Authors’ Reply: Calcium-Based Phosphate Binders and Plasma Oxalate Concentration in Dialysis Patients

We thank Oka and colleagues for their comments on our paper and their suggestion for a possible role for alternative therapeutic interventions to reduce oxalate concentrations and cardiovascular mortality in patients on dialysis. They suggest a low-oxalate diet or calcium-based phosphate binders could decrease oxalate absorption and lead to reduced cardiovascular risk. We agree these measures warrant further evaluation when planning interventional studies examining elevated plasma oxalate concentrations and risk of sudden cardiac death in patients on dialysis. Avoidance of high-oxalate foods makes sense, although the dietary restrictions faced by patients on dialysis are already burdensome.1 Of note, food products containing high amounts of oxalate (nuts, beans, certain vegetables),2 The current Kidney Disease Improving Global Outcomes guidelines3 suggest restricting the dose of calcium-based phosphate binders in adults with CKD stage G3a–G5D receiving phosphate-lowering treatment (2B recommendation), due to a higher mortality risk. For patients on dialysis, this recommendation was made on the basis of a large trial comparing sevelamer to a calcium-containing phosphate binder.4 The eight trials analyzed by Jamal et al.,1 and duly cited by Oka and colleagues, also compared sevelamer with calcium carbonate or acetate. Yet, sevelamer itself may also feature a modest oxalate-lowering effect, as shown in a small trial in patients with enteric hyperoxaluria.6 Future studies could elucidate this issue further.

DISCLOSURES

F. Knauf reports receiving personal fees from Advicenne, Allena Pharmaceuticals, Alnylam Pharmaceuticals, Fresenius Medical Care, Oxtpharma Pharmaceuticals, and Sanofi; receiving research funding from Alnylam Pharmaceuticals, Dicerna Pharmaceuticals, Deutsche Forschungsgemeinschaft, and Else Kröner Fresenius Stiftung; having consultancy agreements with Chinox Pharmaceuticals USA, EcoR1 USA, and Zai Pharmaceuticals China; serving on the scientific advisory board of the Oxalosis and Hyperoxaluria Foundation NYC; and having patents or royalties with PocketDoktor Medical Books. F. Knauf and A. Pfau report being employees of the nonprofit institute Charité-Universitätsmedizin Berlin, which has recently filed a patent for oxalate-lowering agents in patients on dialysis, with A. Pfau and F. Knauf listed as inventors. A. Pfau reports receiving personal fees from Alnylam Pharmaceuticals, outside the submitted work.

FUNDING

None.

AUTHOR CONTRIBUTIONS

F. Knauf provided supervision, reviewed and edited the manuscript, and was responsible for validation; and A. Pfau conceptualized the idea of this manuscript, wrote the original draft, and was responsible for investigation.

REFERENCES


See related letter to the editor, “Calcium-Based Phosphate Binders and Plasma Oxalate Concentration in Dialysis Patients,” on page 1427, and original article, “High Oxalate Concentrations Correlate with Increased Risk for Sudden Cardiac Death in Dialysis Patients,” in Vol. 32, Iss. 9, on pages 2375–2385.

Clinical Studies of Vaccine Efficacy

The study by Bell and colleagues uses linkage between large datasets to analyze severe acute respiratory syndrome
A key finding is a 33% (95% confidence interval, 0%–52%) reduction in infection risk after the second vaccine dose. This estimate is explained in Supplemental Table 1, where the risk of coronavirus disease 2019 (COVID-19) infection is given as 25/235 (11%) in the unvaccinated and 357/5011 (7%) in vaccinated individuals. Real world efficacy of vaccination is an important question, and observational population studies are therefore most welcome, although they face a number of challenges. This study suggests a weaker vaccine effect than has been observed by others, raising the question of whether this finding might reflect study design, rather than a true difference.

A potential problem in the study design is not considering “time.” Infections are counted per person, rather than per person-day, and vaccination status is treated as fixed, although people transition from unvaccinated to vaccinated throughout the study period. These factors lead to differences in “duration at risk” between vaccinated and unvaccinated groups, as well as a large number of excluded events: of the 814 COVID-19 infections in 2021, 357 were “breakthrough,” so 457 non-breakthrough infections (94 of which were fatal) occurred in individuals who were unvaccinated or had received only a single dose. However, only 25 of these are included in Supplemental Table 1.

The study design also leads to difficulty defining groups without bias. Groups are defined within the “adult kidney replacement therapy population as of 19th September 2021.” Intuitively, to be part of this population, a patient should be alive on that date, so it seems as though the 25 unvaccinated cases are COVID-19 survivors (whereas the vaccinated cases include all 357 breakthrough infections, 33 of which were fatal). Alternatively, the population as of 19th September 2021 may include those who died before that date. In this case the outcome (COVID-19 infection) influences group membership (vaccination status) since those who died of COVID-19 had less time in which to get vaccinated (Figure 1).

It would be helpful, therefore, to better understand the definitions and data underpinning the estimate of vaccine efficacy, because it seems unclear what can reliably be concluded from the analysis presented.

**DISCLOSURES**

The author has nothing to disclose.

**FUNDING**

None.

**AUTHOR CONTRIBUTIONS**

D. Ashby conceptualized the study, wrote the original draft, and reviewed and edited the manuscript.

**REFERENCES**


**Figure 1. Timeline of study population.** Simplified timeline in which each patient is a horizontal line, showing mortality and group membership by vaccination status. COVID-19 cases are shown as colored dots, with colored lines indicating survival postinfection. A per-person analysis based on the final population leads to bias, since only COVID-19 survivors are compared. But inclusion of cases circled in a per-person analysis also leads to bias, since dying from COVID-19 may be the reason for nonvaccination, whereas all the pre-vaccination cases (which are excluded) are immortal up to the time of vaccination.
LETTERS TO THE EDITOR www.jasn.org


Damien Ashby
Renal Medicine, Imperial College Healthcare NHS Trust, London, United Kingdom
JASN 33: 1428–1430, 2022
do: https://doi.org/10.1681/ASN.2022030300

Authors’ Reply: Clinical Studies of Vaccine Efficacy

We thank Ashby for his interest in our study. Our data clearly demonstrate a two-dose coronavirus disease 2019 (COVID-19) vaccination regimen is insufficient protection for patients either on dialysis or with a kidney transplant. This finding is entirely in keeping with other emergent data demonstrating higher COVID-19 mortality in double-vaccinated patients with kidney failure when compared with other patients who are clinically vulnerable.1–3 Vaccine efficacy differs between studies in patients with kidney failure depending on the population studied, degree of immunosuppression, vaccination regimen, mechanism of reporting of positive COVID-19 infection, and infectivity of the prevalent variant of severe acute respiratory syndrome coronavirus 2. However, the totality of evidence supports that, although two-dose vaccination may improve outcomes to some degree, there is still an unacceptably high proportion of double-vaccinated patients with kidney failure dying or being hospitalized within 28–30 days of a positive COVID-19 test; this proportion is reported at 9% and 34%, respectively, up until September 21, 2021 in our study1 and 9.5% and 30%, respectively, in Canada, albeit with a follow-up only until June 30, 2021.4 To date, there are still comparatively few reports of the effect of COVID-19 vaccination on clinical outcomes rather than serologic markers of response in this population.

We acknowledge the lack of consideration of time at risk in our study as a potential problem. Although we note the merits of this approach, it does pose challenges when implementing in a highly vaccinated population. We do not feel that including person-time would significantly affect the analyses because the follow-up period is short (March–October) and patients are classed as fully vaccinated 2 weeks after their second dose. We have used March 1, 2021 as the date when we included both patients who were vaccinated and those who were unvaccinated for our vaccine effectiveness calculation because this was the point at which all patients would have had the opportunity to be vaccinated. It was suggested that, by not accounting for person-time exposed, we are underestimating vaccine efficacy. If this is the case, as the population progressively transitions to double-vaccinated status, it is likely that those who are double vaccinated will be slightly less exposed to COVID-19 than those who are unvaccinated, and so vaccinated individuals have slightly less follow-up time, thereby slightly overestimating vaccine effectiveness (if at all) in our study. The total number of infections from the beginning of the pandemic in March 2020 was 814 (apologies for a typographic error in one listing of the date in the paper for which we have submitted a correction). Individuals who had two doses had 357 of the infections, compared with 25 cases among those who were not vaccinated. Individuals who were partially vaccinated were excluded. In terms of the second point with regards to defining groups as of September 19, we have repeated the analyses according to the suggested permutations. Vaccine effectiveness was slightly lower rather than underestimated. We have clearly described the limitations of the methodology we used and presented the accompanying confidence intervals as a measure of precision. We feel that our paper reinforces a very important message: Two doses of COVID-19 vaccine in patients receiving kidney replacement therapy provide insufficient protection. Patients should be encouraged to take up additional vaccine doses and continue to implement other preventive measures.

DISCLOSURES

S. Bell reports receiving honoraria from AstraZeneca. P. Mark reports receiving honoraria from Astellas, AstraZeneca, Boehringer Ingelheim, Napp, Novartis, Pharmacosmos, and Vifor; and receiving research funding from Boehringer Ingelheim. All remaining authors have nothing to disclose.

FUNDING

None.

AUTHOR CONTRIBUTIONS

S. Bell, J. Campbell, E. Lambour, and P. Mark reviewed and edited the manuscript; S. Bell and P. Mark wrote the original draft and were responsible for methodology; J. Campbell was responsible for data curation; and J. Campbell and E. Lambour were responsible for formal analysis.

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Samira Bell, Division of Population Health and Genomics, School of Medicine, University of Dundee, Ninewells Hospital, Dundee, DD1 9SY, Scotland. Email: s.t.bell@dundee.ac.uk
Copyright © 2022 by the American Society of Nephrology