Benefit of extending anticoagulation therapy lost after discontinuation of therapy

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Among patients with a first episode of pulmonary embolism (the obstruction of the pulmonary artery or a branch of it leading to the lungs by a blood clot) who received 6 months of anticoagulant treatment, an additional 18 months of treatment with warfarin reduced the risk of additional blood clots and major bleeding, however, the benefit was not maintained after discontinuation of anticoagulation therapy, according to a study in the July 7 issue of *JAMA*.

When anticoagulant therapy is stopped after 3 to 6 months of treatment, patients with a first episode of unprovoked (no major risk factor) venous thromboembolism (blood clot within a vein) have a much higher risk of recurrence than those with venous thromboembolism provoked by a transient risk factor (e.g., surgery). In this high-risk population, extending anticoagulation beyond 3 to 6 months is associated with a reduction in the risk of recurrence as long as treatment is continued. However, whether this benefit is maintained thereafter has been uncertain because most previous studies did not include follow-up of patients after discontinuation of treatment, according to background information in the article.

Francis Couturaud, M.D., Ph.D., of the Universite de Bretagne Occidentale, Brest, France, and colleagues conducted a study that included 371 adult patients who had experienced a first episode of symptomatic unprovoked pulmonary embolism (i.e., with no major risk factor for a blood clot) and had been treated initially for 6 uninterrupted months with a vitamin K antagonist. The patients were randomly

assigned to warfarin or placebo for 18 months; median follow-up was 24 months. The trial was conducted at 14 French centers.

After randomization, 4 patients were lost to follow-up, all after month 18, and 1 withdrew due to an adverse event. During the 18-month treatment period, the primary outcome (the composite of recurrent venous thromboembolism or major bleeding at 18 months after randomization) occurred in 6 of 184 patients (3 percent) in the warfarin group and in 25 of 187 patients (13.5 percent) in the placebo group, resulting in a relative risk reduction of 78 percent in favor of warfarin. This result was driven by a reduction in the risk of recurrent venous thromboembolism, with the risk of bleeding increasing to a minimal extent.

This benefit of anticoagulation was lost after anticoagulation was discontinued. During the 42-month entire study period (including the study treatment and follow-up periods), the composite outcome occurred in 33 patients (21 percent) in the warfarin group and in 42 (24 percent) in the placebo group. Rates of recurrent venous thromboembolism, major bleeding, and unrelated death did not differ between groups.

The authors note that their results suggest that patients such as those who participated in this study require long-term secondary prevention measures. "Whether these should include systematic treatment with vitamin K antagonists, new anticoagulants or aspirin, or be tailored according to patient risk factors needs further investigation."

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