Cranberries vs Antibiotics to Prevent Urinary Tract Infections

A Randomized Double-blind Noninferiority Trial in Premenopausal Women

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Background: The increasing prevalence of uropathogens resistant to antimicrobial agents has stimulated interest in cranberries to prevent recurrent urinary tract infections (UTIs).

Methods: In a double-blind, double-dummy noninferiority trial, 221 premenopausal women with recurrent UTIs were randomized to 12-month prophylaxis use of trimethoprim-sulfamethoxazole (TMP-SMX), 480 mg once daily, or cranberry capsules, 500 mg twice daily. Primary end points were the mean number of symptomatic UTIs over 12 months, the proportion of patients with at least 1 symptomatic UTI, the median time to first UTI, and development of antibiotic resistance in indigenous *Escherichia coli*.

Results: After 12 months, the mean number of patients with at least 1 symptomatic UTI was higher in the cranberry than in the TMP-SMX group (4.0 vs 1.8; $P = .02$), and the proportion of patients with at least 1 symptomatic UTI was higher in the cranberry than in the TMP-SMX group (78.2% vs 71.1%). Median time to the first symptomatic UTI was 4 months for the cranberry and 8 months for the TMP-SMX group. After 1 month, in the cranberry group, 23.7% of fecal and 28.1% of asymptomatic bacteriuria *E coli* isolates were TMP-SMX resistant, whereas in the TMP-SMX group, 86.3% of fecal and 90.5% of asymptomatic bacteriuria *E coli* isolates were TMP-SMX resistant. Similarly, we found increased resistance rates for trimethoprim, amoxicillin, and ciprofloxacin in these *E coli* isolates after 1 month in the TMP-SMX group. After discontinuation of TMP-SMX, resistance reached baseline levels after 3 months. Antibiotic resistance did not increase in the cranberry group. Cranberries and TMP-SMX were equally well tolerated.

Conclusion: In premenopausal women, TMP-SMX, 480 mg once daily, is more effective than cranberry capsules, 500 mg twice daily, to prevent recurrent UTIs, at the expense of emerging antibiotic resistance.

Trial Registration: *isrctn.org* Identifier: ISRCTN50717094

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URINARY TRACT INFECTIONS (UTIs) are very common, especially in women. Almost half of all women report at least 1 UTI sometime during their lifetime, and after an initial UTI, 20% to 30% of women experience a recurrence with additional concomitant short-term morbidity.[1] For premenopausal women with more than 2 UTIs per year, low-dose antibiotic prophylaxis is commonly recommended.[2] However, this may lead to drug resistance not only of the causative microorganisms but also of the indigenous flora.[3] The increasing prevalence of isolates of *Escherichia coli* (the most prevalent uropathogen) that are resistant to antimicrobial agents has stimulated interest in novel nonantibiotic methods for the prevention of UTIs.[4]

See Invited Commentary at end of article

Cranberries have been used in the prevention of UTIs for many years. The mechanism of action has not been completely elucidated, but cranberries contain fructose and type A proanthocyanidins (PACs), which in urine can inhibit the adherence of type 1 and P fimbriae of *E coli* to the uroepithelial cell receptors.[5-7] A meta-analysis of the results of 2 well-conducted randomized controlled trials showed that, in women with recurrent UTIs (rUTIs), cranberry products reduced the incidence of recurrences at 12 months by 39% (relative risk, 0.61; 95%

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confidence interval, 0.40-0.91) compared with placebo or control interventions.[8] In these trials, cranberries were compared with placebo or no intervention and not with the standard of care prophylaxis, namely, low-dose antibiotics (eg, trimethoprim-sulfamethoxazole [TMP-SMX]). Effectiveness of cranberries in groups other than women with rUTIs is less certain.[8,9]

We herein report a double-blind, double-dummy, randomized noninferiority trial in premenopausal women with rUTIs, comparing 12 months' prophylaxis use with either TMP-SMX, 480 mg once daily, or cranberry capsules, 500 mg twice daily, for the prevention of rUTI.

METHODS

PATIENTS

Premenopausal women, 18 years of age or older, with a medical history of at least 3 symptomatic UTIs in the year preceding enrollment were eligible. The UTIs in the previous years were defined by self-report. Patients were living in the community and recruited through advertisement in women's magazines and in journals, through primary care physicians' referral, and from secondary or tertiary hospitals all over the Netherlands from January 1, 2005, through August 31, 2007. Exclusion criteria were symptoms of a UTI at inclusion, use of antibiotics or cranberries in the previous 2 weeks, relevant interactions with existing medication or contraindications for TMP-SMX (eg, known allergy) or cranberries (oral anticoagulants[10] or renal stones[11]), pregnancy (or desire for pregnancy), breastfeeding, and a history of renal transplantation. The study protocol was approved by the medical ethics committees of all 10 participating centers, and all participants gave written informed consent before inclusion. Procedures were in accordance with the Helsinki Declaration, and this trial is registered in the International Standard Randomised Controlled Trial Number Register (ISRCTN 50717094).

INTERVENTION

The coordinating center (Academic Medical Center, Amsterdam, the Netherlands) prepared drug randomization lists for each study site in advance. Women were randomized to 12 months' ingestion of either (1) 1 tablet with 480 mg TMP-SMX at night and 1 placebo capsule twice daily or (2) 1 capsule with 500 mg cranberry extract (Cran-Max; Proprietary Nutritionals, Inc, Kearny, New Jersey) twice daily and 1 placebo tablet at night. We prescribed a twice-daily capsule with 500 mg cranberry extract on the basis of the results of a previous laboratory study showing antiadhesion activity in the urine within 2 hours and persisting for up to 10 hours following cranberry juice consumption.[12] The amount of type A PACs in the cranberry extract was 9.1 mg/g, quantified by Brunswick Laboratories (Norton, Massachusetts) using a high-performance liquid chromatography method coupled with fluorescence and mass detection.[13] Masking of patients and investigators was achieved by double-dummy dosing. Placebo and active doses of the tablets and of the capsules were identical in appearance and taste (provided they were swallowed whole as instructed) and were sealed in identical lightproof jars with moisture traps in the lid. Patients were instructed to keep the jar in a cool and dry place. Concealed randomization was ensured using computer-aided block randomization (block size was kept secret), with prestratification by center and presence (yes/no) of complicating host factors, defined as functional or structural abnormalities of the urinary tract, metabolic and/or hormonal abnormalities, or impaired host responses.[14] Patients were instructed not to use prophylactic treatment with antibiotics or cranberries during the intervention period and in the 3 months after discontinuation of the study medication.

Table 1. Baseline Characteristics of the Participants[a]

Characteristic	TMP-SMX (n=110)	Cranberry (n=111)
Age, median (IQR), y	36.1 (26.9-46.3)	34.8 (22.8-44.4)
No. of UTIs in preceding year, median (IQR)	6 (4-8)	7 (4-11)
Complicated UTIs[b]	15 (13.6)	15 (13.5)
Anatomic/functional abnormalities of urinary tract	10 (9.1)	11 (9.9)
Medical history with urologic surgery	7 (6.4)	7 (6.3)
Catheter	3 (2.7)	5 (4.5)
Intermittent	3	5
Indwelling	0	0
Diabetes mellitus	1 (0.9)	3 (2.7)
Type 1	1	0
Type 2	0	3
Sexually active	104 (94.5)	99 (89.2)
Use of incontinence material	13 (11.8)	15 (13.5)
Use of antibiotic 3 mo before inclusion		
Any antibiotic	86 (78.2)	85 (76.6)
TMP	9 (8.2)	9 (8.1)
TMP-SMX	8 (7.3)	8 (7.2)
Nitrofurantoin	39 (35.5)	37 (33.3)
Quinolones	17 (15.5)	14 (12.6)
Amoxicillin-clavulanic acid	9 (8.2)	10 (9.0)
Other	20 (18.2)	28 (25.2)
Asymptomatic bacteriuria	24/95 (25.3)	38/104 (36.5)

Abbreviations: IQR, interquartile range; TMP, trimethoprim; TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.

[a]Data are given as number (percentage) of women, unless otherwise indicated. For both the TMP-SMX and the cranberry group, the maximum number of missing values for a characteristic was 3. For the microbiologic characteristics, samples from women who withdrew their consent were not available.

[b]Urinary tract infections in patients with complicating host factors, defined as functional or structural abnormalities of the urinary tract, metabolic and/or hormonal abnormalities, or impaired host responses.

ASSESSMENTS

At baseline, demographic variables and clinical characteristics were collected (**Table 1**). Immediately before the start of the study medication and monthly thereafter, until 3 months after discontinuation of the study medication, the women were asked to collect urine (a dipslide and a sample to measure antibacterial activity) and feces. At these time points, the women also received a questionnaire addressing UTI symptoms, adverse events (AEs), infections other than UTIs, and antibiotic consumption. After discontinuation of the study medication, after 12 months or earlier in case of dropout, women were asked to guess to which intervention they had been assigned (TMP-SMX, cranberries, or don't know). In case of symptoms compatible with a UTI, women were instructed to collect urine using a dipslide and to send this to the laboratory for culture. A urine dipslide is an agar coated–slide that can be dipped in urine and replaced in its sterile container, after which it can be sent by mail.

Although samples were collected monthly, we decided not to analyze antibiotic resistance in all monthly urine and feces samples because preliminary results showed that the increased antibiotic resistance levels of *E coli* were stable from

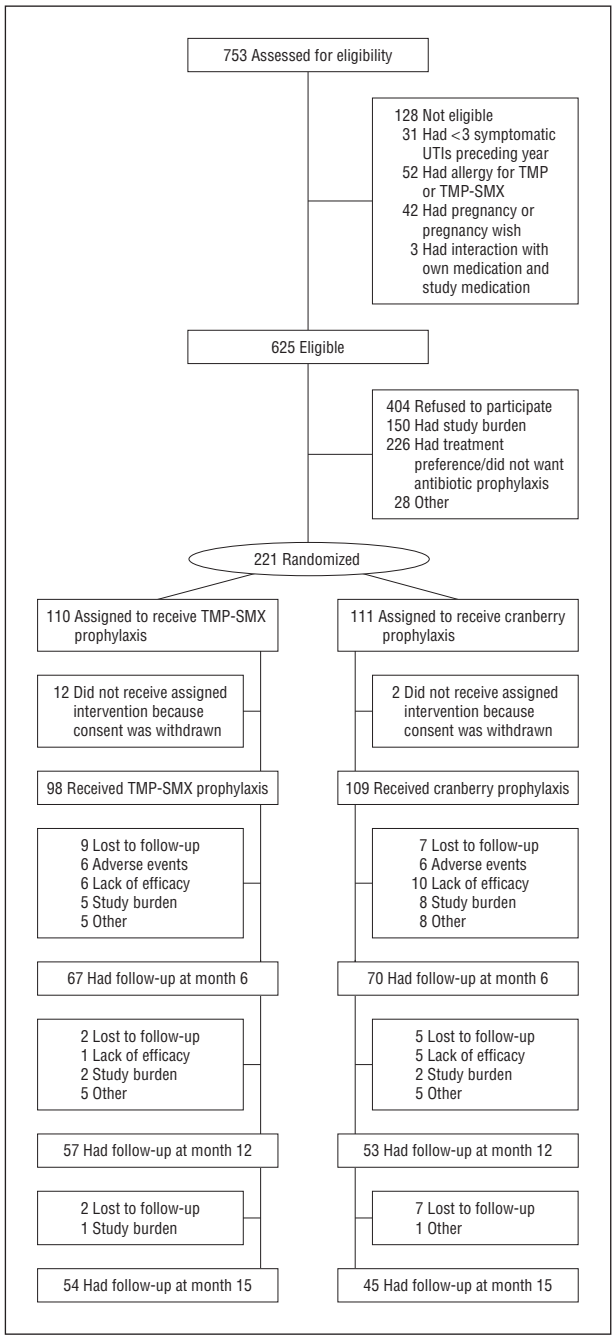

Figure 1. Distribution of participants. The lack of efficacy was determined by the patients. TMP-SMX indicates trimethoprim-sulfamethoxazole.

1 to 12 months. Therefore, only urine and fecal samples obtained at study entry, after 1 and 12 months of prophylaxis use, and 1 and 3 months after discontinuation of study medication were analyzed for antibiotic resistance of *E coli* isolates. Selective (MacConkey agar) plates were used for the bacteriologic analysis of the urine and fecal samples. From 1 to 3 *E coli*–like red colonies were selected and identified using standard bacteriologic methods, which include the urea and indol test, as negative or positive for *E coli*. In case of doubt or inconclusive results, the API 20 (bioMérieux Clinical Diagnostics, Boxtel, the Netherlands) was used. Susceptibility to the antibiotics most commonly prescribed for the treatment of UTIs was determined. Antibiotic susceptibility was determined at the microbiology laboratory of the Maastricht University Medical Center using a microbroth dilution method, following Clinical and Laboratory Standards Institute guidelines.[15] All urine samples were tested for antibacterial activity due to TMP-SMX or other antibacterial substances.[16]

OUTCOME MEASURES

The primary clinical outcomes were the mean number of symptomatic UTIs (clinical recurrences [CRs]) over 12 months, the proportion of patients with at least 1 symptomatic UTI during 12 months of prophylaxis use, and the median time to the first symptomatic UTI. A CR was defined as a UTI on the basis of a woman's subjective report of clinical symptoms, usually dysuria, frequency, and/or urgency. The primary outcome measure evaluating development of resistance was the percentage of *E coli* isolates from feces and urine of asymptomatic women that was resistant to TMP-SMX at 1 and 12 months. In addition, we analyzed these *E coli* isolates to trimethoprim, nitrofurantoin, amoxicillin, amoxicillin-clavulanic acid, gentamicin, ciprofloxacin, and norfloxacin. An additional analysis of the primary outcomes was performed for the 3 months after discontinuation of the study medication.

Secondary outcomes were the mean number of microbiologically confirmed symptomatic UTIs (microbiologic recurrences [MRs]), the percentage of patients with at least 1 MR, and the median time to first MR during the 12 months of prophylaxis use and in the 3 months after prophylaxis use. An MR was defined as a UTI on the basis of the combination of clinical symptoms and bacteriuria ($\geq 1 \times 10^3$ colony-forming units [CFU/mL of urine).[17] If *E coli* was the causative microorganism, susceptibility to the previously mentioned antibiotics was determined.

The prevalence of asymptomatic bacteriuria ($\geq 1 \times 10^5$ CFU/mL of urine) was determined at 1 and 12 months of prophylaxis use. Additional secondary outcomes included the proportion of patients experiencing serious AEs (SAEs). The likelihood of a causal relationship between the study medication and the SAEs or events leading to withdrawal was assessed by an independent masked (not aware of group assignment) data and safety monitoring board. For each woman, we counted the number of prescriptions of antibiotics for the treatment of UTIs and other bacterial infections.

Adherence to antibiotic prophylaxis was assessed by measuring antibacterial activity in urine. Success of masking was assessed by comparing the patient's guesses about treatment assignment with the actual treatment.

POWER CALCULATION

When the sample size in each group is 118, a 2-group, 1-sided *t* test with an α of .05 will have 80% power to reject the null hypothesis that the mean number of annual symptomatic UTIs in the cranberry group is 1.3 greater than in the TMP-SMX group, in favor of the alternative hypothesis of noninferiority, assuming that the expected difference in means is 0 and the common SD is 4.0. A 2-sided *t* test, as required at present by European Medicines Agency, would have required 150 patients per group (nQuery Advisor, version 7.0; Statistical Solutions Ltd, Cork, Ireland).

STATISTICAL ANALYSIS

We analyzed those patients who reported taking at least 1 dose of trial medication. Analysis on main outcome parameters was performed before breaking the treatment code.

To establish noninferiority of cranberry prophylaxis compared with TMP-SMX prophylaxis, the upper 95% confidence

Table 2. CRs and MRs During and After UTI Prophylaxis

Recurrence	At 12-Month Prophylaxis			3 Months After Prophylaxis		
	TMP-SMX (n=95)	Cranberry (n=104)	*P* Value	TMP-SMX (n=69)[a]	Cranberry (n=66)[a]	*P* Value
CRs						
Mean No. of CRs (95% CI)	1.8 (0.8-2.7)[b]	4.0 (2.3-5.6)[b]	.02	0.5 (0.3-0.7)	0.7 (0.4-0.9)	.30
Difference between Kaplan-Meier estimates[c]						
% With ≥1 CR (95% CI)	71.1 (57.9-80.2)	78.2 (66.7-85.7)	.03	32.1 (19.7.42.5)	36.9 (22.9-48.3)	.75
Median time to first CR (95% CI), mo	8 (6-10)	4 (3-6)		>3[d]	>3[d]	
MRs						
Mean No. of MRs (95% CI)	0.8 (0.4-1.1)[b]	1.2 (0.8-1.5)[b]	.15	0.1 (0.0-0.2)	0.1 (0.0-0.2)	.92
Difference between Kaplan-Meier estimates[c]						
% With ≥1 MR (95% CI)	46.7 (33.8-57.2)	47.1 (34.4-57.3)	.48	9.3 (1.9-16.1)	7.1 (0.1-13.6)	.62
Median time to first MR, mo	>12[d]	>12[d]		>3[d]	>3[d]	

Abbreviations: CI, confidence interval; CR, clinical recurrence; MR, microbiologic recurrence; TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.

[a] We intended to collect data from all patients in the 3 months after discontinuation of the study medication, including those who had prematurely discontinued the study medication. Women with a urinary catheter were excluded from the analyses presented in this table.

[b] Numbers based on the analyses using inverse probability of censoring weighting. All other numbers in the table are based on unadjusted analyses. See the "Statistical Analysis" subsection.

[c] We have modeled the probability of being UTI free at each time point during follow-up using Kaplan-Meier estimates for both treatment arms. The significance of the difference between the Kaplan-Meier estimates was tested using the log-rank test. From the Kaplan-Meier estimates, we computed the median time to the first UTI as well as the probability of having 1 or more UTIs after 12 months of prophylaxis use and in the 3 months after prophylaxis use.

[d] Median time to first CR or MR could not be given because the percentage of patients with at least 1 CR or MR was less than 50%.

limit for the between-group difference in the number of CRs at 12 months had to lie below the noninferiority margin (delta) of 1.3 CRs. In accordance with the Consolidated Standards of Reporting Trials and the European Medicines Agency, we report 2-sided 95% confidence intervals of the between-treatment differences.[18]

We used linear regression including only treatment as an independent variable in the model and the total number of either CRs or MRs at 12 months as the dependent variable.

We modeled the probability of being UTI free at each time point during the 12 months of prophylaxis use and in the 3 months thereafter using Kaplan-Meier estimates for both treatment arms. The significance of the difference between these Kaplan-Meier estimates was tested using the log-rank test. From these Kaplan-Meier estimates, we computed the median time to the first UTI as well as the probability of having at least 1 UTI after 12 months of using prophylaxis and in the 3 months after using prophylaxis.

The analyses were also performed using inverse probability of censoring weighting to correct for possible informative censoring.[19] Inverse probability of censoring weighting–adjusted results are presented for the analyses of the mean numbers of CRs and MRs after 12 months of prophylaxis use. For the percentages of patients with at least 1 CR or MR and the median times to these events, the inverse probability of censoring weighting–adjusted estimates did not differ substantially from the unadjusted estimates. Therefore, we present the unadjusted results for these end points.

At the protocol phase, we decided to include women with a urinary catheter in this study because rUTIs are a prevalent problem in this patient group. However, the number of women with a urinary catheter was too small to examine a subgroup effect. To avoid confounding and generalization of our findings to patients with a urinary catheter, we decided to exclude this small group of patients from the analyses of CRs, MRs, and asymptomatic bacteriuria. We retained the women with a urinary catheter in all other analyses.

For statistical analysis, we used SPSS, version 16.0 (SPSS Inc, Chicago, Illinois), and the software package R, version 2.10.1 (Institute for Statistics and Mathematics, University of Vienna, Vienna, Austria).

RESULTS

PARTICIPANT FLOW

From January 1, 2005, to August 31, 2007, we recruited 221 premenopausal women with rUTIs: 110 were randomized to TMP-SMX and 111 to cranberries (**Figure 1**). We planned to stop inclusion after this period. Table 1 shows baseline characteristics of the participants.

PRIMARY OUTCOMES: CRs AND DEVELOPMENT OF RESISTANCE

After 12 months of using prophylaxis, the mean number (95% confidence interval) of CRs was 1.8 (0.8-2.7) in the TMP-SMX and 4.0 (2.3-5.6) in the cranberry group (**Table 2** and **Figure 2**A). The between-group difference of 2.2 CRs after 12 months (95% confidence interval, 0.3-4.2; *P*=.02) was outside our noninferiority margin of 1.3 CRs. The proportion of patients with at least 1 symptomatic UTI was higher in the cranberry than in the TMP-SMX group (78.2% vs 71.1%) (Table 2). The median time to first recurrence was 8 months for the TMP-SMX and 4 months for the cranberry group (*P*=.03, log-rank test) (Figure 2B). In addition, Table 2 shows the mean number of CRs, the percentage of patients with at least 1 CR, and the median time to first CR during the 3 months after prophylaxis use.

After 1 month of using TMP-SMX prophylaxis, resistance to TMP-SMX, TMP, and amoxicillin had increased (from 21.1%-27.8% to 72.5%-90.5%) in both feces and urine (**Figure 3A-D**). A return to the baseline resistance levels was seen 3 months after TMP-SMX discontinuation. Resistance rates for ciprofloxacin and norfloxacin in urinary *E coli* isolates increased from 8.3% at

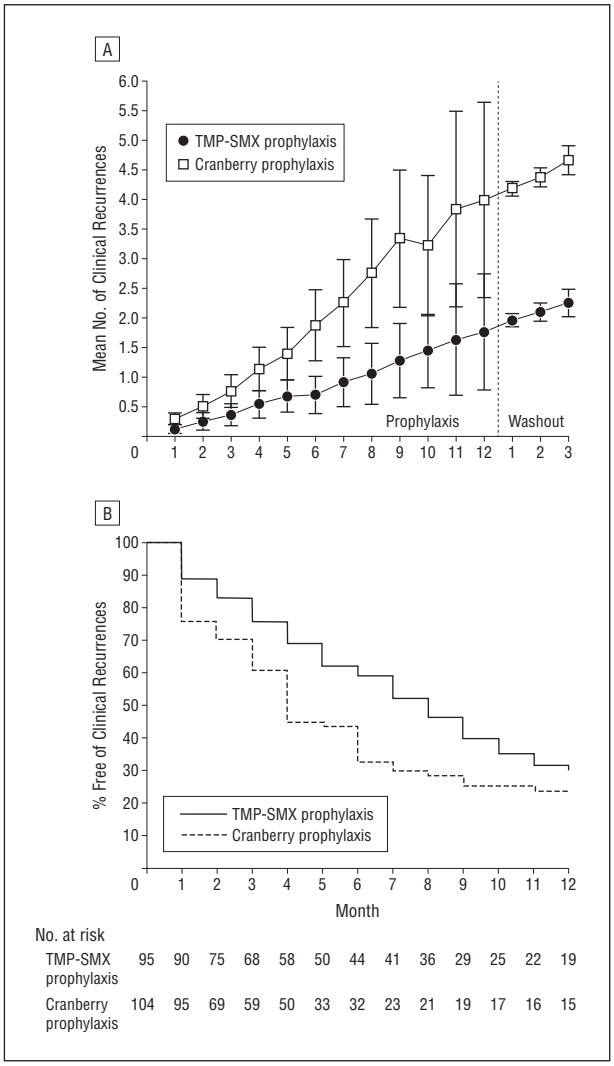

Figure 2. After 12 months of prophylaxis (A) the mean number (95% confidence interval) of clinical recurrences during and after prophylaxis use adjusted for selective dropout (see the "Statistical Analysis" subsection in the "Methods" section), and (B) time to first clinical recurrence. TMP-SMX indicates trimethoprim-sulfamethoxazole.

baseline to 23.1% after 12 months of using TMP-SMX prophylaxis.

SECONDARY OUTCOMES: MRs AND ASYMPTOMATIC BACTERIURIA

Table 2 shows the mean number of MRs, the percentage of patients with at least 1 MR, and the median time to first MR during the 12 months of prophylaxis use and in the 3 months after prophylaxis use. **Table 3** shows causative microorganisms. In both groups, *E coli* was the most prevalent causative microorganism (78.9% in the TMP-SMX and 75.9% in the cranberry group). Resistance percentages of the *E coli* isolates causing UTIs in the TMP-SMX group were similar and in the cranberry group were somewhat lower than the corresponding resistance percentages of *E coli* from feces or urine of asymptomatic women (Figure 3 and **Figure 4**).

After 1 month, 22 of the 83 women in the TMP-SMX group (26.5%) and 32 of the 89 women in the cranberry group (36.0%) had asymptomatic bacteriuria. At 12 months, these percentages were 30.2% (16 of 53) and 37.0% (17 of 46), respectively. Table 3 shows the cultured microorganisms for the entire study period.

ADVERSE EVENTS

There were no statistically significant differences between the TMP-SMX and the cranberry groups in the percentages of patients with any or a specific AE or a SAE (**Table 4**). In the TMP-SMX group, 1 woman had a SAE (Stevens-Johnson syndrome), which led to her withdrawal. There were no SAEs in the cranberry group.

ANTIBIOTIC CONSUMPTION AND OTHER INFECTIONS

The median number (interquartile range) of antibiotic prescriptions for a UTI during the intervention period was 0.5 (0-2) in the TMP-SMX and 1 (0-2) in the cranberry group. Patients received these antibiotics from their primary care physician when they had symptoms of a UTI. In both groups, nitrofurantoin was the most commonly prescribed antibiotic (52.3% and 45.1%, respectively), followed by norfloxacin (13.1% and 14.0%, respectively). The median number of antibiotic prescriptions for other bacterial infections, usually respiratory tract infections, was 0 (0-0) in both groups.

COMPLIANCE WITH TMP-SMX AND EVIDENCE OF MASKING EFFICACY

In 632 of 722 urine samples (87.5%) obtained from women during TMP-SMX prophylaxis use, antibacterial activity was present. At the end of the study, 35 of 77 participants in the TMP-SMX group (45.5%) and 33 of 73 participants in the cranberry group (45.2%) correctly guessed which active treatment they had taken.

COMMENT

In a randomized double-blind noninferiority trial, TMP-SMX was more effective than cranberry capsules for the prevention of rUTIs in premenopausal women. Cranberries and TMP-SMX were equally well tolerated. However, the use of TMP-SMX prophylaxis resulted in a considerable increase in antibiotic resistance. Already after 1 month, 86.3% of *E coli* isolates from the indigenous fecal flora were TMP-SMX resistant. Moreover, a simultaneous increase was seen in resistance to amoxicillin and fluoroquinolones.

Particularly strong points of this study include the relatively long intervention period of 12 months and the inclusion of a washout period after the discontinuation of the study medication. Furthermore, thorough microbiologic testing and rigorous analyses were performed in urine of asymptomatic women and women with symptomatic episodes as well as laboratory-confirmed episodes of a UTI. Finally, the effect of long-term (antibiotic) prophylaxis on the indigenous flora was assessed.

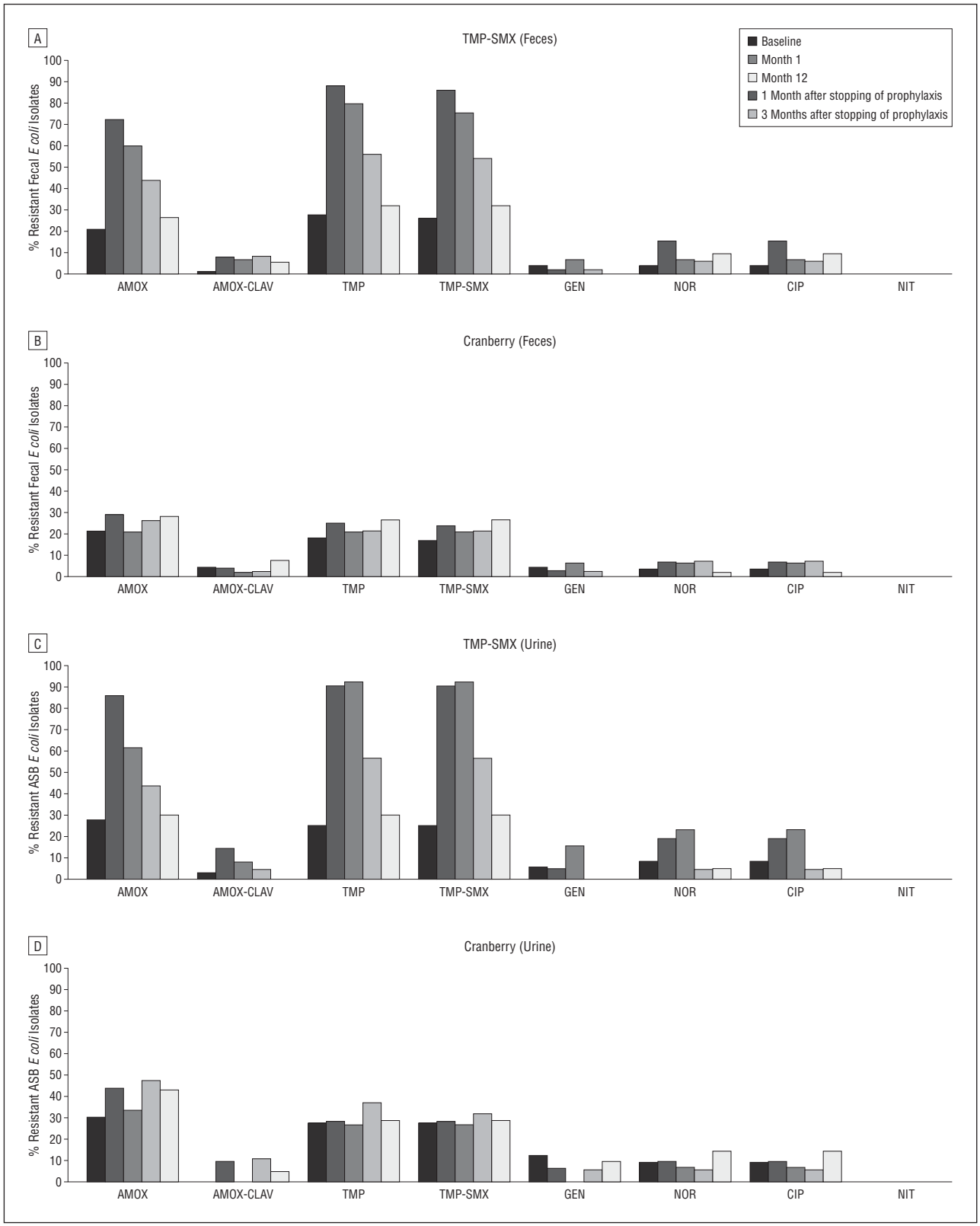

Figure 3. Antibody susceptibility of *Escherichia coli* isolates cultured from feces and from urine of women with asymptomatic bacteriuria (ASB), during and after discontinuation of trimethoprim-sulfamethoxazole (TMP-SMX) and cranberry prophylaxis. AMOX indicates amoxicillin; CIP, ciprofloxacin; CLAV, clavulanic acid; GEN, gentamicin; NIT, nitrofurantoin; NOR, norfloxacin.

Several limitations should be noted. Our target number of 280 participants for this trial (140 in each arm) was based on an incorrect a priori sample size calculation and incorrect assumptions. The sample size calculation was not based on our outcome of primary interest, namely, the mean number of recurrences over 1 year,

Table 3. Bacteria Isolated and Collected Monthly From Urine of Asymptomatic Women and Symptomatic Women Using Prophylaxis

Bacteria	No. (%) of Urinary Isolates			
	Asymptomatic Women		Women With Symptoms of a UTI	
	TMP-SMX (n=526)	Cranberry (n=632)	TMP-SMX (n=71)	Cranberry (n=87)
Escherichia coli	223 (42.3)	271 (42.8)	56 (78.9)	66 (75.9)
Klebsiella species	30 (5.7)	22 (3.5)	5 (7.1)	2 (2.3)
Nonfermentors	51 (9.7)	84 (13.3)	2 (2.8)	4 (4.6)
Proteus species	3 (0.6)	6 (0.9)	0	3 (3.4)
Other gram-negative bacteria	6 (1.1)	45 (7.1)	2 (2.8)	5 (5.7)
Enterococcus faecalis	85 (16.2)	106 (16.7)	4 (5.6)	5 (5.7)
Coagulase-negative *Staphylococcus*	74 (14.1)	59 (9.3)	1 (1.4)	0
Other gram-positive bacteria	16 (3.6)	16 (2.5)	0	1 (1.1)
Other	38 (7.2)	23 (3.6)	1 (1.4)	1 (1.1)

Abbreviations: TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.

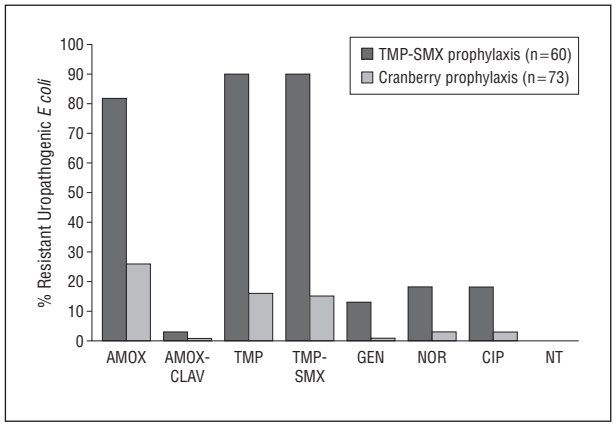

Figure 4. Antibiotic resistance among *Escherichia coli* isolated from patients with symptomatic urinary tract infections. For an explanation of the abbreviations, see the legend to Figure 3.

for which we had no literature reference in 2004. Instead, we based our target number on the published 95% reduction of UTIs per patient-year with use of TMP-SMX prophylaxis[20] and a noninferiority margin of 10% to establish noninferiority of cranberries. The success rates of 95% with TMP-SMX and 85% with cranberry prophylaxis turned out to be far too optimistic. High resistance rates at baseline and the relative high background incidence of UTIs in our study population might have influenced our success rates. However, now that we have the empirical data that allow us to calculate confidence intervals that quantify the numerical imprecision, further discussion about our predefined target number seems futile to some extent. To provide a context for interpreting the accuracy of our results, a post hoc power calculation is presented.

Another significant concern was withdrawal during the trial. High withdrawal rates (≤58%) were also reported in other cranberry trials with maximum follow-up periods of 6 months[8] instead of the 12 months of our trial. We used inverse probability weighting to correct for selective dropout, which in fact was present. In the cranberry group, women experiencing many recurrences were more likely to withdraw.

Table 4. Adverse Events or Serious Adverse Events During Prophylaxis

Event	No. (%) of Patients	
	TMP-SMX (n=98)	Cranberry (n=109)
Adverse events		
Any	51 (52.0)	53 (48.6)
Rash or urticaria	15 (15.3)	9 (8.3)
Nausea, vomiting, or diarrhea	16 (16.3)	13 (11.9)
Constipation	13 (13.3)	11 (10.1)
Vaginal complaints	18 (18.4)	15 (13.8)
Other[a]	42 (42.9)	44 (40.2)
Adverse event resulting in withdrawal	5 (5.1)	6 (5.5)
Relation with treatment unlikely	0	1 (0.9)
Relation with treatment likely[b]	5 (5.1)	5 (4.6)
Serious adverse events		
Any	12 (12.2)	8 (7.3)
Relation with treatment likely: systemic allergic reaction	1 (1.0)	0
Relation with treatment unlikely: UTI requiring hospitalization	1 (1.0)	0
Hospitalization for other reason		
Orthopedic surgery	1 (1.0)	3 (2.6)
Urogynecologic surgery	3 (3.1)	2 (1.8)
Miscellaneous	9 (9.2)	4 (3.7)
Serious adverse event resulting in withdrawal	1 (1.0)	0
Relation with treatment unlikely	0	0
Relation with treatment likely	1 (1.0)	0

Abbreviations: See Table 3.

[a] Heterogeneous group of adverse events. Most occurred only once or just a few times.

[b] The data and safety monitoring board, masked to group assignment, judged that the following 5 withdrawals from the cranberry group could be related to the use of study medication: rash (n=1), painful ankles (n=1), vaginal candidiasis (n=1), headache and dizziness (n=1), and muscular and joint pain (n=1). According to the data and safety monitoring board, in the TMP-SMX group the adverse events leading to withdrawal were rash (n=1), photosensitivity (n=1), vaginal candidiasis (n=2), and nausea and fatigue (n=1).

Furthermore, not all CRs were confirmed microbiologically. However, if women with a history of rUTIs have clinical signs and symptoms consistent with a UTI, the likelihood of a UTI is approximately 86%.[21] Indeed, 85%

of the received urine samples yielded at least 1×10^3 CFU/mL. Therefore, we think that the number of CRs is reliable and the most relevant for patient care. Furthermore, CR has been used as an end point in UTI studies before.[22]

Another limitation is that we did not confirm that all women took the cranberry prophylaxis. However, in 88% of the urine samples obtained from women during TMP-SMX prophylaxis use, antibacterial activity was present. We have no strong reasons to believe that adherence in the cranberry group would be worse than in the antibiotic group. Factors in our study that could possibly influence adherence were comparable in both groups (rate of UTIs below prestudy rate, AEs, and masking efficacy).

Until recently, there was no consensus about the most appropriate method to measure type A PACs. Besides, the dimethylaminocinnamaldehyde method developed by Howell et al[5] was not widely available. Therefore, we used a high-performance liquid chromatography method.[13] Only recently, the Brunswick Laboratories–dimethylaminocinnamaldehyde method, which can serve as the standard industry method, became commercially available.[23]

Furthermore, the optimum dosage of cranberries in vivo is still not clear; a dose-finding study is under way (clinicaltrials.gov Identifier: NCT00100061). Moreover, it is not known whether PAC is the only working antiadherence substance. The results of a recently published in vitro study suggest that the administration of PAC, 72 mg/d, measured by the old dimethylaminocinnamaldehyde method, may offer some protection against bacterial adhesion in the urinary tract until 24 hours after cranberry consumption.[5] This was not known during the start of the present study, and in our batch only 9.1 mg of PAC per gram of cranberry extract was measured. The daily dose of type A PACs that was used in our study is equivalent to a daily dose of 75 mL of Ocean Spray cranberry juice (27% cranberry).[23]

In a comparable study in which cranberry extract, 500 mg once daily, was compared with TMP, 100 mg once daily, in elderly women (mean age, 63 years) with at least 2 UTIs in the previous year, McMurdo et al[24] found that, after 6 months, 25 of 69 women (36%) women in the cranberry group had a symptomatic antibiotic-treated UTI compared with 14 of 68 women (21%) in the TMP group, which is roughly in accordance with our findings. Unfortunately, because these authors described the antibiotic resistance to TMP at baseline only and resistance among microorganisms causing UTIs for both study arms together, a comparison with our resistance percentages was impossible.

Our study compared the effects of 2 different forms of prophylaxis, namely, TMP-SMX and cranberry prophylaxis, on antibiotic resistance among indigenous and uropathogenic *E coli* isolates. We found high resistance rates already after 1 month of TMP-SMX prophylaxis use. This is in concordance with the high percentages (>95%) of TMP-SMX–resistant microorganisms in feces and urine of TMP or TMP-SMX recipients after only 2 weeks.[3] In addition to TMP-SMX resistance, in our study there was also an increase in resistance to amoxicillin and the quinolones during use of TMP-SMX prophylaxis. The former is known to be plasmid linked.[25]

From clinical practice and during the recruitment phase of this study, we learned that many women are afraid of contracting drug-resistant bacteria using long-term antibiotic prophylaxis and preferred either no or nonantibiotic prophylaxis. In those women, cranberry prophylaxis may be a useful alternative despite its lower effectiveness.

For rational decision making at a societal level, we will perform a formal cost-utility analysis, weighing effectiveness of prophylaxis against the costs of increasing antibiotic resistance.

In conclusion, in premenopausal women with rUTIs, TMP-SMX, 480 mg once daily, is more effective than cranberry capsules, 500 mg twice daily, for the prevention of rUTIs. However, this should be weighed against the greater development of antibiotic resistance.

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