Common risk factors for both arterial and venous thrombosis

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Summary

Arterial and venous thromboses have traditionally been viewed as distinct conditions, with differences in risk factors, pathology and treatment. However, recent epidemiological studies have suggested associations between venous thromboembolism, arterial thromboembolism (myocardial infarction and stroke) and atherosclerosis. While several biological mechanisms might contribute to these associations, common risk factors for both arterial and venous thrombosis probably play the major role. This article summarizes the evidence for shared risk factors (clinical, biochemical and haematological) that supports this conclusion. At a practical level, it is suggested that following routine treatment of venous thromboembolism with a course of anticoagulant drugs, patients should be routinely assessed not only for risk of recurrent venous thromboembolism but also for risk of arterial thromboembolism. Appropriate lifestyle advice and medication (including aspirin) should then be considered.

Keywords: thrombosis, risk factors, myocardial infarction, stroke.

You live with atherosclerosis but you die from thrombosis (Anon)

Are arterial and venous thrombosis associated?

Traditional medical teaching has stressed the differences between arterial thrombosis and venous thrombosis. While both are composed of platelets and fibrin, arterial thrombi tend to occur at sites of arterial plaque rupture where shear rates are high, and are platelet-rich 'white thrombi'. In contrast, venous thrombi tend to occur at sites where the vein wall is often normal, but blood flow and shear rates are low, resulting in red cell-rich 'red thrombi'. Likewise, it is still stated that antiplatelet agents are more effective in arterial thrombosis, and anticoagulants in venous thrombosis. Finally, 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).

In recent years however, epidemiological studies have for the first time explored the association between venous thromboembolism (VTE), arterial thromboembolism [coronary heart disease (CHD) including myocardial infarction (MI), and stroke] and atherosclerosis. Reports on the associations between VTE and markers of atherosclerosis have produced conflicting results (Prandoni et al, 2003; Hong et al, 2005; Eliasson et al, 2006; van der Hagen et al, 2006; Reich et al, 2006), and further studies are required. Reports on the associations between VTE and subsequent arterial thrombotic events (MI or stroke), which are more important (see the quote at the start of this article), are more consistent in showing an association (Becattini et al, 2005; Bova et al, 2006; Prandoni et al, 2006; Schulman et al, 2006; Sorensen et al, 2007).

In the largest of these studies, Sorensen et al (2007) compared retrospectively the risks of MI and stroke in 25 199 patients with deep vein thrombosis (DVT), 16 925 patients with pulmonary embolism (PE) and 163 566 population 'controls', using nationwide Danish medical databases. Patients with baseline hypertension, CHD, stroke or transient cerebral ischaemic 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 2.70 [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 (Sorensen et al, 2007). The increased risk of MI and stroke was highest in the first year after diagnosis of VTE (Sorensen et al, 2007), which is perhaps surprising because the standard treatment (3–6 months of oral anticoagulant drugs) should lower the risk of MI (Medical Research Council’s General Practice Framework, 2003).
Possible explanations include increased risk of haemorrhagic 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 (Smeeth *et al*, 2004, 2006).

In summary, there is increasing evidence from epidemiological studies for an association between VTE and arterial thromboembolism (MI and stroke). Further epidemiological studies (especially prospective studies) and systematic reviews are required to establish the magnitude, duration and possible causes of these risks.

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

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 (Rosendaal, 1999; Yusuf *et al*, 2004). For arterial disease, some of these risk factors may be ‘atherogenic’ (promoting progression of occlusive atherosclerosis), while others may be ‘thrombogenic’ (promoting 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 haemostasis (see next section). Furthermore, there is increasing evidence that activation of inflammation and haemostasis plays a role in progression of atherosclerosis (Fowkes *et al*, 1993; Ross, 1999; Tzoulaki *et al*, 2006) as well as in plaque rupture and superadded arterial thrombosis (Libby *et al*, 2002).

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 haemostasis following tissue injury (Fig 1). This risk is reduced by both mechanical devices which increase leg blood flow, or by low-dose heparin (Lowe, 2006a). Chronic peripheral arterial disease also increases the risk of VTE, probably due to reduced leg blood flow (Lowe, 2006a; Fig 1).

Conversely, but rarely, VTE may directly cause arterial thrombosis, for example by ‘paradoxical’ embolism through a right-to-left intracardiac shunt causing an ischaemic stroke (Lowe, 2006a; Fig 1).

In summary, the most likely biological explanation for an association between VTE and arterial thromboembolism (Sorensen *et al*, 2007) is the sharing of common risk factors (Agnelli & Becattini, 2006; Lowe, 2006a). The remainder of this review updates and extends previous reviews of common clinical risk factors (Lowe, 2006a) and haematological risk factors (Lowe, 2006b).

**Cardiovascular risk factors (genetic and environmental)**

- **“Atherosclerotic” risk factors** (e.g. smoking, BP, cholesterol, diabetes)
- **Atherosclerosis**
- **Plaque rupture**
- **Arterial thrombosis**
- **Acute MI/stroke**
- **Peripheral arterial disease**

- **“Thrombotic” risk factors** (e.g. obesity, diabetes, immobility, oestrogens, infections, smoking)
- **Venous thrombosis**

**“Paraphilic” embolism via R → L intracardiac shunt**

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

There is an exponential increase in risk of both arterial and venous thrombotic events with age (Hume et al, 1970; Gordon & Kannel, 1972), and the increase in life expectancy in the second half of the twentieth century is a major cause of the current epidemic of both arterial and venous thrombosis (Hume et al, 1970; Nieto, 1999). Possible mechanisms include cumulative effects of risk factors on the arterial wall, decreased regular exercise, increasing immobility resulting in venous stasis, and increasing systemic activation of blood coagulation (Lowe et al, 1997; Rumley et al, 2006).

Immobility

As with increasing age (and partly because of it), immobility has increased greatly in the second half of the twentieth century. Socio-economic changes promoting immobility include sitting in cars or in front of television or computer screens, and reduced leisure-time activity. Epidemiological studies have shown that the latter is related to both risk of arterial thrombosis, and systemic activation of haemostasis and inflammation (Wannamethee et al, 2002). Immobility is also associated with increased risk of both first and recurrent VTE (Prandoni et al, 2007).

Obesity, metabolic syndrome and diabetes

Increasing immobility, in combination with increasing commercial promotion of a high fat diet (e.g. 'junk food') has resulted in a global epidemic of obesity, the metabolic syndrome (hypertension, dyslipidaemia, hyperglycaemia, hyperinsulinaemia) and type 2 diabetes mellitus (Grundy et al, 2005). Obesity, metabolic syndrome and diabetes increase the risk of arterial thrombosis (Grundy et al, 2005), probably because of many adverse influences on the arterial wall, and systemic effects on inflammation, coagulation and fibrinolysis (Woodward et al, 1997; Juhan-Vague et al, 2000; Wannamethee et al, 2004, 2005a). Several epidemiological studies have also reported associations between obesity, metabolic syndrome and type 2 diabetes with VTE (Goldhaber et al, 1997; Hansson et al, 1999; Tsai et al, 2002; Ageno et al, 2006). In a recent meta-analysis, Ageno et al (2007) 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 I). Significant heterogeneity among studies was detected for obesity, hence caution is required; however the estimated relative risk of VTE in obese persons at present appears comparable to the relative risk of arterial thromboembolism (MI and stroke). No significant heterogeneity among studies was detected for diabetes; and the estimated relative risk of VTE at present appears about half as strong as the relative risk (about 3) of MI and stroke ( Yusuf et al, 2004; Table I). This discrepancy may reflect the major effects of diabetes on the arterial wall (Fig 1), which range from endothelial dysfunction to extensive atherosclerosis.

Table I. Indirect comparisons of associations between ‘arterial’ risk factors and VTE versus MI.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>VTE (OR, 95% CI)</th>
<th>MI (OR, 99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking (current vs. never)</td>
<td>1.42 (1.28–1.58) (Pomp et al, 2007)</td>
<td>2.95 (2.72–3.20)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.51 (1.23–1.85) (Ageno et al, 2007)</td>
<td>2.48 (2.30–2.68)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.42 (1.12–1.77) (Ageno et al, 2007)</td>
<td>3.08 (2.77–3.42)</td>
</tr>
</tbody>
</table>

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

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 identified by the Framingham Study (Gordon & Kannel, 1972). While collectively they have been estimated to account for about 50% of inter-individual risk of CHD among persons of the same age and sex, adjustment for regression dilution bias (single estimates result in under-estimation of associations) in the British Regional Heart Study increased this estimate to 80–90% (Emerson et al, 2004). Meta-analyses of randomized controlled trials of blood pressure reduction (Blood Pressure Lowering Treatment Trialists’ Collaborators, 2003) and cholesterol reduction (Cholesterol Trialists’ Treatment Collaborators, 2005) and observational studies of smoking cessation (Doll et al, 2004) 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 (Wannamethee et al, 2005a,b).

There has been conflicting evidence from epidemiological studies on the associations of smoking habit, blood pressure and cholesterol with risk of VTE (Goldhaber et al, 1983, 1997; Heit et al, 2000; Tsai et al, 2002; Heit, 2005; Kyrle & Eichinger, 2005; Ageno et al, 2006). In a recent meta-analysis, Ageno et al (2007) 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 hypercholesterolaemia (Table I). The significantly increased risk for hypertension may be related to obesity, since hypertension is a component of the metabolic syndrome (see above). The non-significant increased risk for smoking is probably a type 2 statistical error, because of the small number of VTE events (less than 1000) in reported studies. In a recent large population-based case–control study (the MEGA study), 3989 patients with VTE (after exclusion of those with known malignancies) were compared for smoking habit with 4900 controls (Pomp et al, 2007). 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 (Pomp et al., 2007). This may be related to the dose-dependent and reversible associations of smoking habit with activation of coagulation and inflammation (Wannamethee et al., 2005b). However, as with diabetes (see above), 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 (Yusuf et al., 2004; Table I). This discrepancy may reflect the direct effects of smoking and arterial blood pressure on the arterial wall, which range from endothelial dysfunction to atherosclerosis.

At present, the association of serum cholesterol with risk of VTE is unclear (Ageno et al., 2007). While observational studies suggest that treatment with statins (which lower low-density-lipoprotein cholesterol and hence total cholesterol) may be associated with decreased relative risk of VTE (Ray, 2003; Squizzato et al., 2006), the causality of this association remains to be established by randomized controlled trials. In the PROSPER (prospective study of pravastatin in the elderly at risk) trial of pravastatin 40 mg/d versus placebo in men and women aged 70–82 years with cardiovascular disease or risk factors, pravastatin treatment was not associated with decreased risk of VTE (relative risk 1.18; 95% CI 0.75–1.86) (Freeman et al., 2007).

In conclusion, the relative risks for VTE of smoking and blood pressure (but not cholesterol) are becoming established, but are probably about 50% lower than their associations with MI (Yusuf et al., 2004; Table I) 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. (2007).

Cancer

Cancer is well recognized as a risk factor for both arterial and venous thrombosis (Levine et al., 2003). Possible mechanisms include local effects of solid tumours on vessels (compression, invasion), immobility for venous thrombosis, and systemic hypercoagulability – induced by the tumour or by treatments such as chemotherapy (Levine et al., 2003). Tamoxifen (a selective oestrogen receptor modulator used in prevention of recurrent breast cancer) increases the risk of VTE about twofold, and might also increase the risk of stroke (Cuzick et al., 2003). Anticoagulants are increasingly used 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.

Oestrogens

Pregnancy, combined oral contraceptives (COC) and oral hormone “replacement” therapy (HRT) increase the risks of both arterial and venous thrombosis (Rosendaal et al., 2003; Kujovic, 2004; Greer et al., 2007; Lowe, 2007), probably due to systemic hypercoagulability (especially in women with thrombophilias). However, screening for thrombophilias in pregnancy, or prior to prescription of COC or oral HRT, does not appear cost-effective (Wu et al., 2005c, 2006).

Combined oral contraceptives use increases the relative risk of VTE about twofold, and increases the relative risk of arterial thrombosis (MI, ischaemic stroke, or peripheral arterial disease) about threefold. 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 (Bloemenkamp & Helmerhorst, 2007). International guidelines are available to reduce thrombotic risk (World Health Organisation, 2004).

Oral HRT use also increases the relative risk of VTE about twofold, and increases the relative risk of arterial thrombosis (ischaemic stroke, peripheral arterial disease) by about 1.5. 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 (Table II; Lowe, 2007). The absolute risk of venous and arterial thrombosis is 10-fold higher in oral HRT users than COC users, due to their higher age (Table II; Lowe, 2007). 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.

| Table II. Relative risks and estimated absolute risks of cardiovascular events in users of HRT over 5 years, compared to non-users (modified from Lowe, 2007). |
|---|---|---|---|
| Age (years) | Number of cases per 1000 non-HRT users | Relative risk, HRT vs. no HRT (95% CI) | Extra number of cases per 1000 HRT users |
| **VTE** | | | |
| 50–59 | 3 | 2 (1.5–3.0) | 3 |
| 60–69 | 8 | | 8 |
| **Stroke** | | | |
| 50–59 | 5 (1 fatal or disabling) | 1.23 (1.06–1.44) | 1 (0.5 fatal or disabling) |
| 60–69 | 10 (2 fatal or disabling) | | 2 (1 fatal or disabling) |
| **MI** | | | |
| 50–59 | 5 | 1? | |
| 60–69 | 15 | | 0 |
| **Total CV events** | | | |
| 50–59 | 13 | – | 4 |
| (VTE, stroke and MI) | 60–69 | 33 | 10 |

HRT, hormone replacement therapy; VTE, venous thromboembolism; MI, myocardial infarction; CV, cardiovascular; CI, confidence intervals.
Infections

Acute infections transiently increase the risk of both arterial and venous thrombosis (Smeeth et al., 2004, 2006). 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 (Lijfering et al., 2006).

Trauma and surgery

Trauma and surgery are well-established risk factors for venous thrombosis (Hume et al., 1970), 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 (Scottish Intercollegiate Guidelines Network (SIGN), 2007a). This can be reduced by careful assessment of such patients and their medications (including aspirin) prior to surgery (SIGN, 2007a).

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 (Wu et al., 2005a,b; Robertson et al., 2006; Lowe, 2007). 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 (Kim & Becker, 2003; Ye et al., 2006). However, these associations are about 10-fold weaker than their associations with risk of venous thrombosis (odds ratio about 1.2–1.3, compared to 2–3) (Ye et al., 2006). These genetic mutations are associated with the phenotype of resistance to activated protein (Castaman et al., 2001), which has recently been associated with risk of arterial thrombosis (Smith et al., 2005). Acquired thrombophilias – lupus anticoagulants (Greaves et al., 2002), hyperhomocystinaemia (Lowe, 2006b), and polycythaemias including polycythaemia vera – increase the risk of both arterial and venous thrombosis.

Conclusions

There is increasing evidence that arterial and venous thrombosis share several cardiovascular risk factors. Furthermore, global changes in population age, immobility and obesity are increasing the likelihood that risk factors are shared. The clinical message for haematologists 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. 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 (Joint British Societies, 2005; SIGN, 2007b). 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 about 25%) of venous thrombosis, as well as arterial thrombosis, in high-risk patients (Antithrombotic Trialists’ Collaboration, 2002). Randomized trials of aspirin in secondary prevention of VTE are currently in progress (Hovens et al., 2006).

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