Background: The impact of stress on coagulation and diseases associated with perturbed coagulation has been verified in a multitude of studies of the arterial system. For example, heightened level of stress increases the risk for developing incident cardiovascular disease (CVD) and recurrent CVD events. These associations are well known for acute as well as chronic stress. The idea that similar processes might play a role in the development of a venous thromboembolism (VTE) seems conceivable. To the best of my knowledge, only a few studies addressed this issue in the past. Their results are intriguing but raise also further questions, some of which will be addressed in this thesis.

Aims: The main aim of this thesis is to investigate the overarching hypothesis of an association between stress-related psychosocial variables, coagulation factors, and inflammatory markers related to coagulation processes in the venous blood system.

(i) Study 1 tested the factorial stability of most psychometric questionnaires used in the project. It provided valuable information whether they form discriminative constructs or not.

(ii) Study 2 investigated in potential psychological contributors to patients' perceived health-related quality of life (HRQOL). It should help to broaden the concept of HRQOL and to determine further strong predictors of VTE.

(iii) Two further studies eventually focused on the associations between psychosocial variables, coagulation, and inflammatory markers. In **study 3** the associations between psychological distress and the endogenous anticoagulants protein C and protein S were analysed. **Study 4** examined the associations of sleep quality, fatigue, and vital exhaustion with platelet count.

Participants and methods: The overarching study project had a longitudinal design. All data presented in this thesis were collected cross-sectionally. **Study 1** based on a consecutive sample of 242 patients with previous VTE (mean age 46.6 years, standard deviation 13.9; 54,1% men) who underwent thrombophilia work-up at the Central Haematology Laboratory, Bern University Hospital, Inselspital, Bern. For the study, participants completed the Short Form Health Survey-12 (SF-12), the Hospital Anxiety and Depression Scale (HADS), the Maastricht Vital Exhaustion questionnaire (MVEQ), the Effort-Reward-Imbalance Scale (ERI), the Type D Scale –14 (DS-14), and the ENRICHD Social Support Instrument (ESSI). **Study 2** included 205 patients (mean age 47.4 years, standard deviation 14.9; 54,6% men) who filled in the Short Form Health Survey-12 (SF-12), the Multidimensional Fatigue Symptom Inventory (MFSI-SF), and the Hospital Anxiety and Depression Scale (HADS). **Study 3** comprised 126 consecutively enrolled patients (mean age 47.9 years, standard deviation 10.9; 51,6% men). These patients completed the Hospital Anxiety and Depression Scale (HADS). **Study 4** included 205 patients (mean age 47.2 years, standard deviation 14.8; 55% men). For that study, they com-

pleted the Multidimensional Fatigue Symptom Inventory (MFSI-SF), the Maastricht Vital Exhaustion questionnaire (MVEQ), and the Jenkins Sleep Quality Questionnaire (JSQ). Different sample sizes across the 4 studies are explained by the consecutive enrolment of patients and missing data in terms of questionnaires and biological measures.

Results: The correlation matrix in **study 1** showed low-to-medium correlations for most of the psychological questionnaires. A rotated factor analysis revealed ten interpretable factors accounting for 52.7% of the common variance. These ten factors reflected most of the originally used scales. In another rotated factor analysis I found depression and negative affect, but not vital exhaustion to be overlapping but distinct constructs.

In **study 2** multiple regression models controlling for demographic and medical factors were used. Fatigue ($p<.01$), but not psychological distress ($p>.05$), was negatively associated with physical HRQOL, explaining 11.0% of the variance. Fatigue ($p<.001$) and psychological distress ($p<.001$) were significant predictors of mental HRQOL explaining an additional 36.2% and 3.6% of the variance after controlling for age, sex, BMI, oral anticoagulants, aspirin, and time elapsed since last VTE. Further analyses revealed that all subscales of the HADS (i.e., anxiety, depression) and the MFSI-SF (i.e., general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor) were also significant predictors of mental HRQOL. MFSI-SF subscales additionally predicted physical HRQOL.

In **study 3** psychological distress (sum of anxiety plus depression symptoms; p's$\leq$.027), anxiety (p's$\leq$.055), and depression (p's$\leq$.031) were positively associated with protein C, controlling for demographic and medical factors. The different scales explained between 3% and 6% of the common variance in protein C. Total PS antigen showed a direct relationship with psychological distress ($p=.025$) and depression ($p=.005$), explaining 5% and 7% of respective variances. Free protein S showed a positive association with depression ($p=.046$), explaining 3% of the variance. Anxiety showed no independent association with either PS measure.

In **study 4** I controlled for age, sex, body mass index, time since the index event, and medication. After taking into account these covariates, poorer sleep quality ($p=.001$; $\Delta R^2=.046$), high fatigue ($p=.008$; $\Delta R^2=.032$), and vital exhaustion ($p=.050$; $\Delta R^2=.017$) were all associated with elevated platelet count. In addition, high level of fatigue mediated the relationship between poor sleep quality and elevated platelet count ($p=.046$).

Conclusions: The results of **study 1** support the initial assumption of distinguishable and independent, but partially overlapping psychological concepts for most of the scales. The first factor was an accumulation of various items. It includes anxiety and depression items from the HADS, mental subscale items from the SF-12, vital exhaustion items from the MVEQ, and negative affect items from the DS-14. This factor seems to reflect the construct of anxious-

agitated depression. Vital exhaustion was not reflected in one of the factors; its items showed a content-related distribution across the other factors. The findings of **study 2** suggest that fatigue and psychological distress substantially predict HRQOL in patients with previous VTE above and beyond demographic factors. This broadens the concept of HRQOL that is associated with psychological factors, which are important in CVD. The independent associations of psychological distress with enhanced endogenous anticoagulant potential in **study 3** might reflect a counter regulatory mechanism. Individuals under chronic stress with elevated symptoms of anxiety and depression might outweigh the previously observed hypercoagulability in depression and anxiety states by enhancing endogenous anticoagulant activity. In **study 4** were poor sleep quality, high levels of fatigue, and vital exhaustion identified as correlates of an elevated platelet count in patients with a previous episode of VTE. Given the emerging role of inflammatory processes, as is for instance reflected by elevated platelet count, in VTE, the findings suggest a mechanism through which behavioural and chronic psychological stressors might contribute to incident and recurrent venous thromboembolic events.

To sum up, the studies reported in this thesis confirm the main hypotheses of the study. The assumption of independent associations between psychological stress and inflammatory and coagulation markers was shown in studies 3 and 4. Especially study 3 was controversially disputed because it suggests a possible counter regulatory mechanism. Study 4 demonstrates how different psychological variables might interact in their impact on platelet count. To the best of my knowledge a concrete association between psychological scales and physiologic markers in patients with VTE is reported for the very first time. The results provide first and intriguing information in a growing area of research. The limitations of the studies are discussed later in the thesis. Further research and replication are needed to confirm our results.

Keywords: venous thromboembolism; deep vein thrombosis; pulmonary embolism; coagulation; inflammation; psychological distress; quality of life; fatigue; anxiety; depression