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State-of-the-art thrombosis prevention and treatment



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'Pulmonary embolism is a leading cause of death in cancer patients and the risk for venous thromboembolism is significantly increased in patients with solid tumors and hematological malignancies.'

Thrombosis is the leading cause of death in developed countries, with arterial thrombosis presenting as myocardial infarction, stroke or peripheral arterial occlusion. Venous thromboembolism (VTE) is a major cause of mortality worldwide, despite some variations in prevalence of the disease [1]. While the incidence of VTE increases with aging, it is the leading cause of vascular morbidity in young adults.

A multitude of risk factors can contribute to presentation of VTE [2]. This includes transient risk factors such as trauma, surgery, immobilization, long-haul flights, acute medical illness, hormonal therapy and pregnancy. Long-standing risk factors include chronic conditions such as congestive heart failure, chronic lung disease, inflammatory bowel disease and nephrotic syndrome. The discovery of thrombophilic risk factors opened a new era of genetic assessment of the predisposition for VTE with potential ability for better definition of the risk associated with transient risk factors. For example, hormonal therapy in women with thrombophilic risk factors, such as Factor V Leiden and the prothrombin gene polymorphism, multiply the risk for VTE [3]. While testing for thrombophilia is appealing, wider application has been hampered by equivocal cost-effectiveness analysis. A screening test for thrombophilia would be useful, and global assays such as the Protein C Global have been suggested in this regard [4].

In general, VTE is preventable by application of prophylactic measures. Applying early mobilization and physical measures such as elastic stockings and external pneumatic compression devices is useful. The current pharmacological approach is based on unfractionated, low-molecular-weight heparins (LMWH) and fondaparinux. Vitamin K

antagonists are used for longer periods of primary and secondary prophylaxis of thrombosis. Heparins, especially unfractionated, have drawbacks, including the need for subcutaneous injections and the risk for heparin-induced thrombocytopenia and osteoporosis on long-term use. The heparin derivatives require binding to antithrombin in order to exert their anti-coagulant properties.

Vitamin K antagonists have a narrow therapeutic range that necessitates frequent monitoring of the prothrombin time. The pharmacogenetics of the vitamin K epoxide reductase and *CYP219* genes may be helpful to better define the dose and the risk for bleeding on vitamin K antagonists [5].

These limitations led to the development of numerous new antithrombotic agents during the past decade, and to an ongoing effort by the industry to develop novel anticoagulants with improved efficacy and safety profile and better tolerability for patients. Information gained from gene targeting in mice and animal models of thrombosis is useful for a better understanding of the coagulation system and is detrimental for the development of new drugs.

The majority of these new anticoagulant agents are directed either towards factor Xa or factor IIa (thrombin), although a few agents are directed toward the coagulation initiator tissue factor (TF), factor XI or factor XI_a.

While there is an ongoing debate regarding which anticoagulant is theoretically better, the direct anti-Xa or the direct antithrombin, these agents have not been compared in a clinical trial.

The advantage of both classes include oral administration, direct binding and inhibition of factor Xa or thrombin and no need for monitoring. The most advanced agents are rivaroxaban and apixaban among the anti-Xa agents, and the direct antithrombin dabigatran [6]. A potential disadvantage of these drugs is the lack of specific antidote, which may pose a problem in case of bleeding, but in case there is an urgent need for reversal, plasma transfusion can be applied. While clinical trials test the efficacy and safety of new antithrombotics, data on venous thrombosis in real life can be obtained from international multicenter registries, such as the

substantial information gained by the Registro Informatizado de Pacientes con Enfermedad Tromboembólica Venosa en España (RIETE) registry [7].

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Venous thrombosis in the lower extremities can be asymptomatic, as determined by radiological tests such as Doppler sonography and, particularly, venography, which still serves as the gold standard in the diagnosis of asymptomatic clots, as even quantitative Doppler sonography fails to reveal several distal and, occasionally, even proximal clots. Whether distal clots should be treated is still debatable [8]. The duration of anticoagulation after first VTE event depends on the combination of the type and strength of risk factors and the severity of the first event. D-dimer levels and the presence of residual thrombosis can contribute to assessment of the risk for a recurrent event.

Pulmonary embolism is a leading cause of death in cancer patients and the risk for VTE is significantly increased in patients with solid tumors and hematological malignancies. Mechanisms for increased thrombosis risk in cancer patients include procoagulant activity of tumor cells, acquired activated protein C resistance, effect of chemotherapy and immobilization and presence of indwelling central venous lines [9].

TF plays a central role in cancer patients. TF-bearing microparticles tend to be increased in the plasma of patients with solid tumor and hematological malignancies. Heparanase, a key enzyme

that promotes angiogenesis and metastasis, has been shown to increase TF [10].

Recent observations suggest that anti-coagulants, especially heparins and LMWHs, may affect survival in cancer patients, potentially via a multitude of effects including anti-inflammatory and anti-angiogenetic mechanisms as well as their anticoagulant properties [11].

VTE is a major public health issue, as recently declared by the Surgeon General's Workshop [12] and therefore, patient and public education are of the utmost importance. Worldwide efforts are currently applied by a growing number of organizations with the aim of significantly decreasing the burden of venous thrombosis.

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It is expected that the concentrated effort in basic studies and clinical science, together with patients and public education, will result in improved care of patients with thrombosis.

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