



# Risk of future arterial cardiovascular events in patients with idiopathic venous thromboembolism

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Venous and arterial thromboses have traditionally been considered distinct pathophysiologic entities. However, the two disorders have many features in common, and there is evidence that persons with venous thrombosis may be at greater risk for arterial events. The pathogenesis of both disorders includes endothelial injury, platelet activation, elevated levels of intrinsic clotting factors and inflammatory markers, increased fibrinogen, and impaired fibrinolysis. In addition, older age, obesity, dyslipidemia, and smoking predispose to both venous and arterial thrombosis. While the evidence that arterial disease is a risk factor for venous thrombosis is inconclusive, arterial disease does appear to occur with a modestly increased frequency in patients with a history of venous thromboembolism. Reported odds ratios in such patients were 1.2 for myocardial infarction, 1.3 for stroke, 2.3 for carotid plaque, and 4.3 for coronary calcification. Of note, in persons under age 40 with unprovoked venous thrombosis, the odds ratio for acute myocardial infarction was as high as 3.9. In general, however, venous disease is considered to be a weak risk factor for arterial thrombosis, and the use of agents specifically targeted to the prevention of heart attack or stroke in the majority of persons with VTE cannot be recommended at present.

Venous and arterial thromboses have traditionally been considered distinct pathophysiologic entities. Venous thrombi usually develop in low-flow vessels and consist predominantly of erythrocytes and fibrin. Arterial thrombi are found in areas of high shear stress and consist mostly of platelets and fibrin. However, the two disorders have many features in common, and there is evidence that persons with venous thrombosis may be at greater risk for arterial events. Furthermore, there are a few disorders that are characterized by having both venous and arterial thromboses: the antiphospholipid antibody syndrome, heparin-induced thrombocytopenia, myeloproliferative disorders, and hyperhomocysteinemia.

In this paper, the common pathophysiologic features of arterial and venous thrombosis will be described, and the clinical studies examining the association of the two conditions will be reviewed. The clinical studies are divided into those that examined the risk of venous thrombosis in patients with arterial disease, and those that assessed the risk of arterial thrombosis in patients with venous disease. Venous thromboembolism (VTE) may be unprovoked (spontaneous) or secondary to other factors such as trauma or surgery; most studies have focused on patients with unprovoked VTE. Some investigators have compared incidence rates between unprovoked and secondary VTE, without a non-VTE control group. How-

ever, there are important differences between patients with unprovoked and secondary VTE; only studies with well-matched controls (without VTE) are included in this review.

## Commonalities Between Arterial and Venous Thrombosis

There is biological plausibility to the concept that atherosclerosis and VTE may have a similar pathogenesis. In both arterial and venous thrombosis, activation of endothelium, platelets and leukocytes can be demonstrated, setting the stage for thrombus formation in veins as well as arteries. Other factors associated with arterial and venous thrombosis are high levels of clotting components, older age, obesity, smoking, dyslipidemia, and hormonal agents (**Table 1**).

### Factors VIII, IX, and XI

Elevated levels of intrinsic clotting factors are associated with both arterial and venous disease. Large prospective studies have reported an association between factor VIII and cardiovascular events. In the Atherosclerosis Risk in Communities Study, the odds ratio for prevalent cardiovascular disease was 1.15 in men and 1.14 in women ( $P < .05$ ),<sup>1</sup> and in the Cardiovascular Health Study, the hazard ratio for cardiovascular events was 1.06 (95% CI: 1.00-1.12).<sup>2</sup> Retrospective family studies confirm this association. Bank et al<sup>3</sup> examined 584 first-degree relatives of 177 patients with elevated factor VIII concentrations. As compared with

**Table 1. Common features of arterial and venous thrombosis.***Hemostatic Factors*

- Platelet activation
- Depressed endothelial nitric acid production
- High intrinsic clotting factor concentrations
- Increased fibrinogen, dysfibrinogenemia, impaired fibrinolysis

*Lifestyle Factors*

- Older Age
- Obesity
- Smoking

*Others*

- Inflammatory cytokines (ie, IL-6)
- Dyslipidemia
- Hyperhomocysteinemia
- Estrogens, anti-estrogens, oral contraceptives

relatives with normal factor VIII levels, those with high levels had an annual incidence of a first arterial thrombotic event that was 3-fold increased. In particular, the risks for a first myocardial infarction (odds ratio 4.3) and first peripheral arterial thrombosis (odds ratio 8.6) were significantly increased ( $P = .046$ ). While this study suggests that high levels of factor VIII predispose to arterial disease, it is possible that in addition to inheriting a propensity for an elevated factor VIII level, these relatives also may have inherited other risk factors for atherosclerosis. However, in further support for a role of factors VIII, IX, and XI in arterial disease, Doggen et al<sup>4</sup> recently reported that these factors were elevated in men with a history of myocardial infarction.

Serial measurements of factor VIII in persons with VTE demonstrate persistently high concentrations of factor VIII, although other acute phase reactants revert back to normal.<sup>5</sup> More than 19,000 adults were prospectively evaluated in the LITE study<sup>6</sup>; 159 venous thrombotic events occurred. Factor VIII was linearly associated with an increased risk of VTE ( $P$  for trend  $< .0001$ ). The same is true for elevated levels of fibrinogen.<sup>7</sup> That raised factor VIII levels occur on a genetic basis was shown by studies of family members<sup>8</sup>; 40% of first degree relatives had increased factor VIII.<sup>3</sup> While studies of several regions of the *F8* gene were unable to identify polymorphisms,<sup>9</sup> analysis of 13 families with thrombosis and high factor VIII levels showed linkage to imprinted loci on chromosomes 5 and 11.<sup>10</sup> Families with inherited high concentrations of combined factors VIII, IX, and XI have an odds ratio of 4.1 for developing venous thrombotic events, confirming that these are indeed potent risk factors for VTE.<sup>11</sup>

**Age**

Over the past 30 years, considerable effort has been expended to discern the changes in coagulation that may explain the increased frequency of thrombosis in the

elderly. In 1980, Zahavi et al<sup>12</sup> reported that levels of plasma  $\beta$ -thromboglobulin and platelet factor 4, specific platelet proteins released during platelet activation, increased with patient age. In addition, spontaneous platelet activation was found to correlate with age and was independent of hematocrit.<sup>13</sup> These findings of platelet activation in the elderly were confirmed by Bastyr et al,<sup>14</sup> who also observed more active platelet aggregation in response to adenosine diphosphate and increased turnover of platelet phosphoinositides with advancing age. Platelet aggregation and platelet adhesion to ex vivo umbilical artery segments were significantly correlated in elderly, but not young, blood donors.<sup>15</sup> A mechanism that may explain the increased responsiveness of platelets in the elderly is the age-related loss of platelet receptors for the inhibitory prostacyclin, PGI<sub>2</sub>.<sup>16</sup> Platelet activation characterizes both venous and arterial thrombosis (see accompanying article by B Furie, beginning on page 255). However, a clear role for platelets in venous thrombosis has not been established; for example, in the Women's Health Study, long-term, low-dose aspirin had little effect on the prevention of VTE.<sup>17</sup>

Hager et al<sup>18</sup> performed an extensive study of blood coagulation factors in the elderly. They found that partial thromboplastin (aPTT) and thrombin clotting times were slightly shortened in older patients (age 68-92 years) than in younger patients (age 18-41 years). Plasma concentrations of fibrinogen and factors VII, VIII, X, high molecular weight kininogen, and prekallikrein were increased, whereas antithrombin was decreased. Factor IX<sup>19</sup> and the A-subunit of factor XIII<sup>20</sup> also increase with age. Kario et al<sup>21</sup> confirmed the increase in factor VII in those 60 to 98 years old, and attributed this to increased hepatic synthesis and activation of the FVII zymogen. Ibbotson et al<sup>22</sup> studied the consequences of increased clotting factor levels and activity, and observed that thrombin generation strongly correlated with age ( $r = -0.64$ ). More recently, shortening of the aPTT was reported to increase the risk of VTE.<sup>23</sup> Since all clotting factors except factor VII are reflected by the aPTT, it is perhaps not surprising that increased levels of factors VIII,<sup>24,25</sup> IX,<sup>26</sup> XI,<sup>27</sup> and fibrinogen<sup>28</sup> have been associated with a greater risk of VTE. In particular, elevated levels of fibrinogen are associated with an increased risk of VTE in those older than 45 but not in those younger than 45. Certain polymorphisms of the fibrinogen genes also appear to increase the risk of venous thrombosis. Persons homozygous for the FGG-H2 gene had decreased fibrinogen  $\gamma$  levels, and this was associated with an enhanced VTE risk, possibly by removing a binding site for thrombin.<sup>29</sup>

Several investigators have examined the fibrinolytic system with aging. Hashimoto et al<sup>30</sup> reported a marked increase in both tissue plasminogen activator (t-PA) and plasminogen

activator inhibitor (PAI-1) with increasing age, but a decrease in PA activity. The latter was confirmed by Hager et al,<sup>18</sup> who also noted that levels of plasminogen and antiplasmin were unaffected by age. Levels of plasmin-antiplasmin (PAP) complexes rise with age,<sup>31</sup> possibly reflecting increased fibrinolytic activity. This concept is supported by studies of d-dimer, a measure of fibrin degradation, which is also increased in the elderly. Lastly, thrombin activatable fibrinolysis inhibitor (TAFI) also increases with age, especially in women.<sup>32</sup> With the exception of d-dimer, the association of other fibrinolytic factors with venous thrombosis is still tenuous.

Molecular markers of coagulation, such as prothrombin activation fragment F<sub>1+2</sub>, are increased in the elderly as compared to younger individuals.<sup>33,34</sup> Wilkerson and Sane<sup>35</sup> suggest that the elevated levels of F<sub>1+2</sub> in the elderly may be due to excessive factor Xa activity. In keeping with that suggestion, levels of thrombin-antithrombin (TAT) complexes increase with age.<sup>36</sup> However, there is no compensatory increase in natural anticoagulants such as protein C, S, or antithrombin,<sup>37</sup> and this may tip the hemostatic balance toward thrombosis.

Lastly, cytokines associated with inflammation appear to increase with advancing age. Interleukin (IL)-6 has been most studied; it is increased in the elderly<sup>38</sup> and has been found to be a risk factor for venous thrombosis.<sup>39</sup> IL-6 induces the synthesis of fibrinogen, increases platelet counts, and promotes platelet aggregation and thrombosis in experimental animals (summarized by Wilkerson and Sane<sup>35</sup>).

The prevalence of chronic venous disease, especially leg ulcers, increases with age (recently summarized by Bergan et al<sup>40</sup>); this observation is consistent with the increased prevalence of VTE in the elderly, as chronic venous disease is the most common sequel of this disorder. Fronck et al<sup>41</sup> report that the diameter of the common femoral vein declines beginning at age 60, with a decrease in flow velocity. Another factor that may predispose to venous and arterial thrombosis is the age-related decline in endothelial nitric oxide production, as observed in aged human umbilical vein endothelial cells in culture.<sup>42</sup>

### Obesity

Obesity is a risk factor for atheromatous disease, but it is also a risk factor for VTE. Abdollahi et al<sup>43</sup> observed that obesity (body mass index [BMI] > 30) increased the risk of venous thrombosis twofold (CI: 1.5-3.4) in the 454 persons enrolled in the Leiden Thrombophilia Study. There was a larger absolute effect in older age groups. They also found that the use of oral contraceptives in women with BMI > 25 increased the risk of VTE 10-fold, an observation confirmed

by Canonico et al.<sup>44</sup> In another population-based case-control study, the risk of VTE increased linearly with BMI in postmenopausal women (OR per SD increase in BMI 1.34 [CI 1.16-1.55]).<sup>45</sup> The basis for the association of obesity with VTE is unclear; fat is pro-inflammatory and abdominal fat, especially visceral fat, may raise venous pressure in the vena cava and distal veins as well as be a source of PAI-1, a potent inhibitor of fibrinolysis.<sup>46</sup> However, this is not the only alteration in hemostasis; Abdollahi et al<sup>43</sup> noted raised levels of factors VIII and IX in the obese. Thus, several factors in the obese (increased factor VIII, fibrinogen, PAI-1, as well as diabetes and dyslipidemia) predispose to arterial and venous thrombosis.

### Dyslipidemia

Dyslipidemia might be a risk factor for venous as well as arterial disease. Doggen et al<sup>47</sup> reported that elevated triglyceride levels were associated with a doubling of the risk for VTE in postmenopausal women, and another study found that elevated HDL-cholesterol decreased risk.<sup>48</sup> However, a study of over 27,000 women could not confirm that the levels of these lipids affected the risk of incident VTE,<sup>49</sup> and the LITE study, a prospective investigation of nearly 20,000 persons over the age of 45, also was unable to find an association of recurrent VTE with decreased apolipoprotein A1 (a major component of HDL) and lower HDL particle concentrations.<sup>50</sup> Increased Lp(a) is a risk factor for VTE as well as atherosclerosis, although its thrombogenicity may reside in its anti-fibrinolytic activity. Lastly, several recent studies have shown that statin drugs decrease the risk of VTE.<sup>51-53</sup> In a large, randomized, controlled trial (JUPITER), persons who took rosuvastatin were 43% less likely to experience a VTE than non-users.<sup>54</sup> The participants in this trial had LDL cholesterol levels lower than 130 mg/dL, but C-reactive protein concentrations higher than 2.0 mg/L, suggesting that the beneficial effects of statins might be related to their anti-inflammatory effects as well as their lipid lowering activity.

### Smoking

Smoking is a well-established risk factor for arterial disease, but it also contributes to VTE. The Nurses Health Study found smoking to be an independent risk factor for PE, with a relative risk of 1.9 that increased to 3.3 with more intense usage.<sup>55</sup> In middle-aged men, smoking was associated with a relative risk for VTE of 2.8 (CI 1.3-6.1).<sup>56</sup> Pomp et al<sup>57</sup> performed a case-control study of more than 8000 persons, half of whom had VTE. Smoking was associated with an increased risk of VTE (current smokers: OR 1.43; CI: 1.3-1.6; former smokers: 1.2, CI: 1.1-1.4). Those with a higher number of pack-years had a larger OR (4.3), and smoking acted synergistically with oral contraceptive use and prothrombotic genetic mutations to increase risk.

## VTE in Persons with Atherosclerosis

An association between VTE and atherothrombosis was observed in an autopsy study by Eliasson et al,<sup>58</sup> who found an OR of 1.4 (CI: 1.3-1.5) adjusted for age and gender. Of note, the association was observed mainly for cervico-cranial and peripheral arterial disease; coronary artery disease had a negative association. Furthermore, the impact of this study is weakened by the fact that fatal pulmonary embolism (PE) is a common mechanism of death in hospitalized patients, and this study was limited to recording only acute thrombosis in the autopsied subjects.

The Tromso study examined the incidence of VTE in persons with a strong family history of myocardial infarction.<sup>59</sup> The hazard ratio for total VTE was 1.25 (CI: 1.01-1.6) and for unprovoked VTE 1.46 (1.03-2.07) in multivariable analysis. The authors suggested that persons with a high risk of arterial thrombosis were also at risk for venous thrombosis, although the hazard ratio for VTE barely reached statistical significance.

In contrast to these studies pointing to a risk of VTE in persons with atherosclerosis, two observational studies could find no such association. Neither the Cardiovascular Health Study (CHS) nor the Atherosclerosis Risk in Communities (ARIC) study were able to confirm that persons with evidence of subclinical atherosclerosis (carotid ultrasound, ankle-brachial index) had a higher incidence of VTE.<sup>60,61</sup> It should be noted that both of these studies examined only persons older than 45 years.

The conclusion from these studies is that atherosclerosis does not appear to be a risk factor for VTE, except perhaps in younger persons with an unusually large number of other risk factors.

## Association of Arterial Disease with Idiopathic Venous Thromboembolism

Prandoni et al<sup>62</sup> performed carotid ultrasound in 299 patients with VTE and no history of arterial disease. Carotid plaques were observed in 47% of those with idiopathic VTE, 27% in patients with secondary venous thrombosis, and 32% in a control group who were admitted for conditions unrelated to either arterial thrombosis or VTE, and were age/sex matched to the study group. The odds ratio (OR) for carotid plaque in patients with idiopathic VTE as compared with those with secondary thrombosis was 2.3, and 1.8 compared with controls. The relatively high frequency of carotid plaque might have been related to the age and sex of the participants (65 years, 68% men), and that about a third had hypertension or were smokers. However, the strength of the association was unaffected in multivariate analysis for atherosclerosis risk factors.

Hong et al<sup>63</sup> performed a retrospective case-control study of patients with confirmed idiopathic VTE and well-matched controls in whom VTE had been excluded. The VTE group had a higher prevalence of coronary artery calcium, as well as diabetes and hypertension. Which of these several risk factors underlie the coronary disease is not clear from this small retrospective study.

The relationship between unprovoked VTE, age, and acute myocardial infarction was investigated by Spencer et al.<sup>64</sup> The Canadian Institute for Health Information Database was used to identify all patients 20 to 64 years old hospitalized with an unprovoked VTE and followed up for 10 years. Controls were matched 2:1 with cases. While the cumulative rate of acute myocardial infarction was no different in the total sample, patients 20 to 39 years old had a higher rate of myocardial infarction as compared with controls (0.1 vs 0.03 per 100 patient-years; HR 3.92; CI 1.65-9.35). No association was observed in those 40 to 64 years old. Although the investigators stated that the younger patients had no atherosclerotic risk factors at baseline, it is clearly not possible to exclude all potential factors that may increase risk.

A Danish study evaluated the risk of myocardial infarction and stroke in more than 40,000 patients with deep vein thrombosis (DVT) and PE, and 160,000 controls.<sup>65</sup> Between a third and a half of the cohorts were older than 70. At one year follow-up, those with unprovoked DVT had an HR for myocardial infarction of 1.74 and for stroke of 2.01, and patients with unprovoked PE had an HR for myocardial infarction of 2.62 and stroke of 3.17. After 2 to 20 years of follow-up, the HRs were smaller but still significant (**Table 2**). However, in contrast to previous studies, the relative risks for arterial cardiovascular events were similar for those with provoked and unprovoked VTE.

Bova et al<sup>66</sup> conducted a small, retrospective study of 151 consecutive patients with unprovoked VTE and a similar number of controls. During a mean follow-up period of 43 months, there were 16 arterial events in the VTE patients and only 6 in the controls (adjusted HR 2.86 [1.07-7.62]).

In summary, the prevalence of arterial disease in patients with unprovoked VTE appears to be modestly increased. As **Table 2** shows, the largest effect was observed in the smallest studies. It is important to note, however, that the study of Spencer et al<sup>64</sup> did find an impressive hazard ratio of 3.92 when only persons younger than 40 years old were included.

**Table 2. Odds ratio (OR; 95% confidence interval) for arterial disease in persons with unprovoked venous thromboembolism (VTE).**

Arterial Disease	VTE no./total	No VTE no./total	OR (95%CI)	Ref.
Carotid plaque	72/153	48/150	2.3 (1.4-3.7)	62
Coronary artery calcification	46/89	25/89	4.3 (1.9-10.1)	63
Acute myocardial infarction	0.33*/6065	0.30*/12,040	1.1 (0.91-1.34)**	64
Myocardial infarction	961/18,087	3627/66,657	1.18 (1.1-1.27)**	65
Stroke	1118/18,087	3861/66,657	1.29 (1.21-1.38)**	65
Not Specified	16/151	6/151	2.86 (1.07-7.62)**	66

\*rate/100 patient-years

\*\*hazard ratio

## Conclusions

Arterial and venous thromboses have many similar pathogenic mechanisms. Endothelial injury, platelet activation, elevated levels of intrinsic clotting factors and inflammatory markers, increased fibrinogen, and impaired fibrinolysis are characteristic of the two disorders. In addition, older age, obesity, dyslipidemia, and smoking predispose to both venous and arterial thrombosis. However, the evidence that arterial disease, per se, is a risk factor for venous thrombosis is inconclusive. On the other hand, arterial disease does appear to occur with a modestly increased frequency in patients with a history of unprovoked VTE, especially in younger individuals with major risk factors. Nevertheless, venous disease is considered to be a weak risk factor for arterial thrombosis, and the use of agents specifically targeted to the prevention of heart attack or stroke in the majority of persons with VTE is not currently recommended. Some of the uncertainties regarding the value of this approach could be addressed by appropriately designed clinical trials.

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