Risk of Warfarin-Related Bleeding Events and Supratherapeutic International Normalized Ratios Associated with Complementary and Alternative Medicine: A Longitudinal Analysis

Stephen Shalansky, Pharm.D., FCSHP, Larry Lynd, B.S.P., Ph.D., Kathryn Richardson, M.Sc., Andrew Ingasewski, M.D., FRCPC, and Charles Kerr, M.D., FRCPC

Study Objective. To determine the risk of bleeding and supratherapeutic international normalized ratios (INRs) associated with use of complementary and alternative medicine (CAM) in patients receiving warfarin.

Design. Prospective, longitudinal study.

Setting. An acute care, academic and research hospital in Canada.

Patients. A total of 171 adults who were prescribed warfarin anticoagulation therapy for an expected duration of at least 4 months after enrollment.

Intervention. Patients were asked to complete a 16-week diary by recording bleeding events and exposure to factors previously reported to increase the risk of bleeding and supratherapeutic INRs, including CAM consumption.

Measurements and Main Results. Prescription, medical, and laboratory records were reviewed. Risk factors for bleeding events and supratherapeutic INR (at least 0.5 units above the target range) were evaluated longitudinally by using generalized estimating equation (GEE) modeling. Of the 171 patients completing a diary, 87 (51%) reported at least one bleeding event and 36 (21%) had a supratherapeutic INR. Seventy-three patients (43%) indicated they had used at least one CAM product previously reported to interact with warfarin. Warfarin use of less than 3 months' duration was the only statistically significant risk factor identified for supratherapeutic INR. The CAM therapies associated with an increased risk of self-reported bleeding included cayenne, ginger, willow bark, St. John's wort, and coenzyme Q₁₀. Use of more than one CAM while receiving warfarin was also a significant risk factor. Two CAMs were independently associated with an increased risk of self-reported bleeding: coenzyme Q₁₀ (odds ratio [OR] 3.69, 95% confidence interval [CI] 1.88–7.24) and ginger (OR 3.20, 95% CI 2.42–4.24). Other risk factors significantly associated with increased bleeding included high target INR (2.5–3.5), diarrhea, acetaminophen use, increased alcohol consumption, and increased age.

Conclusions. The use of CAM by patients receiving warfarin is common, and consumption of coenzyme Q₁₀ or ginger appears to increase the risk of bleeding in this population.

Key Words: complementary and alternative medicine, CAM, warfarin, bleeding events, international normalized ratio, INR, adverse events, drug interactions, dietary interactions, risk factors.

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Warfarin was first used as an anticoagulant more than 50 years ago. Since then, its efficacy has been established for a wide range of common indications based on well-conducted clinical trials.\textsuperscript{1} Despite the recent development of many new antithrombotic drugs, warfarin remains the most commonly prescribed agent in this class with more than 24 million prescriptions dispensed in the United States in 2006.\textsuperscript{2,3} Although the appropriate use of warfarin is associated with a substantial decrease in morbidity and mortality, anticoagulant effects outside the established therapeutic range increase the risk of bleeding or thrombosis.\textsuperscript{4} Patients often experience warfarin-related adverse events, largely due to the myriad of factors that can influence anticoagulant response, including diet, concomitant diseases, and drug interactions.\textsuperscript{5-6} The use of complementary and alternative medicine (CAM) has increased dramatically in recent years,\textsuperscript{7} and many of the most commonly used products possess properties that could theoretically increase the risk of adverse events from warfarin anticoagulation.\textsuperscript{8-10} Review articles of CAM-drug interactions consistently implicate warfarin in more documented or theoretical interactions than any other prescription or nonprescription drug.\textsuperscript{11-16} However, because CAM use commonly fluctuates over time and is often not disclosed by patients or documented in medical records, studies are difficult and the risk associated with concomitant CAM-warfarin use remains unclear.\textsuperscript{17} Therefore, the objective of this study was to evaluate the risk of bleeding and supratherapeutic anticoagulation associated with the concurrent use of warfarin and CAM in a sample of patients receiving long-term warfarin therapy.

Methods

This was a prospective, longitudinal study in which subjects were enrolled between June 1, 2001 and December 31, 2003, and followed for a target duration of 16 weeks. Potential study participants were identified either during admission to St. Paul's Hospital (Vancouver, British Columbia, Canada), or through review of St. Paul's Hospital outpatient clinic records. Patients were eligible for the study if they were prescribed warfarin for an expected duration of at least 4 months after enrollment, were fluent in reading and writing English (as demonstrated during the initial interview), and were aged 19 years or older. The patient’s medical record was reviewed to determine the specific indication for warfarin, the target international normalized ratio (INR) range, and the duration of warfarin therapy before study initiation.

On enrollment, each patient was provided with a diary containing 16 identical surveys and instructed to fill out one survey on the same day each week for 16 weeks. The diaries were designed to capture information on warfarin use, bleeding events, and exposure to other factors previously reported to increase the risk of bleeding and supratherapeutic anticoagulation. To limit the potential for recall bias, patients were not told that the analysis was to focus on the risk of CAM usage.

Participants were asked about their use of 39 specific CAM therapies previously reported to possess properties that may influence INR or bleeding risk (Appendix 1). Assessment of other potential risk factors included questions on the presence of diseases and symptoms (e.g., fever, diarrhea), exposure to nonprescription drugs (e.g., aspirin, ibuprofen, acetaminophen), and the frequency and amount of vitamin K–rich foods and alcohol consumed. Checklists were used to prompt responses from patients and limit omissions, and space was provided for patients to indicate exposures to CAM, foods, and drugs not listed. Specific INR results were obtained directly from the laboratory, and prescription drug use was determined by using BC PharmaNet, a population-based prescription drug database that captures all prescription dispensations in British Columbia.

To assess adverse events, participants were required to indicate, based on self-assessment, whether they experienced a bleeding event. A checklist of bleeding event types was used, including the following options: excessive bruising beyond what you typically experience while taking warfarin, excessive bleeding from a cut, nosebleed, blood in urine, blood in stool,
blood in vomit, or other (specify). In an attempt to limit dropouts and ensure ongoing completion of the diaries, each participant was contacted by telephone 1 week after enrollment, and every 2 weeks thereafter. If diaries had not been completed, a telephone interview was carried out to collect the missing data.

The Providence Health Care–University of British Columbia Research Ethics Board approved this study, and each patient provided written informed consent before enrollment. Participants were remunerated $25 (Can) after returning their completed diaries.

Statistical Analysis

The characteristics of the study sample in terms of demographics and the prevalence of potential risk factors were evaluated by using mean ± SD or median (interquartile range) as appropriate for continuous variables and proportions for categoric variables. Multivariate analyses were conducted to determine whether CAM use in general, or the use of specific CAM therapies, was independently associated with warfarin-related adverse outcomes, after adjusting for other potential risk factors. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of warfarin-related outcomes associated with CAM exposure were calculated separately for two primary binary outcomes: INR greater than 0.5 above the upper limit of the target range based on indication, and a self-reported bleeding event.

Generalized estimating equation (GEE) modeling was used to control for the correlation of events within individuals over time to facilitate incorporation of sporadic exposure. In this study, it was expected that some patients would use CAM, or be exposed to other risk factors, for part of the 16-week data collection period, whereas others would have consistent use over the 16 weeks. The GEE analysis accounts for the correlation of events within an individual, given that an individual who has experienced one bleeding event or elevated INR may be more likely to experience one or more subsequent events. For the GEE models predicting bleeding events, an m-dependent correlation structure was used, which assumes that the correlation within an individual differs depending on the time (in weeks) between responses. As there were fewer weeks with INR results measured, an exchangeable correlation structure was applied for the GEE models evaluating supratherapeutic INR. This assumes a constant correlation between all pairs of diary responses for each patient. All factors hypothesized to be associated with each outcome were assessed in separate GEE models. To account for the delay in therapeutic response, outcomes were deemed relevant to exposures occurring in the current week if the outcome occurred Thursday through Sunday, whereas outcomes were deemed relevant to exposures in the previous week if the outcome occurred Monday through Wednesday.

The GEE models for each outcome (i.e., either bleeding event or supratherapeutic INR) were developed in two steps. Initially, all potential non-CAM confounders with at least three temporally related adverse events based on the above criteria were entered into separate multivariate GEE models for the two outcomes. A backward stepwise approach was then used to develop models that best fit the data to predict both outcomes. Risk factors were retained in the models if they were deemed clinically relevant or were associated with the outcome with a probability of a type 1 error of a p value less than 0.20. Once all potential non-CAM confounders were incorporated into the model using these criteria, each CAM was entered into the model individually, and adjusted ORs and 95% CIs were then determined for each CAM. Finally, separate fully adjusted models were developed including all potential confounders and all CAM that were associated with the applicable outcome (i.e., either bleeding event or supratherapeutic INR) with a probability of a type 1 error of a p value less than 0.20.

All statistical analyses were performed by using SAS software version 8.2 (SAS Institute Inc., Cary, NC), and 2-sided significance tests were used throughout the analysis.

Results

One hundred seventy-one subjects enrolled in the study, each completing at least 4 weeks of surveys and most (159 [93%]) completing at least 15 weeks. In 155 subjects (91%), the INR was measured at least once (mean 6.1 ± 3.5 measurements) during the period when they were completing their diaries. Among the 171 participants, 68% were male and 32% were female, with atrial fibrillation (46%) and mechanical heart valves (23%) being the most common indications for warfarin (Table 1). Seventy-eight participants (46%) reported using at least one CAM during the data collection
period, including 73 patients (43%) who used a CAM that has been implicated in increasing the risk of bleeding or the occurrence of a supratherapeutic INR (Table 2). Vitamin E, at a median dose of 400 IU/day, was the most commonly used CAM (26% of subjects). A total of 78 CAM treatment courses were recorded, of which 37 (47%) involved the use of CAM for the entire diary period. Approximately half of the participants reported the use of a prescription drug that potentially interacts with warfarin, with amiodarone and omeprazole being the most common. Two thirds reported use of interacting nonprescription drugs, most commonly acetaminophen.

During the survey period, 873 INR measurements were obtained. Of these, 53 (6%) in 36 patients (21%) were at least 0.5 units above the target range. Eighty-seven (51%) of the 171 patients reported a bleeding event in 386 (15%) of the 2660 survey weeks. The 386 bleeding events were categorized by the patients as follows: 159 (41%) excessive bruising beyond what you typically experience while taking warfarin, 58 (15%) nosebleed, 26 (7%) blood in stool, 21 (5%) excessive bleeding from a cut, 7 (2%) blood in urine, 3 (0.8%) hemorrhage in eye, 2 (0.5%) excessive bleeding from tooth extraction, 2 (0.5%) internal bleeding, and 108 (28%) not specified. As hypothesized, a positive, although nonsignificant, association was noted between a supratherapeutic INR and self-reported bleeding events (GEE OR 1.84, 95% CI 0.99–3.41).

The results of two multivariate GEE models evaluating the associations between potential non-CAM confounders and bleeding events or supratherapeutic INRs are illustrated in Tables 3 and 4. The numbers of diary weeks that study patients were exposed to each risk factor are listed in each table, with Table 4 listing the results only for the weeks when an INR result was available. Statistically significant risk factors for bleeding events included high target INR (2.5–3.5), diarrhea, acetaminophen use, increased alcohol consumption, and increased age (Table 3). Completion of the diary during the winter or spring months and an increased warfarin dosage were associated with a lower risk of bleeding events.

Consistent with the results for bleeding events, although not statistically significant, increasing the dosage of warfarin was also associated with a lower risk of supratherapeutic INR, whereas

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**Table 1. Characteristics of the 171 Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD (range)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>66.3 ± 11.4 (20–87)</td>
</tr>
<tr>
<td>Warfarin dosage (mg/week)</td>
<td>33.5 ± 17.5 (9.5–150)</td>
</tr>
</tbody>
</table>

**Table 2. Exposures Reported to Increase the Risk of Bleeding or Supratherapeutic International Normalized Ratio in the 171 Patients**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K–rich foods</td>
<td>8.1 ± 6.3</td>
</tr>
<tr>
<td>Fever</td>
<td>14 (8.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>68 (39.8)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>128 (74.9)</td>
</tr>
<tr>
<td>Use of prescription drug with reported antiplatelet effects</td>
<td>10 (5.8)</td>
</tr>
<tr>
<td>Use of prescription drug reported to increase INR</td>
<td>75 (43.9)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>21 (12.3)</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>12 (7.0)</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>11 (6.4)</td>
</tr>
<tr>
<td>Ramitidine</td>
<td>11 (6.4)</td>
</tr>
</tbody>
</table>

**Use of potentially interacting nonprescription drug**

<table>
<thead>
<tr>
<th>Exposures</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>44 (25.7)</td>
</tr>
<tr>
<td>Glucosamine</td>
<td>19 (11.1)</td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>14 (8.2)</td>
</tr>
<tr>
<td>Garlic, supplemental</td>
<td>13 (7.6)</td>
</tr>
</tbody>
</table>

INR = international normalized ratio; CAM = complementary and alternative medicine.

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*Any exposure during the survey period.

*Only those agents with > 5% exposure are listed.

*Some previous case reports suggest coenzyme Q10 can decrease INR, although the evidence is inconsistent.
short duration of warfarin use (< 3 mo) was an independent risk factor for a supratherapeutic INR (Table 4). The use of acetaminophen, amiodarone, and other prescription drugs reported to increase INR were also associated with an increased risk of a supratherapeutic INR. Although these associations did not reach statistical significance, they were consistent with the hypothesized effect on outcome and therefore the variables were retained in the final model to ensure the maximal explanation of the variance of the dependent variable before adding CAM variables to the model. It should be noted that some patients documented dosage increases during the data collection period for amiodarone (dosage increased during 4 diary wks) and acetaminophen (dosage increased during 100 diary wks). This may have affected the impact of these exposures on INRs measured during subsequent weeks. However, there were relatively few weeks in which both INR measurements and dosage increases occurred. This precluded the use of “dosage compared with previous week” as a separate variable, thus total exposure was used in the analysis for these drugs.

Crude and adjusted ORs for the association between the use of specific CAMs and the occurrence of a bleeding event or a supratherapeutic INR are illustrated in Figures 1 and 2, respectively. Adjusted ORs represent the association between each individual CAM and the specific outcome, adjusted for other potential non-CAM confounders found in Tables 3 and 4 based on the a priori criteria for model inclusion. All
CAMs considered for evaluation are included in the figures, but results are only reported for CAMs with at least three associated adverse events.

In both the crude and adjusted models, all CAM except salmon oil and vitamin E were positively associated with the occurrence of a bleeding event (Figure 1). In the adjusted model, statistically significant associations between the use of several individual CAMs and bleeding events were identified: cayenne (OR 8.0, 95% CI 3.57–17.92), coenzyme Q10 (OR 3.91, 95% CI 2.09–7.31), ginger (OR 6.63, 95% CI 3.49–12.61), St. John’s wort (OR 4.70, 95% CI 1.49–14.79), and willow bark (OR 9.00, 95% CI 6.42–12.62). There was also a significant positive association between the use of two or more CAMs and a bleeding event (OR 2.11, 95% CI 1.07–4.16). No individual CAM significantly increased the risk of a supratherapeutic INR, nor did the number of CAMs used over the 16-week diary period (Figure 2).

In the fully adjusted multivariate model, coenzyme Q10 (OR 3.69, 95% CI 1.88–7.24) and ginger (OR 3.20, 95% CI 1.42–4.24) remained statistically significant independent risk factors for bleeding (Figure 3). No CAMs were independent risk factors for a supratherapeutic INR.

A priori sample size calculations were not carried out, as it was difficult to predict both the usage rate of specific CAMs and the number of outcomes expected over the 16-week data collection period for each patient. Post hoc GEE sample size calculations based on the observed data and the correlation structures used in the analysis suggest that the study sample was large enough to detect a relative risk larger than 1.9 or smaller than 0.52 for bleeds, and larger than 2.3 or smaller than 0.43 for elevated INR. Many of the relative risk ratios observed of individual CAMs were beyond these ranges; however, a larger sample size may have resulted in some of the nonsignificant associations reaching significance.

During the survey period, two patients with bleeding were seen in an emergency department. Neither participant reported having used CAM or any other interacting prescription or nonprescription drugs, during the study period. Both

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Supratherapeutic INRs</th>
<th>Weeks Exposed to Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of time taking warfarin 12 mo (reference)</td>
<td>32</td>
<td>609</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–12 mo</td>
<td>7</td>
<td>125</td>
<td>0.91</td>
<td>0.38–2.14</td>
<td>0.82</td>
</tr>
<tr>
<td>&lt; 3 mo</td>
<td>8</td>
<td>63</td>
<td>2.90</td>
<td>1.10–7.63</td>
<td>0.03</td>
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<tr>
<td>Alcoholic consumption compared with previous week²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased</td>
<td>1</td>
<td>59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>7</td>
<td>83</td>
<td>1.86</td>
<td>0.93–3.73</td>
<td>0.08</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>17</td>
<td>208</td>
<td>1.76</td>
<td>0.85–3.63</td>
<td>0.13</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>10</td>
<td>106</td>
<td>1.63</td>
<td>0.60–4.42</td>
<td>0.34</td>
</tr>
<tr>
<td>Prescription drug that may increase INR²</td>
<td>26</td>
<td>322</td>
<td>1.48</td>
<td>0.60–3.62</td>
<td>0.39</td>
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<tr>
<td>Warfarin dosage compared with previous week²</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Decreased</td>
<td>18</td>
<td>154</td>
<td>0.62</td>
<td>0.38–1.02</td>
<td>0.06</td>
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<tr>
<td>Increased</td>
<td>12</td>
<td>198</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin K servings compared with previous week²</td>
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<tr>
<td>Decreased</td>
<td>21</td>
<td>335</td>
<td>0.95</td>
<td>0.66–1.38</td>
<td>0.81</td>
</tr>
<tr>
<td>Increased</td>
<td>16</td>
<td>286</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

INR = international normalized ratio; OR = odds ratio; CI = confidence interval.
Only weeks in which an INR result was available were evaluated.
²The OR assumes that the risk associated with increased and decreased consumption, dosage, or servings follows a linear pattern, thus one OR is estimated; for example, the OR for increased consumption compared with previous week = 1/OR for decreased consumption.
³Not including amiodarone. In descending order of frequency: allopurinol, omeprazole, ranitidine, levotirothyroxine, glyburide, propafenone, quinidine, paroxetine, celecoxib, lovastatin, sertraline, sulfonamide, phenylbutazone, propranolol, salicylate, sultonylurea, propylthiouracil, flutamide, fenofibrate, ciprofloxacin, rofecoxib, clarithromycin, itraconazole, tetracycline, cotrimoxazole, fluconazole, norfloxacin, influenza vaccine.
patients had a stable warfarin dosage over the previous several months. Another patient with upper gastrointestinal bleeding was admitted to the hospital during the diary period. Although this patient’s warfarin dosage had been stable for several months, he had started taking naproxen 375 mg/day 2 days before the bleeding event and was a frequent user of potentially interacting CAM. Specifically, he reported using vitamin E 800 IU consistently for several months and had recently started supplemental garlic, cayenne, devil’s claw, and coenzyme Q10. His INR measured 4 days before the bleed was 1.5 (target INR range 2.0–3.0). The patient received fresh frozen plasma and vitamin K in the emergency department. Although the INR result from the same day was 1.8, the timing of this measurement relative to administration of fresh frozen plasma and vitamin K was unclear. After a 3-day hospitalization, the patient was discharged and warfarin was restarted.

Discussion

To our knowledge, this is the first longitudinal analysis of risk factors associated with warfarin-related adverse events, and the first prospective study to thoroughly evaluate the risk of CAM usage in this population. Of the 171 study participants, 93% completed at least 15 weeks of follow-up, resulting in a total of 2660 weeks of warfarin exposure included in the analysis. The longitudinal nature of the study in conjunction with essentially complete follow-up and high rate of CAM exposure resulted in a sample that is particularly well suited for evaluation of the potential impact of CAM-warfarin interactions. Specific analytic techniques were used to overcome some common difficulties associated with evaluating risk factors for warfarin-related adverse events in the general population, in particular, the sporadic use of CAM (as illustrated by this study sample) and the variable delay in response to risk factor exposure. The identification of previously reported non-CAM risk factors for bleeding and supratherapeutic INR provides evidence of face validity that thereby lends support to the CAM results. Specifically, after adjusting for the identified non-CAM risk factors, coenzyme Q10 and ginger were significantly associated with self-reported bleeding, whereas no CAM therapy significantly increased the risk of a supratherapeutic INR.

This study sample represents a typical cross

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**Figure 1.** Crude (gray bars) and adjusted (black bars) odds ratios for the association between each individual complementary and alternative medicine (CAM) and the occurrence of a self-reported bleeding event.

**Figure 2.** Crude (gray bars) and adjusted (black bars) odds ratios for the association between each individual complementary and alternative medicine (CAM) and the occurrence of a supratherapeutic international normalized ratio (INR).
section of patients taking warfarin in terms of sex, age, and indication, which supports the external validity and generalizability of the results. The rate of supratherapeutic INRs was also similar to that of previous cohort studies, whereas the rate of bleeding was relatively high. Approximately half of the patients (51%) in this sample reported minor bleeding during their 4-month survey period, whereas previous large randomized trials evaluating warfarin anticoagulation for stroke prevention have estimated the rate of minor bleeding, including ecchymoses, at approximately 21%/patient-year. The lower previously reported minor bleeding rate may reflect the tight control of anticoagulation achieved under the scrutiny of a clinical trial. Conversely, the higher rate of bleeding reported here may represent a reporting bias, in that study participants may have been more diligently monitoring and documenting minor events. It would be expected that those who volunteer to keep detailed weekly diaries over a 4-month period would be more inclined to notice and document minor events than would the general population taking warfarin.

Non-CAM Risk Factors for Bleeding and Supratherapeutic INR

The risk factors for bleeding and supratherapeutic INR identified in this study are consistent with those identified in larger studies. One of the most important risk factors for bleeding identified in this and previous studies is a high target INR. Increased age was also an independent risk factor for bleeding in this study, which is also consistent with previous research. Diarrhea, which can decrease vitamin K absorption, has been reported by others to increase the risk of supratherapeutic anticoagulation and bleeding. Increased warfarin dosage was associated with a lower risk of both bleeding and supratherapeutic INR. Although this may at first seem counterintuitive, it is logical when one considers the delay in therapeutic response associated with warfarin dosage adjustment. Since warfarin dosage would be increased in response to a low INR, it is logical that there was a low risk of a supratherapeutic INR at the point when the warfarin dosage was increased. Since bleeding risk is lower when INR is low, it also makes sense that there was an association between a low bleeding risk and an increased warfarin dose.

Increased alcohol consumption was identified as a risk factor for bleeding, and there was a nonsignificant trend toward increasing the risk of supratherapeutic INR. Increased alcohol consumption by patients without liver disease has been associated with supratherapeutic INR, but not in all studies. Acetaminophen consumption increased the risk of bleeding in this sample, potentially through the nonsignificant trend toward increased risk for supratherapeutic INR among acetaminophen users. Amiodarone use was also associated with a nonsignificant increased risk of supratherapeutic INR. A recent systematic overview of warfarin drug interactions categorized amiodarone’s ability to potentiate warfarin anticoagulation as “highly probable,” whereas acetaminophen was categorized as “probable.”

Study participants were significantly less likely to report bleeding in the winter and spring months compared with summer or fall. Studies evaluating seasonal variation in intensity of
warfarin anticoagulation have produced inconsistent results,\textsuperscript{25,26} and too few supratherapeutic INRs were reported to evaluate a seasonal effect in depth. It is possible that the decreased bleeding rate was the result of decreased activity during colder months, or that patients were less likely to notice bleeding and bruising when they wore heavier clothing.

Use of CAM and the Risk of Warfarin-Related Adverse Events

More than 45\% of patients reported the use of at least one CAM during the survey period, and 43\% had used CAM previously to interact with warfarin, most commonly vitamin E, glucosamine, coenzyme Q\textsubscript{10}, and supplemental garlic. These usage patterns are consistent with those of previous cross-sectional surveys of the general North American population\textsuperscript{7} and cardiovascular patients,\textsuperscript{9,11,27} but higher than those of previous surveys of patients taking warfarin.\textsuperscript{10,28–30}

Although the high rate of vitamin E use in this study allowed precise estimates of the associated risk, there was a neutral effect on both bleeding and supratherapeutic INR, which is consistent with what has been reported previously. Although there are reports that vitamin E use may be associated with an exaggerated response to warfarin, the only published double-blind, randomized study demonstrated negligible effects on INR at moderate-to-large doses (800–1200 IU/day).\textsuperscript{8,31,32}

Several other CAMs were associated with a statistically significant increased risk of bleeding when evaluated by univariate analysis, but none increased the risk of supratherapeutic INR. Those increasing the risk of bleeding included cayenne, ginger, willow bark, St. John’s wort, and coenzyme Q\textsubscript{10}, all of which have been previously reported to interact with warfarin or increase the risk of bleeding.\textsuperscript{31} Although previous studies have reported lower warfarin concentrations associated with the concurrent use of St. John’s wort, it was associated with an increased risk of self-reported bleeding by univariate analysis in the current study.\textsuperscript{31} Since St. John’s wort did not remain a significant predictor of bleeding events in the fully adjusted model, the univariate association may be related to the small number of exposures evaluated (four bleeds over 22 wks of exposure), or confounded due to the relationship between the use of St. John’s wort and other risk factors for bleeding.

Only ginger and coenzyme Q\textsubscript{10} were statistically significant independent risk factors for bleeding when all CAM and non-CAM risk factors were taken into consideration. Previous research evaluating interactions between warfarin and either ginger or coenzyme Q\textsubscript{10} has produced conflicting results. Coenzyme Q\textsubscript{10} is structurally related to menaquinone (vitamin K\textsubscript{2}), and there have been several case reports of a decreased response to warfarin after starting coenzyme Q\textsubscript{10}.\textsuperscript{31} However, in the only published, double-blind, randomized trial, 4 weeks of coenzyme Q\textsubscript{10} 100 mg/day did not affect weekly INR results in 24 patients.\textsuperscript{33} As far as we are aware, our study is the first to report an increased risk of bleeding in patients taking warfarin and coenzyme Q\textsubscript{10}. This may represent a previously undetected interaction, or may be the play of chance owing to the small number of patients (15 patients) reporting consumption of coenzyme Q\textsubscript{10}.

Cases have been reported of altered platelet aggregation and severely supratherapeutic INR thought to be due to the ingestion of large quantities of ginger by patients taking warfarin.\textsuperscript{34,35} Although ginger has been reported to reduce platelet function in some, but not all studies,\textsuperscript{31,35–37} there was no effect on INR, platelet aggregation, or warfarin clearance in 12 healthy male subjects receiving recommended doses of ginger for 7 days.\textsuperscript{38} Unlike most previous studies, the therapeutic constituents of the ginger product were confirmed by high-performance thin-layer chromatography.

The only patient to experience a major bleed in our study reported using multiple CAMs, including several associated with bleeding in this analysis, particularly coenzyme Q\textsubscript{10}. The patient also took vitamin E 800 IU/day; a dosage that has been associated with bleeding and prolonged prothrombin time in at least one case report involving a patient receiving warfarin.\textsuperscript{39} However, the strongest contributor to bleeding risk was likely the recent initiation of naproxen.\textsuperscript{40}

Given the large number of reported potential interactions between warfarin and CAM, it is somewhat surprising that the prevalence of CAM use is so high among patients receiving warfarin. Whereas previous studies have recorded a lower prevalence of CAM use, some queried the use of specific herbal products only, yet the rate of use was still 19–27\%.\textsuperscript{10,28–30} Caregivers may be unaware of CAM use in many cases, whereas both patients and caregivers may be unaware of the potential risks. Previous surveys suggest that most patients receiving warfarin do not disclose
CAM use to the health care providers.28, 29 Furthermore, physicians and pharmacists generally score poorly in surveys designed to test their knowledge of alternative medicines, few regularly ask their patients about CAM use, and even fewer document the use of these agents.41–44 Perhaps CAM usage among patients taking warfarin would decrease with improved communication between patients and caregivers and with more thorough education regarding CAM products.

Limitations

There are several limitations to this study that should be considered. Not every factor that could be associated with bleeding or supratherapeutic INRs was controlled for in the analysis. To avoid multivariate model instability and inconsistent results, a limited number of variables can be assessed. However, data were collected for the most common previously reported risk factors, and all those with a sufficient number of exposures were accounted for in the analysis. Another limitation was the small number of supratherapeutic INR results, which limited the ability to identify significant risk factors for this outcome. Although there were enough bleeding events to draw conclusions regarding risk factors, self-reported bleeding is somewhat subjective and patients’ interpretations of what warranted documentation likely varied. For both of these limitations, however, consistent trends between the bleed and supratherapeutic INR data sets for several variables provide a measure of the face validity of these results. Furthermore, there is no reason to believe that patients using CAM were more likely to report a bleeding event because study subjects were not explicitly informed that the primary focus of the study was CAM use. Finally, some patients may have been consuming very small doses of CAM products that would not be expected to influence the risk of bleeding or supratherapeutic INR. Although the surveys asked patients to record the dosage and brand of all CAM products consumed, this information was not always thoroughly documented, and the actual content of the active component of the CAM product is highly variable.

Conclusion

To our knowledge, this is the first longitudinal analysis of risk factors for bleeding and supratherapeutic INR in patients taking warfarin, along with a comprehensive evaluation of risk associated with CAM use in this population. In support of the validity of the data, several previously identified risk factors for bleeding were confirmed, including high target INR, diarreha, acetaminophen use, increased alcohol consumption, and increased age. These data suggest that the use of some CAM therapies, specifically ginger and coenzyme Q10, appear to increase the risk of bleeding in patients taking warfarin. Although these results need to be confirmed by randomized trials, patients taking warfarin should be cautioned regarding potential CAM and non-CAM interactions reported here and in previous studies.

References


Appendix 1. Complementary and Alternative Medicines Listed in the Study Diary

Angelica root
Arnica flower
Anise
Asafoetida
Bajiaolian
Bogbean
Borage seed oil
Bromelain
Cayenne
Chamomile
Clove
Coenzyme Q10
Danshen (tan seng)
Devil's claw
Don qui
Fenugreek
Feverfew
Gingko biloba
Garlic (beyond that used to flavor foods)
Ginger root (beyond that used to flavor foods)
Ginseng: Siberian
Ginseng: Asian or Oriental
Horse chestnut
Kelp
Licorice root
Meadowsweet
Papain
Papaya
Parsley
Passionflower
Poplar
Quassia
Red clover
Rue
St. John's wort
Sweet clover
Turmeric
Vitamin E
Willow bark
Other complementary and alternative medicines
(please specify):