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Original Article

Prior thromboprophylaxis and outcome in patients experiencing acute venous thromboembolism after an acute medical illness

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ABSTRACT

Background: Even despite the use of thromboprophylaxis, some patients with an acute medical illness develop symptomatic venous thromboembolism (VTE). It is unclear whether the outcome in these patients is different in those in whom prophylaxis was not prescribed.
Patients and methods: We used the RIETE (Registro Informatizado Enfermedad TromboEmbolica) database to compare the 3-month outcome (death, fatal pulmonary embolism, VTE recurrences, major bleeding) of patients with acute VTE after immobilization for an acute medical disease, according to the use of prophylaxis.
Results: Thromboprophylaxis was prescribed in 1313 (37%) of the 3527 patients included in August 2014. Acute infection was the most frequent cause of immobilization. Patients who received prophylaxis were more frequently immobilized in hospital than at home (70% vs. 22%), and fewer patients were immobilized for cancer (13% vs. 22%). During the first 3 months of treatment, the rates of all-cause death (23 vs. 21%), fatal PE (2.6 vs. 3.1%), VTE recurrences (2.4% vs. 2.8%), and major bleeding (4.2% for both) did not differ between the two groups. Thromboprophylaxis was not associated with each outcome in multivariate analysis.
Conclusions: The outcome in patients with VTE provoked by medical immobilization was not influenced by the use of thromboprophylaxis during the period of immobility.

1. Introduction

Pulmonary embolism (PE) is considered the most common preventable cause of death in hospitalized patients [1], and most cases of fatal PE in the hospital occur in medical patients [2]. Several randomized studies in acutely ill medical patients have shown that the risk of venous thromboembolism (VTE) can be reduced by up to two thirds using adequate pharmacologic VTE prophylaxis [3–7]. Accordingly, evidence-based guidelines on the prevention of VTE recommend that at-risk, acutely ill hospitalized medical patients should receive pharmacologic prophylaxis with low-molecular-weight heparin, unfractionated heparin, or fondaparinux [1]. Efforts have focused to help practitioners improving the prevention of hospital-acquired VTE, which is frequently used now as a quality indicator for health authorities [8].

However, a substantial number of patients may experience symptomatic VTE despite adequate VTE prophylaxis [9], and there is little data focused on the outcome of these patients. As illustrated in the clinical vignette, one might ask whether a patient who presented symptomatic VTE despite prophylaxis will have a favorable outcome under anticoagulant therapy, which is frequently the same drug (at least initially) as that used for prevention (LMWH). With the exception of one trial [6], the efficacy end point of the above-mentioned randomized trials combined asymptomatic and symptomatic VTE. Symptomatic VTE was rare in these studies, precluding any analysis of outcome in patients with symptomatic VTE.

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We used the RIETE (Registro Informatizado de Enfermedad TromboEmbólica) database to compare the outcome during the first 3 months of anticoagulant therapy in patients developing acute VTE after being immobilized for an acute medical illness, according to the use of VTE prophylaxis. RIETE is an ongoing, multicenter, international (Spain, Italy, France, Israel, Greece, Switzerland, Czech Republic, and Macedonia), observational registry of consecutive patients with symptomatic acute VTE [10–13]. It provides valuable information on every day practice in the different countries involved. Hence, it represents a unique opportunity to assess this question, as opposed to an administrative database.

2. Methods

2.1. Study population

All enrolled patients in RIETE presented with symptomatic, objectively confirmed VTE. Symptomatic PE was confirmed if it was objectively documented (by positive helical computed tomography scan, high-probability ventilation/perfusion lung scan, positive pulmonary angiography, visualisation of a thrombus in the right ventricle or in the right atrium on echocardiography, or intermediate-probability ventilation/perfusion lung scan associated with a diagnosis of DVT). DVT was diagnosed in the case of acute symptoms of DVT confirmed by compression ultrasound or contrast venography of the lower limbs. If patients were currently enrolled in a clinical therapeutic trial with blinded medication, they were excluded. Every patient (or their legal power of attorney if indicated) submitted oral or written consent to participate in this registry. All patients were managed according to the clinical practice of each participating hospital and not subject to any predetermined procedure.

In the RIETE registry, the participating physicians ensured that eligible patients were consecutively enrolled. Data were recorded in a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. The trial coordinating center assigned patients a unique identification number to maintain patient confidentiality and was responsible for all data management.

2.2. Study design

For this study, we selected all patients older than 39 years, immobilized for at least 4 days during the past 2 months for an acute medical disease (heart or respiratory failure, stroke, infection, or cancer), as in the randomized clinical trials evaluating the efficacy and safety of VTE prophylaxis. Patients were divided in two groups: those who received prophylaxis and those who do not.

2.3. Outcomes

Major outcomes included the development of fatal PE, objectively confirmed recurrent VTE, major bleeding, and overall death in the first 90 days following the symptomatic VTE event. Causes of death were determined by the attending physicians. Fatal PE, in the absence of autopsy, was defined as any death appearing <7 days after PE diagnosis, in the absence of an alternative cause of death. According to the ISTH definition [14], bleeding was classified as 'major' if it was overt, fatal, and/or causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome.

2.4. Variables and definitions

The following parameters were recorded in the RIETE registry: initial VTE presentation, clinical characteristics (age, gender, and weight), concomitant therapies, additional risk factors for VTE, and drugs used in prophylaxis. The cause (heart failure, ischemic heart disease, acute stroke, chronic lung disease, acute infection, and active cancer) and place of immobilization were recorded for each patient. Active cancer is defined as newly diagnosed cancer, metastatic cancer, or cancer that is being treated. We observed the rates of thromboprophylaxis in the patients immobilized for acute medical reasons and then to compare the outcomes of patients who experienced VTE after medical immobilization, according to the thromboprophylaxis group.

2.5. Data collection and monitoring

The attending physicians ensured that eligible patients were consecutively enrolled. Data were captured on a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. Data encryption was used to enhance confidentiality and security. Data quality was regularly monitored and documented electronically 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 who compared the medical records with the data on the web. A data audit was performed at periodic intervals. Patient identity remained confidential because they were identified by a unique number assigned by the trial coordinating center responsible for all data management.

2.6. Statistical analysis

Differences in the distribution of characteristics between patients with and without thromboprophylaxis were assessed using chi-square tests for categorical variables and *t* test for continuous variables. A *p*-value <0.05 was considered to be statistically significant.

Regression models were used to examine whether thromboprophylaxis was associated with the study outcomes. Statistical analyses were conducted with SPSS for Windows Release 17.0 (SPSS, Inc.).

3. Results

Of the 50,325 patients included in the RIETE registry as at August 2014, 3527 (7%) patients had VTE after immobilization for an acute medical illness. Thromboprophylaxis had been prescribed in 1313 (37%) such patients, mainly LMWH in the vast majority of them (92%). Their clinical characteristics are presented in Table 1, according to the use of thromboprophylaxis. Acute infection was the most frequent cause of immobilization. Compared to patients not receiving prophylaxis, patients that did receive it were more likely immobilized in hospital (70% vs. 22%), but less frequently for cancer (13% vs. 22%). The proportion of patients initially presenting with acute PE and the frequency of signs of severity were similar in the two groups. No differences were found in terms of drugs used in the initial therapy (LMWHF, UFH) as in the long-term therapy (Table 2).

During the first 3 months of treatment, the rates of all-cause death (23 vs. 21%), fatal PE (2.6 vs. 3.1%), VTE recurrences (2.4% vs. 2.8%), and major bleeding (4.2% for both) did not differ between the two groups (Table 3). Even when included in multivariate models predicting each outcome (unpresented data), the use of thromboprophylaxis was not associated with a different risk for death, fatal PE, VTE recurrence, or major bleeding.

4. Discussion

Our findings, obtained from a large series of consecutive patients with acute VTE developing after an acute medical illness, reveal that the use of thromboprophylaxis had no influence on their 3-month outcome. Recently, the RIETE investigators found that patients with PE provoked by non-surgical immobilization had a greater risk of dying of PE