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## Risk of warfarin-related bleeding events and supratherapeutic international normalized ratios associated with complementary and alternative medicine: a longitudinal analysis.

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### Abstract

**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 Q(10). 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 Q(10) (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 Q(10) or ginger appears to increase the risk of bleeding in this population.

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