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Author: Timp, J.F.
Title: Risk factors and predictors for recurrent venous thrombosis : building blocks for a prognostic model
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Table 1. Recurrence rate in premenopausal women and the influence of hormonal contraceptive use

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>N recurrence</th>
<th>Follow-up time (years)</th>
<th>IR (per 1000) 95%CI</th>
<th>HR (95%CI)</th>
<th>HR† (95%CI)</th>
<th>HR‡ (95%CI)</th>
<th>HR§ (95%CI)</th>
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<tr>
<td>Non-use at first event</td>
<td>20</td>
<td>1284</td>
<td>15.6 (10.0-24.1)</td>
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<td>1 (reference)</td>
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<td>HC use at first event</td>
<td>60</td>
<td>3870</td>
<td>15.5 (12.0-20.0)</td>
<td>1.0 (0.6-1.7)</td>
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<td>1.0 (0.6-1.7)</td>
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<td>Non-use during follow-up</td>
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<td>4615</td>
<td>13.2 (10.3-17.0)</td>
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<td>19</td>
<td>539</td>
<td>35.2 (22.5-55.2)</td>
<td>2.6 (1.5-4.3)</td>
<td>2.8 (1.6-4.7)</td>
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<td>COC</td>
<td>15</td>
<td>399</td>
<td>37.5 (22.6-62.2)</td>
<td>2.7 (1.5-4.7)</td>
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<td>29</td>
<td>34.4 (4.9-244.5)</td>
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<td>-</td>
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<tr>
<td>Non-oral preparation</td>
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<td>Vaginal ring</td>
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<td>3</td>
<td>269.0 (37.9-1909.4)</td>
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<td>IUD</td>
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<td>0 (0-47.9)</td>
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<td>Injectable</td>
<td>0</td>
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<td>0 (0-153.7)</td>
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<td>-</td>
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<tr>
<td>HC use at first event and non-use during follow-up</td>
<td>43</td>
<td>3378</td>
<td>12.7 (9.4-17.2)</td>
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<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
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<td>HC use at first event and during follow-up</td>
<td>17</td>
<td>491</td>
<td>34.6 (21.5-55.6)</td>
<td>2.6 (1.5-4.6)</td>
<td>2.9 (1.6-5.1)</td>
<td>2.9 (1.6-5.1)</td>
<td>2.9 (1.6-5.1)</td>
</tr>
</tbody>
</table>

COC denotes: combined oral contraceptive, HC: hormonal contraceptive, HR: hazard ratio, IR: incidence rate, POP: progestagen-only pill
*No data on the type of contraceptive used was available in seven women
†Adjusted for anticoagulation
‡Age and anticoagulation adjusted
§Anticoagulation, age and BMI adjusted
Abstract

Background
Several studies have shown an increased risk of venous thrombosis (VT) in otherwise healthy individuals during seated immobility. Temporary thromboprophylaxis during periods of immobility is not justified because of a low risk in absolute terms. This may be different for recurrent VT.

Objectives
To study whether seated immobility, either through exposure to long-haul travel or through prolonged immobility in daily life, increases the risk of recurrent VT.

Patients/ Methods
This study is a case-control study nested within a cohort of 4731 patients with a first VT who were followed for recurrence (MEGA follow-up study). Participants reported via a questionnaire on periods of seated immobility: 1) prolonged travel >4h or seated work >4h/day during a 3 month-period before the recurrence for the cases or a random period for the controls 2) confinement to a wheelchair anytime during the follow-up period. 2723 participants (58%) returned the questionnaire. For the first exposure, odds ratios (OR), adjusted for age, sex, comorbidity at baseline and anticoagulant treatment were estimated to compare risk of recurrence between groups with and without recent immobility. For the second, adjusted hazard ratios (HR) were estimated by means of time-dependent Cox regression analysis to compare risk of recurrence between groups with and without use of a wheelchair.

Results
No association was found between long-haul travel and recurrent VT (adjusted OR 0.8; 95%CI, 0.6-1.1) or daily seated work and recurrent VT (adjusted OR 0.8; 95%CI, 0.6-1.2). Within subgroups of different types and duration of travel or subgroups of days per week of work-related immobility results were similar. Five out of 47 patients who reported to use a wheelchair developed recurrent VT, but did not have an increased recurrence risk as compared with patients without a wheelchair (adjusted HR 1.1; 95%CI, 0.4-2.6).

Conclusions
For several seated immobility exposure categories, i.e. prolonged travel, seated work or confinement to a wheelchair, no association was found with recurrent VT.

Introduction

In 1856, Rudolf Virchow described three broad categories of factors contributing to venous thrombosis; endothelial injury, hypercoagulability and stasis. Stasis as a risk factor for thrombosis has been described predominantly in the context of plaster casts, prolonged bed rest and immobilisation after surgery. However, in these instances other factors like damaged tissue or comorbidities that contribute to hypercoagulability also play a role.

Immobilization per se as a risk factor for venous thrombosis, in otherwise healthy people, has been described for the first time in 1940, during the second World War, when an increase in number of deaths from pulmonary embolism was attributed to prolonged sitting in shelters during the bombardments of London.[1]

More recently, several studies have been published in which seated immobility, such as during work, travel or long haul flights, was found to be a risk factor for a first venous thrombotic event.[2-4] In a study by Healy and colleagues prolonged work- and computer-related seated immobility was associated with an almost three-fold increased risk of a first venous thrombotic event (OR 2.8; 95%CI, 1.2-6.1).[3] A meta-analysis by Chandra and colleagues reports on a three-fold increased risk (pooled RR 2.8; 95%CI, 2.2-3.7) for travellers as compared with non-travellers.[2] Prolonged immobility in a supine position however, has not been related to activation of coagulation.[5]

Although reported relative risks of a first venous thrombotic event during or after seated immobility are moderately high, the absolute risk of a first venous thrombotic event is low (1-2 per 1000 persons per year). [6] This is why clinical interventions such as temporary thromboprophylaxis (for example during long-haul flights) are not justified. This may be different for recurrent venous thrombosis, for which the absolute risk is high. The five-year cumulative incidence of recurrent venous thrombosis is reported to be around 12-25%.[7-9] However, the relation between seated immobility and recurrent venous thrombosis has not been studied before. Knowledge is needed to provide travellers, as well as individuals who are otherwise immobilised in the absence of morbidity, with solid advice regarding their actual risk and to evaluate the utility of prophylactic measures.

We aimed to study whether seated immobility, either through exposure to long-haul travel or through prolonged immobility in daily life, increases the risk of recurrent venous thrombosis.
Methods

Study design

Between March 1999 and August 2004, 4956 patients aged 18-70 with an objectively diagnosed first deep vein thrombosis (DVT) of the leg or pulmonary embolism (PE) were included in a population-based case-control study (MEGA study). All patients filled in an extensive questionnaire on putative risk factors for venous thrombosis. Details of the MEGA study have been described previously.[10] Of the MEGA case-control study, only the cases were further followed for recurrence until 2008-2009 (MEGA follow-up study). For this, 225 of the 4956 patients did not consent, leaving 4731 patients. Of these patients 134 participated in the MEGA follow-up pilot study for which follow-up ended in 2005. The MEGA follow-up study was approved by the Medical Ethics Committee of the Leiden University Medical Center, and all participants gave written informed consent.

Adjudication of immobility status

Data on periods of seated immobility of participants during follow-up came from a detailed questionnaire, filled in by the patients at the end of follow-up. We studied the following self-reported factors regarding seated immobility during follow-up: 1) Long-haul travel for >4 hours; 2) seated work for >4 hours per day, categorized as either seated work or work-related seated travel, and 3) confinement to a wheelchair.

Questions regarding long-haul travel or seated work were asked with regard to a 3 month period before the date of recurrence for the participants with a recurrent venous thrombotic event and a randomly picked three months period during follow-up for the participants without a recurrent venous thrombotic event (Figure 1).

The period of exposure to seated immobility is much longer for patients who are confined to a wheelchair than for patients who took e.g. a long-haul flight. Questions regarding the use of a wheelchair were therefore asked with regard to the complete duration of follow-up and focussed on the first date of using the wheelchair.

Adjudication of recurrent events

Between 2007 and 2009 the vital status of all patients was acquired from the central Dutch population register.[11] For the patients who died, a cause of death (ICD-10-CM) was obtained from the national register of death certificates at the Central Bureau of Statistics. Short answer forms concerning recurrent venous thrombosis were sent by mail to all survivors and consenting individuals between June 2008 and July 2009, and supplemented by telephone interviews. Additional information was acquired from the regional anticoagulation clinics and from hospitals. Deaths due to recurrent venous thrombosis were counted as fatal recurrent events. Based on hospital discharge letters, the information from the anticoagulation clinics, forms filled in by the patients and causes of death, possible recurrences were classified into certain and uncertain recurrences, following a decision rule published previously.[12] In short, reported recurrences were classified into certain recurrences when there was a discharge letter stating a diagnosis of a recurrent event based on clinical and radiological data, or when both the anticoagulation clinic and the patient reported a recurrent event at either a clearly different location than the first event or more than one year has passed since the first event, or when a registered death from a recurrent event at least six months after the first event was found.

Adjudication of use of prophylactic anticoagulant treatment

Information on the use of anticoagulant treatment during the three months exposure period, both for long-haul travel and seated work, was obtained from the SFK register. SFK stands for the Dutch Foundation for Pharmaceutical Statistics and is a register in which over 95% of the community pharmacies in the Netherlands are represented. [13] SFK data contain information about patient specific drugs dispensed; the generic name of a drug, the Anatomical Therapeutic Chemical (ATC) classification, the date of prescription, and the number of days for which a drug was prescribed. Information from this register was available for the years 1999 to 2009. Linkage was based on a combination of age, sex, 4-digit postal code and vitamin K antagonist use within the first month after the initial venous thrombosis. In total 2547 (54%) patients of the MEGA follow-up study could be individually linked with SFK. In analyses on the use of prophylactic anticoagulant treatment during follow-up, information on this use of anticoagulant treatment was derived from the anticoagulation clinics.

Statistical analyses

Patients reported on long-haul travel or seated work with regard to a three months exposure period. To study whether long-haul travel and daily seated work after a first thrombotic event were associated with recurrent venous thrombosis we used a nested case-control design, within the MEGA follow-up study. Cases were the participants with recurrent venous thrombosis and controls participants without recurrent venous thrombosis. Patients reported on the use of a wheelchair during follow-up and the
first date of use. To study whether confinement to a wheelchair was associated with recurrent venous thrombosis we used a traditional follow-up design.

1 Analyses on long-haul travel
For the analyses on long-haul travel participants of the MEGA follow-up pilot study (n=134), participants who did not return the follow-up questionnaire (n=1874), participants who did not fill in the question regarding long-haul travel (n=287) and participants with an uncertain recurrent event (n=50) were excluded. In total, 2386 participants were eligible for analyses. This group contained 402 cases, i.e. participants with a recurrent event and 1984 controls, i.e. participants without a recurrent event.

The cases were 1:1 matched on time since the first thrombotic event until the three months exposure period to take into account that the risk of recurrence decreases over time. After this matching procedure 804 participants were included for analyses, i.e. all 402 cases and 402 controls. Odds ratios (OR) with 95% confidence intervals were estimated with conditional logistic regression analysis to compare the risk of recurrence between groups with and without recent travel.[14] Odds ratios were estimated for long-haul travel for >4 hours yes or no, stratified by type of transport (airplane, bus, car or train), number of travels and duration of travel. Odds ratios were adjusted for age, sex and comorbidity at baseline. Comorbidity at baseline could be diagnoses of cancer, diabetes, liver failure, kidney failure, rheumatoid arthritis, multiple sclerosis, chronic bronchitis or emphysema. Additionally, adjustment for (prophylactic) anticoagulant use during the three months exposure period was performed.

2) Analyses on daily seated work
For the analyses on seated work participants of the MEGA follow-up pilot study (n=134), participants who did not return the follow-up questionnaire (n=1874), participants who did not fill in the question regarding seated work either because they were not employed at the time or because they did not want to answer the question (n=1216) and participants with an uncertain recurrent event (n=31) were excluded, leaving 1476 participants eligible for analyses. This group contained 254 cases and 1222 controls. After the matching procedure 506 participants were included for analyses, of which 253 cases (out of 254) and 253 controls. Odds ratios were estimated for seated work for >4 hours per day, either through seated work or work-related seated travel, stratified by number of days per week. Odds ratios were adjusted for age, sex, comorbidities at baseline and anticoagulant treatment during the 3 months exposure period (as described above).

3) Analysis on use of a wheelchair
For the analyses on the use of a wheelchair participants of the MEGA follow-up pilot study (n=134), participants who did not return the follow-up questionnaire (n=1874), participants who responded with “Yes, I use a wheelchair”, but who did not fill in a starting date (n=7) and participants who did not answer the question regarding use of a wheelchair (n=89), 2627 participants could be included for analyses. Duration of follow-up was counted from date of first thrombotic event to end of follow-up, defined as the date of a recurrence or, in its absence, the date of returning the short answer form. The last form in the current study population was returned on December 31, 2009. Here we limit the analyses to certain recurrent events (n=465) and participants with an uncertain recurrent event (n=86) were censored from the date of the uncertain recurrence onward. Incidence rates of recurrent venous thrombosis were estimated as the number of events over the accumulated follow-up time and with person time split and divided over participants with or without the need for a wheelchair during follow-up. The association between the use of a wheelchair and recurrent venous thrombosis was estimated by means of time-dependent Cox regression analysis with the use of a wheelchair as a time-dependent variable. Hazard ratios with corresponding 95% confidence intervals (CI) were estimated and corrected for age, sex and comorbidity at baseline. Additional adjustments for anticoagulant treatment during follow-up were performed with anticoagulant treatment as a time-dependent variable. Hazard ratios were estimated for confinement to a wheelchair yes or no and stratified for the duration of wheelchair use. As a sensitivity analysis we included patients who responded in the questionnaire “Yes, I use a wheelchair”, but who did not fill in a date (n=7) and considered them exposed over the full follow-up period.

Results
In the MEGA follow-up study 4731 patients with a first episode of venous thrombosis were followed for recurrent events for a median of 5.9 years (interquartile range 1.6-7.8 years, total follow-up 24 064 years). Mean age at enrolment was 48 years and 2164 (46%) patients were men. In 987 (21%) patients comorbidity at baseline was reported, with cancer (9%) accounting for most of the comorbidities. Baseline characteristics for patients who returned the follow-up questionnaire (n=2723) were similar to those of the total group of patients (mean age 48, 45% men) except for the proportion of patients with comorbidities at baseline (15% comorbidities) (Table 1).

Relation between long-haul travel and recurrent venous thrombosis
Of 402 cases with recurrent venous thrombosis, 127 (32%) reported long-haul travel of more than four hours, during the three months period prior to their recurrence. Of the matched 402 controls 148 (37%) reported long-haul travel during the 3 months exposure period. Long-haul travel appeared not related to recurrent venous thrombosis, shown by both the crude and adjusted odds ratios of 0.8 (95%CI, 0.6-1.1) and 0.8 (95%CI, 0.6-1.1) (Table 2). When results were split for either long-haul air travel or long-haul non-air travel, results did not change with adjusted odds ratios of 0.8 (95%CI, 0.5-1.2) and 0.8 (95%CI, 0.5-1.1). Results for number of travels and duration of travel were additionally similar and did not show an association between
travel and recurrent venous thrombosis. Only for patients with long-haul air travel for >12 hours we found a possibly increased risk of recurrence (OR 2.0; 95%CI 0.7-6.2), as compared with patients without long-haul air travel. When we stratified long-haul non-air travel for the type of transport we did not see elevated risks for any means of transport, with an adjusted odds ratio of 0.7 (95%CI; 0.5-1.1) for a trip by car, 0.4 (95%CI; 0.1-2.4) for a trip by train and of 0.9 (95%CI; 0.3-2.7) for travel by bus. In all of abovementioned analyses additional adjustment for (prophylactic) anticoagulant treatment did not change results (Table 2). We had data on other types of prophylactic measures, such as compression stockings or exercise, only for participants who took a long-haul flight. Of 56 cases who took a long-haul flight 17 (30%) reported not to have taken any prophylactic measures, while 21 (38%) reported to have exercised or moved during the flight and 28 (50%) reported to have worn compression stockings. For the 69 controls who took a long-haul flight, these numbers were 30 (43%), 27 (39%) and 24 (35%), respectively.

Relation between seated work and recurrent venous thrombosis

Of 253 cases with recurrent venous thrombosis, 147 (58%) reported to perform seated work of more than four hours, during the three months period prior to their recurrence. Of the matched 253 controls 155 (61%) reported to perform seated work during this period (Table 3). Work-related daily immobility was not associated with recurrent thrombosis, shown by an adjusted odds ratio of 0.8 (95%CI; 0.6-1.2). Also after

<table>
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<tr>
<th>Table 1. Clinical Characteristics</th>
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<td>Multiple sclerosis</td>
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<td>Chronic bronchitis</td>
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<td>Emphysema</td>
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*86 uncertain recurrent events not counted
†219 uncertain recurrent events not counted

Table 2. Odds ratios for risk of recurrent venous thrombosis according to long-haul travel

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95%CI)</th>
<th>OR* (95%CI)</th>
<th>OR† (95%CI)</th>
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<tr>
<td>No</td>
<td>275</td>
<td>254</td>
<td>reference</td>
<td>reference</td>
<td>reference</td>
</tr>
<tr>
<td>Yes</td>
<td>127</td>
<td>148</td>
<td>0.8 (0.6-1.1)</td>
<td>0.8 (0.6-1.1)</td>
<td>0.8 (0.6-1.1)</td>
</tr>
<tr>
<td>Number of travels</td>
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<td>≤2</td>
<td>67</td>
<td>74</td>
<td>0.8 (0.5-1.2)</td>
<td>0.8 (0.5-1.2)</td>
<td>0.8 (0.5-1.2)</td>
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<td>&gt;2</td>
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<td>74</td>
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<td>0.8 (0.5-1.2)</td>
<td>0.8 (0.5-1.2)</td>
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<td>Duration of travel</td>
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<td>≤12 hours</td>
<td>104</td>
<td>111</td>
<td>0.8 (0.6-1.2)</td>
<td>0.9 (0.6-1.2)</td>
<td>0.9 (0.6-1.3)</td>
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<td>&gt;12 hours</td>
<td>17</td>
<td>25</td>
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<td>0.8 (0.4-1.6)</td>
<td>0.7 (0.3-1.5)</td>
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<td>Long-haul air travel &gt;4 hours</td>
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<td>No</td>
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<td>331</td>
<td>reference</td>
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<td>Yes</td>
<td>56</td>
<td>69</td>
<td>0.8 (0.5-1.1)</td>
<td>0.8 (0.5-1.2)</td>
<td>0.8 (0.5-1.3)</td>
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<td>Number of flights</td>
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<tr>
<td>≤2</td>
<td>41</td>
<td>43</td>
<td>0.9 (0.6-1.5)</td>
<td>1.0 (0.6-1.6)</td>
<td>1.0 (0.6-1.7)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>15</td>
<td>26</td>
<td>0.6 (0.3-1.1)</td>
<td>0.5 (0.3-1.3)</td>
<td>0.5 (0.2-1.0)</td>
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<td>Duration of flight</td>
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<td></td>
</tr>
<tr>
<td>≤12 hours</td>
<td>42</td>
<td>60</td>
<td>0.7 (0.5-1.1)</td>
<td>0.7 (0.5-1.1)</td>
<td>0.7 (0.4-1.2)</td>
</tr>
<tr>
<td>&gt;12 hours</td>
<td>9</td>
<td>5</td>
<td>1.8 (0.6-5.4)</td>
<td>2.0 (0.7-6.2)</td>
<td>2.0 (0.6-6.2)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, comorbidity
†Adjusted for age, sex, comorbidity and (prophylactic) anticoagulant treatment
Data on anticoagulant treatment was not available for all participants (linkage successful 54%)
stratification for daily seated work and daily work-related seated travel no association was found (adjusted OR 1.0 (95%CI; 0.7-1.5) and 0.7 (95%CI; 0.4-1.3), respectively). Within subgroups of days per week of work-related immobility results were similar and no association was found between seated immobility and recurrences. In all of abovementioned analyses additional adjustment for (prophylactic) anticoagulant treatment did not change results (Table 3).

Relation between confinement to wheelchair and recurrent venous thrombosis
In the follow-up questionnaire 47 patients reported to have a condition for which they were confined to a wheelchair. Five of these patients developed a recurrent venous thrombotic event for an incidence rate of 22.5 per 1000 person-years (95%CI; 9.5-54.0) while it was 26.9 per 1000 person-years (95%CI; 24.5-29.5) for patients without a wheelchair. Corresponding hazard ratio after adjustments for age, sex and comorbidity at baseline was 1.1 (95%CI; 0.4-2.6) (Table 4). In a sensitivity analysis in which we included seven participants who used a wheelchair but for whom we did not have a date of first use, we found similar results with an adjusted HR of 1.0 (95%CI; 0.4-2.2).

24 Out of 47 patients with a wheelchair started using their wheelchair before the first thrombotic event. They did not have an increased risk of recurrence (HR 1.0; 95%CI, 0.3-3.1) after adjustments for age, sex and comorbidity (Table 4). The other 23 patients who started using a wheelchair after the first thrombotic event developed 2 recurrences and did not have an increased recurrence risk (HR 1.2; 95%, 0.3-4.8 after adjustments). One of these recurrences was within one year after the start of using a wheelchair. Prophylactic anticoagulant treatment does not seem to explain our findings. Additional adjustments for anticoagulant treatment as a time-dependent variable did not change our results (Table 4). Of all 47 patients that reported to be bound to a wheelchair none started prophylactic anticoagulant treatment around the time of first use. Eight out of 24 patients who started using a wheelchair before their first thrombotic event received prophylactic treatment after the event. Three of all 24 patients received only therapeutic anticoagulant treatment shortly after the thrombotic event and thirteen out of 24 patients had one or several periods of prophylactic treatment during follow-up. Out of 23 patients who started using the wheelchair after the first event, 15 patients had no periods of anticoagulant treatment after the start of use, 5 patients had a period of long-term anticoagulant treatment after the start of use and 3 patients had one or several shorter periods of prophylactic treatment after the start of use.

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Table 3. Odds ratios for risk of recurrent venous thrombosis according to immobility in daily life through work

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95%CI)</th>
<th>OR* (95%CI)</th>
<th>OR† (95%CI)</th>
</tr>
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<tbody>
<tr>
<td>Work-related daily immobility</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>106</td>
<td>98</td>
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<tr>
<td>Yes</td>
<td>147</td>
<td>155</td>
<td>0.9 (0.6-1.3)</td>
<td>0.8 (0.6-1.2)</td>
<td>0.8 (0.6-1.2)</td>
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<tr>
<td>Number of days per week</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1-2 days</td>
<td>14</td>
<td>20</td>
<td>0.5 (0.2-1.3)</td>
<td>0.5 (0.2-1.6)</td>
<td>0.5 (0.1-1.5)</td>
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<tr>
<td>&gt;2 days</td>
<td>133</td>
<td>135</td>
<td>1.0 (0.7-1.4)</td>
<td>0.9 (0.6-1.3)</td>
<td>0.9 (0.6-1.3)</td>
</tr>
<tr>
<td>Daily seated work</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>110</td>
<td>110</td>
<td>reference</td>
<td>reference</td>
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<tr>
<td>Yes</td>
<td>141</td>
<td>142</td>
<td>1.0 (0.7-1.4)</td>
<td>1.0 (0.7-1.5)</td>
<td>1.0 (0.7-1.5)</td>
</tr>
<tr>
<td>Number of days per week</td>
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<td></td>
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<td></td>
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<tr>
<td>1-2 days</td>
<td>12</td>
<td>16</td>
<td>0.4 (0.1-1.4)</td>
<td>0.7 (0.2-2.5)</td>
<td>0.7 (0.2-2.5)</td>
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<tr>
<td>&gt;2 days</td>
<td>129</td>
<td>126</td>
<td>1.1 (0.7-1.6)</td>
<td>1.1 (0.7-1.6)</td>
<td>1.1 (0.7-1.6)</td>
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<tr>
<td>Daily work-related seated travel</td>
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<td></td>
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<tr>
<td>No</td>
<td>207</td>
<td>206</td>
<td>reference</td>
<td>reference</td>
<td>reference</td>
</tr>
<tr>
<td>Yes</td>
<td>35</td>
<td>32</td>
<td>1.1 (0.6-1.9)</td>
<td>0.7 (0.4-1.3)</td>
<td>0.7 (0.4-1.3)</td>
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<td>Number of days per week</td>
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<td></td>
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<tr>
<td>1-2 days</td>
<td>9</td>
<td>13</td>
<td>0.5 (0.2-1.5)</td>
<td>0.3 (0.1-0.9)</td>
<td>0.2 (0.1-0.8)</td>
</tr>
<tr>
<td>&gt;2 days</td>
<td>26</td>
<td>19</td>
<td>1.5 (0.8-3.1)</td>
<td>1.0 (0.5-2.2)</td>
<td>1.1 (0.5-2.3)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, comorbidity
†Adjusted for age, sex, comorbidity and anticoagulant treatment
Data on anticoagulant treatment was not available for all participants (linkage successful 54%)
Table 4. Odds ratios for risk of recurrent venous thrombosis according to confinement to a wheelchair

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Obs.yrs (n)</th>
<th>rec events</th>
<th>IR/1000</th>
<th>HR</th>
<th>HR*</th>
<th>HR†</th>
<th>HR‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confined to wheelchair</td>
<td>No</td>
<td>16413 (2580)</td>
<td>441</td>
<td>26.9 (24.5-29.5)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>222 (47)</td>
<td>5</td>
<td>22.5 (9.4-54.0)</td>
<td>0.9 (0.4-2.1)</td>
<td>1.1 (0.4-3.1)</td>
<td>1.0 (0.3-3.3)</td>
</tr>
<tr>
<td>Duration of wheelchair use</td>
<td>Start before the 1st thrombotic event</td>
<td>141 (24)</td>
<td>3</td>
<td>213 (9.6-56.1)</td>
<td>0.8 (0.2-2.4)</td>
<td>1.0 (0.3-3.1)</td>
<td>1.0 (0.3-3.3)</td>
</tr>
<tr>
<td></td>
<td>Start after the 1st thrombotic event</td>
<td>82 (23)</td>
<td>2</td>
<td>245 (6.1-97.9)</td>
<td>1.0 (0.3-4.1)</td>
<td>1.2 (0.3-4.8)</td>
<td>1.4 (0.5-4.5)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, comorbidity
†Adjusted for age, sex, comorbidity and anticoagulant treatment
‡Adjusted for age, sex, comorbidity, anticoagulant treatment, and other factors

Discussion

In this study we found no association between seated immobility, either through long-haul travel, work-related seated immobility or through the use of a wheelchair and recurrent venous thrombosis. Odds ratios for long-haul air travel and long-haul non-air travel as compared with no travel were 0.8 (95%CI, 0.5-1.2) and 0.8 (95%CI, 0.5-1.1). Stratification for the duration of travel did not change results, although long-haul air travel >12 hours may be associated with an increased risk of recurrence. The risk of recurrent venous thrombosis was not increased during periods of daily seated work (OR 1.0; 95%CI, 0.7-1.5) or work-related seated travel (OR 0.7; 95%CI, 0.4-1.3) and results were similar in subgroups of days per week with seated work. For patients confined to a wheelchair the risk of recurrent venous thrombosis was not increased compared with patients who did not use a wheelchair (HR 1.2; 95%CI, 0.4-2.6).

Several studies that demonstrated a positive association between long-haul travel and first events of venous thrombosis have shown a dose-response relation with regard to increasing duration of travel and number of travels. In a large meta-analysis a dose-response relationship was found with a 20% higher risk for venous thrombosis for each 2-hour increase in travel duration.[2] Kuipers et al. have shown that the risk of a first event increases with exposure to more flights in a short time-frame and with increasing duration of flights.[15] A previous study has shown similarly increased risks of a first event after flying or traveling by car, bus or train.[16] For a first venous thrombotic event several studies have reported an association between both work- and computer-related seated immobility.[3,17-19] A severe case of a first venous thrombotic event after periods of prolonged sitting at a computer has even led to the proposal of the term ‘eThrombosis; the 21st century variant of venous thromboembolism associated with immobility’.[18] The association between the use of a wheelchair, use of prophylactic anticoagulation and venous thrombosis has received little attention in the literature. However, a study by Arpaia and colleagues reported a frequency of asymptomatic DVT of over 40% in patients with advanced multiple sclerosis admitted to a neurology center, who were either wheelchair-bound or bedridden.[20] Currently, the ACCP guidelines recommend against the routine use of thromboprophylaxis in chronically immobilized patients who either reside at home or at a nursing home.[21]

Although previous studies on the relation between seated immobility, such as during travel or work, and first venous thrombosis have shown moderately strong associations, we did not find such an association between immobility and recurrences. A factor such as prolonged immobility, leading to stasis of blood in the venous system, which is strongly associated with first venous thrombotic events, could be expected to be a risk factor for recurrences as well. We cannot fully exclude the possibility of an increased recurrence risk during periods of seated immobility. An explanation for our null findings with regard to long-haul travel could be the large proportion of controls...
who undertook long-haul travel. The frequency of long-haul air travel >4 hrs over three months was 17% in our control participants. Controls were asked to report on long-haul travel during a random three-month exposure period over the past few years. Perhaps they did not remember the exact date of travel, and responded ‘yes’ to the question while their actual date of travel was just outside the three months exposure period. This would result in an overestimation of number of travels in controls. However, in a study by Martinielli et al frequencies of long-haul flights of >8hrs and of flights of any duration were approximately 6% and 23%, respectively, over a three months period. [22] Our frequency of 17% for long-haul flights of >4hrs, lies in between these numbers. Another explanation may be that we may not have been able to correct for all potential confounding factors. Probably, patients who are able to travel have an overall better health status than patients who do not travel. We tried to correct for this by adjusting for comorbidities at baseline (at time of the first thrombotic event). However, we may not have had sufficient information on general health throughout the follow-up period. Such a ‘healthy traveller effect’ has been described before in a study on the association between air travel and first thrombotic events.[23] Another explanation for our null findings for both long-haul travel, seated work and confinement to a wheelchair is that we have not been able to correct for other prophylactic measures taken by patients themselves, such as compression stockings, or exercise.

In summary, in a large follow-up study we studied the association between seated immobility and recurrent venous thrombosis. For several exposure categories, like prolonged travel, seated work or confinement to a wheelchair, we did not find an association with recurrences. For participants with long-haul air travel >12 hours the risk of recurrent venous thrombosis may be increased. We cannot make a definite conclusion as to whether preventive measures, like prophylactic anticoagulant treatment, exercise or stockings during periods of seated immobility, would be beneficial in patients with a history of venous thrombosis. Randomized clinical trials are needed to answer this question.

Reference List
1 Simpson K. Shelter deaths from pulmonary embolism. Lancet 1940;2:744.


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**Chapter 9**

Risk of first and recurrent venous thrombosis in individuals treated with antibiotics: Results from the MEGA study

Jasmijn F. Timp, Suzanne C. Cannegieter, Vladimir Y.I.G.V. Tichelaar, Sigrid K. Braekkan, Frits R. Rosendaal, Saskia le Cessie, Willem M. LIjfering

*Submitted for publication*