Supplementary Online Content

Clark WF, Sontrop JM, Huang S et al. Effect of coaching to increase water intake on kidney function decline in adults with chronic kidney disease: A Randomized clinical trial

Final Statistical Analysis for the Chronic Kidney Disease Water Intake Trial

Primary analysis: Continuous variables are summarized as means and standard deviations (SD) or as medians and inter-quartile ranges as appropriate. No statistical tests were used to compare baseline characteristics.[1] Linear regression was used to estimate the between-group difference in eGFR change (hydration minus control) using SAS version 9.3 (SAS Institute Inc., Cary, NC). The following pre-specified covariates[2] (measured at baseline) were adjusted for in the primary analysis: age (in years), sex, obesity (body mass index $\geq$30 kg/m^2), current smoker (yes/no), presence of diabetes, 24-hour urine albumin (mg/day) (log transformed), and use of any of the following medications: an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, diuretic, beta blocker, calcium channel blocker, or statin.[3] Missing baseline data occurred for <0.2% of categorical covariates (if missing, the condition was considered absent) and 6% for 24-hour urine albumin (imputed using fully conditionally specified models[4] as described below). Participants who died within one year of follow-up were excluded from the primary and secondary outcome analyses (12 of 631 participants [1.9%]). Less than 5% of survivors were missing a 12-month eGFR value ($\pm$4 months); missing eGFR data was imputed using fully conditionally specified models[4] as detailed below. SAS PROC MIANALYZE was used to combine results from imputed datasets.[5] The type I error rate was set at 0.05. All analyses were conducted according to the intention-to-treat principle.

Analysis of missing data: Missing baseline data occurred for <0.2% of categorical covariates (if missing, the condition was considered absent) and 6% for 24-hour urine albumin (imputed using fully conditionally specified models[4] as described below). Participants who died within one year of follow-up were excluded from the primary and secondary outcome analyses (12 of 631 participants [1.9%]). Less than 5% of survivors were missing a 12-month post-randomization eGFR ($\pm$4 months); missing eGFR data was imputed using fully conditionally specified models[4] with the following baseline variables: treatment group, center, age (in years), sex, presence of obesity (Body Mass Index $\geq$30 kg/m^2), current smoker (yes/no), presence of diabetes, 24-hour urine albumin (mg/day) (log transformed), and use of any of the

following medications: an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, diuretic, beta blocker, calcium channel blocker, and statin (yes/no). Estimated GFR values at the 3-month and 6-month study time points were also included in the imputation. Twenty datasets were imputed. We assumed that data were missing at random, and that the data were from a multivariate normal distribution. We conducted several sensitivity analyses to examine whether conclusions were sensitive to assumptions about the missing-data mechanism; these analyses included a complete-case unadjusted analysis, simple imputation, and imputation that did not include the treatment group.[6,7] SAS PROC MIANALYZE was used to combine results from imputed datasets.[5] The type I error rate was set at 0.05.

Supporting analyses: Several supplementary analyses were conducted using alternative definitions of change in eGFR. As specified in the protocol,[2] for these analyses, a p-value <0.05 would be interpreted as statistically significant only if there was concordance with the primary results. Supplementary analyses included the between-group difference in (i) eGFR measured with cystatin C *(ii)* the annual percentage change defined as [(final eGFR-baseline eGFR)/baseline eGFR] and *(iii)* the proportion of participants with a one-year eGFR decline ≥20%.[8–10] We also examined whether results were consistent in participants with and without macroalbuminuria at baseline (24-hour urine albumin ≥300 mg/day). Finally, we conducted a per-protocol analysis restricted to participants in the hydration group who maintained a 24-hour urine volume that was at least 0.5 L/day above their baseline value at 6-months and 12-months after randomization, and participants in the control group who maintained a 24-hour urine volume that was <0.5 L/day above their baseline value at each follow-up assessment; participants who missed an assessment or whose final urine sample was collected >16 months after randomization were excluded.

Longitudinal rate of change in eGFR (sensitivity analysis of primary outcome): We conducted a longitudinal analysis of eGFR, estimating the average change in eGFR for each 1-month increase in time, for both groups. To do this, we used a mixed-effects model with a random intercept. The outcome was eGFR measured at one of four time points. The fixed-effects regression coefficients were time (0, 3, 6, and 12 months), and a time-treatment group interaction term. The time coefficient describes the average change in eGFR for a one-month increase in time for participants who were randomized to the hydration group. The time-treatment group interaction term represents the additional change in eGFR for the control group (i.e. the sum of the two coefficients represents the average change in eGFR for a one-month increase in time for participants randomized to the control group). The random intercept

was used to account for within-subject correlation. For this analysis, 3- month eGFR was defined as the eGFR measured closest to 3 months (between 1.5 and 4.5 months after randomization), 6-month eGFR was defined as the eGFR measured closest to 6 months (between 4.5 and 8 months after randomization), and 12-month eGFR was defined as the eGFR measured closest to 12 months (between 8 and 16 months after randomization). We tested whether the coefficient for the time-treatment group interaction term was equal to zero, which would indicate that the change in eGFR over time was equal between the groups. If this term was significantly different from zero, we reported the average change in eGFR for a one-month increase in time for both groups separately. If the time-treatment interaction coefficient was not significantly different from zero at the α=0.05 level, we fit the same mixed-effects regression model, but omitted the interaction term. From this model, we tested the null hypothesis that the average change in eGFR was equal to zero at the α=0.05 level, for both treatment groups simultaneously.

Analyses of secondary outcomes: The one-year changes in plasma copeptin concentration, creatinine clearance, 24-hour urine albumin, and health-related quality of life were compared between groups using the independent-samples t-test or the Mann-Whitney U as appropriate.

References

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