Author's response to reviews

Title: Barriers to Successful Care for Chronic Kidney Disease

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Author's response to reviews: see over
Response to reviewers

Reviewer 1: Gordon Taylor

General:
We have carefully reviewed and revised the statistical analyses and incorporated the suggestions of this reviewer. We acknowledge that in some instances it would be of great interest to perform more sophisticated analyses. However, the size of our dataset limits the number and types of analyses that can be performed without increasing the risk of spurious results. Should this reviewer have any specific suggestions as to what additional tests to perform or what specific flaws in our analyses to correct, we would be willing to tackle these issues. However, we believe that in its current revised form our analyses are suitable for publication.

Detailed responses:
We strongly insist that the two groups, SNC and LNC, were not derived by “artificially splitting” the data or by a “serendipitous post hoc split”. We postulated at the beginning of the study, i.e., at the time the protocol was submitted to our local institutional review board, that nephrologists are likely to do a better job in taking care of these patients and that is why we had to collect data regarding the length of care.

While we hypothesized that outcomes will be different, it was not evident to us that SNC patients should have different baseline characteristics than LNC patients. This may be illustrated by the following example. Say, 2 persons of the same age, gender, and ethnicity develop diabetic nephropathy in January of 2000. They both progress to CKD stage 4 until January 2004, when our study happened to take place. Say, one patient was referred to the nephrologist in January 2000, while the other was referred in January 2004. The former would be a LNC while the latter would be a SNC patient. According to our hypothesis, the outcomes should be different between the two patients, while the baseline characteristics such as age, gender, etc. should not.

There are two notable exceptions to this argument. One is the length of care. The differences in length of care obviously result from the way we split the patients into two groups. Median length of care is 2 and 33 months in the SNC and LNC group, respectively. The second is the GFR at referral. GFR declines over time. Thus, we agree that it is not surprising at all to see a lower GFR at referral in the SNC group compared to the LNC group. We did not feel that a statistical comparison of either of the two variables was needed, since they are a direct result of our splitting the cohort, however, another reviewer wanted to see p-values.

Table 1:
We acknowledge that we performed a very large number of comparisons in table 1, and we are aware that the chance to obtain spurious results increases with the number of comparisons performed. However, we were asked by previous reviewers to attach a p-value to each line, and we complied.
We agree that for age and GFR an overall test is the first step, although the GFR difference is a result of the study design, see above. We have now included that result in table 1.
We split the age groups arbitrarily into decades in order to give the reader a better impression of the age distribution. We noted that one decade was missing from the previous version of table 1 and we corrected that mistake. The p-values in our mind do not contribute much to the overall manuscript; they were added at the request of another reviewer.

The GFR levels may appear odd from a mathematical point of view, but they make sense clinically. The different stages of chronic kidney disease are defined by the stated GFR levels. Again, we showed these data mainly to give the reader a better impression of the GFR distribution. The p-values in our mind do not contribute much to the overall manuscript; they were added at the request of another reviewer.
We added all p-values, no matter whether significant or not, in most tables and figures. This, unfortunately, was not possible in the already complex table 2.

Table 2:
We acknowledge that table 2 is somewhat complex, but we feel strongly that the reader should have an opportunity to see what comes closest to the raw data.
We agree that from a mathematical point of view it is rather odd to show ANOVA results and medians in the same table. The rationale was that this paper will likely be read by clinicians, and we felt that it is easier to grasp the distribution with medians and quartiles rather than means and standard deviations. However, we followed this reviewer’s advice and converted the table so that it now shows means±SD.

Our dataset is rather small and thus we cannot reject the hypothesis that our data are normally distributed. Inspection of the data did not show an obviously non-normal pattern, and since most biological data are normally distributed, we assumed that ours are, too.

The reviewer is correct in the assumption that the Bonferroni correction was applied only within but not across parameters. Given that multiple parameters are tested, caution needs to be exercised as to what p-value is considered acceptable. In this particular case, likely a p<0.001 can be considered significant. Since different readers may have different views of the required stringency, we stated that only p<0.05 are shown, but we avoided to state what we would consider significant.

As mentioned above, we would like to strongly assure the reviewer that the SNC-LNC is not a serendipitous post hoc split. It is hypothesis-driven and supported by the literature in the field. Consider that our hypothesis did not pan out for many parameters in Stage 4 CKD and for all parameters in Stage 5 CKD patients (see tables 3 & 4); if this had been a post-hoc split why should we show negative results?

Table 4.
We decided that from a clinical point of view, having more than half the parameters, i.e., at least 5/9, not at goal would qualify as an undesirable outcome and this is clinically relevant. This is how the outcome was chosen. Obviously, the results will be different the closer one gets to the extremes since the number of patients in one of the two groups will dwindle and it will be impossible to reach any significance. We believe that whether one chooses 4/9 or 6/9 rather than 5/9 depends on ones clinical judgment. We did not try out other cut points because we felt that ours is a clinically relevant one. Given the small sample size, it likely would result in a similar outcome without any significant p-values.

Not all goals are equally difficult to achieve, as table 3 demonstrates. For example, a much higher proportion of patients achieved calcium or phosphate goals than PTH goals. This may be in part due to pathophysiology and in part due to the type of medication used, some of which have a bad taste, have to be taken multiple times a day, or have to be injected. In addition, some parameters by be more important than others in terms outcomes such as survival or progression to end-stage renal disease. Another very important observation made by this reviewer is reflected in the question of independence. From a statistical point of view, the nine parameters collected from each patient are not independent from each other, since they occur in the same individual and thus are subject to the same modifiers, such as gender, age, non-adherence etc. In addition, there are multitudes of interactions between the parameters. To name just a few, treatment of hyperphosphatemia may cause metabolic acidosis, an elevated PTH is likely to be associated with an elevated phosphate, the treatment of anemia can influence blood pressure control, and many more. While it would be highly desirable from a statistical point of view to tease out all these interactions, several thousand subjects would be needed for a robust analysis. For this reason, we view our manuscript more as a tool to generate hypotheses and stimulate further research rather than to provide all the answers. However, we do agree with the reviewer that these shortcomings of the current manuscript need to be mentioned, and we have expanded the section regarding limitations.

Reviewer 2: Bryce Kiberd

We corrected the typos in tables 2 and 3.
Please see response to reviewer 1 in regards to the choice of outcome.

We did separate analyses for the outcomes secondary hyperparathyroidism (combination of calcium, phosphate, calcium-phosphate product, and PTH), anemia, nutrition (combination of metabolic acidosis and hypoalbuminemia), blood pressure, and lipids. In fact, predictors of failure to achieve goals vary among these analyses. However, we decided not to present these data since it would add another layer of multiple comparisons, and the interpretation of statistical significances would become very difficult. We acknowledge that it would be very interesting to know the answer to these questions, but a much larger cohort will be needed.
We revised the sentence on page 12.

Reviewer 3: Wendy St. Peter

We revised tables 2 and 4; we hope this will resolve the lingering questions.
We corrected the sentence on page 5.
We corrected the statement about hyperlipidemia on page 10. In the course of the careful repeat analysis in response to reviewer 1, we found that 3 subjects had not been classified. after correcting this mistake, hyperlipidemia did no longer reach the level of significance.
We expanded the discussion on Vitamin D.
Legend to table 3 was corrected.
“(Stage 4 and 5)” added.
Page 11, sentence added as suggested.