Epidemiology and prevention of venous thromboembolism

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Abstract | Venous thromboembolism, that consists of the interrelated conditions deep-vein thrombosis and pulmonary embolism, is an under-appreciated vascular disease. In Western regions, approximately 1 in 12 individuals will be diagnosed with venous thromboembolism in their lifetime. Rates of venous thromboembolism are lower in Asia, but data from other regions are sparse. Numerous risk factors for venous thromboembolism have been identified, which can be classified as acute or subacute triggers (provoking factors that increase the risk of venous thromboembolism) and basal or acquired risk factors (which can be modifiable or static). Approximately 20% of individuals who have a venous thromboembolism event die within 1 year (although often from the provoking condition), and complications are common among survivors. Fortunately, opportunities exist for primordial prevention (prevention of the development of underlying risk factors), primary prevention (management of risk factors among individuals at high risk of the condition) and secondary prevention (prevention of recurrent events) of venous thromboembolism. In this Review, we describe the epidemiology of venous thromboembolism, including the incidence, risk factors, outcomes and opportunities for prevention. Meaningful health disparities exist in both the incidence and outcomes of venous thromboembolism. We also discuss these disparities as well as opportunities to reduce them.

Venous thromboembolism (VTE), that consists of the interrelated diseases of pulmonary embolism and deep-vein thrombosis (DVT), is among the top five most common vascular diseases in most countries[1]. The lifetime risk of VTE is estimated to be 8% overall among US adults[2]. Approximately 20% of individuals die within 1 year of a VTE diagnosis, sometimes from VTE but often from conditions that provoked the event[3].

VTE is preventable, and the risk of VTE is a marker of adverse conditions at the levels of the individual, society and health systems[4,5]. At the individual level, obesity[6–9] and lack of physical exercise[10,11] increase the risk of VTE. These factors are often caused by adverse societal conditions, such as a lack of access to high-quality nutrition or safe places to exercise[12]. At the health systems level, opportunities are missed to provide effective preventive measures during hospitalization or after selected interventions, or in individuals with a personal or family history of VTE. The pathophysiology of VTE is also distinct among vascular diseases because several established risk factors for atherosclerotic cardiovascular disease, such as hyperlipidaemia, hypertension and diabetes mellitus, are not associated with the risk of VTE independently of established VTE risk factors, such as age and obesity[13].

The risk of VTE is multifactorial[14] (TABLE 1 and FIG. 1). In epidemiological studies, VTE is often defined as provoked or unprovoked. Provoked events occur after triggering factors in the previous 3 months, such as immobilization, trauma, surgery, cancer or hospitalization, whereas unprovoked events occur in the absence of these conditions[8,15–17]. Although the classification of provoked and unprovoked can be useful both epidemiologically and clinically, it is controversial[18]. For instance, some studies might classify pregnancy and hormone-related VTE as provoked. Given that VTE is multifactorial, it can be challenging (or impossible) to identify a single characteristic that led to VTE or to consider as unprovoked an array of smaller thrombotic challenges that led to a VTE event. The 2019 European Society of Cardiology/European Respiratory Society guidelines for the diagnosis and management of acute pulmonary embolism avoided the terminology of 'provoked' and 'unprovoked', instead focusing on the estimated long-term risk of VTE recurrence (<3% per year being low risk, 3–8% per year being intermediate risk and >8% per year being high risk) on the basis of underlying factors[19]. However, given the predominance of the provoked and unprovoked terminology in the published literature, we use this terminology in this Review.

VTE is treated with anticoagulant therapy. VTE treatment is divided into three phases: initial stabilization

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Key points

- Venous thromboembolism (VTE) surveillance systems are lacking, but VTE is estimated to affect one to two individuals per 1,000 person-years in Europe and the USA, with lower rates in other regions.
- Risk factors for VTE are varied, and include triggers (acute and subacute), basal risk factors (demographic, behavioural, anthropometric and genetic) and acquired clinical risk factors.
- Numerous complications can occur after a VTE event, and quality of life can decrease.
- Reduction in the risk of VTE and adverse outcomes after a VTE event will require prevention across the spectrum of prevention stages (primordial, primary and secondary) and increased awareness of this under-appreciated condition.
- Disparities exist in VTE incidence and outcomes; reducing these disparities will require individual, systems-based and societal commitments to equity.

(days to weeks), primary treatment (3–6 months) and secondary prevention (after completion of primary treatment)[20]. The designation of provoked versus unprovoked VTE also guides treatment duration, particularly whether or not to use secondary prevention strategies, which are recommended for individuals with unprovoked VTE and can include surveillance, anticoagulation therapy during high-risk periods or continued anticoagulation therapy[21]. However, the distinction between provoked and unprovoked is inconsistently applied in clinical practice and is often not reflective of management decisions. People with incurable cancer and VTE (a provoked event) are offered indefinite anticoagulation therapy, and women with hormone-associated VTE (an unprovoked event) are offered a finite course of treatment[21]. This inconsistency in VTE management is further confused because minor triggers, such as travel or minor orthopaedic injuries, are often thought of as provoking factors clinically but not in epidemiological studies. The lack of unified definitions and practice recommendations leads to heterogeneity in treatment patterns, prevention and, potentially, outcomes.

VTE is a major cause of morbidity and mortality. Understanding the burden of this condition, as well as its risk factors, is essential to prevent VTE and reduce disparities in VTE incidence and outcomes at the societal level. In this Review, we provide contemporary information on the epidemiology of VTE, including incidence, risk factors and complications. Additionally, we summarize strategies for the primordial, primary and secondary prevention of VTE, and highlight the importance of reducing disparities in VTE incidence and management.

Incidence

Global perspective

The incidence of VTE in Europe and the USA is estimated to be ~1–2 per 1,000 person-years[1], but varies widely by age, sex, race and medical conditions. In Asia, the rates of VTE are thought to be lower than in Europe and the USA. For instance, the incidence of VTE in South Korea was estimated to be 0.2 per 1,000 person-years[22]. Fewer data exist for South America[23] and Oceania. A study from Buenos Aires, Argentina, found a VTE incidence of 0.7 per 1,000 person-years[24], and a study from Perth, Australia, found a VTE incidence of 0.8 per 1,000 person-years[25]. Very little is known about VTE incidence in Africa[26].

The most robust data on VTE incidence come from the USA and Europe. An American Heart Association report from 2021 estimated that approximately 1,220,000 total cases of VTE occur in the USA annually[27]. This estimate was based on previously unpublished data from the National Inpatient Sample, and showed ~370,000 cases of pulmonary embolism and ~857,000 cases of DVT in 2016 and assumed 30% of DVTs were treated in the outpatient setting. A modelling study estimated that the annual VTE incidence in six countries in Europe (total population 310.4 million) was 296,000 cases of pulmonary embolism and ~466,000 cases of DVT[28].

Methodological considerations

Owing to the lack of surveillance for VTE at the population level, estimates of VTE incidence rely on incomplete data and on assumptions to complete the picture. Interpretation of most sources of data on VTE incidence should be viewed in light of secular trends and data characteristics that lead to higher[29,30] or lower[31–33] estimates of VTE incidence (BOX 1). There is a clear need for population-based VTE surveillance, particularly in the developing world and in populations at risk of VTE. These data would guide VTE prevention, screening and management efforts.

Acute triggering risk factors

Surgery, bone fracture and minor injuries

Surgery and bone fracture are established risk factors for VTE. The risk of postoperative VTE varies widely by surgery type, and the best strategies to prevent postoperative VTE are unclear[34]. Risk factors for VTE after surgery include basal risk factors (such as older age and male sex), comorbid conditions (such as obesity, active cancer and malnutrition) and postoperative complications (such as pneumonia, blood transfusions and myocardial infarction)[34]. The epidemiology of VTE after bone fracture also reflects the diversity of patient populations and type of bone fracture studied, and varies widely. In general, the risk is thought to be higher with lower-leg long-bone fractures, trauma-related bone fractures and operatively treated bone fractures[35].

Minor injuries are often an under-appreciated trigger for VTE. The relationship between minor injuries and VTE is difficult to study systematically owing to recall bias in retrospective studies and because most of these minor injuries do not result in medical care. In an analysis from the MEGA study[36], minor injuries were shown to increase the risk of VTE by about fivefold, with a higher risk of VTE with more severe injuries, leg injuries and injuries in the previous 4 weeks. Genetic risk factors for thrombosis have been shown to increase the risk of VTE associated with minor injuries compared with control individuals (for example, a 50-fold increased risk for the factor V Leiden variant in the *F5* gene, a ninefold increased risk for the prothrombin G20210A polymorphism and a 12-fold increased risk for family history of VTE), suggesting supra-additive interactions[36].

Hospitalization

Between 40% and 60% of all VTE events occur during or in the 3 months after a hospitalization, and hospitalization increases the risk of VTE by approximately 100-fold[16,37,38]. The risk of in-hospital VTE is believed to be a function of both underlying medical conditions and immobility, which often characterizes a hospitalization[39–41]. In-hospital VTE is an important indicator of overall health, with even asymptomatic VTE associated with a threefold increased risk of death among hospitalized, acutely ill patients[42]. Although VTE might not be the primary cause of death in many of these individuals, both VTE symptoms and treatment complicate patient care.

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is an idiosyncratic immunothrombotic disorder resulting from exposure to heparins[43]. The aetiology of HIT is thought to be related to IgG antibodies, which bind to platelet factor 4 (PF4) complexed with heparins on the surface of platelets, leading to platelet activation and thrombosis[43]. Seroconversion (developing antibodies to the PF4–heparin complex) occurs more commonly than the clinical syndrome[43], requiring both clinical context and serology to make a diagnosis of HIT. Up to 30–40% of people with confirmed HIT develop arterial and/or venous thrombosis[44]. Owing to the ubiquitous exposure of patients to heparin during hospitalization, HIT complicates 1 in 1,500 hospital admissions, but can also occur with outpatient heparin exposure or after discharge from hospital[43]. Heparin formulations such as low-molecular-weight heparins are associated with a lower risk of HIT than unfractionated heparin[45].

Table 1 | **Risk factors for venous thromboembolism**

Category	Definition	Risk factors
Acute triggers	Factors that lead to an immediate elevation in the risk of venous thromboembolism, which lasts for only a short period of time	Surgery, fracture and minor injuries
		Hospitalization
		Heparin-induced thrombocytopenia
		Infection
		COVID-19 and COVID-19 vaccination
Subacute triggers	States that lead to a persistent elevation in the risk of venous thromboembolism, for the duration of the trigger	Inflammation
		Hormonal states: oral contraceptive use, hormone replacement therapy, pregnancy, exogenous testosterone
Basal risk factors	Factors that tend to be stable or fairly stable in an individual and are related to the risk of venous thromboembolism	Demographic: older age, sex[a], race/ethnicity[b]
		Behavioural: physical inactivity, poor quality diet, smoking
		Anthropometric: taller height, obesity[c], May–Thurner syndrome
		Genetic
Acquired risk factors	Risk factors that are either present or absent in individuals and not present throughout the life course	Cancer and cancer treatments
		Obesity[c]
		Antiphospholipid antibody syndrome
		Autoimmune diseases
		Other clinical conditions, such as heart failure and atrial fibrillation
		Previous venous thromboembolism

[a]Varies across the life course, with women at greater risk during their reproductive years and men at modestly greater risk at older ages. [b]Variation exists, probably predominantly owing to sociological factors. [c]Can fit in multiple categories.

Infection

Acute infection has also been identified as a trigger for VTE, including in two case–crossover studies that evaluated the risk of VTE after hospitalization for infection[46,47]. In one of these studies, which used data from the ARIC study, hospitalization for infection in the previous 30 days was associated with a 2.7-fold (95% CI 1.1-fold to 6.4-fold) greater risk of VTE relative to control periods of the previous 1 year and 2 years[46]. A self-controlled, case series study derived from the MEGA cohort used antibiotic treatment as a surrogate for infection. The risk of VTE was fivefold higher (95% CI 4.0-fold to 6.1-fold) during antibiotic treatment than during periods of no antibiotic use in the same patients[48]. In general, the available studies lack the granularity required to assign individualized risks to specific types of infection.

COVID-19 and COVID-19 vaccination

Early reports from Wuhan, China, suggested a high incidence of thrombosis associated with hospitalization for coronavirus disease 2019 (COVID-19)[49]. This observation led to a rapid escalation of anticoagulation therapy in people hospitalized for COVID-19 and eventually to clinical trials to assess the use of anticoagulant therapy in patients with mild (outpatient-treated), moderate (treated in general medical wards) or severe (treated in intensive care) COVID-19 as well as the use of anticoagulation prophylaxis in patients after hospital discharge[50]. However, over time, the role of therapeutically dosed anticoagulation drugs has evolved from the prevention of thrombosis in people with COVID-19 to the prevention of care escalation in those with moderate COVID-19 (REF.[50]). Treatment of documented VTE in patients with COVID-19 has received less study, but probably should be treated similarly to any provoked VTE event[51].

The risk of thrombosis with adenovirus-based COVID-19 vaccination has raised concerns. The adenovirus vector-based vaccines ChAdOx1 nCoV-19 (AstraZeneca) and Ad26.COV2.S (Johnson & Johnson) are associated rarely with an immune-related syndrome of vaccine-associated thrombosis and thrombocytopenia (VITT)[52]. At the individual level, the risk of VITT is low, with the highest reported incidence of VITT with ChAdOx1 nCoV-19 vaccination (10 per 1 million vaccinated people)[52]. VITT resembles HIT; however, the currently hypothesized mechanism is that the general inflammatory reaction to the vaccine triggers the production of antibodies to components of the adenovirus vector for the vaccine and to platelet PF4 complexes[53]. The unavailability of alternative vaccines for billions of people in resource-poor settings combined with the proven efficacy of the adenovirus-based vaccinations means that strategies to diagnose and treat VITT in these settings must be identified.

Other COVID-19 vaccines that are based on mRNA technology (the COVID-19 vaccines from

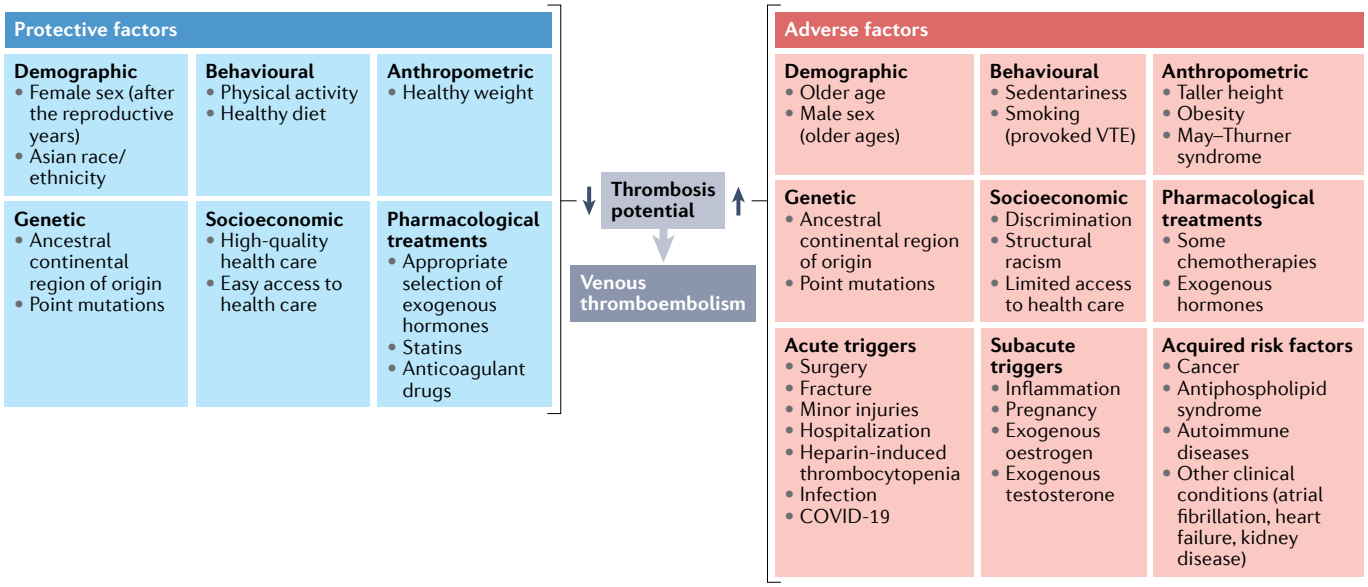

Fig. 1 | **Factors with protective or adverse effects on thrombosis potential and risk of VTE.** The risk of venous thromboembolism (VTE) is multifactorial. Factors that are thought to be protective and associated with a lower thrombosis potential and VTE risk are shown in blue. Factors that are considered to be harmful and associated with greater thrombosis potential and VTE risk are shown in red. Blood lipid levels, hypertension and diabetes mellitus are not shown in the figure because they are not independently associated with the risk of VTE after accounting for obesity and other risk factors.

Pfizer–BioNTech and from Moderna) do not seem to trigger VITT[54,55]. Immune activation through viral infections or vaccinations can lead to inflammation, and inflammation is linked to an increased risk of VTE (see sections 'Infection' and 'Inflammation'). If VTE is triggered by mRNA-based vaccines, the relative and absolute risks are minuscule, because studies with millions of people who received an mRNA-based COVID-19 vaccine have not detected consistent associations with VITT[54,56].

Subacute triggering risk factors

Inflammation

High levels of biomarkers of chronic inflammation, such as serum C-reactive protein and serum albumin, have been consistently associated with a greater risk of VTE[57–59]. Genetic studies that identified coagulation-related gene variants linked to the risk of VTE have also highlighted a role of inflammatory pathways in VTE[60]. However, the most compelling data linking inflammation to the risk of VTE come from randomized, controlled, clinical trials of statins[58]. In addition to their anti-hyperlipidaemic properties, statins are also potent anti-inflammatory agents and might also improve the coagulation profile[61]. In the JUPITER trial[62], rosuvastatin therapy reduced the risk of VTE compared with placebo (HR 0.57, 95% CI 0.37–0.86). Importantly, blood lipid levels are not associated with the risk of VTE[13], suggesting that the role of statins in reducing the risk of VTE is via their anti-inflammatory effects.

Hormonal states

Oral contraceptive use, hormone replacement therapy, and pregnancy. The risk of VTE is elevated in women receiving oestrogen-based contraceptives, hormone replacement therapy or infertility treatment, as well as during pregnancy[63]. In a cohort study of ~1.2 million women from four national registries, women taking combined (oestrogen and progestogen) oral contraceptives or progestin-only oral contraceptives were at approximately sixfold and threefold increased risk, respectively, of VTE compared with women who did not take oral contraceptives[64]. Although the prevalence of exposure to oral contraceptives and the magnitude of the association with VTE is relatively large, owing to the overall low incidence of VTE in this age group, 2,000 women would need to shift from combined oral contraceptives to progestin-only contraceptives to prevent one VTE annually[64]. Oestrogen therapy intensity seems to be important, with the highest risk of VTE in those individuals receiving continuous oestrogen therapy and a lower risk with increasing break periods in the therapy cycle[65]. Exposure to high-intensity exogenous hormones in the context of fertility treatments (for example, to simulate egg development and in vitro fertilization) can lead to ovarian hyperstimulation syndrome. Up to 10% of women with severe ovarian hyperstimulation syndrome develop VTE[66]. Users of hormone replacement therapy have an increased risk of VTE, similar to that observed with oral contraceptives[67]; however, the increased absolute baseline risk of VTE in this older patient population might change the risk–benefit ratio of hormone replacement therapy in this setting[67]. Research in transgender women might also provide additional insights into the role of sex hormones in the risk of VTE[68].

VTE complicates ~1.2 in 1,000 pregnancies[69] and accounts for approximately 9% of pregnancy-associated deaths in the USA[70]. Pregnancy is a procoagulant state and is also associated with greatly elevated steroid hormone levels, mechanical venous obstruction and venous

stasis, which increase the risk of VTE before delivery and during the puerperium[71,72]. In the postpartum period, the risk of VTE is highest during the first week after delivery (~0.9 per 1,000 deliveries)[73]. The risk of VTE drops to ~0.25 per 1,000 deliveries in the second week and continues to drop through to the 12th week. Furthermore, among individuals who are pregnant or postpartum, certain obstetric procedures and complications, such as caesarean delivery, pre-eclampsia, haemorrhage and postpartum infection, are thought to be associated with an increased risk of VTE (OR 1.3–6.4)[73]. Pregnancy-associated VTE differs by race/ethnicity in the USA, but whether this variation is due to differences in risk factors, genetics or access to health care has not been well studied[74].

Testosterone. Endogenous testosterone levels are not associated with VTE risk[75,76]. However, exogenous testosterone therapy might increase the risk of VTE[77–79]. Hypothesized mechanisms include elevated haematocrit levels (which can increase blood viscosity), platelet accumulation and elevated thromboxane A_2 production by platelets and increased concentrations in the blood, all of which can increase the risk of VTE[77–79]. The three largest studies on this topic have all relied on administrative databases. One study that used a case–crossover design determined that testosterone therapy is associated with a doubling in VTE risk[80]. Another study using a cohort design found a 70% greater risk with testosterone therapy[81]. A third study found no significant association[82]. Although the available data for VTE risk and testosterone therapy are not entirely conclusive, these findings, together with those suggesting that testosterone therapy is associated with increased risk of atherosclerotic disease[83–85], suggest that caution should be used when prescribing exogenous testosterone. Research among transgender men might also provide novel insights into the role of testosterone in the risk of VTE[68].

Basal risk factors

Demographic risk factors

Older age. The risk of VTE rises exponentially with age[7,15,86]. For example, in the LITE study[15], the race-adjusted and sex-adjusted incidence of VTE per 1,000 person-years was 0.72 in those aged 40 to <55 years, 1.58 in those aged 55 to <65 years, 2.47 in those aged 65 to <75 years, 3.12 in those aged 75 to <85 years and 6.96 in those aged ≥85 years. In a more recent analysis, the hazard ratios of VTE per decade of age were 2.67 (95% CI 2.45–2.91) (in the Emerging Risk Factors Collaboration (n = 731,728)) and 1.81 (95% CI 1.71–1.92) (in the UK Biobank (n = 421,537))[7]. The greater risk of VTE at older ages might be partly a result of the higher prevalence in older individuals of VTE risk factors, such as obesity, cancer, hospitalization or other comorbid conditions. Coagulation factor concentrations also typically increase with age[87–90], which might partly explain the increased risk of VTE in older adults.

Sex and gender. The risk of VTE according to sex varies by life stage. Women of child-bearing age are at increased risk of VTE, probably as a consequence of exposure to oral contraceptives and pregnancy[91–94] (see section on 'Hormonal states'). At older ages, *cis*-men are at a modestly greater risk of VTE than *cis*-women[16,95,96]. Some of this excess risk might be due to differences in the prevalence of underlying risk factors, particularly height[95]. VTE risk among transgender people is complex and might partially reflect gender-affirming hormone treatments and surgical procedures[97].

Race and ethnicity. The association between race and ethnicity and the risk of VTE is complex[98,99] (FIG. 2). In the USA, the incidence of VTE has been shown to differ by race and ethnicity[100–102]. Black American individuals seem to have the highest risk of VTE, followed by white, Latina/Latino and Asian American individuals, respectively[100–102] (based on US definitions of race and ethnicity[99]). However, VTE rates are similar in Black American and white American individuals after accounting for differences in the prevalence of underlying risk factors[100]. Geography also has a role in both VTE incidence and pulmonary embolism mortality in the USA, with the highest incidence in south-eastern USA[103,104]. Worldwide, differences in the prevalence of risk factors (such as obesity), genetics, overall health and access to health care are all likely to influence the risk of VTE in each region. However, available data are mostly from North America and Europe, with few or no data from Africa, Asia, Australia and South America[4,105]. Cross-national comparisons are difficult owing to differences in (or the lack of) disease surveillance systems and differences in health-care practices. Disentangling the effects of race and geography that are due to social (such as structural racism) and genetic constructs in epidemiological studies might inform efforts to reduce disparities in VTE incidence. There is also a need to include individuals from diverse populations in clinical trials. FIGURE 2 shows potential reasons, at least in the context of the USA, for the racial and ethnic differences and disparities in VTE incidence[98].

Behavioural

Physical inactivity. Numerous observational studies have found that greater physical activity is associated with lower VTE risk, as has been thoroughly reviewed previously[10,11]. In a 2020 meta-analysis of 14 prospective cohorts, the relative risk of VTE in individuals with high

Box 1 | **Factors affecting estimates of VTE incidence**

Higher estimates

- Advances in imaging of pulmonary embolism, which lead to the detection of smaller pulmonary embolisms[29] and poor interobserver agreement on the diagnosis of small pulmonary embolisms[30]
- Increased use of full-leg ultrasonography, which detects distal deep-vein thrombosis
- Co-occurrence of deep-vein thrombosis and pulmonary embolism in the same patient (might be double-counted in some data sources)

Lower estimates

- Outpatient care of ~35% of patients with deep-vein thrombosis[31] and a smaller proportion of patients with pulmonary embolism
- Misdiagnosis or under-diagnosis of venous thromboembolism events, particularly when symptoms are mild
- Low autopsy rates, resulting in a failure to identify fatal pulmonary embolisms

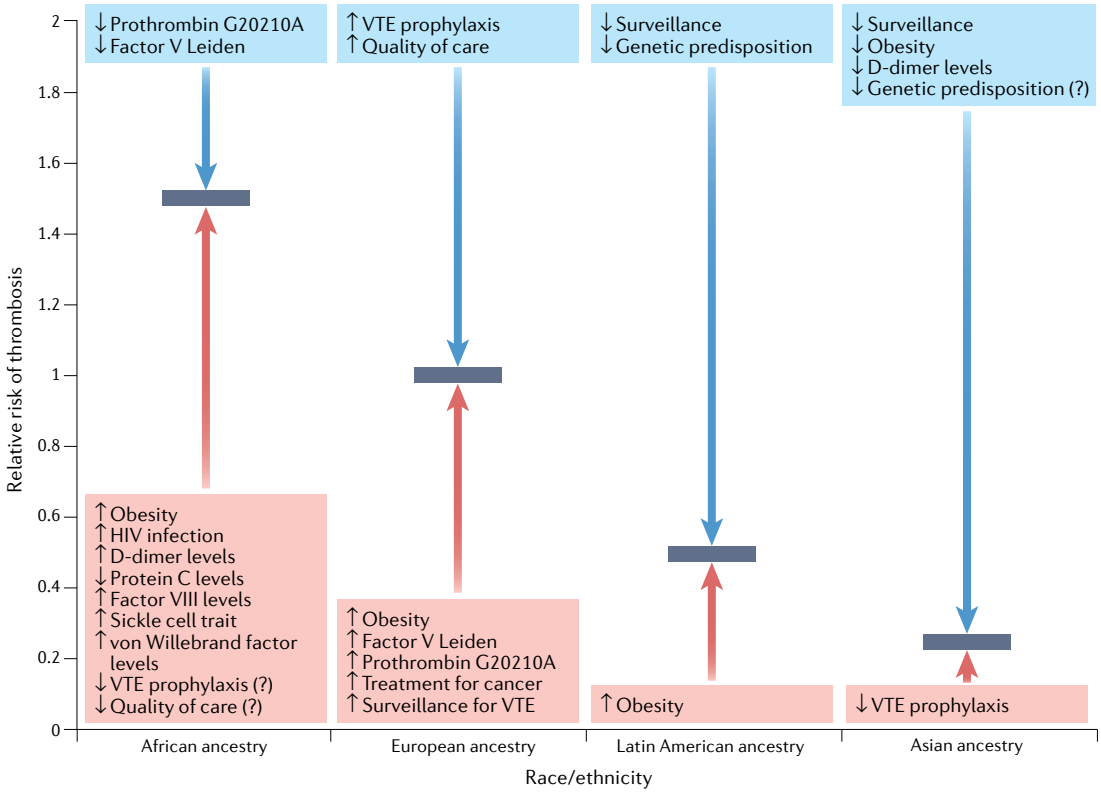

Fig. 2 | **Racial/ethnic differences in VTE incidence and potential underlying factors.** The graph shows the relative risk of venous thrombosis according to racial/ethnic categories. The relative risk is based on a review of the literature on absolute risk of venous thromboembolism (VTE) in various cohort studies (see REF.[98] for more details). The figure shows the factors that might lead to a higher or lower risk of VTE in each racial/ethnic group. Adapted with permission from REF.[98].

physical activity was 0.87 (95% CI 0.79–0.95) compared with those with low physical activity[11]. Greater cardiovascular fitness, objectively measured using a cycle ergonometric test, has also been associated with lower risk of VTE in a study in Swedish men[106]. Mechanisms linking greater physical activity to lower VTE risk include improved endothelial function, lower concentrations of coagulation factors, lower BMI and increased blood flow[11]. Conversely, low physical activity through a sedentary lifestyle, habitual sitting at work and more time spent watching television have all been linked to a greater risk of VTE[107,108]. However, results have not been entirely consistent[109]. The population-attributable risk of VTE owing to physical inactivity might be as high as 4%[110].

Diet. Research assessing diet as a risk factor for VTE has generally yielded neutral, inconsistent or modest findings[111]. This lack of strong evidence might reflect the difficulty in assessing diet as well as the uncertainty about what specific elements of the diet influence the risk of VTE. Diet might modify the risk of VTE through intake of specific nutrients, altering levels of haemostatic and fibrinolytic biomarkers, and/or through being associated with obesity. The strongest evidence linking diet to VTE comes from the Women's Health Initiative, in which women who were randomly assigned to receive vitamin E supplementation (600 IU) were at 21% lower risk of VTE than women receiving placebo[112]. Among observational studies, some, but not all, have found a lower risk of VTE associated with the intake of fruit and vegetables, low or moderate quantities of alcohol, vitamin E, vitamin B_6 and fibre, and a higher risk of VTE with greater intake of a 'Western' diet, red and processed meat, and *trans* fatty acids[111,113–118]. Given the inconsistent and neutral findings, public health messages are unlikely to promote consumption of a healthy diet for VTE prevention. However, dietary patterns that might be beneficial for reducing the risk of VTE are also advantageous for more common conditions, such as coronary heart disease and cancer, and are therefore encouraged in current dietary guidelines.

Smoking. Tobacco smoking has been postulated to increase the risk of VTE, given the potential for smoking to increase coagulability and chronic inflammation[119,120]. However, data evaluating smoking and VTE incidence are less convincing. Smoking was associated with provoked but not with unprovoked VTE events in a large, individual participant data meta-analysis that included validated VTE events[13]. Specifically, fully adjusted hazard ratios for the association between current smoking and provoked or unprovoked VTE events were 1.36 (95% CI 1.22–1.52) and 1.08 (95% CI 0.90–1.29), respectively[13], with similar findings in other studies[8,121]. The stronger association between smoking and provoked VTE might be explained by the well-known association between smoking and numerous health conditions (such as

cancer, respiratory illnesses, myocardial infarction and stroke), which can lead to hospitalization and/or immobilization.

Anthropometric risk factors

Height. Taller height is associated with greater risk of VTE[8,9,122–124]. In general, individuals in the highest height quantile are at 1.5–2.0 times greater risk of VTE than those in the lowest height quantile[8,9,122–124]. Possible explanations for this association include taller people having a greater venous surface area, a higher number of venous valves and greater hydrostatic pressure[125,126]. In one analysis, which included leg length measures, leg length was a VTE risk factor independent of total body height, but height was no longer associated with VTE risk after accounting for leg length[122]. This finding supports the hypothesis that leg length and height are associated with the risk of VTE through blood stasis or changes to the vascular wall rather than through hypercoagulability. A Mendelian randomization analysis that used data from the ARIC, CHS and the Mayo Clinic VTE studies found that single-nucleotide polymorphisms associated with greater height were associated with elevated VTE risk[127], strongly suggesting a causal relationship. A Swedish study that used a co-sibling design, specifically full sibling pairs discordant for height, also suggested a causal association[128].

Obesity. High BMI has been consistently associated with elevated risk of VTE, in a dose–response manner[6–9]. For example, in the LITE study, the hazard ratio for VTE was 1.58 (95% CI 1.20–2.09) for BMI 25 to ≤30 kg/m^2, 2.10 (95% CI 1.57–2.82) for BMI 30 to ≤35 kg/m^2 and 3.09 (95% CI 2.26–4.23) for BMI ≥35 kg/m^2 compared with normal weight (BMI ≤25 kg/m^2)[6]. Weight gain has also been associated with excess VTE risk[129,130]. A 2020 analysis estimated that the population-attributable risk of VTE associated with obesity in the USA was 30%[110]. An important additional assumption of population-attributable risk calculations is that the association is causal. Physiologically, obesity might increase the risk of VTE through venous stasis, elevated concentrations of haemostatic and inflammatory biomarkers, and increased risk of other conditions known to predispose to VTE (such as cancer)[110]. Strong evidence of causality was derived from two Mendelian randomization studies that demonstrated that single-nucleotide polymorphisms associated with increased BMI were linked to a higher risk of VTE[131,132]. Large-scale, randomized, controlled trials have not yet tested whether prevention of weight gain or interventions to lose weight reduce the risk of VTE.

May–Thurner syndrome. Patients with May–Thurner syndrome have an elevated risk of developing an extensive left iliofemoral DVT (localized blood clot) owing to an anatomical variant in which the right common iliac artery compresses the left common iliac vein against the lumbar spine[133]. Determining the population burden of May–Thurner syndrome is challenging because of the specialized imaging techniques required for its diagnosis[134]. However, the extremely limited data available suggest that this syndrome might account for 2–5% of DVT cases in the USA and Europe[134]. Given the complexity of diagnosing May–Thurner syndrome, the relative and absolute risks of VTE in individuals with this anatomical variant are unknown.

Genetic risk factors

Heritability and family history. Studies have estimated that the heritability of VTE is approximately 23%[60] to 30%[135]. These heritability estimates are lower than those that were based on family studies (40–60%)[136,137]. In a multi-generation study of Swedish registry data, the familial odds ratio for VTE was 2.49 (95% CI 2.40–2.58) in siblings, 2.65 (95% CI 2.50–2.80) in children, 2.09 (95% CI 2.03–2.15) in parents, 1.52 (95% CI 1.26–1.85) in maternal half-siblings, 2.34 (95% CI 2.00–2.73) in paternal half-siblings, 1.69 (95% CI 1.57–1.82) in nieces or nephews, 1.47 (95% CI 1.33–1.64) in cousins and 1.14 (95% CI 1.09–1.18) in spouses of individuals diagnosed with VTE[137].

Genetic risk factors. Numerous genetic risk factors have been identified that predispose individuals to VTE, as has been extensively reviewed previously[136,138,139]. A few of the more notable established genetic risk factors are highlighted below. Importantly, genetic discovery work continues[60,135].

The factor V Leiden variant is the cause of the most common monogenetic inherited thrombophilia among populations of European origin, but is rare in non-European populations[140]. In a pooled analysis, the risk of VTE was increased fourfold in individuals who were heterozygous for the factor V Leiden variant and increased 11-fold in those who were homozygous for the factor V Leiden variant compared with non-carriers[141]. The lifetime risk of VTE in those with the factor V Leiden variant is ~17%[2]. Likewise, the prothrombin *F2* gene variant G20210A is often cited as a risk factor for VTE and is associated with a twofold to threefold relative increase in the risk of VTE[142].

Sickle cell disease and trait are genetic risk factors for VTE[2,143–145]. In the USA, 0.2% of Black American individuals have sickle cell disease and 8% of Black American individuals have sickle cell trait[146]. Whereas sickle cell disease is characterized by substantial morbidity, individuals with sickle cell trait are often unaware of their status[147]. Both conditions are also associated with procoagulant abnormalities[148,149]. Several studies have demonstrated that sickle cell trait is a moderately strong risk factor for VTE[2,143–145], with 18% of individuals with sickle cell trait developing VTE in their lifetime[2].

More common genetic variants associated with VTE tend to be associated with a lower magnitude of risk than rare mutations, but might have a substantial effect on the population-level risk of VTE. Some examples include non-O blood group and variants in the *F2*, *F5*, *F11*, *FGG* or *ZFPM2* genes[150].

Genetic risk scores. Genetic risk scores have been created to predict the risk of VTE. In an anlysis of data from the LITE study, an a priori weighted score was created based on five established VTE-associated

single-nucleotide polymorphisms in the *ABO*, *F2*, *F5*, *F11* and *FGG* genes[151]. When this score was used, the risk of VTE in white individuals increased 1.41-fold (95% CI 1.27–1.56) per allele increment. Another study calculated a genetic risk score based on 37 VTE susceptibility gene variants, which showed a robust dose–response association with the risk of VTE[60]. Compared with individuals in the 25th to 75th percentiles of the genetic risk score, the odds ratios for VTE were 0.51 (95% CI 0.43–0.61) in individuals at or below the 5th percentile and 3.19 (95% CI 2.89–3.52) in individuals at or above the 95th percentile[60]. Genetic risk scores are not currently used for VTE risk assessment, but given the familial studies suggesting heritability of VTE risk, there is potential for the use of genetic risk scores to help refine an individual's VTE risk. A huge barrier to implementing genetic risk scores in practice are the limitations in understanding genetic VTE risk in populations of non-European origin as well as how to use them in racially mixed populations.

Acquired risk factors

Cancer

Cancer is the quintessential risk factor for VTE[152]. After the cancer itself, thrombosis is the next leading cause of death in people with cancer, and complicates the care of people with cancer[153]. The mechanism of thrombosis in patients with cancer relates to the cancer itself as well as to cancer treatments and complications of cancer treatment, as has been reviewed previously[153].

The annual incidence of VTE in patients with cancer ranges from 0.5% to 20% depending on the cancer type and cancer treatments offered[153,154]. Risk factors, such as cancer stage, certain cancer treatments, central catheters and surgical procedures, all interact to influence the risk of VTE[153,154]. Specific thrombosis risk scores exist for patients with cancer in general[155] as well as for patients with specific cancer types undergoing selected treatments[156,157]. None of these risk scores incorporate the temporal nature of many risk factors that patients with cancer encounter, such as hospitalization and surgical procedures, which have been shown to be important for VTE risk[158].

Prevention of thrombosis in patients with cancer is under active investigation, and in some individuals with cancer primary prophylaxis might be warranted. Professional medical societies frequently publish guidelines for the management and prevention of thrombosis in patients with cancer and, as we improve our understanding of the risk of VTE in these patients, the indications for VTE prevention will evolve[159].

Autoimmune diseases

Antiphospholipid syndrome (APS), and the related entity catastrophic APS, is an autoimmune disorder that predisposes individuals to thrombosis and is the quintessential thrombotic autoimmune disease[160]. The diagnosis of this clinicopathological entity requires both the appropriate clinical setting, defined by unexplained pregnancy loss or thrombosis, as well as pathological confirmation of the presence of persistent antiphospholipid antibodies (as measured, for example, by anti-cardiolipin antibodies) and/or lupus anticoagulants (as measured, for example, by the dilute Russell's viper venom time)[161]. In APS, autoantibodies disrupt phospholipids protecting the blood vessel wall, leading to thrombosis[161]. The incidence of APS in the general population is approximately 2 per 100,000 person-years[162]. However, the presence of antiphospholipid antibodies is common in the general population, ranging from 1–5% in healthy young populations to 50% in older individuals with multiple comorbidities[163]. In VTE-free individuals with certain autoimmune diseases such as systemic lupus erythematosus, antiphospholipid antibodies and/or lupus anticoagulants might increase the risk of thrombosis by up to threefold[161,162]. About 1% of people with APS develop catastrophic APS[164]. Catastrophic APS can develop in individuals with APS who have uncontrolled activation of the complement system, leading to catastrophic thrombosis, often despite the use of anticoagulation therapy[160].

Numerous other autoimmune diseases have been linked to an increased risk of VTE[165]. For example, a Swedish nationwide study found that the risk of pulmonary embolism was elevated in the first year after hospitalization for 33 different autoimmune disorders[166]. Among the most studied are rheumatoid arthritis, systemic lupus erythematosus and inflammatory bowel disease[165–169]. Some studies have estimated that patients with systemic lupus erythematosus have up to a 26% risk of having a thrombosis event throughout their disease course[165,169]. These autoimmune diseases are thought to increase VTE risk by upregulating the body's procoagulant factors while simultaneously decreasing the levels of physiological anticoagulants via systemic inflammation[165]. Other potential causes include increased VTE risk associated with some treatments for autoimmune diseases as well as a higher prevalence of antiphospholipid antibodies leading to increased incidence of APS in this patient population[165,170].

Hyperlipidaemia, hypertension and diabetes

The role of traditional risk factors for cardiovascular disease, such as hypertension, hyperlipidaemia and diabetes, in the risk of VTE has long been debated. In crude or minimally adjusted analyses, associations are generally present[13]. However, after demographic factors and BMI are accounted for, hypertension, hyperlipidaemia and diabetes are not associated with the risk of VTE[13]. Arguably, the best data evaluating these associations come from a large, individual-level meta-analysis that included nine prospective cohorts including 244,865 participants with a total of 4,910 VTE events occurring during a mean follow-up of 4.7–19.7 years[13]. Hazard ratios adjusted for age, sex and BMI for overall VTE were 0.98 (95% CI 0.89–1.07) for hypertension, 0.97 (95% CI 0.88–1.08) for hyperlipidaemia and 1.01 (95% CI 0.89–1.15) for diabetes[13]. These neutral findings are also supported by a 2021 study showing that a polygenic risk score for coronary artery disease is not related to venous thrombosis[171]. In summary, convincing evidence indicates that hypertension, hyperlipidaemia and diabetes are not VTE risk factors independently of age, sex and obesity.

Other clinical conditions

Numerous other clinical conditions and risk factors have also been associated with an increased risk of VTE. Although some of the increase in VTE risk is likely to be due to confounding comorbidities, immobility and adverse environmental conditions (such as air travel)[172], evidence suggests the involvement of specific pathological mechanisms underlying conditions such as kidney disease[173,174], heart failure[175,176] and atrial fibrillation[177,178].

Previous VTE

Although treatment and secondary prevention of VTE is extraordinarily effective, previous VTE is one of the strongest risk factors for a VTE event[179]. Even superficial thrombophlebitis has been shown to be a risk factor for recurrent VTE[180].

Primary treatment failure occurs within 3 months of the initial VTE diagnosis[20]. In early studies on VTE treatments, radiographic progression of VTE based on various criteria is common with treatment (up to 15%), although usually asymptomatic[181]. In clinical trials comparing direct oral anticoagulant treatment with other anticoagulant strategies, the rate of recurrent symptomatic VTE was ≤3.5% with either treatment strategy[182–187]. Establishing risk factors for primary treatment failure is challenging owing to the differing definitions of treatment failure. In a secondary analysis of clinical trial data, risk factors for the failure of primary treatment with parental heparin bridged to an oral vitamin K antagonist were cancer, chronic cardiovascular disease, chronic respiratory disease, concurrent diseases (renal, hepatic, gastrointestinal, neurological, haematological or multisystem diseases) and younger age[188]. After 3–6 months of primary treatment, individuals should be risk-stratified for secondary prevention of VTE with anticoagulation therapy or observation. In the absence of long-term anticoagulation treatment, approximately 30% of patients have VTE recurrence within the next 10 years[8,189,190]. Predictors of VTE recurrence within 180 days include active cancer and inadequate initial anticoagulation treatment[191].

Outcomes

Mortality

Mortality from VTE is higher after pulmonary embolism events than after DVT events[3,192]. In a study using data from ~100,000 patients from 26 countries who were included in the RIETE registry, 30-day mortality from VTE was 2.6% for distal DVT, 3.3% for proximal DVT and 5.2% for pulmonary embolism[193]. The 30-day mortality was higher for DVT (5.1%)[194] and pulmonary embolism (9.1%)[195] among US Medicare beneficiaries aged ≥65 years, which might be attributable to the older age of this patient population. The same researchers found that the 1-year mortality for DVT was 19.6%[194] and the 6-month mortality for pulmonary embolism was also 19.6%[195]. The 1-year mortality for pulmonary embolism was not reported.

After VTE, 1-year survival varies greatly by underlying VTE cause. In an analysis using administrative data for first-time VTE in Quebec, Canada, the 1-year survival rate for VTE was 77% overall, but when stratified by VTE-provoking status, it was 47% for cancer-associated VTE, 84% for provoked VTE and 93% for unprovoked VTE[196]. Long-term mortality remains elevated after an unprovoked VTE event, as shown by the MEGA study[197].

Additional research is needed to understand the burden of VTE associated with specific health conditions as well as the need for and optimal approaches to VTE prophylaxis. For example, as noted in the section 'Hormonal states', VTE accounts for ~9% of pregnancy-associated deaths in the USA[70]. Additional efforts are need to identify and prevent VTE in the peripartum period.

Even when not clinically recognized, VTE might be an important marker of an increased risk of death. Among patients with acute medical illness, asymptomatic DVT events diagnosed with compression ultrasonography were associated with a threefold increased risk of short-term all-cause death compared with those with no evidence of DVT[198].

Complications

Bleeding. Bleeding is a complication of every anticoagulant therapy. Historically, the incidence of bleeding after diagnosis of VTE has been shown to be >10%, and early bleeding is associated with a greater risk of VTE recurrence and death[199,200]. Data from phase III, randomized, controlled trials suggest that the use of direct oral anticoagulants, instead of warfarin, for the primary treatment of VTE could reduce the risk of bleeding[201,202], but patient characteristics might influence the magnitude of the benefit[203,204]. The risk of bleeding drives many of the recommendations for the use of anticoagulation therapy for the secondary prevention of VTE[20,21].

Post-thrombotic syndrome. Post-thrombotic syndrome refers to symptoms and signs of chronic venous insufficiency that develop after DVT[205]. Post-thrombotic syndrome is a common complication of DVT that develops in 20–50% of patients after proximal DVT and is severe in 5–10% of patients[180]. Moreover, approximately 4% of patients with DVT develop venous stasis ulcers[206].

Post-thrombotic syndrome has specific risk factors that can be identified at the time of or after DVT: recurrent ipsilateral DVT, obesity, chronic kidney disease, more extensive DVT, poor quality of initial anticoagulation therapy, ongoing symptoms or signs of DVT 1 month after diagnosis, and elevated plasma D-dimer levels at 1 month[180,207]. Additionally, in a meta-analysis of patients with DVT who underwent ultrasonography at least 6 weeks after their DVT event, the ultrasonography parameters of residual vein thrombosis and venous reflux at the popliteal level were both predictive of post-thrombotic syndrome[27,208]. Methods for the primary prevention of post-thrombotic syndrome are uncertain[209].

Pulmonary hypertension. Survivors of VTE are at an elevated risk of pulmonary hypertension, which is also referred to as chronic thromboembolic pulmonary hypertension[210,211]. Pulmonary hypertension can occur when pulmonary emboli or thrombi do not resolve and

instead obstruct major pulmonary arteries, leading to increased pulmonary artery pressures, right-sided heart remodelling and pulmonary hypertension[210].

The true incidence of pulmonary hypertension after VTE is unknown[211,212], although some of the strongest studies suggest an incidence of 1–4% in the 2 years after the pulmonary embolism event[212–214]. Few studies have evaluated risk factors for pulmonary hypertension in patients with VTE. However, in the UK Clinical Practice Research Datalink analysis, chronic obstructive pulmonary disease, atrial fibrillation, heart failure and splenectomy were associated with a greater risk of pulmonary hypertension[212]. In a USA-based study using MarketScan administrative claims data, a higher Charlson Comorbidity Index score was associated with greater risk of pulmonary hypertension, and the individual comorbidities associated with the strongest elevation in pulmonary hypertension risk were concomitant heart failure, chronic pulmonary disease and alcohol abuse[214].

Post-VTE quality of life and physical function. Quality of life and physical function after VTE are also crucial considerations[215]. VTE is often viewed as an acute condition, but evidence indicates that survivors of VTE are more likely to be granted permanent work-related disability[216], experience a decline in physical function in the years subsequent to their index event[217], and be frail and have poor physical function long after their initial VTE event compared with similarly aged individuals who did not have VTE[218]. Individuals who have VTE might be a group with a high risk of functional decline who should receive screening and potentially interventions to preserve physical function.

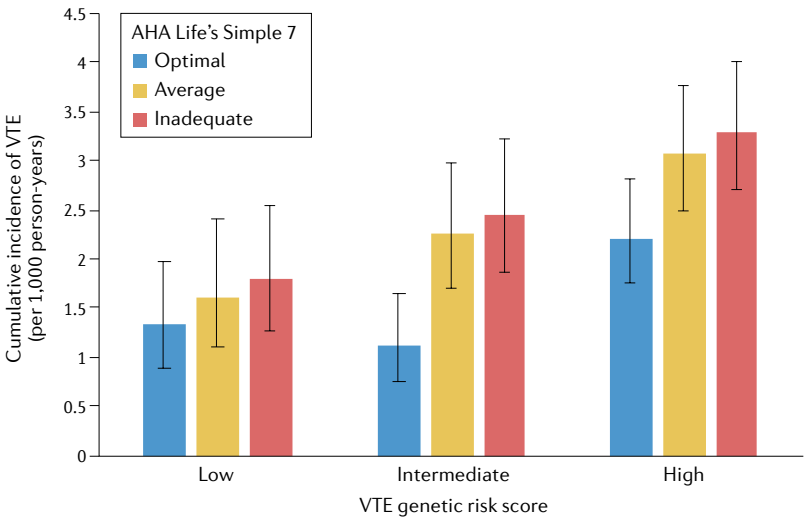

Fig. 3 | **Cumulative incidence of VTE according to genetic risk score and the AHA Life's Simple 7.** Cumulative incidence of venous thromboembolism (VTE) per 1,000 person-years (95% CI) according to VTE genetic risk score category. The genetic risk score categories are classified according to American Heart Association (AHA) Life's Simple 7 categories[219]. The cumulative incidence of VTE is greater among individuals with high VTE genetic risk scores. In each genetic risk score group, lifestyle is also associated with the risk of VTE. Specifically, regardless of genetic predisposition, individuals with optimal Life's Simple 7 scores have the lowest risk of VTE, those with average Life's Simple 7 scores have an intermediate risk and those with inadequate Life's Simple 7 scores have the greatest risk of VTE. The graph is a re-analysis of data from REF.[224].

Prevention

VTE is divided epidemiologically and clinically into provoked and unprovoked events[20]. As described in the Introduction, the terminology is confusing and used inconsistently. Provoked events are those associated with conditions such as cancer, surgery, hospitalization and/or immobility, whereas unprovoked events are those associated with no identifiable trigger but include pregnancy and hormone-associated VTE. Approximately half of all VTE events are associated with a defined trigger and are, therefore, potentially preventable through interventions of finite duration[27]. Unprovoked VTE can theoretically be prevented by healthy lifestyle choices[110,219], and even by off-target effects of cardiovascular disease therapies such as statins[58]. However, this strategy might lack a holistic and patient-centred approach to VTE prevention. One alternative approach is to view VTE risk as a temporally layered set of risk factors. Some risk factors are constant (such as genetics), whereas others increase over time (such as age), with subacute (obesity) and acute (hospitalization) events layering on the risk until a predefined individual thrombosis threshold is crossed (FIG. 1). In this section, we discuss prevention in terms of primordial, primary and secondary prevention.

Primordial prevention

Primordial prevention refers to preventing disease in otherwise healthy people by preventing the development of risk factors for the disease[220,221]. Not all risk factors are amenable to primordial prevention (such as age, sex and genetics). However, interventions that improve health have the potential to reduce the risk of VTE, although they might not have been studied specifically for VTE prevention[220,221]. Ideal levels of physical activity and dietary interventions (see relevant sections) can result in less obesity and fewer hospitalizations, which could reduce the risk of VTE[222]. Preventing individuals from starting to smoke could reduce the risk of VTE by reducing the incidence of and hospitalizations for respiratory diseases, cardiovascular diseases and certain cancers (see section 'Smoking')[13,221]. Equitable lifestyle interventions (by age, sex, race and socioeconomic status) to improve diet and physical activity and prevent smoking in the general population improve health without having to add VTE risk reduction into the equation[223]. Even for static risk factors, such as genetic factors, primordial prevention matters. Healthy lifestyle choices can attenuate the increased risk of VTE associated with adverse genetic variants[224] (FIG. 3). Other opportunities for primordial prevention include a focus on gynaecological and obstetric health in younger women by selecting lower risk methods of contraception, such as cyclic oral contraceptives and intrauterine devices (see section 'Hormonal states').

Primary prevention

Primary prevention of VTE reduces VTE by specific interventions in those individuals at risk of VTE. The most common intervention is pharmacological prophylaxis with low doses of anticoagulation drugs. The two most discussed opportunities for primary prevention of VTE relate to hospitalization and cancer. Given the large

number of VTE events attributable to hospitalization and the finite risk period, hospital-associated VTE risk has become a key target of VTE prevention measures to reduce health-care-associated complications[225–228]. Whereas guidelines exist for the prevention of VTE during the hospital stay, there is limited clarity on how long prophylaxis should be continued after discharge, except for certain orthopaedic procedures for which guidelines are well established[60]. A similar consensus on primary prevention of VTE is evolving for patients with cancer, although the best strategy to prevent VTE in these patients is not known because the risk of VTE varies over time[159,229]. Primary prevention with anticoagulation therapy increases the risk of bleeding, and the risk–benefit balance is not established in many populations at risk of VTE[228].

Another intriguing pharmacological intervention for the primary prevention of VTE is the use of statins. The JUPITER trial[62], which recruited individuals with elevated plasma C-reactive protein levels and normal blood lipid levels, demonstrated that an off-target benefit for rosuvastatin therapy was a reduction in VTE risk. Whether statins can be used in individuals with increased risk of VTE to reduce VTE events has not been tested.

Secondary prevention

Secondary prevention refers to the prevention of recurrent VTE events in individuals with a history of VTE. Traditionally, the strategy for secondary prevention of VTE is anticoagulation therapy[20]. This approach reflects VTE being considered in clinical medicine as an event rather than a lifelong disease. Of note, in clinical practice, one of the strongest risk factors for VTE is a history of VTE. Even individuals with provoked VTE events often have multiple VTE recurrences throughout their life.

Although imperfect guidelines exist for who should be offered secondary VTE prevention with anticoagulation therapy, even, and perhaps especially, individuals who are not receiving anticoagulation therapy for secondary prevention are at risk of VTE recurrence with further provoking events such as pregnancy, hormone therapy, bone fracture, hospitalization and surgery[20]. In women, VTE provoked by exogenous hormone therapy or pregnancy warrants secondary prevention with anticoagulation therapy with subsequent pregnancy or hormone use. For hospitalized people, previous VTE is one of the most consistent risk factors for hospital-acquired VTE. The bottom line is that although the decision to offer anticoagulation therapy for secondary prevention of VTE is made once in the 3–6 months after the initial event, decisions on how best to prevent recurrent VTE during periods of VTE risk should be made throughout the life course. Although there are intriguing findings for non-antithrombotic agents for the secondary prevention of VTE, none are currently recommended for use in clinical practice[61].

Awareness

Improving awareness of VTE is another important avenue to VTE prevention[230]. Awareness of the disease is poor in the general population, and symptoms are often attributed to other disorders, thereby leading to a delay in diagnosis[231]. Unfortunately, even among individuals with a high risk of potentially provoking conditions, awareness of VTE is low. In a survey of patients with cancer, <20% of patients could name the symptoms of VTE and only 3% knew that cancer treatments are associated with a greater risk of VTE[232]. Continued education among medical professionals could also increase VTE awareness and implementation of guideline-based care[230].

Reducing disparities in VTE burden

As noted above, VTE incidence and outcomes vary according to race and ethnicity. As with so many other health conditions, factors underlying these disparities in VTE incidence and outcomes include structural racism, differences in socioeconomic status and disparities in access to health care. Lower individual[105,233] and neighbourhood[4,233] socioeconomic status have been linked to greater VTE risk, even in regions with a universal health-care model (such as Denmark, Netherlands and Sweden). Although men in the general population have a higher risk of VTE recurrence than women, this risk differs by race, with Black and Latina women having a higher recurrence risk of VTE than white women in the USA[234]. For primary prevention of VTE, a US hospital-based project showed that care standardization through implementation of a mandatory computerized clinical decision support tool eliminated disparities in the use of VTE anticoagulation prophylaxis[235]. Also in the USA, Black individuals with VTE were fivefold more likely to experience complications of care after hospitalization for a VTE, including readmission, bleeding and death, than white individuals[236,237]. Reducing disparities in VTE incidence and outcomes will require individual, systems-based and societal commitments to equity.

Conclusions

VTE is an underappreciated source of morbidity and mortality worldwide. In the developed Western world, an estimated 8% of people will develop VTE in their lifetime[2]. However, global estimates of VTE incidence and burden are limited owing to the lack of VTE surveillance systems. VTE risk factors are multifactorial (FIG. 1), including acute triggers, subacute triggers and basal and acquired risk factors. Although the breadth of VTE risk factors make it difficult to determine who will develop VTE, it also yields many pathways amenable to targeting for VTE prevention. As with most conditions, the greatest potential to reduce the societal burden of VTE would be through primordial prevention to prevent the development of risk factors for VTE (such as obesity and common acute triggers). For individuals at risk of VTE or who have previous VTE, primary and secondary prevention are essential to reducing the burden of VTE. Differences related to race, ethnicity and socioeconomic status exist in VTE incidence and outcomes, and approaches to VTE prevention that improve health equity should be prioritized.

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Review criteria
We provide a broad overview of the epidemiology and prevention of venous thromboembolism (VTE). Given the breadth of this topic, including an exhaustive review of the literature for each risk factor and VTE was not possible. Therefore, we tried to identify either a well-performed meta-analysis or a few representative studies for each risk factor. In general, we placed the most weight on randomized controlled trials (when available), followed by large, population-based, cohort studies, and then case–control studies or other designs. With regard to VTE anatomical sites, we focus on the deep veins of the legs and arms as well as of the pulmonary arterial vasculature. Alternative sites of thrombosis, such as cerebral sinus thrombosis and splanchnic vein thrombosis, are not reviewed in this article because, although having some shared risk factors, they are managed differently and often have very specific risk factors. Additionally, treatment is reviewed more extensively in various consensus statements, and a full review of treatment strategies is outside the scope of this Review.