

ORIGINAL ARTICLE

## An Association between Atherosclerosis and Venous Thrombosis

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### ABSTRACT

#### BACKGROUND

In about a third of patients with venous thromboembolism, the cause of the disorder is unexplained. In patients with atherosclerosis, activation of both platelets and blood coagulation and an increase in fibrin turnover are detectable, which may lead to thrombotic complications. Whether atherosclerosis is associated with an increased risk of venous thrombosis is unknown.

#### METHODS

We performed ultrasonography of the carotid arteries in 299 unselected patients who had deep venous thrombosis of the legs without symptomatic atherosclerosis and in 150 control subjects. Patients with spontaneous thrombosis, patients with secondary thrombosis from acquired risk factors, and control subjects were assessed for plaques.

#### RESULTS

At least one carotid plaque was detected in 72 of the 153 patients with spontaneous thrombosis (47.1 percent; 95 percent confidence interval, 39.1 to 55.0), 40 of the 146 with secondary thrombosis (27.4 percent; 95 percent confidence interval, 20.2 to 34.6), and 48 of the 150 control subjects (32.0 percent; 95 percent confidence interval, 24.5 to 39.5). The odds ratios for carotid plaques in patients with spontaneous thrombosis, as compared with patients with secondary thrombosis and with controls, were 2.3 (95 percent confidence interval, 1.4 to 3.7) and 1.8 (95 percent confidence interval, 1.1 to 2.9), respectively. In a multivariate analysis that accounted for risk factors for atherosclerosis, the strength of this association did not change.

#### CONCLUSIONS

There is an association between atherosclerotic disease and spontaneous venous thrombosis. Atherosclerosis may induce venous thrombosis, or the two conditions may share common risk factors.

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**V**ENOUS THROMBOEMBOLISM IS A serious and potentially fatal disease affecting approximately 2 persons per 1000 each year in Western countries.<sup>1-5</sup> Although considerable progress has been made in the diagnosis and treatment of this disorder, many questions remain concerning its pathogenesis. Classic risk factors for venous thrombosis include cancer, surgery, immobilization, fractures, paralysis, pregnancy, childbirth, and use of estrogens.<sup>6-8</sup> These conditions not only predispose apparently normal people to thrombosis but also are likely to trigger episodes in patients with prothrombotic tendencies.<sup>9</sup> Although acquired or inherited risk factors potentially responsible for this disorder are identifiable in most patients, the disease still remains unexplained in up to 30 percent of patients.<sup>6-12</sup>

We hypothesized that patients with atherosclerosis may be at increased risk for venous thrombosis. Indeed, older age (a well-known risk factor for atherosclerosis) has long been identified as an independent risk factor for venous thrombosis.<sup>1,2,6-8</sup> A few case-control and prospective studies have found an association between venous thromboembolic disorders and chronic arterial disease of the legs, hyperlipidemia, or hypertension.<sup>13-16</sup> Furthermore, atherosclerosis is associated with activation of both platelets and blood coagulation as well as an increase in fibrin turnover, which can lead to thrombotic complications.<sup>17-23</sup>

In subjects without symptomatic atherosclerosis, carotid plaques are considered a reliable marker of arterial disease elsewhere in the circulation.<sup>24-28</sup> To determine whether an association exists between asymptomatic atherosclerotic disease and the risk of venous thromboembolism, we assessed whether vessel-wall plaques were present and, if so, quantified them by means of carotid-artery ultrasonography in a consecutive series of patients with acute venous thrombosis and in a control group of subjects without thrombosis. We compared the frequency and characteristics of carotid plaques among patients with spontaneous thrombosis, patients with secondary thrombosis as a result of acquired risk factors, and control subjects without thrombosis.

## METHODS

### STUDY DESIGN AND OBJECTIVE

This was a case-control study to evaluate the potential relation between asymptomatic carotid-wall

plaques and acute spontaneous deep venous thrombosis. The protocol was approved by the institutional review board of Padua University, in Padua, Italy. All subjects provided written informed consent.

### PATIENTS

All consecutive outpatients admitted to our institution between March 1996 and April 2001 with symptomatic proximal-vein thrombosis, as assessed by compression ultrasonography, were eligible for the study. Patients with a history of either venous thromboembolism or symptomatic atherosclerosis (ischemic stroke, transient ischemic attack, acute myocardial infarction, angina, or intermittent claudication) were excluded, as were pregnant patients and those who declined to participate. All recruited patients were hospitalized and received conventional treatment (i.e., unfractionated or low-molecular-weight heparin followed by oral anticoagulant therapy).<sup>10</sup>

Patients were classified as having secondary thrombosis if they had cancer, had given birth within the previous three months, had had leg trauma or fracture, had been immobilized for more than one week, or took estrogens; all other patients were classified as having spontaneous thrombosis. Screening for mutations and conditions associated with thrombophilia (antithrombin, protein C, or protein S deficiency; factor V Leiden; prothrombin G20210A mutation; hyperhomocysteinemia; and lupus-like anticoagulants) was left to the discretion of treating physicians and was performed according to previously described methods.<sup>29-33</sup> Carriers of thrombophilia were classified as having spontaneous or secondary thrombosis according to their clinical presentation.

During the study period, 150 control subjects were randomly selected from patients who were admitted for conditions unrelated to venous thromboembolism or atherosclerosis and who had no clinical evidence or history of such diseases. As each patient with spontaneous venous thrombosis was recruited, the first patient admitted to the same room in the ward who was frequency-matched for age (in five-year age groups) and sex to the qualifying patient was selected as the control. If that patient declined to participate, the next patient admitted who met the requirements was selected as the control.

Before undergoing carotid-artery ultrasonography, patients with thrombosis and control subjects were evaluated for the presence of risk factors for

atherosclerosis.<sup>34</sup> On the basis of a clinical examination, biochemical tests, or both, data on the following variables were recorded on a standard form: smoking status, with smoking defined as habitual, daily use of 10 or more cigarettes, with interruptions of less than one month; hypertension, defined by a systolic blood pressure of more than 160 mm Hg or a diastolic blood pressure of more than 90 mm Hg (or both) on at least two occasions or by the use of hypotensive drugs; obesity, defined by a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 30; diabetes mellitus, defined by a plasma glucose level of at least 126 mg per deciliter (7.0 mmol per liter) after an overnight fast on at least two occasions or a level of at least 200 mg per deciliter (11.1 mmol per liter) 2 hours after the administration of 75 g of oral glucose and at least once between 0 and 2 hours or by the use of antidiabetic drugs; and hyperlipidemia, defined by a fasting venous cholesterol level exceeding 240 mg per deciliter (6.2 mmol per liter), or a fasting venous triglyceride level exceeding 250 mg per deciliter (2.8 mmol per liter) on at least two occasions, or by the use of lipid-lowering drugs.

#### ULTRASONOGRAPHY OF CAROTID ARTERIES

Bilateral assessment of the carotid arteries was performed by a trained operator who was unaware of the patients' clinical status. The test was carried out with an Apogee 800 Plus device (Advanced Technology Laboratories), with an 8.5-MHz probe for B-mode imaging and a 6-MHz probe for pulsed-wave color Doppler imaging according to standardized methods.<sup>35,36</sup> Patients were examined in the supine position with their neck rotated 45 degrees in the direction opposite the site being examined. The carotid trunk was identified with the use of both B-mode and pulsed-wave color Doppler ultrasonography, and the following segments were examined: common carotid artery, carotid bifurcation, and internal and external carotid arteries. All arteries underwent longitudinal and transverse scanning as well as a flow analysis.

Plaque was defined as a protrusion into the vessel lumen of at least 2 mm, as measured from the border between the adventitial and medial layers.<sup>35,36</sup> The percentage of vessel obstruction was measured along the longitudinal axis and classified as stenosis of up to 30 percent, stenosis of 31 to 50 percent, stenosis of 51 to 70 percent, or stenosis of 71 to 100 percent. When more than one plaque was found, the greatest degree of obstruction was re-

corded, as well as the number and site of associated ipsilateral and contralateral smaller lesions. In addition, the measure of the intima-media thickness of the right and left common carotid arteries was obtained 1 to 3 cm proximally to the carotid bifurcation and expressed in millimeters. The higher of the two values was recorded.

The reproducibility of the ultrasonographic assessment of carotid atherosclerosis was evaluated in 100 consecutive patients by having the test repeated by another operator within one hour after the first examination.

#### STATISTICAL ANALYSIS

The clinical characteristics of patients with thrombosis and control subjects were compared with use of the Kruskal-Wallis test for continuous variables and the chi-square test for dichotomous variables. The presence of carotid plaques in the three groups was assessed with logistic-regression analyses. Results were expressed as odds ratios with 95 percent confidence intervals. Initially, the three groups were assessed with use of a pairwise univariate comparison. Then, risk factors for atherosclerosis (age, sex, smoking status, hyperlipidemia, hypertension, obesity, and diabetes) were introduced in a multivariate model in which the three groups were included with the use of dummy variables. In analyses taking into account only the patients with thrombosis, the odds ratio for carotid atherosclerosis in patients with spontaneous thrombosis, as compared with those with secondary venous thrombosis, was adjusted for the presence or absence of thrombophilia and risk factors of atherosclerosis. Finally, the relation between spontaneous thrombosis and the presence of carotid plaques was assessed in subgroups of patients older than 60 years and older than 70 years.

The measure of the intima-media thickness of the common carotid arteries was expressed in each group as the mean  $\pm$ SD, and the analysis of variance was used to compare the study groups. Kappa statistics were used to assess interobserver variability of the ultrasonographic assessment of carotid plaques. Statistical analyses were performed with SPSS statistical software (version 9.0).

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## RESULTS

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#### STUDY POPULATION

Of 378 consecutive outpatients admitted with proximal-vein thrombosis, 76 were excluded, 33 because of previous venous thromboembolism and 43 be-

cause of symptomatic atherosclerosis. Of the remaining 302 patients, 299 provided written informed consent and were included in the study.

On the basis of the clinical presentation, 153 patients had spontaneous thrombosis and 146 had secondary thrombosis (cases associated with active cancer in 65, recent trauma or fracture in 44, recent surgery in 16, prolonged immobilization in 10, use of estrogens in 8, and recent childbirth in 3). During the study period, 150 eligible control subjects gave their consent and were enrolled in the study. They had been admitted to the hospital for the following reasons: infectious diseases in 20, cardiac causes in 18, respiratory conditions in 18, neoplastic conditions in 17, gastrointestinal causes in 16, rheumatic conditions in 15, hematologic conditions in 15, neurologic conditions in 11, hepatic disease in 8, renal disease in 7, and endocrinologic diseases in 5.

Table 1 shows the main characteristics of the study subjects as well as the prevalence of risk factors for atherosclerosis. The three study groups were similar with regard to these features. Sympto-

matic pulmonary embolism was present in 32 patients with spontaneous thrombosis (20.9 percent) and in 33 patients with secondary thrombosis (22.6 percent). Thrombophilic abnormalities were identified in 25 of the 68 patients with spontaneous thrombosis (36.8 percent) who were screened for thrombophilia and in 15 of the 64 patients with secondary thrombosis (23.4 percent) in whom this determination was made (Table 1).

**CAROTID PLAQUES**

At least one carotid plaque was detected in 72 of the 153 patients with spontaneous thrombosis (47.1 percent; 95 percent confidence interval, 39.1 to 55.0), 40 of the 146 with secondary thrombosis (27.4 percent; 95 percent confidence interval, 20.2 to 34.6), and 48 of the 150 control subjects (32.0 percent; 95 percent confidence interval, 24.5 to 39.5). In the univariate logistic-regression analysis, patients with spontaneous thrombosis were more likely to have carotid plaques than those with secondary thrombosis (odds ratio, 2.3; 95 percent confidence interval, 1.4 to 3.7) or controls (odds ratio, 1.8; 95 percent confidence interval, 1.1 to 2.9). Patients with secondary thrombosis had a risk of atherosclerotic lesions similar to that of control subjects (odds ratio, 0.8; 95 percent confidence interval, 0.5 to 1.3).

In the multivariate analysis, after taking into account risk factors for atherosclerosis, the odds ratio for carotid plaques in patients with spontaneous thrombosis as compared with those with secondary thrombosis and with controls was 2.4 (95 percent confidence interval, 1.4 to 4.0). The odds in patients with secondary thrombosis did not differ significantly from those in control subjects (odds ratio, 0.8; 95 percent confidence interval, 0.5 to 1.5).

In logistic-regression models that included only patients with venous thrombosis, the strength of the association between spontaneous thrombosis and the presence of any carotid lesions remained significant and of similar magnitude (odds ratio, 2.3; 95 percent confidence interval, 1.4 to 3.7). The value of this association did not change after adjustment for risk factors for atherosclerosis and thrombophilic abnormalities (adjusted odds ratio, 2.3; 95 percent confidence interval, 1.3 to 3.9). The association between spontaneous thrombosis and the presence of carotid plaques grew stronger with age, with an adjusted odds ratio of 3.0 (95 percent confidence interval, 1.7 to 5.4) among patients older than 60 years and an adjusted odds ratio of 3.9

**Table 1. Main Characteristics of the Study Population.\***

Characteristic	Patients with Spontaneous Thrombosis (N=153)	Patients with Secondary Thrombosis (N=146)	Control Subjects (N=150)
Age — yr	67.0±16.7	65.8±17.4	65.4±15.7
Male sex — no. (%)	71 (46.4)	65 (44.5)	68 (45.3)
Smoker — no. (%)	40 (26.1)	49 (33.6)	45 (30.0)
Hypertension — no. (%)	46 (30.1)	37 (25.3)	46 (30.7)
Hyperlipidemia — no. (%)	25 (16.3)	17 (11.6)	25 (16.7)
Obesity — no. (%)	11 (7.2)	12 (8.2)	16 (10.7)
Diabetes — no. (%)	16 (10.5)	12 (8.2)	18 (12.0)
Screened for thrombophilia — no. (%)	68 (44.4)	64 (43.8)	—
Thrombophilia — no.	25†	15‡	—

\* Plus-minus values are means ±SD. There were no significant differences among the groups.

† The causes of thrombophilia were as follows: antithrombin deficiency in 2, protein C deficiency in 1, protein S deficiency in 3, factor V Leiden alone in 10, prothrombin mutation alone in 2, hyperhomocysteinemia (homocysteine, >15 μmol per liter) alone in 4, and hyperhomocysteinemia in combination with factor V Leiden and prothrombin mutation in 2 and 1, respectively.

‡ The causes of thrombophilia were as follows: protein C deficiency in two, factor V Leiden alone in three, prothrombin mutation in one, lupus-like anticoagulants in five, hyperhomocysteinemia alone in three, and hyperhomocysteinemia in combination with factor V Leiden in one.

(95 percent confidence interval, 1.8 to 8.4) among patients older than 70 years.

#### REPRODUCIBILITY OF ULTRASONOGRAPHIC ASSESSMENTS OF CAROTID PLAQUES

The interobserver variability of the ultrasonographic assessment of carotid atherosclerosis was high ( $\kappa=0.86$ ; 95 percent confidence interval, 0.75 to 0.97).

#### ADDITIONAL OBSERVATIONS

The characteristics of the carotid plaque producing the greatest degree of obstruction are shown in Table 2. The number and location of associated smaller ipsilateral and contralateral plaques are given in Table 3.

The mean intima–media thickness of the common carotid arteries was  $1.06\pm 0.46$  mm in patients with spontaneous thrombosis,  $0.83\pm 0.32$  in those with secondary thrombosis, and  $0.88\pm 0.32$  in the control subjects. A significant difference was found between patients with spontaneous thrombosis and both those with secondary thrombosis and control subjects ( $P<0.001$ ), whereas there was no significant difference between patients with secondary thrombosis and control subjects ( $P=0.80$ ).

#### DISCUSSION

Our study demonstrates a relation between asymptomatic atherosclerotic lesions and spontaneous venous thrombosis of the legs. The prevalence of carotid plaques was significantly higher in patients with unexplained thrombotic events (47.1 percent) than in those with secondary ones (27.4 percent) or in age- and sex-matched subjects without thrombosis (32.0 percent). This association was still present after adjustment for risk factors for atherosclerosis and thrombophilic conditions. When the analysis was confined to elderly patients, the association became even stronger. In addition, other features of atherosclerosis (such as intima–media thickness of the carotid arteries, the degree of carotid stenosis, the number of plaques, the number of carotid segments involved, and the extent of contralateral carotid involvement) were far more frequent among subjects with spontaneous thrombosis than in the other two groups. Since carotid plaques represent a marker of arterial disease elsewhere in the circulation,<sup>24–28</sup> our results suggest either that atherosclerosis can induce venous thrombosis or that the two conditions share common risk factors.

**Table 2. Characteristics of the Plaque Producing the Largest Degree of Obstruction in Subjects with at Least One Plaque.**

Characteristic	Patients with Spontaneous Thrombosis (N=72)	Patients with Secondary Thrombosis (N=40)	Control Subjects (N=48)
Stenosis			
$\leq 30\%$	45 (62.5)	25 (62.5)	29 (60.4)
31–50%	22 (30.6)	13 (32.5)	14 (29.2)
51–70%	5 (6.9)	1 (2.5)	5 (10.4)
$>70\%$	0	1 (2.5)	0
Location			
Common carotid artery	5 (6.9)	2 (5.0)	3 (6.2)
Carotid bifurcation	14 (19.4)	14 (35.0)	15 (31.2)
Internal carotid artery	44 (61.1)	22 (55.0)	26 (54.2)
External carotid artery	9 (12.5)	2 (5.0)	4 (8.3)

**Table 3. Number and Location of Ipsilateral and Contralateral Minor Carotid Lesions.**

Site of Minor Lesion	Patients with Spontaneous Thrombosis (N=45)	Patients with Secondary Thrombosis (N=30)	Control Subjects (N=33)
Common carotid artery	3 (6.7)	2 (6.7)	2 (6.1)
Carotid bifurcation	7 (15.6)	6 (20.0)	7 (21.2)
Internal carotid artery	28 (62.2)	15 (50.0)	18 (54.5)
External carotid artery	7 (15.6)	7 (23.3)	6 (18.2)

Atherosclerosis is associated with activation of platelets and blood coagulation, as well as increased fibrin turnover.<sup>17–23</sup> A role of this prothrombotic state in promoting venous thrombosis is plausible, on the basis of the assumption that activated platelets and coagulation factors appear in the slow-flowing venous system. High D-dimer levels have been found to be associated with an increased risk of venous thromboembolism<sup>37,38</sup> and recurrent venous thromboembolism.<sup>39</sup> In addition, old age, arterial occlusive disease of the legs, hyperlipidemia, and hypertension have been reported to be associated with an increased risk of venous thromboembolism.<sup>1,2,13–16</sup> Finally, two recent studies have shown that, surprisingly enough, the use of statins

reduces the risk of venous thromboembolism.<sup>40,41</sup> Since users of non-statin lipid-lowering agents were not at lower risk of venous thrombosis,<sup>40</sup> the reduction in venous thromboembolism observed in statin users might be explained by the ability of statins to improve endothelial function and prevent the development and destabilization of atherosclerotic lesions.<sup>42</sup>

Hyperhomocysteinemia, factor V Leiden, and lupus anticoagulant are potential risk factors for both atherosclerosis and venous thrombosis.<sup>43-46</sup> In our study, a systematic search for these abnormalities was performed in about half the patients. These factors did not explain the observed association between spontaneous thrombosis and atherosclerotic lesions.

We investigated the relation between atherosclerosis and venous thrombosis by comparing the prevalence of carotid plaques in patients with spontaneous thrombosis and patients with secondary thrombosis. We used patients with secondary thrombosis as a comparison group because these patients have the same disease but have a probable cause of their thrombotic disorder. The prevalence of carotid lesions in patients with secondary thrombosis did not differ significantly from that in control subjects without thrombosis. Our prevalence figures are consistent with findings from several population-based studies in asymptomatic subjects conducted in the United States and European countries, including Italy.<sup>24,47</sup> Since patients with spon-

aneous venous thrombosis had a significantly higher prevalence of asymptomatic carotid plaques than did patients with secondary thrombosis or control subjects, our results suggest that there is a strong relation between atherosclerosis and venous thrombosis of the legs.

Care was taken to avoid bias. The presence of risk factors for atherosclerosis was evaluated and recorded on a standard form before carotid-artery ultrasonography was performed. Ultrasonography was performed according to accepted guidelines by a trained physician unaware of patients' clinical data. The interobserver reproducibility of the ultrasonographic assessment of carotid plaques was established in a subgroup of 100 patients and found to be high. Moreover, in the statistical analysis, adjustments were made for the confounding effects of risk factors for atherosclerosis and thrombophilic abnormalities. Finally, control subjects were randomly selected by enrolling the first patient admitted to the same room in the ward who met the frequency-matching criteria for age and sex.

Although our results do not establish a causative role of atherosclerosis in venous thromboembolism, they suggest the existence of a link between arterial and venous disorders, which opens important new avenues for further research, including the potential role of statins and antiplatelet agents as preventive interventions.

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