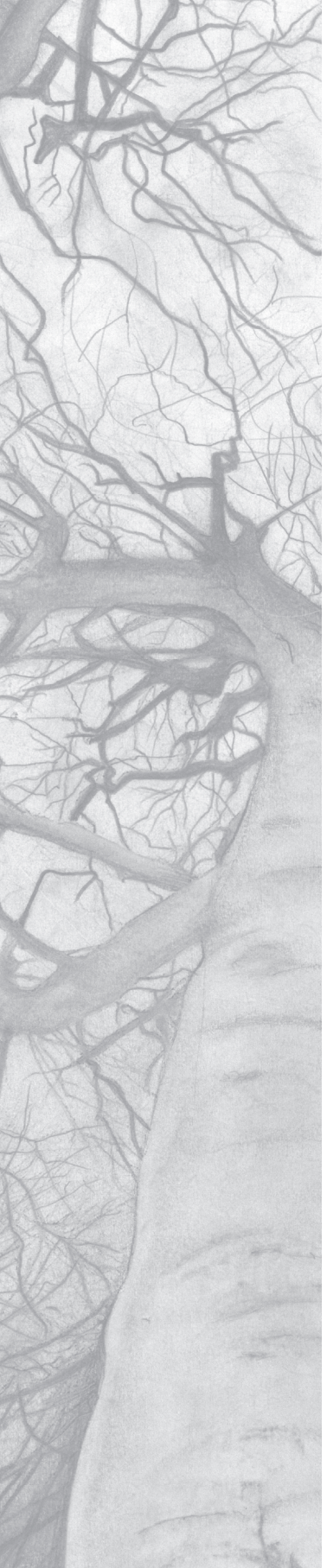
Conventional and age-specific risk factors for venous thrombosis in older people : the AT-AGE study

Engbers, Marissa Josephina



CHAPTER 3

The contribution of immobility risk factors to the incidence of venous thrombosis in an older population

M.J. Engbers
J.W. Blom
M. Cushman
F.R. Rosendaal
A. van Hylckama Vlieg

J Thromb Haemost. 2014; 12: 290-6

ABSTRACT

Background

Venous thrombosis is common in the older population. Assessment of risk factors is necessary in order to implement preventive measures.

Objectives

We studied the associations between immobility-related risk factors and thrombosis, specifically, hospitalisation, surgery, fractures, plaster cast use, minor injuries, and transient immobility at home in an older population.

Methods

Analyses were performed in the Age and Thrombosis, Acquired and Genetic risk factors in the Elderly (AT-AGE) study, a two-centre population-based case-control study. Consecutive cases aged ≥70 years with a first-time thrombosis (n= 401) and control subjects ≥70 years old without a history of thrombosis were included (n= 431). Exclusion criteria were active malignancy and severe cognitive disorders. We calculated odds ratios (OR) with 95% confidence intervals (CI95) after adjustment for age, sex, body mass index and study centre, and population attributable risks (PAR).

Results

There was a 15-fold (OR 14.8; CI95 4.4-50.4) increased risk of thrombosis within two weeks after hospital discharge. Surgery (OR 6.6; CI95 3.7-11.6), fractures (OR 12.7; CI95 3.7-43.7), plaster cast (OR 6.2; CI95 2.0-18.9), minor leg injuries (OR 1.9; CI95 1.1-3.3), and transient immobility at home (OR 5.0; CI95 2.3-11.2) were all associated with thrombosis risk over three months. The PAR for in-hospital immobility was 27%, and for out-of-hospital immobility 15%.

Conclusions

In those over 70 years of age, in-hospital and out-of hospital immobility are strong risk factors for thrombosis. Additional studies on preventive measures during immobilisation in this age group should not focus solely on hospital settings.

INTRODUCTION

Venous thrombosis presents mainly as deep venous thrombosis of the leg (DVT) and pulmonary embolism (PE). The incidence of thrombosis increases sharply with age, being rare in young individuals (<1 per 10 000 per year) and increasing to approximately 1% per year in very old age. [1] More than two thirds of all patients with venous thrombosis are aged 60 years and older, and 25% are older than 80 years. [2] So, increasing age is one of the most important risk factors. As venous thrombosis is a potentially lethal disease, morbidity (e.g. the post thrombotic syndrome) is common, and treatment has frequent side effects, prevention efforts will have large effects in older individuals. [3] However, the risk factors for thrombosis in the older population are not well characterised since studies to date mainly included young and middle aged individuals. [4]

Immobility is associated with reduced venous blood flow, particularly in the pockets of the venous valves, leading to inflammation and hypercoagulability. [5,6] In young and middle-aged individuals, immobility, for example due to hospitalisation or minor injuries, is an established risk factor for thrombosis with relative risk estimates ranging from 3 to 11. [7,8] However, it is unknown to what extent immobilisation increases the risk of venous thrombosis in older individuals. We hypothesised that immobility-related risk factors would be strong risk factors in this population.

The aim of this study was to assess the risk of venous thrombosis associated with hospitalisation, surgery, use of a plaster cast, minor injury, and transient immobility at home in a case-control study of people aged 70 years and older.

METHODS

Identification of participants

The Age and Thrombosis, Acquired and Genetic risk factors in the Elderly (AT-AGE) Study is a two-centre, population based case-control study in Leiden, the Netherlands and Burlington, Vermont, US, designed to study risk factors for venous thrombosis in the older population. From June 2008 to August 2011 in Leiden and December 2008 to July 2011 in Vermont, all consecutive patients 70 years and older with DVT or 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 the University of Vermont Medical Centre in Burlington, Vermont, which are the only diagnostic centres in that geographic area. We defined venous thrombosis as DVT alone or PE with or without a proven DVT by ultrasound (PE±DVT). We were unable to accurately define isolated

PE without DVT since diagnostic measures of thrombosis of the legs are not routinely performed in all PE patients. Control subjects were identified in Leiden and Vermont in the same geographical area as the cases. Control subjects were randomly selected from five primary care practices in Leiden and four in Vermont.

All identified cases and control subjects were mailed an invitation letter, followed by a telephone call to discuss participation. Individuals were excluded from participation if they responded affirmatively that they had an active malignancy, defined as 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. Potential participants with severe psychiatric or cognitive disorder, as judged by the telephone contact, were excluded. We also excluded individuals who self-reported previous DVT or PE within the past 10 years.

Of the 1187 identified cases, 689 (58%) were eligible and 498 (42%) were excluded. (figure 1) Of those excluded, 55 (11%) died before inclusion was possible, 159 (32%) had active malignancy, 108 (22%) had an apparent severe cognitive or psychiatric disorder, and 171 (34%) had a history of venous thrombosis within the last 10 years. Of the 723 identified control subjects, 631 (87%) were eligible and 92 (13%) were excluded: 15 (16%) died before inclusion was possible, 19 (21%) had active malignancy, 34 (37%) had an apparent severe cognitive or psychiatric disorder and 10 (11%) had a history of venous thrombosis within the last 10 years (see figure 2 for participation flowchart by study centre).

All participants provided written informed consent in accordance with the Declaration of Helsinki and gave permission to obtain information about their medical history. The study was approved by the Medical Ethical Committee of the Leiden University Medical Centre and by the Committee of Human Research of the University of Vermont.

Data collection

In Leiden, 398 (71%) of the 561 invited cases and 321 (76%) of the 422 invited control subjects participated. In Vermont, 128 cases were invited and 75 (59%) participated, while 140 (67%) of the 209 invited control subjects participated. For all eligible cases and controls subjects who agreed to participate, home visits were scheduled. During this home visit, an extensive structured interview and blood collection was completed by trained personnel. The index date was defined as the date of diagnosis of the thrombosis for the cases and the date of the in home interview for the control subjects.

The interview assessed thrombosis risk factors that have been established in the young and middle-aged as well as other putative age-specific risk factors that were present within 3 months of the index date. Questions queried hospitalisations, surgery during hospitalisation, fractures and use of plaster cast (or splint), minor injuries of the lower extremities and transient immobility at home, including dates and location.

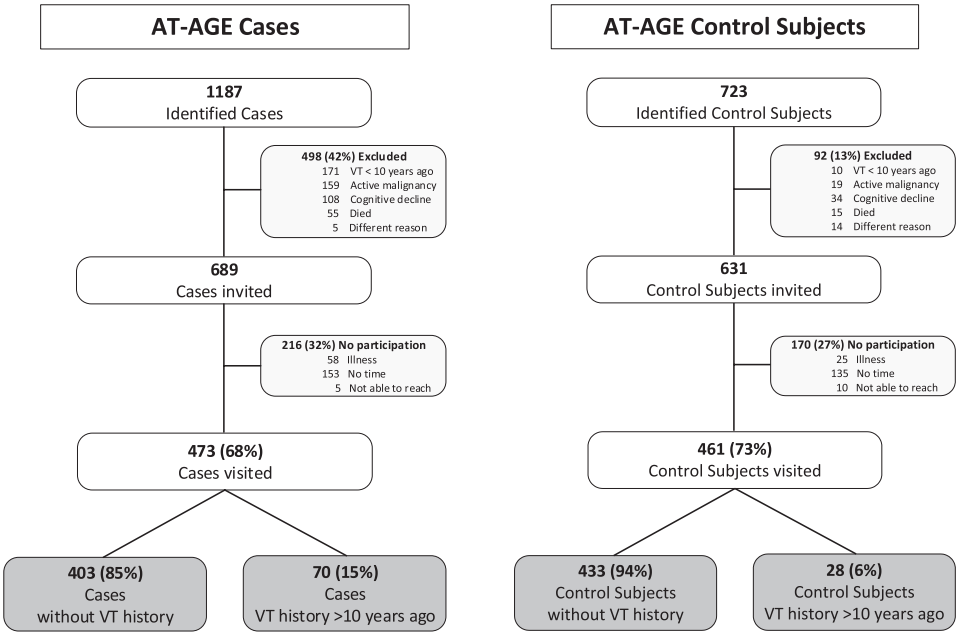


Figure 1. Flowchart of AT-AGE study

Physical measurements were performed including weight (measured with a calibrated scale) and height. Body mass index (BMI) was calculated by dividing body weight (kg) by squared height (m2).

Analyses

For these analyses on the etiology of thrombosis we included only cases and control subjects without a history of venous thrombosis (403 cases and 433 control subjects) who had complete interview data (401 cases and 431 control subjects). Characteristics of the control subjects included in Leiden and in Vermont were analysed separately to provide insight into the source populations. For all further analyses, we combined data from the two sites. We determined associations between transient immobility-related risk factors and venous thrombosis. Transient immobility was defined as a status of immobility that is shortly present in one's life. As estimates of relative risk, we calculated odds ratios (OR) and their 95% confidence intervals (CI95) using logistic regression models. All reported ORs were adjusted for age (continuous), sex, BMI (continuous) and study centre using multivariable logistic regression analysis. Stratified analyses were performed for DVT and for PE±DVT.

Hospitalisation was defined as present when the participant was hospitalised at the index date or the discharge date was within the three months window previous to the

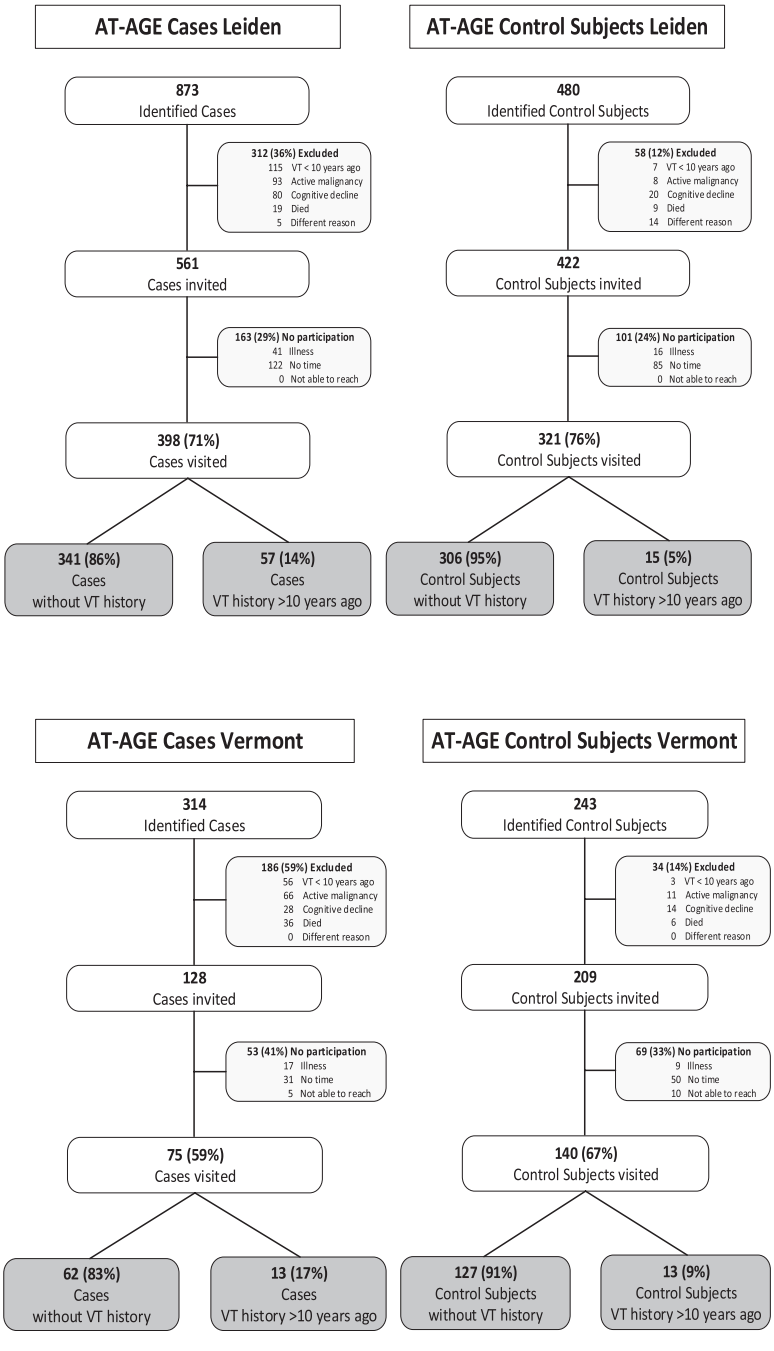


Figure 2. Flowchart of AT-AGE study per center

Table 1. Characteristics of control subjects by center

	Controls NL	Controls VT
	306	125
Median Age, n (Range)	76 (70-94)	76 (70-96)
70-75 years, n (%)	126 (41)	49 (39)
75-80 years, n (%)	90 (29)	39 (31)
80-85 years, n (%)	61 (20)	24 (19)
>85 years, n (%)	29 (10)	13 (11)
Men, n (%)	147 (48)	62 (50)
Ethnicity White, n (%)*	284 (93)	124 (99)
Smoking status*		
Never, n (%)	88 (29)	32 (26)
Former, n (%)	168 (55)	87 (69)
Current, n (%)	49 (16)	6 (5)
Median BMI (kg.m-2) (Range) *	25.9 (17.0-42.0)	27.3 (19.0-49.7)
Hospitalisation, n (%)†	16 (5)	13 (10)
Surgery, n (%)†	12 (4)	4 (3)
Fracture, n (%)†	1 (0.3)	2 (2)
Plaster cast (splint), n (%)†	2 (1)	2 (2)
Minor injury, n (%)*†	18 (6)	8 (7)
Transient Immobility at home, n (%)*†	5 (2)	3 (2)

NL= the Netherlands, VT= Vermont, n = number, BMI = Body Mass Index.

*ethnicity 5 missings, smoking 1 missings, BMI 8 missings, minor injury 1 missing, transient immobility at home 1 missing

† < three months before index date

index date. Hospital admission for both in-patients and day patients were taken into account. Hospitalisation for surgical and non-surgical indications was analysed separately. The presence of a fracture or plaster cast (or splint) in the three months before the index date were analysed as putative risk factors as were minor injuries of the lower extremities and transient immobility at home. A minor injury was defined as an injury of the lower extremities (hip, knee, ankle or foot) such as a sprained ankle or contusion of the lower leg that started within the three months window. A period of transient immobility at home was defined as a period of four or more consecutive days of immobility, such as being bedridden or continuously sitting in a chair, that started within the three months before the index date.

If participants were bed- or chair-ridden for the entire three months prior to the index date they were classified as chronically immobilised and not included in these analyses. To study duration of risk of venous thrombosis after the transient risk factor, we dichotomised the time between the risk factor and venous thrombosis by the median time from the end of the risk period (for hospitalisation) or the start of the risk period (for minor injury or transient immobility at home) in the control subjects. Since the group of

Table 2. Association of transient immobility related risk factors with venous thrombosis

	Cases n = 401	Controls n = 431	OR crude (CI95)	OR adjusted* (CI95)
Hospitalisation, n (%)[†]	126 (31.4)	29 (6.7)	6.4 (4.1-9.8)	7.2 (4.5-11.4)
Surgery, n (%)[†]	79 (19.7)	16 (3.7)	6.4 (3.6-11.1)	6.6 (3.7-11.6)
Thrombosis after discharge, n (%)	84 (67)			
Time after discharge[‡]				
< 2 weeks (%)	28 (9.3)	3 (0.7)	13.6 (4.1-45.3)	14.8 (4.4-50.4)
2-4 weeks (%)	17 (5.9)	3 (0.7)	8.3 (2.4-28.5)	8.8 (2.5-31.5)
>4 weeks - 3 months (%)	38 (12.1)	22 (5.2)	2.5 (1.5-4.4)	2.9 (1.6-5.1)
Fracture, n (%)[†]	27 (6.7)	3 (0.7)	10.3 (3.1-34.2)	12.7 (3.7-43.7)
Plaster cast (splint), n (%)[†]	21 (5.2)	4 (0.9)	5.9 (2.0-17.3)	6.2 (2.0-18.9)
Minor injury, n (%)[†‡]	41 (10.5)	26 (6.1)	1.8 (1.1-3.0)	1.9 (1.1-3.3)
Start of minor injury~				
< 4 weeks (%)	15 (4.1)	15 (3.6)	1.1 (0.6-2.4)	1.3 (0.6-2.7)
> 4 weeks-3 months (%)	26 (6.9)	11 (2.7)	2.7 (1.3-5.6)	2.8 (1.3-5.8)
Transient immobility at home, n (%)[†‡]	34 (8.8)	8 (1.9)	5.1 (2.3-11.1)	5.0 (2.3-11.2)
Start of transient immobility[‡]				
< 9 weeks (%)	25 (6.6)	4 (0.9)	7.5 (2.6-21.7)	7.7 (2.6-22.9)
> 9 weeks - 3 months (%)	9 (2.5)	4 (0.9)	2.7 (0.8-8.8)	2.5 (0.8-8.5)

n = number, OR = oddsratio, CI = confidence interval.

*adjusted for age (continuous), sex, BMI: body mass index (continuous) and study center.

[†] < three months before index date

[‡]time after discharge: cases: 1 missings, controls 1 missings; minor injury 6 missings, transient immobility at home: 6 missings

participants with hospitalisation in the three months prior to the index date was large enough for further stratification, to study the time trend in risk of venous thrombosis in more detail, the time after hospital discharge was divided into three periods (< two weeks, two-four weeks, four weeks-three months). The small number of control subjects with fractures or plaster cast prohibited a detailed analysis of the risk by time from immobilisation.

In addition, sensitivity analyses were performed. Since the index date was defined as the date of the home visit for the control subjects and therefore, per definition, none of the controls was hospitalised on the index date, assessment of the risk of thrombosis during hospitalisation was not directly possible. To estimate the risk of venous thrombosis during hospitalisation, the index date of the controls was moved back by five weeks, i.e, by the median time (in weeks) of the cases between diagnosis of thrombosis and home visit.

We calculated population attributable risk (PAR) as: pd (OR-1)/(OR); in which pd is the proportion of cases exposed to the risk factor of interest. In this case the PAR indicates the proportion of the total incidence of venous thrombosis in those 70 and older who were eligible for this study that can be attributed to the risk factor of interest. [9,10] We calculated the PAR for all immobility related risk factors combined, and for in-hospital

Table 3. Odds ratios of thrombosis over three months with transient immobility risk factors stratified by type of thrombosis

Exposure	N, DVT/total VT (%)	DVT OR (CI95)*	PE±DVT OR (CI95)*
Hospitalisation	43/126 (34)	5.6 (3.2-9-8)	9.1 (5.5-15.2)
Surgery	27/79 (34)	5.3 (2.7-10.4)	7.9 (4.2-14.6)
Fracture	11/27 (41)	14.2 (3.7-55.3)	10.9 (2.9-40.5)
Plaster cast (splint)	6/21 (29)	4.2 (1.1-16.5)	7.6 (2.3-24.9)
Minor injury	24/41 (59)	2.6 (1.4-4.9)	1.4 (0.7-2.6)
Transient immobility at home	7/34 (21)	2.4 (0.8-6.8)	7.4 (3.2-17.2)

N= number, VT = venous thrombosis, DVT= deep venous thrombosis of the leg, PE = pulmonary embolism, OR = odds ratio, CI = confidence interval.
*adjusted for age (continuous), sex, BMI: body mass index (continuous) and study center.

and out-of-hospital immobility, separately. Out-of-hospital immobility was defined as the presence of fractures, plaster cast (or splint), minor injuries, and transient immobility at home within the non-hospitalised population.

RESULTS

For the cases, the median duration between the index date and the home visit was five weeks (range 1-44 weeks), 75% were visited within seven weeks, and 90% within 10 weeks. General characteristics of the control subjects in Leiden and Vermont are shown in table 1. In both centres, ~30% of the control subjects were 80 years and older. Median BMI was slightly higher in Vermont than Leiden. Of the 401 cases, in Leiden, 134 (39%) of the cases had DVT, and 207 (61%) had PE±DVT, and in Vermont 32 (53%) had DVT and 28 (47%) PE±DVT. In 155 of the 166 DVT cases (93%), and in 220/235 of the PE cases (94%) we were able to obtain the diagnostic report of the thrombotic event, and was the thrombosis thus objectively confirmed by ultrasound and PE was confirmed by spiral computed tomography or ventilation-perfusion lung scan.

Table 2 shows the risk of venous thrombosis associated with immobility-related risk factors. Overall, hospitalisation was associated with a more than 7-fold increased risk of venous thrombosis (OR = 7.2, CI95 4.5-11.4). Among cases and controls with hospitalisation, the median duration of hospital stay in the cases was 10 days (range 2-55) and in the control subjects 3 days (range 1-22). Dichotomisation of the time between discharge from hospital and the index date, based on the median time of hospitalisation until the index date in the control subject (48 days, range 4-89) showed that the risk of venous thrombosis was 7.9-fold increased in the first seven weeks after discharge (OR 7.9; CI95 4.2-14.7) and 2.1-fold increased after seven weeks (7 weeks- 3 months, OR 2.1; CI95 1.0-4.4). Further stratification of the time between hospital discharge and the

index date showed a 14.8-fold increased risk of thrombosis within the first two weeks after discharge from the hospital (OR 14.8; CI95 4.4-50.4) and gradually decreasing risk to a 3-fold increased risk between four weeks and three months after discharge (table 2). Performing a sensitivity analysis using the recalculated index date for the controls, 41 (10.1%) cases and 1 (0.2%) control subject was hospitalised during the index date indicating that the thrombotic risk was highest during hospitalisation although the confidence interval was wide (OR 48.7; CI95 6.6-361.0).

Among the cases hospitalised within the three months prior to the index date, 79 of the 126 (63%) had surgery during the hospital admission. When compared with individuals without hospitalisation, the risk of venous thrombosis associated with surgery-related hospitalisations (OR 6.6, CI95 3.7-11.6) was similar to non-surgery hospitalisations (OR 5.5 CI95 2.7-10.4) (OR for surgical versus non-surgical admission = 1.1, CI95 0.4-2.7). Thirty-one (7.8%) of the cases and 4 (0.9%) of the control subjects underwent lower extremity surgery, indicating that lower extremity surgery was associated with an almost 9-fold increased risk of thrombosis (OR = 8.6, CI95 3.0-25.1).

Fracture was associated with a nearly 13-fold increased risk of thrombosis (OR 12.7, CI95 3.7-43.7). In the cases, two-thirds of fractures (n=17) were of the lower extremities of which 8 (47%) presented with a DVT. In 87% of these cases the DVT was diagnosed on the ipsilateral side as the fracture. Use of a plaster cast or a splint was associated with a 6-fold increased risk of thrombosis (OR= 6.2; CI95 2.0- 18.9).

Minor leg injury was associated with a 1.9-fold increased risk of thrombosis (OR = 1.9; CI95 1.1- 3.3). The median time of occurrence of the minor injury until the index date was 43 days (range 1-92) for the cases and 27 days (range 4-93) for the controls. Compared with individuals without a minor injury in the three months prior to the index date, the risk of venous thrombosis was 1.3-fold (CI95 0.6-2.7) increased in the first 4 weeks after start of the minor injury and remained 2.8-fold (CI95 1.3-5.8) increased between four weeks and three months after the start of the immobility. The risk of thrombosis was increased in individuals with sprains of the ankle or knee (OR 1.9; CI95 0.6-6.1) and a contusion of the leg (OR 1.5; CI95 0.7-3.1). In 24 of the 41 cases (59%) with a minor injury a DVT was diagnosed, while 17 cases (41%) had PE±DVT. In 22 of these 24 cases (92%) the DVT was diagnosed on the ipsilateral side as the minor injury.

Transient immobilisation was associated with a 5-fold increased risk of thrombosis (OR = 5.0, CI95 2.3- 11.2). Median duration of transient immobilisation at home in the cases was 8 days (range 4-77 days) and 10 days (range 4-30 days) in control subjects. The median time of the start of transient immobility until the index date, was 27 days (range 2-81) for the cases, and 63 days (range 38-86) for the control subjects. The risk of thrombosis was 7.7-fold increased (CI95 2.6-22.9) within the first 9 weeks (63 days) after the transient immobility, whereas as an OR of 2.5 (CI95 0.8-8.5) was found if transient im-

mobility was more than 9 weeks up to 3 months previous. In 42% of the cases the reason for transient immobilisation at home was an infection, 23% had generalised weakness or "malaise", 17% had fracture, and 9% each had back pain or a minor injury. Of the cases, 5 (1.2%) were chronically immobilised, whereas none of the control subjects were.

All immobility risk factors were similarly associated with both DVT and PE±DVT. (Table 3) Overall, immobilisation from any cause had a PAR of 39%. In-hospital immobility and out-of-hospital immobility had population attributable risks of 27% and 15%, respectively.

DISCUSSION

In the AT-AGE study, a case-control study on venous thrombosis risk in people aged 70 years and older, we determined that immobility-related risk factors, i.e., hospitalisation, surgery, fractures, plaster cast (or splint), minor injuries of the legs, and transient immobility at home were strongly associated with the risk of venous thrombosis (both DVT and PE±DVT) in the 3 months after the start of the immobility (ORs ranging between 2 and 13). The highest risk of thrombosis was for found for immobilisation during hospitalisation (OR 48.7; CI95 6.6-361.0), and the risk of thrombosis out-of hospital was 15-fold increased within the two weeks after hospital discharge, and the risk remained increased for 3 months after hospital discharge. Predefined potential confounders of the risk factors, i.e, age, sex, BMI, and study centre, did not alter any of the associations. Previous studies on immobility and the risk of thrombosis in older populations reported similar risk estimates, ranging from 1.5 up to more than 8-fold increased risks. [4] Based on the PARs we observed, the overall contribution of immobility to thrombotic risk (both in and out of hospital) in this study population was 40%. A PAR of 27% was found for in-hospital related immobility. This contrasts with data previously reported for younger people, where the PAR was only 15% for hospital-related immobility. [4] Importantly, the PAR was 15% for out-of-hospital immobility in the last three months in this older population. These findings indicate that immobility explains part of the age gradient in the incidence of venous thrombosis.

Findings illustrate the large impact of immobility, a common occurrence in the older population. The prevalence of immobility related risk factors in the three months prior to the index date for our control group ranged from 2-8% for the different exposures.

Hospitalisation causes immobilisation. [11] In line with this we found that cases were hospitalised for a longer period than the control subjects. One should take into account that severity and disease entity during hospitalisation can influence the risk of thrombosis, as can the duration of hospitalisation. [12]

As in a younger population, we found that minor injuries were associated with a higher risk of thrombosis over three months. [8] For minor injury the time of highest risk differed than for other types of immobility, with a higher risk after four weeks compared to shortly after the minor injury. For the other studied factors the risk was highest shortly after the exposure of immobility. It is possible that the seriousness of the minor injury, and the long term consequences, leading to more or less immobility, increase the thrombotic risk, rather than the minor injury itself. It is also possible this finding was a chance finding. Transient immobilisation at home increased the risk of thrombosis 5-fold, and this risk was highest in the first two months after immobilisation. Transient immobilisation at home was most frequently due to infection, an important trigger for thrombosis. [13]

The increased risk of thrombosis associated with out-of-hospital immobility indicates that prophylaxis may be beneficial. Home treatment with prophylaxis has effectively been implemented in other high risk groups, such as orthopedic surgical patients. [14] The EXCLAIM trial showed a beneficial effect of a longer duration of treatment within the older population (>75 years). [15] However, in two clinical trials including inpatients, extended thromboprophylaxis after discharge reduced thrombosis rates at the cost of higher bleeding rates (30 days event rate: 0.5-0.8%). [16,17] Other preventive measures that might be considered in this high risk group include the use of graded elastic compression stockings or aspirin. [18,19]

Recruiting older individuals in research is challenging. [20] We overcame this by performing home visits to assess the presence of risk factors. This enabled us to recruit less mobile individuals and achieve a high participation rate (participation rate: cases 68%, control subjects 73%). As in any case-control study, recall bias might have occurred. However, both cases and controls were interviewed by trained personnel using a standardised interview, which minimises the risk of bias. Using an interview for assessment of risk factors for thrombosis within three months before the index date enabled us to determine putative risk factors, such as transient immobility at home, that might be challenging to determine, e.g., as these are not mentioned regularly in medical reports and they might be difficult to recall precisely after a longer period. Unfortunately, data on preventive measures in the hospital (e.g., low molecular heparin injections) were not collected. However, individuals with in-hospital immobilisation were most likely more often treated with thromboprophylaxis as their risk of venous thrombosis is thought to be increased. More frequent treatment with thromboprophylaxis in immobilised individuals compared with individuals who are not immobilised, leads to an underestimation of the true relative risk of venous thrombosis associated with in-hospital immobilisation.

In a case-control study, associations may be biased if the willingness to participate is affected by the presence of the risk factor. We minimised this bias by performing home visits, and achieving a high participation.

Moreover, the sensitivity analysis in which we recalculated the index date of the control subjects, did not alter interpretations of our results. We excluded cancer patients so our results are not generalisable to these individuals. Finally, a number of potential participants died before they could be invited to participate. The impact on our results is difficult to determine, but these participants were more likely immobilised, resulting in an underestimation of the true risk.

In conclusion, the contribution of immobility-related risk factors, defined as hospitalisation, fracture, plaster cast (or splint), minor injury of the leg, and transient immobilisation at home to the risk of venous thrombosis in the older population is high. Studies regarding preventive measures during immobilisation should focus on both in-hospital and out-of-hospital patients.

REFERENCES

1. 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.
2. Rosendaal FR, van Hylckama Vlieg A, Doggen CJ. Venous thrombosis in the elderly. *J Thromb Haemost* 2007; 5 Suppl 1: 310-7.
3. Goldhaber SZ. Venous thromboembolism: Epidemiology and magnitude of the problem. *Best Pract Res Clin Haematol* 2012; 25: 235-42.
4. Engbers MJ, van Hylckama Vlieg A, Rosendaal FR. Venous thrombosis in the elderly: incidence, risk factors and risk groups. *J Thromb Haemost* 2010; 8: 2105-12.
5. Virchow R. Gesammelte Abhandlungen zur Wissenschaftlichen Medizin. Frankfurt: Staatsdruckerei. 1856.
6. Bovill EG, van der Vliet A. Venous valvular stasis-associated hypoxia and thrombosis: what is the link? *Annu Rev Physiol* 2011; 73: 527-45.
7. Rosendaal FR. Risk factors for venous thrombotic disease. *Thromb Haemost* 1999; 82: 610-9.
8. Van Stralen KJ, Rosendaal FR, Doggen CJ. Minor injuries as a risk factor for venous thrombosis. *Arch Intern Med* 2008; 168: 21-6.
9. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health* 1998; 88: 15-9.
10. Rowe AK, Powell KE, Flanders WD. Why population attributable fractions can sum to more than one. *Am J Prev Med* 2004; 26: 243-9.
11. Weill-Engerer S, Meaume S, Lahlou A, Piette F, Saint-Jean O, Sachet A, Beinis JY, Gallinari C, Grancher AS, Vincent JP, Naga H, Belmin J, Salvatore R, Kazes M, Pautas E, Boiffin A, Piera JB, Duviquet M, Knafo D, Piau A, Miric D, Jean A, Bellamy V, Tissandier O, Le Blanche AF. Risk factors for deep vein thrombosis in inpatients aged 65 and older: a case-control multicenter study. *J Am Geriatr Soc* 2004; 52: 1299-304.
12. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, III. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med* 2000; 160: 809-15.
13. Rogers MA, Levine DA, Blumberg N, Flanders SA, Chopra V, Langa KM. Triggers of hospitalization for venous thromboembolism. *Circulation* 2012; 125: 2092-9.
14. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141: e419S-e494S.
15. Hull RD, Schellong SM, Tapson VF, Monreal M, Samama MM, Nicol P, Vicaut E, Turpie AG, Yusen RD. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. *Ann Intern Med* 2010; 153: 8-18.
16. 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.
17. Cohen AT, Spiro TE, Buller HR, Haskell L, Hu D, Hull R, Mebazaa A, Merli G, Schellong S, Spyropoulos A, Tapson V. Extended-duration rivaroxaban thromboprophylaxis in acutely ill medical patients: MAGELLAN study protocol. *J Thromb Thrombolysis* 2011; 31: 407-16.
18. Thigh-length versus below-knee stockings for deep venous thrombosis prophylaxis after stroke: a randomized trial. *Ann Intern Med* 2010; 153: 553-62.

19. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000; 355: 1295-302.
20. Bugeja G, Kumar A, Banerjee AK. Exclusion of elderly people from clinical research: a descriptive study of published reports. *BMJ* 1997; 315: 1059.