

Venous and Arterial Thrombosis: Is there a Link?

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ABSTRACT

Following the demonstration that patients with deep venous thrombosis of the lower extremities have a significant higher prevalence of carotid plaques than matched control individuals, numerous studies have consistently shown that patients with venous thromboembolism – especially those with events of unknown origin – have a remarkably higher risk of developing subsequent arterial thrombotic events than control subjects. The two vascular disorders share several risk factors (including age, obesity, smoking habit, diabetes mellitus, hypertension, hypertriglyceridemia, and metabolic syndrome) and the abnormal elevation of markers of endothelial dysfunction (such as microalbuminuria and the plasma levels of soluble P-selectin and von Willebrand factor). These findings have potential implications for both research and medical practice. Patients with venous thromboembolism could be examined for asymptomatic atherosclerosis, in order to modify the risk profile in those with abnormal test results. Measures could include appropriate counseling about lifestyle changes, control of risk factors for atherosclerosis and the use of drugs, such as statin and aspirin, whose effectiveness in reducing the risk not only of arterial but also of venous thrombotic disorders has recently been shown.

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INTRODUCTION

Venous and arterial thrombotic disorders have long been viewed as separate pathophysiological entities, partly because of the obvious anatomical differences, as well as their distinct clinical presentations. In particular, arterial thrombosis has long been held to be largely a phenomenon of platelet activation, whereas venous thrombosis is largely a matter of activation of the clotting system. However, there is evidence that this dichotomy is likely to be an oversimplification. Fibrin-rich thrombi form in the left atrial appendage of patients with atrial fibrillation and in the coronary artery system of patients with myocardial infarction. Accordingly, anticoagulant drugs are highly effective for prevention of arterial embolism related to atrial fibrillation^[1], and for prevention and treatment of coronary artery disease^[2]. Likewise, platelets play an inevitable role in the formation of thrombi in the venous system, and antiplatelet agents have been shown to be effective for prevention of venous thromboembolic (VTE) disorders, although to a smaller extent than anticoagulant drugs^[3,4]. As another example, subjects who sustain a retinal vein thrombosis commonly have associated cardiovascular risk factors^[5], and the causes of mortality on follow-up are usually arterial vascular events^[6].

GENERATION OF THE HYPOTHESIS

In the second half of the '90s, the author's group published the results of a prospective cohort study dealing with the long-term follow-up of a wide cohort of patients after their first episode of

both unprovoked and provoked acute deep vein thrombosis (DVT) of the lower extremities^[7]. While the predominant interest of this observation focused on the development of recurrent VTE and late post-thrombotic sequelae, we were surprised by the unexpectedly high proportion of patients who died of acute myocardial infarction, ischemic stroke or experienced a sudden otherwise inexplicable death. Although there was not a control group without thrombosis, we had the perception that this proportion would be higher than that expected in matched individual subjects free from thromboembolic disorders.

ASSOCIATION BETWEEN VTE AND ATHEROSCLEROSIS

In order to assess whether an association exists between VTE and atherosclerosis, in 1996, a prospective case-control study was initiated and its results were published in 2003^[8]. Ultrasonography of the carotid arteries was performed in 299 unselected patients with DVT without symptomatic atherosclerosis and in 150 control subjects. In a multivariate analysis taking into account risk factors for atherosclerosis, the odds ratio (OR) for carotid plaques in patients with unprovoked as compared to provoked DVT (i.e., DVT associated with active cancer, recent puerperium, trauma or fracture, prolonged immobilization or estrogens use) and controls was found to be 2.4 (95% CI, 1.4 to 4.0).

Subsequently, three studies have provided further evidence in support of the association between VTE and atherosclerosis. In a case-control study, Hong *et al* found a higher prevalence of coronary artery calcium, as assessed by chest CT scan, in patients with unprovoked VTE than in matched control individuals^[9]. In a series of almost 24 000 consecutive autopsies, Eliasson *et al* found an increased prevalence of VTE in patients with arterial thrombosis, except for those with coronary artery thrombosis^[10]. Finally, in a recent case-control study conducted on subjects older than 50 years, we assessed the prevalence of symptomatic or subclinical atherosclerosis in 100 unselected patients with unprovoked VTE, and compared it with that of 100 patients with provoked VTE and of 100 matched control individuals free from VTE disorders [11]. In patients with unprovoked VTE, the adjusted OR for symptomatic or subclinical atherosclerosis was 5.1 (95% CI, 2.0 to 13.1) in comparison to patients with provoked VTE, and 14.5 (95% CI, 5.8 to 36.3) in comparison to controls. The prevalence of atherosclerosis was higher in patients with provoked VTE than in controls (OR, 3.1; 95% CI, 1.6 to 6.1).

RISK FACTORS OF ATHEROSCLEROSIS AND VENOUS THROMBOEMBOLISM

Ageno *et al* reviewed the evidence favouring the association of the most important risk factors for atherosclerosis and VTE^[12]. After reviewing 21 case-control and cohort studies dealing with a total of 63 552 patients meeting the inclusion criteria, factors that were found to be significantly associated with an increased risk of VTE were obesity, blood hypertension, diabetes mellitus, and hypertriglyceridemia. According to the results of subsequent population-based study, abdominal obesity appears to be the pivotal risk factor among the individual components of the metabolic syndrome^[13-15].

While the review by Ageno *et al.* failed to identify smoking as an additional potential risk factor for VTE, the findings from two more recent population-based studies provided strong evidence that

this is the case^[16,17]. Interestingly enough, in a cross-sectional study a few markers of atherosclerosis (namely, male sex and arterial hypertension) were found to be independently associated also with an increased risk of recurrent VTE after a period of 3 to 6 months of vitamin K antagonist therapy for the first VTE event^[18].

NATURE OF THE ASSOCIATION

Although information coming from the above reported investigations suggests the existence of an association between VTE and atherosclerosis, it does not clarify the nature of this association. On the one hand, atherosclerosis has the potential to promote the development of thrombotic disorders in the venous system. Atherosclerosis is associated with a detectable activation of both platelets and blood coagulation as well as an increased fibrin turnover, which can lead to thrombotic complications^[19-28]. The role of this prothrombotic state in favouring venous thrombotic events is plausible given the assumption that activated platelets and coagulation factors appear in the slow-flowing venous system.

On the other hand, the two clinical conditions may share common mechanisms or risk factors. In addition, there are many examples of conditions accounting for both arterial and venous thromboembolic disorders, such as hyperhomocysteinemia, antiphospholipid antibodies, malignancies, paroxysmal nocturnal haemoglobinuria, infectious states, inflammatory bowel disease, and the use of hormonal therapy^[29].

Interestingly enough, a few markers of endothelial dysfunction have been found to be significantly higher in patients with unprovoked DVT than in matched control individuals^[30,31]. Microalbuminuria, a well know marker of endothelial dysfunction and of arterial cardiovascular events, was found to be independently associated with an increased risk for VTE as well^[32].

IS ATHEROSCLEROSIS PREDICTIVE OF VTE?

In an attempt to assess whether atherosclerotic disease predisposes to VTE, the authors of two similar population-based cohort studies carried out in the USA, the Atherosclerosis Risk in Communities and the Cardiovascular Health Study, evaluated the rate of VTE development in subjects younger and older than 65, respectively, who had carotid ultrasound and the assessment of other subclinical parameters of atherosclerosis, and were then followed-up prospectively for several years^[33,34].

In the former study, 13,081 adults aged 45-64 years underwent carotid ultrasonography to assess the intima-media thickness and the presence of atherosclerotic plaques^[33]. After adjustment for age, sex, ethnicity, body mass index and diabetes, no association was found between ultrasound parameters of subclinical atherosclerosis and VTE development after a mean follow-up of 12.5 years (adjusted hazard ratio (HR) of VTE for presence of carotid plaques, 0.97; 95% CI, 0.72 to 1.29).

In the latter study, 4108 individuals aged at least 65 years underwent non-invasive assessment of subclinical atherosclerosis using carotid ultrasound (intima-media thickness and presence of plaques), ankle-brachial blood pressure index and electrocardiogram, and then were followed-up for a median of 11.7 years^[34]. Surprisingly enough, the adjusted relative risk (RR) of overall and unprovoked VTE for presence of any type of subclinical atherosclerosis was 0.60 (95% CI, 0.39 to 0.91) and 0.32 (95% CI, 0.18 to 0.59), respectively. These unexpected findings were mostly explained by an inverse association of high-risk carotid plaques and arterial events during follow-up.

While in the former of the two above reported studies, the occurrence of cardiovascular and cerebrovascular events was significantly associated with the development of VTE^[33], in the latter the opposite was seen^[34].

In an attempt to determine the impact of cardiovascular risk factors, including family history of myocardial infarction, on the incidence of VTE, investigators from Norway extracted data from more than 21 000 subjects, aged 25-96 years, who had been enrolled in a prospective, population-based study (the Tromsø Study)^[35,36]. In multivariable analysis, family history of myocardial infarction was significantly associated not only with an increased risk of infarction but also of total VTE (HR, 1.27; 95% CI 1.01-1.60) and unprovoked VTE (HR, 1.46; 95% CI: 1.03-2.07). The risk was found to increase with increasing number of affected individuals. The association was not explained by modifiable atherosclerotic risk factors. In another population-based study, having first degree relatives with myocardial infarction before the age of 60 years was positively associated with VTE compared to participants not having a positive family history (OR 1.3; 95% CI 1.1-1.6)^[37]. Finally, in a more recent population-based study conducted in Denmark patients with a history of arterial cardiovascular events had a clearly increased relative risk of VTE events in the first three months following the index event, then the risk decreased yet remained statistically significant^[38].

Based on these findings, asymptomatic atherosclerosis is unlikely to constitute a risk factor of venous thromboembolic disorders. Whether patients developing symptomatic complications of atherosclerosis such as myocardial infarction or stroke are at a higher risk of VTE complications is controversial. A logical explanation for the difference could be that advanced atherosclerosis and complicated atheromas are frequently associated with arterial thrombosis.

IS VTE PREDICTIVE OF ARTERIAL CARDIOVASCULAR EVENTS?

Another scenario assumes that the same biological trigger is responsible for activating coagulation and inflammatory pathways in both arterial and venous thromboembolism, in such a way determining a simultaneous risk of arterial and venous thrombotic complications. This assumption is supported by the results of a cohort

study. Indeed, in an attempt to evaluate whether elevated clotting factors, which have been linked to chronic sub-clinical inflammation and arterial thromboembolic disease, have a high prevalence in patients with VTE as well, Luxembourg *et al* measured the plasma level of fibrinogen, factor VIII, and high-sensitivity C-reactive protein in a cohort of sex- and age-matched patients with unprovoked VTE, patients with provoked VTE and controls^[39]. They found that these markers of inflammation were significantly higher in patients with unprovoked compared to provoked VTE and controls, in such a way providing evidence in support of the hypothesis that VTE and arterial thromboembolism may share common risk factors.

If this is true, subjects with VTE may be at a higher risk of subsequent arterial cardiovascular events than matched control individuals. This hypothesis was tested in 11 studies^[40-50] (Table 1) and summarized in a meta-analysis^[51]. All together, the results of these studies are in keeping with the observation of a higher prevalence of carotid atherosclerosis in patients with unprovoked DVT than in matched control individuals^[8,11], and strongly suggest that patients with VTE have also an increased risk of subsequent symptomatic arterial cardiovascular events. Of particular relevance is a population-based cohort study carried out in Denmark. Using nationwide Danish medical databases, Sorensen *et al* assessed the risk of hospitalization due to myocardial infarction, stroke and transient ischemic attack among 25 199 patients with DVT, 16 925 patients with PE and 163 566 population controls discharged from the Danish hospitals in a 25-year period^[45]. Patients with both DVT and PE were found to have a substantially increased risk of myocardial infarction and stroke during the first year after the thrombotic event. For patients with DVT, the RRs varied from 1.60 for myocardial infarction (95% CI 1.35 – 1.91) to 2.19 (95% CI 1.85-2.60) for stroke. For patients with PE, the RRs were 2.60 (95% CI 2.14-3.14) for myocardial infarction and 2.93 (95% CI 2.34-3.66) for stroke. The RRs were also elevated, though less markedly, during the subsequent 20 years of follow-up, with 20 to 40% increases in risk for arterial cardiovascular events. RRs were similar for those with provoked and unprovoked DVT and PE.

Whether the risk of subsequent arterial thrombotic disorders applies to all VTE patients or to the only patients with unprovoked disease is uncertain. According to the results of a meta-analysis

Table 1 Main studies addressing the risk of arterial cardiovascular events in patients with VTE.

Ref	Study design	Study population	Number	Findings
Becattini ^[40]	Prospective cohort	Idiopathic PE Secondary PE	209 151	Idiopathic PE risk factor of arterial cardiovascular events
Prandoni ^[41]	Prospective cohort	Idiopathic VTE Secondary VTE	1,063 856	Idiopathic VTE risk factor of arterial cardiovascular events
Schulman ^[42]	Extended follow-up of the DURAC study ^[27]	VTE patients General Swedish population	897	Higher mortality from myocardial infarction or stroke in VTE patients
Bova ^[43]	Retrospective cohort	DVT patients Controls	151 151	Idiopathic VTE risk factor of arterial cardiovascular events
Young ^[44]	Prospective cohort	DVT with residual thrombosis DVT with recanalized veins	173 143	Residual thrombosis risk factor of vascular death
Sørensen ^[45]	Population-based	VTE patients Controls	42,124 163,566	VTE risk factor of myocardial infarction or stroke
Spencer ^[46]	Population-based	Idiopathic VTE Controls	6,065 12,040	Idiopathic VTE in patients aged < 40 risk factor of myocardial infarction
Klok ^[47]	Prospective cohort	PE patients Suspected PE (not confirmed)	364 334	Idiopathic PE risk factor of subsequent arterial cardiovascular events
Barsoum ^[48]	Population-based	VTE patients Controls	1311 1511	VTE not a predictor of myocardial infarction
Madridano ^[49]	International RIETE registry	VTE patients	23,370	PE-related mortality lower than mortality due to ischemic events
Pasha ^[50]	Prospective cohort	DVT patients Suspected DVT (not confirmed)	244 991	Idiopathic DVT risk factor of subsequent arterial cardiovascular events

of six studies, the risk appears higher in patients with unprovoked VTE compared to those with provoked VTE (Incidence Rate Ratio 1.86, 95% CI 1.19-2.89)^[51]. Of interest, based on recent findings the persistence of residual thrombosis, as assessed with ultrasonography three months after an episode of proximal DVT, predicts the development of arterial thrombotic disorders both in patients with unprovoked and in those with provoked DVT^[52].

IMPLICATIONS OF THE ASSOCIATION

We speculate that venous and arterial thrombosis are two aspects of the same disease (i.e., thrombosis), and that this disease may electively affect genetically predisposed individuals resulting in clinically manifestations that are, in turn, depending on a variety of elements including the age of patients, their lifestyle, and the occurrence of co-morbidities and circumstantial factors: the venous thrombotic events being more frequent, for example, after triggering risk factors such as surgery or trauma, and the arterial thrombotic events being more frequent in subjects who have developed atherosclerosis.

These findings have several implications for both research and medical practice. Patients with VTE of unknown origin could be examined for asymptomatic atherosclerosis, in order to modify aggressively the risk profile in those with abnormal test results. Measures could include appropriate counselling about lifestyle changes and control of risk factors for atherosclerosis. Interestingly enough, lifestyle factors are likely to have a major impact on the risk of VTE. A diet including greater fish, fruit, and vegetable intakes and less red and processed meat^[53], the Mediterranean diet^[54], the supplementation of vitamin E^[55], and alcohol consumption^[56,57] have recently been found to be associated with a lower incidence of venous thrombosis. Whether regular sport activity decreases this risk as well is controversial, as there data in favour^[58] and against^[59] this association. Consistent with these findings are the results of a prospective cohort study conducted in Sweden on 40 000 Swedish women who were followed-up for a mean of 11 years: women non-smokers who were physically active and who consumed alcohol in moderation were found to have a lower risk of VTE^[60]. Conversely, sedentary life was recently found to increase the risk of unprovoked PE in women^[61].

In addition, a potential role for prophylaxis of both recurrent VTE and arterial cardiovascular events with antiplatelet therapy or statins may be explored. Interest in statins has increased, given recent data that consistently suggest an unexpected role in lowering the risk of venous thromboembolism^[62-67]. As far as the role of aspirin is concerned, according to the results of recent studies, aspirin in low doses when administered for the long-term management of patients with unprovoked VTE reduces by approximately 35% the risk of recurrent VTE while offering a considerable protection against the development of arterial cardiovascular events^[68-70].

In conclusion, the separate nature of arterial and venous thrombotic disorders has been challenged. Future studies are needed to clarify the nature of this association, to assess its extent, and to evaluate its implications for clinical practice.

CONFLICT OF INTERESTS

The author have no conflicts of interest to declare.

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