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# Effect of Coenzyme $Q_{10}$ and Ginkgo biloba on Warfarin Dosage in Stable, Long-term Warfarin Treated Outpatients. A Randomised, Double Blind, Placebo-crossover Trial

Dear Sir,

It has been reported that Coenzyme $Q_{10}$ ($CoQ_{10}$) interacts with warfarin treatment in the form of a decreased response to warfarin (1, 2). Moreover, it has been suggested that Ginkgo biloba causes an increased response to warfarin (3). Food supplements and different herbal remedies have become increasingly popular during the last decade. However, scientific data on action and interaction are lacking in most cases. One particular safety concern is potential interactions of health care products with prescription medicine. This issue is especially important with respect to drugs with a narrow therapeutic window, such as warfarin. The use of oral anticoagulants (OAC) has increased threefold during the last decades in Denmark and presently approximately 0.4 % of the Danish population receives OAC (4). About 5 % of the Danish population take $CoQ_{10}$ and Ginkgo biloba is assumed to be equally popular. $CoQ_{10}$ is used as therapy for a variety of cardiovascular disorders, including heart failure, angina and arrhythmias (5). Many patients with these conditions may also be prescribed warfarin. The elimination half-life of $CoQ_{10}$ is 33-34 h (6).

Ginkgo biloba, a common herbal product, is advertised to improve cognitive function and it is often used against circulatory disturbances. Ginkgo leaves contain two main types of constituents, flavonoids and terpenoids. The elimination half-life of Ginkgo biloba is between 2 and 6 h (7).

The aim of the study was to evaluate a possible interaction between Coenzyme $Q_{10}$ and warfarin, and between Ginkgo biloba and warfarin in a group of middle-aged outpatients on stable long-term warfarin treatment. The trial was designed as a double blind crossover study with three treatment periods of four weeks in random order separated by wash-out periods of two weeks. During each of the three treatment periods, the patients once daily received a capsule of $CoQ_{10}$ 100 mg + a placebo tablet, a placebo capsule + a tablet of Ginkgo biloba 100 mg, and a placebo capsule + a placebo tablet. Pharma Nord ApS, Vejle, Denmark, kindly donated the study medication $CoQ_{10}$ (Bio-Quinone®) and Ginkgo biloba (Bio-Biloba®) and placebo. INR was kept between 2.0 and 4.0 by appropriate adjustment of the warfarin dosage. Twenty-four patients, aged 33-79 years, median 64.5 years, 10 males and 14 females, treated with long-term warfarin for recurrent venous thromboembolism, mechanical heart valves or chronic atrial fibrillation were enrolled into the study. Twenty-one patients completed all three phases of the study. Major bleedings or thromboembolic events were not observed.

The stability of INR values during each treatment period was confirmed by linear regression of INR values on weeks of treatment and the slope of the regression line did not differ significantly from zero (Fig. 1). The mean INR value ± SD was 2.7 ± 0.34 during treatment with $CoQ_{10}$ , 2.7 ± 0.38 during treatment with Ginkgo biloba, and 2.7 ± 0.36 during placebo treatment. The geometric means of warfarin

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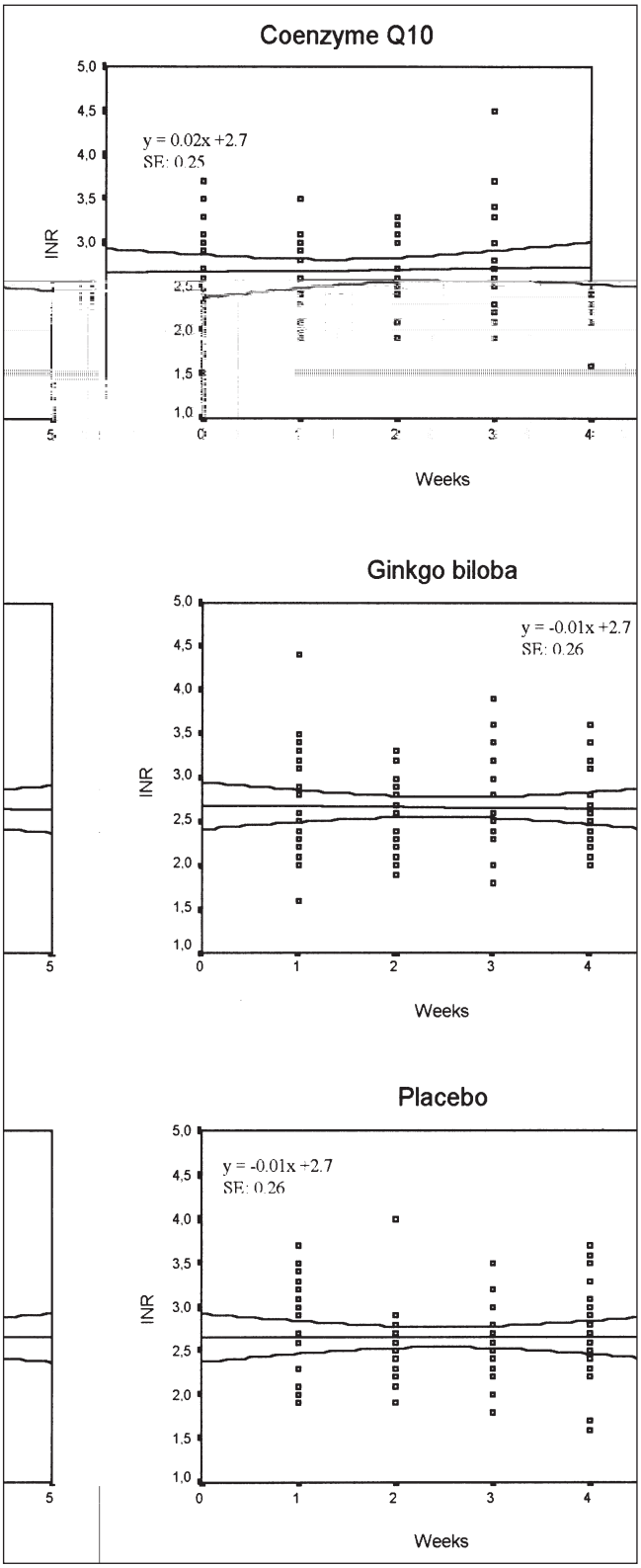


*Fig. 1* Linear regression of INR on time for each of the three treatment periods. The regression lines and 95% confidence interval are shown

dosage were for Ginkgo biloba 36.7 mg/week (95% confidence interval: 29.2-46.0); $CoQ_{10}$ 36.5 mg/week (29.1-45.8) and for placebo 36.0 mg/week (28.6-45.1). The serum concentration of $CoQ_{10}$ increased by approximately a factor two in all patients during the $CoQ_{10}$ treatment period. Routine laboratory and clinical variables did not vary significantly during the study periods.

The aim of our study was to evaluate the possible interaction of OAC with two commonly used health care products. Contrary to previous reports we found that use of $CoQ_{10}$ and Ginkgo biloba had no statistically significant influence on the response to OAC (1-3). The discrepancy may be due to unstable OAC treatment in previous reports, use of the health care products in the treatment of conditions known to influence OAC treatment, or impurities in the used products. The stability of OAC treatment is difficult to ensure in single case reports. In the present study the patients had been on stable warfarin treatment for several months. Interaction observed in case reports may be due to health problems rather than the health care product. Fever, diarrhoea, heart failure, and a number of other health problems are known to influence the response to OAC treatment but may also be the reason that a patient starts to take health care products or non-prescription drugs. Our study does not exclude the possibility that interaction may occur if other brands of Ginkgo biloba had been used. Unlike conventional drugs, herbal products are not regulated for purity and potency. Thus, some of the adverse effects and drug interaction reported could be caused by impurities. Ginkgo leaf contains two main types of constituents, flavonoids and terpenoids. One of the terpenoids, ginkgolide B, inhibits platelet activating factor (PAF) and long term use may cause prolonged bleeding time and spontaneous bleeding (8-10). Although the present study suggest that $CoQ_{10}$ and Ginkgo biloba do not alter the response to warfarin we recommend close monitoring of INR if a patient decides to use these or other health care products to overcome discomfort. The initiative of the patient may shield health problems that can influence the effect of OAC.

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# Variation in Relative Risk of Venous Thromboembolism in Different Cancers

Dear Sir,

Data from a number of epidemiologic studies show significant variation in the risk of venous thromboembolism according to the histological origin of a cancer.

A study of 21,530 Swedish autopsies (1) over a 24-year period showed the highest prevalence of pulmonary embolism for patients with ovarian carcinoma, cancer of the extrahepatic bile duct system or stomach (34.6%, 31.7%, and 15.2%, respectively). Patients with cancer of the oesophagus and larynx, leukaemia, myelomatosis, and malignant lymphoma had the lowest prevalence (0-5.6%).

In a large population registry study of 61,998 patients admitted with acute deep vein thrombosis (DVT) or pulmonary embolism (PE), Barron et al. (2) showed that in occult cancers, the sites most commonly associated with VTE were ovary, pancreas, brain and liver with SIRs of between 11.4 and 6.6. Tumours of the breast, rectum and oesophagus were less frequently associated, with SIRs ranging from 1.8 to 2.0. The hematological malignancies, lymphomas and leukaemias, however had significantly higher VTE risks with SIRs between 4.2 and 7.4. Both these studies show a broadly similar trend in VTE risks by histological origin.

We have sought to estimate the extent of such variation by calculating the relative risk of venous thromboembolism according to the site of origin of cancer.

Data for this study is taken from the dataset presented by Levitan et al. (3), who used the "Medicare Provider Analysis and Review Record" (MEDPAR) database that records the primary discharge diagnosis and an additional 4 discharge diagnoses. The limitations of the MEDPAR database have been previously discussed in detail (3). Further analysis of this data was undertaken with the aim of calculating the relative risk of venous thromboembolism (VTE) for patients with different types of cancer when compared to hospitalised patients without cancer but who were still at risk of developing thrombosis because of their co-morbidities.

The data consists of 9,389,578 patients over the age of 65 years who were hospitalised over a 3-year period from 1988 to 1990 inclusive. Of these, 8,177,634 had a diagnosis of non-malignant disease, of whom 46,848 also had a diagnosis VTE. There were 1,211,944 patients with cancer, of whom 7,238 had VTE. The cancer category was further

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