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Prevalence of risk factors for venous thromboembolism in the Italian population: results of a cross-sectional study from the Master Registry

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Abstract The prevalence of major risk factors for VTE may differ according to age, gender and clinical presentation. We tested this hypothesis in a large Italian VTE population. MASTER is a multicenter registry aimed to prospectively collect information on a large cohort of patients with acute VTE. The presence of major risk factors was captured by an electronic data network in consecutive patients with objectively confirmed acute VTE. We enrolled 2,119 patients (49.8% men) of whom 424 (20%) <40 years, 529 (25%) between 41 and 60 years, 943 (44.5%) between 61 and 80 years, and 223 (10.5%) >80 years. The prevalence of known risk factors in the four age groups is 63.9, 52.6, 54.6, and 58.3%, respectively ($p = 0.002$). Immobilization and severe medical disorders are more commonly associated with VTE in patients >80 years, trauma is significantly more common in patients <40 years than in older patient groups. The prevalence of unprovoked events is the highest in patients 41–60 years, and lowest in patients less than 40 years. After logistic regression analysis, patients with pulmonary embolism are more likely to have known risk factors for VTE than patients with deep vein thrombosis at presentation ($p = 0.0021$), and women are less likely than men to have an unprovoked VTE ($p < 0.0001$). In conclusion, a substantial proportion of VTE events remain classified as unprovoked. Unprovoked events are more common in middle aged patients, in men, and in patients presenting with deep vein thrombosis.

Keywords Venous thromboembolism · Risk factors · Unprovoked venous thrombosis · Age · Gender

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Introduction

The incidence of first-time venous thromboembolism (VTE) rises exponentially with age, ranging from a very low rate of 0.005% per year among children 15 years of age, to a rate of approximately 0.5% per year among individuals over the age of 80 years [1, 2]. VTE is a multicausal disease, and several risk factors may contribute to its pathogenesis. Because VTE is associated with a high risk of recurrence, and because this risk varies according to the presence or absence of major identifiable risk factors [3], secondary prevention strategies start from the assessment of the potential causes of the disease [4]. In some patients, risk factors known to play a major role can be readily identified at the time of the acute event. These

include recent surgical procedures, trauma, immobilization, pregnancy or puerperium, use of oral contraceptives, severe medical disorders, and known cancer. In other patients, the mechanism can be more complex and predisposing factors may be less identifiable. It is reported that as many as 26–47% of VTE events remain classified as idiopathic or unprovoked [5], with this wide variation depending on the study populations and on the definitions of an unprovoked event. The optimal duration of secondary prevention of unprovoked VTE remains controversial, with the guidelines suggesting indefinite anticoagulant treatment for these patients [6]. Thus, a better understanding of the true prevalence of VTE events defined as apparently unprovoked in clinical practice, and of the underlying mechanisms, becomes a major unmet clinical need. Age is associated with an increased risk of VTE: different patterns in the distribution of major risk factors for VTE among age groups may suggest different, age-related, mechanisms to provoke this disease, and may suggest age-specific diagnostic approaches to identify alternative risk factors. There is currently insufficient information on the prevalence of unprovoked VTE and of major risk factors for VTE in patients referred to Italian thrombosis centers. This prevalence has obvious implications on the potential duration of secondary prophylactic strategies in our patients.

To address this issue, we performed a cross-sectional study on the population of the Multicenter Advanced Study for a Thromboembolism Registry (MASTER). MASTER is an Italian, multicenter, observational study aimed to prospectively collect information on VTE patients and treatment practices used in 25 different hospitals [7]. Consecutive patients with objectively documented symptomatic VTE were enrolled between January 2002 and October 2004.

Patients and methods

Inclusion criteria

To be enrolled in the observational registry, consecutive patients with symptomatic acute VTE (either first event or recurrent event) must have met the following criteria: 18 years of age or older, presence of objectively documented symptomatic deep vein thrombosis or pulmonary embolism, and potential availability for a long term follow-up (life expectancy of more than 3 months and possibility of follow up visits). The following diagnostic tests were utilized to make the objective diagnosis: compression ultrasonography, computed tomography scan, and venography to diagnose deep venous thrombosis; computed tomography, ventilation/perfusion scan, perfusion scan, and angiography to diagnose pulmonary embolism. All enrolled patients provided a written informed consent. Both patients with VTE occurring in the outpatient setting, and patients with VTE occurring while in hospital were eligible for the study. Patients with concomitant deep vein thrombosis and pulmonary embolism were categorized according to the first clinical manifestation of the disease. Deep vein thrombosis included proximal and distal vein segments in the lower limbs and upper limb venous thrombosis.

Data collection

Information was captured by an electronic data network at the time of the index event. At each participating center, data were collected by a designated study coordinator on the electronic case report form and submitted to a data management center through a secure website. Patient identities remained as confidential information to the participating hospital. Patients were identified through a number assigned by the study physician at each center. All confidential data were protected by passwords for electronic data and by storing all paper charts in secure facilities at the participating hospitals.

Risk factors assessment

For the aim of this study, the following information was collected: baseline characteristics, site of thrombosis, presence of clinically overt or newly diagnosed cancer at the time of VTE diagnosis, site of cancer, ongoing chemotherapy or hormone therapy, presence of temporary risk factors (surgical procedures or trauma occurring in the previous 3 months, immobilization for more than 7 days, pregnancy or puerperium, use of oral contraceptives, severe medical disorders, central vein catheters) at the time of VTE diagnosis. In the presence of any of the above listed risk factors, VTE was defined as provoked. If none was detected, VTE was defined as unprovoked.

Statistical analysis

Baseline characteristics are reported by descriptive analysis. The Chi-square test was used to evaluate the significance of differences in frequencies in two-way tables. An Odds Ratio was used as a measure of risk of VTE associated with a plausible risk factor; a multiple logistic regression model was used to determine the association between each risk factor and age groups, gender, and clinical presentation, while adjusting for other risk factors. The analysis was adjusted by center. All analyses were performed using the Epi Info 3.3.2 (Center for Disease Control and Prevention, Atlanta, USA) Software.

Results

A total of 2,119 patients were enrolled. Baseline characteristics are summarized in Table 1. In the majority of patients with deep vein thrombosis, the event occurred in the lower limb (92.6%), and in two-thirds of cases (63.8%) it was located in the proximal veins. Only 6.5% of patients had upper limb deep vein thrombosis.

The four age groups (40 years or younger, 41–60 years, 61–80 years and older than 80 years) significantly differed according to gender distribution, overall prevalence of known risk factors, prevalence of known or newly diagnosed cancer, and prevalence of transient risk factors at the time of the index event (Table 2). The prevalence of two transient risk factors, immobilization and severe medical disorders, was significantly higher in patients older than 80 years than in the other age groups, whereas the prevalence of trauma was significantly higher in the group of patients aged 40 years or younger than in other age groups (Table 2). There was no difference in the prevalence of surgical procedures at the time of the index event among age groups (Table 2). The prevalence of unprovoked events was highest in patients aged 41–60 years and lowest in patients aged less than 40 years. A previous history of VTE was present in 14.7% of patients, with no statistically significant differences across groups.

Overall, 18.3% of patients were receiving thromboprophylaxis at the time of the index event. The proportion of patients receiving prophylaxis significantly varied across age groups, being 25.2% in the group of patients aged 40 years or younger, 17.6% in the group of patients aged 41–60 years, 16.3% in the group of patients aged 61–80 years, and 14.8% in patients older than 80 years ($p < 0.001$).

Table 1 Baseline characteristics

Patients	2,119
Male gender (%)	1,056 (49.8)
Deep vein thrombosis (%)	1,541 (72.7)
Pulmonary embolism (%)	578 (27.3)
Known risk factors (transient or permanent) (%)	1,194 (56.3)
Known cancer (%)	381 (18.0)
Newly diagnosed cancer (%)	50 (2.4)
Immobilization (%)	318 (15.0)
Surgery (%)	306 (14.4)
Trauma (%)	202 (9.5)
Severe medical disease (%)	174 (8.2)
Oral contraceptives (%)	114 (10.7[a])
Pregnancy/puerperium (%)	67 (6.3[a])
Central vein catheter (%)	5 (0.2)

[a] The percentage is calculated for the female population only

After logistic regression analysis, we found that women were less likely than men to have an unprovoked VTE event ($p < 0.0001$), and that patients presenting with pulmonary embolism were significantly more likely than patients presenting with deep vein thrombosis to have an identifiable risk factor ($p = 0.0021$). Results did not change when oral contraceptives were not included among major risk factors in the analysis. The association between age groups and risk factors was confirmed (data not shown).

Discussion

VTE remains classified as unprovoked in nearly half of patients. Unprovoked events are more common in male gender, in middle aged populations, and in patients presenting with deep vein thrombosis. The association with known risk factors is highest in the youngest as well in the eldest populations, with a U-shaped curve for distribution. The distribution of cancer reflected the known distribution of the disease in the general population.

Advanced age has been consistently shown to be associated with an increased risk of VTE [1, 2, 5, 8]. In the Study of Men Born in 1913, 855 men were followed up prospectively from the age of 50 years to 80 years [2]. The cumulative probability of having experienced a first thromboembolic event was 0.5% at age 50 years, 2.0% 60 years, 8.2% 75 years, and 10.7% at age 80 years [2]. This finding may suggest that changes in the hemostatic balance producing an increased prothrombotic state with increasing age are sufficiently powerful to play as a major risk factor for VTE in the elderly. Of interest, though, the association between advancing age and thrombosis reported by Anderson et al. [1] is no longer evident when allowances are made for other risk factors, particularly chronic systemic disease. Thus, elderly patients appear to be at increased risk of VTE mainly because of an increased prevalence of major risk factors predisposing to thrombosis, in association with an "acquired hypercoagulable state". As expected, we find cancer to be particularly frequent in the population of elderly patients with VTE, being often newly diagnosed at the time of acute VTE in patients older than 80 years. On the other hand, the majority of patients aged less than 40 years develop thrombosis because of a major, usually transient, risk factor. This appears to be particularly true in women, as it is known that the risk of VTE is higher among women of childbearing age than among men in the same age group [9–11]. This difference clearly relates to the association of VTE with pregnancy or the use of oral contraceptives.

In this study, we find that the highest rates of apparently unprovoked VTE events occur in patients between 41 and

Table 2 Baseline characteristics and prevalence of risk factors among age groups

	≤40 years	41–60	61–80	>80 years	*p**
Number	424	529	943	223	–
Male gender	46.9%	52.9%	52.2%	38.1%	<0.001
Pulmonary embolism	28.8%	23.8%	28.0%	29.6%	0.210
Known risk factors	63.9%	52.6%	54.6%	58.3%	0.002
Known cancer	5.2%	17.8%	24.5%	15.2%	<0.001
Newly diagnosed cancer	0.7%	2.1%	2.4%	5.8%	<0.001
CNS cancer	1.2%	1.5%	1.5%	0.4%	0.634
Hematologic cancer	2.4%	2.1%	5.1%	2.7%	0.006
Gastrointestinal cancer	0.7%	4.3%	5.7%	4.9%	<0.001
Genitourinary cancer	0.7%	4.7%	7.5%	7.2%	<0.001
Lung cancer	0.0%	2.6%	2.7%	0.4%	0.001
Breast cancer[a]	0.4%	7.6%	6.7%	7.2%	0.002
Melanoma	0.2%	0.2%	0.4%	0.4%	0.853
Sarcoma	0.0%	0.4%	0.2%	0.0%	0.520
Transient risk factors	58.7%	38.6%	36.3%	46.6%	<0.001
Central vein catheter	0.5%	0.2%	0.1%	0.4%	0.541
Immobilization	10.6%	10.2%	15.6%	32.3%	<0.001
Oral contraceptives[b]	33.8%	14.1%	0.7%	0.0%	<0.001
Pregnancy[b]	12.0%	1.2%	0.0%	0.0%	<0.001
Puerperium[b]	16.0%	0.4%	0.0%	0.0%	<0.001
Severe medical diseases	3.5%	6.4%	9.4%	16.1%	<0.001
Surgery	13.2%	13.6%	15.8%	13.0%	0.457
Trauma	15.3%	9.6%	7.4%	7.2%	<0.001

CNS Central nervous system

* Chi-square test

[a] The percentage is calculated for the female population only

[b] The percentages are calculated for the female population only

60 years of age. In nearly 50% of these patients no major risk factors can be detected. Because VTE is considered a "multi-causal" disease in which more than one genetic or environmental condition coincide [12], it is possible that in this age group the sum of minor, less evident, prothrombotic conditions may result in clinically apparent thrombosis. On the other hand, we cannot be certain that the search for occult cancer in this age group was as aggressive as it is in older age groups (see below).

Unprovoked events were also more common in men than in women, and are less likely to present as pulmonary embolism. Gender difference may at least in part be attributed to the role of known gender specific risk factors, such as the use of oral contraceptives, pregnancy and the puerperium. However, there may be other women. For example, a recent longitudinal study finds that the metabolic syndrome, a newly identified risk factors for VTE, is significantly associated with VTE in men, but not in women [13].

This study has a number of limitations. First, the results of this study reflect the distribution of risk factors for VTE in the population of patients referred to the Thrombosis Centers of the participating hospitals, which are usually responsible for the long term follow up of the patients, and, in many settings, for the monitoring of therapy with vitamin K antagonists. Thus, there is a chance that these data do not entirely reflect the actual distribution of risk factors in a general population of VTE patients. However, statistical analysis was adjusted by center, and no center effect was observed. Second, this is an observational study, and the accuracy of investigation on risk factors was left to the discretion of the attending physician at each registry hospital. However, the multicenter design of the study, the high number of participating centers, and, most of all, the sample size of the study suggest that potential discrepancies in data collection were sufficiently diluted. Furthermore, we only focused on major risk factors that are commonly and easily investigated in clinical practice, and

which do not require additional, possibly center-specific, procedures. Extensive search for occult cancer was not mandatory in the registry protocol, and some cases of occult cancer were probably missed. Furthermore, information on occult cancer only refers to the initial phase of treatment, and additional cases detected during long term follow up may have been missed. However, the chance of a greatly unbalanced distribution of such cases among age groups is quite unlikely. Similarly, screening for thrombophilia was not mandatory, and some cases of patients with severe thrombophilic abnormalities may have been missed. However, for the purpose of the present study, we decided not to include thrombophilia in the list of risk factors in accordance with the most recent guidelines of the American College of Chest Physicians [6].

In conclusion, we aimed to describe the distribution of risk factors in the population of patients with VTE referred to 25 Italian thrombosis centers. The results of this study confirm that for as many as 44% of patients followed at these centers VTE remains classified as unprovoked, in particular in middle aged groups. These patients are more frequently male, and less frequently present with a pulmonary embolism. Based on current recommendations, these frequent definitions expose these patients to a potentially indefinite treatment with anticoagulant drugs for secondary prophylaxis and leave clinicians with a substantial degree of uncertainty. Rather than simply comparing different treatment durations of secondary prophylactic strategies, additional research is warranted to better explore the pathogenesis of VTE in this large population.

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Conflict of interest None.

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