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Full Length Article

Residual vein thrombosis and serial D-dimer for the long-term management of patients with deep venous thrombosis

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ABSTRACT

Background: The optimal long-term strategy for preventing recurrent venous thromboembolism (VTE) in patients with deep-vein thrombosis (DVT) is uncertain.
Methods: In 620 consecutive outpatients with a first proximal DVT who had completed at least three months of anticoagulation (unprovoked in 483, associated with minor risk factors in 137), the ultrasound presence of residual vein thrombosis (RVT) was assessed and defined as an incompressibility of at least 4 mm. In 517 patients without RVT and with negative D-dimer, anticoagulation was stopped and D-dimer was repeated after one and three months. Anticoagulation was resumed in 63 of the 72 patients in whom D-dimer reverted to positivity.
Results: During a mean follow-up of three years, recurrent VTE developed in 40 (7.7%) of the 517 patients, leading to an annual rate of 3.6% (95% CI, 2.6 to 4.9): 4.1% (95% CI, 2.9 to 5.7) in individuals with unprovoked DVT, and 2.2% (95% CI, 1.1 to 4.5) in those with DVT associated with minor risk factors. Of the 233 males with unprovoked DVT, 17 (7.3%) developed events in the first year of follow-up. Major bleeding complications occurred in 8 patients while on anticoagulation, leading to an annual rate of 1.2% (95% CI, 0.6 to 2.4).
Conclusions: Discontinuing anticoagulation in patients with a first episode of proximal DVT based on the assessment of RVT and serial D-dimer leads to an overall annual rate of recurrent VTE lower than 5.0%, which is the rate deemed as acceptable by the Subcommittee on Control of Anticoagulation of the ISTH. However, in males with unprovoked DVT there is room for further improving the long-term strategy of VTE prevention. (ClinicalTrials.gov number, NCT01285661).

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1. Introduction

Once anticoagulation is stopped, the risk of recurrent venous thromboembolism (VTE) over years approaches 40% of all patients with a first episode of proximal deep venous thrombosis (DVT) [1], irrespective of the duration of anticoagulation [2,3]. Although the risk is highest in patients with unprovoked DVT, it is alarmingly high also in patients with DVT associated with minor risk factors of thrombosis [1,4]. Current guidelines suggest an indefinite anticoagulation in all patients with the first episode of unprovoked proximal DVT, provided the bleeding risk is perceived as being acceptably low [5]. However, in clinical practice this indication is often disregared [6], as the annual incidence of major bleeding from the long-term use of vitamin K antagonists (VKA) is not negligible [7], and the case-fatality rate of major bleeding is considerably higher than that of recurrent VTE [8,9]. Although the use of the novel direct oral anticoagulants in the substitution of VKAs is likely to improve the benefit-to-risk ratio of long-term anticoagulation owing to the considerably lower risk of relevant bleeding [10], identifying patients in whom anticoagulation can be safely discontinued remains a top priority [11].

Following the demonstration that the ultrasound assessment of residual vein thrombosis (RVT) [12–14] and a positive D-dimer test, as measured after discontinuing anticoagulation [15–17], are factors that independently predict the development of recurrent VTE after discontinuing anticoagulation, tailoring the duration of anticoagulation based on the resolution of thrombotic burden [18,19] or serial D-dimer negativity [20,21] led to weak or controversial results. In contrast, in a recent Italian multicenter study, discontinuing anticoagulation in patients with early vein recanalization or stable thrombotic burden and serially negative D-dimer test was found to be applicable in approximately 50% of patients with DVT that was either unprovoked or associated with minor risk factors of thrombosis, and resulted in a subsequent annual recurrence rate as low as 3.0% [22]. In that study, anticoagulation was by definition stopped also in patients with persistent RVT provided they had received 6–9 further months of anticoagulation, the D-dimer determination was scheduled four more times in the three months after VKA discontinuation, and age- and sex-specific cut-off values were adopted for interpretation of D-dimer tests [22].

The current prospective cohort multicenter study was designed to assess the value of a slightly different algorithm for the identification of patients with proximal DVT in whom anticoagulation can be safely discontinued. Anticoagulation was indefinitely prolonged in patients with persistent RVT. Whenever leg veins recanalized, patients were instructed to stop anticoagulation provided D-dimer was negative and remained negative in only two further determinations, one and three months apart. In addition, the D-dimer cut-off values that are recommended by manufacturers for diagnostic purposes were the ones that were adopted for interpretation of D-dimer tests.

2. Methods

2.1. Main study objective

To assess the rate of recurrent VTE over a long-term follow-up period in a cohort of outpatients with a first episode of symptomatic proximal DVT, in whom anticoagulation was discontinued after 3-to-12 months of anticoagulation, based on an algorithm incorporating the ultrasound assessment of RVT and the serial determination of D-dimer (at baseline, after one and three months).

The Institutional Review board of each participating center approved the study protocol. The study was conducted in accordance with the declaration of Helsinki.

2.2. Study patients

Consecutive outpatients who were referred to 19 centers in Italy with a first episode of ultrasonography proven proximal DVT between February 1, 2010 and October 31, 2015 were eligible for the current investigation provided they had received at least three months of anticoagulation. Patients with indication for short term anticoagulation (i.e., with an event triggered by major surgery or trauma) and those with indication for indefinite anticoagulation (i.e., with an event associated with active cancer, medical illnesses resulting in long-term immobilization, antiphosholipid syndrome, strong family history of VTE or known inherited defects in the natural anticoagulants) were excluded, as were those with concomitant conditions (such as atrial fibrillation) requiring indefinite anticoagulation, those who were on anticoagulant therapy for more than one year, those who had experienced an episode of recurrent VTE or major bleeding while on anticoagulation, those with severe post-thrombotic syndrome, those with life expectancy shorter than one year, with age younger than 18, pregnant women, patients who had inaccessibility for long-term follow-up and those who refused to provide their written informed consent. Accordingly, only patients with a first episode of proximal DVT that was either unprovoked or associated with minor risk factors of thrombosis (such as minor injury, arthroscopic or laparoscoic general surgery, short immobilization, long haul flight or estrogen therapy) were recruited for the current investigation, provided they had completed an uneventful 3 to12-month period of anticoagulation with VKAs.

The simultaneity of clinical manifestations suggestive of PE was recorded, as was the presence of a family history of VTE (i.e., occurrence of a venous thromboembolic episode in a first-degree relative). As the search for thrombophilia was not mandatory, it was done occasionally. Accordingly, this parameter was not collected.

Patients had been treated with therapeutic doses of unfractionated heparin, low-molecular-weight heparin or fondaparinux, overlapping with and followed by at least three months of VKA therapy (International Normalized Ratio [INR], 2.0 to 3.0).

2.3. Management procedures

Recruited patients received the ultrasound assessment of the common femoral vein at the groin and of the popliteal vein at the popliteal fossa, which were scanned in the transverse plane. Veins were identified and compressed with the ultrasound transducer. The vein diameters were assessed during compression, and RVT was defined as the persistence of thrombotic material resulting in a diameter of 4 mm or more. This criterion was recently found to possess a high reproducibility [23].

Patients with RVT were instructed to continue anticoagulation and to reassess their veins every six months until a maximum of 24 months since recruitment. Patients with persistent RVT were invited to prolong anticoagulation indefinitely.

Patients whose veins were found to have recanalized, either at baseline or after 6,12,18 or 24 months received the determination of D-dimer. The D-dimer level was assessed with the quantitative assay routinely used in each participating center, the cut-off ranging between 250 and 500 μg/ml depending on the manufacturer's instructions. For the purpose of this investigation, the D-dimer cut-off values that are recommended by manufacturers for diagnostic purposes were the ones that were adopted for interpretation of D-dimer tests. Patients whose D-dimer was positive prior to stopping anticoagulation were invited to prolong anticoagulant treatment indefinitely. Patients with negative D-dimer were invited to discontinue anticoagulation and to repeat this determination two more times, one and three months apart. Whenever D-dimer reverted to positive, patients were instructed to resume anticoagulation and to prolong it indefinitely. All other patients were invited to remain without anticoagulant treatment. At the discretion of single investigators or the attending physicians, low-dose aspirin was prescribed in the substitution for VKAs.