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Original Article

Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients. A retrospective multicenter study

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ABSTRACT

Objective: To analyze the incidence of VTE in hospitalized medical patients and prophylaxis applied in accordance with the 8th ACCP guidelines and the National PRETEMED guide for thromboprophylaxis.
Methods: Discharge lists were reviewed to select the first consecutive 20 patients, aged ≥40 years and admitted ≥4 days to the Internal Medicine Departments of 79 Spanish hospitals. Exclusion criteria were: admission for diagnostic procedures, VTE or surgical illness, or care during hospitalization provided by the local investigator.
Results: From September 2011 to July 2012, 2845 discharge reports were evaluated and 1623 were considered eligible for the study. Overall 930 (57.3%) patients of this group were at risk of VTE according to the ACCP guidelines, 759 (81.6%) received VTE prophylaxis (mechanical or pharmacological) and 159 (17.1%) had at least one risk factor that might contraindicate anticoagulant use. The proportion of patients at VTE risk according to the ACCP and National PRETEMED guidelines with no risk factors of bleeding that did not receive prophylaxis was 16.3% and 17.2%, respectively. During hospitalization, there were 14 (0.9%) episodes of symptomatic VTE, 12 (86%) of which occurred in patients receiving prophylaxis. VTE rate was 1.3% among patients with VTE risk that received prophylaxis and 3.5% in patients that also had one risk factor that might contraindicate anticoagulant use.
Conclusions: In a setting characterized by high thromboprophylaxis compliance most of the episodes occurred in patients receiving pharmacological prophylaxis. Patients with combined VTE and bleeding risk factors showed the highest rate of both symptomatic VTE and prophylaxis failure.

1. Introduction

Clinical trials and meta-analysis confirmed that venous thromboembolism (VTE) prophylaxis in acutely ill medical patients reduces the occurrence of proximal deep vein thrombosis (DVT) and pulmonary embolism (PE). Thus, the evidence-based clinical practice guidelines of the American College of Chest Physicians (ACCP) (9th edition) [1] recommend thromboprophylaxis in patients admitted to hospital with an acute medical illness with an increased risk of thrombosis. However, in spite of that evidence and recommendation, application of VTE prophylaxis is not generalized. There is some skepticism about the benefits of VTE prophylaxis especially in the elderly [2]. During the last decade, studies using either large datasets [3–5] or single center experiences [6,7] reported that between 30 and 74% of the acutely ill medical patients received VTE prophylaxis. In the multinational, cross-sectional ENDORSE study [8] 60.5% of medical patients at risk did not receive prophylaxis according to the ACCP—2004 guidelines. In a sub-analysis [9] of data from the 20 participating Spanish hospitals, the proportion of these patients was smaller (35.9%). During the last five years considerable efforts have been made to implement prophylaxis in patients at risk. Electronic alerts [10–12], seem to be effective for that purpose. Besides, medical societies have produced specific guidelines for the use of prophylaxis. In Spain, the National PRETEMED guide [13] categorizes patient VTE risk according to a number of risk factors and has been in use since 2007. How closely these guidelines are followed in clinical practice and how much increased thromboprophylaxis use influences the occurrence of VTE are not well known. The aim of this study is to analyze the incidence of symptomatic VTE in a sample of consecutive patients admitted to hospital for acute medical illnesses taking into account associated risk factors and prophylaxis used. A secondary aim was to analyze the incidence of bleeding in this population.

2. Methods

MEDITROM is a multicenter retrospective study. The Internal Medicine Services of many centers in Spain were asked to collaborate

Abbreviations: VTE, venous thromboembolism; LMWH, low molecular weight heparin; DVT, deep vein thrombosis; PE, pulmonary embolism; ACCP, American College of Chest Physicians.

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in the study. These centers were selected from 13 of the 15 peninsular regions of the country, depending on the experience of the local investigator and the feasibility of data collection. Both large academic hospitals and small private clinics were considered suitable for participation in the study. Seventy-nine hospitals that admitted patients for acute medical illnesses or exacerbation of chronic diseases were involved in the study. All the cases coming from one center (no. 19) had to be dismissed due to errors in the application of the inclusion criteria, so that finally data from 78 centers were analyzed (a full list of participating centers is included in Appendix A). The protocol was designed by the principal investigator (JAN) and revised after discussion with the study sponsor. Data collection started in September 2011 and finished in July 2012. The study protocol was approved by the Ethics Committee of the principal investigator hospital and by local Ethics Committees of participating hospitals when required by local regulations. The MEDITROM study was funded by Bayer SL.

2.1. Study population

Discharge lists of Internal Medicine services were reviewed in participating centers. Local investigators selected the first consecutive 20 patients (eligible patients), aged ≥40 years and admitted ≥4 days to a medical unit. Patients were considered ineligible or excluded if they were admitted for diagnostic procedures, VTE or surgical illness, if they were treated during hospitalization by the local investigator, or relevant data was missing. We applied the same definitions as used in the ENDORSE study [8] and the 8th ACCP guidelines [14] to classify populations, risk factors for bleeding and VTE, and contraindications for anticoagulation. The "eligible" population contains all patients remaining after application of the selection criteria described above. The "at-risk of VTE" population contains the eligible patients that were not anticoagulated and fulfilled the 8th ACCP criteria [14], and PRETEMED 2007 criteria [13] for VTE risk. Finally, the "assessable" population contains patients "at risk for VTE" but without contraindication to anticoagulation.

2.2. Data collection

Data from discharge reports or medical records were collected on standardized case report forms that were provided to each participating center. In order to handle patients' data in a confidential manner a numeric code was assigned to each case. Patients were not interviewed. Completed case report forms were sent to the coordinating center (Phidea Marvin SLU, Madrid) for entry into a single database and to perform statistical analysis. Double data entry was used to reduce the risk of errors. Potential discrepancies in double entries were resolved by reviewing the case report forms.

Recorded data included patient demographics, medical history, admission diagnosis, risk factors for bleeding and VTE, clinical episodes of bleeding or VTE during hospitalization, reported discharge diagnosis and VTE prophylaxis used.

2.3. Definitions

We considered bleeding risk factors as defined in the 8th ACCP guidelines [14] which were the current guidelines during the observation period. Patients were considered to have a contraindication to anticoagulant prophylaxis if they had recent intracranial hemorrhage, significant hepatic impairment, active bleeding at hospital admission, an active gastrointestinal ulcer [15] or history of intracranial or aortic aneurysm.

We considered VTE prophylaxis to have been provided if the patient received at least a single dose of 2.000–6.000 IU low molecular weight heparin (LMWH), or 2.5 mg fondaparinux for this purpose, or if at any time during hospitalization mechanical prophylaxis methods were used regardless of how long they were maintained.

VTE episodes were included if they were symptomatic and diagnosed by image methods; the episodes of VTE were assigned regardless of the number of days that the patient received prophylaxis. Bleeding episodes were included if they were considered clinically relevant enough to be detailed in the discharge report. No distinctions were made between major or minor bleeding. Cause of death was established by the attending physician. No autopsies were performed.

2.4. Statistical analysis

Based on previous data [9] according to which 64% of the acute medical patients at risk of VTE received prophylaxis, we estimated that a sample size of 1680 patients would be sufficient to show a 2.3% difference in the use of prophylaxis in the assessable population when compared to the ENDORSE historical data for our country at a two-sided alpha level of 0.05. On this basis, it was planned to involve 84 centers, including 20 eligible patients from each of them. As mentioned above, finally 79 centers participated in the study. Missing data was shown in the tables or in the text when appropriate. Student's *t*-test was used to compare continuous variables. Qualitative variables were compared by the Chi-square test or Fisher exact test when appropriate. A two-sided $p < 0.05$ was considered to be statistically significant. SAS version 8.2 was used for the statistical analyses.

3. Results

Discharge reports from 2.845 medical patients were evaluated; 1222 patients did not meet the inclusion criteria (age <40, 188; admitted <4 days, 579) or were excluded (admission for diagnostic procedures, 65; admitted for VTE, 130; surgical illness, 138; treated by the local investigator, 133; missing essential data to make a decision to include or exclude the patient, 57; patients from centre number 19, 20). Eighty-two patients failed 2 criteria and 5 patients 3 criteria.

Data from 1623 (57.1%) eligible patients were included in this analysis. Median age was 78; 78% of the patients were older than 65 years and 22% older than 85. The patients' race was predominantly Caucasian (99.4%). Key characteristics of the eligible population, reasons for hospital admission and secondary diagnosis at discharge are shown

Table 1
Characteristics of the eligible population (n, 1623).

Age (median; range)	78; 40–104
Females (%)	49%
Weight (kg; median; range)	74; 37–147
In-hospital days (median; range)	8; 4–75
Reason for hospitalization n (%)	
Respiratory infection	450 (27.8)
Heart failure (NYHA III or IV)	282 (17.4)
Non-respiratory infection	279 (17.2)
Cardio-vascular disease	233 (14.4)
Gastrointestinal/liver disease	206 (12.7)
Renal disease	109 (6.7)
Neurologic disease	107 (6.6)
Acute non-infectious respiratory disease	99 (6.1)
Malignancy, active	93 (5.7)
Ischemic stroke	68 (4.2)
Endocrine/metabolic disease	68 (4.2)
Hematological disease	55 (3.4)
Rheumatological or inflammatory disease	32 (2.0)
Hemorrhagic stroke	18 (1.1)
Other	94 (5.8)
Secondary diagnosis n (%)	
Death, any cause	87 (5.4)
Bleeding	84 (5.2)
Infection	240 (14.8)
Thromboembolism	19 (1.2)
Venous thromboembolism	14 (0.9)

Some patients had more than one reason for hospitalization.