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The Epidemiology of Venous Thromboembolism in the Community

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The Incidence of Deep Vein Thrombosis and Pulmonary Embolism

Venous thromboembolism is a major health problem. The average annual incidence of venous thromboembolism among whites is 108 per 100,000 person-years[1,2], with about 250,000 incident cases occurring annually among U.S. whites. The incidence appears to be similar or higher among African-Americans and lower among Asian- and Native-Americans[3,4]. Adjusting for the different age and sex distribution of African-Americans, the venous thromboembolism incidence is about 78 per 100,000, suggesting that about 27,000 incident venous thromboembolism cases occur annually among U.S. Blacks. Recent modeling suggests that over 900,000 incident or recurrent, fatal and non fatal VTE events occur in the U.S. annually[5]. The incidence of venous thromboembolism has not changed significantly over the last 25 years[2].

Venous thromboembolism is predominantly a disease of older age[1,2,6]. Incidence rates increase exponentially with age for both men and women and for both deep vein thrombosis and pulmonary embolism[1,2,6]. The overall age-adjusted incidence rate is higher for men (130 per 100,000) then women (110 per 100,000; male:female sex ratio is 1.2:1)[1,2]. Incidence rates are somewhat higher in women during the childbearing years, while incidence rates after age 45 years are generally higher in men. Pulmonary embolism accounts for an increasing proportion of venous thromboembolism with increasing age for both genders[1].

Survival after Deep Vein Thrombosis and Pulmonary Embolism

Observed survival after venous thromboembolism is significantly worse than expected survival for age and gender, and survival after pulmonary embolism is much worse than after deep vein thrombosis alone[7,8]. The risk of early death among patients with symptomatic pulmonary embolism is 18-fold higher compared to patients with deep vein thrombosis alone[7]. Pulmonary embolism is an independent predictor of reduced survival for up to three months after onset. For almost one-quarter of pulmonary embolism patients, the initial clinical presentation is sudden death. The annual number of pulmonary embolism-related deaths in the U.S. may exceed myocardial infarction-related death, and also stroke-related deaths[5].

Venous Thromboembolism Recurrence

Venous thromboembolism is a chronic disease with episodic recurrence; about 30% of patients develop recurrence within the next ten years[9,10]. The hazard of recurrence varies with the time

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since the incident event and is highest within the first 6–12 months. While anticoagulation is effective in preventing recurrence, the duration of anticoagulation does not affect the risk of recurrence once primary therapy for the incident event is stopped[10,11]. Independent predictors of recurrence include male gender[12], increasing patient age and body mass index, neurological disease with leg paresis, and active cancer[6,9,10,13]. Additional predictors include "idiopathic" venous thromboembolism[13], a lupus anticoagulant or antiphospholipid antibody[14,15], antithrombin, protein C or protein S deficiency[16], and possibly persistently increased plasma fibrin D-dimer[17] and residual deep vein thrombosis[18].

Complications of Venous Thromboembolism

The major complications of venous thromboembolism are venous stasis syndrome (i.e., post-thrombotic syndrome) and venous ulcer, and chronic thromboembolic pulmonary hypertension. The overall incidence of venous stasis syndrome and venous ulcer in the U.S. is 76.1 and 18.0 per 100,000 person-years, respectively[19]. Venous thromboembolism accounts for about 12% of all venous stasis syndrome cases occurring in the community[19]. Venous thromboembolism patients have a 17-fold increased risk of venous stasis syndrome[19]. The 20-year cumulative incidence of venous stasis syndrome after venous thromboembolism and after proximal deep vein thrombosis are about 25% and 40%, respectively[10,20,21]. The 20-year cumulative incidence of venous ulcer is 3.7%[21].

The incidence of chronic thromboembolic pulmonary hypertension is 6.5 per million person-years[22]. Applying these incidence rates to the 2000 U.S. white population, approximately 1367 new chronic thromboembolic pulmonary hypertension cases occur in the U.S. annually.

Risk Factors for Venous Thromboembolism

To reduce venous thromboembolism incidence, persons at risk for venous thromboembolism must first be identified. Independent risk factors for venous thromboembolism include increasing patient age, surgery, trauma, hospital or nursing home confinement, active cancer with or without concurrent chemotherapy, central vein catheterization or transvenous pacemaker, prior superficial vein thrombosis, varicose veins, and neurological disease with leg paresis; patients with chronic liver disease have a reduced risk [23,24]. The incidence of VTE increases significantly with age for both idiopathic and secondary VTE, suggesting that the risk associated with advancing age may be due to the biology of aging rather than simply an increased exposure to VTE risk factors with advancing age[25]. Compared to residents in the community, hospitalized residents have over a 100-fold increased incidence of acute venous thromboembolism[26]. Hospitalization and nursing home residence together account for almost 60% of incident venous thromboembolism events occurring in the community[27]. Thus, hospital confinement provides an important opportunity to significantly reduce venous thromboembolism incidence. Of note, hospitalization for medical illness and hospitalization for surgery account for almost equal proportions of venous thromboembolism (22% and 24%, respectively), emphasizing the need to provide prophylaxis to both of these risk groups. Nursing home residence independently accounts for over one-tenth of all venous thromboembolism disease in the community[27].

Active cancer accounts for almost 20% of incident venous thromboembolism events occurring in the community[27]. The risk appears to be higher for patients with pancreatic cancer, lymphoma, malignant brain tumors, cancer of the liver, leukemia, and colorectal and other digestive cancers[28]. Cancer patients receiving immunosuppressive or cytotoxic chemotherapy are at even higher risk for venous thromboembolism[23].

The risk among surgery patients can be further stratified based on patient age, type of surgery, and the presence of active cancer[29,30]. The incidence of postoperative venous

thromboembolism is increased with advancing patient age[30,31]. High-risk surgical procedures include neurosurgery, major orthopedic surgery of the leg, thoracic, abdominal or pelvic surgery for malignancy, renal transplantation, and cardiovascular surgery [30]. After controlling for the type of surgery and active cancer, additional independent risk factors for venous thromboembolism within three months after major surgery include increasing body mass index, intensive care unit admission for six days or longer, a central venous catheter, prolonged immobility, varicose veins and infection[31,32].

Among patients hospitalized for acute medical illness, active cancer is a major venous thromboembolism risk factor. After controlling for cancer, additional independent risk factors for venous thromboembolism within three months after hospitalization for acute medical illness include increasing age and BMI, neurological disease with leg paresis, fracture, chronic renal disease, central venous catheter, prior superficial vein thrombosis, and prolonged immobility[33].

Medical conditions associated with VTE include heparin-induced thrombocytopenia, myeloproliferative disorders (especially polycythemia rubra vera and essential thrombocytosis), intravascular coagulation and fibrinolysis/disseminated intravascular coagulation, nephrotic syndrome, paroxysmal nocturnal hemoglobinuria, thromboangiitis obliterans (Buerger's disease), thrombotic thrombocytopenic purpura, Behcet's syndrome, systemic lupus erythematosus, inflammatory bowel disease, homocystinuria, and possibly hyperhomocysteinemia[34,35]. The risk associated with congestive heart failure, independent of hospitalization, is low[23,24]. Long haul (> 6 hour) air travel is associated with a slightly increased risk for venous thromboembolism that is preventable with graduated compression stockings[36].

Among women, additional risk factors for venous thromboembolism include oral contraceptive use and hormone therapy [37], pregnancy and the postpartum period[24,38], and therapy with the selective estrogen receptor modulator, raloxifene. First and third generation oral contraceptives convey higher risk than second generation oral contraceptives[37]. Hormone therapy is associated with a 2- to 4-fold increased risk of venous thromboembolism [39], but the risk may vary by type of estrogen[40]. The overall incidence of pregnancy-associated venous thromboembolism is about 200 per 100,000 woman-years; compared to non-pregnant women of childbearing age, the relative risk is increased about 4-fold[38]. The risk during the postpartum period is about 5-fold higher than the risk during pregnancy[38].

The Genetic Epidemiology of Venous Thromboembolism

Recent family-based studies indicate that venous thromboembolism is highly heritable and follows a complex mode of inheritance involving environmental interaction[41,42]. Inherited reductions in plasma natural anticoagulants (e.g., antithrombin, protein C, or protein S) have long been recognized as uncommon but potent risk factors for venous thromboembolism[43]. More recent discoveries of impaired downregulation of the procoagulant system (e.g., activated protein C resistance, Factor V Leiden), increased plasma concentrations of procoagulant factors (e.g., factors I [fibrinogen], II [prothrombin], VIII, IX, and XI) and increased basal procoagulant activity, impaired fibrinolysis, and increased basal innate immunity activity and reactivity have added new paradigms to the list of inherited or acquired disorders predisposing to thrombosis (thrombophilia). Inherited thrombophilias interact with such clinical risk factors (e.g., environmental risk factors) as oral contraceptives, pregnancy, hormone therapy, and surgery to increase the risk of incident venous thromboembolism. Similarly, genetic interaction increases the risk of incident and recurrent venous thromboembolism. These findings support the hypothesis that an acquired or inherited thrombophilia may predict the subset of persons exposed to common risk factors who actually develop symptomatic venous thromboembolism.

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