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Protective Effects of Statins Administration in European and North American Patients Infected with COVID-19: A Meta-Analysis

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Abstract

Severe acute respiratory syndrome coronavirus 2 has spread rapidly throughout the world, becoming an overwhelming global health emergency. The array of injuries caused by this virus is broad and not limited to the respiratory system, but encompassing also extensive endothelial and systemic tissue damage. Since statins effectively improve endothelial function, these drugs may have beneficial effects in patients with coronavirus disease 2019 (COVID-19). Therefore, this investigation aimed to provide an updated overview on the interplay between statins and COVID-19, with particular focus on their potentially protective role against progression toward severe or critical illness and death. A systematic electronic search was performed in Scopus and PubMed up to present time. Data on statins use and COVID-19 outcomes especially in studies performed in Europe and North America were extracted and pooled. A total of seven studies met our inclusion criteria, totaling 2,398 patients (1,075 taking statins, i.e., 44.8%). Overall, statin usage in Western patients hospitalized with COVID-19 was associated with nearly 40% lower odds of progressing toward severe illness or death (odds ratio: 0.59; 95% confidence interval: 0.35–0.99). After excluding studies in which statin therapy was started during hospital admission, the beneficial effect of these drugs was magnified (odds ratio: 0.51; 95% confidence interval: 0.41–0.64). In conclusion, although randomized trials would be necessary to confirm these preliminary findings, current evidence would support a favorable effect of statins as adjuvant therapy in patients with COVID-19. Irrespective of these considerations, suspension of statin therapy seems highly unadvisable in COVID-19 patients.

Keywords
- statins
- coronavirus disease
- COVID-19
- meta-analysis

The novel coronavirus disease 2019 (COVID-19) pandemic is sustained by severe acute respiratory syndrome coronaviru 2 (SARS-CoV-2). This is the third coronavirus outbreak that has occurred during the past 20 years, after those caused by SARS and Middle East respiratory syndrome (MERS) coronaviruses (CoVs).[1,2] This new microorganism belongs to the CoV family, a class of enveloped, positive-sense, single-stranded RNA viruses, which typically cause respiratory, enteric, hepatic, and neurological diseases.[3,4]

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SARS-CoV-2 is transmitted principally through respiratory droplets, though contact/fomites and airborne (i.e., aerosol) transmission also plays a role in viral spread.[5] The virus penetrates into the host cells by primarily binding to angiotensin-converting enzyme 2 (ACE2), and initially reproduces in the cells of lower and upper respiratory tracts. Viral invasion might then be followed by a dysregulated host inflammatory response in some genetically or clinically predisposed individuals, leading to life-threatening episodes of acute respiratory distress syndrome (ARDS) and/or multiple organ failure.[6] ACE2 is a type I membrane protein expressed in lung, heart, kidney, and intestine and is mainly associated with cardiovascular disease. The protein consists of an N-terminal peptidase domain P and a C-terminal Collectrin-like domain that ends with a single transmembrane helix and an approximately 40-residue intracellular segment.[7] In addition to cleavage of angiotensin (Ang) I to produce Ang-(1–9) and cleavage of Ang II to produce Ang 1,7, ACE2 also provides a direct binding site for the spike (S) proteins of CoVs. Early studies have shown that SARS-CoV-2 S protein binds to human ACE2 with a 10- to 20-fold higher affinity than SARS-CoV, thus explaining its higher virulence.[8]

The unfavorable progression of COVID-19, which can be seen in 5 to 15% of all patients with SARS-CoV-2 infections, is characterized by a dysregulated inflammatory reaction, which can also be accompanied by downregulation of ACE2 levels.[9,10] On one hand this event may contribute to reduce the likelihood of being infected, on the other hand a lower ACE2 expression is associated with worse disease progression in those who have already been infected by SARS-CoV-2, as will be more specifically explained below.[9,10] The adverse effects of COVID-19 were initially thought to be primarily limited to the respiratory tract (i.e., pneumonia and ARDS), but it is now clear that the virus can extend systematically,[11] impacting a vast array of organs and tissues. The systemic propagation of the infection is frequently associated with development of a prothrombotic state,[12] which manifests as micro- or macrovascular episodes of venous and/or arterial thrombosis,[13,14] associated with unfavorable prognosis.

Recent data show that SARS-CoV-2 could directly infect the vascular endothelium and thereby impair endothelial cell function. Severe endothelial injuries associated with the presence of intracellular viruses, disrupted cell membranes, thrombosis with microangiopathy, and alveolar-capillary microthrombi have been described in COVID-19 patients.[15,16] In accordance with these findings, it is now clear that patients with vascular comorbidities such as hypertension, cardiovascular disease, and even diabetes are at much greater risk of poor outcome.[17–19]

Although no universal pharmacological treatment against SARS-CoV-2 has been established to date, combinations of oxygenation, antiviral agents, immunosuppressive drugs, and anticoagulants, along with other compounds, are individually used.[20,21] Among the various agents investigated, recent evidence has emerged that statins (3-hydroxy-3-methylglutaryl coenzyme A –HMG-CoA– reductase inhibitors) may have a beneficial effect in preventing disease progression.[22] Along with their lipid-lowering activity, statins are known to exert a kaleidoscope of pleiotropic effects on inflammation and oxidative stress,[23] producing beneficial effects on cardiovascular disease and thrombosis.[24–26] Recent evidence has been provided that statins administration may be effective in upregulating ACE2,[27] a mechanism that may lower the risk of developing severe ARDS in patients with SARS-CoV-2 infection,[28] since this enzyme promotes the enzymatic conversion of AngII into Ang 1,7, which then counterbalances the proinflammatory and vasoconstrictive activity of the former peptide.[29] Although the potential efficacy of antiatherosclerotic and antithrombotic mechanisms attributed to statins in COVID-19 requires further investigation, these drugs may represent a potentially promising therapy, at least as potential adjuvant drugs, especially due to their low cost, widespread availability, and relatively modest side effects.[30,31]

Thus, statins have been suggested as part of the arsenal to treat and/or attenuate COVID-19 symptoms and sequelae.[23] Therefore, this work is aimed to provide an overview of recent scientific literature exploring the interplay between statins and outcome of COVID-19, especially in European and North American populations.

Materials and Methods

We performed an electronic search in Medline (PubMed interface) and Scopus, using the keywords "COVID-19" OR "SARS-CoV-2" AND "statin," between 2019 and present time (i.e., September 28, 2020), restricting the search to articles published in English. The reference list of all documents was also reviewed to identify other potentially eligible studies. The title, abstract, and full text of the articles identified according to our search criteria were analyzed by two of the authors (D.O. and M.P.) and were considered eligible for inclusion in this literature review if they were case series (sample size >10) or observational studies reporting clear extractable data on the use of statins in laboratory-confirmed COVID-19 patients, and compared data regarding the use of statins between patients with severe/critical or nonsevere disease (or ARDS, or pulmonary embolism diagnosed by computer tomography pulmonary angiography) or between survivors and nonsurvivors. Severe/critical disease was defined as intensive care unit admission, need for mechanical ventilation, or ARDS, pulmonary embolism diagnosed by computer tomography pulmonary angiography, or death. We also excluded studies that only reported the generic term "lipid-lowering agents" and no specific information on the class of drug along with studies in patients with specific pathologies that could lead to misinterpreting drug effect (i.e., patients with multiple myeloma).[32] Reviews, case reports, and other editorial materials with no original data were also excluded. Disagreement arising during the selection assessment was resolved by discussion and consensus.

The data extracted from each article included authors, year of publication, title of the study, country, number of patients, age, number of patients taking statins or not, percentage of patients under statins use who developed severe disease or death versus those who did not, severity, infection criteria, and conclusions of the study (►**Table 1**).

Studies were selected in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines.[33]

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Table 1 Characteristics of the selected studies in patients hospitalized with COVID-19

Study	Setting	Study design	Sample size (COVID-19 positive)	Age (y)	Statins Yes (*n*) No (*n*)		% Patients on statin with severe disease or death	Endpoints	Conclusions
Wang et al (2020)[32]	United States	Retrospective	67	67 (median)	27	31	79% on statins vs. NA without	Mortality in patients with multiple myeloma	Statin use significantly associated with mortality in patients with multiple myeloma.
De Spiegeleer et al (2020)[35]	Belgium	Retrospective multicenter cohort study	154	79–93	31	123	19.4% on statins vs. 25.2% without	Severe disease or death	The effects of statin were positive but not statistically significant (OR: 0.75; CI: 0.24–1.87)
Mestre-Gómez et al. (2020)[36]	Spain	Retrospective single cohort study	91	56–73	27	64	22% on statins had PE vs. 35% without	PE confirmed at CT	No significant differences in treatment with statins in patients with and without PE
Daniels et al (2020)[37]	CA, United States	Retrospective	170	40–78	46	124	43.4% on statins vs. 56.5% without	Admission in ICU or death	Statin use prior to admission was associated with reduced risk of severe COVID-19
Nguyen et al (2020)[38]	IL, United States	Retrospective	353	50–73	89	264	11.23% on statins vs. 13.2% without	Death	Statin use prior to admission was associated with reduced risk of mortality
Gupta et al (2020)[39]	NY, United States	Retrospective multicenter cohort study	1,296	60–81	648	648	17.2% on statins vs. 31% without	Death	Antecedent statin use in patients hospitalized with COVID-19 was associated with lower inpatient mortality
Rodriguez-Nava et al (2020)[40]	IL, United States	Retrospective cohort Study	87	58–75	47 (on 39 survivors, unknown data for deceased patients)	40	NA 49% on statins vs. 62% without	Death	Slower progression to death associated with atorvastatin
McCarthy et al (2020)[41]	United States	Retrospective multicenter cohort study	247	50–76	187	60	48.0% on statins vs. 36.7% without	Admission in ICU or death	Use of statins is associated with unfavorable outcome.
Zhang et al (2020)[42]	Hubei, China	Retrospective	13,981	45–72	1,219	12,762	NA (reported as incidence rate: 0.21% on statins vs. 0.27 without)	Death during 28-day follow-up	Statin use was associated with a lower risk of all-cause mortality
Yan et al (2020)[43]	China	Retrospective multicenter	578	49 median age	15	563	33% on statins vs. 21% without	Severe disease	Despite low number of statin users, percentage of disease severity is higher in patients with statins
Argenziano et al (2020)[44]	NY, United States	Case series	1,000	50–75	361	639	NA	Severe disease or death	NA
Dreher et al (2020)[45]	Germany	Retrospective	50	58–76	18 (lipid-lowering agents)	32	50.0% on statin vs. 46.8% no statin use	Evolution in ARDS	NA
Zeng et al (2020)[46]	China	Retrospective	1,031	46–74	38	993	3% on statin vs. NA no statin use	Death	NA
Grasselli et al (2020)[47]	Italy	Retrospective multicenter	3,988	55–69	479	3,509	NA	Death	NA

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; CT, computed tomography; ICU, intensive care unit; NA, not available; OR, odds ratio; PE, pulmonary embolism.

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For the purposes of pooling into a meta-analysis, Chinese studies (to limit ethnic and sample heterogeneity) and studies that did not provide useful data for statistical purposes were excluded from our analysis. A separate analysis of Chinese studies was unfeasible, as they lacked the essential data for statistical pooling. A composite endpoint of severe or fatal COVID-19 was employed for this analysis. The meta-analysis was finally performed with calculation of pooled odds ratio (OR) and 95% confidence interval (95% CI) using MetaXL, software Version 5.3 (EpiGear International Pty Ltd., Sunrise Beach, Australia). Heterogeneity among the included studies was probed employing both the chi-square (χ^2) test and the I^2 statistic. For the χ^2 test, significant heterogeneity among the studies was designated with a Cochran's Q p-value of <0.10. The I^2 statistic values were interpreted as 25, 50, and 75%, indicating low, moderate, and high heterogeneity, respectively.[34] To evaluate potential sources for heterogeneity among the studies, subgroup analyses by time of initiation of statin therapy (before or after hospital admission) and by administration of azithromycin (a macrolide drug with significant drug interaction with statins, especially fostering rhabdomyolysis) were performed.

Results

A total of 170 studies could be originally identified, 156 of which were finally excluded because they were duplicates or did not fulfill the above-mentioned eligibility criteria (►**Fig. 1**).

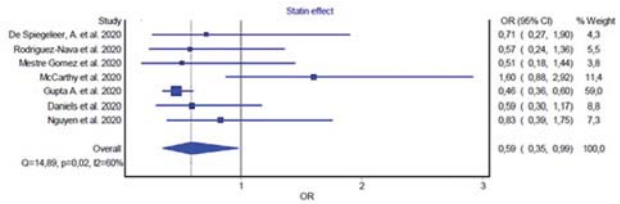

Fig. 2 Forest plot of the meta-analysis.

Overall, 14 studies met the inclusion criteria,[32,35–47] and are summarized in ►**Table 1**. After excluding studies from China or with inadequate data for pooling, the final meta-analysis was limited to seven retrospective studies performed in Western countries,[35–41] totaling 2,398 patients, 1,075 of whom (44.8%) were taking statins (►**Table 1**).

Three of the included studies were based on patients with similar age range (50–76 years old),[36,40,41] while the others included a mix of younger and older patients. Five out of seven studies evaluated patients with statin treatment before hospital admission,[35–39] while the others considered treatments started before admission or during hospital stay.[40,41] Notably, azithromycin[48] was also administered to the vast majority of patients included in the study by McCarthy et al.[41] Two studies applied death as the endpoint, two reported disease severity as the endpoint, and three reported both events.

The result of the meta-analysis of these seven studies performed in Western countries are reported in ►**Fig. 2**,[35–41]

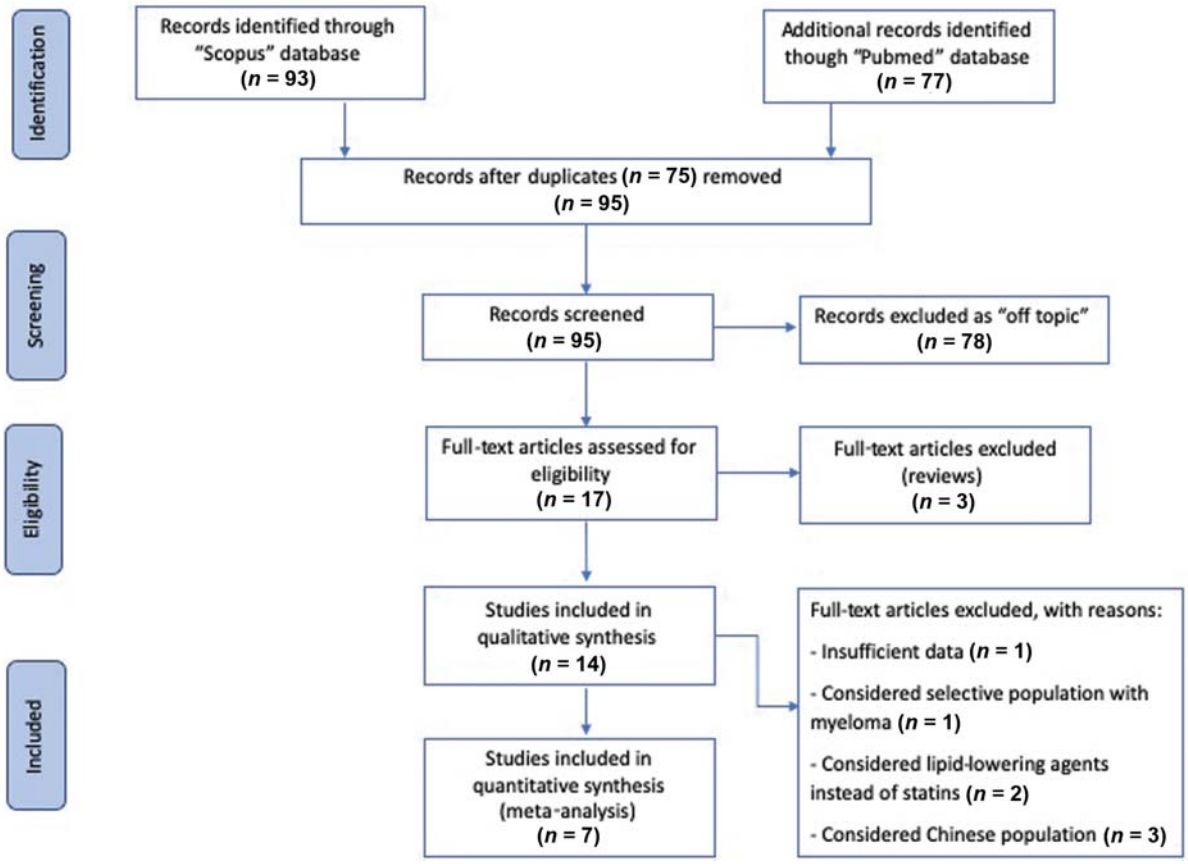

Fig. 1 PRISMA flow diagram of the literature search and selection process.

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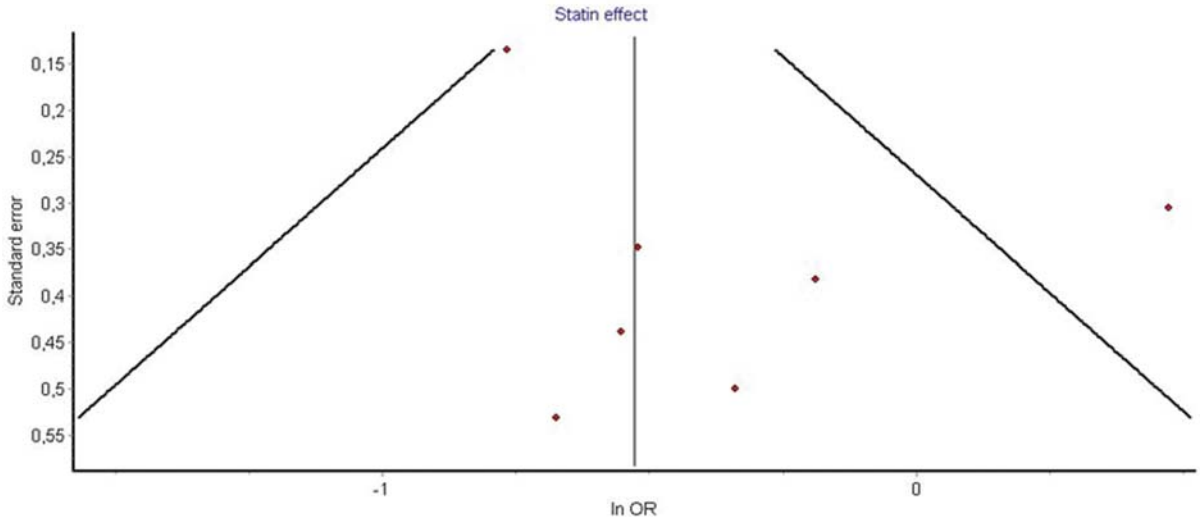

Fig. 3 Funnel plot of the meta-analysis: statins' protective effect versus lack of protection in hospitalized COVID-19 patients.

which demonstrate that COVID-19 patients taking statins had nearly 40% lower odds of progressing to the composite endpoint of severe/critical illness or death (OR: 0.59; 95% CI: 0.35–0.99; Cochran's Q $p = 0.02$; $I^2 = 60\%$). Individually, six of these seven studies reported a reduced OR (i.e., OR < 1; protective effect of statins),[35–40] while in only one study was the OR >1 (i.e., OR: 1.60; 95% CI: 0.88–2.92).[41] After excluding McCartney's study, in which patients were also given azithromycin, the beneficial effect of statins was magnified (OR: 0.52; 95% CI: 0.42–0.64; Cochran's Q $p = 0.73$, $I^2 = 0\%$). The results did not substantially change after excluding both studies in which statin therapy was initiated after hospital admission (OR: 0.51; 95% CI: 0.41–0.64; Cochran's Q $p = 0.61$, $I^2 = 0\%$).[40,41] The funnel plot of all studies is shown in ►**Fig. 3**, which demonstrated slight asymmetry.

Discussion

This article aimed to review the current scientific literature which has explored the potential impact of statins on clinical outcome of COVID-19 to date. Overall, the results of our analysis suggest a beneficial effect of these cardiovascular drugs in North American and European patients with SARS-CoV-2 infection.

In fatal cases of human SARS-CoV-2 (as well as of SARS-CoV-1 and MERS-CoV) infections, patients mostly progress to a severe form of acute respiratory distress, which requires mechanical ventilation and on autopsy demonstrates the classic histopathology findings of ARDS.[49–51] ARDS is a life-threatening lung condition that causes diffuse alveolar damage in the lung, with hyaline membrane formation in alveoli in the acute stage, and subsequent interstitial widening, edema, and fibroblast proliferation in the organizing stage.[52,53]

Convincing evidence has been provided that release of inflammatory cytokines is strictly associated with development and progression of ARDS, thus confirming that the onset of a dysregulated inflammatory response is a primary event in promoting clinical deterioration in COVID-19 patients.[54] The pathogenesis of COVID-19 encompasses hypercoagulability, inflammation, and decreased endothelial integrity,[34] culminating in defective pulmonary vasoconstriction, shunting, and thrombotic microangiopathy.[55–57] A potential beneficial effect of statin use thus possibly entails modulation (i.e., inhibition) of many underlying pathways, leading to potentially powerful anti-inflammatory and antithrombotic effects. In an animal model, atorvastatin was found to inhibit the expression of toll-like receptors, a family of sensor proteins which activate the myeloid differentiation primary response 88 pathway, thus underpinning its potential favorable effect in patients with COVID-19.[58]

Despite numerous investigations, it remains uncertain if statins could have a role in inhibiting the formation of thrombi in human subjects. To date, no study has demonstrated a substantial impact of statins in prevention of thrombosis. As such, statins are not clinically indicated for primary or secondary prevention of venous thromboembolism.[59,60] Thus, the beneficial effects of statins in COVID-19 are more likely to be attributed to its anti-inflammatory properties (as well as improvement in endothelial function) than to any significant antithrombotic direct effect.

Nonetheless, another potential beneficial mechanism of HMG-CoA reductase inhibitors that needs to be mentioned in COVID-19 involves their effect on cholesterol reduction. During viral infections, viruses require host lipid metabolism for survival since lipids are implicated in membrane fusion, envelopment, and transformation.[61] The host plasma membrane contains microdomains rich in proteins, sphingolipids, and cholesterol, named lipid rafts. An in vitro study investigated the role of these molecular structure in modulating the interaction between the spike protein of SARS-CoV-1 with ACE2 receptor,[62] finding that cholesterol is required for efficient S-mediated binding to ACE2-containing cells and its depletion decreased the infectivity by approximately 50% in a single replication cycle. Given this evidence, it is possible that SARS-CoV-2 would benefit from the presence of high cholesterol in the plasma membrane, which may hence facilitate its penetration into host cells. Thus, a statin-mediated inhibition of

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cholesterol biosynthesis pathway would result in decreased lipid raft formation and could hence be seen as a putative protective mechanism against SARS-CoV-2, as well as against other viral infections.[63,64]

Only one out of the seven studies included in our meta-analysis failed to report a favorable effect of statins in patients with SARS-CoV-2 infection. However, the concomitant administration of azithromycin in most patients enrolled in that study may have ultimately biased the outcome. In fact, muscle injury, possibly emerging from combined administration of the two drugs, may have contributed to attenuating the vascular benefits of statins, as clearly highlighted.[41,65] As such, it is not surprising that the favorable outcome of statins in COVID-19 patients increased (i.e., from 40 to ~50% lower risk of unfavorable progression, with narrower 95% CI) when this study was excluded from our meta-analysis. Unfortunately, no specific analysis could be performed to assess whether any single statin formulation would be more beneficial than another, since the type of drug administered was clearly specified in only one study (i.e., Atorvastatin 40 mg).[39] Nonetheless, these findings support the start of new randomized controlled trials investigating statins as adjunctive therapy in COVID-19.

Our meta-analysis has some limitations. First, this pooled analysis had a relatively small sample size. Second, all studies were retrospective; two studies[39,40] included patients in whom statin therapy was only started upon hospital admission, though their exclusion from the meta-analysis suggested an even larger favorable effect of statins. Finally, the use of a composite outcome likely introduced some heterogeneity into the analysis. However, subgroup analysis by study endpoint was unfeasible, as individual studies did not report data required to segregate patients by outcome, with the majority employing their own composite outcomes.

Conclusion

In conclusion, the results of this meta-analysis suggest a potential beneficial effect of statins in patients with COVID-19, especially when these drugs were initiated before hospital admission, but also lead the way to suggest that their administration could be beneficial for all patients hospitalized with COVID-19, as additional treatment for preventing unfavorable disease progression. Whether the favorable effect of statins in patients with SARS-CoV-2 infection may be direct (e.g., lowering lipids and decreasing the high cardiovascular risk characterizing COVID-19 patients),[66] or is more predictably mediated by the pleiotropic effects of these drugs (i.e., anti-inflammatory, anti-thrombotic, anti-hypertensive),[67] requires further investigation. Randomized controlled trials should be undertaken to explore the potentially diversified effects of statins as adjuvant therapy for improving outcomes in patients with SARS-CoV-2 infection. Irrespective of these considerations, it seems reasonable to conclude that statin therapy should at minimum not be suspended in patients with COVID-19.

Conflict of Interest
None declared.

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