Venous thrombosis in the elderly: risk factors and consequences

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CHAPTER 1

General introduction and outline of the thesis

THE COAGULATION SYSTEM

Once a venous blood vessel is damaged, the primary and secondary hemostatic systems are initiated to stop the bleeding. During secondary hemostasis, the coagulation system is activated, and a stable blood clot is formed within the blood vessels to stop the bleeding. In normal hemostasis, there is a dynamic equilibrium between the pro- and anticoagulant and pro- and antifibrinolytic systems. When there is an imbalance between pro-and anticoagulant systems, where the coagulation system is overactivated, this may lead to hypercoagulability and excessive clot formation. A venous thrombosis obstructs the natural flow of blood, resulting in clinical symptoms such as pain, swelling and redness and a subsequent clinically diagnosed venous thrombosis.

VENOUS THROMBOSIS – RISK FACTORS

Venous thrombosis occurs at an annual incidence of about 1-2 per 1000 adults [1]. In the last 60 years, an increasing number of studies focused on causes of venous thrombosis, resulting in a long list of risk factors for venous thrombosis, including genetic risk factors (e.g., factor V Leiden (FVL), the prothrombin G20210A and ABO blood groups) and acquired risk factors (e.g., increasing age, previous thrombosis, trauma, major surgery, malignancy, obesity, immobilization, oral contraceptives and hormonal replacement therapy) reviewed in [2, 3]. The presence of an environmental risk factor just prior to occurrence of venous thrombosis determines whether an episode of venous thrombosis is classified as provoked or unprovoked [4]. A provoked venous thrombosis is associated with acquired risk factors, either transient or persistent. Strong provoking risk factors include major surgery, trauma, immobilization, hormone replacement, oral contraception, and active cancer [5]. Patients without provoking risk factors are referred to as having "unprovoked" venous thrombosis [6]. Several studies have been conducted to assess the combined effect of several genetic risk factors or of genetic risk factors and acquired factors [2, 7-9] in young and middle-aged populations. The most common genetic risk factors are FVL and prothrombin 20210A mutation, with a relatively high prevalence (more than 1%) among Caucasian populations [10, 11]. The combination of these two prothrombotic mutations and several acquired risk factors (obesity, pregnancy, and oral contraceptive use) have been shown to increase the risk of venous thrombosis beyond what was expected based on the individual risks (e.g., the combined effect of factor V Leiden and obesity resulted in a 7.9-fold greater risk than had non-carriers with a BMI <25kg/m^2) [8, 9, 12-15].

The multitude of risk factors for venous thrombosis known today indicate that venous thrombosis is a multifactorial disease. In 1856, Rudolf Virchow proposed three main factors determining the location, nature, and extent of thrombosis formation (Virchow's triad): a decreased blood flow (stasis), an increase in blood coagulability, and damage to the vessel wall, which model is still valid today [16, 17]. When there is stasis, blood circulates with low velocities, creating a low shear field, and allowing red cells to be aggregated. Furthermore, stagnation of the blood leads to hypoxia, which is associated with an increased clotting tendency. Hypercoagulability describes the increased thrombin generating capacity of the blood clotting system. High levels of individual procoagulant factors II (prothrombin), VIII, IX, and XI were shown to increase the risk of venous thrombosis [7, 18-22]. However, global assays, such as the endogenous thrombin potential and the D-dimer assay, measure the overall coagulable state, and both assays have been shown to be associated with the risk of venous thrombosis [23-32]. Damage to the endothelial wall may be caused by a variety of factors: direct disruption of the vessel, trauma, or surgery [33]. In vascular hemostasis, endothelial collagen plays a dynamic function: in addition to synthesizing a number of crucial anticoagulant and fibrinolytic compounds, it also offers a good surface for the positioning of different anticoagulant and antifibrinolytic proteins [34]. Endothelial injury leads to thrombogenesis due to the release of tissue factors.

VENOUS THROMBOSIS – MANIFESTATIONS

Venous thrombosis has two manifestations, i.e., deep vein thrombosis and pulmonary embolism. Deep vein thrombosis occurs when a blood clot forms in a deep vein, usually in the lower leg, thigh, or pelvis. Pulmonary embolism occurs when a clot breaks loose and travels through the bloodstream to the lungs. In patients with a pulmonary embolism, the most concerning complication is the associated high mortality [35]. Pulmonary embolism is associated with a 90-day cumulative incidence of death of 27% [36]. Most risk factors for deep vein thrombosis and pulmonary embolism overlap, indicating deep vein thrombosis and pulmonary embolism are the same disease. However, it was proposed that pulmonary clots may also arise de novo in the lungs due to local inflammation-driven coagulation [37].

Several risk factors for deep vein thrombosis and pulmonary embolism differ [38]: e.g., factor V Leiden, hormonal-related risk factors, obesity, prior venous thrombosis, recent surgery, and cancer are reported to be associated with an increased risk of deep vein thrombosis but much less of pulmonary embolism [39, 40], while others, e.g., pneumonia, COPD and sickle cell disease, chronic lung disease, heart failure, and renal insufficiency, are associated with a larger risk of pulmonary embolism than of deep vein thrombosis [40, 41].

VENOUS THROMBOSIS – THE EFFECT OF AGEING

Most prior research has been conducted in young and middle-aged populations [42]. However, the population is aging rapidly. Over a period of 35 years (from 2015 to 2050), the proportion of the population being older, i.e., aged 60 years and older, has been estimated to increase from 12% to 22% [43]. The incidence of venous thrombosis increases sharply with age: it is rare in young individuals (<1 per 10 000 per year) but increases to approximately 1% per year in very old age, and the case-fatality rate of thrombosis is high in the elderly (the estimated case fatality rate from PE increases with age from 3.6% in patients aged 25-34 years to 17.4% in patients aged >85 years) [44, 45]. Increasing age is, therefore, by far the most important risk factor for venous thrombosis. Explanations for this age gradient in the risk of venous thrombosis include some risk factors that are more prevalent among the elderly than young or middle-aged individuals, e.g., immobilization, or factors having a stronger effect in the elderly than the young. Because of the multicausal character of venous thrombosis, it is likely that multiple factors contribute to the risk of venous thrombosis in the elderly. We previously reported that several risk factors (Factor V Leiden, prothrombin mutation, non-O blood group, family history, hospitalization, surgery, fractures, plaster cast, minor injuries, transient immobility, functional impairment, varicose veins, leg ulcers, leg oedema, valve thickness) were associated with the risk of venous thrombosis in the older population [46-50]. However, for many well-known risk factors described in young and middle-aged populations, the associations with venous thrombosis risk in the elderly are not well described [7, 18-32, 51-67]. Elderly are often excluded from clinical studies on etiology because of comorbidities, short life expectancies, and logistical difficulties [68]. Some studies did include a broad age range, including individuals of older age. However, these had limited reporting of subgroup analyses among older participants and with sample sizes of the elderly often too small for meaningful analyses. Only a few studies, primarily performed in recent years, explicitly focused on the risk factors for venous thrombosis in the elderly [46-50, 53, 69-75].

In older populations, we have previously examined the combined effects of a number of genetic risk factors and acquired risk factors. We showed that the combined effect of ABO blood group, i.e. non-O blood groups, and the presence of either FV Leiden or prothrombin G20210A mutation with non-O blood groups did not lead to more venous thrombosis cases than expected based on the separate risks (those with both risk factors had a similar risk as those with blood group O and a prothrombotic variant); that the combined effect of family history of VT and the presence of either FV Leiden or prothrombin G20210A further increased venous thrombosis risk (individuals with a positive family history of venous thrombosis who also carried either prothrombotic variant had the highest risk of venous thrombosis: odds ratio 7.6, 95%CI: 1.6-35.7, compared with

non-carriers without a positive family history); that the combined effect of the presence of varicose veins, leg ulcer, and leg oedema increased venous thrombosis risk (the risk of venous thrombosis was highest when all three clinical features combined: odds ratio 10.5, 95%CI: 1.3-86.1); and finally, that the combined effect of a prolonged clot lysis time and endogenous thrombin potential further increased venous thrombosis risk (the risk of venous thrombosis was highest for individuals with a prolonged clot lysis time and an elevated endogenous thrombin potential) [46, 49, 76]. Thus, also in the elderly, the risk of venous thrombosis was highest in the presence of multiple risk factors.

LONG-TERM CONSEQUENCES OF VENOUS THROMBOSIS

Venous thrombosis has the potential to have long-term effects on a patient's health. Previous studies mainly reported on the long-term outcomes of venous thrombosis in young and middle-aged populations [77-83]. These studies showed that after venous thrombosis, patients had an increased risk of death, both short and long-term, an increased risk of recurrence of venous thrombosis, of post-thrombotic syndrome, and also that the venous thrombotic event affected long-term health-related quality of life for many years after the initial event. The long-term effects of venous thrombosis in the elderly have received little attention in the literature. Only a few studies have described long-term mortality risk and health-related quality of life in elderly venous thrombosis patients [84, 85]. However, the follow-up time in these studies was relatively short, and the analyses regarding health-related quality of life were often limited to a single measurement instrument.

AIMS OF THIS THESIS

The main objective of this thesis is to gain more insight in the risk factors and long-term consequences of venous thrombosis in people aged 70 years and older. The first aim is to explore the risk of venous thrombosis in the elderly associated with several risk factors known to increase the risk of venous thrombosis in young and middle-aged populations, i.e., procoagulant factors (factor II, VIII, IX, and XI), D-dimer, thrombin generation parameters, and cardiovascular risk factors (body mass index, smoking, alcohol intake, hypertension, and diabetes). In addition, we also assess the association between a remote history of venous thrombosis and the development of venous thrombosis at an older age.

Secondly, we investigate the long-term consequences of a first venous thrombosis in the elderly by assessing the long-term health-related quality of life and assessing long-term mortality risk (up to 12 years) and causes of death.

CLINICAL DATA USED IN THIS THESIS

The AT-AGE study

The Age and Thrombosis, Acquired and Genetic risk factors in the elderly (AT-AGE) study is a two-center, population-based case-control study designed to study risk factors for venous thrombosis in older people. In brief, from June 2008 to August 2011 in Leiden, the Netherlands and December 2008 to July 2011 in Vermont, US, all consecutive patients aged 70 years and older with a first imaging-confirmed deep vein thrombosis of the leg (deep vein thrombosis) or pulmonary embolism (with or without deep vein thrombosis) were identified. Patients were identified from the anticoagulation clinics in Haarlem and Leiden and from the Vascular Laboratory and the Radiology department of the University of Vermont Medical Center (Burlington, Vermont, United States). Control subjects were randomly selected from five primary care practices in Leiden and four in Vermont. Patients with active malignancy, a history of venous thrombosis, or severe cognitive impairment were excluded. Individuals with active malignancy were defined as a diagnosis of cancer within six months before the thrombotic event (or date of telephone call for the control subjects) or chemotherapy or radiation therapy for cancer in the last six months. For all participants, during a home visit, a structured questionnaire on risk factors for venous thrombosis was completed during an interview by a trained research nurse, and a blood sample or buccal swab was collected. For control subjects, the home visit was performed once. For patients, the home visit was performed twice, as soon as possible after the venous thrombosis and one year after the event. In total, 401 patients and 431 controls completed the first interview. However, not all patients were available for the second home visit 1 year after VT, as 21 of them had died after the first visit and some (depending on different research questions) declined to participate or failed to fill in questionnaires in the second home visit. In addition, a few participants failed to have blood collection or coagulation assay measurements or complete the questionnaires. **Chapters 2 to 6** are based on data from the AT-AGE study.

The CBS data

Dates and causes of death were obtained by linking the AT-AGE study with data of Statistics Netherlands (CBS), the national repository for death certificates. Primary causes of death were retrieved. Causes of death were coded according to the ICD-10 classification [86, 87]. **Chapter 7** uses the data from CBS.

OUTLINE OF THIS THESIS

Part I - Risk factors for venous thrombosis in the elderly

Chapter 2 focuses on the association between procoagulant factors and the risk of venous thrombosis. In **chapter 3**, the association between D-dimer and thrombin generation and the risk of venous thrombosis is studied. Next, in **chapter 4**, we investigate the association between cardiovascular risk factors and the risk of venous thrombosis. The association of a remote history of venous thrombosis with the risk of venous thrombosis is described in **chapter 5**.

Part II-Quality of life and long-term survival in older people with venous thrombosis

We study the impact of venous thrombosis on health-related quality of life in **chapter 6** and evaluate the long-term survival in patients with venous thrombosis in **chapter 7**.

Finally, **in chapter 8**, we summarize the results of this thesis and provide a discussion and suggestions for future research.

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