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Epidemiology of venous thromboembolism

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Abstract

Thrombosis can affect any venous circulation. Venous thromboembolism (VTE) includes deep-vein thrombosis of the leg or pelvis, and its complication, pulmonary embolism. VTE is a fairly common disease, particularly in older age, and is associated with reduced survival, substantial health-care costs, and a high rate of recurrence. VTE is a complex (multifactorial) disease, involving interactions between acquired or inherited predispositions to thrombosis and various risk factors. Major risk factors for incident VTE include hospitalization for surgery or acute illness, active cancer, neurological disease with leg paresis, nursing-home confinement, trauma or fracture, superficial vein thrombosis, and—in women—pregnancy and puerperium, oral contraception, and hormone therapy. Although independent risk factors for incident VTE and predictors of VTE recurrence have been identified, and effective primary and secondary prophylaxis is available, the occurrence of VTE seems to be fairly constant, or even increasing.

Introduction

Thrombosis can affect any branch of the venous circulation. This Review is focused on the epidemiology of venous thromboembolism (VTE), including deep-vein thrombosis (DVT) of the leg or pelvis, and its complication, pulmonary embolism (PE). Thrombosis affecting the superficial leg veins (such as the saphenous vein) and other venous circulations (such as those of the arms, and cerebral, mesenteric, renal, hepatic, and portal veins) is beyond the scope of this Review. VTE is a multifactorial disease, involving interactions between clinical risk factors and predispositions to thrombosis, either acquired or inherited (thrombophilias).^{1–5} Moreover, the type of VTE event (PE versus DVT) might also be partly heritable.^{6,7} In this Review, I have attempted to summarize and integrate the data relating to VTE incidence (including trends in incidence), recurrence (including predictors of recurrence), attack rates, survival (including predictors of survival), health-care costs, and risk factors.

Scope of the Review

This Review is focused on comprehensive studies of the epidemiology of objectively-diagnosed VTE, which reported the racial demography and included the full spectrum of disease occurring within a well-defined geographical area over time, separated by event type

Competing interests

The author declares no competing interests.

and incident versus recurrent event, as well as studies of VTE survival and recurrence that included a relevant duration of follow-up. Most epidemiological studies of VTE have addressed populations of predominantly European origin, and the data discussed in this Review primarily relate to these populations. Where they were available, data from populations originating from other continents have also been discussed. The term 'risk factors' relates to characteristics that have been shown by logistic regression to be associated with incident VTE, whereas 'predictors' relates to characteristics associated with VTE recurrence and survival via Cox proportional hazards modelling. 'Independent' risk factors and predictors are those characteristics that have been significantly associated with the occurrence of VTE in multivariable analyses.

Incidence of VTE

The estimated annual incidence rates of VTE among people of European ancestry range from 104 to 183 per 100,000 person-years,^{8–18} rates that are similar to that of stroke.^{19,20} Overall VTE incidence might be higher in African American populations^{21–23} and lower in Asian,²⁴ Asian American,^{25,26} and Native American populations,²⁷ and might vary in the African American population according to US geographical location.²³ Reported incidence rates for PE (with or without DVT), and for DVT alone (without PE), range from 29 to 78, and 45 to 117, per 100,000 person-years, respectively.^{10,12,14–18}

VTE is predominantly a disease of older age, and is rare prior to late adolescence.^{8,10–15,18} Incidence rates increase markedly with age for men and women (Figure 1) and for DVT and PE (Figure 2).^{10,14,15} The overall age-adjusted annual incidence rate is higher for men (130 per 100,000) than for women (110 per 100,000).^{10,15} Incidence rates are somewhat higher in women during childbearing years (16–44 years) compared with men of similar age, whereas incidence rates in individuals aged >45 years are generally higher in men. PE accounts for an increasing proportion of VTE with increasing age in both sexes.¹⁰ In populations of European and African origins, the percentage of incident VTE events that are idiopathic ranges from 25% to 40% (F. A. Spencer, personal communication).^{26,28} In one study, 19% of incident events in a study population from Asia and the Pacific Islands were found to be idiopathic.²⁶

Data relating to trends in VTE incidence are limited. Incidence rates for VTE, DVT, and PE either remained constant or increased from 1981 to 2000, with a substantial increase in the incidence rate of VTE occurring from 2001 to 2009, mostly owing to an increasing incidence of PE (Figure 3).^{10,14,18,29} The rates of incident cancer-associated VTE, secondary VTE not associated with cancer, and idiopathic VTE were fairly constant from 1999 to 2009 (F. A. Spencer, personal communication). The observed increases in the rates of VTE and PE could, at least in part, reflect increased utilization of objective imaging, and improved image resolution, particularly with CT pulmonary angiography and MRI.¹⁸

Recurrence of VTE

VTE recurs frequently, and around 30% of patients with VTE experience recurrence within 10 years.^{16,30–40} Reported rates of recurrent VTE, DVT, and PE are 19–39, 4–13, and 15–29 per 100,000 person-years, respectively.¹⁸ In a study of residents of Olmsted County, MN,

USA with incident VTE diagnosed from 1966 to 1990, the estimated cumulative incidence of first overall VTE recurrence was 1.6% at 7 days, 5.2% at 30 days, 8.3% at 90 days, 10.1% at 180 days, 12.9% at 1 year, 16.6% at 2 years, 22.8% at 5 years, and 30.4% at 10 years.³¹ The risk of first recurrence varies with the time since the incident event, and is highest within the first 6–12 months, with rates per 1,000 person-days of 170 at 7 days, 130 at 30 days, 30 at 90 days, 20 at 180 days and 1 year, 10 at 2 years, 6 at 5 years and 5 at 10 years.³¹ Although secondary prophylaxis is effective in preventing recurrence, the duration of acute treatment does not affect the rate of recurrence beyond an initial 3 months of prophylactic anticoagulation medication.^{33,34,41–45} These observations suggest that VTE is a chronic disease with episodic recurrence.^{31,32,46,47}

Independent predictors of recurrence include increasing patient age,^{31,32,34,35,48–53} increasing BMI,^{31,51,53–56} male sex,^{31,34,50,56–64} active cancer,^{12,30,31,48,65–70} and neurological disease with leg paresis.³¹ Additional predictors of recurrence include idiopathic VTE,^{30,35,43,58,66,67,71–73} persistent lupus anticoagulant or antiphospholipid antibody,^{42,74–76} deficiency of antithrombin, protein C, or protein S,^{77–79} hyperhomocysteinaemia,⁸⁰ persistently elevated plasma D-dimer in patients with idiopathic VTE,^{81–84} and, possibly, residual vein thrombosis.^{85,86} The risk of recurrence is modestly increased in heterozygous carriers of the factor V Leiden (*F5* rs6025) or prothrombin 20210G>A (*F2* rs1799963) mutations, and in patients with blood types other than O.^{87,88} Patients with homozygous factor V Leiden mutations or heterozygous factor V Leiden mutations combined with deficiencies of antithrombin, protein S, or protein C have an increased risk of recurrence. In patients with active cancer, factors associated with increased risk of VTE recurrence are cancer site (pancreatic, brain, lung, and ovarian cancer, myeloproliferative or myelodysplastic disorders), stage IV cancer, cancer stage progression, and leg paresis.⁷⁰

Several risk factors, when present at the time of the incident VTE event, are associated with either a reduced risk of recurrence, or are not predictive of recurrence.^{30–32,44,58,89} In women, pregnancy or puerperium,^{31,38} oral contraception,³¹ hormone therapy,^{62,90} and gynaecological surgery³¹ at the incident VTE are associated with reduced risk of recurrence. HMG-coenzyme A reductase inhibitor (statin) treatment following hospital discharge after PE reduces the risk of recurrent PE.⁹¹ Recent surgery and trauma or fracture have been reported to have no predictive value,³¹ or to predict a reduced risk of recurrence.^{30,92} Additional baseline characteristics that are not predictive of VTE recurrence include recent immobilization, tamoxifen therapy, and failed prophylaxis (incident VTE despite prophylaxis).³¹ For these patients, who do not have an increased risk of recurrence, and for patients with isolated calf-vein thrombosis, a shorter duration of acute therapy (heparin, low-molecular-weight heparin, warfarin or another vitamin K antagonist, or a target-specific oral anticoagulant) is probably adequate.^{44,66} Data relating to the use of the type of incident event as a predictor of recurrence are conflicting.^{31,35,36,44,49,56,93–97} However, a significant association has been found between the type of incident event and the type of recurrent event.⁴⁹ Patients with sub-segmental PE have a similar 3-month recurrence risk to patients with more proximal PE.⁹⁸

Several VTE recurrence prediction algorithms have been derived for the stratification of recurrence risk in patients with incident idiopathic or cancer-associated VTE. In the development of the 'Men continue and HERDOO2' rule, no predictors of a reduced risk of recurrence were identified in men with incident idiopathic VTE. By contrast, women with incident idiopathic VTE who had 1 of a set of risk factors had a significantly lower risk of VTE recurrence than those with >1.⁹⁹ The risk factors were older age (< 65 years), obesity (BMI < 30 kg/m²), increased D-dimer level prior to stopping warfarin therapy, and signs of post-thrombotic syndrome.⁹⁹ In the Vienna prediction model,¹⁰⁰ male sex, incident VTE type (PE and/or proximal DVT versus isolated calf DVT), and increasing D-dimer levels are predictors of recurrence after idiopathic incident VTE. In the DASH prediction model,¹⁰¹ persistently increased D-dimer level after termination of anticoagulation therapy, age <50 years, male sex, and—in women—VTE unrelated to hormonal therapy predicted an increased risk of recurrence after an idiopathic incident VTE. The only inconsistent risk factor in these models is patient age, given that older age is associated with a higher recurrence risk among women in the HERDOO2 model,⁹⁹ younger age is associated with a higher risk in men and women in the DASH model,¹⁰¹ and age is not a predictor of recurrence in the Vienna model.¹⁰⁰ Depending on the model, patients with a low score have recurrence rates of 1.6–4.4% per year.^{102,103} If these recurrence rates were considered to be acceptable, around 50% of patients with idiopathic incident VTE and a low prediction score could avoid secondary prophylaxis, and the associated risk of bleeding complications.^{99–101} Among patients with active cancer and VTE, female sex, cancer site (lung) and previous VTE are high-risk predictors of VTE recurrence, and cancer site (breast) and stage (stage I rather than stage II, III, or IV) are low-risk predictors in patients receiving anticoagulation therapy.^{69,104}

VTE attack rates

Estimated VTE attack rates (including incident and recurrent VTE) range from 142 to >300 per 100,000 person-years. Estimated attack rates for DVT and PE are 91–255 and 51–75 per 100,000 person-years, respectively.^{18,105} VTE attack rates related to current or recent hospitalization are much higher than the rates for people residing in the community (330 versus 8 per 100,000 person-years, respectively).¹⁰⁵

Information is scarce regarding the total number of VTE events (incident and recurrent) occurring each year, and available estimates vary widely. In an incidence-based modelling study, the estimated total number of symptomatic VTE events per year in six European Union countries was 465,000.¹⁰⁶ Using age-specific and sex-specific incidence rates for 1991–1995, projected to 2000, 260,000 incident cases of VTE have been estimated to occur in the US white population annually.¹³ If incidence rates are similar, then around 27,000 additional incident cases will occur in the US African American population annually. In an incidence-based modelling study that included hospital-acquired and community-acquired, incident and recurrent VTE events, 600,000 nonfatal VTE events (370,000 DVT and 270,000 PE) were estimated to occur in the USA in 2005, two-thirds of which were related to current or recent hospitalization.¹³ Using 2007–2009 National Hospital Discharge Survey diagnosis codes, an estimated average of 548,000 hospitalizations with VTE

occurred each year among US residents aged 18 years, of which 349,000 were DVT and 278,000 were PE.¹⁰⁷

Costs attributable to incident VTE

In a population-based study, adjusted mean predicted costs were found to be 2.5-fold higher for patients with VTE related to current or recent hospitalization for acute illness (US \$62,838) than for hospitalized control patients matched by active cancer status (\$24,464; $P < 0.001$).¹⁰⁸ Costs were calculated from the VTE event date (or index date for controls) to 5 years post-index, and cost differences between cases and controls were greatest (\$16,897) within the first 3 months.¹⁰⁸ Similarly, the 5-year costs were predicted to be 1.5-fold higher for patients with VTE related to current or recent hospitalization for major surgery (\$55,956) than for hospitalized control patients matched by the type of surgery and active cancer status (\$32,718; $P < 0.001$).¹⁰⁹ Again, cost differences between cases and controls were greatest (\$12,381) in the first 3 months after the index date. Predicted costs over 5 years were also nearly twofold higher for patients with VTE and active cancer (\$49,351) than for patients with active cancer but no VTE (\$26,529; $P < 0.001$; J. A. Heit, unpublished work). VTE associated with hospitalization was the leading cause of disability-adjusted life-years in low-income and middle-income countries, and the second most common cause in high-income countries.¹¹⁰

Predictors of survival after incident VTE

Overall, survival after VTE is worse than the expected survival in a population of similar age, sex, and ethnic distribution, and survival after PE is much worse than after DVT alone (Figure 4).^{36,111–115} The risk of early death in patients experiencing PE is 18-fold higher than in patients with DVT but not PE.¹¹¹ PE is an independent predictor of reduced survival (compared with patients with incident DVT alone) for up to 3 months after the event, although beyond 3 months, survival after PE is similar to expected survival.^{15,111,112} For almost one-quarter of patients experiencing PE, the initial clinical presentation is sudden death.¹⁰³ Independent predictors of reduced early survival after VTE include older age, male sex, lower BMI, confinement to a hospital or nursing home at the onset of VTE, congestive heart failure, chronic lung disease, serious neurological disease, and active cancer.^{40,111,112,116} Additional clinical predictors of poor early survival after PE include syncope and arterial hypotension.^{116,117} Evidence of right heart failure, on the basis of clinical examination, plasma markers (such as cardiac troponin T and B-type natriuretic peptide), or echocardiography, predicts poor survival among normotensive patients with PE.¹¹⁶ Survival over time might be improving for those patients with PE who are living sufficiently long to be diagnosed and treated.^{111,113,118,119} Mortality is similar in patients with subsegmental PE and those with more proximal PE.⁹⁸

Risk factors for incident VTE

Investigators in a case-control study identified 726 women with incident VTE between 1988 and 2000 in Olmsted County, MN, USA.¹²⁰ In this group, independent risk factors for incident VTE were major surgery (OR 18.95), active cancer with or without concurrent chemotherapy (OR 14.64), neurological disease with leg paresis (OR 6.10), hospitalization

for acute illness (OR 5.07), nursing-home confinement (OR 4.63), trauma or fracture (OR 4.56), pregnancy or puerperium (OR 4.24), oral contraception (OR 4.03), noncontraceptive oestrogen plus progestin (OR 2.53), oestrogen (OR 1.81), progestin (OR 1.20), and BMI (OR 1.08). Among previously identified VTE risk factors, age, varicose veins, and progestin were not significantly associated with incident VTE in this multivariate analysis.¹²⁰ Other risk factors for incident VTE include central vein catheterization or transvenous pacemaker placement, prior superficial vein thrombosis, urinary tract infection, increased baseline plasma fibrin D-dimer, and family history of VTE, whereas patients with chronic liver disease have a reduced risk of VTE.^{121–127} Compared with residents in the community, hospitalized patients have >100-fold increased incidence of VTE.¹²⁸ Hospitalization and nursing-home residence together account for almost 60% of incident VTE events in the community.^{28,129} Notably, hospitalization for illness and hospitalization for surgery account for almost equal proportions of VTE (22% and 24%, respectively).^{28,129} Nursing-home residence independently accounts for over one-tenth of all VTE disease in the community.^{28,129}

The risk of VTE in patients undergoing surgery can be stratified on the basis of patient age, type of surgery, smoking status, and the presence or absence of active cancer.^{130–132} The incidence of postoperative VTE is increased in patients who are aged ≥ 65 years.¹³³ Surgical procedures associated with a high risk of VTE include neurosurgery, major orthopaedic surgery of the leg, renal transplantation, cardiovascular surgery, and thoracic, abdominal, or pelvic surgery for cancer.^{124,133,134} Obesity,^{135–138} and poor physical status according to American Society of Anesthesiology criteria,¹³⁹ are risk factors for VTE after total hip arthroplasty.

The risk of VTE in patients hospitalized for acute illness can be stratified on the basis of age, obesity, previous VTE, thrombophilia, cancer, recent trauma or surgery, tachycardia, acute myocardial infarction or stroke, leg paresis, congestive heart failure, prolonged immobilization (bed rest), acute infection or rheumatological disorder, hormone therapy, central venous catheter, admission to an intensive or coronary care unit, white blood cell count, and platelet count.^{140–146} Although risk-assessment models have been derived for prediction of VTE in hospitalized, nonsurgical patients, these models are highly variable in terms of the number and type of predictors, and the strengths of associations with VTE, and lack generalizability and adequate validation.^{147,148}

Active cancer accounts for almost 20% of all incident VTE occurring in the community.^{28,129} The risk of VTE is higher in patients with cancers of the brain, pancreas, ovaries, colon, stomach, lungs, kidneys, or bones, compared with other locations,^{149,150} and in patients with metastases.¹⁵⁰ Patients with cancer who are receiving immunosuppressive or cytotoxic chemotherapy, including L-asparaginase,^{151,152} thalidomide¹⁵³ or lenalidomide,¹⁵⁴ or tamoxifen,¹⁵⁵ are at even higher risk of VTE.^{121,150} Routine screening for occult (undiagnosed) cancer is controversial and probably not warranted.^{156,157} However, if clinical features suggest a possible occult cancer (such as idiopathic VTE, especially among patients with abdominal-vein or bilateral leg-vein thrombosis,¹⁵⁸ or in whom VTE recurs¹⁵⁹), then the only imaging study shown to be useful is a CT scan of the abdomen and pelvis.¹⁵⁹ Among patients with cancer, the risk of chemotherapy-associated VTE is

increased in patients with pancreatic or gastric cancer, platelet count $350 \times 10^9/l$, haemoglobin $<100 \text{ g/l}$ or use of red cell growth factors, leukocyte count $11 \times 10^9/l$, or BMI 35 kg/m^2 ;¹⁶⁰ biomarkers (plasma soluble P-selectin and D-dimer) add further predictive value.¹⁶¹

A central venous catheter or transvenous pacemaker accounts for 9% of all incident VTE occurring in the community.²⁸ Central venous access via femoral vein catheters is associated with a higher incidence of VTE compared with subclavian vein catheterization.¹⁶² Prior superficial vein thrombosis is an independent risk factor for subsequent DVT or PE, remote from the episode of superficial thrombophlebitis.^{121,163} The risk of DVT associated with varicose veins is uncertain, and seems to vary with patient age.^{121,164,165} Long haul ($>4\text{--}6$ h) air travel is associated with a slightly increased risk of VTE (1 VTE event per 4,656 flights^{166–168}), which is preventable by the use of elastic compression stockings.¹⁶⁹ Statin therapy can result in a 20–50% reduction in the risk of VTE.^{170–172} Hypertriglyceridaemia doubles the risk of VTE in postmenopausal women.¹⁷³ However, the risk associated with atherosclerosis, or other risk factors for atherosclerosis, remains uncertain.^{126,174–178} Diabetes mellitus,¹²⁰ myocardial infarction,¹⁷⁹ current or past tobacco smoking, HDL-cholesterol level, lipoprotein(a) level, and chronic obstructive pulmonary disease are not independent risk factors for VTE.^{121,180,181} The risk associated with congestive heart failure, independent of hospitalization, is low.^{121,130}

In women, additional risk factors for VTE include oral contraception,^{120,130,182–184} hormone therapy,^{120,185,186} pregnancy and puerperium,^{130,183,187} and therapy with the selective oestrogen-receptor modulator, raloxifene.¹⁸⁸ First-generation and third-generation oral contraceptives convey higher risks than second-generation oral contraceptives.¹⁸⁴ Injectable depot medroxyprogesterone acetate contraception is associated with a threefold increased risk of VTE, whereas a levonorgestrel intrauterine device imparts no risk.¹⁸⁹ Hormone therapy is associated with a twofold to fourfold increased risk of VTE,^{120,185} depending on the type of oestrogen and the mode of delivery, with evidence suggesting possibly no risk with transdermal oestrogen.¹⁹⁰ The overall incidence of pregnancy-associated VTE is around 200 events per 100,000 women-years, a fourfold relative risk compared with nonpregnant women of childbearing age.^{187,191} The risk of VTE during the postpartum period is around fivefold higher than the risk during pregnancy.¹⁸⁷ Prior superficial vein thrombosis is an independent risk factor for VTE during pregnancy or puerperium.^{192,193} Additional risk factors for incident VTE associated with pregnancy include varicose veins, urinary tract infection, pre-existing diabetes mellitus, stillbirth, obesity, obstetric haemorrhage, preterm delivery, and delivery by Caesarean section.¹⁹⁴

Other conditions associated with VTE include autoimmune disorders,¹⁷⁸ Behçet's disease, coeliac disease,¹⁹⁵ heparin-induced thrombocytopenia,¹⁹⁶ homocystinuria and hyperhomocysteinaemia,^{197,198} hyperthyroidism,¹⁹⁹ immune thrombocytopenia,^{200,201} infection,¹²³ inflammatory bowel disease,²⁰² intravascular coagulation and fibrinolysis/disseminated intravascular coagulation (ICF/DIC), myeloproliferative neoplasms (especially polycythaemia rubra vera and essential thrombocythaemia),^{203,204} chronic kidney disease with severely reduced glomerular filtration rate,²⁰⁵ nephrotic syndrome,²⁰⁶ paroxysmal nocturnal haemoglobinuria,²⁰⁷ rheumatoid arthritis,^{208,209} obstructive sleep apnoea,^{210,211}

thromboangiitis obliterans (Buerger disease), thrombotic thrombocytopenic purpura, sickle-cell disease,²¹² systemic lupus erythematosus, and granulomatosis with polyangiitis (Wegener's granulomatosis).²¹³

Studies of twins and families show that VTE is highly heritable and follows a complex mode of inheritance, involving interaction with clinical risk factors.^{1,3,4,7} Inherited reductions in plasma levels of natural anticoagulants, such as antithrombin, protein C, or protein S, have long been recognized as uncommon, but potent, risk factors for VTE.^{214–217} More recent discoveries of additional reduced natural anticoagulants^{218–223} or anticoagulant cofactors,²²⁴ impaired downregulation of the procoagulant system (for example, activated protein C resistance, factor V Leiden [*F5* rs6025]),^{29,225–227} increased plasma concentrations of procoagulant factors (such as factor I [fibrinogen], factor II [prothrombin; prothrombin 20210G>A [*F2* rs1799963], factors VIII, IX, and XI, von Willebrand factor [*ABO* rs8176719]),^{56,215,228–245} increased basal procoagulant activity,^{122,246,247} impaired fibrinolysis,²⁴⁸ and increased basal innate immunity activity and reactivity,^{249,250} have added new paradigms to the list of inherited or acquired disorders predisposing to thrombosis (thrombophilias). These plasma haemostasis-related factors, or markers of coagulation activation, correlate with increased thrombotic risk and are highly heritable.^{2,251–255} Inherited thrombophilias interact with obesity and tobacco smoking,^{254,256,257} and clinical risk factors such as oral contraception,^{258–261} pregnancy,^{262,263} hormone therapy,^{264–266} minor trauma,²⁶⁷ surgery,^{268,269} and cancer,²⁷⁰ to compound the risk of incident VTE. Similarly, interactions between genetic risk factors further increase the risk of incident VTE.²⁷¹

Conclusions

VTE is a fairly common disease that recurs frequently, and is associated with reduced survival and substantial health-care costs. Although independent risk factors for VTE and predictors of VTE recurrence have been identified, and effective primary and secondary prophylaxis is available, the occurrence of VTE is generally constant or even increasing. Future research should be directed towards identification of the optimal targets for VTE prophylaxis. Groups currently considered to be at high risk of VTE, such as all patients undergoing hip or knee replacement surgery, include few individuals who would experience VTE in the absence of prophylaxis. The requirement is to identify the individuals within these groups who are at high risk of incident or recurrent VTE, who would benefit most from primary or secondary prophylaxis, thereby minimizing the risk of bleeding complications incurred by treatment of those at low risk.

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Key points

- Venous thromboembolism (VTE) occurs as often as stroke, and recurs frequently, with around 30% of patients with VTE experiencing recurrence within 10 years
- Occurrence of VTE, especially pulmonary embolism (PE), is associated with reduction in survival, and PE is an independent predictor of reduced survival for up to 3 months
- VTE is associated with high health-care costs and increased disability-adjusted life-years
- Despite identification of VTE risk factors, development of new prophylaxis regimens, and improved uptake of VTE prophylaxis, the occurrence of VTE is increasing

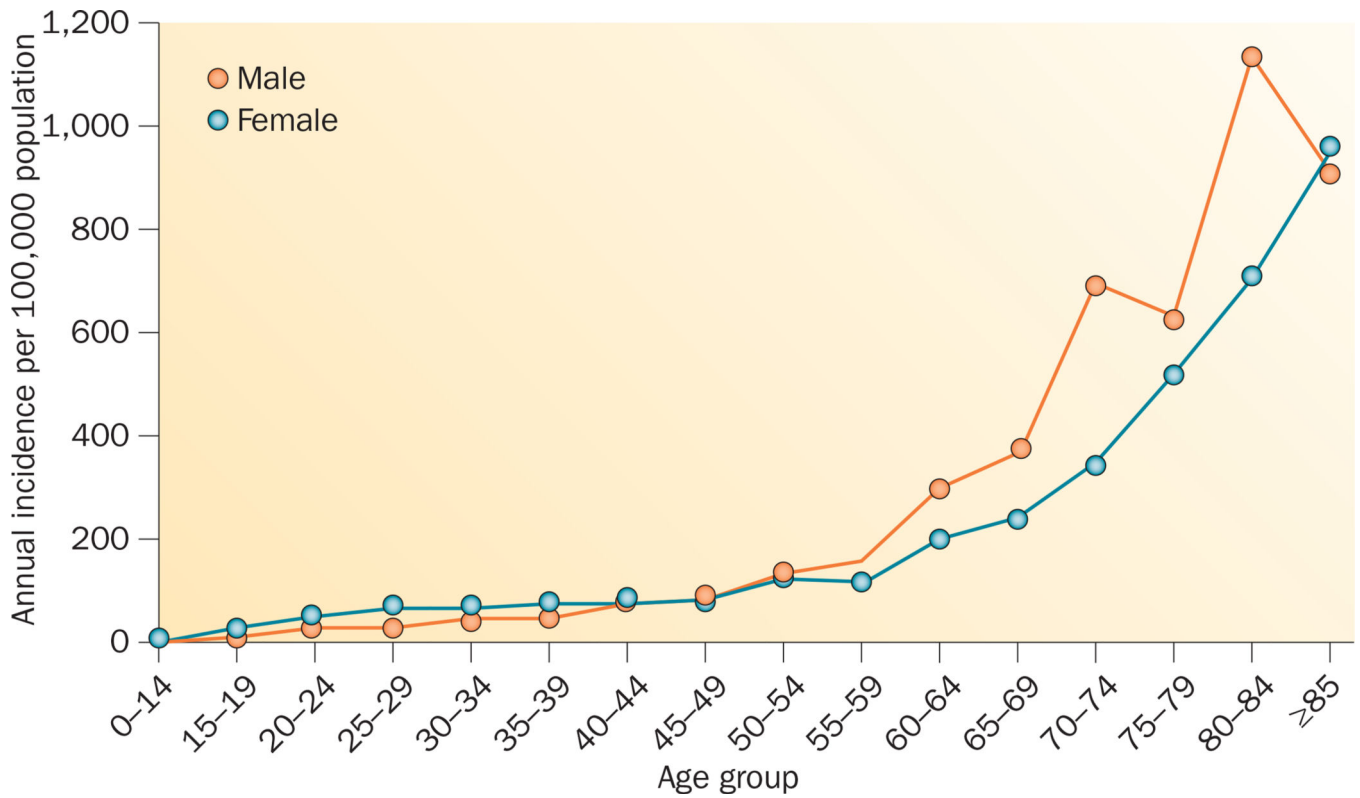


Figure 1. Annual incidence of venous thromboembolism among residents of Olmsted County, MN, USA, from 1966 to 1990, by age and sex. Permission obtained from the American Medical Association © Silverstein, M. D. *et al.* Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch. Intern. Med.* **158**, 585–593 (1998).

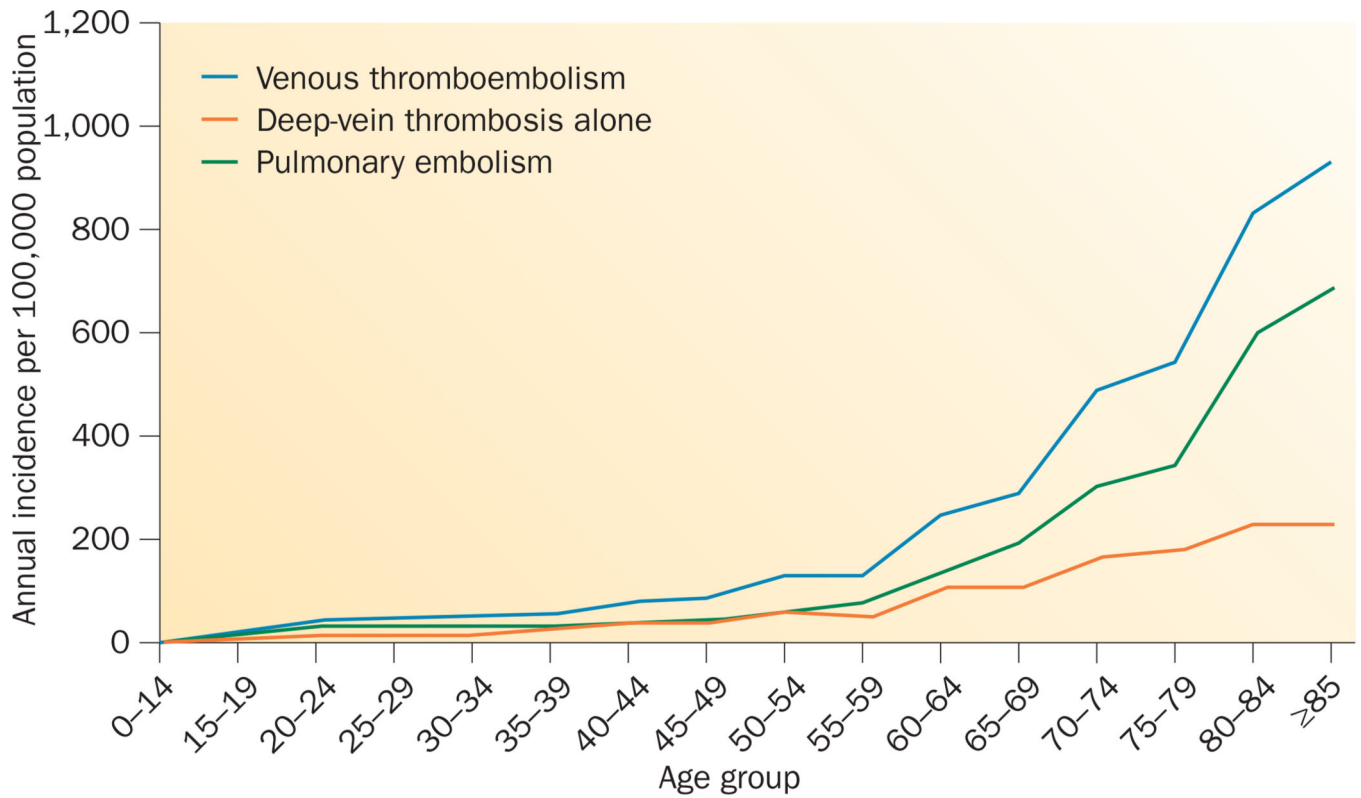


Figure 2.

Annual incidence of venous thromboembolism among residents of Olmsted County, MN, USA, from 1966 to 1990, by age. The overall incidence of venous thromboembolism is shown, along with the incidence of deep-vein thrombosis alone, and pulmonary embolism (with or without deep-vein thrombosis). Permission obtained from the American Medical Association © Silverstein, M. D. *et al.* Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch. Intern. Med.* **158**, 585–593 (1998).

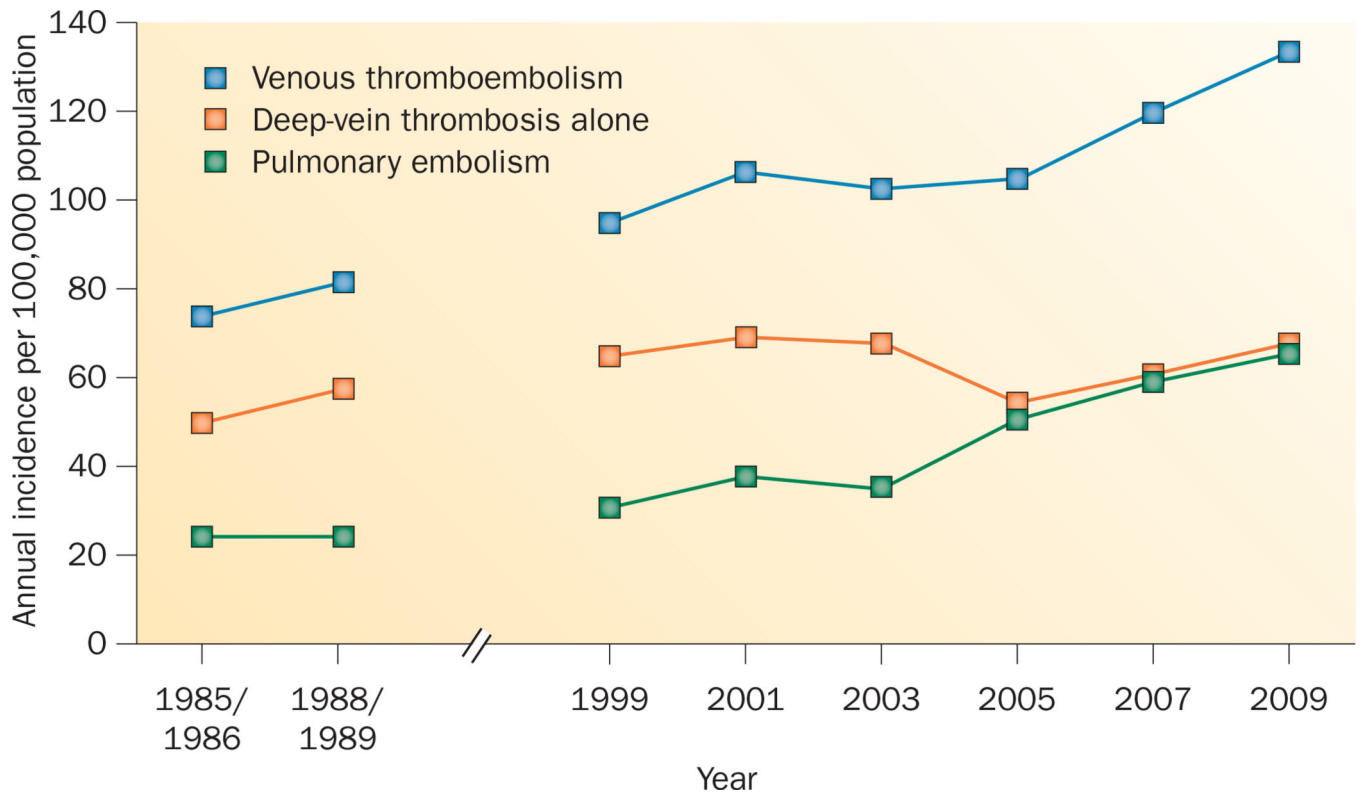


Figure 3. Trends over time in the incidence of venous thromboembolism, deep-vein thrombosis alone, and pulmonary embolism (with or without deep-vein thrombosis) among residents of Worcester, MA, USA. Permission obtained from Elsevier © Huang, W. *et al.* Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985–2009). *Am. J. Med.* **127**, 829–839 (2014).

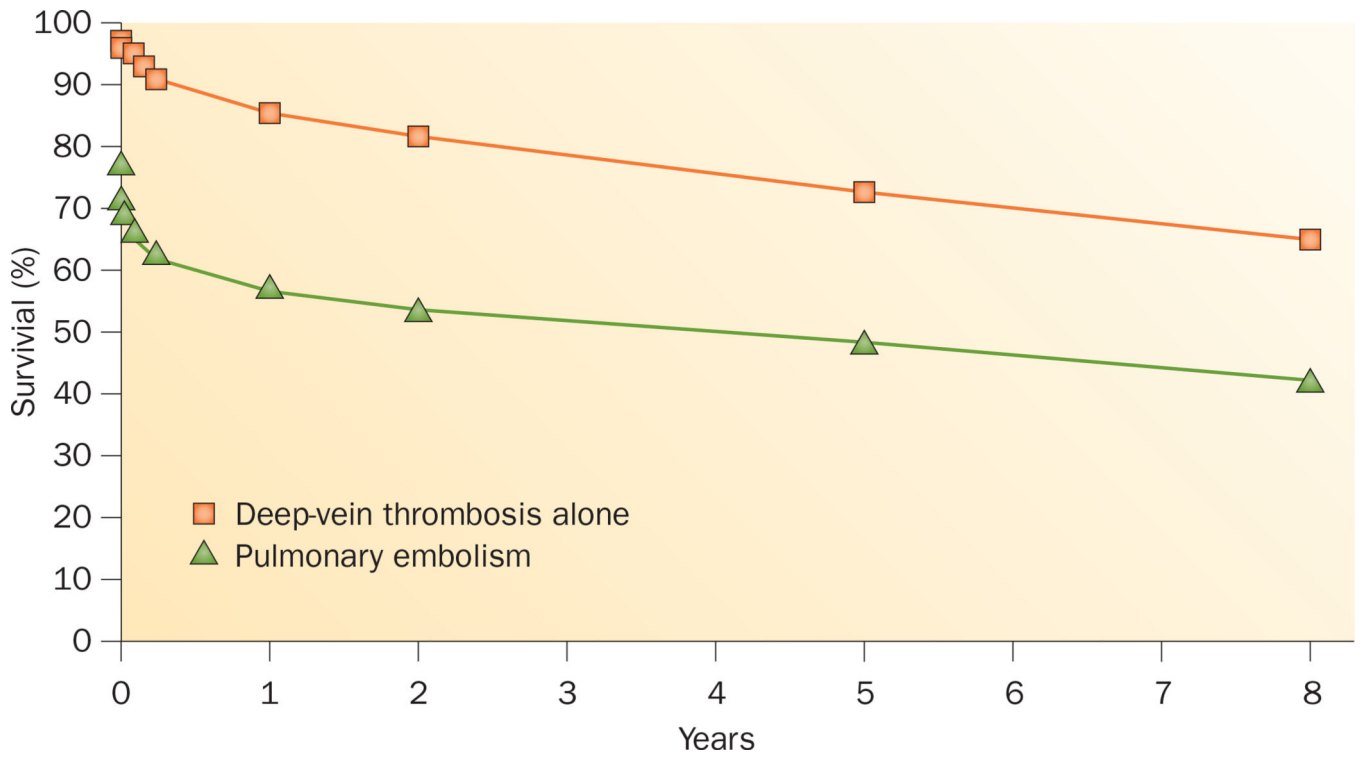


Figure 4. Kaplan–Meier estimates of survival among residents of Olmsted County, MN, USA with incident venous thromboembolism diagnosed 1966–1990.¹¹¹ Pulmonary embolism includes cases with or without deep-vein thrombosis, where pulmonary embolism was the cause of death.