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EDITORIALS

Secondary Prophylaxis with Warfarin
for Venous Thromboembolism

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There are two phases in the treatment of patients with symptomatic venous thromboembolism: initial treatment and secondary prophylaxis. Initial therapy usually consists of either subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin, whereas oral vitamin K antagonists (such as warfarin) are generally prescribed for secondary prophylaxis.

The evidence that an initial five-to-seven-day course of the direct-acting anticoagulant heparin is indeed warranted comes from two clinical trials. The first is the landmark 1960 study by Barritt and Jordan, who compared a combination of heparin and warfarin with no treatment in patients with symptomatic pulmonary embolism.[1] The study was stopped prematurely after only 35 patients had undergone randomization, because approximately 25 percent of the patients in the no-treatment group had died of recurrent pulmonary embolism and another 25 percent had had a nonfatal recurrence during the first weeks after entry into the trial, whereas there had been no recurrences in the treated patients.

The second study compared a combination of heparin and vitamin K antagonists with vitamin K antagonists alone.[2] This study was also stopped prematurely, since the patients who were not treated initially with heparin had an incidence of recurrent venous thromboembolic complications during the three months after randomization that was three times as high as that in the group that received heparin.

The evidence supporting the need for secondary prophylaxis with vitamin K antagonists is provided by two comparative studies. In one study, by Lagerstedt et al.,[3] patients with deep calf-vein thrombosis who were initially treated with full-dose heparin were randomly assigned to receive no further treat-ment or vitamin K antagonists. In the other study, Hull and colleagues[4] compared vitamin K antagonists with a fixed low dose of subcutaneous unfractionated heparin (5000 IU twice a day) after initial heparin treatment in patients with deep venous thrombosis. Both studies clearly indicated that the risk of recurrent venous thromboembolism with no or inadequate secondary prophylaxis was higher than the risk among patients who received vitamin K–antagonist therapy (i.e., about 27 percent vs. about 4 percent during the first three months of observation).[3-5]

Therefore, vitamin K antagonists have become the standard for secondary prophylaxis for most patients with venous thromboembolism. Two aspects of vitamin K–antagonist therapy in this setting are frequently debated — the intensity and the duration of treatment. In this issue of the *Journal*, Kearon et al.[6] present interesting data regarding the intensity of anticoagulant therapy. They hypothesized that extended secondary prophylaxis with low-intensity warfarin therapy (i.e., with a target international normalized ratio [INR] of 1.5 to 1.9) might be as effective as conventional-intensity warfarin therapy (INR, 2.0 to 3.0) but associated with a lower risk of bleeding. In their randomized, double-blind study involving patients with unprovoked venous thromboembolism who had completed three or more months of conventional-intensity warfarin therapy, they compared these two intensities and followed their patients for recurrent venous thromboembolism and bleeding. Contrary to their expectations, the risk of recurrent thrombosis was clearly higher among patients assigned to low-intensity therapy (1.9 episodes per 100 person-years, as compared with 0.7 episode per 100 person-years among patients treated with conventional-intensity warfarin),

with no significant difference in the frequency of major bleeding or overall bleeding between the two groups.

The findings of this elegant and convincing study should be interpreted together with the observations reported recently by Ridker et al.[7] In their study, low-intensity warfarin therapy (INR, 1.5 to 2.0) was compared with placebo in patients with idiopathic venous thromboembolism who had received full-dose warfarin therapy (INR, 2.0 to 3.0) for a median of 6.5 months. The authors concluded that, in comparison with placebo, "low-intensity warfarin therapy is a highly effective method of preventing recurrent venous thromboembolism." The observations of Ridker and colleagues with respect to the rates of recurrence and bleeding in the low-intensity–warfarin group are consistent with those reported by Kearon et al.

Hence, it appears that the debate about the intensity of warfarin therapy for venous thromboembolism is now settled. The target INR should be 2.0 to 3.0. Lowering the INR results in more recurrences with no advantage in terms of the risk of bleeding. Target INRs above 3.0 were previously shown to result in more bleeding, without any benefit in the prevention of recurrent thrombotic episodes.[5,8]

The remaining debate therefore focuses on the optimal duration of secondary prophylaxis with vitamin K antagonists. It is becoming increasingly clear that patients with venous thromboembolism go through three phases, each associated with a different risk of recurrence. The first is the period of treatment with vitamin K antagonists, the second is the first 6 to 12 months after the discontinuation of this therapy, and the third reflects a more constant, long-term risk during the subsequent years.

During therapy with vitamin K antagonists, the risk of recurrence is very effectively reduced — by approximately 90 percent, to 0.7 episode per 100 person-years.[5,6] In the 6 to 12 months immediately after the discontinuation of therapy, a catch-up phenomenon occurs, resulting in an absolute incidence of recurrence of venous thromboembolism of 5 to 10 percent.[5,9,10] This phenomenon has been observed after 3, 6, and 12 months of vitamin K–antagonist therapy[9,10] and therefore suggests that prolonging this therapy simply delays recurrence until the therapy is stopped, rather than reducing the risk of recurrence. During the subsequent years, the risk of recurrence stabilizes, and the annual incidence of recurrence is 1 to 2 percent.

Besides the complex assessment of the risk of recurrent venous thromboembolism, including consideration of this catch-up phenomenon, two other elements dominate the decision about how long to continue treatment with vitamin K antagonists. The first concerns the risk of bleeding, and the second the patient's valuation of health states related to venous thromboembolism and its treatment with vitamin K antagonists. The frequency of major bleeding is about 1 episode per 100 person-years, whereas the risk of nonmajor, but still clinically relevant, bleeding is four to five times as high.[5,6,8] In order to obtain optimal efficacy and safety with vitamin K–antagonist therapy, it is mandatory to perform careful and regular laboratory monitoring with subsequent adjustments of the dose, which makes this therapy inconvenient. On the basis of the balance between the risk of recurrence and the risk of bleeding, the current recommendation is to provide secondary prophylaxis with vitamin K antagonists to patients with unprovoked venous thromboembolism for a period of 6 to 12 months.

To continue therapy beyond this period is probably not beneficial for all patients and should depend on the preference of the individual patient. It is becoming increasingly clear that patients are able to balance the benefits and risks of treatment with vitamin K antagonists, when appropriately informed, and that patients have different thresholds for accepting further treatment. Subsequent research in this area should focus on two aspects: the development of reproducible, simple, and accurate instruments for the assessment of patients' treatment preferences, and better ways to identify patients who have the highest risk of recurrence. It will then be possible to tailor the duration of treatment individually and to avoid both overanticoagulation and underanticoagulation.

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Disparity between Solid-Organ Supply and Demand

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More patients die awaiting solid-organ transplantation than currently receive viable organs. Perhaps a victim of its own success, transplantation is the treatment of choice for failed organ function. Despite the burgeoning demand for transplanted organs, the number of available cadaveric organs has remained essentially static over the past decade. As a result, the waiting list for renal transplants in the United States has grown to more than 52,000 patients, with average waiting times exceeding 1000 days.

In this issue of the *Journal*, Sheehy et al.[1] tackle the critical issue of the shortage of cadaveric donors, attempt to ascertain where the shortfalls are greatest, and suggest strategies for addressing the problem. Although it does not include all regions of the United States, this analysis provides the most extensive estimation to date of the potential number of organ donors. Several of the authors' findings confirm and substantiate the conclusions of previous reports. The use of trained "experts" in lieu of untrained health professionals to obtain consent from families may have increased the rate of consent slightly in comparison with that in earlier studies.[2] The reported 54 percent consent rate, however, remains unacceptably low for patients awaiting transplants.

Suggested mechanisms for increasing the consent rate and ultimately the rate of "conversion" of potential donors to actual donors include the offering of financial inducements to families and the presumption of consent. The concept of presumed consent, although it is an obvious potential answer to the shortage of donors, would be a difficult "sell" in the United States, where individual freedom of choice is intrinsic to our self-definition. Offering financial inducements to families in order to increase the frequency of organ donation is problematic and might paradoxically lower donation rates.[3] Surveys

of the families of previous donors corroborate that altruism is the most important motivation for these families and that payment would be viewed negatively.[4] One acceptable financial inducement may be the elimination of financial disincentives to donation such as the need to pay any travel and lodging costs in the case of living donors or funeral expenses in the case of cadaveric donors.[5]

Surprisingly, the donor-card initiative (a program intended to increase the rate of organ donation by making it easier for potential donors to offer their organs simply by signing a card, such as the back of a driver's license) has had little effect on the number of cadaveric donors in the United States. Currently, there is no uniform legal protection afforded to the physician or the organ-procurement organization that attempts to uphold the will of the potential cadaveric donor against the dissent of a living family member.[6,7] The greatest positive effect on the conversion rate might come from the passage of the revised Uniform Anatomical Gift Act (1987) and the federal Patient Self-Determination Act (1991), which reinforce the concept of the autonomy of the patient. Unfortunately, despite the validation of advance directives, donor cards, and other instruments of consent to donation, physicians and organ-procurement organizations still insist on consulting the families of potential donors and following their wishes.

An additional area for improvement whose potential may be deduced from previous studies is a reduction in the proportion of potential donors who do not become actual donors because consent is never sought. Given that this proportion is currently reported to be 16 percent, there are approximately 2000 additional potential donors in the United States who could become actual donors. Several states have adopted legislation that puts the onus on hospitals to report deaths to their local organ-procurement