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

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Introduction:

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

Methods:

We used data from The Health Improvement Network (THIN), 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. [7] 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 Idiopathic Pulmonary Fibrosis Clinical Syndrome (IPF-CS).

Cases were included if they were first diagnosed after January 1st 2000 and at least 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, gender and general practice. Each case was assigned an index date which 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 PE or DVT after diagnosis of IPF-CS, excluding those who had a PE or DVT prior to the index date. Cox regression was used to estimate incidence rate ratios of PE and DVT in people with IPF-CS compared to 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 (Texas).

Results:

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

Conclusion:

In this large population based study, we found that people with IPF have higher incidence rates of PE and DVT and are more likely to be prescribed warfarin compared to the general population. Possible explanations for our finding include a) IPF increasing the risk of VTE or b) a prothombotic 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.[2,8]

Table 1: Incidence rates and rate ratios for pulmonary embolus and deep vein thrombosis

Outcome	Number of events in cases	Person-years	Crude rate in cases (per 1000 pyrs) (95% CI)	Number of events in controls	Person-years	Crude rate in controls (per 1000 pyrs) (95% CI)	Rate ratio* (95% CI)	p value
Pulmonary embolus	72	7.8	9.3 (7.4-11.7)	74	48.4	1.53 (1.2-1.9)	6.42 (4.30-9.57)	<0.001
Deep Vein Thrombosis	33	7.7	4.3 (3.0-6.0)	106	48.1	2.2 (1.8-2.7)	2.11 (1.37-3.27)	<0.001

*Rate ratios stratified for matching variables, smoking habit, and warfarin prescription

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Author's contributions:

VN, HAP, AWF and RBH conceived and designed the study. WD, HAP, RBH and VN were involved in the analyses of the data. WD, HAP, AWF, RBH and VN were involved in the interpretation of the data and in writing or revising the manuscript before submission.

VN takes responsibility for the integrity of the work in this manuscript and is the guarantor of the manuscript.