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Review

Venous thromboembolism: Diagnosis, treatment and the prevention of long-term complications ☆

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ABSTRACT

Venous thromboembolism encompasses a wide spectrum of illness, including deep venous thrombosis and pulmonary embolism. Appropriate recognition and treatment is critical to preventing serious recurrent thromboembolism events. Use of clinical prediction tools, such as the modified Well's criteria, is critical to rapid and efficient diagnosis of venous thromboembolism. Similarly, use of clinical prediction tools can help to identify patients for whom thromboembolism recurrence necessitates extended anticoagulation therapy. Choosing an appropriate anticoagulant for the acute management and potential extended therapy requires assessing patient and physician preferences given the recent expansion of treatment choices. In this document, we review the spectrum of disease as well as guideline-based recommendations for diagnosis and management of venous thromboembolism.

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Background

Venous thromboembolism (VTE) encompasses a spectrum of disorders characterized by thrombosis in the peripheral venous and pulmonary arterial beds [1]. At the core of the thrombotic

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process are three key elements described by Virchow over 100 years ago [2]. These include abnormalities in blood flow (stasis), abnormalities in blood properties (hypercoagulability) and injury to a vessel's wall. While our understanding of these elements has been expanded and refined over the last century, the core principals remain true today. We have also begun to understand the important role inflammation plays on thrombogenesis through thrombus organization and amplification [3,4].

Disease spectrum

As a spectrum of diseases, VTE represents a range of different, but related, diagnoses [2,5]. Deep venous thrombosis (DVT), the most common form of VTE, includes thrombus in the deep veins of the legs, pelvis or upper extremities. In the legs and pelvis, DVT is commonly divided into proximal veins (popliteal, femoral and iliac) and distal veins (anterior tibial, posterior tibial and peroneal). In the upper extremities, DVT usually involves the axillary and/or subclavian veins, most often in patients with malignancy and/or indwelling venous catheters. Pulmonary embolism (PE) includes any thrombus in the pulmonary arteries, either forming de novo or after embolization from a peripheral vein. The longer-term consequence of DVT, especially when involving the iliofemoral venous segment, is termed post-thrombotic syndrome (PTS). PTS is characterized by chronic pain, swelling, and sometimes hard to heal venous ulcer wounds. Less common than DVT, superficial venous thrombosis (SVT) of the legs usually involves thrombus in the great or small saphenous veins.

Acute PE is commonly categorized as being massive (with a systolic blood pressure <90 mmHg, a drop in systolic blood pressure of at least 40 mmHg, syncope or cardiac arrest), submassive (evidence of right ventricular dysfunction despite normal blood pressure) and non-massive (normal blood pressure and right ventricular function) [6]. Chronic accumulation of thrombus in the pulmonary arteries can lead to the development of elevated pulmonary artery pressures, termed chronic thromboembolic pulmonary hypertension (World Health Organization Type IV) [7].

Epidemiology

VTE is a serious health care concern, representing over 900,000 annual cases in the United States and the third leading cause of cardiovascular death after myocardial infarction and stroke [2,6]. First-time VTE are diagnosed in 1.92/1000-persons yearly, more often in men and more often in the elderly [8,9]. In fact, population studies have demonstrated a relative risk for developing VTE of 1.9 for each increasing decade of age [9]. VTE can also be associated with other medical conditions, commonly malignancy, hospitalizations, surgery, major trauma or immobilization [8]. When a VTE occurs in conjunction with one of these conditions, it is referred to as "provoked."

While SVT may be less common than DVT, it still carries a potential risk. DVT or PE are estimated to occur in up to 25% of SVTs at the time of diagnosis and 10% will develop subsequent DVT within the following three months [10]. SVT are often associated with the presence of varicose veins, which can occur both in the setting of the post-thrombotic syndrome and in the development of primary varicose veins [10].

Post-thrombotic syndrome

The post-thrombotic syndrome (PTS), also known as chronic venous insufficiency, is a common sequela of VTE. The presence of thrombus can damage venous valves leading to valve dysfunction and venous hypertension, while the inflammation associated with thrombosis can lead to a stiff and fibrotic vein wall and subsequent valvular dysfunction from that mechanism. This process often results in the development of telangiectasia (spider veins), edema, hyperpigmentation, varicosities and in severe cases, venous ulcerations [11]. PTS is associated with a negative quality of life and significant increases in the cost of treatment and lost productivity for affected patients [12]. PTS develops in 20–40% of patients with DVT, most commonly in patients with iliofemoral DVT [5].

Diagnostic approach

The use of clinical prediction tools is key to a thoughtful and prudent approach toward diagnosing VTE [13]. Simple tools have been developed for determining the pre-test probability of a patient having either a DVT [14] or PE [15] (Table 1). In patients with a low pre-test probability score, a negative d-dimer effectively rules out the diagnosis of VTE. When a patient's pre-test probability is moderate or high, the d-dimer is not negative, or when biomarkers are not obtained, use of compression venous ultrasound, V/Q scanning or CT pulmonary angiography is appropriate to diagnose a suspected DVT or PE. Invasive venography or pulmonary angiography are rarely used today, and are reserved for select cases performed at experienced centers or in conjunction with the use of thrombolytic therapy for both DVT and PE. Use of the Well's prediction rule, along with a d-dimer, has been shown effective in both emergency department and primary care settings [16]. However, the Well's prediction tool for DVT diagnosis appears to be less useful for hospitalized patients [17].

Table 1
Modified Well's scores for DVT and PE diagnosis.

DVT		PE	
Active cancer (received treatment within 6 months or currently on palliative treatment)	1	Clinical signs and symptoms of DVT	1
Paralysis, paresis or recent plaster immobilization of the lower extremities	1	Tachycardia	1
One of: Recently bedridden for 3 days or more Major surgery within the prior 12 weeks requiring general or regional anesthesia	1	Immobilization or surgery in the prior four weeks	1
Localized tenderness along the distribution of the deep venous system	1	Previous DVT or PE	1
Entire leg swollen	1	Hemoptysis	1
Calf swelling at least 3 cm larger than the asymptomatic side (measure 10 cm below tibial tuberosity)	1	Malignancy	1
Pitting edema confined to the symptomatic leg	1	An alternative diagnosis is less likely than PE	1
Collateral superficial veins (non-varicose)	1		
Previously documented DVT	1		
Alternative diagnosis at least as likely as DVT	−2		

DVT or PE is "unlikely" for a score of ≤ 1 using either system. DVT – deep venous thrombosis, and PE – pulmonary embolism.

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