

The first ambulatory screening on thromboembolism: a multicentre, cross-sectional, observational study on risk factors for venous thromboembolism

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Summary. *Objectives:* To assess the prevalence of risk factors for venous thromboembolism (VTE) and the prevalence of recent (< 1 year) VTE [including superficial vein thrombosis (SVT), deep vein thrombosis (DVT) and pulmonary embolism (PE)] amongst patients attending general practitioner (GP) surgeries. *Design:* Multicentre, cross-sectional, observational study. *Setting:* A total of 1536 GP surgeries. *Participants:* A total of 15 180 adult, co-operative subjects, who had consulted their GP for a health disorder and signed the informed consent form. *Interventions:* None. *Main outcome measures:* Prevalence of known VTE risk factors graded according to importance and prevalence of recent (< 1 year) VTE events (including SVT), based on interviews. *Results:* About 1:5 patients had at least one strong risk factor and about 1:20 had at least two risk factors, with no difference between sexes. The prevalence of strong risk factors increased with age. Most were related to medical conditions: history of SVT and/or DVT/PE, heart failure and malignancy. About 3:4 women and 2:3 men had at least one moderate to weak risk factor; nearly 1:2 women and 1:3 men had at least two moderate to weak risk factors. The most common were: history of VTE, smoking, history of miscarriage, estrogen therapy, obesity, and varicose veins. Overall, 80% women and 67% men had at least one risk factor, and 50% women and 35% men had at least two risk factors. The prevalence of recent (< 1 year) VTE was 3.4% in women and 2.4% in men, and increased with age. The majority of cases

were SVT in both sexes (2.5% in women and 1.5% in men). *Conclusions:* The prevalence of risk factors for VTE amongst patients attending GP surgeries is high. GPs should bear this in mind during their daily practice.

Keywords: general population, general practitioners, risk factors, venous thromboembolism.

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is the most common cardiovascular disease after myocardial infarction (MI) and stroke. It is also an important cause of mortality and morbidity [1,2]. PE not only may result in death in the short-term, but may lead to the development of pulmonary hypertension in the long-term. In addition, a post-thrombotic syndrome may follow DVT, causing discomfort to the patient and compromising limb function. Interestingly, the incidence of post-thrombotic syndrome after DVT of the legs varies between 20% and 100% [1].

VTE is the main cause of mortality and morbidity in hospitalized patients [1–3], but may also affect patients not admitted to hospital, including young adults [1–3]. The annual incidence in the general population is estimated to be about 1 per 1000 inhabitants [2].

The pathogenesis of VTE involves different factors that may be either acquired or inherited. Some of these risk factors are already well known (age, surgery, cancer, immobilization, pregnancy, fractures, oral contraceptives, the antiphospholipid antibody syndrome, and medical illnesses, such as MI, congestive heart failure and ischemic stroke), while others are still under investigation [3–6]. A genetic predisposition to VTE (inherited thrombophilia) (antithrombin, protein C and protein

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S deficiency, heparin cofactor II deficiency, resistance to activated protein C, G20210A prothrombin gene polymorphism, dysfibrinogenemia) should be considered when VTE occurs in the post-natal period, in infancy, in patients with mesenteric, cerebral or portal venous thrombosis, and especially in patients with a positive family history for VTE [3–10]. Increased levels of coagulation factor VIII have also been studied as a cause of thrombophilic syndromes [3–6]. Hyperhomocysteinemia is also associated with the occurrence of venous thrombosis [3–6,11]. Knowledge of the main risk factors is essential for the diagnosis and the correct prevention of VTE. As to the diagnosis of VTE, the investigations performed may be negative in about 70%–75% of outpatients with signs and symptoms of acute DVT; conversely, at least between 30% and 50% of cases of DVT are asymptomatic [6,12], the percentage being much higher in the hospital setting, and very high in patients undergoing surgery (90%–95% of post-operative DVT cases are asymptomatic). Physicians should be aware that the knowledge of the main risk factors and an appropriate diagnostic work-up is essential to establish the presence of DVT in patients presenting with suggestive symptoms, so that prophylactic anticoagulant treatment can be instituted.

Notwithstanding major progress in the identification of the main risk factors for VTE in recent years, few prevalence data are available in the population presenting for surgery with general practitioners (GPs).

The aims of the present study, the first ambulatory screening on thromboembolism (FAST), were to assess the prevalence of VTE risk factors and the prevalence of recent (<1 year) VTE in subjects presenting for surgery with their GPs.

Materials and methods

The FAST study was a multicentre, cross-sectional, non-intervention, observational trial. It was performed with the support of 107 centers belonging to the 'SOS Phlebitis' network, which are involved in educational activities on VTE. The survey was carried out by trained GPs during their usual daily practice.

The Italian Scientific Board of the 'SOS Phlebitis' network approved the study protocol and the Case Report Form (CRF). The main investigators prepared the educational material on VTE and relevant risk factors to be used for the study implementation and conduction. In each case, definition of risk factors (e.g. congestive heart failure) was based on the WHO definitions and reported in detail on the CRF.

After the National Meeting (May 2003) the representatives of the 'SOS Phlebitis' Centres acted as tutors, within their geographical areas, by training (as to the diagnosis, epidemiology, risk factors, prevention and treatment of VTE), assisting and coordinating the invited GPs who decided to participate in the survey. Local kick-off meetings were held with 4173 invited GPs; 1936 GPs accepted to take part in the survey and 1536 GPs (79.3%) completed the study.

The GPs participating in the study had to enroll two patients per day over a period of five consecutive days of activity (i.e.

each GP had to enroll a total of 10 patients week⁻¹), starting on the first working day after the local meeting.

To be eligible, the patients had to present at the doctor's office for a consultation related to a health disorder and to meet the following inclusion criteria: age ≥18 years, cooperative attitude, and signature of the informed consent form granting permission to use their personal health data.

The examination consisted of an interview regarding the presence/absence of known VTE risk factors graded according to their importance (strong or, moderate to weak) (Tables 1 and 2) on the basis of an extensive literature review and expert ratings [5,13–35]; the presence/absence of a history of VTE events [including superficial vein thrombosis (SVT), DVT and PE] (If positive, further information was collected on the nature and timing of event.); personal demographic and lifestyle information; the reason for consulting the GP and for any ongoing antithrombotic therapy.

Body weight (kg) and height (m) were noted and body mass index (BMI; kg m⁻²) was calculated.

The data were collected and entered into a SAS system (version 8).

The primary endpoint was the assessment of the prevalence of known VTE risk factors, subdivided into strong and moderate to weak, in the patient population presenting at the surgery of their GP because of a health problem. A history of recent (<1 year) VTE (including SVT) was also assessed.

All data were stratified according to sex and age (young 18–45 years; middle-aged 46–74 years; elderly ≥75 years). The prevalence data were age-adjusted with respect to the corresponding distribution of the Italian population (2001 census) [36].

Overall prevalence rates were obtained for each risk factor, as well as specific prevalence rates by sex and age, together with 95% confidence intervals (CI) related to the whole patient population, stratified by sex.

The study was performed in accordance with the tenets of the Declaration of Helsinki and subsequent amendments (up to Edinburgh 2000).

Results

Patients

Data on a total of 15 208 patients were collected by September 2003; 15 180 (99.8%) were valid for the statistical analysis. The data were collected throughout Italy: 40.7% in the North, 23.8% in the Centre and 35.5% in the South.

The FAST patient population included more women (62.8%) than men (37.2%). Women were on average slightly younger than men, their mean ± SD age being 56.3 ± 16.4 years vs. 59.7 ± 15.7 years in men; this was also clear in age distribution (women: 18–45 years 28.5%; 46–74 years 57%; >75 years 14.5%; men: 18–45 years 20.5%, 46–74 years 61.8%, >75 years 17.7%).

On average, both sexes were overweight (mean ± SD BMI 25.6 ± 4.8 in women, 26.5 ± 3.7 in men).

Table 1 Prevalence of strong risk factors by sex and age

Risk factor	Sex	18–45 years	46–74 years	≥75 years	Prevalence* (95% CI)
History of DVT/PE [14,20]	F	1.5	5.8	11.1	4.4 (4.0–4.8)
	M	1.5	4.1	10.8	3.2 (2.7–3.7)
History of SVT [14]	F	4.2	14.5	23.8	10.8 (10.2–11.5)
	M	2.8	6.2	12.1	4.9 (4.2–5.5)
Puerperium (<8 weeks from delivery) [30]	F	0.6	0.1		0.3 (0.2–0.5)
Recent [†] major surgery or orthopedic surgery [14,21]	F	2.1	3.0	2.9	2.6 (2.2–2.9)
	M	2.8	4.1	3.7	3.4 (2.8–4.0)
Recent [†] major trauma/fracture of lower limbs or pelvis [14,21]	F	0.4	1.1	1.5	0.8 (0.6–1.0)
	M	1.7	0.9	1.1	1.4 (0.9–1.8)
Malignancy [14,32]	F	0.8	3.3	4.9	2.3 (2.0–2.6)
	M	0.7	5.3	10.3	3.3 (2.8–3.7)
Recent [†] MI [13,21]	F	0.1	0.2	0.6	0.2 (0.1–0.3)
	M	0.4	0.7	1.3	0.6 (0.4–0.8)
Stroke or other neurological disorder associated with paralysis [21]	F	0.2	0.9	2.1	0.7 (0.6–0.9)
	M	0.8	1.9	2.2	1.4 (1.0–1.7)
Heart failure [23]	F	0.6	7.5	20.6	5.9 (5.4–6.3)
	M	0.9	11.5	26.2	7.1 (6.5–7.6)
Recent immobilization in bed or wheelchair for more than 3 days [14,20–22]	F	0.7	1.6	3.2	1.4 (1.2–2.6)
	M	2.2	2.2	3.3	2.3 (1.8–2.8)

*Standardized by age.

[†]In last 3 months.**Table 2** Prevalence of moderate to weak risk factors by sex and age

Risk factor	Sex	18–45 years	46–74 years	≥75 years	Prevalence* (95% CI)
Family history of VTE [14,20]	F	16.8	18.6	12.5	17.0 (16.1–17.9)
	M	11.1	12.9	7.0	11.6 (10.5–12.7)
Smoking (> 15 cigarettes daily) [29]	F	15.5	9.8	2.3	11.5 (10.8–12.3)
	M	23.9	18.8	7.1	20.6 (19.0–22.2)
Ongoing pregnancy [30]	F	4.6	0.1	–	2.5 (2.0–2.9)
History of miscarriage [30]	F	11.7	14.0	8.2	12.2 (11.5–13.0)
	M				
Estrogen treatment [24–28]	F	30.8	9.4	0.7	18.3 (17.3–19.4)
	M				
Obesity [20,29]	F	13.5	26.2	23.0	19.9 (19.0–20.8)
	M	12.3	18.4	14.2	14.9 (13.7–16.1)
Varicose veins [14,20]	F	30.8	54.2	56.4	43.6 (42.2–44.9)
	M	9.9	28.3	35.9	19.3 (18.1–20.5)
Chronic inflammatory disease involving the intestine [31]	F	1.2	1.8	1.5	1.4 (1.0–1.8)
	M	1.4	1.3	2.5	1.5 (1.2–1.8)
Recent hospital stay for more than 10 days [14,20]	F	1.3	2.2	3.2	1.9 (1.6–2.2)
	M	1.6	4.2	4.1	2.9 (2.4–3.3)
Recent long-distance travel (> 6 h) [20]	F	10.4	6.5	1.9	7.7 (7.1–8.4)
	M	19.9	10.4	3.3	14.8 (13.4–16.3)
Diabetes mellitus [20]	F	1.9	10.2	14.5	6.8 (6.3–7.3)
	M	3.2	15.4	15.2	9.1 (8.3–9.8)
Chronic obstructive pulmonary disease [34,35]	F	1.7	8.0	12.0	5.5 (5.1–6.0)
	M	3.0	15.3	24.9	9.6 (8.9–10.4)
Current myeloproliferative disorders [14,20]	F	0.2	0.4	1.2	0.4 (0.3–0.5)
	M	0.2	1.1	1.2	0.6 (0.4–0.8)

*Standardized by age.

Almost all patients had concomitant diseases (99.5%) and half of them (44.2%) had more than one. The most common concomitant diseases involved the cardiovascular (44%) and the musculoskeletal (32.6%) systems; these diseases usually were the reason for the consultation. There were no important differences between the sexes.

Risk factors

Strong risk factors About 1:5 patients had at least one strong risk factor and about 1:20 had at least two, with no difference between sexes (Fig. 1). The most common strong risk factors were related to medical conditions. The prevalence of the

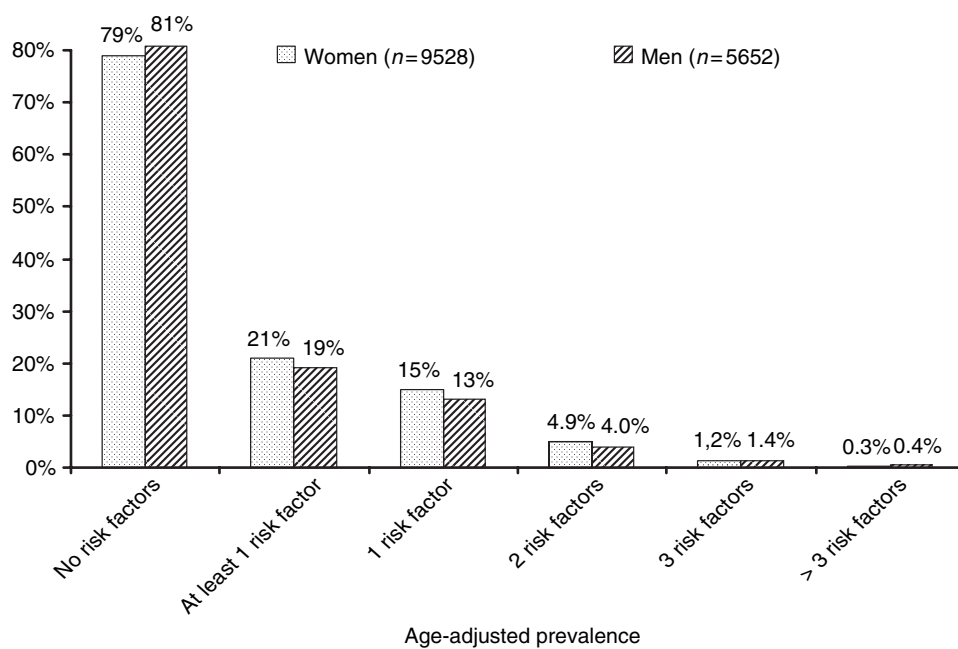


Fig. 1. FAST population: prevalence of strong risk factors for VTE by sex.

various strong risk factors stratified according to age and sex is shown in Table 1. The prevalence of a few risk factors differed in the two sexes. The prevalence of SVT was twice as high in women than men (10.8% vs. 4.9%), the difference being highest in the group of elderly patients (23.8% vs. 12.1%). In contrast, the prevalence of recent trauma/fractures of lower limbs or pelvis was higher in men (1.4% vs. 0.8%), especially in the group of young patients (1.7% vs. 0.4%). Not only heart failure, but also recent MI – a related condition, was more common in men, especially in the elderly group (1.3% vs. 0.6%). Also stroke and related neurological disorders were more common in men (1.4% vs. 0.7%), but only in the young and middle-aged groups; the same was true for immobilization.

The prevalence of all strong risk factors increased with age: nearly half of the patients older than 75 years had at least one strong risk factor and nearly 20% had at least two, independently of sex, whereas nearly all patients aged 45 years or younger did not have any.

Moderate to weak risk factors Several of these risk factors were more common than strong risk factors, their prevalence ranging from 11.5% to 43.6%: history of VTE, smoking, history of miscarriage, estrogen therapy, obesity, varicose veins and long-distance travels (only males). The prevalence of the various moderate to weak risk factors by age and sex is shown in Table 2. The proportion of women with at least one moderate to weak risk factor was higher than the corresponding proportion of men (78% vs. 63%) and the same was true amongst the patients who had at least two moderate to weak risk factors (44% vs. 28%). The most common risk factor in women was by far varicose veins (43.6%), followed by obesity (19.9%) and estrogen treatment (18.3%), whereas the most common in men was smoking

(20.6%), varicose veins (19.3%), obesity (14.9%) and long-distance travels (14.8%).

Unlike strong risk factors, moderate to weak risk factors did not increase in frequency with age in either sex. A number of them varied according to age: smoking and family history diminished with age, together with the risk factors associated with fertility in women (ongoing pregnancy, estrogen therapy), whereas medical conditions [diabetes, chronic obstructive pulmonary disease (COPD)] increased with age in parallel with the medical conditions that represent strong risk factors. The prevalence of obesity was related to age, but in a different way, reaching its peak in middle-age (46–74 years). Others differed according to sex: family history, obesity and, above all, varicose veins were more common in women, whereas smoking, diabetes (except in the elderly) and COPD were more common in men.

Taking all risk factors into consideration, 80% of women and 67% of men had at least one risk factor (Fig. 2), and 51% of women and 35% of men had at least two risk factors. The number of patients with risk factors increased with age in men. However, the proportions of women with risk factors were similar in the three age categories with the exception of patients with more than three risk factors (7% amongst young patients, 16% in middle-aged patients, 18% in elderly patients).

VTE history

When standardized by age, the prevalence of recent VTE (< 1 year) was higher in women ($n = 380$) than in men ($n = 172$) (3.4% vs. 2.4%). Such figures varied with age, arguing for an age-dependent effect: the prevalence reached 8.2% in elderly women (≥ 75 years) and 5.1% in men (≥ 75 years) (Fig. 3). The majority of cases were SVT in both sexes (2.5% in women vs. 1.5% in men).

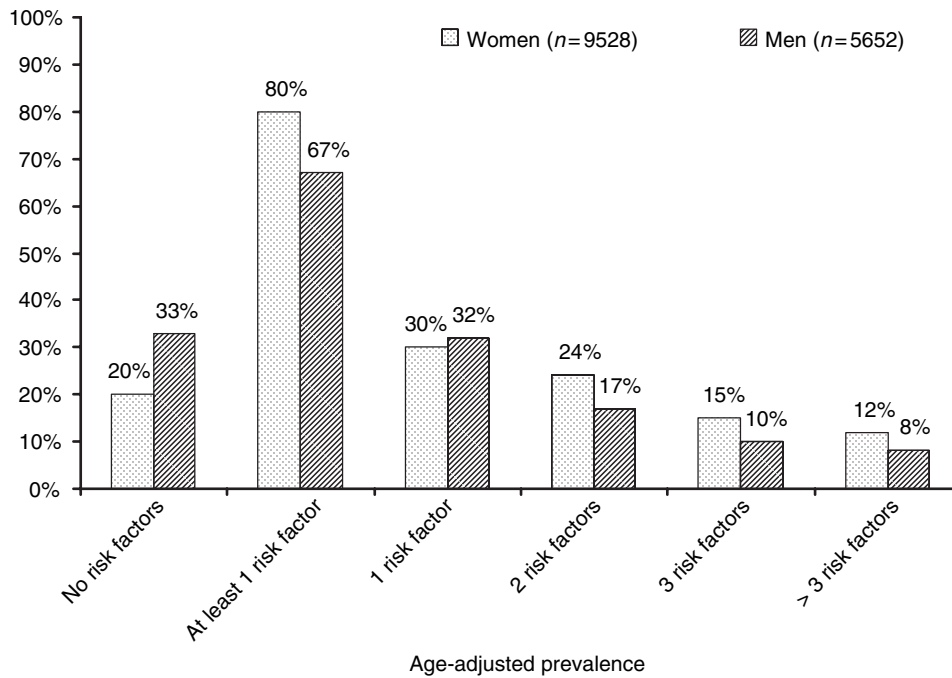


Fig. 2. FAST population: prevalence of risk factors for VTE of any grade by sex.

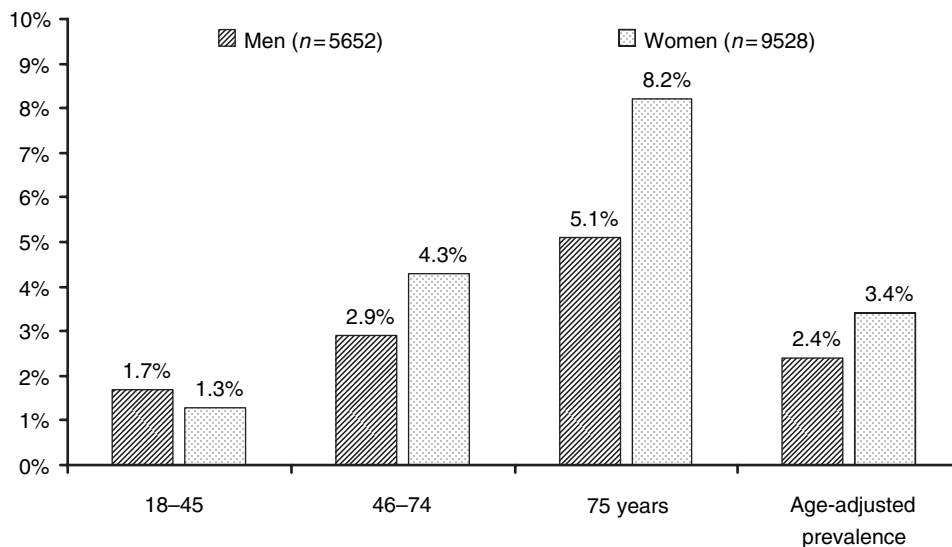


Fig. 3. FAST population: prevalence of recent (< 1 year) VTE by sex and age class.

Several risk factors reported in the previous section were more common among subjects with a recent VTE than in the rest of the population (Table 3). As in similar reports [3,20], three or more risk factors very commonly coexisted in patients with recent VTE (48.3% in women and 33.7% in men).

Discussion

This multicentre, cross-sectional, observational study reports the high prevalence of risk factors for VTE (including a prior history of VTE) amongst 15 180 adult patients who consult

their GP at his/her surgery for a health disorder. Their prevalence is higher in women and increases with age; on the other hand, the prevalence of recent VTE in elderly patients (≥ 75 years) is fairly high, especially in women.

The GPs recruited a large number of patients throughout Italy and within a short period of time, following rigorously standardized methods. In this respect, the present data should provide reliable prevalence data in the Italian patient population consulting GPs. However, this population is subject to the bias of GP consultation and may not reflect the general Italian population.

Table 3 Risk factors in subjects with a recent VTE: Mantel-Haenszel standardized odds ratios (M-H a-OR)

Risk factor	Sex	M-H a-OR	95% CI	P
Previous DVT/PE	F	11.1	8.8–14.1	<0.0001
	M	20.4	14.3–29.0	<0.0001
Previous SVT	F	19.6	15.4–25.1	<0.0001
	M	16.7	12.1–23.2	<0.0001
Cancer	F	1.31	0.79–2.18	0.296
	M	1.83	1.10–3.04	0.0181
Heart failure	F	2.59	1.98–3.38	<0.0001
	M	1.69	1.15–2.50	0.0074
Family history	F	2.90	2.32–3.62	<0.0001
	M	2.70	1.87–3.89	<0.0001
Cigarette smoking	F	1.32	0.94–1.87	0.110
	M	1.17	0.78–1.75	0.438
Obesity	F	2.29	1.85–2.84	<0.0001
	M	1.97	1.40–2.78	<0.0001
Varicose veins	F	6.59	4.86–8.95	<0.0001
	M	8.22	5.77–11.72	<0.0001
Inflammatory bowel disease	F	1.11	0.52–2.41	0.781
	M	1.04	0.33–3.34	0.943
Diabetes mellitus	F	1.73	1.31–2.30	<0.0001
	M	1.04	0.68–1.63	0.813
COPD	F	1.63	1.19–2.24	0.002
	M	1.30	0.88–1.91	0.188
Myeloproliferative disorders	F	1.81	0.64–5.10	0.249
	M	0.54	0.07–3.97	0.540

Standardized by age.

A comparison with the data of the 2001 census [36] shows that the population in this study was on average older and included a larger proportion of females (62.7% vs. 50.9%). For this reason the prevalence data presented were adjusted for age and stratified by sex.

To our knowledge, no other observational studies have been performed with the aim of assessing the prevalence of risk factors for VTE in the patients who consult their GP at his/her surgery. However, the prevalence of a few of the risk factors taken into consideration was assessed during the 2001 census [36].

The prevalence of diabetes according to the census was similar and almost the same in the elderly population (≥ 75 years): 14.7% vs. 15.2% in our study in men and 15.0% vs. 14.5% in women. Also the data related to COPD were similar. The proportion of smokers was higher in the 2001 census: 31.5% vs. 20.6% in men and 17.2% vs. 11.6% in women. These differences are probably due to the definition of smoker: only subjects smoking more than 15 cigarettes daily were considered smokers in this study, whereas no cut-off number was set in the census.

It is of interest to relate the present data with relevant information in the area. A certain number of subjects evaluated in the present investigation had a recent (<1 year) VTE. GPs involved in this study had received extensive education of a series of concepts concerning VTE appropriate diagnosis. This might have caused a selection bias. However, the information has been obtained through patient interview using a standardized CRF. On the other hand, the large number of GPs

involved is likely to have diluted/cancelled potential selection bias. Finally, the data obtained are on line with information from other such studies [3,20]: in keeping with the finding that the risk of VTE is higher in women than in men and increases exponentially with advancing age [3,20], recent VTE was higher in women than in men (3.4% vs. 2.4%), and increased with age (Fig. 3) in the present report; the incidence of VTE increases in proportion to the number of risk factors and risk factors interact cumulatively to create high-risk individuals [20]. A cumulative effect of multiple risk factors was detected in the FAST report: three or more risk factors very commonly coexist in patients with recent (<1 year) VTE (48.3% in women and 33.7% in men) in the present setting. In the Sirius Study [20] as well as in the report by Anderson and Spencer [3], several of the risk factors reported in the previous section were more common among subjects with a recent VTE than in the rest of the population (Table 3): this is also true in this setting. On the other hand, probably due to the sample size, in the Sirius study as well as in the report by Anderson, no stratification of the risk factors as to patient's sex was possible [3,20]. Our very large sample size and breadth of collected data on a wide range of thromboembolic risk factors, allows for such stratification: with few exceptions (cancer, diabetes mellitus) the prevalent risk factors did not differ in men and women with a recent VTE (Table 3).

Limitations of the present study

At variance with the Sirius Study [20], the design of our investigation can only reveal association but not causality between risk factors and recent (<1 year) VTE. A potential limitation is that the data are mostly based on historical information reported by the patient and not checked in any way; this limitation regards not only the risk factors, but also the prevalence of recent VTE. Another possible limitation may be imparted by selection bias. In an effort to ensure a random sampling study, GPs were asked to enroll the first two cooperative consenting patients from their clinic per day. As a matter of fact, GPs received extensive education on the epidemiology, risk factors, diagnosis of VTE as recently as the day before enrolling patients: this is conceivable to have influenced their patient selection. While it is not clear what direction this potential selection bias may take (e.g. patients with more or less risk factors), the differing selection bias may be cancelled each other out by the large number of GPs participating. On the other hand our data stress the potential impact of GP education on their subsequent enrolment of subjects at risk as well as with a recent history of VTE.

Meaning of the study: possible explanations and implications for policy makers

This study provides prevalence data in an Italian population of subjects consulting GPs in their surgery. This study shows not only that the prevalence of risk factors for VTE is high amongst the patients consulting their GP, but also identifies the nature

of such risk factors. Most of these risk factors may be corrected either by treatment (heart failure, diabetes, COPD) or by changes in lifestyle (smoking, estrogen treatment, obesity) that could be implemented by the GP. GPs are in a position to identify patients at high risk for VTE and to implement prophylactic measures, provided that they are aware of the issue.

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Conflict of interests

Di Minno G, Mannucci PM, Tufano A, Palareti G, Moia M, Baccaglini U have received honoraria (speaker's fees) from Sanofi-Synthelabo S.p.A. They also have had the costs of travel for the study paid by Sanofi-Synthelabo S.p.A. within the past 2 years.

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