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LOW INTENSITY WARFARIN THERAPY

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ABSTRACT

Background and Objective. Several studies comparing different intensities of oral anticoagulant treatment have clearly shown a relationship between bleeding complications and prolongation of prothrombin time. In the early '50s, de Takats suggested that low-dose oral anticoagulants might be as effective as higher doses in preventing thrombosis, at a lower risk of bleeding. This review article examines the potential of low dose warfarin therapy.

Information sources. The authors have been working in this field, contributing original papers. In addition, the material examined in this article includes articles published in the journals covered by the Science Citation Index® and MedLine®.

State of art and Perspectives. The hypothesis that low-dose oral anticoagulants can be effective in preventing thrombosis was first proven by experiments in animal models, and showed that a prothrombin time ratio as low as 1.14 using rabbit brain thromboplastin was still able to confer some inhibition of experimental thrombosis. Low-dose or very low-dose warfarin were subsequently demonstrated to be effective in patients with morbid obesity and decreased antithrombin III functional and antigenic levels, in patients with indwelling catheters, in patients undergoing gynecological surgery, as well as in patients with stage IV breast cancer. Low-dose warfarin is also effective in the prevention of embolic strokes in patients with nonrheumatic atrial fibrillation. However, older patients (>75 years), who have a very high risk of bleeding, might be safer taking a very low dose of warfarin (i.e., a daily dose of 1-1.25 mg). Moreover, after a period of run-in, a fixed, very low-dose warfarin schedule does not need further laboratory control, which is a factor that could contribute to the full acceptance of treatment by patients and could stimulate a broader prescription of warfarin for the primary prevention of stroke in older patients with nonrheumatic atrial fibrillation.

Therefore, we have organized a multicenter clinical trial in which 1000 patients with non-rheumatic atrial fibrillation will be randomized to receive either a fixed mini-dose of warfarin or a standard dose. Positive results might permit the treatment of most older patients with non-rheumatic atrial fibrillation, creating a benefit for the community as a consequence of its effective prevention of disabling strokes.

Key words: anticoagulant treatment, warfarin

Various aspects of venous thromboembolism and the use of heparin and oral anticoagulants for its treatment were discussed extensively at the *First International Winter Meeting on Basic, Laboratory and Clinical Aspects of Thromboembolic Diseases,* held in Cortina d'Ampezzo, Italy, on March 9-12, 1994.[1-10] Two years later, during the second Meeting in La Thuile, the question of low-dose anticoagulant therapy for prevention of thromboembolic disorders was examined.

Several studies comparing different intensities of oral anticoagulant treatment showed a relationship between bleeding complications and the prolongation of prothrombin time. In fact, Hull *et al.*,[11] found more bleeding complications in patients with deep vein thrombosis when higher INR values between 3.0 and 4.5 were maintained. Accordingly, a study by Turpie *et al.*[12] about patients with substituted tissue heart valve, and studies by Saour *et al.*[13] and Altmann *et al.*[14] concerning patients with mechanical prosthetic heart valves, demonstrated an increased number of hemorrhagic events in patients treated at higher intensity. On the other hand, in all the above-mentioned studies, there was no observed increase in thrombotic complications in patients undergoing a lower intensity treatment. These findings underline the importance of determining the intensity of anticoagulant treatment that is sufficient to prevent thromboembolic events. It may depend on the thromboembolic risk of each clinical setting considered: an INR value of below 2.5 is not safe in very high-risk patients such as those bearing mechanical prosthetic heart valves,[15] while an INR value as low as 1.0 might be indicated in very low-risk patients.

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Animal models

The first indication that thromboembolism could be prevented by low-dose oral anticoagulants arose in the early fifties from a study performed by de Takats,[16] who suggested that low doses of oral anticoagulants might be effective in preventing thrombosis before intravascular coagulation was initiated. Support for this hypothesis came from studies using an animal model of thrombosis. In fact, Gitel and Wessler[17,18] studied the *in vivo* antithrombotic effect of warfarin, and found a dose-dependent effect following infusion of tissue thromboplastin in rabbits. Some inhibition occurred even at the lowest doses of warfarin, when the prothrombin time ratio was 1.14 and was accompanied by a small depression of factor II, VII and X. Other relevant data suggested that warfarin required 6 days to fully express its antithrombotic effect, an event that was not related to prothrombin time, but to factor Xa inhibition.

From these experiments, it is possible to conclude that low- or very low-dose warfarin treatment might be as effective as standard treatment in preventing thromboembolism with little prolongation of prothrombin time.

Low-dose warfarin and biological markers of blood coagulation

When very low-dose warfarin is administered to patients, interesting variations in the biological markers of coagulation can be observed. For example, 1 mg of warfarin per day is able to reduce elevated Factor VII levels, a possible risk factor for cardiovascular disease, with minimum increase in prothrombin time.[19] Accordingly, in patients with a history of myocardial infarction, very low-dose warfarin (1.25 mg daily) significantly reduced F1+2, which is a marker for activation of coagulation *in vivo*, without affecting the prothrombin time; F1+2 returned to basal levels after suspension of treatment.[20] These data are confirmed by Millenson *et al*.[21] who measured F1+2 and INR in warfarin-treated patients with previous ischemic strokes. A decrease in F1+2 levels was observed with no or very little increase in INR values. These data support the concept that the *in vivo* inhibition of coagulation, which might support the antithrombotic activity, cannot be measured by a global test such as prothrombin time, especially if performed with low-sensitive thromboplastins.

Clinical trials have shown that very low-dose warfarin can prevent thromboembolic events

To support these biological findings, clinical trials have shown that very low-dose warfarin can prevent thromboembolic events. This hypothesis was tested by Bern *et al*.[22] in patients at risk of thrombosis associated with chronic indwelling central venous catheters for delivery of antineoplastic chemotherapy. Patients were randomly assigned to receive 1 mg of warfarin daily, beginning 3 days before catheter insertion and continuing for 90 days. The end point was angiographically-proven thrombosis. Four out of 42 (9.5%) patients receiving warfarin and 15 out of 40 (37.5%) not receiving this drug had thrombosis, which is a highly significant difference. There was no measurable change in prothrombin times in either group.

In another international cooperative study,[23] patients receiving chemotherapy for metastatic breast cancer, and therefore at high risk for thromboembolism and at the same time prone to bleeding complications, were randomly assigned to receive very low-dose warfarin or placebo. Patients in the warfarin group received 1 mg daily for the first 6 weeks, and then a dose sufficient to stabilize the INR at 1.5. There were 7 thromboembolic events in the placebo group and 1 in the warfarin group, which can be considered a statistically significant difference.

Very low-dose warfarin in non-rheumatic atrial fibrillation (NRAF)

The Framingham study[24] has taught us that atrial fibrillation constitutes a high risk factor for stroke in patients with rheumatic heart disease, posing a relative risk of 17.56. A much lower risk of 5.6 is present in patients with NRAF, and the question of whether to use oral anticoagulants in these patients has been debated for quite a long time. Five trials recently confirmed that oral anticoagulants are indeed useful in these patients; however, there remains concern as to the applications of these results in the general population. In fact, although these studies showed a significant reduction of stroke, the number of randomized compared to total considered patients was only 7% in two large trials, and not specified in 2 other trials. Therefore, it seems fair to conclude that the results were obtained in a highly selected patient subgroup. Another important point refers to the age of the patients; most of the trials considered patients that were younger compared to the total population of patients with NRAF.[25]

When patients older than 75 years were considered separately, as in the SPAF II trial,[26] it is interesting to observe that moderate-intensity warfarin treatment still benefited patients in comparison to aspirin, but at the cost of a significant increase in bleeding complications. Similar to cancer patients treated with chemotherapy, older patients with NRAF constitute yet another clinical setting in which oral anticoagulants are effective and at the same time burdened with a higher risk of bleeding. Thus, low-dose or very low-dose warfarin treatment might also be beneficial in this group of patients. Another piece of information that encourages this strategy is that the mean effective daily dosage of

Table 1. A trial for the prevention of thromboembolism in patients with NRAF.

- Name: minidose warfarin in nonrheumatic atrial fibrillation (MIWAF)
- Objective: prevention of ischemic stroke, vascular death and intacranial bleeding in patients with nonrheumatic atrial fibrillation.
- Selection of patients: patients over 60 years of age with chronic atrial fibrillation.
- Treatment: Test = Fixed Mini-dose warfarin (1.25mg/day)
  Control = Standard-dose warfarin (INR 2.0-3.0)
- Design of the study: open, multicenter with local randomization
- Primary end points: ischemic stroke, systemic embolism, intracranial bleeding, fatal bleeding, vascular death
- Sample size: 500 patients in each group
- Follow-up: 2 years
- Coordinating Center: Università di Padova, Divisione e Cattedra di Cardiologia, Servizio di Prevenzione e Terapia della Trombosi, via Gattamelata 64, 35128 Padova, Italia.
- Secretary: Dr. Antonella Zasso (phone: international +39.49. 8212315 or 8215658)

warfarin decreases with age. In fact, while patients in the fourth or fifth decade necessitate a mean daily dose of 6 mg of warfarin, patients 80 years or older require a much lower mean daily dose of approximately 4 mg.[27]

Moreover, when a survey of the use of warfarin in elderly people was carried out in our city out of 100 patients discharged from the hospital in 1993 with NRAF and no counterindications to oral anticoagulant treatment, only 14 (14%) were treated (*Nante, personal communication*).

Taken together, these data convinced us to propose a strategy to increase the number of treated patients: very low-dose warfarin could be effective and safer, and appreciated by physicians; a fixed daily dose could be attractive for patients because they would not need frequent laboratory controls, which was the main reason for refusal in participating in previous trials.

Therefore, we have organized a multicenter clinical trial (Table 1) in which 1000 patients with NRAF will be randomized to receive either a fixed mini-dose of warfarin or a standard dose. Positive results might permit the treatment of most older patients with NRAF, benefiting the community as a consequence of the effective prevention of disabling strokes.

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