EDITORIALS

COPD and Declining FEV_1 — Time to Divide and Conquer?

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In 1976, Fletcher et al. published a monograph summarizing the results of an 8-year observational study of the relationship between cigarette smoking, chronic expectoration, and the development of irreversible airflow obstruction.[1] At that time, the nomenclature for chronic obstructive pulmonary disease (COPD) was confusing. COPD was understood to include chronic bronchitis and emphysema, but the definitions of these two entities contained no mention of airflow obstruction. The clinical paradigm described patients as either "blue bloaters," who had chronic airway inflammation and a propensity for resting hypercapnia, and "pink puffers," who had airspace destruction and preserved resting arterial oxygenation.

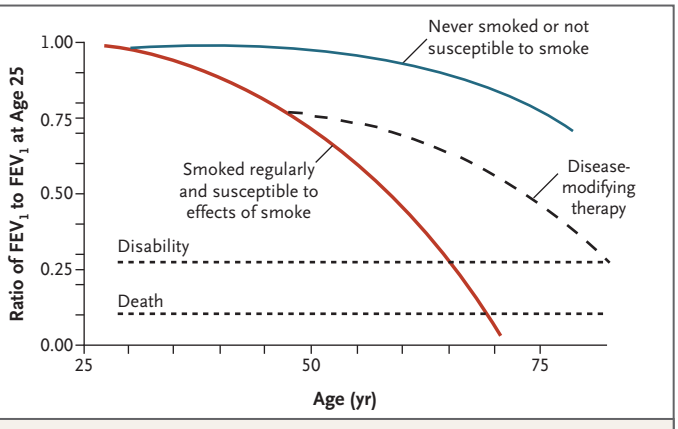

Figure 1. Association between the Ratio of FEV_1 to FEV_1 at the Age of 25 Years and Disability or Death.

The graph shows two subgroups of persons: those who have never smoked tobacco or who have smoked but are not susceptible to airflow obstruction (blue line) and those who have smoked and are susceptible to airflow obstruction (red line). The effects of disease-modifying therapy, such as smoking cessation, are depicted by the dashed line, showing a change in the rate of decline in the forced expiratory volume in 1 second (FEV_1) associated with the intervention. The change in the rate of decline in FEV_1 has been used as the end point in a number of large clinical trials involving patients with COPD. Data are adapted with permission from Fletcher and Peto.[2]

The study by Fletcher et al. showed that a subgroup of smokers had an accelerated rate of decline in rates of maximal forced expiratory flow, represented by the forced expiratory volume in 1 second (FEV_1). This finding shaped subsequent investigative activities in two areas: a search for the factors that underlie an apparent susceptibility to the effects of cigarette smoking and a search for therapies that slow the accelerated rate of decline. Since the introduction of this concept, modification of this trajectory, which is the first-time derivative of FEV_1 during a period of years, $d(FEV_1)/dt$, has been adopted as a clinical standard for disease-modifying therapy (Fig. 1). The acceptance of this concept is reflected by its inclusion as one of five proposed primary efficacy end points in the Guidance to Industry draft document prepared by the Food and Drug Administration on the development of drugs for the treatment of patients with COPD.[3]

More recently, the Global Initiative for Chronic Obstructive Lung Disease has agreed on a single definition of COPD, which is characterized "by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases."[4] This statement reinforced the notion that COPD is a single disease, which is operationally defined by results on spirometry and more specifically by the FEV_1.

In this issue of the *Journal*, Tashkin and colleagues report the results of a large, randomized trial of the long-acting anticholinergic medication tiotropium in patients with COPD.[5] The trial was designed to test the hypothesis that the

regular use of tiotropium, in addition to standard therapy for COPD, would favorably alter the rate of decline in FEV_1. This trial, known as the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study (ClinicalTrials.gov number, NCT00144339), illustrates the challenges of using FEV_1 as an end point.

Given the magnitude of the rate of decline in FEV_1, along with its variability among patients and the variability of FEV_1 measures, an adequately powered trial requires the enrollment of a large number of patients who are observed for a period of at least 3 years. This factor creates challenges in recruitment, retention, and expense, all of which are formidable hurdles for clinical investigators. The UPLIFT investigators secured appropriate resources, organized a network of 490 centers in 37 countries, and recruited a total of 5993 patients. Despite their best efforts, about 40% of enrollees dropped out before the study was completed, a rate that is similar to those of other recent, large COPD trials.[6] For the coprimary end points — the rates of decline in FEV_1 before and after bronchodilation — there were no significant differences between tiotropium and placebo.

One could argue that this outcome was predictable, since previous trials of a short-acting anticholinergic drug, a number of inhaled corticosteroids, and an antioxidant have all shown no positive effect on the rate of decline in FEV_1.[6-11] To date, the only intervention that has met this criterion of disease-modifying therapy is smoking cessation, as shown in the Lung Health Study, sponsored by the National Institutes of Health.[8] In retrospect, the accomplishments of the investigators in the Lung Health Study are all the more impressive, since they achieved a 5-year follow-up rate of 94% among 5887 subjects and had the foresight to select smoking cessation among their interventions.

The UPLIFT investigators also noted a trend suggesting a decline in mortality among the tiotropium-treated patients that came tantalizingly close to achieving statistical significance. This is the second large trial to have this result. Last year, the Towards a Revolution in COPD Health (TORCH) trial (NCT00268216) also showed a reduction in mortality in the active-treatment group (in which patients received a combination of fluticasone and salmeterol) that came close to but did not achieve conventional statistical criteria for significance.[6] To date, only smoking cessation and, in appropriately selected subgroups of patients, oxygen therapy and surgery for lung-volume reduction have been shown to reduce mortality.

Other than the clinical conclusion that tiotropium should not be prescribed with the goal of disease modification but rather for the alleviation of symptoms, what have we learned from the UPLIFT trial? The pessimistic perspective might be that we have yet to show that any pharmacologic intervention alters the natural history of COPD. A different perspective might be that the issue with this trial, and other recent large trials, is a signal-to-noise problem. In our efforts to simplify and clarify our definition of COPD, we have promulgated an inclusive definition that relies primarily on spirometric measures to establish the diagnosis. There is increasing recognition that FEV_1 alone, while important, does not capture and communicate the heterogeneity of COPD.[12]

In fact, COPD in the singular is probably a misnomer. It is more appropriate to view COPD as a syndrome that encompasses a variety of obstructive diseases that share a common exposure but differ in terms of mechanism of disease and response to therapy. This concept is expressed in the mathematical notation

$$\mathrm{COPD} \stackrel{?}{=} \sum_{n=1} (\mathrm{COPD}_n),$$

in which $COPD_n$ represents subgroups of COPD. As a reflection of this recognized heterogeneity, investigators have developed new classification systems, such as the BODE index, which evaluates the body-mass index, the degree of airflow obstruction and dyspnea, and exercise capacity to create a 10-point scale in which higher scores indicate a higher risk of death. In addition, investigators have attempted to define other homogeneous subgroups of patients with COPD.[12]

The definition of meaningful subgroups will be crucial to achieving two goals. First, it will help to ensure that therapies that are effective in a subgroup of patients with COPD (such as oxygen therapy and lung-volume reduction) will not be discarded on the basis of results of studies that included patients with various types of COPD. Second, the use of highly refined entry criteria will facilitate genetic and mechanistic studies

and should allow for the conduct of meaningful trials with smaller numbers of patients.

This process will be an iterative one, in which the use of post hoc analyses of large data sets, such as those in the UPLIFT trial, will be used to generate proposed definitions of subgroups that can be prospectively tested. Although the characteristics that will define these subgroups remain to be determined and will probably include clinical, physiological, radiologic, and genetic measures, it is clear that the use of FEV_1 alone is not sufficient.

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UKPDS and the Legacy Effect

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The United Kingdom Prospective Diabetes Study (UKPDS) continues to produce important evidence concerning the evolution of type 2 diabetes and its management. Two studies published in this issue of the *Journal* provide some answers to two questions of fundamental importance to patients with diabetes and to physicians alike. In one article, Holman et al. (UKPDS 80)[1] provide data that confirm a so-called legacy effect associated with intensive glucose control in patients with type 2 diabetes, long after the cessation of randomized intervention. This finding provides a fitting parallel to the observations of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications (DCCT/EDIC) study in patients with type 1 diabetes.[2] In the other article, Holman et al. (UKPDS 81)[3] present the opposite conclusion with respect to blood pressure, reporting that there is no such sustained effect with intensive control of blood pressure and that good blood-pressure control must be continued if the benefits are to be maintained.

In the original UKPDS, which involved 5102 patients with newly diagnosed type 2 diabetes, 4209 patients were randomly assigned to receive either conventional therapy (diet alone) or intensive therapy (either sulfonylurea or insulin or, in overweight patients, metformin) for glucose control, whereas 1148 patients who also had hypertension were randomly assigned to tight or less-tight regimens for blood-pressure control.[1,3-5] In post-trial monitoring, patients returned to community- or hospital-based diabetes care with no attempt to maintain their previously randomized therapies. Patients were seen annually for