The handle http://hdl.handle.net/1887/39596 holds various files of this Leiden University dissertation.

**Author:** Timp, J.F.
**Title:** Risk factors and predictors for recurrent venous thrombosis : building blocks for a prognostic model
**Issue Date:** 2016-05-12


---

**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*
Abstract

Background
Previous studies have suggested a role for transient infections in the etiology of venous thrombosis (VT). We aimed to study whether individuals who receive antibiotic treatment (as a proxy for infections) have an increased risk of first or recurrent VT and what the joint effect is of antibiotics and genetic thrombophilia.

Methods and Results
4731 patients with a first VT from 1999-2004 were included in the MEGA-study and followed for a median of 5.9 years for recurrence (1999-2010 MEGA follow-up study). Information on antibiotic use was obtained via linkage to SFK-data (Dutch Foundation for Pharmaceutical Statistics). We used the self-controlled case-series method to study the risk of first VT during antibiotic prescriptions. VT, either PE or DVT, might at first sight be misdiagnosed as an infection. Therefore, patients for whom misclassification certainly played a role were excluded and we stratified for types of antibiotics for which misclassification is unlikely. 2547 VT patients could be individually linked to SFK-data, in whom 114 first events occurred during antibiotic use. After exclusion of patients who were misclassified we found a five-fold increased risk of first VT during antibiotic treatment: (incidence-rate-ratio [IRR] 5.0; 95%CI, 4.0-6.1). The IRR of DVT in patients receiving antibiotics for urinary tract infections (no misclassification) was 3.2 (95%CI, 1.9-5.6). By means of time-dependent Cox-regression, with correction for age and sex, antibiotic use was associated with a 2.0-fold (95%CI, 1.1-4.0) increased risk of recurrent VT, compared with no use. A joint risk of about 9 was found for antibiotic use and genetic thrombophilia (factor V Leiden or prothrombin G20210A mutation).

Conclusion
Individuals who receive antibiotics have a two to three-fold increased risk of a first VT or a recurrent VT during their antibiotic use, with highest risks during the first week of use.

Introduction
Venous thrombosis, defined as deep vein thrombosis (DVT) of the leg or pulmonary embolism (PE), is a major cause of mortality and morbidity. The incidence of venous thrombosis in the population is 1-2 per 1000 individuals per year[1], and the cumulative incidence of recurrent venous thrombosis within five years after a first event is 20-25%. [2-4] In about half of the patients with venous thrombosis no provoking risk factor can be identified. This is clinically important, as such patients are considered candidates for long term anticoagulant treatment.[5]

In 2006, Smeeth and colleagues observed an increased risk of venous thrombosis in patients who had a transient respiratory or urinary tract infection. The risk was highest in the first three months after diagnosis of an infection.[6] Also, as many as 36% of patients with acute venous thrombosis report, when asked, symptoms or signs of a transient infectious or inflammatory disease during the four weeks prior to presentation.[7] This adds credence to the suggestion that transient infectious diseases are associated with an increased risk of venous thrombosis. Nevertheless, infectious diseases are currently not considered as a provoking factor for venous thrombosis.[5] Moreover, the influence of infection on risk of recurrence has only received anecdotal attention in the literature and little formal study.[8] The mechanism that underlies the association has only been obtained in patients with sepsis[9], or in laboratory studies. [10]

We aimed to study whether individuals who receive antibiotic treatment (as a proxy for infection), have an increased risk of first and recurrent venous thrombosis. Additionally, we aimed to study whether the risk of venous thrombosis during antibiotic use is further increased in individuals with genetic thrombophilia. For this purpose we used three different study designs; a self-controlled case series design, a prospective follow-up design and a case-only analysis.
Methods

Patients
Consecutive patients aged 18 to 70 years with a first DVT or PE were included in the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study. Details of the MEGA study have been described previously. In short, 4956 patients were recruited in the period between February 1999 to September 2004.

Of the patients included, 225 did not consent to participate in a follow-up study on recurrent venous thrombosis. Therefore, 4731 patients were followed from their first venous thrombotic event until 2008-2010 when they completed a questionnaire on recurrent venous thrombotic events. This study has been approved by the Medical Ethics Committee of the Leiden University Medical Center, and all patients gave written informed consent.

Outcome classification first venous thrombosis
Patients with a first objectively identified DVT of the leg or a first PE were identified at six anticoagulation clinics in the Netherlands. The anticoagulation clinics monitor the anticoagulant therapy of all patients in a well-defined geographical area, which allowed the identification of consecutive and unselected patients with venous thrombosis. Unprovoked venous thrombosis was defined as venous thrombosis without surgery, trauma, plaster cast, pregnancy or immobilization in the first three months before the event, prolonged travel in the first two months before the event, active malignancies in the first five years before the event or hormone use (oral contraceptives or hormone replacement therapy) at the time of the event. Patients who had one or more of these risk factors at time of their thrombotic event were classified as having had a provoked venous thrombosis.

Outcome classification recurrent venous thrombosis
During the same period when patients were asked to self-report on any recurrent thrombotic events during follow-up, information about recurrences was additionally retrieved from the anticoagulation clinics and from hospital discharge letters. Furthermore, between 2007 and 2009 the vital status of all patients was acquired from the central Dutch population register. For the patients who died, the cause of death (ICD-10-CM encoded) was obtained from the national register of death certificates at the Central Bureau of Statistics. Deaths due to recurrent venous thrombosis were counted as fatal recurrent events. Information from the anticoagulation clinics, hospital discharge letters, questionnaires filled in by the patients and death certificates was combined and based on this, recurrences were classified into certain and uncertain recurrences, following a decision rule as described previously.

Antibiotic exposure definition
Information on antibiotic use was obtained by linkage to the SFK register (the Dutch Foundation for Pharmaceutical Statistics). In the Netherlands, antibiotics are only available by prescription, and over 95% of the community pharmacies in the Netherlands are represented in this register. SFK contains 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 study could be individually linked with SFK. After linkage to the SFK register, all MEGA patients with one or more prescriptions of antibiotics in the period 1999-2009 were identified.

Clinically, an early presentation of PE may at first be misdiagnosed as an infection. Early symptoms of PE are sometimes mistaken for a respiratory tract infection and antibiotics are prescribed. This misclassification would lead to spurious associations between antibiotic use and PE. For DVT and infections of the skin of the leg the same may be true. We reduced this possibility of misclassification step by step. First, we excluded patients in whom it was likely that such misclassification had taken place, from information of discharge letters. Second, we performed a subgroup analysis involving patients with DVT only, PE only or PE with or without DVT as the pathophysiology of DVT might be different from that of PE and as misclassification (of for example an acute lung infection) is likely to be less for DVT than for PE. Furthermore, we stratified results for different types of antibiotics since misclassification will play a different role for different types of antibiotics. For example, we expect virtually no misclassification for antibiotics prescribed for urinary tract infections. We defined three main groups of antibiotics based on the condition for which these antibiotics are most often prescribed in the outpatient setting in the Netherlands: 1) penicillins, tetracyclines and macrolides (wide range of infections); 2) nitrofurane derivatives, sulphonamides and trimethoprim and quinolones (primarily urinary tract infections); 3) fluoxacillin (primarily skin infections).

Genetic thrombophilia testing
Venous blood was collected at least three months after discontinuation of anticoagulant therapy following the first event, or during anticoagulant treatment in patients who continued for more than one year. Blood was collected in trisodium citrate and processed within four hours. For logistic reasons this was done until June 2002. Patients who were unable or unwilling to provide blood samples or were recruited after June 1, 2002 were sent buccal swabs to collect DNA for genetic profiling and blood group determination. DNA from either buccal swab or blood samples was obtained by standard methods. Blood group was determined by a 5′nuclease assay (Taqman;Applied Biosystems, Foster City, California) using a standard PCR reaction mix
Chapter 9

This synergy index is the

Antibiotic use and recurrent venous thrombosis as compared with the baseline period. Subgroup analyses were performed in patients (with 95% confidence intervals [CIs]) for events occurring within the period of exposure in Figure 1. Conditional Poisson regression was used to estimate incidence rate ratios period (i.e., without exposure). This method and the time intervals used are illustrated considered exposed person-time. All other observation time was taken as the baseline use during the observation period from February 1999 to September 2004 (inclusion period for MEGA case-control study) were included in this analysis (n=1584).

We derived measures of the relative incidence of events during exposure to antibiotics as compared with all other observed time periods for each patient. The null hypothesis was that venous thrombotic event rates remain constant from day to day and are not affected by an acute exposure of antibiotic use. The period of exposure was defined as extending up to end of treatment with antibiotics. Additional analyses were performed in which only the first week after the prescription of an antibiotic was considered exposed person-time. All other observation time was taken as the baseline period (i.e., without exposure). This method and the time intervals used are illustrated in Figure 1. Conditional Poisson regression was used to estimate incidence rate ratios (with 95% confidence intervals [CIs]) for events occurring within the period of antibiotic exposure as compared with the baseline period. Subgroup analyses were performed in patients

Design and statistical analyses

Three designs were used to answer our research questions.

1) Antibiotic use and first venous thrombosis risk

We used the self-controlled case-series (SCCS) method to study whether patients who received antibiotic treatment have an increased risk of first venous thrombosis. The SCCS method relies on intra-person comparisons in a population of individuals who have had the outcome of interest, thereby eliminating fixed confounding.[17] Only those patients with a first venous thrombosis and at least one prescription of antibiotic use during the observation period from February 1999 to September 2004 (inclusion period for MEGA case-control study) were included in this analysis (n=1584).

We derived measures of the relative incidence of events during exposure to antibiotics as compared with all other observed time periods for each patient. The null hypothesis was that venous thrombotic event rates remain constant from day to day and are not affected by an acute exposure of antibiotic use. The period of exposure was defined as extending up to end of treatment with antibiotics. Additional analyses were performed in which only the first week after the prescription of an antibiotic was considered exposed person-time. All other observation time was taken as the baseline period (i.e., without exposure). This method and the time intervals used are illustrated in Figure 1. Conditional Poisson regression was used to estimate incidence rate ratios (with 95% confidence intervals [CIs]) for events occurring within the period of antibiotic exposure as compared with the baseline period. Subgroup analyses were performed in patients

2) Synergy between antibiotic use with genetic thrombophilia to venous thrombosis risk

The combination of genetic and environmental factors is often accountable for the development of venous thrombosis.[18] It is therefore likely that if infections increase the risk of venous thrombosis, the risk will be highest in combination with thrombophilic abnormalities such as factor V Leiden. We therefore assessed the extent of a joint effect on a multiplicative scale between antibiotic use and the presence of factor V Leiden, blood group non-O or prothrombin G20210A mutation to the risk for venous thrombosis in a case-only study.[19,20] In a case-only study one examines the association between an exposure and a genotype among case subjects only. The case-only study relies on the assumption that the two factors of interest are independently distributed in the general population which is a reasonable assumption for genetic risk factors and infectious diseases. Patients with first venous thrombosis were divided into those with a venous thrombotic event during a period of antibiotic use and patients who did not use antibiotics at the moment of the event. The odds ratios for genetic thrombophilia (i.e., factor V Leiden, the prothrombin mutation or blood group) then estimate the synergy index on the multiplicative scale.[20] This synergy index is the factor by which the odds ratios of genetic thrombophilia and antibiotic use have to be multiplied to obtain the joint odds ratio.

3) Antibiotic use and subsequent recurrent venous thrombosis risk

In a cohort study design we tested whether antibiotic use is associated with recurrent venous thrombosis. Duration of follow-up for recurrent venous thrombosis was estimated as the time at risk from the date of the index (first) thrombotic event to the end of follow-up. The end of follow-up was defined as the date of a recurrent event and in the absence of a recurrence, the date of filling in the follow-up questionnaire. If a patient did not fill in a questionnaire, they were censored at the last date we knew them to be recurrence free. This could be date of death (n=49), date of emigration (n=1), date of the last visit to the anticoagulation clinic (n=264) or the last moment known to be recurrence free from information of the MEGA case-control study (n=198). Details of assessment of end of follow-up have been described previously.[13] In the analyses we considered certain recurrent events only (n=367). Patients with uncertain recurrent events (n=120) were censored from this uncertain recurrent event 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 for periods with antibiotic treatment and periods without antibiotic treatment, without a wash-out period. This means that a patient with antibiotic use during follow-up contributes with one or several observation periods of exposed and non-exposed person-time. The association between antibiotic use and recurrent venous thrombosis was estimated

Figure 1. Risk periods in the self-controlled case series analysis

As shown in this example, the effect of each infectious stimulus was analyzed separately for the outcome of venous thrombosis. All individuals had at least one exposure to the stimulus (prescription of antibiotic), and had at least one venous thrombotic event. Risk periods were defined as total period of antibiotic drug use (not drawn to scale), which was further divided into the first week of use.

with either DVT only, PE only or PE with or without DVT and in patients with either a provoked or unprovoked first event. Additionally, incidence rate ratios were estimated for the three types of antibiotics.
by means of Cox regression analysis with antibiotic use entered as a time-varying variable. Hazard ratios with corresponding 95% confidence intervals were estimated and corrected for age and sex. Exposure to antibiotics was first set at the total period of antibiotic use by the patient and additionally set at the first week of antibiotic use. The rest of the time was set at non-exposed person-time.

All statistical analyses were performed using SPSS, version 20.0 (IBM Corp., Armonk, NY) and Stata, version 12 (Stata Corp., College Station, Texas).

Results

2547 patients could be linked to the SFK data register and were included for analyses. Characteristics of these patients at the first venous thrombotic event are shown in Table 1. Median age of the patients was 51 years and 1197 (47%) patients were men. Most first venous thrombotic events were deep vein thrombosis (59%) and most first events were provoked by a provoking risk factor (68%). Baseline characteristics did not differ between those who could and could not be linked to SFK (Table 1).

1) Antibiotic use and first venous thrombosis risk

1584 patients with a first venous thrombotic event had at least one prescription of antibiotics in the period from February 1999 to September 2004. These patients were included in the SCCS analysis. During the aggregated period of antibiotic use the risk of a first venous thrombotic event was five-fold increased (Incidence rate ratio (IRR) 5.1; 95%CI, 4.1-6.3) as compared with periods without antibiotic use (Table 2). During the first week of antibiotic use the IRR was 5.3 (95%CI, 4.2-6.6)).

Clinically, a presentation of PE, and to a lesser extent DVT, may at first be misdiagnosed as an infection. We tried to reduce misclassification step by step. We excluded 13 individuals in whom such misclassification certainly played a role, based

| Table 1. Clinical Characteristics* |
|-------------------------------|-------------------------------|-------------------------------|
|                               | Patients linked to SFK | Patients not linked to SFK | Total                      |
| N (%)                         | 2547 (54%)                | 2184 (46%)                  | 4731 (100%)                |
| Median age, years (range)     | 51 (18-70)                | 47 (18-70)                  | 50 (18-70)                 |
| Male sex, n (%)               | 1197 (47%)                | 967 (44%)                   | 2164 (46%)                 |
| DVT only, n (%)               | 1490 (59%)                | 1257 (58%)                  | 2747 (58%)                 |
| PE +/- DVT, n (%)             | 1057 (41%)                | 927 (42%)                   | 1984 (42%)                 |
| PE only, n (%)                | 826 (32%)                 | 723 (33%)                   | 1549 (33%)                 |
| Provoked†                     | 1732 (68%)                | 1565 (72%)                  | 3297 (70%)                 |
| Malignancy                    | 247 (14%)                 | 174 (11%)                   | 421 (13%)                  |
| Trauma/surgery/Immobilisation | 1033 (60%)                | 869 (56%)                   | 1902 (58%)                 |
| Plaster cast                  | 107 (6%)                  | 112 (7%)                    | 219 (7%)                   |
| Estrogen use (women)          | 663 (61%)                 | 687 (67%)                   | 1350 (64%)                 |
| Pregnancy/puerperium (women) | 86 (8%)                   | 87 (8%)                     | 173 (8%)                   |
| Travel >4 hours               | 367 (21%)                 | 350 (22%)                   | 717 (22%)                  |
| Unprovoked                    | 742 (29%)                 | 559 (26%)                   | 1301 (28%)                 |
| Factor V Leiden, n (%)        | 344 (14%)                 | 308 (14%)                   | 652 (14%)                  |
| Prothrombin G20210A, n (%)    | 112 (4%)                  | 106 (5%)                    | 218 (5%)                   |
| Blood group non-O, n (%)      | 1590 (62%)                | 1323 (61%)                  | 2913 (62%)                 |

* At time of first venous thrombotic event
† Data were missing for some patients in some subgroups
on information from discharge letters. When we excluded these patients, the overall risk of venous thrombosis was 4.5-fold increased during antibiotic use (IRR 4.5; 95%CI, 3.6-5.6). For DVT only, the IRR remained 3.2-fold increased (95% CI, 2.2-4.7) during antibiotic use. Incidence rate ratios for a first provoked venous thrombotic event were somewhat higher than for a first unprovoked thrombosis.

Incidence rate ratios for the three types of antibiotics are shown in Table 3. There were 1357 patients who had at least one prescription of antibiotics for a wide range of infections, 218 patients who had at least one prescription of antibiotics mainly used for skin infections and 622 patients had at least one prescription of antibiotics mainly used for urinary tract infections. The risk of venous thrombosis was almost five-fold increased (IRR 4.7; 95%CI, 3.6-6.1) for the first group of antibiotics with a substantial difference between DVT (IRR~3) and PE (IRR~7). For antibiotics used mainly for infections of the skin the risk of venous thrombosis was about four-fold (IRR 4.1; 95%CI, 1.7-10.0) increased, with roughly similar risks for DVT and PE. For antibiotics used mainly for urinary tract infections the risk of both DVT and PE was three-fold increased, with IRR’s of 3.2 (95%CI, 1.9-5.6) and 3.0 (95%CI, 1.3-6.8) for DVT and PE, respectively.

2) Synergy between antibiotic use with genetic thrombophilia

There were 114 patients with a first venous thrombotic event during a period of antibiotic use. Odds ratios, estimating the synergy indices for Factor V Leiden and prothrombin mutation, were both 1.0 (95%CI, 0.6-1.8) and 1.0 (95%CI, 0.4-2.5) respectively. This implies that the joint effect of both genetic factors and antibiotic use is equal to the product of the separate effects of both antibiotic use and the genetic factors (Table 4).[21] Given the effects of genetic variants and antibiotic use, this implies a high joint risk, which is about 9 for the joint presence of a genetic variant and antibiotics use. The synergy index for blood group non-O was somewhat lower (0.7; 95%CI, 0.5-1.1) and therefore the joint effect of both antibiotic use and blood group non-O does not become high.

3) Antibiotic use and subsequent recurrent venous thrombosis risk

Of 2547 patients included in this analysis 367 had a recurrent thrombosis, yielding an incidence rate of 29.1 /1000 person-years (95%CI, 26.3-32.3). During follow-up 1401 patients (55%) had at least one prescription of antibiotics. The incidence rate of recurrent venous thrombosis was 56.2/1000 person-years (95%CI, 29.2-108.0) during antibiotic use, while it was 28.8/1000 person-years (95%CI, 25.9-31.9) for periods without antibiotic use. The recurrence risk was two-fold increased during the use of antibiotics (HR 2.0; 95%CI, 1.1-4.0). During the first week of antibiotic use, the risk was 2.9-fold (95%CI, 1.4-6.1) increased.

### Table 2. Incidence rate ratios of first venous thrombosis during exposure to all types of antibiotics

<table>
<thead>
<tr>
<th>Patients</th>
<th>Total duration of antibiotic use</th>
<th>First week of antibiotic use</th>
<th>Baseline period</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients included</td>
<td>1357</td>
<td>4.7 (3.4-6.5)</td>
<td>2.9 (1.8-4.3)</td>
</tr>
<tr>
<td>of whom misclassification was certain, based on information from discharge letters, were excluded from these analyses.</td>
<td>1357</td>
<td>4.7 (3.4-6.5)</td>
<td>2.9 (1.8-4.3)</td>
</tr>
</tbody>
</table>

### Table 3. Incidence rate ratios of first venous thrombosis during exposure to different types of antibiotics

<table>
<thead>
<tr>
<th>Patients</th>
<th>Total duration of antibiotic use</th>
<th>First week of antibiotic use</th>
<th>Baseline period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins, tetracyclines, macrolides (antibiotics prescribed for a wide range of infections)</td>
<td>1357</td>
<td>4.7 (3.4-6.5)</td>
<td>2.9 (1.8-4.3)</td>
</tr>
<tr>
<td>Of whom misclassification was certain, based on information from discharge letters, were excluded from these analyses.</td>
<td>1357</td>
<td>4.7 (3.4-6.5)</td>
<td>2.9 (1.8-4.3)</td>
</tr>
</tbody>
</table>

### Table 4. Incidence rate ratios of first venous thrombosis during exposure to different types of antibiotics

<table>
<thead>
<tr>
<th>Patients</th>
<th>Total duration of antibiotic use</th>
<th>First week of antibiotic use</th>
<th>Baseline period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors V Leiden and prothrombin mutation</td>
<td>1357</td>
<td>4.7 (3.4-6.5)</td>
<td>2.9 (1.8-4.3)</td>
</tr>
<tr>
<td>Of whom misclassification was certain, based on information from discharge letters, were excluded from these analyses.</td>
<td>1357</td>
<td>4.7 (3.4-6.5)</td>
<td>2.9 (1.8-4.3)</td>
</tr>
</tbody>
</table>
Table 4. Multiplicative interaction between antibiotic use and genetic thrombophilia to venous thrombosis risk

<table>
<thead>
<tr>
<th>Genetic thrombophilia</th>
<th>Venous thrombosis during antibiotic use</th>
<th>Odds ratio for joint effect (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>+</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>84</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>+</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>95</td>
</tr>
<tr>
<td>Blood group non-O</td>
<td>+</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>35</td>
</tr>
</tbody>
</table>

*Per 1000 person-years
†Adjusted for age and sex

Table 5. Age and sex adjusted risk of recurrent venous thrombosis in risk periods after antibiotic use

<table>
<thead>
<tr>
<th>Observation years (N)</th>
<th>Recurrent events</th>
<th>Incidence rate* (95%CI)</th>
<th>Hazard ratio† (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total duration of antibiotic use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline period</td>
<td>12439 (2547)</td>
<td>358</td>
<td>28.8 (25.9-31.9)</td>
</tr>
<tr>
<td>Antibiotic use</td>
<td>160 (1401)</td>
<td>9</td>
<td>56.2 (29.2-108.0)</td>
</tr>
<tr>
<td>First week of antibiotic use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline period</td>
<td>12511 (2547)</td>
<td>360</td>
<td>28.8 (26.0-31.9)</td>
</tr>
<tr>
<td>Antibiotic use</td>
<td>89 (1401)</td>
<td>7</td>
<td>78.7 (37.5-165.0)</td>
</tr>
</tbody>
</table>

*Per 1000 person-years
†Adjusted for age and sex

Discussion

Summary of findings
We found an increased risk for both first and recurrent venous thrombosis during periods of antibiotic use. Both for first and recurrent venous thrombosis relative risks were highest during the first week of use.

Incidence rate ratios of a first venous thrombotic event ranged from three to seven. Since symptoms of a venous thrombotic event might mimic an infection, we took several steps to reduce misclassification. After exclusion of patients for whom misclassification was likely and including patients with DVT only (for which we expect less misclassification than in patients with PE) we still found a three-fold increased risk of venous thrombosis, indicating that our results are robust. For antibiotics prescribed mainly for urinary tract infection, for which we expect no misclassification, we found an increased risk of DVT of 3.2 (95%CI, 1.9-5.6) and an increased risk of PE of 3.3 (95%CI, 1.7-6.5). In addition, we found a synergy index of around 1 between antibiotic use and both factor V Leiden and the prothrombin mutation, which leads to high joint relative risks. This appeared not to be the case for blood group non-O. We found a two-fold increased recurrence risk for patients with a history of venous thrombosis using antibiotics as compared with those patients not using antibiotics.

Previous studies
In the last decade several studies have been published that investigated the risk of a first venous thrombotic event after infections and inflammatory diseases.[6, 7, 22-24] In a large register study from Denmark over 15 000 cases with venous thrombosis were matched to controls from the general population.[24] Within three months after a hospital diagnosed infection the risk of venous thrombosis was increased three-fold as compared with patients without infection (IRR 3.3; 95%CI, 2.9-3.8). The risk of venous thrombosis was almost three-fold increased after antibiotic treatment in the community (IRR 2.6; 95%CI, 2.5-2.8), with higher risks for antibiotics prescribed for both respiratory tract and skin or soft tissue infections than for antibiotics prescribed for urinary tract infections. The associations were strongest within the first two weeks and gradually declined thereafter. These results are quite similar to our findings. Ribeiro et al showed in the MEGA case-control study that self-reported pneumonia substantially increased the risk of venous thrombosis in the subsequent year (OR 4.8; 95%CI, 3.6-6.2) after adjustment for many confounding factors.[23] It was shown that the association could only partially be explained by a concurrent period of immobilization or lifestyle. In a large case-control study based on a general practice database from the UK 4.0% of DVT cases was reported to have a respiratory infection in the year before the index date as opposed to 2.3% in the controls.[22] An increased risk of DVT was found in the month following infection (OR 2.6; 95%CI, 1.6-4.3). In this study urinary tract infections were less strong risk factors for venous thrombosis than respiratory infections. There was only weak evidence for an association with subsequent DVT and no evidence of an
increased risk of PE following urinary tract infections. The authors suggest these latter findings might be explained by small numbers.

Misclassification of symptoms of either DVT or PE as an infection might have affected all of abovementioned studies. The study based on the UK general practice database[22] reduced possible misclassification by excluding patients with a respiratory infection in the month before PE. The other studies were not able to reduce misclassification. People with and without diagnosed infections probably are different in other aspects besides their infection, therefore comparison between individuals could be misleading and correction for potential confounders is crucial. In the large registry study from Denmark[24] correction for confounders affected results considerably and the covariate with the most influence was a measure of frailty or immobility. Although most of abovementioned studies corrected for many potential confounders, residual confounding remains possible. Smeeth and colleagues solved the part of the problem caused by intransient confounders by performing a self-controlled case study.[6] During the first week of a urinary tract infection the risk of both DVT and PE was increased two-fold. During the first week of a respiratory tract infection the risk of DVT was also increased two-fold (IRR 1.9; 95%CI, 1.5-2.4). Relative risks that we found are somewhat higher than the results from Smeeth (IRR ~3). This may be explained by the inclusion of objectively identified thrombotic events only, while events by Smeeth et al. came from an electronic database.

One previous study showed a moderately strong relation between inflammatory bowel disease and recurrent venous thrombosis[25] with a relative risk of 2.5 (95%CI, 1.4-4.2). This supports the hypothesis that infection/ chronic inflammation increases the risk of recurrent venous thrombosis as well.

Interpretation of our findings
Several explanations are possible for our findings of an increased risk of venous thrombosis during antibiotic use: 1) infections increase the risk of venous thrombosis through a systemic effect; 2) infections increase the risk of venous thrombosis through immobilisation/ bedrest; or 3) antibiotics have a direct effect on the risk of venous thrombosis. It has been described that oral application of some of the antibiotic drugs (i.e. macrolides, penicillins) can lead to overgrowth of Gram-negative bacteria in the gut.[26] This shift has been causally associated with entrance of Gram-negative bacteria into the bloodstream and ultimately increased circulatory levels of lipopolysaccharides (LPS) inducing a pro-coagulant state.[27-29] This could lead to the hypothesis that some antibiotics might contribute to the development of clinical venous thrombosis by changing the gut microbiome. However, we have seen increased risks of venous thrombosis for all types of antibiotics and side-effects are rarely a class-effect. Since we have seen increased thrombosis risks for all types of antibiotics, amongst others antibiotics prescribed for urinary tract infection, immobilisation as the explanation for the increased risks is also improbable. This suggests the first explanation might be the right one.

Limitations
Some potential limitations should be mentioned as well. First, an early presentation of PE might be misdiagnosed as a respiratory tract infection. For DVT and infections of the skin of the leg the same may be true. To reduce this possibility of misclassification, we excluded patients for whom we were sure that such misclassification took place, from information of discharge letters. Furthermore, such misclassification will be unlikely for urinary tract infections and DVT and PE, and for skin infections and PE. During treatment for urinary tract infections the risk of both DVT only and PE only was still 3.2- and 3.3-fold increased in our study. In addition, the risk of PE during treatment for skin infections was 3.2-fold increased. Some misclassification of infectious diseases might have occurred since our definition of an infection was solely based on the antibiotic class that was prescribed. Second, our results may not be generalizable to all types of infection since we did not have data on antibiotic use during hospital stays and since we used antibiotic use as a proxy for infectious diseases, we do not have data on viral infections and the risk of venous thrombosis. Third, as cancer might increase the risk of both infections and venous thrombosis a diagnosis of cancer could account for some of the associations we observed. However, the results for patients with an unprovoked first venous thrombosis (in whom no patients with cancer were present) were in the same line as for total venous thrombosis; i.e. an increased risk of venous thrombosis at time of antibiotic use, especially in the first week after the start of antibiotic use. Therefore, cancer diagnoses do not explain our findings. Fourth, although we have used the self-controlled case series method to study the association between antibiotic use and first venous thrombotic events, in which intransient confounders do not play a role, residual transient confounders might account for some of the association we observed. Fifth,
in our analyses on recurrent venous thrombosis we were, because of small numbers, unable to correct for additional variables besides age and sex and residual confounding factors might play a role in the association we found there. Additionally, because of small numbers, we were not able to study different types of venous thrombosis and/or different types of antibiotics, so that we can not exclude misclassification of events. For the same reason we were not able to study the combined effect of antibiotic use and genetic thrombophilia on the risk of recurrences.

Conclusion
To conclude, individuals who receive antibiotics (which we used as a proxy for infection), have an approximately three-fold increased risk of a first venous thrombotic event and a two-fold increased risk of recurrent venous thrombosis. Our results should increase awareness of the risk of venous thrombosis in patients with infections, in treating physicians in and out of hospital. Furthermore, accuracy of treatment strategies might be improved by a revision of the current definition of ‘unprovoked’ events. Future clinical trials may be required to determine whether patients with prior venous thrombosis who use antibiotics should or should not receive thromboprophylaxis to decrease their risk of recurrence.

Reference List


