Reviewer’s report

Title: Clinical and cost-effectiveness of oral sodium bicarbonate therapy for older patients with chronic kidney disease and low-grade acidosis (BiCARB): a pragmatic randomised, double blind, placebo-controlled trial

Version: 0 Date: 27 Nov 2019

Reviewer: Claudine Jurkovitz

Reviewer's report:

The objectives of this double-blind randomized clinical trial were to evaluate the clinical and cost effectiveness of oral sodium bicarbonate therapy in older patients with advanced CKD. The primary outcome was the between-group difference at 12 months in physical performance assessed by the validated Short Physical Performance Battery Protocol. Secondary outcomes included comparisons of quality of life, comparisons of anthropometric measurements, renal function, walk distance, blood pressure, bone and cardiovascular risks markers. Adverse events including death, cardiac events were compared between the 2 arms.

This is a well-designed RCT unique in the context of bicarbonate supplementation because it is double-blinded, and focuses on older adults with CKD, a specifically vulnerable population. However, the methods and description of results have some limitations as follows:

1) Major comments:

1.1. Some information is missing from the methods section both from the current paper and from the 2015 study protocol publication.

Were there any exclusion criteria related to very low serum concentration of bicarbonate?

Were there any recommendations given to physicians for the management of low serum bicarbonate in patients in the control group?

Were medications other than sodium bicarbonate included in the calculation of health care costs?

1.2. The authors mention in the results section that multiple imputations were used to account for missing data (line 9, page 11), however there is no information on which variables have missing data, and the percentage of missing data, both for the primary outcome and the secondary outcomes analyses. How many patients were included in the linear mixed model for the primary outcome analysis? Likewise, how many patients were included in the cox proportional regression analyses for adverse events (lines 33-57 page 11; lines 13-14 page 12)? Which strategy was used to handle missing data in the repeated measures models?
1.3. The number of patients who completed the one year follow-up is 220 (116 in bicarbonate group, 104 in placebo group). However, it seems that only 187 patients completed the SPPB (primary outcome). How many of those are in the bicarbonate group versus the placebo group? Are the characteristics of those who completed the SPPB similar to the characteristics of those who completed the one year follow-up for each treatment group?

1.4. What is the time frame of the analysis of the secondary outcomes, 12 months or 24 months (table 2)? Were all the time to event analyses done at 24 months?

1.5. More information about the 18 control patients who crossed-over would be helpful to better understand figure 2. Did these patients complete the 24-months follow-up? The increase in serum bicarbonate level in the placebo group over time is surprising. Is there any information about the management of acidosis in the placebo group?

1.6. Was the mean (median) length of follow-up similar between the 2 treatment arms? This is important for the comparison of adverse events considering that the follow-up was truncated for 22 patients.

1.7. Assuming that the length of follow-up is similar between the 2 arms, was the proportion of participants with at least one adverse event statistically different between the 2 arms (table 3)? What is the distribution of adverse events within each arm (% of participants with 1, 2, 3 or 4 adverse events or other type of stratification according to the distribution).

1.8. One limitation of the cost-effectiveness analysis is that only 80% of those who completed the 12 months follow-up had complete cases. Was the proportion of missing data balanced between the 2 arms?

1.9. Table 4 is not very clear. The number of complete cases at 24 months is n=114, but when the participants in renal replacement therapy are added, the total number of cases becomes 161, which is the number of participants who attended the 24 month follow-up visit. Are the missing data only related to renal replacement therapy?

2) Other comments
2.1. Could the number of patients present at each time point be added to figure 2?

2.2. Were the 18 control patients who were switched to bicarbonate treatment included in the "Bad adherence group" or were they excluded from this analysis?

2.3. On page 10 line 29, the standard deviation should be provided with the mean, as well as the median and IQR.

2.4. One of the categories used in the minimization algorithm is age ≥75, but this is not a category described in table 1. Could this information be also provided in table 1?

2.5. In table 1, there seems to be a typo in the value provided for SF36 MCS in the placebo column.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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Yes

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