Supplementary Online Content

Juthani-Mehta M, Van Ness PH, Bianco L, et al. Effect of cranberry capsules on bacteriuria plus pyuria among older women in nursing homes: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2016.16141

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Serious and Non-serious Adverse Events by Treatment Group (Per Event Analysis)

Adverse Event Type[a]	Related[a]	Anticipated[b]	Treatment N (Rate)[c]	Control N (Rate)	Total
Serious	**Unrelated**	**Anticipated**	50.0 (60.1)	66.0 (78.6)	116.0 (69.4)
		Unanticipated	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
	Related	**Anticipated**	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
		Unanticipated	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Subtotal Serious			*50.0 (60.1)*	*66.0 (78.6)*	*116.0 (69.4)*
Non-serious	**Unrelated**	**Anticipated**	1,731.0 (2,080.6)	1,966.0 (2,341.7)	3,697.0 (2,211.7)
		Unanticipated	3.0 (3.6)	0.0 (0.0)	3.0 (1.8)
	Related	**Anticipated**	7.0 (8.4)	7.0 (8.3)	14.0 (8.4)
		Unanticipated	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Subtotal Non-serious			*1,741.0 (2,092.7)*	*1,973.0 (2,350.0)*	*3,714.0 (2,221.9)*
Grand Total:			***1,791.0 (2,152.8)***	***2,039.0 (2,428.6)***	***3,830.0 (2,291.3)***

[a] Unrelated = unrelated or unlikely related to the study protocol; related = possible, probable, or definitely related to the study protocol.

[b] Anticipated = the adverse event was identified before study initiation as anticipated to occur over the course of the study period

[c] Adverse event rate per 100 person years of follow-up by treatment group, calculated as (number of events / total person years of follow-up for surveillance: 83.20 for Treatment and 83.96 for Control) x 100.

eTable 2. Subset of 127 participants without bacteriuria plus pyuria at baseline[a]

	Treatment	Control	Total urine specimens
Bacteriuria plus pyuria	39 (15.0%)	28 (11.4%)	67 (13.2%)
No bacteriuria plus pyuria	221 (85.0%)	218 (88.6%)	439 (86.8%)
Total urine specimens	260	246	506

Frequency of missing urine specimens: 256

[a] total anticipated urine specimens were 127*6=762; 506 specimens obtained; 256 missing

eAppendix. Supplemental Methods Appendix

All analyses were performed by intent-to-treat (i.e., participants were analyzed as randomized, regardless of adherence). A p-value of 0.05 (two-sided) was used for the level of statistical significance in confirmatory analyses. SAS® 9.4 statistical software (SAS/STAT Version 14.1) was used for analyses.

Sample Size

Sample size was determined to detect a difference between the proportion with bacteriuria plus pyuria over time in the treatment versus placebo group using the method of Diggle et al. for repeated binary outcomes. The following assumptions were made for this sample size calculation: Type 1 error of 5% (2-sided), 80% power, a serial correlation of 0.35 between six repeated participant outcomes, an overall bacteriuria plus pyuria rate of 0.45 in the control group, a 33% reduction in the rate in the treatment group (i.e., bacteriuria plus pyuria rate of 0.30), and 20% inflation for deaths, transfers and missing cultures. Based on these assumptions, the total sample size was 180 participants (90 per group).

Analysis of Baseline Characteristics

Baseline characteristics (Table 1) were summarized as counts and percentages for discrete data and as means, standard deviations, medians and interquartile ranges for continuous data. No tests of significance were conducted for differences in baseline characteristics between treatment groups. Instead, the following set of pre-specified baseline variables were used for covariate adjustment: bacteriuria, incontinence, age at enrollment, and number of comorbidities.

Unadjusted Analysis of the Primary Outcome

The unadjusted percentage of study participants with bacteriuria plus pyuria at baseline and at each follow-up time point by treatment group was calculated as the number of study participants having bacteriuria plus pyuria divided by the number participants assessed multiplied by 100 (Table 2). The overall percentages were determined as the total number of episodes of bacteriuria plus pyuria over the six follow-up time points divided by the total number of assessments multiplied by 100. 95% confidence intervals for baseline percentages were estimated by a generalized linear model using a logit link in which treatment group maximum likelihood confidence intervals were re-transformed to the original scale by an inverse link function and then multiplied by 100. The 95% confidence intervals for bi-monthly percentages were estimated by a GEE model using an independent correlation structure for repeated bacteriuria plus pyuria outcomes and covariates for treatment group, follow-up time, and their interaction. These confidence intervals were re-transformed to the original scale by an inverse link function and multiplied by 100. The GEE model without the interaction term was used to generate 95% confidence intervals for the overall percentage with bacteriuria and pyuria in each treatment group. The unadjusted analyses did not include imputation or weighting for missing values.

Handling of Missing Data

The quantity, pattern, nature, and mechanism of missing data were investigated. Of the 1110 (=185*6) primary outcome assessments scheduled to be collected across six follow-up time points, 723 (65%) were actually obtained, 353 in the treatment group and 370 in the control group. Thus, 35% of the scheduled outcome assessments were missed.

The pattern included approximately 5% intermittent missing values; the remainder was monotone missing values. Approximately 10% of study participants had no observed follow-up outcome observations. Missing values occurred because of death as well as other losses to follow-up. The missing data mechanism was modeled using an indicator variable for missing primary outcome values as the outcome of a logistic regression model; explanatory variables were then sought that were strongly associated with missingness. Of the variables examined, baseline incontinence and incontinence that developed during follow-up were strongly associated with missing values. Since incontinence during follow-up was not a variable present in the original trial data set, information about toileting from the Medicare Minimum Data Set was integrated into the trial data set. A lagged time-varying variable for incontinence best characterized the missing data mechanism.

Adjusted Analysis of the Primary Outcome

Adjusted analyses for the association of treatment status and bacteriuria plus pyuria were conducted for baseline, for individual follow-up times, and for the overall follow-up period, respectively (Figure 2). Baseline percentages and 95% confidence intervals for treatment groups were estimated by a generalized linear model adjusted for a pre-specified set of baseline covariates (incontinence, age at enrollment, and number of comorbidities) using a logit link. These estimates were re-transformed to the original scale by an inverse link function and then multiplied by 100.

The adjusted analysis of the primary outcome was conducted using a generalized estimating equations (GEE) model with inverse probability weighting (IPW) at the observation level for missing monotone values. We used the SAS PROC GEE procedure,

which permits explicit modeling of the missing data mechanism as the means for determining inverse probability weights. Missing intermittent values and two-month values for participants with no recorded outcomes were singly imputed using the fully conditional specification (FCR) method, a prerequisite for using the IPW GEE method. This regression modeling approach for handling missing values under the assumption of data missing at random (MAR) was chosen because it allowed for the explicit modeling of the missing data mechanism without the necessity of adding covariates to the regression model that were not pre-specified. Additional reasons included the generation of population-averaged model results that are generally regarded as more pertinent for clinical trials than individual-specific results and the avoidance of unreasonable assumptions regarding random effects that would be needed for a generalized linear mixed model (GLMM) with binary outcomes. The use of the GEE approach instead of the GLMM approach was anticipated in the final study protocol: "If required by considerations of poor model fit or convergence problems, we will explore other methods for handling MAR data."

Pre-specified baseline variables for bacteriuria, incontinence, age at enrollment, and number of comorbidities were included in the model as adjustment covariates. A covariate for follow-up time was also added and assessed both for its linear association with the outcome and for its interaction with treatment. Because there was no clear linear association between follow-up time and outcome, follow-up time was treated as a categorical variable in the modeling. Because of the large number of nursing homes, many of which had sparse data, it was not feasible to adjust for nursing home as a fixed effect in the GEE modeling because of convergence issues.

An unstructured correlation matrix was used to model the serial correlation of repeated participant outcomes to avoid forcing unjustified structure on the correlation matrix. Adjusted percentages and 95% confidence intervals for each treatment group generated from the GEE model were re-transformed to the original scale using an inverse link function and then multiplied by 100. The same GEE model without the treatment by time interaction term was used to generate overall percentages and 95% confidence intervals.

Exploratory analyses were conducted to investigate the addition of higher-order terms to the regression model and the impact of alternative correlation structures and weighting schemes. Residual analysis was used to assess model fit. However, model fit assessment is somewhat limited by the use of inverse probability weights. Thus, we also examined plots of the distributions of different schemes of inverse probability weights; observation weighting, as contrasted with study participant weighting, provided less extreme differences in weight values.

Other approaches for assessing the impact of missing data were considered but were not performed because they were judged unlikely to yield meaningful changes in statistical inference regarding the trial's primary hypothesis. Specifically, joint modeling of survival and the study's longitudinal outcome was not undertaken nor were extensive sensitivity analyses regarding the occurrence of data missing not at random (MNAR) using pattern mixture modeling.

Analysis of Secondary Outcomes

The secondary outcomes were analyzed as rates or counts of the outcomes per person years of follow-up (PYF) for each treatment group (Table 3). Counts for mortality

represent individual events; counts for hospitalization and MDR GNB represent the number of episodes such that individual study participants may have had more than one episode; and counts for antibiotics for suspected UTI and total antimicrobials represent counts of days of usage. Estimates of rates (number of episodes per PYF) and rate ratios (treatment vs. control) and corresponding 95% confidence intervals were generated by generalized linear regression models with Poisson distributions, treatment status as explanatory variables, and natural logarithms of the time at risk (PYF) as offsets. These estimates were exponentiated to return them to the original measurement scale. These model-based rates and rate ratios were virtually identical to those obtained by calculating crude rates as number of events per PYF. Standard errors were adjusted to account for overdispersion. Rates for mortality, hospitalizations and MDR GNB were expressed as events per 100 PYF; rates for antibiotics for suspected UTI and total antimicrobials were expressed as usage days per PYF. Adjustment for pre-specified covariates was attempted, but because of lack of model fit the results were statistically questionable and, therefore, only the unadjusted results were reported. In addition, mortality was also analyzed by a Cox model that yielded a hazard ratio and p-value that were virtually identical to the rate ratio results from the generalized linear model. Per protocol, the four other secondary outcomes were also analyzed using a Wilcoxon rank sum statistic and none was statistically significant.