

The Absence of an Interaction Between Warfarin and Cranberry Juice: A Randomized, Double-Blind Trial

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The question of potentiation of warfarin anticoagulation by cranberry juice (CJ) is a topic of biomedical importance. Anecdotal reports of CJ-warfarin interaction are largely unconfirmed in controlled studies. Thirty patients on stable warfarin anticoagulation (international normalized ratio [INR], 1.7-3.3) were randomized to receive 240 mL of CJ or 240 mL of placebo beverage, matched for color and taste, once daily for 2 weeks. The INR values and plasma levels of R- and S-warfarin were measured during the 2-week period and a 1-week follow-up period. The CJ and placebo groups ($n = 14$ and 16 , respectively) did not differ significantly in mean plasma R- and S-warfarin concentrations. Eight patients (4 on CJ, 4 on placebo) developed minimally elevated INR (range, 3.38-4.52) during the treatment period.

Mean INR differed significantly ($P < .02$) only on treatment day 12; at all other time points, the groups did not differ. Cranberry juice has no effect on plasma S- or R-warfarin plasma levels, excluding a pharmacokinetic interaction. A small though statistically significant pharmacodynamic enhancement of INR by CJ at a single time point is unlikely to be clinically important and may be a random change. Enhanced warfarin anticoagulation attributed to CJ in anecdotal reports may represent a chance temporal association.

Keywords: Warfarin; anticoagulation; drug interactions; supplements

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Oral anticoagulation with the vitamin K antagonists, predominantly warfarin in North America, is fraught with difficulties because of the need for frequent monitoring to maintain the antithrombotic effect within a therapeutic range.¹ The international normalized ratio (INR), the measure of warfarin's antithrombotic effect, may be influenced by factors such as medications, nutritional supplements, and

diet. S-warfarin, the pharmacologically active enantiomer of racemic warfarin, is metabolized mainly by hepatic cytochrome P450-2C9 (CYP2C9).²⁻⁵ A medication or natural substance that inhibits the activity of CYP2C9 could impair S-warfarin clearance, elevate its plasma levels, and increase the INR due to a pharmacokinetic interaction. Natural substances or medications also could have a potentiating (or inhibiting) effect on the INR due to a mechanism other than pharmacokinetic. Polymorphisms in the vitamin K epoxide reductase complex 1 gene, the target of warfarin's effect, can influence warfarin sensitivity on a pharmacodynamic basis independent from pharmacokinetics. It may be possible that an interaction could be mediated through this target.

The ability of a substance to interact with warfarin through pharmacokinetic or pharmacodynamic mechanisms is often difficult to confirm, and the evidence of an interaction is frequently anecdotal and based on single case reports.⁶ In a recent review of this topic, Holbrook et al classify drug interactions with warfarin based on the quality of the literature

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that supports the claim. They estimated that 84% of reported interactions were of poor quality and 86% were based on single case reports.⁶

Recently, several case reports have implicated cranberry juice (CJ) as a food item that potentiates warfarin and increases the INR.⁷⁻¹¹ These published reports were preceded by a small number of unpublished reports from the United Kingdom describing patients with a variety of illnesses who consumed CJ and experienced, in most cases, an elevated INR, although in 1 case, the INR was reduced.¹² As a result of these anecdotal reports, warnings have been issued by the Committee on Safety of Medicines in the United Kingdom and have been inserted in the warfarin packaging label in the United States with regard to potential interactions with CJ. Since then, 3 prospective controlled trials have been conducted but with conflicting results.

To provide more definitive information on this issue, we evaluated the effect of administration of CJ, or matching placebo beverage, on the pharmacokinetics and antithrombotic effect of warfarin in patients already receiving the drug for clinical treatment.

METHODOLOGY

Patients

The protocol and consent form were reviewed and approved by the Institutional Review Board serving Boston Medical Center. All patients provided written informed consent.

Patients on warfarin for a variety of indications from a population of anticoagulation clinic patients were selected based on their past history of stable anticoagulation and willingness to participate in the study. Inclusion criteria required patients to be >18 years old and to have a therapeutic INR range of 2.0 to 3.0, no hepatic or renal dysfunction, and a stable INR (defined as an INR between 1.7-3.3 on at least 2 measurements within 8 weeks prior to study entry). Patients took their customary warfarin dosage, which was constant throughout the course of the study, at the same time each day (morning).

Study Design

The study was a randomized, double-blind, placebo-controlled, parallel group trial. It consisted of a 2-week lead-in phase with weekly INRs in range, a 2-week intervention phase with INR measurements every 3 days, and a 1-week follow-up phase (36 days total). Any patient with an out-of-range INR value

(greater than 3.3) during the intervention phase ceased the intervention but continued through follow-up. Patients with an out-of-range INR during the lead-in phase were not entered into the study.

Intervention

Ocean Spray (Lakeville, Massachusetts) provided CJ cocktail from concentrate, containing 27% CJ. Matching placebo contained similar quantities of high-fructose corn syrup, ascorbic acid, other organic acids, and other phenolics but did not contain cranberry ingredients. The CJ and placebo were similar in color and taste and packaged in identically appearing single-dose bottles identified only by code.

Patients were randomly assigned by computer to CJ or placebo with neither the investigators nor patients knowing the assignment. During the intervention phase, patients were instructed to drink an 8-oz glass of either placebo or CJ at the same time each morning. In most but not all instances, consumption of the CJ was done in the presence of one of the investigators. In all cases, empty bottles of CJ or placebo were collected and monitored by the investigators. Patients were advised to maintain a consistent diet throughout the study.

Blood Sampling for INR and Plasma Warfarin Analysis

Venous blood samples were drawn by venipuncture prior to warfarin dosage or CJ consumption beginning with the lead-in phase on the following days: day 1, 8, 15, 19, 23, 26, 29, 32, and 36. One aliquot of blood was used for INR measurements, which were done immediately following venipuncture in the Boston Medical Center-accredited laboratories using a thromboplastin with an international sensitivity index (ISI) of 0.92.

A second blood aliquot was centrifuged, and the plasma was separated and frozen immediately at -80°C until the time of plasma warfarin concentration determination. Levels of R- and S-warfarin in all samples were determined by an enantioselective high-pressure liquid chromatographic (HPLC) method¹³ with minor modifications. The internal standard (oxybenzone, 1.0 μg) was added to study sample tubes and to a series of calibration tubes containing varying known amounts of R-, S-, or R,S-warfarin. Plasma (0.25 mL) from study patients was added to study sample tubes; 0.25 mL of drug-free control serum or plasma was added to calibration tubes. To each tube was added 0.1 mL of 1 N HCl,

Table I Characteristics of Patients in the Study

	Number or Mean \pm SE (with range)		
	All Patients	Placebo Group	Cranberry Juice Group
Number	30	16	14
Gender, M/F	16/14	6/10	10/4
Age, y	59 \pm 3 (32-84)	57 \pm 4 (32-77)	61 \pm 4 (33-84)
Warfarin dose, mg/wk	39.9 \pm 3.6 (8.75-84.0)	37.3 \pm 5.2 (8.75-82.5)	43.0 \pm 5.0 (19.0-84.0)
Indication for warfarin			
Atrial fibrillation	9	4	5
Deep vein thrombosis	9	4	5
Pulmonary embolism	4	3	1
Valvular heart disease	3	2	1
Cerebrovascular disease	4	2	2
Congestive heart failure	1	1	–

followed by 2.5 mL of ethyl acetate. Samples were extracted by vortex mixing. After centrifugation, the organic layer was separated and evaporated to dryness. The residue was reconstituted in 0.25 mL of HPLC mobile phase. The limits of sensitivity were 100 ng/mL for R- and S-warfarin.

The analytic instrument was an Agilent HPLC system (Santa Clara, California) consisting of a solvent delivery pump, autosampler, ultraviolet detector (305 nm), and data processor. The chiral separation column was 25 cm in length \times 4.6 mm in internal diameter containing 5- μ m, 100- \AA spherical silica (Whelk-O 1, Regis Technologies, Morton Grove, Illinois). The mobile phase was 55% methanol, 15% acetonitrile, 30% water, and 0.1% glacial acetic acid; the flow rate was 1.0 mL/min.

Calibration curves were linear and passed through the origin. The sensitivity limit was 50 ng/mL for R- and S-warfarin. Within-day coefficients of variation (CVs) for identical samples did not exceed 9%. Between-day CVs were 11% to 12% for S-warfarin and 10% to 13% for R-warfarin.

Statistical Analysis

The number of patients in each group was sufficient to detect a between-group difference of 0.5 INR units with $\alpha = .05$ and power = .80. The principal statistical procedure was the Student *t* test for independent groups.

RESULTS

A total of 56 patients entered the lead-in phase of the study. Of these, 26 did not qualify for randomization

due to an unstable INR. Of 30 patients that entered the randomization phase, 14 were randomized to receive CJ and 16 to receive placebo. Patient characteristics are shown in Table I. The groups did not differ significantly in age or gender composition. The overall mean weekly dose of warfarin was 39.9 mg (range, 8.75-84.0 mg) and did not differ significantly between CJ and placebo groups.

Plasma Warfarin Concentrations

Consistent with previous studies,¹⁴ plasma concentrations of R-warfarin exceeded those of the active enantiomer, S-warfarin (Figure 1). There was no significant difference between CJ and placebo groups in R- or S-warfarin concentrations at any time point. Maximum plasma warfarin concentrations did not differ between lead-in and treatment phases nor between CJ and placebo groups (Table II).

Effects on INR

Eight of the 30 patients developed an INR exceeding 3.3 (range, 3.38-4.52) during the treatment phase (CJ or placebo). Four of these patients were in the CJ group and 4 in the placebo group. In these 8 individuals, treatment was discontinued, and they entered the follow-up phase. In 7 of the 8 patients, INR values declined between the final treatment sample and the first follow-up sample; in 1 patient, however, the INR increased (Figure 2). In 1 additional patient in the CJ group, an INR of 1.69 was measured during the ninth treatment day (day 23). This patient remained in the study, and the next INR value (treatment day 12; study day 23) was 2.39.

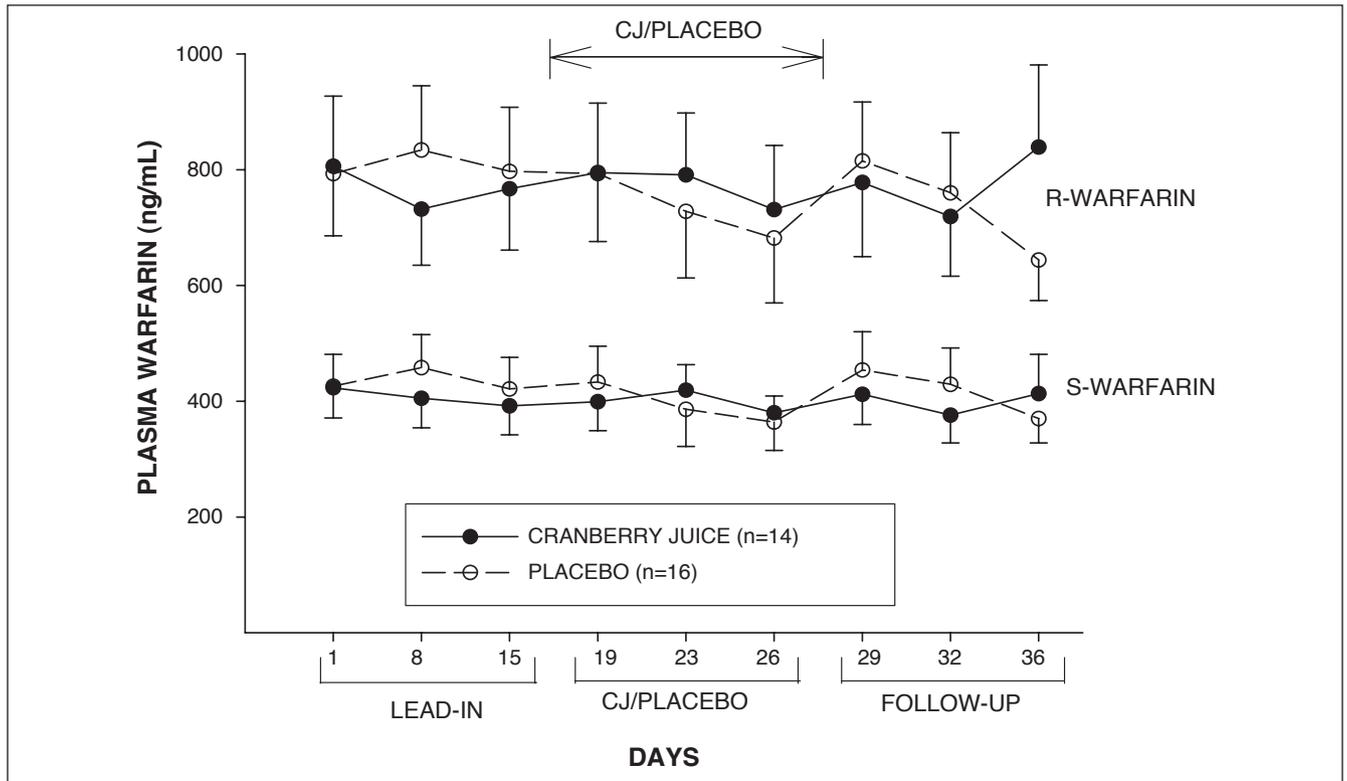


Figure 1. Mean (\pm SE) plasma concentration of R- and S-warfarin at corresponding points in the study for cranberry juice (CJ) and placebo groups. CJ/placebo consumed from day 15 to day 28. The groups did not differ significantly at any of these time points.

Table II Mean Maximum R- and S-Warfarin Levels During the Lead-in and Treatment Phases of the Study

	Mean (\pm SE) Plasma Warfarin, ng/mL		Value of Student <i>t</i> ^a
	Placebo Group	Cranberry Juice Group	
S-warfarin			
Maximum during lead-in	538 (\pm 58)	497 (\pm 53)	0.51 (NS)
Maximum during treatment	473 (\pm 58)	480 (\pm 49)	0.09 (NS)
Difference	-65 (\pm 31)	-17 (\pm 29)	1.11 (NS)
R-warfarin			
Maximum during lead-in	931 (\pm 121)	893 (\pm 121)	0.22 (NS)
Maximum during treatment	849 (\pm 113)	874 (\pm 118)	0.15 (NS)
Difference	-82 (\pm 34)	-19 (\pm 39)	1.25 (NS)

a. A Student independent *t* test was used

Figure 3 shows mean INR values in the CJ and placebo groups during the screen, lead-in, treatment, and follow-up phases of the study. The groups did not differ significantly at any time, with the exception of the final day of the treatment phase. At this single time point, the CJ group was significantly higher than placebo ($t = 2.79$; $P < .02$). However, on the first follow-up day (24 hours after the last dose

of CJ or placebo), the INR values were essentially identical between groups (Figure 3).

DISCUSSION

Single case reports are well recognized as having serious weaknesses in terms of identifying cause-and-effect relationships.¹⁵⁻¹⁷ Since 2003, there have

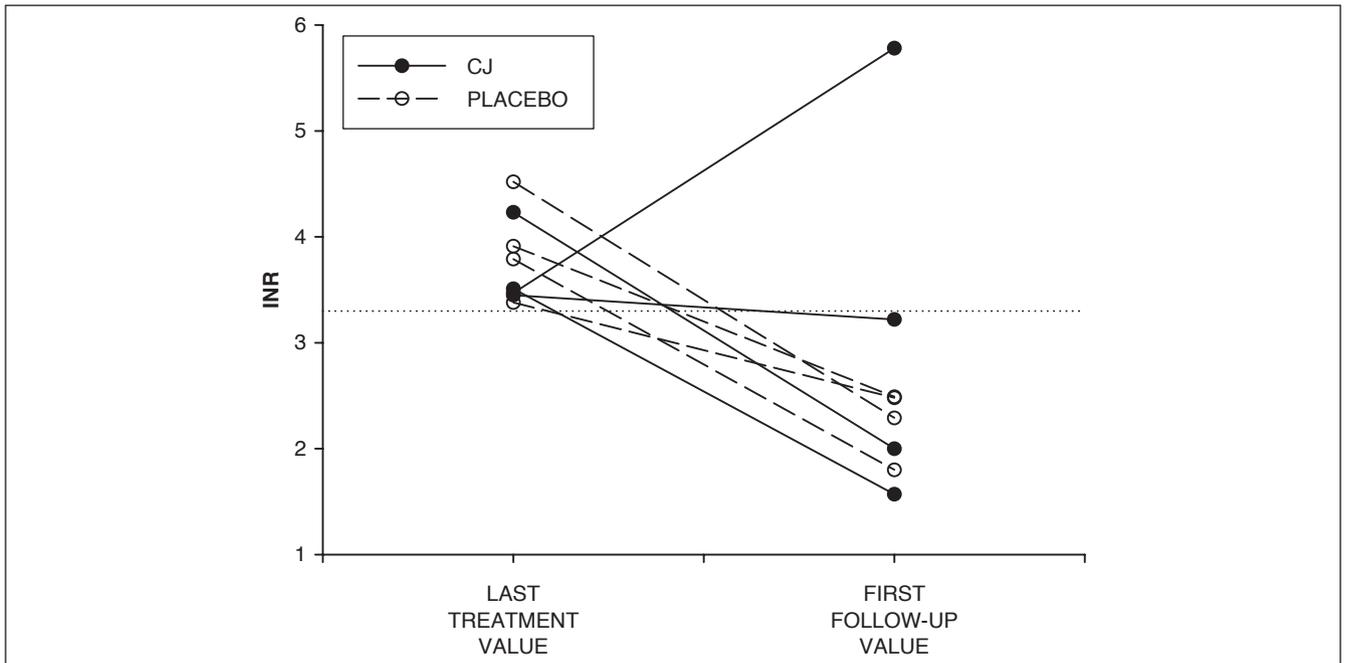


Figure 2. Eight patients (4 receiving cranberry juice [CJ], 4 receiving placebo) developed international normalized ratio (INR) values exceeding 3.3 during the treatment phase of the study. The picture shows individual INR values for the final sample during the treatment phase and the first sample in the follow-up phase.

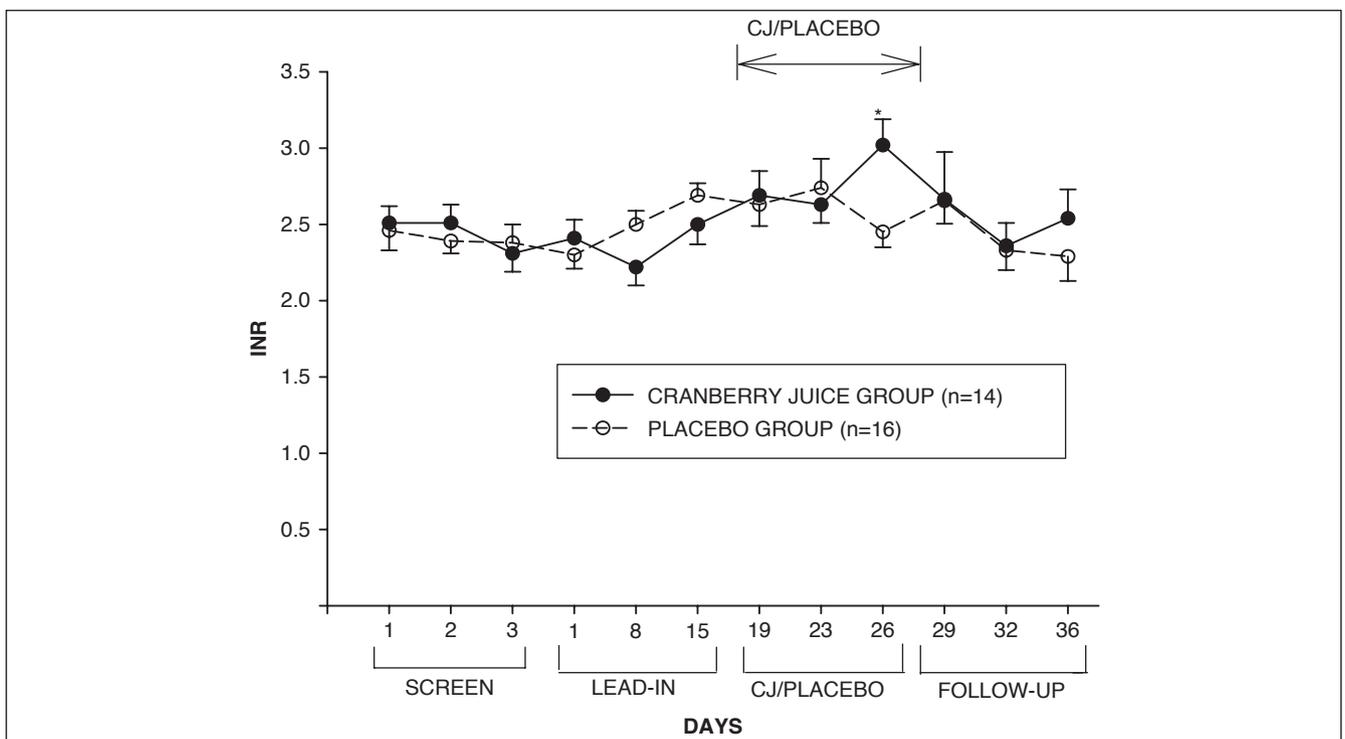


Figure 3. Mean (\pm SE) international normalized ratio (INR) values at corresponding times in the cranberry juice (CJ) and placebo groups. CJ/placebo consumed from day 15 to day 28. The values are significantly different (* $P < .02$) only on the final measurement during the treatment phase but returned to therapeutic range on the next morning INR. At all other points, the differences are not significant.

Table III Summary of Controlled Studies on Cranberry Juice (CJ) With Warfarin or CYP2C9 Substrates

Study	Substrate	Duration of CJ Exposure	Kinetic Result (Plasma Levels of Substrate)	Dynamic Result
Lilja, 2007 (18)	Warfarin (single dose)	Extended	No effect	No effect (thromboplastin time)
Li, 2006 (19)	Warfarin (steady-state)	Extended	(Not determined)	No effect (INR)
Abdul, 2008 (20)	Warfarin (single dose)	Extended	No effect	↑ INR AUC by 28% (maximum 8% difference at any individual time point)
Greenblatt, 2006 (21)	Flurbiprofen (single dose)	Short-term	No effect	N/A

INR, international normalized ratio; AUC, area under the concentration-time curve.

been 5 single case reports of CJ associated with a supertherapeutic INR in patients on warfarin therapy. The cases involved a malnourished individual recently on antibiotics drinking only CJ for a 6-week period,⁷ a subject drinking almost 2 L of CJ daily to prevent urinary infections for approximately 2 weeks,⁸ an individual drinking 24 oz of CJ daily for approximately 2 weeks,⁹ an individual drinking approximately half a liter of CJ daily for 1 month, and a patient who consumed half a gallon of cranberry/apple juice in the week prior to the elevated INR.¹¹ In 4 of the cases, the INR returned to therapeutic range after stopping the CJ (the fifth patient died of hemorrhage). In each of these case reports, the association between the CJ and the elevated INR was circumstantial. The quantities of CJ in 1 of the cases were exceptional, and in at least 2 of the cases, there were other reasonable causes for a supertherapeutic INR.

Controlled clinical, pharmacokinetic, and pharmacodynamic studies have not confirmed a meaningful interaction between warfarin and CJ. Three such studies have been published in the scientific literature (Table III). Two of these show no effect of CJ on the antithrombotic response to warfarin.^{18,19} Li et al¹⁹ conducted a small randomized, placebo-controlled, double-blind crossover study in 7 patients on a stable dose of warfarin for atrial fibrillation. Patients received a 7-day course of CJ or placebo, followed by a washout period of 7 days, and then a final 7 days of opposite therapy. The INR did not change significantly from baseline for all test points in either group. In a second study of 10 healthy volunteers on warfarin who consumed 200 mL of CJ or water 3 times daily, Lilja et al¹⁸ measured the R- and S-warfarin enantiomers. They found no increase in the peak plasma concentration or area under the

concentration-time (AUC) curve for R-warfarin and a slightly decreased AUC (7%; $P = .051$) for S-warfarin. There was no measurable difference in the anticoagulation effect of warfarin with CJ or water based on coagulation testing. Abdul et al²⁰ pretreated 12 healthy volunteers with CJ concentrate capsules for 2 weeks. Compared to no treatment, the cranberry capsules had no effect on the kinetics of R- or S-warfarin following a single 25-mg dose of racemic warfarin. The area under the warfarin effect curve (INR vs time) was increased by 24%, with an 8% increase in the maximum INR. Finally, Greenblatt et al²¹ studied the effect of CJ on CYP2C9 function in 14 healthy volunteers by measuring the clearance of flurbiprofen, an antiinflammatory analgesic, almost exclusively metabolized by CYP2C9. They found no change in CYP2C9-mediated clearance of flurbiprofen in subjects given CJ.

The present study presents additional evidence in the context of a robust study design (randomized, double-blind) that the daily consumption of 8 oz of CJ does not interfere with warfarin therapy. In this study, stability of anticoagulation was assured by a lead-in phase of 2 weeks. Patients consumed one 8-oz glass of CJ, or matching placebo, daily at the same time each day, and INRs were drawn at this time. The INRs were checked for 1 week after CJ or placebo exposure (follow-up phase) to exclude a delayed effect and to assess posttreatment INR. Eight patients (4 each in CJ and placebo groups) developed a minimally elevated INR during the trial (range, 3.38-4.52), and 1 patient in the CJ group developed a minimally reduced INR. At a single time point during the intervention phase, the last day of CJ consumption, the mean INR in the CJ group was significantly higher than in the placebo group, but mean INRs were essentially identical between groups at

the next measurement point (just 24 hours later). When plasma R- and S-warfarin levels were measured, placebo and CJ groups did not differ at any time point, suggesting that CJ does not affect warfarin metabolism via CYP2C9. This is consistent with other studies that uniformly demonstrate CJ to have no detectable effect on clearance of warfarin or flurbiprofen in humans.^{18,20,21} The reasons for the slightly elevated INR values (greater than 3.3) in 4 CJ and 4 placebo patients remain unclear. An interaction attributable to altered warfarin protein binding, caused by one or more acidic components present both in CJ and placebo beverages, seems unlikely. Abdul et al²⁰ found that cranberry extract capsules did not alter plasma protein binding (free fraction) of warfarin in humans.

The present study evaluated consumption of “reasonable” quantities of CJ (one 8-oz glass or 240 mL/d over a 2-week period), and we cannot exclude the possibility of an effect with larger amounts of CJ. There is also the possibility that not all patients took CJ as required; however, most consumption was monitored, and emptied containers were collected. The 2-week intervention may also have been too short to detect an interaction. However, if interference with the metabolism of warfarin was the basis for an interaction, one would expect to see a change in S-warfarin plasma concentrations, which was not observed in the present study or in other controlled pharmacokinetic studies (Table III). If the vitamin K oxide reductase complex 1 were affected (eg, making the enzyme more sensitive to warfarin), the above warfarin studies would not have detected this possibility, but the INR would have. Although the sample size in both groups was relatively small, this is the largest study to date assessing the interaction between CJ and warfarin.

Based on this study and those in Table III, we believe that there is no clinically important interaction between CJ and warfarin and that other factors were likely responsible for the findings in the anecdotal case reports.

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