

## The Optimal Long-Term Treatment of Venous Thromboembolism

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### Summary

It has been clearly demonstrated that patients with acute venous thromboembolism (VTE) who are treated with full doses of unfractionated or low molecular weight heparin (LMWH) have a very high rate of recurrence unless effective anticoagulant therapy is continued after the initial treatment. The observed difference in recurrence rates between patients with and without reversible risk factors is relevant to the issue of optimal duration of oral anticoagulant therapy. The long-term prognosis of patients in whom VTE occurs following exposure to temporary risk factors is excellent. Accordingly, they do not require further anticoagulation following the initial 3-week period. Patients with continuous risk factors and those with idiopathic thrombosis have a 2- to 3-fold increased risk of recurrence as compared with patients who developed a thrombotic event in association with a transient risk factor. Several randomized clinical trials have clearly demonstrated that long-term anticoagulant therapy is effective in preventing recurrences in these patients, but it carries a risk of bleeding and is inconvenient.

Accordingly, the optimal duration of oral anticoagulant therapy is still controversial. Recent studies suggest that low-intensity warfarin therapy, after an initial 3- to 6-month period of conventional anticoagulation, may confer an additional protection without an excessive bleeding risk. New categories of drugs, such as pentasaccharides and thrombin inhibitors, are emerging that have the potential to simplify the long-term treatment of patients with VTE by obviating the need for periodic laboratory monitoring and that seem associated with a more favorable benefit-to-risk ratio. Furthermore, recent studies suggest that the risk for late recurrences can be carefully predicted on an individual basis by strategies that include the ultrasound assessment of thrombotic burden or the laboratory evaluation of D-dimer.

### Available Strategies

Randomized controlled trials have established that patients with acute VTE who are treated with an initial course of heparin therapy have a very high rate of recurrence unless effective anticoagulant therapy (ie, a therapy that produces a targeted international normalized ratio [INR] of 2.0–3.0) is continued for weeks or months after hospital discharge.<sup>1–3</sup> Recent investigations suggest that, for this indication, oral anticoagulants can be effectively and safely replaced by subcutaneous heparin, adjusted to maintain the mid-interval activated partial thromboplastin time (aPTT), determined 6 hours after injection at 1.5 times the control value, or by LMWH in fixed doses.<sup>4–11</sup> Both unfractionated heparins and LMWHs are highly recommended for patients in whom oral anticoagulants are contraindicated (eg, during pregnancy) and in those who for any reason cannot undergo the regular determination of INR.

### Three Months or Less?

The optimal duration of oral anticoagulant therapy after a first episode of VTE is still controversial. For most patients it is recommended that warfarin be continued for 3 months.<sup>12</sup> A number of investigators have evaluated shorter durations of warfarin treatment,<sup>13–16</sup> but the results have been inconclusive because of the small number of patients or suboptimal study design. Furthermore, 3 major studies have provided convincing evidence against the generalized shortening of the duration of oral anticoagulant treatment.

The British Thoracic Society performed a study evaluating the optimal duration of oral anticoagulant therapy for VTE, in which patients with deep venous thrombosis (DVT) or pulmonary embolism (PE) were randomized to receive either 4 or 12 weeks of therapy.<sup>17</sup> They found a remarkably higher recurrence rate of recurrent thromboembolism in patients who were treated for 4 weeks (7.8%) than for 12 weeks (4.0%) during an unspecified period of follow-up. Post hoc analysis suggested a qualitative difference between “postoperative” and “medical” cases of VTE, the former having a considerably lower recurrence risk regardless of the duration of anticoagulation.

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Based on the hypothesis that a normal impedance plethysmography (IPG) following DVT defines a group of patients at low risk of recurrent VTE, Levine et al<sup>18</sup> conducted a prospective controlled double-blind trial to evaluate the efficacy of only 4 weeks of warfarin in patients with an already normalized IPG test at that time. During the 8 weeks following randomization, 9 of the 105 placebo patients (8.6%) developed recurrent VTE compared with 1 of the 109 warfarin patients (0.9%;  $P=.009$ ). In patients with proximal DVT who were given warfarin for 3 months and were then followed for an additional 9 months (including both patients who were randomized and those who presented with an abnormal IPG test after 4 weeks), the rate of recurrent thromboembolic events was much higher in patients who had either permanent risk factors or idiopathic DVT than in those with transient, reversible risk factors.

Schulman et al<sup>19</sup> performed a multicenter trial comparing 6 weeks of oral anticoagulant treatment with 6 months of such therapy in 897 patients who had had a first episode of VTE. After 2 years of follow-up, there were 80 recurrences among the 443 patients randomized to the 6-week group (18.1%), and 43 among the 454 randomized to the 6-month group (9.5%). This trial showed, therefore, a substantial reduction in the risk for recurrent thromboembolism among patients who were administered 6 months of anticoagulation. However, there was no difference in the incidence of recurrent events in the 2 groups from 6 to 24 months after the initial episode in both groups of patients. Furthermore, the overall rate of recurrence after 2 years was much lower among patients with temporary risk factors than among those with permanent risk factors (6.6% vs 18%).

As a result of these 3 major studies, the generalized reduction of overall anticoagulation beyond the currently recommended 3 months is not acceptable. According to the results of a recent clinical trial, this finding is true not only for patients with idiopathic VTE but also for those with secondary VTE from reversible risk factors, such as surgery, trauma, temporary immobilization, or hormonal therapy.<sup>20</sup>

### Three Months or More?

In order to assess the risk for recurrent thromboembolic events in patients suffering the first episode of DVT, we observed prospectively 528 consecutive symptomatic patients.<sup>21,22</sup> A surprisingly high risk of recurrent thromboembolism that persisted after the period of treatment was found, and resulted in a cumulative incidence of almost 30% after 8 years of follow-up. Of the 101 patients who experienced at least 1 recurrent thrombotic event, 47 (46.6%) occurred in a leg initially involved, 33 (32.7%) in the contralateral leg, and 21 (20.8%) were pulmonary emboli, which were fatal in 11 (10.9%) patients. These results are fully consistent with those reported by other studies.<sup>23,24</sup> Of the evaluated potential risk factors and clinical characteristics, the presence of malignancy and of impaired coagulation inhibition increased the risk of recurrent venous thromboembolism (RR=1.5 and 2.0, respectively). In contrast, surgery and recent trauma or fracture were associated with a diminished risk of recurrent

venous thromboembolism (RR=0.65 and 0.4, respectively).

After the publication of the randomized study by Schulman et al,<sup>19</sup> other recent studies have addressed the potential for prolonged anticoagulation in selected categories of patients. Kearon et al<sup>25</sup> randomized consecutive patients to receive 3 months or 2 years of oral anticoagulant therapy following an episode of acute VTE. A prespecified interim analysis led to early termination of the trial after 162 patients had been enrolled for an average of 10 months. Of 83 patients assigned to continue to receive placebo, 17 had a recurrent episode of venous thromboembolism (27% per patient-year), as compared with 1 of 79 patients assigned to receive warfarin (1.3% per patient-year). There was a nonsignificant trend toward a higher risk of nonfatal major bleeding in patients assigned to warfarin as compared to those assigned to the placebo group (3.8% vs 0% per patient-year;  $P=.09$ ).

In a recent Italian multicenter study, 267 patients with a first episode of idiopathic proximal DVT who had completed 3 months of anticoagulant treatment were randomized either to withdraw anticoagulation or to continue for 9 additional months.<sup>26</sup> Of the 134 patients assigned to extended anticoagulation, 21 had a recurrence of VTE (5.0% per patient-year, average follow-up 37.8 months) as compared with 21 of the 133 patients randomized to withdrawal of anticoagulation (5.1% per patient-year, average follow-up 37.2 months). Four patients had nonfatal major bleeding during extended anticoagulant treatment (3.0%). The results of this study suggest that extending to 1 year the 3-month course of anticoagulant treatment in patients with idiopathic proximal DVT is not associated with long-term clinical benefit. These conclusions have been supported by a French multicenter clinical trial, which addressed the comparison between 3 and 6 months of anticoagulation in patients with proximal DVT, and the comparison between 6 and 12 weeks in patients with isolated calf DVT.<sup>27</sup> Pinede et al failed to show appreciable differences between the study groups in terms of recurrent thromboembolic complications after a 12-month follow-up period.

The benefit of extending the duration of oral anticoagulation beyond the currently recommended 3-month period in selected patients with clinically symptomatic PE has recently been addressed by another Italian multicenter trial.<sup>28</sup> In this study, 326 patients with a first episode of PE who had completed 3 months of oral anticoagulant therapy were randomly assigned to the discontinuation of anticoagulation or to its continuation for 3 or 9 additional months, depending on the presence or the absence of transient risk factors. Among 165 patients assigned to extended anticoagulant therapy, 15 had a recurrent event (9.1%; 3.1% per patient-year; average follow-up 31.8 months), as compared with 18 of 161 patients assigned to treatment discontinuation (11.2%; 4.1% per patient-year; average follow-up 29.8 months), resulting in a relative risk of 0.81 (95% confidence interval [CI], 0.42–1.56). It is interesting to note that in neither patient category (idiopathic or secondary PE) was extending anticoagulant treatment associated with long-term

clinical benefit. Three major bleedings were observed during extended anticoagulation (1.8%). The results of this study, therefore, are fully consistent with those observed in patients with DVT.

In a multicenter trial addressing the optimal duration of oral anticoagulant therapy after a second episode of VTE, Schulman et al<sup>29</sup> found a considerable reduction in the risk for recurrent thromboembolism (from 21% to 3%) in patients allocated to receive 4 years as compared with 6 months of warfarin. Surprisingly, this benefit was offset by a remarkably higher incidence of major bleeding (8.6% vs 2.7%).

Summarizing the results of these studies, it can be concluded that prolonged treatment with oral anticoagulants reduces the risk of recurrence during its use (relative risk reduction, approximately 90%), but is associated with a clinically important risk of major bleeding complications (1–4% per year).<sup>30</sup>

### Current Recommendations

The observed difference in recurrence rates between patients with and without reversible risk factors is relevant to the issue of optimal duration of oral anticoagulant therapy. The long-term prognosis of patients in whom DVT occurs following exposure to temporary risk factors (namely, recent surgery, trauma or fracture, puerperium, hormonal therapy) is excellent. According to the guidelines delivered by the American College of Chest Physicians, they do not require further anticoagulation following the initial 3 months.<sup>12</sup>

According to the same guidelines, a 12-month or longer period of anticoagulation should be considered in patients with malignancy or other medical illnesses requiring prolonged immobilization, in patients with multiple episodes of spontaneous thrombotic episodes, and in those with antiphospholipid antibody syndrome, antithrombin defects, protein C and S defects, double heterozygosity for factor V Leiden and G20210A prothrombin variant, and homozygosity for either defect.<sup>12</sup> At present, lifelong anticoagulant therapy remains a clinical judgment in the individual patient.

A 6-month or longer period of anticoagulation is currently recommended for patients with the first episode of idiopathic DVT, even in the presence of a heterozygosity for factor V Leiden or G20210A prothrombin variant.<sup>12</sup>

### Future Perspectives

#### *New Strategies*

In a recent prospective cohort study, we have shown that the persistence of residual thrombosis after an episode of proximal DVT as detected by repeated ultrasonography is an independent risk factor for recurrent thromboembolism.<sup>31</sup> Veins were considered recanalized with a vein diameter of less than 2.0 mm in a single determination, or less than 3.0 mm in 2 consecutive determinations in patients with DVT. Among 313 consecutive patients with proximal DVT who were followed prospectively for up to 6 years after a 3- to 6-month period of anticoagulation, those with persistent

venous obstruction were at a higher risk of recurrence (hazard ratio, 2.4; 95% CI, 1.3–4.4) after adjustment for thrombophilia and spontaneous clinical presentation. A similar prognostic value of the resolution of the thrombus was observed by Piovella et al<sup>32</sup> in 179 patients with symptomatic first episode of DVT and in 104 patients with DVT occurring after hip replacement surgery serially monitored by ultrasonography over a period of 12 months. Of interest, a recent meta-analysis of clinical trials comparing unfractionated heparin with LMWH for the treatment of DVT, in which ascending phlebography had been used as a tool to assess thrombus evolution, showed an important correlation between thrombus regression and recurrent VTE.<sup>33</sup> Strategies that include such an assessment of thrombotic burden are intuitively attractive, since a patient can potentially be managed based on the individual course of his thrombotic disease, rather than by broad guidelines alone.

An elegant study by Palareti et al<sup>34</sup> has opened perspectives for the inclusion of a marker of a thrombotic tendency (D-dimer) in the risk stratification, and thus ultimately therapeutic guidance, of an individual patient. In 396 patients with a first episode of DVT and/or PE, a D-dimer test was performed at the discontinuation of the secondary prophylaxis with vitamin K antagonists, after 21–30 days, and at 3 months. In the most clinically interesting subgroup, that is, patients with idiopathic VTE, patients with a normal assay at 3 months had a 3.7% recurrence rate during follow-up (NPV=96.3%; 95% CI, 87.2–99.5), compared with 10.2% in the patients with elevated D-dimer concentration (PPV=10.2; 95% CI, 4.8–18.5). On the basis of these results it seems justified to evaluate the potential role of a normal D-dimer concentration to guide safely the cessation of anticoagulant therapy in a substantial number of patients with idiopathic thrombosis after an initial period of treatment. Of interest, preliminary data provided by Fattorini et al<sup>35</sup> also suggest that D-dimer measurements during oral anticoagulant treatment may have a predictive value in the assessment of the risk of DVT recurrence.

#### *Old and New Drugs*

In a recent multicenter, double-blind, randomized trial, Ridker et al<sup>36</sup> have convincingly demonstrated that low-intensity warfarin prophylaxis, using a targeted INR of 1.5–2.0, is superior to placebo in preventing recurrent VTE in patients with idiopathic VTE who have previously been treated for at least 3 months with warfarin at the conventional level of intensity. The trial was terminated early after 508 patients had undergone randomization and had been followed for up to 4.3 years (mean, 2.1 years). Of 253 patients assigned to placebo, 37 had recurrent VTE (7.2 per 100 person-years), as compared with 14 of 255 patients assigned to low-intensity warfarin (2.6 per 100 person-years), a risk reduction of 64% (HR, 0.36; 95% CI, 0.19–0.67). There was no significant increase in the rate of major bleeding complications in patients receiving low-intensity warfarin therapy.

Surprisingly enough, Kearon et al<sup>37</sup> have simultaneously reported the results of a different randomized, double-

blind trial of similar size that found that low-intensity warfarin (INR 1.5–1.9) was significantly less effective than conventional-intensity warfarin (INR 2.0–3.0) for extended prevention of recurrent VTE, without significant differences in the rate of bleeding complications. It is difficult to reconcile these findings and to make definitive recommendations regarding the optimal intensity of anticoagulation therapy for long-term secondary prevention without data from a risk-benefit analysis in a 3-way comparison of conventional-intensity, low-intensity, and no anticoagulation therapy following at least 3 months of conventional-intensity warfarin therapy for an initial episode of idiopathic VTE.<sup>38</sup>

In recent years, new categories of drugs have emerged that have the potential to rapidly change the therapeutic scenario of VTE. They include anti-Xa inhibitors, such as pentasaccharide, and antithrombin inhibitors, such as ximelagatran (Exanta, AstraZeneca). The once-weekly administration of 2.5 mg of a long-active formulation of pentasaccharide (idraparinux, Sanofi-Aventis) has recently been shown in a phase II study to be at least as effective and safe as warfarin for the secondary prevention of DVT.<sup>39</sup> Furthermore, according to the results of a recent randomized clinical trial, the oral administration of fixed doses of ximelagatran has been shown to be more effective than and as safe as placebo for the prevention of recurrent VTE following the administration of 6 months of warfarin in patients with DVT.<sup>40</sup> However, before introducing the results of these studies into routine clinical practice, the results of wider studies, which are currently underway, should be awaited.

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