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Association of Hospitalization and Forced Vital Capacity Endpoints with Survival in Idiopathic Pulmonary Fibrosis: Analysis of a Pooled Cohort from Three Clinical Trials

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¹⁰For a complete listing of the IPFnet members, see Supplemental Figure 1

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AUTHOR CONTRIBUTIONS

Author contributions: MTD drafted and critically revised the manuscript, and participated in data analysis and interpretation. HRC, KKB, KRF, TEK, SMP, GR, LDS, and FJM, designed the study and critically revised the manuscript. RSR analyzed the data and critically revised the manuscript. KJA designed the study, analyzed the data and critically revised the manuscript. All authors had access to the raw data.

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Abstract

Background—Mortality is an impractical primary endpoint for idiopathic pulmonary fibrosis (IPF) clinical trials in patients with mild to moderate physiological impairment due to low event rates. Change in forced vital capacity (FVC) is widely accepted as a surrogate for mortality in patients with IPF, and has been the most common primary endpoint in IPF clinical trials. The role of hospitalization as a predictor for mortality independent of FVC decline has not been well defined. In a pooled cohort of subjects with IPF, we determined the independent and combined association of hospitalization and a categorical 10% decrease in FVC with all-cause mortality.

Methods—The incidence of non-elective hospitalization and 10% decrease in FVC was compared across strata of baseline physiologic impairment. Cox proportional hazards models were used to evaluate the risk of all-cause mortality associated with hospitalizations and 10% decrease in FVC occurring up to a pre-defined time point.

Findings—Hospitalization and categorical 10% decrease in FVC occurred frequently across strata of baseline physiologic impairment. The majority of hospitalized patients did not have a 10% decrease in FVC, a finding that was not explained by missed spirometry visits. Both surrogate events were associated with subsequent time to death from any cause. When causes of hospitalizations were considered, only respiratory hospitalizations remained associated with mortality.

Interpretation—Hospitalizations may be appropriate components of a clinically meaningful composite endpoint that improves feasibility in IPF clinical trials.

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal interstitial lung disease.¹ Historically, no effective disease-modifying therapy has been available; however, two agents have now been shown to slow disease progression, as defined by decline in forced

vital capacity (FVC),^{2, 3} and many other potential therapeutic agents are under development. This has led to substantial interest in the choice of endpoints used in clinical trials in IPF.^{4–8}

The feasibility of all-cause mortality as a primary endpoint in trials of patients with IPF and mild to moderate physiological impairment is limited by low event rates, requiring large sample sizes or long trial durations.^{9, 10} In this context, there is a need to identify surrogate endpoints with higher event rates. Potential surrogates for mortality include events such as disease progression, as defined by categorical changes in pulmonary function, and hospitalizations.

FVC has become an accepted primary endpoint in phase 3 clinical trials in IPF^{2, 3, 11} given its efficiency and its consistently strong association with mortality in cohort studies and previous trials.^{7, 12–15} A 10% or greater decline in FVC is widely used to define disease progression and has been used as a component of an event-driven endpoint in recent clinical trials^{2, 3}. Non-elective hospitalization is a frequent clinical event in IPF,^{10, 15–17} and represents another potential endpoint for clinical trials that may capture a distinct population from FVC decline.^{18, 19} Some authors have called for wider use of hospitalization as an endpoint;⁸ however, concerns remain about its robustness and, in particular, whether all-cause or respiratory-related hospitalizations should be included.⁹ A recent report has suggested that hospitalizations are independently associated with decreased survival in IPF, and that respiratory hospitalizations portend especially poor long-term outcomes.²⁰

The current study investigates the independent and combined association of non-elective hospitalizations (both all-cause and respiratory-related) and disease progression (as defined by a 10% decline in FVC), with all-cause mortality in a large, pooled cohort of patients from the IPF Clinical Research Network (IPFnet) clinical trials.

METHODS

Study Population

An overview of the study design is shown in Figure 1. The study population included subjects from the IPFnet clinical trials: STEP-IPF,²¹ ACE-IPF,¹⁹ and PANTHER-IPF.¹¹ All patients met consensus diagnostic criteria for IPF at the time of study enrollment.²² STEP-IPF was a randomized controlled trial of sildenafil vs. placebo in patients with advanced IPF, defined as diffusion capacity for carbon monoxide (D_LCO) < 35% of the predicted value. ACE-IPF was a randomized controlled trial of warfarin vs. placebo in patients with progressive IPF, defined as worsening dyspnea, worsening physiologic impairment (decline in FVC by 10%, decline in D_LCO by 15%, or decrease in arterial oxygen saturation by 5%) or worsening radiographic findings. PANTHER-IPF was a three-arm randomized controlled trial of N-acetylcysteine alone, combination therapy with N-acetylcysteine, prednisone and azathioprine, or placebo; enrolled patients had mild to moderate IPF as defined by FVC 50% predicted and D_LCO 30% predicted. Local institutional review boards approved the study protocols at all sites, and all patients provided written informed consent.

In the current study, patients who were randomized to warfarin in ACE-IPF or the combination of prednisone, azathioprine and N-acetylcysteine (NAC) in PANTHER-IPF

were excluded in initial analyses, as these therapies were shown to be harmful. Sensitivity analyses were then carried out using the full IPFnet cohort, to determine if this exclusion resulted in significant changes in the primary findings.

Landmark Statistical Method and Endpoint Definition

The landmark statistical method²³ classifies patients on the basis of events occurring before a specific time point during study followup, rather than the groups to which patients are randomized. Timepoints were chosen to enable classification of patients by the occurrence of two different events—“early hospitalization” as defined by non-elective hospitalization, and “early disease progression” as defined by a relative decrease in FVC of 10%—and to allow sufficient follow-up time after these events for assessment of subsequent mortality. Here, we use the term “early” to refer to events occurring early during study followup, rather than early in a patient’s overall disease course. Because the assessment schedules for spirometry differed among the three IPFnet trials, the landmark time point was set at 12, 15 and 16 weeks for STEP-IPF, PANTHER-IPF and ACE-IPF, respectively (Figure 1B). In other words, patients enrolled in STEP-IPF were assessed for 10% relative decrease in FVC and for occurrence of non-elective hospitalization over the first 12 weeks of the study, with survival analyses using 12 weeks as time zero; patients in PANTHER-IPF were assessed over the first 15 weeks, and patients in ACE-IPF over the first 16 weeks. These time points (12, 15, or 16 weeks, depending on the parent trial) are referred to as the “landmark time point” for a given patient in the current study.

All hospitalizations and their primary causes were centrally adjudicated by the IPFnet investigators as part of the primary endpoint in ACE-IPF. Hospitalizations representing potential acute exacerbations of IPF were adjudicated as secondary endpoints in STEP-IPF and PANTHER-IPF. No additional centralized adjudication of hospitalizations was performed. For the current study, the specific causes were categorized as respiratory or non-respiratory as described in the appendix. Patients with missing spirometry visits were categorized as not having early disease progression in the primary analysis; a sensitivity analysis was performed with these patients classified as having early disease progression.

Statistical Analysis

Baseline continuous variables were expressed as means (standard deviations); categorical variables as frequencies and percentages. We compared subjects who experienced early hospitalization or early disease progression with those who did not via the Wilcoxon test or Chi-square (χ^2) test as appropriate.

Before assessing the association of hospitalization or disease progression with mortality, we examined the cumulative incidence rates of these events across the entire study followup period. In these analyses, death was treated as a competing risk (that is, patients who died could not subsequently have hospitalizations or declines in FVC), and patients were grouped by GAP index to illustrate the frequency of these events across strata of baseline physiologic impairment. The GAP index is a validated risk stratification model that incorporates baseline FVC, DLCO, age and sex, with higher scores associated with increased risk of mortality.^{24, 25} Using the GAP index, patients were classified into three stages: stage I (0–3

points), stage II (4–5 points), or stage III (6–8 points) based on enrollment values. Because the GAP index incorporates only baseline (not longitudinal change in) FVC, this risk score does not preclude using change in FVC as a definition for categorical disease progression in multivariable models.

The association of early hospitalization or early disease progression with time to death from any cause, adjusting for baseline GAP index, duration of IPF diagnosis, and smoking history was performed using Cox proportional hazards models, stratified by the parent clinical trial (i.e., STEP-IPF, PANTHER-IPF, or ACE-IPF). Tests of proportional hazards and linear functional forms for covariates demonstrated no violations of model assumptions (Supplemental Tables 9–11). Subsequent analyses considered respiratory- or non-respiratory-related early hospitalizations, and composite events comprised of early hospitalization and early disease progression. As described above, the trial-specific landmark point served as time zero for these analyses. Results of the models were reported as hazard ratios and 95% confidence intervals. Unadjusted estimates of event rates for all-cause mortality following the landmark point were computed using the Kaplan-Meier estimator, with comparisons between groups based on the log-rank test statistic. Because early hospitalization and disease progression status was determined for each patient at this time zero, and all-cause mortality was the sole outcome of interest, a competing risk analysis was unnecessary and not used in these models.

Finally, because we lacked the ability to validate these models in an independent cohort and wished to assess the effects of *a priori* exclusion criteria on our results, a sensitivity analysis was carried out by adding all patients randomized to warfarin in ACE-IPF and prednisone, azathioprine and N-acetylcysteine in PANTHER-IPF to the original pooled cohort. Cox models assessing the association of early hospitalization or early disease progression with time to death from any cause were repeated in this larger cohort. These results are reported in the appendix.

Role of the funding source

An independent committee appointed by the NHLBI approved the protocols for the IPFnet clinical trials from which this pooled cohort was derived. None of the funding sources had any role in the study design, analysis or interpretation of the data, or writing of the report for these analyses. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

RESULTS

Study Populations

Five hundred seventeen patients were included in the study cohort. Seven patients died prior to the landmark time point, leaving 510 patients for the remaining survival analyses (Figure 1).

Event rates for hospitalization, disease progression, and death

Event rates for non-elective all-cause hospitalization, categorical disease progression, and death for the entire study population (N = 517) are shown in Figure 2. Compared with GAP stage I patients, GAP stage II was associated with twice the risk of non-elective hospitalization and three times the risk of disease progression during followup, after accounting for the competing risk of death. Patients in GAP stage III had over five times the risk of hospitalization and twice the risk of disease progression compared with patients in GAP stage I (Table 2).

Landmark Population Characteristics and Events

Thirty-eight of the 510 patients (7%) who survived past the landmark time point experienced early hospitalization, and 58 (11%) experienced early disease progression (Table 1). Thirty patients experienced early hospitalization without early disease progression, and 50 patients experienced early disease progression without early hospitalization (Table 3). Only eight patients had both early disease progression and early hospitalization. Seven total patients had missing spirometry at the landmark time point. Sensitivity analysis showed no classification effect (data not shown); none of these seven patients experienced early hospitalization. Of the 38 early hospitalizations, 19 (50%) were for respiratory causes (Supplemental Table 1).

Hospitalization and Disease Progression as Risk Factors for Mortality

All-cause mortality rates among subgroups are shown in Supplemental Table 2. Five (19%) of patients with early hospitalization died, compared with 16 (4%) of patients without early hospitalization. Nine (23%) of patients with early disease progression died compared with 12 (3%) of patients without early disease progression.

Early hospitalization and early disease progression were associated with reduced survival time in unadjusted analyses ($p = 0.0002$ and $p < 0.0001$, respectively, Figure 3). After adjustment for GAP index, duration of IPF and smoking history, the risk of all-cause mortality was higher in patients with early disease progression (HR 4.68 [95% CI 1.83, 11.99], $p = 0.0013$) or early non-elective hospitalization (HR 4.05 [95% CI 1.36, 12.11], $p = 0.0012$) (Table 4). C-statistics for these models were 0.805 and 0.808, respectively. While respiratory hospitalizations were associated with increased all-cause mortality (adjusted HR 5.42 [95% CI 1.62, 18.12], $p = 0.006$), non-respiratory hospitalizations were not (HR 1.16 [95% CI 0.15, 8.92], $p = 0.8885$).

Because there was minimal overlap between patients with early hospitalizations and early disease progression, we then tested the impact of composite endpoints combining the two events (Table 4, Figure 4). Patients who had early hospitalization from any cause, early disease progression, or both had a nearly six-fold increase in risk of mortality (HR 5.81 [95% CI 2.23, 15.11], $p = 0.0003$) compared to patients with neither early hospitalization nor early disease progression. The C-statistic for this model was 0.849. A composite of early respiratory hospitalization or disease progression had a similar association with subsequent mortality (HR 5.65 [95% CI 2.19, 14.56], $p = 0.0003$, c-statistic 0.843).

Sensitivity Analyses

To determine if the *a priori* exclusion of patients randomized to warfarin in ACE-IPF or to the combination of prednisone, azathioprine and N-acetylcysteine in PANTHER-IPF had a significant impact on the primary results, sensitivity analyses were performed by adding these two groups to the original pooled study cohort (Supplemental Tables 3 and 4). Eleven patients from these groups were excluded due to death prior to the landmark time point. In this larger cohort, early disease progression was associated with a three-fold higher risk of all-cause mortality (HR 3.01 [95% CI 1.31, 6.90], $p = 0.0095$), whereas the relationship between early all-cause hospitalization approached statistical significance (HR 2.64 [95% CI 0.98, 7.16], $p = 0.0561$). A composite of early disease progression or early all-cause, non-elective hospitalization was also associated with higher risk of all-cause mortality in these models (HR 3.04 [95% CI 1.39, 6.61], $p = 0.0052$).

DISCUSSION

We investigated the frequency of non-elective hospitalization and disease progression (defined by categorical decrease in FVC) across IPF disease severity, and their potential use as surrogate endpoints for mortality in IPF clinical trials. Both non-elective hospitalizations and disease progression occurred frequently, with 17% of all patients experiencing at least one early event in spite of the relatively short time period of three to four months imposed by the landmark statistical method. Higher incidence of all events was associated with more severe GAP index stages, which represent older patients with more physiologic impairment from their disease. Early hospitalization—either all-cause or respiratory-related—and early disease progression were both associated with increased risk of death from any cause. Composite endpoints comprised of early disease progression and early hospitalization identified a greater number of patients subject to higher risk of all-cause mortality.

Useful surrogate events must occur more frequently than the true outcome of interest—in our case, mortality—to be useful for reducing the size or duration of a clinical trial.²⁶ Because clinical trials tend to include a limited subset of the overall disease population, we first examined the frequency of potential surrogate events across strata of baseline physiologic impairment, to evaluate their plausibility as endpoints in a range of potential clinical trial populations. To this end, we used the GAP index^{24, 25} to stratify baseline risk in lieu of other indices such as the composite physiologic index (CPI).²⁷ The GAP index provides a discreet stage which could more easily be used to assess trial eligibility for individual patients. The observed correlation between frequency of both hospitalization and categorical disease progression and higher GAP stage in this cohort highlights the need to carefully account for baseline risk in the design of clinical studies in IPF.

Prior studies have demonstrated that, when considered individually, both acute hospitalizations^{17, 20} and decline in FVC^{7, 12–5} are associated with decreased survival in IPF. Interestingly, in our study there was little overlap (10%) between patients with early hospitalization and early disease progression; in fact, patients who experienced one surrogate event were more likely not to experience the other, a finding that did not appear to be explained by missing FVC data. These results suggest that considering both hospitalization and disease progression simultaneously might increase sensitivity to patients

at increased risk of death and improve trial efficiency.¹⁷ Our data do not offer an explanation for this lack of overlap, but they suggest that hospitalizations (in particular respiratory hospitalizations) are not preceded by gradual declines in FVC and may most commonly be due to acute respiratory worsenings from infection or acute exacerbation. While we observed a strong association between respiratory hospitalizations and subsequent mortality risk, adjudicated acute exacerbations of IPF accounted for only seven of these hospitalizations, limiting our assess the significance of more specific event definitions. It is possible that disease progression (as defined by 10% FVC decline) would capture a substantially higher number of hospitalized patients in the absence of the landmark analysis (which excludes post-landmark disease progression as an event). However, even after accounting for all events occurring during the entire trial followup periods, the majority of hospitalized patients did not experience categorical disease progression (Supplemental Tables 6 and 7). Taken together, we believe that these results suggest that composite endpoints incorporating both clinical events (such as hospitalizations) and physiologic measures of disease progression deserve further consideration in future clinical trials in IPF.

Concerns about the use of hospitalization as an endpoint in IPF clinical trials have focused on regional variability in criteria for hospitalization and the uncertain significance of non-respiratory causes.⁶ Regional variability is difficult to address, but limiting hospitalizations included in an endpoint to respiratory-specific hospitalizations, or even more narrowly defined events such as acute exacerbations, is one way trialists have tried to address this concern. Our data support this qualified approach, demonstrating that early non-respiratory hospitalizations contribute little to the subsequent risk of death during a trial, a finding which is in keeping with other recent reports.²⁰ Further studies are needed to clarify the appropriate definition of hospitalizations to be used as endpoints in various IPF clinical trial settings.

Several limitations to the current study should be considered. The choice of landmark time point is inherently arbitrary, and the strategy excludes patients who die prior to that time.²³ Our landmark time points were chosen *a priori*, based on the assessment schedules in the IPFnet studies, to allow patients to be classified on the basis of both hospitalizations and changes in FVC. While causes for hospitalizations in the IPFnet studies were prospectively adjudicated, there was no explicit *a priori* classification of respiratory or non-respiratory causes; accordingly, we have reported results for both all-cause and respiratory-specific hospitalizations and, despite the finding that non-respiratory hospitalizations did not appear to be associated with subsequent mortality, have stopped short of recommending a specific definition for a hospitalization endpoint based on our data. Furthermore, the threshold for non-elective hospitalization may differ by medical provider, geographic region or other factors. The current study cannot, by itself, argue for the appropriateness of any surrogate endpoint for a specific clinical trial; an ideal surrogate endpoint must have a biologically and clinically plausible relationship with the true endpoint of interest, i.e. mortality, in addition to a statistical relationship. Different surrogate endpoints may be appropriate for different clinical trials, depending on the drug or other intervention being studied.

Twelve to 16 weeks is a relatively short period of time to observe for significant changes in pulmonary function; however, categorical disease progression occurred in over 10% of the

study population during this early period. By definition, the landmark method compares groups of patients who are not defined by a randomized exposure; whereas comparison groups in a randomized study would be expected to be similar with regard to baseline characteristics, markers of baseline disease severity in our study differed between patients with and without surrogate events occurring during followup. We have controlled for these differences to the extent reasonable, based on our sample size.

The IPFnet clinical trials were designed before the adoption of the current consensus guidelines for diagnosis.¹ However, study participants met contemporary diagnostic criteria,²² and the study inclusion criteria required specific combinations of imaging, clinical and histopathologic findings that are equivalent to those in the current guidelines.

Finally, comparing FVC decline and hospitalizations with other potential endpoints, such as changes in D_LCO or six-minute walk distance was not possible due to the differing assessment schedules of the three IPFnet trials.

In conclusion, in a pooled study population combining patients from three major clinical trials in IPF, non-elective hospitalization and disease progression as defined by 10% relative decrease in FVC were independently associated with increased risk of all-cause mortality. Composite endpoints incorporating disease progression and hospitalization were also highly predictive of reduced survival and identified a substantially larger population of patients at risk than either measure alone. Non-elective hospitalizations and disease progression as defined by categorical change in FVC may be practical and clinically relevant components of a composite endpoint in future event-driven IPF clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Systematic Review

All-cause mortality is a clinically relevant but impractical primary endpoint for idiopathic pulmonary fibrosis (IPF) clinical trials in patients with mild to moderate physiologic impairment. Forced vital capacity (FVC) has become the standard primary endpoint in such trials, as it is a widely accepted surrogate for mortality; hospitalization represents another potential surrogate endpoint that may complement FVC. We searched PubMed for studies evaluating the associations between FVC changes, hospitalizations and mortality among patients with IPF. We used the search terms, “IPF and hospitalizations and mortality” and “IPF and FVC and mortality,” without language or date restrictions. Both hospitalizations and categorical decreases in FVC have been shown to be associated with mortality in the context of clinical trials in IPF, and respiratory hospitalizations have been shown to portend particularly poor survival in a recent retrospective cohort. To our knowledge, ours is the first study to directly evaluate the associations between these two surrogate events, both alone and in the form of a composite surrogate endpoint, with subsequent mortality in a population of patients with IPF enrolled in clinical trials.

Interpretation

We show that hospitalizations and categorical decreases in FVC are common clinical events across a range of baseline physiologic impairments in IPF. Both events are significantly and independently associated with mortality. When cause-specific hospitalizations were considered, only respiratory-related hospitalizations remained associated with subsequent mortality. A composite outcome comprised of hospitalization (either all-cause or respiratory-related) plus 10% change in FVC has a substantially higher event rate than either event alone and a similar risk of mortality. Hospitalization plus categorical FVC change may represent a clinically relevant composite endpoint in IPF that improves feasibility.

Figure 1. Study Design

Patients from the IPFnet clinical trials formed the study population. Patients from the ACE-warfarin and PANTHER-prednisone/azathioprine/N-acetylcysteine arms were excluded to form the sample for overall time-to-event analyses. Seven additional patients were excluded for the remaining analyses, for which patients needed to be alive at the trial-specific landmark points.

Figure 2. Rates of hospitalization, disease progression and death

Plots show time to (A) disease progression as defined by 10% relative decrease in FVC, (B) first non-elective hospitalization from any cause, and (C) death from any cause. All are stratified by GAP index staging system: stage I, stage II, or stage III²⁴. Trial enrollment serves as time zero.

Figure 3. Impact of Hospitalizations and Decreases in FVC on All-Cause Mortality

Kaplan-Meier plots show time to death from any cause, stratified by (A) early disease progression as defined by 10% relative decrease in FVC, and (B) early hospitalization from any cause. The trial-specific landmark point serves as time zero. Number of subjects at risk is shown below the horizontal axis.

Figure 4. Impact of Composite Non-Fatal Endpoints on All-Cause Mortality

Kaplan-Meier plots show time to death from any cause, stratified by (A) composite of early non-elective, all-cause hospitalization or disease progression, and (B) composite of early respiratory hospitalization or disease progression. The trial-specific landmark point serves as time zero. Number of subjects at risk is shown below the horizontal axis.

Table 1

Baseline patient characteristics by non-elective, all-cause hospitalization and by disease progression (as defined by 10% decrease in FVC) occurring prior to or at the trial-specific landmark point.

Characteristic	Non-Eventive, All-Cause Hospitalization			Disease Progression		
	Hospitalization (n = 38)	No Hospitalization (n = 472)	p-value	Disease Progression (n = 58)	No Disease Progression (n = 452)	p-value
Age, yr	71.51 ± 7.4	67.7 ± 8.5	0.004	67.6 ± 8.8	68.1 ± 8.4	0.533
Female sex	5 (13)	99 (21)	0.250	10 (17)	94 (21)	0.527
Black	1 (3)	10 (2)	0.577	1 (2)	10 (2)	>0.999
White	36 (95)	441 (93)	>0.999	52 (90)	425 (94)	0.249
History of smoking	25 (66)	299 (64)	0.498	35 (60)	289 (64)	0.838
Time since diagnosis, yr	1.7 (0.5, 2.5)	10 (0.3, 20)	0.086	0.9 (0.3, 20)	1.0 (0.4, 2.1)	0.910
FVC % predicted	58.6 ± 14.7	66.0 ± 16.8	0.010	57.8 ± 15.3	66.4 ± 16.7	<0.001
D _L CO % predicted	28.6 ± 8.4	38.0 ± 13.6	<0.001	33.2 ± 11.8	37.9 ± 13.6	0.006
P _a O ₂ , mm Hg	70.1 ± 12.0	76.0 ± 13.7	0.012	69.2 ± 12.3	76.4 ± 13.7	<0.001
Supplemental O ₂ use at rest	11 (29)	84 (18)	0.089	20 (35)	75 (17)	<0.001
6-minute walk distance, m	273.3 ± 134.0	328.0 ± 125.5	0.018	275.4 ± 133.8	3300 ± 124.7	0.005
St. George's Respiratory Questionnaire, total score (range 0–100)	55.8 ± 18.2	44.5 ± 17.7	<0.001	51.7 ± 15.6	44.5 ± 18.1	0.004
Congestive Heart Failure	1 (3)	7 (2)	0.505	1 (2)	7 (2)	>0.999
Gastroesophageal Reflux Disease	23 (61)	285 (60)	>0.999	43 (74)	265 (59)	0.056
Coronary Artery Disease	12 (32)	103 (22)	0.282	12 (21)	103 (23)	0.883
Parent trial	27 (71)	147 (31)	<0.001	26 (45)	148 (33)	0.084
• STEP-IPF	3 (8)	70 (15)	<0.001	10 (17)	63 (14)	0.084
• ACE-IPF	8 (21)	255 (54)	<0.001	22 (38)	241 (53)	0.084
• PANTHER-IPF						

Values are presented as mean ± SD, median (IQR), or N (%). P-values are for Wilcoxon rank-sum test (time since diagnosis), two-sample t-tests (all other continuous variables), or χ^2 tests (categorical variables), respectively.

Table 2

Risk of non-elective hospitalization and disease progression by FVC criterion at any point during followup, accounting for death from any cause as a competing risk.

	Non-Elective, All-Cause Hospitalization		Non-Fatal Disease Progression	
	HR (95% CI)	P-value	HR (95% CI)	P-value
GAP II (compared with GAP I)	2.02 (1.04, 3.94)	0.0391	3.01 (1.31, 6.90)	0.0095
GAP III (compared with GAP I)	5.73 (3.06, 10.73)	<0.0001	2.29 (1.49, 3.50)	0.0001

Table 3

Concordance between patients with hospitalization and disease progression by FVC criterion occurring prior to or at the trial-specific landmark point (12–16 weeks, depending on parent trial).

Early hospitalization	Early disease progression		
	No		Yes
	<10% FVC decrease	Missed spirometry visit	10% FVC decrease
No	415	7	50
Yes	30	0	8

Table 4

All-Cause Mortality. Cox proportional hazards models for risk of all-cause mortality associated with surrogate events occurring prior to or at the landmark point (12–16 weeks, depending on parent trial).

Surrogate Event	HR (95% CI)	P-value
Disease progression (non-fatal 10% relative decrease in FVC)	4.68 (1.83, 11.99)	0.0013
• Without hospitalization in model	4.20 (1.63, 10.83)	0.0030
• With early hospitalization in model		
All-cause , non-fatal, non-elective hospitalization	4.05 (1.36, 12.11)	0.0122
• Without disease progression in model	3.41 (1.12, 10.38)	0.0312
• With early disease progression by FVC in model		
Respiratory non-fatal, non-elective hospitalization	5.97 (1.81, 19.74)	0.0034
• Without disease progression in model	5.42 (1.62, 18.12)	0.0060
• With early disease progression in model		
Non-respiratory, non-fatal , hospitalization	1.16 (0.15, 8.92)	0.8885
Composite of disease progression or all-cause hospitalization	5.81 (2.23, 15.11)	0.0003
Composite of disease progression or respiratory hospitalization	5.65 (2.19, 14.56)	0.0003

All models were stratified by parent trial, and adjusted for baseline GAP index (which includes age, sex, FVC and DLCO), duration of IPF diagnosis and smoking history in pack-years.