Daily Home Spirometry: An Effective Tool for Detecting Progression in Idiopathic Pulmonary Fibrosis

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Abstract

Rationale: Recent clinical trial successes have created an urgent need for earlier and more sensitive endpoints of disease progression in idiopathic pulmonary fibrosis (IPF). Domiciliary spirometry permits more frequent measurement of FVC than does hospital-based assessment, which therefore affords the opportunity for a more granular insight into changes in IPF progression.

Objectives: To determine the feasibility and reliability of measuring daily FVC in individuals with IPF.

Methods: Subjects with IPF were given handheld spirometers and instruction on how to self-administer spirometry. Subjects recorded daily FEV_1 and FVC for up to 490 days. Clinical assessment and hospital-based spirometry was undertaken at 6 and 12 months, and outcome data were collected for 3 years.

Measurements and Main Results: Daily spirometry was recorded by 50 subjects for a median period of 279 days (range, 13–490 d). There were 18 deaths during the active study period. Home spirometry showed excellent correlation with hospital-obtained readings. The rate of decline in FVC was highly predictive of outcome and subsequent mortality when measured at 3 months (hazard ratio [HR], 1.040; 95% confidence interval [CI], 1.021–1.062; $P \leqslant 0.001$), 6 months (HR, 1.024; 95% CI, 1.014–1.033; $P < 0.001$), and 12 months (HR, 1.012; 95% CI, 1.007–1.016; $P = 0.001$).

Conclusions: Measurement of daily home spirometry in patients with IPF is highly clinically informative and is feasible to perform for most of these patients. The relationship between mortality and rate of change of FVC at 3 months suggests that daily FVC may be of value as a primary endpoint in short proof-of-concept IPF studies.

Keywords: interstitial lung disease; clinical trials; biomarker; personalized medicine

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic lung disease of unknown etiology (1). Although the median survival for IPF from diagnosis is 3 years, the progression of the disease is highly variable. In most cases, the condition leads to a gradual but inexorable decline in exercise capacity. This decline reflects the on-going accumulation of the extracellular matrix, which, in turn, results in architectural destruction of the lung and ultimately terminates in respiratory failure. This gradual decline is punctuated by unheralded, rapid-onset, catastrophic, acute exacerbations in approximately 5 to 8% of patients with IPF per year (2). These episodes, which are characterized histologically by diffuse alveolar damage with a background of interstitial pneumonia, are a major cause of morbidity and mortality in IPF (3). In addition to

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At a Glance Commentary

Scientific Knowledge on the Subject: Change in FVC is the best established measure of worsening disease in individuals with idiopathic pulmonary fibrosis (IPF). Home monitoring of daily spirometry is used successfully in lung transplantation recipients to detect episodes of acute rejection. The feasibility and clinical usefulness of daily FVC monitoring in individuals with idiopathic pulmonary fibrosis has not been previously assessed.

What This Study Adds to the Field: Daily monitoring of FVC in IPF is highly clinically informative. Home measurements correlate well with hospital-based assessment of FVC. Daily measurement confirms that in most people with the condition, IPF is inexorably progressive, but a small number of those with the disease experience unheralded acute and irreversible declines in FVC. Assessment of daily home FVC provides a more accurate determinant of disease behavior and subsequent outcome than do periodic hospital-based measurements.

these episodes, an estimated 5 to 10% of those with IPF have a rapidly progressive form of the disease, with death occurring within 12 to 18 months of diagnosis (2).

Understanding of the natural history of IPF has been greatly informed by both retrospective analyses of large, specialist center cohorts and through observations derived from prospective clinical trials (4, 5). It has become increasingly clear that measurements of FVC provide the best assessment of progression of fibrosis in IPF (6–8). In clinical trial populations, FVC decline has been shown to be uniform across different baseline severities of disease, and meta-analysis suggests that slowing of FVC decline ultimately translates into improvements in survival (7, 9). However, variability inherent in the measurement of FVC (10), combined with the unpredictable nature of IPF disease progression, hinders the use of serial FVC measurement in the assessment of individual patients and limits its usefulness as an endpoint for short, early phase, proof-of-concept clinical trials.

Home monitoring of physiological variables has become increasingly practicable with the miniaturization and falling costs of devices, and corresponding improvements in wireless electronic connectivity. Within respiratory medicine, home disease monitoring in the form of peak flow measurement is already a feature of asthma self-management, and in lung transplantation recipients, daily surveillance spirometry is used for the detection of episodes of acute rejection (11). It is not known whether the adoption of a similar approach in IPF might be either feasible or clinically useful. Potential clinical advantages of routine home monitoring in IPF include early detection of rapidly declining FVC (which would enable prompt assessment of patients with potential acute exacerbations) and monitoring of response to novel therapies. From a clinical trial perspective, increased frequency of FVC monitoring may well provide an earlier efficacy signal than the one that is obtained with current hospital-based approaches, which typically necessitate a 52-week period of observation. The aim of this study was to assess the feasibility, reliability, and potential value of monitoring patient-administered daily FVC in a cohort of subjects with IPF. Some of the results of this study have been previously reported in the form of an abstract (12).

Methods

Study Subjects

Subjects with a consensus diagnosis of IPF [made in accordance with current international criteria (13)] were recruited as a subgroup of the PROFILE (Prospective Observation of Fibrosis in the Lung Clinical Endpoints) study (14), from the interstitial lung disease unit at Royal Brompton Hospital, London. The study was approved by the Royal Free Hospital and Medical School Research Ethics Committee (10/H0720/12), and all subjects provided signed, informed consent. Clinical assessment and full hospital-based lung function testing (spirometry, plethysmography, and gas transfer) were undertaken at baseline. Clinical assessment was repeated at 3-month intervals, whereas lung function testing was undertaken at 6 and 12 months. Subjects were followed until death or April 1, 2015.

Spirometry

Study subjects were provided with a portable hand-held Micro spirometer (CareFusion, Kent, United Kingdom). The Micro spirometer measures FEV_1 and FVC using a turbine volume transducer and provides a digital read out registered in liters at BTPS. Each spirometer was factory calibrated. The accuracy of the Micro spirometer when measuring FVC is reported to be $\pm 3\%$ in the range of 0.1 to 9.99 L. The Micro spirometer conforms fully with current American Thoracic Society and European Respiratory Society standards (15).

Subjects were given 60 minutes dedicated instruction on how to perform spirometry. Refresher training was provided after 1 month. Subjects were asked to perform a single spirometry reading at approximately the same time each day and to record the results in a dedicated diary. All FVC readings were recorded in liters and to two decimal places. Readings were reviewed at each visit by study staff and were entered in to an electronic database. Subjects were asked to contact study staff if their FVC reading fell by $>10\%$ from baseline for 3 or more consecutive days. Hospital-based spirometry was obtained according to current international standards, with the values used being the best obtained from three technically adequate forced expiratory maneuvers (15).

Statistical Analysis

Values are expressed as mean $\pm$ SD or median and range. Statistical analyses were performed using GraphPad Prism version 6.01 for Windows (GraphPad Software, San Diego, California) or MedCalc for Windows, version 13.6.1 (MedCalc software, Ostend, Belgium). Comparison of baseline home and hospital spirometry was performed using the Bland–Altman method. Rate of FVC change (Δ) was calculated using all available values, within the time windows considered and as described in the figure legends, by linear regression analysis without any imputation of missing values. Rate of change in FVC is presented as the percentage change relative to baseline values. For home-based spirometry, the baseline value was taken to be the mean of the values obtained between

baseline and Day 7. Survival analyses were assessed using Kaplan–Meier plots. The association between ΔFVC and subsequent survival was tested using Cox proportional hazards regression. Where relevant, disease progression was defined as death or a >10% decline in hospital-based FVC at 12 months. A P value of <0.05 was considered statistically significant.

Results

Patient Characteristics

Fifty subjects with IPF (mean age, 66.7 ± 7.9 yr; 45 [90%] men) were recruited for the study. Detailed baseline characteristics are provided in Table 1. Thirteen subjects completed a full 70 weeks (490 d) of home monitoring. The median duration for subjects remaining in the study was 279 days (range, 13–490 d). Eighteen patients died during the first 70 weeks of the study. Of the remaining subjects, 19 discontinued spirometry before 490 days (with 11 discontinuing before 6 mo and a further 2 before 12 mo) due to disease progression, intolerance of the procedure, or distress caused by observing deterioration in spirometry readings. For the 50 enrolled subjects, there was a median of 174 (range, 13–488) separate daily spirometry readings available for evaluation. The mean proportion of daily readings completed by each subject during the time they were participating in the study was 82.7 ± 17.3%.

Table 1. Baseline Characteristics of the Study Cohort

	Mean ± SD*
Male, n (%)	45 (90)
Age	66.7 ± 7.9
FEV_1, L/min	2.21 ± 0.61
FEV_1, % predicted	74.8 ±17.0
FVC, L	2.71 ± 0.82
FVC, % predicted	71.6 ± 18.3
FEV_1/FVC	0.82 ± 0.07
D_{LCO}, % predicted	39.2 ± 12.7
Modified MRC score	2.9 ± 0.9

Definition of abbreviations: D_{LCO} = diffusing capacity of the lung for carbon monoxide; MRC = Medical Research Council.
Lung function values are those obtained in the hospital physiology department immediately before study initiation.
*Unless otherwise indicated.

Validity and Reproducibility of Home Measurements

To avoid daily spirometry becoming too intrusive, study subjects were asked to undertake a single forced maneuver each day. To compare the accuracy of home readings with hospital-based measurements, the mean of all the daily readings recorded by subjects during the first 7 days of the study was compared with the hospital-based FVC obtained immediately before study initiation. Bland–Altman plots comparing home FVC and FEV_1 with hospital-based readings (Figure 1) show overall good agreement with a slight bias toward higher readings for both FEV_1 (bias 0.20 L/min; 95% limits of agreement, −0.35 to 0.75 L/min) and FVC (bias 0.20 L; 95% limits of agreement, −0.28 to 0.68 L) measured in the hospital lung physiology department. Agreement between home- and hospital-based spirometry remained equally good at later time points. At 6 months, FVC bias was 0.22 L with 95% limits of agreement of −0.23 to 0.68 L.

To assess within-subject reproducibility, only the readings for the first 28 days for each subject were

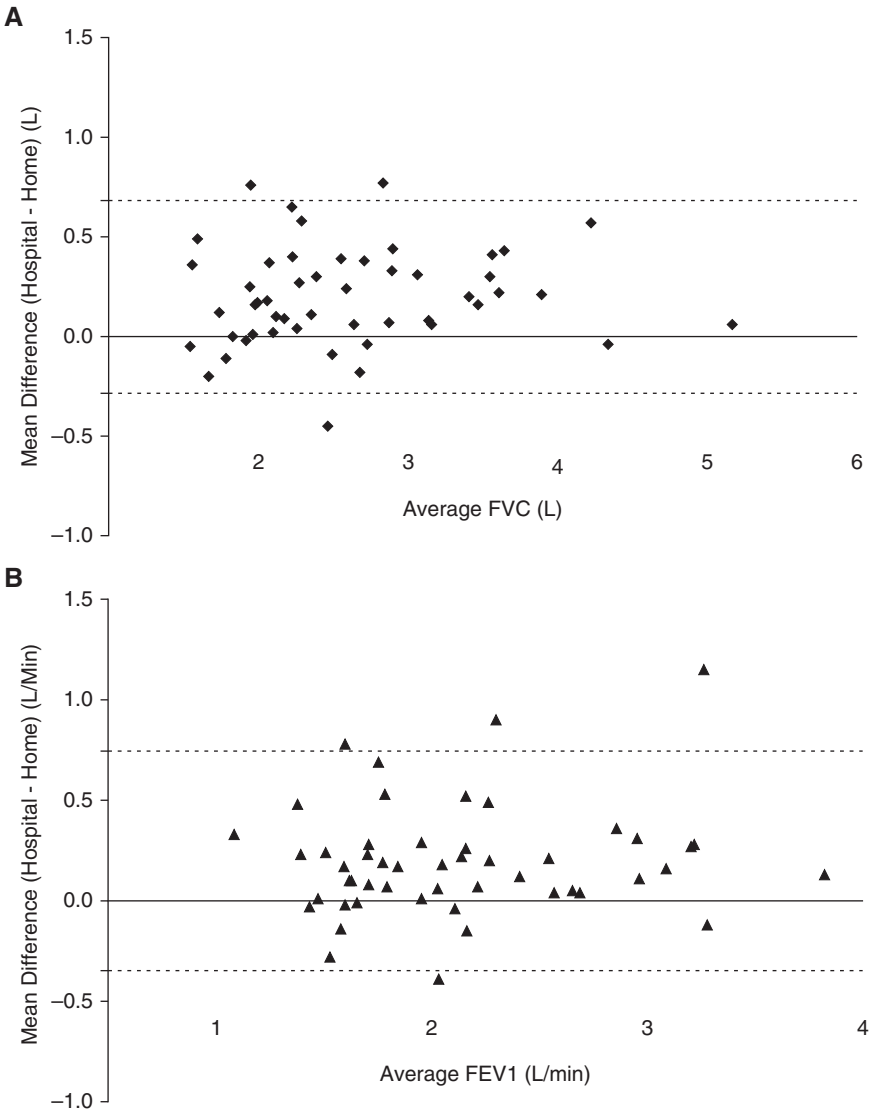

Figure 1. Comparison of hospital- and home-based spirometry readings. Bland–Altman plots comparing hospital- and home-based readings of (*A*) FVC and (*B*) FEV_1. Hospital-based readings were those obtained immediately before enrollment of subjects into the study. The value for home-based readings was taken as the mean of all the daily readings recorded by subjects during the first 7 days of the study.

considered (to avoid the influence of disease progression as far as possible). The median SD for repeated measurements by the same subject was 0.13 L (range, 0.04–0.38 L), which provided a median coefficient of variation of 4.96% (range, 2.06–20.09%). These readings were comparable to those obtained with daily supervised spirometry undertaken in healthy individuals and in those with chronic obstructive pulmonary disease.

Patterns of Disease Behavior

Analysis of individual plots disclosed disease behavior in keeping with that previously reported for IPF. As such, it was possible to identify subjects with inexorably progressive disease, those with rapidly progressive disease, and a small number who experienced acute exacerbations (Figure 2). Five (10%) of the subjects had an extremely rapid rate of disease progression (Figure 2B) with a projected annualized decline in FVC of >95% of baseline value. As might be expected, all died within 12 months of enrollment in the study. Four (8%) subjects exhibited accelerated periods of lung function loss with >10% FVC decline occurring in a 10- to 14-day period (Figure 2C). Three of these four subjects had symptoms, signs, and radiographic findings consistent with an acute exacerbation of IPF, and none subsequently recovered their lost vital capacity. The fourth subject was diagnosed with a lower respiratory tract infection and recovered back to baseline after treatment. Individual regression lines demonstrating the 1-year rate of FVC change for each of the 50 subjects in the study are shown in Figure 3. The median annualized rate of FVC decline was 306 ml.

Predicting Subsequent Outcome

Categorical change in FVC over 12 months in individuals with IPF has previously been demonstrated to predict subsequent survival in several retrospective studies (6, 8, 16). To determine whether change in FVC was predictive of mortality in the present study, the rate of change in FVC was calculated by using linear regression for all available values from baseline to 28 days, 3 months, 6 months, and 1 year. For initial analyses, the rate of change in FVC was assessed categorically using thresholds of 5 and 10%, relative to baseline values. In keeping with the literature, a 1-year rate of decline in FVC of ⩾10% strongly predicted outcome

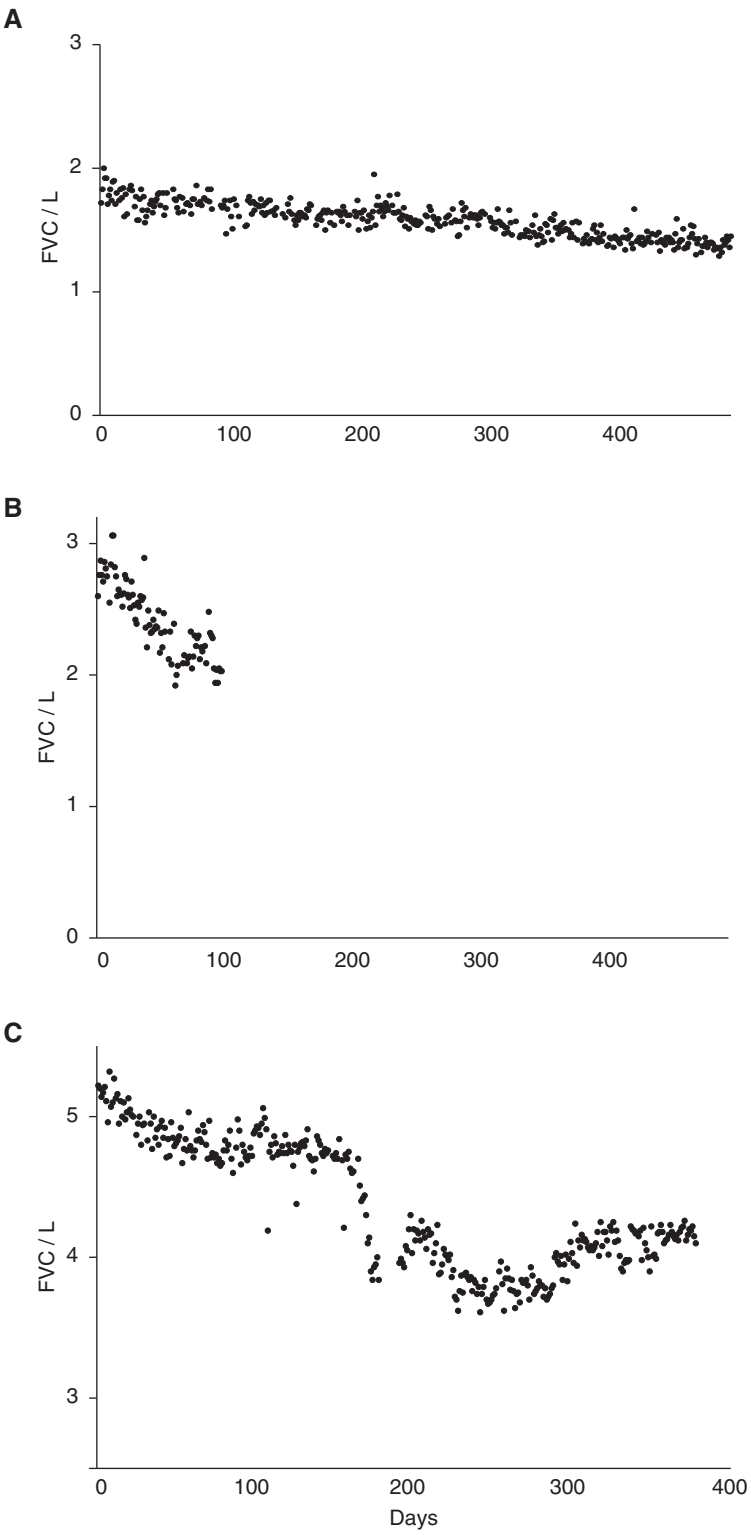

Figure 2. Individual examples of disease behavior. Daily FVC measurements for subjects with (*A*) inexorably progressive disease, (*B*) rapidly progressive disease, and (*C*) an acute exacerbation. Each point represents a single FVC measurement. The subject in *A* died of respiratory failure at 725 days. The subject in *B* died at Day 202, and the subject in *C*, despite losing 20% of FVC in a 3-week period, survived until Day 952.

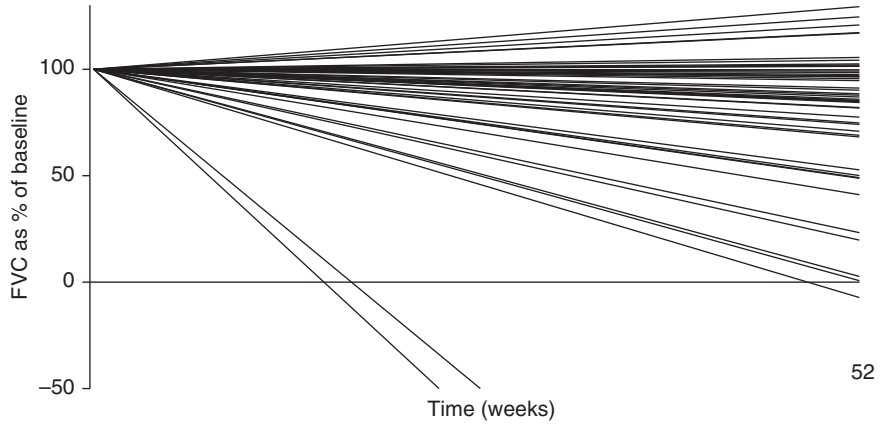

Figure 3. Rate of decline in FVC. Linear regression lines for each study subject demonstrate the rate of annual decline in FVC relative to baseline. Linear regression was performed using all readings available between baseline and Day 365 without imputation.

(Figure 4). For the group with a >10% rate of decline in FVC at 1 year, median survival was 598 days compared with a median survival of 1,084 days for the group with a <10% rate of decline ($P = 0.0010$). Rate of change from baseline to 6 months was similarly predictive of outcome when both a 5 and 10% threshold were applied. For an FVC threshold of >5% rate of decline, median survival was 598 days (compared with 985 d for those with <5% rate of decline; $P = 0.0068$), whereas for >10% rate of decline, it was 297 days (compared with a median survival of 1,487 d for the remaining subjects; $P < 0.0001$). Rate of decline at 3 months when dichotomized at a 5% threshold strongly predicted subsequent outcome (Figure 5). The subjects (n = 31) with a <5% rate of decline had a median survival of 930 days compared with a median survival of 334 days for the 19 subjects with a decline >5% rate of decline at 3 months ($P = 0.0015$). Only 9 subjects had a 10% rate of FVC loss at 3 months; median survival for this group was 228 days compared with 904 days for the <10% group ($P < 0.0001$). Dichotomized rate of change at 28 days was not predictive of subsequent outcome ($P = 0.1148$ when comparing groups with >5% and <5% rate of change).

When rate of FVC change was considered as a continuous variable and analyzed using a Cox proportional hazards model correcting for age, sex, baseline FVC, and baseline diffusion capacity for carbon monoxide, the rate of change in FVC assessed at 3 months, 6 months, and 1 year was predictive of subsequent mortality (Table 2). Only the rate of change between baseline and Day 28 failed to carry any prognostic value. The strongest relationship between rate of FVC decline and mortality was seen between baseline and 3 months (hazards ratio [HR], 1.040; 95% confidence interval [CI], 1.021–1.062; $P < 0.0001$).

IPF clinical trials have frequently reported a composite outcome of disease progression defined as death or >10% FVC decline at 12 months. This endpoint is judged to be both clinically meaningful and important to patients (17). Rate of change in patient-administered daily FVC over 3 months was strongly predictive of subsequent disease progression at 1 year as defined by a composite of >10% change in hospital-measured FVC or death (Figure 5). Subjects with progressive disease had a significantly greater rate of decline at 3 months (median decline, −7.9%; 95% CI, −4.98 to −20.81%) compared with those with stable disease (median change, +0.10%; 95% CI, +4.41 to −1.21%; Mann–Whitney $P = 0.0002$). On receiver-operating characteristic analysis, 3-month change in FVC was strongly predictive of disease progression (area under the curve, 0.796; $P < 0.001$) with a >5% rate of change at 3 months having a specificity and sensitivity of 90.5% and 62.1%, respectively, for predicting patients likely to have progressive disease at 12 months.

Twelve-month hospital-based FVC was available for 37 of 50 subjects, with the remaining 13 having died before 365 days. Although survival was poorer in the group of subjects with >10% loss in FVC relative to baseline (Figure 6A), the difference between the progressive and stable groups did not reach statistical significance ($P = 0.14$). By contrast, a landmark analysis (18) of the 12-month rate of change in home-measured FVC (Figure 6B) for those subjects still alive at 12 months demonstrated that a 12-month rate of change of >10% remained strongly predictive of a poorer outcome ($P = 0.01$).

Discussion

Daily, unsupervised, patient-performed, domiciliary spirometry is highly clinically informative in individuals with IPF. Although some subjects found daily FVC unpleasant to perform, the rate of discontinuation was comparable to the rate of dropouts seen in clinical trials, which suggests that regular home measurement of FVC in the context of a clinical study is feasible. Furthermore, the increased frequency of measurement permitted by undertaking home readings provided information over and above that obtained through periodic hospital-based measurement of FVC. Our data confirmed previously suspected disease paradigms (2, 19), with most of the subjects showing an inexorable, near-linear decline in FVC over time, with a smaller number experiencing extremely rapid progression, and an even smaller percentage (6%) showing evidence of acute irreversible decline in FVC associated with the onset of an acute exacerbation. Furthermore, the prospective daily evaluation of FVC was much more sensitive than hospital-based measurements in predicting subsequent prognosis, and at time points much earlier than have hitherto been possible with hospital-based readings (6, 8, 16).

Challenges in Conducting Home Spirometry

Bland–Altman analysis of both FVC and FEV_1 comparing hospital- and home-based readings demonstrated that home spirometry, in general, underestimated the values obtained when readings were supervised by a respiratory physiologist and obtained on hospital-based lung function equipment. The extent of the underestimate was consistent across all levels of baseline FVC and remained stable over time. We did not test whether this underestimate was

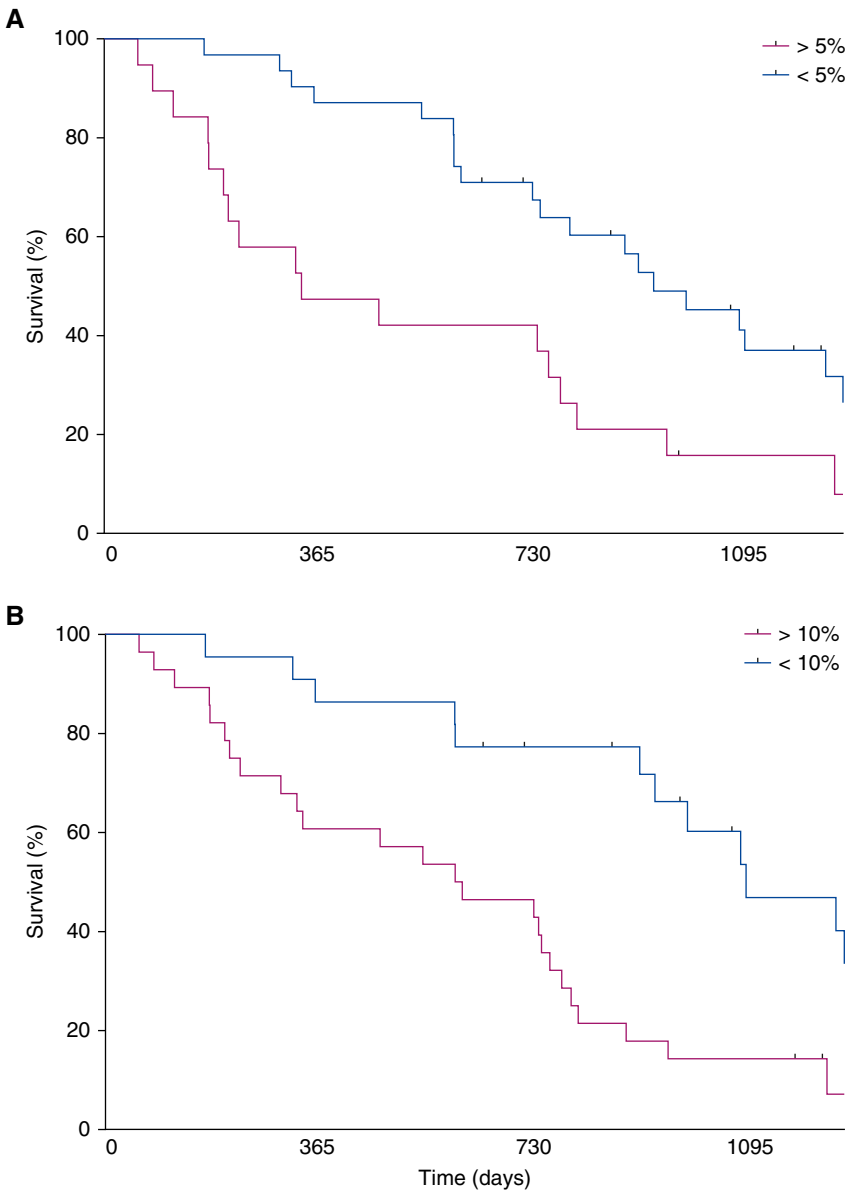

Figure 4. Relationship between 3- and 12-month rate of FVC change and subsequent survival. Kaplan–Meier plots demonstrate the effect of rate of change in FVC on subsequent survival at (*A*) 3 months and (*B*) 12 months. At 12 months, subjects were dichotomized into those with >10% rate of decline in FVC (*red line*) (n = 28) or <10% FVC rate of change (*blue line*) (n = 22). At 3 months, subjects were dichotomized into those with >5% rate of change in FVC (*red line*) (n = 19) or <5% rate of change in FVC (*blue line*) (n = 31). Rate of change was calculated by linear regression analysis of all points between baseline and 3 and 12 months, respectively. Rate of change is reported relative to baseline values, which were calculated by taking the mean of all the daily readings recorded by subjects during the first 7 days of the study.

effort- or equipment-related. Nonetheless, as demonstrated by the longitudinal data, this underestimation of FVC did not affect, to any important extent, the predictive value of serial measurement of FVC. Furthermore, the variability seen in day-to-day readings obtained by the same subject was comparable to that observed in reproducibility studies performed with hospital-based spirometry in both healthy individuals and those with chronic obstructive pulmonary disease (10).

Feedback from subjects who undertook the study confirmed, for the most part, that daily spirometry was straightforward to measure. This observation was validated by the fact that, on average, subjects completed spirometry on 4 of every 5 days during the time they actively participated in the study. However, some subjects did report that spirometry triggered fits of coughing, and this was cited as a reason by some for why they prematurely discontinued participating in the study. Concern about cough was also a reason for some potential subjects to decline participation in the study in the first place. The spirometer used for the study provided a visual readout of FEV_1 and FVC (and subjects manually recorded this in a dedicated study diary). Again, many study subjects reported value in knowing their daily FVC measurement. However, a consequence of asking patients to record their own FVC was that it provided them with considerable insight into the nature and rapidity of their own disease progression, and for a minority this proved to be psychologically distressing. (It is worth noting that the study was conducted before the advent of antifibrotic therapy; therefore, knowledge about disease decline did not influence therapy, as might now be the case.) If daily spirometry is to be used in clinical trials, it may be prudent to blind subjects to their own readings, although in short studies of 3 months or less, the changes seen will be less stark than those observed in this study of 70 weeks.

The information provided by home spirometry also created challenges in terms of managing short-term change in values. *A priori*, we instructed subjects to contact us if they observed a >10% drop in FVC from baseline on any 3 consecutive days or if they noted a drop in their FVC associated with a change in symptoms. Four subjects experienced an acute decline in FVC, which in each case was associated with increased symptoms of dyspnea and cough, and 3 cases showed radiographic changes consistent with an acute exacerbation. Whether early identification and intervention (all were treated with antibiotics and short-course oral corticosteroids) was beneficial is unknown; however, our data suggested that home spirometry could be used as a means for identifying acute exacerbations of IPF at an early stage and could therefore be used as the basis for conducting a clinical trial in this subject group.

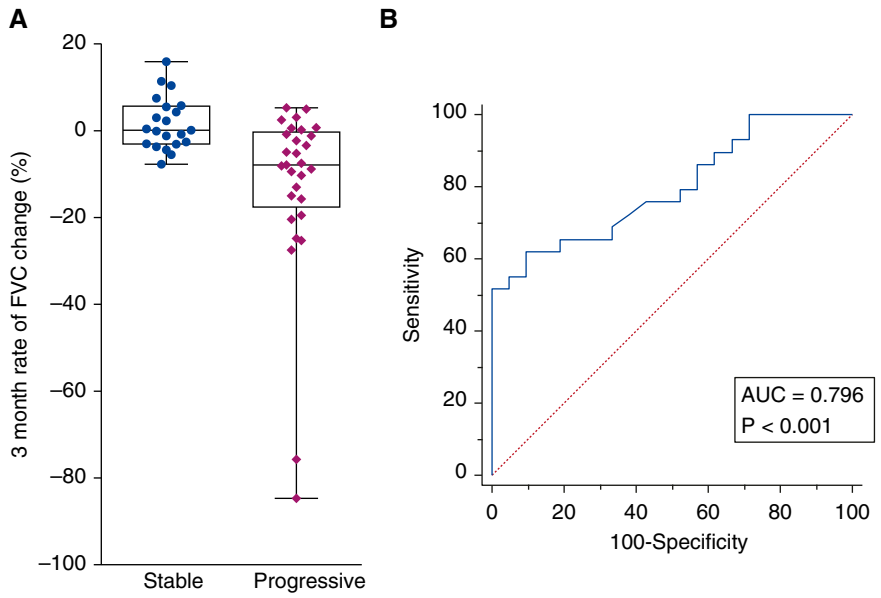

Figure 5. Three-month rate of change predicts disease progression at 1 year. Disease progression at 1 year was defined as death or >10% relative decline in hospital-measured FVC at 12 months. (*A*) Scatter plot with box and whiskers demonstrating the relationship between rate of change in FVC at 3 months as measured by daily home spirometry and subsequent disease progression at 12 months. (*B*) Receiver-operating curve analysis assessing predictive value of 3-month FVC rate of change in determining subsequent disease progression. A 5% rate of change in 3-month FVC had a 62.1% sensitivity (i.e., two-thirds of those with disease progression at 1 yr could be identified at 3 months on the basis of having a 5% rate of FVC decline) and a specificity of 90.5% (i.e., <1 in 10 subjects with a 5% rate of decline in FVC at 3 months subsequently failed to fulfill the criteria for disease progression at 1 yr). AUC = area under the curve.

Disease Insights Provided by Daily Home FVC

The rate of FVC decline measured by daily spirometry was highly predictive of subsequent prognosis and was informative of outcome from as early as 3 months. The relationship between FVC rate of change and outcome was considerably greater than that reported in retrospective cohort studies and in prospective clinical trials (6, 8, 16, 20–23). The reasons for this are several-fold. First, the subjects in the present study had a mortality akin to that seen in real-world clinical cohorts, which is greater than that observed in clinical trials. Second, retrospective studies require, by their very nature, that subjects have had lung function tested both at baseline but also at a given time point thereafter. This creates an inclusion bias that excludes those with the most rapidly progressive disease (in the present study, 13 subjects did not perform hospital-based spirometry at 12 months because they had died). Nonetheless, for the 37 subjects alive at 12 months, the rate of decline in home-measured FVC was predictive of subsequent outcome, whereas a change in hospital-based FVC was not. This speaks to the third advantage of performing daily spirometry, which is that the increased number of readings available had the effect of smoothing out measurement variation and dramatically improved the precision of the estimate of rate of disease change compared with periodic hospital-based assessments.

Although home-based spirometry was predictive of subsequent outcome at 3 months, no relationship was seen between rate of FVC decline at 28 days and mortality. It might be that any effective signal was lost due to measurement variability (although, as noted, the variability seen in the first 28 days was comparable to that historically reported for repeated hospital-based measurements). Alternatively, it might be that, on average, IPF did not progress at a fast enough rate to be detectable by FVC measurement at 28 days. FVC represents a proximate measurement for change in the burden of fibrosis, and it can be assumed that a certain burden of additional fibrosis has to develop before an impact on FVC becomes detectable. Therefore, there will ultimately be a limit to the resolution of FVC to detect change at the molecular level. Further studies are required before the true threshold at which FVC can be used to detect change in fibrosis can be determined. For the time being, our study suggests that 3 months represents a feasible period of time during which to detect change, whereas 28 days remains insufficient.

Table 2. The Effect on Survival of Magnitude of Rate of Change in Daily FVC over Specified Time Periods Measured by Cox Proportional Hazards Regression

Period for Rate of Change	Hazard Ratio	95% CI	*P* Value
0–28 d	0.975	0.937–1.014	0.20
0–3 mo	1.040	1.021–1.062	<0.0001
0–6 mo	1.024	1.014–1.033	<0.0001
0–1 yr	1.012	1.007–1.016	<0.0001

Definition of abbreviation: CI = confidence interval.
The gradients are on the original linear scale; therefore, the hazard ratio for this variable relates to the change in hazard for every 1% rate of decline in the slope of change over the given time period. All analyses are adjusted for age, sex, and baseline FVC.

Future Uses for Home Spirometry in IPF

The increased sensitivity of daily spirometry compared with interval hospital-based spirometry for predicting subsequent disease progression and survival suggests that home FVC could be used as an efficacy endpoint that would enable shorter early phase clinical trials. Importantly, only four subjects discontinued spirometry within the first 90 days of the study (two because of rate of their disease progression) with only one subject having less than 30 evaluable FVC readings. This suggests that a 3-month time window would be acceptable to clinical trial participants while being informative. Home

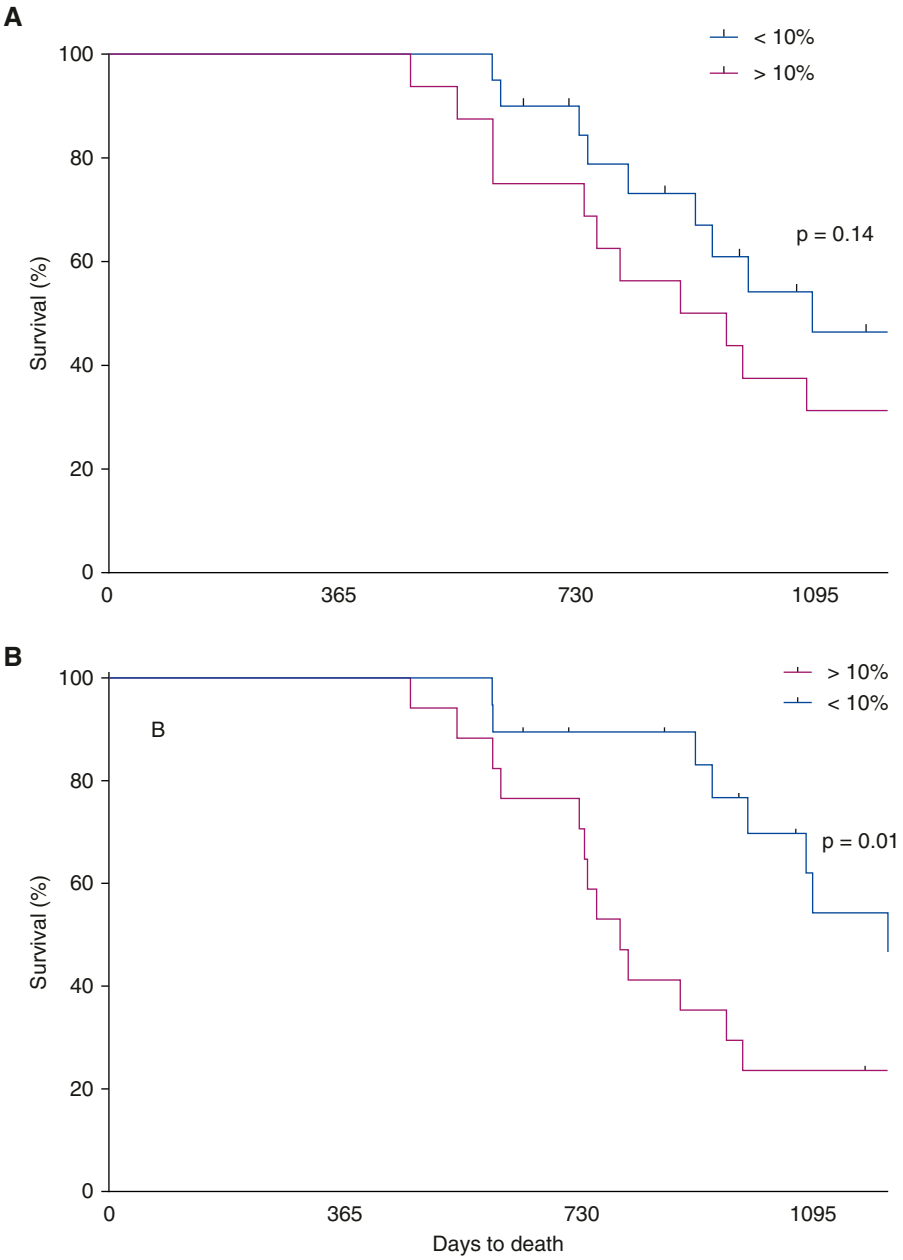

Figure 6. Twelve-month change in home- but not hospital-based spirometry is strongly predictive of subsequent outcome. Subjects were dichotomized into those with progressive (>10% change in hospital-based FVC between baseline and 12 months or >10% annual rate of change in home-based FVC) and relatively stable (<10% change in hospital-based FVC between baseline and 12 months or <10% annual rate of change in home-based spirometry) disease. (*A*) Kaplan–Meier plot of stable and progressive patients based on hospital-measured FVC (n = 37; 13 patients died before 12 months and were therefore unevaluable). (*B*) Kaplan–Meier landmark analysis of 12-month rate of change in home FVC (n = 37 as the 13 deaths before 12 months are excluded from the landmark analysis).

spirometry may also have a role in the early detection of infection or acute exacerbations (24). Such a use of spirometry merits prospective, protocolized assessment. The one impediment to the widespread, long-term use of daily measurements is that of tolerability and compliance. This may be possible to overcome by using less frequent measurement (e.g., weekly) of spirometry. In an era of effective antifibrotic therapy, early detection of disease progression should provide the opportunity to tailor therapy to an individual's disease. As such, this may offset some of the psychological morbidity associated with monitoring an inexorably progressive and ultimately fatal disease.

Strengths and Limitations

Major strengths of this study included its prospective design, the inclusion of subjects with an incident diagnosis of IPF, and limited exclusion criteria. Hitherto, the only prospective evaluation of the relationship between FVC and outcome has been in clinical trials.

However, our study did have a number of potential limitations. All subjects were recruited from a single center; therefore, these observations merit repeating across other centers to ensure generalizability. Subjects underwent limited training on performing spirometry. Variability in readings might have been reduced by more intensive and repeated training before initiation of home measurements. However, this did not prevent home FVC from being predictive of outcome. The current international guidelines on spirometry recommend that subjects perform three good quality maneuvers and that the best readings be used to determine subjects' "true" FEV_1 and FVC (15). To try and minimize intrusiveness and to limit intolerable effects (e.g., cough), we simply asked subjects to perform a single daily reading. Although this might have had an impact on accuracy, our anticipation was, as demonstrated by the data presented, that this would be compensated for by the number of readings undertaken over time. An alternative approach to the one that we took would be to undertake weekly spirometry, but when doing so, to mandate three high quality spirometry maneuvers. This could potentially reduce the intrusiveness of measurements while at the same time retaining the benefit gained through increased frequency of readings. The spirometer used for this study did not record flow-volume loops and nor did it store data; therefore, all daily readings had to be transcribed into a paper diary by subjects. The lack of flow-volume loops meant that it was not possible to validate the quality of individual daily readings. The use of paper diaries might have introduced error, which could not be corrected for by data cleaning, because there were no electronic records of results. Newer, internet connected spirometers should enable these limitations to be overcome in the future and may also provide a way of permitting real-time

identification of patients who are poorly compliant or misperforming spirometry, and those patients who are experiencing an acute exacerbation or with rapidly worsening disease. Finally, in analyzing individual disease behavior, we used a regression model that assumed linearity of disease decline. This approach is in keeping with that used in recent registration clinical trials in IPF (20, 21). A small number of subjects, particularly those who had exacerbations, violated the assumptions of linearity. It could be that using nonlinear models of disease progression over time might provide additional insights into IPF disease behavior. We hope to explore this possibility with larger cohorts in the future.

Conclusions

We demonstrated that daily home monitoring of FVC was highly clinically informative. In addition, it was feasible for most of the subjects to provide daily readings, on at least 4 of every 5 days, for periods of up to 1 year. Daily measurements of FVC provide a more sensitive and earlier prediction of disease behavior and outcome than do traditional periodic hospital-based readings. Home monitoring could be used to deliver personalized patient care, enabling early identification and treatment of IPF-related complications. Furthermore, we believe that the use of home spirometry offers the potential to transform early phase clinical trials by providing an efficacy readout in a time scale better suited to drug discovery than that provided by current hospital-based approaches. ■

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

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