Title: Associations of serum and dialysate electrolytes with arrhythmic risk in incident hemodialysis: The Predictors of Arrhythmic and Cardiovascular Risk in End-Stage Renal Disease (PACE) Study

Version: 0 Date: 04 Dec 2018

Reviewer: Patrick Hank Pun

Reviewer’s report:

This is an analysis of the longitudinal PACE study examining the relationship between serum and dialysate electrolytes with QT interval at baseline and again at 1 yr followup. The study is relatively straightforward and generally well written. I have the following suggestions and comments:

1. "Arrhythmic risk" in the title of the manuscript is too broad and has many possible meanings. For clarity of communication, it should be replaced with the exact measure of arrhythmic risk that was measured here: QT interval and prolongation.

2. Although QT interval may be an important measure of arrhythmic risk in the non-dialysis population, to my knowledge QT prolongation and QTc interval (a marker of susceptibility to ventricular arrhythmias) has not been convincingly shown to be independently associated with SCD risk in the hemodialysis population. Instead, non-ventricular bradyarrhythmias are increasingly implicated as more prevalent clinically significant arrhythmias. The authors should devote a section in the discussion to what is known about the clinical significance of the QT interval and hard outcomes specifically in this population.

3. It seems like there is an opportunity in the longitudinal analyses to examine how changes in the electrolyte levels associate with changes in QTc interval between baseline and followup, not just static QT measurement at a later timepoint. If present, this would make a more powerful argument for the causal link between these factors. It would also be a great opportunity to see how changes in other longitudinal measures (such as LVMI and EF) associated with changes in QT interval.

4. The finding of an association with ionized calcium levels, and not total calcium levels could be explained by differences in the timing of measurement. Ionized calcium levels and ECG analyses were done at very nearly the same time (on nondialysis days) , whereas total calcium levels could have been drawn days or weeks prior to QTc measurement. Since QT interval is a dynamic measurement and calcium levels can vary by day and in relationship to the timing of dialysis treatment, its not a surprise that the more coincident measurement of calcium showed better correlation. A similar argument could be made for the relationship between dialysate Ca levels, and also gradients. One would hypothesized effect of these factors on the QT to be primarily observed in the immediate post dialysis period when electrolyte levels change rapidly,
and dissipate over time. Thus, ECG measurements done at a different time could miss any potential effects altogether. These important limitations should be included in the discussion, and appropriate caution should be applied to the discussion on total vs ionized calcium levels, as well as dialysate levels in the manuscript.

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