 factorial design,[21,22] a test of interaction between the two interventions was performed for the main efficacy and the main safety outcomes. No significant interaction was found between the assigned prophylactic anticoagulant regimen and the assigned statin regimen for the 90-day main efficacy ($p = 0.75$) or the main safety outcome ($p = 0.27$). Therefore, results of the statin randomization are presented independently.

For comparisons of 90-day functional status between patients assigned to atorvastatin versus placebo, a mixed-effects ordinal logistic regression model with random intercepts for enrolling centers was used, resulting in odds ratios (ORs) and corresponding confidence intervals (CIs). Higher ORs represent the odds of ending up in a higher PCFS category (i.e., worse functional status). For comparison of PHQ-2 at 90-day follow-up between the two assigned treatments, a mixed-effects binary logistic regression model with random intercept for centers was used.

A p-value <0.05 was considered significant for the main outcome. No adjustment for multiplicity of comparisons was prespecified. Therefore, assessment of the findings for other outcomes and within subgroups should be considered exploratory. Statistical analyses were performed via Stata 16 (for Mac OS, StataCorp, Texas, United States).

Results

From the predefined 626 target sample size, 605 patients were enrolled in the INSPIRATION-S study (303 randomized to atorvastatin and 302 randomized to placebo) between July 29, 2020 and April 4, 2021. Premature termination was due to limited study funds and excessive strain on the study

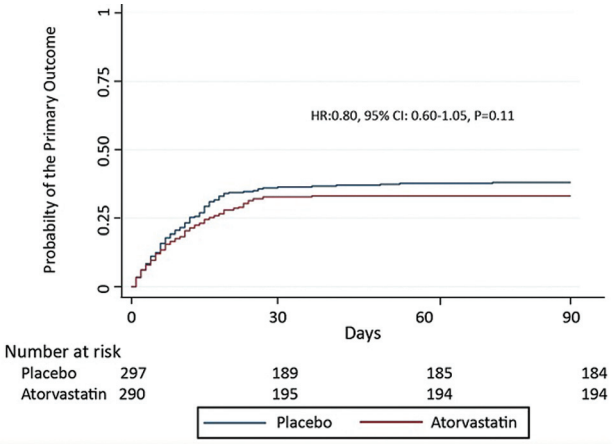


Fig. 1 Composite efficacy outcome in the prespecified primary cohort. Composite of adjudicated acute arterial thrombosis, venous thromboembolism, extracorporeal membrane oxygenation, or all-cause mortality during 90 days from enrollment. The prespecified primary cohort consisted of patients who received at least one dose of the study drug, were not excluded, and did not withdraw consent.

personnel. Baseline patient characteristics of the trial participants have been described previously.[21] Briefly, the median (Q1, Q3) age in the atorvastatin and placebo groups were 57 (45, 67) and 57 (45, 68) years, respectively. Women constituted 43.1% versus 44.1% of study participants in the atorvastatin and placebo groups. Other baseline characteristics, comorbidities, and background therapies were comparable in both groups, except for history of smoking, which was more common in patients assigned to atorvastatin than to placebo (31 [10.7%] vs. 10 [3.4%] patients).

Efficacy Outcomes

By 90-day follow-up, the composite efficacy outcome occurred in 96 (33.1%) patients assigned to atorvastatin 20 mg once daily and 113 (38.0%) patients assigned to placebo (HR: 0.80, 95% CI: [0.60–1.05], $p = 0.11$) (►**Fig. 1**, ►**Table 1**). There were six new adjudicated events from day 31 to 90 of follow-up, five in those assigned to placebo and one in those assigned to atorvastatin. Ninety-day all-cause mortality was adjudicated in 91 (31.3%) patients assigned to atorvastatin and 108 (36.3%) patients assigned to placebo (HR: 0.78, 95% CI: [0.59–1.04], $p = 0.09$; ►**Table 1** and ►**Fig. 2**).

Adjudicated VTE events occurred in 6 (2.1%) patients assigned to atorvastatin and 9 (3.0%) patients assigned to placebo (HR: 0.61, 95% CI: [0.21–1.72]; $p = 0.35$). There were no cases of myocardial infarction or acute peripheral arterial thrombosis. Ischemic stroke occurred in one patient in the placebo group. New atrial fibrillation was diagnosed in 2 (0.6%) and 5 (1.6%) patients assigned to atorvastatin and placebo, respectively (HR: 0.38, 95% CI: [0.07–1.99]; $p = 0.25$). New renal replacement therapy at 90-day follow-up occurred in 10 (3.4%) patients assigned to atorvastatin and 8 (2.6%) patients assigned to placebo group (HR: 1.20, 95% CI: [0.47–3.06]; $p = 0.69$).

Functional Status and Depressive Symptoms

For the functional status analysis, of the 605 enrolled patients, 524 were recruited after August 28, 2020, of whom 101 patients did not consent to be interviewed for the functional status assessment. Therefore, 423 patients (median age: 58 (45,67) years; 43% women) were included in the functional status analysis (►**Supplementary Fig. S1**, available in the online version): 209 patients assigned to atorvastatin and 214 patients to placebo (►**Supplementary Table S1**, available in the online version). In the mixed-effects ordinal regression model with random intercept for centers, use of atorvastatin versus placebo showed a tendency for improved 90-day functional status grading, although the upper bound CI crossed 1.0 ($OR_{ordinal}$: 0.64, 95% CI: [0.41–1.01], $p = 0.05$; ►**Fig. 3A**).

For depressive symptoms screening, only patients who survived and agreed to the 90-day follow-up were included (119 and 115 patients in atorvastatin and placebo groups, respectively). The proportion of patients with 90-day PHQ-2 score $\geq$3 was higher yet not significantly different in those assigned to statin versus placebo (20/119 [16.8%] vs. 11/115 [9.6%]) (►**Fig. 3B**). In the mixed-effects binary logistic regression model with random intercept for centers, there was no significant association between atorvastatin versus placebo on reduced odds of PHQ-2 $\geq$3 at 90-day follow-up (OR_{binary}: 1.86, 95% CI: [0.77–4.55]; $p = 0.16$).

Safety Outcomes

By 90-day follow-up, rise in liver enzymes >3 times upper normal limit was identified in 5 (1.7%) patients who were assigned to atorvastatin compared with 7 (2.3%) on placebo. There were no cases of clinically diagnosed hepatotoxicity or myopathy in either study group.

Fatal bleeding occurred in 2 (0.6%) of patients assigned to atorvastatin compared with 2 (0.6%) patients in the placebo group (HR: 1.02, 95% CI: [0.14–7.27]; $p = 0.98$). Eleven patients randomized to receive atorvastatin (3.7%) and five randomized to placebo (1.6%) were diagnosed with major bleeding (HR: 2.14, 95% CI: [0.74–6.19]; $p = 0.15$). Clinically relevant nonmajor bleeding occurred in 7 (2.4%) patients randomized to atorvastatin versus 9 (3.0%) patients in the placebo group (HR: 0.84, 95% CI: [0.3–2.32]; $p = 0.74$). Severe thrombocytopenia, defined as platelet counts less than 20,000/fL occurred in 4 (1.3%) in the atorvastatin group versus 3 (1.0%) of those in the placebo group.

Sensitivity Analysis

In the sensitivity analyses of all nonduplicative eligible randomized patients ($N = 605$), or all patients who met the eligibility criteria ($N = 591$), and per-protocol cohort ($N = 444$), the results were similar to the primary analyses (►**Supplementary Tables S2–S4**, available in the online version). An exploratory landmark analysis showed that the composite efficacy outcome was not significantly different in those assigned to atorvastatin versus placebo from day 31 to day 90 of follow-up (HR: 0.18, 95% CI: [0.02–1.62]) (►**Supplementary Fig. S2**, available in the online version).

Subgroup Analysis

In the assessment of the prespecified subgroups, the outcomes were similar for most subgroups including in women

Table 1 Ninety-day outcomes in the prespecified primary analysis population

Outcome	Atorvastatin ($n=290$), n (%)	Placebo ($n=297$), n (%)	Risk difference (95% CI)*	Hazard ratio (95% CI)**	p-Value
Composite efficacy outcome					
Composite of adjudicated acute venous thrombosis[a], arterial thrombosis[b], treatment with extracorporeal membrane oxygenation[c], or all-cause mortality	96 (33.1)	113 (38.0)	−4.9 (−12.6 to 2.7)%	0.80 (0.60–1.05)	0.11
Secondary outcomes					
All-cause mortality	91 (31.3)	108 (36.3)	−4.9 (−12.6 to 2.6)%	0.78 (0.59–1.04)	0.09
Venous thromboembolism	6 (2.0)	9 (3.0)	−0.9 (−3.5 to 1.5)%	0.61 (0.21–1.72)	0.35
Exploratory outcomes					
Type I acute myocardial infarction[d]	0[f]	0			
Stroke	0	1 (0.3)	−0.3 (−0.9 to 0.3)%		0.32
Peripheral arterial thrombosis	0	0			
Incident atrial fibrillation	2 (0.6)	5 (1.6)	−0.9 (−2.7 to 0.7)%	0.38 (0.07–1.99)	0.25
New in-hospital renal replacement therapy	10 (3.4)	8 (2.6)	0.7 (−2.0 to 3.5)%	1.20 (0.47–3.06)	0.69
Safety outcomes					
Fatal bleeding (BARC 5)	2 (0.6)	2 (0.6)	0 (−1.3 to 1.3)%	1.02 (0.14–7.27)	0.98
Major bleeding (BARC 3 or 5)[e]	11 (3.7)	5 (1.6)	2.1 (−0.5 to 4.7)%	2.14 (0.74–6.19)	0.15
Clinically relevant nonmajor bleeding[g] (BARC 2)	7 (2.4)	9 (3.0)	−0.6 (−3.2 to 2.0)%	0.84 (0.30–2.32)	0.74
Severe thrombocytopenia[h]	4 (1.3)	3 (1.0)	0.3 (−1.3 to 2.1)%	1.16 (0.25–5.29)	0.84
Myopathy[i]	0	0			
Rise in liver enzymes[j]	5 (1.7)	7 (2.3)	−0.6 (−2.9 to 1.6)%	0.69 (0.21–2.17)	0.52

Abbreviations: BARC, Bleeding Academic Research Consortium; CI, confidence interval; ICU, intensive care unit.
Note: *,**Risk differences are crude measurement and HRs are from mixed-effects models; p-values are for HRs.
[a]All the venous thromboembolism events were adjudicated by the online clinical event committee. Each event was only confirmed by presenting a guideline-recommended imaging test (see Appendix).
[b]Acute arterial thrombosis defined as type I acute myocardial infarction, ischemic stroke, and acute peripheral arterial thrombosis.
[c]No patients received extracorporeal membrane oxygenation.
[d]Type I myocardial infarction was defined as rise and/or fall in cardiac troponin values with at least one value above the 99th percentile upper reference limits 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 ischemic etiology; confirmed by coronary angiography, intravascular imaging or autopsy. Myocardial injury was noted in six patients with a combination of cardiac biomarker rise and electrocardiographic 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.
[e]Major bleeding consisted of Bleeding Academic Research Consortium (BARC) type 3 and 5, which defines as type 3a for overt bleeding plus hemoglobin drop of 3 to 5 g/dL, or any transfusion with overt bleeding; type 3b for overt bleeding plus hemoglobin drop 5 g/dL, cardiac tamponade or bleeding requiring surgical intervention for control, type 3c for intracranial hemorrhage, and type 5 for fatal bleeding.[36]
[f]For events with zero incidence in one group, only absolute risk difference was reported.
[g]Clinically significant bleeding that warranted attention from the medical personnel, but not fulfilling criteria for major bleeding.
[h]Platelet count <20,000/fL.
[i]New myopathy diagnosed by the treating clinicians based on clinical and laboratory results.
[j]Acute rise in liver enzymes >3 times the upper reference limit.

and men, those with or without obesity, those with or without diabetes, and those with and without obstructive airway disease (►**Fig. 4**). However, there was an association between atorvastatin use and improvement in the main composite outcome in those assigned to atorvastatin within the first 7 days of symptoms ($N=342$), but not in those randomized after 7 days of symptoms onset ($N=245$) (HR: 0.60, 95% CI: [0.42–0.86] vs. HR: 1.20, 95% CI: [0.78–1.86], $p_{\text{interaction}}=0.02$). In the mixed-effects ordinal regression model with random intercept for centers, use of atorvastatin versus placebo was associated with improved 90-day PCFS in those assigned to atorvastatin within the first

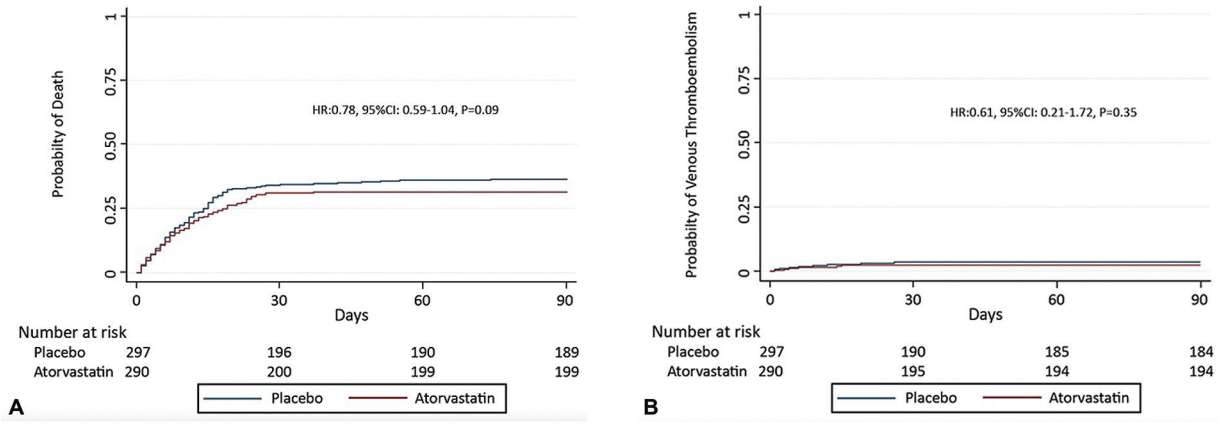


Fig. 2 Kaplan–Meier curve for all-cause mortality (**A**) and VTE (**B**). The prespecified primary cohort consisted of patients who received at least one dose of the study drug, were not excluded, and did not withdraw consent. For panel (B), competing risk of mortality was addressed. VTE, venous thromboembolism.

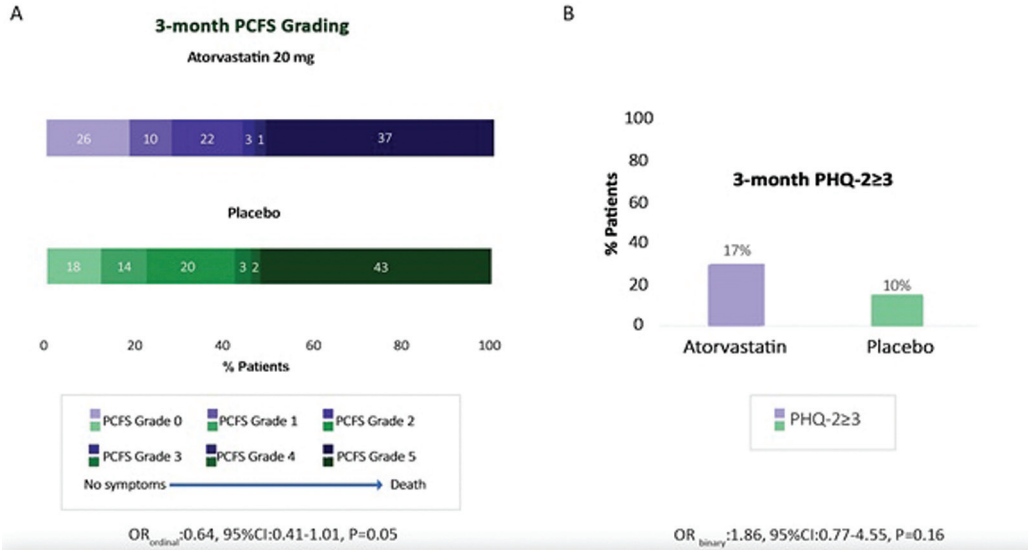


Fig. 3 Three-month PCFS grading and proportion of patients PHQ-2 ≥3 in the two study groups. Comparison of PCFS grading (**A**) and proportion of patients PHQ-2 ≥3 (**B**) analyzed via the mixed-effects regression model with random intercept for centers were depicted. Patients' percentages in each class of PCFS were compared between atorvastatin (purple) versus placebo (green). Darker colors designated worse outcomes. PCFS, Post-COVID-19 Functional Scale; PHQ-2, Patient Health Questionnaire-2.

7 days of symptoms ($OR_{ordinal}$: 0.69, 95% CI: [0.49–0.97], $p = 0.03$).

Discussion

In this study of acutely ill patients, atorvastatin 20 mg daily was not associated with the significantly lower rate of the 90-day composite of all-cause death, treatment with ECMO, or venous or arterial thrombosis. However, there was an association between starting atorvastatin within the first 7 days of symptom onset and lower rates of adverse events as well as better functional outcomes. No changes were observed in depressive symptoms. It is therefore possible that the use of atorvastatin, compared with placebo, has positive impact on the outcomes of patients with COVID-19, especially when they present early in the course of disease. Notably, in INSPIRATION-S, only 605 out of the target of predefined 626 patients were enrolled. In addition, the pooled actual event rate in INSPIRATION-S was lower than expected event rate at the time of trial design. While a clinically meaningful treatment effect is possible, the results of this trial were not definitive and should be verified by findings from other ongoing randomized controlled trials (RCTs).[29]

Despite an association between antecedent statin use and reduced in-hospital mortality among patients admitted with COVID-19 in a prior retrospective analysis (OR = 0.47, 95% CI [0.36–0.62], $p < 0.001$),[30] in this trial atorvastatin use was not associated with significantly improved survival at 90-day follow-up (HR: 0.78, 95% CI [0.59–1.04], $p = 0.09$). The potential reasons for this discrepancy may include lack of sufficient statistical power in the current study (type II error), lower dose of statin therapy in INSPIRATION-S (chosen because of drug–drug interactions) compared with observational studies which applied high-intensity statins,[31]

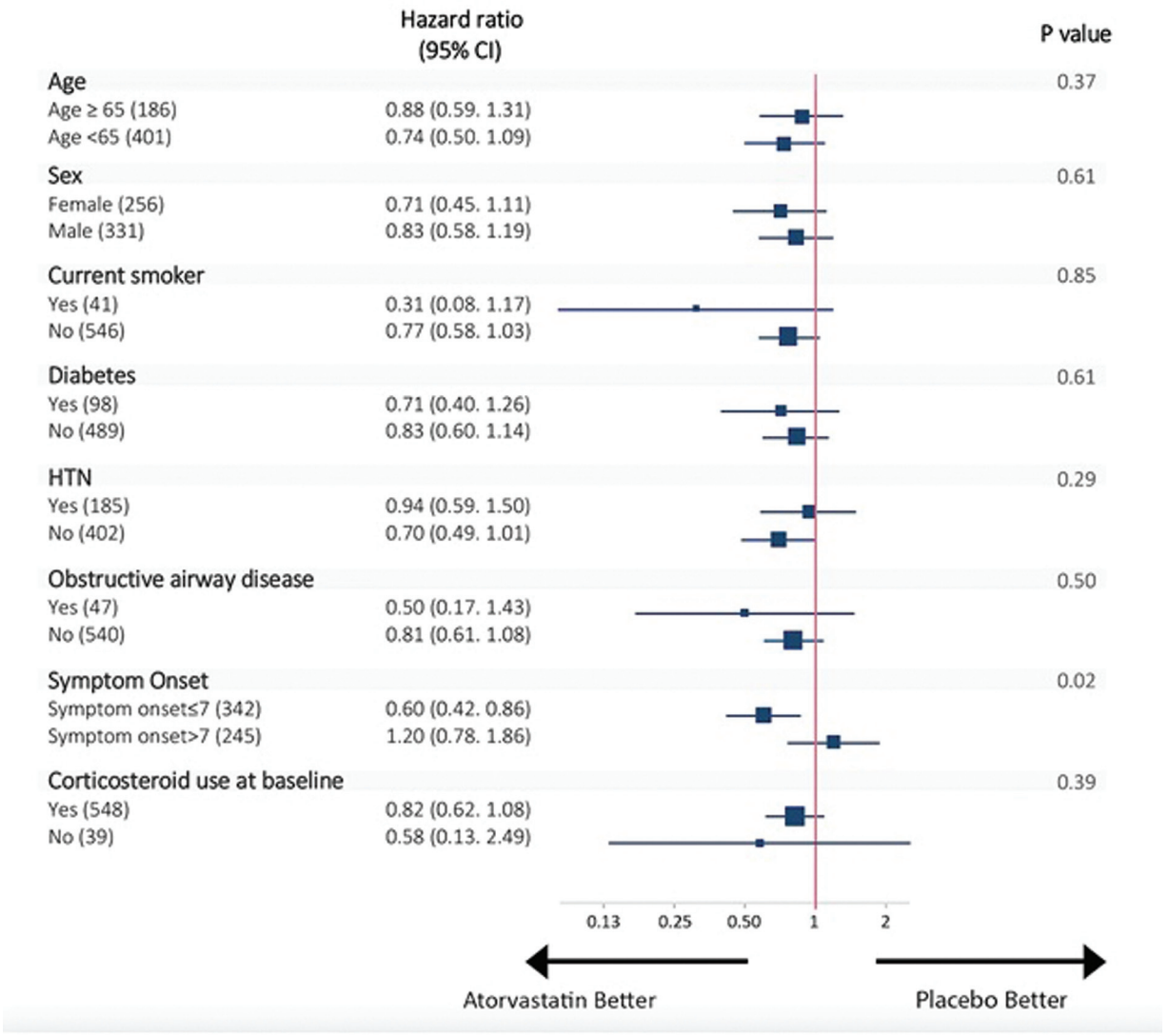


Fig. 4 Subgroup analysis for the main composite outcome.

differential impact based on the timing of administration of statins (antecedent vs. during acute illness), patient population (patients in ICU may be too sick to benefit from statins), or a true lack of treatment effect for statins.

There was no significant reduction in the incidence of venous/arterial thrombosis with atorvastatin 20 mg daily versus placebo at 90-day follow-up. Notably, the pooled actual event rates were lower than expected at the time of trail design, possibly because patients were not routinely screened for VTE. Imaging tests were implemented only in cases of clinical suspicion. Thrombotic event rates may have also been reduced in more recent periods of the pandemic as a result of other effective therapies targeting thrombo-inflammation.

Early use of atorvastatin 20 mg daily, within the first 7 days of symptoms onset, was associated with an improvement in the composite study outcome, consistent with the hypothesis-generating findings reported previously.[12] Lipid rafts have a crucial role in virus entry during the early phases of severe acute respiratory syndrome. Their disruption by statins may help reducing angiotensin-converting enzyme 2-mediated virus infection. Consequently, early initiation of statins could impact the modulation of virus entry.[32] Furthermore, most inflammatory markers are increased within the first 7 days of infection,[33] which supports the idea of improved outcomes associated with early statin treatment. In addition, early administration of statins may protect the vascular endothelium by enhancing endothelial nitric oxide synthase activity and diminishing the release of systemic endothelial-derived microparticles. This effect is also associated with reducing inflammatory cytokines.[34] Similarly, in the HARP-2 trial, the administration of simvastatin within 48 hours in the hyper-inflammatory phase of acute respiratory distress syndrome was associated with improving 28- and 90-day survival.[35]

In the current trial, there was a hypothesis-generating improvement of functional limitation with statin therapy, whereas atorvastatin use was not associated with significant difference in depressive symptoms compared with placebo. The results of studies that have examined the effect of statins on functional status in different settings are heterogenous. However, a systematic review and meta-analysis of RCTs of non-COVID-19 patients suggested a positive effect of statins (in particular the lipophilic ones due to better penetration to

blood–brain barrier) on mitigating the severity of depression.[19]

This study has several limitations. First, the study was stopped prematurely before meeting its target sample and the event rates were lower than expected. Consequently, this study was not sufficiently powered to assess the effect of atorvastatin on the composite efficacy outcome given the observed event rates. Also, functional outcomes could not be assessed in all patients because they were only included in the study protocol during the course of the study and a considerable number of patients refused the necessary interview. There are at least 15 other RCTs on the use of statins (atorvastatin [20 and 40 mg], simvastatin [40 and 80 mg], rosuvastatin [5 and 40 mg]) in different settings of ICU (three studies), non-ICU (11 studies), and postdischarge (1 study) patients with COVID-19.[11] These studies will help elucidate the effect of statins on patient outcomes. Second, it is possible that a higher dose of statin therapy would have been associated with improved outcomes. Furthermore, atorvastatin was only used for 30 days. A longer duration of treatment in future studies may be associated with sustained improvement. While the duration of treatment is a limitation of this study for the assessment of long-term effects of atorvastatin, we believe that targeting the inflammation in the early phase of COVID-19 is the most determining factor in patients' outcomes. Additionally, most patients were co-treated with steroids with stronger anti-inflammatory properties, which may have affected the treatment effect of statins. We also did not assess the patients' medications from 31 to 90 day of follow-up. However, at the time of the conduct of the trial, no other medications were known to improve durable outcomes in patients with COVID-19. In addition, since the study groups were randomized and received blinded therapies, it is probable that no imbalance occurred between the groups. In addition, we did not check inflammatory biomarkers (such as high sensitivity C-reactive protein) or cholesterol levels to elucidate the potential mechanism of atorvastatin action in the study population. Finally, although the results among subgroups are interesting and prespecified, they were not adjusted for multiplicity of comparisons, and should be considered hypothesis-generating.

Conclusion

Use of atorvastatin versus placebo for 30 days in patients with COVID-19 admitted to the ICU was not superior to placebo in preventing the composite of venous or arterial thrombosis, treatment with ECMO, or all-cause mortality at 90-day follow-up. However, treatment with atorvastatin was associated with improvement in 90-day functional status, especially when applied within the first 7 days of symptom onset; in this patient subgroup, atorvastatin use was also associated with a reduction in the incidence of the efficacy outcomes. These findings support that a clinically important treatment effect associated with atorvastatin use was not shown beyond doubt in our trial, but cannot yet be excluded. Results from ongoing statin trials in COVID-19 are highly awaited with respect to the overall population, including those who present early in the disease course, especially with regard to functional outcomes.

What is known about this topic?

- Statins reduce platelet thrombogenicity and modestly inhibit coagulation which may decrease the incidence of thrombotic complications.
- Statins have pleiotropic effects which may attenuate the worsening inflammatory process in patients with COVID-19.
- In the INSPIRATION-S trial, atorvastatin versus placebo was associated with a nonsignificant 16% reduction in 30-day composite of venous/arterial thrombosis or death in ICU patients with COVID-19.
- Thromboinflammatory response in COVID-19 may last beyond the first 30 days.

What does this paper add?

- Atorvastatin 20 mg compared with placebo did not significantly reduce the 90-day composite of death, treatment with ECMO, or venous/arterial thrombosis. However, statin therapy may have potential effects on the outcomes of critically ill patients admitted to the ICU with COVID-19 who presented early after infection.
- Atorvastatin use was associated with improved 90-day functional status assessed by Post-COVID-19 Functional Scale (PCFS) *in critically ill patients admitted to the ICU*. These findings should be verified in upcoming studies.

Note

Tweet: #atorvastatin did NOT ↓composite of venous/arterial thrombosis/ECMO/mortality in 90-days F/U of #INSPIRATION-S in patients w #COVID19 admitted to ICU. Potential improvement in PCFS & hypothesis-generating improvement in pts presenting within 7 days need further validation.

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Conflict of Interest

D. V. reports consultant and speaker for BMS/Pfizer, Daiichi-Sankyo, Rovi, and Sanofi. Dr. Gupta received payment from the Arnold & Porter Law Firm for work related to the Sanofi clopidogrel litigation and from the Ben C. Martin Law Firm for work related to the Cook inferior vena cava filter litigation. A. G. holds equity in a health care telecardiology startup, Heartbeat Health, Inc., and received consulting fees from Edwards LifeSciences. M. V. M. has received support from an institutional grant by the National Institutes of Health/National Heart, Lung, and Blood Institute to Columbia University Irving Medical Center (T32 HL007854). S. S. S. reports honoraria from Janssen and Chiesi and research grant support from the American Heart Association. G. P. has received research support from Bristol-Myers Squibb/Pfizer Alliance, Bayer, Janssen, Alexion, Amgen, and Boston Scientific Corporation, and consulting fees from Bristol-Myers Squibb/Pfizer Alliance, Boston Scientific Corporation, Janssen, Namsa, Prairie Education and Research Cooperative, Boston Clinical Research Institute, and Amgen. S. A. P. reports being on the Advisory Board for Abbott, Boston Scientific, Medtronic, CSI, Philips, Janssen; research grants: Abbott, Boston Scientific, Surmodics, TriReme Medical, Shockwave Medical; and receiving consulting fees from Terumo and Abiomed. M. M. received an unrestricted educational grant for research from Sanofi, Leo, and Rovi, and fees for participating in advisory meetings from Sanofi. A. J. K. reports institutional funding to Columbia University and/or Cardiovascular Research Foundation from Medtronic, Boston Scientific, Abbott Vascular, Amgen, CSI, Philips, ReCor Medical, Neurotronic, Biotronik, Chiesi, Bolt Medical, Magenta Medical, Canon, SoniVie, Shockwave Medical, and Merck. In addition to research grants, institutional funding includes fees paid to Columbia University and/or Cardiovascular Research Foundation for consulting and/or speaking engagements in which Dr. Kirtane controlled the content. Personal: consulting from IMDS; Travel Expenses/Meals from Medtronic, Boston Scientific, Abbott Vascular, CSI, Siemens, Philips, ReCor Medical, Chiesi, OpSens, Zoll, and Regeneron. S. B. reports unrestricted research grants from Bayer, Concept Medical, INARI, Boston Scientific, Bard, and Sanofi; honoraria from Bayer, Concept Medical, INARI, and Boston Scientific. B. W. V. T. has received research support from Novartis, Swedish Orphan Biovitrum, Olatec Therapeutics, Serpin Pharm, and R-Pharm. He has been a consultant of R-Pharm and Serpin Pharma. G. W. S. has received speaker or other honoraria from Cook, Terumo, and Orchestra Biomed; served as a consultant to Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, Matrizyme, and Cardiomech; and has received equity or options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, MedFocus family of funds, and Valfix. G. Y. H. L. reports consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are received personally. H. M. K. reports personal fees from UnitedHealth, personal fees from IBM Watson Health, personal fees from Element Science, personal fees from Aetna, personal fees from Facebook, personal fees from Siegfried & Jensen Law Firm, personal fees from Arnold & Porter Law Firm, personal fees from Ben C. Martin Law Firm, personal fees from National Center for Cardiovascular Diseases, Beijing, ownership of HugoHealth, ownership of Refactor Health, contracts from the Centers for Medicare & Medicaid Services, grants from Medtronic and the Food and Drug Administration, grants from Medtronic and Johnson and Johnson, grants from Shenzhen Center for Health Information, and is a Venture Partner at FPrime. Outside the submitted work. B. B. is supported by a research grant from The Mary Horrigan Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital. B. B. reports that he is a consulting expert, on behalf of the plaintiff, for litigation related to two specific brand models of IVC filters. All other authors report no relevant disclosures.

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