Literature Review

Arterial and venous thrombosis: shared risk factors and pathophysiology

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Introduction

Thrombosis is a common pathology underlying ischemic heart disease, ischemic stroke, and venous thromboembolism (VTE). It is a major contributor to the global disease burden and a leading cause of mortality, being responsible for approximately one in four deaths worldwide.[1] Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two expressions of the same disease and are collectively called VTE. Venous thrombosis is traditionally associated with red blood cell and fibrin-richred clot formed under low flow-rate conditions, whereas arterial thrombi, formed at higher flow rates, are rich in platelets, often giving the appearance of white clot. This simple but dogmatic concept has had important therapeutic implications over the past decades, with anticoagulant therapy considered the treatment of choice for the management and prevention of venous thrombosis, whereas antiplatelet therapy is the cornerstone for the treatment and prevention of arterial thrombosis. In addition, major risk factors for arterial thrombosis (e.g. tobacco smoking, blood pressure and cholesterol) are contrasted with major risk factors for venous thrombosis (e.g. trauma, surgery and cancer). However, the concept that VTE and arterial thrombosis are two completely distinct entities has recently been challenged.

Are arterial thrombosis and venous thrombosis associated?

Recent studies have reported on the coexistence of venous and arterial thrombotic events with a 2 to 3 fold risk of ischemic events among subjects with VTE in the prior year, compared to those that did not have a VTE. Risk of ischemic events was particularly elevated in those that had unprovoked VTE or PE. In the largest of these studies, Sorensen et al compared retrospectively the risks of myocardial infarction (MI) and stroke in 25,199 patients with DVT, 16,925 patients with PE and 163,566 population 'controls', using nationwide Danish medical databases.[2] Patients with baseline hypertension, coronary heart disease (CHD), stroke or transient cerebral ischemic attack were excluded. Compared to population controls, patients with VTE had a substantially increased risk of MI and stroke during the first year after the VTE event. Patients with DVT had a relative risk for MI of 1.60 [95% confidence interval (CI) 1.35-1.91] and for stroke of 2.19 (1.85-2.60). Patients with PE had a relative risk for MI of 2.60 (2.14-3.14) and for stroke of 2.93 (2.34-3.66). Relative risks of MI and stroke remained elevated, but less markedly (1.2-1.4), during the subsequent 20 years of follow-up. In contrast to some previous reports from smaller studies, these relative risks were similar for those with idiopathic VTE and those with VTE associated with malignancy, trauma, surgery or pregnancy. The increased risk of MI and stroke was highest in the first year after diagnosis of VTE, which is perhaps surprising because the standard treatment (3-6 months of oral anticoagulant drugs) should lower the risk of MI and ischemic stroke. Possible explanations include increased risk of hemorrhagic stroke during anticoagulant therapy, rebound hypercoagulability and/or failure to re-start aspirin after cessation of anticoagulants, or a transient hypercoagulable state induced by common exposures such as acute infection, which increases the risk of both venous and arterial thrombosis for several weeks or months.

Classic cardiovascular risk factors such as obesity, diabetes, hypertension and smoking increase the odds

of VTE by up to 3 folds.[3] Furthermore, a recent study demonstrated an association between the severity of coronary artery disease and the occurrence of VTE.[4] Hypercoagulability and inflammation are postulated mechanisms by which traditional cardiovascular risk factors impact both venous and arterial thrombosis. Histopathological analysis of retrieved pulmonary emboli supports this hypothesis and reveals presence of both platelets and polymorphonuclear neutrophils.[5]

In addition, studies testing statin therapy to reduce atherothrombotic events in patients at risk for atherosclerosis have also demonstrated reductions in VTE possibly through anti-inflammatory mechanisms. In the prospective randomized controlled study of rosuvastatin in apparently healthy persons, rosuvastatin 20 mg/d significantly reduced the occurrence of symptomatic VTE. The rates of VTE were 0.18 and 0.32 event per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio with rosuvastatin, 0.57; 95%CI: 0.37 to 0.86; p = 0.007).[6]

Although anticoagulation is the most effective treatment for VTE, several studies have demonstrated that aspirin monotherapy is effective for primary and secondary prevention of VTE.[7-11] The efficacy of an antiplatelet agent for preventing VTE is biologically plausible because of the involvement of platelets in the formation of venous thrombi and the evidence of increased levels of markers of platelet and endothelial activation in patients with VTE. In the setting of primary prevention, a meta-analysis by the Antiplatelet Trialists' Collaboration observed a reduction in the incidence of DVT by 20% and of PE by 69% in surgical and high-risk medical patients receiving aspirin monotherapy.[6] The combined results of the WARFASA (Warfarin and Aspirin) and ASPIRE (Aspirin to Prevent Recurrent Venous Thromboembolism), randomized trials of aspirin versus placebo for secondary prevention in patients with prior VTE, demonstrated a highly significant 32% reduction in the rate of recurrent VTE and a 34% reduction in the rate of major vascular events, without significantly increasing the risk of bleeding in patients randomized to aspirin versus placebo administered after 6 to 24 months of oral anticoagulation.[9,10] This 32% risk reduction corresponds to less than 50% of the degree of risk reduction achieved by oral anticoagulants but with the benefit of lower bleeding rates (approximately 1.35% per patient-year during treatment with aspirin). Whether these benefits driven primarily by the antiplatelet effects of aspirin is unknown. A recent study demonstrates that more intensive antiplatelet therapy, vorapaxar (a PAR-1 antagonist) or ticagrelor (a P2Y12 inhibitor), when added to aspirin alone or aspirin plus clopidogrel is associated with a further 29% risk reduction in VTE.[4]

The COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies) has recently shown that, in patients with coronary artery disease or peripheral arterial disease, low-dose anticoagulation with rivaroxaban 2.5 mg twice daily added to low-dose aspirin resulted in a 24% relative risk reduction in the incidence of cardiovascular death, MI, and stroke compared with aspirin alone.[12] In addition, a trend also occurred for reduction in VTE (HR, 0.61; 95%CI: 0.37-1.00; p = 0.05). These observations further underscore the role of the platelet in the pathogenesis of VTE and the cross-talk between platelet activation and the coagulation cascade. Indeed, much debate regarding the white clot/red clot paradigm is expected in the near future.

What biological mechanisms might be responsible for an association between arterial and venous thromboembolism?

Figure 1 summarizes potential biological mechanisms linking atherosclerosis, arterial thromboembolism (MI and stroke) and VTE. The first possibility is that arterial disease and VTE share common risk factors. Both arterial disease and VTE are common and multifactorial diseases, whose risks increase exponentially over the lifecourse, and which are associated with multiple interacting genetic and environmental risk factors.[13,14] For arterial disease, some of these risk factors may be 'atherogenic' (promot-

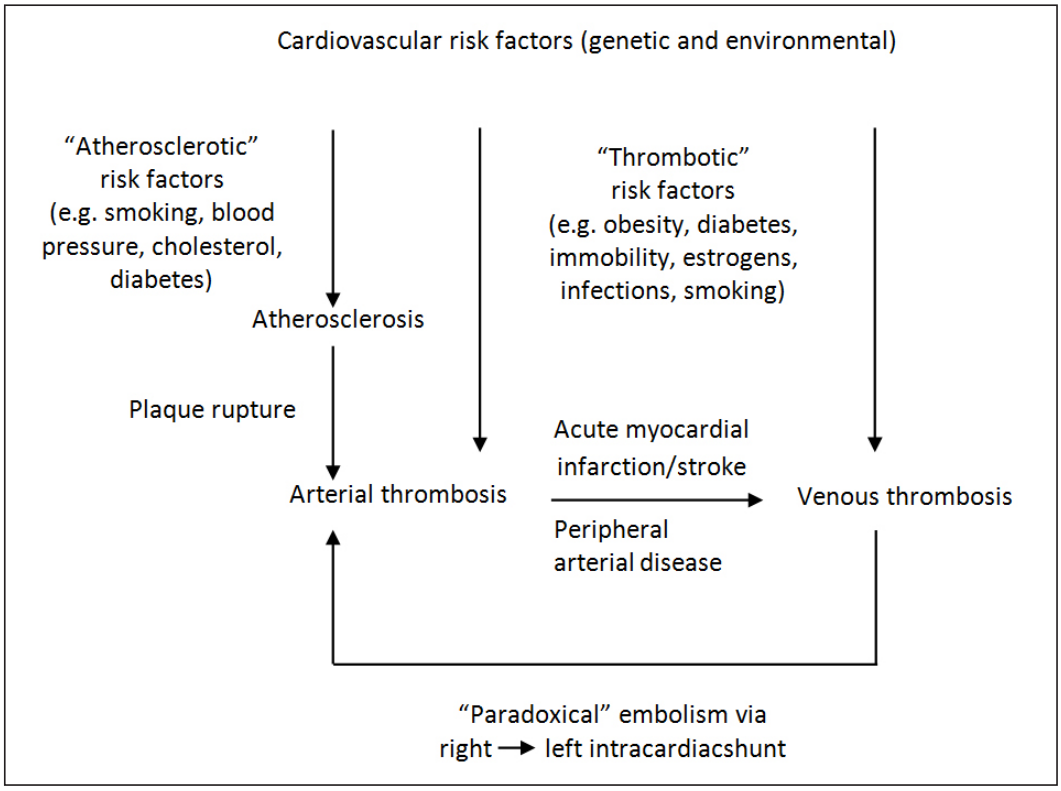

Figure 1 Possible mechanisms for associations between atherosclerosis, arterial thrombosis and venous thrombosis.

ing the progression of occlusive atherosclerosis), while others may be 'thrombogenic' (promoting the rupture of atheromatous plaques and superadded thrombosis). Figure 1 suggests that 'thrombotic' risk factors may increase the risk of VTE as well as arterial thromboembolism, whereas 'atherogenic' risk factors may be more relevant to atherothrombosis. However, there is increasing evidence that many 'arterial' risk factors are associated not only with atherosclerosis (at necropsy or imaging) but also with circulating markers of activated inflammation and hemostasis. Furthermore, there is increasing evidence that activation of inflammation and hemostasis plays a role in progression of atherosclerosis as well as in plaque rupture and superadded arterial thrombosis. New research has identified signaling pathways that intertwine thrombotic and inflammatory pathways with the development and progression of atherosclerosis. These signaling pathways contain positive feedback loops that propagate atherogenesis (Figure 2).[15]

In certain circumstances, arterial disease may directly promote VTE. For example, there is a transient increased risk of VTE following MI or stroke, probably due to the combination of leg stasis in immobilized patients and the systemic activation of inflammation and hemostasis following tissue injury. This risk is reduced by both mechanical devices which increase leg blood flow, or by low-dose heparin. Chronic peripheral arterial disease also increases the risk of VTE, probably due to reduced leg blood flow. Conversely, but rarely, VTE may directly cause arterial thrombosis, for example by 'paradoxical' embolism through a right-to-left intracardiac shunt causing an ischemic stroke.

In summary, the most likely biological explanation for an association between VTE and arterial thomboembolism is the sharing of common risk factors.

Age

There is an exponential increase in the risk of both arterial and venous thrombotic events with age. The possible mechanisms include cumulative effects of risk factors on the arterial wall, decreased regular exercise with decreased mobility resulting in venous stasis, and increasing systemic activation of blood coagulation.[16]

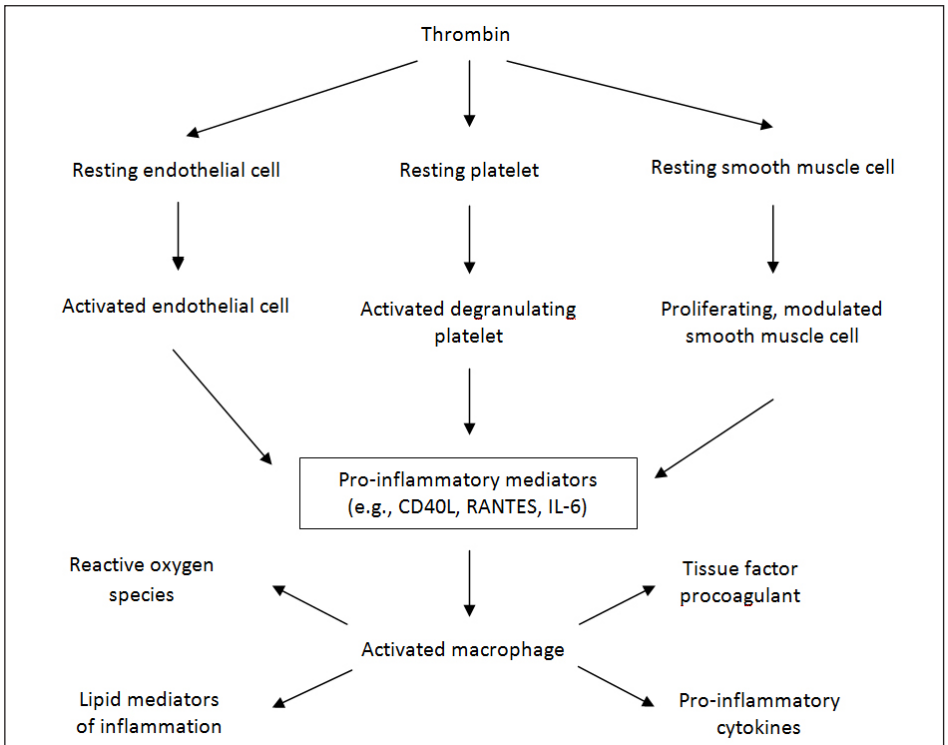

Figure 2 Thrombin-induced inflammatory processes play a central role in the development and complications of atherosclerotic vascular disease

Table 1 Indirect comparisons of associations between arterial risk factors and VTE *versus* MI.

Risk factor	VTE (OR, 95% CI)	MI (OR, 99% CI)[14]
Smoking (current vs. never)	1.42 (1.28-1.58)[19]	2.95 (2.72-3.20)
Hypertension	1.51 (1.23-1.85)[3]	2.48 (2.30-2.68)
Diabetes	1.42 (1.12-1.77)[3]	3.08 (2.77-3.42)

VTE, venous thromboembolism; MI, myocardial infarction; OR, odds ratio; CI, confidence intervals

Immobility

Epidemiological studies have shown that immobility is related to both risk of arterial thrombosis, and systemic activation of hemostasis and inflammation.[17] Immobility is also associated with increased risk of both first and recurrent VTE.[18]

Obesity, metabolic syndrome and diabetes

Obesity, metabolic syndrome and diabetes increase the risk of arterial thrombosis, probably because of many adverse influences on the arterial wall, and systemic effects on inflammation, coagulation and fibrinolysis. Several epidemiological studies have also reported associations between obesity, metabolic syndrome and type 2 diabetes with VTE. In a recent meta-analysis, Ageno et al reported the relative risk of VTE as 2.33 (95%CI: 1.68-3.24) for obesity; and 1.42 (1.12-1.77) for diabetes (Table 1).[3]

Smoking, blood pressure and cholesterol

Tobacco smoking, arterial blood pressure and serum cholesterol are the classical risk factors for arterial disease in the heart, brain, and leg. The meta-analyses of randomized controlled trials of blood pressure and cholesterol reduction and the observational studies of smoking cessation proved that these three risk factors play causal roles in arterial disease. This may be partly through atherogenesis, and partly through systemic activation of coagulation and inflammation.

There has been also evidence from epidemiological studies on the associations of smoking habit, blood pressure and cholesterol with risk of VTE. In a recent meta-analysis, Ageno et al reported the odds ratios of VTE as 1.51 (95%CI: 1.23-1.85) for hypertension, 1.18 (0.95-1.46) for smoking and 1.16 (0.67-2.02) for hypercholesterolemia.[3] The significantly increased risk for hypertension may be related to obesity, since hypertension is a component of the metabolic syndrome. In a recent large population-based case-control study (the MEGA study), 3,989 patients with VTE (after exclusion of those with known malignancies) were compared for smoking habit with 4,900 controls.[19] 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). Hence, this large study establishes a clear dose-dependent and reversible association of smoking habit with risk of VTE. This may be related to the dose-dependent and reversible associations of smoking habit with activation of coagulation and inflammation. However, as with diabetes, the relative risks for VTE of blood pressure and current smoking (1.4-1.5) appear about half as strong as the relative risks (about 2.5-3) of MI and stroke (Table 1). This discrepancy may reflect the direct effects of smoking and arterial blood pressure on the arterial wall, which range from endothelial dysfunction to atherosclerosis.

The association of serum cholesterol with risk of VTE is emerging. Recent studies suggest that treatment with statins (which lower low density-lipoprotein cholesterol and hence total cholesterol) is associated with decreased relative risk of VTE.[6,20,21]

In conclusion, the relative risks for VTE of smoking, blood pressure and cholesterol are becoming established, but are probably about 50% lower than their associations with MI or stroke. However, together with obesity and diabetes, they may account for much of the association of VTE with subsequent risk of MI or stroke reported by Sorensen et al.[2]

Cancer

Cancer is well recognized as a risk factor for both arterial and venous thrombosis.[22,23] Possible mechanisms include local effects of solid tumors on vessels (compression and/or invasion), immobility for venous thrombosis, and systemic hypercoagulability-induced by the tumor or by treatments such as chemotherapy. Tamoxifen (a selective estrogen receptor modulator used in prevention of recurrent breast cancer) increases the risk of VTE about two fold, and might also increase the risk of stroke. Anticoagulants are used increasingly for primary or secondary prevention of VTE in cancer patients; the effects of anti-thrombotic therapy in prevention of arterial thrombosis in cancer patients remain to be established. A recent study showed that an elevated absolute neutrophil count and higher soluble P-selectin levels were associated with an increased risk of arterial thrombosis in patients with cancer.[23]

Estrogens

Pregnancy, combined oral contraceptives (COC) and oral hormone replacement therapy (HRT) increase the risks of both arterial and venous thrombosis, probably due to systemic hypercoagulability (especially in women with thrombophilias).[13,24] However, screening for thrombophilias in pregnancy, or prior to prescription of COC or oral HRT, does not appear cost-effective.[25]

Combined oral contraceptives use increases the relative risk of VTE approximately two folds, and increases the relative risk of arterial thrombosis (MI, ischemic stroke, or peripheral arterial disease) approximately three folds. The risk of VTE increases with age, obesity and thrombophilias. The risk of arterial thrombosis increases with age, obesity, smoking, blood pressure, serum cholesterol and diabetes.[26]

Oral HRT use also increases the relative risk of VTE about two folds, and increases the relative risk of arterial thrombosis (ischemic stroke, peripheral arterial disease) by about 1.5 fold. Oral HRT use does not reduce the relative risk of MI, and may confer a small increase in risk. There is now no doubt that oral HRT increases the overall risk of venous and arterial thrombosis.[24] The absolute risk of venous and arterial thrombosis is 10 folds higher in oral HRT users than COC users, due to their higher age. As with COC use, the risk of VTE also increases with age, obesity and thrombophilias. The risk of arterial thrombosis increases with age, obesity and classical risk factors.

Infections

Acute infections transiently increase the risk of both arterial and venous thrombosis.[27,28] Possible mechanisms include systemic hypercoagulability, and immobility for venous thrombosis. There is increasing interest in a possible increased risk of both arterial and venous thrombosis in persons with human immunodeficiency virus (HIV) infection, perhaps due to effects of the virus, or of antiretroviral therapy.[29]

Trauma and surgery

Trauma and surgery are well-established risk factors for venous thrombosis, due to immobility and systemic hypercoagulability. There is increasing interest in the increased risk of arterial thrombosis following surgery, especially in patients with clinical evidence of arterial disease. This can be reduced by careful assessment of such patients and their medications (including aspirin) prior to surgery.

Thrombophilias

Congenital thrombophilias are established risk factors for venous thrombosis, especially during periods of increased risk, such as pregnancy, COC use, HRT use and surgery.[24] There has been increasing interest in their association with arterial thrombosis. While further studies are required, recent meta-analyses suggest that the two common prothrombotic genetic mutations (factor V Leiden and the prothrombin G20210A mutation) are associated with increased arterial thrombotic risk.[30,31] However, these associations are about 10 folds weaker than their associations with risk of venous thrombosis (odds ratio approximately 1.2-1.3, compared to 2-3). These genetic mutations are associated with the phenotype of resistance to activated protein, which has recently been associated with risk of arterial thrombosis.[32] Acquired thrombophilias - lupus anticoagulants, hyperhomocysteinemia, and polycythemia vera - increase the risk of both arterial and venous thrombosis.[33]

Conclusions

There is increasing evidence that arterial and venous thrombosis share several risk factors and pathophysiology. Cardiovascular risk factors are associated with an increased risk of VTE. This association between VTE and atherothrombosis has great clinical relevance with respect to individual screening, risk factor modification, and the primary and secondary prevention of VTE. Global changes in population age, immobility and obesity are increasing the likelihood that risk factors are shared. The clinical message for clinicians is that patients with arterial or venous thrombosis increasingly share risk factors, hence clinical management of thrombosis should address the 'total thrombotic risk' (arterial and venous) of the individual patient. This should be considered when evaluating (and discussing with the patient) secondary prevention with antithrombotic therapies. Clinicians should abandon a "silo" approach for the prevention of venous or arterial thrombosis and promote a holistic approach for risk stratification and prevention of vascular

disease. For example, following routine treatment of VTE with a course of anticoagulant drugs, patients should be routinely assessed not only for risk of recurrent VTE but also for risk of arterial thromboembolism (MI and stroke). Appropriate lifestyle advice and medication should then be considered. In particular, low-dose aspirin might be considered in those with a 10-year risk of MI or stroke greater than 20%, because it is effective in reducing the risk (by approximately 32%) of venous thrombosis, as well as arterial thrombosis, in high-risk patients.

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