

Official Title of Study:

Randomized Trial of Empiric Versus Selective Prevention Strategies for Kidney Stone Disease

NCT number:

NCT05365477

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STATISTICAL DESIGN AND POWER

Number of subjects expected to enroll

We expect to enroll 56 subjects.

Expected effect size, power, and statistical methods

The primary outcomes are calculated calcium oxalate supersaturation and calcium phosphate supersaturation at baseline compared to 2 months.

For calcium oxalate supersaturation, prior studies have shown that a supersaturation difference of 3.3 between study arms is clinically meaningful and associates with stone events.^{24,25,71} We estimate the standard deviation of calcium oxalate supersaturation at 3.6 based on prior studies.^{29,72,73} With a per-group sample size of $n=28$, we will have 92% power to detect the clinically meaningful effect while controlling type I error rate at 5%. We will maintain 80% power with 8 or fewer dropouts per group.

For calcium phosphate supersaturation, a difference of 1.0 between study arms is considered clinically meaningful.²⁵ The reported standard deviation ranges from 0.83 to 1.0.⁷³⁻⁷⁵ With these parameter settings, we will have at least 95% power with a type I error rate of 5%. We will maintain >85% power with 8 or fewer dropouts per group.

Patient characteristics on all randomized patients will be summarized. For each primary endpoint, a regression model will be fit with treatment as the primary covariate and sex, race (white/non-white), and co-morbid conditions (modified Charlson comorbidity index⁷⁶ score 0-1 versus ≥ 2), and treatment-sex interaction as the additional variables. As the total sample size is 56, we will have a large enough sample size for stable estimation of the treatment effect. The treatment difference will be estimated using this regression model and will be reported with a 95% confidence interval.

Sex as a biological variable: In the primary analysis, an interaction between treatment and sex will be added to the regression model so a systematic comparison of the treatment effect between sexes becomes possible.

Missing data: We will use the following approach to handle missing data. Assuming there will not be any missing baseline data, we will follow the recommendations by Jacobson et al.⁷⁷ and not use the multiple imputation method, which may increase the standard errors by introducing additional uncertainty.⁷⁸ As suggested by Jacobson et al.,⁷⁷ we will use a single imputation by plugging in the missing data by the other group's mean ± 2 standard deviation to create a "best-worst-case" and "worst-best-case" scenario data sets. If these data sets do not give qualitative contradicting results, then we will report the conservative single-imputation-based result (smaller group difference) as the imputation-based intention-to-treat analysis. If the results are significantly different, then we will use the observed data only and report the best-worst and worst-best case analyses.

We will perform a complete accounting for all participants including dropouts (e.g. those who did not complete the trial). The data for each of the measures will be summarized for each treatment arm.

For diet therapy, we will construct a table to compare empiric and selective therapy with respect to adherence. Then, to explore changes in dietary intakes between the two groups, we will analyze each of the following outcomes: energy, water, sodium, potassium, calcium, phosphorus, fiber, and servings of fruits, vegetables, meats and dairy. We will fit a regression models (analysis of covariance) for each time point (week 4 or week 8) with the baseline intake and treatment group as the covariate. We will also include their interaction. Using this model, we will be able to estimate the treatment-group difference accounting for the baseline measurement.

For pharmacologic therapy, a table of adverse events and adherence will be constructed with empiric and selective intervention arms forming columns for comparison. We report the following measures:

- Dropouts due to adverse events versus administrative reasons
- Participants taken off study medication
- Participants with reduced dosage and reason
- Type and severity of participant symptoms or complaints

- Abnormal laboratory measurements