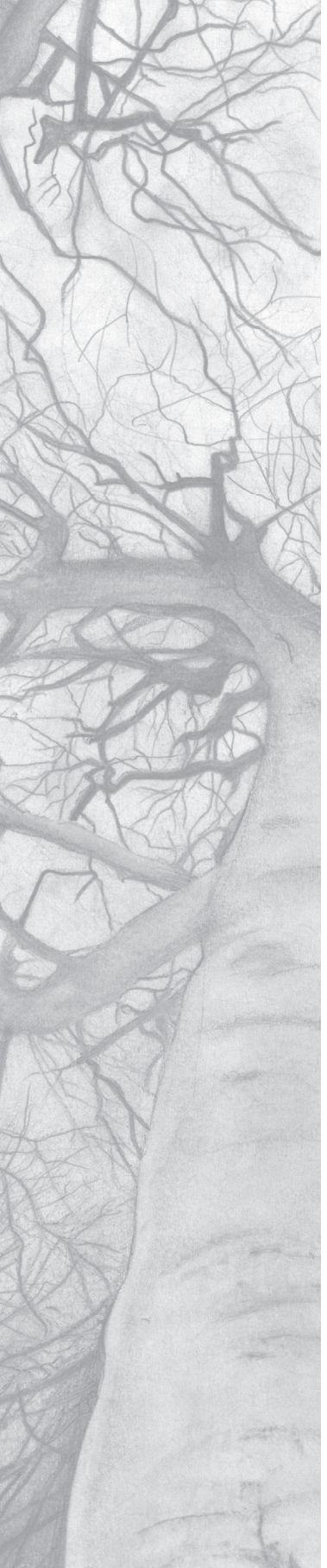
Conventional and age-specific risk factors for venous thrombosis in older people : the AT-AGE study

Engbers, Marissa Josephina



CHAPTER 9

Summary and general discussion

In this discussion section we will summarise the main results of this thesis and possible implications of the findings, discuss methodological considerations and focus on future perspectives in the AT-AGE study.

In **chapter 2** we provided an overview of the available publications (up to 2010) on the effect of conventional risk factors as well as age-specific risk factors for venous thrombosis in the older population. Many conventional risk factors for venous thrombosis established in the young and middle-aged population appeared to increase the risk of thrombosis in the older population as well. Previous reports showed that immobilisation by hospital admission, malignant diseases, heart failure and genetic mutations ((factor V Leiden (FVL, rs6025) and prothrombin 20210A mutation (PT20210, rs1799963)) are risk factors for venous thrombosis in older individuals. As the prevalence of acquired risk factors is higher in the older than in the younger population we found higher population attributable risks (PAR). However, it must be noted that most risk estimates in the older population were based on studies with a small sample size or on subgroup analyses. Furthermore, only a limited number of studies concerning age-specific risk factors such as functional decline and endothelial dysfunction have been published. So, there was limited knowledge regarding risk factors for venous thrombosis in the older population. In order to study the effect of conventional and age-specific risk factors for venous thrombosis in the older population, the "Age and Thrombosis, Acquired and Genetic risk factors in the Elderly" (AT-AGE) study was performed. The AT-AGE study is a population based case-control study among individuals aged 70 years and older for whom home visits were performed. [1]

In **chapter 3** we demonstrated that short-term immobility at home, e.g., due to minor injuries or infections, is a risk factor for venous thrombosis in the older population (2- to 5-fold increased risk). Furthermore, we illustrated that also hospitalisation is a major risk factor in older individuals, similar as in the young and middle aged individuals. Recent hospital discharge was identified as a risk factor, as the risk of venous thrombosis within two weeks after hospitalisation was still increased up to 15-fold. Surgery and plaster cast increased the risk of thrombosis up to 7-fold and fractures increased the risk up to 13-fold. We demonstrated that the relative contribution of in-hospital immobility and out-hospital immobility to the incidence of venous thrombosis is high. Preventive drugs, i.e., thrombosis prophylaxis with low-molecular weight heparin is frequently given to older individuals during hospitalisation. [2] Our results indicate that extended thromboprophylaxis after discharge may be beneficial. This notion is supported by results from the EXCLAIM trial, which included individuals aged 75 years and older. [3] Prolonged duration of treatment after discharge reduced thrombosis rates (absolute difference in the 30 days thrombosis rate −4.2% [95% CI: −6.5-2.0]) but this came at the cost of increased bleeding rates (30 days event rate: 0.5-0.8%). Prolonged use of thromboprophylaxis may

be justified in older individuals who are at particularly high risk of venous thrombosis in whom the benefit of treatment will outweigh the risk of major haemorrhage. Future studies need to carefully examine for which patients and risk circumstances the balance of treatment would be beneficial.

In **chapter 4** we showed that genetic risk factors also play a role in the risk of venous thrombosis in older individuals. Factor V Leiden (FVL, rs6025) and the prothrombin 20210A mutation (PT20210, rs1799963) increased the risk of thrombosis 1.5 to 2-fold in the older population. Also a positive family history of venous thrombosis remained associated with an increased risk of venous thrombosis in 70 years and older individuals (OR 2.3, 95% CI 1.6-3.3) These results indicate that genetics play a role in the etiology of venous thrombosis in older people, and that the effect is not limited to the young.

In **chapter 5 and 6** we showed that age-specific risk factors are relevant in the development of thrombosis. Venous stasis, a risk factor for thrombosis described already by Virchow, can be present due to diminished venous function or a damaged venous wall, causing venous insufficiency. Clinical features of venous insufficiency increased the risk of thrombosis in individuals aged 70 years and older. Varicose veins were associated with a 1.6-fold increased risk of venous thrombosis, and both a leg ulcer and leg oedema increased the risk of thrombosis 3-fold. The combination of these three clinical features showed a 10-fold increased risk of thrombosis compared to none of the clinical features. These increased risks could not be explained by the presence of other major risk factors of thrombosis in the older population, such as recent hospitalisation and surgery. We showed in **chapter 6** that an impaired functional status, more specifically the disability to perform activities of daily living, having an impaired mobility, having a sedentary life, or an impaired hand grip strength were associated with a 2- to 4-fold increased risk of thrombosis. Therefore, in the older population not only short term immobility due to hospitalisation and minor injuries, (**chapter 2**), but also a long term state of decreased mobility and functioning was shown to increase the risk of thrombosis.

METHODOLOGICAL CONSIDERATIONS OF THE AT-AGE STUDY

In the AT-AGE study we achieved high participation rates in cases (69%) and control subjects (73%) for questionnaires combined with blood sampling at first visit (**chapter 3**). In **chapter 7** we demonstrate that performing home visits rather than inviting participants to a study centre is an effective approach to increase the participation rate of older patients in research studies. Home visits enabled us to conduct an extensive, structured interview and to obtain a blood sample. We were able to visit less mobile individuals which diminished the threshold for participating. However, immediate processing of blood samples in the laboratory is not feasible when conducting home visits.

For this reason we determined optimal sample handling, i.e., blood sample storage time and temperature prior to centrifugation with regard to the measurement of coagulation factor levels at a later stage in the study (**chapter 8**). We concluded that determination of coagulation factor levels was reliable when blood samples were stored at room temperature for up to 2.5 hours.

In the AT-AGE study, individuals with an active malignancy were excluded. Exclusion of individuals with an active malignancy preserved internal validity, as we anticipated that control subjects with an active malignancy would be less likely to participate in a research study than cases who suffered from a malignant disease. Moreover, selection bias was a potential problem due to recruitment of cases in the Netherlands via anticoagulation clinics, which only treat patients with vitamin K antagonists. Since 2007, patients with venous thrombosis and a malignancy are increasingly using low-molecular weight heparin injections instead of vitamin K antagonists, which would have led to an undersampling of venous thrombosis patients with a malignancy. [2]

In each case-control study there is a chance of recall bias. The risk of recall bias is not similar for all risk factors in our study. A risk factor such as a history of oedema of the legs in DVT patients probably has a higher chance to be affected by recall bias than the presence of more severe diseases such as leg ulcera. We performed standardised interviews by trained personnel, instead of a questionnaire by mail, which enabled us to clarify the questions for each participant, and determine more precisely the presence of risk factors in cases and control subjects. With this we reduced the chance of recall bias occurring in the AT-AGE study.

Relative risks found in etiological research within the older population tend to be lower than relative risks found in a younger population, due to the higher baseline risk of diseases in the older population. To be able to compare the relative influence of a risk factor on the incidence of venous thrombosis between the younger and the older population, we assessed the population attributable risk (PAR). This enabled us to identify risk factors for venous thrombosis that exhibit major consequences on a population level, albeit with a mild relative risk of thrombosis.

FUTURE PERSPECTIVES

Multimorbidity is frequently present in the older population, and therefore it would be useful to evaluate within the AT-AGE study population, the role of the medical history of diseases in the older individuals. For example, it could be hypothesised that arterial disease, lung disorders such as chronic obstructive pulmonary diseases (COPD), chronic kidney disease, or hypothyroidism influence the risk of thrombosis in older individuals. Recent analyses in the AT-AGE study show that individuals with COPD have a 1.8-fold

increased risk of thrombosis compared with individuals without COPD (CI95 1.1-2.9: 1.1-2.9). (*Karasu et al, manuscript in preparation*) Furthermore, it is currently not known what the effect is of multimorbidity on the risk of thrombosis, i.e., is interaction between these risk factors present? More insight into medication use as a potential risk factor or as a preventive factor for thrombosis in the older population is needed, as polypharmacy is frequently present in the older population. For instance, the potential protective effect of statin use on thrombosis risk in the older population could be determined. With age, plasma levels of many hemostatic factors are increasing, such as of fibrinogen, FVIII, FVII, D-dimer and homocysteine. [4,5] With the AT-AGE study we will gain insight in the role of these elevated levels of coagulation factors and the risk of venous thrombosis in the older population. In the younger population a venous thrombotic event most frequently presents itself as a DVT, whereas in the older population PE is more frequently diagnosed. [6] PE and DVT have long been thought to have the same etiology. However, recently it was shown that risk factors for DVT and PE sometimes differ. [7] The Factor V Leiden paradox is the well-established notion that this genetic variant affects predominantly the risk of DVT and not of PE. Lung disorders such as pneumonia and COPD, however, are risk factors for PE, but have little or no effect on DVT in the middle-aged population. A similar difference was recently demonstrated in the 70 years and older population of the AT-AGE study (COPD: OR_{PE} 2.5, 95%CI: 1.4-4.3; OR_{DVT} 1.0, 95%CI: 0.5-2.1). (*Karasu et al, manuscript in preparation*) In older individuals it would be interesting to define more risk factors specifically for PE, as PE is more common and is associated with higher mortality rates as compared to DVT. [6]

Follow up of the participating patients in the AT-AGE study has taken place one year after the thrombotic event when we revisited the patients and obtained data from questionnaires and a blood sample. With these data, we will able to evaluate the prevalence and severity of the post-thrombotic syndrome in patients aged 70 years and older. Furthermore, the effect of the occurrence of venous thrombosis on the quality of life within older individuals can be evaluated. It will be interesting to perform additional follow-up of the AT-AGE study patients and focus on the recurrence risk of thrombosis, the development of co-morbidities, and the mortality risk after thrombosis at higher age.

In a separate project, patients with deep venous thrombosis of the leg (n= 76) and control subjects (n=97) of the AT-AGE study are included to study the process of ageing of the venous valves (valve thickness and function) and the risk of venous thrombosis (BATAVIA study). (*Karasu et al, manuscript in preparation*) These subjects underwent an ultrasound examination of the venous valves in the popliteal veins.

In general, future research should focus on the use of preventive measures of venous thrombosis within the highest risk groups in the older people. In this thesis we indicate that extended thromboprophylaxis might be beneficial in older individuals who are at

high risk of thrombosis. However, the risk of major hemorrhage needs to be taken into account. The role of direct oral anticoagulant (DOAC) drugs within specific risk groups can be explored. These DOACs are used as thromboprophylaxis in orthopedic surgery. However, beneficial effects on prevention of venous thrombosis in the older population are currently unknown. The ADOPT trial showed that apixaban was associated with more major bleeding events than enoxaparin in middle aged and older people (>40 years). [8] Moreover, an antidote is not yet available. Other medications that have been suggested to prevent thrombosis are aspirin and statins. Aspirin may be a good option for prevention in the older population. [9] The preventive effect is lower than that of low molecular weight heparin and oral anticoagulants; however, the bleeding risk is low. If further research confirms the protective effect of statins, this would be, if well-tolerated by the patients, an elegant alternative in the prevention of thrombosis in the older population. [10,11] The effect of preventive measures for thrombosis other than medication, such as compression stockings, frequent ambulation, or the use of electrical calf muscle stimulation are important targets of future research in the older population. For now, physicians could advise patients with in and out-of-hospital immobility to walk a few times per day, or to perform exercises of the calf muscles even while being bedridden, to prevent stasis. [12]

Currently,' the primary care rule', a clinical decision rule, is used to rule out DVT in primary care together with the point of care D-dimer assay. [13] Recently, it was found that in older patients the primary care rule showed a higher failure rate than in younger patients. [14] This might indicate that other predictors of thrombosis are present and needed in the older individuals. It would be interesting to investigate the addition of age-specific risk factors, such as functional impairment, short-term immobility at home, or minor injuries in order to improve the clinical decision rule in the older population.

CONCLUSIONS

Venous thrombosis will lead to increasing medical and economic burdens in the near future, given the worldwide growth of the older population. Determining risk factors of thrombosis specific in older individuals provides insight in opportunities to prevent thrombosis in this age group. Research studies in older individuals are challenging; however, we showed that performing home visits rather than inviting participants to a study centre can be an effective approach to increase the participation rate of older patients. In this thesis we showed that conventional risk factors such as immobilisation due to hospital admission and also immobility at home, due to for instance infection and minor injury, increase the risk of venous thrombosis also in 70 years and older individuals. We report the presence of age-specific risk factors: venous insufficiency and

functional impairment. The relative contribution of these risk factors to the incidence of venous thrombosis in this population is high. We identified new high risk groups in older people, e.g., recent hospital discharge in which preventive measures could be of special interest. In the upcoming years the AT-AGE study will provide information on additional risk factors for venous thrombosis in the older population. With further identification of risk factors and high-risk groups within the older population we can put effort into research focusing on adaptation of diagnostic rules and the safe use of preventive measures.

REFERENCES

1. Engbers MJ, Blom JW, Cushman M, Rosendaal FR, van H, V. The contribution of immobility risk factors to the incidence of venous thrombosis in an older population. *J Thromb Haemost* 2014; 12: 290-6.
2. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133: 381S-453S.
3. Yusen RD, Hull RD, Schellong SM, Tapson VF, Monreal M, Samama MM, Chen M, Deslandes B, Turpie AG. Impact of age on the efficacy and safety of extended-duration thromboprophylaxis in medical patients. Subgroup analysis from the EXCLAIM randomised trial. *Thromb Haemost* 2013; 110: 1152-63.
4. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Tracy RP, Aleksic N, Folsom AR. Coagulation factors, inflammation markers, and venous thromboembolism: the longitudinal investigation of thromboembolism etiology (LITE). *Am J Med* 2002; 113: 636-42.
5. Koster T, Blann AD, Briet E, Vandenbroucke JP, Rosendaal FR. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. *Lancet* 1995; 345: 152-5.
6. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost* 2007; 5: 692-9.
7. van Langevelde K, Flinterman LE, van H, V, Rosendaal FR, Cannegieter SC. Broadening the factor V Leiden paradox: pulmonary embolism and deep-vein thrombosis as 2 sides of the spectrum. *Blood* 2012; 120: 933-46.
8. Goldhaber SZ, Leizorovicz A, Kakkar AK, Haas SK, Merli G, Knabb RM, Weitz JI. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med* 2011; 365: 2167-77.
9. Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini E, Silingardi M, Bianchi M, Moia M, Ageno W, Vandelli MR, Grandone E, Prandoni P. Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med* 2012; 366: 1959-67.
10. Glynn RJ, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Ridker PM. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. *N Engl J Med* 2009; 360: 1851-61.
11. Adams NB, Lutsey PL, Folsom AR, Herrington DH, Sibley CT, Zakai NA, Ades S, Burke GL, Cushman M. Statin therapy and levels of hemostatic factors in a healthy population: the Multi-Ethnic Study of Atherosclerosis. *J Thromb Haemost* 2013; 11: 1078-84.
12. Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, Cook DJ, Balekian AA, Klein RC, Le H, Schulman S, Murad MH. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141: e195S-e226S.
13. Oudega R, Moons KG, Hoes AW. Ruling out deep venous thrombosis in primary care. A simple diagnostic algorithm including D-dimer testing. *Thromb Haemost* 2005; 94: 200-5.
14. Schouten HJ, Koek HL, Oudega R, van Delden JJ, Moons KG, Geersing GJ. Validation of the Oudega diagnostic decision rule for diagnosing deep vein thrombosis in frail older out-of-hospital patients. *Fam Pract* 2015; 32: 120-5.