

# The Association between Idiopathic Pulmonary Fibrosis and Vascular Disease

## A Population-based Study

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**Rationale:** Previous studies have suggested that people with idiopathic pulmonary fibrosis (IPF) may be at increased risk of vascular disease.

**Objectives:** To quantify the risk of cardiovascular disease before and after a diagnosis of IPF.

**Methods:** We used computerized primary care data from the Health Improvement Network to quantify the relative risk of having a cardiovascular event (acute coronary syndrome, angina, atrial fibrillation, deep-vein thrombosis, and cerebrovascular accident) either before or after having a diagnosis of IPF in comparison to age, sex, and community-matched general population control subjects.

**Measurements and Main Results:** Our study included 920 incident case subjects of IPF (mean age at diagnosis, 71 yr; 62% male) and 3,593 matched control subjects. There was an increased risk of acute coronary syndrome (odds ratio [OR], 1.53; 95% confidence interval [CI], 1.15–2.03), angina (OR, 1.84; 95% CI, 1.48–2.29) and deep-vein thrombosis (OR, 1.98; 95% CI, 1.13–3.48) in the period before the diagnosis of IPF. During the follow-up period, there was a marked increased risk of acute coronary syndrome (rate ratio [RR], 3.14; 95% CI, 2.02–4.87) and deep-vein thrombosis (RR, 3.39; 95% CI, 1.57–7.28). None of these estimates were confounded by smoking habit or modified by age or sex.

**Conclusions:** People with IPF have an increased risk of vascular disease in comparison with the general population. This effect is most marked for acute coronary syndrome and deep-vein thrombosis after the diagnosis of IPF has been made.

**Keywords:** idiopathic pulmonary fibrosis; cardiovascular disease; deep vein thrombosis

Our best current estimates of the incidence of idiopathic pulmonary fibrosis (IPF) suggest that there are more than 21,000 new cases diagnosed each year in the United States and that the equivalent figure for the United Kingdom is 4,200 (1, 2). The median survival after diagnosis for these people is about 3 years, and there are no treatments that have been shown to improve survival (1, 3–5). IPF is therefore a significant public health problem in the United States and Europe.

The most common cause of death in people with IPF is progression of their underlying lung disease, but there is evidence that the incidence of other diseases, such as lung cancer, may be increased in people with IPF (6–11). This is interesting, because such associations may shed light on the etiology and/or pathogenesis of IPF, and highlight the need for a comprehensive approach to the care of people with IPF. A previous review by

### AT A GLANCE COMMENTARY

#### Scientific Knowledge on the Subject

There is concern among interstitial lung disease specialists that patients with IPF may have an increased incidence of acute vascular disease. To date, no controlled studies have attempted to quantify this relationship.

#### What This Study Adds to the Field

Our results show that patients with IPF have an increased risk of acute coronary syndrome and deep-vein thrombosis.

Panos and colleagues (6) highlighted a possible increase in cardiovascular disease in people with IPF, and evidence supporting this observation comes from a recent uncontrolled autopsy study in which 9 out of 42 people with IPF died from a cardiovascular event (8). Furthermore, in a study of 630 people referred for lung transplantation, Kizer and colleagues (12) found that people with IPF were more than twice as likely to have angiographic evidence of coronary artery disease as people with nonfibrotic lung diseases.

The aim of this study was to quantify the risk of cardiovascular disease in people with IPF in comparison to the general population, both before and after the time of the IPF diagnosis. The results will help to determine whether heightened surveillance and/or prevention strategies are needed in people with IPF, and whether management guidelines should be modified accordingly. Some of the results of this study have previously been reported in the form of an abstract at the British Thoracic Society Winter Meeting 2007 (13).

### METHODS

In this study, we have used data from the Health Improvement Network that is a longitudinal, computerized, primary-care dataset. The dataset for this study has previously been used to determine the incidence and survival of IPF in the United Kingdom (1).

Our overall study design included a case-control analysis to quantify the risk of having an acute coronary syndrome, and a range of other cardiovascular outcomes, in people with IPF before their diagnosis compared with the general population, and a cohort analysis to determine whether the incidence of these outcomes was increased during the follow-up period.

The methods for defining the study populations have been described elsewhere in detail (1). Briefly, we used data from the Health Improvement Network to identify a cohort of 920 incident case subjects with IPF and 3,593 age-, sex-, and community-matched control subjects. Cases were defined as being incident if the subject's first recorded diagnosis of IPF was preceded by at least 12 months of computerized data. We have previously validated this method using hospital records (10).

Each case was assigned an index date corresponding to the first recorded diagnosis of IPF, and matching control subjects were assigned

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an identical date. This enabled us to divide the data into the period before IPF diagnosis (pre-index date) for the case-control study, and subsequent follow-up time (post-index date) for the cohort analysis.

We extracted data on diagnoses of acute coronary syndromes (coded as acute myocardial infarctions, acute coronary syndromes, and unstable angina), cerebrovascular accidents, stable angina, atrial fibrillation and deep-vein thrombosis, prescriptions for warfarin, aspirin,  $\beta$  blockers, amiodarone, angiotensin-converting enzyme (ACE) inhibitors, statins, and smoking habit, both before and after the index date for both case and control subjects. For our case-control study, we compared the odds of pre-index date exposures/events between case and control subjects using conditional logistic regression (STATA version 9; StataCorp, LP, College Station, TX). In these analyses, we looked for evidence of confounding by smoking habit by adding this variable to our model. We also looked for evidence of effect modification by age and sex.

For our cohort analysis of disease incidence during follow-up time, we used the Cox regression. In these analyses, we used the index date as the start date, and the date of the outcome or last data collection as the finish date. These cohort analyses were stratified to allow for the cohort matching (14). For each of the cohort analyses, we excluded people who had the relevant outcome before the index date to ensure that we were only studying new, first-time incident outcomes. We used a similar strategy to that outlined above to look for evidence of confounding and effect modification.

With 920 case subjects and 3,593 control subjects available for our case-control study, we had in excess of 90% power to detect odds ratios (ORs) of 1.75 or greater for exposures affecting 5% of control subjects or more, and to detect ORs of 1.5 or greater for exposures affecting 10% of control subjects or more. The study protocol was reviewed and approved by the Nottingham Research Ethics Committee.

## RESULTS

The demographic details of our 920 case subjects and 3,593 matched control subjects have been reported before (1). The mean age of case subjects at diagnosis was 71 years (SD, 11 yr), and 568 (62%) were male. Case subjects were marginally more likely to be a current or ex-smoker than were control subjects, but this difference was not significant at the 5% level (Table 1).

### Case-Control Analysis of the Association between Acute Coronary Syndromes and Idiopathic Pulmonary Fibrosis

The mean duration of computerized records before index date was 7.8 years (SD, 3.9 yr) for case subjects and 7.7 years (SD, 3.9 yr) for control subjects. The distribution of medical diagnoses and drug use during this time is shown in Table 1. Case subjects had a 50% increase in the risk of having a diagnosis of an acute coronary syndrome recorded compared with control subjects (OR, 1.53; 95% confidence interval [CI]: 1.15–2.03) before receiving a diagnosis of IPF. Case subjects were also approximately twice as likely as control subjects to have a diagnosis recorded of deep-vein thrombosis (OR, 1.98; 95% CI, 1.13–3.48) or angina (OR, 1.84; 95% CI, 1.48–2.29), but had no increase in the risk of having atrial fibrillation or a cerebrovascular accident. The use of warfarin, aspirin, and ACE inhibitors was increased in people with IPF compared with the general population control subjects, but use of statins and  $\beta$  blockers was similar between the two groups. Our case subjects were more likely than control subjects to have a prescription for amiodarone—this is an important observation, because amiodarone is a cause of fibrotic lung disease (15). On the basis of the exposure rate among our control subjects, we expected that 15 of our case subjects would have amiodarone exposure, but the observed number was 34 (OR, 2.33; 95% CI, 1.50–3.63). There was no evidence of confounding by smoking habit, or effect modification by age and sex for any of our findings.

**TABLE 1. THE ASSOCIATION BETWEEN IDIOPATHIC PULMONARY FIBROSIS AND ACUTE CORONARY EVENTS AND OTHER OUTCOMES/EXPOSURES IN THE TIME BEFORE THE DIAGNOSIS OF IDIOPATHIC PULMONARY FIBROSIS: CASE-CONTROL ANALYSIS**

Characteristic	Case Subjects n (%) (n = 920)	Control Subjects n (%) (n = 3,593)	OR (95% CI)
<b>Cardiovascular outcome</b>			
Acute coronary syndrome	72 (8%)	192 (5%)	1.53 (1.15–2.03)
Angina	143 (16%)	339 (9%)	1.84 (1.48–2.29)
Atrial fibrillation	54 (6%)	160 (4%)	1.34 (0.98–1.85)
Deep-vein thrombosis	19 (2%)	38 (1%)	1.98 (1.13–3.48)
Cerebrovascular accident	53 (6%)	191 (5%)	1.09 (0.79–1.50)
<b>Medication</b>			
Warfarin	73 (8%)	159 (4%)	1.86 (1.39–2.48)
Aspirin	275 (30%)	890 (25%)	1.36 (1.14–1.61)
Amiodarone	34 (4%)	61 (2%)	2.33 (1.50–3.63)
$\beta$ -blocker	194 (21%)	820 (23%)	0.91 (0.76–1.09)
ACE inhibitor	235 (26%)	512 (14%)	2.16 (1.79–2.59)
Statin	82 (9%)	305 (8%)	1.08 (0.82–1.41)
<b>Smoking status</b>			
Nonsmoker	355 (39%)	1,420 (40%)	1.00 (—)
Current or ex-smoker	432 (47%)	1,591 (44%)	1.11 (0.94–1.31)
Missing data	133 (14%)	582 (16%)	

*Definition of abbreviations:* ACE = angiotensin-converting enzyme; CI = confidence interval; OR = odds ratio.

### Incidence of Cardiovascular Disease during Follow-up

For people with a diagnosis of IPF, the mean years of follow-up after index date was 2.7; the equivalent figure for control subjects was 3.9 years. During the follow-up period, the incidence rate for new, first-time acute coronary syndromes in people with IPF was 19.3 per 1,000 person-years, compared with a general population rate of 8.5 per 1,000 person-years. This means that the additional rate of acute coronary syndromes occurring in association with a diagnosis of IPF was 10.8 per 1,000 person-years for people with IPF. In relative terms, the rate ratio (RR) for this increase was 3.14 (95% CI, 2.02–4.87; Table 2). The cumulative incidence for acute coronary syndromes for the two cohorts is shown in Figure 1.

A similar, large increase in the incidence of deep-vein thrombosis was present, with an incidence rate of 5.9 per 1,000 person-years in people with IPF and 2.1 per 1,000 person-years in the general population. The incidence of both new cerebrovascular accidents and atrial fibrillation was higher in people with IPF compared with the general population, but the 95% CIs for these included unity. None of these RRs were changed appreciably by adjusting our analyses for smoking habit or use of statins, aspirin, amiodarone,  $\beta$  blockers, warfarin, or ACE-inhibitors. In a *post hoc*, restricted analysis, in which case and control subjects with exposure to amiodarone were excluded, we found that the association between IPF and incidence of acute coronary syndromes remained very similar to our inclusive estimate (RR, 3.29; 95% CI, 2.11–5.13). In addition there was no evidence of effect modification by age or sex, or that the proportional hazards assumptions for our final models were not met.

In order to investigate whether people with IPF had a lower level of treatment with cardioprotective drugs during follow-up, we examined the distribution of use of a number of medications during the time before the acute coronary syndrome using data from both before and after the index date (Table 3). The results of this analysis show that, overall, the rates of aspirin use were similar between people with and without IPF, although the use of ACE inhibitors and warfarin was higher in people with IPF, and the use of statins and  $\beta$  blockers was lower. Overall, the use of amiodarone was marginally higher in people with IPF, but

**TABLE 2. INCIDENCE OF NEW CARDIOVASCULAR EVENTS DURING FOLLOW-UP TIME: COHORT ANALYSIS**

Incident cardiovascular outcomes*	No. of Case Subjects	No. of Control Subjects	No. of New Events in Case Subjects	No. of New Events in Control Subjects	RR (95% CI)
Incident cardiovascular outcomes*					
Acute coronary syndrome	848	3,401	43	113	3.14 (2.02–4.87)
Angina	777	3,254	30	747	1.23 (0.79–1.89)
Atrial fibrillation	866	3,433	24	842	1.55 (0.95–2.54)
Deep-vein thrombosis	901	3,555	14	29	3.39 (1.57–7.28)
Cerebrovascular accident	867	3,402	25	125	1.60 (0.98–2.62)

Definition of abbreviation: CI = confidence interval; RR = rate ratio.

\* Case and control subjects with a prior diagnosis recorded before the index date are excluded from the follow-up analysis, and so the number of case and control subjects varies between analyses.

this was entirely explained by the higher rate of exposure before the diagnosis of IPF. During the follow-up period, the rate of exposure to amiodarone was 1.7% for case subjects and 1.9% for control subjects.

**DISCUSSION**

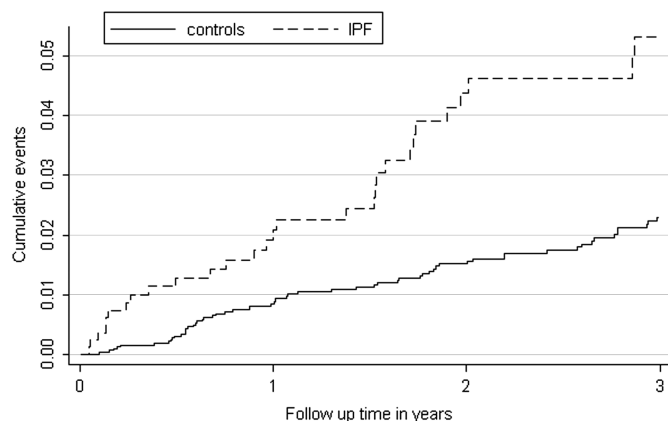
In this large, general population-based study of people with IPF, we have found a small increase in the risk of having an acute coronary event before the diagnosis of IPF was made, and a larger increase in risk during the subsequent follow-up period. We have also found that the risk of having a deep-vein thrombosis is increased in people with IPF compared with the general population both before and after the diagnosis of IPF is first recorded. In absolute terms, our results show that, if a cohort of 100 people with newly diagnosed IPF were followed for 3 years, they would have six acute coronary events and two deep-vein thromboses, whereas an age- and sex-matched general population cohort of the same size would have three acute coronary events and one deep-vein thrombosis. People with IPF were less likely to be prescribed statins and  $\beta$  blockers than the general population, and more likely to be prescribed ACE inhibitors, amiodarone, and warfarin.

**Strengths and Limitations of Our Data**

The main strengths of our study are its large size and the ability to study drug use and medical outcomes over a prolonged period of time. The validity of interstitial lung disease diagnoses has previously been examined in computerized, general-practice databases, and been found to be high; in addition, the age

distribution and survival of individuals in our study population with a diagnosis of IPF is similar to that seen in other general population-based cohorts of people with IPF (3, 10, 16). Interestingly, we found that our case subjects were more likely to have had a prescription for amiodarone than their matched control subjects. We had 34 exposed case subjects, although we only expected to have 15. Because amiodarone can cause lung fibrosis, it is possible that the additional 19 case subjects (2% of the total case subjects) were diagnosed as such due to amiodarone exposure, and did not have IPF. On the other hand, given that the risk of having had an acute coronary syndrome was higher in people with IPF even before the diagnosis of lung disease was made, it is possible that some of the excess prescription of amiodarone merely reflects the increased prevalence of coronary artery disease in the population of people with as-yet undiagnosed IPF. Importantly, removal of all people with amiodarone exposure did not change the association between IPF and acute coronary syndrome in our subsequent cohort study.

The validity of diagnoses of death and acute myocardial infarction have also been tested in computerized, general-practice databases, and have been found to be high (17, 18). The data on drug exposures are derived directly from the software used to generate the prescriptions, and so the validity of these data is also likely to be high, although we cannot be sure that individuals take all of the drugs that they are prescribed. For the case-control analysis the information on exposure status was collected before the diagnosis of IPF was first recorded, and so there should be no recall or other information bias. It seems likely, however, that some cases of IPF may be misdiagnosed initially as left ventricular failure, and this may well explain the increase in exposure to ACE inhibitors. We have previously shown similar effects for diuretics (19). For the



**Figure 1.** The cumulative incidence of first-time acute coronary syndromes in people with idiopathic pulmonary fibrosis (IPF) and control subjects during the follow-up period.

**TABLE 3. PRESCRIPTIONS FOR DRUGS AT ANY POINT BEFORE INCIDENT ACUTE CORONARY EVENT**

Drug	Case Subjects n (%) (n = 848)*	Control Subjects n (%) (n = 3,401)	P Value <sup>†</sup>
Statins	115 (14)	597 (18)	0.006
Aspirin	311 (37)	1199 (35)	0.500
Amiodarone	29 (3.4)	89 (2.6)	0.200
$\beta$ -blockers	187 (22)	989 (29)	0.0001
ACE-inhibitors	253 (30)	774 (23)	0.0001
Warfarin	98 (12)	221 (7)	0.0001

Definition of abbreviation: ACE = angiotensin-converting enzyme.

\* Data set excludes case and control subjects with an acute coronary event before index date.

<sup>†</sup> Chi-square test.

cohort analysis, however, it is possible that people with IPF are investigated in more detail than the general population, and so there may be some ascertainment bias, which may have led to an overestimate of the association between cardiovascular disease outcomes and the presence of IPF. It is unlikely that any ascertainment bias will be specific to any particular cardiovascular outcome, and, thus, the lack of association between IPF and incident angina argues against a strong effect of ascertainment bias in this dataset.

### Findings from Other Studies

In a previous review of a number of natural history studies, Panos and colleagues (6) highlighted a possible increase in deaths from ischemic heart disease and pulmonary embolism in people with IPF. Data supporting these findings come from a series of post-mortem reports, and the interesting observation that, after lung transplantation, pulmonary embolism appears more common in people with IPF (8, 20). Kizer and colleagues (12) reviewed the clinical data of 630 people referred for lung transplantation at the Hospital of the University of Pennsylvania. They divided this population into 186 people with fibrotic lung disease, in which IPF was the most common diagnosis ( $n = 76$ ), and 444 people with nonfibrotic lung disease, in which chronic obstructive pulmonary disease was the most common diagnosis ( $n = 330$ ). After adjusting carefully for age, sex, smoking habit, race, blood pressure, cholesterol, diabetes, and family history of heart disease, they found an increased prevalence of coronary artery disease detected by angiography in people with fibrotic lung disease (OR, 2.18; 95% CI, 1.17–4.06). This increase remained in the subgroup of people with IPF (OR, 2.31; 95% CI, 1.11–4.82). The risk of coronary artery disease was also higher in the subset of people with granulomatous fibrotic lung disease compared with people with nonfibrotic lung disease, although this increase was not statistically significant at the 5% level (OR, 1.56; 95% CI, 0.47–5.16). The authors concluded that the prevalence of coronary artery disease was higher in people with end-stage fibrotic lung diseases compared with people with other end-stage lung diseases, but highlighted that this increase in risk may not be the same for all types of fibrotic lung diseases.

### Possible Mechanisms

Our finding of an association between diagnoses of angina, acute coronary syndromes, and deep-vein thrombosis may have a number of explanations. First, it is possible that reverse causation is present such that the presence of IPF increases the incidence of these outcomes. Certainly, the results of the subsequent survival analysis suggest that the increased risk of acute coronary syndromes is, if anything, greater after the diagnosis of IPF than before the diagnosis. Even allowing for the presence of some ascertainment bias, this supports the hypothesis that IPF causes acute coronary syndromes rather than the other way around. If this is the case, a number of mechanisms might be important, such as hypoxia exacerbating angina and decreased mobility causing deep-vein thrombosis. In addition, it is possible that the presence of a serious lung disease might distract medical attention from routine cardiovascular care, and mean that primary and secondary prevention interventions are neglected. In keeping with this hypothesis, people with IPF were less likely to receive statins and  $\beta$  blockers than the general-population control subjects.

Alternatively, it is possible that IPF, acute coronary syndromes, deep-vein thromboses, and angina all share common etiological factors. Such factors might include environmental factors, such as early-life experience or host factors, such as genetic makeup (21, 22). One emerging and potentially important shared

host risk factor may be an increased tendency to clot. Data from the Copenhagen City Heart Study has shown that people with factor V Leiden genes, who are genetically predisposed to hypercoagulability, have an accelerated decline in lung function, and that this tends to result in a restrictive defect (23). Furthermore, there is evidence that the clotting cascade is activated in lung fibrosis (24). In addition one small prospective study by Kudo and colleagues (25) reported that individuals with IPF who received anticoagulation therapy had a reduction in mortality over a median follow-up period of approximately 1 year.

### Conclusions

Our findings suggest that patients with IPF have a marked relative increase in the risk of vascular disease, and this should be considered during the routine care of these patients. Our findings also provide further support for a possible trial of anticoagulation in people with IPF to determine whether this has a beneficial effect on the outcome of this devastating disease.

**Conflict of Interest Statement:** None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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