Venous thrombosis in the elderly: risk factors and consequences

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CHAPTER 8

Summary and general discussion

The work described in this thesis had two objectives, specifically focusing on people aged 70 years and older: first, we aimed to investigate the associations between several thrombosis- related risk factors described in young and middle-aged populations and the risk of venous thrombosis (VT) in the elderly; second, we aimed to provide insight into several long-term consequences (i.e., health-related quality of life (HRQoL) and long-term risk of mortality) after a first VT at old age. In this discussion section, we summarize and interpret the main findings of this thesis. In addition, we discuss methodological considerations, as well as limitations and strengths of the AT-AGE study. Furthermore, we discuss the clinical implications of the results and future perspectives.

SUMMARY OF MAIN FINDINGS

Part I: The association between known risk factors in young and middle-aged populations and the risk of venous thrombosis in the elderly

In **Chapter 2**, we studied the association between the levels of procoagulant factors (F) VIII, IX, XI, and prothrombin and the risk of a first VT in the elderly. We demonstrated that high levels of coagulation factors FVIII, FIX, and FXI were positively associated with the risk of VT, both combined as well as for deep vein thrombosis (DVT) and pulmonary embolism (PE [with or without DVT]) separately. No association was found between high prothrombin levels and the risk of VT. These results were in line with the conclusions drawn from the Cardiovascular Health Study (CHS) study in which the authors reported an association between the levels of factor VIII and IX and the risk of VT in people aged 65 years and older but no association between prothrombin levels and the risk of VT (1, 2). Our hypothesis was that increasing levels of procoagulant factors would increase the risk of VT in the elderly as was observed in young and middle-aged populations. With the exception of prothrombin, the associations between procoagulant factors and VT risk, as reported in our elderly population, were consistent with those in young and middle-aged populations. No clear dose-response association was observed between an increasing number of elevated coagulation factors (for those individually associated with the risk of VT in the elderly: FVIII, FIX, and FXI) and the risk of VT in the elderly, i.e., when levels of multiple coagulation factors were increased, this did not lead to a further excess VT risk. Since coagulation factor levels increase with age, we expected these levels to have an important role in the development of VT in the elderly (3).

While our observed associations were modest, with ORs slightly lower than those reported in young and middle-aged populations, in this age group, the population attributable risks (PARs) associated with high levels of coagulation factors were not trivial (the PAR was 37.6%, 23.3%, and 12.4% for FVIII, FIX, and FXI, respectively). This is because of the

increased prevalence of elevated coagulation factor levels with age. This emphasizes the importance of these risk factors in the elderly population. Our results on the association between procoagulant factors and the risk of VT in the elderly may guide physicians in identifying high-risk individuals and subsequent targeted prophylactic treatment in those at high risk.

In **Chapter 3**, we studied the association between hypercoagulability measured using a thrombin generation assay and D-dimer levels and the risk of VT in the elderly. We showed that D-dimer levels and parameters of hypercoagulability, i.e., peak thrombin, time-to-peak (ttPeak), endogenous thrombin potential (ETP), and velocity index, but not lag time were associated with the risk of VT. As observed for the association between the levels of individual coagulation factors and the risk of VT, similar risk patterns were observed for DVT and PE [with or without DVT] and for provoked and unprovoked VT separately, albeit the relative risks of VT were more pronounced for unprovoked events than for provoked events. Few studies have reported on the association between D-dimer levels or thrombin generation parameters and the risk of VT in the elderly, and the results have been inconsistent (4-6). There is extensive variation in assay criteria when measuring the thrombin generation potential, i.e., the substrate type, sample preparation, data processing, presence or absence of thrombomodulin and activated protein C, and tissue factor trigger concentration (6, 7), making it difficult to compare results obtained from individual studies. Individuals with both high thrombin generation levels (peak thrombin or ETP) and high D-dimer levels had the highest risk of VT. Furthermore, for all prothrombotic markers (peak thrombin, ETP, and D- dimer), the risk of VT was highest in the presence of a prothrombotic mutation (factor V Leiden and prothrombin G20210A). Our results suggest that hypercoagulability and D-dimer play a role in the etiology of VT in the elderly, and that the effect is not limited to the young. VT is a multicausal disease and the risk of first VT is strongly influenced by the combined effects of several risk factors in a particular patient (8). Our findings suggest that combining thrombin generation parameters with either D-dimer level or a prothrombotic mutation could aid a physician in assessing the risk of first VT in the elderly.

In **Chapter 4**, we studied the association between cardiovascular risk factors (i.e., body mass index (BMI), smoking, alcohol intake, hypertension, and diabetes) and the risk of VT in the elderly. We found no association between smoking, alcohol intake, or diabetes, and the risk of VT. Height and weight were positively associated with the risk of VT, and the risk further increased in individuals with a genetic predisposition of VT, i.e., in the presence of factor V Leiden, prothrombin G20210A mutation, family history of VT, or non-O blood group. To increase the power of the analysis, we chose to combine the common genetic risk factors to indicate a genetic predisposition of venous thrombosis.

Hypertension was inversely associated with the risk of VT, i.e., the risk of VT was decreased in elderly individuals with hypertension compared with those with normal or low blood pressure, both in general as well as separately for systolic and diastolic blood pressure. However, hypertension was not associated with a protective effect of VT in individuals with a genetic predisposition (i.e., compared with individuals without hypertension and without a genetic predisposition). Our results show that there was no clear association between BMI and the risk of VT in older individuals. However, body weight by itself was positively associated with the risk of VT. Potentially, differences in fat distribution affect the risk of venous thrombosis in this age group, which is not adequately captured by BMI.

In **Chapter 5**, we explored the association between self-reported remote history of VT (occurring >10 years before enrollment) and the development of VT in people aged 70 years and older. A remote history of VT was associated with an increased risk of VT after adjustment for other risk factors, i.e., age, sex, BMI, study center, and family history of VT. Our aim was to assess the added value of asking older individuals their personal VT history in order to identify those at increased risk of VT. We did not aim to infer causality in this study, and we performed subgroup analysis merely to assess the robustness of the estimates and for descriptive purposes. Similar risk patterns were observed in DVT and PE [with or without DVT] and provoked and unprovoked VT separately. In clinical practice, this quantification could assist clinicians in the identification of the elderly who are at increased risk of VT and in advising older patients on VT prevention in risk settings, such as surgery. These results underline the importance of taking older individuals´ lifetime history of VT into account.

Part II: Long-term consequences of a first venous thrombosis at older age

In **Chapter 6**, we investigated the potential change in generic health-related quality of life (HRQoL) and disease-specific HRQoL in elderly patients one year after the VT. Based on literature, we know that QoL is decreased due to VT, particularly in the acute phase (9). We studied whether the generic HRQoL in elderly patients with VT increased to the level before the event by comparing levels one year after the VT with those of control subjects. We measured HRQoL using the generic SF-36 questionnaire and disease-specific HRQoL using VEINES-QOL/Sym and PEmb-QoL questionnaires. An increase was observed in HRQoL in the year after VT using both the generic SF-36 and the PEmb-QoL questionnaires. No increase in HRQoL was observed with the VEINES-QOL/Sym questionnaire. Quality of life of those who had experienced VT, one year after the event, was worse than that of the controls after adjustment for comorbidities. These results indicate a major long-term impact of a VT diagnosis on the elderly. For the interpretation of the results of the generic HRQoL, we considered a difference of 5 points in any subscale as clinically or socially relevant. We found that the mean scores of PCS

(physical component summary scores) and MCS (mental component summary scores) in patients over one year after the VT event were clinically improved and 177 (56%) patients had clinically meaningful improvement of more than 5 points for the two summary scores. It may be important to consider approaches to improve physical and mental health shortly after VT diagnosis. Implementing approaches to improve physical and mental health may involve a multi-disciplinary approach that includes medical management, lifestyle modifications, and psychological support. This may include interventions such as exercise programs, dietary changes, and counseling services to address anxiety and depression (10). Early intervention may help prevent complications (e.g., post- thrombotic syndrome (PTS) (11, 12) and improve the overall quality of life of patients with VT. Close monitoring and ongoing support from healthcare providers may also be necessary to ensure the successful implementation of these approaches. Our findings are a call to action for doctors to increase awareness of the long-term effects of VT in elderly patients.

In **Chapter 7**, we determined the long-term (up to 12 years) mortality risk in VT patients aged 70 years and older and assessed the main causes of death after VT. This 12-year span is significantly longer than that performed in previous studies. In general, the cumulative incidence of death was higher in patients than in controls at 2, 5, and 12 years. VT patients had a 1.4-fold (95% CI: 1.1-1.7) increased risk of death compared with controls, and this risk remained increased for up to 5 years after the thrombotic event. Similar to results from previous studies, the main causes of death in our study were diseases of the circulatory system, neoplasms, and diseases of the respiratory system. Close communication with other healthcare providers may be necessary to ensure coordinated care and effective management of any comorbid conditions that could contribute to increased mortality risk. In the future, using data from Statistics Netherlands (CBS), we can assess the risk of morbidity after a first VT in the elderly, for example, by assessing the incidence of cardiovascular events (myocardial infarction, Transient Ischemic Attack (TIA), and recurrent VT) and non- cardiovascular events during the long-term follow-up.

Methodological considerations

Strengths of the AT-AGE study are: 1) this is one of the largest studies to investigate the associations between several risk factors and the risk of VT in individuals aged 70 years and older; 2) we performed home visits as an effective method to recruit elderly patients and achieved a high participation rate; 3) the large amount of data collected, enabled us to assess the role of multiple risk factors.

Limitations of the AT-AGE study are: 1) the restriction of the population to mostly Caucasian people, which means results may not be generalizable to other ethnicities; 2) in most studies described in this thesis, the confidence intervals for risk estimates in subgroup

analyses were wide, so differences between those subgroups should be interpreted with caution; 3) inherent to the case-control design, blood was sampled in the cases after the VT resulting in the potential problem of reverse causality. However, blood samples were obtained more than one year after the VT event, so the associations between risk factors and risk of VT were unlikely to be due to the acute-phase effects; 4) the exclusion of participants due to death, unwillingness to participate, failed blood collection, unsuccessful assay measurements, and use of vitamin K anticoagulants may have led to selection bias and reduced sample size for subgroup analysis. However, multiple imputation analysis was used to impute the missing values in **Chapter 2**, and the results after imputation were similar to the initial results; 5) in **Chapter 6**, we could not obtain complete data for the PEmb-QoL questionnaire in participants from Vermont, USA, so the interpretation of the results may only be valid for Dutch participants. Moreover, the controls may not represent the Dutch general population or the US general population, i.e., participants may be healthier and having a higher HRQoL than the general population with the same age, which may have led to an overestimation of the HRQoL in the control group and an underestimation of the improvement of HRQoL; 6) we only included patients who survived the initial period after their VT event until registration at the anticoagulant clinic. Therefore the overall mortality, which we calculated, is not representative of the whole population of elderly patients experiencing VT after the age of 70 years.

Sources of bias in the AT-AGE study

Both information bias (particularly recall bias) and selection bias may have affected our findings. In the design of the case-control study, we tried to overcome these problems.

Selection bias

Selection bias often arises in case-control studies, with the biggest challenge being the selection of the control group. We selected elderly controls from the files of general practitioners in the catchment area of the anticoagulation clinics where the patients were treated. The response rate among controls was high (i.e., 73%), and the reason for not willing to participate was rarely because of illness (13). To increase the response rate, which is usually low among elderly individuals, home visits were conducted. This also reduced the possibility of selection bias, as also less mobile elderly individuals were able to participate in our study. Since patients were included from the files of anticoagulant clinics, we miss patients who died soon after the VT or who were treated solely in the hospital. The latter are mostly cancer patients, as these patients are often treated only with heparin and not registered to an anticoagulant clinic. This was one of the reasons we excluded individuals with malignancies from our study. The selection of the patients indicates that we have to be careful with the extrapolation of our findings to all elderly VT patients. For example, the risk of death after VT in the elderly is most likely an underestimation as we miss early

deaths. Furthermore, causes of death only apply to patients who survive long enough to be registered at an anticoagulant clinic.

A study design with restriction to elderly individuals could potentially be affected by a specific selection bias: index event bias. When multiple risk factors contribute to the risk of an outcome, conditioning on a consequence of these risk factors during selection of the patients (in this specific case looking at risk factors that also associate with survival while restricting to older age) may induce dependence between the risk factors, even when they are independently distributed in the general population (14). Because of conditioning on age, observed risk estimates may underestimate the true effect of a risk factor and even result in a reversed effect, i.e., risk factors appearing protective and vice versa (15). Figure 1 explains index event bias. In the general population, risk factor A may affect the selection into the study (i.e., reaching an old age) but not be associated with the risk of VT. When we select a group of older patients with a first VT (conditioning on a collider), an inverse association (the association was not present in the general population) is created between risk factor A and the other risk factors (associated with both age and VT), opening the pathway (a-b-c). As a result, risk factor A appears to be negatively associated with the risk of VT. Index event bias is a well-known problem in epidemiology that can lead to biased estimates of the effect of exposures on health outcomes. Several articles have reported on the impact of index event bias in epidemiological studies: Index event bias is a common occurrence in observational research, according to Yaghootkaar et al., but the extent to which this bias affects those studies varies on a number of variables (i.e., disease prevalence, sample size and the effect size,) (16). A simulation study further has shown that index event bias would have a minor impact on observational studies when the risk factors have modest effects as observed in most studies (17), and a subsequent study in Crohn's disease supports this (18). Furthermore, UK researchers recently presented a number of statistical methods that can be used to detect (including the use of negative controls and an inspection of Miami plots) and adjust (including inverse probability weighting, Slope-Hunter method, and Dudbridge et al. method) for index event bias in studies of disease progression (19).

In our study, due to the selection of older patients with first VT, risk estimates may, to some extent, be affected by index-event bias. In **Chapter 2,** the absence of an association between prothrombin and the risk of VT in the elderly may be explained by index event bias. Also, for risk factors that are associated with VT risk in the elderly, e.g., high levels of factors VIII, IX, and XI, the risk estimates may be an underestimation of the true effect. However, for the association between elevated coagulation factors and the risk of VT, this explanation seems unlikely since elevated coagulation factors are not, or at most weakly associated with the risk of death before reaching the age of inclusion (i.e., reaching old age allowing inclusion in our study). The problem of index event bias could

be minimized by adjusting for as many other risk factors as possible, thereby closing the pathway a-b-c. However, the results only marginally changed after we adjusted for other risk factors in **Chapter 4,** again indicating that index-event bias did not have a major effect on our results.

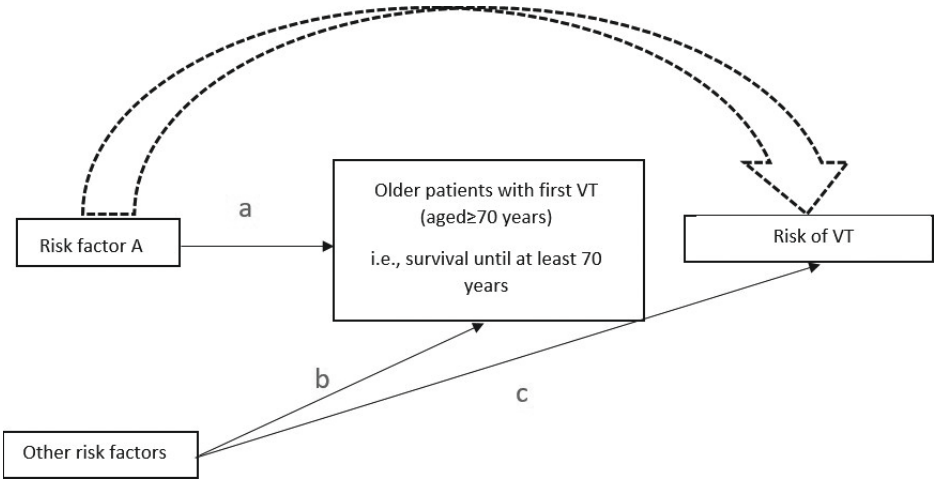

Figure 1. Directed Acyclic Graph (DAG) for index event bias.

Information bias

During data collection, systematic errors may occur. There are two types of misclassification: differential and nondifferential misclassification. Nondifferential misclassification is a misclassification that is unrelated to other study variables. In contrast, with differential misclassification, the misclassification differs according to the exposure or outcome. There are three specific forms of information bias: self-reporting bias, the measurement bias and confirmation bias. In this thesis, we mainly discussed the self-reporting bias.

Self-reporting is a typical method used in epidemiologic and medical research to collect data. Participants must respond to the researcher's questions using this way without the researcher's assistance. Interviews, surveys, and questionnaires are certain types of self-reporting. However, self-reported data are frequently considered to be unreliable and threatened by self-reporting bias in comparison to other sources of information, such as medical records or laboratory measurements (20). Recall bias and social desirability are two examples of self-reporting bias that are explored in AT-AGE study.

Recall bias is a common type of information bias. Recall bias is a differential misclassification because the exposure information is misclassified differentially for those

with or without disease. The possibility of recall bias is inherent to a case-control design, and occurs when cases and controls differentially recall the presence or absence of risk factors prior to the index date. This can lead to biased results, as the reported data may not accurately reflect the true exposure status of the participants. While recall bias may have occurred in the AT-AGE study, this was limited to a minimum by performing home visits (where for example, medical information and medication wrappings could be checked) and by conducting standardized interviews by trained research nurses. The use of standardized interviews enabled us to clarify each question in the questionnaires, reducing the chance of recall bias. Furthermore, in our study, we visited the participants soon after the first VT event, which renders recall bias unlikely.

Regarding remote VT history (Chapter 5), which was also self-reported in our study, the time since a previous event was more than 10 years. This is therefore not limited to a short recall period as stated above. However, we hypothesized that the remoteness of the previous event did not occur to patients as a cause of their current event so differential recall in patients and controls is less likely. Furthermore, a VT has an impact on health and requires anticoagulant therapy (standard therapy >10 years ago was the use of Vitamin K antagonists (VKAs), Sintromitis and Marcoumar prescribed in the Netherlands, and Warfarin in the US), which was burdensome, suggesting that this may be something that people most likely remember.

To minimize the recall bias in case-control studies, studies can use a variety of methods to collect data on anticoagulant therapy use, including medical records, pharmacy records, and interviews with healthcare providers. It is possible that non-differential misclassification affected the results to some extent, particularly in the analysis regarding a remote history of VT where the time since a previous event was more than 10 years, making the recall of such a remote event difficult regardless of current disease status. Non-differential misclassification may have led to an underestimation of the true effect.

Future researchers may be able to mitigate recall bias by using repeated measures, i.e., collecting data on risk factors multiple times during repeated interviews, using detailed questionnaires (questionnaires that ask about specific behaviors), and using proxy respondents (such as family members or friends, who can provide information about a participant's smoking or alcohol use when the participant is unable to do so accurately), and using information from medical records instead of using the interview information.

The questions that are asked when researchers employ surveys, questionnaires, or interviews to gather data may be private or sensitive, such as self-reports of dietary intake, drug use, income, and violence. Therefore, self-reporting data may be influenced by external

bias brought on by social desirability or approbation, particularly in situations where anonymity and confidentiality cannot be ensured at the time of data collection. For instance, results obtained when estimating drug usage among a sample of people could underestimate the actual usage. Social desirability bias may be used to describe the bias in this situation (20). Smoking, alcohol use, and diabetes were self-reported, so results may have been affected by social desirability bias. The patients who had a first VT may be ashamed of their smoking and alcohol intake , more so than the controls.

Validating the self-reporting instrument before using it for data collection is the main approach of preventing social desirability bias. Such validations could be internal or external. Internal validation compares the results of the self-reporting instrument with other ways of gathering data, such as laboratory tests. Examples of frequently used validation techniques for drug testing include blood and hair analysis. However, because the participants in our study had history of smoking and alcohol intake long time ago, there are no laboratory measurements available for our study. Potentially, external validation could be used, such as examining medical records or obtaining input from friends and family.

Relative risks versus absolute risks

We can obtain both absolute and relative risk in etiological research. Absolute risks and relative risks are two important epidemiological measures that help quantify the association between exposure and outcome. However, caution should be taken when interpreting different effect sizes on an absolute or relative scale. When the disease is uncommon, a relative effect may be quite large but has minimal impact on the absolute risk difference and on public health. Only relative effects (i.e., odds ratios) can be directly obtained from case- control studies. However, using the relative risk acquired from case-control studies, the absolute risk can be inferred by taking into account the population's overall background rate or risk of disease occurrence. The overall incidence of first VT ranges from 1-2 per 1000 person-years in the general population to nearly 8 per 1000 in those aged 85 years and older. (21) This indicates a lower relative risk in the elderly might still result in a larger effect on an absolute scale as the background incidence of VT in the elderly is high.

Most case-control studies, such as ours, are sampled from a dynamic population. Therefore, the odds ratio is a perfect estimation of the rate ratio (22). While it is generally not possible to calculate the absolute risk of VT directly in the case-control study, it is possible to assess the population attributable risk (PAR), which was estimated as PAR = pd * (OR – 1)/(OR), in which pd refers to the proportion of patients exposed to the risk factor of interest. The PAR indicates the proportion of the total incidence of VT which can be attributed to

a particular risk factor in older individuals who were eligible for the AT-AGE study. In **Chapter 2** and **Chapter 5** (23, 24), even though we observed the odds ratios were slightly lower than those reported in young and middle-aged populations, the PARs associated with certain risk factors (factor VIII (PAR: 37.6%), IX (PAR: 23.3%), and XI (PAR: 12.4%), and a remote history of VT (PAR: 7.7%)) were evident, indicating the importance of those risk factors in the elderly.

Association versus Causality

In epidemiology, causality refers to the relationship between an exposure or risk factor and a health outcome. It is the concept of establishing a causal effect relationship between two variables, where one variable is believed to influence or determine the occurrence of the other. To establish causality, epidemiologists often consider several criteria, commonly referred to as the Bradford Hill criteria. Establishing causality in epidemiology is a complex process that requires careful consideration of multiple factors while meeting all the criteria is not always feasible. An association between an exposure and an outcome does not necessarily mean that the exposure is causally associated with the outcome, as this can be explained by different factors, e.g., confounding. When inferring causality, one has to therefore take all confounding factors into account.

Although we observed that procoagulant factors, hypercoagulability, D-dimer, cardiovascular risk factors, and self-reported remote history of VT were associated with the risk of VT in the elderly, it remains difficult to draw conclusions regarding the causality of the association (25). However, whether to infer association or causality mainly depends on the objectives of the study. For example, in our study on the risk of VT associated with the levels of procoagulant factors in elderly patients, the initial objective was to ascertain whether these risk factors play a causal role in the disease. These findings could potentially aid in the discovery of targets to develop novel anticoagulant drugs. In the study on the role of self- reported remote history on VT, the goal was to determine whether the exposure (the self- reported remote history of VT) could be used to predict the outcome (current VT) rather than to determine the causal relationship between the exposure and the outcome. Since a cause is a condition without which an event would not have happened, it is irrelevant whether the remote history of VT is a cause or not since it cannot be removed.

Future perspectives

Future studies should focus on the association between a broader range of environmental and genetic risk factors (e.g., deficiencies of antithrombin, protein C, protein S, long-distance travel, acute infection, and air pollution) (26) and the risk of VT in the elderly and also investigate the effect of gene-environmental interactions on the risk of VT in the

elderly. Furthermore, genome-wide association studies (GWAS) have been employed in recent years to identify genetic variations that are associated with a risk for a disease or a certain trait. Even though several genetic risk factors for VT have already been discovered in the elderly, utilizing GWAS could identify more genetic determinants.

In the elderly, VT is often provoked (45%), with malignancy-related events accounting for 26% of all events (27). As stated previously, the problem of the index event bias could be minimized by adjusting for as many other risk factors as possible. However, many more events are provoked than unprovoked in the elderly, which indicates that preventing index event bias by controlling for all other risk factors is difficult. We showed that the results of the association between cardiovascular risk factors and VT in the elderly, as described in Chapter 4, only marginally changed after adjusting for other risk factors. Nonetheless, it may be interesting for future studies to adjust the associations between risk factors and VT more extensively in order to infer causality and also to assess to what extent risk estimates are affected by index event bias.

For the AT-AGE study, we recruited VT patients from anticoagulant clinics since at that time vitamin K antagonists (VKA) were the only oral treatments for VT and for which monitoring was necessary. Currently, direct oral anticoagulants (DOACs) are the preferred treatment option after VT, regardless of the age of the patient (28-32), which implies that recruitment of (elderly) patients in a similar way as described here is no longer possible. Novel recruitment strategies, therefore, need to be explored. VT patients may be included from hospital records based on ICD-10 coding, but as there are many diagnosing hospitals, this is more elaborate than inclusion via anticoagulation clinics. The feasibility of such an approach was demonstrated in a recent study, which identified patients from hospital records (33). Other strategies that may be explored include using large population registers or databases of general practitioners. In general, we excluded participants with active malignancy in the AT- AGE study as these are only rarely registered at anticoagulant clinics for VKA treatment. Other recruitment strategies may result in a better way to include all patients, including cancer patients and patients who have a short life expectancy after the VT event.

In recent years, researchers have focused more on the development of VT and provided different VT prediction models, mainly in young and middle-aged populations (27, 34-37). The elderly have received little attention. Several factors that increase the risk of VT in the elderly have been found in our prior research. We identified additional risk factors in the same population in this thesis. As a result, a prediction model for VT recurrence in the elderly may be created. It is possible to incorporate all risk factors discovered thus far and in this thesis into the prediction model, which will help healthcare professionals

to identify the elderly who are at increased risk of developing VT. This, in turn, can lead to early intervention and prevention of potentially life-threatening complications. At the same time, it is conceivable that larger studies in elderly people with VT identify other risk variables, which may prove to be valuable in a prediction model.

Conclusions

In this thesis, we showed that multiple risk factors such as procoagulant proteins (factor VIII, factor IX, and factor XI), thrombin generation parameters (peak thrombin, ttPeak, ETP, and velocity index), D-dimer, several cardiovascular risk factors (body height and body weight), and a remote history of VT, increase the risk of VT in people aged 70 years and older.

Furthermore, we studied the long-term consequences of VT, i.e., health-related quality of life after a first venous thrombosis in individuals aged 70 years and older and long-term mortality and causes of death in elderly after a first venous thrombosis, indicating the long-term effects of venous thrombosis on the lives of elderly. In the near future, the AT-AGE study will provide information on additional risk factors as a large amount of data was collected through questionnaires, and blood samples are still available for analysis. More genetic risk factors may be identified by utilizing GWAS for venous thrombosis in the elderly.

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