Patient-reported Outcomes for Clinical Trials in Idiopathic Pulmonary Fibrosis: New Opportunities to Understand How Patients Feel and Function

In recent years, our understanding of the pathogenesis of idiopathic pulmonary fibrosis (IPF) has grown enormously, and this new knowledge has underpinned major clinical trials testing novel treatment approaches (1). These scientific advances have resulted in the approval of two antifibrotic therapies (2, 3), which have changed the landscape of IPF care. At the same time, our knowledge of the physical, emotional, and social impacts of IPF has also grown, primarily from the application of qualitative methods in IPF research (4). The burden of dyspnea and cough are well established, with the impact of fatigue increasingly recognized (5). Many patients with IPF also experience anxiety, frustration, sadness, a loss of independence and important life roles, financial stress, and social stigma (4). Although the emergence of antifibrotic treatments has made us feel better about the future of IPF treatments, to date we do not have convincing evidence that these therapies have delivered better health-related quality of life (HRQL) for patients (2, 3).

The development and testing of interventions to improve HRQL in people with IPF across the disease course has been hampered by a lack of confidence in our measurement tools, many of which were adopted or adapted from those for other lung diseases (6). Although purpose-designed tools are emerging (7), a comprehensive HRQL measure for IPF that is ready for use in clinical trials remains a gap in our clinical trial toolbox. In this issue of the Journal, Swigris and colleagues (pp. 1689–1697) describe the first steps toward this important outcome (8). The Living with IPF (L-IPF) questionnaire has 35 items scored on a five-point numerical rating scale that address important symptoms (dyspnea, cough, and low energy) and impacts of IPF. This study provides evidence that the L-IPF has excellent test-retest reliability in stable patients, together with good psychometric, concurrent, and known-groups validity. The authors have worked with the U.S. Food and Drug Administration to ensure the

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development and testing of the L-IPF questionnaire meets the requirements of U.S. Food and Drug Administration qualification, which, if achieved, will increase the likelihood that this HRQL measure is used in clinical trials.

The strengths of this study include the genesis of the questionnaire from patients’ perspectives, which were gained from interviews and focus groups of people with IPF. The methods are robust and well described, including item generation, assessment of clinimetric properties, and optimization of scales and scoring. When compared with other HRQL measures such as the King’s Brief Interstitial Lung Disease questionnaire, the L-IPF questionnaire has fewer items (6) and assesses a broader range of symptoms, with separate domain scores for shortness of breath, cough, and energy. This may mean that patients are asked to complete fewer questionnaires to achieve a comprehensive assessment of HRQL, which is certainly an important consideration. However, the L-IPF does not assess mood disturbance, a common and important burden associated with IPF (9), so other patient-reported outcomes will remain necessary. Because the L-IPF domains are focused on the common symptoms of IPF, more general symptoms that impact HRQL (e.g., nausea related to drug treatment) would not be detected. The inclusion of an energy domain in the L-IPF questionnaire is a valuable contribution given the burden of fatigue for many patients with IPF (5). The authors intend to place the L-IPF questionnaire in the public domain (8), which increases the likelihood that a wide range of researchers and clinicians will choose this tool to measure patient-reported outcomes, in turn generating new knowledge about HRQL in this patient group.

The L-IPF was developed to assess HRQL in IPF, a well-characterized patient group that has been a major focus of clinical trials in interstitial lung disease (1). However, this research paradigm may be changing, with the recognition that other progressive fibrotic interstitial lung diseases exhibit similar disease behavior (10) and response to treatment (11). In future clinical trials, our HRQL tools may need to be applied to a broader range of patients with progressive lung fibrosis, and it will be important to understand the performance of the L-IPF in this context. In the current study (8), Swigris and colleagues applied the L-IPF to a patient group typical of those currently considered for clinical trials of drug treatments, with 81% receiving antifibrotic therapy and few patients in GAP (gender, age, and physiology) stage III. Whether the L-IPF is useful across a broader range of patients remains to be established.

It is important to be able to measure a health outcome, but it is equally as important to know whether we can change that outcome with treatment. Future research must address the responsiveness of the L-IPF questionnaire. Although the broad range of items included in the questionnaire is valuable to accurately reflect the range of patient experiences, it is possible that this may affect the ability of the L-IPF to detect changes with treatments that do not affect all domains (for example a treatment that does not impact cough). HRQL is a critical outcome for clinical trials of both drug and nondrug treatments (e.g., pulmonary rehabilitation, symptom management, and supportive care), so it will be necessary to assess responsiveness across a range of interventions. The minimal important difference for the L-IPF should also be established so that we can assess whether observed changes are meaningful to patients.

Researchers and healthcare professionals have made important advances in the diagnosis and treatment of people with IPF in recent years, but the journey toward better outcomes for patients is far from over. The study of Swigris and colleagues illustrates the importance of partnerships across patients, researchers, health professionals, and policy makers to better understand where we should be headed and how we might know if we have gotten there.

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Understanding the cardiovascular (CV) impact of obstructive sleep apnea (OSA) is now a mature research field. After more than four decades of experimental, translational, and clinical studies (most of them observational or small randomized trials) showing a myriad of OSA consequences such as hypertension, heart failure, arrhythmias, and coronary artery disease (CAD), we were recently challenged for reaching the top of the scientific evidence (1). Like in any other field, randomization reduces bias and provides a rigorous tool to examine cause–effect relationships between an intervention and outcome (2). The obvious initial strategy is to select patients with a high-CV-risk profile to increase the chance of detecting differences during a relatively short period of time and aiming for feasibility; events in the primary prevention scenario usually have lower incidence, requiring greater than twofold the number of patients and follow-up time than secondary prevention studies. However, expectations based on promising previous observational studies in primary prevention (3–5) did not come true for secondary prevention: recent randomized trials comprising patients with OSA with previous CAD or cerebrovascular disease (SAVE [Sleep Apnea Cardiovascular Endpoints]) (6), CAD only (RICCADSA [Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnea]) (7), and acute coronary syndrome (ACS) (ISAACC [Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome]) (8) showed neutral results in their primary outcomes. Although subanalysis suggested significant effects in patients with good adherence of continuous positive airway pressure (CPAP) for preventing cerebrovascular events in SAVE (6) and composite CV endpoints in RICCADSA (7), the ISAAC trial resulted in a tough scenario: not only did CPAP not prevent CV events, untreated patients with OSA did not have a poorer prognosis than a control group without OSA (8). Therefore, it is natural to ask whether we should ignore the aforementioned evidence because it did not fit the most recommended evidence. What kind of previous lessons and reflections do we consider before determining OSA to be a nonrelevant cardiology issue? Recently, at least three reviews highlighted this matter and proposed alternatives for future studies (1, 9, 10). Beyond CPAP compliance issues, these randomized studies shared a common profile: patients with OSA were minimally or not sleep. Although the inclusion of sleepy patients sounds unethical, they may prevent us from understanding the impact of treating symptomatic patients on cardiovascular outcomes. Indeed, recent evidence in the Sleep Heart Health Study showed that excessive sleepiness is associated with poor CV outcomes in patients with OSA (11). Moreover, it is reasonable to speculate that physiological traits, characteristics of the nocturnal hypoxemia, biomarkers, and the baseline characteristics of patients may modulate clinical response and outcomes in OSA treatment (12).

In this issue of the Journal, Zapater and colleagues (pp. 1698–1706) shed light upon the phenotypes and therapeutic opportunities for mitigating CV risk in OSA (13). They reported the results of a secondary analysis of the ISAACC study, aimed at understanding the impact of moderate–severe OSA on the incidence of CV disease in 1,701 patients with ACS of different CV risk phenotypes (13). The authors define CV risk phenotypes using unsupervised approaches to help tease out the known clinical heterogeneity of OSA, a strategy that has been demonstrated to be valuable in understanding CV disease risk in other clinical domains in OSA such as clinical symptoms (11) and polysomnographic characteristics (14). In the current study, the authors used latent class analysis on categorized representation of 12 clinical factors commonly associated with CV risk (e.g., age, sex, lifestyle habits, comorbidities, and lipid levels) and identified two distinct CV risk phenotypes: “no previous CVD” and “previous CVD.” These distinct subgroups of patients with ACS differed mostly based on the prevalence of previous CV diseases, but they also differed in age, smoking status, and prevalence of other comorbidities.

The main findings of the study indicate a significant effect of moderate–severe OSA on the risk of recurrent CV events observed only in patients in the “no-previous-CVD” subgroup (13). Patients with OSA in this subgroup had an increased risk of recurrent CV events with an adjusted hazard ratio (HR) of 1.54 (95% confidence interval [95% CI], 1.06–2.24). Conversely, this effect was not
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