Gastroesophageal Reflux Therapy Is Associated with Longer Survival in Patients with Idiopathic Pulmonary Fibrosis

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Rationale: **Gastroesophageal reflux (GER) is highly prevalent in patients with idiopathic pulmonary fibrosis (IPF). Chronic microaspiration secondary to GER may play a role in the pathogenesis and natural history of IPF.**

Objectives: **To investigate the relationship between GER-related variables and survival time in patients with IPF.**

Methods: **Regression analysis was used to investigate the relationship between GER-related variables and survival time in a retrospectively identified cohort of patients with well-characterized IPF from two academic medical centers.**

Measurements and Main Results: **Two hundred four patients were identified for inclusion. GER-related variables were common in this cohort: reported symptoms of GER (34%), a history of GER disease (45%), reported use of GER medications (47%), and Nissen fundoplication (5%). These GER-related variables were significantly associated with longer survival time on unadjusted analysis. After adjustment, the use of GER medications was an independent predictor of longer survival time. In addition, the use of gastroesophageal reflux medications was associated with a lower radiologic fibrosis score. These findings were present regardless of center.**

Conclusions: **The reported use of GER medications is associated with decreased radiologic fibrosis and is an independent predictor of longer survival time in patients with IPF. These findings further support the hypothesis that GER and chronic microaspiration may play important roles in the pathobiology of IPF.**

Keywords: pulmonary fibrosis; respiratory aspiration; idiopathic interstitial pneumonia; survival

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrotic lung disease with a median survival from the time of diagnosis of 2 to 3 years (1). The cause of IPF remains unknown (2). It has been hypothesized that chronic microaspiration (i.e., tracheobronchial aspiration of small amounts of gastric secretions) due to gastroesophageal reflux (GER) may cause repetitive subclinical injury to the lung leading to pulmonary fibrosis (3, 4). Evidence from experimental models in animals and descriptive studies in humans supports this concept (3, 5–9).

GER is highly prevalent in patients with IPF. Esophageal pH monitoring has estimated the prevalence of distal GER in IPF at 67 to 88% and proximal GER at 30 to 71% (10–14). Although the pathobiological significance of GER in IPF remains unclear, two small case series have suggested stabilization of pulmonary function with medical or surgical treatment of GER (5, 9). These two studies are limited by their small size and the lack of adequate controls.

In the current study, we sought to further investigate the relationship between GER and IPF using a large cohort of patients with well-defined disease identified from the longitudinal cohorts of patients with interstitial lung disease (ILD) seen at two major academic medical centers. Specifically, we asked whether reported GER-related variables, including GER symptoms, a diagnosis of GER disease, and the use of medical and/or surgical therapies for GER, were associated with survival time in patients with IPF.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Gastroesophageal reflux (GER) is prevalent in patients with idiopathic pulmonary fibrosis (IPF). However, the significance of GER in IPF is unclear.

What This Study Adds to the Field

This study confirms that GER-related findings are common in IPF and suggests that the reported use of GER medications is associated with less radiologic fibrosis and longer survival time in these patients. Although preliminary, these findings further support the hypothesis that GER and silent microaspiration may play a role in the pathobiology of IPF.

METHODS

Study Design and Patient Population

Patients with IPF were identified retrospectively from two longitudinal cohorts of patients with ILD seen at the University of California San Francisco (UCSF) and the Mayo Clinic (Rochester, MN), from April 2001 until July 2008. These cohorts involve the prospective and systematic collection of symptoms, comorbidities, and medication use via standardized questionnaires and physician review. Enrollment into these cohorts included informed consent giving permission to record clinical data and review medical records. Demographics, clinical features, medication history, pulmonary function, and high-resolution computed tomography (HRCT) data were obtained for all patients. The Institutional Human Subject Review Committee at each institution approved the protocol.

(*Received in original form January 24, 2011; accepted in final form May 25, 2011*)

Supported by National Heart, Lung, and Blood Institute grants HL086516 (H.R.C.) and HL097383 (J.S.L.).

Author Contributions: Involvement in conception, hypothesis, and design of the study (J.S.L., J.H.R., P.J.W., T.E.K., H.R.C.); acquisition of the data (J.S.L., J.H.R., B.M.E., C.P.L., K.D.J.); analysis and interpretation of the data (J.S.L., J.H.R., P.J.W., T.E.K., H.R.C.); substantial involvement in the writing and/or revision of the article (J.S.L., J.H.R., P.J.W., T.E.K., H.R.C.)

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 184. pp 1390–1394, 2011

Originally Published in Press as DOI: 10.1164/rccm.201101-0138OC on June 23, 2011
Internet address: www.atsjournals.org

TABLE 1. BASELINE DEMOGRAPHICS (N = 204)

Variable	Value
Age, y	70 (SD, 9)
Female sex	63 (31%)
BMI, kg/m^2	29 (SD, 5)
Underweight (BMI < 18.5)	1 (1%)
Healthy weight (18.5 ≤ BMI < 25)	42 (21%)
Overweight (25 ≤ BMI < 30)	80 (40%)
Obese (BMI ≥ 30)	75 (38%)
Cough	172 (86%)
Dyspnea	176 (89%)
Ever smoker	144 (71%)
Surgical lung biopsy	78 (39%)
Prednisone	40 (20%)
Azathioprine	9 (4%)
N-acetylcysteine	7 (3%)
Warfarin	9 (4%)
Long-term oxygen	63 (31%)
FVC, % predicted	69 (SD, 18)
D_{LCO}, % predicted	47 (SD, 14)
Total lung capacity, % predicted	68 (SD, 12)
Radiologic fibrosis score, %	17 (9, 27)
Gastroesophageal reflux symptoms*	68 (34%)
Gastroesophageal reflux disease†	91 (45%)
Gastroesophageal reflux medication use‡	96 (47%)
Nissen fundoplication	11 (5%)

Definition of abbreviations: BMI = body mass index; D_{LCO} = diffusing capacity for carbon monoxide; FVC = forced vital capacity.

Data are expressed as mean (SD), n (%), or median (25th percentile, 75th percentile).

* Patient reported symptoms of heartburn or regurgitation.

† Patient or physician reporting of this diagnosis.

‡ Either proton pump inhibitor (n = 86) or H2 blocker (n = 12); two patients were taking both.

TABLE 2. UNADJUSTED PREDICTORS OF SURVIVAL TIME

Variable	HR (95% CI)	*P* Value
Age	1.03 (1.01–1.05)	<0.01
Female sex	0.64 (0.42–0.99)	0.05
BMI	0.97 (0.94–1.01)	0.21
Cough	1.73 (0.93–3.25)	0.09
Dyspnea	1.75 (0.91–3.37)	0.09
Ever smoker	1.07 (0.72–1.60)	0.74
Prednisone	1.66 (1.05–2.62)	0.03
Azathioprine	1.23 (0.54–2.80)	0.63
N-acetylcysteine	0.65 (0.15–2.62)	0.54
Warfarin	1.16 (0.37–3.68)	0.80
Long-term oxygen	2.38 (1.61–3.52)	<0.01
FVC, % predicted	0.97 (0.96–0.98)	<0.01
D_{LCO}, % predicted	0.97 (0.95–0.98)	<0.01
Total lung capacity, % predicted	0.97 (0.95–0.99)	<0.01
Radiologic fibrosis score, %	1.03 (1.02–1.05)	<0.01
Gastroesophageal reflux symptoms*	0.62 (0.40–0.96)	0.03
Gastroesophageal reflux disease†	0.56 (0.37–0.83)	<0.01
Gastroesophageal reflux medication use‡	0.51 (0.34–0.76)	<0.01
Nissen fundoplication	0.29 (0.09–0.92)	0.04

Definition of abbreviations: BMI = body mass index; CI = confidence interval; D_{LCO} = diffusing capacity for carbon monoxide; FVC = forced vital capacity; HR = hazard ratio.

* Patient reported symptoms of heartburn or regurgitation.

† Patient or physician reporting of this diagnosis.

‡ Either proton pump inhibitor (n = 86) or H2 blocker (n = 12); two patients were taking both.

In both cohorts, the diagnosis of IPF was made by multidisciplinary review according to consensus criteria (1). The diagnosis of IPF required the absence of an identifiable etiology for ILD and histopathologic or radiologic usual interstitial pneumonia pattern. All patients with IPF in these cohorts who had HRCT and pulmonary function tests within 12 and 3 months, respectively, of the date of diagnosis (defined as the date of initial clinic visit), were eligible for inclusion. Eligible patients were excluded only if survival data were unobtainable (missing in five subjects). Patient demographics, symptoms (dyspnea, cough, heartburn/regurgitation), history of tobacco use (categorized as never or ever smokers), body mass index (BMI), and pulmonary function values were recorded. At both UCSF and the Mayo Clinic, GER symptoms, GER disease, and GER medication use were recorded and reviewed in a prospective manner by the treating physician at the time of the clinic visit. Lung transplant data and vital status were obtained using the medical record and the Social Security Death Index (http://ssdi.rootsweb.ancestry.com/).

Radiology Review

HRCTs were obtained as part of the clinical evaluation of all patients. All studies were performed using standardized protocols and had adequate quality images available. HRCTs were prospectively reviewed as part of this study by two radiologists (B.M.E., C.P.L.) who were blinded to all clinical features of the patient. A semiquantitative analysis of the severity of fibrosis on HRCT was calculated by estimating the percentage of lung affected by fibrosis (i.e., reticular abnormality and/or honeycombing) to the nearest 5% in three zones for each lung, as previously described by Best and colleagues (15). These numbers were averaged to obtain a net radiologic fibrosis score.

Statistical Analysis

Descriptive statistics are presented as mean and standard deviation (SD) or median (25th percentile, 75th percentile). Comparisons between groups were performed using the *t* test, Mann-Whitney rank sum test, chi-square test, or Fisher exact test as appropriate. Survival time was calculated from the initial visit (i.e., time of diagnosis) until the primary outcome was achieved, either death or lung transplantation (i.e., transplant-free survival). Patients were censored if there was no lung transplant or death recorded in the medical record or on query of Social Security Death Index. Kaplan-Meier curves were constructed for selected variables and compared using the log rank test. Survival time (in days) is reported as median (25th percentile, 75th percentile). Unadjusted and adjusted Cox proportional hazards regression analyses were performed. The adjusted Cox regression modeling was performed using two methods: one using all significant predictors on unadjusted analysis and a second using backward selection. Model assumptions of log-linearity and proportional hazards were checked using standard approaches. All data analysis was performed using STATA Version 11.1. All tests were two-sided and were performed at a significance level of 0.05.

RESULTS

Study Population

The study cohort consisted of 204 patients (84 from UCSF and 120 from Mayo Clinic) (Table 1). Patients were primarily men (69%) with a mean age of 70 years. Most patients were overweight, with a mean BMI of 29. The majority of patients were current or former smokers (71%). Twenty percent of patients reported use of prednisone at the time of diagnosis. Mean baseline forced vital capacity (FVC) was 69% predicted and diffusing capacity for carbon monoxide (D_{LCO}) was 47% predicted. The median radiologic fibrosis score was 17%. The intraclass correlation coefficient for the fibrosis score was 0.97 (95% confidence interval, 0.96–0.98). Surgical lung biopsy was performed in 39% of the study cohort. In general, the UCSF patients with IPF were similar to the Mayo Clinic patients with IPF and overall were similar to other reported cohorts of patients with IPF (*see* Table E1 in the online supplement).

GER-Related Variables

Symptoms of GER were present in 34% of patients (Table 1). Patient- or physician-reported history of GER disease was present in 45% of patients. At the time of diagnosis, approximately

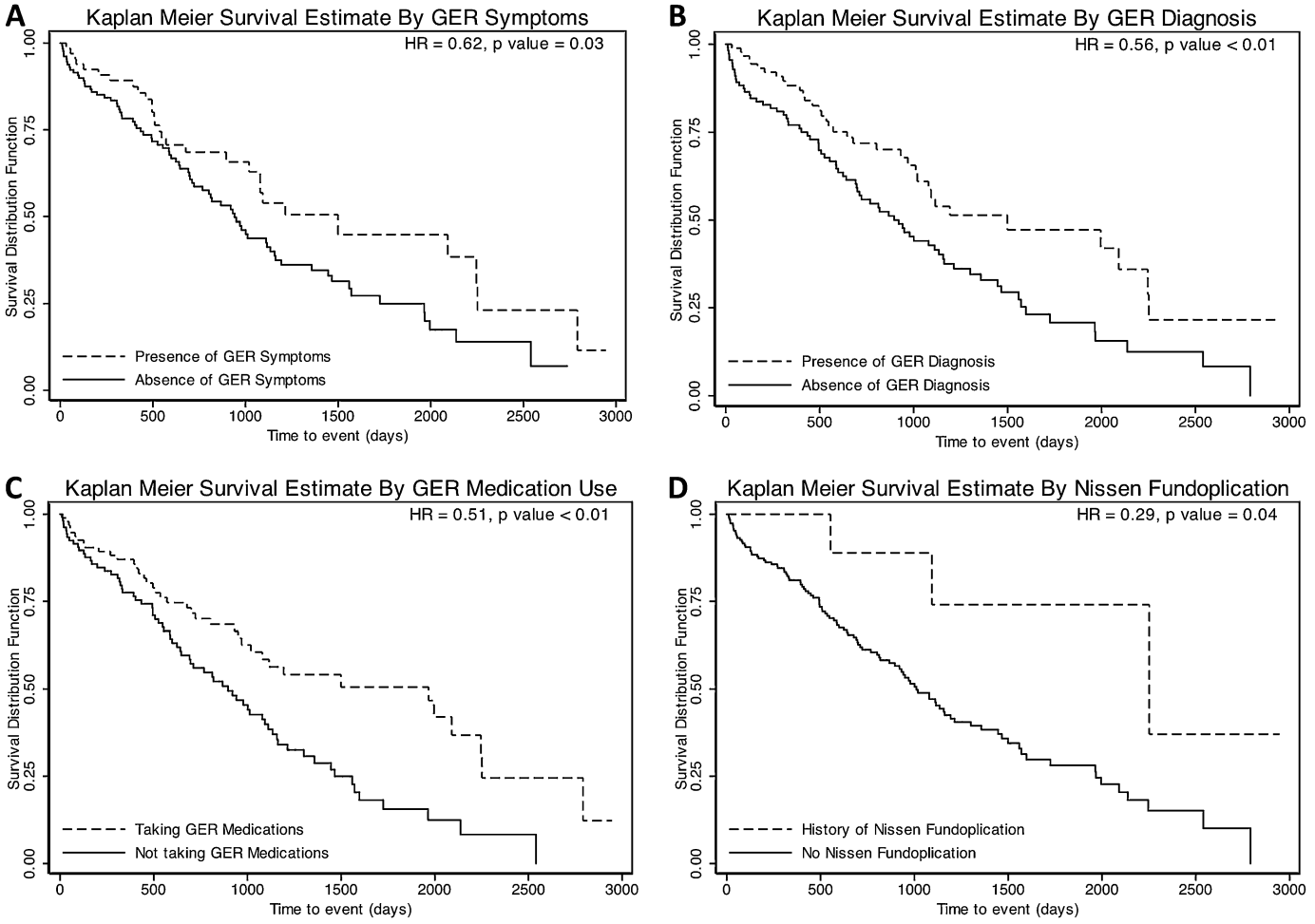

Figure 1. (*A*) Survival time estimates based on presence or absence of gastroesophageal reflux (GER) symptoms. Median survival time for those with GER symptoms was 1,499 days and median survival time for those without GER symptoms was 941 days. (*B*) Survival time estimates based on presence or absence of reported GER disease. Median survival time for those with GER disease was 1,499 days and those without GER disease was 920 days. (*C*) Survival time estimates based on reported GER medication use (either proton pump inhibitors or H2 blockers). Median survival time for those taking GER medications was 1,967 days and median survival time for those not taking GER medications was 896 days. (*D*) Survival time estimates based on presence or absence of a history of Nissen fundoplication. Median survival time for those with a history of Nissen fundoplication was 2,252 days and median survival time for those without a history of Nissen fundoplication was 1,019 days.

half of patients reported current treatment with GER therapy (either proton pump inhibitor [n = 86] or H2 blocker [n = 12]). Eleven patients reported a history of Nissen fundoplication. The indication for Nissen fundoplication was for the treatment of GER disease (*see* online supplement). There were no significant differences in these features between the UCSF and Mayo Clinic cohorts (Table E1). Three patients reported a history of Barrett esophagus, one patient a history of gastritis, and one patient a remote history of peptic ulcer disease.

Survival Analysis

The median survival time for this cohort was 1,079 days (495–2,091) and did not differ by center (Figure E1). Unadjusted predictors of survival time are listed in Table 2. The reported presence of GER symptoms, GER diagnosis, GER medication use, and Nissen fundoplication were all associated with longer survival time (Figure 1). These relationships were present in both the UCSF and Mayo Clinic patients (Table E2).

On adjusted analysis, higher FVC % predicted, higher D_{LCO} % predicted, and the use of GER medications were associated with longer survival time in both regression models (Table 3). In the backward selection model, higher BMI was also found to be a significant predictor of longer survival time.

Comparison of Patients Taking and Not Taking GER Medications

Patients reporting GER medication use were significantly more likely to be women, have a history of cough, have lower HRCT fibrosis score (14 vs. 19%), and have undergone surgical lung biopsy. There were no significant differences in age, BMI, history of smoking, dyspnea, use of prednisone, long-term oxygen use, or pulmonary physiology between those with and those without reported GER medication use. As expected, those reporting GER medication use were more likely to have GER symptoms, GER disease, and history of Nissen fundoplication (Table 4).

DISCUSSION

There is equipoise among pulmonologists as to how aggressively to diagnose and treat GER in patients with IPF. There are no convincing data demonstrating a clinical benefit to treatment

TABLE 3. ADJUSTED PREDICTORS OF SURVIVAL TIME

Variable	HR (95% CI)	*P* Value
Age	1.02 (1.00–1.05)	0.08
Female sex	0.87 (0.54–1.42)	0.58
Long-term oxygen	1.18 (0.72–1.95)	0.65
Prednisone	1.05 (0.61–1.82)	0.85
FVC, % predicted	0.98 (0.96–0.99)	<0.01
D_{LCO}, % predicted	0.98 (0.96–1.00)	0.03
Radiologic fibrosis score, %	1.00 (0.98–1.02)	0.83
Gastroesophageal reflux symptoms*	0.80 (0.45–1.44)	0.46
Gastroesophageal reflux disease†	1.78 (0.90–3.51)	0.10
Gastroesophageal reflux medication use‡	0.47 (0.24–0.93)	0.03
Nissen fundoplication	0.74 (0.21–2.59)	0.64

Definition of abbreviations: CI = confidence interval; D_{LCO} = diffusing capacity for carbon monoxide; FVC = forced vital capacity; HR = hazard ratio.

Data shown are for the regression model constructed by including significant variables from the unadjusted survival analysis (Table 2).

* Patient reported symptoms of heartburn or regurgitation.

† Patient or physician reporting of this diagnosis.

‡ Either proton pump inhibitor (n = 86) or H2 blocker (n = 12); two patients were taking both.

TABLE 4. COMPARISON OF PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS TAKING AND NOT TAKING GASTROESOPHAGEAL REFLUX MEDICATIONS (N = 203)

Variable	Taking GER Medications (*n = 96*)	Not Taking GER Medications (*n = 107*)	*P* Value
Age, y	69 (SD, 10)	70 (SD, 8)	0.17
Female sex	37 (39%)	25 (23%)	0.02
BMI, kg/m^2	29 (SD, 5)	29 (SD, 6)	0.81
Cough	87 (92%)	84 (81%)	0.03
Dyspnea	82 (88%)	93 (89%)	0.78
Ever smoker	64 (67%)	80 (75%)	0.20
Surgical lung biopsy	44 (46%)	34 (32%)	0.04
Follow-up time	694 (325, 1,213)	624 (292, 1,134)	0.43
Prednisone	20 (21%)	20 (19%)	0.70
Azathioprine	5 (5%)	4 (4%)	0.61
N-acetylcysteine	4 (4%)	3 (3%)	0.60
Warfarin	4 (4%)	5 (5%)	0.86
Long-term oxygen	27 (28%)	36 (34%)	0.40
FVC, % predicted	70 (SD, 17)	68 (SD, 19)	0.27
D_{LCO}, % predicted	48 (SD, 14)	46 (SD, 14)	0.37
Total lung capacity, % predicted	68 (SD, 13)	69 (SD, 12)	0.66
Radiologic fibrosis score, %	14 (8, 23)	19 (12, 32)	0.01
Gastroesophageal reflux symptoms*	53 (57%)	15 (14%)	<0.01
Gastroesophageal reflux disease†	78 (81%)	13 (12%)	<0.01
Nissen Fundoplication	8 (8%)	3 (3%)	0.08

Definition of abbreviations: BMI = body mass index; D_{LCO} = diffusing capacity for carbon monoxide; FVC = forced vital capacity; GER = gastroesophageal reflux.

Data are expressed as mean (SD), n (%), or median (25th percentile, 75th percentile). GER medications: either proton pump inhibitor (n = 86) or H2 blocker (n = 12); two patients were taking both.

* Patient reported symptoms of heartburn or regurgitation.

† Patient or physician reporting of this diagnosis.

of GER in this setting and there are risks to medical and surgical treatment (4). In this study, approximately half of patients with IPF reported taking GER medications at the time of initial diagnosis. The use of GER medications was associated with lower HRCT fibrosis score and was an independent predictor of longer survival time. Although preliminary, these findings support the hypothesis that GER and chronic microaspiration may play important roles in the pathobiology of IPF.

Although the indication for GER medication use in this cohort is unknown, GER symptoms and diagnosis were more common in patients reporting GER medication use, suggesting the indication was likely for the treatment of GER. It is possible that GER medications were prescribed for gastro-protection in patients also receiving prednisone. However, there was no difference in prednisone use among those reporting and not reporting GER medication use, making this explanation unlikely.

Our results are consistent with two previous reports suggesting stabilization of IPF with medical or surgical therapy for GER (5, 9). In a study of four patients with IPF, aggressive medical management of GER resulted in apparent physiological stabilization (5). One of the cases demonstrated physiologic stabilization with GER medications, then worsening with cessation of therapy, followed by restabilization after resuming therapy once again. A second study demonstrated stabilization of oxygen requirements in pretransplant patients with IPF who underwent Nissen fundoplication for GER, although no change in pulmonary function was observed (9). Our study adds substantially to these results by linking GER-related variables to the extent of HRCT fibrosis and survival time in a large, two-center cohort of well-characterized patients with IPF.

There are several possible explanations for the results of our study. The most straightforward is also the most controversial: that the treatment of GER is beneficial to survival in IPF. It is hypothesized that GER may impact progression in IPF through microaspiration of gastric droplets either causing slowly progressive lung injury and fibrosis or by triggering acute exacerbation of IPF (4). Suppressing the acidity of gastric contents may reduce the injury caused by microaspiration. However, acid suppression alone does not prevent microaspiration of weakly acidic reflux, and this may also contribute to lung fibrosis (16). Nissen fundoplication is a surgical intervention that reduces both acid and weakly acidic GER. An additional survival benefit to Nissen fundoplication is suggested by our data, which would support a role for both acid and weakly acidic GER. Our small sample size limits any firm conclusions that can be made from this data.

Our results could also be due to confounding by unmeasured associated variables. For example, patients receiving GER therapy might also be more likely to receive other medical interventions (e.g., pulmonary rehabilitation, influenza vaccination, or simply more comprehensive care) that could impact survival. Arguing against this somewhat is that any confounder would have to exist at both centers involved in the study. Another possible explanation for our findings is lead-time bias. GER could cause patients to seek medical attention sooner than those who do not have GER, leading to the diagnosis of IPF earlier in the course of disease. Although most measures of disease severity (e.g., pulmonary function values) were similar between groups, the association between lower percent of radiologic fibrosis on HRCT and GER medication use could suggest lead-time bias. However, after adjustment for the degree of radiologic fibrosis, the relationship between GER medication use and survival time remained significant.

Finally, it is possible that the association between GER and survival time in IPF is real, but that GER may develop as a consequence of progressive fibrotic lung disease, rather than vice versa. Architectural distortion and increased traction on mediastinal structures may lead to weakening of the lower esophageal sphincter and increased GER (4, 12). The association of GER medication use with less radiologic fibrosis and the lack of an association with standard measures of thoracic restriction (e.g., pulmonary function tests) argue against this hypothesis.

The results of our study need validation to confirm the association between reported GER medication use and survival time. Although large and well-defined, our cohort had limited

information on GER diagnosis and responsiveness to treatment. Information on 24-hour pH and/or esophageal impedance testing, dosing, duration, and compliance with GER therapy, and effectiveness of acid suppression with therapy should be collected in future studies. A prospective longitudinal cohort of patients with carefully recorded GER-related variables would address these issues more rigorously. If our results are validated, future studies should look beyond association and address how the treatment of GER might affect survival in IPF.

Author Disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgments: The authors thank Eric Vittinghoff for statistical assistance, Sally McLaughlin and Jane Berkeley for assistance with patient identification and data retrieval, the physician members of the UCSF Interstitial Lung Disease Consortium for referring their patients for evaluation by our program, and the many patients who generously agreed to participate in our longitudinal cohort study.

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