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REGULAR ARTICLE

D-dimer and factor VIII are independent risk factors for recurrence after anticoagulation withdrawal for a first idiopathic deep vein thrombosis

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Abstract

Background and objectives: To assess the predictive value of D-dimer (D-d) and Factor VIII (FVIII) in combination for recurrent venous thromboembolism (VTE) after vitamin K antagonist (VKA) therapy suspension.
Design and methods: Consecutive outpatients with a first episode of idiopathic proximal deep vein thrombosis of the lower limbs were enrolled on the day of VKA suspension. After 30+/−10 days, D-d (cut-off value: 500 ng/mL), chromogenic FVIII activity and inherited thrombophilia were determined. Follow-up was 2 years.
Results: Overall recurrence rate was 16.4% (55/336; 95% CI:13–21%). The multivariate hazard ratio (HR) for recurrence was 2.45 (95% CI: 1.24–4.99) for abnormal D-d and 2.76 (95% CI:1.57–4.85) for FVIII above the 75th percentile (2.42 U/mL) after adjustment for age, sex, thrombophilia, VKA duration and residual venous obstruction. When compared with normal D-d and FVIII, the multivariate HR was 4.5 (95% CI: 1.7–12.2) for normal D-d with FVIII above 2.42 U/mL and 2.7 (95% CI: 1.2–6.6) and 7.1 (95% CI:2.8–17.6) for abnormal D-d with FVIII, respectively, below and above 2.42 U/mL.
Interpretation and conclusions: D-d and FVIII at 30+/−10 days after VKA withdrawal are independent risk factors for recurrent VTE.

Abbreviations: D-d, D-dimer; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; FVIII, Factor VIII; VKA, vitamin K antagonists; CI, Confidence intervals; HR, hazard ratio; CUS, compression ultrasound; RVO, residual venous obstruction.

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Introduction

Vitamin K antagonists (VKA) for venous thromboembolism (VTE) are highly effective in reducing mortality by pulmonary embolism (PE) and recurrences [1]. VKA for at least 3 months after symptomatic VTE are generally recommended for the high risk of early recurrence [1,2]. Currently the recommended duration of VKA is based on the clinical characteristics of the index event. VKA are recommended for 3 months after VTE due to a triggering transient risk factor and for at least 6 months after unprovoked or idiopathic VTE [2]. However, VTE tends to recur after VKA withdrawal whatever the duration of treatment. Several studies have investigated different lengths of VKA treatment and have shown that VKA extension after unprovoked VTE reduces the risk of recurrence by 90% [4–7] but it is associated with a clinically relevant risk of major bleeding (2.74% per patient-years after 3 months) [8]. Several studies have also shown that the benefit associated with VKA prolongation was not maintained after therapy was discontinued [9–11]. As a result the optimal duration of VKA after a first episode of VTE is still uncertain [3].

The risk of recurrence after VKA withdrawal differs individually and markers of individual risk prediction could help tailor VKA duration. In addition to the characteristics of the index event, several factors have emerged as predictors of risk for recurrence after VKA withdrawal, such as D-dimer (D-d), residual venous obstruction, thrombophilia and factor VIII [12–23]. Our previous observation that altered D-d after VKA withdrawal is associated with a low risk of recurrent VTE [12] has been confirmed by other authors [13] and also by the randomized clinical study PROLONG [14]. The role of inherited thrombophilia and residual venous obstruction (RVO) as risk factors for recurrent VTE is still controversial [15–20]. However, we have observed that in inherited thrombophilia, altered D-d (above 500 ng/mL) at 1 month after VKA withdrawal is associated with a significantly higher risk of recurrence than normal D-d [17]. We have also shown that RVO, when measured at the time of VKA withdrawal, is neither associated with late recurrences nor it increases the risk of recurrences in the presence of abnormal D-d [20].

High Factor VIII levels have been shown to be associated with an increased risk in VTE recurrence [21–23]. In a prospective study following patients with a first idiopathic venous thrombosis, Kyrle et al. [22] found a 27% rate of recurrent VTE in patients with Factor VIII coagulant activity above the 90th percentile. We observed that in patients with a first idiopathic VTE, the risk of recurrence was more than 5-fold higher when FVIII chromogenic activity exceeded the 90th percentile and 3-fold higher with FVIII levels above the 75th percentile [23]. Elevated plasma factor VIII and D-dimer levels were shown to be predictors of poor outcomes (e.g. lack of thrombus resolution, recurrent thrombosis or post-thrombotic syndrome) after venous or arterial thromboembolic events in children [24].

So far it is unknown whether D-d and FVIII chromogenic activity are independent risk factors for recurrent VTE in adults.

The specific objective of the study was to assess the risk for VTE recurrence conferred by D-d and FVIII in combination after VKA withdrawal for symptomatic idiopathic proximal deep vein thrombosis (DVT) over a two-year follow-up.

Materials and methods

Study design

Consecutive patients with a first episode of objectively documented symptomatic idiopathic proximal DVT of the lower limbs (with or without PE) were prospectively investigated after VKA discontinuation. The study complied with the Declaration of Helsinki. The institutional review board of S. Orsola-Malpighi University Hospital, Bologna, Italy, approved the research protocol and informed consent was obtained from all the participating subjects.

All consecutive outpatients attending our anticoagulation clinic for a first episode of idiopathic DVT of the lower limbs between February 1995 and July 2004 were evaluated from the time of referral for VKA surveillance. We report the data obtained in a larger cohort of patients already evaluated in a previous paper [23]. The index VTE event was considered idiopathic if it occurred in the absence of any established clinical triggering/favouring (e.g. surgery, trauma, immobilization, pregnancy, puerperium, oral contraceptives, hormone replacement therapy) or non removable (e.g. cancer, chronic inflammatory disease) risk factors as previously described [12]. Patients with VTE were referred after discharge from our hospital or by general practitioners in our health district. On the first day of patient attendance at our clinic, the duration of VKA was suggested for at least 6 months. A clinical evaluation was then arranged at the end of the scheduled VKA course for its possible suspension along with compression ultrasonography (CUS) of the lower limbs. During the course of VKA, CUS was not routinely performed.

Inclusion criteria were: a single objectively documented unprovoked proximal DVT of the lower limbs, isolated or associated with PE, VKA duration of at least 3 months, and ability to return for follow-up visits. Exclusion criteria were: isolated iliac DVT or a disease requiring indefinite anticoagulation (such as atrial fibrillation, malignancy requiring chemotherapy and/or radiotherapy, known antiphospholipid syndrome).

On the day of VKA withdrawal (T1), CUS of the lower limbs was performed along with blood sampling as indicated below. The investigators were blinded to D-d and CUS results and the decision for VKA withdrawal was based solely on the type of index event as indicated above: at least 6 months after DVT and 6–12 months after PE (isolated PE or DVT with PE).