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Risk Factors for Venous Thromboembolism

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Introduction

There are many risk factors reported to increase the risk of venous thromboembolism (VTE), as shown in Table 1.1.

Large national registries for VTE patients have helped to elucidate and quantify the relative risk of individual factors. The risk factors for deep vein thrombosis (DVT) and pulmonary embolism (PE) are largely similar, as DVT and PE represent a spectrum of the same disease process. There is also some overlap between venous and arterial thrombotic risk, with age, smoking and obesity common to both, although they are much more important factors in arterial disease. Part of this may be an indirect association – for example, smoking increases cancer risk, and hence VTE, while medical in-patients with heart failure have a marked increase in risk for pulmonary embolism. Figure 1.1 shows the increasing rate of VTE with age, from the UK VTE registry, VERITY. Overall, the risk for VTE is increasing, with an ever aging population, receiving multiple medications many of which increase thrombotic risk, particularly in the field of cancer medicine.

The most important risk factors for VTE are a history of previous VTE, recent surgery, hospital in-patient stay and cancer. While there is much comment around factors such as long-haul travel and inherited risk factors for VTE, these represent less common and less important factors. In general the more risk factors present, the greater will be the cumulative risk for VTE.

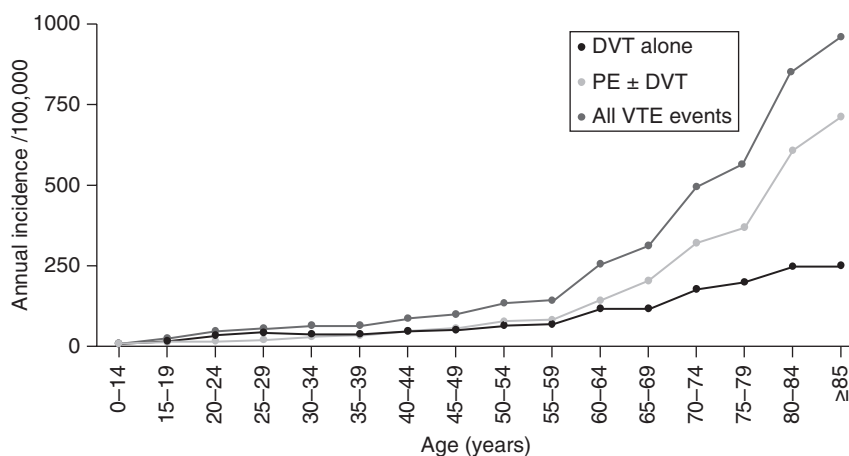
Previous VTE

For patients with a known history of VTE, it is important to identify if the previous event was provoked, in association with temporary risk factors, or unprovoked. The risk of recurrence is less than 3% if provoked, but is near 10% in unprovoked VTE within 12 months of discontinuing anticoagulant therapy. It can be difficult to determine what is and is not provoked; for example, a DVT post orthopaedic surgery is clearly provoked, while a female on the combined pill preparation for three years without previous thrombosis is not necessarily a provoked event. A VTE within three months of starting the pill however, would be provoked.

Provoking factors can be further divided into surgical, with a recurrence rate of 1% within 12 months of treatment, and non-surgical factors, with a 6% risk in this time period. For patients with unprovoked VTE, the risk persists with time, with 40% recurrence within ten years. For a cohort of young male patients presenting with unprovoked PE, there is a 20% risk of recurrence of PE within 12 months which persists, making recurrence almost inevitable.

Table 1.1 Risk factors for venous thromboembolic disease.

Patient Related	Additional factors
Increasing age	Surgery within 90 days
Previous history VTE	Lower limb cast
Family history 1st degree relative	Hospital stay > 3 days
Thrombophilia	Cancer in past six months/ongoing disease
Pregnancy	Medical comorbidities
Obesity > 30 kg/m ²	Extended travel
Smoking/alcohol/substance abuse	Medication related

**Figure 1.1** VTE risk increases with age. Taken from UK VERITY (Venous Thromboembolism registry).

Surgery

Pulmonary embolism remains the most widely reported preventable cause of death in patients undergoing surgery. It is the most common cause of death within 30 days of surgery, with 40% of VTE events occurring later than three weeks post-operatively. Even for low-risk general gynaecological abdominal surgery for non-malignant disease, the risk for VTE extends up to at least 90 days post-surgery. Previous autopsy studies in surgical patients report VTE to be present in 5–10% of cases. Surgery, therefore, requiring general anaesthesia for over one hour, is a major risk factor for VTE. Surgical risk is compounded by many concomitant medical risk factors – for example, a further doubling of risk in cancer surgery. See Table 1.2.

Orthopaedic Surgery

Patients undergoing lower limb surgery are among the highest risk patients (odds ratio > 10), and this includes total hip and knee arthroplasty, hip/leg fractures, major orthopaedic trauma and spinal surgery. With improved surgical procedures and shorter time for anaesthesia, there is some recent risk reduction. The risk for VTE partly relates to prolonged stasis associated with immobility, and the release of tissue fragments of collagen and fat, which can directly activate coagulation factors. Furthermore, direct blood vessel damage during retraction of soft tissues can act as a nidus for thrombus formation.

Table 1.2 Surgical risk factors for VTE.

Personal	Surgical
Age > 60	Prolonged anaesthesia
Medical comorbidities	Major trauma
Previous VTE	Lower limb surgery
Thrombophilia	Major abdominal surgery
Obesity	Cancer surgery
	Post-operative admission to ITU
	Bariatric surgery

Lower limb immobilisation in casts, with or without surgery, increases the risk of VTE. The prevalence of lower limb injury-related DVT with cast immobilisation is reported to occur in 4–40% of cases. Further confirmation of the importance comes from studies using chemical thromboprophylaxis, which results in a 50% reduction in DVT rate. On this basis, NICE guidance recommends that all patients with lower limb immobilisation should be assessed for chemical thromboprophylaxis.

Other Surgeries

Other high-risk surgery includes major abdominal procedures, particularly in cancer patients. Evidence confirming the importance of general surgery as a major risk factor for VTE is provided from studies evaluating the efficacy of thromboprophylaxis. For example, a systematic review of cancer patients undergoing surgery showed a reduction in VTE events from 35% to 13% in patients receiving pharmacological thromboprophylaxis.

Additional risk factors for thrombus and surgery include the increasing use of indwelling venous catheters and filters for prolonged periods of time in the post-operative period. It is estimated that 14% of patients undergoing cardiac surgery without thromboprophylaxis develop VTE. As many of these patients are already on antiplatelet or anticoagulant therapy, the true risk associated with surgery is difficult to assess. Similarly, the risk with vascular surgery, while increased, is difficult to quantify in a largely elderly group with reduced mobility, on anti-platelet therapy and often with comorbidities. A careful VTE risk assessment is needed for all patients undergoing surgery, particularly where this involves general anaesthesia and prolonged hospital admission, evaluating the bleeding risk due to the procedure against the reduction in thrombotic events.

Hospitalised Medical Patients

Approximately 70–80% of fatal hospital acquired thrombosis (HAT) occurs in medical patients. Venous thrombosis is increased in most acute medical conditions, necessitating hospital admission. The risk of VTE is also increased in a number of chronic medical disorders (see Table 1.3). Medical inpatients are usually elderly, often with several conditions to compound VTE risk.

Stroke patients, whether due to ischaemic or haemorrhagic events, are at increased risk of VTE, with a wide range of estimates reported, namely, 15–60%. Prevention with chemical thromboprophylaxis is dependent on safety, with haemorrhagic risk often high. In the absence of haemorrhage, the presence of additional factors, such as severity of immobilisation and comorbidities, are important for risk assessment. Acute respiratory infection in hospitalised patients is a particularly high risk for VTE. Other medical conditions included in

Table 1.3 Medical conditions with increased risk of VTE.

Acute	Chronic
Congestive heart failure	Disorders of mobility (mechanical/ neurological)
Respiratory failure	Nephrotic syndrome
Severe infection/ sepsis	Sickle-cell disease
Rheumatological conditions	Paraproteinaemia
Inflammatory bowel disorders	Paroxysmal nocturnal haemoglobinuria
Stroke	Bechet's disease
Cancer	Porphyria

clinical trials for thromboprophylaxis in medical patients include congestive heart failure, respiratory failure, acute rheumatological and inflammatory bowel disorders.

Clinical studies have shown the risk of DVT to be between 4–5%, with mortality at 90 days 6–14%. Congestive heart failure patients commonly develop DVT in the absence of thromboprophylaxis, affecting 20–40% of patients, with a similar risk for medical intensive care patients. All hospitalised medical inpatients, therefore, require a risk assessment for VTE in order to reduce morbidity and mortality from HAT.

Several chronic medical conditions carry an increased life-time risk of VTE. Rheumatological disorders such as systemic lupus erythematosus, particularly associated with the anti-phospholipid syndrome, are pro-thrombotic conditions. Inflammatory bowel disease is associated with a 2–3 fold increased VTE risk. Less common medical conditions at high risk include Bechet's disease, nephrotic syndrome, sickle cell disease, and some porphyrias. Paroxysmal nocturnal haemoglobinuria, while rare, is complicated by thrombotic problems in over 50% of cases. Medical treatments may also be associated with VTE, with hormone therapies and erythropoietin being common examples. These medical conditions should evoke a high index of suspicion for VTE, particularly in those with a previous proven event.

Cancer Associated Thrombosis (CAT)

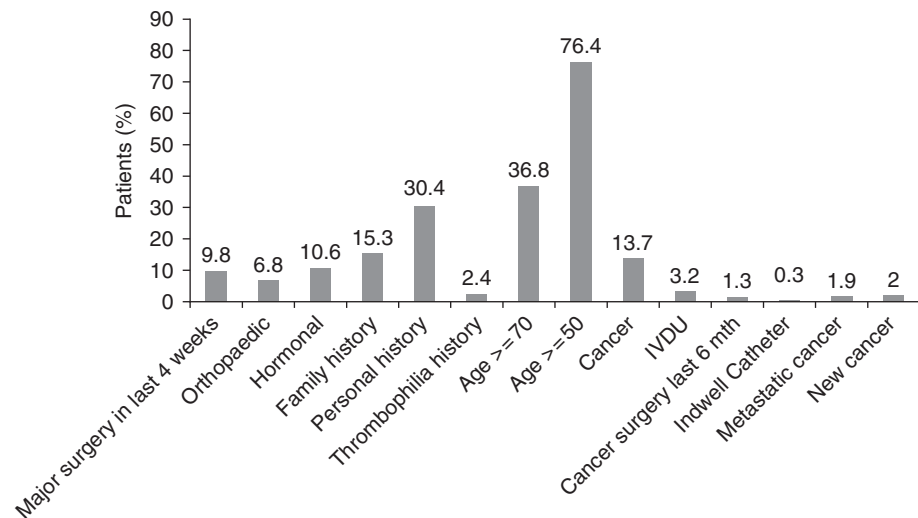
Twenty percent of all VTE cases occur in patients with cancer (those diagnosed within the previous six months or with ongoing disease or treatment for cancer). VTE is the second most common cause of death in cancer patients, and is associated with a very poor prognosis. Nearly 50% of cancer patients die within six months of developing VTE. CAT has a different pathogenesis, a different additional risk profile, and requires different management from non-cancer VTE. CAT is often undiagnosed, as it is found in 50% of cancer patients at autopsy. Important risk factors need to be considered for CAT, including the tumour site and the presence of metastatic disease. These risk factors are shown in Table 1.4 below.

Tumour sites with the highest thrombotic risk include pancreas, brain, stomach and lung. Rare tumours, such as head and neck plus endocrine, are also high risk for CAT – see Figures 1.2 and 1.3 from the UK VERITY registry.

While breast and prostatic cancer are the most commonly seen malignancies in patients presenting with CAT, this is due to their increased prevalence, with overall moderate to low risk, respectively, for these sites. The risk of VTE is greatly increased in the presence of metastatic disease, with increased tumour burden an important factor in promoting the pro-thrombotic state. This is illustrated in breast cancer, where the risk for localised Stage 1 disease not requiring adjuvant treatment for VTE is low, but increases 15 fold for those with Stage 4 disease requiring chemotherapy.

Table 1.4 Risk factors for cancer-associated VTE.

All cancer patients	Cancer patients receiving chemotherapy
Site of tumour high/intermediate/low risk	Platelets $> 350 \times 10^9/l$
Metastatic disease	Haemoglobin $< 100 g/l$
Surgery	White blood count $> 11 \times 10^9/l$
Chemotherapy	BMI $> 35 kg/m^2$
Radiotherapy	High D-dimer
Hormone treatment	High serum P-selectin
Anti-angiogenic therapy	
Indwelling venous catheter	

Figure 1.2 Risk factors for VTE. Taken from UK VERITY (Venous Thromboembolism registry).

There is also a 28 fold increase in CAT patients with haematological malignancy, compared with population controls. This figure not only reflects the underlying pro-thrombotic state, but also the intensity and need for several modalities of treatment. Nearly all modalities of treatment increase the thrombotic risk in cancer patients. Many chemotherapeutic agents increase damage to the vascular endothelium, while radiotherapy also increases VTE. Many adjuvant treatments, such as hormone therapy, anti-angiogenic agents such as thalidomide, lenalidomide and anti- VEGF therapy, are associated with high risk for thrombosis. The use of indwelling lines for prolonged venous access, together with the additional risk where surgery is needed, all contribute to CAT. Supportive therapies, such as G-CSF, erythropoietin and even blood transfusion, have been reported to increase VTE risk.

The presence of malignancy appears such a significant risk factor for VTE that the risk profile is very different from non-cancer patients with VTE. In one large registry study, factors such as personal history of VTE, Thrombophilia, IV drug abuse and smoking were only significantly raised in non-cancer patients, with medical in-patient stay with immobilisation for more than three days in the last four weeks more common in CAT patients. In many, CAT is asymptomatic with increasing numbers of cases identified, due to improved imaging techniques. All cancer patients, as part of the multi-disciplinary treatment assessment at presentation, should have an appraisal of VTE risk in order to reduce the very high mortality with CAT. See Figure 1.4.

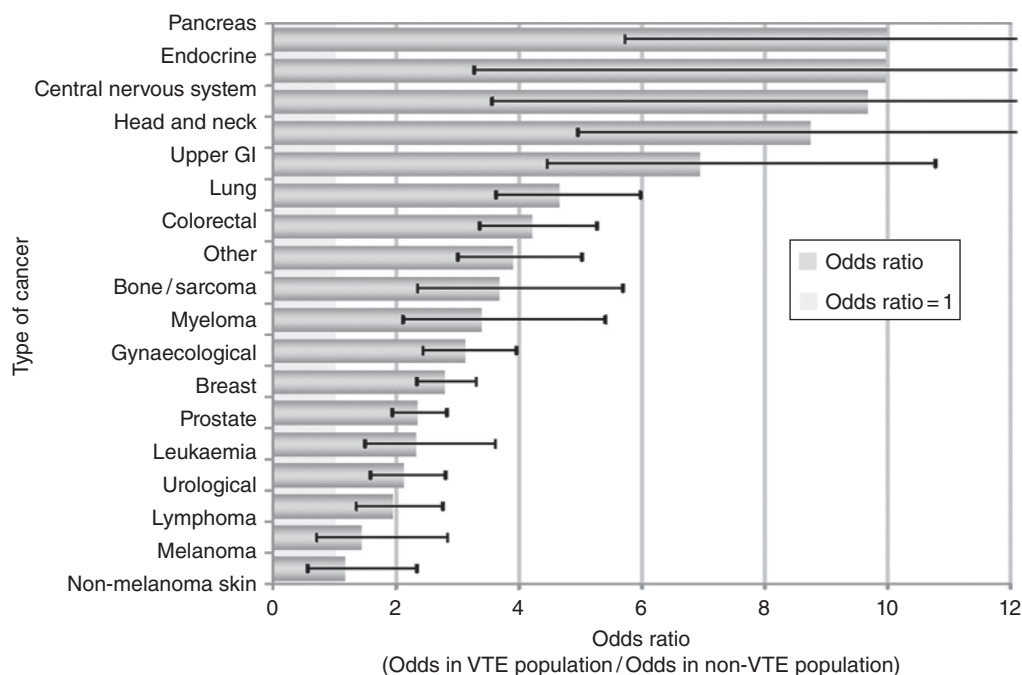


Figure 1.3 Rates of different cancers in the non-VTE and VTE population; odds ratios for different types of cancer. Taken from UK VERITY (Venous Thromboembolism registry).

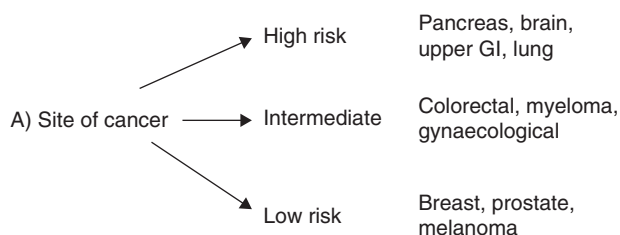


Figure 1.4 Risk assessment for VTE in cancer patients.

Pregnancy

Pregnancy is a pro-thrombotic state from the first trimester onwards, and is associated with a 4–5 fold increase in risk for VTE. The highest risk period is in the immediate eight weeks post-partum, with a 20 fold increased risk. The prevalence of all thrombotic events in pregnancy is two per 1000 deliveries, with 80% venous and 20% arterial. It is suggested that the pro-thrombotic state has evolved to reduce the haemorrhagic complications with childbirth. VTE accounts for approximately 10% of all maternal deaths, and is the most common cause in the western world. The risk of VTE increases with maternal age and multi-parity, and is higher in black females. The risk factors are shown in Table 1.5.

The clinical presentation is usually with an extensive clot in the proximal veins of the left leg. The predilection for the left leg is due to narrowing of the left common iliac vein, as it compresses between the lumbar vertebral body and right common iliac artery. There have also to be additional mechanical or hormonal factors in pregnancy to affect this change.

Table 1.5 Pregnancy and risk factors for VTE.

Patient-related	Additional factors
Increasing age > 35	Caesarean section
Previous VTE	Dehydration (hyperemesis)
Multi-parity	Pre-eclampsia
Varicose veins	Previous fertility treatment
Thrombophilia	Puerperal sepsis
Ethnicity (> Afro-Caribbean)	Ante-partum haemorrhage
Obesity	
Smoking	

Reduced venous flow in pregnancy is multi-factorial, with hormones mediating a reduction in venous tone and increased risk of varicosities. This is abetted by the expanding uterus and reduced mobility. The higher risk post-delivery is the result of increased tissue and vessel damage. A number of coagulation factors are significantly increased, including factors V, VIII, IX, XI and fibrinogen. There are changes in the natural anticoagulant free protein S, which reduces throughout pregnancy due to increased levels of binding protein C-4b, increasing thrombotic risk. Reduced fibrinolysis with increased levels of plasminogen activator inhibitors (PAI-1) and (PAI-2), is also seen in pregnancy. PAI-2 is produced in the placenta, and markedly increases in the third trimester. All of these changes contribute to the pro-thrombotic condition.

There are several additional risk factors to increase VTE in pregnancy. A personal history of VTE increases the risk by a further 3–4 fold. Dehydration and hyperemesis can be an important factor from early in pregnancy. Surgical intervention, with caesarean section, post-partum haemorrhage and puerperal sepsis, all increase thrombotic risk. While pregnancy can be considered an acquired form of thrombophilia, the risk for VTE increases further in the presence of a heritable thrombophilia. The risk varies dependent on the thrombophilia but, for those homozygous for Factor V Leiden or the Prothrombin mutation, there is a 30 fold increase in risk, while heterozygosity is associated with a 6–8 fold increase.

Patients with anti thrombin deficiency are high risk, with 50% risk for VTE in pregnancy. Protein C and S deficiency are reported to increase risk during pregnancy by 3–10% and 0–6%, respectively, with higher risk post-partum between 7–20%. Patients with thrombophilia, particularly with a proven history of VTE, would require specialist input to assess management.

Those who become pregnant as a result of fertility treatment have an added risk of VTE, sometimes presenting with thrombosis at unusual sites, resulting in subclavian and/or jugular vein thrombosis. A proper risk assessment for VTE in pregnancy is therefore essential, in order to avoid preventable morbidity and mortality. Combined assessment at an obstetric and haematology clinic is needed for patients at high risk, particularly those with a previous history of VTE.

Combined Oral Contraceptive Use

The highest risk period for VTE in users of the combined oral contraceptive (COC) is in the first few months of starting. The individual risk for VTE is very low but, as there are over 100 million users of reproductive age, it has an important impact on the incidence of VTE. The incidence in non-COC users is reported to be 0.16 per 1000 person years, while the relative risk in COC users compared to non-users is reported, in a Cochrane database study, to be 3.5. Similar to pregnancy, there are increased levels of several coagulation factors, and

reduced levels of some natural anticoagulants in particular protein S. These changes have been reported to be more pronounced in some COC preparations than in others, most notably third generation COCs.

While all COC preparations increase VTE risk to some extent, studies have identified the dose of ethinylestradiol to be critical, with an important risk reduction in the dose from 150 to 30 micro grammes. The thrombotic risk is also dependent on the progestogen used in the preparation. Changes in the progestogen component have been made to try to reduce side-effects of COCs. Second-generation, from the 1970s, and third-generation COCs, together with further preparations, have had varying VTE risk outcomes. Overall, the most recent Cochrane review still reported the second-generation COC with 30 microgrammes of ethinylestradiol and levonorgestrel to have the lowest risk for VTE.

For all COC users of low-dose ethinylestradiol in combination with either gestodene, desogestrel, cyproterone acetate or drospirone, the risk of VTE is 50–80% higher than with the second-generation COC. More recent studies, with the exception of norgestimate, also confirm the risk to be higher for the newer drug preparations. To date, there is limited information on the progestin-only contraceptive, although a recent meta-analysis concluded that VTE risk is not increased.

For postmenopausal women, increasing age is an important compounding factor and, for those taking hormone replacement therapy, there is a 2–5 fold increased risk for VTE. This risk is highest in the first 12 months of starting, when the risk is increased six-fold. The risk varies by preparation, but is higher in oestrogen-progestin preparations and increases with higher oestrogen dose. There is also a significant difference dependent on the mode of delivery, with transdermal patches safer. Overall, the risk, particularly when there are additional comorbidities, needs to be assessed when considering optimal therapy.

Family History of VTE and Thrombophilia

A family history of an unprovoked VTE in a first-degree relative is associated with an additional risk for VTE. Screening for a significant heritable thrombophilia in patients with a proven history will, however, fail to identify an abnormality in nearly 50% of cases. The increased VTE risk remains, whether or not the screen is positive. For younger patients with an unprovoked PE, a thrombophilia screen should be considered if it is planned to stop anticoagulant treatment. This would also be the case where there is a known high-risk thrombophilia in a first-degree relative and the patient is due to be exposed to additional risk factors.

Heterozygosity for Factor V Leiden can be identified in approximately 5% of people in the UK. It carries only a two-fold risk for VTE, and is the most commonly found abnormality in studies where thrombophilia screening has been undertaken in proven VTE patients, present in 30% of cases. For very rare cases homozygous for Factor V Leiden, the risk of VTE increases nearly 80 fold. The absolute risk for non-COC users heterozygous for Factor V Leiden is 35 per 100 000, rising to 285 per 100 000 for COC users. To put this in context, it compares to an absolute risk with fracture of femur of 6000 per 100 000. Overall, the risk of COC usage is not an absolute contraindication in carriers of Factor V Leiden, as the risk would be higher if pregnant. If known, it should, however, be part of the discussion around the most appropriate and safest form of contraception.

Overall, the risk of a first DVT in carriers of Factor V Leiden or Prothrombin gene mutation, and those with increased levels of FVIII, is under 0.5% per year, not high enough to warrant consideration for thromboprophylaxis. This is particularly the case as there is no difference in recurrence rate to patients with first DVT who have not had thrombophilia testing. Higher VTE risk is seen in deficiency of the natural anticoagulants protein C, protein S and antithrombin. The annual risk for VTE is reported as between 1.5 and 1.9%, with a recurrence risk at five years of 40%. The risk with deficiency of these factors in pregnancy, as previously discussed, is significantly higher and warrants expert input. While high levels of other coagulation factors, FIX, FXI and hyperhomocysteinaemia, have been reported to increase VTE risk, they are not independent risk factors and are usually seen in association with increased FVIII. The combination of two or more thrombophilia factors would increase risk, and would require further expert input.

Obesity

A strong association between obesity and VTE has been reported. In a large population-based study, DVT risk increased with BMI, showing a hazard ratio of 1.3 in those overweight, 1.8 in moderate obesity, and 3.4 in severe obesity, compared with normal-weighted individuals. The risk is present for both males and females. Obese women using the COC, however have been reported to have a 24 fold increased VTE risk, compared with non-obese females not taking a COC.

Obesity risk for VTE is also increased in combination with a heritable thrombophilia – for example, it is associated with an eight- and seven-fold risk with heterozygosity for Factor V Leiden and Prothrombin 20210A mutations, respectively. For those with concomitant medical problems, the risk is high, as is the risk associated with bariatric surgery. Of the measures to quantify obesity, it is reported that waist circumference in males, and hip circumference in females, equate best with VTE. This contrasts with arterial and myocardial risk, in which waist-hip and waist to height are better measures. This emphasises differences in body fat distribution for venous and arterial disease and, perhaps, a different underlying cause. Obesity has been suggested to correlate with increased thrombin generation in females with VTE, with increased fibrinogen and prothrombin associated with a pro-thrombotic state. Overall, the cause, independent of reduced mobility, still needs to be defined.

Travel

Extended travel is associated with an increased risk of venous thrombosis. The most compelling evidence relates to a study at Charles de Gaulle airport, where passengers diagnosed with acute pulmonary embolism were assessed in terms of distance travelled. For travellers of less than 5000 km, the event rate was 0.01 cases per million, compared with 4.8 cases per million for travel greater than 10 000 km. Overall there is a 2–4 fold increase in VTE events for air-travellers for flights greater than four hours, compared with non-travellers.

The absolute risk of a spontaneous VTE event within four weeks of flight is very low, at one per 4600 flights. The risk is increased with the frequency of flights within a short time frame, with a significant increase for two or more flights of over eight hours within six weeks. Additional risk factors are important, and can increase the event rate three-fold. These include increasing age, obesity, recent surgery, recent VTE off anti-coagulants, malignancy and pregnancy. The mechanism is likely to be multi-factorial, but prolonged immobilisation resulting in venous stasis, and changes in air pressure, are most important. While dehydration in flight has been suggested as a risk factor, there is currently no body of evidence to support this.

In conclusion, a VTE episode occurring within eight weeks of extended flight can be considered to have a role in causation. Risk associated with car travel, bus or train is highest in the week after travel. The greatest risk is reported in those with a BMI of more than 30 kg/m^2 , those over 1.9 m tall, or those with Factor V Leiden.

Substance Abuse

There is a marked increase in risk for DVT in users of opioid drugs. The prevalence of previous DVT in opioid users is reported to be 14%, with an annual incidence rate of 3%. The rate increases with age, female use, sex-worker status and intravenous administration. There is a high risk with iliac and femoral injection, often in combination with severe groin infection. High rates of venous leg ulceration (15%) are reported in young drug abusers which are usually chronic and recurring. *Staphylococcus bacteraemia* is a common problem with IV drug abuse and VTE; however, it is also a proven independent risk for VTE within 90 days of community acquired infection.

While moderate alcohol consumption has been suggested to reduce the risk of VTE, alcohol abuse and its associated medical complications increase the risk of DVT. The risk is increased, even in those without associated medical complications.

The magnitude of risk with smoking and VTE is much less than that seen with arterial disease. While VTE risk is small, smoking is very common, and is an additional risk factor for COC users and those with raised BMI. There is also a reported dose response relationship for smoking and VTE, with return to normal risk on discontinuation. The association is seen in patients with provoked and unprovoked VTE, and may be attributable to the reduced fibrinolysis, inflammation and raised viscosity seen in smokers.

Conclusion

VTE risk is multi-factorial, and requires a careful clinical appraisal in order to reduce the unacceptable high rates of morbidity and death currently seen in clinical practice. Early intervention in high risk patients is essential, and it is to be hoped that greater awareness of the important risk factors for VTE can reduce the incidence of a largely preventable problem.

Further Reading

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