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Effect of Cranberry Capsules on Bacteriuria Plus Pyuria Among Older Women in Nursing Homes
A Randomized Clinical Trial

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Editorial

Supplemental content

IMPORTANCE Bacteriuria plus pyuria is highly prevalent among older women living in nursing homes. Cranberry capsules are an understudied, nonantimicrobial prevention strategy used in this population.

OBJECTIVE To test the effect of 2 oral cranberry capsules once a day on presence of bacteriuria plus pyuria among women residing in nursing homes.

DESIGN, SETTING, AND PARTICIPANTS Double-blind, randomized, placebo-controlled efficacy trial with stratification by nursing home and involving 185 English-speaking women aged 65 years or older, with or without bacteriuria plus pyuria at baseline, residing in 21 nursing homes located within 50 miles (80 km) of New Haven, Connecticut (August 24, 2012-October 26, 2015).

INTERVENTIONS Two oral cranberry capsules, each capsule containing 36 mg of the active ingredient proanthocyanidin (ie, 72 mg total, equivalent to 20 ounces of cranberry juice) vs placebo administered once a day in 92 treatment and 93 control group participants.

MAIN OUTCOMES AND MEASURES Presence of bacteriuria (ie, at least 10^5 colony-forming units [CFUs] per milliliter of 1 or 2 microorganisms in urine culture) plus pyuria (ie, any number of white blood cells on urinalysis) assessed every 2 months over the 1-year study surveillance; any positive finding was considered to meet the primary outcome. Secondary outcomes were symptomatic urinary tract infection (UTI), all-cause death, all-cause hospitalization, all multidrug antibiotic–resistant organisms, antibiotics administered for suspected UTI, and total antimicrobial administration.

RESULTS Of the 185 randomized study participants (mean age, 86.4 years [SD, 8.2], 90.3% white, 31.4% with bacteriuria plus pyuria at baseline), 147 completed the study. Overall adherence was 80.1%. Unadjusted results showed the presence of bacteriuria plus pyuria in 25.5% (95% CI, 18.6%-33.9%) of the treatment group and in 29.5% (95% CI, 22.2%-37.9%) of the control group. The adjusted generalized estimating equations model that accounted for missing data and covariates showed no significant difference in the presence of bacteriuria plus pyuria between the treatment group vs the control group (29.1% vs 29.0%; OR, 1.01; 95% CI, 0.61-1.66; $P = .98$). There were no significant differences in number of symptomatic UTIs (10 episodes in the treatment group vs 12 in the control group), rates of death (17 vs 16 deaths; 20.4 vs 19.1 deaths/100 person-years; rate ratio [RR], 1.07; 95% CI, 0.54-2.12), hospitalization (33 vs 50 admissions; 39.7 vs 59.6 hospitalizations/100 person-years; RR, 0.67; 95% CI, 0.32-1.40), bacteriuria associated with multidrug-resistant gram-negative bacilli (9 vs 24 episodes; 10.8 vs 28.6 episodes/100 person-years; RR, 0.38; 95% CI, 0.10-1.46), antibiotics administered for suspected UTIs (692 vs 909 antibiotic days; 8.3 vs 10.8 antibiotic days/person-year; RR, 0.77; 95% CI, 0.44-1.33), or total antimicrobial utilization (1415 vs 1883 antimicrobial days; 17.0 vs 22.4 antimicrobial days/person-year; RR, 0.76; 95% CI, 0.46-1.25).

CONCLUSIONS AND RELEVANCE Among older women residing in nursing homes, administration of cranberry capsules vs placebo resulted in no significant difference in presence of bacteriuria plus pyuria over 1 year.

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Urinary tract infection (UTI) is the most commonly diagnosed infection among nursing home residents. Distinguishing symptomatic UTI from asymptomatic bacteriuria is problematic among nursing home residents because of challenges with symptom assessment.[1] Bacteriuria is prevalent in 25% to 50% of women living in nursing homes, and pyuria is present in 90% of those with bacteriuria.[2] A randomized trial of antibiotic treatment vs no treatment of bacteriuria in nursing home women showed no decrease in genitourinary morbidity or mortality with treatment.[3] This study along with others[4] led to the recommendation that bacteriuria should not be treated with antibiotics in older institutionalized adults.[3] Bacteriuria plus pyuria is a necessary but not sufficient condition to make the diagnosis of UTI in this population.[5,6]

Cranberry products represent a potential nonantimicrobial method for UTI prevention. Cranberry proanthocyanidins have been shown to inhibit adherence of P-fimbriated *Escherichia coli* to uroepithelial cells,[7] and this effect on virulence is dose dependent.[8] Because *E coli* represents the majority of urinary isolates among nursing home residents, cranberry products remain an appealing UTI prevention strategy, but evidence is conflicting.[9,10] Most published reports have used cranberry juice and postulated reasons for lack of benefit have included insufficient participant adherence to cranberry juice consumption and insufficient proanthocyanidins in the tested cranberry product.[9] Among older women (ie, mean age, 78.5 years), 300 mL (ie, approximately 10 ounces) of cranberry juice cocktail containing 36 mg of proanthocyanidins reduced bacteriuria plus pyuria over 6 months.[11] However, the acrid flavor of cranberry juice is difficult to tolerate in large volumes,[12] especially for nursing home residents because of swallowing disorders, exacerbation of incontinence, and impaired thirst.[13]

Prior studies showed that cranberry capsule administration and urine collection is feasible, and 2 cranberry capsules (each containing 36 mg proanthocyanidins [total 72 mg proanthocyanidins], equivalent to 20 ounces of cranberry juice) are an optimal dose to test among women living in nursing homes.[14,15] The primary aim of this trial was to test the effect of 2 oral cranberry capsules once a day, compared with placebo, on the presence of bacteriuria plus pyuria among older women nursing home residents.

Key Points

Question Do cranberry capsules with sufficient proanthocyanidin content affect the presence of bacteriuria plus pyuria in older women living in nursing homes?

Findings In this randomized clinical trial of 185 women nursing home residents, after adjusting for missing data and covariates, there was no statistically significant difference in presence of bacteriuria plus pyuria between the treatment (29.1%) and control (29.0%) groups over 1 year.

Meaning Among older women living in nursing homes, cranberry capsules, compared with placebo, did not have a significant effect on the presence of bacteriuria plus pyuria over 1 year.

Methods

Study Design and Oversight

This study was a double-blind, randomized, placebo-controlled efficacy trial comparing 2 cranberry capsules vs 2 placebo capsules once per day. The unit of randomization was each participant. Nursing homes targeted for participation had at least 90 beds, within a 50-mile (80 km) radius of New Haven, Connecticut, that had UTI rates and sociodemographic characteristics similar to national averages. The Yale Human Investigation Committee approved the study; all nursing home administrators signed letters of participation and signed consent was obtained from participants or their surrogates.

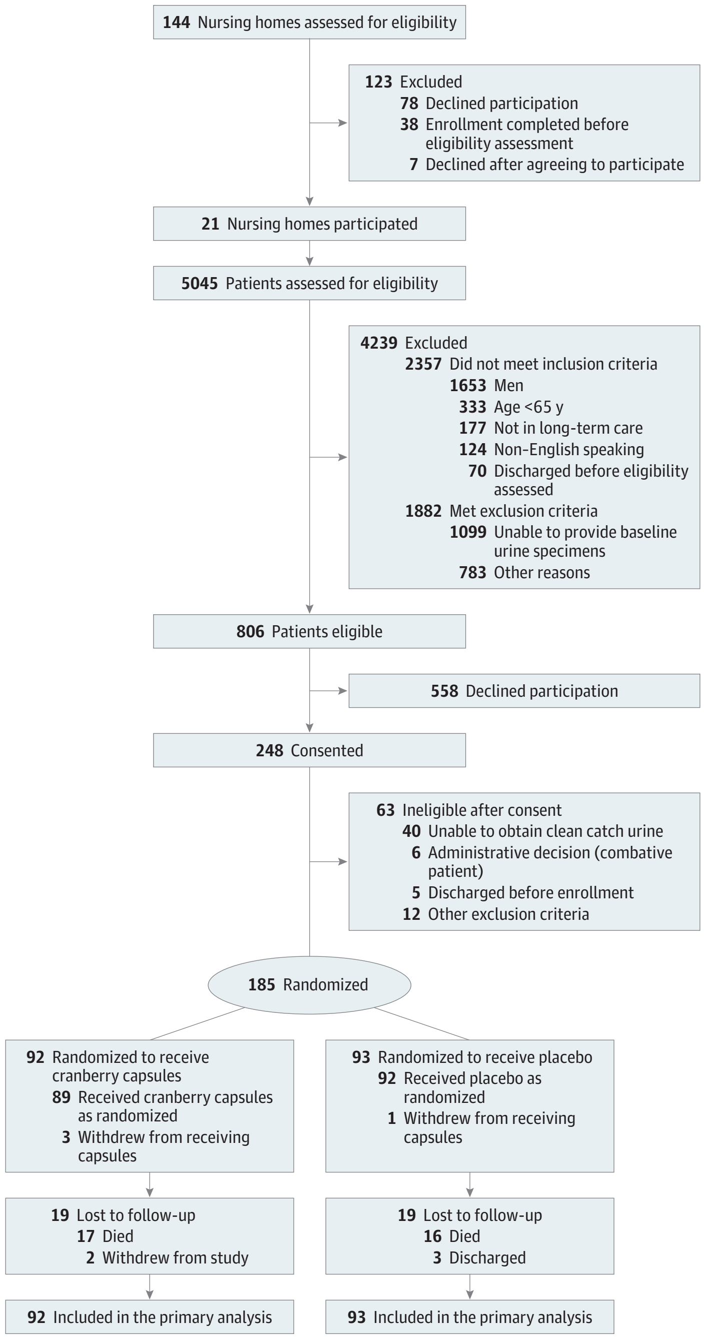
Participants

Nursing homes were approached sequentially, and all residents in participating facilities were screened. Once enrollment was initiated at one nursing home, screening began at the next home. A Health Insurance Portability and Accountability Act waiver (http://www.hhs.gov/hipaa/for-professionals/privacy) was obtained for recruitment purposes. Inclusion criteria were (1) female; (2) long-term care residents; (3) English speaking; and (4) 65 years or older. Only women were included in this study for the following reasons: (1) a prior study included women only[11]; (2) women are the majority of nursing home residents; (3) there is limited evidence that cranberry products reduce bacteriuria plus pyuria in men; (4) the predominant risk factor for UTI in men is underlying structural or functional abnormalities of the urinary tract; and (5) the prevalence of bacteriuria plus pyuria is lower in men.

Exclusion criteria were (1) not expected to be in the nursing home for at least 1 month (ie, short-term rehabilitation, pending discharge, terminal life expectancy <1 month); (2) taking chronic suppressive antibiotic or anti-infective (ie, mandelamine) therapy for recurrent UTI; (3) undergoing dialysis for end-stage renal disease; (4) unable to produce a baseline clean catch urine specimen; (5) receiving warfarin therapy, which could cause an interaction with cranberry juice[16]; (6) history of nephrolithiasis because cranberry products may increase the risk of nephrolithiasis[17]; (7) presence of an indwelling bladder catheter; (8) allergy to cranberry products; (9) treatment with cranberry products; and (10) nursing home residence for less than 4 weeks. Women with and without bacteriuria plus pyuria were eligible for the study.

Nursing home staff identified whether a resident was able to provide self-consent or required surrogate consent. Assent was attempted for residents with surrogate consent. After written consent, a baseline urine specimen was obtained to ensure that subsequent clean catch urine collection was possible. Subsequent waves of recruitment occurred in each nursing home every 3 months.

Figure 1. Flow Diagram of a Randomized Trial Comparing the Effect of Cranberry Capsules vs Placebo on Bacteriuria Plus Pyuria in Women Residents of Nursing Homes



Randomization and Intervention

Participants were randomly assigned to take 2 cranberry capsules (manufactured by Pharmatoka, each containing 36 mg of proanthocyanidins, confirmed by BL-DMAC)[18] or 2 placebo capsules, once a day, using a permuted block design with a variable block size (randomly set to 4 or 6) and equal allocation (**Figure 1**). Stratification by nursing home accounted for potentially different standards of care. The trial statistician designed the randomization scheme, the statistical programmer implemented it, and the Investigational Drug Services pharmacist made treatment assignments. Only the statistical programmer and pharmacist had access to the randomization codes during enrollment. Cranberry or placebo capsules were administered for 360 days (ie, 12 thirty-day blister packs per participant), and the total surveillance of each participant was 365 days.

Data and Outcomes

Research nurses recorded baseline descriptive characteristics from review of the medical chart including age, race, ethnicity, medications, comorbidities, and history of UTI. The primary nurse or certified nursing assistant (CNA) was asked questions adapted from the Minimum Data Set regarding cognitive status, behavior, activities of daily living, continence, and degree of mobility, similar to previously conducted studies.[15,19,20] At study initiation in each nursing home, the senior intervention nurse educator organized a series of "in-service" training sessions for nurses and CNAs regarding methods of urine specimen collection and capsule administration. Clean catch urine specimens were targeted for collection in containers with Boritex (boric acid preservative tablet keeping urine stable for up to 96 hours) by nursing home staff between 5 and 7 AM to optimize pharmacokinetic properties of proanthocyanidins[8] and feasibility of collection and then were refrigerated once obtained. If the specimen was not collected on the due date, attempts at specimen collection continued for 2 additional weeks at any time of the day before classifying the specimen as missing. All specimens were transported in a cooler to Yale New Haven Health on the day obtained for processing at a single central laboratory.

Surveillance for the primary outcome (ie, the presence of bacteriuria plus pyuria) occurred every 2 months after randomization for a total of 6 assessments over 12 months. Urine specimens were obtained by clean catch since catheterization of participants requiring surrogate consent was not authorized by the institutional review board (IRB). Presence of bacteriuria was defined as at least 10^5 colony-forming units (CFUs) per milliliter of 1 or 2 organisms. Absence of bacteriuria was defined as a urine culture with no growth, mixed flora (≥3 organisms), or less than the highest quantitation of bacteriuria reported by the laboratory. Pyuria was defined as any number of white blood cells on urinalysis as in a previous study.[11] Any positive specimen during the surveillance period was considered a positive primary outcome. Two members of the outcome adjudication committee, blinded to treatment assignment, reviewed the primary outcomes. Urinary tract–specific symptoms were assessed at each bimonthly assessment.

Secondary outcomes included symptomatic UTI, all-cause death, all-cause hospitalization, all multidrug antibiotic-resistant organisms, antibiotics for suspected UTI, and total antimicrobial prescriptions. Symptomatic UTI, adapted from National Healthcare Safety Network criteria, was defined as

1. (a) acute dysuria or (b) fever or leukocytosis and at least 1 of the following symptoms: acute costovertebral angle pain or tenderness; suprapubic pain; gross hematuria, new or marked increase in incontinence, urgency, or frequency or (c) 2 or more of new or marked increase in incontinence, urgency, frequency, suprapubic pain, new gross hematuria; and

2. (a) a voided urine culture with 10^5 CFUs/mL or more of a single predominant organism or 2 gram-negative organisms or (b) a specimen collected by in and out catheter with 10^2 CFUs/mL or more of any number of organisms (criteria 1 and 2 must be met).[21] All antimicrobials administered during the trial were recorded via chart review. Multidrug-resistant organisms were defined as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and multidrug-resistant gram-negative bacilli (ie, defined as resistance to ≥3 of the following antibiotics: ampicillin-sulbactam, cefazolin, ceftriaxone, ceftazidime, fluoroquinolones, piperacillin-tazobactam, meropenem, imipenem, and trimethoprim-sulfamethoxazole).[22]

Adherence was determined by the number of capsules administered to each participant relative to the prescribed number. Thirty-day blister packs were delivered each month; adherence was determined from the number of capsules remaining from the previous 30-day supply. Reasons for lack of adherence were obtained from review of the medication administration record. High adherence was defined as administration of 80% or more of prescribed capsules. All adverse events were recorded based on chart review and discussion with nursing staff on a monthly basis. A safety report was generated every 6 months and reviewed by an independent safety monitor.

Statistical Analyses

All analyses were performed by intention to treat (ie, participants were analyzed as randomized, regardless of adherence). A 2-sided *P* value of .05 was used for the level of statistical significance. SAS 9.4 statistical software[23] was used for analyses. Sample size was determined to detect a difference between the proportion with bacteriuria plus pyuria over time in the treatment vs placebo group using the method of Diggle et al[24] for repeated binary outcomes. The following assumptions were made for this sample size calculation: type I error of 5% (2-sided), 80% power, a serial correlation of 0.35 between 6 repeated participant outcomes, an overall bacteriuria plus pyuria rate of 0.45 in the control group,[15] a 33% lower rate of bacteriuria plus pyuria in the treatment group (ie, bacteriuria plus pyuria rate of 0.30),[11] and 20% inflation for deaths, transfers, and missing cultures. Based on these assumptions, the total sample size was 180 participants (90 per group).

The adjusted analysis of the primary outcome was conducted using generalized estimating equations (GEE) with inverse probability weighting at the observation level for missing monotone values. The SAS PROC GEE procedure, which permits explicit modeling of the missing data mechanism as the means for determining inverse probability weights, was used instead of the initially planned generalized linear mixed model. Missing intermittent values and 2-month values for participants with no recorded outcomes were singly imputed using the fully conditional specification method, a prerequisite for using the inverse probability weighting GEE method.[25] This regression-modeling approach for handling missing values under the assumption of data missing at random was chosen because of the unexpected amount and mechanism of the missing data because it allowed for the explicit modeling of the missing data mechanism without adding covariates to the regression

Table 1. Baseline Characteristics, Overall and by Treatment Status[a]

Characteristics	Total No. of Participants (N = 185)	Treatment Group (n = 92)	Control Group (n = 93)
Demographics			
Age, mean (SD), y	86.4 (8.2)	87.1 (8.4)	85.6 (8.0)
Hispanic ethnicity	6 (3.2)	3 (3.3)	3 (3.2)
White race	167 (90.3)	83 (90.2)	84 (90.3)
Coexisting conditions			
Hypertension	152 (82.2)	74 (80.4)	78 (83.9)
Dementia	145 (78.4)	70 (76.1)	75 (80.6)
Psychiatric disorder	125 (67.6)	57 (62.0)	68 (73.1)
Connective tissue disease	112 (60.5)	56 (60.9)	56 (60.2)
Other endocrine disorder	87 (47.0)	42 (45.7)	45 (48.4)
Coronary artery disease	60 (32.4)	30 (32.6)	30 (32.3)
Congestive heart failure	57 (30.8)	30 (32.6)	27 (29.0)
Diabetes	51 (27.6)	25 (27.2)	26 (28.0)
COPD	41 (22.2)	18 (19.6)	23 (24.7)
Kidney disease	40 (21.6)	17 (18.5)	23 (24.7)
Arrhythmia	38 (20.5)	12 (13.0)	26 (28.0)
Cancer	35 (18.9)	16 (17.4)	19 (20.4)
Peripheral vascular disease	33 (17.8)	15 (16.3)	18 (19.4)
Stroke	26 (14.1)	14 (15.2)	12 (12.9)
Peptic ulcer disease	23 (12.4)	13 (14.1)	10 (10.8)
Hemiplegia	9 (4.9)	1 (1.1)	8 (8.6)
Liver disease	4 (2.2)	2 (2.2)	2 (2.2)
Coexisting conditions, median (IQR)[b]	5 (4-7)	5 (4-7)	6 (5-7)
Incontinence status			
Bladder	126 (68.1)	57 (62.0)	69 (74.2)
Bowel	82 (44.3)	38 (41.3)	44 (47.3)
Bacteriuria plus pyuria	58 (31.4)[c]	26 (28.3)[c]	32 (34.4)
History of infection			
Episodes of UTI in the past year			
0	128 (69.2)	68 (73.9)	60 (64.5)
1	40 (21.6)	19 (20.7)	21 (22.6)
2	12 (6.5)	4 (4.3)	8 (8.6)
≥3	5 (2.7)	1 (1.1)	4 (4.3)
Courses of antibiotics in the past year			
0	78 (42.2)	43 (46.7)	35 (37.6)
1	53 (28.6)	25 (27.2)	28 (30.1)
2	26 (14.1)	13 (14.1)	13 (14.0)
≥3	28 (15.1)	11 (12.0)	17 (18.3)
Functional and behavioral status			
No. of ADL disabilities in the past 7 days[d]			
0	126 (68.1)	65 (70.7)	61 (65.6)
1-4	48 (25.9)	21 (22.8)	27 (29.0)
5-8	11 (6.0)	6 (6.5)	5 (5.4)
Resists care	16 (8.6)	9 (9.8)	7 (7.5)
No. of prescribed medications, median (IQR)	10 (7-13)	10 (7-13)	10 (8-13)
Cognitive and mental status			
Nonalert	7 (3.8)	4 (4.3)	3 (3.2)
Delirium			
Periods of altered perception[e]	35 (18.9)	18 (19.6)	17 (18.3)
Periods of lethargy[f]	14 (7.6)	5 (5.4)	9 (9.7)
Episodes of disorganized speech[g]	11 (5.9)	8 (8.7)	3 (3.2)

Abbreviations: ADL, activities of daily living; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; UTI, urinary tract infection.

[a] Data are presented as number (%) unless otherwise indicated.

[b] The coexisting conditions variable was defined as the number of coexisting conditions among the 17 listed in this table.

[c] There was 1 participant with bacteriuria alone at baseline (no pyuria). This 1 additional participant with bacteriuria was in the treatment group (ie, 27 participants total).

[d] The ADL disabilities variable was defined as total dependence in the number of 8 ADLs (ie, bed mobility, transfer, dressing, eating, toilet use, personal hygiene, bathing, and walking in room).

[e] The study participant moves lips or talks to someone not present, believes he/she is somewhere else, or confuses day and night.

[f] The study participant shows sluggishness, staring into space, difficulty to arouse, or little body movement.

[g] The study participant's speech is incoherent, nonsensical, irrelevant, or rambling, or he/she loses a train of thought.

Table 2. Bimonthly and Overall Observed Counts and Percentages of Bacteriuria Plus Pyuria Specimens by Treatment Status (n = 185)

	Treatment Group		Control Group	
Time Point	Count/Total	% (95% CI)[a,b]	Count/Total	% (95% CI)[a,b]
Baseline	26/92	28.3 (20.0-38.3)	32/93	34.4 (25.5-44.6)
2 mo	21/76	27.6 (18.8-38.7)	27/78	34.6 (24.9-45.8)
4 mo	15/63	23.8 (14.9-35.8)	26/65	40.0 (28.9-52.3)
6 mo	13/64	20.3 (12.2-31.9)	20/67	29.9 (20.1-41.8)
8 mo	14/55	25.5 (15.7-38.5)	14/60	23.3 (14.3-35.6)
10 mo	15/51	29.4 (18.6-43.2)	13/54	24.1 (14.5-37.2)
12 mo	12/44	27.3 (16.2-42.1)	9/46	19.6 (10.5-33.5)
Overall	90/353	25.5 (18.6-33.9)[c]	109/370	29.5 (22.2-37.9)[c]

[a] The percentages represent the number of study participants at each time point (baseline or follow-up time) having a specimen with bacteriuria plus pyuria divided by the number of study participants enrolled and followed up at the specified time point multiplied by 100.

[b] The CIs for binomial proportions were estimated using the logit method. For further details, consult the eAppendix in Supplement 2.

[c] The percentage represents the sum of the number of specimens with bacteriuria plus pyuria occurring during the 6 follow-up periods (months 2-12) divided by the sum of the number of study participant assessments during the 6 follow-up time points (ie, the sum of the total counts) multiplied by 100. A total of 1110 (= 185 × 6) observations were scheduled to be collected across 6 follow-up time points, of which 723 were actually obtained, 353 in the treatment group and 370 in the control group.

model that were not prespecified and because it avoided making unreasonable assumptions regarding random effects needed for a generalized linear mixed model with binary outcomes. Prespecified baseline variables for bacteriuria, incontinence, age at enrollment, and number of comorbidities were included in the model as covariates. A covariate for surveillance time was also added and assessed both for its linear association with the outcome and for its interaction with treatment. An unstructured correlation matrix was used to model the serial correlation of repeated participant outcomes.

The adjusted percentage with bacteriuria plus pyuria for each treatment group at each surveillance time point was estimated by transforming the GEE model estimates using an inverse logit link function. The secondary outcomes were analyzed by a generalized linear regression model with a Poisson distribution, a treatment status explanatory variable, a natural logarithm of the time at risk as an offset, and adjustments for overdispersion (see Protocol in Supplement 1 and the eAppendix in Supplement 2 for additional details of all methods). Because the primary proposed mechanism of action of cranberry products is targeted toward *E coli*, exploratory analyses examined the percentage of *E coli* urinary isolates vs others that met the criteria for bacteriuria in bimonthly urine specimens. Additionally, exploratory analyses of participants without bacteriuria plus pyuria at baseline were conducted. No tests of significance were conducted for exploratory analyses.

Results

Figure 1 shows the flow of nursing homes and study participants. From August 24, 2012, through October 7, 2014, 5045 nursing home residents in 21 nursing homes were screened for participation, 806 (16.0%) of whom were eligible, 248 (30.8%) of those consented, and 185 (74.6%) of those who consented were able to provide a baseline clean catch urine specimen and be randomized. Surrogate consent had to be obtained for 93.5% of participants. Surveillance for all outcome and safety data ended on October 26, 2015. **Table 1** displays the baseline demographic characteristics of participants. The mean age of participants was 86.4 years (SD, 8.2). The treatment and control groups were generally comparable. Rates of incontinence, bacteriuria, and number of episodes of UTI in the past year were similar; however, the control group had more coexisting conditions, specifically arrhythmia and hemiplegia.

One hundred forty-seven participants completed 1 year of surveillance, and 33 participants died. Twenty participants, 9 in the treatment group and 11 in the control group, became incontinent prior to the first outcome assessment and were unable to provide any of the scheduled urine specimens. Over the course of the study, 45 participants stopped taking the capsules, 24 in the treatment and 21 in the control groups; 21 refused, 19 transitioned to hospice care, 4 started taking warfarin, and 1 refused via family.

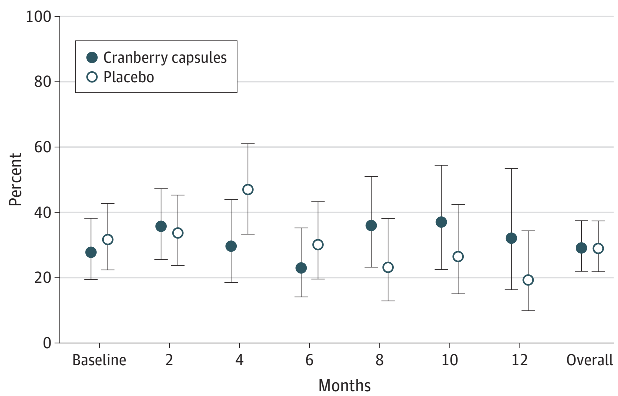
Overall adherence to capsule administration was 80.1%, 77.5% in the treatment group and 82.6% in the control group. Adherence was 83.7% (n = 185) in the first 6 months and 76.7% (n = 168) in the second 6 months.

Table 2 depicts the percentage of urine specimens that met the primary outcome of bacteriuria plus pyuria over 12 months of surveillance. The overall unadjusted results showed rates of 25.5% (95% CI, 18.6%-33.9%) in the treatment group vs 29.5% (95% CI, 22.2%-37.9%) in the control group. The adjusted analysis, accounting for missing data and prespecified covariates, showed no significant difference between groups (29.1% vs 29.0%; OR, 1.01; 95% CI, 0.61-1.66; P = .98; **Figure 2**). Of the 723 urinary specimens obtained, 9 participants (7 with 1 symptom [3 in treatment group, 4 in control group] and 2 with 2 symptoms [1 in each group]) had urinary tract-specific symptoms at a bimonthly assessment.

Of 350 episodes of clinically suspected UTI in 131 participants, there were 10 symptomatic UTIs in the treatment group (8 participants with 1 episode and 1 participant with 2 episodes) and 12 symptomatic UTIs in the control group (7 participants with 1 episode, 1 participant with 2 episodes, and 1 participant with 3 episodes). Although blood cultures were requested for 35 episodes of clinically suspected UTI, there was only 1 episode of septicemia, which occurred in the control group. **Table 3** shows that there were no significant differences in rates of death, hospitalization, multidrug-resistant gram-negative bacilli bacteriuria (from scheduled and suspected UTI urine cultures), antibiotics administered for suspected UTI, or total antimicrobial utilization. There was one MRSA urinary isolate identified in the treatment group and no VRE urinary isolates identified. There were a total of 3830 adverse events (eTable 1 in Supplement 2), 116 serious (83 hospitalizations and 33 deaths, all protocol-unrelated and anticipated) and 3714 nonserious (14 protocol-related and anticipated). The frequency of the 14 protocol-related and anticipated nonserious adverse events (ie, altered mental status, gastrointestinal disturbance, oral cavity disturbance, skin and soft tissue event, weight loss) was similar in both treatment groups.

Exploratory analyses of the percentage of *E coli* isolates showed that in the treatment group, the percentage of *E coli* at study start was 19.6%, at month 2 was 25%; month 4, 20.6%; month 6, 15.6%; month 8, 20.0%; month 10, 17.7%; and month 12, 22.7%. In the control group, the percentage of *E coli* at study start was 21.5%, at month 2 was 23.1%; month 4, 24.6%; month 6, 22.4%; month 8, 18.3%; month 10, 18.5%; and month 12, 17.4%. Exploratory analyses in the subset of 127 women (n = 66 in the treatment group, n = 61 in the control group) who did not have bacteriuria plus pyuria at baseline showed that the overall rate of bacteriuria plus pyuria over 1 year was 15% (n = 39) in the treatment group and 11.4% (n = 28) in the control group (eTable 2 in Supplement 2).

Figure 2. Bimonthly and Overall Adjusted Percentages of Bacteriuria Plus Pyuria Specimens by Treatment Status (N = 185)



Percentage with bacteriuria plus pyuria and corresponding 95% confidence intervals (error bars) were adjusted for the following prespecified baseline variables: bacteriuria, incontinence, age at enrollment, and number of comorbidities (eAppendix in Supplement 2 for additional details). The baseline and bimonthly data represent study participants with bacteriuria plus pyuria while the overall data represent all specimens of bacteriuria plus pyuria over the 6 follow-up time points (months 2-12). See the total number of participants contributing data at each time point in Table 2.

Discussion

Despite prior studies demonstrating that cranberry juice reduced bacteriuria plus pyuria in older women and that 2 cranberry capsules with 72 mg of proanthocyanidins (equivalent to 20 ounces of cranberry juice) was an appropriate dose to test,[11,15,26] the findings from this trial demonstrated no significant difference in presence of bacteriuria plus pyuria among women who received cranberry capsules vs placebo over 1 year. The lack of statistically significant differences in any of the secondary outcomes is consistent with this finding. Many studies of cranberry products have been conducted over several decades with conflicting evidence of its utility for UTI prevention. The results have led to the recommendation that cranberry products do not prevent UTI overall but may be effective in older women.[9,27] This trial did not show a benefit of cranberry capsules in terms of a lower presence of bacteriuria plus pyuria among older women living in nursing homes.

Some studies evaluated cranberry products solely among older adults. In a recent Cochrane review,[9] 2 reports showed a reduction in bacteriuria plus pyuria,[11,26] whereas 2 others did not show a clinical benefit of cranberry products.[14,16] In 1 study of older women in nursing homes and assisted living facilities, 300 mL of cranberry juice cocktail containing 36 mg of proanthocyanidins showed a benefit, but the placebo group had a higher rate of prior history of UTI and likely higher risk of bacteriuria plus pyuria.[28] A more recent study of 1 cranberry capsule twice a day (18 mg proanthocyanidins total) in long-term care facility residents with high risk of UTI (ie, need for long-term catheterization, diabetes mellitus, or at least 1 UTI in the preceding year) showed that participants receiving cranberry capsules had a lower incidence of clinically defined UTI (ie, one of the following: specific and nonspecific micturition-related symptoms and signs; a positive nitrite, leukocyte esterase, dipslide, or culture; antibiotic treatment for UTI; or UTI reported in the medical record). The UTI definition used was very broad, and there was no difference between the treatment and control groups using a strict UTI definition or for either definition in the low risk UTI group. Hence, cranberry capsules have not shown meaningful clinical benefit and have not been cost-effective.[29,30]

There are several potential explanations for why cranberry capsules, compared with placebo, did not result in a difference in the presence of bacteriuria plus pyuria in this trial. First, there appeared to be an initial effect on bacteriuria plus pyuria in the first 6 months, but these rates returned to baseline in the second 6 months of study. Slightly lower adherence in the second 6 months could have contributed to this finding. Additionally, it is possible that because of worsening incontinence and changes to the vaginal microbiome with age, the effects of cranberry capsules were not sustained. Although the exploratory analysis of those without bacteriuria plus pyuria at baseline is limited because the benefit of randomization is lost, it did not support the premise

Table 3. Unadjusted Rates and Rate Ratios for Secondary Outcomes[a]

	Mortality[b]		Hospitalization[b]		MDR GNB Bacteriuria[b,c]		Antibiotics for Suspected UTI[d]		Total Antimicrobials[d]	
	Treatment Group	Control Group	Treatment Group	Control Group	Treatment Group	Control Group	Treatment Group	Control Group	Treatment Group	Control Group
Count	17	16	33	50	9	24	692	909	1415	1883
Person-years	83.2	84.0	83.2	84.0	83.2	84.0	83.2	84.0	83.2	84.0
Rate (95% CI) per 100 person-years	20.4 (12.7-32.9)	19.1 (11.7-31.1)	39.7 (22.3-70.4)	59.6 (37.4-95.0)	10.8 (3.4-34.2)	28.6 (14.1-57.8)	8.3 (5.5-12.6)	10.8 (7.6-15.5)	17.0 (11.7-24.8)	22.4 (16.2-31.1)
Rate ratio (95% CI)	1.07 (0.54-2.12)		0.67 (0.32-1.40)		0.38 (0.10-1.46)		0.77 (0.44-1.33)		0.76 (0.46-1.25)	
P value	.84		.28		.16		.34		.28	

Abbreviations: MDR GNB, multidrug-resistant gram-negative bacilli; UTI, urinary tract infection.

[a] Estimates and CIs are from generalized linear regression models with Poisson distributions, offsets for the natural logarithm for the time at risk, and adjustments for overdispersion. Mortality counts are for individuals; counts for other outcomes are for episodes (ie, counts of the number of hospitalizations, isolates of MDR GNB bacteriuria, uses of antibiotics for suspected UTI, and uses of total antimicrobials).

[b] Rates and CIs are in counts per 100 person-years.

[c] Multidrug-resistant gram-negative bacilli are defined as urinary isolates (*Escherichia coli*, *Klebsiella*, *Proteus*, *Providencia*, *Pseudomonas*, *Citrobacter*, or *Enterobacter* species) having resistance to 3 or more of the following antibiotics: ampicillin-sulbactam, cefazolin, ceftriaxone, ceftazidime, fluoroquinolones, piperacillin-tazobactam, meropenem, imipenem, or trimethoprim-sulfamethoxazole.

[d] Rates and CIs are in antimicrobial days per person-year. Multiple antimicrobials on a given day are counted as 1 antimicrobial day. Antimicrobial classes include cephalosporins, fluoroquinolones, penicillins, oseltamivir, sulfonamides, macrolides, nitrofurantoin, vancomycin, aminoglycosides, carbapenems, metronidazole, tetracycline, fluconazole, mycostatin, daptomycin, and antivirals: acyclovir and valacyclovir.

that cranberry capsules prevented bacteriuria plus pyuria over the surveillance period. Second, cranberry capsules do not provide the hydration of cranberry juice. A recent study among women undergoing elective gynecological surgery with urinary catheter removal showed that 2 cranberry capsules twice a day (equivalent to 16 ounces of cranberry juice) over 6 weeks were able to reduce the rate of UTI by half.[31] However, all participants were instructed to drink 8 ounces of water twice a day with each capsule administration, so it is possible that the fluid load was necessary along with cranberry product. Hydration may also be a necessary component to reduce bacteriuria and urinary symptoms in older women.[5] Third, although adherence was high as measured by capsules removed from the blister pack, participants might not have actually ingested the capsules.

This trial had several strengths. Nursing home residents exclusively were enrolled, the dose of proanthocyanidins was standardized, adherence to capsule administration by the planned assessment method was high, and nursing home staff were trained to optimize outcome assessments. However, this trial also had limitations. First, since participants could not be catheterized to obtain bimonthly urine specimens, only residents capable of providing a clean catch urine specimen were randomized. Exclusion of residents for complete incontinence limited the generalizability of these findings. For randomized participants, 20 became incontinent prior to the first outcome assessment and were unable to provide any urine specimens. Others became incontinent or were transitioned to hospice care, so urine specimens were not obtained. Nevertheless, 65% of planned urine specimens were collected. Second, 78 nursing homes either did not respond or declined to participate and 7 agreed to participate but subsequently declined. Third, antiadhesion of *E coli* to uroepithelial cells in the urine specimens of participants in the trial was not tested. Adhesion studies to date have been conducted on patients enrolled for relatively short observation periods.[7,8] Since there were multiple assessment time points and it was not possible to ensure adherence to capsule ingestion on the day prior to obtaining a urine specimen for adhesion testing, the antiadhesion testing was not feasible. Fourth, the baseline rate of bacteriuria plus pyuria and percentage of *E coli* bacteriuria in this trial population was lower than in the pilot dosing study.[15] Fifth, this study enrolled women with or without bacteriuria plus pyuria at baseline. Therefore, it was not possible to definitively determine the specific role of cranberry capsules for prevention of new occurrence of bacteriuria plus pyuria among women without bacteriuria plus pyuria at baseline nor for reduction of bacteriuria plus pyuria among women with prevalent bacteriuria plus pyuria at baseline.

Conclusions

Among older women residing in nursing homes, administration of cranberry capsules compared with placebo resulted in no significant difference in presence of bacteriuria plus pyuria over 1 year.

ARTICLE INFORMATION

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