PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Associations of statin use with 30-day adverse outcomes among 4,801,406 U.S. Veterans with and without SARS-CoV-2: An observational cohort study
AUTHORS	Wander, Pandora; Lowy, Elliott; Beste, Lauren A.; Tulloch-Palomino, Luis; Korpak, Anna; Peterson, Alexander; Kahn, Steven E.; Danaei, Goodarz; Boyko, Edward J.

VERSION 1 – REVIEW

REVIEWER	Kragholm, Kristian Aalborg University Hospital, Unit of Epidemiology and Biostatistics
REVIEW RETURNED	28-Oct-2021

GENERAL COMMENTS	In this large, retrospective cohort study of >4.8 million Veterans with and without SARS-CoV-2 seen during March 1 and 10, 2020, Wander et al. found that associations of statin use with lower adverse 30-day outcomes were weaker among individuals who tested positive for SARS-CoV-2 compared to individuals without a positive test, indicating that statins do not exert SARS-CoV-2–specific effects. While the study is well-conducted, there are some issues that I encourage the authors to take into account: 1. The introduction suggests that observational studies only have found associations between statin use and more favorable COVID-19 outcomes. The authors should search Pubmed for negative studies as well, including PMID: 33277291 and PMID: 33748678. In addition, this issue should be mentioned in the introduction and the authors are encouraged to more thoroughly argue why this/their study of novelty in a revised introduction. 2. Regarding exposure, is there any data available on continuous versus halted statin use following a positive SARS-CoV-2 and how this relates to outcomes? 3. The results section lacks descriptions of characteristics of the study participants. 4. The interaction between statin use and SARS-CoV-2 status implies that results should be reported stratified by SARS-CoV-2 status and by statin exposure/non-exposure, as accurately done by the authors. The caveat of stratifying results is often that results are more difficult to communicate. I think this is indeed the case here. I wonder whether results could be communicated more clearly by shortly explaining this interaction more clearly both in the abstract and results sections, followed by emphasis on results on patients with positive SARS-CoV-2 status and statin exposure (+/-) and lastly, a brief mentioning of results among patients with negative SARS-CoV-2 status to underline the conclusion that outcomes were weaker among individuals who tested positive for SARS-CoV-2. Minor:

	5. It should be emphasized in the outcomes section in the methods section that 30-day outcomes are assessed. 6. I believe Conclusions on page 10 should be changed to Discussion and then the last section of the Discussion should be the Conclusions

REVIEWER	Vergaro, G Fondazione Toscana Gabriele Monasterio per la Ricerca Medica e di Sanita Pubblica
REVIEW RETURNED	06-Nov-2021

GENERAL COMMENTS	In the present paper, Wander and Colleagues aimed to "quantify the independent association of statin use at diagnosis with adverse outcomes from COVID-19 at 30 days, including hospitalization, intensive-care unit (ICU) admission, and mortality". Starting from a data repository derived from VHA's integrated electronic medical record, the Authors identified 231,154 subjects with ≥ 1 positive nasal swabs for SARS-CoV-2 between March 2020 and March 2021. Subjects (n= 4,570,252) without a positive nasal swab for SARS-CoV-2. Among individuals who tested positive for SARS-CoV-2, statin use was associated with lower odds of death but not hospitalization or ICU admission. The same associations were stronger among individuals without a positive test for SARS-CoV-2. There is indeed a rational for the possible usefulness of statin therapy during COVID-19 infection, but controversy exists on their clinical role. The manuscript is rather clear and well written, but some major issues in the study design and selection of population (as listed below) limit the value of the findings. - The comparator group is rather weak. First, an negative swab was not deemed necessary, thus possible leading to the inclusion of patients with asymtpomatic /mildly symptomatic disease, therefore not experiencing any of the event considered. Moreover, follow-up duration was set arbitrarily in this population - Why a formal matching was not performed to identify the control population? This cold have helped to reduce the effect of confounders. - Apparently, the Authors considered all-cause death, ICU admission and hospitalizations as end-point. As the point here is the possible protective effect of statins in patients with COVID, disease specific outcome should have been (also) considered. The feeling here is that the protective effect of statins in the general population was mitigated in patients with SARS-Cov2 infection, who were more prone to have disease-related hospitalizations and ICU admissions. - Hospital access outside VHA facilities may have not been captured. This is disclosed by the Authors, but may indeed be a major limitation to the present study.

REVIEWER	De Spiegeleer, Bart University of Ghent
REVIEW RETURNED	15-Nov-2021

GENERAL COMMENTS	This is an interesting observational study, adding additional data to the others already published, investigating the statin use

	association with 3 health-outcomes (hospitalisation, ICU and death) within a defined time frame. An important methodological aspect is the inclusion of COVID-negative individuals. The OR found for death in COVID-positive patients of 0.81 is consistent with previous studies where a positive health effect was observed. The authors did not find a statistically significant OR effect for hospitalisation or ICU. However, similar or even better OR results were observed with statin use in the COVID-negative individuals. The limitations of this study are well described, including the different situation of the negative control group in this study compared to the example of the association of influenza vaccination with all-cause mortality seen in elderly individuals. In this study, we can assume that COVID-positive patients are not more “health-conscious” individuals. As with most, if not all, observational studies, randomized controlled trials ultimately can show whether and to what extent statin use contributes to a lower risk of ARDS as observed with COVID-19. A remaining question is the possible relation between hospitalisation -> ICU -> death. For example, does hospitalisation means that they recovered within the time frame? Also, from these data, we should be careful to not draw the conclusion to stop statin use when prescribed; quite on the contrary. It would be instructive to compare the results of this study to those previously published of statin use on all-cause health effects (ie not in the COVID-era). I strongly recommend publishing this study, with only some minor elucidation of the few comments given above.

REVIEWER	Norrie, John Edinburgh Clinical Trials Unit, University of Edinburgh No. 9, Bioquarter, Usher Institute
REVIEW RETURNED	05-Dec-2021

GENERAL COMMENTS	This is a well written article on a topical issue in COVID-19. The authors have used appropriate statistical methods, and these are clearly described. What isn't completely clear is the objective. The conclusion appears to be that statins are not a promising treatment for COVID-19, since the associations for adverse outcomes (hospitalisation, admission to ICU, and 30-day mortality) do not appear to be as favourable for statin users with COVID-19 compared with a 'negative control' group of those without COVID-19. The stated objective is 'to estimate associations', which is fair enough, but it isnt as clear how these associations can be interpreted as likely implying treating with statins is not useful as a specific intervention for COVID. For that, a randomised trial would be ideal. Obviously that would be difficult, but despite a good discussion of the limitations (and strengths) of this analysis, it isnt sufficiently well covered as to the leap from those associations to the conclusion. A couple of specific major issues: 1. Around 30% of both the SARS-CoV-2 positive and negative cohorts are taking statins of various descriptions - from the Table the statin exposure is defined as 'receipt of a statin prescription with a fill date prior to the index date and a quantity

	prescribed that would extend past the index date'. But, recognising that most (the vast majority?) of this 30% will have been on statins for a while, the authors then adjust for 'statins >6 months before index event' - but I couldnt see any summary statistics for this? So, what is the interpretation of the 'current statin' term in the model, in the presence of this 'statin >6 months'? Is it just picking up those prescribed statins in the most recent six months, or is it picking up those who were initiated on statins as a result of getting infected with COVID-19 - or both? It is difficult to see how this set-up mimics treating people with statins to see if they are beneficial for COVID-19? It is not at all obvious how those who have been on statins for years can contribute to the analysis as interpreted - that is why it is crucial to be clear about the study objective here? 2. The authors need to explain more fully the concept of a negative control and how it might apply to this context. Its a good idea, for sure; but it isnt clear that although the outcomes are superficially similar - hospitalisations, admissions to ICU, and 30-day deaths - that the authors are comparing like with like across the positive and negative cohorts? Taking hospitalisations - these might be very strongly weighted towards respiratory conditions for the positives, against a whole range of conditions for the negatives? How does it make sense to compare these with a view to making a statement about the protective capability of statins wrt to COVID? Minor issues 3. There is no mention of compliance. Was there only 'prescriptions issued' data available, no data on actual consumption? 4. Likewise, no data on dose. The authors just use 'potency' as a surrogate. Indeed, it could be that as say a treatment for COVID-19 very large doses given IV might be appropriate - and that isnt possible to address with these data, for example? 5. The authors acknowledge the issue of diagnostic misclassifcation, and the additional problem of not requiring a negative test to be classified in the negative cohort, but there is no quantification of the likely false positives and false negatives rates? This would seem important before it can be claimed that the net effect will be to dilute the associations? 6. There is no mention of vaccination - the study took place over 12 months up to March 2021? 7. The authors mention adjusting for time (month) and region (VHA site) - more detail is needed - was this an important adjustment? 8. The authors should discuss further the apparent attenuation of the 'benefits' of statins going from the negative to the positive group. What is the logic of the original comparison i.e. that oif there is no benefit, then the hazards for the 3 outcomes might be expected to be the same? So, does an attenuation perhaps indicate that statins are doing some 'harm' in this context and consideration be given to stopping them?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Kristian Kragholm, Aalborg University Hospital
Comments to the Author:
In this large, retrospective cohort study of >4.8 million Veterans with and without SARS-CoV-2 seen during March 1 and 10, 2020, Wander et al. found that associations of statin use with lower adverse 30-day outcomes were weaker among individuals who tested positive for SARS-CoV-2 compared to individuals without a positive test, indicating that statins do not exert SARS-CoV-2–specific effects. While the study is well-conducted, there are some issues that I encourage the authors to take into account:

1. The introduction suggests that observational studies only have found associations between statin use and more favorable COVID-19 outcomes. The authors should search Pubmed for negative studies as well, including PMID: 33277291 and PMID: 33748678. In addition, this issue should be mentioned in the introduction and the authors are encouraged to more thoroughly argue why this/their study of novelty in a revised introduction.

Thank you for this suggestion. We have looked again at the literature and added the references recommended by the reviewer. To more thoroughly argue why this study is of novelty, we have revised the Introduction (p. 4, line 14) to state: “Therefore, observational studies with comprehensive strategies to examine potential bias from unmeasured confounding—such as the use of negative control populations2—are needed to improve estimates of the potential causal effect of statin use at diagnosis on mortality after COVID-19.”

2. Regarding exposure, is there any data available on continuous versus halted statin use following a positive SARS-CoV-2 and how this relates to outcomes?

This is an interesting question. There are data available, but methodological issues (most importantly residual confounding by indication and heterogeneity of the populations studied) limit the conclusions that can be drawn. Masana et al. examined associations of statin use with in-hospital mortality in a cohort of hospitalized Spanish patients with a positive test for SARS-CoV-27 comparing statin non-users, users who continued statins during hospitalization, and users who stopped statins during hospitalization. Overall, 25.7% of non-users died, while 19.8% of continued users died, and 17.4% of stoppers died. In that analysis, matching was used to account for differences in pre-admission characteristics; however, the authors were not able to account for characteristics (e.g., severity of COVID-19 illness, perceived prognosis, goals of care, etc.) that might impact the decision to stop statin therapy at the time of admission. In a meta-analysis, Permana et al. examined associations of pre-admission statin use and in-hospital statin use among patients hospitalized after a positive test for SARS-CoV-28, which is a related question. In-hospital but not pre-admission statin use was associated with a lower risk of mortality; however, these pre-admission and in-hospital study populations differed in characteristics such as age and sex that are strongly associated with adverse COVID-19 outcomes, limiting direct comparisons between the groups. Given the many possible determinants of statin cessation or continuation following the diagnosis of COVID-19 potentially related to adverse outcomes that would be difficult to extract from medical records (electronic or otherwise), we believe that the question of whether to cease or initiate statins following COVID diagnosis will be best determined by a clinical trial. For these reasons, we did not examine in-hospital statin continuation in the current analysis but instead focused on the association between statin use prior to COVID diagnosis and outcomes, where use of this medication would not have been confounded by the onset of COVID. We believe that our focus on prior use provides data that might

be plausibly used to justify conducting or not conducting a post-COVID statin trial. Our findings in our opinion best support the latter plan.

3. The results section lacks descriptions of characteristics of the study participants.

We have added further description of the characteristics of study participants in the first paragraph of Results to now include (by SARS-CoV-2 test results) race, BMI categories, high-potency use, urban/rural residence, and co-morbid conditions (p. 8, line 12) as follows: “Statin users were more likely to be of white race/ethnicity, have BMI of 30 kg/m2 or greater, be former smokers, and reside in a rural zip code regardless of SARS-CoV-2 test result. Not surprisingly, statin use was higher among cardiometabolic conditions but lower in alcohol use disorder. A higher proportion of statin users were receiving hi potency therapy among participants testing positive for SARS-CoV-2.”

4. The interaction between statin use and SARS-CoV-2 status implies that results should be reported stratified by SARS-CoV-2 status and by statin exposure/non-exposure, as accurately done by the authors. The caveat of stratifying results is often that results are more difficult to communicate. I think this is indeed the case here. I wonder whether results could be communicated more clearly by shortly explaining this interaction more clearly both in the abstract and results sections, followed by emphasis on results on patients with positive SARS-CoV-2 status and statin exposure (+/-) and lastly, a brief mentioning of results among patients with negative SARS-CoV-2 status to underline the conclusion that outcomes were weaker among individuals who tested positive for SARS-CoV-2.

As requested by the reviewer, we have revised the abstract to state: “We also examined whether associations differed between individuals with and without a positive test for SARS-CoV-2. RESULTS: Among individuals who tested positive for SARS-CoV-2, statin use was associated with lower odds of death at 30 days (OR 0.81 [95%CI 0.77–0.85]) but not with hospitalization or ICU admission. Associations were similar comparing use of specific statins to no statin. Compared to low-/moderate-intensity statin use, high-intensity statin use was not associated with lower odds of ICU admission or death. Over the same time period, associations of statin use with 30-day outcomes were significantly stronger among individuals without a positive test for SARS-CoV-2: hospitalization OR 0.79 (95%CI 0.77–0.80), ICU admission OR 0.86 (95%CI 0.81–0.90), and death 0.60 (95%CI 0.58–0.62), p for interaction all <0.001.”

We have revised and reordered the Results section (p. 8, line 18) to state: “Among SARS-COV-2 positive individuals, statin use was associated with lower odds of death at 30 days (OR 0.81 [95%CI 0.77–0.85]), but not with hospitalization or ICU admission. … Compared to persons with SARS-CoV-2 infection, OR for all three outcomes were significantly lower in persons without SARS-CoV-2 infection, as reflected by p<0.001 for the interaction term of SARS-CoV-2*statin use in all three models. Among SARS-COV-2 negative individuals, statin use was associated with lower odds of hospitalization (OR 0.79 [95%CI 0.77–0.80]), ICU admission (OR 0.86 [95%CI 0.81–0.90]), and death at 30 days (OR 0.60 [95%CI 0.58–0.62]). (Table 2a).”

Minor:
5. It should be emphasized in the outcomes section in the methods section that 30-day outcomes are assessed.

We have revised the outcomes description (p. 6, line 25) to state: “We collected data on 30-day hospitalizations, ICU admissions, and deaths occurring through March 10, 2021.”

6. I believe Conclusions on page 10 should be changed to Discussion and then the last section of the Discussion should be the Conclusions

We have made the suggested revision.

Reviewer: 2
Dr. G Vergaro, Fondazione Toscana Gabriele Monasterio per la Ricerca Medica e di Sanita Pubblica
Comments to the Author:
In the present paper, Wander and Colleagues aimed to “quantify the independent association of statin use at diagnosis with adverse outcomes from COVID-19 at 30 days, including hospitalization, intensive-care unit (ICU) admission, and mortality”. Starting from a data repository derived from VHA’s integrated electronic medical record, the Authors identified 231,154 subjects with ≥ 1 positive nasal swabs for SARS-CoV-2 between March 2020 and March 2021. Subjects (n= 4,570,252) without a positive nasal swab for SARS-CoV-2. Among individuals who tested positive for SARS-CoV-2, statin use was associated with lower odds of death but not hospitalization or ICU admission. The same associations were stronger among individuals without a positive test for SARS-CoV-2.
There is indeed a rational for the possible usefulness of statin therapy during COVID-19 infection, but controversy exists on their clinical role. The manuscript is rather clear and well written, but some major issues in the study design and selection of population (as listed below) limit the value of the findings.

- The comparator group is rather weak. First, an negative swab was not deemed necessary, thus possible leading to the inclusion of patients with asymtpomatic /mildly symptomatic disease, therefore not experiencing any of the event considered. Moreover, follow-up duration was set arbitrarily in this population

We acknowledge the reviewer’s concern that SARS-CoV-2–positive individuals with asymptomatic or mildly symptomatic disease might have been inappropriately included in the SARS-CoV-2 negative group. We have added the following language to the study limitations to emphasize the importance of this issue (p. 12, line 9): “Finally, not all individuals in the comparator group were tested for SARS-CoV-2, so we were unable to exclude the possibility that some SARS-CoV-2–positive participants with asymptomatic or mild disease were misclassified as SARS-CoV-2–negative.” Follow-up duration was chosen to allow direct comparison of the magnitude of the association of statin use with 30-day outcomes between with the SARS-CoV-2 positive and negative/not tested groups. We have added the following language to the Methods section (p. 6, line 25): “In both groups, we collected data on 30-day hospitalizations, ICU admissions, and deaths occurring through March 10, 2021.”

- Why a formal matching was not performed to identify the control population? This cold have helped to reduce the effect of confounders.

We agree that matching is one way to approach the issue of confounding, which can also be addressed via carefully specified modeling using adjustment covariates9. It has been shown in cohort studies that matching can reduce efficiency in terms of precision of multiplicative effect estimates such as the odds ratio10. We therefore selected instead multivariable analysis to control for confounding.

- Apparently, the Authors considered all-cause death, ICU admission and hospitalizations as end-point. As the point here is the possible protective effect of statins in patients with COVID, disease specific outcome should have been (also) considered.
The feeling here is that the protective effect of statins in the general population was mitigated in patients with SARS-Cov2 infection, who were more prone to have disease-related hospitalizations and ICU admissions.

We chose to compare adverse outcomes such as mortality, hospitalization, and ICU admission as opposed to disease-specific outcomes as these best reflect overall harm or benefit. It is possible that statins might reduce CVD events in COVID-19 but unexpectedly exacerbate pulmonary complications or have other deleterious effects in this infection that might outweigh CVD benefits. Our approach here is similar to that taken in many randomized controlled trials of a new intervention in order to capture unexpected untoward effects that might outweigh expected benefits.

- Hospital access outside VHA facilities may have not been captured. This is disclosed by the Authors, but may indeed be a major limitation to the present study.

We agree that this is an important limitation with regard to the 30-day hospitalization and ICU admission outcomes. We have added the following language to strengthen the wording of this limitation (p. 11, line 26): “This is an important source of potential bias should propensity to seek outside care be associated with likelihood of receiving a statin, although VHA users are asked to provide notification within 72 hours of an outside hospital admission, and when possible are transferred to a VHA facility, which would then be captured in the VHA electronic health record.”

Reviewer: 3
Dr. Bart De Spiegeleer, University of Ghent
Comments to the Author:
This is an interesting observational study, adding additional data to the others already published, investigating the statin use association with 3 health-outcomes (hospitalisation, ICU and death) within a defined time frame. An important methodological aspect is the inclusion of COVID-negative individuals. The OR found for death in COVID-positive patients of 0.81 is consistent with previous studies where a positive health effect was observed. The authors did not find a statistically significant OR effect for hospitalisation or ICU. However, similar or even better OR results were observed with statin use in the COVID-negative individuals.

The limitations of this study are well described, including the different situation of the negative control group in this study compared to the example of the association of influenza vaccination with all-cause mortality seen in elderly individuals. In this study, we can assume that COVID-positive patients are not more “health-conscious” individuals.
As with most, if not all, observational studies, randomized controlled trials ultimately can show whether and to what extent statin use contributes to a lower risk of ARDS as observed with COVID-19.

A remaining question is the possible relation between hospitalisation -> ICU -> death. For example, does hospitalisation means that they recovered within the time frame?

“Hospitalization” refers to an inpatient hospital admission within 30 days of the positive SARS-CoV-2 test independent of whether ICU care or death subsequently occurred. We interpret your question about “recover” to mean that you are asking whether the hospitalized participants were discharged from hospital during the 30-day time window. We did not assess this as an outcome as the immediate

consequences of COVID-19 in relation to statin use were our highest priority in this paper. We interpret the question you are asking to relate to so-called long COVID which is not the subject of our paper but which is under consideration by us as the subject of a future publication.

Also, from these data, we should be careful to not draw the conclusion to stop statin use when prescribed; quite on the contrary. It would be instructive to compare the results of this study to those previously published of statin use on all-cause health effects (ie not in the COVID-era).

We appreciate this point. Statins have historically been associated with a lower risk of a wide range of health outcomes, although some of the association has been attributed to residual confounding due to healthy user bias 11. We have added the following language to the Discussion section (p. 9, line 27): “It is important to note, however, that the current study does not demonstrate a harmful effect of statin use among individuals with COVID-19, only that statins may not exert a SARS-CoV-2–specific protective effect and/or that positive findings in previous observational studies may be due to residual confounding. Current findings therefore do not support statin cessation among individuals with COVID-19.”

I strongly recommend publishing this study, with only some minor elucidation of the few comments given above.

Reviewer: 4
Prof. John Norrie, Edinburgh Clinical Trials Unit, University of Edinburgh No. 9, Bioquarter
Comments to the Author:
This is a well written article on a topical issue in COVID-19. The authors have used appropriate statistical methods, and these are clearly described.

What isn't completely clear is the objective. The conclusion appears to be that statins are not a promising treatment for COVID-19, since the associations for adverse outcomes (hospitalisation, admission to ICU, and 30-day mortality) do not appear to be as favourable for statin users with COVID-19 compared with a 'negative control' group of those without COVID-19. The stated objective is 'to estimate associations', which is fair enough, but it isnt as clear how these associations can be interpreted as likely implying treating with statins is not useful as a specific intervention for COVID. For that, a randomised trial would be ideal. Obviously that would be difficult, but despite a good discussion of the limitations (and strengths) of this analysis, it isnt sufficiently well covered as to the leap from those associations to the conclusion.

A couple of specific major issues:

1. Around 30% of both the SARS-CoV-2 positive and negative cohorts are taking statins of various descriptions - from the Table the statin exposure is defined as 'receipt of a statin prescription with a fill date prior to the index date and a quantity
prescribed that would extend past the index date'. But, recognising that most (the vast majority?) of this 30% will have been on statins for a while, the authors then adjust for 'statins >6 months before index event' - but I couldnt see any summary statistics for this? So, what is the interpretation of the 'current statin' term in the model, in the presence of this 'statin >6 months'? Is it just picking up those prescribed statins in the most recent six months, or is it picking up those who were initiated on statins as a result of getting infected with COVID-19 - or both? It is difficult to see how this set-up mimics treating people with statins to see if they are beneficial for COVID-19? It is not at all obvious how those who have been on statins for years can contribute to the analysis as interpreted - that is why it is crucial to be clear about the study objective here?

Among both SARS-CoV-2 positive and negative groups, 75% of “current” statin users were also “prior” statin users. We have moved these statistics up in Table 1 to make them easier to locate. Because the prescription fill date was prior to the index date, “current” statin users do not include any individuals who initiated their statin only after being diagnosed with COVID-19. To clarify the definitions of “current” and “prior” statin use, we have revised and consolidated these definitions in the Methods section (p. 6, line 1): “Current statin use was defined as receipt of a statin prescription with a fill date prior to the index date and a quantity prescribed that would extend past the index date. … We defined prior statin use as receipt of a statin prescription with a fill date that included the time period six months prior to the index date.” To clarify the interpretation of “current” statin use term, we moved the following language to the Methods, Statistical Analyses section (p. 7, line 15): “We also controlled for prior statin use to approximate a comparison of incident users and non-users.”

2. The authors need to explain more fully the concept of a negative control and how it might apply to this context. Its a good idea, for sure; but it isnt clear that although the outcomes are superficially similar - hospitalisations, admissions to ICU, and 30-day deaths - that the authors are comparing like with like across the positive and negative cohorts? Taking hospitalisations - these might be very strongly weighted towards respiratory conditions for the positives, against a whole range of conditions for the negatives? How does it make sense to compare these with a view to making a statement about the protective capability of statins wrt to COVID?

We agree with the reviewer’s concern about the dissimilarity between reasons for hospitalization and ICU care between the COVID patients and controls. We believe that the comparison of mortality is the most methodologically sound outcome to estimate benefit of statins in our participants with and without COVID infection. We do see limitations in the comparison of hospitalizations and ICU admissions but believe there is some value to be derived from it. Given that elective hospitalizations and surgical procedures were postponed for the first year of the pandemic, the hospitalizations in the non-COVID infected controls were likely due to chronic medical conditions some of which are potentially preventable by statins. The following source confirms this by showing 3 CV conditions in the top 10 causes of hospitalization in the US in 2018 (https://www.hcup-us.ahrq.gov/faststats/NationalDiagnosesServlet)

Since CV conditions predispose to COVID hospitalizations, though, there would be some expected overlap with statin benefit between those with and without this infection12. We discuss this issue further in our response to your comment #8 below. We now include the following sentences in the limitations acknowledging this issue (p. 12, line 5). “The comparison of all-cause mortality is in our opinion the best outcome by which to assess whether statin use benefitted patients with versus without SARS-CoV-2 infection. The comparison of admission to hospital or ICU is of less value given that the reasons for hospitalization likely differed greatly by presence of infection, but, nevertheless, are of value in demonstrating that no apparent benefit is seen that might not be reflected in overall mortality.

Minor issues
3. There is no mention of compliance. Was there only 'prescriptions issued' data available, no data on actual consumption?

Participant-level information was not available on statin adherence; however, statin discontinuation rates have previously shown to be low in VHA patients relative to discontinuation rates for other lipid-lowering medications13. We have added the following limitation (p. 12, line 3): “No data were

available on prescription adherence; however, statin discontinuation rates have previously shown to be low in VHA patients relative to discontinuation of other lipid-lowering medications13."

4. Likewise, no data on dose. The authors just use 'potency' as a surrogate. Indeed, it could be that as say a treatment for COVID-19 very large doses given IV might be appropriate - and that isnt possible to address with these data, for example?

Thank you for the opportunity to clarify this point. The dose of each statin dose was included in intensity categories that were used. For example, an individual with a prescription for atorvastatin 20 mg would be classified as receiving a moderate-intensity statin (see Supplementary Table). The reviewer is correct that we are not able to look at associations of IV statin use with COVID outcomes in this dataset as no parenteral statin formulation is currently approved by the US FDA. This is an interesting area of future investigation. We have added the following language to the Methods section (p. 6, line 2): "Statin intensity was defined as low, moderate, or high using definitions from the American Heart Association/American College of Cardiology guidelines on management of cholesterol14 and was calculated based on the specific statin and dosage prescribed."

Supplementary Table. Statin intensity (potency) in relation to dose according to American College of Cardiology/American Heart Association guidelines

High-intensity	Moderate-intensity	Low-intensity
LDL-C lowering ≥50%	30–49%	<30%
Atorvastatin (40 mg) 80 mg	Atorvastatin 10 mg (20 mg)	Simvastatin 10 mg
Rosuvastatin 20 mg (40 mg)	Rosuvastatin (5 mg) 10 mg	Pravastatin 10–20 mg
Simvastatin 20–40 mg	Lovastatin 20 mg	
Pravastatin 40 mg (80 mg)	Fluvastatin 20–40 mg	
Lovastatin 40 mg (80 mg)		
Fluvastatin XL 80 mg		
Fluvastatin 40 mg BID		
Pitavastatin 1–4 mg		

5. The authors acknowledge the issue of diagnostic misclassifcation, and the additional problem of not requiring a negative test to be classified in the negative cohort, but there is no quantification of the likely false positives and false negatives rates? This would seem important before it can be claimed that the net effect will be to dilute the associations?

The false positive rate of the RT-PCR tests used to diagnose SARS-CoV-2 infection in this population are very small and estimated at 1-2% (https://www.cap.org/member-resources/articles/how-good-are-covid-19-sars-cov-2-diagnostic-pcr-tests). As this minimal misclassification would have negligible effect on the test positive predictive value we have chosen to not discuss this in the paper.

RT-PCR sensitivity is estimated at 80% and hence would result in missing true cases of SARS-CoV-2 infection. The bias caused by missing these cases is similar to that caused by not testing and assuming absence of infection. We realize that the description of the dilution of effect as described in the original manuscript was not accurate. The dilution of effect that we wanted to refer to is the difference between the statin-outcome associations in the SARS-CoV-2 infected and non-infected comparator populations. If the associations, say, between statins and mortality differed between the infected and non-infected in reality, then it stands to reason that falsely classifying infected as non-infected would make these two groups more similar, resulting in a diminution in the difference between them. We have revised the sentence in limitations (p. 12, line 14) addressing this to read as

follows: “Further, based on the current results, inclusion of individuals with undiagnosed COVID-19 in the SARS-CoV-2–negative comparator group would be expected to attenuate observed differences in the associations of statin use with adverse outcomes between the SARS-CoV-2 infected and negative comparator groups.”

6. There is no mention of vaccination - the study took place over 12 months up to March 2021?

Unfortunately, given the timing of this study, only 698 individuals in the sample had received both vaccinations in a two-vaccination series or one vaccination in a one-vaccination series by the index date. We are therefore unable to examine the association of vaccination with outcomes due to very limited vaccination coverage of our population at the time of this analysis. We have added the following limitation to the paper: “Given the timing of this study, we were unable to evaluate mediating or moderating effects of vaccination use due to very limited vaccination coverage of our population by the index date.” (p. 12, line 1).

7. The authors mention adjusting for time (month) and region (VHA site) – more detail is needed – was this an important adjustment?

We have added the following language to the Methods section (p. 7, line 11): “Index month was included as a precision variable. Facility location was included because both patterns of statin use and COVID-19 outcomes are expected to differ by region in the US.”

8. The authors should discuss further the apparent attenuation of the ‘benefits’ of statins going from the negative to the positive group. What is the logic of the original comparison i.e. that oif there is no benefit, then the hazards for the 3 outcomes might be expected to be the same? So, does an attenuation perhaps indicate that statins are doing some ‘harm’ in this context and consideration be given to stopping them?

We agree with this point and believe that the attenuation of the hazards for hospital and ICU admission are perhaps further evidence of lack of COVID-specific beneficial effect for statins. The reasons for hospitalization following COVID infection are most likely due to complications of this infectious disease, whereas in the non-infected population, the reasons are mainly for treatment of chronic conditions more likely to be prevented by statins. We speculate that this is the reason for lower odds of hospital and ICU admission in the non-COVID infected comparison population. We feel that this is too speculative to include in the paper, but see a need to state that the attenuated associations are not in our opinion due to deleterious statin effects. Therefore, we have added the following language to the Discussion section (p. 9, line 27): “It is important to note, however, that the current study does not demonstrate a harmful effect of statin use among individuals with COVID-19, only that statins may not exert a SARS-CoV-2–specific protective effect and/or that positive findings in previous observational studies may be due to residual confounding. Current findings therefore do not support statin cessation among individuals with COVID-19.”

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VERSION 2 – REVIEW

REVIEWER	Kragholm, Kristian Aalborg University Hospital, Unit of Epidemiology and Biostatistics
REVIEW RETURNED	03-Jan-2022

GENERAL COMMENTS	The authors have responded well to my comments. I have one last suggestion:

	I recommend that the important messages mentioned by the authors in their response to my second comment are added to the manuscript Discussion section.

REVIEWER	De Spiegeleer, Bart University of Ghent
REVIEW RETURNED	27-Dec-2021

GENERAL COMMENTS	The comments were adequately addressed, and the revised manuscript can be published.

REVIEWER	Norrie, John Edinburgh Clinical Trials Unit, University of Edinburgh No. 9, Bioquarter, Usher Institute
REVIEW RETURNED	07-Jan-2022

GENERAL COMMENTS	The authors have satisfactorily addressed all the statistical queries, and have made appropriate changes where necessary.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Kristian Kragholm, Aalborg University Hospital

Comments to the Author:

The authors have responded well to my comments. I have one last suggestion:

I recommend that the important messages mentioned by the authors in their response to my second comment are added to the manuscript Discussion section.

We have added the following text to the Discussion section (p. 11, line 5): “We did not examine in-hospital statin continuation in the current analysis—a question which remains unaddressed—but instead focused on the association between statin use prior to COVID diagnosis and outcomes, where use of this medication would not have been confounded by the onset of COVID. Methodological issues (most importantly residual confounding by indication and heterogeneity of the populations studied) limit the conclusions that can be drawn from earlier observational studies of statin continuation at hospitalization. Masana et al. examined associations of statin use with in-hospital mortality in a cohort of hospitalized Spanish patients with a positive test for SARS-CoV-228 comparing statin non-users, users who continued statins during hospitalization, and users who stopped statins during hospitalization. Overall, 25.7% of non-users died, while 19.8% of continued users died, and 17.4% of stoppers died. In that analysis, matching was used to account for differences in pre-admission characteristics; however, the authors were not able to account for characteristics (e.g., severity of COVID-19 illness, perceived prognosis, goals of care, etc.) that might impact the decision to stop statin therapy at the time of admission. In a meta-analysis, Permana et al. examined associations of pre-admission statin use and in-hospital statin use among patients hospitalized after a positive test for SARS-CoV-221, which is a related question. In-hospital but not pre-admission statin use was associated with a lower risk of mortality; however, these pre-admission and in-hospital study populations differed in characteristics such as age and sex that are strongly

associated with adverse COVID-19 outcomes, limiting direct comparisons between the groups. Given the many possible determinants of statin cessation or continuation following the diagnosis of COVID-19 potentially related to adverse outcomes that would be difficult to extract from medical records (electronic or otherwise), the question of whether to cease or initiate statins following COVID diagnosis will be best determined by a clinical trial."

Reviewer: 3

Dr. Bart De Spiegeleer, University of Ghent

Comments to the Author:

The comments were adequately addressed, and the revised manuscript can be published.

Reviewer: 4

Prof. John Norrie, Edinburgh Clinical Trials Unit, University of Edinburgh No. 9, Bioquarter

Comments to the Author:

The authors have satisfactorily addressed all the statistical queries, and have made appropriate changes where necessary.