Aetiology and treatment of venous thromboembolism
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General Introduction and Outline of this Thesis

Ivan Bank and Saskia Middeldorp
General Introduction

Venous thromboembolism (VTE) is a common disease with an incidence of 2 to 4 per 1000 inhabitants per year in Western societies. This entity comprises a wide spectrum of clinical manifestations varying from thrombosis in the deep veins of the leg to fatal pulmonary embolism. VTE may lead to recurrences and to sometimes very disabling states such as the post-thrombotic syndrome and pulmonary hypertension.

Care for patients with acute disease or complications caused by VTE or its treatment has improved remarkably during the past decades. For example, objective diagnostic methods for VTE have been established and become more accurate, institution of different forms of anticoagulant treatment has become more defined and nowadays treatment at home is feasible in the great majority of patients. On the other hand, the relationship between various transient and thrombophilic risk factors and the development of VTE is not well understood, the long-term management of patients has not been established, and it is not yet possible to tailor treatment based on individual characteristics.

Since the three main pathophysiologic concepts in the aetiology of VTE (e.g. stasis of blood, changes in the vessel wall and hypercoagulability of blood) were postulated by Rudolph Virchow (1821-1902), a well known pathologist, anthropologist, social reformer, politician and archaeologist, attention concerning aetiology of VTE was initially focussed on transient risk factors. These transient risk factors include surgery, trauma, pregnancy and immobilisation, as well as the use of oral contraceptives and hormone replacement therapy. Later on, there was increasing interest in the familial causes of thrombosis causing hypercoagulability, and the term ‘thrombophilia’ was initially introduced for families with inherited antithrombin deficiency. This term is now used for all acquired and inherited disorders associated with an increased tendency to VTE.

Since the sixties of the last century, an increasing number of thrombophilic factors has been discovered (Table 1). Like arterial thrombotic disease, VTE is a disease in which genetic and acquired risk factors interact dynamically with transient risk factors.

Inherited thrombophilic defects are common in patients with VTE, and these defects are increasingly tested for in both patients and asymptomatic individuals, usually from affected families. In the setting of other conditions such as premature atherosclerosis and pregnancy-related complications, patients are widely screened too. However, whether the presence of these risk factors has any consequences for the management of symptomatic and asymptomatic individuals is not
established, because of the lack of knowledge that makes it possible to balance the risks and benefits of screening. For estimating such a balance, the risk of recurrent VTE and anticoagulant prophylaxis or other types of preventive strategies, as well as the preference of the individual counseled, should be known. With respect to the treatment of VTE, major progress has been made since Maurice Doyon (1863-1934) was able to extract ‘antithrombin’ from dog livers, the first anticoagulant, in 1911. At present, unfractionated or low-molecular weight heparin, followed by a course of vitamin K antagonists, constitute the cornerstone of treatment of patients with acute VTE.

Mortality caused by VTE has decreased since the introduction of anticoagulants, and the development of low-molecular weight heparins has revolutionised the standard of care. Presently, most patients can be treated outside the hospital, but only if several essential requirements for home treatment are available. Despite this progress, anticoagulants do increase the risk of (major) bleeding, while other complications like osteoporosis, heparin induced thrombocytopenia and skin complications may occur. Furthermore, patients using vitamin K antagonists need to be frequently monitored for optimal dosing. Finally, whether quality of life in patients treated for VTE has really improved or how decisions on treatment can be tailored by taking patients characteristics into account, still need to be evaluated. This thesis focuses on the aetiology and treatment of VTE. Part one describes several aetiological aspects of VTE, whereas part two focusses on present and future treatment of VTE. In part three psychological and social issues associated with thrombophilia and treatment of VTE are discussed.

Table 1 Discovery over time of well-known acquired and inherited thrombophilic factors.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1865</td>
<td>Trousseau recognises the association between cancer and VTE.</td>
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<tr>
<td>1965</td>
<td>First family identified with hereditary tendency to thrombosis (antithrombin deficiency).</td>
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<tr>
<td>1978</td>
<td>Heparin induced thrombocytopenia (HIT) was postulated to be associated with VTE.</td>
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<td>1981</td>
<td>First study on protein C deficiency and VTE.</td>
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<td>1983</td>
<td>First suggestion of the existence of a syndrome with lupus anticoagulant.</td>
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<td>1984</td>
<td>Protein S deficiency was found to be a risk factor for VTE.</td>
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<tr>
<td>1991</td>
<td>First report on a possible association between mild hyperhomocysteinemia and VTE.</td>
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<tr>
<td>1993</td>
<td>Dahlback et al. studied the role of activated protein C and its association with VTE.</td>
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<tr>
<td>1994</td>
<td>First study on the association between Factor V Leiden mutation and VTE.</td>
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<tr>
<td>1995</td>
<td>Koster et al. found that elevated levels of FVIIIc were associated with VTE.</td>
</tr>
<tr>
<td>1996</td>
<td>Prothrombin 20210A mutation was revealed as a risk factor for VTE.</td>
</tr>
<tr>
<td>2000</td>
<td>Elevated FXI and FIX were associated with increased risk for VTE.</td>
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</table>
Outline of this Thesis

The first part of this thesis concerns risks in individuals with inherited or acquired thrombophilic disorders for (recurrent) VTE and the post-thrombotic syndrome. In Chapter 2 the underlying mechanisms, diagnosis, clinical manifestations and management of hereditary and acquired thrombophilic factors are reviewed. Chapter 3 and 4 describe the results of two retrospective family studies on the absolute risk for venous and arterial thrombosis in first degree relatives of patients with the prothrombin 20210A mutation or elevated levels of factor VIII. In Chapter 5 co-segregation of thrombophilic factors such as elevated levels of TAFI and factor XI in factor V Leiden mutation carriers is explored. In Chapter 6 the role of thrombophilia in the occurrence of residual thrombosis after treatment is investigated. Chapter 7 addresses the question whether location of deep venous thrombosis of the lower limbs predicts the occurrence of the post-thrombotic syndrome. In Chapter 8 the role of oral contraceptives in the multifactorial aetiology of both venous and arterial diseases is reviewed. The second part addresses the treatment of VTE. In Chapter 9, the daily practice of home treatment of deep venous thrombosis is discussed. Chapter 10 reports the results of a trial on the efficacy and safety of a novel anticoagulant in comparison to vitamin K antagonists in the secondary prevention of deep venous thrombosis. In Chapter 11 a complication in pregnant women using low-molecular weight heparins is reported. The third part of this thesis deals with psychosocial aspects of thrombophilia, VTE and its complications. In Chapter 12 and 13 two qualitative studies that explored social aspects of screening for the factor V Leiden mutation are presented. Finally, in Chapter 14 utilities of patients with acute VTE, the post-thrombotic syndrome or a history of bleeding due to anticoagulants are assessed as well as their treatment preferences.

References


