Venous thromboembolism in people with idiopathic pulmonary fibrosis: a population-based study

To the Editor:

Laboratory studies and animal models have suggested that the activation of the clotting cascade may be important in the pathogenesis of idiopathic pulmonary fibrosis (IPF) [1–3]. Epidemiological studies have also suggested a strong association between IPF and venous thromboembolism (VTE) [4–6]. We estimated the incidence of pulmonary embolus and deep vein thrombosis (DVT) in people with IPF and the general population, and compared these with the prevalence of a warfarin prescription.

We used data from THIN (The Health Improvement Network; www.thin-uk.com), a UK longitudinal database of electronic primary care records containing information recorded in routine clinical care, from face-to-face consultations, and following communication from secondary care. Medical and diagnostic data are entered using medical Read codes, a comprehensive list of medical terms for signs, symptoms, diagnoses, procedures and investigations. We used the Read codes H563.00 (idiopathic fibrosing alveolitis), H563.11 (Hamman–Rich syndrome), H563.12 (cryptogenic fibrosing alveolitis), H563100 (diffuse pulmonary fibrosis) and H563z00 (idiopathic fibrosing alveolitis NOS) to identify incident cases of IPF clinical syndrome (IPF-CS).

Cases were included if they were first diagnosed after January 1, 2000, and ≥12 months after registration. We excluded people under 40 years at diagnosis, as well as those with co-existing connective tissue disease, extrinsic allergic alveolitis, sarcoidosis, pneumoconiosis and asbestosis because it is not clear in this subset which diagnoses were correct. For each incident case of IPF-CS, we randomly selected up to four general population controls, matched on age, sex and general practice. Each case was assigned an index date that corresponded to their first diagnosis of IPF-CS; matched controls were assigned the same date as their case.

We identified individuals with a record of pulmonary embolus or DVT after diagnosis of IPF-CS, excluding those who had a pulmonary embolus or DVT prior to the index date. Cox regression was used to estimate incidence rate ratios of pulmonary embolus and DVT in people with IPF-CS compared with controls, adjusting for the matching variables, smoking and warfarin prescription. We also compared the prevalence of warfarin prescription between cases and controls prior to the index date using conditional logistic regression. Proportional hazards assumption was confirmed graphically. Likelihood ratio tests were used for all hypothesis testing. Statistical analyses were conducted using Stata version 12 (StataCorp, College Station, TX, USA).

We identified 3211 incident cases of IPF-CS and 12 307 matched controls. The cases were mainly male (63.9%) and mean ± SD age at diagnosis was 75.7 ± 9.8 years. Median (interquartile range) follow-up after the index date was 1.7 (0.6–3.6) years in cases and 3.3 (1.5–5.8) years for controls. During this time, 2.4% of cases and 0.6% of controls had a recorded pulmonary embolus and 1.1% of cases and 0.9% of controls had a diagnosis of DVT. Cases were more likely to have been prescribed warfarin (OR 1.52, 95% CI 1.34–1.73; p<0.001) prior to the index date. After adjusting for matching factors, smoking and warfarin prescription, the rates of pulmonary embolus and DVT were six and two times higher, respectively, in people with IPF compared with controls (table 1). There was no evidence that the proportional hazards assumptions were not met.

In this large population based study, we found that people with IPF have higher incidence rates of pulmonary embolus and DVT, and are more likely to be prescribed warfarin, compared with the general population. Possible explanations for our finding include 1) IPF increasing the risk of VTE, and 2) a prothrombotic state leading to the development of IPF and VTE. This study supports the hypothesis that activation of the coagulation cascade may be involved in the pathogenesis of IPF [2, 7].
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cases</th>
<th></th>
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<th>Controls</th>
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<th>Rate ratio# (95% CI)</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>Events n</td>
<td>Person-years</td>
<td>Crude rate per 1000 person-years (95% CI)</td>
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<td>Person-years</td>
<td>Crude rate per 1000 person-years (95% CI)</td>
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<tr>
<td>Pulmonary embolus</td>
<td>72</td>
<td>7.8</td>
<td>9.3 [7.4–11.7]</td>
<td>74</td>
<td>48.4</td>
<td>1.53 [1.2–1.9]</td>
<td>6.42 [4.30–9.57]</td>
<td>&lt;0.001</td>
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<tr>
<td>Deep vein thrombosis</td>
<td>33</td>
<td>7.7</td>
<td>4.3 [3.0–6.0]</td>
<td>106</td>
<td>48.1</td>
<td>2.2 [1.8–2.7]</td>
<td>2.11 [1.37–3.27]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\# adjusted for matching variables, smoking habit and warfarin prescription.
References