

Relation of Statin Use Prior to Admission to Severity and Recovery Among COVID-19 Inpatients



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The impact of statins, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (ARBs) on coronavirus disease 2019 (COVID-19) severity and recovery is important given their high prevalence of use among individuals at risk for severe COVID-19. We studied the association between use of statin/angiotensin-converting enzyme inhibitors/ARB in the month before hospital admission, with risk of severe outcome, and with time to severe outcome or disease recovery, among patients hospitalized at University of California San Diego Health between February 10, 2020 and June 17, 2020 (n = 170 hospitalized for COVID-19, n = 5,281 COVID-negative controls). Logistic regression and competing risks analyses were used to investigate progression to severe disease (death or intensive care unit admission), and time to discharge without severe disease. Severe disease occurred in 53% of COVID-positive inpatients. Median time from hospitalization to severe disease was 2 days; median time to recovery was 7 days. Statin use prior to admission was associated with reduced risk of severe COVID-19 (adjusted OR 0.29, 95% CI 0.11 to 0.71, $p < 0.01$) and faster time to recovery among those without severe disease (adjusted HR for recovery 2.69, 95% CI 1.36 to 5.33, $p < 0.01$). The association between statin use and severe disease was smaller in the COVID-negative cohort (p for interaction = 0.07). There was potential evidence of faster time to recovery with ARB use (adjusted HR 1.92, 95% CI 0.81 to 4.56). In conclusion, statin use during the 30 days prior to admission for COVID-19 was associated with a lower risk of developing severe COVID-19, and a faster time to recovery among patients without severe disease. © 2020 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>) (Am J Cardiol 2020;136:149–155)

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the clinical syndrome of coronavirus disease 2019 (COVID-19), which has caused significant morbidity and mortality worldwide. Individuals with underlying cardiovascular disease (CVD), hypertension, and diabetes have been identified as groups at particularly high risk for developing severe COVID-19.^{1,2} Because a large proportion of patients with these conditions are on statins and either angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), there has been speculation about whether these cardiovascular medications may

influence COVID-19 risk.³ ACE2 may be a mechanistic link between CVD, use of statins, ACE inhibitors or ARBs, and COVID-19. ACE2 is an enzyme with multiple roles, serving as the receptor through which SARS-CoV-2 enters human cells, as well as playing an integral part in countering activation of the renin-angiotensin-angiotensinogen system.⁴ ACE2 is a membrane-bound aminopeptidase expressed broadly in humans, including in the heart and on lung alveolar epithelial cells.⁵ ACE2 acts on angiotensin II to form angiotensin-(1 to 7) which has anti-inflammatory, anti-fibrotic, and vasodilatory effects.⁶ ACE inhibitors and ARBs may increase the expression of ACE2, leading some to speculate that these medications may increase susceptibility to COVID-19; others have postulated protective effects via anti-inflammatory actions.^{3,7–9} Statins upregulate ACE2 as well, and have additional pleotropic effects to counter inflammation and oxidative stress.¹⁰ Further, statins may block SARS-CoV-2 infectivity via direct binding to the main protease.¹¹ The purpose of this single-center observational study of patients hospitalized for COVID-19 was to investigate the association of use of statins, ACE inhibitors, or ARBs, with (1) progression to severe disease (death or intensive care unit [ICU] admission), and (2) time to the onset of severe disease or to recovery, defined as hospital discharge without development of severe disease.

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Methods

The study population included all patients hospitalized for treatment of COVID-19 between February 10 and June 17, 2020 at University of California San Diego Health (UCSDH), as ascertained by data capture within the system-wide electronic health record (EHR) system (Epic Systems, Verona, Wisconsin).¹² Patients were designated as COVID-positive if there was history of positive COVID-19 polymerase chain reaction. Beginning in mid-March 2020, UCSDH policy was to ascertain COVID-19 status of all admitted patients. Patients were excluded if they were hospitalized for reasons unrelated, and exhibited no symptoms attributable, to COVID-19 ($n = 28$). We also excluded 21 patients in whom medications prior to admission could not be verified. In sensitivity analyses, we included all patients admitted during this timeframe who were negative for COVID-19, as contemporaneous negative controls. The study was approved by the Institutional Review Board at UCSD; a waiver of informed consent was granted.

Data collected via automatic extraction from the EHR included demographics, COVID-19 test dates and results, past medical diagnoses, outpatient medication history, dates of hospitalization, reason for hospitalization, dates of ICU admission, and vital status. Data were verified manually for all COVID-positive patients, and for a random sample of COVID-negative patients. The primary exposures of interest were use of statins, ACE inhibitors, and ARBs within the 30 days prior to admission. Medication use was considered present if the patient had regularly taken the medication during the 30 days prior to hospital admission, as reported by the patient or a caregiver. We excluded patients in whom we were unable to verify the medication history. In sensitivity analyses including hospitalized COVID-negative patients, medication use was also considered present if the patient had filled a prescription in the 30 days prior to admission based on dispense data. Comorbid conditions included obesity, hypertension, CVD (defined as history of coronary artery disease, stroke and/or transient ischemic attack, peripheral arterial disease, or heart failure), diabetes mellitus, and chronic kidney disease (CKD).

The primary outcome was severe disease, defined as either admission to the ICU or death. Patients discharged from the hospital without ever experiencing a severe outcome were considered to be recovered from COVID-19. Patients who had not reached either severe status or been discharged at the time of data lock were considered to have unresolved status and were censored.

For each predictor of interest, means or proportions are presented, stratified by presence or absence of severe disease. The mean difference between severe and non-severe subjects are presented for each predictor, with a 95% confidence interval (CI) computed using t tests for continuous variables and Fisher's exact tests for categorical variables. Among COVID-positive patients, association between the presence of severe disease and use of statins, ACE inhibitors and ARBs was investigated using a multivariable logistic regression, adjusting for potential confounders including age, sex, and a list of comorbid conditions (obesity, hypertension, diabetes, CKD and CVD) which were considered a

priori to be potentially related to both severe disease and use of medications of interest. Patients with unresolved status were omitted from this analysis. As sensitivity analyses, the same logistic regression model was fit for (1) COVID-negative hospitalized patients, and (2) COVID-negative hospitalized patients who were part of the UCSDH registry prior to February 1, 2020. We also checked for a significant interaction term between COVID-19 status and each variable in these models. A competing risks analysis¹³ was used to investigate the time to onset of severe disease or to recovery, whichever came first, among COVID-positive patients; the starting timepoint was the earliest date of either first positive COVID-19 test or hospitalization. Cause-specific cumulative incidence curves for severe disease and recovery were calculated using Aalen-Johansen estimators. We investigated the association of statins, ACE inhibitors and ARBs with time to recovery and time to onset of severe disease. For each of these 2 outcomes, a Cox proportional hazards regression model was used in which the competing outcome was treated as a censoring event. Patients with unresolved status were also censored. Models were adjusted for the same potential confounders as in the logistic regression analysis. Additional sensitivity analyses included competing risk analyses with statin, ACE inhibitor, and ARB use modelled separately. The proportional hazards assumption was tested by examining Schoenfeld residuals and all variables passed except hypertension in the recovery model for ACE inhibitors and obesity in the recovery model for all 3 drugs. For all analyses, associations with $p < 0.10$ are reported along with 95% CIs; $p < 0.05$ was considered statistically significant. All analyses were conducted using R v3.4.4.

Results

The primary study population included 170 patients hospitalized with a diagnosis of COVID-19 at UCSDH, including 90 (53%) with a severe outcome (ICU or death), 78 (46%) who recovered, and 2 (1%) with unresolved status at the time of analysis. Of the 90 with a severe outcome, there were 22 deaths. A total of 88 of the 90 severe patients required ICU admission. Of these 88 patients, 61 (69%) required invasive mechanical ventilation. We also analyzed 5281 COVID-negative subjects, including 1278 (24%) with a severe outcome.

Among COVID-positive patients, 58% were male; the average age was 59 ± 19 years (Table 1). Just over half (55%) were of Hispanic race and/or ethnicity, with the remainder non-Hispanic white (21%), African-American (6%), Asian (5%), or other and/or mixed race (12%). Among comorbid conditions, 56% of patients were obese, 44% had a history of hypertension, 21% had CVD, and 20% had diabetes. Other comorbid conditions with 5% or greater prevalence included asthma (8%), CKD (18%), and cancer (14%).

Considering primary exposures of interest, 27% were actively taking statins on admission, while 21% were on an ACE inhibitor and 12% on an ARB. Median length of hospital stay was 9.7 (IQR 3.9 to 19.7) days, and was higher

Table 1
Baseline characteristics of COVID-positive patients by outcome

Characteristic n (%)	Outcome		OR	95%CI	p
	Mild (n = 80)	Severe (n = 90)			
Men	44 (55%)	54 (60%)	1.23	0.64-2.36	0.54
Black	5 (6%)	5 (6%)	0.88	0.20-4.00	1.00
Non-Hispanic white	19 (24%)	17 (19%)	0.75	0.33-1.67	0.46
Asian	4 (5%)	5 (6%)	1.12	0.23-5.84	1.00
Hispanic	45 (56%)	49 (54%)	0.93	0.48-1.78	0.88
Other/mixed	7 (9%)	14 (16%)	1.91	0.68-5.94	0.24
Age (years)*	58.7 ± 19.9	60.1 ± 17.3	1.44	-4.24-7.12	0.62
Current smoker	7 (9%)	1 (1%)	0.12	0.00-0.96	0.03
Obesity†	41 (51%)	54 (60%)	1.42	0.74-2.74	0.28
Diabetes mellitus	12 (15%)	22 (24%)	1.83	0.79-4.40	0.18
Hypertension	32 (40%)	43 (48%)	1.37	0.71-2.64	0.35
CVD	17 (21%)	18 (20%)	0.93	0.41-2.09	0.85
Heart failure	4 (5%)	8 (9%)	1.85	0.47-8.73	0.38
Stroke	5 (6%)	4 (4%)	0.70	0.13-3.38	0.74
CKD	13 (16%)	17 (19%)	1.20	0.50-2.91	0.69
Asthma	4 (5%)	9 (10%)	2.10	0.56-9.74	0.26
COPD	3 (4%)	4 (4%)	1.19	0.20-8.40	1.00
Cancer	12 (15%)	11 (12%)	0.79	0.29-2.10	0.66
HIV	3 (4%)	4 (4%)	1.19	0.20-8.40	1.00
Statin	26 (32%)	20 (22%)	0.60	0.28-1.24	0.17
ACE inhibitor	15 (19%)	20 (22%)	1.24	0.55-2.83	0.70
ARB	8 (10%)	12 (13%)	1.38	0.49-4.14	0.63

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; CI = confidence interval; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; HIV = human immunodeficiency virus; OR = odds ratio for severe disease.

Comparing presence vs absence of the characteristic.

* Mean ± standard deviation; mean difference severe population - mild population.

† Obesity defined as body mass index ≥ 30 kg/m².

among those with severe infection (median 16.8 vs 5.0 days, Wilcoxon rank sum p value <0.001).

Compared to patients without severe disease, those with severe COVID-19 were more likely to be male and obese, were slightly older, and a greater proportion had a history of diabetes and hypertension (Table 1), although these differences were not statistically significant. A smaller proportion of those with severe disease were non-Hispanic white, and more were in the category “other/mixed.”

Associations between patient characteristics and the development of severe COVID-19 were investigated using multivariable logistic regression. Covariates included age, sex, and comorbid conditions including obesity, hypertension, diabetes, CVD, and CKD. Indicators for the use of statins, ACE inhibitors, and ARB medication within the past 30 days prior to admission were included in the model. Diabetes was independently associated with increased risk of severe COVID-19 (adjusted odds ratio [aOR] 3.36, 95%CI 1.14 to 10.87) (Figure 1). Use of statins prior to admission was associated with a 71% reduction (95%CI 29% to 89%) in the adjusted odds of developing severe disease. Use of ACE inhibitors (aOR 1.31, 95%CI 0.55 to 3.19) or ARBs (aOR 1.77, 95%CI 0.60 to 5.59) were not significantly associated with risk of severe disease in these adjusted models. In a sensitivity analysis with death as the outcome, results were similar except use of ACE inhibitors or ARBs showed a potential protective effect (Appendix Figure 1). Results were also unchanged when the outcome was limited to ICU patients requiring invasive mechanical ventilation.

As an additional sensitivity analysis, we performed logistic regression analysis on the COVID-negative hospitalized population, with results summarized in Appendix Table 1. Among COVID-negative inpatients, statins were associated with a 21% reduction (95%CI 7% to 34%) in the adjusted odds of developing severe disease and there was evidence that this association was weaker than in COVID-positive inpatients (p value for interaction 0.07). ARBs

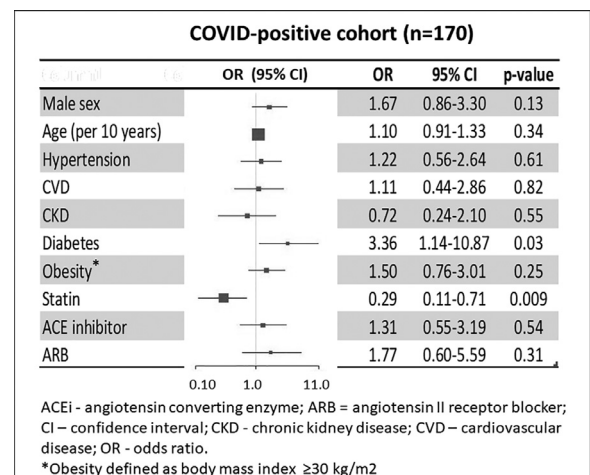


Figure 1. Predictors of severe outcome (death or intensive care unit admission) among COVID-positive inpatients in a multivariable logistic regression model.

were associated with increased risk of severe outcome (aOR 1.35, 95%CI 1.11 to 1.65, $p = 0.003$.) In addition, there was a significant interaction between COVID-status and obesity with respect to risk of developing severe disease ($p = 0.03$ for interaction). Although obesity was associated with increased risk of severe outcomes among COVID-positive patients (aOR 1.50, 95%CI 0.76 to 3.01) it was associated with decreased risk among those who were COVID-negative (aOR 0.94, 95%CI 0.82 to 1.07). To investigate the possibility of misclassification bias, we performed an additional sensitivity analysis limiting the COVID-negative hospitalized patients to those who were already in the UCSDH Registry as of February 1, 2020 ($n = 1,313$) at which time there was little COVID circulating in San Diego. This subpopulation represents a well-characterized cohort, thus limiting confounding by patients seeking care at UCSDH for the first time due to COVID-related disease in whom the electronic health record may be less reliable. Results were not materially changed (Appendix Table 2).

The association of time to recovery or to severe COVID-19 with outpatient use of statins, ACE inhibitors, and ARBs was investigated using a competing risks analysis. Cause-specific cumulative incidence curves, stratified by statin use, are displayed in Figure 2. Among the 46% who recovered, median time to recovery was 7 days overall, but was shorter among those on statins. Among the 53% who developed severe disease, median time to severe disease was 2 days.

Multivariable Cox proportional hazards regression was used to investigate the association of each outcome (severe disease and recovery) with outpatient use of statin, ACE inhibitor or ARB medication, treating the competing outcome as a censoring event and adjusting for potential confounders (Table 2). Statin use was associated with an increased rate of recovery from COVID-19 among subjects who had not yet experienced severe disease (cause-specific adjusted HR [aHR] for recovery 2.69, 95%CI 1.36 to 5.33, $p = 0.004$). In adjusted models, neither ARB use (aHR 1.92, 95%CI 0.81 to 4.56, $p = 0.14$), nor ACE inhibitor use (aHR

Table 2

Multivariable cox regression models for time to severe outcome and time to recovery, treated as competing risks, in COVID-positive inpatients

	Severe Outcome (n = 90)			Recovery (n = 78)		
	HR	95%CI	p value	HR	95%CI	p value
Men	1.20	0.76-1.89	0.43	0.65	0.40-1.07	0.09
Age (per 10 years)	0.98	0.86-1.13	0.79	0.73	0.63-0.86	<0.001
Hypertension	1.12	0.68-1.85	0.67	0.98	0.56-1.73	0.94
CVD	1.11	0.59-2.08	0.74	0.70	0.35-1.40	0.31
CKD	0.79	0.42-1.50	0.47	0.86	0.38-1.90	0.70
Diabetes	1.84	0.94-3.61	0.07	0.78	0.34-1.80	0.56
Obesity	1.31	0.81-2.11	0.27	0.70	0.42-1.17	0.18
Statins	0.55	0.28-1.08	0.08	2.69	1.36-5.33	0.004
ACE inhibitors	1.14	0.65-1.98	0.65	1.32	0.69-2.50	0.39
ARBs	1.57	0.78-3.17	0.21	1.92	0.81-4.56	0.14

ACEi = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; CI = confidence interval; CKD = chronic kidney disease; CVD = cardiovascular disease; HR = cause-specific hazard ratio.

1.32, 95%CI 0.69 to 2.50, $p = 0.39$) was significantly associated with increased rate of recovery. There was some evidence that statin use was also associated with reduced rate of development of severe disease (aHR 0.55, 95%CI 0.28 to 1.08, $p = 0.08$). Use of ACE inhibitors (aHR 1.14, 95%CI 0.65 to 1.98, $p = 0.65$) or ARBs (aHR 1.57, 95%CI 0.78 to 3.17, $p = 0.21$) was not significantly associated with rate of development of severe disease in these adjusted models. Considering covariates, with recovery as the outcome, older age was associated with a significantly reduced rate of recovery, and there was some evidence that male sex was associated with a reduced rate of recovery.

Results of the sensitivity analyses with each of the 3 medication exposures modeled separately are shown in Appendix Tables 3a-c. Statin use was again associated with faster recovery ($p = 0.002$). ARB demonstrated a trend towards increased recovery ($p = 0.06$), and ACE inhibitor use showed no association ($p = 0.78$). Effect sizes were overall similar to the primary analysis.

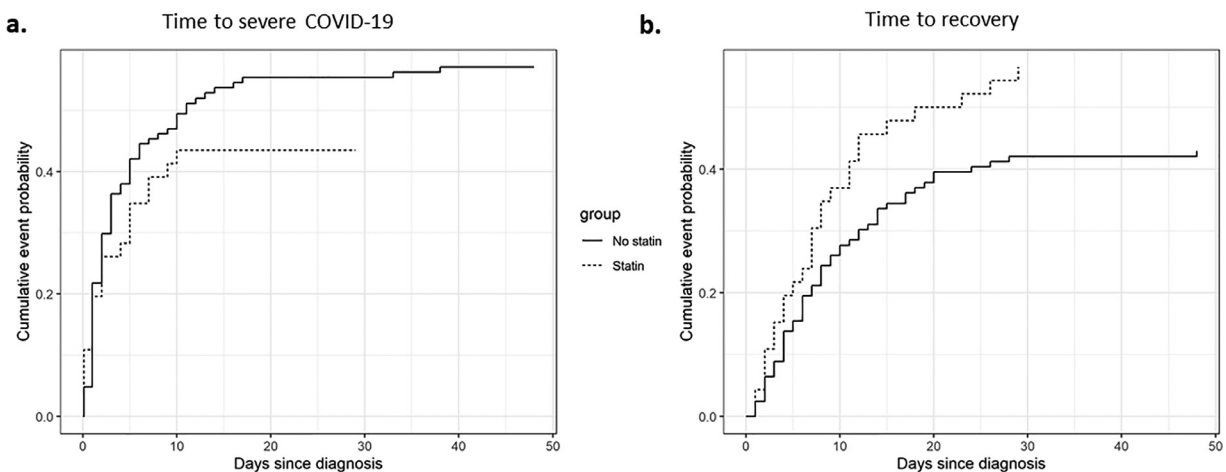


Figure 2. Cause-specific cumulative incidence curves for (A) time to severe COVID-19, and (B) time to recovery, stratified by statin use, with starting time-point the earlier of first positive COVID-19 test or hospitalization for COVID-19. Severe COVID-19 was defined as death or admission to the Intensive Care Unit; recovery was defined as discharge from the hospital without ever experiencing a severe outcome. Includes all patients hospitalized for treatment of COVID-19 at UC San Diego Health from February 10, 2020 to June 17, 2020; 90 with severe outcome and 78 recovered. Two patients were censored at the time of analysis.

Discussion

In this series of 170 patients hospitalized for treatment of COVID-19 at UCSDH, use of statins prior to admission was associated with a more than 50% reduction in risk of developing severe COVID-19, after controlling for associated comorbid conditions and for concomitant use of ACE inhibitors or ARBs. In a competing risks time-to-event analysis, there was strong evidence that statin use was associated with considerably faster time to recovery; there was weaker evidence for association with a reduced rate of progression to severe COVID-19. These effects on timing combine to account for the overall reduction in the occurrence of severe outcomes among patients who used statins. Among all hospitalized patients, median time from hospitalization to severe disease was only 2 days, while median time to recovery was 7 days.

There is some biologic plausibility for a protective role of statins in COVID-19 through known anti-inflammatory and immunomodulator effects as well as via upregulation of ACE2 and direct effects on the virus.^{10,14} Statins may inhibit SARS-CoV-2 infectivity by direct binding and inhibition of the main protease, a key coronavirus enzyme.¹¹ Coronaviruses can induce an inflammatory cascade through activation of the toll like receptor 4 myeloid differentiation response protein 88-nuclear factor kappa B pathway.¹⁰ In murine models under periods of stress, statins can disrupt this pro-inflammatory response through inhibition of toll like receptor 4 expression and stabilization of myeloid differentiation response protein 88 expression levels.^{15,16} Although SARS-CoV viruses employ ACE2 for cell entry, they have been shown *in vivo* to reduce ACE2 expression upon binding of the viral spike protein to the ACE2 receptor.¹⁷ ACE2 down-regulation leads to excessive production of angiotensin, which has been causally linked to severe respiratory failure.¹⁷ Therefore, upregulation of ACE2 is another potential mechanism whereby statins (as well as ACE inhibitors and ARBs) might protect against COVID-19 lung injury.⁸ In observational studies, statins were associated with reduced influenza-related hospitalizations,^{10,18–20} and with improved outcomes in community acquired pneumonia and sepsis.²¹

In time-to-event analysis, when considered alone ARB medication use prior to admission was not a predictor of severe disease, but similar to statins, was associated with faster time to recovery. In multivariable analyses when both ARB and statin use were entered jointly in the model of time to recovery, the effect of ARB use was attenuated, while statin use retained a robust effect. As a significant percentage of patients use both medications, it is plausible that a major portion of the observed effect of ARB use is in fact attributable to statins. On the other hand, in the logistic regressions a higher risk of severe disease with ARBs was seen in both COVID-positive and COVID-negative cohorts.²² This comparison to negative controls suggests that any residual confounding in the logistic regression models is biased toward increased risk of severe disease, whereas we found a significant beneficial effect in models of time to recovery, lending some support to beneficial effect of ARBs. In contrast, ACE inhibitor use was not predictive of time to either severe disease or recovery. Previous observational studies have found no association

between outpatient use of ARBs or ACE inhibitors and either susceptibility to or severity of COVID-19.^{9,23,24} Some observational studies of inpatient use of these medications have suggested a possible beneficial effect, which appears more robust in ARBs than ACE inhibitors.^{25–27} Ongoing clinical trials are evaluating the use of these medications to speed recovery and improve outcomes.

Our findings that obesity and diabetes are risk factors for severe outcomes in COVID-19 are consistent with prior reports.^{1,28,29} In addition, male sex consistently had estimated effects consistent with increased risk. There was an interaction between COVID-status and obesity, with obesity emerging as protective in the COVID-negative cohort but a risk factor among COVID-positive inpatients. A novel finding is that younger age was associated with a shorter time to recovery. This may reflect a more resilient population, though it could also be due to younger individuals presenting later in the time course of disease. Although current smoking was more prevalent among those with mild as opposed to severe COVID-19, the very low prevalence of smoking in this cohort (only 8 current smokers were identified) makes the validity of this finding questionable. Given some evidence that nicotine may play a role in the ACE2 pathway, further investigation is warranted.³⁰

Limitations of the present study include its observational design which cannot prove causality and which leaves open the possibility of residual confounding, and the relatively small sample size. The sensitivity analysis including COVID-negative hospitalized patients also showed beneficial effects of statins on severe outcomes, and we cannot exclude residual confounding as a contributing factor; however the effect size for statin use was much larger in the COVID-positive cohort, and there was evidence for a difference in effect sizes between the COVID-positive and -negative cohorts. In addition, statins would be expected to affect CVD outcomes favorably in non-COVID-19 patients. The COVID-negative cohort is a heterogeneous group which is a limitation, however this is also a strength in that it allows us to control for some biases that may be broadly present. Although extensive manual chart review was performed, misclassification remains a possibility. We used date of hospitalization (or date of first positive COVID-19 test if earlier) as the beginning timepoint for our time-to-event analyses, which does not account for variation in the duration of symptoms prior to hospitalization. Our study did not evaluate the in-hospital use of statins, ACE inhibitors or ARBs and these data should not be extrapolated to the use of these medications for treating acute COVID-19. We also did not have reliable data on dose or duration of medication use; some of the effects of statins, ACE inhibitors or ARBs may be time-dependent. Similarly, with the present study design we are unable to assess the impact of statins, ACE inhibitors, or ARBs on susceptibility to COVID-19 infection, which would require widespread, systematic testing of asymptomatic individuals.

This study also has many strengths. By restricting the analysis to those with documented medication use via careful manual chart review, we eliminated the misclassification bias that can occur among the most ill patients who, since intubated and often transferred from outside facilities, often have incomplete documentation of medications and

medical history. We also were able to leverage a large negative control population of all COVID-negative inpatients during the same time period, which enabled us to assess for confounding and bias.²²

In summary, among patients hospitalized for COVID-19, use of statin medication prior to admission was associated with a reduced risk of severe disease and a faster time to recovery, after adjusting for demographics and comorbid conditions in this single-center observational study. Randomized clinical trials are underway to assess whether statin medications may improve outcomes among COVID-19 patients.

Authors' Contribution

Lori B. Daniels: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization, Supervision, Project Administration, Funding Acquisition; Amy M. Sitapati: Data Curation, Writing – Review & Editing; Jing Zhang: Formal Analysis; Jingjing Zou: Formal Analysis; Quan M. Bui: Writing – Conceptualization, Review & Editing; Junting Ren: Formal Analysis, Writing – Review & Editing, Visualization; Christopher A. Longhurst: Writing – Resources, Review & Editing, Project Administration, Funding Acquisition; Michael H. Criqui: Conceptualization, Methodology, Writing – Review & Editing; Karen Messer: Conceptualization, Methodology, Formal Analysis, Writing – Original Draft, Writing – Review & Editing.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2020.09.012>.

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