Warfarin's Real Impact Less Than in Trials

BY MITCHEL L. ZOLER

ORLANDO — Warfarin was not nearly as effective in the real world as it has been in clinical trials for reducing the risk of stroke in patients with atrial fibrillation, in a review of about 50,000 patients.

Analysis of the same database also showed that fewer than half of the atrial fibrillation patients who were apparently ideal candidates for warfarin received it, Stephen D. Sander, Pharm.D., said at the annual meeting of the American College of Cardiology.

The unexpectedly low benefit from warfarin therapy "indicates that even when prescribed, the level of anticoagulation achieved may not be optimal to obtain the dramatic effect [from warfarin] observed in clinical trials," said Dr. Sander, associate director of health economics and outcomes research at Boehringer Ingelheim Pharmaceuticals Inc.

In the patients included in the review, warfarin cut the stroke rate by 15% relative to patients not on warfarin (a 1.2% absolute reduction) in an analysis that controlled for clinical and demographic differences among the patients in the two treatment groups. In contrast, clinical trial results showed that warfarin treatment drops the stroke rate by 60%-70% compared with no anticoagulant treatment, said Dr. Frederick A. Masoudi, a cardiologist at Denver Health Medical Center.

The study used data collected by HealthCore in its Integrated Research Database of more than 20 million commercially insured beneficiaries during January 2004–February 2008. The database included more than 100,000 patients aged 18 or older with atrial fibrillation, with at least two medical claims for the condition and continuous medical insurance coverage during at least 6 months before and at least 6 months after the index atrial fibrillation claim.

From this group, the analysis identified slightly more than 50,000 patients who had no transient cause of atrial fibrillation and no valvular disease. In this subgroup, 41% received at least two prescriptions for warfarin.

Dr. Sander and his associates further reduced the study group by focusing on the nearly 19,000 patients with no apparent pre-

cautions in their medical charts against warfarin use and with at least one risk factor for stroke based on guidelines from the American College of Chest Physicians. Among these patients who constituted an "ideal" population for warfarin treatment, 42% received two or more prescriptions and 57% received no prescriptions. (The remaining 1% received a single warfarin prescription.)

Patients were less likely to receive warfarin if they were

> 'The level of anticoagulation achieved may not be optimal to obtain the dramatic effect' seen in trials.
>
> DR. SANDER

women, and if they were older than 75. In addition, warfarin use fell with increasing CHADS$_2$ score (congestive heart failure, hypertension, age greater than 75, diabetes, and prior stroke or transient ischemic attack), a measure of the likelihood of stroke occurring in atrial fibrillation patients. This finding is especially surprising because ideally warfarin use should increase as patients' CHADS$_2$ scores increase, an indication of a higher stroke risk, Dr. Masoudi said.

Warfarin use was above average for patients located in the northeastern and western United States, and below average in the midwest and southern regions, Dr. Sander said.

The findings also inexplicably showed that the incidence of hemorrhagic strokes and of bleeding episodes requiring hospitalization were significantly lower in patients who received warfarin, compared with those who did not get the anticoagulant.

Data on testing for the international normalized ratio, available for 748 patients on warfarin, showed that on average these patients spent 55% of the time they were followed in the INR target range of 2.0-3.0, 30% of the time with an INR less than 2.0, and 15% of the time with an INR greater than 3.0. About a quarter of the patients were in the INR target range more than 70% of the time they were tested, and 46% of the patients were in the INR target range less than 40% of the time, Dr. Sander said. ∎

MINDFUL PRACTICE

Vitamin K for Excessive Anticoagulation

BY JON O. EBBERT, M.D., AND ERIC G. TANGALOS, M.D.

The Problem
A 61-year-old man with a history of atrial fibrillation on anticoagulation with warfarin, hypertension, and type 2 diabetes mellitus presents to you with an international normalized ratio of 5.8. He has had an INR in the range of 2.0-3.0 on 5 mg of warfarin daily, and 5 days ago he was started on levofloxacin for community-acquired pneumonia. He says he is not bleeding more easily than usual, and reports no hematochezia. Your clinic recently initiated a nurse-protocol INR adjustment, and your nurse is inquiring as to whether you would like to give the patient vitamin K to reduce his risk for bleeding. Your colleague mentions recent evidence suggesting that vitamin K does not reduce bleeding events. You decide to review the evidence.

The Question
In patients with excessive anticoagulation on warfarin, does vitamin K reduce the risk of bleeding events, compared with holding and reducing the warfarin dose?

The Search
You log on to PubMed (www.pubmed.gov) and search "anticoagulation AND vitamin K," limiting the search to randomized, controlled trials. You find a relevant study. (See box at right.)

Our Critique
This clinical trial was well-designed, with appropriate randomization. Impressively, only 1.7% of patients were lost to follow-up. Although some readers may have concerns about the lack of study control over subsequent management of INR interventions by treating clinicians, randomization theoretically balances unknown variables such as heterogeneity in clinical approaches in the two study arms. In other words, both groups can be considered to be balanced for all interventions apart from receiving the vitamin K or placebo. By study design, only patients with an elevated INR who had not bled were enrolled, which leaves open the possibility of a "healthy cohort" bias. This study has great value in the presentation of contemporary data on the rate of major bleeding in a population of anticoagulated patients in North America and Italy. Reassuringly, the rate of major bleeding is low. However, clinicians may still be inclined to prescribe vitamin K in the hope that it will prevent a subsequent major bleed.

Clinical Decision
You discuss the situation with the patient. You agree to hold warfarin for 1 day and restart him on 3 mg per day with a recheck in 3 days.

DR. EBBERT and DR. TANGALOS are with the Mayo Clinic in Rochester, Minn. They have no conflict of interest to report. To respond to this column or suggest topics for consideration, write to Dr. Ebbert and Dr. Tangalos at our editorial offices or e-mail them at imnews@elsevier.com.

Crowther MA, et al.
Oral vitamin K versus placebo to correct excessive anticoagulation in patients receiving warfarin: A randomized trial. Ann. Intern. Med. 2009;150:293-300.

▶ **Design and Setting:** Randomized, blinded clinical trial conducted at outpatient anticoagulation therapy clinics in Canada, Italy, and the United States.

▶ **Subjects:** Potential subjects were eligible for inclusion if they were currently receiving warfarin with a target INR of 2.0-3.5, and had an INR value greater than 4.49 drawn within last 24 hours. Potential subjects were excluded if they electively discontinued warfarin, were under 18 years of age, had a life expectancy of less than 10 days, had an indication for the acute normalization of INR (e.g., active major bleeding), had severe liver disease, had a recent (within 1 month) history of a major bleeding episode, had a known bleeding disorder or thrombolytic therapy within 48 hours, had a known allergy to vitamin K, were unable to take oral medications, had known significant thrombocytopenia, and were unable to return for follow-up evaluations.

▶ **Intervention:** Subjects were instructed to stop warfarin for 1 day and then were randomly assigned to 1.25 mg vitamin K or placebo. Additional INR sampling necessary to manage the patient was completed at the discretion of the treating physician. Clinics were advised to reinstitute warfarin therapy once the INR was within the therapeutic reference interval.

▶ **Outcomes:** The primary outcome measure was frequency of bleeding events at 90 days. "Major bleeding" was defined as fatal bleeding, bleeding requiring at least 2 units of blood, bleeding resulting in a therapeutic intervention, or confirmed bleeding into a closed space. "Minor bleeding" was defined as bleeding resulting in a medical assessment and not meeting the definition of major bleeding. Secondary outcome measures included major bleeding, thromboembolism, and death at 90 days.

▶ **Results:** A total of 724 subjects were randomized (355 to vitamin K, 369 to placebo), and subjects were similar at baseline. No significant difference was observed between the groups in the number of subjects who had at least one bleeding complication (15.8% vitamin K vs. 16.3% placebo), and no significant difference was observed in major bleeding between the vitamin K and placebo groups (2.5% vs. 1.1%). In addition, no significant difference was observed in thromboembolism between the two groups (1.1% vs. 0.8%). As expected, mean INR decreased more in the vitamin K group than in those who received placebo.