Aetiology and treatment of venous thromboembolism

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Summary
In this thesis, several aspects of venous thromboembolism (VTE) and its treatment are described in three parts. In chapter 1 a general introduction and outline are presented.

The first part describes studies with regard to the aetiology of VTE, and for some risk factors attention is paid to arterial thrombotic diseases as well.

Chapter 2 reviews the inherited and acquired thrombophilic factors that are associated with (recurrent) VTE. Not only the prevalence and presumed mechanisms of these factors, but also the clinical manifestations and potential prophylactic and therapeutic strategies in carriers of these thrombophilic factors are discussed.

Chapter 3 describes the results of a large retrospective study that studied the risk for VTE, arterial thrombotic events and pregnancy-related complications in 407 first-degree relatives of 123 consecutive patients with VTE or premature atherosclerosis who were carriers of the prothrombin 20210A mutation (probands). The annual incidence of a first event of VTE was 0.35% in relatives with the prothrombin mutation and 0.18% in relatives without this mutation (odds ratio (95% confidence interval): 1.9 (0.9-4.1)). Homozygous carriers showed to be at increased risk for VTE as compared to non-carriers (annual incidence: 1.10%/year; OR: 6.0 (1.3-27.2)). Furthermore, relatives of probands who had experienced VTE were at increased risk for VTE as compared to relatives of probands with premature atherosclerosis. During or after surgical proceedings, periods of immobilisation, trauma, pregnancy or use of oral contraceptives, carriers and non-carriers had a statistically similar risk for VTE. The annual incidence of a first episode of arterial thrombosis was 0.22% in carriers and 0.15% in relatives without the mutation (OR: 1.5 (0.6-3.6)); when adjusted for major risk factors for arterial disease, the odds ratio was 2.3 (0.8-6.3). However, carriers of the mutation had an almost fivefold, borderline significant increased risk for a first myocardial infarction as compared to non-carriers (OR: 4.7 (1.0-22.5); p=0.06). Carriers had a comparable risk for pregnancy-related complications such as miscarriages and pregnancy-related hypertension. Therefore, we conclude that the prothrombin mutation is a mild risk factor for VTE in relatives of carriers, but it does not play a major role in the aetiology of arterial thrombotic disease or pregnancy-related complications, with a possible exception of acute myocardial infarction.
Chapter 4 reports the results from another large retrospective family study aimed to estimate the incidences of both VTE and arterial thrombotic events in 584 first-degree relatives of 177 consecutive patients with elevated levels of FVIII:c and VTE or premature atherosclerosis (proband). Forty percent of all relatives also had elevated levels of FVIII:c which supports the hypothesis that elevated levels of FVIII:c are, at least partially, determined genetically. The annual incidence of a first episode of VTE was 0.34% and 0.13% in relatives with elevated levels of FVIII:c and those with normal levels respectively (OR: 3.7 (1.9-7.5)). Furthermore we observed a dose-response effect of FVIII:c for VTE. Concerning arterial thrombotic risks, relatives with elevated levels were also at increased risk as compared to relatives with normal levels (adjusted OR: 3.1 (1.1-6.6)). We thus conclude that elevated levels of FVIII:c occur in 10% of first degree relatives of probands with elevated FVIII:c, and that elevated levels of FVIII:c are associated with an increased risk for both VTE and arterial thrombotic events.

Chapter 5 describes the co-segregation of thrombophilic disorders in factor V Leiden mutation carriers. Of 153 factor V Leiden mutation carriers, 60% had one or more concomitant thrombophilic factors. Increased levels of FVIII:c and TAFI substantially contributed to the risk of VTE in factor V Leiden mutation carriers. This findings support the hypothesis that the clinical expression of factor V Leiden mutation depends on co-segregation of other thrombophilic factors.

Chapter 6 reports a study to investigate whether thrombophilia is associated with residual thrombosis after three months of anticoagulant treatment for acute deep venous thrombosis (DVT). Patients with thrombophilia were found to be at increased risk for residual thrombosis as compared to patients without thrombophilia. Acquired thrombophilia was more frequently associated with residual thrombosis than inherited thrombophilia. In particular lupus anticoagulant, active malignant disease, protein C deficiency and the prothrombin 20210A mutation increased the risk for residual thrombosis. These findings may explain why for example patients with malignancy or lupus anticoagulant are at increased risk for recurrent VTE.

Chapter 7 details the findings of a study investigating whether the location of DVT is related to the risk of post-thrombotic syndrome, a syndrome that develops in about 50% of patients with a first episode of DVT. The initial flebographic results of 90 patients with DVT who had never used compression stockings and
who were followed for at least 5 years, were evaluated in order to find out the location of DVT. The incidence rate of post-thrombotic syndrome in patients with a popliteal vein thrombosis was 4.8% per month of follow-up, while these rates were 3.0% and 5.5% for femoral, respectively iliofemoral thrombosis. Location of thrombosis however was no risk factor for the development of post-thrombotic syndrome.

Chapter 8 extensively reviews the effects of oral contraceptives on the cardiovascular system. Most of the effects are type-dependent, and they interact with individual characteristics of the users. Third-generation oral contraceptives cause an increased risk for VTE as compared to second-generation preparations, which is probably due to a stronger negative effect of the progestagens on the natural anticoagulant and antifibrinolytic system. Furthermore, women with thrombophilia are at increased risk for VTE as compared to women without thrombophilia. Women using oral contraceptives are also at increased risk for myocardial infarction and stroke, a risk even more pronounced in the presence of classical risk factors such as smoking. Although third-generation oral contraceptives have a beneficial effect on lipid profiles, this does not translate into a lower risk for arterial thrombotic events.

The second part of this thesis (chapters 9, 10 and 11) describes the present treatment of VTE and shows the results of a trial investigating the efficacy and safety of a new anticoagulant for the long-term treatment of DVT.

Chapter 9 focuses on home treatment of DVT. Home treatment became possible after the introduction of low-molecular weight heparins (LMWH), but is only adequate if some essential requirements are fulfilled. For example, there are strict selection criteria for patients with DVT who can be considered for treatment outside the hospital, adequate control of anticoagulant therapy, and follow-up of patients are necessary. Furthermore, a 24 hours service has to be available in case patients develop complications at home.

Chapter 10 details the results of a phase II study comparing the efficacy and safety of a novel synthetic factor Xa inhibitor (Pentasaccharide; SanOrg34006) with a standard vitamin K antagonist. SanOrg34006 has predictable pharmacokinetics and is administered once-a-week without dose adjustments. Patients with acute DVT were randomised to 4 dosages of SanOrg34006 and warfarin. The
primary efficacy outcome was the composite of change in thrombotic burden, as assessed by ultrasonography and perfusion lung scanning at baseline and after 12 weeks of treatment in 659 patients. The safety outcome was measured by occurrence of major or clinically relevant bleedings. The 2.5mg of SanOrg34006 appeared as effective as the vitamin K antagonist for the secondary prevention of DVT and was not associated with major bleeding, so it might be a suitable alternative to dose-adjusted vitamin K antagonists.

Chapter 11 describes the occurrence of skin complications due to the use of LMWH during pregnancy. Of all studied women, 29% developed skin complications. These skin complications included (generalised) itching or erythematous rash and local redness. The clinical course was self-limiting in most of the women after switching to another LMWH or a vitamin K antagonist, although about one-third of the women who had switched also had skin complications induced by the second LMWH. Physicians should be aware of skin complications and should instruct pregnant women using these drugs to seek advice when these occur.

The third part of this thesis (chapters 12, 13 and 14) deals with psychosocial aspects of screening for the factor V Leiden mutation and describes utilities of patients with acute VTE, post-thrombotic syndrome or a history of bleeding due to use of anticoagulants.

Chapter 12 presents the findings of a qualitative study on social aspects of asymptomatic carriership of the factor V Leiden mutation, in particular how these carriers have experienced the procedure of screening for this mutation. Knowledge of carriership of the factor V Leiden mutation did have impact on the daily life of carriers. Carriers were concerned about their future and the future of their children. Stigmatisation and problems with insurance companies had occurred as well. For the daily clinical practice of screening for the factor V Leiden mutation it is of importance to realise that these negative aspects of screening may occur. Furthermore, guidelines should be developed to optimise the procedure of screening for the factor V Leiden mutation; screening comprises more than only the collection of a blood sample.

Chapter 13 outlines the fact that the factor V Leiden mutation may induce more
uncertainty than that it provides benefits for individuals who never have experienced VTE. The various types of stigmatisation that might be involved in carrieryship are reviewed. Finally, it is argued that the only way to avoid the negative effects induced by knowledge of carrieryship of factor V Leiden mutation is to clarify the paradigm of the gene-environment interaction to both carrierys and health professionals.

Finally, chapter 14 shows the results of a study on utilities of health states related to VTE and its treatment with vitamin K antagonists in 53 patients who had experienced an episode of VTE, 23 patients who had experienced a major bleeding during treatment with anticoagulants, and 48 patients with post-thrombotic syndrome. Also patients’ preferences for either continuation or cessation of treatment after three months of treatment with vitamin K antagonists were evaluated. About 25% of studied patients wanted to continue use of vitamin K antagonists despite possible complications in order to prevent a new episode of VTE. Furthermore, patients were very well able to value health states related to VTE and vitamin K antagonists, and to balance the benefits and risks associated with treatment. So, recommendations concerning duration of treatment with anticoagulants should be tailored to patient’s specific values and concerns rather than only as recommended in tentative guidelines for duration of treatment in case of VTE.