The risk of venous thromboembolism in systemic inflammatory disorders: a UK matched cohort study

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Abstract

Background
Venous thromboembolism (VTE), comprising pulmonary embolism (PE) and deep vein thrombosis (DVT), are common and associated with significant morbidity and mortality. VTE risk is higher in chronic inflammatory conditions including inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) compared to the general population. Evidence for differential VTE risk in other inflammatory diseases, notably psoriatic arthritis (PsA) and vasculitis, is more limited. Risk factors for VTE have been described in the general population, but there has been little interrogation of VTE risk factors for individuals with chronic inflammatory conditions and their association with subsequent VTE.

Objective
We aim to describe the prevalence of VTE risk and risk factors in individuals with systemic inflammatory disorders in a contemporary real-world population, by disease type (IBD, RA, and PsA) and relative to a control population without systemic inflammatory disease. In the same cohorts we will further compare the influence of VTE risk factors on risk of VTE events in individuals with systemic inflammatory disorders.

Method
We will perform a retrospective cohort study to compare VTE risk and VTE risk factors in adults with IBD, RA, and PsA and matched controls between January 1, 1998 and January 1, 2018, within the RCGP RSC network. In the cohorts with and without inflammatory conditions we will estimate the risk of VTE overall, and for PE and DVT separately, using unadjusted Cox proportional hazards models, stratified by matched set (exposed cohort versus unexposed cohort), to provide overall hazard ratios for the association with each outcome. Models will be subsequently adjusted for sociodemographic and clinical and VTE risk factors in multivariable analysis to explore potentially important associations with VTE. We will then repeat the same analyses for each autoimmune condition separately. We will perform prespecified sensitivity analyses to explore the robustness of any potential associations.
Lay summary

Blood clots occurring in the legs and in the lungs are relatively common; they occur in around 3 in a 1000 people per year. They can cause disability and are also potentially life threatening. When a clot occurs in the legs it is called a deep vein thrombosis or DVT. When they occur in the lungs they are called a pulmonary embolism or PE. The risk for DVT and PE is higher in people with conditions which cause inflammation. The most common of these are inflammatory bowel disease (ulcerative colitis and Crohn’s disease), rheumatoid arthritis, and psoriatic arthritis (a condition comprised of psoriasis and joint inflammation).

What is not known is how much higher the risk of DVT and PE is in these groups compared with people without inflammatory disease, and what causes the excess risk in these people. This study aims to assess the measure the exact increase in risk for DVT and PE in people with these inflammatory conditions and to identify which risk factors are most strongly associated with the increased risk. These data should help us understand the causes of blood clot risk in these inflammatory conditions and identify targets for reducing risk.
**Introduction**

Venous thromboembolism (VTE), comprising pulmonary embolism (PE) and deep vein thrombosis (DVT), is relatively common, with an incidence in the general population of around 3 cases per 1000 patient years.\(^1\) It is associated with significant morbidity and mortality.

Systemic inflammation is a risk factor for VTE,\(^2\) and risk of VTE has been shown to be increased amongst individuals with chronic inflammatory conditions including inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) compared to the general population.\(^3\)\(^\text{-}\)\(^6\) Evidence for differential VTE risk in other inflammatory diseases, notably psoriatic arthritis (PsA) and vasculitis, is more limited.\(^4\) Risk factors for VTE have been described in the general population, and include C-reactive protein (CRP), obesity, fractures, surgery and use of oral corticosteroids and hormone therapy,\(^7\)\(^,\)\(^8\) but there has been little interrogation of patterns of VTE risk factors for individuals with chronic inflammatory conditions and their association with subsequent VTE.\(^9\)

In this context we will set out to describe the prevalence of VTE risk factors in individuals with systemic inflammatory disorders in a contemporary real-world population, by disease type (IBD, RA, and PsA) and relative to a control population without systemic inflammatory disease. In the same cohorts we will further compare the influence of VTE risk factors on risk of VTE events in individuals with systemic inflammatory disorders.

**Methods**

**Study design**

We will perform a retrospective cohort study to compare VTE risk and VTE risk factors in adults with IBD, RA, and PsA and matched controls between January 1, 1998 and January 1, 2018, using a large UK primary care database.

**Data source**

The Royal College of General Practitioners Research (RCGP) and Surveillance Centre (RSC) database will be used for this study. The RCGP RSC cohort derives from a large network of GP
practices distributed across England and provides representative sample of the UK population.\textsuperscript{10}

The RCGP RSC database contains information on clinical diagnoses, anthropometric measurements (e.g., body mass index; BMI), laboratory tests results, and prescriptions, coded with the Read coding system (a thesaurus of clinical terms).\textsuperscript{11} UK general practice lends itself to this type of study because it is a registration-based system (each patient can only be registered with a single GP), it has been computerised since the 1990s, and pay-for-performance targets introduced in 2004 have resulted in consistent high-quality clinical data entry about chronic disease.\textsuperscript{12} All RCGP RSC registered practices have electronic laboratory links; meaning all test results are automatically coded and uploaded to the GP computer system. Studies using RCGP RSC data have been published across a range of chronic diseases.\textsuperscript{13-15}

**Study population**

Adult patients (aged $\geq 18$) contributing to RCGP RCS primary care database between January 1, 1998 and January 1, 2018, will be eligible for inclusion.

**Definition of the exposed cohort with systemic inflammatory disease**

The exposed cohort will include all individuals with an existing or incident diagnosis of IBD, RA or PsA (systemic inflammatory diseases) in the RCGP RCS over the study period. IBD, RA or PsA will be identified using Read diagnostic codes previously validated in UK primary care studies.\textsuperscript{16-18} Follow-up for exposed individuals will begin on the latest of the date of diagnosis indicated by first diagnostic code, January 1 1998 or 180 days after practice registration.

**Definition of the matched unexposed cohort**

The matched unexposed cohort will be defined by matching individuals in the exposed cohort with individuals who were never diagnosed with a systemic inflammatory disease either prior to or during the study period by age and sex at GP practice level. Unexposed individuals will require at least one year of follow-up when matched to minimise the risk they had a non-
recorded existing diagnosis of a systemic inflammatory disease of interest. Follow-up for each matched individual will begin at the start of follow-up of their exposed counterpart.

Follow-up will end at the earliest of the study end-date (January 1, 2018), the date of patient transfer from an included practice, date of death, or the date an individual developed an outcome of interest.

Outcomes
The pre-specified outcomes include the time to incident VTE (either PE or DVT), time to PE, and time to DVT. These outcomes will be defined using Read codes that have been previously validated in a similar UK primary care database. Time to each outcome will be compared between individuals with a systemic inflammatory disorder and the matched control population, and across IBD, RA and PsA subgroups.

Baseline characteristics and VTE risk factors
Baseline measures will comprise sociodemographic characteristics, clinical features and biomarkers, selected based on clinical expertise and existing literature demonstrating an established association with VTE or evidence to support an association with VTE among individuals with systemic inflammatory disorders. Socioeconomic status will be defined using the official national measure; the index of multiple deprivation (IMD). This will be calculated at the point of data extraction, using patient postcode, with the resultant scores stratified by deprivation quintile. Ethnicity will be extracted from the primary care record and grouped into the major UK ethnic groups; white, black, Asian, mixed, and others. BMI will be defined as the most recently recorded measurement prior to the study start date. Smoking status and alcohol use will be defined using the most recently recorded data prior to the study start date. Diagnostic codes will be used to define the presence of comorbidities at baseline: hypertension, hyperlipidaemia, diabetes, peripheral vascular disease, cardiovascular disease (Atrial fibrillation, angina, myocardial infarction, congestive heart failure), cerebrovascular disease, cancer, chronic obstructive pulmonary disease, chronic kidney disease (stages 3–5), liver disease, recent hospitalisation, joint replacement, and fractures. Diabetes and diabetes type will be identified using an algorithm developed for use within the RCGP RSC database.
The Read codes used to describe cardiovascular disease within the RCGP RSC database have been previously reported. We will also extract records of pregnancy and reduced mobility. Biomarkers and laboratory tests including cholesterol and blood pressure will be derived by taking the most recent value in the year before cohort entry.

We will examine the following medications commonly used for the management of systemic inflammatory disorders: non-steroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, disease modifying anti-rheumatic drugs (DMARDs), other non-biologic immunosuppressant medications, and biologic therapies (where recorded). We will also include hormone therapy (hormonal contraceptives, hormone replacement therapy). We will also extract information on prescribing of antiplatelet agents (aspirin or adenosine diphosphate receptor inhibitors) and lipid lowering therapy (statins, fibrates, or ezetimibe). Prescribing at the study start date will be defined as the presence of an issued prescription in the three months preceding or one month after the date of diagnosis.

**Statistical Analyses**

We will describe the characteristics at baseline for individuals with IBD, RA and PsA separately in comparison to the matched unexposed cohort. We will evaluate differences in characteristics at entry between those with and without systemic inflammatory disease using the $\chi^2$ test for categorical variables and the unpaired t-test for continuous data. All reported $P$-values will be two-sided.

Event rates for the primary and secondary outcomes will be compared in individuals with and without systemic inflammatory disease, calculated as the number of events divided by the total person-years of follow-up, and expressed as the number per 1000 person-years.

**Risk of VTE**

We will estimate the risk of VTE overall, and for PE and DVT separately, using unadjusted Cox proportional hazards models, stratified by matched set (exposed cohort versus unexposed cohort), to provide overall hazard ratios for the association with each outcome. Models will be subsequently adjusted for sociodemographic and clinical and VTE risk factors in
multivariable analysis. We will then repeat the same analyses for each autoimmune condition separately.

**Predictors of VTE**
Subsequently, we will run multivariable Cox models to examine the relative influence of individual VTE risk factors in the cohort with systemic inflammatory disease and control cohort. We will then explore the impact of changing platelet count over the study follow-up on VTE risk by including platelet count as a time varying exposure in survival models.

**Sensitivity analysis**
To check the sensitivity of findings to the date of introduction of the quality and outcomes framework (QOF), we will repeat the main analyses with the study follow-up for exposed individuals beginning on the latest of the date of diagnosis indicated by first diagnostic code, January 1 2004 or 180 days after practice registration.

All statistical analyses will be performed in R statistical package.

**Ethics approval**
Study approval will be requested from the Research Committee of the RCGP RSC. The study does not meet the requirements for formal ethics board review as defined using the NHS Health Research Authority research decision tool (http://www.hra-decisiontools.org.uk/research/).

**Contributors**
Research support for this project in several areas including data analysis, literature searching, and medication writing will be provided by Momentum Data. John Dennis and Andrew McGovern of Momentum Data have contributed to the writing of this protocol and to the study design. Funding for these studies has been provided by Pfizer UK.
Scientific rigor and study registration

The team ethos at Momentum Data is to support the highest quality research, for patient benefit, with rigorous scientific standards. Publication bias remains an issue in observational studies. Therefore, if approval is granted the protocol will be registered as an observational study with ClinicalTrials.gov and made publicly available prior to the commencement of data analysis. Any protocol amendments will be published alongside this public record of the study and will be noted in any final publication with the rationale for the modification. Any changes will be assessed for the need for ethics approval and further RCGP RSC study approval; these will be sought if required.
References


2. Branchford BR, Carpenter SL. The Role of Inflammation in Venous Thromboembolism. *Frontiers in pediatrics* 2018; 6: 142-.


