Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting

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Summary

Background Acute infection increases the risk of arterial cardiovascular events, but effects on venous thromboembolic disease are less well established. Our aim was to investigate whether acute infections transiently increase the risk of venous thromboembolism.

Methods We used the self-controlled case-series method to study the risk of first deep vein thrombosis (DVT) (n=7278) and first pulmonary embolism (PE) (n=3755) after acute respiratory and urinary tract infections. Data were obtained from records from general practices who had registered patients with the UK’s Health Improvement Network database between 1987 and 2004.

Findings The risks of DVT and PE were significantly raised, and were highest in the first two weeks, after urinary tract infection. The incidence ratio for DVT was 2.10 (95% CI 1.56–2.82), and that for PE 2.11 (1.38–3.23). The risk gradually fell over the subsequent months, returning to the baseline value after 1 year. The risk of DVT was also higher after respiratory tract infection, but possible diagnostic misclassification precluded a reliable estimate of the risk of PE after respiratory infection.

Interpretation Acute infections are associated with a transient increased risk of venous thromboembolic events in a community setting. Our results confirm that infection should be added to the list of precipitants for venous thromboembolism, and suggest a causal relation.

Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are major causes of morbidity and mortality.1 A systematic review of published studies, mostly undertaken in the USA and Sweden, estimated the overall population incidence of DVT to be 0.5 per 1000 person-years.2 Although several studies have focused on the mechanisms and causes of atherothrombosis and acute cardiovascular events, less is known about venous thromboembolic disease. In 1856, Virchow proposed three precipitants for venous thrombosis: venous stasis; increased coagulability of the blood; and damage to the vessel wall.3 Infection could affect venous stasis or increase coagulability of the blood. Furthermore, parallels with the arterial system suggest that damage to the vessel wall might not be limited to physical damage but could also affect endothelial function. Inflammation is a key determinate of endothelial function in both arteries and veins,4 and a link between infection and venous thrombosis via endothelial activation has been suggested.5 Thus, there are several mechanisms by which acute infections could increase the risk of venous thromboembolism. Acute infections have been associated with a transient increase in the risk of myocardial infarction and stroke.6 Using a similar approach, we tested the hypothesis that acute infections trigger a transient increase in the risk of venous thromboembolic disease.

Methods

Participants

The Health Improvement Network is an electronic database of medical records from general practice, and includes complete prescribing and diagnostic information. Recorded rates of consultations and drug prescriptions as well as pregnancy and death rates are equivalent to UK national data.8 The database information is anonymous.

Patients were derived from the population for whom data was available in the database between 1987 and 2004—this comprised more than 20 million person-years of observation from 220 general practices. Eligible participants were those who had had a first-ever diagnosis of DVT or PE at least 18 months after initial registration to the database. Because of the possibility that infections recorded in the first 6 months occurred before the patient joined the database and were recorded retrospectively, the observation period for events began 6 months after the patient was first registered. The 18-month criterion thus allowed 12 months of observation before each outcome. If patients had consulted their general practitioner in the 6 weeks before their diagnosed thromboembolism with symptoms likely to indicate the thromboembolic event, such symptoms were “calf pain” for DVT or “pleuritic chest pain” for PE, their date of onset was altered to the date of the first symptom.

For the analysis of PE, cases with a previous DVT were excluded, to ensure that PE was the first clinical manifestation of venous thromboembolism. Cases with a diagnosis of PE were not included in the analysis of DVT, because of possible misdiagnosis of early signs of PE as a respiratory infection.

Individuals were excluded if they were younger than 18 years at the time of their first DVT or PE (because the aetiology of their venous thromboembolism could have
differed from adults), if they were likely to have been pregnant at the time of their DVT or PE, or if they had had major surgery or lower limb surgery in the 6 weeks before the event. Individuals were also excluded if they had been prescribed warfarin before their event, because it would have suggested that the thromboembolism was not a new event. The only exception to this rule was for patients who had been prescribed warfarin prescriptions more than a year before their recorded event, and who then resumed warfarin at the time of their recorded DVT or PE. This means that a few cases included might have had a DVT or PE in the past.

Cases were also excluded if their medical records indicated that the venous thromboembolic event was likely to have been retrospectively recorded. For example, if the patient's DVT or PE was recorded along with other diagnoses on the day of a new patient or "well-person" screen. We also excluded people whose only diagnostic entry for their event appeared when the general practice received a post-mortem report because we were concerned that the date recorded would not accurately reflect the date of the venous thromboembolic event.

Ethical approval for our study was given by the South Thames Multi-centre Research Ethics Committee.

**Procedures**

We investigated two common infections affecting different organ systems: acute urinary tract infections (UTIs) and acute systemic respiratory tract infections (RTIs) such as pneumonia, acute bronchitis, chest infections, and influenza. Minor illnesses and symptoms such as sore throat or coryza were not included as RTIs. These criteria are the same as those previously used to test the link between infections and risk of myocardial infarction.¹⁰⁰

Assessing differences between people with and those without diagnosed infections can be difficult, meaning that comparison between individuals could be misleading. We therefore used the self-controlled case-series method,¹¹¹² which relies on intra-person comparisons in a population of individuals who have had the outcome of interest. Then, one can derive incidence ratios of events in defined intervals after an exposure relative to all other observed time periods for each person.¹³ Our null hypothesis was that venous thromboembolic event rates are not affected by an acute infection, but remain constant from day to day. 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 was taken as the baseline (unexposed) period. Venous thromboembolic events recorded on the same day as an infection were excluded from the baseline periods. This was because these events might have been recorded retrospectively when the patient attended the general practice for the infection.¹⁴

Participants included had at least one infectious exposure and at least one venous thromboembolic event. Participants with both RTIs and UTIs were included in each analysis.

**Statistical analyses**

We adjusted for age in five-year age bands (18–24 years, 25–29, 30–34, and so on). Our primary analyses were restricted to cases who had been exposed to an infection at least once during follow-up. In the case-series analysis, participants who did not have either a UTI or RTI during the observation period were not included in estimates of the association between exposure and outcome, but were included in adjustments for effects of age. We therefore repeated the analyses including unexposed cases to ensure that the estimates did not vary. We undertook analyses stratified by age (people older than 60 years, or those aged 60 years or younger) at the time of DVT or PE to assess whether the effect differed by age.

Although a seasonal pattern in venous thromboembolic event rates has not been established, any such pattern could lead to a temporal association between DVT or PE and infection simply because of seasonal variation in infections. We therefore analysed the effect of respiratory infections acquired in warmer months (April–September) and in cooler months (October–March). Cancer is a known risk factor for venous thromboembolism, and some cancers can increase the risk of some infection. Recently diagnosed cancer might therefore have increased the risk of both venous thromboembolism and infections. To remove the portion of risk that might have been due to cancer, we repeated the analyses excluding people with a first diagnosis of cancer (except non-melanoma skin cancer) in the year before their DVT or PE.

Incidence ratios and 99% CIs were calculated for events occurring within each stratum of the exposed period compared to baseline periods using the within-person case series method.¹¹¹²

We estimated that for respiratory infection, we would be able to include more than 2000 exposed cases for DVT,

<table>
<thead>
<tr>
<th>Urinary tract infection ( (n=2258)^* )</th>
<th>Systemic respiratory tract infection ( (n=3375)^* )</th>
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<tr>
<td><strong>Post-infection risk period</strong></td>
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<td>Baseline period</td>
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IR-age-adjusted incidence ratio. *Includes those who had a recorded DVT on the day of diagnosis of infection, and who were thus not included in the analysis, because the DVT could have been recorded retrospectively. Individuals who had both a UTI and an RTI are represented in each analysis. Incidence during the baseline period served as the reference. †Significantly higher incidence than at baseline.

Table 1: Age-adjusted incidence ratios of a first deep vein thrombosis after respiratory or urinary tract infections
sufficient to provide over 90% power at 5% significance to detect an incidence ratio of 1·4 in the first 2 weeks after exposure. Data were analysed with Stata (version 8.0).

Role of the funding source
The sponsor had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and took full responsibility for the decision to submit for publication.

Results
10 284 people with a first DVT were identified from the database, of whom 7278 people were included in the analysis. The median age at the time of diagnosis of DVT was 67·6 years (IQR 53·4–77·5), 41·6% were male, and the mean observation period was 10·2 years. 5574 people with a first PE were identified, of whom 3755 were included in our analysis. The median age at the time of diagnosis of PE was 67·9 years (IQR 54·9–77·6), 42·6% were male, and the mean observation period was 9·6 years.

During the observation period, of the people with a DVT, 3375 (46·4%) had one or more respiratory infections and 2258 (31·0%) had one or more urinary tract infections diagnosed. In people with a PE, 1042 (2·7%) had one or more urinary tract infections. Tables 1 and 2 show the numbers of exposed individuals who had a first DVT or a first PE and the age-adjusted incidence ratios after infection.

The rates of both DVT and PE were much higher after a diagnosis of urinary tract infection than before infection. The rates were highest in the first 2 weeks after exposure (around double that at baseline), gradually falling over the subsequent months until returning to baseline after 1 year. Rates were also raised to a similar extent for DVT after respiratory infection. The observed incidence ratio for PE after respiratory infection was extremely high—an 11-fold increased risk in the first 2 weeks after infection. However, since the increase could be an artifact because of misdiagnosis of an early presentation of PE as respiratory infection, the results for PE and respiratory infection were not included in our analyses.

Including unexposed cases did not alter the estimates of the effect of infection on DVT or PE. The incidence ratio of DVT in the first 2 weeks after a UTI was 2·15 (95% CI 1·56–2·82) including both exposed and unexposed cases compared with 2·10 (1·56–2·82) including only exposed cases. There was no evidence of seasonal variation in the incidence of venous thromboembolic events, with 50% of DVTs and 48% of PEs occurring in the 6 warmest months of the year (April–September). The significant graded effect of respiratory infection remained even after analyses were restricted to events occurring in summer. The incidence ratio of DVT in the first 2 weeks after an RTI was 2·86 (2·05–3·97) during the summer months compared to 1·91 (1·49–2·44) overall.

Our results did not differ by age at diagnosis of DVT or PE, with similar rates in people older than 60 years at the time of event compared with those aged 60 years or younger. For example, the incidence ratio of DVT in the first 2 weeks after a UTI in people aged 60 years or younger was 2·06 (1·12–3·78), compared with 2·33 (1·59–3·13) in people older than 60 years. Excluding cases with a diagnosis of cancer in the 12 months before their DVT or PE did not affect the results: the incidence ratio of DVT in the first 2 weeks after a UTI was 2·29 (1·70–3·07) compared with 2·10 (1·56–2·82) when these cases were included.

Discussion
Our results show that in a community setting, acute infection is linked to a transient increase in the risk of venous thromboembolism—both DVT and PE—suggesting a role for acute infections in triggering such events. Using a large data set we were able to identify the magnitude of the association and its temporal resolution. The effect we observed was similar for respiratory and urinary tract infections, suggesting the effect of infections on risk of venous thromboembolism might be generic and not linked to specific types of infection.

Infection had already been identified as a potential risk factor for venous thromboembolism.15,16 In a case-control study of medical outpatients, in which 636 people with a DVT were compared with 636 matched controls,2 the odds ratio for DVT associated with the presence of infectious disease was 1·95 (95% CI 1·31–2·92). This ratio was adjusted for potential risk factors such as immobilisation, which was defined as confinement to a bed, or to a bed and armchair. A secondary analysis of a randomised controlled trial5 of low molecular weight heparin for the prevention of venous thromboembolism in 866 hospitalised patients, all of whom were acutely ill and immobilised, showed that...
by day 14 of follow-up, the adjusted odds ratio for venous thromboembolism associated with acute infectious disease was 1.74 (1.12–2.75). The type of infection was not described in either study.

Further evidence for an important role for infection in venous thromboembolism comes from studies showing that in people with infectious disease, thromboprophylaxis reduced the risk of subsequent venous thromboembolism. In both the previous studies, the association between infection and venous thromboembolism was based on the comparison of people with a DVT or PE with those who had not had such an event. Thus, in spite of adjustment, the results could have been prone to residual confounding. Indeed in studying the association between venous thromboembolism and infection, there is great potential for confounding because individuals who do and those who do not develop infections are likely to differ substantially in their underlying risk of the condition.

The advantage of our method is in removing the variation between individuals in risk factors for venous thromboembolism, by ensuring that comparisons are intra-person. Our study design also meant that infections were diagnosed before knowledge of the subsequent venous thromboembolism, removing the possibility of biased ascertainment of exposure. Ours is more statistically powerful than previous studies, allowing a more precise estimate of the effect of infection. We were also able to identify the timing of the increased period of risk following infection as well as show its gradual dissipation. Thus, our findings indicate that acute infection could precipitate venous thromboembolism, and might cause a large, if temporary, increase in risk. In the same way as arterial disease, the risk of venous thromboembolism seems to fluctuate in response to external factors, such as infection.

We found evidence that early presentations of PE might be misdiagnosed as respiratory infections, producing a misleadingly strong association between respiratory infection and subsequent PE. However, such diagnostic misclassification would be highly unlikely to have occurred for DVT and either respiratory or urinary infections, or for PE and urinary infections.

We also explored potential temporal confounders. The effects of infection were not explained by seasonal patterns in exposure and outcome. Intra-person risk factors for venous thromboembolism that change with time, could, if also associated with an increased risk of infection, have contributed to the observed temporal association between infection and thromboembolism. However, people who were pregnant or who had had recent surgery in the 6 weeks before the thrombotic event were excluded from our primary analyses. Further exclusion of people diagnosed with cancer in the 12 months before a thrombotic event, and extending the period of exclusion for major surgery to 3 months, did not affect our findings.

We cannot totally exclude the possibility of increased ascertainment of venous thromboembolism in the weeks following an infection, when for example, patients might have attended for review of their infection. We also cannot exclude the possibility that increased bed-rest during infection might account for some of the association observed. However, many of the infections included in our study would not have been severe enough to lead to prolonged bed-rest, and in previous studies adjustment for bed-rest did not alter the association between infection and venous thromboembolic event.

Our study used routine clinical data, the quality of which might have been a weakness. However, the research database we used overlaps considerably with the well-established General Practice Research Database (GPRD). The clinical software system used by clinicians to enter data is the same, and over 100 general practices (more than a third of the total) that contribute data to the Health Improvement Network also contribute the same data to the GPRD. It seems reasonable to assume that the quality of data is the same for both databases. The recorded diagnosis of venous thromboembolism in the GPRD has been validated in a sample of 169 cases. The diagnosis had been confirmed by positive venogram, Doppler ultrasound, ventilation perfusion scan or post-mortem findings for 141 cases (83%). For the remaining 28 cases, the diagnosis and decision to treat with anticoagulants were made on clinical grounds after inconclusive investigation.

A limitation of our study is that we used the date of diagnosis rather than date of onset for both venous thromboembolism and infection. However, most patients, even those with upper respiratory tract infections, visit their general practitioner within three days of onset of symptoms, so we are unlikely to have underestimated the duration of the increased risk of venous thrombosis by more than a few days. In addition, we would not have identified all infections because some patients with infections would not have consulted their general practitioner. For the sake of practicality, we defined exposure as infections severe enough to prompt the patient to consult their doctor, and these will inevitably have varied in severity between individuals.

In our previous study of acute arterial cardiovascular events, we could be reasonably sure that the thrombotic event occurred on the day the patient presented with symptoms. By contrast, in the diagnosis of venous thromboembolism, several days or even weeks can pass before symptoms and signs are evident, and some patients never consult their doctor. This possible imprecision in onset date was the reason we used longer risk periods. However, the effect of imprecision in onset date, incomplete ascertainment of infections, and the inclusion of some mild infections would probably have led to an underestimation of the effect of infection on subsequent thrombotic events. Thus, the link between
infectious episodes and risk might in fact be even more striking than the one we report.

Our finding that two infectious processes in different organ systems are associated with a substantial, reversible increase in the risk of venous thromboembolism suggests that acute infections may have a causal role in triggering events. We do not know whether the transient increase in risk is due to a short-term alteration of endothelial function or to other mechanisms such as white-cell activation or dehydration. However, infection is always associated with inflammation, and C-reactive protein is raised in patients diagnosed in a primary-care setting with respiratory tract infection.2 Several studies have identified an increased risk of venous thromboembolism in patients with non-infectious inflammatory disorders, such as inflammatory bowel disease and rheumatoid arthritis.15–17,22 Our earlier study6 confirmed a link between infectious episodes and risk of arterial events and this study shows that the risk is also present for venous thrombosis. Together, our data support the notion that systemic infections increase the risk of thromboembolic events. We now need to uncover the mechanism that underlies the risk we propose. Whatever the mechanism, our study confirms that acute infection should be considered in the list of precipitants for venous thromboembolic disease.

Contributors
L Smeeth and P Vallance had the idea for the study, and drafted the report. C Cook analysed the data, supervised by L Smeeth. All authors contributed to the design and interpretation of results. All authors commented on drafts and approved the final version of the report.

Conflict of interest statement
P Vallance is a member of GlaxoSmithKline’s research advisory board, for which he receives payment. The other authors declare that they have no conflict of interest.

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