Received: 12 February 2021 | Revised: 6 May 2021 | Accepted: 28 May 2021

DOI: 10.1111/ijcp.14434

ORIGINAL PAPER

Infectious diseases

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

Promising effects of atorvastatin on mortality and need for mechanical ventilation in patients with severe COVID-19; a retrospective cohort study

Mohammad Haji Aghajani[1] | Omid Moradi[2] | Hamed Azhdari Tehrani[3] | Hossein Amini[2] | Elham Pourheidar[2] | Firouze Hatami[4] | Mohammad Mahdi Rabiei[4] | Mohammad Sistanizad[1,2]

[1]Prevention of Cardiovascular Disease Research Center, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2]Department of Clinical Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[3]Department of Hematology and Medical Oncology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[4]Clinical Research Development Unit of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Correspondence
Mohammad Sistanizad, Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Valiasr St, Tehran, Iran.
Email: sistanizadm@sbmu.ac.ir

Funding information
This study was performed in prevention of cardiovascular disease research centre, under the supervision of vice chancellery of research and technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran, and did not receive any financial support from other sources.

Abstract

Purpose: Considering the anti-inflammatory effect of atorvastatin and the role of medical comorbidities such as hypertension and coronary artery disease on the prognosis of the COVID-19 patients, we aimed to assess the effect of atorvastatin add-on therapy on mortality caused by COVID-19.

Methods: We conducted a retrospective cohort study, including patients who were hospitalised with confirmed diagnosis of severe COVID-19. Baseline characteristics and related clinical data of patients were recorded. Clinical outcomes consist of in-hospital mortality, need for invasive mechanical ventilation and hospital length of stay. COX regression analysis models were used to assess the association of independent factors to outcomes.

Results: Atorvastatin was administered for 421 of 991 patients. The mean age was 61.640 ± 17.003 years. Older age, higher prevalence of hypertension and coronary artery disease reported in patients who received atorvastatin. These patients have shorter hospital length of stay ($P = .001$). Based on COX proportional hazard model, in-hospital use of atorvastatin was associated with decrease in mortality (HR = 0.679, $P = .005$) and lower need for invasive mechanical ventilation (HR = 0.602, $P = .014$).

Conclusions: Atorvastatin add-on therapy in patient with severe COVID-19 was associated with lower in-hospital mortality and reduced the risk of need for invasive mechanical ventilation which supports to continue the prescription of the medication.

1 | INTRODUCTION

The COVID-19 pandemic is still growing around the world and more than 90 million cases around the world with over 2 million deaths have been identified.[1] Immune dysregulation and cytokine release associated with SARS-COV-2 infection are considered as an important cause of mortality in this population and it could induce hyper-inflammatory state, vasculitis and cardiovascular events.[2-4]

In previous studies, the anti-inflammatory role of statins in the reduction in cytokines, in some conditions other than infectious diseases, has been confirmed.[5,6] Also, studies have been shown that patients who have received atorvastatin had a better prognosis in viral and bacterial pneumonia.[7,8] In some studies, it is hypothesised that decreasing the synthesis of cholesterol by statins and depletion of cell membrane cholesterol content could disturb the entry of the virus into the cells.[9] SARS-COV-2 also generates multi-proinflammatory cytokines by activating Toll-like receptors (TLRs) on T lymphocytes.[10] This TLR-MYD88-NFκB pathway promotes cytokine release. Statins also block this pathway; inhibit T-cell activation and proliferation, so they have immunomodulatory effects.[11]

Furthermore, this class of medication is linked to a rise in IL-18 levels and mortality in patients with acute respiratory distress syndrome which could be harmful in this population and deteriorate the condition of the patients.[12]

By considering the effect of underlying conditions such as hypertension, diabetes, cardiovascular diseases and hyperinflammation associated with COVID-19, statins could affect the prognosis of the patients who have been hospitalised because of COVID-19.[13-15] Therefore, we aimed to assess the effect of atorvastatin use in the outcomes of the patients with severe-to-critical COVID-19.

What's known

Previous studies showed that patients who used statins may have decreased rate of mortality caused by COVID-19. Results about the effect of statins on other outcomes including need for mechanical ventilation and hospital length of stay were inconsistent.

What's new

In our large-scale retrospective cohort study, we examined the effect of atorvastatin, as a lipophilic statin, on outcomes of patients with severe-to-critical form of COVID-19. In addition to decrease in mortality, we observed lower risk of need of invasive mechanical ventilation associated with atorvastatin administration and also shorter hospital length of stay in patients who received atorvastatin.

2 | PATIENTS AND METHODS

2.1 | Study design and patient selection

In this retrospective cohort study, all adult patients (age ≥18 years old) who were hospitalised because of severe-to-critical COVID-19, from March 2020 to July 2020, in the Imam Hossein medical centre affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran, were evaluated.[16] Patients without positive reverse transcriptase-polymerase chain reaction (RT-PCR) results were excluded and data from patients with a diagnosis of COVID-19 based on RT-PCR were included. The study was conducted based on the declaration of Helsinki and the institutional review board committee approved the study.

2.2 | Data collection

For each patient, demographic and laboratory data including past medical and drug history, outcomes, baseline complete blood count and inflammatory markers including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin and lactate dehydrogenase (LDH) and liver function tests were recorded. Also, vital signs on admission and selected pharmacotherapy for management of COVID-19, besides the administration of atorvastatin and other cardiovascular medications, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and beta-blockers, were documented. Atorvastatin use was defined as the administration of the medication on first day of admission and the medication continued during the hospitalisation period if no contraindication was present.

2.3 | Outcomes

In hospital mortality was defined as the primary outcome for the study. The need for invasive mechanical ventilation including ventilation via endotracheal or tracheostomy tubes and length of hospital stay are considered as the secondary outcomes.

2.4 | Statistical analysis

Statistical analysis was performed by STATA software version 14 (StataCorp). All included patients stratified as they received atorvastatin or not during hospitalisation. The parametric or non-parametric distribution of the quantitative data was analysed using the Kolmogorov-Smirnov test. Data description of parametric quantitative variables was reported as means ± standard deviation and non-normally distributed data reported as median (interquartile range = IQR). Qualitative variables were reported as frequency (percentage). Continues variables were compared using independent *t* test or Mann-Whitney *U*-test for normally and non-normally distributed data in bivariate analysis respectively. Categorical variables were analysed using chi-square or Fisher's exact test (in the situation in which more than 25% of the categories had frequencies below five). A *P*-value of less than .05 is considered significant.

The crude association between atorvastatin administration and occurrence of outcomes including the need for invasive mechanical ventilation and in-hospital mortality was performed using the univariate COX proportional hazards regression model. For the selection of the best predictors, variables with a *P*-value of less than .2 are were considered to be analysed in multivariable COX regression analysis using a stepwise selection approach. Confounders were selected based on the recommendation of previously published epidemiological studies that reported the probable prognostic value of underlying conditions and also medications that were being used.[17] This included age, gender, body mass index (BMI) in demographics, hypertension, diabetes mellitus, coronary artery disease, chronic respiratory conditions, malignancies, immunocompromised and chronic kidney disease in comorbidities. Also, we adjusted the model for using beta-blockers and ACEIs or ARBs.[18,19] The model was adjusted for the medications which were used to treat COVID-19. Patients with negative time to event were removed from the analysis. A

TABLE 1 Patient demographics and related clinical and laboratory findings

Characteristics	Total (n = 991)	Received atorvastatin (n = 421)	Not received atorvastatin (n = 570)	*P*-value
Age (y)	61.640 ± 17.003	65.46 ± 14.94	58.82 ± 17.88	<.001
Gender				
Male (%)	544 (54.89)	225 (53.44)	319 (55.97)	.431
Female (%)	447 (45.11)	196 (46.56)	251 (44.03)	
Body mass index (kg/m^2)	27.051 ± 4.854	27.34 ± 26.49	26.81 ± 4.74	.119
Vital signs				
Systolic blood pressure (mmHg)	117.59 ± 20.71	118.55 ± 19.65	116.95 ± 21.49	.219
Diastolic blood pressure (mmHg)	74.69 ± 27.19	74.70 ± 11.76	74.71 ± 34.58	.985
Pulse rate (beats/min)	89.55 ± 15.71	89.01 ± 15.83	89.94 ± 15.41	.538
Respiratory rate (breath/min)	20.64 ± 7.92	20.80 ± 10.69	20.51 ± 5.06	.670
O_2 saturation (%)	88.29 ± 7.82	88.35 ± 7.04	88.25 ± 8.38	.924
Comorbidities				
Hypertension (%)	407 (41.07)	233 (55.34)	174 (30.53)	<.001
Diabetes (%)	303 (30.58)	117 (27.79)	186 (32.81)	<.001
Coronary artery disease (%)	194 (19.58)	133 (46.08)	61 (10.70)	<.001
Chronic kidney disease (%)	102 (10.29)	37 (8.79)	65 (11.40)	<.001
Malignancy (%)	42 (4.24)	32 (7.60)	10 (1.75)	.012
COPD/asthma	87 (8.78)	38 (9.03)	49 (8.60)	.813
Baseline laboratory data				
WBC (cell/μL)	6.90 (4.63)	7.20 (4.80)	6.60 (4.40)	.020
Lymphocyte (cell/μL)	821.75 (1588.10)	828.00 (1596.00)	821.50 (1587.20)	.780
Haemoglobin (g/dL)	12.41 ± 2.08	12.30 ± 2.17	12.28 ± 2.14	.898
INR	1.20 ± 0.48	1.22 ± 0.52	1.08 ± 0.20	.239
PT	13.09 ± 5.09	13.26 ± 5.30	12.94 ± 4.96	.415
PTT	28.25 ± 12.79	27.39 ± 10.87	28.93 ± 14.22	.126
Lactate dehydrogenase	645.00 (403.00)	643.00 (404.00)	659.00 (525.25)	.282
Ferritin	621.30 (964.00)	579.10 (812.10)	750.95 (1134.40)	.508
C-reactive protein	54.00 (53.10)	55.30 (53.30)	51.50 (51.65)	.040
Erythrocyte sedimentation rate	52.74 ± 28.41	48.20 ± 29.01	60.17 ± 26.12	.021
Creatine phosphokinase	130.00 (211.00)	130.00 (206.00)	136.00 (264.00)	.203
Serum creatinine	1.40 (1.20)	1.40 (1.20)	1.45 (1.08)	<.001
Serum urea	50.00 (45.00)	48.20 (41.90)	52.30 (55.88)	<.001
Procalcitonin	0.73 (1.85)	0.49 (1.31)	1.16 (2.41)	.873
D-dimer	799.20 (2434.00)	709.00 (1257.00)	1712.50 (3756.75)	.365
Aspartate aminotransferase	26.00 (27.00)	25.00 (25.40)	29.60 (38.13)	.470
Alanine aminotransferase	37.00 (29.50)	40.00 (26.40)	34.40 (39.78)	.490
Medication used to treat COVID-19				
Hydroxychloroquine	553 (55.80)	213 (89.67)	340 (59.65)	.005
Lopinavir/ritonavir	557 (56.21)	236 (56.06)	321 (56.32)	.935
Corticosteroid	287 (28.96)	141 (33.49)	146 (25.61)	.007
Interferon beta-1a	372 (37.54)	170 (40.38)	202 (35.44)	.112
Remdesivir	46 (4.64)	21 (4.99)	25 (4.39)	.656
Favipiravir	40 (4.04)	23 (5.46)	17 (2.98)	.050

95% confident interval of hazard ratio was reported. The proportional hazard assumption for COX analysis was tested using scaled Schoenfeld residuals and the *P*-value of .05 or more was considered as no serious violations of the proportional hazards assumption.

3 | RESULTS

Nine hundred and ninety-one patients were included in the study. The mean age was 61.640 ± 17.003, and 544 (54.89%) and 447 (45.11%) of the patients were men and women respectively. Four hundred and twenty-one patients (42.48%) received atorvastatin, whereas five hundred and seventy (57.52%) did not. Of those who received atorvastatin, 169 (40.14%) were taking the medication prior to hospital admission and atorvastatin was initiated for the rest of the patients on the first day of hospital admission.

Regarding demographics, patients who received atorvastatin were older ($P < .001$), but no significant differences were observed in gender distribution and BMI between the two groups. Considering comorbidities, except for diabetes and CKD, which were more prevalent in patients who did not receive atorvastatin ($P < .001$), and others including hypertension ($P < .001$), coronary artery disease ($P < .001$) and malignancy ($P = .012$) were significantly higher in the group of patients who received atorvastatin. From laboratory data collected at baseline, CRP was significantly higher in the group of patients who received atorvastatin ($P = .040$). Patients who did not receive atorvastatin had a higher baseline ESR, serum creatinine and urea levels compared with those who did not. Except for hydroxychloroquine ($P = .005$) and corticosteroids ($P = .007$), there were no significant differences between the two groups in medications used to treat COVID-19. Baseline demographics, clinical and laboratory data are presented in Table 1.

Based on the crude analysis, no significant differences were observed in mortality rate between two groups (26.84% vs 25.09%, $P = .221$). Patients who received atorvastatin have a significantly lower hospital length of stay ($P < .001$). Also, this group had a lower but non-significant need for mechanical ventilation ($P = .563$). Results for primary and secondary outcomes are represented in Table 2.

In unadjusted COX proportional analysis, atorvastatin was associated with a decreased in-hospital mortality (0.820 [0.639-1.054]) and need for mechanical ventilation (0.709 [0.486-1.034]). Stepwise COX regression proportional hazard ration analysis revealed that atorvastatin is associated with reduced risk of in-hospital mortality (0.679 [0.517-0.890]) and the need for mechanical ventilation (0.602 [0.401-0.903]), independently. From demographics, age, obesity, coronary heart disease and malignancy were included in the multivariable analysis to evaluate the need for invasive mechanical ventilation. Also, utilisation of beta-blockers, ACEIs/ARB, atorvastatin, corticosteroid, hydroxychloroquine and lopinavir/ritonavir were analysed. In the stepwise model for the analysis of survival, age, hypertension, coronary heart disease, malignancy and medication, ie beta-blockers, ACEIs/ARB, atorvastatin, corticosteroid, hydroxychloroquine and lopinavir/ritonavir, remained in the multivariable model. The association of factors with mortality and the need for invasive mechanical ventilation in COX proportional analysis is represented in Table 3.

4 | DISCUSSION

In our retrospective cohort study, among 991 patients suffering from severe-to-critical COVID-19, atorvastatin which was administered for 421 of the patients was associated with a significant decrease in mortality (HR = 0.679), the need for mechanical ventilation (HR = 0.602) and hospital length of stay. Very little was found in the literature about the role of statins in the management of patients with COVID 19. In line with our study, data from the largest cohort study from China by Zhang et al demonstrated that in-hospital use of statins improved survival among COVID-19 patients (HR = 0.58). In this retrospective study, which included 1219 patients who used a statin, 28-day all-cause mortality risk was 5.2% and 9.4% in the statin and non-statin users respectively.[20] The lower mortality rate in this study compared with our results could be as a result of including moderate cases in the study by Zhang et al which were not included in our study. Another study enrolled 71 patients with a preexisting chronic cardiovascular disease, and in accordance with our findings, the mortality rate of patients who received statins was lower compared with the group of patients without statins (21.4% vs 34.5%; $P < .05$), and in their subgroup analysis, it is reported as a significant reduction in mortality in the patients who were taking atorvastatin compared with non-statin users and patients who were taking other statins ($P = .025$).[21] In another retrospective cohort study, which compared intensive care unit (ICU) admission, invasive mechanical ventilation rate and death between statin users and non-statin users, ICU admission was lower in the statin group but other outcomes were not different between the two groups.[22] Another

TABLE 2 Primary and secondary outcomes

Variable	Total (n = 991)	Received atorvastatin (n = 421)	Not-received atorvastatin (n = 570)	*P*-value
Need for mechanical ventilation (%)	144 (14.53)	58 (13.78)	86 (15.09)	.563
Hospital length of stay (days) [range]	6.00 (6.00) [1-80]	6.00 (5.00)	7.00 (6.00)	<.001
In-hospital outcome (%)				
Death	256 (25.83)	113 (26.84)	143 (25.09)	.221
Recovery	735 (74.17)	308 (73.16)	427 (74.91)	

TABLE 3 Association of factors with outcomes in COX proportional hazard regression model

Variable	Crude HR, 95% CI	*P*-value	Adjusted HR, 95% CI	*P*-value
In hospital mortality				
Age (y)	1.034 [1.025-1.043]	<.001	1.036 [1.026-1.045]	<.001
Gender	1.197 [0.930-1.541]	.162		
Obesity	0.982 [0.957-1.009]	.188		
Hypertension	1.535 [1.199-1.965]	.001	1.227 [0.916-1.644]	.170
Diabetes	0.982 [0.755-1.277]	.890		
Coronary heart disease	1.331 [1.004-1.764]	.047	0.980 [0.719-1.337]	.901
Chronic kidney disease	1.002 [0.688-1.459]	.992		
Malignancy	1.370 [0.784-2.396]	.269	1.706 [0.961-3.031]	.068
Chronic respiratory disease	1.194 [0.962-1.482]	.107		
Immunosuppressive disorders	1.205 [0.674-2.152]	.530		
Smoking	0.932 [0.667-1.302]	.679		
Beta-blocker	1.375 [1.052-1.794]	.020	1.327 [0.981-1.795]	.066
ACEIs/ARB	1.067 [0.808-1.407]	.647	0.754 [0.553-1.029]	.075
Atorvastatin	0.820 [0.639-1.054]	.121	0.679 [0.517-0.890]	.005
Corticosteroid	1.205 [0.930-1.561]	.159	1.245 [0.941-1.649]	.125
Hydroxychloroquine	0.814 [0.635-1.045]	.106	0.813 [0.629-1.051]	.113
Lopinavir/ritonavir	1.220 [0.945-1.574]	.128	1.250 [0.951-1.641]	.110
Remdesivir	0.815 [0.456-1.457]	.489		
Favipiravir	0.739 [0.430-1.273]	.276		
Mechanical ventilation				
Age (y)	1.019 [1.007-1.028]	.001	1.026 [1.014-1.038]	<.001
Gender	1.259 [0.868-1.825]	.225		
Obesity	0.994 [0.969-1.029]	.744	1.390 [0.903-2.140]	.134
Hypertension	1.190 [0.781-1.811]	.418		
Diabetes	1.141 [0.779-1.672]	.499		
Coronary heart disease	1.115 [0.750-1.657]	.592	0.704 [0.422-1.174]	.179
Chronic kidney disease	0.750 [0.405-1.390]	.361		
Malignancy	1.652 [0.768-3.552]	.199	1.963 [0.894-4.312]	.093
Chronic respiratory disease	1.470 [0.838-2.577]	.179		
Immunosuppressive disorders	0.924 [0.340-2.508]	.877		
Smoking	1.008 [0.624-1.629]	.972		
Beta-blocker	1.639 [1.110-2.418]	.013	2.071 [1.334-3.217]	.001
ACEIs/ARB	0.823 [0.545-1.242]	.252	0.670 [0.426-1.054]	.084
Atorvastatin	0.709 [0.486-1.034]	.074	0.602 [0.401-0.903]	.014
Corticosteroid	1.507 [1.034-2.196]	.033	1.445 [0.962-2.170]	.076
Hydroxychloroquine	0.711 [0.489-1.033]	.073	0.707 [0.482-1.036]	.076
Lopinavir/ritonavir	1.367 [0.934-2.000]	.108	1.357 [0.904-2.037]	.141
Remdesivir	0.944 [0.414-2.152]	.892		
Favipiravir	1.577 [0.859-2.893]	.141		

Note: The model was fitted based on the Schoenfeld residual test for the evaluation of the proportional hazard assumption with $P = .253$ and $P = .218$ respectively.

Abbreviation: HR, hazard ratio.

retrospective multi-centre cohort study showed a significant association between statin intake in 31 subjects and the absence of symptoms during COVID-19 with an odds ratio of 2.91; nevertheless, there were no effects on serious clinical outcomes.[23]

Based on the result from our study, which is in accordance with the previously performed studies, reduced need for mechanical ventilation as two important measures for pulmonary function, we could say that atorvastatin administration strongly reduces the disease severity by inhibition of the inflammatory process during the disease course. Also, these effects alongside to reduction in mortality rate, which was statistically significant, make the medication an important choice of add-on therapy. Based on the significance of the mechanisms involved in the beneficial effect of the atorvastatin in the course of COVID-19, and the clinically proven efficacy, we could consider it in the treatment of patients who suffer from a severe form of the disease. It is important to note that we studied the effect of the atorvastatin on the outcome of the patients as add-on therapy and we should not forget about the importance of early antiviral agents administration as potent inhibitors of the viral replication which could reduce the hospital length of stay,[24] and the role of potent anti-inflammatory agents such as corticosteroids and interleukin pathways inhibitors on mortality and severity in the treatment of the COVID-19.[25-28] As an important pharmacokinetic consideration in the administration of atorvastatin, antiviral agents such as lopinavir/ritonavir and remdesivir could increase serum level of atorvastatin and increase the probability of adverse reactions such as myopathy.[29,30]

By considering the result of the study, we should be aware of the limitation we are facing in this study. First, this study was performed by a retrospective method which complicates control of all confounders and makes further randomised controlled trials emerge. Second, we could not evaluate the possible adverse effects of atorvastatin and also the relation between statin dose and duration with the effect and side effects of the drug. Finally, extrapolation of the results to non-hospitalised patients with moderate disease severity may not be possible as we included data related to severe form of the disease.

5 | CONCLUSION

In conclusion, we found that atorvastatin therapy has positive effects on the course of hospitalisation in patients with severe COVID-19. Mostly, these effects were seen in important outcomes of these patients, ie mortality rate, duration of hospitalisation and needs for mechanical ventilation caused by COVID-19. Prospective randomised, controlled trials are to be recommended to confirm the effect of statins on patients with viral infections, especially severe COVID-19.

DISCLOSURES

The authors declare no conflict of interest.

AUTHORS CONTRIBUTIONS

MHA, study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content and study supervision; OM, statistical analysis, drafting of the manuscript, technical support and acquisition of data; HAT, drafting of the manuscript and technical support; HA, drafting of the manuscript, statistical analysis and critical revision of the manuscript for important intellectual content; Elham Pourheidar, drafting of the manuscript, critical revision of the manuscript for important intellectual content and technical support; Firouze Hatami, drafting of the manuscript and technical support; Mohammad Mahdi Rabiei, drafting of the manuscript and technical support; Mohammad Sistanizad, study concept and design, acquisition of data, drafting of the manuscript, statistical analysis, administrative and material support, critical revision of the manuscript for important intellectual content and study supervision.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy restrictions.

ORCID

Omid Moradi https://orcid.org/0000-0001-5754-535X
Mohammad Sistanizad http://orcid.org/0000-0002-7836-6411

REFERENCES

1. World Health Organization. WHO coronavirus disease (COVID-19) dashboard. 2021. https://covid19.who.int/. Accessed January 20 2021.
2. Gustine JN, Jones D. Immunopathology of hyperinflammation in COVID-19. *Am J Pathol*. 2021;191(1):4-17. https://doi.org/10.1016/j.ajpath.2020.08.009
3. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. 2020;17(5):259-260. https://doi.org/10.1038/s41569-020-0360-5
4. Becker RC. COVID-19-associated vasculitis and vasculopathy. *J Thromb Thrombolysis*. 2020;50(3):499-511. https://doi.org/10.1007/s11239-020-02230-4
5. Wassmann S, Faul A, Hennen B, Scheller B, Böhm M, Nickenig G. Rapid effect of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibition on coronary endothelial function. *Circ res*. 2003;93(9):e98-e103. https://doi.org/10.1161/01.RES.0000099503.13312.7B
6. Fang CH, Li JJ, Hui RT. Statin, like aspirin, should be given as early as possible in patients with acute coronary syndrome. *Med Hypotheses*. 2005;64(1):192-196. https://doi.org/10.1016/j.mehy.2004.06.018
7. Novack V, Eisinger M, Frenkel A, et al. The effects of statin therapy on inflammatory cytokines in patients with bacterial infections: a randomized double-blind placebo controlled clinical trial. *Intensive Care Med*. 2009;35(7):1255-1260. https://doi.org/10.1007/s00134-009-1429-0
8. Mortensen EM, Restrepo MI, Anzueto A, Pugh J. The effect of prior statin use on 30-day mortality for patients hospitalized with community-acquired pneumonia. *Respir Res*. 2005;6(1):82. https://doi.org/10.1186/1465-9921-6-82
9. Radenkovic D, Chawla S, Pirro M, Sahebkar A, Banach M. Cholesterol in relation to COVID-19: should we care about it? *J Clin Med*. 2020;9(6):1909. https://doi.org/10.3390/jcm9061909

10. Minz MM, Bansal M, Kasliwal RR. Statins and SARS-CoV-2 disease: current concepts and possible benefits. *Diabetes Metab Syndr*. 2020;14(6):2063-2067. https://doi.org/10.1016/j.dsx.2020.10.021
11. Fajgenbaum DC, Rader DJ. Teaching old drugs new tricks: statins for COVID-19? *Cell Metab*. 2020;32(2):145-147. https://doi.org/10.1016/j.cmet.2020.07.006
12. Rogers AJ, Guan J, Trtchounian A, et al. Association of elevated plasma interleukin-18 level with increased mortality in a clinical trial of statin treatment for acute respiratory distress syndrome. *Crit Care Med*. 2019;47(8):1089-1096. https://doi.org/10.1097/CCM.0000000000003816
13. Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. *Lancet*. 2020;395(10229):1014-1015. https://doi.org/10.1016/S0140-6736(20)30633-4
14. Holman N, Knighton P, Kar P, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *Lancet Diabetes Endocrinol*. 2020;8(10):823-833. https://doi.org/10.1016/S2213-8587(20)30271-0
15. Bae S, Kim SR, Kim M-N, Shim WJ, Park S-MJH. Impact of cardiovascular disease and risk factors on fatal outcomes in patients with COVID-19 according to age: a systematic review and meta-analysis. *Heart*. 2021;107(5):373–380. https://doi.org/10.1136/heartjnl-2020-317901
16. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in china: summary of a report of 72 314 cases from the chinese center for disease control and prevention. *JAMA*. 2020;323(13):1239-1242. https://doi.org/10.1001/jama.2020.2648
17. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3
18. Zhang P, Zhu L, Cai J, et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res*. 2020;126(12):1671-1681.
19. Vasanthakumar N. Beta-adrenergic blockers as a potential treatment for COVID-19 patients. *BioEssays*. 2020;42(11):2000094. https://doi.org/10.1002/bies.202000094
20. Zhang X-J, Qin J-J, Cheng X, et al. In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. *Cell Metab*. 2020;32(2):176–187.e4. https://doi.org/10.1016/j.cmet.2020.06.015
21. Rossi R, Talarico M, Coppi F, Boriani GJI, Medicine E. Protective role of statins in COVID 19 patients: importance of pharmacokinetic characteristics rather than intensity of action. *Intern Emerg Med*. 2020;15(8):1573-1576. https://doi.org/10.1007/s11739-020-02504-y
22. Tan WY, Young BE, Lye DC, Chew DE, Dalan R. Statin use is associated with lower disease severity in COVID-19 infection. *Sci Rep*. 2020;10(1):1-7. https://doi.org/10.1038/s41598-020-74492-0
23. De Spiegeleer A, Bronselaer A, Teo JT, et al. The effects of ARBs, ACEis, and statins on clinical outcomes of COVID-19 infection among nursing home residents. *J Am Med Dir Assoc*. 2020;21(7):909-914.e902. https://doi.org/10.1016/j.jamda.2020.06.018
24. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of covid-19 — final. *Report*. 2020;383(19):1813-1826. https://doi.org/10.1056/NEJMoa2007764
25. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with covid-19 – preliminary report. *N Engl J Med*. 2021;384(8):693-704. https://doi.org/10.1056/NEJMoa2021436
26. Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol*. 2020;2(8):e474-e484. https://doi.org/10.1016/S2665-9913(20)30173-9
27. Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol*. 2020;2(7):e393-e400. https://doi.org/10.1016/S2665-9913(20)30164-8
28. Ziaie S, Koucheck M, Miri M, et al. Review of therapeutic agents for the treatment of COVID-19. *J Cell Mol Anesth*. 2020;5(1):32-36. https://doi.org/10.22037/jcma.v5i1.29760
29. Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. *Am J Cardiol*. 2004;94(9):1140-1146. https://doi.org/10.1016/j.amjcard.2004.07.080
30. Aleissa MM, Silverman EA, Paredes Acosta LM, Nutt CT, Richterman A, Marty FM. New perspectives on antimicrobial agents: remdesivir treatment for COVID-19. *Antimicrob Agents Chemother*. 2020;65(1):e01814-e01820. https://doi.org/10.1128/AAC.01814-20

How to cite this article: Haji Aghajani M, Moradi O, Azhdari Tehrani H, et al. Promising effects of atorvastatin on mortality and need for mechanical ventilation in patients with severe COVID-19; a retrospective cohort study. *Int J Clin Pract*. 2021;75:e14434. https://doi.org/10.1111/ijcp.14434