Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

Should statins be used as adjunctive treatment in patients with COVID-19?

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RECOMMENDATION

There is insufficient evidence to recommend statins as adjunctive treatment in patients with COVID-19. *(Very low certainty of evidence)*

Consensus Issues
Due to perceived risk of harm, two panelists were inclined to suggest against the use of statins as adjunctive treatment in patients with COVID-19.

Key Findings

Statins are lipid-lowering drugs known to have pleiotropic effects against inflammation and thrombosis. Very low quality of evidence from two randomized clinical trials showed that among COVID-19 patients admitted to the ICU, the only significant finding was a decrease in hospital stay. There was no significant benefit for the following outcomes: composite risk for adjudicated venous or arterial thrombosis, the risk for ECMO treatment, the risk for all-cause mortality, or the individual components of adjudicated venous thromboembolism, all-cause mortality, or need for mechanical ventilation.

Introduction

Coronavirus disease (COVID-19) is characterized by a hyperactive immune system and a prothrombotic state.[1] Severe inflammation and thrombotic events, such as arterial thrombosis and venous thromboembolism, have been implicated in mortality of some COVID-19 patients.[2,3] Patients with a higher risk of COVID-19 disease include those with cardiovascular disease, many of whom are on maintenance statin therapy. Statins are a class of drugs known to decrease risk of thrombosis and are also known to have anti-inflammatory effects.[4] However, statins also upregulate the ACE2, which is the receptor through which the SARS-CoV-2 virus enters human cells.[5] Hence, it is important to establish whether statins can be continued during treatment for COVID-19 and whether statins can be used as an adjunct to COVID-19 treatment. This review aimed to study the effects of statins on clinical outcomes of COVID-19 patients.

There are several meta-analyses of observational studies that showed reduced mortality and reduced risk for severe COVID-19 among patients treated or maintained on statins, 6,7,8,9 with the meta-analyses of Diaz-Arocutipa et al. 6, Kollias et al. 7 and Yetmar et al. adjusting for other factors. All these reviews included studies that had high variability in the type, dose, and duration of the statin that was used, the chronicity of intake, as well as patient admission type (outpatients, inpatients and/or ICU patients only). Several patients had comorbidities such as hypertension,

coronary heart disease, and diabetes. Effect estimates were adjusted by methods such as propensity matching to reduce the effect of confounding factors but there was still risk of residual confounding in the observational studies. This highlights the need for more robust evidence on statin use in COVID-19 patients, particularly from randomized controlled trials.

Review Methods

We conducted a literature search for studies published in 2019 to September 16, 2021. Databases searched were Pubmed, Cochrane Central Register of Controlled Trials (CENTRAL), Epistemonikos, and Google Scholar. Registries for ongoing or completed clinical trials were also searched (Clinicaltrials.gov, ISRCTN registry, World Health Organization International Clinical Trials Registry Platform). The following search terms were used: “statin”, “atorvastatin”, “ lovastatin”, “pravastatin”, “simvastatin” or “meglutol” together with “COVID-19”, “coronavirus”, “SARS-Cov-2” or “nCoV”. References of all studies were reviewed to identify other studies. Searches were limited to human studies, but were not limited in terms of language or country. The study types included were randomized controlled trials, systematic review and meta-analysis of randomized controlled trials as well as observational studies.

The PICO was as follows: Population – patients diagnosed with COVID-19; Intervention – statin therapy, whether as continuing maintenance medication or initiated only during hospitalization for COVID-19; Comparator – standard of care, no control, placebo; Outcomes – mortality, ICU admission, need for mechanical ventilation, length of hospital stay, days to recovery, viral load or cycle threshold, and worsening of symptoms. Adverse events were also included.

Results

Of 272 records identified from the search, only two randomized controlled trials were available for review: one by Bikdelli et al. [1,10] and another by Davoodi et al. 11 The former, though unpublished at this current time, was presented at the American College of Cardiology Scientific Session on May 16, 2021 in sufficient detail to allow appraisal and inclusion in this review.

It studied the clinical outcomes of critically-ill COVID-19 patients treated with atorvastatin versus placebo. The overall design was a 2x2 factorial design randomized controlled trial, where researchers investigated the safety and efficacy of two pharmacological regimens on outcomes of critically-ill patients with COVID-19. The first randomization involved an open-label assignment to intermediate versus standard dose prophylactic anticoagulation, and the second was a double-blind assignment of the included patients to atorvastatin 20mg daily versus matching placebo. The hypothesis was that statin therapy, compared to placebo, would reduce the composite of VTE, need for ECMO, or all-cause mortality.

The primary efficacy outcome was the composite adjudicated venous thromboembolism, arterial thrombosis, treatment with ECMO or all-cause mortality. Secondary efficacy outcomes included the individual components of all-cause mortality and adjudicated venous thromboembolism, ventilator-free days, objectively clinically-diagnosed type I acute myocardial infarction and objectively clinically-diagnosed stroke. The safety outcomes assessed were fatal bleeding, major bleeding, or clinically-relevant non-major bleeding (BARC 2 to 5), clinically diagnosed myopathy and rise in liver enzymes.[10]

The certainty of the evidence was assessed to be low for both the primary efficacy outcome and all-cause mortality due to serious imprecision and suspected publication bias. For the adjudicated

venous thromboembolism, there was a very wide confidence interval. Hence, imprecision was classified as very serious and the evidence was assessed to be of very low certainty.

Though the manuscript of the trial by Bikdeli et al. is still unpublished, the study results were presented in the American College of Cardiology Scientific Session on May 16, 2021. Hence, we were able to include the results of the trial in this evidence summary. Results of the study are presented in the GRADE evidence profile (see Appendix 5). For the primary efficacy outcome, there was decreased risk in the statin group but this was not statistically significant (RR 0.90, 95% CI 0.72-1.13; p=0.36). For the all-cause mortality, the risk ratio of statin use was 0.89 (95% CI 0.71-1.13; p=0.35). For the adjudicated venous thromboembolism, the risk ratio was 0.68 (95% CI 0.25-1.89; p=0.46). The mean ventilator-free days for both intervention and control was 30 days (p=0.08). There was no incident of clinically diagnosed myocardial infarction. There was only one incident of clinically-diagnosed stroke in the placebo group and none in the statin group (RR 0.34, 95% CI 0.01-8.35; p=0.51). The outcome for the individual component of arterial thrombosis was not presented.[10]

In terms of safety outcomes, there was no significant difference between the intervention and control for fatal bleeding, clinically-relevant non-major bleeding, and rise in liver enzymes. There was signal for harm, but it was noted that the effects of the anticoagulation therapy could not be extricated from the statin analysis. It must be noted that there was increased risk for the statin group for major bleeding (RR 2.25, 95% CI 0.79-6.4; p=0.13) but this was not statistically significant, perhaps due to the small number of events that occurred.[10]

On the other hand, the double-blind, randomized controlled trial by Davoodi et al. studied the effect of atorvastatin plus lopinavir/ritonavir on newly hospitalized adult COVID-19 patients without cardiovascular diseases.[11] The control was lopinavir/ritonavir which is a standard of care in Iran, where the study was held. The primary outcome was the duration of hospitalization. The secondary outcomes included the need for interferon or immunoglobulin, need for invasive mechanical ventilation, oxygen saturation and C-reactive protein levels. Atorvastatin 40mg daily was given along with lopinavir/ritonavir for five days.

The certainty of evidence from the Davoodi et al. trial was assessed to be moderate for length of hospital stay and low for need for mechanical ventilation due to serious imprecision, and suspected publication bias. Results of the Davoodi et al. trial are shown in Appendix 5. The duration of hospitalization was decreased by a mean of 1.8 days (p value 0.012) in the atorvastatin group. For the need for mechanical ventilation, the relative risk of the atorvastatin group was 0.33 (95% CI 0.01 to 7.72, p=0.49).

Recommendations from Other Groups

On August 4, 2021, the NIH COVID-19 Treatment Guidelines Panel recommended that COVID-19 patients who were already on statins prior to infection should not discontinue taking the statin during acute management of COVID-19 (Strong recommendation based on Expert Opinion).[12] It also recommended against the off-label use of statins to treat COVID-19, except in a clinical trial (Strong recommendation based on Expert Opinion).[12] Currently, there are no local guidelines providing recommendations on the use of statins in COVID-19 patients.

Evidence to Decision

There are no cost-effectiveness studies available to further evaluate the use of statins. It was only identified in some reviews that costs are one of the common causes of nonadherence to chronic statin use aside from its side effects, presence of comorbidities, and lack of health

insurance.[13, 14] The estimated cost of statins ranges from PHP 138.60 to PHP 1,115.10 for 30 days of treatment [15] while the estimated cost of hospitalization or in-patient management for probable or confirmed case of COVID-19 varies from Php 143, 267 to Php 786,384 for moderate to critical cases [16]. Actual costs may still vary.

Research Gaps

The outcomes for patients with asymptomatic or mild COVID-19 is unknown. We also do not know if the continuation of statins in patients already taking the drug is beneficial. As of the time of this review, there were eight records of other randomized clinical trials but their results have not been reported or published (see Appendix 6).

References

[1] Bikdeli B, Talasaz A, Rashidi F, et al. Intermediate versus standard-dose prophylactic anticoagulation and statin therapy versus placebo in critically-ill patients with COVID-19: Rationale and design of the INSPIRATION/INSPIRATION-S studies. Thrombosis Research. 2020 Sept 24. Available from: https://doi.org/10.1016/j.thromres.2020.09.027

[2] Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19. Ann Intern Med. 2020 June 16. Available from: https://doi.org/10.7326/M20-2003

[3] Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. 2020 May 21. N Engl J Med. Available from: https://doi.org/10.1056/NEJMoa2015432

[4] Minz MM, Bansal M, Kasliwal RR. Statins and SARS-CoV-2 disease: Current concepts and possible benefits. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020 Oct 20. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7582042/

[5] Daniels L, Sitapati A, Zhang J, et al. Relation of Statin Use Prior to Admission to Severity and Recovery Among COVID-19 Inpatients. 2020 Sept 16. Am J Cardiol. Available from: https://doi.org/10.1016/j.amjcard.2020.09.012

[6] Diaz Arocutipa C, Melgar-Talavera B, Alvarado-Yarasca A, et al. Statins reduce mortality in patients with COVID-19: an updated meta-analysis of 147 824 patients. Int J Infect Dis. 2021 Aug 4. Available from https://www.ijidonline.com/article/S1201-9712(21)00636-6/fulltext.

[7] Kollias A, Kyriakoullis K, Kyriakoulis I, et al. Statin use and mortality in COVID-19 patients: Updated systematic review and meta-analysis. Atherosclerosis. 2021 Jun 25. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8233054/

[8] Yetmar Z, Chesdachai S, Kashour T et al. Prior Statin Use and Risk of Mortality and Severe Disease From Coronavirus Disease 2019: A Sytematic Review and Meta-analysis. Open Forum Infectious Diseases. 2021 May 26. Available from: https://academic.oup.com/ofid/article/8/7/ofab284/6287994

[9] Zein AFMZ, Sulistiyana CS, Khasanah U, et al. Statin and mortality in COVID-19: a systematic review and meta-analysis of pooled adjusted effect estimates from propensity-matched cohorts. Postgrad Med J. 2021 May 30. Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8249178/

[10] Bikdeli Behnood, Talasaz A, Rashidi F, et al. Atorvastatin vs Placebo in Patients with COVID-19 Admitted to the ICU: The INSPIRATION-S Trial. In: American College of Cardiology Annual Scientific Session [Internet]; 2021 May 16; Virtual. Available from https://www.acc.org/education-and-meetings/image-and-slide-gallery/media-detail?id=9DF17809F35C4CA6B149C64C9D700AC6

[11] Davoodi L, Jafarpour H, Oladi Z et al. Atorvastatin therapy in COVID-19 adult inpatients: A double-blind, randomized controlled trial. IJC Heart & Vasculature. 2021 Sept 14. Available from: https://www.sciencedirect.com/science/article/pii/S2352906721001639?via%3Dihub

[12] National Institutes of Health USA. COVID-19 Treatment Guidelines: Considerations for Certain Concomitant Medications in Patients with COVID-19 [Internet]. National Institutes of Health; 2021 Aug 4 [cited 2021 Sept 19]. Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/concomitant-medications/

[13] Alonso R, Cuevas A, Cafferata A. Diagnosis and Management of Statin Intolerance. J Atheroscler Thromb. 2018 Dec 3. Available from: https://www.jstage.jst.go.jp/article/jat/26/3/26_RV17030/_pdf/-char/ja

[14] Ingersgaard, MV, Andersen TH, Norgaard O, et al. Reasons for Nonadherence to Statins – A Systematic Review of Reviews. Patient Preference and Adherence. 2020 Apr 2. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7135196/

[15] Department of Health. The Philippine Drug Price Reference Index (DPRI) 8th edition. 2020. Philippines. Page 9.

[16] Asian Development Bank. Health System Enhancement to Address and Limit COVID-19: Report and Recommendation of the President [PRP PHI 54171-002]: Economic Analysis. 2020 August.

[17] Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Inf Dis [Internet]. 2021 Sept 27 [cited 2021 Sept 27]; 20(5):533-534. Available from: https://coronavirus.jhu.edu/map.html

[18] Department of Health. COVID-19 tracker [Internet] . 2021 Sept 27 [cited 2021 Sept 27]. Available from: https://doh.gov.ph/covid19tracker

[19] MIMS. Lipitor atorvastatin. MIMS Pte Ltd. 2021. [cited 2021 Sept 29]. Available from: https://www.mims.com/philippines/drug/info/lipitor

[20] MIMS. Saatin atorvastatin. MIMS Pte Ltd. 2021. [cited 2021 Sept 29] Available from: https://www.mims.com/philippines/drug/info/saatin

Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the actual panel meeting: statins (N = 8)

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS
Problem	No (1)	Yes (7)				
Benefits	Large (1)	Moderate (2)	Small (4)	Uncertain (1)		• INCONCLUSIVE BENEFITS and HARM (adjudicated venous thromboembolism, arterial thromboembolism, arterial thrombosis, treatment with ECMO, all-cause mortality); need for interferon or immunoglobulin, need for invasive mechanical ventilation, major bleeding, fatal bleeding • BENEFIT: decrease of length of hospital stay (days) • *Experience: Do not lower cholesterol level even with good compliance (n =1)* • *Needs wider or larger study group (n = 1)*
Harm	Large (1)	Small (7)	Uncertain	Varies		• INCONCLUSIVE BENEFITS and HARM (adjudicated venous thromboembolism, arterial thromboembolism, arterial thrombosis, treatment with ECMO, all-cause mortality); need for interferon or immunoglobulin, need for invasive mechanical ventilation, major bleeding, fatal bleeding
Certainty of Evidence	High	Moderate	Low (4)	Very low (4)		• The overall certainty of evidence: VERY LOW
Balance of effects	Favors drug (4)	Does not favor drug	Uncertain (4)	Varies		• Most outcomes show inconclusive benefits and harm. • Moderate quality of evidence shows benefit in terms of length of hospital stay (reduction of 2 days) among hospitalized non-ICU patients without cardiovascular diseases.
Values	Important uncertainty or variability (4)	Possibly important uncertainty or variability (2)	Possibly NO important uncertainty or variability	No important uncertainty or variability (2)		

Resources Required	Uncertain	Large cost	Moderate Cost (6)	Negligible cost	Moderate savings	Large savings (2)	• **No cost-effectiveness studies available.** Price range: PHP 138.60 – PHP 1,115.10 (estimated cost of drug for 30 days of treatment); Estimated cost of hospitalization (ADB, 2020) for in-patient management for probable or confirmed case of COVID-19: Php 143, 267 to Php 786,384 – moderate to critical cases (Actual costs may vary) • *Panel: It is an added cost. (n = 1)*
Certainty of evidence of required resources	No included studies (4)	Very low (2)	Low (2)	Moderate	High		• No cost-effectiveness studies available.
Cost effectiveness	No included studies (6)	Favors the comparison	Does not favor either the intervention or the comparison (1)	Favors the intervention (1)			• No cost-effectiveness studies available.
Equity	Uncertain (5)	Reduced (1)	Probably no impact (2)	Increased			• No local studies available.
Acceptability	Uncertain (4)	No	Yes (4)	Varies			• Common causes of nonadherence to chronic statin use are costs, side effects, presence of comorbidities, and lack of health insurance. • *Panel: Acceptability depends on ability to control dyslipidemia, decreased or no adverse reactions, and purchasing capacity. (n =1)*
Feasibility	Uncertain (3)	No	Yes (5)	Varies			• No local studies available.

Appendix 2. Search Yield and Results

Database	Date of Last Search	Search strategy	Yield	Matching articles
Pubmed	September 16, 2021	((((((((((statin[MeSH Terms]) OR (atorvastatin[MeSH Terms])) OR (lovastatin[MeSH Terms])) OR (pravastatin[MeSH Terms])) OR (simvastatin[MeSH Terms])) OR (meglutol[MeSH Terms])) OR (statin [tiab])) OR (atorvastatin [tiab])) OR (lovastatin [tiab])) OR (pravastatin [tiab])) OR (simvastatin [tiab])) OR (meglutol [tiab])) AND (((((((COVID-19[MeSH Terms]) OR (coronavirus[MeSH Terms])) OR (sars-cov-2[MeSH Terms])) OR (nCoV [tiab])) OR (COVID-19)) OR (COVID-19 [tiab])) OR (coronavirus [tiab])) OR (SARS-CoV-2 [tiab]))	222	41
Cochrane Library CENTRAL	September 16, 2021	(statin):ti,ab,kw AND (covid-19):ti,ab,kw	27	10
Clinicaltrials.gov	September 20, 2021	COVID-19 AND statin	23	11
Epistemonikos	September 26, 2021	(title: (statin) or abstract:(statin)) AND (title:(covid-19) OR abstract:(covid-19))	111	48

Appendix 3. Characteristics of Included Studies

Study ID	Setting	Population	Intervention	Control	Outcomes
Bikdeli 2021	Iran	Adult patients (≥18 years old) with RT-PCR confirmed COVID-19 admitted at ICU within 7 days of hospitalization	Atorvastatin 20 mg/day initiated at admission Exact duration of intervention not specified.	Matching placebo	Primary efficacy outcome: Composite of adjudicated venous thromboembolism, arterial thrombosis, treatment with ECMO, or all-cause mortality within 30 days Secondary efficacy outcome: Individual components of primary outcome, ventilator free days Safety outcomes: rise in liver enzymes >3x times upper normal limit, myopathy, BARC 3 or 5 bleeding, CRNMB, severe thrombocytopenia
Davoodi 2021	Iran	Adult patients (between 20 and 50 years old), hospitalized, with RT-PCR confirmed COVID-19, CT scan findings of COVID-19, and respiratory symptoms <10 days	Atorvastatin 40 mg 1 tablet per day plus lopinavir/ritonavir 400/100 mg 2 tablets per day Duration of treatment was 5 days	Matching placebo 1 tablet per day plus lopinavir/ritonavir 400/100 mg 2 tablets per day	Primary: duration of hospitalization Secondary: Need for interferon or immunoglobulin, need for invasive mechanical ventilation, O2 saturation on Days 1 and 6, CRP on Days 1 and 6

Appendix 4. Detailed Study Appraisal

A. Bikdeli et al. Trial

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	Yes
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	Yes
3. Were baseline characteristics similar at the start of the trial?	Yes
4. Were patients blinded to treatment assignment?	Yes
5. Were caregivers blinded to treatment assignment?	No
6. Were outcome assessors blinded to treatment assignment?	Yes
7. Were all patients analyzed in the groups to which they were originally randomized?	Yes
8. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE evidence profile
2. How precise was the estimate of the treatment effect?	See GRADE evidence profile
Assessing Applicability	
1. Are there biologic issues that may affect applicability of treatment? (Consider the influence of sex, co-morbidity, race, age and pathology)	Yes. Study is mainly composed of adults 40-60 years old.
2. Are there socio-economic issues affecting applicability of treatment?	No
Individualizing the Results	
1. What is the likely effect of the treatment on your individual patient?	
2. Would you offer the treatment to your patients?	No

B. Davoodi et al. Trial

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	Yes
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	Yes
3. Were baseline characteristics similar at the start of the trial?	Yes
C. Were patients blinded to treatment assignment?	Yes
D. Were caregivers blinded to treatment assignment?	No

E. Were outcome assessors blinded to treatment assignment?	Yes
F. Were all patients analyzed in the groups to which they were originally randomized?	Yes
G. Was follow-up rate adequate?	No. Treatment was only up to 5 days. After discharge, patients were not able to be followed up.
Appraising Results	
1. How large was the effect of treatment?	See GRADE evidence profile
2. How precise was the estimate of the treatment effect?	See GRADE evidence profile
Assessing Applicability	
1. Are there biologic issues that may affect applicability of treatment? (Consider the influence of sex, co-morbidity, race, age and pathology)	No
2. Are there socio-economic issues affecting applicability of treatment?	No
Individualizing the Results	
1. What is the likely effect of the treatment on your individual patient?	
2. Would you offer the treatment to your patients?	

Appendix 5. GRADE Evidence Profile

A. Efficacy Outcomes

Author(s): Furqaan Lim, Maria Teresa Sanchez-Tolosa, Myzelle Infantado
Question: Should statins be used as adjunctive treatment in patients with COVID-19?
Setting: Iran
Bibliography: Bikdeli Behnood, Talasaz A, Rashidi F, et al. Atorvastatin vs Placebo in Patients with COVID-19 Admitted to the ICU: The INSPIRATION-S Trial

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies (no. of patients)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statin	Placebo	Relative (95% CI)	Absolute (95% CI)		
Composite of adjudicated venous thromboembolism, arterial thrombosis, treatment with ECMO, or all-cause mortality (follow-up: 30 days; assessed with: Number of events)												
1	randomised trials	not serious	not serious	not serious	serious [a]	publication bias strongly suspected [b]	95/290 (32.8%)	108/297 (36.4%)	**RR 0.90** (0.72 to 1.13)	**36 fewer per 1,000** (from 102 fewer to 47 more)	⊕⊕◯◯ Low	CRITICAL
All-cause mortality (follow-up: 30 days)												
1	randomised trials	not serious	not serious	not serious	serious [a]	publication bias strongly suspected [b]	90/290 (31.0%)	103/297 (34.7%)	**RR 0.89** (0.71 to 1.13)	**38 fewer per 1,000** (from 101 fewer to 45 more)	⊕⊕◯◯ Low	CRITICAL
Adjudicated venous thromboembolism (follow-up: 30 days)												
1	randomised trials	not serious	not serious	not serious	very serious [c]	publication bias strongly suspected [d]	6/290 (2.1%)	9/297 (3.0%)	**RR 0.68** (0.25 to 1.89)	**10 fewer per 1,000** (from 23 fewer to 27 more)	⊕◯◯◯ Very low	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. The risk ratio has a wide confidence interval

b. Only 1 randomized controlled trial is available for review and is currently unpublished. There are 9 ongoing or possibly finished trials that have not yet reported their results.

c. The risk ratio has very wide confidence interval and touches the line of null effect

d. Only 1 randomized controlled trial studying this effect is available for review and is currently unpublished.

Author(s): Furqaan Lim, Maria Teresa Sanchez-Tolosa, Myzelle Infantado

Question: Should statins be used as adjunct treatment in patients with COVID-19?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	atorvastatin plus lopinavir/ritonavir	lopinavir/ritonavir	Relative (95% CI)	Absolute (95% CI)		
length of hospital stay												
1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected[a]	20	20	-	MD **1.8 lower** (3.14 lower to 0.46 lower)	⨁⨁⨁◯ Moderate	IMPORTANT
need for mechanical ventilation												
1	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	0/20 (0.0%)	1/20 (5.0%)	**RR 0.33** (0.01 to 7.72)	**33 fewer per 1,000** (from 50 fewer to 336 more)	⨁⨁◯◯ Low	CRITICAL

Setting: Iran

Bibliography: Davoodi L, Jafarpour H, Oladi Z et al. Atorvastatin therapy in COVID-19 adult inpatients: A double-blind, randomized controlled trial. IJC Heart & Vasculature 14 Sept 2021. Available from https://www.sciencedirect.com/science/article/pii/S2352906721001639?via%3Dihub

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	atorvastatin plus lopinavir/ritonavir	lopinavir/ritonavir	Relative (95% CI)	Absolute (95% CI)		
length of hospital stay												
1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected[a]	20	20	-	MD **1.8 lower** (3.14 lower to 0.46 lower)	⊕⊕⊕◯ Moderate	IMPORTANT
need for mechanical ventilation												
1	randomised trials	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[a]	0/20 (0.0%)	1/20 (5.0%)	**RR 0.33** (0.01 to 7.72)	**33 fewer per 1,000** (from 50 fewer to 336 more)	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Only two randomised controlled trials are available for review and one is currently unpublished. There are eight ongoing or possibly finished trials that have not yet reported their results.

b. The risk ratio has wide confidence interval and touches the line of null effect

B. Safety Outcomes

Author(s): Furqaan Lim, Maria Teresa Sanchez-Tolosa, Myzelle Infantado

Question: [Should statins be used as adjunctive treatment in patients with COVID-19?

Setting: Iran

Bibliography: Bikdeli Behnood, Talasaz A, Rashidi F, et al. Atorvastatin vs Placebo in Patients with COVID-19 Admitted to the ICU: The INSPIRATION-S Trial

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Statin]	[Placebo]	Relative (95% CI)	Absolute (95% CI)		
Fatal bleeding (follow-up: 30 days)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	publication bias strongly suspected [b]	2/290 (0.7%)	2/297 (0.7%)	**RR 1.02** (0.15 to 7.22)	**0 fewer per 1,000** (from 6 fewer to 42 more)	⨁◯◯◯ Very low	CRITICAL
Major bleeding BARC 3 or 5 (follow-up: 30 days)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	publication bias strongly suspected [b]	11/290 (3.8%)	5/297 (1.7%)	**RR 2.25** (0.79 to 6.40)	**21 more per 1,000** (from 4 fewer to 91 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. There is a wide confidence interval

b. Only one randomized controlled trial is available for review and is currently unpublished. There are eight ongoing or possibly finished trials that have not yet reported their results.

Appendix 6. Characteristics of Ongoing Studies

Randomized Controlled Trials

Study ID	Setting	Title	Intervention	Control	Outcomes
NCT04380402	USA	Prospective Randomized Open-label Trial of Atorvastatin as Adjunctive Therapy of COVID-19 (STATCO19)	Atorvastatin 40 mg	Standard care	Proportion of patients progressing to severe or critical requiring ICU admission and/or emergency salvage therapy or death within 30 days Clinical status at Day 7 and 30 Proportion of patients who test negative for SARS-CoV-2 on Day 7
IRCT20210426051090N1	Iran	The effect of atorvastatin on on inflammatory factors and prognosis outcomes in patients with Covid 19, hospitalized in Hajar Hospital, Shahrekord University of Medical Sciences, 2021	Atorvastatin 40 mg	Placebo	ALT, AST, Alkaline phosphatase, bilirubin, BUN, Na, K, Creatine, CBC, CRP, ESR, FBS, Ferritin, IL-6, LDH, O2 saturation, PT/PTT, INR, Lipid profile on Day 1, 7 and 14
NCT04904536	Australia	An International, Investigator Initiated and Conducted, Pragmatic Clinical Trial to Determine Whether 40mg Atorvastatin Daily Can Improve Neurocognitive Function in Adults With Long COVID Neurological Symptoms	Atorvastatin 40 mg for 18 months	Standard care	Neurologic Recovery Brain imaging
IRCT20200408046990N3	Iran	Evaluation of atorvastatin tablet efficacy as an adjuvant treatment for patients with mild to moderate COVID-19 in Qaem Hospital, Mashhad: A double-blind randomized placebo controlled clinical trial	Atorvastatin 40 mg	Placebo	Fever, clinical response, radiologic response, laboratory response (CBC and CRP), adverse reaction, duration of hospitalization, clinical outcome
EUCTR2020-001319-26-ES	Spain	Multicenter, randomized, controlled, open-label clinical trial to assess the prognostic implications of rosuvastatin treatment in patients discharged after	Rosuvastatin	Not indicated	Death, MI, Stroke within 12 months Admission due to heart failure, readmission from any cause

		hospitalization for COVID-19 Positive			
IRCT20201128049508N1	Iran	Evaluation of statin effect on COVID 19 duration and complications	Statin	Standard care	Mortality, lung fibrosis, recovery
CTRI/2020/07/026791	India	A Randomised Control Trial of Statin and Aspirin as Adjuvant Therapy in Patients with SARS-CoV-2 Infection (RESIST Trial) - RESIST Trial	Atorvastatin 40 mg Aspirin	Standard care	Clinical deterioration (intubation, mechanical ventilation, pressor agents, dialysis, ECMO, mortality) Inflammatory markers ICU admission Length of hospital stay Length of ICU stay Progression to ARDS, shock Safety concerns
NCT04801940	UK	HElping Alleviate the Longer-term Consequences of COVID-19 (HEAL-COVID): a National Platform Trial	Atorvastatin 40 mg for 12months Apixaban	Standard care	Survival, mortality, readmission, adverse reactions, FACIT-fatigue, modified MRC dyspnoea scale, COVID-19 core outcome measure for recovery, PHQ-2, GAD-2, PTSD, quality of life, intervention tolerability