**Title:** Preclinical atherosclerosis and other determinants of venous thromboembolism in patients with thrombophilias

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**Short title:**

Preclinical atherosclerosis and venous thromboembolism

**Summary**

At present, the supposed association between venous thromboembolism and atherosclerosis has yet to be proven. However, no data are available from patients with thrombophilias. We evaluated the association between preclinical atherosclerosis and prevalence of thromboembolic events in patients with thrombophilias.

Presence of preclinical atherosclerosis in common carotid and femoral arteries measured by ultrasound was assessed by Belcaro score (based mainly on presence of plaques) and by measurements of intima media thickness in the same location in 109 patients (43 men, mean age 41.5 ± 13 years) with established thrombophilias. Other parameters under study were age, presence of traditional cardiovascular risk factors, anthropometric and clinical data including blood pressure measurements and medication. The differences between patients with (n=47) and without (n=62) thromboembolic events were assessed by paired t-test and chi square tests.

In patients with a history of venous thromboembolism, body mass index and the prevalence of antihypertensive treatment were significantly higher than in patients without history of thromboembolism (26.5 ± 5.0 vs 24.4 ± 3.7 $kg*m^{-2}$; p=0.04, and 25.5 % vs 8.1 %; p=0.013).

No significant between-group differences were found regarding preclinical atherosclerosis. Overweight and hypertension, but not preclinical atherosclerosis, were more prevalent in patients with thrombophilias suffering from thromboembolism.

**Key words:** preclinical atherosclerosis, ultrasonography, venous thromboembolism, thrombophilia

## Introduction

Venous thromboembolism (VTE) represents one of the most common cardiovascular diseases in developed countries (Gillum *et al.* 1987, Nordström *et al.* 1992). Among the most powerful risk factors for this clinical event are thrombophilias. However, not all patients with established diagnosis of thrombophilia develop VTE (Crowther and Kelton 2003). On one hand, VTE is a potentially fatal condition and on the other hand, anticoagulation therapy is not without risk. Therefore, the detection of other factors that may help to stratify patients at risk of development of VTE is of great importance. Among most recently discussed risk factors is atherosclerosis in its preclinical form, potentially responsible for the activation of coagulation cascade and activation of platelets.

Although atherosclerosis and VTE are traditionally viewed as separate conditions, both share common characteristics. The common feature of atherosclerosis and VTE is endothelial dysfunction (Migliacci *et al.* 2007) and both atherosclerosis and VTE share common risk factors such as age, obesity, increased waist circumference and metabolic syndrome (Ageno *et al.* 2006, Ageno *et al.* 2008). In addition, it has been found that thrombophilias, such as Leiden mutation of factor V, prothrombin mutation and protein C and S deficiency, are risk factors not only for VTE but also for atherosclerosis (Rosendaal *et al.* 1997, Eitzman *et al.* 2005, Marchiori *et al.* 2007, Bank *et al.* 2004, Mahmoodi *et al.* 2008). Other proposed common risk factors for VTE and atherosclerosis include arterial hypertension, smoking, diabetes mellitus and dyslipidemia (Lowe 2008).

The hypothesis that VTE and atherosclerosis share common pathways is supported by recently published study in which the potent hypolipemic/antiatherogenic drug – rosuvastatin - significantly reduced not only clinical complications of atherosclerosis but also symptomatic VTE (Glynn *et al.* 2009). Therefore, it could be possible that atherosclerosis besides local

procoagulative action exerts systemic procoagulative activity that may contribute to thrombus formation in the distant vascular bed (Prandoni 2007).

However, other studies addressing the issue of the relation between atherosclerosis and VTE revealed controversial results. In a prospective case - control study of 299 unselected patients with deep vein thrombosis (DVT), more carotid plaques had been found in patients with unprovoked DVT compared to patients with DVT of known origin (Prandoni *et al.* 2003). In accordance with this finding, in a retrospective case – control study, more coronary calficifications were found in patients with unprovoked VTE compared to controls without VTE (Hong *et al.* 2005). In other studies, more cardiovascular events have been found in patients after VTE (Becattini *et al.* 2005, Bova *et al.* 2006, Sørensen *et al.* 2007). In contradiction with these findings, results of two population - based studies did not reveal that atherosclerosis is predictive of VTE (van der Hagen *et al.* 2006, Reich *et al.* 2006).

If patients with thrombophilias and preclinical atherosclerosis are at a higher risk for VTE has not been studied so far. We evaluated whether the presence of preclinical atherosclerosis in peripherally located arteries and other common cardiovascular risk factors are associated with VTE in patients with thrombophilias.

**Methods**

Participants of the study were patients with defined thrombophilias recruited through the department of hematology. The ethics committee of the Institute approved the study and all participants signed an informed consent.

All participants were interviewed about their medical history according to a standardized protocol. Medical history was focused on the type of thrombophilias confirmed by a hematologist. In addition, information about history of myocardial infarction, angina pectoris, transient ischemic attack, stroke, intermittent claudication, arterial revascularization, smoking, presence of diabetes mellitus, hypertension, dyslipidemia, cancer and current

medication including hormonal therapy was obtained. Body height, weight, waist circumference and blood pressure were also measured according to a standardized protocol. Body mass index was calculated as weight in kg over squared height in meters.

For statistical analyses, patients with a history of regular smoking were defined as smokers, hypertension was defined as the use of antihypertensive drugs and/or systolic blood pressure above 140 mmHg and/or diastolic blood pressure above 90 mmHg, diabetes mellitus was defined as self-reported regular use of diabetic diet and/or anti-diabetic drugs, and dyslipidemia was defined as self-reported use of lipid-lowering drugs or knowledge of higher blood lipids, also reported by the patients.

Data regarding a history of VTE, localization of venous thrombosis, the cause of the VTE and use of anticoagulant treatment were obtained from the medical records of each subject. Provoked venous thrombosis was defined if it had occurred after exposure to exogenous risk factors (immobilization including trauma or surgery, cancer, pregnancy and the use of oral steroids).

All subjects underwent bilateral ultrasound assessment of the carotid and femoral arteries by Toshiba APLIO 50 XV (Tochigi, Japan) ultrasound system with a 7.5-10 MHz linear array transducer. The carotid arteries were examined with the patient in the supine position and the neck rotated 45 degrees in the direction opposite the site being examined. The images of the common, internal and external carotid arteries were obtained at the end of diastole (onset of the R wave on the electrocardiogram). Subsequently, the femoral arteries were examined with the supine patient. The images of the common femoral arteries and their bifurcations were obtained at the end of diastole (onset of the R wave on the electrocardiogram). All arteries were scanned by transverse and longitudinal projection. The images were subsequently digitalized and read offline (using vPACS DS software, version

6.9.25, Czech Republic). Both the sonographer and the reader were blinded with regard to presence/absence of history of VTE and concomitant use of anticoagulant medications.

The presence of preclinical atherosclerosis was defined by semiquantitative classification – the Belcaro score - and by the intima-media thickness measurements. The classification was based on measurements obtained in common carotid arteries and their bifurcations and in common femoral arteries and their bifurcations. The classification by Belcaro has been described elsewhere (Belcaro *et al.* 1996). This classification evaluates the degree of preclinical atherosclerosis based on ultrasound criteria as follows:

Class I: normal - three ultrasonic layers (intima-media, adventitia, and periadventitia) clearly separated, no disruption of lumen-intima interface for at least 3.0 cm, and/or initial alterations (lumen-intima interface disruption at intervals of < 0.5 cm).

Class II: intima-media granulation, granular echogenicity of deep, normally unechoic intimal-medial layer and/or increased intima-media thickness (> 1 mm).

Class III: plaque without hemodynamic disturbance, localized wall thickening and increased density involving all ultrasonic layers, intima-media thickness > 2 mm.

Class IV: stenotic plaque, as in 3, but with hemodynamic stenosis on duplex scanning (sample volume in the center of the lumen), indicating stenosis > 50 %.

The highest value of the Belcaro score found in the arterial system (either in carotid or in femoral arteries) in each subject was used for further analyses.

Digitized images in end–diastole were used to trace the media-adventitial and intima-lumen interfaces and for calculations of mean intima media thickness in arteries under study. A mean of four measurements in the far wall of a distal (10 mm) segment of both common carotid arteries (two in the right and two in the left common carotid artery) and both common femoral arteries (two in the right and two in the left femoral artery) was used as an outcome for statistical analyses. The mean intima-media thickness used for statistical analyses thus was

the average of 8 measurements (4 from common carotid and 4 from common femoral arteries).

The variability of assessment of the highest value of the Belcaro score found in the arterial system (either in carotid or in femoral arteries) was assessed in 10 randomly chosen patients (5 men, 5 women; age 20-73 years) by two independent observers (O.A, and J.P.), who classified the Belcaro score in 1 week interval. The inter-observer variability (assessed within 1 week interval) was 2 %, with an intra-class correlation coefficient = 0.96.

The study data are presented as percentages for categorical variables and means for continuous ones. Between groups comparison of continuous variables was calculated using paired t-test; for discrete variables, a chi square test was applied, for subgroups a Fisher exact test was used. Partial correlation analyses were performed to detect variables significantly associated with VTE status after stratifying for body mass index and hypertension.

**Results**

The primary study population consisted of 134 patients. Twenty five subjects were subsequently considered as not being carriers of a thrombophilia. From those, sixteen patients had established diagnosis of isolated methylenetetrahydrofolate reductase mutations with or without hyperhomocysteinemia that were considered to be at low risk for VTE (Lijfering *et al.* 2007), and in nine subjects no laboratory defect consistent with a diagnosis of thrombophilia was confirmed. Data from resulting 109 patients (43 men, mean age 41.5 ± 13 years) were used for the final analysis. Forty seven (43.1 %) patients had a history of VTE, from these in 19 (40.4 %) the VTE was regarded as unprovoked. Characteristics of the study subjects based on the two patients´ groups divided according to the presence or absence of a history of VTE are presented in Table 1 and in Table 2. There were more subjects with homozygous mutation of the factor V Leiden in the VTE group and more subjects with

heterozygous mutation of the factor V Leiden in the non-VTE group. These differences were of borderline statistical significance, however, the overall prevalence of the factor V Leiden mutations was not different between the study groups (p=0.34). Among the study patients, six were treated with beta sympatholytics, nine with angiotensin converting enzyme inhibitors, three with angiotensin receptor blockers, eight with calcium channel blockers, one with diuretic (patient without history of VTE), and one with antihypertensive drug from other class.

A Belcaro score above I indicating the presence of preclinical atherosclerosis was found in 68.1 % of patients with a history of VTE and in 59.7 % of the patients without a history of VTE. After stratifying for body mass index and antihypertensive treatment, the trend to more prevalent preclinical atherosclerosis based on the Belcaro score in patients with the history of VTE was more pronounced but did not reach statistical significance (Table 3).

In detailed analysis, a Belcaro score I both in carotid and femoral artery was found in 31.9 % (n=15) patients with a history of VTE and in 40.3 % (n=25) patients without history of VTE. A Belcaro score II in carotid or femoral artery was found in 23.4 % (n=11) patients with a history of VTE and in 9.7 % (n=6) patients without the history of VTE. Finally, a Belcaro score III in carotid or femoral artery was found in 23.4 % (n=11) patients with a history of VTE and in 25.9 % (n=16) patients without history of VTE. These distributions were not significantly different between groups under study.

The intima media thickness in the VTE group was higher than in non-VTE group (0.577± 0.170 mm respective 0.558 ± 0.123 mm); however, this difference was of borderline significance (p-value = 0.07) (Table 2).

In a subgroup of patients with factor V Leiden mutation results did not differ from results of the whole study population (Table 4).

**Discussion**

In this study, hypertension and overweight were strongly associated with a history of VTE in patients with thrombophilias. Nevertheless, preclinical atherosclerosis expressed as a Belcaro score or intima media thickness in carotid and femoral arteries were not found to be strongly associated with the history of VTE.

Hypertension is accompanied with prothrombotic state (Remkova and Remko 2009) and it is considered to be one of possible contributors to the risk of VTE, but in different studies different results were reported. While in some studies (Hong *et al.* 2005) hypertension was significantly associated with VTE of unknown origin, this association was not confirmed by others (Tsai *et al.* 2002, Glynn and Rosner 2005). We found more prevalent antihypertensive treatment in patients with a history of VTE and this finding might be also associated with their higher body mass index.

Our study has been done in younger population than is population generally described in literature. Therefore, obesity and hypertension as potential predecessors of atherosclerosis were associated with VTE, but not preclinical atherosclerosis measured by ultrasound. This finding is supported by other published studies in older population (Prandoni *et al*. 2003, Hong *et al.* 2005). In these studies the mean age of the patients with VTE was 67 and 61 years; in contrast the mean age of the patients in our study was 43 years. An additional, to our opinion more important difference is that these studies recruited more participants from general population compared to our study, in which only patients with thrombophilias were recruited. Therefore, our study indicate, that life style modification focused on cardiovascular risk factors – based on our data mainly on the weight reduction and blood pressure - might not only prevent atherosclerotic complications but also thromboembolic events.

More than a half of the VTE cases in our study were secondary thromboses. Therefore, the lack of the association between preclinical atherosclerosis and VTE may be also explained

by a higher proportion of secondary causes in our VTE cohort compared to other studies published so far. In two published studies (Bilora *et al.* 2003, Prandoni *et al*. 2003) secondary thromboses were not associated with more prevalent atherosclerosis. In our study, 40.4 % of the cases of VTE were unprovoked, other were secondary thromboses attributable to immobilization and hormonal use.

The strength of the study is the focus on patients with well defined thrombophilias, who have not been studied so far. The limited size of the study population and the absence of control group of age-matched subjects without thrombophilias is a certain draw-back of our study. Other limitation might represent a somewhat asymmetric distribution of the subjects with factor V Leiden mutations, particularly homozygous mutation known to be a stronger risk factor for VTE than heterozygous mutation. Nevertheless, the study results did not change after the exclusion of the subjects with a homogenous mutation of factor V Leiden. Large, prospective and because of relative low number of patients with particular thrombophilias, multi-centre studies should be performed to improve the risk stratification of patients with thrombophilias and to definitely confirm the absence/presence of an association between preclinical atherosclerosis and venous thromboembolism.

In conclusion, we found obesity and hypertension to be strongly associated with a history of venous thromboembolism in patients with thrombophilias. We did not find strong association between preclinical atherosclerosis and venous thromboembolism in this group of patients.

## Conflict of Interest

There is no conflict of interest.

**Acknowledgement**

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Table 1

Prevalence of thrombophilias within the study population

Data are expressed as n (%)

| | History of venous thromboembolism n = 47 | No history of venous thromboembolism n = 62 | p ($\chi^2$ or t-test) |
|---|---|---|---|
| Factor V Leiden heterozygous mutation | 30 (68.1) | 50 (80.6) | 0.05 |
| Factor V Leiden homozygous mutation | 6 (12.8) | 2 (3.0) | 0.06 |
| Prothrombin G20210A heterozygous mutation | 8 (17.0) | 15 (24.2) | 0.36 |
| Protein C, S deficiency | 2 (4.3) | 1 (1.6) | 0.58 |
| Antithrombin deficiency | 2 (4.3) | 0 | 0.19 |
| Lupus anticoagulans antibodies | 2 (4.3) | 0 | 0.19 |
| More than 1 trombophilic state | 3 (6.4) | 6 (9.7) | 0.73 |

Table 2

Clinical characteristics of patients with thrombophilias

Data are expressed as n (%) if not stated differently

| | History of venous thromboembolism n = 47 | No history of venous thromboembolism n = 62 | p ($\chi^2$ or t-test) |
|---|---|---|---|
| Age, years (mean ± SD) | 42.9 ± 13.0 | 40.3 ± 12.9 | 0.80 |
| Male sex | 22 (46.8) | 21 (33.9) | 0.17 |
| History of cardiovascular disease | 2 (4.2) | 2 (3.2) | 1.0 |
| History of diabetes/impaired fasting glucose | 0 (0) | 2 (3.2) | 0.51 |
| Ever smoker | 17 (36.2) | 24 (38.7) | 0.92 |
| Hypolipidemic treatment | 5 (10.6) | 7 (11.3) | 0.91 |
| Antihypertensive treatment | 12 (25.5) | 5 (8.1) | 0.013 |
| Hormonal therapy (%) | 4 (8.5) | 8 (12.9) | 0.68 |
| Body height, cm, (mean ± SD) | 174.9 ± 9.2 | 173.9 ± 9.7 | 0.61 |
| Body weight, kg, (mean ± SD) | 81.6 ± 18.0 | 74.6 ± 16.3 | 0.04 |
| Waist circumference, cm, (mean ± SD) | 89.3 ± 15.0 | 84.1 ± 13.6 | 0.06 |
| Hip circumference, cm, (mean ± SD) | 103 ± 10.3 | 100 ± 9.1 | 0.12 |
| Body mass index $kg*m^{-2}$, (mean±SD) | 26.5 ± 5.0 | 24.4 ± 3.7 | 0.04 |

| | | | |
|---|---|---|---|
| Systolic blood pressure, mmHg, (mean ± SD) | 119.1 ± 14.1 | 119.8 ± 16.6 | 0.84 |
| Diastolic blood pressure, mmHg, (mean ± SD) | 73.8 ± 10.2 | 73.3 ± 9.5 | 0.78 |
| Pulse rate, n/min, (mean ± SD) | 69.4 ± 7.8 | 69.7 ± 7.6 | 0.81 |
| IMT, mm (mean ± SD) | 0.577 ± 0.170 | 0.558 ± 0.123 | 0.07 |

IMT, intima media thickness; SD, standard deviation

Table 3

Preclinical atherosclerosis expressed as Belcaro score more than 1 and associated intima media thickness values in patients with thrombophilias

| | History of venous thromboembolism | No history of venous thromboembolism | p ($\chi^2$ or t-test) |
|---|---|---|---|
| **All patients** | **n=47** | **n=62** | |
| Belcaro score more than I*, n (%) | 32 (68.1) | 37 (59.7) | 0.37 |
| IMT, mm (mean ± SD) | 0.613 ± 0.189 | 0.592 ± 0.141 | 0.17 |
| **Patients with BMI less than 30 kg*m$^{-2}$** | **n=33** | **n=59** | |
| Belcaro score more than I*, n (%) | 23 (69.7) | 34 (57.6) | 0.25 |
| IMT, mm (mean ± SD) | 0.586 ± 0.181 | 0.586 ± 0.135 | 0.97 |
| **Patients with BMI less than 30 kg*m$^{-2}$ and no antihypertensive therapy** | **n=31** | **n=55** | |
| Belcaro score more than I*, n (%) | 21 (67.7) | 30 (54.5) | 0.23 |
| IMT, mm (mean ± SD) | 0.568 ± 0.097 | 0.574 ± 0.132 | 0.59 |

*Defined as the highest value found in the arterial system (carotid or femoral).

IMT, intima media thickness; BMI, body mass index; SD, standard deviation

Table 4

Intima media thickness and preclinical atherosclerosis expressed as Belcaro score more than 1 in patients with factor V Leiden mutation

| | History of venous thromboembolism n=36 | No history of venous thromboembolism n=52 | p ($\chi^2$ or t-test) |
|---|---|---|---|
| Intima media thickness, mm (mean ± SD) | 0.574 ± 0.179 | 0.560 ± 0.109 | 0.20 |
| Belcaro score more than 1*, n (%) | 25 (69.4) | 32 (61.5) | 0.455 |

*Defined as the highest value found in the arterial system (carotid or femoral).

SD, standard deviation