

**Pulmonary Fibrosis is Associated with an Elevated Risk of Thromboembolic Disease**

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**List of Abbreviations:**

<b>AE-IPF</b>	<b>Acute exacerbation of idiopathic pulmonary fibrosis</b>
<b>COPD</b>	<b>Chronic obstructive pulmonary disease</b>
<b>DVT</b>	<b>Deep-venous thrombosis</b>
<b>ICD</b>	<b>International classification of diseases</b>
<b>ILD</b>	<b>Interstitial lung disease</b>
<b>IPF</b>	<b>Idiopathic pulmonary fibrosis</b>
<b>NCHS</b>	<b>National Center for Health Statistics</b>
<b>PE</b>	<b>Pulmonary embolism</b>
<b>PF</b>	<b>Pulmonary fibrosis</b>
<b>PIPF</b>	<b>Post-inflammatory pulmonary fibrosis</b>
<b>UCD</b>	<b>Underlying cause-of-death</b>
<b>VTE</b>	<b>Venous thromboembolism</b>

**Abstract:**

*Rationale: Recent epidemiologic studies have suggested an increased risk of venous thromboembolic disease (VTE) in lung fibrosis. Large-scale epidemiologic data regarding the risk of VTE in pulmonary fibrosis-associated mortality have not been published.*

*Methods: Using data from the National Center for Health Statistics from 1988-2007, we determined the risk of VTE in decedents with pulmonary fibrosis in the United States.*

*Main Results: We analyzed 46,450,489 records, of which 218,991 met our criteria for "Idiopathic Pulmonary Fibrosis." Among these, 3,815 records also contained a diagnostic code for VTE (1.74%). The risk of VTE in pulmonary fibrosis decedents was 34% higher than in the background population, and 44% and 54% greater than among decedents with COPD and lung cancer, respectively. Those with VTE and pulmonary fibrosis died at a younger age than those with pulmonary fibrosis alone (for women: 74.3 years vs. 77.4 years,  $p < 0.0001$ ; for men: 72 years vs. 74.4 years,  $p < 0.0001$ ).*

*Conclusions: Decedents with pulmonary fibrosis have a significantly greater risk of VTE. Those with VTE and pulmonary fibrosis die at a younger age than those with pulmonary fibrosis alone. These data suggest a link between a pro-fibrotic and a pro-coagulant state.*

**Keywords:****Epidemiology****Idiopathic Pulmonary Fibrosis****Mortality****Pulmonary Fibrosis****Venous Thromboembolism**

**Introduction:**

Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias, and recently published epidemiologic data suggest that the burden of disease is rising. The incidence and mortality rates for IPF – and pulmonary fibrosis (PF) in general – have been increasing steadily. [1-6] IPF is a deadly disease, with a median survival after diagnosis ranging from 3 to 5 years [7] and no therapy other than lung transplantation has been shown to prolong survival.

In a recently conducted epidemiologic study of 920 subjects, an increased risk for venous thromboembolism (VTE) was found among people both before and after the onset of PF. [8] In a separate study that included all Danish PF patients from 1980 to 2007, a prior history of VTE was found to increase the risk of developing interstitial lung disease (ILD). [9] Although these studies hint at a relationship between VTE and PF, large-scale epidemiologic data about the risk of VTE in PF-associated mortality has not been published.

At the molecular level, activation of the coagulation cascade, via the tissue factor-dependent extrinsic pathway, and as evidenced by elevated levels of tissue factor and fibrin (the main component of clots), occurs in lung tissue from patients with IPF. [10] Data also suggest abnormalities in intrinsic anti-coagulation pathways: bronchoalveolar lavage fluid from patients with IPF reveals decreased protein C activation. [11] Further, fibrinolysis appears to be dysregulated: models of lung fibrosis have revealed elevated levels of plasminogen activator inhibitor-1 (PAI-1), thus promoting fibrin persistence. [12]

Based on these data, we hypothesized that an excessive number of VTE would be found in patients with IPF in U.S. decedents from 1988-2007, and that among IPF decedents, the presence of VTE would be associated with a younger age of death.

**Methods:**

*Database:* Details of the database and methods have been published previously. [6] Briefly, we used the U.S. Multiple Cause-of-Death mortality database (Centers for Disease Control and Prevention, National Center for Health Statistics) [13], for which the National Center for Health Statistics (NCHS) compiles data from all death certificates in the United States and releases the figures in yearly public-use files. For this study, we analyzed files from 1988-2007. [13,14] An annual file contains over two million decedent records, and each record contains decedent demographics, up to 20 conditions related to death within a section of the record the NCHS calls the “record axis,” and the ultimate underlying cause-of-death (UCD) – defined by the World Health Organization as “the disease or injury which initiated the train of events leading to death.” [14,15]

From 1988 to 1998, the NCHS coded conditions related to death using the Ninth Revision of the International Classification of Diseases (ICD-9). [16] Thereafter, the NCHS coded conditions related to death using the Tenth Revision of the ICD (ICD-10). [14] All data contained in these database files have been de-identified and are of public record; therefore, Institutional Review Board (IRB) approval for this study was not required.

***Case definitions:***

We included files from any U.S. decedent with “Idiopathic Pulmonary Fibrosis” (IPF) as defined by the following ICD codes: from 1988 to 1998, ICD-9 codes 515 (post-inflammatory pulmonary fibrosis [PIPF]) or 515.6 (IPF), and thereafter, ICD-10 code J84.1 (a code that combines both PIPF and IPF). We then excluded patients with record axis codes for any condition that might be associated with secondary PF including connective tissue diseases, radiation fibrosis, asbestosis, pneumoconiosis (including coal workers’ pneumoconiosis, silicosis, talcosis, and berylliosis), sarcoidosis, and/or extrinsic allergic alveolitis (hypersensitivity pneumonitis). In addition, we excluded patients with a concurrent diagnosis of COPD or lung cancer. We identified three groups for comparison purposes: 1) the background population, that included decedents without IPF, lung cancer, or COPD; 2) decedents with COPD (but not IPF or lung cancer); and 3) decedents with lung cancer (but not IPF). Venous thromboembolic (VTE) disease was defined as either venous thrombosis or pulmonary embolism. From 1988 through 1998, we defined venous thrombosis by ICD-9 codes 451 through 451.8 or 453 through 453.9) and pulmonary embolism by ICD-9 code 415.1, while after 1998 we used ICD-10 codes I80 through I80.9, I82.8, or I82.9 to define venous thrombosis and ICD-10 codes I26 through I26.9 to define pulmonary embolism. Specifics of additional ICD-9 and ICD-10 codes are included in the Appendix.

***Statistical analysis:***

We used Chi-Square (or Mantel-Haenszel statistic where appropriate) to determine the risk of VTE in decedents with IPF in reference to the three comparators groups. We then performed logistic regression to determine the adjusted risk of VTE in decedents with IPF in reference to

the three comparator groups. When comparing the risk of VTE in decedents with IPF to the background population, we assessed for second order interactions between IPF and gender, age, and year of diagnosis. We also used the Chi-Square statistic to compare differences in the UCD between PF decedents with or without VTE. A two-sample t-test was used to compare the mean age of death between PF decedents with or without VTE. A *p-value* of  $< 0.05$  was considered to represent statistical significance in all analyses. All data were analyzed using SAS® version 9.1 (SAS Institute, Cary, NC).



**Results:**

From 1988 to 2007, there were 46,450,489 deaths in U.S. residents. A total of 218,991 records met our criteria for a diagnosis of IPF. Among these, 3,815 records also contained a diagnostic code for VTE (Table 1), yielding a prevalence of VTE in IPF that was significantly greater than in the background population (1.74% vs. 1.33%,  $p < 0.0001$ ). Thus, the overall odds of being diagnosed with a VTE was significantly greater in decedents with IPF than in decedents in the background population (overall OR 1.34; 95% CI = 1.29-1.38). In the year-by-year analysis, the risk of VTE was greater for IPF than the background population in every year except 2005 ( $p = 0.25$ ).

After stratifying on sex and age, female decedents with IPF in age strata 65-74 years, 75-84 years, and those 85 years and older – but not females younger than 65 years – had a significantly greater risk of VTE than the background population (Figure 1). Among male decedents with IPF, the risk of VTE was significantly greater than the background population for all age strata. (Figure 2)

Using logistic regression and adjusting for sex, age, and year of death, the risk of VTE remained significantly greater in decedents with IPF than to the background population (adjusted OR = 1.34; 95% CI 1.29-1.38). Among all decedents, men had a significantly lower risk of VTE (OR = 0.75; 95% CI = 0.74-0.75) than females; and increasing age conferred a slightly lower, but significant, risk of VTE (OR = 0.99; 95% CI = 0.99-.099). From 1988 to 2007, the overall risk of VTE increased slightly with each passing year (OR = 1.01; 95% CI = 1.01-1.01).

When interactions between IPF and sex, age, and year of death were assessed, each two-way interaction was found to be statistically significant. The risk of VTE in decedents with IPF was modified by age, sex, and year of death: among decedents with IPF, increasing age, female gender, and later year of death reduced the risk of VTE. Beta coefficients, standard errors, and p values for the model that included these second order interactions are reported in Table 2.

We assessed the effects of race and gender on the risk of VTE in decedents with IPF compared to the background population. Using logistic regression, we found that the risk of VTE remained greater for IPF decedents than those in the background population when adjusting for ethnicity and race (adjusted OR = 1.39; 95% CI = 1.34-1.43). Among all decedents, when using non-Hispanic whites as the reference population, Hispanics and non-Hispanic others (including Asians) had a lower risk of VTE (OR = 0.75; 95% CI = 0.74-0.76 and OR = 0.56; 95% CI = 0.54-0.57, respectively), while non-Hispanic black decedents had an elevated risk of VTE (OR = 1.33; 95% CI = 1.32-1.34). There were no significant two-way interactions between IPF and ethnicity or race, suggesting that the risk of VTE among IPF decedents is not further altered by the decedent's race or ethnicity.

There were 3,980,364 decedents with COPD. Of these, 48,441 records also contained a code for VTE, yielding a prevalence of VTE that was significantly lower for COPD than for IPF (1.22% vs. 1.74%,  $p < 0.0001$ ) and a risk for VTE that was significantly greater in decedents with IPF (overall OR = 1.44; 95% CI = 1.39-1.49) than in those with COPD. (Figure 3, Table 3) The risk of VTE was greater for IPF than COPD in every year studied. Using logistic regression and adjusting for age (OR = 0.98; 95% CI = 0.98-0.99), male gender (OR = 0.96; 95% CI = 0.94-

0.97), and year of death (OR = 1.01; 95% CI = 1.01-1.01), the risk of VTE in decedents with IPF was found to be significantly greater than in those with COPD (adjusted OR = 1.41, 95% CI = 1.34-1.46)

There were 3,233,845 decedents with lung cancer. Of these, 36,876 records also contained a code for VTE, yielding a prevalence of VTE that was significantly lower than for IPF (1.14% vs. 1.74,  $p < 0.0001$ ) and a risk for VTE that was significantly greater in decedents with IPF (OR = 1.54; 95% CI = 1.49-1.59) than in those with lung cancer (Table 4). The risk of VTE was greater for IPF than lung cancer, in every year except 2004 ( $p = 0.53$ ) and 2005 ( $p = 0.65$ ). (Figure 4) Using logistic regression and adjusting for age (OR = 0.98; 95% CI = 0.98-0.98), male gender (OR = 0.96; 95% CI = 0.96-0.99), and year of death (OR = 1.04; 95% CI = 1.04-1.04), the risk of VTE in decedents with IPF was found to be significantly greater than in those with lung cancer (adjusted OR = 1.66, 95% CI = 1.61-1.72).

Regardless of gender, decedents with IPF and VTE were significantly younger at the time of death than those without VTE (for women, 74.3 years vs. 77.4 years,  $p < 0.0001$ ; for men, 72.0 years vs. 74.4 years,  $p < 0.0001$ ). IPF decedents with VTE were more likely than those without VTE (73.2% vs. 69.3%,  $p < 0.0001$ ) to have either VTE or IPF coded as the UCD. All other candidate conditions examined were less likely to be the UCD in the IPF decedents with VTE than in those without VTE. (Table 5)

Compared with the background population, the overall risk of VTE was lower for those with lung cancer (1.14% vs. 1.31%; OR = 0.87; 95% CI = 0.86-0.88) or COPD (1.22% vs. 1.31%; OR

= 0.93; 95% CI = 0.92-0.94). The risk of VTE was greater among decedents with COPD than those with lung cancer (lung cancer, 1.14% vs. 1.22%, OR = 1.07, 95% CI = 1.05 vs. 1.08).

**Discussion:**

Using mortality data from all United States decedents between 1988 and 2007, we found that the risk of VTE in those with IPF at the time of death was at least 34% higher than the risk of VTE in the background decedent population. We also found that the overall risk of VTE in decedents with IPF was 54% greater than for decedents with COPD, and 44% greater than for decedents with lung cancer – two conditions previously identified to confer an increased risk of VTE; [17-19]

Only a few studies have examined the relationship between VTE and IPF. Using primary care data from the United Kingdom from 1991 to 2003, Hubbard and colleagues identified a cohort of 920 patients with IPF and found that, in comparison to the general population, the risk of deep-venous thrombosis (DVT) was greater both before (OR = 1.98, 95% CI = 1.13-3.48) and even greater after (RR = 3.39, 95% CI = 1.57-7.28) the diagnosis of IPF. [8] Using hospital discharge and mortality data from 1980 through 2007, Sode and colleagues examined the association between VTE and ILD in the entire Danish population. [9] They found an increased risk for the development of ILD—many of whom likely had IPF—in people ever diagnosed with VTE. In contrast to our study, in theirs they did not exclude subjects with known-cause PF, including those with conditions that might confound the relationship between VTE and PF (e.g., connective tissue diseases and obstetrical conditions).

The risk of VTE in decedents with IPF was significantly greater than the background population for women older than 64 years and for men in every age group. In fact, male decedents with IPF appeared to be at particularly high risk for developing VTE. The reasons for these findings is

unclear. Although younger women (due to hormonal influences from the menstrual cycle, pregnancy, and contraceptives) are in a pro-coagulant state and have an elevated risk for developing VTE, we believe that in certain individuals (apparently in men more than women) particularly beyond a certain age, the fibrotic process confers an even more profound risk for VTE. [20] Although among all U.S. decedents from 1988-2007, the risk of VTE differed across race/ethnic groups, among those with IPF, the risk of VTE was not further effected by a decedent's race or ethnicity.

Somewhat surprisingly, we found a significantly greater risk for VTE in IPF than either lung cancer or COPD. Using a case-control design, Blom and colleagues studied subjects within a Dutch population and found a nearly 25-fold increased risk of VTE in patients with lung cancer when compared with control [21]. Levitan and colleagues analyzed a Medicare database and found VTE occurred more frequently in lung cancer patients (6.1 events per 1,000 lung cancer patients) than in patients with various other malignancies. [18] In another study, investigators observed that among patients who required hospital admission for an exacerbation of COPD, 25% had a pulmonary embolism. [19] Although the risk for VTE is elevated in patients with lung cancer, and emerging data suggests the same is true for certain patients with COPD, results here place IPF patients at even greater risk for mortal VTE events. The data leave little room for questioning the clinical significance of these VTE events: decedents with IPF and VTE died younger age than decedents with IPF alone, and in greater than 20% of IPF decedents with VTE, VTE itself was the underlying cause of death.

We found that the risk of VTE in both decedents with lung cancer and those with COPD was significantly lower than the background population. There are several possible explanations for this observation: the first is that the background population indeed possessed a greater risk for mortality-related VTE than decedents with COPD or lung cancer; however, because the database did not allow us to determine the presence or absence of most VTE risk factors (i.e., hereditary causes and other acquired causes of thrombophilia including tobacco abuse) or VTE therapies (i.e., anticoagulation), we could not account for these potential confounders—in any of the subgroups—in our analyses. The data for the current study concern VTE events at the time of death; thus, we know nothing of the number, type, severity, or treatment of VTE events that occurred earlier in the lives of people with COPD or lung cancer – or those in the background population. Our data should not be used to make inferences about life-long risk of VTE.

Not only is lung cancer a known risk for VTE, but once VTE is diagnosed in a patient with malignancy, current guidelines recommend that patients receive anti-coagulation for life or until the malignancy has resolved. [22] This practice could reduce the rates of VTE at the time of death in patients with lung cancer. As more data emerge regarding the risk of VTE in patients with COPD, similar trends may ensue and thus may also explain the slightly, but significantly, higher risk of VTE in patient with COPD than lung cancer. [19]

Finally, we suspect that in a great number of decedents with lung cancer, many conditions possibly contributing to death (like VTE) do not get mentioned on death certificates: the underlying malignancy simply overshadows them, and death certifiers do not write them down. We suspect the same is true for decedents with COPD: at least historically, patients with COPD

suffering a respiratory-related mortal event were overwhelmingly likely to have that event attributed to an acute exacerbation of COPD—perhaps an alternative cause (like VTE) would not have even be investigated.

If true, why would IPF patients be at risk for developing VTE? Mounting evidence suggests that the IPF micro-environment is both pro-coagulant and anti-fibrinolytic and that components in these hematologic pathways contribute to the milieu that drives the fibrotic process. [23] In fact, pro-coagulant moieties (including elevated levels of protein C and reduced thrombomodulin) have been found in the systemic circulation of some patients with IPF during abrupt disease accelerations—so-called acute exacerbations. [24] These data suggest that IPF is a hypercoaguable state.

Recognizing that IPF may be a hypercoaguable condition and that components of the coagulation cascade are either directly involved in—or activated by—fibrosis-producing machinery, Kubo and colleagues tested the hypothesis that inhibiting the coagulation cascade would lead to improved outcomes in patients with IPF. [25] They randomized 56 hospitalized Japanese patients with IPF to receive either prednisolone alone or prednisolone plus oral warfarin. Although the study did not meet its primary outcome, subjects receiving warfarin had a 3-year survival of 63% compared to 35% for subjects receiving only prednisolone ( $p=0.04$ ). In addition, when the authors examined acute exacerbations within this cohort, they found that the resultant mortality from an acute exacerbation (as well as d-dimer levels) was significantly lower in the group receiving warfarin therapy. The IPF-net, a network of U.S. institutions sponsored by the



National Institutes of Health and charged with conducting trials of therapy for IPF, is currently conducting a randomized, placebo-controlled trial of warfarin for the treatment of IPF.

Like other investigators using ICD-coded mortality data, we faced several limitations in this study; these were largely imposed by the dataset we chose to use. First, we had to rely on death certifiers to correctly identify cases and then code them appropriately. In some decedents with IPF (e.g., those whose IPF goes undiagnosed; those who are misdiagnosed as having some other lung disease), the correct diagnosis of IPF will not make it onto the death certificate. For these reasons, we believe, and others have previously demonstrated, [3,26] that PF is underreported on death certificates. Further, we could not assess the accuracy of a VTE diagnosis, and the modalities used to diagnose VTE are not captured in this data set. Clinically significant VTE is likely under-reported when clinical criteria are used, and likely over-reported when autopsy data are used. [27] Indeed, pulmonary emboli are commonly found at autopsy, and in 50-70% of cases, they were not suspected by the clinician. [28] If VTE was either under-reported or over-reported in this database, we would expect any such misclassification to be independent of whether a person had IPF or not, thus biasing the association toward the null. However, it remains possible that reporting occurred: we have no way to determine this.

Acute exacerbations of IPF (AE-IPF) have only recently gained widespread recognition in the U.S. [29]. Given this, in the past, death certifiers could have labeled IPF patients, who abruptly declined and died, with VTE (pulmonary embolism)—a reasonable potential explanation for acute decompensation and death. However, the year-by-year analysis in our study argues against this: decedents with IPF were more likely than decedents in the background population to have

VTE in every year studied, including years since the entity AE-IPF first gained traction in the U.S. If, in more recent years, decedents were being “pulled” from the VTE-as-UCD group and placed in the IPF-as-UCD group, we would have expected a steady decline in VTE rates among IPF decedents—this was not the case.

The database restricted us from identifying risk factors for VTE, including the number of episodes of VTE any decedent had in his life, heritable hypercoaguable conditions, smoking status, and the use of oral contraceptives or female sex hormones. The fact that the association between IPF and VTE held in elderly women (a group perhaps less likely to be prescribed oral contraceptives) and in men argues strongly against any confounding by female sex hormone use.

In summary, using all U.S. death certificate records from 1988 to 2007, we found that the risk of VTE in decedents with IPF was significantly greater than in 1) decedents in the background population, 2) those with lung cancer, or 3) those with COPD. These findings add to a growing data pool on the links between pro-fibrotic and pro-coagulant pathways, but should be viewed as hypothesis-generating. Nonetheless, we believe VTE should be considered in any IPF patient whose respiratory status is declining, particularly those in whom the decline is abrupt or no other cause can be identified. Research is needed to discern the interdependencies of the pro-fibrotic and pro-coagulant cascade, to determine whether IPF induces a systemic hypercoaguable state and to discover whether therapeutic disruption of coagulation leads to improved outcomes in patients with IPF.

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**Appendix :***Details of the ICD codes for excluded records*

From 1988 to 1998, records were excluded if they contained ICD-9 codes for the following conditions: connective tissue disease or rheumatoid arthritis (ICD-9 codes 710 through 710.9, or 714 through 714.9), radiation fibrosis (ICD-9 code 508.1), asbestosis (ICD-9 code 501), coal workers' pneumoconiosis (ICD-9 code 500), silicosis or talcosis (ICD-9 code 502), berylliosis and other inorganic dusts (ICD-9 code 503), unspecified pneumoconiosis (ICD-9 code 505), sarcoidosis (ICD-9 code 135), and/or extrinsic allergic alveolitis (hypersensitivity pneumonitis) (ICD-9 code 495 through 495.9).

After 1998, records were excluded if they contained an ICD-10 code for the following conditions: connective tissue disease or rheumatoid arthritis (ICD-10 codes M32 through M35, M35.1, M35.5, M35.8, M35.9, and M36, or M05 through M05.9, M06 through M06.9, or M08 through M08.9), radiation fibrosis (ICD-10 code J70.1), asbestosis (ICD-10 code J61), coal workers' pneumoconiosis (ICD-10 J60), silicosis or talcosis (ICD-10 codes J62 through J62.8), berylliosis and other inorganic dusts (ICD-10 codes J63 through J63.8), unspecified pneumoconiosis (ICD-10 codes J64 through J65), sarcoidosis (ICD-10 codes D86 through D86.9), and/or extrinsic allergic alveolitis (hypersensitivity pneumonitis) (ICD-10 codes D67 through D67.9).

*Details of the UCD classifications*

From 1992 through 1998, the following ICD-9 codes were analyzed to determine the UCD: ischemic heart disease (ICD-9 codes 410 through 414.9), heart failure ICD-9 codes 428 through



428.9), pneumonia (ICD-9 codes 480 through 487.8), and cerebrovascular disease (ICD-9 codes 430 through 438). After 1998, the following ICD-10 codes were used to determine the underlying UCD: ischemic heart disease (ICD-10 codes I20 through I25), heart failure (ICD-10 codes I50 through I50.9), pneumonia ICD-10 codes J09 through J18.9) and cerebrovascular disease (ICD-10 codes I60 through I69.8).

**Table 1: Numbers (and percentages) of decedents in the background population or with idiopathic pulmonary fibrosis (IPF), and without and with venous thromboembolic (VTE) disease mentioned on their death certificates as contributing to death. \* Overall OR = 1.34, 95% CI = 1.29-1.38, p<0.0001 for association between PF and VTE.**

YEAR	Background Population			Idiopathic Pulmonary Fibrosis		
	VTE absent	VTE present	= %	VTE absent	VTE present	= %
1988	1831827	25295	1.36	6762	136	1.97
1989	1805702	24821	1.36	7321	151	2.02
1990	1797405	23709	1.30	7432	147	1.94
1991	1811245	22855	1.25	7839	133	1.67
1992	1813359	22095	1.25	8240	154	1.83
1993	1888488	21468	1.12	8661	135	1.53
1994	1898205	20944	1.09	9086	131	1.42
1995	1926144	21740	1.12	9494	149	1.55
1996	1924032	21218	1.09	10059	157	1.54
1997	1918141	20659	1.07	10719	148	1.36
1998	1932077	21203	1.09	11210	190	1.67
1999	1973552	27218	1.36	11585	220	1.86
2000	1984046	28100	1.40	12347	245	1.95
2001	1993694	28929	1.43	12664	235	1.82
2002	2015339	29426	1.44	13268	245	1.81
2003	2016149	30276	1.48	13639	251	1.81
2004	1972413	29228	1.46	13572	239	1.73
2005	2011508	30195	1.48	13736	223	1.60
2006	1997942	30670	1.51	13686	261	1.87
2007	1995092	30880	1.52	13856	265	1.88
<b>Totals</b>	38506360	510929	1.31*	215176	3815	1.74*

**Table 2: Logistic regression model for venous thromboembolism (VTE) in decedents with idiopathic pulmonary fibrosis (IPF) compared to the background population, when adjusting for age, gender, year of death, and two-way interactions between IPF and age, gender, and year of death.**

<b>Parameter</b>	<b>Estimate</b>	<b>Standard Error</b>	<b>p value</b>
Intercept	-3.4873	0.00703	p < 0.0001
Disease (Reference = IPF)	0.6192	0.1021	p < 0.0001
Age (Per year, > 25 years of age)	-0.0112	0.000084	p < 0.0001
Gender (Reference = Male)	-0.2956	0.00294	p < 0.0001
Year of Death (Reference = 1988 [coded as 1])	0.0134	0.000248	p < 0.0001
Disease*Age	-0.00505	0.00127	p < 0.0001
Disease*Gender	0.3207	0.0331	p < 0.0001
Disease*Year of Death	-0.00926	0.00296	p = 0.0018

**Table 3: Numbers and percentages of decedents with chronic obstructive pulmonary disease (COPD) or idiopathic pulmonary fibrosis (IPF), and without and with venous thromboembolic (VTE) disease mentioned on their death certificates as contributing to death. \* Overall OR = 1.44, 95% CI = 1.39-1.49, p<0.0001 for association between PF and VTE compared to COPD.**

YEAR	COPD		%	Idiopathic Pulmonary Fibrosis		%
	VTE absent	VTE present		VTE absent	VTE present	
1988	156682	2021	1.27	6762	136	1.97
1989	161287	2283	1.40	7321	151	2.02
1990	164755	2138	1.28	7432	147	1.94
1991	170028	2063	1.20	7839	133	1.67
1992	172495	2035	1.17	8240	154	1.83
1993	187491	1991	1.05	8661	135	1.53
1994	187828	1955	1.03	9086	131	1.42
1995	190306	1886	0.98	9494	149	1.55
1996	193942	2070	1.06	10059	157	1.54
1997	198026	2027	1.01	10719	148	1.36
1998	204277	2047	0.99	11210	190	1.67
1999	214645	2526	1.16	11585	220	1.86
2000	211138	2601	1.22	12347	245	1.95
2001	212783	2710	1.26	12664	235	1.82
2002	215402	2723	1.25	13268	245	1.81
2003	217888	2971	1.35	13639	251	1.81
2004	212259	2914	1.35	13572	239	1.73
2005	225543	3110	1.36	13736	223	1.60
2006	217401	3218	1.46	13686	261	1.87
2007	217747	3152	1.43	13856	265	1.88
<b>Totals</b>	3931923	48441	1.22*	215176	3815	1.74*

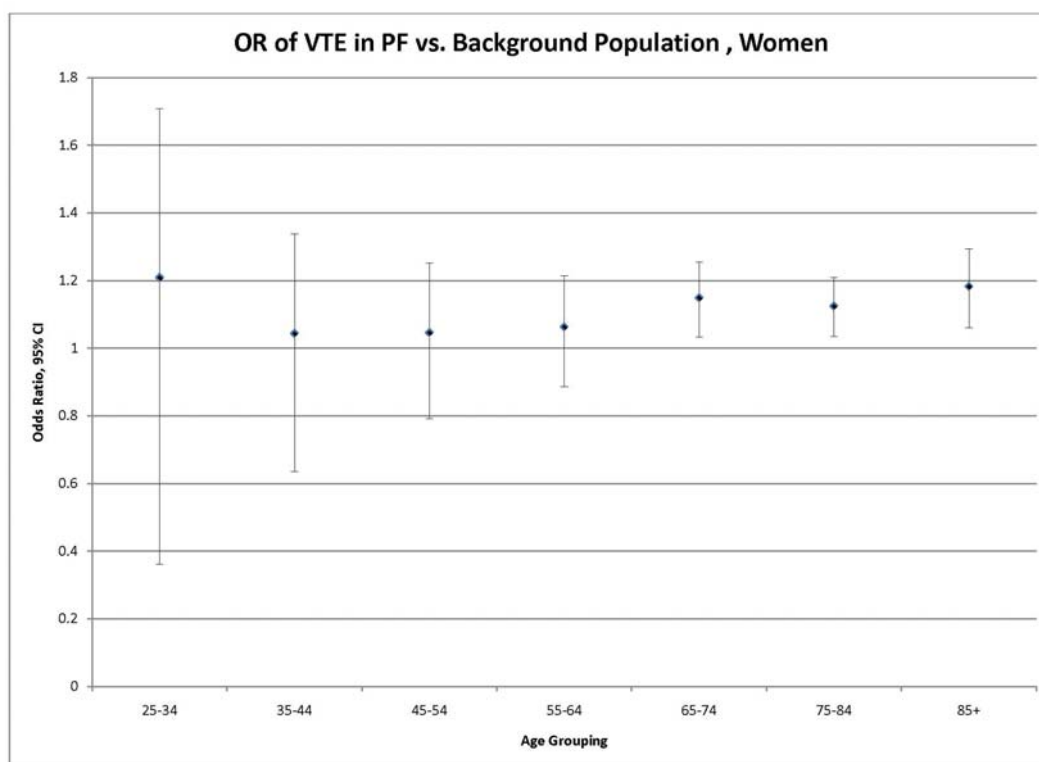
**Table 4: Numbers and percentages of decedents with lung cancer or idiopathic pulmonary fibrosis (PF), and without and with venous thromboembolic (VTE) disease mentioned on their death certificates as contributing to death. \* Overall OR = 1.54, 95% CI = 1.49-1.59, p<0.0001 for association between PF and VTE compared to lung cancer.**

YEAR	Lung Cancer			Idiopathic Pulmonary Fibrosis		
	VTE absent	VTE present	%	VTE absent	VTE present	%
1988	143813	1463	1.01	6762	136	1.97
1989	147379	1522	1.02	7321	151	2.02
1990	151442	1435	0.94	7432	147	1.94
1991	153958	1397	0.90	7839	133	1.67
1992	155896	1339	0.85	8240	154	1.83
1993	159031	1288	0.80	8661	135	1.53
1994	159542	1303	0.81	9086	131	1.42
1995	161091	1322	0.81	9494	149	1.55
1996	161790	1422	0.87	10059	157	1.54
1997	163112	1413	0.86	10719	148	1.36
1998	164794	1458	0.88	11210	190	1.67
1999	159765	1888	1.17	11585	220	1.86
2000	162813	2061	1.25	12347	245	1.95
2001	163088	2322	1.40	12664	235	1.82
2002	164647	2337	1.40	13268	245	1.81
2003	164747	2367	1.42	13639	251	1.81
2004	164452	2538	1.52	13572	239	1.73
2005	165793	2606	1.55	13736	223	1.60
2006	165002	2694	1.61	13686	261	1.87
2007	164814	2701	1.61	13856	265	1.88
<b>Totals</b>	3196969	36876	1.14*	215176	3815	1.74*

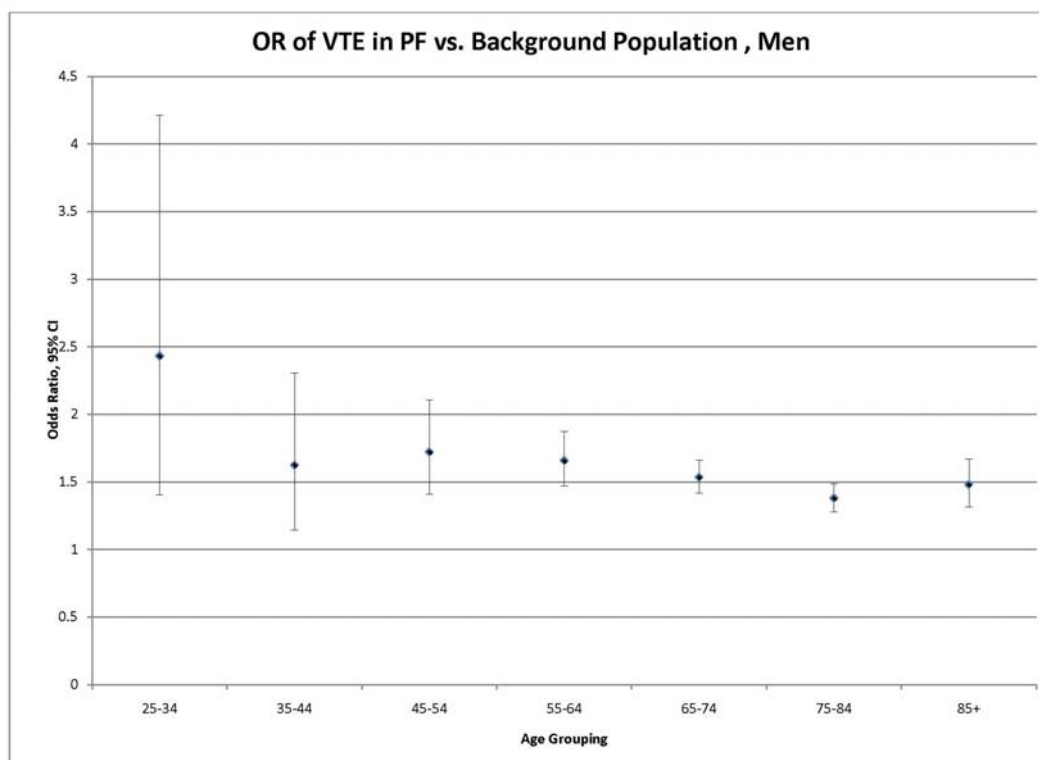
**Table 5: The underlying cause-of-death for decedents with VTE-PF and IPF alone (excluding lung cancer and COPD) over the entire study period. ICD-9 and ICD-10 codes used for each of the following categories are located in the Appendix.**

<b>Underlying Cause-of-Death</b>	<b>PF with VTE, % N = 3,815</b>	<b>PF alone, % N = 215,176</b>	<b>OR (95% CI)</b>	<b>p-value</b>
<b>Venous Thromboembolism</b>	<b>20.9%</b>	-	-	-
<b>Pulmonary Fibrosis</b>	<b>52.3%</b>	<b>69.3%</b>	<b>0.48 (0.45-0.51)</b>	<b>p &lt; 0.0001</b>
<b>Total VTE and PF</b>	<b>73.2%</b>	<b>69.3%</b>	<b>1.21 (1.13-1.30)</b>	<b>p &lt; 0.0001</b>
<b>Cardiac Diseases</b>				
Acute MI	1.7%	3.0%	0.56 (0.46-0.71)	p < 0.0001
Chronic Ischemic Heart Disease	2.6%	5.9%	0.43 (0.35-0.53)	p < 0.0001
Congestive Heart Failure/ Cardiomyopathy	0.8%	2.0%	0.41 (0.29-0.59)	p < 0.0001
<i>Total Cardiac Diseases</i>	<i>5.2%</i>	<i>10.9%</i>	<i>0.45 (0.39-0.51)</i>	<i>p &lt; 0.0001</i>
<b>CVA/Stroke</b>	0.9%	1.3%	0.68 (0.48-0.96)	p = 0.02
<b>Infectious Diseases</b>				
Pneumonia	1.3%	2.3%	0.55 (0.41-0.73)	p < 0.0001
Sepsis	0.3%	0.6%	0.56 (0.31-0.98)	p = 0.04
<i>Total Infectious Diseases</i>	<i>1.6%</i>	<i>2.8%</i>	<i>0.55 (0.42-0.71)</i>	<i>p &lt; 0.0001</i>
<b>Other</b>	18.3%	14.9%	1.28 (1.18-1.39)	p < 0.0001

**Figure 1: The overall risk (odds ratio [OR], 95% CI) of venous thromboembolic (VTE) disease in idiopathic pulmonary fibrosis (IPF) when compared to the background population for women by age grouping. The OR was only significant for those in the older age groups (age groupings 65-74, 75-84, and those over 85) ( $p < 0.05$ ), while the risk was not significantly elevated in the younger age groupings (25-34, 35-44, 45-54, and 55-64,  $p$  values = 0.4830, 0.7966, 0.6809, and 0.4339, respectively).**

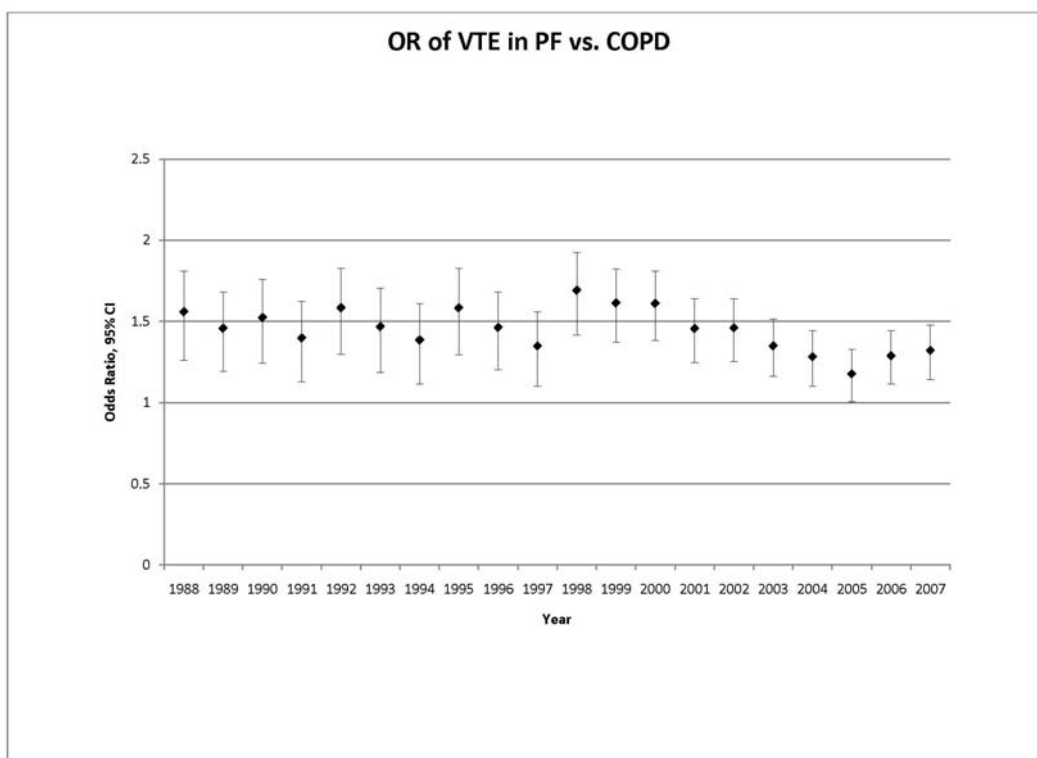


**Figure 2: The overall risk (odd ratio [OR], 95% CI) of venous thromboembolic (VTE) disease in idiopathic pulmonary fibrosis (IPF) when compared to the background population for men by age grouping. All age grouping were statistically significant ( $p < 0.05$ ).**





**Figure3: The annual risk (odd ratios [OR], 95% CI) of venous thromboembolic (VTE) disease in idiopathic pulmonary fibrosis (IPF) when compared to chronic obstructive pulmonary disease (COPD). The OR was statistically significant for all years analyzed ( $p < 0.05$ ).**



**Figure 4: The annual risk (odds ratio [OR], 95% CI) of venous thromboembolic (VTE) disease in idiopathic pulmonary fibrosis (IPF) when compared to lung cancer. The OR was statistically significant ( $p < 0.05$ ) for all years except 2004 ( $p = 0.53$ ) and 2005 ( $p = 0.65$ ).**

