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Outcome after discontinuing anticoagulant therapy in women with venous thromboembolism during hormonal use

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ABSTRACT

Introduction: Whether women developing venous thromboembolism (VTE) while using hormonal therapy should be classified as having "unprovoked" or "provoked" VTE is controversial.
Methods: We used the RIETE (Registro Informatizado Enfermedad TromboEmbólica) database to compare the rate of symptomatic VTE recurrences after discontinuing anticoagulation in 3 subgroups of women aged ≤50 years without cancer, pregnancy or puerperium: (1) those with hormonal therapy and no additional risk factors (hormonal users only); (2) those with unprovoked VTE; and (3) those with additional risk factors, with or without hormonal therapy.
Results: As of March 2016, 1513 women had been followed-up for at least one month after discontinuing anticoagulation. Of these, 654 (43%) were hormonal users only, 390 (26%) had unprovoked VTE and 469 (31%) had transient risk factors with or without hormonal therapy. After discontinuing anticoagulation, the rate of VTE recurrences in women with hormonal use only (2.44 per 100 patient-years; 95% CI: 1.53–3.69) was significantly lower than in those with unprovoked VTE (6.03; 95% CI: 3.97–8.77) and similar to those with transient risk factors (2.58; 95% CI: 1.50–4.13). Interestingly, the rate of VTE recurrences presenting as pulmonary embolism in women with hormonal use only (0.55 per 100 patient-years; 95% CI: 0.18–1.29) was similar to those with transient risk factors (0.46; 95% CI: 0.09–1.33) and 4-fold lower than in women with unprovoked VTE (2.23; 95% CI: 1.07–4.10).
Conclusions: After discontinuing anticoagulation, the rate of VTE recurrences in hormonal users only was significantly lower than in women with unprovoked VTE and similar to the rate in women with additional risk factors.

1. Introduction

Venous thromboembolism (VTE) is a common complication in women using hormonal therapy because of excessive uterine bleeding, polycystic ovary, contraception or replacement therapy [1,2]. It has been calculated that over 100 million women use hormonal treatment worldwide [3], and the mortality rate due to pulmonary embolism (PE) in users has been estimated around 10.5 (95% CI: 6.2–16.6) deaths per million woman-years [4]. Around 70% of these women develop VTE in the absence of additional risk factors, and most often after few months of starting hormonal use [5]. In the literature, whether these women should be classified as having "unprovoked" or "provoked" VTE is controversial [6–11]. This is important since current guidelines from the American College of Chest Physicians (ACCP) recommend anticoagulant therapy for 3 months in VTE patients with only transient risk factors, and beyond the third month for those with unprovoked VTE (if they are not at increased risk for bleeding) [12].

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The RIETE (Registro Informatizado de Enfermedad Trombo-Embólica) Registry is an ongoing, multicenter, international (Spain, Italy, France, Israel, Portugal, Germany, Switzerland, Czech Republic, Republic of Macedonia, Greece, Canada and Ecuador), observational registry of patients with symptomatic, objectively confirmed, acute VTE(ClinicalTrials.gov identifier: NCT02832245). Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, bleeding and mortality, and risk factors for these outcomes [13–16]. In the current study, we compared the rate of VTE recurrences after discontinuing anticoagulant therapy in women with a first episode of VTE, according to the use of hormonal therapy and additional risk factors for VTE.

2. Methods

2.1. Inclusion criteria

Consecutive patients with symptomatic, acute deep vein thrombosis (DVT) or PE, confirmed by objective tests (contrast venography or ultrasonography for suspected DVT; pulmonary angiography, lung scintigraphy, or helical computed tomography for suspected PE), were considered in RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their relatives) provided written or oral consent to their participation in the registry, in accordance with local Ethics Committee requirements.

In the RIETE registry, participating physicians ensured that eligible patients were consecutively enrolled. Data were recorded using a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. The study coordinating center assigned patients a unique identification number to maintain patient confidentiality and was responsible for all data management. Data quality was regularly monitored electronically, including checks to detect inconsistencies or errors, which were resolved by the local coordinators. Data quality was also monitored by periodic visits to participating hospitals by contract research organizations that compared medical records with the submitted data.

2.2. Study design

In this study, only women aged $\leq$50 years with no cancer, pregnancy or puerperium, that had received at least 3 months of anticoagulant therapy and had been followed-up at least 30 days after discontinuing anticoagulation were included. They were classified into three subgroups: (1) those with hormonal therapy and no additional risk factors for VTE (hormonal users only); (2) those with unprovoked VTE; and (3) those with additional risk factors, with or without hormonal therapy.

The major outcome was the development of symptomatic, objectively confirmed VTE recurrences after discontinuation of anticoagulant therapy. Secondary outcomes were major bleeding and death. Major bleeding was defined as any overt bleed that required a transfusion of two or more units of blood, was retroperitoneal, spinal or intracranial, or was fatal.

2.3. Study variables

The following parameters were recorded: patient's baseline characteristics, risk factors for VTE, clinical status including any coexisting or underlying conditions, diagnostic tests, the type and dose of treatment received upon VTE diagnosis and the outcome during at least the first 3 months and after withdrawing of anticoagulant treatment. Immobilized patients were defined in this analysis as nonsurgical patients who had been immobilized (total bed rest with bathroom privileges) for $\geq$ 4 days in the 2-month period prior to VTE diagnosis. Surgical patients were defined as those who had undergone an operation in the 2 months prior to VTE diagnosis. Active cancer was defined as newly diagnosed cancer, metastatic cancer, or cancer that was being treated (with surgery, chemotherapy, radiotherapy, support therapy, or combined treatments).

2.4. Treatment and follow-up

Patients were managed according to the clinical practice of each participating hospital (there was no standardization of treatment). The type, dose and duration of anticoagulant therapy, as was the insertion of an inferior vena cava filter, were recorded. After discharge, all patients were followed-up for in the outpatient clinic. During each visit, any signs or symptoms suggesting VTE recurrences or bleeding complications were noted. Each episode of clinically suspected recurrent DVT or PE was investigated by repeat ultrasonography, venography, lung scanning, helical-CT scan or pulmonary angiography as appropriate. Most outcomes were classified as reported by the clinical centers. However, if staff at the coordinating center were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events). Patients who had recurrent VTE or major bleeding events within 3 months of enrolment remained under surveillance until 3 months of follow-up was completed.

2.5. Statistical analysis

All variables were calculated as absolute numbers and proportions, and then compared with the Student's t-test or χ^2 test (or Fisher's Exact Test where appropriate) in case of quantitative or qualitative variables. A p value < 0.05 was considered statistically significant. Incidence rates were calculated as cumulative incidence (events/100 patient-years) and compared using the rate ratio [17]. These analyses were completed with the Statistical Package for Social Sciences program (version 15.0. for Windows, 2006 SPSS Inc. Chicago, IL, USA).

3. Results

As of March 2016, 63698 consecutive patients with symptomatic VTE were enrolled in RIETE. Of these, 2401 (3.8%) were women aged $\leq$50 years, with no cancer, pregnancy or puerperium. All of them received anticoagulant therapy, and 1513 (63%) were followed-up for at least one month after discontinuing anticoagulation. There is no information on follow-up after discontinuation of therapy in most of the remaining patients (692 of 888, 78%) because at the very beginning of RIETE patients had to be followed-up for only 3 months. Moreover, 31 patients died, 67 were still receiving therapy and 98 were lost for follow-up. Of the 2401 women followed-up after discontinuing anticoagulation, 390 (26%) had unprovoked VTE, 654 (43%) were hormonal users only and 469 (31%) had transient risk factors (with or without hormonal therapy). The most commonly used compounds were combined contraceptives containing ethinylestradiol and drospirenone (34%) and third-generation progestins (etonorgestrel, gestodene or desogestrel) (34%), then ciproterone (19%) and second generation progestins (norgestimate or levonorgestrel) (10%). There was no information on the compound in 278 women (32%).

Hormonal users only were significantly younger, weighed less and were less likely to have co-morbidities than those with unprovoked VTE or with additional risk factors (Table 1). Among those who underwent thrombophilia testing, hormonal users only were less likely to have protein C deficiency or antiphospholipid syndrome but more likely to have prothrombin mutation. As to the initial VTE presentation, hormonal users only and those with