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Association Between Chronic Statin Use and 30-Day Mortality in Hospitalized Patients With COVID-19

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Abstract

Objective: To determine the association between chronic statin use and mortality in patients hospitalized with coronavirus disease 2019 (COVID-19).

Patients and Methods: We identified a retrospective cohort of patients requiring admission at the Mayo Clinic using our enterprise-wide COVID-19 registry from March 1, 2020, through September 30, 2020. Available information included age, sex, use of statins, medical comorbidities, and 30-day mortality. We estimated the association of statins with 30-day mortality using odds ratios and 95% CIs from logistic regression modeling.

Results: Patients (N=1295) between the ages of 30 and 80 years tested positive for COVID-19 and required admission during the study period, of whom 500 (38.6%) were taking statins at admission. Patients taking statins were older and more likely to have diabetes mellitus or congestive heart failure. Within 30 days of diagnosis, 59 (4.6%) died. In multivariable analysis, statin users did not have statistically different odds of death within 30 days with an odds ratio of 1.14 (95% CI, 0.64 to 2.03; P=.67) compared to nonusers.

Conclusion: Patients with COVID-19 taking statins had similar 30-day mortality to those not taking statins after adjusting for relevant covariates. Although this is partly influenced by a higher prevalence of risk factors for more severe COVID-19 presentation not entirely adjusted for by the Charlson comorbidity index, these data would not support statins as a likely therapeutic intervention for COVID-19 in the hospital setting.

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Since its emergence in Wuhan, China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the agent causing coronavirus disease 2019 (COVID-19), has infected more than 79 million people.[1,2] Given the extent of the pandemic, there has been much investigation of risk factors for severe disease, mortality, and preventive strategies.

The use of statins, a class of medications commonly used to treat hyperlipidemia and atherosclerotic disease, has been a subject of debate. Statins have several properties that theoretically have an impact on the pathophysiology of COVID-19, with possible positive or negative effects on outcomes. In particular, expression of angiotensin-converting enzyme 2, the receptor used by SARS-CoV-2, is augmented by statin medications.[3,4] However, lipid metabolism plays a role in viral replication and statins alter this process while also inhibiting the SARS-CoV-2 main protease in vitro.[5,6] Patients with COVID-19 have a high rate of thromboembolism and statins have been identified to have antithrombotic properties and potentially reduce this risk.[7-9] Statins also display anti-inflammatory properties through a number of actions, including downregulation of toll-like receptors and inhibition of T-cell activation.[10,11] These effects may improve a dysregulated inflammatory response; however,

studies have been mixed on the effect of statins in influenza,[12,13] acute respiratory distress syndrome,[14,15] and sepsis.[16] Furthermore, several factors for severe COVID-19 are strongly associated with use of statin therapy such as older age, male sex, systemic hypertension, and cardiovascular disease.[11,17-20] Aspirin, another medication commonly prescribed for patients taking statins, is also postulated to affect outcomes in COVID-19.[21,22]

Our group has previously analyzed published data about statins and effect in infections[23] and community-acquired pneumonia.[24] Data from nine cohorts addressed the role of prior statins in patients with different infections with a pooled adjusted risk ratio (RR) of 0.55 (95% CI, 0.36 to 0.83; I^2=76.5%) were in favor of statins.[23] In another meta-analysis of 13 observational studies, we observed that prior statins were associated with a lower short-term mortality in patients with community-acquired pneumonia (odds ratio [OR], 0.68; 95% CI, 0.59 to 0.78; I^2=75.7%).[24] However, a recent systematic review and meta-analysis analyzed 14 randomized controlled trials using statin initiation as an adjunctive treatment for hospitalized adults with sepsis. De novo statin therapy did not reduce 30-day all-cause mortality in all patients (RR, 0.96; 95% CI, 0.83 to 1.10), nor in a subgroup of patients with severe sepsis (RR, 0.97; 95% CI, 0.84 to 1.12).[25]

The association between statin use and outcomes of patients with COVID-19 has been recently examined in multiple studies with conflicting results.[26-35] Therefore, we sought to examine the association of chronic statin use and COVID-19 outcome in a large hospitalized cohort from the multicenter Mayo Clinic COVID-19 registry.

PATIENTS AND METHODS

Early in the pandemic, an institutional registry was created to identify patients who were diagnosed with COVID-19. This registry contains patients diagnosed at Mayo Clinic sites including Arizona, Florida, and Minnesota. The Mayo practices see approximately 1.2 million patients in the large primary, secondary, and tertiary care practice across more than 70 hospitals and clinics on a yearly basis. The registry contains information regarding comorbidities, 10-year probability of survival based on the Charlson comorbidity index (10-CCI), hospital admission, intensive care unit admission, mechanical ventilation, experimental treatments, and mortality. For this study, the registry was queried for all patients diagnosed with COVID-19 through September 30, 2020 to allow 30 days of follow-up for each patient at the time of analysis. Patients prescribed a statin at the time of their COVID-19 diagnosis were identified by querying an institutional registry, which drew the prescription data from the electronic medical record. Patients without record of statin prescription at this time of admission were assumed not to be taking a statin. Statin prescriptions were organized into high, moderate, and low intensity. High-intensity statins included atorvastatin 40 to 80 mg daily and rosuvastatin 20 to 40 mg daily. Moderate-intensity statins included atorvastatin 10 to 20 mg daily, fluvastatin 40 mg twice daily, lovastatin 40 mg daily, pitavastatin 2 to 4 mg daily, pravastatin 40 to 80 mg daily, rosuvastatin 5 to 10 mg daily, and simvastatin 20 to 40 mg daily. All lower-dosed statins were included in the low-intensity group.[36] Patients with record of statin prescription but without dosage data were excluded from the analysis that examined the association of different statin intensity and mortality. The cohort was restricted to those aged 30 to 80 years at the time of COVID-19 diagnosis to limit confounding by age, as patients outside of this range are unlikely to be prescribed statins. We also limited to those requiring hospitalization to avoid exclusion of asymptomatic or mild cases that did not undergo testing. All patients were followed for 30 days after diagnosis. Some patients did not have complete data on statin intensity (N=42, 8.4%); otherwise there was no missing data in this database. As this was a retrospective chart review, the institutional review board granted waiver of consent, and Minnesota patients without research authorization were excluded.

The associations of statin use at diagnosis with risk of death within 30 days of diagnosis were estimated using ORs and 95% CIs from logistic regression modeling. Our multivariable model was adjusted for 10-CCI, sex, COVID-19 treatment trial enrollment, and aspirin use. The 10-CCI was chosen because

TABLE. Patient Characteristics[a,b]

Characteristic	On statin (n=500)	Not on statin (n=795)	P
Age, median (IQR)	65 (57-73)	55 (43-65)	<.01
Male	307 (61)	410 (52)	<.01
Diabetes mellitus	249 (50)	141 (18)	<.01
Congestive heart failure	77 (15)	37 (5)	<.01
Coronary artery disease	62 (12)	28 (4)	<.01
Aspirin use	258 (52)	126 (16)	<.01
High-intensity statin	129 (26)	0	<.01
Moderate-intensity statin	311 (62)	0	<.01
Low-intensity statin	19 (4)	0	<.01
Unknown-intensity statin	41 (8)	0	<.01
10-year probability of survival by CCI (IQR)	53.4% (2.2%-77.5%)	90.1% (53.4%-95.9%)	<.01
Anti-inflammatory clinical trial	27 (5)	33 (4)	<.01
Antiviral clinical trial	199 (40)	264 (33)	<.01
30-day mortality	35 (7)	24 (3)	<.01

[a]CCI, Charlson comorbidity index; IQR, interquartile range.
[b]Values are n (%) unless otherwise stated.

it incorporates many variables associated with outcomes in COVID-19 such as age and comorbidities. We did perform an exploratory subgroup analysis of this model by separating statin use by intensity. Patients without statin intensity data (n=41 of 500 with statin use, 8.2%) were excluded from this subgroup analysis. All analyses were performed using JMP Pro 14.0 (SAS Institute Inc, Cary, NC).

RESULTS

We identified 1295 patients hospitalized with COVID-19 through September 30, 2020. At diagnosis, 500 (38.6%) were identified as prescribed a statin. In the total cohort, 114 (8.8%) patients had received a diagnosis of congestive heart failure, 390 (30.1%) diabetes mellitus, and 90 (6.9%) coronary artery disease. Three-hundred eighty-four (29.7%) patients were taking any dose of aspirin before admission. Patients on a statin were older, more likely to be male, had a much higher prevalence of diabetes mellitus, congestive heart failure, coronary artery disease, and aspirin use. These patients also had a lower 10-CCI. Patient characteristics by statin use are shown in the Table.

Within 30 days of diagnosis, 59 (4.6%) of patients had died. This included 35 (7.0%) patients with statins and 24 (3.0%) patients

without statins. After adjusting for 10-CCI, sex, clinical trial enrollment, and aspirin use, patients taking statins did not have a statistically different odds for 30-day mortality compared to nonusers (OR, 1.14; 95% CI, 0.64 to 2.03; P=.67). In the subset of patient in which statin intensity dosing was available, a separate analysis was performed with statin intensity as predictors. The ORs were similar for each dose of statin and the quality of the model was lower than the model using statin as a binary predictor, as indicated by significantly increased Akaike information criterion.

DISCUSSION

There remains a desperate need to determine optimal strategies for managing patients with COVID-19. While many new treatment regimens are being developed, the effect of existing medications should continue to be evaluated for efficacy or harm. Statins have plausible mechanisms for both improving and worsening outcomes in COVID-19 while also being widely used. However, our study did not identify a difference in odds of 30-day mortality for statin users, regardless of the intensity of statin therapy.

Although our cohort had inferior 30-day crude mortality on statins, much of this appeared to be related to confounding as many indications for statins are risk factors for more severe disease from COVID-19.[11,17-20] Indeed, after adjustment for 10-CCI, sex, clinical trial enrollment, and aspirin use, there was essentially no association of statin use with 30-day mortality. A prior study indicated that glycemic control correlated with outcomes in COVID.[37] It would follow that diabetic medications act both as a marker of illness and a marker for higher likelihood of controlled illness. Thus, diabetes medications may correlate with both positive and negative effects. Similarly, continuing statins in those with an indication may also contribute to controlling these risk factors for more severe COVID-19. However, interferon responses play a critical role in controlling SARS-CoV-2[38] and statins appear to impair the interferon response.[39]

Study Limitations

Our study has several limitations. The retrospective nature of our review likely has

inherent sources of bias. We also had an overall low number of patients meeting some outcomes, such as 30-day mortality. Another limitation of this study is potential misclassification of patient attributes as these were based on billing codes. Our registry also did not include complete data on the type or dosage of statin medication. This limited our analysis of statin intensity's potential effect on mortality. Finally, our data do not directly answer the question of whether starting a statin at diagnosis of COVID-19 would impact outcomes.

Ultimately, we did not identify statin users as having higher or lower odds of 30-day mortality as compared to nonusers. In the context of the previously noted limitations, this study does not support statin initiation or discontinuation as a therapeutic intervention in patients with COVID-19.

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REFERENCES

1. Shah A, Kashyap R, Tosh P, Sampathkumar P, O'Horo JC. Guide to understanding the 2019 novel coronavirus. *Mayo Clin Proc.* 2020;95(4):646-652.

2. Coronavirus disease (COVID-19) Weekly Epidemiological Update - 29 December 2020. WHO Rep. https://www.who.int/publications/m/item/weekly-epidemiological-update—29-december-2020. Accessed January 2, 2021.

3. South AM, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences. *Am J Physiol Heart Circ Physiol.* 2020;318(5):H1084-H1090.

4. Lee KCH, Sewa DW, Phua GC. Potential role of statins in COVID-19. *Int J Infect Dis.* 2020;96:615-617.

5. Abu-Farha M, Thanaraj TA, Qaddoumi MG, Hashem A, Abubaker J, Al-Mulla F. The role of lipid metabolism in COVID-19 virus infection and as a drug target. *Int J Mol Sci.* 2020;21(10):3544.

6. Reiner Ž, Hatamipour M, Banach M, et al. Statins and the COVID-19 main protease: in silico evidence on direct interaction. *Arch Med Sci.* 2020;16(3):490-496.

7. Moll M, Zon RL, Sylvester KW, et al. Venous thromboembolism in COVID-19 ICU Patients. *Chest.* 2020;158:2130-2135.

8. Violi F, Calvieri C, Ferro D, Pignatelli P. Statins as antithrombotic drugs. *Circulation.* 2013;127(2):251-257.

9. Glynn RJ, Danielson E, Fonseca FAH, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. *N Engl J Med.* 2009;360(18):1851-1861.

10. Karalis DG. Are statins safe in patients with COVID-19? *J Clin Lipidol.* 2020;14:396-397.

11. Alijotas-Reig J, Esteve-Valverde E, Belizna C, et al. Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: a comprehensive review. *Autoimmun Rev.* 2020;19(7):102569.

12. Kwong JC, Li P, Redelmeier DA. Influenza morbidity and mortality in elderly patients receiving statins: a cohort study. *PLoS One.* 2009;4(11):e8086.

13. Vandermeer ML, Thomas AR, Kamimoto L, et al. Association between use of statins and mortality among patients hospitalized with laboratory-confirmed influenza virus infections: a multistate study. *J Infect Dis.* 2012;205(1):13-19.

14. McAuley DF, Laffey JG, O'Kane CM, et al. Simvastatin in the acute respiratory distress syndrome. *N Engl J Med.* 2014; 371(18):1695-1703.

15. Calfee CS, Delucchi KL, Sinha P, et al. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomized controlled trial. *Lancet Respir Med.* 2018;6(9):691-698.

16. Patel JM, Snaith C, Thickett DR, et al. Randomized double-blind placebo-controlled trial of 40 mg/day of atorvastatin in reducing the severity of sepsis in ward patients (ASEPSIS Trial). *Crit Care.* 2012;16(6):R231.

17. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ.* 2020;368:m1091.

18. Jordan RE, Adab P, Cheng KK. COVID-19: risk factors for severe disease and death. *BMJ.* 2020;368:m1198.

19. Zhang J, Wang X, Jia X, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. *Clin Microbiol Infect.* 2020;26(6):767-772.

20. Yetmar ZA, Issa M, Munawar S, et al. Inpatient care of patients with COVID-19: a guide for hospitalists. *Am J Med.* 2020; 133(9):1019-1024.

21. Chow JH, Khanna AK, Kethireddy S, et al. Aspirin use is associated with decreased mechanical ventilation, intensive care unit admission, and in-hospital mortality in hospitalized patients with coronavirus disease 2019. *Anesth Analg.* 2021; 132(4):930-941.

22. Bianconi V, Violi F, Fallarino F, Pignatelli P, Sahebkar A, Pirro M. Is acetylsalicylic acid a safe and potentially useful choice for adult patients with COVID-19? *Drugs.* 2020;80(14):1383-1396.

23. Tleyjeh IM, Kashour T, Hakim FA, et al. Statins for the Prevention and Treatment of Infections. *Arch Intern Med.* 2009; 169(18):1658.

24. Khan AR, Riaz M, Abdulhak AAB, et al. The role of statins in prevention and treatment of community acquired pneumonia: a systematic review and meta-analysis. *PLoS One.* 2013;8(1): e52929.

25. Pertzov B, Eliakim-Raz N, Atamna H, Trestioreanu AZ, Yahav D, Leibovici L. Hydroxymethylglutaryl-CoA reductase inhibitors (statins) for the treatment of sepsis in adults — a systematic review and meta-analysis. *Clin Microbiol Infect.* 2019; 25(3):280-289.

26. Zhang XJ, Qin JJ, 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.

27. Masana L, Correig E, Rodriguez-Borjabad C, et al. Effect of statin therapy on SARS-CoV-2 infection—related mortality in hospitalized patients. *Eur Hear J Cardiovasc Pharmacother.* 2020. https://doi.org/10.1093/ehjcvp/pvaa128 [online ahead of print].

28. Daniels LB, Sitapati AM, Zhang J, et al. Relation of statin use prior to admission to severity and recovery among COVID-19 inpatients. *Am J Cardiol.* 2020;136:149-155.

29. Rossi R, Talarico M, Coppi F, Boriani G. 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.

30. Song SL, Hays SB, Panton CE, et al. Statin use is associated with decreased risk of invasive mechanical ventilation in COVID-19 patients: a preliminary study. *Pathogens.* 2020;9(9):759.

31. Saeed O, Castagna F, Agulliu I, et al. Statin use and in-hospital mortality in patients with diabetes mellitus and COVID-19. *J Am Heart Assoc.* 2020;9(24):e018475.

32. Hariyanto TI, Kurniawan A. Statin therapy did not improve the in-hospital outcome of coronavirus disease 2019 (COVID-19) infection. *Diabetes Metab Syndr.* 2020;14(6):1613-1615.

33. Cariou B, Goronflot T, Rimbert A, et al. Routine use of statins and increased COVID-19 related mortality in inpatients with type 2 diabetes: results from the CORONADO study. *Diabetes Metab.* 2020;47(2):101202.

34. Rodriguez-Nava G, Trelles-Garcia DP, Yanez-Bello MA, Chung CW, Trelles-Garcia VP, Friedman HJ. Atorvastatin associated with decreased hazard for death in COVID-19 patients admitted to an ICU: a retrospective cohort study. *Crit Care.* 2020;24(1):429.

35. 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.e2.

36. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 — full report. *J Clin Lipidol.* 2015; 9(2):129-169.

37. Chang T, Wu J, Chang L. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell Metab.* 2020;31(6):1068-1077.

38. Zhang Q, Bastard P, Liu Z, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science.* 2020;370(6515):eabd4570.

39. Koike A, Tsujinaka K, Fujimori K. Statins attenuate antiviral IFN-β and ISG expression via inhibiting IRF3/JAK/STAT signaling in poly(I:C)-treated hyperlipidemic mice and macrophages. *FEBS J.* 2021. https://doi.org/10.1111/febs.15712.