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Risk factors of arterial cardiovascular complications in patients with prior venous thromboembolism

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ABSTRACT

Background. The effect of cardiovascular risk factors (CVRs) and thrombophilic defects on the risk of arterial cardiovascular complications in patients with prior venous thromboembolism (VTE) is unclear.

Objective. We investigated whether the risk of arterial cardiovascular complications is increased after VTE and whether CVRs and thrombophilic defects influence this risk.

Methods. Subjects were selected from three family cohorts of probands with VTE or arterial cardiovascular complication before the age of 50 and thrombophilic defects (i.e. hyperhomocysteinaemia, prothrombin G20210A or elevated FVIII). For this analysis, probands with arterial cardiovascular complications before inclusion and their relatives as well as relatives without the studied thrombophilic defects were excluded. We calculated the incidence of arterial cardiovascular complications (e.g. myocardial infarction, ischaemic stroke, transient ischaemic attack or peripheral arterial disease) in subjects with and without VTE and adjusted the relative risk for at least one CVR, two or more thrombophilic defects and quintiles of a propensity score (considering risk factors conditional to VTE history).

Results. 861 subjects were included, of whom 399 had experienced VTE before inclusion. Twelve arterial cardiovascular complications occurred in subjects with and nine in subjects without VTE history. Hence the annual incidence was 1.0 (95% CI 0.5 to 1.7) and 0.7 (0.3 to 1.2) in subjects with and without VTE (RR 1.5, 0.6 to 3.6). Adjusting for possible confounders did not change this relative risk.

Conclusion. The mildly elevated risk of arterial cardiovascular complications in patients with prior VTE appears to be independent of cardiovascular risk factors and thrombophilic defects.

KEYWORDS

Cardiovascular diseases, risk factors, thrombophilia, venous thromboembolism

INTRODUCTION

Following the observation of higher prevalence of subclinical atherosclerosis in patients with previous idiopathic venous thromboembolism (VTE) in 2003,[1] several studies have investigated the association between venous and arterial thrombosis. A mildly increased risk of arterial cardiovascular complications in patients with previous VTE has consistently been demonstrated.[2-6] A plausible explanation for such an association might be the presence of shared risk factors between VTE and arterial cardiovascular complications.[7-9] However, two large cohort studies were unable to establish a link between atherosclerosis at baseline and venous thrombosis during follow-up.[10,11] As the study populations in various published cohorts differ, we intended to confirm the increased risk of arterial cardiovascular complications after an episode of VTE in three prospective cohorts of thrombophilic

families. More important, we aimed to investigate whether the presence of multiple conventional cardiovascular risk factors and thrombophilic defects is able to explain the risk increase.

MATERIALS AND METHODS

Study population

The study subjects were selected from three cohorts of thrombophilic families which were identified by probands with documented VTE or premature arterial cardiovascular complications (any event before 50 years of age) and either hyperhomocysteinaemia, prothrombin G20210A or persistently elevated levels of factor VIII. Subjects were recruited between August 1997 and May 2004 from three academic hospitals: Academic Medical Center, Amsterdam, University Medical Center, Groningen and Academic Hospital Maastricht. Details of these studies have been published previously.[12-14] The study was approved by the institutional review boards of the participating hospitals. Additional thrombophilia tests for factor V Leiden and deficiencies of antithrombin, protein S and protein C were performed in all participants. Detailed information about previous episodes of VTE and arterial cardiovascular complications, exposure to exogenous risk factors for thrombosis and anticoagulant treatment was collected by validated questionnaire and by reviewing medical records at baseline. Also, cardiovascular risk factors namely smoking, diabetes mellitus, hyperlipidaemia and hypertension were recorded at inclusion.

Outcome

The outcome of this analysis was the first arterial cardiovascular complication, such as myocardial infarction (MI), ischaemic stroke, transient ischaemic attack (TIA) or peripheral arterial disease. Coronary and peripheral arterial disease had to be symptomatically and angiographically proven while MI was diagnosed according to clinical, enzymatic and electrocardiographic criteria. Ischaemic stroke was defined as the onset of rapidly developing symptoms and signs of cerebral function loss which lasted at least 24 hours and had an apparent vascular cause, as demonstrated by computed tomography scan or magnetic resonance imaging. If a cerebral event completely resolved within 24 hours without cerebral lesions at scanning, it was classified as TIA.[12] We contacted subjects every six months until April 2006, with a detailed questionnaire to identify new episodes of VTE and arterial cardiovascular complications, exposure to risk factors and medication use.

Statistical analysis

To evaluate whether the risk of an arterial cardiovascular complication is higher in subjects with or without history of VTE than those without, we excluded probands who had had an arterial cardiovascular complication prior to enrolment, as well as their relatives, because of higher risk of a recurrent event or the possible hereditary inclination to develop an event. Similarly, relatives with an arterial cardiovascular complication before baseline were excluded. Furthermore, in order to compare subjects with comparable genetic backgrounds regarding thrombophilic defects, we excluded relatives with none of the three thrombophilic defects originally qualifying for inclusion. The annual incidence (95% confidence interval [95% CI]) of the outcome was computed for two groups of subjects, with and without a history of VTE. The follow-up period was defined as years between the inclusion date and the date of death, last contact visit or when an arterial cardiovascular complication occurred. The relative risk of an arterial cardiovascular complication was computed by dividing the incidences of two groups. Potential confounders for the observed relative risk were considered as the presence of conventional cardiovascular risk factors (i.e. smoking, diabetes mellitus, hyperlipidaemia and hypertension and obesity (BMI ≥25 kg/m^2)) and thrombophilic defects. We computed the Mantel-Haenszel adjusted relative risk for the presence of at least one cardiovascular risk factor and two or more thrombophilic defects. We also developed a propensity score which is the probability of experiencing VTE, based on individual characteristics (i.e. age, cardiovascular risk factors and thrombophilic defects) using binary logistic regression model and subsequently computed the Mantel-Haenszel adjusted relative risk for the quintals of the propensity score.[15] Finally, to exclude the protective effect of anticoagulation on the development of arterial thrombosis, we subtracted periods of anticoagulation treatment from the follow-up period.

RESULTS

A total of 861 subjects met the inclusion criteria for this analysis (*figure 1*): 399 subjects (317 probands and 82 relatives) had experienced VTE prior to enrolment and 462 subjects (all relatives) had not. During follow-up, 21 subjects experienced an arterial cardiovascular event, of whom 12 had a history of VTE and nine did not. The median follow-up duration was three years (range: 0.1 to 7) and did not differ between subjects with and without VTE. The annual incidence rate of arterial cardiovascular events was 1.0 (95% CI 0.5 to 1.7) in subjects with previous VTE, and 0.7 (0.3 to 1.2) in those without past VTE (RR 1.5; 95% CI 0.6 to 3.6). *Table 1* shows the baseline characteristics of the two groups. Sex and age were balanced between the two groups as were classical cardiovascular risk factors except for obesity, which was more prevalent in subjects

Figure 1. *Applied selection for current analysis*

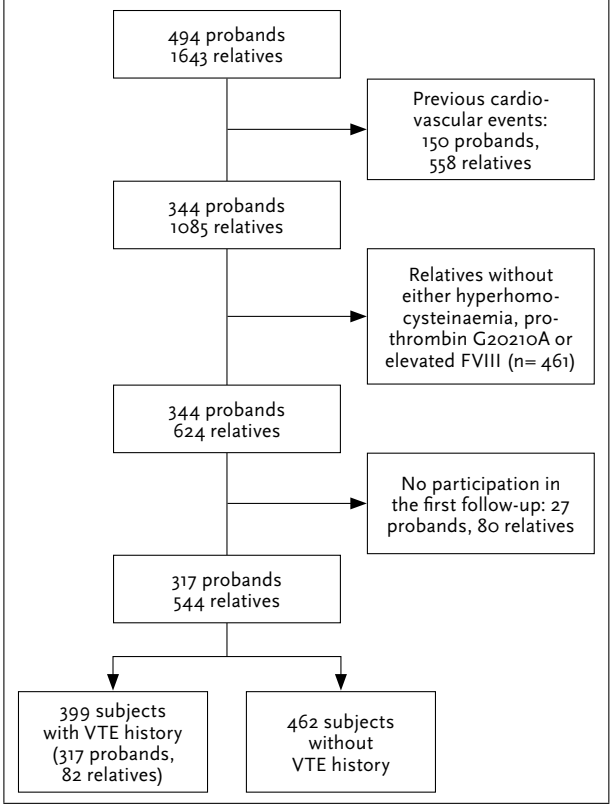

Table 1. *Baseline characteristics and number of arterial cardiovascular outcomes stratified for history of venous thromboembolism (VTE)*

	Subjects without VTE history (N=462)	Subjects with VTE history (N=399)
Sex, M/F (%)	40/60	36/64
Age, year (mean±SD)	47±17	49±16
Hypertension (%)	82 (18)	82 (21)
Hyperlipidaemia (%)	47 (10)	45 (11)
Diabetes mellitus (%)	16 (4)	15 (4)
Obesity, BMI≥30 (%)	72 (16)	86 (22)
Smoking (%)	177 (38)	132 (33)
Hyperhomocysteinaemia (%)	178 (39)	120 (30)
Prothrombin G20210A (%)	160 (35)	131 (33)
Factor VIII elevation (%)	225 (49)	232 (58)
Factor V Leiden (%)	68 (15)	97 (24)
Protein S deficiency (%)	6 (1)	13 (3)
Protein C deficiency (%)	4 (1)	6 (2)
Antithrombin deficiency (%)	1 (0.2)	8 (2)
Number of arterial cardiovascular events (N)	9	12
Number of person-years of follow-up (years)	1367	1199
Annual incidence of arterial cardiovascular events (%) (95% CI)	0.7 (0.3-1.2)	1.0 (0.5-1.7)
Relative risk of arterial thrombotic events in subjects with VTE *vs* those without (95% CI)		1.5 (0.6-3.6)

with a history of VTE (22 *vs* 16%). The thrombophilic defects that were qualified for inclusion, i.e. hyperhomocysteinaemia, prothrombin G20210A mutation and elevated levels of FVIII, were present in 30%, 33% and 58% of subjects with a history of VTE, and in 39%, 35% and 49% in the subjects without previous VTE. Overall, the prevalences of co-inherited thrombophilic defects were somewhat higher in the group with a history of VTE, i.e. 24 *vs* 15% for the FV Leiden mutation, 3 *vs* 1% for protein S deficiency, 2 *vs* 1% for protein C deficiency and 2 *vs* 0.2% for antithrombin deficiency.

Table 2 shows the distribution of cardiovascular risk factors and thrombophilic defects of the subjects who experienced arterial cardiovascular events during follow-up, stratified for a history of VTE. Adjusting the observed relative risk for arterial cardiovascular events in subjects with a history of VTE versus those without previous VTE for the presence of at least one cardiovascular risk factor and for two or more thrombophilic defects did not change the relative risk estimate (1.5; 95% CI 0.7 to 3.3 and 1.5; 0.7 to 3.3 respectively). Likewise, the adjusted relative risk for quintiles of the propensity score was 1.4 (95% CI 0.5 to 3.5). The relative risk of arterial cardiovascular events adjusted for quintiles of propensity score after subtracting periods of anticoagulation use from the follow-up was 1.7 (0.7 to 4.1).

Table 2. *Cardiovascular risk factor and thrombophilic defect distributions in subjects who developed arterial cardiovascular events stratified for venous thromboembolism (VTE) history*

	Subjects without VTE history (N=9)	Subjects with VTE history (N=12)
Sex M/ F (%)	67/33	67/33
Age, year (Mean±SD)	53±18	68±11
Hypertension (%)	1 (11)	4 (33)
Hyperlipidemia (%)	1 (11)	0 (0)
Diabetes mellitus (%)	0 (0)	1 (8)
Obesity BMI≥30 (%)	1 (11)	0 (0)
Smoking (%)	4 (44)	3 (25)
Hyperhomocysteinaemia (%)	3 (33)	3 (25)
Prothrombin G20210A (%)	4 (44)	5 (42)
Factor VIII elevation (%)	3 (33)	8 (67)
Factor V Leiden (%)	2 (22)	4 (33)
Protein S deficiency (%)	0 (0)	0 (0)
Protein C deficiency (%)	0 (0)	0 (0)
Antithrombin deficiency (%)	0 (0)	0 (0)

DISCUSSION

In this prospective analysis of subjects from three prospective family cohort studies we observed that patients with previous VTE have a 1.5 times higher risk of developing arterial cardiovascular complications than their

first-degree relatives who do not have a history of VTE. The estimated relative risk did not alter by adjusting for cardiovascular risk factors or the presence of thrombophilic defects. To our knowledge, this analysis is the first that evaluated simultaneously the effect of cardiovascular risk factors and thrombophilic defects on the risk of arterial cardiovascular complications in patients with previous VTE.

Three other cohort studies of patients with either unprovoked and provoked venous thrombosis or pulmonary embolism have also confirmed the increased risk of arterial cardiovascular complications after VTE.[6,16,17] Among which, one study adjusted the risk for age and cardiovascular risk factors where they did not notice a difference by adjustment.[16]

Our study is different from the previous ones because we included first-degree relatives of the patients with a history of VTE as the control cohort, implicitly expressing the highest possible similarity between the exposed (probands and relatives with VTE) and the control cohort for the environmental variables such as lifestyle and known and unknown genetic variables that are burdensome to adjust for and can produce residual confounding in any association under study. On the other hand, having strict inclusion criteria resulted in a small number of arterial cardiovascular complications. Hence, we could not investigate whether type of VTE (unprovoked *vs* provoked) modulates the risk of arterial cardiovascular complications. This may have led to underestimation of the observed increased risk as some but not all studies have shown that only subjects with unprovoked VTE had an increased risk of subsequent arterial cardiovascular complications.[2,3,6,17] Furthermore our results are only applicable in a highly selected cohort of thrombophilic families.

In conclusion, conventional cardiovascular risk factors and multiple thrombophilic defects do not seem to explain the mildly increased risk for arterial cardiovascular complication in subjects with a history of VTE.

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