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Duration of Anticoagulant Treatment after Venous Thromboembolism

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Key Words

Venous thromboembolism · Deep vein thrombosis · Pulmonary embolism · Oral anticoagulants

The current recommended treatment of venous thromboembolism (VTE) consists of an initial treatment with heparin (either subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin) relayed with a long-term treatment with oral anticoagulants (INR 2.0 - 3.0) given for at least three months [1].

The majority of the studies on the long-term treatment of VTE included patients with deep vein thrombosis (DVT). Based on the assumption that DVT and pulmonary embolism (PE) are two manifestations of the same disease, information available for patients with DVT are commonly translated to patients with PE. Recently, several differences regarding the risk for recurrent VTE in patients with DVT and PE have been reported. In particular, it has been shown that patients with PE are at slightly higher risk of dying from recurrent PE than are patients with DVT [2-3]. For this reason, more prolonged anticoagulation has been proposed for patients with PE, but this choice is not evidence based.

Need for Short- and Long-Term Anticoagulant Treatment

The need for initial anticoagulant treatment in patients with symptomatic PE was demonstrated more than 40 years ago in a placebo-controlled trial [4]. This study showed the high risk of PE-related death in patients receiving placebo. Subsequent studies provided evidence for the need of long-term anticoagulation after the initial anticoagulant treatment. Patients with acute DVT not receiving long-term anticoagulant treatment had a 15% to 50% incidence of symptomatic extension of thrombosis and/or recurrent VTE [5-6]. A randomized trial in which patients with symptomatic calf-vein thrombosis were randomized to receive heparin or placebo after initial treatment with intravenous unfractionated heparin, showed a 20% rate of symptomatic extension and/or recurrence of thrombosis in the placebo group [5]. A subsequent randomized trial evaluated subcutaneous low-dose unfractionated heparin (5000U bid) as an alternative to oral anticoagulants for long-term treatment of patients with DVT. In this trial the low-dose unfractionated heparin regimen was shown to be ineffective and resulted in a high rate (47%) of recurrent VTE [6]. More recently, randomized trials compared the conventional 3 months duration of treatment with oral anticoagulants with shorter periods of 4 to 6 weeks [7-9]. All these studies showed an increase in recurrent thromboembolic events associated with the reduction of treatment duration.

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Risk Stratification for Recurrence of Venous Thromboembolism

A prospective cohort study that included 355 consecutive patients who received anticoagulant treatment for three months for a first-episode of VTE and were followed for up to 8 years provided important information about the long-term clinical course of patients with DVT [7]. This study showed a cumulative incidence of recurrent VTE at 2, 5, and 8 years of 17.5%, 25%, and 30% respectively. The presence of cancer was associated with an increased risk of recurrent VTE (hazard ratio 1.7), as it was the presence of molecular thrombophilic abnormalities as deficiency of antithrombin, protein C, or protein S, or the presence of lupus-like anticoagulants (hazard ratio 1.4). On the other hand, patients with VTE associated with transient risk factors (e.g. surgery or recent trauma) presented a low risk of recurrent thromboembolism.

The finding of a lower incidence rate of recurrent VTE in patients with a first episode of VTE associated with transient risk factors than in those of idiopathic VTE has been confirmed in three recent randomized trial on the optimal duration of oral anticoagulants in patients with VTE [8-10]. In the first of these trials 6.7% of patients with VTE associated with transient risk factors had a recurrent VTE during the 2-year follow-up with respect to 18.1% of patients with VTE associated with a permanent risk factor or idiopathic VTE [8]. In a study including patients with a first episode of PE the incidence of recurrence was 12.2% in patients with idiopathic PE as respect to 7.6% in patients with PE associated with transient risk factors [10].

Based on the different risk for recurrent VTE, three categories of VTE has been established: VTE associated with transient risk factors, VTE associated with persistent risk factors and idiopathic or unprovoked VTE. The recommended duration of oral anticoagulation is different for these three categories. Due to the relatively low recurrence rate of VTE, 3 months of anticoagulation seems to be sufficient in patients with a first episode of DVT associated to a transient risk factor. The high risk for recurrence observed in patients with continuing risk factors for VTE support an indefinite anticoagulant treatment in this patients category. The optimal duration of anticoagulant treatment in patients with an episode of idiopathic venous thromboembolism remains more uncertain.

Duration of Long-Term Treatment

Several randomized trials have been conducted in an attempt to establish the optimal duration of oral anticoagulant treatment after an episode of acute VTE [8-14]. Three randomized trials [8,11,12] were designed to evaluate whether the duration of anticoagulant treatment could be shortened to less than 3 months. For this purpose, 4 to 6 weeks courses of anticoagulant treatment were compared with 3 to 6 months. All these studies revealed a higher incidence of recurrent VTE after treatment discontinuation in patients receiving shorter anticoagulation after a follow-up ranging between 6 months and one year: the increase of the absolute risk with the shorter duration was approximately 8%. Therefore, patients with VTE should receive anticoagulant treatment for at least 3 months. Further studies evaluated the clinical benefit of an extension of anticoagulant treatment beyond this period.

Four studies [9-10,13,14] evaluated the risk-benefit of an extended course of anticoagulant therapy for patients with idiopathic VTE. In all these trials the tested short duration was three months while the extended treatment varied between 6 months and two years. These studies showed that oral anticoagulant treatment is effective for the prevention of recurrent VTE when adjusted to maintain the INR between 2.0 and 3.0. Actually, the rate of recurrence during anticoagulant treatment was extremely low and the majority of recurrences were observed after treatment was discontinued. About 15% of patients treated for idiopathic DVT experience a recurrence of VTE in the two-three years after treatment discontinuation. Two of these studies with a long-term follow-up after anticoagulant treatment discontinuation showed that the incidence of recurrent VTE after treatment withdrawal is similar in patients receiving three months and one year of treatment [9-10, 14]. It seems that prolonging oral anticoagulant treatment beyond the recommended period simply delays recurrences without reducing the risk for recurrence after treatment discontinuation. As a consequence, indefinite anticoagulation has been proposed after a first episode of idiopathic VTE in order to avoid recurrent VTE after treatment discontinuation. However, two points have to be considered regarding the benefit of an indefinite oral anticoagulant treatment. First, the benefit of extended oral anticoagulant treatment is partially offset by the risk of major bleeding. The incidence of major bleeding in studies evaluating oral anticoagulant treatment (INR levels 2.0 - 3.0) for the treatment of idiopathic VTE was approximately 3% during one year of extended treatment [9-14]. In these trials the annual incidence of intracranial bleeding was 0.3% and the case-fatality rate of major bleeding approximately 10%. In addition, 5-15% of patients experienced minor bleeding each year. The risk of bleeding with long-term warfarin treatment outside clinical trials could be even higher. In fact, patients at increased risk of bleeding are often ineligible for inclusion in clinical trials and laboratory monitoring of anticoagulant therapy is generally more accurate in patients included in clinical trials. An additional lim-

itation of indefinite oral anticoagulant treatment is the inconvenience for the patient because of the need for anti-coagulation monitoring and dose adjustment.

To reduce the incidence of bleeding complications and the frequency of monitoring two recent trials evaluated the possibility to extend oral anticoagulation with low-intensity warfarin (INR 1.5 - 2.0) after an initial treatment of three to six months of conventional-intensity anticoagulation (INR 2.0 - 3.0) [15,16]. The first of these studies showed a superior efficacy of low-intensity anticoagulant regimen with respect to placebo in the prevention of recurrent VTE [15]. However, in a subsequent study low-intensity anticoagulant regimen has been shown to be less effective than the conventional-intensity regimen for the prevention of recurrent VTE without providing any advantage in terms of reduction of bleeding complications [16]. In conclusion, extending anticoagulant treatment is associated with an increased incidence of bleeding complications and reducing the level of anticoagulation does not reduce these complications.

Potential risk factors for recurrent VTE have been evaluated in order to define whether patients with presumed idiopathic VTE could be further stratified in different categories for the risk of recurrence. A number of biochemical and instrumental findings have been reported to be associated with an increased risk of recurrent VTE [17-25]. The biochemical markers include thrombophilic abnormalities and D-dimer levels. Different studies indicated as factor predisposing to thrombosis abnormalities of the naturally occurring inhibitors of coagulation (antithrombin, protein C and protein S), specific gene mutations (factor V Leiden and prothrombin 20210A), elevated levels of coagulation factors (factor VIII), elevated levels of homocysteine, presence of antiphospholipid antibodies. However, the specific risk for recurrent VTE associated with each of these abnormalities seems to be different and need to be further clarified in prospective studies. A sub-group analysis of the PREVENT study showed that extended low-intensity warfarin treatment is of benefit in patients with the factor V Leiden or prothrombin 20210A gene mutations [15]. In this study, the annual incidence of recurrent VTE was reduced from 8.6% to 2.2% per year in patients receiving the extended warfarin treatment. More definite evidence exists for the need of an extended anticoagulant treatment in patients with VTE associated with antiphospholipid antibodies. Sub-group analyses of the DURAC studies [8,25]. showed a 29% incidence of recurrent VTE in patients with a first episode of VTE and anti-cardiolipin antibodies as compared with 14% among patients without anti-cardiolipin antibodies (p<0.01). In patients with VTE and anti-cardiolipin antibodies the recommendation for an extended anticoagulant regimen is also based on the evidence of an increased mortality due to thromboembolic causes [22,25]. In fact, all causes four-year

mortality was 15% among patients with anti-cardiolipin antibodies, and 6% among patients without anti-cardiolipin antibodies (p=0.01).

Recently, the presence of elevated plasma D-dimer levels after discontinuing anticoagulant therapy [23] has been associated with an increased incidence of recurrent VTE, as it was for the presence of residual DVT assessed by compression ultrasonography [24]. Prospective trials are currently ongoing in patients with high D-dimer or residual DVT to evaluate different durations of treatment.

The optimal duration of oral anticoagulant treatment after a second episode of VTE has been also evaluated [25]. In the only randomized trial that assessed this issue, patients with a second episode of VTE were randomized to receive six months or indefinite anticoagulant treatment at INR 2.0 - 3.0. Overall, 227 patients were included in the study and followed for 4 years; the cumulative incidence of recurrent VTE was 20.7% and 2.6% in patients who received a six-month anticoagulation and in patients who continued anticoagulant treatment indefinitely (p<0.001), respectively. The cumulative incidence of major bleeding was 8.6% and 2.7% for the indefinite treatment and the six months group, respectively (p=0.084). Therefore, an absolute risk reduction of 18.1%, with an absolute risk increase 5.9%.

Conclusions

In the majority of patients with a first episode of VTE associated with temporary risk factors an anticoagulant treatment of 3-month seems to be appropriate. Indefinite anticoagulation is required in patients with VTE associated with permanent risk factors. Six-month to 1-year of anticoagulation should be recommended in the large majority of patients with idiopathic VTE although further study are required to better stratify the risk of recurrence in these patients. Patients with more than an episode of VTE should be treated indefinitely with oral anticoagulants. The issue of the optimal duration of anticoagulation could be made less critical by the availability of new oral anticoagulant drugs with a safer profile and no need for monitoring.

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