

## Clinical Focus

# Venous thromboembolism and arterial thromboembolism. Many similarities, far beyond thrombosis *per se*

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Venous and arterial thromboembolic disorders are usually considered as two distinct disease entities. At first this belief appears to be indisputable. Arterial thrombi consist mainly of platelets and are induced by arterial plaque ruptures which tend to occur at sites where shear rates are high. Conversely, venous thrombi mainly consist of red blood cells and fibrin and tend to occur at sites where the vein wall is often normal, but blood flow and shear rates are low (1). Furthermore, major, known risk factors for arterial thrombosis (e.g. tobacco smoking, arterial hypertension, diabetes, and dyslipidemia) are completely different from risk factors that are known to provoke venous thrombosis, such as trauma, surgery and cancer. However, mechanisms beyond the development of venous and arterial thrombi are far more complex and certainly have more links, such as endothelial dysfunction and inflammation. Moreover, there also remains much to be understood about risk factors of venous thrombosis, given that currently as many as 26% to 47% of all venous thromboembolic events remain classified as “unprovoked” or “idiopathic” (2).

## Evidence of the association between venous and arterial thrombosis

In the last five years, owing to the results of a number of clinical studies, the hypothesis has been made that, at least in some patients, there may actually be an association between venous and arterial thrombosis. This has opened a number of potential clinical implications. In 2003, Prandoni et al. showed that patients with spontaneous venous thromboembolism (VTE) have a significantly higher prevalence of atherosclerosis, defined by the presence of asymptomatic carotid atherosclerotic lesions, than patients with VTE secondary to known risk factors and control subjects (3). Carotid plaques were detected in 47.1% of patients in the former group and in 27.4% and 32.0%, of the patients in the two control groups, respectively. The odds ratio for carotid plaques in patients with unprovoked deep vein thrombosis (DVT) was 2.3 (95% CI, 1.4–3.7) when compared with patients

with secondary DVT, and 1.8 (95% CI, 1.1–2.9) when compared with control subjects. In a multivariate analysis that took risk factors for atherosclerosis into account, the strength of this association did not change. The association between spontaneous thrombosis and carotid plaques increased with age.

Following the results of this pivotal study, at least five studies have subsequently explored the incidence of symptomatic arterial cardiovascular events after VTE (4–8). In a prospective study on the long-term clinical outcome of patients with a first episode of pulmonary embolism (PE) (4), Becattini et al. showed a higher incidence of arterial cardiovascular events in patients affected by unprovoked PE than in those with PE associated with transient risk factors (relative risk [RR] 7.2; 95% CI, 1.71 – 30.45). Interestingly, PE was confirmed to be an independent risk factor for arterial cardiovascular events after adjusting for age and the unprovoked nature of the index event. Prandoni and colleagues assessed the incidence of fatal and non-fatal symptomatic atherosclerotic disease (including coronary heart disease, ischemic stroke, symptomatic peripheral artery disease, fatal heart failure from ischemic and/or hypertensive cardiopathy, and sudden otherwise inexplicable death) in 1,063 patients with VTE of unknown origin and in 856 patients with secondary VTE (5). After a median follow-up of 48 and 51 months, respectively, the primary end-point was detected in 15.1% of the patients with VTE of unknown origin, and in 8.5% of the patients with secondary VTE (adjusted hazard ratio [HR] 1.6; 95% CI, 1.2–2.0). When the analysis was confined to patients without previous symptomatic atherosclerosis, the hazard ratio became 1.7 (95% CI, 1.1–2.4). In the extended 10-year follow-up of the DURAC study (6), Schulman et al. found that the mortality associated with acute myocardial infarction and stroke was higher in patients with previous VTE than the mortality rate expected in the general population (standardized incidence ratio, 1.28; 95% CI, 1.00 – 1.56). In a retrospective cohort study (7), Bova et al. compared the rate of acute myocardial infarction, ischemic stroke or peripheral arterial disease in 151 consecutive patients with objectively confirmed unprovoked VTE and in 151 control subjects randomly selected from the database of two family physicians.

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During follow-up, the incidence of arterial cardiovascular events was significantly higher in patients with VTE than in controls (hazard ratio, 2.84; 95% CI, 1.11 – 7.27) and this difference remained significant after adjusting for age and other cardiovascular risk factors (hazard ratio, 2.86; 95% CI, 1.07 – 7.62). All these results were recently confirmed by the publication of a 20-year population-based cohort study using data from nationwide Danish medical databases in which the risk of subsequent myocardial infarction and stroke was assessed (8). In this study, 25,199 patients with deep venous thrombosis, 16,925 patients with pulmonary embolism, and 163,566 population controls were evaluated. Patients and controls with known cardiovascular disease were excluded. The relative risk of cardiovascular events in the first year after VTE was significantly higher in both patients with DVT (relative risk for myocardial infarction 1.60; 95% CI 1.35–1.91; relative risk for stroke 2.19; 95% CI 1.85–2.60) and in patients with PE (relative risk for myocardial infarction 2.60; 95% CI 2.14–3.14 and relative risk for stroke 2.93 95% CI 2.34–3.66) in comparison to controls and was also raised, though less markedly, during the subsequent 20 years of follow-up, with 20 to 40% increases in the risk for arterial cardiovascular events. Taken all together, these five studies appear to support the hypothesis that patients with VTE are at increased risk of subsequent symptomatic atherothrombosis. However, the true consistency of these results requires further evaluation. In fact, cases, controls, and the selected end-points of the studies are rather heterogeneous. For example, cases were represented by patients with unprovoked VTE in the studies by Becattini et al. (4), Prandoni et al. (5), and Bova et al. (7), whereas in the study by Schulman et al. (6) and in the Danish registry (8) both patients with unprovoked and provoked events were included. Controls were represented by patients with provoked VTE in the first two studies (4, 5), and by heterogeneous populations without VTE in the latter three studies (6–8). Finally, end-points included cardiovascular mortality only (6), major cardiovascular events (4, 8), or a combination of different arterial disorders, including peripheral vascular disease (5, 7), and hypertensive cardiopathy (5).

If patients with VTE, in particular patients with unprovoked VTE, appear to be at increased risk of subsequent cardiovascular events, there is currently no evidence to support that patients with atherosclerotic lesions are at increased risk of subsequent VTE. In the Atherosclerosis Risk in Communities study (9), 13,081 adults aged 45–64 years underwent carotid ultrasonography to assess the intima-media thickness and the presence of atherosclerotic plaques. After a mean follow-up of 12.5 years, patients with subclinical atherosclerosis did not have an increased risk of VTE as compared to patients without (adjusted hazard ratio 0.97; 95% CI, 0.72 – 1.29). In the Cardiovascular Health Study (10), subclinical atherosclerosis was non-invasively evaluated in 4,108 patients aged at least 65 years using carotid ultrasound (intima-media thickness and presence of plaques), ankle-brachial blood pressure index and electrocardiogram. After a median of 11.7 years, the presence of subclinical atherosclerosis was associated with a lower risk of overall or unprovoked VTE (adjusted relative risk 0.60; 95% CI, 0.39 – 0.91). The authors of both studies concluded that their findings are in contrast with those of the case-control study published by Prandoni et al. (3). However, the use of antiplatelet or other anti-thrombotic therapies was not assessed in

these studies and an increased use of these drugs in patients with subclinical atherosclerosis may have contributed to these negative findings. Finally, in a retrospective case-control study Hong et al. found a higher incidence of coronary artery calcium on pulmonary computed tomography angiographic images in 89 randomly selected VTE patients (51.7%) in comparison to 89 patients without VTE (28.1%), matched for gender and age (11). This association remained significant after multivariate analysis (OR, 4.3; 95% CI, 1.9 – 10.1).

## Evidence of the association between cardiovascular risk factors and venous thrombosis

Thus, there is currently some clinical evidence that indicates an association between venous and arterial thrombosis. This evidence obviously challenges the common view that the etiology of VTE differs from that of atherosclerotic cardiovascular disease. Indeed, both arterial disease and VTE are multi-factorial disorders, whose risks increase exponentially over the duration of life, and that are associated with multiple interacting genetic and environmental risk factors (12, 13). But what common risk factors are there between venous and arterial disorders which may place some patients at increased risk for both diseases? We know that some thrombophilic abnormalities, including antiphospholipid syndrome and hyperhomocysteinemia, may predispose to both venous and arterial events (14–17). Among traditional cardiovascular risk factors, only obesity and age have consistently been demonstrated to be independent risk factors also for venous thromboembolic events (18, 19). However, a few observational studies have also reported a positive association between diabetes and deep vein thrombosis (20), arterial hypertension and the risk of PE (21) and dyslipidemia and VTE (22–24). Elevated levels of triglycerides and low high-density lipoprotein (HDL) were also found to increase the risk of VTE, whereas increased HDL levels may protect against VTE (22–24). Finally, in a recent case-control study (25), we observed a significantly higher prevalence of the metabolic syndrome, a cluster of cardiovascular risk factors associated with an increased risk of cardiovascular disease and mortality, in patients with unprovoked deep vein thrombosis than in patients with secondary deep vein thrombosis and in controls without VTE. These results were subsequently confirmed in a study performed by Ay et al. in which the metabolic syndrome was found to be significantly associated with recurrent VTE (26).

To further assess the strength of the evidence supporting the association between cardiovascular risk factors and VTE, we recently carried out a systematic review of the literature and a meta-analysis (27). The prevalence of five major established risk factors for atherosclerosis (obesity, arterial hypertension, diabetes mellitus, smoking and dyslipidemia) was compared in patients with VTE and in controls based on the data ascertained from 21 selected case-control and cohort studies including a total of 63,552 patients. The results of this meta-analysis support the hypothesis that some major risk factors for atherothrombotic disease are also significantly associated with VTE. Compared with control subjects, the odds ratio for VTE was 2.33 for obesity (95% CI, 1.68 – 3.24), 1.51 for hypertension (95% CI, 1.23 –

1.85), and 1.42 for diabetes mellitus (95% CI, 1.12 – 1.77). We did not find a significant association between smoking and VTE (1.18; 95% CI, 0.95 – 1.46), although this finding may be explained by the small number of VTE events (less than 1000) reported in the selected studies. In a more recent, large population-based case-control study (the MEGA study), 3,989 patients with VTE (after the exclusion of those with known malignancies) were compared for smoking habit with 4,900 controls (28). The relative risk of VTE was 1.42 (95% CI 1.28–1.58) in current smokers, and 1.23 (1.10–1.37) in ex-smokers, compared to those who had never smoked. Those who smoked most or longest had the highest relative risk 4.30 (2.95–7.14), thus suggesting a dose-dependent and reversible association of smoking habit with the risk of VTE.

In our meta-analysis, hypercholesterolemia was not associated with an increased risk of VTE (odds ratio 1.16; 95% CI, 0.67 – 2.02), but we found that the weighted mean in high-density lipoprotein cholesterol levels was significantly lower in VTE patients than in controls (- 2.86 mg/dl, 95% CI from - 4.34 to - 1.38,  $p < 0.05$ ). Likewise, triglyceride levels were on average 21.0 mg/dl (95% CI 10.0–31.0) higher in patients with VTE than in controls. Finally, no significant difference was observed for low-density lipoprotein cholesterol levels in the two groups although the small number of included studies did not allow any meaningful conclusion.

Whilst such a meta-analytical approach has a number of intrinsic limitations that need to be taken into account, and although we found a significant heterogeneity among studies for

all variables apart from diabetes, these results are important because if confirmed by properly designed clinical trials they have the potential to be clinically relevant and they may open new perspectives in the management of patients with VTE. Clinical relevance is supported by the assumption that although estimated odds ratios for these variables were less robust than those reported for established major risk factors for VTE, such as cancer or surgery, cardiovascular risk factors are far more common, often coexist and, as is well known for atherosclerotic disorders, their coexistence is associated with an additive causative effect. Furthermore, there is a good biological plausibility to explain such potential association. Both obesity and diabetes are known to predispose patients to hypercoagulable and inflammatory states, hypertension may induce endothelial dysfunction, and dyslipidemia is also associated with hypercoagulability and endothelial dysfunction. All such effects, in particular when combined, may induce a prothrombotic effect that could also predispose patients to an increased risk of venous thrombosis. This association might in particular help us to explain the pathogenesis of those VTE events that remain currently classified as idiopathic. Should this association be confirmed, recognition of cardiovascular risk factors in patients with VTE may support new strategies for both primary prevention of cardiovascular disease and for secondary prevention of VTE. In particular, the role of weight loss, anti-platelet and lipid lowering therapy will need to be specifically assessed. Further studies are warranted in order to explore other common links, such as genetic risk factors between cardiovascular disease and VTE.

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