Associations between cardiovascular risk factors, hyper- and hypocoagulability
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Summary
SUMMARY

This thesis focuses on the associations between cardiovascular risk factors, hyper- and hypocoagu-
ability. In the first part, associations between novel risk factors, venous and arterial thrombosis
are described. In the second part of the thesis, the risk of cardiovascular disease and quality of life
in patients with hemophilia are evaluated.

Part I. Risk factors for cardiovascular disease

In chapter 1 the association between venous and arterial thrombosis was assessed in a retrospec-
tive study among 456 patients with venous thrombo-embolism (VTE) and 197 controls without
VTE. The presence of calcium deposits, which represent an advanced stage of atherosclerosis, on
the aortic arch was evaluated on the chest X-ray of all subjects. Aortic calcifications were present
in 33% of the VTE patients, compared to 18% of the controls (adjusted odds ratio 1.86, 95%CI
1.18-2.95). The calcifications were most pronounced among patients with unprovoked VTE. Since
calcifications of the aorta are associated with an increased risk of future atherosclerotic events,
these results support an increased risk of cardiovascular events in patients with VTE. Mutual
causal pathways may underlie the association between venous and arterial thrombosis and this
may also imply common therapeutic options. Statin therapy, which has proven highly effective
in the prevention of cardiovascular disease is thought to provide additional protection against
VTE. In chapter 2 using a large population-based registry consisting of 3093 PE patients, in which
hospitalization data have been linked to pharmacy records, the effect of statin therapy on the
occurrence of recurrent pulmonary embolism (PE) was assessed. After a median follow-up period
of 5.6 years, recurrent PE occurred in 285 (9%) of the patients. Statin therapy significantly reduced
the occurrence of recurrent PE (HR 0.48, 95%CI 0.35-0.67), and the protective effect was present
during and after stopping VKA treatment. The present study shows protective effects of statin
therapy are also seen for recurrent PE.

In chapter 3 the effect of statin therapy on a first episode of VTE was further assessed in a
meta-analysis of previous large randomized controlled trials. Twenty-one trials of statin therapy
versus placebo (105 636 participants) showed that statin therapy did not significantly reduce the
risk of VTE (464 vs 520 statin vs control OR 0.89, 95%CI 0.78-1.01, p=0.07). In seven trials (40
594 participants) an intensive versus a standard dose statin regimen was studied. There was no
evidence that higher dose statin therapy reduced the risk of VTE (167 vs 152, OR 1.10, 95%CI 0.88-
1.37, p=0.41). In contrast to previous findings, these results do not support a role of statin therapy
in the prevention of a first episode of VTE. In chapter 4 in a multicentre study, consisting of 157
VTE patients and 394 controls, the total number of subjects with either documented CVD, statin
use, or with an increased risk of CVD, assessed using an established European risk prediction
algorithm (SCORE), was compared between VTE patients and controls. Overall, 45% of the VTE
patients had an indication for statin therapy compared to 33% of the controls (p=0.008). Although
the exact role of statin therapy in the prevention VTE remains to be elucidated, the present study
Summary illustrates that in a substantial proportion of VTE patients, statin therapy is already indicated for the prevention of CVD.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed drugs for the treatment of acute and chronic conditions in which pain and inflammation predominate. Recently, Rofecoxib (Vioxx®) and Valdecocixib were removed from the market due to an increased risk of stroke and myocardial infarctions. In chapter 5 the association between NSAIDs and VTE was studied. In a large population based registry, consisting of 4495 VTE patients and 16802 controls, current use of NSAIDs was significantly associated with PE (OR 2.39, 95% CI 2.06-2.77). The risk was highest for traditional NSAIDs, and the overall risk for NSAIDs was highest in the first 30 days of exposure (OR 4.77, 95% CI 3.92-5.81), as compared to chronic (<1 year) (OR 1.83, 95% CI 1.47-2.28), or long-term use (>1 year) (OR 2.14, 95% CI 1.48-3.09). NSAIDs are associated with an increased risk of symptomatic PE, although the association may be partially explained by underlying medical conditions, as suggested by a similarly increased thrombotic risk in patients receiving acetaminophen and tramadol. Nevertheless, clinicians should be aware of the potentially higher risk of PE in patients who receive these frequently prescribed painkillers.

Thyroid disease is associated with haemostatic abnormalities, but it is uncertain whether this also affects the risk of venous thromboembolism. In chapter 6 the association between pulmonary embolism (PE) and thyroid disease, as well as the influence of treatment with thyroid medication was assessed in a population based registry consisting of 3479 PE patients and 11830 controls. New use of antithyroid agents or hospitalization for thyrotoxicosis within 6 months after the index date were significantly associated with PE (adjusted OR 3.22; 95% CI 1.12-9.22), whereas a relation between thyreomimetic agents and PE was observed for new use before the index date, especially within the first 3 months after treatment onset (adjusted OR 4.58; 95% CI 1.28-16.43). These findings suggests that both patients with untreated hyperthyroidism and patients that recently started with thyreomimetic agents for hypothyroidism are at increased risk of pulmonary embolism.

Patients with venous-thromboembolism (VTE) and myocardial infarction (MI) have elevated prothrombin fragment 1+2 (F1+2) levels. We postulated that uF1+2 is elevated in patients with suspected venous or arterial thrombotic events and therefore performed a pilot study in patients with VTE and MI which is described in chapter 7. In 20 patients with VTE, 20 with MI, and 25 age- and sex-matched healthy controls. Compared to controls, patients with VTE had higher levels of both plasma F1+2 and uF1+2 levels, although the latter difference was not significant. Patients with acute MI had the same F1+2 levels as controls in both plasma and urine. Overall, D-dimer and F1+2 levels in urine were extremely low in all groups. Although urine F1+2 levels may be associated with postoperative venous thrombosis, we found no clear association in patients with acute VTE or MI.

Part II. Hemophilia, cardiovascular risk and quality of life

Chapter 8 provides a systematic overview of literature on cardiovascular disease (CVD) in patients with hemophilia and von Willebrand disease (VWD). Fifteen longitudinal and cross-sectional
studies consisting of 19,242 patients were included. Mortality due to arterial thrombosis was non-significantly reduced in patients with haemophilia compared to healthy controls (SMR 0.51, 95% confidence interval (CI) 0.24-1.09). Haemophilia reduced non-fatal coronary events, and severe haemophilia offered better protection, but these results were based on a single study. No results were available for VWD. Although intima media thickness (IMT) of the carotid and femoral arteries was similar between VWD and haemophilia patients and healthy controls, atherosclerotic plaques of the large arteries were less prevalent in haemophilia patients. Although a clear protective effect on atherothrombosis is found, whether or not hemophilia patients are protected against atherosclerotic disease remains unclear. The reduced cardiovascular mortality in hemophilia may be the result of a lifelong deficiency of factor VIII or IX or the prevalence of risk factors may differ in these chronically ill patients compared to the general population. In chapter 9 the prevalence of risk factors and expected risk of CVD in 100 hemophilia A and B patients was compared to 200 healthy controls. The number of hemophiliacs with hyperglycemia (24%) and hypertension (51%) was higher than in the controls (p-values 0.001 and 0.03, respectively). The mean LDL cholesterol level in cases was lower than the controls (3.02 mmol/L (0.69-6.57) and 3.60 mmol/L (1.68-5.95), respectively, p < 0.001). Fewer cases had increased LDL levels (p=0.045). No difference was found in the ten-year cardiovascular mortality risk >10% between cases and controls (12% and 7% respectively, p = 0.18). The prevalence of risk factors and expected risk of CVD in hemophilia patients was found to be comparable to the general population. This finding strengthens the hypothesis that hypocoagulability may reduce cardiovascular mortality in hemophilia patients. Whether or not hemophilia patients are protected against atherogenesis was studied in the following chapter.

In chapter 10 the prevalence of atherosclerosis and endothelial function was assessed in fifty-one obese (body mass index (BMI) ≥30 kg/m²) and 47 non-obese (BMI ≤25 kg/m²) hemophilia A patients, and 42 obese and 50 matched non-obese male controls. Carotid IMT was increased in obese (0.77 ± 0.22 mm) compared to non-obese subjects (0.69 ± 0.16 mm). No differences in mean carotid and femoral IMT between obese hemophilia patients and obese controls were found (mean Δ 0.02 mm (95% CI -0.07-0.11, p=0.67) and 0.06 mm (95% CI -0.13-0.25, p=0.55), respectively). Thirty-five percent of the obese hemophilia patients and 29% of the obese controls had an atherosclerotic plaque (p=0.49), irrespective of the severity of hemophilia. Since hemophilia A patients had the same degree of atherosclerosis and endothelial function as their matched controls, these findings suggest that the lower cardiovascular mortality in hemophilia patients is likely caused by a decreased risk of arterial thrombosis.

Using the same study population in chapter 11 hemostatic changes associated with obesity were compared in men with and without hemophilia A. In hemophilia patients, mean endogenous thrombin potential (ETP) and median F1+2 levels were lower than in controls (1272 vs. 1625 nM.min (p<0.001) and 120 vs. 153 pmol/l (p<0.001), respectively). Mean vWF:ag levels were higher in hemophilia patients as compared to controls (132 vs. 115%, p=0.011). The obesity-related increase in PAI-1 levels and decrease in PAP levels were comparable between hemophilia patients...
and controls. This study shows that in hemophilia patients a similar obesity-related decrease in fibrinolysis was seen as in non-hemophilic men.

In chapter 12 obesity related impairments in daily life were assessed in hemophilia A patients. Obesity is equally prevalent in hemophilia patients as in the general population and is an important risk factor for osteoarthritis. In hemophilia patients these effects may be even more pronounced since they are already prone to joint damage. The Hemophilia Activities List (HAL) was used to assess the impairment in daily activities in fifteen obese (BMI≥30 kg/m$^2$) and fifteen normal weight (BMI≤25 kg/m$^2$) hemophilia A patients matched for severity and age. Compared to the normal weight hemophilia patients, obese hemophiliacs had a significantly lower overall sum score (88/100 and 98/100, respectively, p-value=0.02), which was mainly caused by an impaired lower limb function. A higher frequency of bleeds requiring treatment with factor VIII concentrate occurred in the obese hemophiliacs (17 bleeds in 8 individuals) compared to the controls (3 bleeds in 3 individuals) (p=0.045). These results show that prevention of overweight and weight reduction requires special attention from physicians treating hemophilia patients.