Acquired and hereditary disorders predisposing to venous thromboembolism (VTE) may coexist in an individual and result in latent or overt thrombophilia. Hereditary risk factors are detectable in approx 50% of patients with VTE events and a positive family history. Deficiencies of antithrombin, protein C, and its cofactor protein S, were the first disorders found to increase the risk of recurrent thrombotic events among carriers. Among Caucasians, resistance against activated protein C caused by factor V Leiden (factor V R506Q), and the mutation in the prothrombin promoter region (G20210A), are the most common hereditary prothrombotic defects, with a prevalence of 3 to 5% in the general population. In addition, several other rare defects have been reported. In heterozygous carriers, these disorders increase the risk of suffering a thromboembolic event between 2- and 10-fold. The risk is clearly higher in homozygous individuals, and in those with combined defects. To result in acute VTE, however, inherited deficiencies of hemostasis usually have to interact with acquired transient or permanent risk factors, such as perioperative bedrest, intake of oral contraceptives, or malignancy. Laboratory methods for the diagnosis of the most relevant hereditary defects, and for some acquired thrombophilic disorders such as the antiphospholipid syndrome, have been established and are available at present. Preliminary studies suggest that the laboratory detection of thrombophilic risk factors may not only help explain the cause of VTE in an individual but also affect the management strategy for these patients. This is particularly true for the recommended duration of secondary prophylaxis with vitamin K antagonists after a first thromboembolic event, which needs to take into account the overall risk of recurrence vs that of anticoagulation-related hemorrhage.
Key Words: Thrombophilia; venous thromboembolism; laboratory diagnosis; anticoagulation therapy.

INTRODUCTION

Thrombophilia is generally defined as an increased risk for developing thrombosis that may be caused by hereditary or acquired disorders (Tables 1 and 2). It may affect the arterial side, the venous side, or both, but the term thrombophilia is commonly (and in this chapter) used in association with venous thromboembolism (VTE). Accordingly, acquired risk factors for thrombophilia include diseases, conditions, or laboratory abnormalities that predispose to the development of venous thrombosis and pulmonary embolism (PE). On the other hand, inherited thrombophilia is a genetically fixed tendency to develop VTE, usually characterized by (recurrent) thromboembolic episodes within several members of a given family.

When considering the issue of thrombophilia, it needs to be mentioned that the risk of developing recurrent thromboembolism is usually determined by an interaction of both permanent and temporary risk factors. To make the issue even more complicated, both prothrombotic and prohemorrhagic, hereditary and acquired risk factors may exist in an individual or kindred. These factors interact with each other and define the overall balance of hemostasis.

Anticoagulants are highly effective for primary prevention of PE in high-risk situations (e.g., perioperatively), for treatment in the acute phase of thromboembolic events (to prevent further thrombus extension or embolization), and for secondary long-term prevention. An increase in the intensity of anticoagulation does decrease the risk of recurrent thromboembolism (see Chapter 14) but may cause minor, severe, or even life-threatening bleeding (1-3). A treatment plan must therefore not only consider the underlying provoking condition and the possible existence of a thrombophilic disorder, but also take into account the treatment-associated bleeding risk, which may vary widely depending on the predisposition and the clinical condition of the individual patient.

HEREDITARY THROMBOPHILIA

The main causes of hereditary thrombophilia (4–9) may be classified into: (1) loss of function of inhibitors of hemostasis; and (2) gain of function of procoagulants. In addition, very rare hereditary defects resulting in disturbance of the fibrinolytic system or in enhanced platelet aggregation have been described. Hereditary risk factors are detectable in a relative high percentage (40 to 60%) of patients with VTE events and a positive family history. Typical clinical features include a first thromboembolic event at an early age (<50 yr) and positive family history of thrombosis or recurrent thromboembolism.

Deficiencies of Specific Coagulation Inhibitors

DEFICIENCY OF ANTITHROMBIN, PROTEIN C, AND ITS COFACTOR, PROTEIN S

These were the first hereditary disorders found to increase the risk of recurrent thrombotic events among carriers as opposed to noncarriers (5,7,10,11). Overall, these deficiencies are rare, being found in less than 1% of the population (Table 1), and a very small proportion of patients with VTE carry one of these defects. Thus, most of the data currently available in the literature have been obtained in family studies. These findings must be interpreted with caution, however, because thrombophilic patients may harbor more