Chapter 1: Introduction

Definition of Venous Thromboembolism

Venous thromboembolism (VTE) refers to all forms of pathologic thrombosis occurring on the venous side of the circulation. When it occurs in its most common location, the deep veins of the leg, it is referred to as deep venous thrombosis (DVT). Less common sites include the veins of the upper extremities, pelvis, abdomen and cerebral venous sinuses. The most life-threatening manifestation of VTE is embolization of venous thrombi to the pulmonary circulation, pulmonary embolism (PE). Up to 30 percent of patients with DVT suffer a symptomatic PE and another 40 percent have asymptomatic PE demonstrated on objective radiological tests.[1,2] Other complications associated with VTE include recurrent thromboembolism and post-phlebitic syndrome. Recurrent DVT occurs in about 20 percent of patients at 5 years and 30 percent after 10 years of followup.[3,4] Post-phlebitic syndrome is characterized by the development of lower extremity pain and swelling, stasis dermatitis, and venous ulceration due to the disrupted venous outflow after a DVT. Almost 30 percent of patients with DVT develop post-phlebitic syndrome after 20 years of followup.[5] Patient presentation varies markedly with some patients being entirely asymptomatic with a small calf vein thrombosis, and others having sudden death from hemodynamic compromise resulting from a large PE.

Epidemiology

VTE and its complications are a common cause of morbidity and mortality in the United States. Data from the Rochester Epidemiology Project estimate that the annual age and sex-adjusted incidence of isolated DVT is 48 per 100,000 people and the incidence of PE , with or without DVT, is 69 per 100,000, respectively.[6] Others estimate the incidence as being higher and suggest that 450,000 cases of DVT, 350,000 cases of non-fatal PE and 250,000 cases of fatal PE may occur annually in the United States.[7]

Etiology

The occurrence of VTE is generally triggered by a confluence of environmental and constitutional risk factors. Environmental risk factors for thrombosis include trauma, surgery, or immobility. Constitutional risk factors for thrombosis may be genetic or acquired. Genetic risk factors include deficiencies of endogenous anticoagulant proteins (such as antithrombin III, protein C or protein S); excessive function of procoagulant proteins (such as is associated with the factor V Leiden or prothrombin 20210 mutations), or elevated levels of factors VIII, IX and XI.[8] Although disturbances of normal fibrinolytic function (e.g., tissue plasminogen activator (TPA) deficiency, excessive levels of plasminogen activator inhibitor 1 (PAI-1) or a_2-antiplasmin, or factor XII deficiency) would be expected to contribute to a hypercoaguable state, clinical evidence of such is lacking.[9-11] Rarely, dysfibrinogenemia is associated with an increased tendency toward clot formation.[12] Hyperhomocysteinemia is associated with an

increased risk for both venous and arterial thrombosis and can result from inherited enzymopathies, or from acquired disorders of homocysteine metabolism including renal failure or folate or vitamin B12 deficiency.[13] Hyperhomocysteinemia has diverse effects on the coagulation cascade; it induces acquired resistance to activated protein C, up regulates tissue factor production and damages the vascular endothelium.[13-15]

Systemic illnesses, particularly cancer, nephrotic syndrome, paroxysmal nocturnal hemoglobinuria, and the antiphospholipid syndrome greatly increase the risk of VTE. Patients with myeloproliferative disorders, such as polycythemia vera and essential thrombocythemia are at an increased risk of thrombosis.[8] Congenital anemias, including sickle cell anemia and thalassemia, also heighten the risk of VTE.[16] Oral contraceptives or estrogen therapy raises the risk for VTE, as does pregnancy.[8] Heparin-induced thrombocytopenia is associated with venous or arterial thrombosis in up to 50 percent of patients in whom it develops.[17]

Diagnostic Approaches

The reference standard for VTE diagnosis remains clot visualization with contrast venography or pulmonary angiography. However, the invasiveness and the risks of these modalities have led to a steady increase in the use of non-invasive or minimally invasive VTE testing. Once popular, impedance plethysmography has become considerably less important in recent years since studies demonstrated its inferiority to duplex ultrasound in the diagnosis of DVT.[18] New methods of venography are now being investigated.[19,20]

Clinicians have relied heavily upon ventilation/perfusion (V/Q) scanning for the diagnosis of PE although they are using helical computed tomography (CT) more and more. Investigators are now examining the usefulness of magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) for diagnosis of PE, as well as the usefulness of coagulation tests (particularly D-dimer assays). All of these tests are optimally used after clinical examination and estimation of the pre-test likelihood of disease.

Therapeutic Approaches

The optimal approach to VTE is prevention. Much effort, with considerable success, has been devoted to VTE prophylaxis in patients known to be at high risk, such as surgical patients and patients with prior VTE. These approaches have included minimization of other contributing risks, such as discontinuing estrogen perioperatively, early ambulation, the use of physical systems to reduce blood stasis (such as sequential venous compression devices and foot pumps), and use of anticoagulant medications perioperatively.[21]

Once VTE has occurred, management is divided into acute and maintenance therapy. Generally, acute management involves anticoagulation with intravenous unfractionated heparin (UFH) or, more recently, subcutaneous low molecular weight heparin (LMWH) to prevent further clot formation and to allow endogenous thrombolysis to proceed. Thrombolytic therapy with intravenous tissue plasminogen activator, urokinase, or streptokinase to rapidly reduce clot burden has typically been reserved for patients with life threatening PE. The benefits of expanding the indications for systemic thrombolytic therapy to include patients with smaller

pulmonary emboli and the use of catheter-directed thrombolysis for DVT are unclear. Once adequate anticoagulation is achieved with heparin, oral vitamin K antagonists such as warfarin are initiated. Warfarin therapy is continued for a variable duration depending upon the clinical situation.

Purpose of Evidence Report

Despite VTE being a very common disease with relatively few diagnostic and treatment options, there remains significant uncertainty about optimal patient management. The purpose of this report is to review and synthesize the evidence on key issues in the diagnosis and treatment of VTE. The report should be a resource for clinicians and policy makers who must make decisions about the management of patients with VTE.