Infections and inflammatory diseases as risk factors for venous thrombosis

A systematic review

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Summary

Inflammation and venous thrombosis are intertwined. Only in the recent 15 years clinical epidemiological studies have focussed on inflammatory or infectious diseases as risk factors for venous thrombosis. Although a few reviews and many case reports or studies on these topic has been written, a review reporting relative or absolute risks for venous thrombosis has not been published yet. We performed a systematic review using Medline, Pubmed and Embase and found 31 eligible articles. Inflammatory bowel disease, ANCA-associated vasculitis, infections in general and more specifically, human immunodeficiency virus, pneumonia and urinary tract infections are associated with an increased risk of venous thrombosis.

Keywords

Venous thrombosis, inflammatory diseases, infections, risk factors

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Introduction

Venous thrombosis is a multicausal disease (1). Many risk factors have been established including acquired and environmental causes (2). One of these is inflammation. That inflammation and coagulation are closely related to each other was found by two early studies performed in the 1990s (3, 4). In the same period Tabib et al. described as one of the first the association between an infectious agent and an increased risk of (arterial) thrombosis in humans. At autopsy, they reported a strikingly high prevalence of coronary lesions in eight young (23–32 years old) patients who died of the human immunodeficiency virus (HIV) (5). It took a further 10 years before an annual incidence or absolute risk of venous thrombosis in HIV-infected patients was reported. Cytomegalovirus was also described as a potential risk factor for venous thrombosis, as demonstrated by many case-reports on this topic (see the review by Abgueguen et al. in 2003 [6]). Thus, only in the last 15 years infectious (and inflammatory) diseases have been linked to venous thrombosis in clinical studies in humans. However, epidemiological reviews of inflammatory and infectious diseases as risk factors for venous thrombosis are still lacking.

The purpose of this review is to provide an overview of studies, performed in the last 15 years, in which infectious and inflammatory diseases were identified as risk factors for venous thrombosis.

Methods

We performed a systematic review of studies reporting on infectious or inflammatory risk factors for venous thrombosis. Papers were eligible if they presented original research in adults, and reported a relative risk or an absolute risk of venous thrombosis, or if these measures could be calculated. Case series or case reports were not included in this study. Studies had to have been published in peer-reviewed journals.

We started searching Pubmed using the following search terms: ((("Pulmonary Embolism"[Mesh]) OR pulmonary embolism) OR (("Venous Thrombosis"[Mesh]) OR venous thromboembolism)) AND ("Risk"[Mesh]) AND ((("Inflammation"[Mesh]) OR inflammation* OR inflammatory diseases) OR ("Virus Diseases"[Mesh] OR viral infection*) OR ("Bacterial Infections and Mycoses"[Mesh])). Embase and Medline were also searched using the following search term: 'thrombosis'/exp AND ('deep vein thrombosis'/de OR 'lung embolism'/de OR 'thromboembolism'/de OR 'vein thrombosis'/de OR 'venous thromboembolism'/de) AND 'risk'/exp AND factor AND ('infection'/exp AND ('bacterial infection'/de OR 'infection'/de OR 'virus infection'/de) OR ('inflammation'/exp AND 'disease'/exp)). Limits were: human, and time ranging from 1996 till 2011 (1st of June). This search revealed 1808 hits, yielding 18 eligible articles for the study (▶Fig. 1) (denoted 1 in ▶Table 1). Also, by checking the bibli-

ographies of these articles, we identified 10 other relevant articles (1R in ▶Table 1).

Consequently, a second search was performed, using similar limits as the first one. The search phrase we used was: ("*" [Mesh]) AND (("Pulmonary Embolism"[Mesh]) OR (pulmonary embolism) OR ("Venous Thrombosis"[Mesh]) OR (venous thromboembolism)) AND ("Risk"[Mesh]), or the equivalent search phrase used in Embase / Medline, in which the "*" was separately replaced by one of the risk factors identified by the first search. In this way, we identified three additional articles (denoted by "2" in ▶Table 1). When performing this search for tuberculosis, psoriasis and Behçet's disease, no eligible studies were found.

We assessed the quality of the studies reviewed by using the Newcastle-Ottawa Quality Assessment Scale for cohort and case-control studies (7). A maximum of nine points can be assigned for the following items. For case-control studies: case and control definition (1 point each), the representativeness of the cases and the selection of the controls (1 point each), ascertainment of exposure and whether this was applied for cases and controls (1 point each), and non-response rate (1 point). For cohort-studies: the representativeness of the exposed cohort, the selection of the non-exposed cohort, ascertainment of the exposure and demonstration that the outcome of interest was not present at the start of the study, all 1 point each. Assessment of outcome, length of follow-up and the adequacy of the follow-up (drop-out rate) gave also 1 point each. Finally, for both kinds of study-designs a maximum of two points could be assigned for comparability of cohorts or cases and controls (1 point for controlling or matching for the main confounder, and another point when a second or more factors were controlled for). In this way, a maximum of nine points can be achieved. Studies with 7–9 points were judged of good quality, studies with 4–6 points were judged of average quality and those with <4 points were judged of poor quality.

Results

Inflammatory diseases and venous thrombosis

Rheumatoid arthritis

Three retrospective cohort studies compared the prevalence of venous thrombosis in patients with rheumatoid arthritis (RA) to that in controls. In 1999 Seriolo et al. described a cohort of 184 female patients and 74 female age-matched controls (8). In patients with RA, 25 (14%) ever had an event of venous thrombosis while only three of the controls (4%) had experienced such an event during their lifetime. We calculated an odds ratio (OR) of 3.7 for the risk of venous thrombosis in patients with RA. However, the quality of this study was low (▶Table 1).

In 2004 Miehsler et al. performed a cohort study of average quality (▶Table 1) with an age- and sex-matched control group to identify the risk of RA, inflammatory bowel disease and coeliac disease for venous thrombosis (9). In 243 patients with RA they did

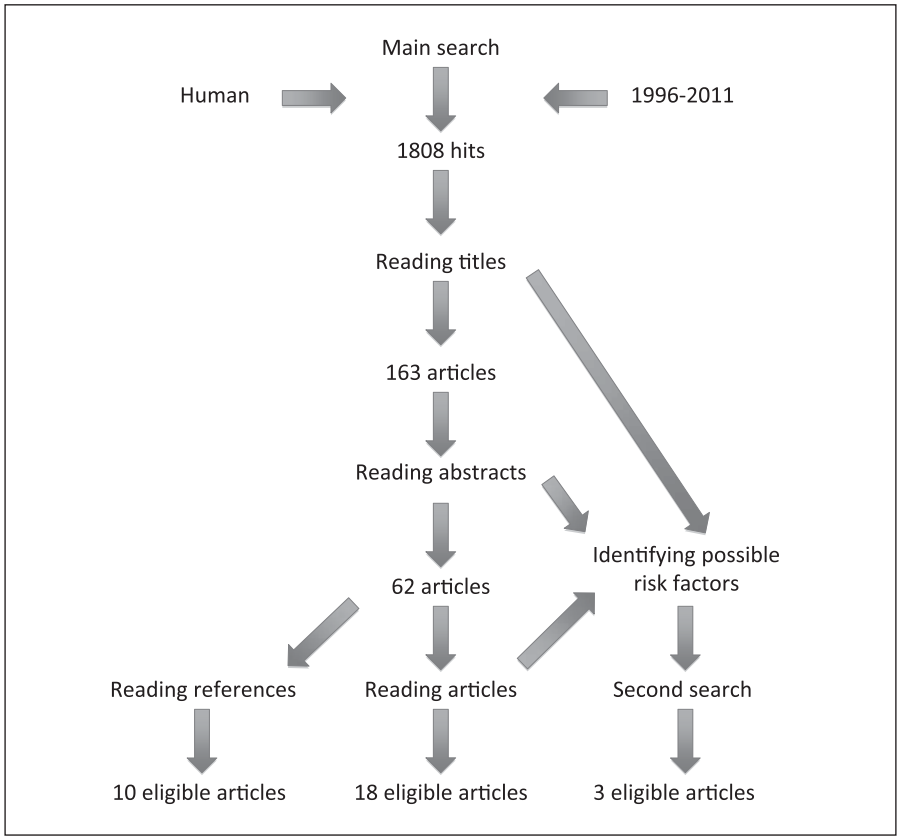

Figure 1: Search strategy.

not find an increased risk for venous thrombosis (n=5) (OR 0.7; 95% confidence interval [CI], 0.2–2.9).

In 2004, Alikahn et al. performed a post-hoc analysis of the Medenox study, a randomised controlled double-blind trial, comparing two doses of low-molecular-weight heparin to placebo in acute ill, immobilised, general medical patients. They found in the entire cohort (n=866) a relative risk of 1.64 (95%CI, 0.96–2.69) of venous thrombosis for RA. However, after multivariate analysis this association disappeared. Results were not different in the high risk subgroup of not-effective treated patients (n=575) (10).

Matta et al. found in 2009 a relative risk of 1.99 (95%CI, 1.98–2.00) for venous thrombosis related to RA, in a study of average quality (▶Table 1) (11). They retrospectively examined almost 895 million patient discharges from hospital, of which about 5 million had RA, by using the National Hospital Discharge Survey. They reported that 0.85% of RA patients had ever had a pulmonary embolism (PE), compared to 0.38% in non-RA patients (relative risk [RR] 2.25; 95%CI, 2.23–2.27). For deep-vein thrombosis (DVT) these numbers were 1.64% and 0.86%, respectively (RR 1.90; 95%CI, 1.89–1.92). Based on these data, we might conclude that RA increases the risk of venous thrombosis at least two-fold, but the quality of these studies is not convincing.

Inflammatory bowel disease

Five cohort studies and one case-control study were identified reporting an association between inflammatory bowel disease (IBD) and venous thrombosis, one of which had a prospective and four a retrospective design. Four were of good quality and one of average quality (▶Table 1). In 2001, Bernstein et al. reported an annual incidence of 4.98 and 4.17 per 1,000 person-years (py) of venous thrombosis for patients with ulcerative colitis and Crohn's disease, respectively (12). Theirs was a retrospective cohort study of over 6,000 patients with IBD with 20,000 py follow-up. Patients were matched to controls from the community 1:10 by age, sex, postal area and year of entry in the administrative database. They concluded that patients with IBD had a three- to four-fold increased risk of venous thrombosis compared to the normal population.

Miehsler et al. (2004) found in a retrospective cohort study with an age and sex matched control group an increased risk of venous thrombosis for patients with IBD (OR 3.6; 95%CI, 1.7–7.8), with a prevalence of 6.15% in the IBD patients and 1.62% in the controls (9).

Huerta et al. described many risk factors for venous thrombosis in a nested case-control study (6,550 cases and 10,000 controls) based on the General Practice Research Database (13). Patients were age, sex and calendar year matched. They reported a multi-adjusted OR of 1.84 (95%CI, 1.29–2.63) for IBD.

More recently, Nguyen et al. (2008) showed a 1.85-fold increased risk of venous thrombosis for ulcerative colitis (95%CI, 1.70–2.01) and a 1.48-fold increased risk for Crohn's disease (95%CI, 1.35–1.62) (14). Data were retrieved from a discharge database (Nationwide Inpatient Sample). This retrospective cohort consisted of hospitalised IBD-patients and was compared to a 1% random sample of non-IBD, non-primary diagnosis of venous thromboembolism (VTE), hospital discharges.

In about 13,000 patients with IBD, prospectively recorded in the General Practice Research Database (UK), Grainge et al. found in 2010 a 3.4-fold (95%CI, 2.7–4.3) increased risk of venous thrombosis compared to 1:5 age, sex and general practitioner matched controls (15). Flare-ups of the IBD increased this risk further, up to 8.4-fold (95%CI, 5.5–12.8). The risk of venous thrombosis was even higher when the flare-up was experienced being ambulatory (hazard ratio [HR] 15.8; 95%CI, 9.8–25.5). In the end, patients in remission of IBD kept an elevated risk of venous thrombosis compared to non-IBD controls (HR 2.1; 95%CI, 1.6–2.9). Overall, an annual incidence of 2.6 per 1,000 py was found, increasing to 9.0 per 1,000 py during a flare-up (hospitalised and ambulatory patients together).

In 2010, Novacek et al. prospectively identified 86 IBD-patients with a first unprovoked VTE, and compared them to 1,255 non-IBD patients with a first unprovoked VTE (16). After cessation of anticoagulation therapy, median follow-up was 41.8 months (interquartile range, 9.7–86.8 months). Recurrent VTE was detected in 27 of IBD-patients (31.4%), compared to 204 of 1,255 in non-IBD patients (16.3%). After adjustment for age, sex, factor V Leiden mutation, prothrombin mutation, factor VIII level, duration of anticoagulation and body mass index, a relative risk of 2.5 (95%CI, 1.4–4.2) for recurrent VTE persisted in IBD-patients. Annual incidence of recurrent VTE was 67.3 per 1,000 py in IBD patients with first unprovoked venous thrombosis.

Overall, there is good evidence that patients with Crohn's disease or ulcerative colitis have a two- to four-fold increased risk of (recurrent) venous thrombosis, with a peak incidence of venous thrombosis when having a flare up of the disease.

Coeliac disease

Only two retrospective cohort studies were found on this topic. Miehsler et al. (9) included 207 consecutive patients and 207 age- and sex-matched controls. Only 1% of patients with coeliac disease ever had venous thrombosis, compared to 1.9% of the controls. An adjusted odds ratio of 0.4 (95%CI, 0.1–2.5) was reported. The quality of this study was average (▶Table 1).

In 2007 Ludvigsson et al (17) identified 406 patients (2.6%) and 1105 controls (1.4%) with venous thrombosis out of 14,207 patients with coeliac disease and 69,048 controls (matched by age, sex, county and calendar year of entry in the database) using the National Inpatient Register and the National Total Population Register. They calculated a HR of 1.86 (95%CI, 1.54–2.24) as an estimate of the RR of venous thrombosis for coeliac disease. The incidence of venous thrombosis in these patients was 1.02 per 1,000 py.

The quality of the last study was good, and included a larger number of subjects, of which the controls were population-based. Therefore, we might conclude that coeliac disease has the potential to increase the risk of venous thrombosis about two-fold.

Table 1: Recent studies on inflammatory and infectious diseases and the risk of venous thrombosis.

First author	Year	Relative risk	95% CI	Absolute risk [1]	Comment	Quality [2]	Search	N (case/control)	Study design
Rheumatoid arthritis									
Seriolo	1999	3.7	n/a	n/a	females only, RR calculated for this review	2	1R	258	RC with MCG
Miehsler	2004	0.7	0.2–2.9	n/a		5	1	1,686	RC with MCG
Alikhan	2004	1.61	0.96–2.69	n/a	univariate only	9	1	866	PC
Matta	2009	1.99	1.98–2.00	n/a		4	2	895,873,000	RC
Inflammatory bowel disease									
Bernstein	2001	3.04 / 4.10	2.43–3.81 / 3.21–5.25	4.98 / 4.17	UC / CD	8	1R	60,819	RC with MCG
Miehsler	2004	3.6	1.7–7.8	n/a		5	1	1,686	RC with MCG
Huerta	2007	1.84	1.29–2.63	n/a		7	1R	6,550 / 10,000	NCC
Nguyen	2008	1.85 / 1.48	1.70–2.01 / 1.35–1.62	n/a	UC / CD	7	1R	639,545	RC
Grainge	2010	3.4 / 8.4	2.7–4.3 / 5.5–12.8	2.6 / 9.0	overall / flare-up	9	1	85,428	RC with MCG
Novacek	2010	2.5	1.4–4.2	67.3	risk of recurrent venous thrombosis	8	1	1,341	PC with MCG
Coeliac disease									
Miehsler	2004	0.4	0.1–2.5	n/a		5	1	1,686	RC
Ludvigsson	2007	1.86	1.54–2.24	1.02		8	1	83,255	RC with MCG
Sarcoidosis									
Crawshaw	2011	1.87	0.96–3.27	n/a		6	1	52,7109	RC with MCG
ANCA-associated vasculitis									
Merkel	2005	n/a	n/a	70	active disease in 81%	6	1R	167	PC
Weidner	2006	n/a	n/a	43	patients with active disease	5	1R	105	RC
Stassen	2008	n/a	n/a	18 / 67	overall / active disease	7	1	198	RC
Human immunodeficiency virus									
Sullivan	2000	n/a	n/a	6.2 / 1.3	AIDS yes / no	7	1R	42,935	RC
Fultz	2004	1.39 / 1.33	1.26–1.52 / 1.24–1.43	11.3 / 5.7	pre-1996 / post-1996	6	1	75,070	RC with MCG
Lijfering	2006	n/a	n/a	7.2 / 5.8	cART yes / no	7	1R	519	RC
Matta	2008	1.21	1.20–1.22	n/a		5	1	465,395,000	RC
Malek	2010	1.4	1.37–1.43	n/a		5	1	293,104,652	RC
Cytomegalovirus									
Lijfering	2008	1.7 / 2.0 [3]	0.6–4.7 / 0.9–5.2	8.1 / 9.8	seroconversion / -positive	8	2	52 / 554	[4] NCC
Atzmony	2010	16.9	2.46–116.12	n/a		7	2	280	RC with MCG
Tichelaar	2011	n/a	n/a	n/a	5 cases, 0 controls with CMV	7	1	258 / 139	CC
Influenza									
van Wissen	2007	0.22	0.03–1.72	n/a	Influenza A only	5	1R	102 / 395	NCC
Zhu	2009	0.74	0.57–0.97	n/a	risk of VT after influenza vaccination	5	1	727 / 727	CC
Chlamydia									
Lozinguez	2000	6.7	3.6–12.2	n/a		6	1	176 / 197	CC
Koster	2000	1.1	0.9–1.4	n/a		8	1	474 / 474	CC

Table 1: Continued

First author	Year	Relative risk	95% CI	Absolute risk [1]	Comment	Quality [2]	Search	N (case/control)	Study design
Pneumonia									
Smeeth	2006	1.91	1.49–2.44	n/a	risk of DVT for 2 weeks after infection	8	1	7,278	SCC
Gangireddy	2007	2.7	2.1–3.5	n/a		7	1	805 / 117,453	[5] NCC
Urinary tract infection									
Smeeth	2006	2.10 / 2.11	1.56–2.82 / 1.38–3.23	n/a	risk of DVT / PE for 2 weeks after infection	8	1	7,278 / 3,755	SCC
Gangireddy	2007	1.8	1.3–2.5	n/a		7	1	805 / 117,453	[5] NCC
Infections not otherwise specified									
Samama	2000	1.95	1.31–2.92	n/a		6	1R	494 / 494	CC
Alikhan	2004	1.74	1.12–2.75	n/a		9	1	866	PC
Cimminiello	2010	1.86	1.16–2.97	n/a		7	1	1,624 / 370,376	NCC
Tichelaar	2010	2.5	1.4–4.8	n/a		8	1	123 / 115	CC

RC – retrospective cohort, MCG – matched control group, PC – prospective cohort, CC – case-control study, SCC – self-controlled case series. CSD – cross-sectional design, NCC – nested case-control study, N/a – not available, UC – ulcerative colitis, CD – Crohn's disease, DVT – deep-vein thrombosis. PE – pulmonary embolism, AIDS – acquired immuno deficiency syndrome, cART – combined anti-retroviral therapy, VT – venous thrombosis, CI - confidence interval. [1]Cases per 1,000 person-years. [2]Number of points out of a maximum of 9, according to the Newcastle-Ottawa Quality Assessment scale. [3]Compared to seronegative patients. [4]In a cohort of renal transplant patients. [5]In a cohort of 30-days post-operative patients.

Sarcoidosis

We found one recent study by Crawshaw et al. (2011) who found an increased risk of venous thrombosis for sarcoidosis (18). In this study of average quality, they retrospectively analysed 52,7109 patients from the Oxford Record Linkage Study, a hospital discharge database with data from 1963 till 1998. Of these, 1,002 had sarcoidosis, which were matched with subjects without sarcoidosis, for age, sex, district and year of admission. A rate ratio of 1.87 (95%CI, 0.96–3.27) was calculated as an estimate of the relative risk of venous thrombosis for sarcoidosis.

Although a large number of patients was included in this study of average quality, the point estimate of the RR did not reach statistical significance. We therefore cannot conclude that sarcoidosis indeed increases the risk of venous thrombosis based on these data only.

ANCA-associated vasculitis

Finally, we found one study of good quality describing that ANCA-associated vasculitis increased the risk of venous thrombosis about 18 times (compared to the general population), and even more when the disease is active or a relapse is present (absolute risk 67 per 1,000 py) (19). This was based on an analysis of a retrospective cohort of 198 patients with ANCA-associated vasculitis from one hospital. Median follow-up was 6.1 years (range 0.2–17.6). Another retrospective study of average quality was performed by Weidner et al. in 2006 (20). They included 105 patients treated for a newly diagnosed ANCA-associated vasculitis between 1986 and 2001, from the Department of Nephrology and Hypertension. The incidence of venous thrombosis was 43 per 1,000 py, within a total time of follow-up of 367.5 py. All patients had active disease at the moment of venous thrombosis. A third study of average quality from 2005 by Merkel et al., reported an incidence rate of first venous thrombosis of 70 per 1,000 py in 167 patients with Wegener's granulomatosis, in 228 py of follow-up (21). Eighty-one patients had active disease at the moment of venous thrombosis. Initially, the study was designed as a randomised controlled trial on the efficacy of etanercept in addition to conventional therapy.

Overall, there is evidence that ANCA-associated vasculitis is associated with an increased risk of venous thrombosis, especially when patients have active or newly diagnosed disease. This risk might be as high as 70 events per 1,000 py. However, one has to keep in mind that these studies were relative small, had a retrospective design, lacked a control group or non-exposed cohort, and that we have no information on the relative risk of venous thrombosis.

Infectious diseases associated with venous thrombosis

Human immunodeficiency virus

One of the first infectious agents associated with an increased risk of venous thrombosis was the human immunodeficiency virus (HIV) (5). However, it took till the year 2000 before an incidence of venous thrombosis was reported. We found five retrospective cohort studies of average to good quality (▶Table 1) reporting annual incidences or relative risks. Sullivan et al. studied 42,935 HIV-infected patients and found an incidence of 1.3 per 1,000 py of ve-

nous thrombosis, increasing to 6.2 per 1,000 py in patients with full-blown acquired immunodeficiency syndrome (AIDS) (mean observation years 2.4, from 1990 till 1998) (22).

Four years later, Fultz et al. analysed 75,070 veterans in the US (23). The authors divided the cohort into two groups, one before and one after 1996 (mean ± SD age 44 ± 9 and 48 ± 11 years, respectively), because in this year combination antiretroviral therapy (cART) was introduced. A RR of 1.39 (95%CI, 1.26–1.52) and 1.33 (95%CI, 1.24–1.43) of HIV infection for venous thrombosis was established before and after 1996, respectively. The incidence of venous thrombosis in HIV-infected veterans was 11.3 per 1,000 py in 1996 and 5.3 per 1,000 py after 1996. Another interesting observation in this study was that the incidence of venous thrombosis also declined in the control group but still remained elevated compared to the general population as reported by Naess et al. (24), from 7.6 to 3.3 per 1,000 py after 1996. This is probably caused by the higher proportion of Afro-Americans in this cohort (49% in the pre-1996 cohort and 35% in the post-1996 cohort), which appear to have a higher baseline risk of venous thrombosis compared to Caucasians (25, 26).

In 2006, Lijfering et al. found an incidence of venous thrombosis of 5.8 per 1,000 py when patients were not on cART, and 7.2 per 1,000 py for patients on cART, in 519 consecutive HIV infected patients, registered in the outpatient clinic from January 1989 till December 2004 (27). Median time of onset of venous thrombosis after HIV diagnosis was one year. However, instead of cART, this association may reflect the underlying severity of HIV-disease.

Matta et al. used the National Hospital Discharge Survey to extract data from 1990 till 2005 about venous thrombosis in patients with an ICD9-CM code for HIV infection (28). They found almost 2.5 million patients with HIV and about 463 million patients without HIV being hospitalised between 1990 and 2005. Venous thrombosis had occurred in 42,000 HIV-infected patients, and in 6.6 million non-HIV patients. A crude RR of 1.21 (95%CI, 1.20–1.22) was calculated as an estimate of the risk of venous thrombosis for HIV infection (in subjects above the age of 18 years).

The most recent study was performed by Malek et al. (29). They also used data from the National Hospital Discharge Survey from 1996 till 2004, identifying over 293 million hospital discharges of which over 1.3 million were HIV positive. Venous thrombosis was found in nearly 7,000 HIV-positive patients and in about 1,5 million HIV-negative patients. An age-adjusted RR of 1.40 (95%CI, 1.37–1.43) was calculated as a risk of venous thrombosis for HIV infection.

Although the estimates of the relative risk of venous thrombosis appear to be mildly elevated by HIV, regarding the absolute risks we can conclude that patients with HIV have a six- to seven-fold increased risk of venous thrombosis when compared to the general population (24), especially when having full-blown AIDS or being on cART.

Cytomegalovirus

There are many case-reports in the literature about concurrent cytomegalovirus (CMV) infection and venous thrombosis. It took until 2008 before a relative or absolute risk of venous thrombosis for CMV infection was described. We found two (nested) case-control studies and one cohort study of good quality (▶Table 1). Lijfering et al. followed a prospective cohort of about 600 renal transplant patients (52 cases with venous thrombosis and 554 controls) who had received their renal transplant between October 2001 and November 2005 (30). The cohort was split in three groups, CMV negative, CMV seroconversion after renal transplant, and CMV seropositive. A first event of venous thrombosis was found in 52 patients after their renal transplant (13, 23 and 16 in each group respectively). The authors reported a RR of venous thrombosis of 1.7 (95%CI, 0.6–4.7) for patients who were CMV seroconverted, and 2.0 (95%CI, 0.9–5.2) for patients who were CMV seropositive, compared to patients who were still CMV seronegative. Corresponding incidences of venous thrombosis were 8.1 per 1,000 py for CMV seroconversion and seronegative patients and 9.8 per 1,000 py for seropositive patients. The authors stated that renal transplant patients have an increased risk of venous thrombosis, but the role of CMV remains a matter of debate, as RRs were based on small numbers and did not reach statistical significance.

In 2010, Atzmony et al. assessed the presence of venous thrombosis in a cohort of 140 consecutive patients with suspected acute CMV infection visiting the hospital in 2005 or 2006, and 140 matched patients without CMV infection (31). A venous thrombotic event was included when it occurred directly after establishing or excluding the diagnosis of acute CMV infection until one month afterwards. Patients were matched for age and sex. They found a hazard ratio of 16.9 (95%CI, 2.46–116.52) as an estimate of the RR of venous thrombosis for CMV-infected patients, compared to CMV-negative patients. However, these estimates are based on small numbers (n=4 for cases with venous thrombosis and acute CMV).

Thirdly, in 2011 we published a case-control study of (258 cases and 139 controls) consecutive patients suspected of venous thrombosis, in which five cases and 0 controls had an acute cytomegalovirus infection (32). To detect this, we used the polymerase chain reaction and serology. Interestingly, all five patients were female and below 37 years of age, and had another acquired risk factor for venous thrombosis. It might be that in young patients cytomegalovirus contributes to a procoagulant state. Due to the non-detection of cytomegalovirus infection in the controls, we could not calculate an OR.

In conclusion, cytomegalovirus may indeed increase the risk of venous thrombosis, but in two studies a statistically significant effect was not found, and the third study reported rather broad CIs, probably due to small numbers of subject included.

Influenza

To our knowledge, there are currently two studies which focused on the risk of venous thrombosis in patients with influenza, both of average quality (▶Table 1). The first, by van Wissen et al., was a nested case-control study of 497 patients (102 cases and 395 controls) in a prospective cohort of patients who were suspected to

have PE (33). Patients were enrolled from 1999 till 2001. At baseline, they recorded symptoms of respiratory tract infection and calculated a score for the influenza-like illness scale. Furthermore, influenza was detected in serum using a complement fixation assay. In 102 patients, an acute PE was confirmed. Only one patient had a positive serum test. Based on the serum diagnostics, an OR of 0.22 (95%CI, 0.03–1.72) was found as an estimate of the RR of PE. Based on the influenza-like illness score an OR of 1.16 (95%CI, 0.67–2.01) was reported. Also, the authors did not find a clear association between this clinical score and the serum test. It might be that in this relatively small group of patients, there were more infectious agents causing respiratory complaints / symptoms than influenza, thereby explaining the low prevalence of a positive serum test for influenza. However, recording the history of respiratory complaints did not show an increased risk of venous thrombosis either.

In 2009 Zhu et al. performed a case-control study of over 1,400 patients with proven first venous thrombosis, matched with controls without arterial or venous thrombotic disease (matched for age and sex) (34). At inclusion they interviewed patients about demographic and clinical characteristics including vaccination against influenza in the past 12 months. They found a decreased risk of venous thrombosis in patients who were vaccinated against influenza (OR 0.74; 95%CI, 0.57–0.97). This risk reduction was equal for unprovoked and provoked venous thrombosis.

Considering the current evidence, there is only one study indirectly indicating that influenza (vaccination) is associated with (a decreased risk of) venous thrombosis. More directly evidence is needed to estimate the real risk of venous thrombosis in influenza patients.

Chlamydia pneumoniae species

We found two case-control studies on *Chlamydia pneumoniae* and the risk of venous thrombosis, both from the year 2000. Lozinguez et al. determined immunoglobulin (Ig) G and when positive, also IgM against *Chlamydia pneumoniae* in 176 patients with objectively confirmed venous thrombosis from a case-control cohort enrolled earlier (35). In this study of average quality, age- and sex-matched controls without venous or arterial thrombosis (n=197) were recruited from a health care centre, where they were referred to for routine check-up. In 87 cases blood sampling took place within three months (median 1 day), while in the other 89 cases the median time between blood sampling and venous thrombosis was 12 months. They found a 6.7-fold increased risk of venous thrombosis in patients with a *Chlamydia pneumoniae* IgG titer of 256 IU/ml or more (age, sex, factor V Leiden and prothrombin mutation adjusted 95%CI 3.6–12.2), in patients from whom the blood was sampled within three months after venous thrombosis, which did not differ significantly from the risk estimate of patients with blood sampling >3 months after the index event.

Koster et al. analysed IgG titers of *Chlamydia pneumoniae* in a case-control study [the Leiden Thrombophilia Study (LETS)] of good quality (36). Cases were consecutive patients with a first objectively confirmed venous thrombosis; controls were age- and sex-matched friends or partners (n=474 for both groups). Median time between blood sampling for serology and the occurrence of venous thrombosis was 19 months (range 6–68). They reported an OR of 1.1 (95%CI, 0.9–1.4) as an estimate of the risk of venous thrombosis for a positive *Chlamydia pneumoniae* IgG titer. This large time interval might have influenced the results, as acute *Chlamydia pneumoniae* infections could have occurred after diagnosis of venous thrombosis and thereby increasing IgG titres.

Overall, we can not conclude that *Chlamydia pneumoniae* is associated with venous thrombosis because of the conflicting results from these two studies. Although the latter included more patients and was of better quality, the large time between the index event and the blood sampling might have biased their findings towards the null.

Pneumonia and urinary tract infections

We found two studies of good quality (▶Table 1) reporting increased risks of venous thrombosis for pneumonia and urinary tract infections. Smeeth et al. used the self-controlled case series method (37–39) in 7,278 patients with DVT and 3,755 patients with PE to assess the risk of venous thrombosis for pneumonia and urinary tract infection (40). Data were derived from an electronic database of medical records from general practices. The null hypothesis was that venous thrombotic event rates would not be influenced by an acute infection. The exposed period was defined as up to 52 weeks after the infection and was subdivided into the following periods: 0–2 weeks, 3–4, 5–8, 9–12, 13–26, 27–39, and 40–52. All other observation time (before and after the exposure) was taken as the baseline (unexposed) period. In this way, incidence ratios of events in the above defined intervals after an exposure (i.e. the infection) relative to all other observed events in the unexposed periods can be calculated for each person with a venous thrombotic event. Mean observation time was 10.2 and 9.6 years for DVT and PE, respectively. They found a two-fold increased risk of DVT after urinary tract infection or pneumonia, for the first two weeks after the infection (age adjusted incidence ratios 2.10; 95%CI, 1.56–2.82 and 1.91; 95%CI, 1.49–2.44, respectively). For urinary tract infection, they also found a 2.11-fold increased risk of PE in the first two weeks after the infection (age adjusted incidence ratio 2.11; 95%CI, 1.38–3.23). Further adjustments for cancer and seasonal effect did not change the risk estimates.

In a prospective cohort of US veterans, the National Surgical Quality Improvement Program, Gangireddy et al. performed a nested case-control study using pre- and postoperative data to assess risk factors of postoperative symptomatic venous thrombosis (41). They included 117,453 controls and 805 cases and found an increased risk of venous thrombosis in a 30-day postoperative period for pneumonia and urinary tract infection (multiple adjusted OR 2.7; 95%CI, 2.1–3.5 and 1.8; 95%CI, 1.3–2.5, respectively).

Together, these two studies of good quality with large numbers of subjects provide convincing evidence that pneumonia and urinary tract infections are associated with a two-fold increased risk of venous thrombosis.

Table 2: Summary of risks of venous thrombosis.

	Relative risk	Absolute risk [1]
Inflammatory bowel disease	1.5 – 8.4	2.6 – 9.0
ANCA-associated vasculitis	n/a	43 – 70
Human immunodeficiency virus	1.2 – 1.4	1.3 – 5.8
Pneumonia	1.9 – 2.7	n/a
Urinary tract infections	1.8 – 2.1	n/a
Infections NOS	1.7 – 2.5	n/a

[1] Cases per 1,000 person-years

Infections, not otherwise specified

Finally, we found four studies indicating that infections not otherwise specified do increase the risk of venous thrombosis, one of average quality and three of good quality (▶Table 1). In the SIRIUS study, Samama et al. (42) found an OR of 1.95 (95%CI, 1.31–2.92) of venous thrombosis for infectious disease. This was a case-control study conducted in general practitioner centres in 494 cases and 494 controls. Of note, patients who had had a plaster cast or were within three weeks post-operatively before inclusion were excluded. Cases were consecutive patients with DVT; controls were consecutive patients without venous thrombosis who visited the general practitioner with an influenza like or rhinopharyngeal syndrome, directly after the visiting index patient. Controls were matched for age and sex.

The MEDENOX study is a randomised controlled double-blind trial, comparing two doses of low-molecular-weight heparin to placebo in acute ill, immobilised, general medical patients. In a post-hoc analysis of the entire cohort (866 patients), Alikhan et al. detected a 1.74-fold (95%CI, 1.12–2.75) increased risk of venous thrombosis for acute infectious disease, using multivariate logistic regression (10).

Cimminiello et al. published in 2010 a nested case-control study using a national general practitioners database including 1,624 cases and 370,376 controls from 2001 until 2004. Controls were age-, sex- and physician-matched (43). They reported a multiple-adjusted OR of 1.86 (95%CI, 1.16–2.97) for acute infectious disease as a risk factor for venous thrombosis.

We performed a prospective case-control study from May 2008 until September 2009 using referred patients to the emergency department who were suspected of DVT (44). Using a standardised questionnaire, we asked patients about signs and symptoms of infectious diseases in the four preceding weeks before presentation at the emergency department. Cases (n=123) were patients with objectively confirmed DVT; controls (n=115) were patients in whom this was ruled out. In this way, we found a 2.5-fold increased risk of venous thrombosis for patients who had experienced infectious symptoms (age and sex adjusted OR, after exclusion of patients with malignancy [95%CI, 1.4–4.8]).

Overall, these studies point out that a two-fold increased risk of venous thrombosis may exist in patients with (acute) infectious diseases.

Discussion

There is now convincing evidence from basic science as well as clinical epidemiological studies that inflammation and venous thrombosis are related. This association appears to be strongest when time between the exposure and the outcome is short; i.e. when the inflammatory or infectious disease was experienced recently or, more specific, while an inflammatory or auto-immune disease was active (flare-up). In ▶Table 2 we provide an overview of the range of the relative or absolute risk of those risk factors for which convincing evidence of an association with venous thrombosis was found in this review.

Studies of good quality showed that inflammatory bowel disease is associated with a two- to four-fold increased risk of first venous thrombosis, as well as a 2.5-fold increased risk of recurrent venous thrombosis. Second, a flare-up of the disease increases this risk even more, up to eight times compared to the general population. There appears to be no difference in elevation of these risks between ulcerative colitis and Crohn's disease.

A little weaker but still convincing was the evidence of three studies on ANCA-associated vasculitis and venous thrombosis. Patients with active disease may have an increased risk of venous thrombosis with an absolute risk of 43–70 per 1,000 py. More information might be contributing, especially to the RR compared to the general population or age- and sex-matched controls.

Studies of average quality showed that HIV was associated with a slightly increased risk of venous thrombosis (RR ranging from 1.21–1.40). Full-blown AIDS or receiving cART might be associated with even a higher risk of venous thrombosis. However, this RR might be an underestimation, because the absolute risks of venous thrombosis reported in these studies (ranging from 5.7 to 11.3 per 1,000 py) are much higher than the incidence rate of venous thrombosis of one per 1,000 py in the general population (24). This discrepancy between relative and absolute risk increase might be due to using subjects with a higher baseline (absolute) risk as controls (i.e. patients discharged from hospital, Afro-Americans) and not subjects from the "real"general population (who have a baseline absolute risk of venous thrombosis of one per 1,000 py).

In two studies of good quality pneumonia and urinary tract infections increased the risk of venous thrombosis about two-fold, in the general population as well as in a highly selected group of post-operative patients. These findings are supported by four other studies of overall good quality, reporting that infections in general (not otherwise specified) indeed increase the risk of venous thrombosis two-fold.

Rheumatoid arthritis might be associated with venous thrombosis, but the current data are not convincing and have poor quality. Second, data on coeliac disease, sarcoidosis, influenza or *Chlamydia pneumoniae* are limited and studies report conflicting results. More studies are needed to draw a conclusion.

Finally, cytomegalovirus appears to be associated with an increased risk of venous thrombosis in three studies of good quality. However, statistical significance was not reached in two studies, probably due to small numbers, and a rather broad confidence interval was reported in the third study.

Pathophysiology

Our findings are supported by several experimental studies, thereby providing pathophysiologic pathways of the association between inflammation, infection and venous thrombosis (3, 45–55). Some authors have proposed the term "endothelial stunning" for referral to inflammation and activation of the vessel wall (45, 46, 56, 57) which appears to play a key-role in the mechanism. Other evidence for an association between infection, inflammation and venous thrombosis comes from the study by van Deventer et al., who showed that infusion with endotoxins led to the activation of coagulation (52). Infusion of (recombinant) interleukin (IL)-6 led to more thrombin generation in patients in another study (58), and administration of recombinant tumour necrosis factor induced activation of factor X and, later on, also thrombin generation (4).

There is also some evidence for C-reactive protein (CRP), a liver synthesised acute phase protein (59–61), as a causative agent in the association between inflammation and coagulation, coming from basic and experimental studies. Bisoendial et al. infused recombinant human CRP in seven healthy volunteers and observed a marked and significant rise of von Willebrand factor (VWF) (mean 82% to 127%), prothrombin fragments 1 and 2 (about three-fold), D-dimer (3.5-fold) and plasminogen activator inhibitor type 1 (PAI-1) (from 35 to 71 ng/ml) (62). Chen et al. demonstrated that PAI-1 concentrations increased significantly after stimulation of endothelial cells of diverse origins with CRP (63). There is also evidence that CRP inhibits expression of tissue plasminogen activator in human aortic endothelial cells (64). In another study, monomeric CRP stimulated platelet adhesion and thrombus growth under arterial flow conditions. CRP was visualised to be present by confocal microscopy on platelets surface and within the thrombus (65). Finally, a misbalance of tissue factor (TF) and tissue factor pathway inhibitor (TFPI) might contribute to a procoagulant state, as CRP increases TF and decreases TFPI levels (66).

On confounding and bias

Most of the studies reported in this review were retrospective cohort studies, case-control studies or nested case-control studies. In particular, cohort studies without a (matched) control group are susceptible to confounding without the statistical possibility to correct for these. However, by carefully describing the kind of population the cohort (sample) was derived from, authors can make readers aware of potential confounders, but the size of the effect of a confounder can not be determined in this way. In (nested) case-control studies, there is much more possibility to adjust the effect for potential confounders, which will only be limited by sample size and study design.

By using the Newcastle-Ottawa Quality Assessment Scale, the possibility to adjust for confounders is included. When authors have not done this or the study design did not allow for this (in the case of cohort studies), or when the sample is hardly representative for the community, the study will receive less points on the scale (up to three points), which in ultimo will categorise it down from" good" to "average" although the design further has not any flaws and received the maximum of the other (six) points. This is also the case for (nested) case-control studies. Thus, by looking at the score on the Newcastle-Ottawa Quality Assessment Scale and the study design, the reader can judge the study on its general quality as well as the possibility to correct for confounding. However, our results should be interpreted with caution as not many studies had the maximum score on the Newcastle-Ottawa Quality Assessment Scale.

Another issue we are not able to control for is publication bias. This could mean that studies finding no (significant) association between infectious or inflammatory diseases and venous thrombosis will not have been published, because of these negative findings, thereby increasing the impact of positive studies on this topic which do have been published. We found for at least three potential risk factors (*Chlamydia pneumoniae*, RA and coeliac disease) some studies reporting that there might be no association between the risk factor of interest and venous thrombosis. One of these studies was of good quality and the others of average quality. Also, for cytomegalovirus as a risk factor of interest, we found a study reporting a relative risk of 1.7–2.0, which was not significant.

Overall, there is some evidence pointing towards a real association between inflammatory or infectious diseases and venous thrombosis, but not all studies agree with this hypothesis nor has this hypothesis been tested for many typical diseases. Therefore, any study of at least average quality on this topic would really add to the existing evidence, whether it contributes pro or contra the null-hypothesis. Therefore, we think that publication bias on this topic is not very likely.

Conclusion

In conclusion, a systematic review of the literature of the last 15 years reveals that inflammatory bowel disease and ANCA-associated vasculitis increase the risk of venous thrombosis, as well as infections in general and more specifically HIV, pneumonia and urinary tract infections. By identifying these new risks and adding them to the more established risk factors, treating physicians can assess the individual risk of venous thrombosis of patients and adequately apply thromboprophylaxis in high-risk situations, in in-hospital settings as well as in ambulatory patients. Near-future research could focus on the benefits and disadvantages of thromboprophylaxis in high-risk patients by a randomised-controlled trial.

Conflicts of interest
None declared.

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