Different circumstances of the first venous thromboembolism among younger or older heterozygous carriers of the G20210A polymorphism in the prothrombin gene

VALERIO DE STEFANO, ELENA ROSSI, KATIA PACIARONI, ANDRIA D'ORAZIO, GREGORIO CINA, ELSA MARCHITELLI, RITA PEPE, GIUSEPPE LEONE

Background and Objectives. The G20210A polymorphism in the prothrombin gene is a common cause of inherited thrombophilia. Scarce information is available about the circumstances of the heralding thrombotic manifestation at different ages. The aim of this study was to determine the risk of spontaneous or secondary venous thromboembolism (VTE) among younger and older carriers of the G20210A prothrombin polymorphism.

Design and Methods. We performed a case-control study, investigating 650 patients with a first objectively documented deep venous thrombosis of the legs or pulmonary embolism and 703 individuals with no history of vascular disease. In all of them we carried out laboratory screening for antithrombin III, protein C and protein S deficiencies, and for the presence of the factor V Leiden and the G20210A prothrombin polymorphisms.

Results. After adjustment for other inherited causes of thrombophilia (deficiency of antithrombin III, protein C or S, factor V Leiden) the overall risk for VTE associated with the prothrombin polymorphism was 3.4 times higher than in the controls (95% CI, 2.0 to 5.8). Stratification according to the age and to the circumstances of the first event revealed an increased risk of spontaneous VTE only among the patients older than 45 years in comparison with age-matched controls (odds ratio 4.4, 95% CI 1.8 to 10.6); among the younger individuals the risk was increased for secondary VTE (odds ratio 4.8, 95% CI, 2.3 to 9.8) but not for spontaneous VTE.

Interpretation and Conclusions. The clinical penetrance of the thrombotic tendency associated with the G20210A prothrombin polymorphism is more expressed in the presence of a circumstantial risk factor (oral contraceptives, pregnancy, surgery, trauma) and in the presence of older age, which acts as an additional circumstantial risk factor. Accordingly, such situations should not discourage from carrying out laboratory screening.

Key words: venous thromboembolism, inherited thrombophilia, prothrombin G20210A, age.

Haematologica 2003;88:61-66
http://www.haematologica.org/2003_01/88061.htm

From the Institute of Hematology (VDS, KP, GL, AD, ER), Department of Cardiovascular Medicine (GC), Catholic University, Rome; and Unit of Angiology, Sant'Eugenio Hospital, Rome;(EM, RP), Italy.

Correspondence: Prof. Valerio De Stefano, Istituto di Ematologia, Università Cattolica, largo Gemelli 8, 00168 Rome, Italy. E-mail: v.destefano@eudoramail.com

A G20210A transition in the 3'-untranslated region of the prothrombin gene is present in 2% of the general population[1] and is a common cause of venous thromboembolism (VTE).[2] A combined analysis of 14 case-control studies,[2-15] including 6,267 controls (3% heterozygous carriers of the mutant allele) and 3,356 patients with VTE (7.3% heterozygous carriers of the mutant allele, $p < 0.001$) produced a pooled odds ratio of 2.5 (95% CI 2.1 to 3.1). In spite of the large number of studies so far published, a thorough analysis of the clinical characteristics of the venous thromboembolic episodes occurring in the carriers of the prothrombin gene polymorphism is lacking. In general, most investigations were aimed to estimate the overall risk associated with the prothrombin gene polymorphism and no study analyzed the circumstances of the first VTE after stratification according to age at the time of the clinical event. In order to investigate whether the age of the carriers of the prothrombin gene polymorphism is relevant in producing different clinical presentations of a first VTE, we carried out a case-control study.

Design and Methods

Patients

We investigated 650 unrelated Italian patients (297 men and 353 women) who had previously had a deep vein thrombosis of the legs or a pulmonary embolism. Two hundred and seventy-two patients were consecutively admitted to our hospital from the emergency ward for an acute venous thrombotic event during the period November 1995 through February 2002; in the same period another 378 patients diagnosed in hospital by their physicians were consecutively referred to our Thrombosis Center for investigation of possible causes of thrombophilia. All patients were of Italian ancestry. A preliminary evaluation had ruled out patients with overt forms of neoplasia, autoimmune diseases (including primary antiphospholipid syndrome) and overt myeloproliferative disorders. All patients were interviewed by physicians who collected their medical history and evaluated the available objective documentation before any laboratory investigation, so that a diagnosis of VTE was recorded without knowledge of the results of the thrombophilia screening. The presence of circumstantial risk factors at the time of VTE, such as pregnancy or puerperium, oral contraceptive use, surgery, prolonged immobilization (bed rest for at least ten days, or plastering of the legs) and trauma was also recorded. A diagnosis of deep vein thrombosis was accepted if it had been established by objective methods such as phlebography or ultrasound

examination; a diagnosis of pulmonary embolism was accepted if proven by perfusion lung scanning, computerized tomography, or nuclear magnetic resonance. Pulmonary embolism was diagnosed in 215 patients, 57 of whom were without objective evidence of deep vein thrombosis of the legs.

A control group of 703 unrelated individuals with Italian ancestry and with no history of previous thromboembolism (410 men and 293 women) was also investigated at the same time as the patients. The control subjects were recruited from among blood donors (n= 330), members of the hospital staff (n= 139), and outpatients with diagnoses other than malignant or autoimmune diseases (n=234). Their mean age was 42 years (median 41, range 7 to 93).

Laboratory tests

Informed consent for laboratory screening was given by all the individuals (or by their parents in the case of children). The screening for thrombophilia has been previously described.[16,17] Antithrombin heparin cofactor activity was measured by an amidolytic assay (Coamate Antithrombin, Chromogenix AB, Molndal, Sweden). Protein C activity was assayed by an amidolytic assay (Coamatic Protein C, Chromogenix) after Protac® activation. Total protein S antigen was measured by ELISA using polyclonal antibodies (Dako A/S, Glostrup, Denmark), and free protein S was measured in the same way after precipitation of the C4b-binding protein-protein S complex with polyethyleneglycol 6000 (3.5% final concentration) or directly by ELISA using a commercial kit with a specific monoclonal antibody (Asserachrom® Free Protein S, Stago, Asnières, France). Diagnosis of antithrombin, protein C or protein S inherited deficiency was established if the plasma level was below the normal lower limit (75 % for antithrombin and 70 % for protein C and protein S) and at least one other first-degree relative of the proband had decreased plasma levels. DNA samples were analyzed for the presence of factor V Leiden and the G20210A prothrombin polymorphisms by specific amplification and digestion.[2,18]

Statistical analysis

Differences between groups were estimated by Fisher's exact test. Univariate odds ratios were calculated as an approximation of the relative risk for putative risk factors by simple cross-tabulation, with 95 % confidence intervals.

Results

Control groups

Among the control individuals 21 were carriers of factor V Leiden (20 heterozygotes, 15 men and 5 women, and 1 female homozygote) (3%) and 21 were heterozygous carriers of the G20210A polymorphism in the prothrombin gene (12 men and 9 women, 3%). No control individual was homozygous for the prothrombin gene polymorphism or carried both factor V Leiden and the prothrombin gene polymorphisms.

Clinical and laboratory features of the patients

The main clinical and laboratory features of the population of patients are reported in Table 1. Thirty-eight per cent of the first venous thromboembolic episodes occurred spontaneously in the absence of a circumstantial risk factor (pregnancy and puerperium, oral contraceptives, surgery, trauma, bed rest). A condition associated with thrombophilia was detected in 33% of the cases; heterozygosity for the G20210A polymorphism in the prothrombin gene was found in 63 patients (9.7%), 16 of them (2.5%) carrying another thrombophilic trait (in 2 cases antithrombin deficiency, in 1 case protein S deficiency, in 1 case homozygosity for factor V Leiden and in 12 cases heterozygosity for factor V Leiden). These latter were excluded from further estimates concerning the prothrombin polymorphism, since the thrombotic risk could be attributed in part to the associated abnormality. Among the consecutive patients the percentage of patients with inherited thrombophilia was 26%, and among the referred patients it was 39% (p=0.001). This difference was due to the higher percentage of patients with antithrombin, protein C, protein S deficiency or factor V Leiden among the referred patients (31%) in comparison with among the consecutive patients (19%, $p < 0.001$), whereas the carriers of the G20210A polymorphism in the prothrombin gene without other plasma abnormalities were similarly distributed between the two groups (7% among both the consecutive and the referred patients, p= 1.00).

The overall risk of VTE estimated in the whole patient cohort after adjustment for other causes of inherited thrombophilia was 3.4 times higher than that in controls (Table 2); the magnitude of the increase in risk did not change substantially for spontaneous VTE or for VTE associated with circumstantial risk factors (Table 2). The circumstantial risk factors associated with VTE among the individuals carrying the prothrombin gene polymorphism were surgery (n= 11), prolonged bed immobilization (n= 5), a previous trauma (n= 4), plastering of the legs (n= 2), oral contraceptive use (n= 4), puerperium (n= 4), and pregnancy (n= 1). One patient had a popliteal (Baker's) cyst in the leg with venous thrombosis.

The first venous thromboembolic episode occurred in 441 patients before 45 years of age (180 males and 261 females, mean age at the first thrombosis 30 years, median 31, range 1 to 45); they were compared to the 422 controls younger than 45 years (242 males and 180 females, mean

Table 1. Clinical and laboratory characteristics of the patients with venous thromboembolism (VTE).

Patients	*Consecutive (n= 272)*	*Referred (n= 378)*	*Overall (n= 650)*
Males/females (ratio)	128/144 (0.88)	169/209 (0.80)	297/353 (0.80)
Mean age (median, range) - yrs at the first VTE	43 (41.2–80)	37 (34.1-84)	39 (37.1-84)
Mean age (median, range) - yrs at observation	43 (41.2–80)	47 (47.14-86)	45 (45.2-86)
Spontaneous first VTE, n (%)	104 (38)	143 (38)	247 (38)
Risk factors associated with first VTE, n (%):			
pregnancy or puerperium *	29 (20)	62 (30)	91 (26)
oral contraceptives *	36 (25)	38 (18)	74 (21)
surgery	39 (14)	60 (16)	99 (15)
trauma and plastering of the legs	19 (7)	39 (10)	58 (9)
bed rest	38 (14)	30 (8)	68 (10)
other causes	7 (3)	6 (1)	13 (2)
Total secondary first VTE, n (%)	168 (62)	235 (62)	403 (62)
Antithrombin deficiency, n (%)	6 (2)	2 (1)	8 (1)
Protein C deficiency, n (%)	8 (3)	15 (4)	23 (4)
Protein S deficiency, n (%)	4 (1)	7 (2)	11 (2)
Heterozygosity for factor V Leiden, n (%)	26 (10)	73 (19)	99 (15)
Homozygosity for factor V Leiden, n (%)	2 (1)	5 (1)	7 (1)
Heterozygosity for prothrombin G20210A, n (%)	20 (7)	27 (7)	47 (7)
Combined defects, n (%)	5 (2)	17 (5)	22 (3)
Total patients with thrombophilia, n (%)	71 (26)	146 (39)	217 (33)

**percentage of female patients.*

Table 2. Relative risk for venous thromboembolism (VTE) associated with the heterozygous G20210A polymorphism in the prothrombin gene (odds ratio, OR, with 95% confidence interval, CI). The odds ratio was estimated after exclusion of the subjects with other causes of inherited thrombophilia.

	All thrombotic episodes	*Spontaneous VTE*	*Secondary VTE*
All ages, OR (95% CI)	3.4 (2.0–5.8)	3.1 (1.5-6.1)	3.6 (2.0–6.4)
Age ≤ 45 years, OR (95 % CI)	3.7 (1.8–7.6)	1.3 (0.4–4.8)	4.8 (2.3–9.8)
Age > 45 years, OR (95% CI)	3.1 (1.4–6.8)	4.4 (1.8–10.6)	1.9 (0.7–5.5)

age 32 years, median 32, range 7 to 45). The remaining 209 patients with a first VTE after 45 years (117 males and 92 females, mean age at the first thrombosis 58 years, median 58, range 46 to 84) were compared to the 281 controls older than 45 years (168 males and 113 females, mean age 57 years, median 56, range 46 to 93). The overall increase in risk of a first VTE associated with the G20210A prothrombin gene polymorphism was similar in both younger and older individuals (3.7-fold and 3.1-fold, respectively) (Table 2).

Further stratification according to the circumstances of the first VTE among younger or older patients in comparison with the respective age-matched control groups revealed, among the younger carriers of the G20210A prothrombin polymorphism, a significant increase in the risk of secondary VTE (odds ratio 4.8, 95% CI 2.3 to 9.8), but not of spontaneous VTE (Table 2). In contrast, the older individuals carrying the prothrombin polymorphism had a significantly increased risk of spontaneous VTE (odds ratio 4.4, 95% CI 1.8 to 10.6) but not of secondary VTE (Table 2). Seventy-six patients had their first VTE after 60 years of age and 87 controls were older than 60 years; among them, there were, respectively, 7 (9.2%) and 1 (1.1%), heterozygotes for the prothrombin polymorphism; in this age subgroup the estimate of the associated risk of spontaneous VTE rose to 19.6-fold (95% CI 2.2 to 170.5). Among the 247 patients having suffered from a spontaneous VTE as their heralding manifestation, 93 (38%) carried a thrombophilic genetic trait; the median age of the first spontaneous VTE was 33 years among the 23 carriers of deficiency of natural anticoagulants (antithrombin, protein C, protein S), 33 years among the 8 carriers of multiple abnormalities, 44 years among the 47 carriers of factor V Leiden, and 59 years among the 15 carriers of the G20210A prothrombin gene polymorphism. The age of a first spontaneous VTE was before 45 years in 74% of the probands with deficiency of antithrombin, protein C, or protein S, in 75% of the probands with multiple abnormalities, in 57% of the probands with factor V Leiden, and in only 25% of the probands with the G20210A prothrombin polymorphism.

Discussion

Conflicting data are available about the circumstance of the first VTE among heterozygous carriers of the G20210A polymorphism in the prothrombin gene. The risk of first VTE has been suggested to be significant only in the elderly population[6] but in other studies the risk associated with the mutant genotype was increased in all age groups[2,9,11,13] or was marginally increased only in the younger population.[15] Analysis of the circumstances of the first VTE (spontaneous or secondary to circumstantial risk situations such as pregnancy, surgery, oral contraceptive use) did not show any variation in the increased risk in two stud-

ies,[11,13] whereas the risk was increased only for secondary thromboses and not for spontaneous ones in another study.[10]

A reason for such discrepancies could be a difference in the selection procedures of the series of patients, including patients referred for screening to specialized Thrombosis Centers[3,7,9,10,13] or consecutive patients,[4,5,6,8,11,12] or patients derived from population-based studies.[2,14,15] Moreover, several studies excluded individuals aged more than 60 to 70 years, so that their conclusions are biased as regards the effect of thrombophilic traits among the elderly population.[2,11,12,15]

In our study the prevalence of inherited thrombophilia among the individuals referred to our Thrombosis Center was higher than that among the patients consecutively admitted to our hospital; yet this difference was due to an overrepresentation of individuals with deficiency in antithrombin, protein C, protein S or resistance to activated protein C. Such alterations can nowadays be easily diagnosed by commercial kits and a number of patients had been probably referred by their physicians not only on the basis of the clinical history but also on the basis of an abnormal preliminary plasma screening. On the other hand the prevalence of the G20210A polymorphism in the prothrombin gene was similar among referred and consecutive patients; this might be due to the fact that DNA analysis is available only in specialized laboratories, so that a referral bias related to preliminary laboratory results can be excluded. Since the thrombotic risk associated with the G20210A prothrombin polymorphism was estimated after exclusion of all the individuals carrying other plasma or gene abnormalities, the effect of the aforementioned referral bias was considered negligible.

Our findings fit with most previous reports, since stratification for age or for the circumstances of the first VTE did not produce any significant variation in the 3.4-fold increase in thrombotic risk associated with the prothrombin polymorphism (Table 2). Yet further stratification according to both age and circumstances of the first VTE revealed that among the younger carriers of the prothrombin gene polymorphism, VTE is for the most part associated with circumstantial risk factors, with a 4.8-fold increase in risk of secondary events. This suggests that the G20210A polymorphism in the prothrombin gene is a relatively weak risk factor which needs a concomitant acquired risk circumstance for clinical expression. In contrast, carriers of the prothrombin polymorphism are significantly more prone to spontaneous VTE only in an older age range, with a 4.4-fold increase in risk after 45 years and 19.6-fold increase in risk after 60 years. The age at the first spontaneous VTE was before 45 years in the large majority of patients with deficiency of antithrombin, protein C or protein S; on the other hand, a substantial portion (43%) of the carriers of factor V Leiden with spontaneous VTE had their first episode after 45 years. This is in agreement with previous observations that factor V Leiden is associated with a less severe thrombotic risk than that due to deficiency of antithrombin, protein C, or protein S.[19] The first spontaneous VTE occurred after 45 years in 75% of the symptomatic carriers of the G20210A prothrombin polymorphism. In the general population the risk of VTE increases with age;[20,21] accordingly, in carriers of the prothrombin polymorphism, advanced age (i.e. the prolonged exposure to the mutant genotype) seems to acts as a concomitant acquired risk circumstance, leading to an increased risk of spontaneous VTE. A similar positive interaction between age and a genetic risk factor has been previously reported for factor V Leiden.[22]

Our findings contrast with those of two studies, which reported only a marginally increased risk of VTE associated with the prothrombin polymorphism. The first, derived from the cohort enrolled in the Physician's Health Study, found a modest increase in risk of primary or secondary VTE among male individuals aged 40 to 84 years carrying the prothrombin polymorphism.[14] The general design of this investigation, enrolling a special group of male physicians, who self-reported thrombotic events, should induce caution when considering such negative results.[23] Moreover, at variance with most studies concerning this issue, cancer as a cause of secondary VTE was not excluded, so that the impact of the mutant genotype could have been reduced in comparison with a strong prothrombotic factor such as neoplasia; finally, the estimate of the relative risk was not adjusted for other causes of inherited thrombophilia, so that the ratio between the venous thrombotic episodes occurring among the carriers of the prothrombin polymorphism alone and those occurring among the individuals with no detected cause of thrombophilia was likely underestimated. Another study was a cross-sectional investigation on a large random population sample;[15] only among individuals younger than 45 years did the carriers of the prothrombin polymorphism have a marginally increased risk of spontaneous VTE. Yet this investigation excluded all the inhabitants aged less than 18 years and more than 65 years, probably leading to an underestimation of the role of the prothrombin polymorphism among elderly individuals. In our series, out of 47 heterozygotes for the prothrombin polymorphism, 10 (21%) had a first VTE outside this age range (4 before 18 years and 6 between 66 and 73 years of age).

In conclusion we confirmed that the G20210A polymorphism in the prothrombin gene is associated with an increased risk of VTE; such a risk is rel-

atively weak, so that the clinical penetrance of the defect is fully expressed in the presence of a concomitant acquired risk circumstance, including older age. Therefore laboratory screening should not be selective, since exclusion of elderly patients may lead to a significant part of subjects with inherited thrombophilia being overlooked. The finding of a significant risk for VTE associated with exposure to triggering situations in the young should prompt family screening in order to identify the asymptomatic carriers of the prothrombin polymorphism and offer them short-term antithrombotic prophylaxis during risk situations.

References

1. Rosendaal FR, Doggen CJ, Zivelin A, Arruda VR, Aiach M, Siscovick DS, et al. Geographic distribution of the 20210 G to A prothrombin variant. Thromb Haemost 1998;79:706-8.
2. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3' untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood 1996;88:3698-703.
3. Cumming AM, Keeney S, Salden A, Bhavnani M, Shwe KH, Hay CR. The prothrombin gene G20210A variant: prevalence in a U.K. anticoagulant clinic population. Br J Haematol 1997;98:353-5.
4. Brown K, Luddington R, Williamson D, Baker P, Baglin T. Risk of venous thromboembolism associated with a G to A transition at position 20210 in the 3'-untranslated region of the prothrombin gene. Br J Haematol 1997;98:907-9.
5. Corral J, Gonzalez-Conejero R, Lozano ML, Rivera J, Heras I, Vicente V. The venous thrombosis risk factor 20210A allele of the prothrombin gene is not a major risk factor for arterial thrombotic disease. Br J Haematol 1997;99:304-7.
6. Hillarp A, Zoller B, Svensson PJ, Dahlback B. The 20210A allele of the prothrombin gene is a common risk factor among Swedish outpatients with verified deep venous thrombosis. Thromb Haemost 1997;78:990-2.
7. Arruda VD, Bizzacchi JM, Gonçalves MS, Costa FF. Prevalence of the prothrombin gene variant (nt20210A) in venous thrombosis and arterial disease. Thromb Haemost 1997;78: 1430-3.
8. Leroyer C, Mercier B, Oger E, Chenu E, Abgrall JF, Ferec C, et al. Prevalence of the 20210A allele of the prothrombin gene in venous thromboembolism patients. Thromb Haemost 1998;80:49-51.
9. Souto JC, Coll I, Llobet D, del Rio E, Oliver A, Mateo J, et al. The prothrombin 20210A allele is the most prevalent genetic risk factor for venous thromboembolism in the Spanish population. Thromb Haemost 1998;80:366-9.
10. Margaglione M, Brancaccio V, Giuliani N, D'Andrea G, Cappucci G, Iannaccone L, et al. Increased risk for venous thrombosis in carriers of the prothrombin G→A20210 gene variant. Ann Intern Med 1998;129:89-93.
11. Alhenc-Gelas M, Arnaud E, Nicaud V, Aubry ML, Fiessinger JN, Aiach M, et al. Venous thromboembolic disease and the prothrombin, methylene tetrahydrofolate reductase and factor V genes. Thromb Haemost 1999;81:506-10.
12. Lindmarker P, Schulman S, Sten-Linder M, Wiman B, Egberg N, Johnsson H. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. DURAC Trial Study Group. Thromb Haemost 1999;81:684-9.
13. Cattaneo M, Chantarangkul V, Taioli E, Santos JH, Tagliabue L. The G20210A mutation of the prothrombin gene in patients with previous first episodes of deep-vein thrombosis: prevalence and association with factor V G1691A, methylenetetrahydrofolate reductase C677T and plasma prothrombin levels. Thromb Res 1999;93:1-8.
14. Ridker PM, Hennekens CH, Miletich JP. G20210A mutation in prothrombin gene and risk of myocardial infarction, stroke, and venous thrombosis in a large cohort of US men. Circulation 1999;99:999-1004.
15. Tosetto A, Missiaglia E, Frezzato M, Rodeghiero F. The VITA project: prothrombin G20210A mutation and venous thromboembolism in the general population. Thromb Haemost 1999;82:1395-8.
16. De Stefano V, Finazzi G, Mannucci PM. Inherited thrombophilia: pathogenesis, clinical syndromes, and management. Blood 1996;87:3531-44.
17. De Stefano V, Rossi E, Paciaroni K, Leone G. Screening for inherited thrombophilia: indications and therapeutic implications. Haematologica 2002;87:1095-108.
18. Bertina RM, Koeleman BPC, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature 1994;369:64-7.
19. Martinelli I, Mannucci PM, De Stefano V, Taioli E, Rossi V, Crosti F, et al. Different risks of thrombosis in four coagulation defects associated with inherited thrombophilia: a study of 150 families. Blood 1998;92:2353-8.
20. Nordstrom M, Lindblad B, Bergqvist D, Kjellstrom T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. J Intern Med 1992;232: 155-60.
21. Hansson PO, Welin L, Tibblin G, Eriksson H. Deep vein thrombosis and pulmonary embolism in the general population. "The study of men born in 1913". Arch Intern Med 1997;157: 1665-70.
22. Ridker P, Glynn RJ, Miletich JP, Goldhaber SZ, Stampfer MJ, Hennekens CH. Age-specific incidence rates of venous thromboembolism among heterozygous carriers of factor V Leiden mutation. Ann Intern Med 1997;126:528-31.
23. Andreotti F, Burzotta F, De Stefano V, Maseri A, Iacoviello L. The G20210A prothrombin mutation and the Physicians' Health Study. Circulation 2000;101:E207-8.

Pre-publication Report & Outcomes of Peer Review

Contributions

VD was reponsible for the conception of the study, data analysis, and development of the text; ER contributed to the conception of the study and to the interpretation of the data. VD and ER should be equally considered as the principal authors. VD, GC, EM, RP, ER, and KP selected the patients and were responsible for their clinical management; VD, ER, and KP performed the medical interviews of the patients; ER and KP selected the controls and performed their medical interviews; AD, ER, and KP performed the laboratory tests; ER was responsible for the overall clinical and laboratory data collection and the statistical analysis; GL supervised the study and critically reviewed the manuscript giving important intellectual contribution as senior author.

Funding

The research programs on inherited thrombophilia of the Institute of Hematology of the Catholic University are supported by a grant from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (40%) (project MM06157335.002) and the Funds of the Catholic University.

Disclosures

Conflict of interest: none

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Vicente Vicente, Deputy Editor. The final decision to accept this paper for publication was taken jointly by Professor Vicente and the Editors. Manuscript received August 30, 2002; accepted November 13, 2002. In the following paragraphs, professor Vicente summarizes the peer-review process and its outcomes.

What is already known on this topic

The G20210A polymorphism of the prothrombin gene has been associated with a thrombophilic status. However, an accurate evaluation of risk of venous thromboembolism among carriers of this polymorphism has not been established.

What this study adds

This study confirms that the thrombotic risk associated with the G20210A polymorphism is weak. However, the clinical prenetrance of this polymorphism is clearly more relevant in the presence of concomitant acquired risk circumstances, such as oral contraceptive use, pregnancy, surgery, and trauma, especially in older patients.