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Efficiency of Systematic Thrombophilia Screening in Idiopathic Venous Thrombosis: A Prospective Study in Internal Medicine

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Summary: In case of unprovoked venous thromboembolism (VTE), the screening of thrombophilia is recommended whatever the age of the patient and the type of risk factors (RF). This prospective study was conducted in patients with unprovoked VTE to detect some predictive factors to have a higher risk of thrombophilia, focusing on age, history of venous thromboembolism, and the existence of a triggering event. From July 2000 to July 2002, in an Internal Medicine Department, unrelated patients with unprovoked VTE were included. Those unprovoked thromboembolic events were defined by the absence of association between permanent and transient RF. The primary outcome measure was the positivity of the thrombophilia screening for any type of abnormality detected (deficit of protein C, S, antithrombin, presence of a lupus anticoagulant, research of V and II mutations). Seventy-four patients were included. Eight died during

the follow-up. A higher risk of thrombophilia was found in patients younger than 40 ($p=0.03$), or with a family but not personal history of VTE ($p=0.01$) or with transient RF ($p=0.02$). The most frequent abnormality of coagulation found in patients younger than 40 was the presence of a lupus anticoagulant. As a new strategy for the screening of thrombophilia, one could propose the following attitude: only patients with transient RF or family history of VTE could undergo a complete screening; for all the remaining patients who are younger than 40, a research of a lupus anticoagulant would be only performed. This strategy should now be balanced against the currently recommended systematic attitude in further studies.

Key Words: Inherited blood coagulation disorders—Risk factors—Thromboembolism.

Thrombophilia is defined as an acquired or inherited predisposition to thrombosis. In most of countries, the screening of an underlying thrombophilia is currently recommended in case of a first venous thromboembolism (VTE) for patients younger than 50 or, no matter the age, in recurrent arterial or venous thrombotic events, a first-degree family history of VTE, VTE at unusual anatomic sites, multiple adverse pregnancy outcomes, and unprovoked idiopathic VTE (1).

A recent cost-effectiveness analysis concerning the indications to test factor V Leiden showed that two different populations should be considered: patients with VTE triggered by a “clear precipitant” where prevalence of Leiden mutation is low and patients with “no obvious precipitant” for whom testing the mutation is cost-effective because of its high prevalence (2).

Several authors (3,4) recently tried to define the concept of unprovoked or idiopathic VTE more precisely. Recent studies (5–9) tend to demonstrate the importance of a chronological analysis of risk factors (RF) in the etiologic investigation of VTE, distinguishing transient and permanent RF. So that, an idiopathic VTE is now defined by the absence of transient risk factors.

However, in internal medicine, although transient RFs are frequent and often associated with each other, the incidence of VTE remains low

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(less than 1%) (6). We previously demonstrated that the association of transient RF with permanent RF is required to satisfactorily explain a thrombotic event (7,8). Thrombophilia would actually be a permanent RF in the same way as obesity, venous insufficiency, chronic loss of walking ability, nonacute cardiac insufficiency, etc.

The main objective of this prospective study carried out in internal medicine was to refine the literature recommendations about the indications of thrombophilia screening in idiopathic VTE. We can wonder if this screening must be systematically performed or if it should be kept for young patients or patients with a history of VTE.

The secondary objective was to validate our etiologic approach of thrombogenesis based on a chronological stratification of RF. If we assume that thrombophilia is a permanent RF and that VTE could be explained by the association of transient and permanent RF, we should find an increase in the prevalence of thrombophilia in patients with only transient RF.

MATERIALS AND METHODS

Study Design

This was a prospective and evaluative study without any additive invasive test since all investigations carried out fitted in with the present recommendations.

Eligible Criteria

All unrelated patients admitted in a 65-bed department of internal medicine for an acute venous thrombosis (deep or superficial, whatever its anatomic site) or for a pulmonary embolism were eligible. In each case, deep vein thrombosis and pulmonary embolism were diagnosed with color Doppler ultrasonography and with lung ventilation-perfusion scan.

Inclusion and Non-inclusion Criteria

Only patients with unprovoked thromboembolic events were enrolled. In each patient, all well-established RF for thromboembolism were listed. As it was used in previous studies (5–9), a chronological evaluation of RF was made, separating permanent and transient RF. The separation of non-major and major RF was based on the level of associated risk. Only two RF had actually demonstrated a strong association with venous thromboembolism (total paralysis of the lower limb and recent orthopedic, or abdominal surgery). In the absence of any further demonstration, all other RF could be considered as non-major RF (Table 1).

The assessment of an unprovoked thromboembolic event was performed in two steps:

First, during the initial medical examination, clinical RF were identified and classified as follows (Table 1):

- Major transient RF: RF with a clearly established very high risk of thromboembolism detected in the last 3 months (and still persistent).

TABLE 1. Classification of Risk Factors

Permanent (detected more than 3 months before)	Non-major Transient (detected in the last 3 months)	Major
Age over 60	Acute loss of walking ability*	Total paralysis of the lower limb
Body mass index >27	Bedrest	Recent surgery
Personal history of unexplained VTE	Acute cardiac insufficiency	
Familial history of recurrent VTE	Clinical signs of dehydration	
Chronic loss of walking ability*	Acute inflammatory state	
Chronic cardiac insufficiency	(not bound to venous thrombosis)	
Progressive malignancy	Thrombocytopenia > 800,000/mm ³	
Oestrogenotherapy	Puerperium	
Pregnancy	Prolonged travel	
Venous insufficiency		
Varicosis of the lower limb		
Post-phébitic syndrome		

*Incapacity to walk around the bed.

- Non-major transient RF: all other acute RF of VTE detected in the last 3 months (and still persistent).
- Permanent RF: all known RF of VTE detected more than 3 months before.

At this stage, patients with major RF or an association between clinical permanent and transient RF were excluded.

Second, the other patients underwent an etiologic investigation including:

- All necessary complementary tests in case of a suspected clinical sign discovered during the first clinical examination to detect a progressive malignancy.
- Systematically: a blood cell count, chest tomography, abdominal and pelvic echography, and measurement of the C reactive protein to detect thrombocytopenia, polycythemia vera, lymphoma, deep abdominal or pelvic cancer and an inflammatory state.

At the end of this etiologic investigation, patients were finally included if no association between transient and permanent RF could have been demonstrated.

So three groups of included patients were identified:

- Patients with no RF
- Patients with only permanent RF
- Patients with only non-major transient RF

Outcome Measure

The primary outcome measure was the positivity of the thrombophilia screening. The complete screening included the research of a lupus anticoagulant (LA), antithrombin, protein C and protein S concentrations and the detection of factors V and II mutations by the following methods:

- The detection of antiphospholipid antibodies was performed by the prolongation of the activated partial thromboplastin time (aPTT, Biomérieux, France), mixing studies (Rosner index), diluted aPTT (PTTLA, Diagnostica Stago, France), and by detecting anticardiolipin antibodies (ELISA method). Cut-off levels of positivity for anticardiolipin were more than 20 U M.PL. and 20 U G.PL. These tests were carried out during the initial hospitalization.
- Antithrombin activity (normal values 80–120%) was measured by a functional method based on its heparin cofactor activity (Stachrom Antithrombin, Diagnostica Stago, France).

- Protein C level (normal values 70–130%) was quantified by clotting method (Staclo Protein C, Diagnostica Stago, France), confirmed by protein C antigenic assay by ELFA (Vidas Protein C, Biomérieux, France).

- Free protein S level (normal values 70–130%) was tested by clotting method (Staclo Protein S, Diagnostica Stago, France), confirmed by immunoturbidimetry assay (Liatest Free Protein S Diagnostica Stago, France).

- The modified test of Dahlback (with dilution in factor V-deficient plasma) was used (Coatest APC Resistance, Chromogenix, IL) for detection of activated protein C resistance. In case of positivity, a confirmation of factor V Leiden mutation was performed by molecular biology (digestion by restriction enzyme *TAQ I* of PCR-amplified fragments)

- The research of the 20210 A prothrombin gene mutation was carried out by the same molecular biology method.

At this stage, patients were excluded if they refused to sign the consent form, which was a legal necessity to carry on with tests based on molecular biology.

In case of long-term oral anticoagulation, only anticardiolipin antibodies, antithrombin activity, factor-V Leiden mutation and prothrombin gene mutation were tested.

Treatment Regimens and Follow-up

All included patients received anti-vitamin K (AVK) treatment for at least 6 months. A follow-up visit was then systematically performed during which the length of the treatment was decided and the thrombophilia screening prescribed.

In case of a second unprovoked thromboembolic event, a long-term AVK treatment was administered and the screening of an inherited thrombophilia was immediately performed. In case of a first unprovoked thromboembolic event with post-phlebotic syndrome or a persistent and progressive RF as malignancy, AVK therapy was prolonged for 6 months and the thrombophilia screening was delayed until the next visit.

In all other cases, AVK treatment was discontinued and the inherited thrombophilia screening was performed after a “wash-out” period of 1 month.

Statistical Analysis

To complete the objectives of this study, the frequency of the primary outcome measure was compared by means of a chi-square test in several groups:

- Patients under 50 and under 40
- Patients with a personal history of thromboembolic events, unprovoked or not
 - Patients with a personal history of unprovoked thromboembolism
 - Patients with a family history of thromboembolic events

Postulating that thrombophilia acts as a permanent RF and to validate our analysis of thrombotic events based on the identification of transient and permanent RF, the frequency of the primary outcome measure was compared in three other groups:

- Patients with permanent RF
- Patients with transient RF
- Patients with no RF

A Student's test (in case of normal population) or a Wilcoxon's test (in case of nonnormal population) was used to compare the average age in each group. The normality of the populations was tested by a Kolmogorov's test. The kurtosis was calculated to detect a possible bimodal character of age curves.

RESULTS

Duration of the Study, Number of Patients

This study was conducted from July 2000 to July 2002 (Fig. 1). Two hundred five patients were eligible. After analysis, 82 thromboembolic events remained unexplained. Among these 82 patients, eight patients refused blood sampling for the thrombophilia research and were excluded. During follow-up, eight patients died. (Two deaths attributed to colorectal cancer, one to stomach cancer, one to myeloma, two to cachexia complicating very old age—92 and 95 years old—one to acute leukemia and one to a medullar haematoma.) So, the statistical analysis was carried out on 66 patients.

Repartition of Risk Factors

Among the 123 excluded patients, 13 had a major RF, 110 had one or more transient RF associated with one or more permanent RF (Table 2).

Prevalence of Each Protein-coagulating Deficiency and Number of Positive Thrombophilia Screenings

For patients 5 and 14, although thrombophilia screening couldn't be completed (patients lost

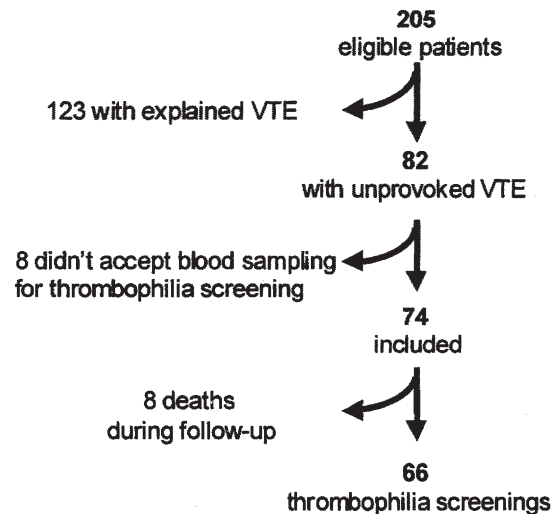


FIG. 1. Number of eligible, excluded, included patients and number of thrombophilia screenings.

to follow-up), it has been considered as positive because of the existence of a lupus anticoagulant discovered at admission (Table 3). Among the 66 patients with an unprovoked VTE, 26 patients (39.3%) had a thrombophilia (whatever the type of deficiency). The prevalence of LA, antithrombin III, activated protein C resistance and prothrombin gene mutation was respectively 9.1%, 3.1%, 18%, and 9.3%. We have found a high level of protein S deficiency (12%) contrasting with a low level of protein C deficiency (less than 1%). The rate of protein S was not higher in patients with transient RF.

Thrombophilia Screenings and Age

The distribution of age values was bimodal (kurtosis <1.8) (Table 4). Two groups of age were tested according to those considered in the literature as discriminant one; i.e., 50 (1) and 40 (10–12). The prevalence of positive thrombophilia screening was only increased in patients under 40 ($p=0.03$). Among the nine patients younger than 40 with thrombophilia, five had a LA.

Patients with a LA were younger (39.7 years \pm 17) than those without a LA (63 years \pm 18; $p=0.02$). We have supposed that the bimodal character of the distribution was probably due to patients with a LA and checked this hypothesis excluding patients with a LA from the data analysis. The frequency of thrombophilia then did not differ in both groups (4/9 vs. 15/50, $p=0.39$).

Table 2. Risk Factors Repartition in Patients with Explained and Unexplained Venous Thromboembolism

Risk Factors	Included Patients n=82 (%)	Excluded Patients n=123 (%)
Age over 60	46 (56)	104 (84%)
Body mass index over 27	25 (30)	44 (36%)
Personal history of unexplained VTE	27 (33)	16 (13)
Familial history of VTE	21 (25)	12 (10)
Prolonged travel	2 (2)	3 (2)
Bedrest	1 (1)	32 (26)
Loss of walking ability less than 90 days	3 (4)	53 (43)
Loss of walking ability more than 90 days	6 (7)	14 (11)
Progressive malignancy	5 (6)	38 (31)
Chronic cardiac insufficiency	10 (12)	19 (15)
Acute respiratory insufficiency	0	14 (11)
Clinical signs of dehydration	0	1 (1)
Post-phlebotic syndrome	0	3 (2)
Acute inflammatory state	3 (4)	57 (46)
Oestrogenotherapy	4 (5)	3 (2)
Venous insufficiency	27 (32)	59 (48)
Varicosis of the lower limb	2 (2)	46 (37)
Pregnancy	1 (1)	2 (2)
Puerperium	1 (1)	1 (1)
Recent surgery	0	7 (6)
Total paralysis	0	6 (5)

Thrombophilia Screenings and History of Venous Thromboembolism

To compare the prevalence of positive inherited thrombophilia screenings in patients with a family history of VTE, patients with a lupus anti-coagulant (and no other deficiency) were excluded from the statistical analysis (n=5) since it couldn't be considered as an inherited disorder of the coagulation (Table 4). Positive thrombophilia screenings were not more frequent in patients with a personal history of VTE ($p=0.92$), even if we focus on the unexplained one ($p=0.48$). Thrombophilia was more frequent in patients with a family inherited history of VTE (59% vs. 25% $p=0.01$).

Thrombophilia Screenings and Risk Factors

A great majority of patients (50/66) had only permanent RF (see Table 4). The prevalence of positive thrombophilia screenings, evaluated in each group defined by the chronological analysis

of RF (described subsequently), was only increased in patients with transient RF. It was two times higher in that group in comparison with patients with permanent or no RF (75% vs. 34% $p=0.02$).

DISCUSSION

With an overall prevalence of thrombophilia about 40%, we confirm the good efficiency of this screening in patients with unprovoked venous thromboembolism.

Even if it is difficult to find exactly the same tested population and the same methodology for thrombophilia detection, our prevalence is consistent with literature data. Milgic and colleagues (14) in 121 patients and Mateo and colleagues (12) in a large group of 2132 consecutive patients found a lower prevalence than ours (about 12%) but in both studies, mutations on factor V and II were not tested.

TABLE 3. Results of Thrombophilia Screening

Patient	acc	at3	protc	protsi	rpca	Leiden	20210 A	Conclusion
1	N	N	N	N	1.5	h	N	positive
2	N	N	N	N	2.2		N	negative
3	N	N	AVK	AVK	2.4		N	negative
4	N	P	N	N	2.5		N	positive
5	P	LFU	LFU	LFU	LFU	LFU	LFU	positive
6	N	N	N	N	2.6		N	negative
7	N	N	AVK	AVK	2.2		N	negative
8	N	N	AVK	AVK	NP	N	N	negative
9	N	N	N	N	2.3		h	positive
10	N	N	N	N	2.2		N	negative
11	N	N	AVK	AVK	2.3		N	negative
12	N	N	N	N	2.2		N	negative
13	N	N	AVK	AVK	2.1		N	negative
14	P	LFU	LFU	LFU	LFU	LFU	LFU	positive
15	N	N	N	N	2.4		N	negative
16	N	N	N	N	1.9	N	N	negative
17	N	N	N	P	2.2		N	positive
18	N	N	N	N	2.3		N	negative
19	N	N	AVK	AVK	2		N	negative
20	N	N	N	N	2.6		N	negative
21	N	N	N	N	2.3		h	positive
22	N	N	N	N	2.3		N	negative
23	N	N	AVK	AVK	NP	N	h	positive
24	N	N	AVK	AVK	2.3		N	negative
25	N	N	N	N	1.6	h	N	positive
26	N	N	N	N	2.2		N	negative
27	N	N	N	P	2.3		N	positive
28	N	N	N	N	2.3		N	negative
29	N	N	N	N	1.6	h	h	positive
30	N	N	N	N	2.3		N	negative
31	N	N	N	N	1.6	h	h	positive
32	N	N	AVK	AVK	2.1		N	negative
33	N	N	N	N	2.3		N	negative
34	N	P	N	N	2.2		N	positive
35	P	N	N	N	2.1		N	positive
36	P	N	N	N	2.1		N	positive
37	N	N	N	N	1.6	h	N	positive
38	N	N	N	N	2.6		N	negative
39	N	N	N	N	1.5	H	N	positive
40	N	N	N	N	2.3		N	negative
41	N	N	AVK	AVK	2.2		h	positive
42	N	N	N	N	2.1		N	negative
43	N	N	N	N	2.3		N	negative
44	N	N	N	N	2.3		N	negative
45	N	N	AVK	AVK	2.2		N	negative
46	N	N	N	N	2.3		N	negative
47	N	N	N	N	1.5	h	N	positive
48	N	N	N	P	2.2		N	positive
49	N	N	N	N	2.3		N	negative
50	N	N	AVK	AVK	2.3		N	negative
51	P	N	N	N	2.4		N	positive
52	N	N	AVK	AVK	2.3		N	negative
53	N	N	N	P	2.1		N	positive
54	N	N	AVK	AVK	NP	N	N	negative
55	N	N	N	P	2.3		N	positive
56	N	N	N	N	2.3		N	negative
57	N	N	N	N	2.2		N	negative
58	P	N	N	P	2.1		N	positive
59	N	N	N	N	2.2		N	negative
60	N	N	N	N	1.5	h	N	positive
61	N	N	N	N	2.5		N	negative
62	N	N	N	N	1.7	h	N	positive
63	N	N	N	N	2.2		N	negative
64	N	N	N	N	2.2		N	negative
65	N	N	N	N	2.3		N	negative
66	N	N	AVK	AVK	2.3		N	negative
Fq	(6/66)	(2/64)	(0/50)	(6/50)	(10/50)	(9/50)	(6/64)	

LFU, lost to follow-up; NP, not performed; AVK, patients treated with antivitamin K; h, heterozygote; H, homozygote; N, negative test; P, positive test.

TABLE 4. Effect of Age, History of Venous Thromboembolism, and Type of Risk Factors on Frequency of Thrombophilia

Risk Factors	Present (%, n/total)	Absent (%, n/total)	p*
Age <40	64% (9/14)	32% (17/52)	0.03
Age <40, CCA excluded	45% (4/9)	30% (15/50)	0.39
Age <50	47% (11/23)	34% (15/43)	0.30
Personal history of VTE	40% (12/30)	38% (14/36)	0.92
Personal history of unexplained VTE	45% (10/22)	36% (16/44)	0.48
Familial history of VTE (CCA excluded)	59% (10/17)	25% (11/44)	0.01
Permanent RF	36% (18/50)	50% (8/16)	0.31
Transient RF	75% (6/8)	34% (20/58)	0.02
No RF	25% (2/8)	41% (24/58)	0.37

*Chi-square test.

In non-white populations (15–17), the overall prevalence of thrombophilia in patients with VTE varied from 22% to 58% but it is difficult to compare results based on a genetic transmission in different ethnic groups. In non-selected outpatients, i.e., patients with unexplained and explained VTE, the combined prevalence of antithrombin III, protein C, and protein S is lower than ours (18) (8% vs. 18%). This result is consistent with the results of Eckman and colleagues (2), who showed because of a low prevalence, the uselessness to perform thrombophilia case finding in non-selected patients with VTE.

Bombeli and colleagues (19) found a similar prevalence of thrombophilia (39%) in patients with thrombosis in other venous systems such as the upper extremity or portal veins, which remains unexplained in most cases.

In our study, the prevalences of a LA (9.1%), antithrombin III deficiency (3.1%), activated protein C resistance (18%) and mutation 20210A of the prothrombin gene (9.3%) were similar to those reported in the literature; i.e., respectively 4% to 16% (11,12,16,20); 1.4% to 7.1% (14–17,21–23); 5% to 40% (11,13,16,17,19,22,24–27), and 4% to 18% (11,13,19,25–28). We found a relatively high prevalence of protein S deficiency (12%) usually not noticed in our white countries, quite similar to those observed in Asia (15,21,22,29). Here, we must bear in mind that, in internal medicine, a certain number of deficiencies can be acquired. For example, it is well known that an acquired protein S deficiency can occur in particular acute pathologies as sys-

temic lupus (30,32), Behcet's disease (33), nephrotic syndrome (34), or myeloma (35) for example. That's why our results must be balanced and consequently the observed prevalence must perhaps be lowered.

Including LA, we have found an increase in the prevalence of thrombophilia only in patients younger than 40 (64% vs. 32%, $p=0.02$), but this high prevalence was exclusively due to the high prevalence of LA in that population (5/9, 55%) because after having excluded patients with LA from the data analysis, the prevalence of thrombophilia did not differ in both groups (4/9 vs. 15/50, $p=0.39$). So, we confirm the literature data that recommend to carry out the thrombophilia screening in all patients whatever their age, in that particular case of unprovoked VTE. Our prevalence of thrombophilia in young patients is consistent with that of Swiatkiewicz and colleagues (10), who found thrombophilia in 50% of patients with the same inclusion criteria. Mateo and colleagues found a lower prevalence (17.5%) but patients with thrombosis were not selected and the research of the two mutations was not carried out.

Family but not personal history of deep vein thrombosis was associated with a high risk of thrombophilia (56% vs. 23%; $p=0.01$). Even when we focused on the unexplained personal history of VTE, we failed to demonstrate an increase of the thrombophilia rate. It suggests that these unprovoked events might actually be caused by some triggering factors forgotten or not noticed by the patients.

In patients with only transient RF, we found a high prevalence of thrombophilia (75%) confirming that the explanation of a thromboembolic event required the presence of a high risk ground on which the occurrence of a transient RF will act as a trigger toward thrombogenesis. In the specific context of our study, the chronic high risk ground is here represented by thrombophilia in 75% of the cases because we have excluded all other known permanent RF such as loss of walking ability, obesity, age over 60, venous insufficiency, etc. In women with unexplained VTE during pregnancy and puerperium, Martinelli and colleagues (13) found a lower prevalence of inherited thrombophilia of 39.5% but although those clinical contexts can be considered as transient RF, they represent very high-risk situations, which might explain this discrepancy.

In conclusion, taking into account all the results of this study, in the specific context of unprovoked VTE, we could propose to test thrombophilia only in patients with transient RF in first line of decision, or with a family history of VTE in second line and in third line, to solely perform a research of a LA only if they are younger than 40.

If we had applied this strategy to the patients included in this study, we would have diagnosed 19 thrombophilia in 31 patients (61%) instead of the 26 diagnosed here in 66 patients. It will now be very interesting to perform a prospective study aimed at evaluating this new strategy in terms of efficiency and usefulness compared to the currently recommended systematic attitude.

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