Arterial and venous thromboembolic diseases have historically been viewed as separate pathophysiological entities until recently, partly as a result of the obvious anatomical differences and divisions of the arterial and venous systems, as well as their separate, distinct clinical presentations. However, it has become increasingly clear that this dichotomy of vascular disease is over simplistic and probably hinders rather than promotes our understanding of the underlying pathogenesis of the condition.

Indeed, some generalisations are often readily made by the uninitiated. Agreed, venous thromboembolic disease is predominantly fibrin-rich clot (‘red clot’), related to stasis or venous wall damage in deep veins, and embolising to the pulmonary vasculature; thus, ‘venous clots’ respond well to anticoagulation therapy. In contrast, arterial thrombus within the coronary or peripheral artery is considered predominantly platelet-rich clot (‘white clot’) and in this ‘high flow’ arterial system, antiplatelet therapies are beneficial, for example, in the setting of acute coronary syndromes (ACS). As always, these generalisations can be overtly misleading. In atrial fibrillation (AF), which is a common and important cause of intracardiac thrombus – resulting in stroke and systemic (arterial) thromboembolism – stasis within the left atrial appendage and a preponderance of coagulation abnormalities results in fibrin-rich thrombus (‘red clot’) formation (1). Hence, the superiority of anticoagulation as thromboprophylaxis in AF and in keeping with the observation that the benefit of antiplatelet therapy in AF is not much beyond what would be expected from the effect of co-existent vascular disease. Similarly, anticoagulation can sometimes be complementary or an alternative to antiplatelet therapy in ACS (2). As another example, subjects who sustain a retinal vein thrombosis commonly have associated cardiovascular risk factors and the causes of mortality on follow-up are usually arterial vascular events, such as myocardial infarction and stroke (3).

Perhaps an appreciation of the underlying prothrombotic mechanisms may improve our understanding of the common pathophysiological features with both venous and arterial thromboembolism. With arterial disease, the processes of endothelial damage/dysfunction, inflammation and thrombogenesis (with coagulation/platelet abnormalities) are well-recognised, resulting in the dynamic, progressive disease of atherothrombotic disease (4). Indeed, thrombogenesis and atherogenesis are closely related. Compared to arterial thrombosis, the pathogenesis of venous thromboembolism (VTE) is probably less well understood, where the classic risk factors (such as malignancy, pregnancy, oestrogen use, immobilization) are absent. As atherosclerosis is known to involve platelet and coagulation activation, as well as fibrin turnover, it is not unreasonable to suggest that a plausible pathophysiological link exists between VTE and atherosclerosis. This notion is given further credence as both conditions have many risk factors in common, including older age, obesity, diabetes mellitus, hyperlipidaemia and hypertension (5).

In this issue of *Thrombosis and Haemostasis*, Bova et al. (see pages 132-6) explore the potential association between idopathic VTE and adverse arterial events. Their choice of idopathic VTE is significant, as it represents 25%-50% of all VTEs (7). Their case-control study is well-designed, with the patient and control groups being evenly-matched for number and gender, as well as known arteriovenous disease risk factors, whilst follow-up was prospective and lasted an average of 40 months. Bova et al. (6) conclude that there is a higher risk of adverse cardiovascular outcomes in idopathic VTE patients (HR:2.84; 95% CI:1.11–7.27; p=0.03), compared to the control population. Of note, all VTE patients were treated with anticoagulation for approximately 13.9 months, thereby further reducing the risk of cardiovascular adverse events, such as ischaemic stroke and myocardial infarction.

Their findings are in keeping with their previous report (8), where the risk of atherosclerosis (as defined by carotid ultrasonography) was higher in spontaneous (idopathic) VTE when compared to secondary VTE patients (OR:2.3; 95%CI:1.4–3.7) or controls (OR: 1.8; 95%CI: 1.1–2.9). However, the obvious limitations of a cross-sectional analysis apply, and such a study design reveals associations rather than causality. Also, statistical
adjuncts are unlikely to fully account for all biological and pathophysiological processes. On a practical note, a considerable proportion of patients presenting with idiopathic VTE will ultimately reveal occult malignancy at follow-up, and this should be borne in mind when treating such patients (7).

How might atherosclerosis per se contribute directly or indirectly to risk of VTE? Presumably, this would involve activation of clotting pathways, perhaps induced by the presence of released factors from atherosclerotic plaques. Indeed, cells present in atherosclerotic plaques (such as macrophages, monocytes, endothelial cells) release factors such as tissue factor, IL-6, IL-8 and tumour necrosis factor (9–11), and these very same inflammatory plasma markers are abnormally raised in VTE patients (12, 13), although this could well be a response rather than a cause of VTE. Other abnormalities exist in blood constituents common to related artery-vein abnormalities, with similar abnormalities in plasma viscosity, haematocrit, haemoglobin, plasma fibrinogen, PAI, fibrin D-dimer and serum Lp(a) being present in patients with retinal vein occlusion and retinal artery occlusion (14). Interestingly, statin therapy has been shown to reduce the risk of VTE in patients with atherosclerosis, which is perhaps a reflection of their ‘stabilising’ effect on the endothelium, as well as their putative antithrombotic effects (15).

Does arterial and venous thrombosis have a common origin in abnormalities of various blood constituents? Instead of a ‘cause and effect’ scenario, a more likely one assumes that the same ‘biological trigger’ is responsible for activating coagulation and inflammatory pathways in both arterial and venous thromboembolism. This would be in keeping with elevated inflammatory mediators in both conditions, as well as the increased risk of cardiovascular events in idiopathic VTE patients. As research continues in the attempt to decipher the vagaries of atherothrombotic disease, a more immediate consideration is the clinical impact of such an association. Potentially, patients with idiopathic VTE should undergo long-term or even, indefinite anti-coagulation, as prophylaxis against future cardiovascular events. Alternatively, extended treatment with anti-platelet agents might well be the answer, as would adjunct statin therapy, with similar risk-benefit considerations.

With their study, Bova et al. (6) continue to challenge the common assumption of the separate nature of arterial and venous disorders, and by doing so, will stimulate further research two-fold: firstly, the need for prospective clinical trials to positively confirm an increased risk with a view to treat prophylactically, and secondly, research to precisely determine a pathophysiological relationship, allowing for novel treatment avenues. Despite the considerable advances in understanding and treating these diseases, it is sobering to realise that there continues to be a great need for further medical development, made all the more pertinent in the context of an ageing population, as the incidence of atherothrombotic disease continues to rise.

References