

# Is there a Link Between Atherothrombosis and Deep Venous Thrombosis?

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## ABSTRACT

*Venous and arterial thromboses have traditionally been regarded as separate diseases with different causes. Clinical experience shows, that the arterial atherothrombotic disease can be associated with venous thrombotic disease, but there is insufficient evidence to prove and explain the nature of this association.*

*This review focuses on the risk factors associated with both arterial and venous thrombotic events, and recent epidemiological studies have documented an association between these vascular complications.*

*According to the results of recent studies, atherosclerosis and venous thrombosis share common risk factors, including age, obesity, cigarette smoking, and metabolic syndrome.*

*Several studies have demonstrated that subjects with idiopathic venous thrombosis have an increased risk of cardiovascular events compared with subjects with secondary thrombosis or control group. On the other hand, atherosclerosis has the potential to promote the development of thrombotic disorders in the venous system. Based on the results of population studies carried out in the United States, atherosclerosis is unlikely to constitute a risk factor for venous thrombosis. In conclusion, the separate nature of arterial and venous disorders has been challenged. Future studies are needed to clarify the nature of this association, and to evaluate its implications for clinical practice.*

**Keywords:** atherosclerosis, deep venous thrombosis, risk factor, prospective study

## INTRODUCTION

**A**rterial atherothrombotic disease (acute myocardial infarction, ischemic stroke and peripheral artery disease) and venous thromboembolism (deep venous thrombosis) are generally considered as separate entities from mechanistic and clinical points of view. While venous thrombosis has been traditionally associated with red blood cells, arterial thrombi are mainly composed of platelets, giving the appearance of white thrombs (1).

The different role played by platelets and fibrin in arterial and venous thrombosis contributes to the concept of these disease as distinct entities. The different role of antiplatelet and anticoagulant agents in the prevention and treatment of venous and arterial thromboembolism is often emphasized to reinforce the paradigm of this clear-cut distinction (2).

However, recent epidemiological studies have suggested associations between venous thromboembolism and atherothrombosis. Studies have indicated that patients with athero-

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Ref.	Study design	Study population	Number	Findings
Rumley A (5)	Prospective cohort	Men aged 60-79	3861	Age, risk factor for atherosclerosis is risk factor for DVT
Heit JA (6)	Population-base			
Jezovnik MK (7)	Case-control	Idiopathic DVT	47	Higher recurrence of idiopathic DVT in men versus women
Kyrle PA (8)		Healthy controls DVT	44	
Hansson PO (9)	Prospective cohort	Men aged > 50	855	Waist circumference and smoking are risk factors for DVT
Goldhaber SZ (10)	Prospective cohort	Women aged 30-55	112822	Obesity, hypertension and smoking are risk factors for DVT
Stein PD (11)	Population-base			
Glynn RJ (12)	Prospective cohort			
Petrauskiene V (13)	Case-control	Patients with diabetes	56	Diabetes is risk factor for DVT
Hong C (14)	Case-control	Control without diabetes	246	
		Idiopathic DVT	89	Diabetes and hypertension are risk factors for DVT
		Healthy controls	89	
Deguchi H (15)	Case-control	Males < 55 with DVT	49	Low HDL and high LDL cholesterol are risk factors for DVT
Doggen CJ (16)	Case-control	Age-matched controls	49	
		Postmenopausal women with a first venous thrombosis	477	Triglycerides are a risk factor for DVT
Vaya (17)	Case-control	Postmenopausal women	1986	Hypercholesterolemia and obesity are risk factors for DVT
		Patients with DVT	143	
		Healthy controls	194	
Marcucci R (18)	Case-control	Patients with DVT	603	Lipoprotein(a) is a risk factor for DVT
	Case-control	Healthy controls	430	
Vormittag R (19)		Patients with DVT	128	No association between lipoprotein(a) and DVT
		Healthy controls	122	
Ageno W (20)	Case-control	Patients with DVT	97	
		Healthy controls	103	Metabolic syndrome is a risk factor for DVT
Ay C (21)		Patients with DVT	116	
		Healthy controls	129	
Tsai AW (22)	Prospective cohort	Subject >45	19293	Diabetes and obesity, but not hypertension, hyperlipaemia or smoking risk factors of DVT
Glynn RJ (23)	Prospective cohort	Male physicians	18662	Obesity, but not hypertension, hypercholesterolaemia, diabetes or smoking risk factors of DVT
Sigrid K (24)	Population-base	Subject >25	27158	Smoking, hypertension, dyslipidemia and diabetes are not risk factors of DVT

**TABLE 1.** Studies that assessed the potential association between deep venous thrombosis and common risk factors of atherosclerosis.

DVT: deep venous thrombosis; HDL: high-density lipoproteins; LDL: low-density lipoproteins

sclerosis may be at increased risk of venous thromboembolism and that thrombogenic factors are involved in the development of atherosclerosis (3).

While several biological mechanisms might contribute to these associations, common risk factors for both arterial and venous thrombosis probably play the major role (4).

### Common risk factors for atherothrombosis and venous thrombosis

It is already known that atherothrombosis and deep venous thrombosis have many common risk factors.

Taken together, these data indicate that some risk factors for arterial thrombosis, such as obesity and, probably, diabetes, may also

have a role in deep venous thrombosis, while uncertainty remains for other risk factors such as smoking, hypertension and hyperlipidemia. Also, these studies do not provide data regarding the timing of occurrence of deep venous thrombosis and its nature as idiopathic or associated with temporary risk factors.

### Deep venous thrombosis predisposes to atherosclerosis?

The potential association between venous thromboembolism and atherosclerosis was described for the first time in 2003, by Prandoni et al, through a study that began in 1999 (prospective case control study) that required five years for its execution. This study demonstrates a relation between asymptomatic atherosclero-

sis lesions and deep venous thrombosis of the leg, even if the predominant interest was focused on the development of recurrent deep venous thrombosis and the postthrombotic sequelae (25).

In another study published in 2006, by Prandoni et al, a number of 1919 patients with a first episode of deep venous thrombosis, were followed up for the incidence of symptomatic arterial disease (such as: ischemic stroke, ST-elevation or non ST-elevation acute coronary syndromes, peripheral arterial disease, and systemic hypertension). After a median follow-up of about 4 years, at least one arterial event occurred in 15.1% of patients with idiopathic deep vein thrombosis when compared to 8.5% in patients with secondary deep venous thrombosis (26).

Schulman et al, by extending up to 10 years the follow-up of a large number of patients with acute deep venous thrombosis previously enrolled in the Duration of Anticoagulation (DURAC) Study, observed a mortality rate associated with myocardial infarction and stroke that was significantly higher than that expected in general population (SIR 1.28; 95% CI 1-1.56) (27).

In a case-control study, Hong et al, found a higher prevalence of coronary artery calcium, as assessed by chest computed tomography scan, in patients with idiopathic deep venous thrombosis (51.7%) than in matched control individuals (28.1%) (14).

In a cohort of 23 796 consecutive autopsies, Eliasson et al, found an increased incidence of deep venous thrombosis in patients with atherosclerosis, but not by coronary artery thrombosis (OR 0.7; 95% CI 0.6-0.8) (28).

In a population-based cohort study using nationwide Danish medical databases, Sorensen et al, (2007) assessed the risk due to myocardial infarction, stroke and transient ischemic attack among 25 199 patients with deep venous thrombosis, 16 925 patients with pulmonary embolism and 163 566 population controls. Patients with deep venous thrombosis and pulmonary embolism were found to have a substantially increased risk of myocardial infarction and stroke during the first year after the thrombotic event (29).

### Is atherosclerosis a predictive factor of deep venous thrombosis?

With the aim to assess whether or not atherosclerotic disease predisposes to deep venous thrombosis, two similar population-based cohort studies carried out in the US (the Atherosclerosis Risk in Communities and the Cardiovascular Health Study), investigated subjects younger and older than 65, respectively (30,31).

In the former study, by Reich et al, a number of 13 081 adults underwent carotid ultrasonography to assess the intima-media thickness and the presence of atherosclerotic plaques, but no association was found between ultrasound parameters of subclinical atherosclerosis and deep venous thrombosis development after a mean follow-up of 12.5 years (HR 0.97; 95% CI 0.72-1.29) (32).

In the latter study, by van der Hagen et al, 4108 individuals underwent non-invasive assessment of subclinical atherosclerosis using carotid ultrasonography, ankle-brachial blood pressure index and electrocardiography, and then were followed-up for a median of 11,7 years. Surprisingly, the adjusted risk ratio of overall and idiopathic deep venous thrombosis for the presence of any type of subclinical atherosclerosis was 0.6 (95% CI 0.39-0.91) and 0.32 (95%CI 0.18-0.59), respectively. These unexpected findings were mostly explained by an inverse association of high-risk carotid plaques and arterial events during follow-up (33,34).

Based on these findings, asymptomatic atherosclerosis is unlikely to constitute a risk factor of venous thromboembolic disorders. The results of these two recent studies do not confirm the results previously reported by Prandoni et al. (25) this inconsistency may appear difficult to explain. However, differences in the study design (case-control study versus prospective investigations), diagnosis of deep venous thrombosis (objective versus medical records), and features of the control population (in-hospital versus population-based controls) may explain the differences in the results. □

### CONCLUSIONS

These findings have several implications for medical practice. Patients with idiopathic deep venous thrombosis could be examined for asymptomatic atherosclerosis, in order to

modify aggressively the risk profile in those with abnormal test results, and is also important role of prevention of both recurrent deep venous thrombosis and arterial and cardiac events with antiplatelet therapy or statins.

In conclusion, the separate nature of arterial and venous disorders has challenged. Future

studies are needed to clarify the nature of this association, assess its extent, and evaluate its implications for clinical practice.

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