

Arterial and venous thrombosis: more in common than previously thought

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Traditionally, arterial and venous thrombotic disease are regarded as separate disease entities. Indeed, the clinical manifestation of each of these types of thrombosis is quite different. Arterial thrombosis usually leads to obstruction of organ perfusion with resulting tissue ischaemia and necrosis and subsequent organ dysfunction, whereas venous thrombosis is merely associated with congestion and consequent symptoms, such as swelling or pain. There only seems to be a connection between the two diseases when venous thrombi switch from the venous to the arterial side (as occurs in case of pulmonary embolism). Interestingly, the two types of thrombosis are also usually seen by different medical professionals, whereby arterial thrombotic complications are usually taken care of by the specialist who handles the threatened end-organ (i.e. cardiologists, neurologists, etc.) in contrast to venous thromboembolism, which is most often covered by internists, sometimes specialised in haematology or vascular medicine. The separation between arterial and venous thrombosis is further accentuated by very different insights into pathogenesis, whereby arterial thrombosis is regarded as a result of vascular damage, platelet-vessel wall interaction, and high shear stress, and venous thrombosis may result from immobilisation, changes in blood composition, and (surgical) trauma.¹ However, recent studies point to the fact that arterial and venous thrombosis have more in common than previously thought. There is increasing evidence that there is a link between arterial atherothrombotic disease and venous thrombosis, as these two conditions occur in similar patients and share common risk factors, such as age and obesity. Prandoni *et al.* were the first to demonstrate a higher prevalence of subclinical atherosclerosis in patients with previous idiopathic venous thromboembolism (VTE) in 2003 and in patients with previous VTE an increased risk of arterial cardiovascular complications has been consistently shown.²⁻⁴ Vice-versa, large population-based studies demonstrated that the presence of thrombophilia (known to increase the risk of venous thromboembolism)

also increased the risk of atherothrombosis, albeit to a modest extent.^{5,6} A recent study showed that microalbuminuria, traditionally seen as a risk factor for atherothrombotic disease, was associated with a higher risk of venous thromboembolism.⁷ Conversely, patients with haemophilia were shown to have less extensive atherosclerosis as compared with controls.⁸ Importantly, interventions aimed at reducing atherothrombotic events in a high-risk population by means of the administration of statins were also effective in preventing venous thromboembolism. This study was the first to show this effect of statins and the results were obtained in the setting of a large prospective trial with a strong study design. It should be mentioned, however, that despite a significant 43% reduction in venous thromboembolism in patients using a statin, the absolute risk reduction was quite modest. In fact, over a median two-year follow-up the absolute incidence of thrombosis was 3.8 per 1000 in the statin group as compared with 6.7 per 1000 in the placebo group, which means that 342 patients should be treated with statins over a two-year period to prevent one venous thromboembolic event. However, it would be interesting to see whether this beneficial effect of statins would be confirmed in a population with a higher risk of venous thrombosis, such as in patients with a previous episode of venous thromboembolism. Prospective evaluation of this question and validation of the previous results are planned in a large Dutch multicentre study.

Further insight into the link between arterial and venous thrombosis is provided by the interesting study by Roshani *et al.* in this issue of the Netherlands Journal of Medicine.⁹ The authors studied whether patients with prior venous thromboembolism had a higher risk of arterial cardiovascular complications. They recruited 861 subjects from families in which patients experienced venous thromboembolism or arterial thrombosis before the age of 50 years. The authors show that there is a mildly elevated risk of arterial cardiovascular complications in patients with prior venous thromboembolism; however,

this cannot be ascribed to the presence of risk factors for arterial cardiovascular disease or thrombophilic defects. Hence, based on these observations, traditional risk factors cannot be held responsible for the link between arterial and thrombotic disease.

A common pathogenesis for venous and arterial thrombosis cannot easily be found along the lines of established mechanisms of disease. New pathogenetic pathways need to be identified that may better explain this connection. One of these potential mechanisms that links arterial and venous thromboembolism may be mediated by inflammation-induced effects on the vessel wall, which appear to be important in both the pathogenesis of atherosclerosis and venous thromboembolism.¹⁰ Inflammation is a known risk factor for venous thrombosis, either by changes in blood composition rendering it hypercoagulable, or by direct effects on the vessel wall. Simultaneously, the involvement of inflammation in the pathogenesis of atherosclerosis and arterial thrombosis becomes increasingly clear from recent studies. Interestingly, it seems that these effects are indeed modified by the use of statins, which then may explain the statin effect on venous thromboembolism.

What does this notion of a more close relationship between arterial and venous thrombosis mean for individual patients? A more integral approach in (secondary) prevention of thrombotic events may be warranted. Also, (pharmaceutical) preventive strategies could possibly be more integrated. Obviously, statins cannot be considered as adequate prophylaxis for venous thrombosis if this is indicated, although patients who have an indication for statin treatment may benefit from the additional (albeit modest) lowering of the risk of venous thromboembolism.¹¹ Similarly, aspirin cannot be considered adequate prophylaxis for venous thrombosis; however, large studies point to some (additional) benefit for patients with (risk of) venous thromboembolism.¹²

The days of a clear separation between arterial and venous thrombosis seem to be over. In the next years we will have to find out how this insight can be translated into better strategies to prevent or treat both arterial and venous thrombosis.

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