# An Epidemiologic Study of Risk Factors for Deep Vein Thrombosis in Medical Outpatients

## *The Sirius Study*

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**Background:** Little information is available concerning risk factors for venous thromboembolism (VTE) in nonhospitalized patients.

**Participants and Methods:** An epidemiologic case-control study of deep vein thrombosis (DVT) risk factors was conducted in 1272 outpatients by general practitioners. The case population (636 patients presenting with DVT) was paired with the control population (636 patients presenting with influenzal or rhinopharyngeal syndrome) according to sex and age. Deep vein thrombosis was to be documented by at least 1 objective test. Risk factors were classified into "intrinsic" ("permanent") and "triggering" ("transient") factors and were evidenced using univariate analysis.

**Results:** In the *medical population*, defined as patients who had not undergone surgery or application of a plaster cast to the lower extremities within the 3 weeks preceding inclusion (494 cases and 494 controls), intrinsic factors such as history of VTE, venous insufficiency, chronic heart failure, obesity, immobile standing position, history of more than 3 pregnancies, and triggering factors such as pregnancy, violent effort, or muscular trauma, deterioration of general condition, immobilization, long-distance travel, and infectious disease were significantly more frequent in the case patients than in the controls (odds ratio, $>1$; $P<.05$). In the overall population, additional risk factors were cancer, blood group A, plaster cast of the lower extremities, and surgery. In both populations, the number of risk factors per patient was greater in the case patients than in the controls.

**Conclusion:** Several risk factors for DVT were identified in medical outpatients presenting with DVT, and their comprehension may improve appropriateness and efficiency of the different methods available for thromboprophylaxis.

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DEEP VEIN thrombosis (DVT) remains a frequent disease in which the major complication is pulmonary embolism (PE)—both DVT and PE occurring most frequently in nonsurgical (medical) patients.[1] The incidence of venous thromboembolism (VTE) in general medical patients ranges from 10% to 30%.[2,3] In addition, autopsy series of hospitalized patients have shown that PE was the cause of 4% to 11% of deaths and that only 1 in 4 of these patients had recent surgery.[4,5] As sudden death is often the first and only clinical sign of VTE,[5] and as most deaths occur within 30 minutes of the acute event, systematic prophylaxis has been advocated as the most convenient and logical answer to this threat.[6]

Although there are extensive data to support both the clinical benefit[7,8] and cost-effectiveness[9-11] of prophylaxis in surgical patients according to the level of the risk for VTE, the situation is far less clear in general medical patients.[2,3] Owing to the heterogeneous characteristics of medical patients, an approach based on the prevention of VTE solely in patients at risk may represent a safer and more cost-effective alternative to systematic prophylaxis. Indeed, most fatal PEs occur in patients presenting with several risk factors.[12] However, in contrast to hospitalized surgical patients for whom risk factors have been well defined, only scant information is available for outpatients and in particular medical patients.[2,3]

Since knowledge of the patient's risk profile may help in the identification of individuals who are likely to benefit from VTE prophylaxis, the aim of the present epidemiologic study was to elucidate the factors associated with DVT in outpatients, with special attention to medical patients.

## PARTICIPANTS AND METHODS

This was a multicenter case-control study conducted between October 1990 and December 1991 (total duration of the study, 14 months) in 624 general practitioner centers.

### DEFINITION OF PATIENTS AND CONTROLS

Consecutive patients with a DVT of the lower extremities (case patients) were included in the study. Deep vein thrombosis was to be documented using at least 1 of the following objective tests: venography, duplex ultrasonography, B-mode ultrasonography, and/or impedance plethysmography.

Case patients and control patients were matched according to sex and age (±10 years). The general practitioner was required to pair each case patient with the first patient presenting with an influenzal or rhinopharyngeal syndrome (control patient) immediately after the inclusion of the case patient.

### RISK FACTORS FOR VENOUS THROMBOEMBOLISM

The following variables were prospectively recorded on separate case report forms for case patients and control patients: sociodemographic characteristics, location of DVT, methods for DVT diagnosis, whether the patient was hospitalized for treatment, and potential predefined risk factors. These factors were those commonly cited as risk factors for VTE in hospitalized patients.[13-16]

Potential risk factors were classified into 2 categories (**Table 1** and **Table 2**). *Permanent (intrinsic) factors*, represented by intrinsic patient characteristics, comprised 23 items, including menopause and history of pregnancies. *Triggering factors*, appearing transiently, were defined as events occurring within 3 weeks prior to inclusion and consisted of 24 items, 6 of which concerned female patients only.

### STATISTICAL ANALYSIS

Two study populations were defined. The overall study population comprised all patients with evaluable case report forms. A case patient was not considered if DVT was not confirmed by objective tests, age or sex was missing in one or both (patient and/or control) case report forms, and one or both case report forms were not completed or matching for age and/or sex. The medical (nonsurgical) study population comprised all patients who had not undergone any surgery within 3 weeks prior to inclusion, including application of a plaster cast to the lower extremities.

Determination of VTE risk factors was based on comparison of the incidence of each predefined risk factor in case patients with the corresponding incidence in the control patients (univariate analysis). Calculated odds ratios (ORs) and corresponding 95% confidence intervals were adjusted for age and sex using logistic regression, and $P<.05$ was considered as statistically significant.

## RESULTS

### STUDY POPULATIONS

A total of 1582 patients were included, 791 case patients and 791 control patients. Among the 791 case patients, 155 (19.6%) could not be considered in the analysis for the following reasons: DVT was not documented in 53, the case patient's age was not reported in 4, the case report form was not completed in 1, and matching for age and/or sex with a control patient was not done or was inadequate in 97. Thus, 636 case patients and their corresponding controls (1272 patients in all) were considered in the overall study population. As 142 case patients (22.3%) had undergone surgery or application of a plaster cast to the lower extremities within the 3 weeks preceding inclusion, the medical patient population comprised 494 case patients and 494 controls (988 patients in all).

The demographic characteristics of the 636 case patients were similar to those of their corresponding controls, in terms of blood group and ethnic origin. Mean ± SD age was 59.1 ± 17.3 years in the case patients and 58.1 ± 16.8 years in the control patients ($P=.29$), and there was no difference between the 2 groups in regard to the distribution by class of age, showing that matching for age was successful (**Figure 1**). Overall, there were 818 women (64.3%) and 454 men (35.7%), with no difference between case and control patients in regard to distribution by sex (409 women in each group). Among the women for whom information was available, 537 (66.4%) of 809 had reached menopause (268 for cases and 269 for controls), and 687 (85.9%) of 800 had experienced at least 1 previous pregnancy (329 in cases and 358 in controls). These distributions were similar in the medical population with 658 women (66.6%), 329 in each group.

### DEEP VEIN THROMBOSIS

A total of 854 objective tests was performed on 636 case patients for the diagnosis of DVT: duplex ultrasonography, 481; venography, 229; B-mode ultrasonography, 101; and plethysmography, 43. Venography and duplex ultrasonography were coupled in 116 patients, and this association of objective tests was most frequently observed. Among the 636 case patients, 594 (93.4%) underwent either venography or duplex ultrasonography or both.

**Table 3** shows DVT locations and the number of patients hospitalized for DVT treatment. Deep vein thrombosis was distal in 57.9% and proximal in 23.9% of case patients. Overall, 280 (44.0%) of 636 case patients were hospitalized for the treatment of their DVT. The percentage of patients hospitalized for such treatment was 32.9% (121/368), 53.9% (82/152), and 69.2% (72/104), respectively, for patients with distal, proximal, and both proximal and distal DVT.

**Table 1. Risk Factors in Descending Order of Importance of a Medical Study Population***

| Risk Factors | Case Patients, No. (%) | Control Patients, No. (%) | Odds Ratio (95% CI) | P |
|---|---|---|---|---|
| Intrinsic factors | | | | |
| History of DVT or PE | 105 (21.3) | 12 (2.4) | 15.6 (6.77-35.89) | <.001 |
| Venous insufficiency | 346 (70.0) | 203 (41.1) | 4.45 (3.10-6.38) | <.001 |
| Chronic heart failure | 51 (10.3) | 22 (4.5) | 2.93 (1.55-5.56) | .001 |
| Obesity† | 72 (14.8) | 34 (7.0) | 2.39 (1.48-3.87) | <.001 |
| Standing position >6 h/d | 104 (38.7) | 69 (31.9) | 1.85 (1.12-3.06) | .02 |
| History of >3 pregnancies‡ | 54 (16.5) | 32 (9.8) | 1.74 (1.06-2.87) | .03 |
| Triggering factors | | | | |
| Pregnancy‡ | 8 (2.4) | 1 (0.3) | 11.41 (1.40-93.29) | .02 |
| Violent effort or muscular trauma | 39 (7.9) | 5 (1.0) | 7.59 (2.95-19.53) | <.001 |
| Deterioration in general condition | 31 (6.3) | 6 (1.2) | 5.75 (2.20-15.01) | <.001 |
| Immobilization§ | 38 (8.0) | 10 (2.0) | 5.61 (2.30-13.67) | <.001 |
| Long-distance travel | 62 (12.6) | 31 (6.3) | 2.35 (1.45-3.80) | <.001 |
| Infectious disease | 95 (19.2) | 63 (12.8) | 1.95 (1.31-2.92) | .001 |

*CI indicates confidence interval; DVT, deep vein thrombosis; and PE, pulmonary embolism.
†Obesity was defined as a body mass index of more than 30 kg/m$^2$.
‡In 325 women.
§Total confinement to bed or to bed and armchair.

## RISK FACTOR DETERMINATION IN THE MEDICAL STUDY POPULATION

Univariate analysis of potential predefined risk factors for DVT in the medical study population indicated that some of these factors were significantly more frequently observed in case patients than in control patients (Table 1).

Among the predefined intrinsic factors, a history of DVT or PE, venous insufficiency, chronic heart failure, obesity, immobile standing position more than 6 hours per day and a history of 3 or more pregnancies (n=325) were significantly more frequent in case patients than in control patients. The triggering factors that were identified more frequently in case patients than in controls were pregnancy, violent effort or muscular trauma, deterioration of the general condition, immobilization, long-distance travel, and infectious disease. Among factors that could not be unequivocally identified as risk factors for DVT (Table 2), there was a trend toward statistical significance for cancer in progression or history of cancer, blood group A as compared with group O, and inflammatory bowel disease in regard to intrinsic factors. Similarly, with respect to triggering factors, a tendency to reach statistical significance was seen for rheumatologic disease occurring within 3 weeks prior to inclusion.

Some predefined potential intrinsic factors (drug addiction, circulating anticoagulant, collagen disease, hemopathy, polycythemia, thrombophilia, nephrotic syndrome) or triggering factors (neurologic event, varicosclerosation, spontaneous abortion, post partum of normal delivery, post partum of caesarean section, elective abortion) could not be evaluated due to the small number of patients in these categories.

This model theoretically allows determination of factors protecting against DVT. In the medical study population, regular smoking emerged as a protective factor (OR, 0.66; P=.04), since only 71 patients (14.4%) in the case patient population vs 101 patients (20.5%) in the control patient population were smokers (Table 2). Similarly, the use of oral contraceptive agents tend to appear as a protective factor (OR, 0.60; P=.08; Table 2).

**Table 2. Factors Not Identified as Risk Factors in a Medical Study Population**

| Factors | Cases, No. (%) | Controls, No. (%) | Odds Ratio | P |
|---|---|---|---|---|
| Intrinsic factors* | | | | |
| Regular smoking use | 71 (14.4) | 101 (20.5) | 0.66 | .04 |
| Cancer in progression or history of cancer | 37 (7.5) | 23 (4.7) | 1.77 | .054 |
| Blood group A | 89 (52.4) | 75 (43.1) | 1.71 | .06 |
| Inflammatory bowel disease | 26 (5.3) | 14 (2.8) | 1.89 | .09 |
| Menopause† | 219 (68.0) | 220 (67.3) | 0.60 | .33 |
| Immobile sitting position >6 h/d | 58 (21.6) | 57 (26.4) | 0.79 | .39 |
| Alcohol consumption | 112 (22.7) | 112 (22.7) | 1.08 | .72 |
| Chronic respiratory failure | 39 (7.9) | 35 (7.1) | 0.97 | .91 |
| Diabetes | 45 (9.1) | 44 (8.9) | 1.02 | .92 |
| White | 476 (98.1) | 473 (97.7) | 1.03 | .96 |
| Triggering factors‡ | | | | |
| Rheumatologic disease | 44 (8.9) | 25 (5.1) | 1.64 | .07 |
| Use of oral contraceptive agents† | 41 (12.5) | 61 (18.5) | 0.60 | .08 |
| Neuroleptic or antidepressive agent consumption | 77 (15.6) | 53 (10.7) | 1.36 | .14 |
| Estrogen consumption | 12 (2.4) | 7 (1.4) | 2.62 | .16 |
| Sportive event/competition | 7 (1.4) | 9 (1.8) | 0.71 | .50 |
| Progesterone consumption | 13 (2.6) | 14 (2.8) | 0.95 | .92 |

*Drug addiction, circulating anticoagulant, collagen disease, hemopathy, polycythemia, thrombophilia, and nephrotic syndrome are not displayed due to the small number of patients in these categories.
†In 325 women in both groups.
‡Neurologic event, varicosclerosation, spontaneous abortion, post partum of normal delivery, post partum of caesarean section, and elective abortion are not displayed due to the small number of patients in these categories.

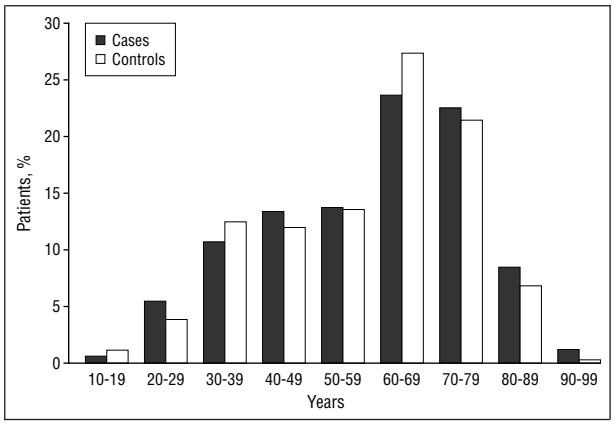


**Figure 1.** *Distribution of case and control patients according to class of age in the overall study population.*

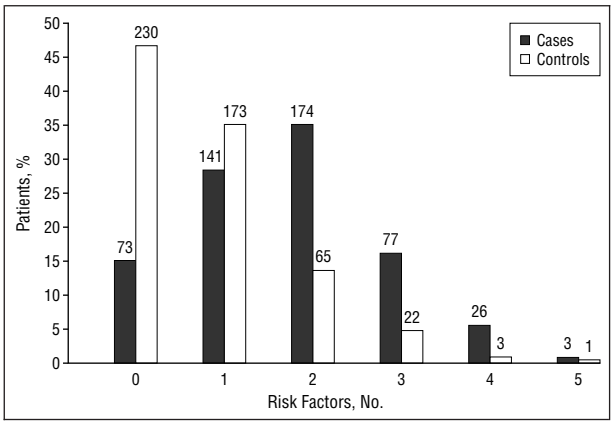


**Figure 2.** *Distribution of patients according to number of risk factors in the medical study population. The numbers above the bars indicate total number of patients.*

**Table 3. Deep Vein Thrombosis (DVT) Location and Hospitalization for DVT Treatment in Case Patients**

| | DVT Patients, No. (%) | DVT Hospitalized Patients, No. (%) |
|---|---|---|
| Distal DVT | 368 (57.9) | 121 (43.2) |
| Proximal DVT | 152 (23.9) | 82 (29.3) |
| Proximal and distal DVT | 104 (16.3) | 72 (25.7) |
| Missing | 12 (1.9) | 5 (1.8) |
| **Total** | **636 (100.0)** | **280 (100.0)** |

## RISK FACTOR DETERMINATION IN THE OVERALL STUDY POPULATION

Similar results were found in the overall study population. Additional corresponding intrinsic risk factors were cancer in progression or history of cancer (OR, 2.33; $P=.001$) and blood group A (OR, 0.006). Other triggering risk factors associated with DVT included application of a plaster cast to the lower extremities (OR, 36.47; $P<.001$), orthopedic surgery (OR, 16.25; $P<.001$), and general surgery (OR, 9.46; $P<.001$).

Among the triggering factors almost reaching significance, rheumatologic disease had been experienced by 50 (7.9%) cases vs 30 (4.7%) controls (OR, 1.62; $P=.06$), an infectious disease by 102 (16.1%) cases vs 83 (13.1%) controls (OR, 1.4; $P=0.06$), a pregnancy by 8 (2.0%) cases vs 3 (0.7%) controls (OR, 3.37; $P=.08$), and urologic surgery by 11 (1.7%) cases vs 3 (0.5%) controls (OR, 3.30; $P=.08$). The number of patients who had undergone vascular surgery was too small to allow statistical analysis.

The use of oral contraceptive agents was identified as protective in nonmenopausal women (OR, 0.57; $P=.04$). Indeed, in the population of patients with DVT, 53 women (13%) were using oral contraceptive agents vs 77 women (19%) in the control group. Smokers comprised 104 (16.4%) cases and 136 (21.4%) controls (OR, 0.74; $P=.07$). The number of women smoking was greater in the controls (16.1%) than in the case patients (12.5%). In addition, there was a significant relationship between regular smoking and the use of oral contraceptive agents ($P<.001$): the number of women who smoked and were using oral contraceptive agents in the controls (43.4%) was greater in the case patients (32.5%).

## CUMULATIVE RISK FACTOR ANALYSIS

All factors common to both sexes and identified in the univariate analysis as risk factors for DVT were considered for this analysis, except those with a high incidence of missing data. This applied to the factors "immobile standing position more than 6 h/d," and "A blood group." Thus, 9 and 12 risk factors, respectively, were included in this analysis for the medical and overall study populations.

The distribution of cases and controls by number of risk factors, for the medical study population, is presented in **Figure 2**. More than 80% of the control patients presented with no or only 1 risk factor, whereas 85% of the case patients presented with at least 1 risk factor, more than 50% of them presenting at least 2 risk factors. Similar findings were observed in the overall study population. In the medical study population, the mean±SD number of risk factors was 1.70±0.05 and 0.78±0.04, respectively, in case and control patients. The corresponding figures for the overall study population were 1.71±0.04 and 0.75±0.03, respectively. The distribution of case and control patients according to the number of risk factors was similar in the 2 study populations (**Figure 3**).

## COMMENT

In the absence of extensive knowledge of clinical risk factors in medical patients, the factors prospectively defined as potential risk factors for DVT in the present study were those usually cited in surgical patients.[13-16] Studies addressing the issue of clinical risk factors in medical patients are scarce.[17-21] Most were retrospective studies conducted in hospitalized patients,[17-19] and the majority did not compare the incidence of a risk factor in patients with VTE to that observed in a control population.[17,18,20] A recent study was a population-based case-control study in both inpatients and outpatients.[22] To our knowledge, only 1 study was a case-control study in 426 consecutive out-

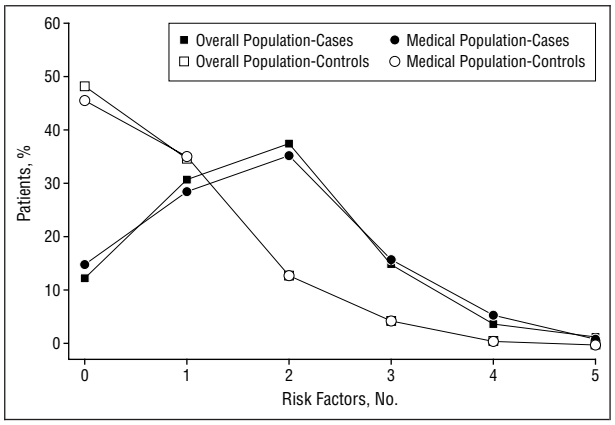


**Figure 3.** *Distribution of case and control patients according to number of risk factors in the overall and medical study populations.*

patients, including medical patients, with clinically suspected DVT referred to hospital by their general practitioner.[21] The Sirius study was also a case-control study assessing clinical risk factors for DVT in 636 nonselected outpatients, of whom 77.7% were medical patients. In addition, diagnosis of DVT could be considered as reliable since 93.4% of patients underwent duplex ultrasonography or venography or both. Only 44% of these patients were hospitalized for the treatment of their DVT, a practice now supported by results of recent studies showing that even proximal DVT can be treated outside the hospital.[23,24]

Most studies have shown that the risk of VTE increases exponentially with advancing age.[17,19-20] Although the Sirius study was not designed to evaluate age or sex as risk factors for DVT, the mean age of the case patients was 59 years, more than 80% of them being older than 40 years and 50% older than 60 years. Nevertheless, it has been argued that the relationship between age and VTE might be due to underlying comorbidities that could be the actual risk factors for VTE.[16-18] With respect to distribution of sex, data are conflicting as in some studies, the incidence of VTE was higher in male patients,[17,21] whereas in others no difference between men and women could be determined. [19,20] In the present study, 66.6% of patients were female patients. This finding may be explained by the high incidence of pregnancy-related DVT observed in our outpatient population, which was on average younger than a comparable hospitalized population, characterized by a more even distribution of other risk factors between sexes.[16] Indeed, in the Sirius study, pregnancy emerged as a triggering risk factor for DVT.

Among the factors that emerged as associated with DVT in the medical population of our study, most were also found in other studies, such as a history of VTE,[19-21,25] venous insufficiency,[22,25] cardiac failure,[17,20,21] and obesity.[17,26] Paralysis, prolonged confinement to bed, and other forms of immobilization have long been recognized as risk factors for the occurrence of VTE.[14,15,22] In our study, immobilization (total confinement to bed or to bed and armchair) and also immobile standing position more than 6 hours a day and long-distance travel emerged as factors associated with DVT. Travel has recently been identified as a risk factor for VTE.[27] Another triggering factor identified, deterioration of the general condition, may be related to immobilization. The number of patients with neurologic disorders including lower limb paralysis was too small to allow statistical analysis. Malignant diseases were associated with an increased risk of VTE in the vast majority of studies involving medical patients.[17,19-21,22,25] In our study, cancer in progression or history of cancer tended to reach statistical significance in the medical patients but was a significant triggering risk factor in the overall population. Infective episodes was also associated with DVT in the medical patients, but the significance threshold was not reached in the general population. It is likely that in the latter population this factor was outweighed by other triggering factors such as orthopedic or general surgery and application of a plaster cast to the lower limbs.[21] Similarly, inflammatory diseases such as rheumatologic and inflammatory bowel disease tended to emerge as risk factors in the medical patients. Finally, as observed in other studies,[20,28,29] blood group A showed a tendency to be a risk factor. Congenital or acquired thrombophilia was reported in too small a number of patients to allow statistical analysis. It should be noted that a systematic search for thrombophilia by laboratory tests was not mandatory in this study.

Oral contraceptive use was evidenced as a protective factor in the present study, whereas it is usually described as a risk factor for VTE.[14-16,20,30] Regular smoking was also described as a protective factor, which is consistent with previous studies showing a lower incidence of DVT in medical and surgical patients,[19] or in patients with acute myocardial infarction.[31-33] However, the mechanism of this possible protective effect remains speculative[19] and controversial as it has also been shown that cigarette smoking increased the risk of VTE.[25,34,35] Our unexpected findings may be explained by the nature of the control group. Indeed, patients who smoke are more prone to develop influenzal or rhinopharyngeal syndromes, and there was a significant relationship between smoking and the use of oral contraceptive agents in our female study population.

Cumulative effects of multiple risk factors could be evidenced in our study. In both study populations, the mean number of risk factors was higher in case patients than in controls. The percentage of patients with more than 1 risk factor was close to 60% in the case patients, whereas it was only 18% in the controls. Thus, the risk of DVT appeared to be higher in patients presenting with more than 1 risk factor than in those with no or only 1 risk factor. Several other studies have suggested that the incidence of VTE increases in proportion to the number of risk factors.[17,18] In both our study populations, the mean number of risk factors per patient was 1.7, without taking age into consideration. According to the Arcellus et al[36] classification of the risk for VTE, the Sirius study population would be at moderate risk (overall score between 2 and 4), if age were added to the list of risk factors. As stated by the National Institutes of Health consensus as early as 1986, management of VTE in nonsurgical patients requires identification of risk factors and their cumulative effect to determine the most effective and safest method of prevention to be used.[13] Recent evidence suggests that a high-dose regimen of low-molecular-

weight heparin, which proved effective in high-risk surgical patients, is required for moderate-risk medical patients.[37]

Our study has several limitations. Patients with influenzal or rhinopharyngeal syndrome were chosen as controls as they probably represent the least severe condition requiring ambulatory health care. However, these patients might significantly differ from a general population control group on a variety of factors and it cannot be excluded that some of these factors might affect the risk of developing DVT. In addition, appreciation of some risk factors such as violent effort or muscular trauma, deterioration in general condition, long-distance travel, infectious disease, and regular smoking were determined by the investigator. Although this approach appears to be more representative of the everyday practice in the management of outpatients, the assessment of the etiologic importance of these factors is difficult. Finally, multivariable regression analysis could not be performed due to the large number of interaction tests, which were unexpectedly significant. However, we believe that our data support the hypothesis that risk factors can be identified in outpatients, especially medical patients, at moderate risk of DVT. Although a cause-effect relation between DVT and these factors was not demonstrated, an analysis of risk factors may help in defining which patients should benefit from prophylaxis.

In conclusion, the results of the present study indicate that intrinsic factors and triggering situations associated with DVT can be identified in medical outpatients with objectively confirmed DVT, as previously shown in other groups of patients. Knowledge of these factors might help to define the medical patients who may benefit from thromboprophylaxis.

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