
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Clinical Lipidology (2021) 15, 399–401

Journal of Clinical Lipidology

Editorial

# Statins in COVID-19 infection: A rehash of old themes or truly a new hope?



The COVID-19 pandemic, caused by SARS-CoV-2, has compelled a global mobilization of resources for medical innovation to combat the substantial morbidity and mortality of the disease. Due to the need for expediency, significant efforts have been appropriated towards repurposing of existing medications as therapies for COVID-19 infection. Thus far, some efforts have led to moderate success – i.e. remdesivir, while others have not quite panned out – i.e. hydroxychloroquine.[1,2]

## What do we know?

While patients with COVID-19 often present with respiratory symptoms, the infection is a systemic illness with significant impact to the cardiovascular system most likely as an indirect effect from the ensuing cytokine storm.[3] Multiple studies have shown presence of myocardial injury in COVID-19 patients as evidenced by increases in cardiac biomarkers such as troponins and B-type natriuretic peptide (BNP) as well as via histology and imaging.[4–6] Importantly, patients with pre-existing cardiovascular disease (CVD) present with more severe disease and have an increased risk for mortality.[7] COVID-19 infection is thought to cause direct myocardial injury as well as microvascular or macrovascular thrombosis, endothelial dysfunction and a pro-inflammatory response.[3]

Given the significant cardiovascular impact, it is not surprising that there is interest in the role of statins as a part of COVID-19 management. Statin therapy has been a well-established and foundational therapy for the primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) for the better part of two decades.[8] Apart from effectively reducing low density lipoprotein cholesterol (LDL-C), statins have been postulated to have multiple pleotropic effects including improving endothelial function and attenuating vascular inflammation. In the JUPITER trial, Ridker et al. demonstrated that treatment with rosuvastatin in primary prevention patients with mildly elevated LDL-C and elevated high-sensitivity C-reactive protein (hs-CRP), a biomarker of inflammation, resulted in ASCVD risk reduction. Moreover, the absolute risk reduction attributable to rosuvastatin increased with increasing levels of baseline hs-CRP.[9] Statins have been shown in animal models to modulate the Toll-like receptor (TLR)-MYD88 pathway, which in turn attenuates NF-kB activation.[10] Experimental data have found that SARS-CoV-1 triggers this pathway during infection, and inhibition of NF-kB improves survival in animal models.[11]

The anti-inflammatory properties of statins in acute respiratory infections have been evaluated in a number of prior studies before the COVID-19 pandemic. Results from several observational studies in influenza have suggested that statin use may be protective in the setting of viral pneumonia. For instance, Frost el al. noted significant reduction in influenza/pneumonia mortality among statin users.[12] However, other studies have shown no benefit in respiratory infection outcome from statin use.[13] Among patients with ventilator associated pneumonia (VAP), one small randomized, open-label trial of 152 patients showed a signal towards improved outcomes among critical care patients treated with pravastatin.[14] Yet a much larger randomized placebo-controlled trial enrolling over 1000 VAP patients found no significant effect of simvastatin on mortality and other VAP outcomes.[15] Meanwhile, meta-analysis of randomized trials of statins in sepsis did not show an improvement in mortality compared with placebo.[16] Taken as a whole, there has been insufficient evidence prior to the COVID-19 pandemic to support the use of statin in an acute infection setting.

## What does this study add?

Thus far, several observational studies have assessed the association of statin use in patients with COVID-19 infection. In the current issue, Lohia et al. performed a retrospective cohort study of COVID-19 patients presenting for care at 2 hospitals in Detroit, Michigan.[17] Analyses were conducted using both traditional multivariable regression and propensity score matching. Interestingly, no association with mortality was seen with statin use in the unadjusted regression analyses, and the association between statin therapy and mortality became evident only after adjusting for several covariates in multivariable regression. The authors then

1933-2874/Published by Elsevier Inc. on behalf of National Lipid Association.
https://doi.org/10.1016/j.jacl.2021.04.002

conducted propensity score matching between statin users and non-users to evaluate outcomes. Overall, the authors found that among COVID-19 patients, statin use as part of their home medication regimen was associated with a 34% lower odds for mortality compared with those not on a statin after adjusting for multiple comorbidities in the multivariable regression models (OR 0.66, 95% CI 0.46-0.95, $p = 0.03$) and 44% lower odds for mortality in a propensity score matched analysis (OR 0.56, 95% CI 0.37-0.83, $p = 0.004$). The authors also showed that compared to non-users, patients on moderate or high-intensity statin therapy showed lower mortality in propensity score matched analyses. No such association was seen with low-intensity statin therapy. While the association with decreased mortality seen in this study is impressive, the previous body of work on statins in acute infectious processes advocate for caution when interpreting the results. Finally, the association between statin use and clinical markers of disease severity (need for ICU admission or the need for mechanical ventilation) was not significant, and therefore, what drove a reduction in mortality in this study is not very clear.

## Where do we go from here?

The authors should be commended on meticulous analyses adjusting for a wide variety of comorbidities and for employing propensity score matching to account for selection bias as result of known confounders. Yet with any observational study, residual confounders and unknown confounders undoubtedly remain. A healthy user bias cannot be excluded either as patients on statins may be more health conscious, have better health care access, and present earlier during their clinical course. Furthermore, assessing only the admitted patients, though pragmatic, in itself introduces selection bias. Indeed, other observational studies assessing antecedent statin use and in-hospital morbidity and mortality outcomes have found different results. One such study led by Mitacchione et al. noted that statin use was not associated with significantly lower risk for mortality and was associated with more severe COVID-19 disease after propensity score matching.[18] These studies highlight the limitation associated with observational studies – i.e., despite employing the best available analytic techniques, these studies can only account for known confounders. Randomization on the other hand accounts for both known and unknown confounders. Therefore, until randomized controlled trial data becomes available, there is insufficient evidence to support the repurposing of statin therapy to treat patients with COVID-19 infections.

In most COVID-19 patients who are already on statins for primary or secondary prevention of ASCVD, there is no convincing data suggesting that continuing therapy through the course of the infection is unsafe. Interestingly, several studies assessing the lipid profile of patients during COVID-19 infection show a downtrend of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and LDL-C likely as a negative acute phase reactant response.[19,20] Some have speculated that further reduction of blood cholesterol by statins in the setting of acute infection may contribute to worsening disease severity. However, no causal relationship between low cholesterol levels and increase in COVID-19 disease severity has been demonstrated. Thus, continuing statin therapy in most cases of COVID-19 is likely safe. Of course, in the case of severe liver injury or rhabdomyolysis, which have been described in COVID-19 infection, holding statin therapy until these processes resolve seems prudent. While evaluating patients with COVID-19 who have established ASCVD, diabetes or high-risk primary prevention, clinicians should also ask themselves whether these patients need to be initiated on statin therapy based on current cholesterol treatment guidelines if not already on statin therapy. This approach is likely safe and will reduce clinical inertia in cholesterol management, especially for these high-risk patients.

Being preventive cardiologists, we would love to see statins as a panacea of all maladies. Alas this is not the case. The efficacy of statins in the risk reduction in ASCVD, however, is ironclad. COVID-19 patients with clinical ASCVD and CVD risk factors have increased morbidity and mortality. Therefore, while statins may not be the silver bullet, preventing ASCVD becomes even more paramount in the era of COVID-19.

## Declaration of Competing Interest

XJ: Nothing to declare.

SSV: Grant Support: Department of Veterans Affairs, World Heart Federation, Tahir and Jooma Family. Honorarium, American College of Cardiology (Associate Editor for Innovations, acc.org).

Xiaoming Jia
*Section of Cardiology, Department of Medicine, Baylor College of Medicine, Houston, TX, United States*
Salim S. Virani*
*Section of Cardiology, Department of Medicine, Baylor College of Medicine, Houston, TX, United States*
*Health Policy, Quality & Informatics Program, Michael E. DeBakey Veterans Affairs Medical Center Health Services Research and Development Center for Innovations, Houston, TX 77030, United States*
*Section of Cardiology, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, United States*
*Section of Health Services Research, Department of Medicine, Baylor College of Medicine, Houston TX, United States*
*Corresponding author at: Michael E. DeBakey Veterans Affairs Medical Center Health Services Research and Development, Center for Innovations, 2002 Holcombe Blvd, Houston, TX 77030, United States.
*E-mail address:* virani@bcm.edu (S.S. Virani)

Received March 18, 2021
Accepted April 11, 2021

## CRediT authorship contribution statement

**Xiaoming Jia:** Conceptualization, Writing - original draft, Writing - review & editing. **Salim S. Virani:** Conceptualization, Writing - original draft, Writing - review & editing.

## Reference

1. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of COVID-19 - final report. *N Engl J Med*. 2020;383(19):1813–1826.
2. Self WH, Semler MW, Leither LM, Casey JD, Angus DC, Brower RG, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: a randomized clinical trial. *JAMA*. 2020;324(21):2165–2176.
3. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. COVID-19 and cardiovascular disease. *Circulation*. 2020;141(20):1648–1655.
4. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, 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.
5. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(11):1265–1273.
6. Fox SE, Li G, Akmatbekov A, Harbert JL, Lameira FS, Brown JQ, et al. Unexpected features of cardiac pathology in COVID-19 infection. *Circulation*. 2020;142(11):1123–1125.
7. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;5(7):802–810.
8. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;73(24):e285–e350.
9. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359(21):2195–2207.
10. Yuan X, Deng Y, Guo X, Shang J, Zhu D, Liu H. Atorvastatin attenuates myocardial remodeling induced by chronic intermittent hypoxia in rats: partly involvement of TLR-4/MYD88 pathway. *Biochem Biophys Res Commun*. 2014;446(1):292–297.
11. DeDiego ML, Nieto-Torres JL, Regla-Nava JA, Jimenez-Guardeno JM, Fernandez-Delgado R, Fett C, et al. Inhibition of NF-kappaB-mediated inflammation in severe acute respiratory syndrome coronavirus-infected mice increases survival. *J Virol*. 2014;88(2):913–924.
12. Frost FJ, Petersen H, Tollestrup K, Skipper B. Influenza and COPD mortality protection as pleiotropic, dose-dependent effects of statins. *Chest*. 2007;131(4):1006–1012.
13. Fleming DM, Verlander NQ, Elliot AJ, Zhao H, Gelb D, Jehring D, et al. An assessment of the effect of statin use on the incidence of acute respiratory infections in England during winters 1998–1999 to 2005–2006. *Epidemiol Infect*. 2010;138(9):1281–1288.
14. Makris D, Manoulakas E, Komnos A, Papakrivou E, Tzovaras N, Hovas A, et al. Effect of pravastatin on the frequency of ventilator-associated pneumonia and on intensive care unit mortality: open-label, randomized study. *Crit Care Med*. 2011;39(11):2440–2446.
15. Papazian L, Roch A, Charles PE, Penot-Ragon C, Perrin G, Roulier P, et al. Effect of statin therapy on mortality in patients with ventilator-associated pneumonia: a randomized clinical trial. *JAMA*. 2013;310(16):1692–1700.
16. Deshpande A, Pasupuleti V, Rothberg MB. Statin therapy and mortality from sepsis: a meta-analysis of randomized trials. *Am J Med*. 2015;128(4):410–417 e1.
17. Lohia P, Kapur S, Benharam S, Mir T. Association between antecedent statin use and severe disease outcomes in COVID-19: a retrospective study with propensity score matching. *J Clin Lipidol*. 2021;S1933-2874(21):53–62.
18. Mitacchione G, Schiavone M, Curnis A, Arca M, Antinori S, Gasperetti A, et al. Impact of prior statin use on clinical outcomes in COVID-19 patients: data from tertiary referral hospitals during COVID-19 pandemic in Italy. *J Clin Lipidol*. 2021;15(1):68–78.
19. Wei X, Zeng W, Su J, Wan H, Yu X, Cao X, et al. Hypolipidemia is associated with the severity of COVID-19. *J Clin Lipidol*. 2020;14(3):297–304.
20. Hu X, Chen D, Wu L, He G, Ye W. Declined serum high density lipoprotein cholesterol is associated with the severity of COVID-19 infection. *Clin Chim Acta*. 2020;510:105–110.