

# Novel Risk Factors for Venous Thromboembolism

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## KEYWORDS

- Metabolic syndrome • *JAK2* mutation • Hyperthyroidism
- Cushing syndrome • Venous thromboembolism • Risk factors

Venous thromboembolism (VTE), such as deep venous thrombosis (DVT) of the leg, pulmonary embolism (PE), and unusual-site thrombosis, is a common disorder.<sup>1</sup> Vein thrombus either arises spontaneously or is caused by well-known clinical conditions.<sup>2</sup> Orthopedic and cancer surgery, trauma and spinal cord injury, metastatic cancer, and acute medical illness are the most common settings in which thromboembolism occurs.<sup>3</sup> Besides major risk factors of VTE, several genetic and acquired minor risks have been identified.<sup>2,3</sup> Indeed, VTE is currently best understood as a multicausal disease in which more than one genetic or environmental condition coincides to produce clinically apparent thrombosis.<sup>1</sup> Therefore, weak thromboembolic risk factors may also be clinically relevant, especially if treatable. Novel risk factors for VTE, which were previously not described, are frequently reported. This article discusses the most promising risk factors for VTE: traditional cardiovascular risk factors, *JAK2* mutation, and endocrine disorders (**Box 1**).

## TRADITIONAL CARDIOVASCULAR RISK FACTORS

Arterial atherothrombotic disease and VTE were generally considered as separate entities from mechanistic and clinical points of view. However, several studies have recently challenged this dichotomy, suggesting a closer link between these 2 clinical conditions.<sup>4-8</sup>

Among traditional cardiovascular risk factors, only obesity and age have consistently been demonstrated to be independent risk factors for VTE.<sup>9,10</sup> In a prospective cohort study on 855 men, waist circumference greater than 100 cm was found to be associated with VTE (odds ratio [OR], 3.92; 95% confidence interval [CI], 2.10–7.29).<sup>9</sup>

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**Box 1**  
**Novel persistent risk factors for VTE**

*Cardiovascular risk factors*

- Hypertension
- Obesity
- Diabetes mellitus
- Dyslipidemia
- Smoking
- Metabolic syndrome

*Ph– myeloproliferative disorders and JAK2V617F mutation*

*Endocrine disorders*

- Thyroid dysfunction: hyperthyroidism and subclinical hypothyroidism
- Cushing syndrome
- Hyperprolactinemia

These results were confirmed by a similar study performed in 112,822 women in whom obesity was an independent predictor of PE<sup>11</sup> and by a population-based study in which obesity was strongly associated with the risk of DVT in men and women.<sup>12</sup>

Recently, several observational studies have also reported a positive association between dyslipidemia and VTE. Elevated levels of triglycerides and low levels of high-density lipoprotein (HDL) were found to increase the risk of VTE, whereas increased HDL levels may protect against VTE.<sup>13–15</sup> Doggen and colleagues<sup>15</sup> found that elevated serum triglyceride levels are associated with a doubling of the risk of VTE in postmenopausal women. Another study identified a link between increased levels of lipoprotein (a), a marker of atherosclerosis, and the risk of unprovoked VTE (OR, 2.1; 95% CI, 1.4–3.2).<sup>16</sup> Observational studies have also reported a positive association between DVT and/or PE and diabetes,<sup>17</sup> arterial hypertension, and smoking.

However, other studies have failed to find a significant association between these traditional cardiovascular risk factors and VTE. For example, in a study on 19,293 subjects, a higher incidence of VTE was associated with obesity (OR, 2.27; 95% CI, 1.57–3.28) and diabetes (OR, 1.7; 95% CI, 1.2–2.4) but not with hypertension at 8 years of follow-up,<sup>18</sup> and in another study that enrolled 18,662 male physicians, VTE was associated with obesity but not with hypertension, hypercholesterolemia, diabetes, or smoking at 20 years of follow-up.<sup>19</sup>

To further assess the strength of the evidence supporting the association between cardiovascular risk factors and VTE, Ageno and colleagues<sup>20</sup> recently performed a systematic review and a meta-analysis of the literature. The prevalence of 5 major established risk factors for atherosclerosis (obesity, arterial hypertension, diabetes mellitus, smoking, and dyslipidemia) was compared in patients with VTE and in controls based on data from 21 selected case-control and cohort studies, including a total of more than 60,000 patients and controls. Obesity (OR, 2.33; 95% CI, 1.68–3.24), hypertension (OR, 1.51; 95% CI, 1.23–1.85), and diabetes mellitus (OR, 1.42; 95% CI, 1.12–1.77) were associated with VTE. There was no significant association with smoking (OR, 1.18; 95% CI, 0.95–1.46). Hypercholesterolemia was not associated with an increased risk of VTE (OR, 1.16; 95% CI, 0.67–2.02), but the weighted mean in HDL cholesterol levels was significantly lower in patients with VTE than in

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