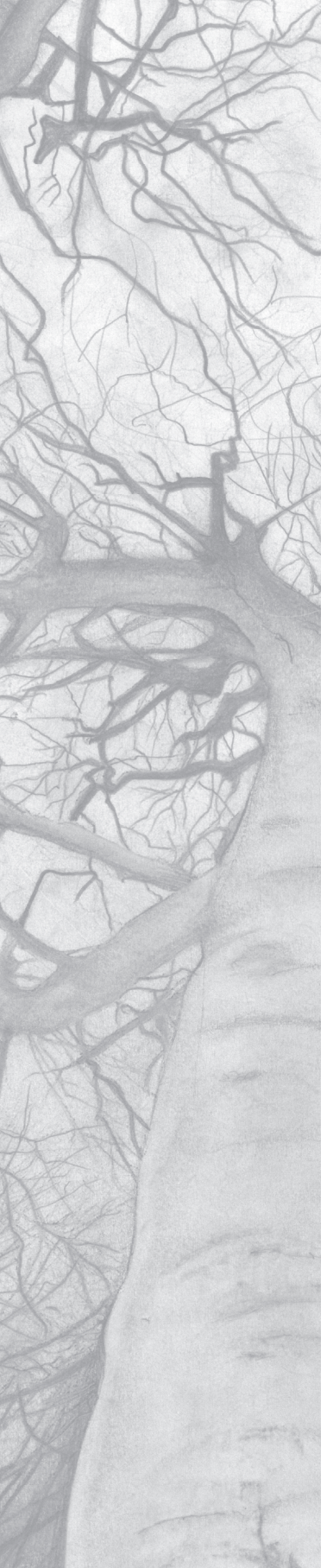

CHAPTER 1

General introduction and outline of thesis

VENOUS THROMBOSIS

Clot formation is a natural and vital mechanism in quickly sealing disruption of vessel walls, thereby preventing excessive bleeding. Vessel wall disruption leads to tissue factor exposure to the blood which induces factor X conversion into factor Xa, subsequent activation of prothrombin into thrombin, and finally activation of fibrinogen into insoluble fibrin. Platelets aggregate at the site of the injury and together with fibrin a blood clot is formed. Once in place, a clot is not a passive entity but the result of a delicate balance between pro- and anticoagulant activity. When the vessel wall is sufficiently repaired, procoagulant activity is reduced again by plasmin, which degrades fibrin clots. This will reduce and eventually eliminate the clot. However, if coagulation is overactivated or if inhibition is incomplete or fails, excessive clot formation occurs. [1] Situations in which this excessive thrombus formation blocks the vein and hinders blood flow, are called venous thrombosis. The two main clinical manifestations of venous thrombosis are deep vein thrombosis of the lower extremities (deep venous thrombosis of the leg, DVT) and embolisation of a dislodged clot to the pulmonary arteries (pulmonary embolism, PE).

Venous thrombosis is a common disease of which the annual incidence is approximately 1 per 1000 persons. [2] In young and middle-aged individuals many risk factors have been established such as immobilisation, oral contraceptives, surgery, fractures, and the use of plaster casts. Furthermore, genetic risk factors such as the factor V Leiden mutation are known to increase the risk of venous thrombosis. [3] With age, the incidence of venous thrombosis increases sharply. [4] E.g., the incidence of venous thrombosis is more than 10-fold higher in octogenarians than in middle-aged individuals (40-50 years). Venous thrombosis will pose an increasing medical and economic burden in the future, given the worldwide growth of the older population. In developed countries, in the upcoming five decades the number of people of 70 years and older will quadruple. [5] In the Netherlands, 15% of the population is 65 years and older, which will increase to 25% in de next 30 years. [6] This shift in the age distribution in the population will lead to an increase in the prevalence and incidence of diseases such as venous thrombosis, which will be challenging for policy makers and healthcare professionals. Due to the increased incidence of venous thrombosis in older age, an improved understanding of the etiology of this disease is specifically needed in the older population in order to target adequate preventive measures.

Virchow has described three mechanisms that contribute to thrombus formation. Stasis of blood flow, damage to the vessel wall (e.g., by hypoxia) and changes in blood composition. [7] It is unknown what causes the increase of the incidence of venous thrombosis in the older people, i.e., what is the role in older individuals of the well-known ''conventional' risk factors of thrombosis, such as immobilisation due to hospital admission and surgery, and whether we can distinguish age-specific risk factors for thrombosis.

In general, there is a lack of studies involving older people. This phenomenon, referred to as "ageism", has occurred in several fields of medical research. This may have practical reasons, e.g., when researchers anticipate mobility problems for older people to reach the study centre, or when excluding older people is inherent to the study question, e.g., researchers expect genetic risk factors to stand out most in young individuals. The difficulties of recruiting older people for research are illustrated by the 'Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis' (MEGA) study [8], a large case-control study on risk factors of venous thrombosis in 18-80 years old individuals performed in the Netherlands (1999-2004). This study discontinued the recruitment of individuals aged 70 to 80 after one year due to a low participation rate (*MEGA-study, data not published*). In 2007, our study group reported that few risk factors have been studied in older people. [9] Knowledge about conventional and age-specific risk factors for venous thrombosis in the older population is insufficient. This was the rationale behind the "Age and Thrombosis, Acquired and Genetic risk factors in the Elderly", or AT-AGE study, a case-control study among older individuals.

THE AT-AGE STUDY

The AT-AGE study is a two-centre, population based case-control study in Leiden, the Netherlands and Burlington, Vermont, US. From June 2008 to August 2011 in Leiden and December 2008 to July 2011 in Vermont, all consecutive patients aged 70 years and older with deep venous thrombosis (DVT) in the leg or a pulmonary embolism (PE), were identified. In Leiden, cases were identified from two anticoagulation clinics in a defined geographical area in the western part of the Netherlands. In Vermont, cases were identified in the Vascular Laboratory and the Radiology department of University of Vermont Health Centre, Burlington. Control subjects were randomly selected from primary care practices in Leiden and Vermont. The AT-AGE study was specifically designed to optimise the participation-rate in the older population. Therefore, we performed home visits to all participants. A home visit enabled us to perform an interview, rather than sending a questionnaire, since the latter is often difficult for older individuals leading to a decrease in the participation rate. The interview assessed conventional thrombosis risk factors that have been established in young and middle-aged people and putative age-specific risk factors, e.g., the presence of varicose veins and functional status. The interview was conducted by trained research assistants, in order to minimise missing data and potential misinterpretation of questions by the participant. In addition, during the home visits a blood sample was drawn and we performed multiple anthropometric measurements and physical tests relevant in the older population, e.g., hand grip strength and gait speed.

OUTLINE OF THIS THESIS

The main objective of this thesis is to determine the risk of venous thrombosis associated with conventional and age-specific risk factors in older people. Moreover, the contribution of these risk factors to the increased incidence of venous thrombosis in older people is assessed. To this aim, we review, in **chapter 2**, the current literature (until 2010) on the effects of conventional risk factors as well as age-specific risk factors for venous thrombosis in older people. In **chapter 3** we elucidate to what extent immobility is a risk factor for thrombosis in older people. We assess the risk of venous thrombosis associated with hospitalisation, surgery, fracture, plaster cast (or splint) use, minor injuries, and transient immobility at home. In **chapter 4** we assess whether the two common genetic risk factors in younger people, i.e. factor V Leiden (FVL, rs6025) and prothrombin 20210A mutation (PT20210, rs1799963) are risk factors for a first venous thrombosis at older age. Moreover, the association of non-O blood type, and a positive family history of thrombosis and thrombosis is determined. In **chapter 5 and 6** we focus on "age-specific" risk factors. In **chapter 5** we determine the risk of venous thrombosis associated with clinical features of venous insufficiency, specifically a history of varicose veins, leg ulcer, and the presence of leg oedema. In **chapter 6** we focus on the presence of functional impairment in older individuals and the risk of venous thrombosis. In **chapter 7** we study the participation rate of older patients in research studies with a focus on practical aspects of the study design (i.e., home visits instead of inviting participants to a study centre). Because in the AT-AGE study blood samples are obtained at home, these could not be processed directly. In **chapter 8**, we study whether the time between venipuncture and blood processing and difference in storage temperature affected the levels fibrinogen, prothrombin, factors VIII, IX, XI and anti-thrombin. Finally, in **chapter 9**, we summarise the main results of this thesis and reflect on the strength and limitations of our findings and we translate our findings into implications and recommendations for future research.

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