hypertension (16). A more precise assessment of donor smoke exposure, passive or active, may provide more information for safer donor-recipient matching.

Overall, this study provides guidance for the design of future ARDS therapeutic drug trials. This study adds to the preponderance of evidence suggesting that clinical trials must begin to integrate precise phenotyping of ARDS patients into patient selection, including their tobacco exposure, to identify effective patient-specific therapeutics for ARDS. Finally, and perhaps most importantly, ongoing public health efforts to highlight the profound impact of tobacco smoke exposure on ARDS risks are integral to decreasing the population-based risk of a syndrome with high morbidity, mortality, and societal cost. ■

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References

1. Afshar M, Netzer G, Mosier MJ, Cooper RS, Adams W, Burnham EL, *et al.* The contributing risk of tobacco use for ARDS development in burn-injured adults with inhalation injury. *Respir Care* 2017;62:1456–1465.
2. Calfee CS, Matthay MA, Kangelaris KN, Siew ED, Janz DR, Bernard GR, *et al.* Cigarette smoke exposure and the acute respiratory distress syndrome. *Crit Care Med* 2015;43:1790–1797.
3. Diamond JM, Lee JC, Kawut SM, Shah RJ, Localio AR, Bellamy SL, *et al.*; Lung Transplant Outcomes Group. Clinical risk factors for primary graft dysfunction after lung transplantation. *Am J Respir Crit Care Med* 2013; 187:527–534.
4. Hsieh SJ, Zhuo H, Benowitz NL, Thompson BT, Liu KD, Matthay MA, *et al.*; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network. Prevalence and impact of active and passive cigarette smoking in acute respiratory distress syndrome. *Crit Care Med* 2014;42:2058–2068.
5. Moazed F, Hendrickson C, Conroy A, Kornblith LZ, Benowitz NL, Delucchi K, *et al.* Cigarette smoking and ARDS after blunt trauma: the influence of changing smoking patterns and resuscitation practices. *Chest* 2020; 158:1490–1498.
6. Panzer AR, Lynch SV, Langelier C, Christie JD, McCauley K, Nelson M, *et al.* Lung microbiota is related to smoking status and to development of acute respiratory distress syndrome in critically ill trauma patients. *Am J Respir Crit Care Med* 2018;197:621–631.
7. Moazed F, Hendrickson C, Jauregui A, Gotts J, Conroy A, Delucchi K, *et al.* Cigarette smoke exposure and acute respiratory distress syndrome in sepsis: epidemiology, clinical features, and biologic markers. *Am J Respir Crit Care Med* 2022;205:927–935.
8. Sinha P, Delucchi KL, Chen Y, Zhuo H, Abbott J, Wang C, *et al.* Latent class analysis-derived subphenotypes are generalisable to observational cohorts of acute respiratory distress syndrome: a prospective study. *Thorax* 2022;77:13–21.
9. Polubriaginof F, Salmasian H, Albert DA, Vawdrey DK. Challenges with collecting smoking status in electronic health records. *AMIA Annu Symp Proc* 2018;2017:1392–1400.
10. Hsieh SJ, Ware LB, Eisner MD, Yu L, Jacob P III, Havel C, *et al.* Biomarkers increase detection of active smoking and secondhand smoke exposure in critically ill patients. *Crit Care Med* 2011;39: 40–45.
11. Emmons KM, Hammond SK, Fava JL, Velicer WF, Evans JL, Monroe AD. A randomized trial to reduce passive smoke exposure in low-income households with young children. *Pediatrics* 2001; 108:18–24.
12. World Health Organization. WHO report on the global tobacco epidemic 2019: offer help to quit tobacco use. World Health Organization; 2019.
13. Liu A, Zhang X, Li R, Zheng M, Yang S, Dai L, *et al.* Overexpression of the SARS-CoV-2 receptor ACE2 is induced by cigarette smoke in bronchial and alveolar epithelia. *J Pathol* 2021;253:17–30.
14. Lowe KE, Zein J, Hatipoglu U, Attaway A. Association of smoking and cumulative pack-year exposure with COVID-19 outcomes in the Cleveland Clinic COVID-19 Registry. *JAMA Intern Med* 2021;181: 709–711.
15. Sinha P, Furfaro D, Cummings MJ, Abrams D, Delucchi K, Maddali MV, *et al.* Latent class analysis reveals COVID-19-related acute respiratory distress syndrome subgroups with differential responses to corticosteroids. *Am J Respir Crit Care Med* 2021;204: 1274–1285.
16. Shah RJ, Diamond JM, Cantu E, Flesch J, Lee JC, Lederer DJ, *et al.* Objective estimates improve risk stratification for primary graft dysfunction after lung transplantation. *Am J Transplant* 2015;15: 2188–2196.

The Shorter, the Better: Can We Improve Efficiency of Idiopathic Pulmonary Fibrosis Trials?

Idiopathic pulmonary fibrosis (IPF) is the prototypic fibrosing lung disease, characterized by relentless progression and poor prognosis (1). Patients gradually deteriorate despite treatment with the current standard of care, nintedanib or pirfenidone (2). These drugs have been approved after decades of failed trials and heated discussion on the choice of the best efficacy endpoint. Endpoints have been investigated in thousands of patients before it was decided that the change of FVC over 1 year was the right one, a decision based mainly on the correlation between FVC changes and mortality and accepting that studies with mortality as endpoint were not feasible (3).

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Measuring FVC is a simple, reproducible, and widely available tool to monitor IPF progression. Both substantial (⩾10%) and marginal (between 5% and 10%) declines in FVC at 6 months are associated with increased risk of death (4–6). One challenge in current clinical trials is allocation of patients to true placebo when approved treatments are available. The alternative strategy of identifying a treatment effect on top of antifibrotic treatment leaves smaller margins to detect differences and requires more patients and long trial duration. Therefore, novel strategies to improve trial efficiency in IPF are most needed.

In this issue of the *Journal*, Khan and colleagues (pp. 936–948) used a solid statistical approach to assess the reliability of a 3-month change in functional parameters as a surrogate efficacy endpoint in IPF trials (7). The authors performed a systematic review and meta-analysis using individual patient data from large IPF trials (certainly a strength of their study) to explore the relationships between a 3-month change in physiological parameters and clinically relevant outcomes. The data generated from almost 2,000 patients with IPF indicate that a 2.5% relative FVC decline at 3 months is associated with a 15% increased risk of mortality and a 30% increased likelihood of disease progression. An optimal threshold of 5.7% in FVC change at 3 months is predicting a significantly higher risk of death: the accuracy of this 3-month FVC change is comparable to a 10% change in a 12-month period.

In the treatment arms of six trials evaluating currently approved antifibrotics, a 2.5% relative FVC decline at 3 months is associated with a 20% risk increase in mortality and 46% greater likelihood of disease progression. Importantly, the comparison of FVC decline between treatment arms and their corresponding placebo arms showed that a statistically significant treatment effect is present after 3 months (40.9-ml difference between placebo and treatment arms, a relative change difference of 1.6%). The authors conclude that 3-month declines in lung function are predictive of disease progression, irrespective of antifibrotic treatment, and could serve as an earlier endpoint or a prognostic enrichment tool for future IPF trials.

Khan and colleagues should be praised for the methodological robustness of their study, providing an unbiased insight into the extent to which FVC change could be exploited. An efficacy endpoint measurable in a shorter timeframe could more rapidly provide evidence of (in)efficacy, optimizing the resources needed in IPF trials and making study participation more sustainable. Improving the efficiency of trials in IPF and pulmonary fibrosis in general should be a priority for the respiratory community. New opportunities are on the horizon, including the use of Bayesian approaches (8) and the implementation of home spirometry; 3-month change in FVC measured via handheld spirometers showed high sensitivity for predicting subsequent survival and could be used as an efficacy endpoint in short proof-of-concept trials (9), although recent findings suggest that this approach needs further validation (10, 11).

The findings of Khan and colleagues will also help to enroll patients with a more "progressive" disease. It will be important to validate these results in other nonidiopathic fibrotic lung diseases, as this additional evidence would also contribute to the ongoing process of defining what is "progressive" in patients with pulmonary fibrosis.

The advantages of using a 3-month interval in FVC change come at a price though. The authors estimate that a hypothetical trial using FVC decline at 3 months as the primary efficacy endpoint should approximately double the number of patients, as compared with a "standard" 12-month trial. Although more patients could feel encouraged to participate in shorter trials, this should be carefully balanced with the challenge of a most intensive recruitment phase, a challenge even more critical in the current coronavirus disease (COVID-19) pandemic era.

The current study included trials of a bygone IPF era when placebo arms were entirely formed by naive, untreated patients. Pirfenidone or nintedanib are now an essential component of the placebo groups in IPF trials, thus sensibly decreasing the rate of functional decline of this group. As such, it could be argued that a 3-month window to detect a treatment effect may not be the best fit, as separation of functional trend slopes of placebo and treatment arms could be delayed in time owing to smaller effect sizes. However, recent studies in IPF have also shown that the patients in the placebo arms with background therapy were more progressive than would have been expected (12). These patients were not (yet) included by the authors in their analyses. On the other hand, a short trial duration might increase acceptance of a "pure" placebo group of patients, at least in phase 2 trials.

The choice of using FVC decline as a standalone primary endpoint should not be taken for granted. The incorporation of alternative outcomes could enhance trial efficiency. If backed by validation and consensus on implementation strategies (13), patient-reported outcomes will be given higher priority in the design of future IPF trials. Quantitative assessment of chest imaging via computer-aided imaging analysis could increase sensitivity to capture subtle changes in lung parenchyma indicating progressive disease (14–16). The radiological extent of pulmonary fibrosis was included as secondary endpoint in the recent successful phase 2 trial of pamrevlumab, which showed to decrease fibrotic progression on computed tomography scan at 12 months (17). Change over time in lung function will probably remain the mainstay for assessing drug efficacy in IPF. Khan and colleagues show that shorter trials may be a way forward. Nonetheless, a shorter timeframe for change in lung function should be complemented by other outcomes of interest to maximize trial effectiveness and capture a range of benefits beyond slowing down disease progression, as our goal is to halt and ideally reverse pulmonary fibrosis, making patients feel better. ■

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References

1. Wijsenbeek M, Cottin V. Spectrum of fibrotic lung diseases. N Engl J Med 2020;383:958–968.
2. Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. *N Engl J Med* 2018;378:1811–1823.
3. Karimi-Shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis–FDA review of pirfenidone and nintedanib. *N Engl J Med* 2015;372:1189–1191.
4. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, *et al.* Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;184: 459–466.
5. Zappala CJ, Latsi PI, Nicholson AG, Colby TV, Cramer D, Renzoni EA, *et al.* Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. *Eur Respir J* 2010;35:830–836.
6. Richeldi L, Ryerson CJ, Lee JS, Wolters PJ, Koth LL, Ley B, *et al.* Relative versus absolute change in forced vital capacity in idiopathic pulmonary fibrosis. *Thorax* 2012;67:407–411.
7. Khan FA, Stewart I, Moss S, Fabbri L, Robinson KA, Johnson SR, *et al.* Three-month FVC change: a trial endpoint for idiopathic pulmonary fibrosis based on individual participant data meta-analysis. *Am J Respir Crit Care Med* 2022;205:936–948.
8. Zampieri FG, Casey JD, Shankar-Hari M, Harrell FE Jr, Harhay MO. Using Bayesian methods to augment the interpretation of critical care trials. An overview of theory and example reanalysis of the alveolar recruitment for acute respiratory distress syndrome trial. *Am J Respir Crit Care Med* 2021;203:543–552.
9. Russell AM, Adamali H, Molyneaux PL, Lukey PT, Marshall RP, Renzoni EA, *et al.* Daily home spirometry: An effective tool for detecting progression in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2016;194:989–997.
10. Noth I, Cottin V, Chaudhuri N, Corte TJ, Johannson KA, Wijsenbeek M, *et al.*; INMARK trial investigators. Home spirometry in patients with idiopathic pulmonary fibrosis: data from the INMARK trial. *Eur Respir J* 2021;58:2001518.
11. Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M, *et al.* Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Respir Med* 2020;8:147–157.
12. Raghu G, van den Blink B, Hamblin MJ, Brown AW, Golden JA, Ho LA, *et al.* Effect of recombinant human pentraxin 2 vs placebo on change in forced vital capacity in patients with idiopathic pulmonary fibrosis: a randomized clinical trial. *JAMA* 2018;319:2299–2307.
13. Aronson KI, Danoff SK, Russell A-M, Ryerson CJ, Suzuki A, Wijsenbeek MS, *et al.* Patient-centered outcomes research in interstitial lung disease: an official American Thoracic Society research statement. *Am J Respir Crit Care Med* 2021;204:e3–e23.
14. Jacob J, Bartholmai BJ, Rajagopalan S, Kokosi M, Nair A, Karwoski R, *et al.* Automated quantitative computed tomography versus visual computed tomography scoring in idiopathic pulmonary fibrosis: validation against pulmonary function. *J Thorac Imaging* 2016;31:304–311.
15. Jacob J, Bartholmai BJ, Rajagopalan S, Kokosi M, Nair A, Karwoski R, *et al.* Mortality prediction in idiopathic pulmonary fibrosis: evaluation of computer-based CT analysis with conventional severity measures. *Eur Respir J* 2017;49:1601011.
16. Maldonado F, Moua T, Rajagopalan S, Karwoski RA, Raghunath S, Decker PA, *et al.* Automated quantification of radiological patterns predicts survival in idiopathic pulmonary fibrosis. *Eur Respir J* 2014;43: 204–212.
17. Richeldi L, Fernández Pérez ER, Costabel U, Albera C, Lederer DJ, Flaherty KR, *et al.* Pamrevlumab, an anti-connective tissue growth factor therapy, for idiopathic pulmonary fibrosis (PRAISE): a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2020;8:25–33.

Hypoxia and Sleep-disordered Breathing
Friend or Foe?

Hypoxia is a hallmark feature of respiratory disease and has multiple effects on the central nervous system. For example, experimentally induced acute sustained isocapnic hypoxia (oxygen saturation as measured by pulse oximetry [Sp_{O_2}], 80–85%) blunts respiratory sensation (1) and symptom perception in asthma (2) and suppresses cough reflex sensitivity (3) and arousal responses to airway closure during sleep in healthy individuals (4). The effects of repetitive intermittent hypoxia, as occurs nightly in sleep-disordered breathing, are generally considered deleterious for the cardiovascular system. For instance, 2–4 weeks of nightly intermittent hypoxia increases daytime blood pressure and sympathetic nerve activity in healthy individuals (5, 6), potentially via renin-angiotensin mechanisms (7). In addition, the overnight sleep apnea–related hypoxic burden metric, which includes both hypoxemia frequency and magnitude components, predicts cardiovascular mortality (8–10).

However, as highlighted in this issue of the *Journal* in the current proof-of-concept physiology study conducted in a group of hypertensive men with obstructive sleep apnea (OSA) by Panza and colleagues (pp. 949–958) (11) and by others (12, 13), not all aspects of hypoxemia are necessarily deleterious. The rationale for the current study was based largely on the authors' prior work that investigated specific hypercapnic intermittent hypoxia regimes and the subsequent facilitatory effects on respiratory and upper airway neurons (14, 15) and the work of others that indicates that mild intermittent hypoxia during wakefulness can reduce blood pressure via nitric oxide mechanisms in untreated hypertensive patients in whom OSA status is unknown (16). The three key study findings were that intermittent hypoxia

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