Can venous thromboembolism navigate the prevention of cardiovascular complications?

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Traditionally venous and arterial thrombosis has been viewed as two separate pathophysiological and clinical entities. It is widely accepted that venous thrombi are "red thrombi" being predominantly formed from red blood cells and fibrin (1). "Red thrombi" usually develop in areas with slow blood flow, such as veins or left atrial appendage of patients with atrial fibrillation. Consequently anticoagulant agents are highly effective for prevention of embolism secondary to venous thrombosis or atrial fibrillation (2-4). Although anticoagulants could exert some beneficial effect in arterial thrombosis (e.g., in patients with ischemic heart disease) they have not become a routine part of management of such patients (5).

In contrast arterial thrombi tend to be "white thrombi" with their content largely contributed by aggregated platelets with relatively little fibrin or red cells (1). Arterial thrombi usually develop in areas of high shear stress, which are more prone to endothelial damage, such as stenotic arteries. These distinct roles of fibrin and platelets in the formation of venous and arterial thrombosis, as well as clinical presentations have resulted to a "separation" of these two clinical conditions. Do they have anything in common?

The clear-cut distinction between the pathological states leading to arterial or venous thrombosis is likely to be an oversimplification. Over the last decade emerging data indicate that it is not uncommon for those two types of thrombosis to occur in the same patients within a short period of time.

An association between venous thromboembolism and atherosclerosis has been suggested about a decade ago. Of interest, the venous thrombosis and atherosclerosis (i.e., the leading cause of arterial thrombosis) share a number of common risk factors including obesity, cigarette smoking, and hypertension (6-10). The same is true for the feared complication of the venous thrombosis, venous thromboembolism. A well powered meta-analysis by Ageno *et al.* that included 21 case-control and cohort studies with a total of 63,552 participants has unambiguously confirmed increased body mass index, hypertension and diabetes mellitus as principle factors associated with venous thromboembolism [odds ratio (OR) =2.33; 95% confidence interval (CI), 1.68-3.24 for obesity; OR =1.51; 95% CI, 1.23-1.85 for hypertension, and OR =1.42; 95% CI, 1.12-1.77 for diabetes] (11).

More recently, several epidemiological studies have suggested a link between metabolic syndrome, a recognized risk factor for cardiac events, and increased rates of venous thromboembolism (12-15). Furthermore, increased levels of proatherogenic lipoprotein(a) have been recently reported to be independently predictive for idiopathic venous thromboembolism (16). Although the nature of these associations is not always clear common risk factors definitely play a role in both types of thrombosis (6). The common pathogenic mechanisms identified thus far include activation of endothelium, platelets and leukocytes that lead to endothelial dysfunction and thrombogenesis in both arteries and veins (6).

Considering these biological mechanisms and given that arterial and venous thrombosis are complex and multifactorial disorders, it is unsurprising that they share more common risk factors than has thus far been recognized (1). Advanced age, a major risk factor for atherothrombosis, is also a powerful predictor for thrombi generation within the venous system (17). The increase in life expectancy, observed in

developed countries has been largely achieved by reduction in atherothrombotic events (18-20). As the result more and more people with prevented (or merely postponed) coronary and cerebrovascular events survive to the life phase of limited mobility, a major contributor to deep vein thrombosis and venous thromboembolism. Under these circumstances the combination of venous and arterial thrombotic events becomes rather expected (21,22).

Emerging data show that pathogenesis of both types of thrombosis has multiple similarities at cellular and molecular levels. Despite the somewhat artificial subdivision into "red" and "white" clits thrombosis in both part of the vascular bed is accompanied by activation of blood coagulation and platelets.

Subsequently, several studies have provided further insights into this topic. Analysis of epidemiological data has shown that patients with atherosclerosis are not only at higher risk of venous thromboembolism, but reciprocally prothrombotic factors are implicated in atherogenesis (23). Indeed, a retrospective case-control study has reported higher prevalence of coronary artery calcification in subjects with unprovoked venous thromboembolism (52%) compared to venous thromboembolism-free matched volunteers (28%) (8).

However, the data supporting the link between atherosclerosis and venous thromboembolism are not entirely consistent (24,25). A cross-sectional analysis of 23,796 autopsies had inconclusive results (26). The study found increased incidence of deep venous thrombosis in patients with cervico-cranial artery and peripheral artery thrombosis (OR adjusted for gender and age 1.4; 95% CI, 1.3-1.5) whilst opposite trend was seen regarding the coronary artery thrombosis (OR =0.8; 95% CI, 0.7-1.0). The discrepancy may at least partly depend on etiology of the venous thrombosis in patients included in a study. In a large case-control study with 5-year follow up, patients with unprovoked venous thromboembolism had a higher prevalence of asymptomatic carotid atherosclerosis (47.1%) than did patients with secondary thrombosis (27.4%) and age-matched and sex-matched hospital controls (32.0%) without venous thrombosis (27). These observations are supported by Becattini *et al.* who performed a systematic review and meta-analysis of arterial cardiovascular events after venous thromboembolism, which included 6 studies (n=104,141 patients) (28). The analysis showed that the risk of arterial cardiovascular events was increased in subjects with unprovoked venous thromboembolism *vs.* venous thromboembolism-free controls for both unprovoked venous thromboembolism (incidence rate ratio =1.87; 95% CI, 1.32-2.65) and provoked venous thromboembolism (incidence rate ratio =1.86; 95% CI, 1.19-2.89).

Most of the published evidence that associate atherosclerosis with increased risk of venous thrombosis derives from clinic-based studies within large referral centers and have with few outcome events (29-32). However, these data were confirmed by a large nationwide population-based study from Denmark showing the patients with venous thromboembolism are at higher risk of cardiovascular events comprised of combination of myocardial infarction, stroke and transient ischemic attack compared with general population. Of interest the maximal excess risk was noted within the first year after the venous thrombotic events perhaps indicating the common pathophysiological background, rather than simple aging playing the role. However, the relationship persisted for decades thus suggesting that the presence of a low intensity chronic process was present in venous thromboembolism and thus predisposing the arterial complications. The fact the relative risks of arterial events were similarly high in subjects with provoked and unprovoked venous thromboembolism confirms hypothesis that predisposing factors for venous thrombosis (e.g., those defined by Virchow's triad) lead to systemic disturbances (e.g., inflammation and endothelial dysfunction) predisposing to arterial complications (33).

Nonetheless, the magnitude of impact of venous thromboembolism for risk of major arterial cardiovascular events although statistically significant may not be necessarily very high. For example, extended 10-year follow-up of the DURAC study found the excess in mortality secondary to myocardial infarction and stroke in patients with previous venous thromboembolism was of borderline significance compared to the general population (standardized incidence ratio 1.28; 95% CI, 1.00-1.56) (31).

The study by Katz *et al.* (34) reported in a recent issue of the *American Journal of Medicine* expands the evidence for an association between venous thrombosis with cardiovascular events, by providing prospective data from a randomized clinical trial settings with a large sample size. The study was done in a population of patients with impaired glucose tolerance who have high risk for cardiovascular events showing benefits from a prolonged 5-year follow up with analysis based on hard events (i.e., death, myocardial infarction, and stroke). The study shows that subjects with history of venous thromboembolism are at almost 2-fold higher risk of cardiovascular events compared those with no

prior history of venous thromboembolism.

The findings reported by Katz *et al.* (34) have important clinical implication. Firstly, they indicate that patients with venous thromboembolism should be assessed for presence of atherosclerotic changes, particularly in the heart. However, the analysis provides limited information on symptomatic status of venous thromboembolism in patients who also experienced cardiovascular event. However 'silent' ischemia is not uncommon, particularly in patients with diabetes and low threshold should be employed for non-invasive ischemia testing in patients with unprovoked venous thromboembolism.

Although not yet specifically tested in clinical trials it appears reasonable to ensure more "aggressive" management of cardiovascular risk factors in patients with spontaneous venous thrombosis. This approach has potential to prevent arterial thrombotic events, but also to reduce risk of venous thromboembolism recurrence as many risk factors are shared by both conditions. This is particularly relevant for adequate management of hypertension and diabetes. Every effort should be made to achieve and maintain "healthy" weight. In this view it is important to provide adequate counseling about lifestyle changes and where appropriate pharmaceutical support (e.g., antihypertensive and glucose lowering agents and statins).

The optimal antithrombotic management in those people remains to be established (35). With recent introduction of non-vitamin K oral anticoagulants (NOACs) with favorable antithrombotic efficacy and safety profile the role of longer-term oral anticoagulation and possibly its combination with antiplatelet agents in venous thromboembolism survivors may need to be re-considered in the future, to have an impact on atherothrombotic events. Nonetheless, we need to remember that VKAs have protective effects against cardiac ischaemic events, and that combination therapy with any anticoagulant and antiplatelet confers an increase in serious bleeding risks (especially intracranial haemorrhage) (36,37). Also, we now recognize that the maximal efficacy and safety with VKA use requires a high percentage time in therapeutic range (e.g., >70%) as recommended in guidelines and position documents (38-40).

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