Duration of anticoagulant treatment for unprovoked deep-vein thrombosis – is prolonged long enough?

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Patients presenting with deep-vein thrombosis or pulmonary embolism are often considered together as having one clinical syndrome, called venous thromboembolism. From a pathophysiological perspective this makes sense, as both entities have their origin in the veins, most often the deep leg veins.[1] In line with this, recent trials evaluating the direct oral anticoagulants have included both patients presenting with proximal deep-vein thrombosis (deep-vein thrombosis in the popliteal vein or more proximal leg veins) and pulmonary embolism.[2-5] However, looking at the natural history, there are some important differences between patients with deep-vein thrombosis and those with pulmonary embolism. First, in a meta-analysis, patients who initially presented with deep-vein thrombosis had more deep-vein thrombosis as recurrent disease (79%) than pulmonary embolism (21%); patients with initial pulmonary embolism, had more recurrent pulmonary embolism (81%) than deep-vein thrombosis (19%).[6] Second, whereas the rate of recurrent venous thromboembolism after acute pulmonary embolism closely resembles that of recurrent venous thromboembolism after a deep-vein thrombosis, the case fatality rate of recurrent deep-vein thrombosis or pulmonary embolism, after stopping anticoagulant treatment, in patients who presented with pulmonary embolism (5.7% to 12.3%) seemed to be higher than that of patients who presented with deep-vein thrombosis (3.8% to 8.5%).[7] Of note, in a more recent meta-analysis focusing solely on patients with unprovoked venous thromboembolism, this difference was not replicated.[8] Even so, it seems logical after all to evaluate antithrombotic treatment for pulmonary embolism and deep-vein thrombosis separately.

As patients with unprovoked venous thromboembolism have a high risk of recurrent venous thromboembolism after stopping anticoagulant treatment, guidelines advocate continuing treatment after the initial 3 to 6 months.[9] The basis for this recommendation was laid in a triad of trials comparing 3 months of anticoagulant therapy with a longer period up to 12 months.[10-12] It became clear from these trials that the protection against recurrent venous thromboembolism provided by the prolonged therapy came at the obvious cost of (major) bleeding during anticoagulant treatment with vitamin K antagonists. Furthermore, the benefit of extended therapy subsided as soon as the treatment was stopped.

In the randomized PADIS-PE study[13] in patients with acute unprovoked pulmonary embolism, which was performed by the same investigators as the PADIS-DVT study, after an initial period of 6 months of anticoagulation, an additional 18 months of warfarin therapy was compared to placebo; the benefit of the extended therapy was lost during a 2-year follow-up period after discontinuing anticoagulation. Subsequently, the same authors set out to evaluate the benefit of extended therapy, using a similar design, in patients with unprovoked deep-vein thrombosis,[14] for which they are to be commended. So, were the differences observed in the two earlier meta-analyses[6,7] also apparent in this study?

The PADIS-DVT trial recruited 104 patients with acute unprovoked proximal deep-vein thrombosis without apparent major reversible risk factors for venous thromboembolism, including active cancer, within the 3 months preceding the diagnosis of the deep-vein thrombosis. During the 18-month treatment period, recurrent deep-vein thrombosis occurred in none of the 50 patients in the warfarin-group and in 16 out of 54 patients (cumulative risk, 29.6%) in the placebo group. During the first 12 months, this risk was greatest in the placebo group after anticoagulation discontinuation (cumulative risk, 38.7% at 12 months). As the authors indicate, this risk, albeit comparable to the risk of recurrent venous thromboembolism in their PADIS-PE study, may well have been the result of the selection of study patients with a (very) high recurrence risk. Importantly, there is no mention of the location of the recurrent deep-vein thrombosis and how it was assessed, other than that ultrasonography was applied. The objective diagnosis of recurrent ipsilateral deep-vein thrombosis is particularly challenging, especially if prior ultrasound indicates residual thrombosis.[15] Of note, in the PADIS-DVT study, more than 50% of patients had residual clots after the index deep-vein thrombosis. This may have caused an overestimation of the deep-vein thrombosis recurrence rate. Magnetic resonance direct thrombus imaging, a technique that can differentiate acute from chronic thrombosis, might have led to an overall lower, more realistic estimate of the cumulative incidence of recurrent deep-vein thrombosis.[16]

The advantage of continued anticoagulant treatment was lost upon discontinuation of the anticoagulation; during the entire 42-month study period, the composite outcome occurred in 14 patients in the warfarin group (cumulative risk, 36.8%) and 17 patients in the placebo-group (cumulative risk, 31.5%) (hazard ratio, 0.72; 95% confidence interval: 0.35-1.46). When the data from the PADIS-PE and PADIS-DVT studies were pooled, a non-significant hazard ratio of 0.68 indicated a potential overall benefit of prolonging anticoagulant treatment.[14]

The PADIS-DVT study has some limitations, of which, as noted by the authors, the most prominent one was the small sample size, due to the slow recruitment of patients and the study's premature discontinuation. A remarkable finding was the low major bleeding rate over the whole 42-month study period, with only one major bleed in the warfarin group after treatment cessation (2.0%). This low rate may have been the result of patient selection and small sample size although in the PADIS-PE study, the major

bleeding rate in the treated group was 2.2% *versus* 0.5 % in the placebo group.[13] Another limitation, although inherent due to the time the study was designed, was the use of vitamin K antagonists. Whether direct oral anticoagulants, in full or reduced dose, will provide the same results has to be demonstrated in future studies.

In conclusion, prolonging anticoagulant therapy after an initial period of 6 months leads to a significant reduction of recurrent venous thromboembolism in patients with unprovoked deep-vein thrombosis, a benefit, which is not maintained after stopping the anticoagulant treatment. This study underlines the relevance of current guidelines that recommend considering indefinite anticoagulation in patients with unprovoked venous thromboembolism.[9] Indeed, only prolongation of anticoagulant treatment is not enough in these high-risk patients.

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