Letter to the Editor

Effects of statins on clinical outcomes in hospitalized patients with COVID-19

Dear editor,

Statins are lipid-lowering drugs that have been evaluated as a potential treatment for COVID-19 due to their pleiotropic effects, including anti-inflammatory, immunomodulatory, antioxidant, antithrombotic, and endothelium-stabilizing properties. A recent meta-analysis pooling results from 25 cohort studies suggested that statins may improve prognosis and decrease mortality in patients with COVID-19 [1]. Nevertheless, it is well known that observational studies may be misleading to build an evidence-based clinical practice. Moreover, statin use in most cohorts was driven by cardiovascular reasons rather than by COVID-19, and the associations between treatment effect and clinical outcomes may be spurious. Therefore, evidence from randomized clinical trials (RCTs) is needed to confirm these findings. In this study, we summarized the current evidence from RCTs on the effects of statins on clinical outcomes in patients with SARS-CoV-2 infection.

Searches were performed in PubMed, Web of Science, Embase, medRxiv, Google Scholar, and the website ClinicalTrials.gov from January 1, 2020, to April 19, 2022 (Supplementary file). The reference lists of all eligible studies and reviews were also scanned to identify additional studies for inclusion. Reports were screened in two stages: titles and abstracts followed by full-text articles.

The following elements were used to define eligibility criteria:

(1) Population: Hospitalized patients with COVID-19.
(2) Intervention: Statins (atorvastatin, simvastatin, lovastatin, pravastatin or rosuvastatin).
(3) Comparison: Placebo or standard protocol.
(4) Outcomes: Length of stay, intensive care unit (ICU) admission, death, and any adverse events.
(5) Study type: RCTs. Eligible studies must report at least one of the outcomes of interest. Potential overlapping populations and observational studies were excluded.

Data from publications were extracted by two authors and cross-checked for accuracy. Risk of bias was judged according to the Cochrane guidelines for RCTs. Treatment effects were reported as relative risk (RR) for dichotomous variables (ICU admission and death) and mean difference (MD) for continuous variables (length of stay) with 95% confidence intervals (CI). Data on adverse events were provided descriptively. A random-effects model was used to pool the results and a 2-tailed $p < 0.05$ was used to determine significance. Analyses were conducted using Review Manager, version 5.3 (Cochrane IMS).

Search strategy yielded 496 potentially relevant records and six full-text articles were assessed for eligibility. Five RCTs [2–6] were selected for the meta-analysis (Supplementary file) and a total of 1132 patients were included, 556 in the intervention group and 576 in the control group (placebo or standard protocol). Of the included trials, four used atorvastatin (20 mg/day [2,3] or 40 mg/day [4,5]) and one used rosuvastatin (40 mg/day) [6] as treatment for hospitalized patients with COVID-19 (Supplementary file). Overall, the RCTs had a low risk of selection and attrition bias, but 40% presented a potential risk for performance, detection, and reporting bias. Three RCTs [3,4,6] clearly reported the exclusion of patients with prior statin use before randomization. There was a high risk for small-sample bias in most studies (Supplementary file).

In the meta-analysis, we found no difference in length of stay (MD = 0.25; 95% CI -1.13 to 1.62; $I^2 = 84\%$) and risk of ICU admission (RR = 1.72; 95% CI 0.61 to 4.85; $I^2 = 59\%$) and death (RR = 0.90; 95% CI 0.73 to 1.11; $I^2 = 0\%$) between patients treated with statins and the control group (Table 1). The influence of intervention protocol and statin type on the results of the meta-analysis can be found in the Supplementary file. Three studies provided information on adverse events. In the INSPIRATION-S Investigators trial [3], 6.6 and 5.1% of patients receiving atorvastatin 20 mg/day and placebo, respectively, had bleeding complications. No cases of myopathy were confirmed and severe thrombocytopenia was diagnosed in four (1.4%) patients using atorvastatin. In the study by Matli et al. [5], six patients had adverse events (bradycardia, nausea/vomiting, and hypotension), three (17.7%) among patients receiving atorvastatin 40 mg/day and three (15%) in the placebo group. Gaitán-Duarte et al. [6] reported a two-fold increased risk of adverse events among patients receiving rosuvastatin, especially gastrointestinal symptoms and hepatic injuries.

This meta-analysis compared the effects of statins on clinical outcomes in hospitalized patients with SARS-CoV-2 infection. The major findings were derived from a population of 1132 participants of five RCTs and the best available evidence has not shown that statins reduce the length of stay and decrease the risk of ICU admission and death associated with COVID-19. Moreover, statins were well tolerated and the occurrence of adverse effects was relatively low. These results

Table 1
Treatment effects of statins on clinical outcomes in patients with COVID-19.

Outcomes	MD (95% CI)	RR (95% CI)	*p*-value	I^2
Length of stay (days)	0.25 (-1.13 to 1.62)	-	0.73	84%
ICU admission	-	1.72 (0.61 to 4.85)	0.31	59%
Death	-	0.90 (0.73 to 1.11)	0.33	0%

MD, mean difference; RR, risk ratio; CI, confidence interval. Negative results for MD indicate decreased length of stay among patients receiving statins.

indicate that statins do not appear to provide clinical benefits in a complex pro-inflammatory scenario as seen in COVID-19.

Several observational studies [7,8] have shown an association between antecedent statin use and lower risk of intubation, ICU admission, and mortality in hospitalized patients with COVID-19. On the other hand, other observational studies showed that antecedent statin exposure in hospitalized patients with COVID-19 was not associated with a decreased risk of severe endpoints, including the need for mechanical ventilation and mortality [9,10]. These conflicting data supported the realization of a large systematic review and meta-analysis performed by Diaz-Arocutipa et al. [1], which included 25 cohort studies and 147,824 patients, and showed that the chronic use of statins was associated with reduced mortality among COVID-19 patients. Despite the importance of this review, observational studies are not the best source of evidence for assessing the efficacy of treatments and the main findings were likely to be affected by residual confounding. To the best of our knowledge, our study is the first meta-analysis including only RCTs to examine the effects of statin in hospitalized patients with COVID-19.

Three studies in our review provided information on adverse events associated with statin use including bleeding complications, bradycardia, nausea/vomiting, hypotension, gastrointestinal symptoms, and hepatic injuries. Statins are well-tolerated drugs with few side effects. Among them, myopathy constitutes the most relevant event at the clinical level and the mildest form of this disorder is characterized by myalgia without an increase in creatine kinase. Prothrombin activity is also significantly reduced in COVID-19 patients, which is associated with a higher incidence of thrombotic and hemorrhagic events. Therefore, statin use may increase the likelihood of coagulopathy during the clinical course of the disease. The uncertainty of the clinical course of COVID-19, the interactions with other treatments, and the potential adverse effects of statins in this clinical context imply close monitoring of possible complications.

Statins represent a pharmacological class that has been used for many years with undoubted therapeutic efficacy and safety profile in the management of hyperlipidemia and prevention of atherosclerotic vascular disease. Therefore, based on the neutral findings of our investigation, hospitalized patients with COVID-19 using statins should continue to use this medication, following cardiovascular guideline recommendations. On the other hand, the available evidence does not support initiating the drug to specifically treat SARS-CoV-2 infection.

Our study had some limitations, including some trials with small samples and high risk for performance, detection, and reporting bias. Moreover, the doses of atorvastatin used in some RCTs may have limited the expected beneficial pleiotropic effects in the inflammatory setting of COVID-19. In summary, available evidence based on the results of RCTs showed no clinical benefits of statins as a treatment for COVID-19.

However, patients using statins should be closely monitored for potential adverse effects during the hospital stay.

Authors contributions

All authors contributed equally to this manuscript.

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Declaration of Competing Interest

The authors declare they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.06.007.

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