Author's response to reviews

Title: High Serum Bicarbonate Level within the Normal Range Prevents the Progression of Chronic Kidney Disease in Elderly Chronic Kidney Disease Patients

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Author's response to reviews: see over
Dear Dr. Henderson:

Thank you very much for your letter with the reviewers’ comments and for your helpful remarks concerning our paper. Included are our point-by-point responses to the reviewers’ comments, which we hope to have addressed in full.

To Dr. Julia Scialla (1384410480844984_comment):

Major Compulsory Revisions
1. Since this study occurred in a real life clinical setting and not in the setting of a study protocol, the number of eGFR measurements for each participant likely varied based on how closely a patient needed monitoring. This may dramatically affect when patients achieve the endpoint of a 25% reduction in eGFR. Can you please provide information on the distribution of eGFR frequency and how this differed in the two groups? I am concerned that the low bicarbonate group had more advanced CKD, more refractory acidosis and may have had much more frequent measurement of eGFR.

We measured the intervals of GFR measurements in days as an index of care. The results were as follows.
This table shows that the mean intervals of GFR measurements were from 32.2 to 34.1 days. The difference in the interval of GFR measurements between the two groups was about 1 or 2 days. The mean interval of GFR measurements between the groups showed no statistically significant difference (two-way ANOVA, $p=0.4491$). In stage 4, the mean interval of GFR measurements in the low-bicarbonate group was lower than that in the control group; however, no statistically significant difference was observed (t-test, $p=0.53$). There was also no statistically significant difference in the mean interval of GFR measurements in stage 5 ($p=0.82$). We have added the description that most of the patients usually visited the Shiigai Clinic every month. Page 5, paragraph 2, line 9.

2. How many events were eGFR versus ESRD events by group?

The distributions of the patients are shown in the following tables.

<table>
<thead>
<tr>
<th></th>
<th>Low-bicarbonate group</th>
<th>Control group</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 3</td>
<td>32.2</td>
<td>34.1±3.2</td>
<td>34.1±3.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34.5 (32.0, 36.3)</td>
<td></td>
</tr>
<tr>
<td>Stage 4</td>
<td>32.6±2.2 (30.9, 33.4)</td>
<td>33.3±3.4</td>
<td>33.1±3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33.3 (30.9, 35.4)</td>
<td></td>
</tr>
<tr>
<td>Stage 5</td>
<td>33.5±3.0 (30.9, 35.3)</td>
<td>33.3±2.1</td>
<td>33.4±2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33.4 (31.4, 35.4)</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>33.1±2.6 (30.9, 34.2)</td>
<td>33.6±3.1</td>
<td>33.5±3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34.2 (31.6, 35.5)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 Intervals of GFR measurements in days
Values are shown as mean±SD and median (25%, 75%). There was one patient in the stage 3 and low-bicarbonate group.

Table 2 Outcome (a decrease of 25% or higher in eGFR or starting dialysis)
The patients with a decrease of 25% or higher in eGFR showed the same distribution.
Table 3 Dialysis

<table>
<thead>
<tr>
<th></th>
<th>Low-bicarbonate group</th>
<th>Control group</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 3</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>1 (8.3%)</td>
<td>1 (2.6%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Stage 5</td>
<td>5 (33.3%)</td>
<td>3 (21.4%)</td>
<td>8 (27.6%)</td>
</tr>
<tr>
<td>All</td>
<td>6 (21.4%)</td>
<td>4 (4.7%)</td>
<td>10 (8.9%)</td>
</tr>
</tbody>
</table>

The patients in the low-bicarbonate group tended to show CKD progression to the outcome. In the control group, more patients in stage 4 tended to show progression to the outcome, that is, a decrease of 25% or higher in eGFR, than patients in stage 3 and 5. More patients in stage 5 tended to progress dialysis. These findings suggest that CKD progression was more rapid in stage 4 than in stage 3, and that patients in stage 5 tended to start dialysis before their eGFR decreased by more than 25%. However, because the number of patients in the stage 3 and low-bicarbonate group was very small, we were unable to examine the relationship between CKD stage and CKD progression in both groups. The imbalance of patient distribution in CKD stages was described as a limitation of this study in the Discussion. Page 13, paragraph 2, line 2.

3. I am not convinced of the usefulness of the univariate logistic model. What is the contribution of this result? There are large differences in eGFR across bicarbonate levels so without adjustment for GFR, no real inference can be made about the importance of the bicarbonate here.

The logistic models have been eliminated.

4. The discussion needs to address the fact that this population includes both treated and untreated subjects. In fact the proportion treated and dose of bicarbonate used is much higher in the low serum bicarbonate group. It could be that aggressive sodium loading with sodium bicarbonate is harmful in this study or that "refractory" acidosis is harmful whereas easily treated is not. Ideally the treated and untreated populations would be evaluated separately but the sample size is probably not large enough to do this.

We agree that the treatment with sodium bicarbonate needed to be discussed. As you
indicated, the sample size in this study was not large enough to evaluate the treated and untreated patients separately. This was described as a limitation of this study in the Discussion. Page 13, paragraph 2, line 6.

Minor Essential Revisions:
1. The description of the study protocol remains somewhat confusing. This was a retrospective study and therefore I would not expect that patients were treated according to any pre-specified study protocol. This is somewhat misleading in the study design and study population section of the manuscript. In particular the following statement may require clarification: "We treated CKD in accordance with the CKD practice guideline of the Japanese Society of Nephrology. A high serum bicarbonate level was treated in accordance with K/DOQI guidelines 2000. By administration of only sodium bicarbonate, serum bicarbonate level was maintained from 22-32 mEq/L." It might be more appropriate to state that this was the general practice of the clinic to follow such clinical practice guidelines, but I suspect this was not protocolized for this study.

We agree with your suggestion. The expression has been changed as you suggested. Page 5, paragraph 2, line 11.

2. Several places in the manuscript use the language that "an increase in serum bicarbonate level decreased the risk of CKD progression." This suggests cause and effect and should be revised to state that "a higher serum bicarbonate level was associated with lower risk of CKD progression." This language is used throughout the manuscript; abstract, results and discussion.

We agree with your suggestion. The expression has been changed as you suggested in the following pages. Page 2, paragraph 3, line 2. Page 2, paragraph 3, line 5. Page 2, paragraph 4, line 1. Page 9, paragraph 3, line 5. Page 10, paragraph 1, line 1. Page 10, paragraph 1, line 5. Page 11, paragraph 2, line 2.

To Dr. Donald Wesson (1258021813843650_comment):

Thank you very much for your review.
To Sankar D Navaneethan (1520959347861682_comment):

Thank you very much for your review.

We thank the reviewers for the very thorough but fair review and hope that the revisions address all your concerns.

Sincerely,

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