Modifiable Risk Factors for Venous Thromboembolism

Subjects: Peripheral Vascular Disease

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Venous thromboembolism (VTE), which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant cause of morbidity and mortality worldwide. There are many factors, both acquired and inherited, known to increase the risk of VTE. Most of these result in increased risk via several common mechanisms including circulatory stasis, endothelial damage, or increased hypercoagulability.

deep vein thrombosis pulmonary embolism venous thromboembolism risk factors thrombophilia

1. Previous Venous Thromboembolism

Individuals with a history of venous thromboembolism (VTE) are at an increased risk of recurrent thrombosis. A prospective cohort of 355 patients reported an incidence of recurrent VTE at 17.5% after two years of follow up, 24.6% after four years, and 30.3% after eight years [1]. Likewise, in a large observational study of 1231 patients with VTE, 19% of the patients reported at least one prior clinically recognized VTE event [2]. However, the risk of recurrence is highly dependent upon patient-specific factors. Patients with a history of VTE in the setting of a transient, reversible risk factor (i.e., immobilization or surgery) have a lower rate of recurrence compared to those with no known risk factors (i.e., unprovoked) or with permanent risk factors (i.e., malignancy). In the study noted above, the presence of cancer was associated with an increased risk of recurrent VTE (hazard ratio (HR) 1.72) while surgery and recent trauma or fracture were associated with a decreased risk of recurrent VTE (HR 0.36) [1]. Similarly, a prospective cohort study of 570 patients followed over 2 years noted zero recurrence of VTE in those whose first VTE occurred within six weeks of surgery compared to 19.4% recurrence in those whose first VTE had no identifiable clinical risk factors [3]. As such, while a previous VTE is a risk factor for a future VTE, the ultimate risk is highly dependent on patient-specific factors, which are further outlined below.

2. Family History of Venous Thromboembolism

Similar to a personal history of VTE, a family history of VTE has also been identified as a risk factor for VTE development. A large national cohort study noted that having a sibling with a history of VTE incurred a relative risk (RR) of 3.08 for developing a VTE event compared to the general population [4]. It appears that the risk increases based on the number of family members with a prior VTE. In a case–control study of 505 patients, a positive family increased the risk of VTE more than 2-fold (odds ratio (OR) 2.2), with the risk increasing up to 4-fold (OR 3.9) when

more than one relative has a history of VTE [5]. Interestingly, this research also noted that those with hereditary thrombophilia and a family history of VTE had a higher risk of VTE compared to those with heredity thrombophilia and no family history. Specifically, in those with a factor V Leiden mutation, a positive family history of VTE incurred a 2.9-fold higher risk compared to a negative family history [5]. These findings underscore that there are likely other inherited thrombophilias present that have yet to be discovered.

3. Immobility

Prolonged periods of immobility, such as postoperative bed rest, paralysis, hospitalization, or long-haul travel, are well-established risk factors for VTE. Immobility leads to venous stasis, particularly in the legs, which promotes thrombosis. A prior autopsy study noted that 15% of patients on bed rest for less than one week before death were found to have a venous thrombosis, with the incidence increasing to 80% for those in bed for a longer period [6]. Likewise, in a large international registry, chronically immobile elderly patients were noted to have an increased risk of recurrent VTE [7]. As immobility can be caused by numerous different factors, the risk of VTE ultimately depends on the cause and length of immobility.

The risk of VTE after an acute cerebrovascular accident (CVA) resulting in paralysis is quite high. The current rates of symptomatic VTE in patients with acute CVA ranges from 1–10%, whereas asymptomatic VTE is even higher, with a report of 11% at 10 days post CVA and 15% at 30 days post CVA [8][9][10]. Likewise, the rates of DVT within 3 months of paralytic spinal cord injury are also high, with the reported incidence of DVT being greater than 30% in those who are screened for DVT [11][12]. The risk of VTE development after spinal cord injury appears to be greatest during the first two weeks after injury, with fatal PE being rare beyond 3 months after injury [13]. Interestingly, chronic immobility in the setting of CVA or spinal cord injury does not appear to confer the same degree of risk as acute immobility. This difference is likely due to the physiologic changes that occur with chronic immobility, including leg muscle atrophy and changes in venous anatomy [13].

Transient immobility both during hospitalization and upon discharge to home or rehabilitation facility also represents an important risk factor for VTE. In addition to venous stasis due to immobility, acute illness can increase the risk of VTE due to increased alterations in the hypercoagulable state and damage to endothelial cells in the setting of increased inflammation. Common medical illnesses associated with VTE in hospitalized patients include infection, CVA, inflammatory bowel disease, and autoimmune diseases [14]. When compared to patients in the community, those hospitalized for any reason appear to have a 100 times greater incidence of VTE [15]. Likewise, factors associated with institutionalization, defined as current or recent hospitalization within the past three months or being a nursing home resident, independently account for over 50% of all cases of VTE in the community [16].

Prolonged travel, including in the car and by air, also appears to confer an increased risk of VTE. A meta-analysis of 14 studies noted that the pooled RR for VTE in travelers was as high as 2.8 [17]. Additionally, there was a dose–response relationship identified with an 18% higher risk for VTE for each 2 h increase in the duration of travel by any mode and a 26% higher risk for every 2 h of air travel.

Lastly, prolonged sitting such as at a computer for a prolonged period also appears to confer an increased risk. In a series of patients admitted for DVT/PE, 34% reported seated immobility for a prolonged period of time (8–12 h) at work [18].

4. Surgery

Surgical procedures have long been associated with an increased risk of VTE, as surgery can result in damage to blood vessels, activation of the coagulation cascade, and venous stasis due to immobility, both during the surgery and in the post-operative period. However, not all surgery carries the same risk of VTE, with thrombotic risk being the highest amongst orthopedic, major vascular, neurosurgery, and cancer surgery. Hip and knee arthroplasty are considered amongst the highest-risk surgeries for VTE development. Initial reports have demonstrated that the VTE incidence is as high as 30% in patients undergoing major orthopedic surgery who were not receiving thromboprophylaxis [19]. However, during more recent studies, where anticoagulation was used for VTE prophylaxis, the incidence is much lower, typically less than 5% [20][21]. The American College of Chest Physicians (ACCP) estimates the baseline perioperative, 35-day risk at 4.3% after major orthopedic surgery, with the risk highest within the first 7–14 days [22]. As such, several guidelines, including the International Consensus Meeting on VTE in 2022 (Strength of Recommendation: Strong), the American Society of Hematology in 2019 (conditional recommendation based on very low certainty), and the National Institute for Health and Care Excellence (NICE) in 2018, recommend the use of chemoprophylaxis for the prevention of VTE in this patient population [23][24][25].

In non-orthopedic surgery, open abdominal and open pelvic surgery, particularly for those associated with cancer, are also considered high risk [26][27]. Neurosurgical interventions have also reported increased rates of VTE, with a meta-analysis reporting approximately one in four patients developing VTE after neurosurgery [28][29]. Other surgeries reporting an elevated risk of VTE in the post-operative setting include coronary artery bypass, major urologic surgery, thoracic surgery, and bariatric surgery [30][31][32].

In contrast, laparoscopic surgery does not appear to confer the same degree of risk compared to open surgery. A retrospective study of 750,159 patients demonstrated an incidence of VTE of 0.32% within 30 days of abdominal laparoscopic surgery, with the highest incidence among patients undergoing colorectal surgery at 1.12% [33]. Similarly, another retrospective study of over 138,595 patients demonstrated that the incidence of VTE among patients undergoing laparoscopic surgery was lower compared to those undergoing open surgery (0.28% versus 0.59%, respectively) [34].

5. Trauma

Trauma resulting in fracture and severe injury elevates the risk of VTE, often due to blood stasis in the setting of immobilization and via endothelial activation in the setting of injury, resulting in the activation of the clotting cascade. Like surgery, not all trauma confers the same degree of risk of thrombosis. Major trauma is associated with a significantly increased risk of VTE. A study of 716 patients with major trauma, defined as an Injury Severity

Score of at least 9, who underwent screening evaluation for DVT reported a DVT incidence of 58%, with 18% occurring in the proximal veins [35][36]. Of note, these patients did not receive prophylactic anticoagulation. Interestingly, while the use of prophylactic anticoagulation does reduce the risk of VTE in patients with major trauma, the reported rates of VTE in this patient population remain high, with a reported incidence of VTE of 44% with the use of low-dose heparin and of 31% with the use of low-molecular-weight heparin [37]. Trauma resulting in fracture, particularly those involving the lower limb, is a strong VTE risk factor. The incidence differs based on the location of the fracture, with the highest risk locations including the hip (16.6%), tibial plateau (16.3%), and tibial shaft (13.3%) [38].

In contrast, minor trauma does not appear to confer the same degree of risk. In a cohort of 294 cancer-free patients with VTE admitted to hospital, the adjusted incidence rate ratio (IRR) for VTE for open wounds was 0.46 (95% CI, 0.15–1.39), for sprains 1.15 (95% CI, 0.44–3.04), and for dislocations 1.54 (95% CI, 0.37–6.48). In contrast, the adjusted IRR in the same cohort was elevated for fractures (2.45, 95% CI 1.29–4.68) and immobility (3.84, 95% CI 2.39–6.15) [39]. Likewise, a systematic review of 15 studies demonstrated an incidence of VTE of 4.8% in patients undergoing temporary lower limb immobilization due to isolated trauma [40].

6. Cancer

Malignancy is a well-established risk factor for the development of VTE. Cancer is known to create a hypercoagulable state via the expression of hemostatic proteins on tumor cells, the release of inflammatory cytokines, and the activation of the clotting system [41]. Additionally, depending on the location and size of the tumor, the local mass effect can lead to the compression of veins with the stasis of venous flow. Amongst patients with symptomatic DVT, approximately 20% will have a known active malignancy [16][42]. The risk of cancer-associated thrombosis (CAT) varies due to several factors, including cancer site and stage, malignancy treatment, and other patient-specific factors. The risk of VTE varies broadly by cancer type. In a large registry study, the cancers associated with the highest 6-month cumulative VTE incidence were pancreatic cancer (4.4%), ovarian cancer (3.1%), Hodgkin lymphoma (2.9%), and non-Hodgkin lymphoma (2.7%); in contrast, melanoma (0.36%) and breast cancer (0.64%) were amongst the malignancies with the lowest risk [43]. Other significant risk factors for VTE development included a prior history of VTE (subdistribution HR (SHR) 7.6), distant metastasis (SHR 3.2), and the use of chemotherapy (SHR 3.4). These findings have been confirmed elsewhere with metastatic disease and the use of high-risk treatment, including surgery, radiotherapy, and chemotherapy, being associated with an increased risk of VTE [44].

The risk of VTE is highest in the first 3 months after cancer diagnosis [43][45][46]. This increased risk is likely related to cancer treatments, as several treatments, including chemotherapy, protein kinase inhibitors, antiangiogenic therapy, and immunotherapy, as well as the use of central venous catheters, have been associated with an increased risk of thrombosis [43][47]. Aside from the increased morbidity associated with VTE, CAT is reported to be the second leading cause of death after disease progression amongst patients with cancer [48].

Given the clear association of malignancy as a risk factor for VTE, the question often arises about screening for malignancy in a patient with VTE without other identified risk factors with the goal of the earlier detection of malignancy and thus decreasing the cancer-related mortality and improving the quality of life. Of note, the majority of cancers associated with thromboembolic events have previously been diagnosed at the time of VTE diagnosis [49]. In those without a known history of malignancy, the rate of occult cancer detection for unprovoked VTE was ~5% within 12 months of VTE diagnosis [50][51][52]. Despite this, there has been no data demonstrating improved patient-specific outcomes [52]. As such, the 2017 International Society on Thrombosis and Haemostasis recommend performing age- and gender-specific cancer screening (breast, cervical, colon, and prostate) while more intensive screening with whole-body CT or PET scan is not routinely recommended [53].

7. Pregnancy and Postpartum

Pregnancy and the postpartum period are associated with an increased risk of VTE via several different mechanisms. Venous stasis frequently occurs in pregnancy due to the compression of the pelvic vein by the gravid uterus and due to pregnancy-associated changes in venous capacitance. Additionally, pregnancy can result in an alteration in several coagulation factors, resulting in a hypercoagulable state, as well as result in vascular injury at the time of delivery [54]. The overall incidence of VTE in pregnancy is relatively low with reports of VTE diagnosis during 1 in 1000 to 2000 pregnancies [55][56]. The incidence of DVT is reported to be three times higher than that of PE and the majority of VTE events occur in the postpartum period [55][56]. Compared to non-pregnant patients, pregnant patients have a 5-fold increased risk of VTE during pregnancy, with the risk increasing substantially to 60-fold during the first three months after delivery [57]. Additional reported risk factors associated with pregnancy-related VTE include increasing age (age > 40) and the use of assisted reproductive technology [58][59][60].

8. Hormone-Based Contraception and Hormone Replacement Therapy

Estrogen-containing contraceptives and hormone replacement therapy (HRT) have been associated with an increased risk of both arterial and venous thrombosis. The mechanism is not fully understood but appears to be related to the effect that estrogen has on inducing prothrombotic and fibrinolytic changes in hemostatic factors as well as impacting the regulation of endothelial function [61]. Given their widespread use, oral contraceptives (OCPs) are one of the most important causes of thrombosis in young women. It is reported that OCPs increase the relative risk of VTE by approximately threefold [60][62][63]. The risk of VTE development with the use of OCPs appears to be highest in the first 6–12 months after the initiation of OCPs [64]. At the time of cessation of OCPs, the risk of VTE is felt to return to the level prior to OCP initiation within one to three months. Overall, the risk of VTE is considerably lower with the use of OCPs compared to the risk seen in pregnancy and the postpartum period. Additional factors that are felt to increase the risk of VTE during OCP use include smoking, obesity, polycystic ovary syndrome, older age, venous compression, and immobilization [65][66][67].

HRT is also associated with increased risk; however, this risk appears to be lower than that of OCPs, potentially due to the lower estrogen doses used in HRT compared to OCPs. Studies suggest that HRT causes an approximate twofold increase in the VTE risk [68][69][70]. Similar to OCPs, the risk of VTE development appears to be highest in the first year of HRT treatment [70]. Other risk factors associated with VTE in the setting of HRT use include older age, overweight/obesity, and factor V Leiden mutation [71].

9. Obesity

Obesity is a recognized risk factor for VTE, likely due to its association with inflammation and the enhanced production of clotting factors. There are numerous studies demonstrating that obesity is associated with an increased risk of DVT and PE, and conversely, that underweight patients are at a reduced risk. In a study of 19,293 patients evaluating cardiovascular risk factors and venous thromboembolism, a body mass index (BMI) of greater than 40 had a sex-adjusted HR of 2.7 [72]. Likewise, a national database study demonstrated an RR of 2.5 for DVT and 2.21 for PE when comparing obese patients to non-obese patients [73]. Conversely, results from the EDITH study demonstrated underweight patients had a statistically significant reduction in risk for VTE compared with normal weight (OR 0.55) [74].

10. Smoking

Cigarette smoking is linked to endothelial damage and inflammation and thus a heightened risk of VTE, especially in combination with other risk factors. Smoking is a well-established risk factor for atherosclerosis but has a less established link with VTE. There are several studies that have demonstrated no significant relationship between smoking and VTE [72][75]. However, others have demonstrated a link between smoking and VTE, with several demonstrating a dose-dependent link between smoking and non-smoking, with those having a higher pack year and currently smoking being at the highest risk [76][77].

11. Age

Advancing age has been demonstrated in numerous studies to be associated with VTE, with proposed mechanisms including changes within the venous system and less effective inherent anticoagulation mechanisms. A prior study has demonstrated an exponential increase in VTE risk with age, with the annual incidence rate for DVT increasing from 17 per 100,000 persons/years for patients between the ages of 40 to 49 to 232 per 100,000 persons/year for those between the ages of 70 and 79 [78]. Similarly, it has been noted that the risk of VTE approximately doubles with each decade, starting at age 40 [13]. With this, VTEs in children and young adults are rare. When they do occur, they are usually associated with a strong predisposing risk factor, such as trauma/fracture or surgery.

12. Male Sex

Male sex has been demonstrated in several studies to be a risk factor for VTE recurrence; however, there is no reported sex differences in the risk of the first VTE event. In a meta-analysis of 2554 patients with a first VTE, the incidence of recurrence was higher in men than women, both at one year (9.5% vs. 5.3%) and at three years (11.3% vs. 7.3%) [79]. Likewise, another large meta-analysis of over 2185 demonstrated a 2.8-fold higher risk of VTE recurrence in men compared to women [80]. The mechanism behind this difference is unclear but has been reported to be due to differences in other VTE risk factors between the sexes. One prior study noted a factor V Leiden mutation as a risk factor for VTE recurrence in male patients, while the age at the first event and obesity were noted as risk factors for female patients [81].

13. SARS-CoV-2 Disease (COVID-19)

Since the start of the COVID-19 pandemic, there have been numerous reports demonstrating an increased risk of VTE. Mechanistically, SARS-CoV-2 is felt to increase the risk of VTE via the release of proinflammatory cytokines which activate platelet aggregation, tissue factor, and the coagulation cascade, as well as via the interaction with the angiotensin converting enzyme (ACE)-2 receptor on endothelial cells, resulting in endothelial dysfunction as well as the release of vasoconstrictor angiotensin-II [82][83]. With this, numerous studies have reported increased rates of VTE in patients hospitalized with COVID-19. A large meta-analysis demonstrated that the overall prevalence of PE/DVT in hospitalized patients with COVID-19 who underwent a screening assessment for VTE was approximately 30% [84]. Moreover, a meta-analysis of twelve studies demonstrated a VTE prevalence of 31% among ICU patients, despite the use of prophylactic or therapeutic anticoagulation [85]. In contrast, the incidence of VTE in non-hospitalized patients with COVID-19 does not appear to be increased. In a large cohort of 398,000 patients, the overall incidence of VTE in non-hospitalized patients with COVID-19 was reported to be 0.1%. Likewise, in a retrospective cohort comparing COVID-19-positive patients with COVID-19-negative controls, the 30-day prevalence of VTE events was not different between the two groups (1.4% vs. 1.3%, respectively) [86]. Interestingly, it appears that the risk of VTE also differs by the strain of SARS-CoV-2 virus [87]. While there is still much left to understand about the role of COVID-19 in the VTE risk, it does appear that both the severity of COVID-19 illness and the strain of COVID-19 virus do impact the risk.

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