

## Thrombosis prophylaxis in medical patients: a retrospective review of clinical practice patterns

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**Background and Objectives.** The risk of venous thromboembolism in medical patients is comparable to the risk in general surgical patients. Thromboprophylaxis is recommended for specific medical patients, but its use in clinical practice is unknown.

**Design and Methods.** We conducted a retrospective review of the charts of consecutive patients discharged from 2 departments of Internal Medicine, one in the teaching hospital of Varese and one in the non-teaching hospital of Angera, Italy, from October to December 2000. We selected the charts of patients with clinical conditions at increased risk of venous thromboembolism requiring thromboprophylaxis according to consensus statements. The use of antithrombotic drugs and contraindications to prophylaxis were documented.

**Results.** We screened a total of 516 charts, 265 in Varese and 251 in Angera and we identified 165 patients (103 and 62, respectively) at risk of venous thromboembolism because of malignancy (53), heart failure (34), stroke (33), acute infections (23), acute respiratory failure (18), acute rheumatic disorders (3), and inflammatory bowel disease (1). Forty-two patients had contraindications to antithrombotic drugs and 11 were already on long-term oral anticoagulant treatment. Among the 112 remaining patients, prophylaxis was prescribed to 52 patients (46.4%), 35 of 60 in Varese (58.3%) and 17 of 52 in Angera (32.7%,  $p=0.0067$ ). Patients with stroke and heart failure were significantly more likely to receive thromboprophylaxis than other groups of patients.

**Interpretation and Conclusions.** Prophylaxis of venous thromboembolism is underused in medical patients and the proportion of patients receiving antithrombotic drugs varies with the medical condition which precipitated hospital admission. The low rate of usage of prophylaxis suggests that preventable cases of thromboembolism are occurring and that better education of physicians is required to increase the usage of thromboprophylaxis.  
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## Thrombosis

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Venous thromboembolism (VTE) is a common cause of morbidity and mortality in the United States and approximately 200,000 patients die annually from pulmonary embolism as a direct or a contributing cause.<sup>1</sup> In particular, pulmonary embolism is responsible for 10% of overall deaths in hospitalized patients.<sup>2</sup> However, the real incidence, prevalence and mortality rates of the disease are likely to be underestimated because of its clinically silent nature.<sup>3</sup> The rationale for thromboprophylaxis has been supported over the years by overwhelming evidence from several clinical trials, mainly conducted in surgical patients.

Epidemiological data have shown that the risk of VTE in medical patients is comparable to the risk in surgical patients, varying from 60% in ischemic stroke patients<sup>4</sup> to 24% in myocardial infarction patients,<sup>5</sup> and to 19% in other medical patients.<sup>6</sup> Moreover, *post-mortem* data suggest that 75% of all in-hospital deaths from pulmonary embolism (PE) occur in non-surgical patients.<sup>2</sup> Although the prevention of VTE has been less extensively studied in medical patients than in surgical patients, there are now sufficient data to support the use of pharmacologic prophylaxis in several medical conditions, and the Sixth Consensus Conference on Antithrombotic Therapy of the American College of Chest Physicians (ACCP) recommended either low molecular weight heparin or low dose unfractionated heparin for patients with acute myocardial infarction, acute ischemic stroke and in general medical patients.<sup>5</sup> These are patients with heart failure, acute respiratory failure, acute infectious diseases, acute rheumatic disorders, inflammatory bowel diseases and cancer.

A significant underuse of routine prophylaxis has been reported in the population of patients undergoing surgery,<sup>7-9</sup> with the proportion of treated patients varying according to the surgical procedure.<sup>10</sup> Clinical guidelines and educational programs for VTE prevention in the general medical population are far less developed than those in the surgical population. Little is known about the actual use of VTE prophylaxis in medical patients. To assess

the routine use of VTE prophylactic therapy in medical patients, we retrospectively reviewed the charts of patients discharged from two Italian departments of Internal Medicine, one in a teaching hospital and one in a non-teaching hospital.

### Design and Methods

This was a retrospective study conducted in two departments of Internal Medicine at the hospitals of Varese and Angera, Italy. The former is a university-based teaching hospital, the latter is a non-teaching hospital. The total number of beds is 94, 48 in Varese and 46 in Angera. The charts of all patients discharged in the months of October, November, and December 2000 were screened. To assess the prevalence of clinical conditions requiring VTE prophylaxis and to evaluate the adherence to published clinical guidelines, patients were selected on the basis of the ACCP consensus statements<sup>5</sup> and the criteria used in the MEDENOX study.<sup>11</sup> Accordingly, the presence of at least one of the following conditions at risk for VTE was required: heart failure (NYHA class III or IV), acute respiratory failure revealing or complicating chronic respiratory insufficiency, acute infectious disease, acute rheumatic disorders, active episode of an inflammatory bowel disease, malignancy, and acute ischemic stroke with lower limb paralysis. Patients were excluded if they had been bedridden for more than 3 days prior to hospital admission.

All patients selected had the following data extracted from their hospital charts: age, gender, and the presence of concomitant risk factors for VTE such as being overweight or obese defined on the basis of the body mass index, personal history of VTE, varicose veins, heart failure with NYHA class I and II, concomitant hormone therapy, and known thrombophilia including antithrombin, protein C and protein S deficiencies, mutations in factor V or factor II, hyperhomocysteinemia, and the antiphospholipid antibodies syndrome. Information on drugs and regimens for VTE prophylaxis during hospitalization were recorded for all patients, as well as according to the clinical condition requiring VTE prophylaxis. The presence of contraindications to antithrombotic treatment was documented. A contraindication to antithrombotic therapy was defined by the presence of any of the following conditions: impaired hepatic function, active or recent bleeding, hemorrhagic tendency or a bleeding dyscrasia, active peptic ulcer disease or known esophageal varices, hypersensitivity to heparin or personal history of heparin-induced thrombocytopenia, and a platelet count of less than

$100 \times 10^9/L$ . Patients presenting with clinical contraindications to antithrombotic treatment as well as patients who were already receiving long-term treatment with oral anticoagulant drugs were excluded from the primary analysis.

Information on suspected deep venous thrombosis or pulmonary embolism during hospitalization and on diagnosis or exclusion of the disease based on objective tests was also collected.

For statistical analysis we used the  $\chi^2$  test to compare the rates of VTE prophylaxis use between the two departments of Internal Medicine and among the different clinical conditions requiring prophylaxis. An unpaired t-test was used to compare the mean age of patients with clinical conditions requiring VTE prophylaxis according to hospital location. For all analyses, a 2-sided  $p$ -value  $< 0.05$  defined statistical significance.

### Results

A total of 516 charts were examined, 265 in the department of Internal Medicine of the hospital of Varese and 251 in the department of Internal Medicine of the hospital of Angera. Clinical indications for VTE prophylaxis were identified in 165 of 516 patients (32%), with a mean age of 74.5 years. In particular, we identified 103 patients in the hospital of Varese (38.9%) and 62 patients in the hospital of Angera (24.7%). The mean age of the patients was not significantly different between the 2 groups. The prevalences of the single disorders requiring VTE prophylaxis are summarized in Table 1. Data on the presence of concomitant risk factors are reported in Table 2. Information on concomitant risk factors was inadequate in some charts and, thus, results may underestimate the actual prevalence of concomitant risk factors.

We identified 42 patients with clinical contraindications to VTE prophylaxis, 33 in Varese and 9 in Angera. The most common clinical contraindication was recent or active bleeding, reported in 18 patients. Thirteen patients had a platelet count of less than  $100 \times 10^9/L$  and 11 had severe liver dysfunction (9 admitted with metastases to the liver, all of whom died within 7 days of admission). Eleven patients (10 in Varese and 1 in Angera) were already on long-term oral anticoagulant treatment because of chronic atrial fibrillation. Thus, excluding all patients with clinical contraindications to anticoagulation, and patients who were on oral anticoagulants prior to hospital admission, the number of eligible patients for our primary analysis was 112, 60 in Varese and 52 in Angera.

Pharmacologic prophylaxis was prescribed to 52

**Table 1. Prevalence of pathologies placing patients at high risk of venous thromboembolism.**

	Total	Teaching Hospital	Non-teaching Hospital
Total	165	103	62
Acute ischemic stroke	33 (20%)	18 (17.5%)	15 (24.2%)
Cancer	53 (32.1%)	42 (40.8%)	11 (17.7%)
Congestive heart failure	34 (20.6%)	18 (17.5%)	16 (25.8%)
NYHA class III	19	8	11
NYHA class IV	15	10	5
Acute respiratory failure	18 (10.9%)	9 (8.7%)	9 (14.5%)
Acute infectious disease	23 (13.9%)	15 (14.6%)	8 (12.9%)
Acute rheumatic disorder	3 (1.9%)	1 (0.9%)	2 (3.3%)
Inflammatory bowel disease	1 (0.6%)	–	1 (1.6%)

of 112 patients (46.4%) who met consensus guidelines for the use of antithrombotic therapy. The overall rate of use of this therapy differed statistically between the department of Varese and the department of Angera (58.3% and 32.7%, respectively,  $p < 0.0067$ ). Patients admitted for acute ischemic stroke or heart failure were more likely to receive prophylaxis than other groups of patients, with an odds ratio of 2.20 and 2.40, respectively, as compared to cancer patients, and of 2.59 and 2.83 as compared to patients with acute infectious disease. In particular, the difference was statistically significant when these patients were compared to patients with acute respiratory failure (stroke patients versus patients with acute respiratory failure  $p = 0.0219$ , odds ratio 5.60, patients with heart failure versus patients with acute respiratory failure  $p = 0.0163$ , odds ratio 5.19) (Table 3). Patients with malignancy or acute respiratory failure were not considered for VTE prophylaxis at the department of Internal Medicine of Angera (Table 3).

Low molecular weight heparins (nadroparin and enoxaparin) were prescribed to a total of 47 out of 52 patients who received antithrombotic prophylaxis. Five patients received unfractionated heparin (5,000 IU three times daily), all in the department of Internal Medicine in Angera. Patients on enoxaparin received a 40 mg daily dose, patients on nadroparin received either a 0.3 mL or a 0.4 mL daily dose. Eight patients received low molecular weight heparins at higher doses (enoxaparin 60 mg or nadroparin 0.6 mL) because of obesity. No patients received mechanical prophylaxis with elastic stockings or intermittent pneumatic compression.

During hospitalization, deep venous thrombosis was suspected in 5 of the 165 patients presenting with clinical conditions at increased risk for VTE

**Table 2. Identified risk factors for VTE in patients enrolled in the study.**

	Total	Teaching Hospital	Non-teaching Hospital
	N:165	N:103	N:62
History of VTE	12	12	–
Overweight or obese	29	27	2
Varicose veins	18	17	1
Heart failure (NYHA I and II)	29	15	14
Hormone therapy	3	3	–
Thrombophilia	–	–	–

Abbreviations: VTE: Venous thromboembolism.

(3%). Three were receiving prophylaxis and 2 were not receiving prophylaxis. In 4 patients deep vein thrombosis was subsequently ruled out by objective testing, in 1 patient proximal vein thrombosis of a lower limb was diagnosed (0.6%). This patient had prostate cancer and was not receiving any prophylactic strategy because of concomitant active bleeding (macrohematuria).

## Discussion

The results of this retrospective chart review demonstrate that VTE prophylaxis in medical patients is still significantly underused, despite compelling evidence for its efficacy. According to the current recommendations of the Sixth Consensus Conference of the ACCP,<sup>5</sup> at least one third of our patients presented with clinical conditions at moderate or high risk of VTE. Only 31.5% of them received adequate prophylaxis, 46.4% after the exclusion of patients with clinical contraindications and patients who were on oral anticoagulants prior to hospital admission. The use of VTE prophylaxis was higher in patients with acute ischemic stroke and heart failure than it was in patients with malignancies, acute infectious diseases or acute respiratory failure. However, the use of prophylaxis was still inadequate in all groups of patients, irrespective of their risk profile. We also found different rates of use of VTE prophylaxis between patients admitted to a teaching hospital and those admitted to a non-teaching hospital. In the latter there was a lower prescription rate of antithrombotic prophylaxis, suggesting the risk of VTE in patients with malignancy or acute respiratory failure was less appreciated.

The results of our study are not surprising. Several reports from clinical practice have described a

**Table 3. Use of prophylaxis of venous thromboembolism in the eligible medical population.**

	Total	Teaching Hospital	Non-teaching Hospital
Total	52/112 (46.4%)	35/60 (58.3%)	17/52 (32.7%)
Acute ischemic stroke	17/29 (58.6%)	10/15 (66.7%)	7/14 (50%)
Cancer	9/23 (39.1%)	9/16 (56.2%)	0/7
Congestive heart failure	17/28 (60.7%)	10/13 (76.9%)	7/15 (46.7%)
Acute respiratory failure	3/14 (21.4%)	3/5 (60%)	0/9
Acute infectious disease	6/17 (35.3%)	3/10 (30%)	3/7 (42.9%)
Acute rheumatic disorder	0/1	0/1	0/0
Inflammatory bowel disease	0/0	0/0	0/0

significant underuse of VTE prophylaxis in surgical patients even in the presence of multiple risk factors.<sup>5</sup> In particular, surveys on patients undergoing general surgery have produced results that are almost identical to those reported in our study. Bratzler *et al.*<sup>8</sup> performed a retrospective review of the medical records of 419 patients older than 65 years undergoing major abdominothoracic surgery and found that only 38% received VTE prophylaxis. This occurred despite the conclusive results of a number of clinical trials that have been carried out in more than 100,000 surgical patients<sup>12,13</sup> and despite the availability of clear clinical guidelines produced by several consensus conferences. Evidence for the utility of antithrombotic prophylaxis in medical patients is less overwhelming, however, it is convincing. Thus, approximately 16,000 patients have been included in mostly small clinical trials,<sup>6,11</sup> and fewer clinical guidelines have been produced for these patients than for surgical patients. Moreover, consensus on clinical guidelines is sometimes unclear and the recommendations can be heterogeneous and thus confusing. For instance, the Sixth Consensus Conference of the ACCP<sup>5</sup> recommends the routine use of low dose unfractionated heparin, low molecular weight heparin, or danaparoid for all patients with ischemic stroke and immobility, whereas the guidelines published by the Stroke Prevention and Educational Awareness Diffusion (SPREAD)<sup>14</sup> only recommend VTE prophylaxis in stroke patients with hemiplegia, obesity, history of previous VTE, or impaired consciousness. For all other stroke patients, antithrombotic prophylaxis is clearly not recommended by this group.

In our study, the rate of use of thromboprophylaxis varied between clinical conditions. This finding was surprising since patients who would appear to be at high risk of thrombosis (such as those with acute respiratory failure or malignancy) seemed to be systematically excluded from thromboprophylaxis in one center in our study. The importance of VTE prophylaxis is heightened by the observation that VTE is often clinically silent, but this aspect can be misleading in medical patients even more than it is in surgical patients. Thus, in the Mednox study,<sup>11</sup> objectively documented, symptomatic DVT occurred in only 0.7% of both patients receiving active prophylaxis and patients receiving placebo, whereas overt bleeding events occurred in 12% of patients receiving prophylaxis and 8.6% of patients receiving placebo. We cannot, therefore, expect an internist to prescribe antithrombotic drugs on the basis of his daily practice. Thus, appropriate diffusion of consensus conference recommendations is necessary to increase the awareness of the risk of VTE also in medical patients. However, consensus statements alone are insufficient to ensure the routine use of prophylactic strategies in clinical practice.<sup>10</sup> Anderson *et al.*<sup>15</sup> demonstrated that the application of educational strategies significantly increased by almost twofold the frequency with which physicians prescribe VTE prophylaxis. These findings, coupled with our observation of a very low rate of VTE prophylaxis usage, suggest that educational programs should be locally developed and designed to increase the use of prophylaxis both in teaching and non-teaching hospitals.

In conclusion, the results of this retrospective study show that prophylaxis of VTE is underused in medical patients and that the proportion of patients receiving antithrombotic drugs varies with the medical disease. Broader recognition and dissemination of the results of clinical trials and the recommendations of consensus statements is required, if the burden of preventable complications of thromboembolism in medical inpatients is to be minimized.

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WA was the major contributor to this work and was primarily responsible for it, from conception to submitted manuscript. He should be considered as the principal author. The remaining authors qualified for authorship according to the World Association of Medical Editors (WAME) criteria, and have taken specific responsibility for the following parts of the content: AS, FA, FD, CM, VM and LS: collection of clinical data; AV had a major role as the senior

author in designing the study, interpreting the data and preparing the article. We are indebted to Dr. Mark Crowther for his critical review of the manuscript and his invaluable suggestions.

#### Disclosures

*Conflict of interest: none.*

*Redundant publications: no substantial overlap with previous papers.*

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#### PEER REVIEW OUTCOMES

##### Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Vicente Vicente, Deputy Editor. The final decision to accept this paper for publication was taken jointly by Prof. Vicente and the Editors. Manuscript received February 27, 2002; accepted April 11, 2002.

##### What is already known on this topic

The real incidence, prevalence and mortality rates of venous thromboembolism (VTE) are underestimated.

##### What this study adds

This retrospective study adds information on the routine use of VTE prophylactic therapy in medical patients.

##### Potential implications for clinical practice

Prophylaxis of VTE is underused in medical patients. Better education of physicians involved in this field should reduce the burden of preventable complications of thromboembolism in medical patients.

Vicente Vicente, Deputy Editor